

Mini Review

*Corresponding author

Vincent PAVOT, PhD

Postdoctoral Research Scientist
The Jenner Institute
University of Oxford
Old Road Campus Research Building
Roosevelt Drive
Oxford OX3 7DQ, UK
Tel. +44 (0)1865 617637
E-mail: vincent.pavot@ndm.ox.ac.uk

Volume 1 : Issue 1

Article Ref. #: 1000VROJ1101

Article History

Received: January 26th, 2016

Accepted: February 13th, 2016

Published: February 17th, 2016

Citation

Pavot V. Leading Ebola vaccine candidates. *Vaccin Res Open J.* 2016; 1(1): 1-6. doi: [10.17140/VROJ-1-101](https://doi.org/10.17140/VROJ-1-101)

Copyright

©2016 Pavot V. This is an open access article distributed under the Creative Commons Attribution 4.0 International License (CC BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Leading Ebola Vaccine Candidates

Vincent Pavot, PhD*

The Jenner Institute, University of Oxford, Oxford, OX3 7DQ, UK

The ongoing outbreak of Ebola Virus Disease (EVD) in West Africa is the largest outbreak ever recorded with a total number of 28,602 confirmed, probable, or suspected cases in Guinea, Liberia, and Sierra Leone, including 11,301 reported deaths since December 2013 (as of January 17, 2016).¹ A meeting convened by the World Health Organization (WHO) in September, 2014, concluded that an urgent unmet need exists for efficacy and safety testing of the EVD vaccine candidates and that clinical trials should be expedited. These vaccines could be used both in an outbreak setting and to provide long-term protection in populations at risk of sporadic outbreaks.

A number of vaccines have been evaluated in phase 1 trials including DNA vaccines, virus-like particles and viral vectors,² but the two most advanced first-generation Ebola vaccine candidates are the live replicating Vesicular Stomatitis Virus (rVSV) and the replication-defective chimpanzee adenovirus 3 (ChAd3).

rVSV-ZEBOV

The replication-competent recombinant vesicular stomatitis virus (rVSV)-based vaccine expressing the Glycoprotein (GP) of a Zaire strain of Ebola virus (ZEBOV) is among the leading Ebola vaccine candidates and has been rapidly progressed to a phase 3 efficacy trial in Guinea.

A key determinant of VSV pathogenicity is the surface GP which is also the predominant target for immune responses. The rVSV Ebola vaccine (rVSV-ZEBOV) is designed to exploit this by replacing the VSV-GP with a GP from the Zaire Ebola virus (strain Kikwit-95). This chimeric design with switching of GPs attenuates the pathogenicity of the virus while allowing the vaccine virus to replicate using the Ebola GP to attach and enter cells.³

The vaccine was developed by the Public Health Agency of Canada, licensed to Bio-Protection Systems (NewLink Genetics, IA, USA), and most recently sublicensed to Merck, which is responsible for ongoing research and development.

The rVSV-ZEBOV vaccine has been assessed in eight phase 1 studies in Europe, Africa, and North America; a large phase 2 study (the PREVAIL study, NCT02344407) in Liberia; and an ongoing phase 3 study in Sierra Leone (the STRIVE study, NCT02378753) and more than 9000 volunteers have received this vaccine so far.

Preliminary results from open-label, dose-escalation phase 1 trials and randomized, double-blind, placebo-controlled phase 1 trials have been reported in April 2015 in *The New England Journal of Medicine*.^{4,5} These trials assessed safety, side-effect profiles, and immunogenicity of rVSV-ZEBOV at various doses in healthy adults in Europe, Africa and US. Participants were injected intramuscularly (IM) with doses of vaccine ranging from 300,000 to 50 million Plaque-Forming Units (PFU) or placebo.

