



Universiteit
Leiden
The Netherlands

Evaluation of waning of IgG antibody responses after rVSVΔG-ZEBOV-GP and Ad26.ZEBOV, MVA-BN-Filo Ebola virus disease vaccines: a modelling study from the PREVAC randomized trial

Valayer, S.; Alexandre, M.; Prague, M.; Beavogui, A.H.; Doumbia, S.; Kieh, M.,; ... ;
PREVAC study team

Citation

Valayer, S., Alexandre, M., Prague, M., Beavogui, A. H., Doumbia, S., Kieh, M. , , ...
Lhomme, E. (2024). Evaluation of waning of IgG antibody responses after rVSVΔG-ZEBOV-GP and Ad26.ZEBOV, MVA-BN-Filo Ebola virus disease vaccines: a modelling study from the PREVAC randomized trial. *Emerging Microbes & Infections*, 14(1).
doi:10.1080/22221751.2024.2432353

Version: Publisher's Version

License: [Creative Commons CC BY 4.0 license](#)

Downloaded from: <https://hdl.handle.net/1887/4296542>

Note: To cite this publication please use the final published version (if applicable).



Evaluation of waning of IgG antibody responses after rVSVΔG-ZEBOV-GP and Ad26.ZEBOV, MVA-BN-Filo Ebola virus disease vaccines: a modelling study from the PREVAC randomized trial

Simon Valayer^{a,b}, Marie Alexandre^{b,c}, Mélanie Prague^{b,c}, Abdoul Habib Beavogui^d, Seydou Doumbia^e, Mark Kieh^f, Brian Greenwood^g, Bailah Leigh^h, Marie Poupelin^b, Christine Schwimmerⁱ, Samba O. Sow^j, Irina Maljkovic Berry^k, Jens H. Kuhn^k, Daniela Fusco^{l,m}, Natasha Dubois Cauwelaertⁿ, Deborah Watson-Jones^g, Rodolphe Thiébaut^{b,c,i,o}, Yves Lévy^{c,n,p}, Yazdan Yazdanpanah^{a,n,q}, Laura Richert^{b,c,i,o}, Edouard Lhomme^{b,c,i,o} and the PREVAC Study Team*

^aInfection, Antimicrobials, Modelling, Evolution (IAME), Université Sorbonne Paris Nord, Université Sorbonne Paris Cité, and Institut national de la santé et de la recherche médicale (Inserm), Paris, France; ^bBordeaux Population Health Research Centre, Université de Bordeaux, Inserm, and Inria, Bordeaux, France; ^cVaccine Research Institute, Faculté de Médecine, Université Paris-Est Créteil, Créteil, France; ^dCentre National de Formation et de Recherche en Santé Rurale (CNFRSR) de Mafèrinyah, Ministère de la Santé et de l'Hygiène Publique, Mafèrinyah, Guinea; ^eUniversity Clinical Research Center, University of Sciences, Technique and Technology of Bamako, Bamako, Mali; ^fPartnership for Research on Ebola Virus in Liberia (PREVAIL), Monrovia, Liberia; ^gLondon School of Hygiene & Tropical Medicine (LSHTM), London, UK; ^hCollege of Medicine and Allied Health Sciences (COMAHS), University of Sierra Leone, Freetown, Sierra Leone; ⁱEuropean Clinical Trials Platform & Development (EUCLID), Université de Bordeaux, Centre Hospitalier Universitaire Bordeaux, and Inserm, ISPED, Bordeaux, France; ^jCentre pour le Développement des Vaccins, Ministère de la Santé et du Développement Social du Mali, Bamako, Mali; ^kIntegrated Research Facility at Fort Detrick, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Frederick, MD, USA; ^lFrench Agency for Research on AIDS and Viral Hepatitis (ANRS), Emerging Infectious Diseases, Paris Santé Campus, Paris, France; ^mDepartment of Infectious Diseases Epidemiology, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany; ⁿInserm, Paris Cedex 13, France; ^oPôle de Santé Publique, Centre Hospitalier Universitaire Bordeaux, Bordeaux, France; ^pService d'Immunologie Clinique et Maladies Infectieuses, Hôpital Henri-Mondor, Créteil, France; ^qService de Maladies Infectieuses et Tropicales, Hôpital Bichat, Paris, France

ABSTRACT

rVSVΔG-ZEBOV-GP and Ad26.ZEBOV, MVA-BN-Filo are WHO-prequalified vaccination regimens against Ebola virus disease (EVD). Challenges associated with measuring long-term clinical protection warrant the evaluation of immune response kinetics after vaccination. Data from a large phase 2 randomized double-blind clinical trial (PREVAC) were used to evaluate waning of anti-Ebola virus (EBOV) glycoprotein (GP_{1,2}) antibody concentrations after rVSVΔG-ZEBOV-GP or Ad26.ZEBOV, MVA-BN-Filo vaccination with linear mixed-effect regression models. After a post-vaccination peak, each vaccination strategy was associated with a decrease of anti-EBOV GP_{1,2} antibody concentrations with distinct kinetics, highlighting a less-rapid decline in antibody levels after vaccination by rVSVΔG-ZEBOV-GP. One year after administration of the vaccine, antibody concentrations were higher in children compared to adults for both vaccines, although with different effect sizes: 1.74-fold higher concentrations (95% confidence interval [CI] [1.48; 2.02]) for children 12–17 years old to 3.10-fold higher concentrations (95% CI [2.58; 3.69]) for those 1–4 years old compared to adults for Ad26.ZEBOV, MVA-BN-Filo versus 1.36-fold (95% CI [1.12; 1.61]) to 1.41-fold (95% CI [1.21; 1.62]) higher than these values for adults, with relatively small changes from one age category to another, for rVSVΔG-ZEBOV-GP. Antibody concentrations also differed according to geographical location, pre-vaccination antibody concentration, and sex. In combination with knowledge on memory response, characterization of the major determinants of immune response durability of both vaccinations may guide future EVD control protocols.

Trial registration: [ClinicalTrials.gov identifier: NCT02876328](https://clinicaltrials.gov/ct2/show/study/NCT02876328).

ARTICLE HISTORY Received 16 July 2024; Revised 28 October 2024; Accepted 17 November 2024

KEYWORDS Ebola virus disease; vaccine; immunogenicity; antibody; Western Africa; modelling

Introduction

Ebola virus (EBOV) has caused recurrent outbreaks of Ebola virus disease (EVD) for more than four decades.

The Western African outbreak (2013–2016) prompted a global research response that included the rapid acceleration of vaccine clinical trials [1,2].

CONTACT Edouard Lhomme ✉ edouard.lhomme@u-bordeaux.fr ✉ SISTM Team – Inserm U1219 Bordeaux Population Health, 146 Rue Léo Saignat, 33000 Bordeaux, France

*Study Group team members are listed in the Acknowledgments.

Supplemental data for this article can be accessed online at <https://doi.org/10.1080/22221751.2024.2432353>.

© 2024 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group, on behalf of Shanghai Shangyixun Cultural Communication Co., Ltd This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. The terms on which this article has been published allow the posting of the Accepted Manuscript in a repository by the author(s) or with their consent.

Two vaccines – rVSVΔG-ZEBOV-GP (based on a recombinant vesicular stomatitis Indiana virus) and Ad26.ZEBOV, MVA-BN-Filo (dose 1 based on a recombinant human adenovirus type 26, followed by dose 2 of modified vaccinia virus Ankara) – have been prequalified by the World Health Organization (WHO) and have received marketing authorization by the European Medicines Agency (EMA) [3]. Also, rVSVΔG-ZEBOV-GP has been licensed by the US Food and Drug Administration (FDA). Both vaccines have been shown immunogenic and safe in numerous clinical trials [4–11]. However, the sporadic nature of EVD outbreaks has limited the ability to conduct large phase 3 efficacy trials, with the notable exception of rVSVΔG-ZEBOV-GP having been shown to provide protection in an immediate-versus-deferred ring vaccination trial, conducted during the 2013–2016 outbreak in Guinea [12]. Efficacy was recently reaffirmed by a study conducted during the 2018–2020 outbreak in the Democratic Republic of the Congo [13]. Although definitive correlates of protection have not yet been demonstrated, previous studies have suggested that immunoglobulin G (IgG) antibodies targeting EBOV glycoprotein (GP_{1,2}) are associated with protection against EVD, albeit without a validated protective threshold [14]. The marketing authorization for Ad26.ZEBOV, MVA-BN-Filo has therefore been primarily based on extrapolation from experimental nonhuman primate efficacy studies and vaccine immunogenicity assessed by antibody responses in human clinical trials. However, the exact level of protection remains unknown.

