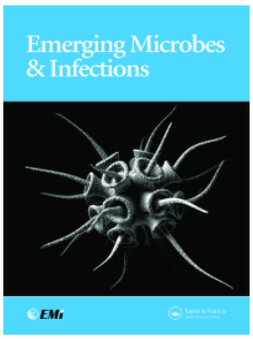

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Evaluation of waning of IgG antibody responses after rVSVΔG-ZEBOV-GP and Ad26.ZEBOV, MVA-BN-Filo Ebola virus disease vaccines: a modelling study from the PREVAC randomized trial

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 Schwimmer[i], Samba O. Sow[j], Irina Maljkovic Berry[k], Jens H. Kuhn[k], Daniela Fusco[l,m], Natasha Dubois Cauwelaert[n], 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*

[a]Infection, 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; [b]Bordeaux Population Health Research Centre, Université de Bordeaux, Inserm, and Inria, Bordeaux, France; [c]Vaccine Research Institute, Faculté de Médicine, Université Paris-Est Créteil, Créteil, France; [d]Centre National de Formation et de Recherche en Santé Rurale (CNFRSR) de Mafèrinyah, Ministère de la Santé et de l'Hygiène Publique, Mafèrinyah, Guinea; [e]University Clinical Research Center, University of Sciences, Technique and Technology of Bamako, Bamako, Mali; [f]Partnership for Research on Ebola Virus in Liberia (PREVAIL), Monrovia, Liberia; [g]London School of Hygiene & Tropical Medicine (LSHTM), London, UK; [h]College of Medicine and Allied Health Sciences (COMAHS), University of Sierra Leone, Freetown, Sierra Leone; [i]EUropean CLInical Trials Platform & Development (EUCLID), Université de Bordeaux, Centre Hospitalier Universitaire Bordeaux, and Inserm, ISPED, Bordeaux, France; [j]Centre pour le Développement des Vaccins, Ministère de la Santé et du Développement Social du Mali, Bamako, Mali; [k]Integrated Research Facility at Fort Detrick, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Frederick, MD, USA; [l]French Agency for Research on AIDS and Viral Hepatitis (ANRS), Emerging Infectious Diseases, PariSanté Campus, Paris, France; [m]Department of Infectious Diseases Epidemiology, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany; [n]Inserm, Paris Cedex 13, France; [o]Pôle de Santé Publique, Centre Hospitalier Universitaire Bordeaux, Bordeaux, France; [p]Service d'Immunologie Clinique et Maladies Infectieuses, Hôpital Henri-Mondor, Créteil, France; [q]Service 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 of children 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.

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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.

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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 log_{10}-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 clinicals 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