The most common adverse events were injection-site pain, myalgia, and fatigue. Transient VSV viremia was detected within 3 days in most participants receiving 3 million PFU or more. Fever was observed in up to 35% of vaccinees. At the Geneva trial site where participants were dosed with 10 million or 50 million PFU of rVSV-ZEBOV, 11/51 participants developed

arthralgia in the second week after injection.⁴ Reducing the dose of rVSV-ZEBOV from 10 million (or greater) to 300,000 PFU improved its early tolerability but lowered antibody (Ab) responses and did not prevent vaccine-induced arthritis, dermatitis, or vasculitis.⁵ Thus, although the mechanism of this arthritis remains unclear, it is likely that local VSV replication may play a role. It will be critical to confirm the frequency of these side effects in the large phase 3 efficacy trial being run in Guinea to enable a more informed evaluation of the risk of live rVSV vaccination.

Regarding the induction of specific Abs, the rVSV-ZEBOV vaccine generated GP-binding Abs in all participants at all doses (as few as 300,000 PFU may be sufficient), showing its immunogenicity in humans. In the study undertaken in the US, Ab titers against the Ebola Zaire GP, at day 28, were higher in the group receiving 20 million PFU than in the group receiving 3 million PFU.⁶ These data support continued development of the rVSV-ZEBOV Ebola vaccine candidate in general and the selection of a dose of 20 million PFU for phase 2 and 3 trials.

It was noteworthy that despite similar GP-binding Ab titers between groups administered with doses between 3 million and 50 million PFU, higher vaccine doses elicited higher titers of neutralizing Abs to the Ebola Zaire GP. Since the relative roles of neutralizing and GP-binding Abs in protection against Ebola virus disease are unknown, it is difficult to conclude whether higher vaccine doses are required for optimal protection. However, a preliminary comparison of data from Non-Human Primates (NHPs) vaccinated with the same doses (3 million or 20 million PFU) used in the US trials, then subsequently challenged with Ebola-Kikwit strain virus, showed that survivors had significant pre-challenge IgG-Ab responses against Ebola GP, as seen in vaccinated human volunteers.⁵

Further follow up from these studies to determine the durability of Ab responses is awaited. One important unanswered question is whether rVSV induces any cellular immunity and how these immune responses correlate with protection.

The *Ebola ça Suffit* ("Ebola this is enough") phase 3 trial is currently underway in Guinea to assess the efficacy of the rVSV-ZEBOV candidate vaccine for the prevention of EVD. The preliminary report of the Guinea trial, published in August 2015 in *The Lancet*, reported very encouraging results following a planned interim analysis.⁷ The trial tested a ring vaccination design, a strategy that was borrowed from successful smallpox eradication efforts in the 1970s; after one patient contracts the disease, close contacts are identified and those who are eligible to receive vaccination and can give consent are vaccinated in the hope of stemming the onward spread of the virus.

The Guinea trial included two arms: one in which adults who had been in contact with someone infected with Ebola and their subsequent contacts were vaccinated shortly after the original patient developed Ebola, and a second in which contacts instead received the vaccine three weeks later (one dose of 20

million PFU, administered IM).

Between April 1, 2015, and July 20, 2015, 7651 people were included in the planned interim analysis. Four-thousand one-hundred and twenty-three people were randomly assigned to immediate vaccination with rVSV-ZEBOV, and 3528 people were randomly assigned to delayed vaccination. In the immediate vaccination group, there were no cases of Ebola virus disease with symptom onset at least 10 days after randomization, whereas in the delayed vaccination group there were 16 cases of EVD. The findings mean that the vaccine provided 100% protection from the virus, though the study's small size means that the vaccine's true protection rate may be slightly lower. The authors of the paper estimate its true effectiveness at between 75% and 100%. No new cases of EVD were diagnosed in vaccinees from the immediate or delayed groups from 6 days post-vaccination. Forty-three serious adverse events were reported; one serious adverse event was judged to be causally related to vaccination (a febrile episode which resolved without sequelae).