Both rVSVΔG-ZEBOV-GP and Ad26.ZEBOV, MVA-BN-Filo vaccination strategies have been used widely in recent EVD outbreaks [15–17]. In the absence of trials to assess longer-term efficacy, the characterization of the durability of antibody responses provides an important, albeit partial, indicator of the durability of protection. Additionally, it is important to characterize the host factors that may be associated with the magnitude, kinetics, and durability of the antibody responses to each vaccine. The Partnership for Research on Ebola Vaccinations (PREVAC) [18] has recently published results of its randomized trial evaluating the immunogenicity and safety of antibody responses in adults and children from several Western African countries over a 12-month period following vaccination with either rVSVΔG-ZEBOV-GP or Ad26.ZEBOV, MVA-BN-Filo [19]. Here, we report the results of a modelling study, based on the PREVAC data, that evaluated the kinetics of antibody responses among participants with different demographic characteristics throughout the 12-month period after vaccination.

Materials and methods

Study design and population

The PREVAC trial (NCT02876328) was an international, randomized, double-blinded, placebo-controlled clinical trial that assessed three vaccination strategies in healthy adults and children older than 1 year in Guinea, Liberia, Mali, and Sierra Leone. Vaccine strategies included: (1) one dose of rVSVΔG-ZEBOV-GP, with a second dose at day 56; (2) one dose of rVSVΔG-ZEBOV-GP, followed by a placebo dose at day 56 (referred to as rVSVΔG-ZEBOV-GP-placebo arm); and (3) a dose of Ad26.ZEBOV, followed by a dose of MVA-FN-Filo at day 56. Because rVSVΔG-ZEBOV-GP is approved as a one-dose vaccine regimen, the experimental two-dose arm was not included in this modelling study; rather, modelling was based on data from participants of rVSVΔG-ZEBOV-GP-placebo; Ad26.ZEBOV, MVA-BN-Filo; and pooled “placebo-placebo” arms as defined by the protocol. The primary endpoint of the trial was the anti-EBOV GP_{1,2} IgG antibody concentrations measured 12 months after vaccination [18]. After the initial dose of vaccine or placebo, participants were scheduled for follow-up visits at day 7 (± 3 days), day 14 (± 3 days), and day 28 (± 7 days). All participants were administered a second dose of a vaccine or placebo on day 56 (53–66 days), followed by visits at day 63 (7 ± 3 days after the second dose), month 3 (± 14 days), month 6 (± 1 month), and month 12 (± 1 month).

Antibody assay

Serum concentrations of IgG binding antibodies against EBOV GP_{1,2} were measured before vaccination and at each follow-up visit by the Filovirus Animal Non-Clinical Group (FANG) enzyme-linked immunosorbent assay (ELISA). Details and results from the formal validation of the FANG assay were previously described [20] and discussed in supplementary section S3.6.1 of the PREVAC trial primary publication [19]. The standard operating procedure that contains the FANG assay for the PREVAC trial is in the Supplementary Material. Analyses were performed by two separate laboratories according to the country of participant origin: the Liberian Institute for Biomedical Research (LIBR) in Liberia analyzed samples from Guinea and Sierra Leone, and the National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID) Integrated Research Facility at Fort Detrick (IRF-Frederick) in Maryland, USA, analyzed samples from Liberia and Mali.

Statistical analysis

Linear mixed-effect regression models were used to investigate anti-EBOV GP_{1,2} IgG dynamics after the post-vaccination peak and to determine any association with participant characteristics. Two models were used to independently evaluate the two active vaccination strategies: model A for rVSVΔG-ZEBOV-GP-placebo and pooled placebo arms; model B for Ad26.ZEBOV, MVA-BN-Filo and pooled placebo arms. The dependent variable was the log₁₀-transformed anti-EBOV GP_{1,2} IgG concentrations over time. Modelling began at the peak of anti-EBOV GP_{1,2} IgG concentrations (day 28 for model A and month 3 for model B) and ended at month 12. Time was modelled as a linear trend with one slope for model A (rVSVΔG-ZEBOV-GP) and two slopes for model B (Ad26.ZEBOV, MVA-BN-Filo), with a transition at month 6 to better consider the specific dynamics. The following variables were analyzed as fixed-effect covariates (single-effect and interaction with time): vaccine arm (vaccine versus pooled placebo arms, with placebo as reference), age category (1–4 years, 5–11 years, 12–17 years, ≥18 years [reference]), sex (women, men [reference]), country (Guinea, Liberia, Sierra Leone, Mali [reference]), laboratory for FANG assay analyses, anti-EBOV GP_{1,2} IgG concentrations prior to vaccination, vaccination time (hour in the day) for dose 1 and dose 2, body mass index (BMI; for adults) or Z score (for children), malaria status (defined as a known clinical malaria case within a month prior to the boost), HIV-1 infection status, lymphopenia, neutropenia, and eosinophilia. The analyses were performed on available data; only 5.2% of antibody response measurement data were missing (all time points considered) and considered missing at random. To build the multivariate model and to find the best trade-off between the goodness of fit and model simplicity, the final selection among the multivariable models was guided by the Akaike Information Criterion (AIC). An effect was considered significant if the *p*-value was less than 0.05 using a Wald test. Both models included a random effect on the intercept, and model A included a random effect on the slope. Both models were fitted using restricted maximum-likelihood estimation (REML). The fixed-effect covariates in the final model were determined to be age category, sex (only for the rVSVΔG-ZEBOV-GP-placebo arm), country, and pre-vaccination anti-EBOV GP_{1,2} IgG concentrations. The performance of the models in predicting the anti-EBOV GP_{1,2} IgG concentrations at month 12 was evaluated by a leave-one-out cross-validation.

For both models, the effect of each covariate is presented as a ratio of the geometric mean concentrations (GMCs) in a natural scale between the category of interest and its reference. In addition, tables were

created for the probability of reaching a concentration threshold (200; 600; and 1000 EU/mL, corresponding to empirical thresholds used in previous clinical trials [19,21] with unknown clinical significance) at the end of the study and the time required after the beginning of the vaccination strategy for 50% of the population to drop below the anti-EBOV GP_{1,2} IgG GMC threshold, according to the age category (and sex for the rVSVΔG-ZEBOV-GP arm). Additional details regarding the analyses are provided in the Supplementary Material. All analyses were performed with R, version 4.1.3 (R Foundation for Statistical Computing).

Results

Study population

The PREVAC randomized trial enrolled 1400 adults and 1401 children. Participants with administration errors, missing covariate data, and total missing data on the antibody levels within the model timeframe were removed from the analyses. Thus, we utilized data from 781 (out of 802) participants randomized to the single-dose rVSVΔG-ZEBOV-GP arm (administered as rVSVΔG-ZEBOV-GP-placebo), 779 (out of 799) participants randomized to the Ad26.ZEBOV, MVA-BN-Filo arm, and 791 and 786 (out of 801) participants randomized to the pooled placebo arm in models A and B, respectively. The age, sex, country, and an anti-EBOV IgG concentration of >200 EU/mL prior to vaccination were well-balanced among arms [19].

Anti-EBOV GP_{1,2} IgG dynamics

Both vaccination strategies resulted in robust peak IgG responses when measured approximately 28–34 days after completion of the respective vaccination regimen. Graphical representations of the multivariable models' outputs are presented for the overall population, by age, sex (Figure 1), country, and pre-vaccination antibody concentrations (see Supplementary Material). Very slow waning anti-EBOV GP_{1,2} IgG (GMCs) were observed after rVSVΔG-ZEBOV-GP vaccination from the peak (28 days) to month 12. Although the early post-vaccination peak was higher after Ad26.ZEBOV, MVA-BN-Filo vaccination, anti-EBOV GP_{1,2} IgG GMCs decreased at two different rates from the peak (month 3, after dose 1), with rapid decline to month 6 and slower decline from month 6 to month 12.

Determinants of rVSVΔG-ZEBOV-GP single-dose vaccination and antibody concentration

The anti-EBOV GP_{1,2} IgG response after a single dose of rVSVΔG-ZEBOV-GP varied according to