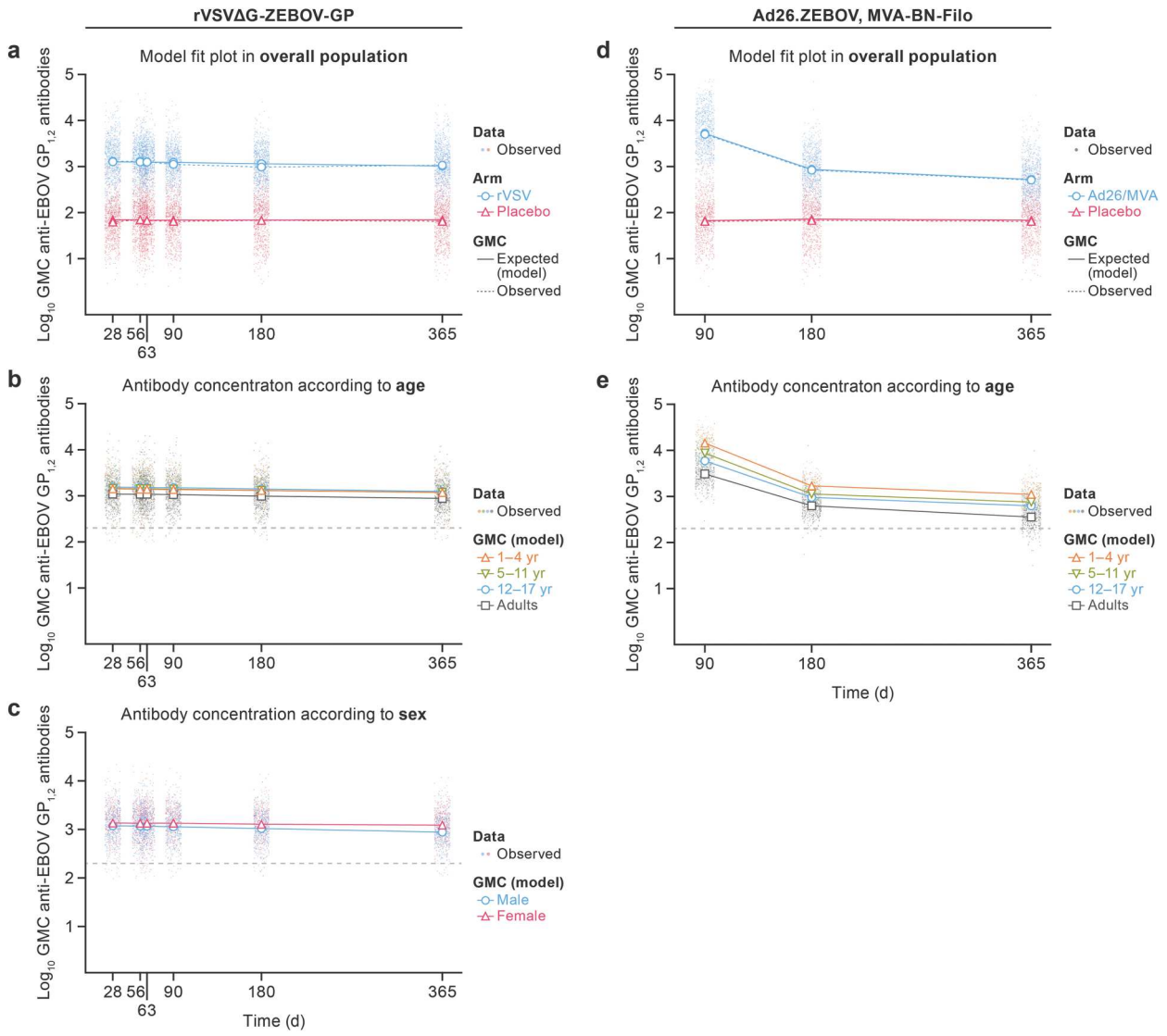

Figure 1. Anti-EBOV $GP_{1,2}$ IgG response (EU/mL) from the post-vaccination peak to 12 months after the first dose of rVSVΔG-ZEBOV-GP or Ad26.ZEBOV, MVA-BN-Filo, respectively. (a) (rVSVΔG-ZEBOV-GP) and (d) (Ad26.ZEBOV, MVA-BN-Filo): Observed and modelled (multivariable models) antibody GMCs over time 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.

	Anti-EBOV $GP_{1,2}$ antibody	Anti-EBOV $GP_{1,2}$ antibody
	Peak[a]	End of study[a]
Variable	Ratio of geometric mean concentration [95% CI]	Ratio of geometric mean concentration [95% CI]
Age category		
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]
Sex		
Males	Reference	Reference
Females	1.15 [1.01; 1.30]	1.40 [1.22; 1.59]
Country (laboratory)		
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]
Pre-vaccination antibody level		
<200 EU/mL	Reference	Reference
>200 EU/mL	1.31 [1.07; 1.57]	1.19 [0.99; 1.41]

[a]The 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.

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
Females			
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]
Males			
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.

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 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	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]
Age category		
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]
Country (*laboratory*)		
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]
Pre-vaccine antibody concentration		
<200 EU/mL	Reference	Reference
>200 EU/mL	0.93 [0.75; 1.13]	1.38 [1.12; 1.68]

[a]The 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.

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.

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

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.