This study enables some cautious preliminary conclusions and suggests that rVSV confers protection between 6-21 days after vaccination; how much longer vaccine-induced protection lasts is unknown. Vaccine failures within the first 6 days would suggest that vaccine-induced protection needs at least a week to reach effective levels and raises some doubt on the claim that rVSV could work rapidly and provide post exposure prophylaxis. A non-significant indirect protective effect among unvaccinated individuals was also observed. The magnitude of this effect and whether it was mediated through a reduced viral load and transmission remains to be determined. Lastly, this study offers a unique opportunity to identify vaccine-induced correlates of protection. In phase 1 trials, the Ab titers induced by rVSV vaccination reached titers associated with protection in NHPs only by 28 days post vaccination,⁸ implying that the Ab titer required for protection of humans against naturally acquired infection is likely lower than that required for protection of NHPs against controlled challenge.

In the wake of the trial results, the WHO has decided that the rVSV-ZEBOV vaccine will continue to be used in the outbreak in Guinea as part of the clinical trial. A combined phase 2 and phase 3 clinical trial designed to assess the safety of the rVSV-ZEBOV candidate (20 million PFU) is being conducted in Sierra Leone (STRIVE: Sierra Leone Trial to Introduce a Vaccine against Ebola).

rVSV-ZEBOV remains a 'first-generation' vaccine that is not ideal for stockpiling: it must be stored at -80 °C and only protects against a limited number of species of the Ebola virus. Gavi, the vaccine alliance in Geneva, Switzerland, will work with researchers and industry to support the development of second-generation Ebola vaccines that target other Ebola virus species, as well as the closely related Marburg virus, and which do not require storage in expensive, laboratory-grade freezers. Gavi has signed an advance purchase agreement with Merck that gives the drug company \$5 million to develop the

rVSV-ZEBOV-GP Ebola Zaire vaccine. The agreement is based on the understanding that 300,000 doses of the vaccine will be available for clinical trials or emergency use by May 2016 and that the vaccine will be submitted for full licensure by the end of 2017.⁹

ChAd3-ZEBOV

The monovalent, replication-deficient, chimpanzee adenovirus type-3 vector-based Ebola Zaire vaccine (ChAd3-ZEBOV, also known as ChAd3-EBO-Z or cAd3-ZEBOV) encoding the Ebola GP from the Zaire strain has undergone extensive preclinical development and is now among the leading Ebola vaccine candidates. The original clinical-development plan for this Ebola vaccine, primarily for biodefense, included the use of a bivalent vaccine formulation of Zaire and Sudan strains¹⁰ that would use both ChAd3 and Modified Vaccinia virus Ankara (MVA) viral vectors. The ChAd3 vaccine encoding just the Zaire strain appeared to be a potentially advantageous monovalent formulation for outbreak control on the basis of efficacy data in macaques and was thus selected for phase 1 clinical testing.

The ChAd3-ZEBOV was developed by the Vaccine Research Center (VRC) of the National Institute of Allergy and Infectious Diseases (NIAID) in collaboration with Okairios (now a division of GlaxoSmithKline).¹¹

The ChAd3-ZEBOV had already been manufactured to clinical grade at the time of the acceleration of the EVD outbreak in early August 2014. These events provided the opportunity to design a rapid clinical development program that could lead to deployment of the vaccine. In September 2014, two phase 1 clinical trials began and have reported preliminary results on the use of a single dose of ChAd3. The dose-escalation clinical trial, called VRC 207, was performed in the US (conducted at the National Institutes of Health – NIH), to determine the safety, side-effect profile, and immunogenicity of the bivalent vaccine that included ChAd3-EBO glycoprotein Zaire and ChAd3-EBO glycoprotein Sudan, in a 1:1 ratio.¹⁰ A total of 20 participants were enrolled and vaccinated with a single dose of vaccine administered IM at a dose of 2×10^{10} particle units (pu) or 2×10^{11} pu. This bivalent vaccine was well tolerated with self-resolving mild to moderate side effects. As expected, the higher dose induced significantly higher magnitude of Abs and T-cells compared with the lower dose, with responses peaking 4 weeks after vaccination. The authors found that Ab titers in individuals vaccinated with the higher dose were within the range associated with protection in NHP models.^{11,12}

The second phase 1 clinical trial, called EBL01, began in the UK at the Jenner Institute (University of Oxford). EBL01 was a dose-escalation, open-label study assessing the safety and immunogenicity of the monovalent ChAd3-ZEBOV.¹³ Three dose-specific groups of 20 volunteers each were recruited for the trial and were assigned to receive the ChAd3 vaccine as a single IM injection: 1×10^{10} pu, 2.5×10^{10} pu or 5×10^{10} pu.