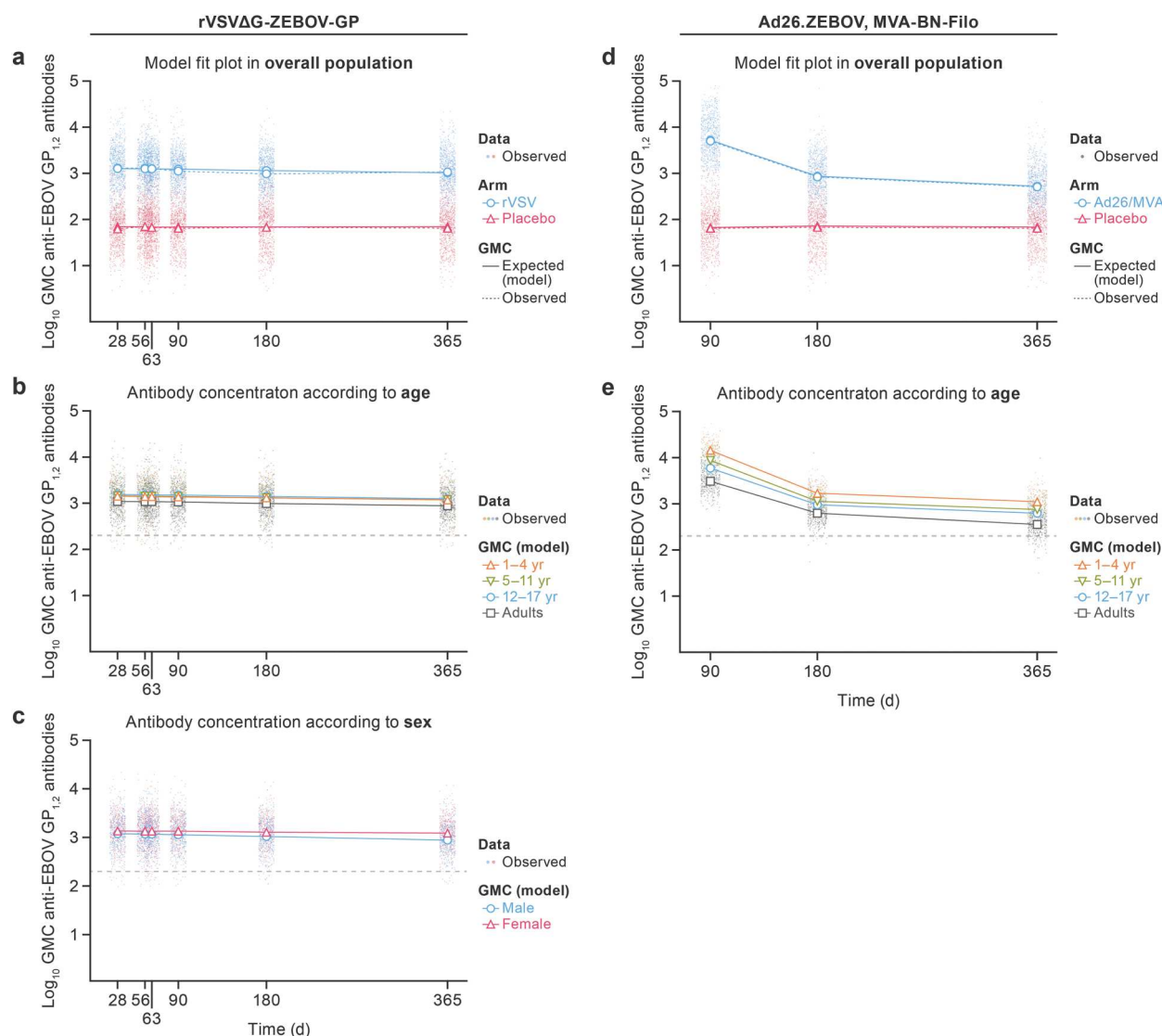


Figure 1. Anti-EBOV GP_{1,2} IgG response (EU/mL) from the post-vaccination peak to 12 months after the first dose of rVSVΔG-ZEBOV-GP or Ad26.ZEBOV, MVA-BN-Filo, respectively. (a) (rVSVΔG-ZEBOV-GP) and (d) (Ad26.ZEBOV, MVA-BN-Filo): Observed and modelled (multivariable models) antibody GMCs over time in vaccine arm and pooled placebo arms in overall population. (b) (rVSVΔG-ZEBOV-GP) and (e) (Ad26.ZEBOV, MVA-BN-Filo): modelled (multivariable models) IgG GMCs over time in active vaccine arm according to age category. (c) (rVSVΔG-ZEBOV-GP): modelled (multivariable models) IgG GMCs over time in active vaccine arm according to sex. IgG GMCs over time after (Ad26.ZEBOV, MVA-BN-Filo) vaccination is not presented according to sex, as sex was not included in the model (not significantly associated). Dots represent individually observed serum samples. The dashed horizontal line in each panel indicates 200 EU/mL anti-EBOV GP_{1,2} IgG concentration. GMC = geometric mean concentration. GP_{1,2} = glycoprotein. EBOV = Ebola virus.

age, sex, country, and IgG titer prior to vaccination. At peak and month 12, higher GMCs were associated with a younger age, female sex, and higher GMCs prior to vaccination. All age categories of children had higher IgG GMCs than adults: the model outputs, expressed as GMC ratios, estimated that GMCs for children were 1.32-fold higher (95% confidence interval [CI] [1.10; 1.57]) to 1.41-fold higher (95% CI [1.22; 1.64]) at peak and 1.36-fold (95% CI [1.12; 1.61]) to 1.41-fold higher (95% CI [1.21; 1.62]) at month 12 than these values for adults, with relatively small changes from one age category of children to another. Women had estimated 1.15-fold higher (95% CI [1.01; 1.30]) GMCs than men at peak, with an increase to 1.40-

fold higher (95% CI [1.22; 1.59]) at the end of the study. Compared to participants from Mali, GMCs of participants from Sierra Leone were lower with a ratio of 0.80 (95% CI [0.67; 0.95]) at peak and 0.69 (95% CI [0.58; 0.81]) at month 12, and GMCs of participants from Guinea were lower with a ratio of 0.73 (95% CI [0.62; 0.85]) at peak and of 0.74 (95% CI [0.63; 0.86]) at month 12. No difference was seen in GMCs from Liberia and Mali. Antibody concentrations higher than 200 EU/mL prior to vaccination were associated with a 1.31-fold higher (95% CI [1.07; 1.57]) response at peak and up to a 1.19-fold higher (95% CI [0.99; 1.41]) response at the end of the study. All GMC ratios for rVSVΔG-ZEBOV-GP are presented in Table 1.

Table 1. Mixed-model analysis of variables associated with anti-EBOV GP_{1,2} IgG antibody concentrations after rVSVΔG-ZEBOV-GP vaccination.

Variable	Anti-EBOV GP _{1,2} antibody	Anti-EBOV GP _{1,2} antibody
	Peak ^a	End of study ^a
	Ratio of geometric mean concentration [95% CI]	Ratio of geometric mean concentration [95% CI]
<i>Age category</i>		
Adults	Reference	Reference
Children 1–4 yr	1.32 [1.10; 1.57]	1.36 [1.12; 1.61]
Children 5–11 yr	1.35 [1.14; 1.57]	1.37 [1.16; 1.61]
Children 12–17 yr	1.41 [1.22; 1.64]	1.41 [1.21; 1.62]
<i>Sex</i>		
Males	Reference	Reference
Females	1.15 [1.01; 1.30]	1.40 [1.22; 1.59]
<i>Country (laboratory)</i>		
Mali (IRF-Frederick)	Reference	Reference
Guinea (LIBR)	0.73 [0.62; 0.85]	0.74 [0.63; 0.86]
Sierra Leone (LIBR)	0.80 [0.67; 0.95]	0.69 [0.58; 0.81]
Liberia (IRF-Frederick)	1.07 [0.87; 1.30]	1.01 [0.81; 1.24]
<i>Pre-vaccination antibody level</i>		
<200 EU/mL	Reference	Reference
>200 EU/mL	1.31 [1.07; 1.57]	1.19 [0.99; 1.41]

^aThe peak and the end of the study were defined as 90 days and 12 months after receipt of the prime vaccination, respectively. EBOV = Ebola virus. IRF-Frederick = Integrated Research Facility at Fort Detrick. GP_{1,2} = glycoprotein. LIBR: Liberian Institute for Biomedical Research. yr = years. EU/mL = enzyme-linked immunosorbent assay units per milliliter. CI = confidence interval.

The model allowed estimation of the percentage of the IgG GMCs at month 12 remaining above different empirical thresholds (>200, >600, and >1000 EU/mL) (Table 2). For rVSVΔG-ZEBOV-GP, there was a very high and homogenous percentage of GMCs above 200 EU/mL at the end of study for children (99% for females and 97% for males) and for adults (97% for females and 94% for males). A 600 EU/mL threshold increased the difference in percentage for adults, diminishing to 75% for females and to 61% for males at end of the study; in contrast, at the 600 EU/mL threshold, the percentage for children decreased less than adults and remained homogenous within each age category compared to adults. At the 1000 EU/mL threshold, the percentage dropped to 54% for female adults, 38% for male adults, 66% for female children, and 53% for male children. Overall, a higher estimated percentage of females reached the designated threshold compared to males, regardless of age

category. Additional probability explorations with a continuous threshold scale and time after vaccination required for 50% of the population to drop below the same three anti-EBOV GP_{1,2} GMC thresholds are shown in the Supplementary Material.

Determinants of Ad26.ZEBOV, MVA-BN-Filo vaccination and antibody concentration

The anti-EBOV GP_{1,2} IgG GMCs after vaccination with Ad26.ZEBOV, MVA-BN-Filo differed according to age, country, and IgG titer prior to vaccination. At peak and month 12, significantly higher IgG GMCs were associated with a younger age and location in Mali. Higher IgG GMCs prior to vaccination were associated with higher antibody concentrations at month 12. In contrast to the rVSVΔG-ZEBOV-GP model, sex was not associated with the antibody response after Ad26.ZEBOV, MVA-BN-Filo vaccination.

