Published in final edited form as:

Lancet. 2015 June 06; 385(9984): 2229–2230. doi:10.1016/S0140-6736(15)60613-4.

An updated Ebola vaccine: immunogenic, but will it protect?

Andrea Marzi and

Laboratory of Virology, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, MT, USA (AM)

Darryl Falzarano

VIDO-InterVac, University of Saskatchewan, Saskatoon, SK S7N 5E3, Canada (DF)

Graphical Abstract

The largest outbreak of Ebola virus ever recorded has been ongoing for about 16 months in west Africa. In the past week, Liberia, which had nearly reached the halfway point to being declared Ebola free, has reported a new case, and new Ebola infections continue to be confirmed in Sierra Leone and Guinea.¹ With more than 24 000 cases and almost 10 000 fatalities,¹ this outbreak is one of the biggest public health crises so far this century. When the outbreak was first confirmed in March, 2014, none of the experimental vaccine platforms with promising results in non-human primate studies² had advanced beyond assessment in phase 1 clinical trials in human beings, let alone been approved for human use. But only a few months later, with the epidemic spreading and thousands of people infected in west

We declare no competing interests.

Africa, the international community pulled together to accelerate phase 1 clinical trials in humans for vaccine platforms based on recombinant adenovirus ([ClinicalTrials.gov](https://clinicaltrials.gov) numbers NCT02289027, NCT02368119, NCT02231866, NCT02354404, NCT02240875, NCT02267109) and vesicular stomatitis virus (NCT02287480, NCT02269423, NCT02296983, NCT02314923, NCT02280408, NCT02374385, NCT02283099).

The timely study by Feng-Cai Zhu and colleagues³ in *The Lancet* is the fourth report of a phase 1 trial in humans using either recombinant adenovirus-based or DNA-based vaccination strategies.^{4–6} The recombinant adenovirus type-5 vaccine platform has previously been tested by other investigators with a prototypic Ebola virus glycoprotein.² The present study updated the vaccine vector to encode the glycoprotein from the 2014 west African Ebola virus isolate, making it the first Ebola vaccine report to use an immunogen that matches that of the currently circulating Ebola virus strain.

In the study, 120 healthy Chinese individuals were randomly assigned to receive placebo (n=40), or a low dose (4×10^{10} viral particles; n=40) or high dose (1.6×10^{11} viral particles; n=40) of the recombinant adenovirus type-5 vaccine.³ In each group, roughly 60% of the participants had pre-existing neutralising antibody titres greater than 1:200 to adenovirus type-5. In a previous phase 1 trial based on a different recombinant adenovirus type-5-based Ebola vaccine vector with promising data in non-human primates, pre-existing adenovirus type-5 neutralising antibodies negatively affected the immune response to the vaccine (55% vs 100% response).^{2,7} These data provided the basis for replacement of the adenovirus-type-5 vector with a chimpanzee adenovirus vector.⁵

The increased vaccine doses used in Zhu and colleagues' study³ seem to partly circumvent pre-existing immunity to the vector, because participants in the high-dose group had a 100% response rate, with no resultant increase in adverse events. Glycoprotein-specific antibody titres significantly increased in the low-dose and high-dose vaccine groups at both day 14 (geometric mean titre 421.4 [95% CI 249.7–711.3] and 820.5 [598.9–1124.0], respectively) and day 28 (682.7 [424.3–1098.5] and 1305.7 [970.1–1757.2], respectively), with T-cell responses peaking at day 14 in both these groups (median 465.0 spot-forming cells [IQR 180.0–1202.5] and 765.0 cells [400.0–1460.0], respectively). The antigen-specific immunoglobulin-G responses in participants in the high-dose group with low pre-existing adenovirus type-5 immunity (1:200) resulted in geometric mean titres of 2231.8 (95% CI 1268.6–3926.2) at 4 weeks after vaccination, but titres decreased to 946.5 (705.4–1270.1) when the immunised individuals had pre-existing neutralising titres greater than 1:200. This finding is a major concern about this vaccine platform, because 80% of the target population in Africa are expected to have adenovirus type-5 neutralising antibody titres.⁸ Furthermore, findings from previous studies^{9,10} in nonhuman primates suggest that with adenovirus-based vaccines, an Ebola virus glycoprotein-specific ELISA 90% effective concentration (the metric also used in the present study) titre of 3000 is required for protection, and this concentration was not reached in the present trial, particularly in participants with pre-existing adenovirus type-5 immunity. This recombinant adenovirus-based type-5 Ebola virus vaccine also elicits a similar T-cell response in humans to that shown with the chimpanzee adenovirus vector, peaking 14 days after vaccination.⁵

The glycoprotein from the present outbreak strain has 97% similarity to previously known Ebola virus vaccine isolates,¹¹ and vaccines using the prototypic antigen are expected to protect against infection with the west African isolates. Data from preclinical animal studies will hopefully provide information about the importance of having a vaccine antigen that is identical to that of circulating viruses.