The safety profile was similar to that observed in the US study, with no vaccine-related serious adverse event at any of the dose levels studied (fever developed in 2 of the 59 participants who were evaluated).

Ab responses were higher at 4 weeks in the high-dose group. However, in contrast to the US study, GP-specific Ab titers were lower than those induced in macaques protected by the same vaccine. At the vaccine doses tested, T-cell responses were detected (more CD4⁺ than CD8⁺ T-cell responses according to the secretion of IFN- γ , IL-2, or TNF- α) and peaked at 14 days rather than 28 days as observed in the US study.

Between October 24, 2014, and June 22, 2015, a third phase 1/2a trial evaluating safety and immunogenicity of ChAd3-ZEBOV was performed at the Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (trial number NCT02289027).¹⁴ In this randomized, double-blind, placebo-controlled, dose-finding trial, participants received a single IM dose of low-dose vaccine (2.5×10^{10} pu), high-dose vaccine (5×10^{10} pu) or placebo.

A sample size of 100 vaccinated participants was calculated to achieve a total of 250 vaccinated participants, taking into account all three concurrent phase 1 trials of the ChAd3-ZEBOV vaccine (Lausanne, Oxford, and Mali). This sample size was expected to produce reliable data for the incidence of frequent adverse events.¹⁴ Although the safety data were roughly similar to those reported in the Oxford trial, with headache, fatigue, and malaise being the most common adverse events, the frequency of adverse events was higher in the Lausanne study. Only 5% (n=2) of participants had objective fever in the Oxford study, compared with 28% of participants in the Lausanne study. Overall, the ChAd3-ZEBOV was safe and well tolerated, although mild to moderate systemic adverse events were common. All vaccine recipients had humoral immune responses that peaked at day 28, and then decreased by about half 6 months after vaccination but still significantly present.

The Lausanne trial was the only one that was placebo-controlled, allowing for the most accurate assessment of safety and reactogenicity. Among all Ebola vaccine trials, this is the only one that has so far reported safety and immunogenicity results up to 6 months after injection, which provides some insight into the value of the vaccine over the course of an epidemic. When compared with results of the rVSV-vectored Ebola vaccine at 20 million or 50 million PFU, the safety profile of the ChAd3-ZEBOV at doses of 10^{10} pu is slightly better, but the humoral responses 1 month after injection are slightly lower. In view of the good safety profile of ChAd3-ZEBOV at doses of 10^{10} pu in the present trial, the authors state that the 10^{11} pu dose would seem appropriate to use when proceeding to phase 2 and 3 trials in Africa as planned, especially because the few available safety data with ChAd3-ZEBOV at 10^{11} pu show an acceptable adverse events profile and, more importantly, similar Ab responses, as those obtained with the 20 million PFU dose of the rVSV-ZEBOV. Assuming that the anti-GP antibody concentration is correlated with protection, the promising efficacy results

reported in the preliminary report of the rVSV-vectored vaccine in the phase 3 trial in Guinea could also be obtained with the ChAd3-ZEBOV vaccine at a dose of 10^{11} pu. The persistence of Abs at month 6, although at a reduced concentration, might suggest that some protection remains. However, this theory needs to be confirmed in a thorough phase 3 trials. Detailed correlation of immunological data and protection in NHP studies might also give some insight into efficacy, if a phase 3 trial becomes impossible to do due to an insufficient number of new cases of EVD.