Age had a major effect on the IgG GMCs at peak (90 days after dose 1), with 4.68-fold higher (95% CI [3.82; 5.64]) IgG GMCs for children 1–4 years old compared to adults. With increased age, the difference in peak GMCs compared to adults was diminished to 2.82-fold higher (95% CI [2.32; 3.38]) for children 5–11 years old and 1.93-fold higher (95% CI [1.57; 2.35]) for those 12–17 years old. Similar trends were found at the end of the study, with 1.74-fold higher (95% CI [1.48; 2.02]) concentrations for children 12–17 years old and 3.10-fold higher (95% CI [2.58; 3.69]) concentrations for those 1–4 years old compared to adults. Participants from Guinea and Sierra Leone had a lower peak IgG GMCs than those from Mali with ratios of 0.59 (95% CI [0.49; 0.72]) and 0.38 (95% CI [0.30; 0.47]), respectively. These differences were maintained at month 12 with ratios of 0.80 (95% CI

Table 2. Probability of having an antibody concentration above threshold 12 months after rVSVΔG-ZEBOV-GP vaccination (one dose).

	Probability of reaching anti-EBOV GP _{1,2} antibody threshold (EU/mL) at day 365 [95% CI]		
	>200	>600	>1000
<i>Females</i>			
Children 1–4 yr	0.99 [0.97; 1.00]	0.84 [0.78; 0.90]	0.67 [0.59; 0.74]
Children 5–11 yr	0.99 [0.97; 1.00]	0.84 [0.78; 0.90]	0.66 [0.58; 0.74]
Children 12–17 yr	0.99 [0.98; 1.00]	0.85 [0.79; 0.90]	0.68 [0.60; 0.76]
Adults	0.97 [0.96; 0.99]	0.75 [0.71; 0.80]	0.54 [0.49; 0.60]
<i>Males</i>			
Children 1–4 yr	0.97 [0.95; 0.99]	0.73 [0.66; 0.80]	0.51 [0.43; 0.60]
Children 5–11 yr	0.97 [0.95; 0.99]	0.74 [0.67; 0.80]	0.53 [0.45; 0.60]
Children 12–17 yr	0.97 [0.95; 0.99]	0.76 [0.69; 0.82]	0.55 [0.47; 0.63]
Adults	0.94 [0.91; 0.96]	0.61 [0.56; 0.66]	0.38 [0.33; 0.43]

Note: EBOV = Ebola virus. GP_{1,2} = glycoprotein. yr = years. EU/mL = enzyme-linked immunosorbent assay units per milliliter. CI = confidence interval.

Table 3. Mixed-model analysis of variables associated with anti-EBOV GP_{1,2} antibody concentrations after Ad26.ZEBOV, MVA-BN-Filo vaccination.

	Anti-EBOV GP _{1,2} antibody	
	Peak ^a	End of study ^a
	Ratio of geometric mean concentration [95% CI]	Ratio of geometric mean concentration [95% CI]
<i>Age category</i>		
Adults	Reference	Reference
Children 1–4 yr	4.68 [3.82; 5.64]	3.10 [2.58; 3.69]
Children 5–11 yr	2.82 [2.32; 3.38]	2.09 [1.78; 2.44]
Children 12–17 yr	1.93 [1.57; 2.35]	1.74 [1.48; 2.02]
<i>Country (laboratory)</i>		
Mali (IRF-Frederick)	Reference	Reference
Guinea (LIBR)	0.59 [0.49; 0.72]	0.80 [0.67; 0.95]
Sierra Leone (LIBR)	0.38 [0.30; 0.47]	0.61 [0.49; 0.74]
Liberia (IRF-Frederick)	0.57 [0.44; 0.73]	0.57 [0.45; 0.72]
<i>Pre-vaccine antibody concentration</i>		
<200 EU/mL	Reference	Reference
>200 EU/mL	0.93 [0.75; 1.13]	1.38 [1.12; 1.68]

^aThe peak and the end of the study were defined as 90 days and 12 months after receipt of the prime vaccination, respectively. EBOV = Ebola virus. IRF-Frederick = Integrated Research Facility at Fort Detrick. GP_{1,2}: glycoprotein. LIBR: Liberian Institute for Biomedical Research. yr = years. EU/mL = enzyme-linked immunosorbent assay units per milliliter. CI = confidence interval.

[0.67; 0.95]) and 0.61 (95% CI [0.49; 0.74]), respectively, compared to Mali. The IgG GMCs were also lower in Liberia compared to Mali with a ratio of 0.57 (at both peak and at month 12, 95% CI [0.44; 0.73] and [0.45; 0.72], respectively). Furthermore, pre-vaccination IgG GMCs higher than 200 EU/mL were associated with 1.38-fold higher (95% CI [1.12; 1.68]) IgG GMCs at the end of the study. All GMC ratios for Ad26.ZEBOV, MVA-BN-Filo are presented in Table 3.

There was a much higher percentage of minimum IgG GMCs of 200 EU/mL at month 12 for children compared to adults (76%), a difference which slightly decreased with increased age (from 98% for children 1–4 years old to 91% for those 12–17 years old). In addition, the percentage for adults dropped to 28% for the 600 EU/mL GMC threshold and to 12% for the 1000 EU/mL GMC threshold. With higher thresholds, the effect of age on the estimated percentage in children was even clearer. For the threshold 600 EU/mL, the percentages were 53% (12–17 years) and 77% (1–4 years); for the 1000 EU/mL threshold, the percentages were 30% (12–17 years) and 56% (1–4 years). The percentage table is shown in Table 4. Additional probability explorations with a continuous threshold scale and time after vaccination required for 50% of

the population to drop below the same three anti-EBOV GP_{1,2} GMC thresholds are available in the Supplementary Material.

Discussion

This modelling study, based on a large international randomized clinical trial, provides new information on the longitudinal dynamics of immune responses for the two currently approved EVD vaccination strategies. A more rapid decline in antibody levels after vaccination by Ad26.ZEBOV, MVA-BN-Filo was observed. Higher IgG responses were observed in children than adults, with a more prominent difference after Ad26.ZEBOV, MVA-BN-Filo vaccination. Higher IgG responses were seen in participants with higher pre-vaccination antibody concentrations for both vaccination strategies and in women for rVSVΔG-ZEBOV-GP vaccine only.

The observed differences in antibody response kinetics between the two vaccines may be explained by their distinct features, including different platforms and vectors, the surface GP_{1,2} used in the vaccine, and the dosage. Our study confirms that vaccine-specific features are not the only variables responsible for differential response profiles, but host demographic characteristics also have a major impact on the immune response after vaccination. This impact differed between the two vaccination strategies, with greater variability for the Ad26.ZEBOV, MVA-BN-Filo vaccine.

Age was particularly associated with the humoral response to Ad26.ZEBOV, MVA-BN-Filo, with IgG GMCs at 12 months three times higher in the youngest children (1–4 years old) than in adults. The overall trend of higher immune responses in younger children is consistent with similar findings reported previously [22]. It has been well-documented in the context of other vaccines that age at

Table 4. Probability of having an antibody concentration above threshold 12 months after Ad26.ZEBOV/MVA-BN-Filo vaccination.

	Probability of reaching anti-EBOV GP _{1,2} antibody threshold (EU/mL) at day 365 [95% CI]		
	>200	>600	>1000
Children 1–4 yr	0.98 [0.96; 0.99]	0.77 [0.70; 0.82]	0.56 [0.48; 0.63]
Children 5–11 yr	0.94 [0.91; 0.97]	0.61 [0.54; 0.68]	0.38 [0.30; 0.45]
Children 12–17 yr	0.91 [0.88; 0.94]	0.53 [0.45; 0.60]	0.30 [0.24; 0.36]
Adults	0.76 [0.72; 0.79]	0.28 [0.24; 0.32]	0.12 [0.09; 0.14]

Note: EBOV = Ebola virus. GP_{1,2} = glycoprotein. yr = years. EU/mL = enzyme-linked immunosorbent assay units per milliliter. CI = confidence interval.

vaccine receipt greatly influences subsequent vaccine-specific immune responses that are generally lower with increased age and extremely low in the elderly [23]. In this study, factors contributing to IgG response differences between adults and children include the lack of dose adaptation for participant age or BMI. Additionally, pre-existing memory responses to environmental adenoviruses may impair immune responses to adenovirus-based vaccines [24,25]. However, pre-existing immunity to Ad26 did not have an effect on vaccine-induced immune response in EVD or coronavirus disease 2019 (COVID-19) studies [26].

Sex was found to influence the humoral response to the rVSVΔG-ZEBOV-GP vaccination strategy, with women exhibiting higher IgG GMCs than men across age categories, in line with what had already been described [27,28]. Although this difference was significant but relatively small at peak, it reached 40% at 1 year after vaccination, putting it at the same order of magnitude as the effect of age on this vaccination strategy.