Because Zhu and colleagues' report³ is preliminary, antibody responses have only been assessed up to day 28 after vaccination. Thus, the durability of a single-dose recombinant adenovirus type-5 vaccination is still unknown, and assessment of whether subsequent boosts will be necessary to maintain or establish sufficient long-term immunity will be important. 82 (68%) participants reported at least one solicited adverse reaction within 7 days of vaccination (19 in the placebo group vs 27 in the low-dose group vs 36 in the high-dose group). The only reported adverse event in all three groups was mild pain at the injection site (eight in the placebo group, 14 in the low-dose group, and 29 in the high-dose vaccine group),³ a minor side-effect, suggesting that administration of the high dose probably needed in Africa would be acceptable. However, follow-up was only for 28 days and no conclusion about long-term side-effects can be made.

This adenovirus type-5 Ebola vaccine vector is an example of how quickly existing vaccine platforms can be modified to incorporate a new virus strain, and moved, with minimum testing in animals, into trials in humans during a crisis situation. However, for this vector, efficacy testing in non-human primates to establish whether the high-dose vaccine would be effective against homologous and heterologous Ebola virus strains still needs to be done. The outstanding question remains as to whether DNA, recombinant adenovirus, or recombinant chimpanzee adenovirus vaccine platforms will be more effective than a recombinant vesicular stomatitis virus-based vaccine, which by contrast is fast acting and not affected by pre-existing vector immunity.¹² Ultimately, the effectiveness of all these vaccines will only become clear when they proceed to phase 2 efficacy trials in outbreak regions.

References

1. WHO. Ebola situation report—11 March 2015. 2015 <http://apps.who.int/ebola/current-situation/ebola-situation-report-11-march-2015> (accessed March 16, 2015).
2. Marzi A, Feldmann H. Ebola virus vaccines: an overview of current approaches. *Expert Rev Vaccines* 2014; 13: 521–31. [PubMed: 24575870]
3. Zhu F-C, Hou L-H, Li J-X, et al. Safety and immunogenicity of a novel recombinant adenovirus type-5 vector-based Ebola vaccine in healthy adults in China: preliminary report of a randomised, double-blind, placebo-controlled, phase 1 trial. *Lancet* 2015; published online 3 25 10.1016/S0140-6736(15)60553-0.
4. Kibuuka H, Berkowitz NM, Millard M, et al. Safety and immunogenicity of Ebola virus and Marburg virus glycoprotein DNA vaccines assessed separately and concomitantly in healthy Ugandan adults: a phase 1b, randomised, double-blind, placebo-controlled clinical trial. *Lancet* 2014; published online 12 22 10.1016/S0140-6736(14)62385-0.
5. Ledgerwood JE, DeZure AD, Stanley DA, et al. Chimpanzee adenovirus vector Ebola vaccine—preliminary report. *N Engl J Med* 2014; published online 11 26 DOI:10.1056/NEJMoa1410863.
6. Sarwar UN, Costner P, Enama ME, et al. Safety and immunogenicity of DNA vaccines encoding ebolavirus and marburgvirus wild-type glycoproteins in a phase I clinical trial. *J Infect Dis* 2015; 211: 549–57 [PubMed: 25225676]

7. Ledgerwood JE, Costner P, Desai N, et al. A replication defective recombinant Ad5 vaccine expressing Ebola virus GP is safe and immunogenic in healthy adults. *Vaccine* 2010; 29: 304–13. [PubMed: 21034824]
8. Nwanegbo E, Vardas E, Gao W, et al. Prevalence of neutralizing antibodies to adenoviral serotypes 5 and 35 in the adult populations of The Gambia, South Africa, and the United States. *Clin Diagn Lab Immunol* 2004; 11: 351–57. [PubMed: 15013987]
9. Geisbert TW, Bailey M, Hensley L, et al. Recombinant adenovirus serotype 26 (Ad26) and Ad35 vaccine vectors bypass immunity to Ad5 and protect nonhuman primates against ebolavirus challenge. *J Virol* 2011; 85: 4222–33. [PubMed: 21325402]
10. Stanley DA, Honko AN, Asiedu C, et al. Chimpanzee adenovirus vaccine generates acute and durable protective immunity against ebolavirus challenge. *Nat Med* 2014; 20: 1126–29. [PubMed: 25194571]
11. Baize S, Pannetier D, Oestereich L, et al. Emergence of Zaire Ebola virus disease in Guinea. *N Engl J Med* 2014; 371: 1418–25. [PubMed: 24738640]
12. Lai L, Davey R, Beck A, et al. Emergency postexposure vaccination with vesicular stomatitis virus-vectored Ebola vaccine after needlestick. *JAMA* 2015; published online 3 5 DOI:10.1001/jama.2015.1995.