PRIME-BOOST STRATEGIES

ChAd3-ZEBOV/MVA-BN-Filo

Findings from studies in NHPs have shown that both immunogenicity and duration of high-level protection against challenge can be extended by administration of a dose of MVA-encoding Zaire Ebola virus GP.¹¹ Then, the effect of boosting in humans with a heterologous vector, MVA-BN-Filo vaccine (developed by Bavarian Nordic A/S) – which encodes Zaire Ebola virus and Sudan Ebola virus GP, Marburg virus GP, and Tai-Forest Ebola virus nucleoprotein – was assessed in Malian and US adults.¹⁵

The phase 1, single-blind, randomized trial of ChAd3-ZEBOV was performed in the US and the phase 1b, open-label and double-blind, dose-escalation trial in Bamako (Mali) (trial numbers NCT02231866 (US) and NCT02267109 (Malian)).

Between October 8, 2014, and February 16, 2015, participants were randomly allocated to different single doses of IM immunization with ChAd3-ZEBOV: 91 Malians received 1×10^{10} pu, 2.5×10^{10} pu, 5×10^{10} pu, or 1×10^{11} pu; 10 US participants received 1×10^{10} pu or 1×10^{11} pu. Fifty-two of the 91 Malians received a single boost-dose of 2×10^8 PFU of MVA-BN-Filo or placebo.

The primary outcome was safety, measured with occurrence of adverse events for 7 days after vaccination. The results in both Malian and US participants document that the 1×10^{11} pu dose of ChAd3-ZEBOV is well tolerated and significantly more immunogenic than are low doses in elicitation of anti-GP antibodies. Ninety-one percent of Malian and 60% of US participants given a single dose of ChAd3-ZEBOV attained titers that are associated with protection of NHPs. A single booster dose of MVA-BN-Filo stimulated anamnestic anti-GP antibody and CD4/CD8 T-cell responses, suggesting, by extrapolation from results in NHPs, that this booster might extend the duration of high-level protection.

With optimistic extrapolation of these results, a single 1×10^{11} pu dose of ChAd3-ZEBOV, used as part of a ring vaccination strategy, might be sufficiently well tolerated and immunogenic to be effective in interrupting Ebola virus transmission to family members and other close contacts of index patients. A heterologous prime and boost regimen consisting of a ChAd3-

ZEBOV prime followed 2-3 months afterwards by a boost with MVA-BN-Filo could confer long-term protection to subgroups that need extended protection (e.g. health-care workers and populations that are likely to be repeatedly exposed).

Ad26-ZEBOV/MVA-BN-Filo

NIAID and other funding partners supported the development, preclinical and clinical testing of an investigational vaccine regimen designed to specifically protect against the Ebola virus strains responsible for the recent outbreak in West Africa. The vaccine candidate combines the Ad26-ZEBOV vector (based on the AdVac platform developed by Crucell Holland B.V., one of the Janssen Pharmaceutical Companies of Johnson & Johnson) with the MVA-BN-Filo. This product commenced a phase 1 clinical trial in Oxford during January 2015. Preliminary data from the first-in-human study, presented by Janssen in May 2015, indicated that the prime-boost vaccine regimen is immunogenic, regardless of the order of vaccine administration, and provoked only temporary adverse reactions normally expected from vaccination.¹⁶

Additional phase 1 trials are underway in Africa. In July 2015, Crucell initiated a phase 2 clinical trial of the investigational vaccine in the UK and France. The study is evaluating the safety, tolerability and immunogenicity of the heterologous prime-boost regimen. In total, the studies enrolled 612 healthy adult volunteers, all receiving the Ad26-ZEBOV prime or placebo on day 1 and then the MVA-BN-Filo boost or placebo on days 29, 57 or 85.