Pre-vaccination IgG concentrations influenced responses for both vaccination strategies, with higher humoral response at month 12 among participants with higher baseline concentrations. It should be noted that a history of EVD or previous vaccination against EVD were both exclusion criteria for the PREVAC trial but were self-reported. The unexpectedly notable baseline antibody concentrations were also found in previous clinical studies [21,29] and prompted use of centralized analysis of the samples conducted in an independent laboratory (Q2 Solutions, which is validated for regulatory purposes) [30]. Pre-vaccination IgG may derive from prior unrecognized, unrecalled, or subclinical (or asymptomatic) EBOV infection, as suggested in previous studies [31,32]. This phenomenon aligns with the trial's geographic context, conducted in the three Western African countries most severely affected by the extensive 2013–2016 EVD outbreak. Notably, pre-existing antibodies were more common in participants from these countries than those from Mali and rare in the youngest children born post-epidemic. Alternatively, though scored as “positive,” detection of low concentrations of IgG in the assay may represent prior exposure to cross-reacting antigens.

Since the FANG antibody assay was performed in two different laboratories, it is difficult to discriminate between country-specific and laboratory-related variation in the PREVAC trial. The FANG assay performance is associated with some degree of variability between laboratories despite use of similar method protocols and reagents [33]. The FANG assay has been commonly used in multiple vaccine trials [4,6,8,11], and its limitations have

largely been addressed in the annex of a previous PREVAC paper [19]. However, a difference was observed between Malian and Liberian participants after the Ad26.ZEBOV, MVA-BN-Filo vaccine; notably, this geographic variation was observed despite analysis in the same central laboratory and confirmed in a second centralized analysis of the same data [29]. This geographic variation, unexplained by levels of baseline antibody concentrations, might be resultant of unmeasured genetic or exposure factors.

While this modelling is drawn from a single study, one of its main strengths is the design, as it relies on data from a multi-country randomized double-blind clinical trial that incorporated two authorized vaccination strategies, was based on a large recruitment population from several Western African countries and included rural and urban participants with balance across sex and age strata.

Our results provide important insight to the longitudinal dynamics of the anti-EBOV GP_{1,2} IgG response, which, while not a validated correlate of protection, can be considered the best immunological marker associated with vaccine efficacy against EVD [34]. The probability of having an IgG titer above the empirical threshold of 200 EU/mL IgG at 1 year remained above 90% in most cases, except in adults vaccinated with Ad26.ZEBOV, MVA-BN-Filo. However, at higher thresholds, the probability decreased, raising questions about the level of immune response necessary for optimal protection. It remains to be determined whether the same host characteristics also impact the memory immune response in previously vaccinated individuals. Current data suggest that vaccinated individuals are likely protected one-year post-vaccination, but it is still too early to recommend changes to the EVD vaccination program, including adaptations for specific populations. However, it is crucial to closely monitor the waning of immune responses over time to ensure sustained vaccine efficacy longitudinally across different populations.

Recent EVD outbreaks are sporadic and rapidly brought under control due to a well-coordinated response that includes vaccination campaigns. Thus, it is challenging to detect infectious breakthroughs, cases that could prompt the need for additional injections. Our modelling data highlight the need for research on future EVD vaccination strategies, especially evaluating the value of follow-up doses with the same or different vaccine. The ongoing PREVAC trial (PREVAC-UP) will characterize the durability of immune response up to 5 years post-vaccination and will not be published before 2025; results from this trial will be particularly useful in assessing the antibody level dynamics after 1 year, estimating the durability of humoral response over time

and if, when, and for whom follow-up vaccination might be appropriate.

Acknowledgements

We are grateful to the Ministries of Health of Guinea, Liberia, Sierra Leone, and Mali, which permitted the conduct of the trial. We furthermore thank The Alliance for International Medical Action and all site collaborators for their contribution in the implementation of the trial. The authors and study team thank the participants who consented to the trial. We also thank Anya Crane (Integrated Research Facility at Fort Detrick, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Fort Detrick, Frederick, MD, USA) for critically editing the manuscript and Jiro Wada (Integrated Research Facility at Fort Detrick, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Fort Detrick, Frederick, MD, USA) for preparing figures. Part of the experiments presented in this paper were carried out using the PlaFRIM experimental testbed, supported by Inria; Centre National de la Recherche Scientifique; Laboratoire Bordelais de Recherche en Informatique and Institut de Mathématique de Bordeaux, Université de Bordeaux; Bordeaux INP; and Conseil Régional d'Aquitaine (see <https://www.plafrim.fr>).

YY and YL conceptualized the study. AHB, SD, MK, BG, BL, SOS, LR, and EL contributed to the study design. SV, MPo, and MA accessed and verified the data, did the data linkage, and conducted the formal analysis. EL, LR, and MPr supervised the analyses and verified the data. All authors contributed to data interpretation. SV created the first drafts of the figures and wrote the first draft of the manuscript. All authors critically revised and edited the manuscript and approved the final version for submission. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

PREVAC study team:

Jamila Aboulhab² MD, Michelle Aguirre-MacKenzie¹² BS, Pauline Akoo³ MB, ChB, Esther Akpa² MSN, MPH, RN, Robert Akpata¹ MD, Sara Albert¹⁷ BA, MPH, Boni Maxime Ale⁴ MD, MSc, MPH, Serry Alimamy-Bangura¹¹ MB, ChB, Pierre Andong¹ MSt, Benetta C. Andrews¹⁰ MD, Stephane Anoma⁶ MD, Negin Atri² MPH, CPH, Augustin Augier⁶ MCom, Ken Awuondo³ MSc, Achidjo Ayoub³⁰ PhD, Moses Badio¹⁰ MSc, Aminata Bagayoko¹ MD, Abby Balde¹⁷ MPH, Joséphine Balssa^{1,8} PharmD, Lamin Molecule Bangura¹¹ BSc, Keshia Barrington¹⁷ MPA, Eric Barte de Saint Fare⁶ BA, Beth Baseler¹⁷ MS, Ali Bauder¹² BA, PMP, Claire Bauduin⁴ MSc, Luke Bawo¹⁰ MSc, Abdoul Habib Beavogui⁹ MD, PhD, Michael Belson² BS, Safaa Ben-Farhat⁴ MEng, Marion Bererd⁶ BS, Nicolas Bernaud^{1,18} MSc, Teedoh Beyslow¹⁰ PharmD, Neirade Biai³⁰ MSc, Jeanne Billioux² MD, Shere Billouin-Frazier¹⁷ MSc, Blandine Binachon⁴ MD, MPH, Julie Blie¹⁰ MSc, Viki Bockstal¹³ PhD, Patricia Boison¹⁷ MS, Fatorma Bolay¹⁰ PhD, Aliou Boly⁶ MM, Rachael Elizabeth Bonawitz¹² MD, MS, Anne-Gaëlle Borg⁶ MCM, Samuel Bosompem² PharmD, MSc, Courtney Bozman²⁸ MSc, Tyler Brady² MPH, Sarah Browne¹⁰ RN, BSN, Ryan Bullis¹² PhD, Barbara Cagniard¹ PhD, Kelly Cahill² RN, MSc, CCRC, RAC, Yingyun Cai²⁸ PhD, Aissata Abdoulaye Camara⁶ MSc, Aboubacar Keira Camara¹ MD, Alseny Modet