In October 2015, Crucell launched a second phase 2 study in 1,200 volunteers in Sierra Leone. The first stage of the study called “EBOVAC-Salone” includes approximately 40 adults aged 18 years or older. In stage 2, approximately 400 individuals across different age groups will be vaccinated, including children and adolescents.¹⁷

CONCLUSION

The recent Ebola epidemic has galvanized the development of filovirus vaccines and presented a unique set of challenges that required extraordinary collaboration, flexibility, and innovation among a number of entities with a broad range of expertise to secure global health. These entities included government agencies, especially health officials from the affected West African countries, non-governmental organizations, academic research groups, pharmaceutical companies, and the WHO. This led to an unprecedented speed of Ebola vaccine testing since late 2014 with multiple candidates in advanced stages of clinical development.

Current efforts to develop a vaccine are focused on the viral GP encoded by the virus. The most advanced first-generation Ebola vaccines candidates tested so far are the live replicating rVSV-ZEBOV and the replication-defective ChAd3-ZE-

BOV based on the GP from the Zaire strain of Ebola virus. Trials being undertaken in Africa, Europe and US have already shown that these vaccines are safe and well-tolerated and, although a human correlate of protection remains unknown, a single dose of rVSV-ZEBOV or ChAd3-ZEBOV is able to generate putatively protective Ab titers. ChAd3 vaccine on its own especially at 10^{11} should be effective as it produces Ab titers at least as high as VSV and greater cellular immunity (which is relevant at least in NHPs).

These immune responses are significantly enhanced in prime-boost regimes using MVA-based virus vectors as a boosting vaccination, although the optimal interval between the priming and boosting vaccination has not yet been determined.

Although the promising efficacy of rVSV vaccine is encouraging, challenges remain in improving vaccines to provide durable efficacy and identifying optimal ways for vaccine deployment. Moreover, as a general rule, live-replicating viruses such as VSV-vectored vaccines are contraindicated in people with an immunodeficiency (e.g. HIV⁺) and children, since the vaccine strain could be pathogenic, particularly when non-replicating viral vectors such as adenoviruses have shown good safety in those two groups. Clinical assessment should continue to allow a full comparison of ChAd3 alone, ChAd3/MVA, Ad26/MVA and rVSV for safety, with particular emphasis on the rate of post-vaccination fevers and arthritis, and for immunogenicity, preferably in African populations where the vaccine will be needed in future.

Some 300,000 doses of rVSV-ZEBOV vaccine against EVD will be available from May 2016 for use in emergency situations and clinical trials, under a deal signed by the drug company Merck and by Gavi, a vaccine provider to the poorest countries in the world.