Camara⁶ MD, Antoine Campagne¹ PhD, Cécilia Campion⁴ MSc, Alexandre Cantan^{4,29} BSc, Jennifer Cash¹⁷ BS, Siew Pin Chai¹³ BBio-MedSc, Francois Chambelin¹ MHist, Michael Chea¹⁰ BSc, Geneviève Chêne⁴ MD, PhD, Edouard Choi³ PhD, Michelle Chouinard⁶ MSW, Florence Chung¹ PhD, Lucy Chung² PharmD, Séverine Ciancia¹ MJ, Papa Ndiaga Cisse¹⁴ PhD, Elfrida Cline-Cole¹⁷ MA, Céline Colin⁴ MSc, Beth-Ann Collier¹² PhD, Djélikan Siaka Conde¹ MD, Katherine Cone² MSW, LCSW-C, C-SWHC, Laurie Connor¹² MS, Nicholas Connor³ MSc, Joseph Boye Cooper¹⁰ MSc, Sandrine Couffin-Cardiergues¹ PhD, Fatoumata Coulibaly¹ BS, Mariam Coulibaly²⁰ PharmD, MSc, Page Crew² PharmD, MPH, BCPS, Sandrine Dabakuyo-Yonli⁴ PharmD, PhD, Djeneba Dabita²⁰ PharmD, PhD, Thierry Damerval¹ PhD, Bionca Davis⁵ MPH, Gibrilla Fadlu Deen¹¹ MD, MSc, Eline Dekeyster¹³ PhD, Jean-François Delfraissy¹ MD, PhD, Christelle Delmas¹ MSc, Mahamadou Diakite²⁰ PharmD, DPhil, Alpha Diallo^{1,8} MD, MPH, Fatoumata Abdoulaye Diallo⁶ MD, Mamadou Saliou Diallo⁶ MD, MPH, Ayoubia Diarra²⁰ MSc, Samba Diarra²⁰ MSc, PhD, Oualy Diawara¹⁹ BS, Bonnie Dighero-Kemp²⁸ BSc, Samba Diop²¹ MSc, PhD, Waly Diouf¹⁴ PhD, Saurabh Dixit² PhD, Barry Djenabou⁶ MSc, Laurie Doepele² BA, Eric D'Ortenzio^{1,7,8} MD, MPH, Seydou Doumbia²⁰ MD, PhD, Moussa Moise Doumbia¹⁹ MD, Macaya Douoguih¹³ MD, MPH, Nelson Dozier²⁸ MSc, Natasha Dubois Cauwelaert^{1,8} PhD, Alain DuChêne⁵ BS, Michael Duvenhage¹⁷ NDIPIT, Risa Eckes² RN, Elizabeth Elliott² MSc, Luisa Enria³ PhD, Hélène Espérou¹ MD, Cécile Etienne¹ MSc, Allison Eyler¹⁷ HSD, Lawrence Fakoli¹⁰ MSc, Mosoka Fallah¹⁰ PhD, Marie-Alix Fauvel¹ MSc, Sylvain Faye¹⁴ PhD, John Fayiah¹⁰ MSc, Suzanne Fleck³ PhD, Vemy Fofana⁶ BComp, Karine Fouth Tchoss² MD, MPH, Kokulo Franklin¹⁰ MPhil, MSc, Daniela Fusco¹ PhD, Auguste Gaddah¹³ PhD, Marylène Gaignet¹ MSc, Katherine Gallagher³ PhD, Julie Gardner¹² BS, Harrison Gichini²⁸ MSc, Julia Garcia Gozalbes¹ MD, Greg Grandits⁵ MS, Maima Gray¹⁰ BPharm, Brian Greenwood³ MD, Nico Grobler¹³ PhD, Robin Gross²⁸ MSc, Louis Grue¹⁷ RN, BS, BSN, Birgit Grund²⁷ PhD, Oumar Guindo²⁰ MSc, PharmD, Swati Gupta¹² DrPH, MPH, Fadima Haidara¹⁹ MD, Benjamin Hamzé¹ PharmD, Emma Hancox³ MSc, Jean-Christophe Hébert¹ MSL, Jenny Hendriks¹³ PhD, Patricia Hensley³ MPh, Lisa E Hensley²⁸ PhD, MSPH, Betsey Herpin² MSN, Elisabeth Higgs² MD, DTMH, MIA, Trudi Hilton³ BPharm, MSc, Mickael Hneino¹ PhD, Tracey-Ann Höeltermann²⁸ BSc, MPH, Horace Preston Holley¹⁷ MD, Marie Hoover¹⁶ PhD, Natasha Howard³ PhD, Melissa Hughes¹² BA, MBA, CPM, PMP, Dicko Ilo²⁰ MD, MPH, Skip Irvine¹² BS, David Ishola³ MD, PhD, Yvonne Jato² MPH, Madison Joe¹⁰ MSc, Melvin Johnson¹⁰ MSc, Aboubacar Sidiki Kaba⁶ MD, Jonathan Kagan² PhD, Kade Kallon¹⁷ MSc, Michael Kamara³ MBChB, MSc, Myriam Kante⁴ BS, Judith Katoudi⁶ MD, MPH, Cheick Mohamed Keita⁶ MD, Sakoba Keita¹⁵ MD, Seykou Keita²² MD, Stephen B. Kennedy¹⁰ MD, MSc, Babajide Keshinro¹³ MBBS, FWACP, Hassan Kiawu¹⁰ MSc, Mark Kieh¹⁰ MD, MSMHC, Brent Killinger¹² BA, Moumouni Kinda⁶ MD, MBA, Matthew Kirchoff² PharmD, MSc, MBA, Gregory Kocher²⁸ MSc, Mamoudou Kodio¹⁹ PharmD, Brian Kohn³ BSc, Lamine Koivogui²³ PharmD, PhD, Richard Kojan⁶ MD, Cece Francis Kolié⁶ PharmD, Jacques Seraphin Kolié⁶ MD, David Kollie¹⁰ BSc, Stacy Kopka¹⁷ MS, Bockarie Koroma¹¹ BPharm, Dickens Kowuor³ BSc, MSc, PhD, Catherine Kpayieli-Freeman¹⁰ MSc, Liane Kwast¹³ MSc, Christine Lacabaratz^{1,18} PhD, Boris Lacarra¹ MD, Laurie Lambert¹⁷

BS, Courtney Lambeth¹² BS, Solange Lancrey-Javal^{1,8} PharmD, H. Clifford Lane² MD, Shadrach Langba¹⁰ BSc, Bolarinde Lawal³ MSc, Andrew Wen-Tseng Lee¹² MD, Shona Lee³ PhD, Shelley Lees³ PhD, Annabelle Lefevre¹ MD, Bailah Leigh¹¹ MD, MSc, Frederic Lemarcis¹ PhD, Yves Lévy^{1,18} MD, PhD, Claire Levy-Marchal¹ MD, Maarten Leyssen¹³ MD, PhD, Edouard Lhomme²⁶ MD, PhD, Janie Liang²⁸ MSc, Mameni Linga¹⁰ MSc, Ken Liu¹² PhD, Brett Lowe³ MPhil, Julia Lysander¹⁰ MSc, Ibrah Mahamadou⁶ PharmD, Irina Maljkovic-Berry²⁸ PhD, Marvington Mambiah¹⁰ ASC, Daniela Manno³ MD, PhD, Jonathan Marchand^{2,17} MS, Lindsay Marron²⁸ MSc, Moses B.F. Massaqoi¹⁰ MD, MSc, Laure Masson¹ MIBL, Charly Matard⁴ BS, Steven Mazur²⁸ BS, John McCullough¹⁶ BS, Katherine McFadyen¹³ MPH, Chelsea McLean¹³ PhD, Noémie Mercier¹ PharmD, Pauline Michavila⁶ BBus, Tracey Miller¹⁷ RN, BSN, Niouma Pascal Millimouno⁶ MD, Alejandra Miranda¹⁷ MS, Soumaya Mohamed⁶ BJ, Tom Mooney³ BA, Dally Muamba⁶ MD, James Mulbah¹¹ BPharm, Rita Lukoo Ndamenyaa⁶ MD, MSc, James Neaton⁵ PhD, Désiré Neboua¹ MD, Micki Nelson¹² BSN, MS, Kevin Newell¹⁷ MPH, MEd, Vinh-kim Nguyen²⁴ MD, Yusupha Njie³ BSc, Wissedi Njoh¹⁷ MSN, Anna Novotney-Barry¹³ MSC, Matthew Onorato¹² BS, Uma Onwuchekwa²² BSc, Susan Orsega² MSN, FNP-BC, Inmaculada Ortega-Perez^{1,8} PhD, MPH, Cynthia Osborne¹⁷ BS, Tuda Otieno³ MSC, Davy Oulai⁴ MD, Sushma Patel¹² MS, PMP, Danielle Peart² BS, Martine Peeters³⁰ PhD, James Pettitt²⁸ MSc, Nathan Peiffer-Smadja¹ MD, PhD, Robert Phillips³ MSc, Jerome Pierson² PhD, Peter Piot³ MD, PhD, Micheal Piziali² JD, MSc, Stéphany Pong^{1,8} PharmD, Elena Postnikova² PhD, Calvin Proffitt¹⁷ MA, Alexandre Quach¹ MD, Sinead Quigley¹ MSSc, Nadeeka Randunu^{2,17} BSc, MBA, Laura Richert²⁶ MD, PhD, Priscille Rivière¹ MSc, Cynthia Robinson¹³ MD, Céline Roy^{4,29} PhD, Amy Falk Russell¹² MS, Philip Sahr¹⁰ MD, Katy Saliba² MSc, PhD, Mohamed Samai¹¹ MBBS, PhD, Sibiry Samake²⁰ PharmD, MSc, Jen Sandrus¹⁷ AA, Ibrahim Sanogo²⁰ MsP, MD, Yeya Sadio Sarro²⁰ PharmD, PhD, Serge Sawadogo⁶ MD, MSc, Sani Sayadi⁶ MD, MPH, Maxime Schvartz¹ MD, Christine Schwimmer⁴ PhD, Fatou Secka³ BSc, MSc, MBChB, Heema Sharma²⁸ MSc, Denise Shelley¹⁷ MS, Bode Shobayo¹⁰ MSc, Sophia Siddiqui² MD, MPH, Jakub Simon¹² MD, Shelly Simpson¹⁷ MS, Billy Muyisa Sivahera⁶ MD, Karen Slater³, Mary Smolskis² BSN, MA, Elizabeth Smout³ MD, MSc, Emily Snowden³ MA, Anne-Ayglie Southiphong^{4,29} MSc, Amadou Sow⁶ MSc, Samba O. Sow²² MD, MSc, Ydrissa Sow² MD, MPH, Michael Stirratt²⁵ PhD, Jeroen Stoop¹³ PhD, Guna Subramaniam¹³ MSc, Léa Surugue¹ MJ, Nathalie Swales¹³ MSc, Sienné Tamba¹⁰ RN, BSN, Chan Tang¹³ BSc, Cheick Tangara²⁰ MSc, Milagritos D. Tapia²² MD, Julius Teahton¹⁰ MSc, Jemee Tegli¹⁰ MSc, Monique Termote⁴ MSc, Guillaume Thaurignac³⁰ MSc, Rodolphe Thiebaut⁴ MD, PhD, Greg Thompson⁵ BS, John Tierney² BSN, MPM, Daniel Tindanbil³ MSc, Abdoulaye Touré²³ PharmD, MPH, PhD, Elvis Towalid¹⁰ BPharm, Stacey Traina¹² BS, Awa Traore¹⁹ PharmD, Tijili Tyee¹⁰ PharmD, David Vallée¹ PharmD, Renaud Vatrinet¹ PhD, Corine Vincent⁴ MSc, Susan Vogel² RN, BSN, Cedrick Wallet⁴ MSc, Travis Warren² PhD, Deborah Watson-Jones³ MD, PhD, Wade Weaver²⁸ MSc, Deborah Wentworth⁵ MPH, Cecelia Wesseh¹⁰ BSc, Hilary Whitworth³ PhD, Jimmy Whitworth³ PhD, Aurelie Wiedemann^{1,18} PhD, Wouter Willems¹³ PhD, Bartholomew Wilson¹⁰ MSc, Jayanthi Wolf¹² PhD, Alie Wurie¹¹ MD, MSc, Delphine Yamadjako¹⁷ MS, Marcel Yaradouno⁶ MSc, Quiawiah Yarmie¹⁰ MSc, Yazdan Yazdanpanah^{1,7,8}

MD, PhD, Shuiqing Yu²⁸ BS, Zara Zeggani⁶ MSc, Huanying Zhou²⁸ BS.

Affiliations

- ¹French Institute for Health and Medical Research (Inserm), 75013 Paris, France
- ²National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA or under contract/subcontract to NIAID
- ³London School of Hygiene & Tropical Medicine, London, UK
- ⁴Univ. Bordeaux, INSERM, Institut Bergonié, CHU de Bordeaux, CIC-EC 1401, Euclid/F-CRIN clinical trials platform, F-33000 Bordeaux, France
- ⁵School of Public Health, University of Minnesota, Minneapolis, MN, USA
- ⁶The Alliance for International Medical Action, Alima, B.P.15530 Dakar, Sénégal
- ⁷AP-HP, Hôpital Bichat-Claude Bernard, Service de Maladies Infectieuses et Tropicales, Paris F-75018, France
- ⁸ANRS Emerging Infectious Diseases, Paris, France
- ⁹Centre National de Formation et de Recherche en Santé Rurale de Maferinyah, Maferinyah, Guinea
- ¹⁰Partnership for Research on Ebola Virus in Liberia (PRE-VAIL), Monrovia, Liberia
- ¹¹College of Medicine and Allied Health Sciences (COMAHS), University of Sierra Leone, Freetown, Sierra Leone
- ¹²Merck Sharp & Dohme Corp, Inc., Kenilworth, NJ, USA
- ¹³Janssen Vaccines and Prevention BV Leiden, The Netherlands
- ¹⁴Département de Sociologie, FLSH, Université Cheikh Anta DIOP, Dakar, Sénégal
- ¹⁵Agence Nationale de Sécurité Sanitaire, Conakry, Guinea
- ¹⁶Advanced BioMedical Laboratories, L.L.C., 1605 Industrial Hwy, Cinnaminson, NJ, USA
- ¹⁷Leidos Biomedical Research, Inc. Frederick, MD 21704, USA
- ¹⁸Vaccine Research Institute, Univ. Paris Est Créteil, Henri Mondor Hospital, Créteil, France
- ¹⁹Centre pour le Développement des Vaccins, Ministère de la Santé, Bamako, Mali
- ²⁰University Clinical Research Center (UCRC), University of Sciences, Techniques and Technologies of Bamako (USTTB), Bamako, Mali
- ²¹Liberia Institute for Biomedical Research Ethics Committee/National, Monrovia, Liberia
- ²²Center for Vaccine Development and Global Health, University of Maryland School of Medicine, 685 West Baltimore Street Baltimore, MD 21201-1509, USA
- ²³INSP (Institut Nationale de Santé Publique), Conakry, Guinea
- ²⁴École de santé publique de l'Université de Montréal, Montréal, Canada
- ²⁵National Institute of Mental Health, Bethesda, MD, USA
- ²⁶Univ. Bordeaux, INSERM, Institut Bergonié, CHU de Bordeaux, CIC-EC 1401, Euclid/F-CRIN clinical trials platform and U1219 BPH Inria Sism, F-33000 Bordeaux, France
- ²⁷School of Statistics, University of Minnesota, Minneapolis, MN, USA
- ²⁸Integrated Research Facility at Fort Detrick (IRF-Frederick), National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), Fort Detrick, Frederick, MD, USA
- ²⁹Univ. Bordeaux, INSERM, MART, UMS 54, F-33000 Bordeaux, France

³⁰Recherche Translationnelle Appliquée au VIH et aux Maladies Infectieuses, Institut de Recherche pour le Développement, University of Montpellier, INSERM, 34090, Montpellier, France.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the Innovative Medicines Initiative 2 Joint Undertaking (IMI2JU) under grant number 115854, EBOVAC1. This project has also received support from the European Union's Horizon 2020 research and innovation programme and EFPIA. The dissemination represents only the authors' views and IMI2JU is not responsible for any use of the information contained in the dissemination. This work was also supported by a dedicated Institut national de la santé et de la recherche médicale (Inserm) allocation on behalf the French Research Ministry. This work was supported in part by the National Institutes of Health (NIH), by Inserm, and by the London School of Hygiene and Tropical Medicine (LSHTM). The clinical trial was conducted with the support of Janssen, Bavarian Nordic, and Merck Sharp & Dohme Corp., which provided the vaccines. This work was also supported in part by the National Cancer Institute contract number HHSN261201500003I through the Frederick National Laboratory for Cancer Research. This work was supported in part through the Laulima Government Solutions, LLC, prime contract with NIH National Institute of Allergy and Infectious Diseases (NIAID) under contract number HHSN272201800013C. IMB performed this work as an employee of Laulima Government Solutions, LLC. JHK performed this work as an employee of Tunnell Government Services (TGS), a subcontractor of Laulima Government Solutions, LLC, under contract number HHSN272201800013C. The views and conclusions contained in this document are those of the authors and should not be interpreted as necessarily representing the official policies, either expressed or implied, of the US Department of Health and Human Services or of the institutions and companies affiliated with the authors, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government. PREVAC-UP trial was part of the EDCTP2 programme supported by the European Union (grant number RIA2017S-2014 - PREVAC-UP) and by the US National Institute of Allergy and Infectious Diseases of the National Institutes of Health.

Data availability statement

All data used are from the recently published PREVAC trial [19]. Data from this study can be accessed by submitting a request to Professor Yazdan Yazdanpanah (yazdan.yazdanpanah@aphp.fr). The data availability begins one year after completion of the 5-year follow-up of the PREVAC trial.

Code availability

The code to reproduce the analyses can be accessed via https://github.com/sistm/PREVAC_UP_WP_Modeling.git.