REFERENCES

1. 2014 Ebola outbreak in West Africa - case counts. Centers for Disease Control and Prevention. Web site. <http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/case-counts.html>. Updated February 10, 2016. Accessed February 15, 2016.
2. Sridhar S. Clinical development of Ebola vaccines. *Therapeutic Advances in Vaccines*. 2015; 3:125-138. doi: [10.1177/2051013615611017](https://doi.org/10.1177/2051013615611017)
3. Jones SM, Feldmann H, Stroher U, et al. Live attenuated recombinant vaccine protects nonhuman primates against Ebola and Marburg viruses. *Nature Medicine*. 2005; 11: 786-790. doi: [10.1038/nm1258](https://doi.org/10.1038/nm1258)
4. Agnandji ST, Huttner A, Zinser ME, et al. Phase 1 trials of rVSV Ebola vaccine in Africa and Europe - preliminary report. *The New England Journal of Medicine*. 2015. doi: [10.1056/NEJMoa1502924](https://doi.org/10.1056/NEJMoa1502924)
5. Regules JA, Beigel JH, Paolino KM, et al. A recombinant vesicular stomatitis virus ebola vaccine - preliminary report. *The New England Journal of Medicine*. 2015. doi: [10.1056/NEJMoa1414216](https://doi.org/10.1056/NEJMoa1414216)
6. Huttner A, Dayer JA, Yerly S, et al. The effect of dose on the safety and immunogenicity of the VSV Ebola candidate vaccine: a randomised double-blind, placebo-controlled phase 1/2 trial. *The Lancet Infectious Diseases*. 2015; 15: 1156-1166. doi: [10.1016/S1473-3099\(15\)00154-1](https://doi.org/10.1016/S1473-3099(15)00154-1)
7. Henao-Restrepo AM, Longini IM, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. *Lancet*. 2015; 386: 857-866. doi: [10.1016/S0140-6736\(15\)61117-5](https://doi.org/10.1016/S0140-6736(15)61117-5)
8. Geisbert TW, Feldmann H. Recombinant vesicular stomatitis virus-based vaccines against Ebola and Marburg virus infections. *The Journal of Infectious Diseases*. 2011; 204 Suppl 3: S1075-S1081. doi: [10.1371/journal.pntd.0001567](https://doi.org/10.1371/journal.pntd.0001567)
9. Gulland A. Ebola vaccine will be made available for emergency use. *BMJ*. 2016; 352: i386. doi: [10.1136/bmj.i386](https://doi.org/10.1136/bmj.i386)
10. Ledgerwood JE, DeZure AD, Stanley DA, et al. Chimpanzee Adenovirus Vector Ebola Vaccine - Preliminary Report. *The New England Journal of Medicine*. 2014. doi: [10.1056/NEJMoa1410863](https://doi.org/10.1056/NEJMoa1410863)
11. Stanley DA, Honko AN, Asiedu C, et al. Chimpanzee adenovirus vaccine generates acute and durable protective immunity against ebolavirus challenge. *Nature Medicine*. 2014; 20: 1126-1129. doi: [10.1038/nm.3702](https://doi.org/10.1038/nm.3702)
12. Sullivan NJ, Martin JE, Graham BS, Nabel GJ. Correlates of protective immunity for Ebola vaccines: implications for regulatory approval by the animal rule. *Nature Reviews Microbiology*. 2009; 7: 393-400. doi: [10.1038/nrmicro2129](https://doi.org/10.1038/nrmicro2129)
13. Rampling T, Ewer K, Bowyer G, et al. A Monovalent Chimpanzee Adenovirus Ebola Vaccine - Preliminary Report. *The New England Journal of Medicine*. 2015. doi: [10.1056/NEJMoa1411627](https://doi.org/10.1056/NEJMoa1411627)
14. De Santis O, Audran R, Pothin E, et al. Safety and immunogenicity of a chimpanzee adenovirus-vectored Ebola vaccine in healthy adults: a randomised, double-blind, placebo-controlled, dose-finding, phase 1/2a study. *The Lancet Infectious Diseases*. 2015. doi: [10.1016/S1473-3099\(15\)00486-7](https://doi.org/10.1016/S1473-3099(15)00486-7)
15. Tapia MD, Sow SO, Lyke KE, et al. Use of ChAd3-EBO-Z Ebola virus vaccine in Malian and US adults, and boosting of Malian adults with MVA-BN-Filo: a phase 1, single-blind, randomised trial, a phase 1b, open-label and double-blind, dose-escalation trial, and a nested, randomised, double-blind, placebo-

bo-controlled trial. *The Lancet Infectious Diseases*. 2016; 16: 31-42. doi: [10.1016/S1473-3099\(15\)00362-X](https://doi.org/10.1016/S1473-3099(15)00362-X)

16. Johnson & Johnson Announces Major Commitment to Speed Ebola Vaccine Development and Significantly Expand Production. Johnson & Johnson. Web site. <http://www.jnj.com/news/all/Johnson-Johnson-Announces-Major-Commitment-to-Speed-Ebola-Vaccine-Development-and-Significantly-Expand-Production>. Accessed January 25, 2016.

17. Staged phase 3 Study to Assess the Safety and Immunogenicity of Ebola Candidate Vaccines Ad26.ZEBOV and MVA-BN-Filo During Implementation of Stages 1 and 2 (EBOVAC-Salone). ClinicalTrials.gov. Web site. <https://clinicaltrials.gov/ct2/show/NCT02509494>. Accessed January 25, 2016.