References

- [1] Jacob ST, Crozier I, Fischer WA II, et al. Ebola virus disease. *Nat Rev Dis Primers*. 2020 Feb 20;6(1):13. doi:10.1038/s41572-020-0147-3
- [2] Kuhn JH, Amarasinghe GK, Perry DL. Filoviridae. In: Howley PM, Knipe DM, Whelan SPJ, editors. *Fields virology*. Vol. 1, Emerging viruses. 7th ed. Philadelphia (PA): Wolters Kluwer/Lippincott Williams & Wilkins; 2020. p. 449–503.
- [3] European Medicines Agency. Ebola; 2022. Available from: <https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/ebola>
- [4] Bolay FK, Grandits G, Lane HC, et al. PREVAIL I cluster vaccination study with rVSVΔG-ZEBOV-GP as part of a public health response in Liberia. *J Infect Dis*. 2019 Apr 19;219(10):1634–1641. doi:10.1093/infdis/jiy698
- [5] Dahlke C, Kasonta R, Lunemann S, et al. Dose-dependent T-cell dynamics and cytokine cascade following rVSV-ZEBOV immunization. *EBioMedicine*. 2017 May;19:107–118. doi:10.1016/j.ebiom.2017.03.045
- [6] Halperin SA, Das R, Onorato MT, et al. Immunogenicity, lot consistency, and extended safety of rVSVΔG-ZEBOV-GP vaccine: a phase 3 randomized, double-blind, placebo-controlled study in healthy adults. *J Infect Dis*. 2019 Aug 30;220(7):1127–1135. doi:10.1093/infdis/jiz241
- [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 Aug 29;386(9996):857–866. doi:10.1016/S0140-6736(15)61117-5
- [8] Huttner A, Agnandji ST, Combescure C, et al. Determinants of antibody persistence across doses and continents after single-dose rVSV-ZEBOV vaccination for Ebola virus disease: an observational cohort study. *Lancet Infect Dis*. 2018 Jul;18(7):738–748. doi:10.1016/S1473-3099(18)30165-8
- [9] Ishola D, Manno D, MO A, et al. Safety and long-term immunogenicity of the two-dose heterologous Ad26.ZEBOV and MVA-BN-Filo Ebola vaccine regimen in adults in Sierra Leone: a combined open-label, non-randomised stage 1, and a randomised, double-blind, controlled stage 2 trial. *Lancet Infect Dis*. 2022 Jan;22(1):97–109. doi:10.1016/S1473-3099(21)00125-0
- [10] Milligan ID, Gibani MM, Sewell R, et al. Safety and immunogenicity of novel adenovirus type 26- and modified vaccinia Ankara-vectored Ebola vaccines: a randomized clinical trial. *JAMA*. 2016 Apr 19;315(15):1610–1623. doi:10.1001/jama.2016.4218
- [11] Pollard AJ, Launay O, Lelievre J-D, et al. Safety and immunogenicity of a two-dose heterologous Ad26.ZEBOV and MVA-BN-Filo Ebola vaccine regimen in adults in Europe (EBOVAC2): a randomised, observer-blind, participant-blind, placebo-controlled, phase 2 trial. *Lancet Infect Dis*. 2021 Apr;21(4):493–506. doi:10.1016/S1473-3099(20)30476-X
- [12] Henao-Restrepo AM, Camacho A, Longini IM, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). *Lancet*. 2017 Feb 4;389(10068):505–518. doi:10.1016/S0140-6736(16)32621-6

- [13] Meakin S, Nsio J, Camacho A, et al. Effectiveness of rVSV-ZEBOV vaccination during the 2018–20 Ebola virus disease epidemic in the Democratic Republic of the Congo: a retrospective test-negative study. *Lancet Infect Dis.* 2024 Aug 20;S1473-3099(24)00419-5. doi:10.1016/S1473-3099(24)00419-5
- [14] Medaglini D, Santoro F, Siegrist C-A. Correlates of vaccine-induced protective immunity against Ebola virus disease. *Semin Immunol.* 2018 Oct;39:65–72. doi:10.1016/j.smim.2018.07.003
- [15] World Health Organization. WHO adapts Ebola vaccination strategy in the Democratic Republic of the Congo to account for insecurity and community feedback; 2019. Available from: <https://www.who.int/news/item/07-05-2019-who-adapts-ebola-vaccination-strategy-in-the-democratic-republic-of-the-congo-to-account-for-insecurity-and-community-feedback>
- [16] World Health Organization. Strategic Advisory Group of Experts (SAGE) on immunization. Interim recommendations on vaccination against Ebola virus disease (EVD); 2019 May 7. Available from: https://cdn.who.int/media/docs/default-source/immunization/ebola/interim-ebola-recommendations-may-2019.pdf?sfvrsn=c54ce264_9
- [17] World Health Organization. Ebola virus disease – Democratic Republic of the Congo. *Wkly Epidemiol Rec.* 2020;95(27):301–306.
- [18] Badio M, Lhomme E, Kieh M, et al. Partnership for Research on Ebola VACcination (PREVAC): protocol of a randomized, double-blind, placebo-controlled phase 2 clinical trial evaluating three vaccine strategies against Ebola in healthy volunteers in four West African countries. *Trials.* 2021 Jan 23;22(1):86. doi:10.1186/s13063-021-05035-9
- [19] PREVAC Study Team, Kieh M, Richert L, et al. Randomized trial of vaccines for Zaire Ebola virus disease. *N Engl J Med.* 2022 Dec 29;387(26):2411–2424. doi:10.1056/NEJMoa2200072
- [20] Rudge TL Jr, Sankovich KA, Niemuth NA, et al. Development, qualification, and validation of the Filovirus Animal Nonclinical Group anti-Ebola virus glycoprotein immunoglobulin G enzyme-linked immunosorbent assay for human serum samples. *PLoS One.* 2019;14(4):e0215457.
- [21] Kennedy SB, Bolay F, Kieh M, et al. Phase 2 placebo-controlled trial of two vaccines to prevent Ebola in Liberia. *N Engl J Med.* 2017 Oct 12;377(15):1438–1447. doi:10.1056/NEJMoa1614067
- [22] Afolabi MO, Ishola D, Manno D, et al. Safety and immunogenicity of the two-dose heterologous Ad26.ZEBOV and MVA-BN-Filo Ebola vaccine regimen in children in Sierra Leone: a randomised, double-blind, controlled trial. *Lancet Infect Dis.* 2022 Jan;22(1):110–122. doi:10.1016/S1473-3099(21)00128-6
- [23] Siegrist C-A, Aspinall R. B-cell responses to vaccination at the extremes of age. *Nat Rev Immunol.* 2009 Mar;9(3):185–194. doi:10.1038/nri2508
- [24] Barouch DH, Pau MG, Custers JHHV, et al. Immunogenicity of recombinant adenovirus serotype 35 vaccine in the presence of pre-existing anti-Ad5 immunity. *J Immunol.* 2004 May 15;172(10):6290–6297. doi:10.4049/jimmunol.172.10.6290
- [25] Shiver JW, Emini EA. Recent advances in the development of HIV-1 vaccines using replication-incompetent adenovirus vectors. *Annu Rev Med.* 2004;55:355–372. doi:10.1146/annurev.med.55.091902.104344
- [26] Le Gars M, Sadoff J, Struyf F, et al. Impact of preexisting anti-adenovirus 26 humoral immunity on immunogenicity of the Ad26.COV2.S coronavirus disease 2019 vaccine. *J Infect Dis.* 2022 Sep 21;226(6):979–982. doi:10.1093/infdis/jiac142
- [27] Simon JK, Kennedy SB, Mahon BE, et al. Immunogenicity of rVSVΔG-ZEBOV-GP Ebola vaccine (ERVEBO®) in African clinical trial participants by age, sex, and baseline GP-ELISA titer: a post hoc analysis of three Phase 2/3 trials. *Vaccine.* 2022 Nov 2;40(46):6599–6606. doi:10.1016/j.vaccine.2022.09.037
- [28] Zimmermann P, Curtis N. Factors that influence the immune response to vaccination. *Clin Microbiol Rev.* 2019 Mar 20;32(2):e00084-18. doi:10.1128/CMR.00084-18
- [29] McLean C, Barry H, Kieh M, et al. Immune response of a two-dose heterologous Ebola vaccine regimen: summary of three African clinical trials using a single validated Filovirus Animal Nonclinical Group enzyme-linked immunosorbent assay in a single accredited laboratory. *EBioMedicine.* 2023 Apr 24;91:104562. doi:10.1016/j.ebiom.2023.104562
- [30] Lee AW, Liu K, Lhomme E, et al. Immunogenicity and vaccine shedding after 1 or 2 doses of rVSVΔG-ZEBOV-GP Ebola vaccine (ERVEBO®): results from a phase 2, randomized, placebo-controlled trial in children and adults. *Clin Infect Dis.* 2024 Apr 10;78(4):870–879. doi:10.1093/cid/ciad693
- [31] Glynn JR, Bower H, Johnson S, et al. Asymptomatic infection and unrecognised Ebola virus disease in Ebola-affected households in Sierra Leone: a cross-sectional study using a new non-invasive assay for antibodies to Ebola virus. *Lancet Infect Dis.* 2017 Jun;17(6):645–653. doi:10.1016/S1473-3099(17)30111-1
- [32] Thom R, Tipton T, Strecker T, et al. Longitudinal antibody and T cell responses in Ebola virus disease survivors and contacts: an observational cohort study. *Lancet Infect Dis.* 2021 Apr;21(4):507–516. doi:10.1016/S1473-3099(20)30736-2
- [33] Anderson MS, Niemuth NA, Sabourin CL, et al. Interlaboratory comparison for the Filovirus Animal Nonclinical Group (FANG) anti-Ebola virus glycoprotein immunoglobulin G enzyme-linked immunosorbent assay. *PLoS One.* 2020;15(8):e0238196. doi:10.1371/journal.pone.0238196
- [34] Grais RF, Kennedy SB, Mahon BE, et al. Estimation of the correlates of protection of the rVSVΔG-ZEBOV-GP Zaire ebolavirus vaccine: a post-hoc analysis of data from phase 2/3 clinical trials. *Lancet Microbe.* 2021 Feb;2(2):e70–e78. doi:10.1016/S2666-5247(20)30198-1