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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 Aboulhab[2] MD, Michelle Aguirre-MacKenzie[12] BS, Pauline Akoo[3] MB, ChB, Esther Akpa[2] MSN, MPH, RN, Robert Akpata[1] MD, Sara Albert[17] BA, MPH, Boni Maxime Ale[4] MD, MSc, MPH, Serry Alimamy-Bangura[11] MB, ChB, Pierre Andong[1] MSt, Benetta C. Andrews[10] MD, Stephane Anoma[6] MD, Negin Atri[2] MPH, CPH, Augustin Augier[6] MCom, Ken Awuondo[3] MSc, Ahidjo Ayouba[30] PhD, Moses Badio[10] MSc, Aminata Bagayoko[1] MD, Abby Balde[17] MPH, Joséphine Balssa[1,8] PharmD, Lamin Molecule Bangura[11] BSc, Kesha Barrington[17] MPA, Eric Barte de Saint Fare[6] BA, Beth Baseler[17] MS, Ali Bauder[12] BA, PMP, Claire Bauduin[4] MSc, Luke Bawo[10] MSc, Abdoul Habib Beavogui[9] MD, PhD, Michael Belson[2] BS, Safaa Ben-Farhat[4] MEng, Marion Bererd[6] BS, Nicolas Bernaud[1,18] MSc, Teedoh Beyslow[10] PharmD, Neirade Biai[30] MSc, Jeanne Billioux[2] MD, Shere Billouin-Frazier[17] MSc, Blandine Binachon[4] MD, MPH, Julie Blie[10] MSc, Viki Bockstal[13] PhD, Patricia Boison[17] MS, Fatorma Bolay[10] PhD, Aliou Boly[6] MM, Rachael Elizabeth Bonawitz[12] MD, MS, Anne-Gaëlle Borg[6] MCM, Samuel Bosompem[2] PharmD, MSc, Courtney Bozman[28] MSc, Tyler Brady[2] MPH, Sarah Browne[10] RN, BSN, Ryan Bullis[12] PhD, Barbara Cagniard[1] PhD, Kelly Cahill[2] RN, MSc, CCRC, RAC, Yingyun Cai[28] PhD, Aissata Abdoulaye Camara[6] MSc, Aboubacar Keira Camara[1] MD, Alseny Modet Camara[6] MD, Antoine Campagne[1] PhD, Cécilia Campion[4] MSc, Alexandre Cantan[4,29] BSc, Jennifer Cash[17] BS, Siew Pin Chai[13] BBio-MedSc, Francois Chambelin[1] MHist, Michael Chea[10] BSc, Geneviève Chêne[4] MD, PhD, Edouard Choi[3] PhD, Michelle Chouinard[6] MSW, Florence Chung[1] PhD, Lucy Chung[2] PharmD, Séverine Ciancia[1] MJ, Papa Ndiaga Cisse[14] PhD, Elfrida Cline-Cole[17] MA, Céline Colin[4] MSc, Beth-Ann Coller[12] PhD, Djélikan Siaka Conde[1] MD, Katherine Cone[2] MSW, LCSW-C, C-SWHC, Laurie Connor[12] MS, Nicholas Connor[3] MSc, Joseph Boye Cooper[10] MSc, Sandrine Couffin-Cardiergues[1] PhD, Fatoumata Coulibaly[1] BS, Mariam Coulibaly[20] PharmD, MSc, Page Crew[2] PharmD, MPH, BCPS, Sandrine Dabakuyo-Yonli[4] PharmD, PhD, Djeneba Dabitao[20] PharmD, PhD, Thierry Damerval[1] PhD, Bionca Davis[5] MPH, Gibrilla Fadlu Deen[11] MD, MSc, Eline Dekeyster[13] PhD, Jean-François Delfraissy[1] MD, PhD, Christelle Delmas[1] MSc, Mahamadou Diakite[20] PharmD, DPhil, Alpha Diallo[1,8] MD, MPH, Fatoumata Abdoulaye Diallo[6], MD, Mamadou Saliou Diallo[6] MD, MPH, Ayouba Diarra[20] MSc, Samba Diarra[20] MSc, PhD, Oualy Diawara[19] BS, Bonnie Dighero-Kemp[28] BSc, Samba Diop[21] MSc, PhD, Waly Diouf[14] PhD, Saurabh Dixit[2] PhD, Barry Djenabou[6] MSc, Laurie Doepel[2] BA, Eric D'Ortenzio[1,7,8] MD, MPH, Seydou Doumbia[20] MD, PhD, Moussa Moise Doumbia[19] MD, Macaya Douoguih[13] MD, MPH, Nelson Dozier[28] MSc, Natasha Dubois Cauwelaert[1,8] PhD, Alain DuChêne[5] BS, Michael Duvenhage[17] NDIPIT, Risa Eckes[2] RN, Elizabeth Elliott[2] MSc, Luisa Enria[3] PhD, Hélène Espérou[1] MD, Cécile Etienne[1] MSc, Allison Eyler[17] HSD, Lawrence Fakoli[10] MSc, Mosoka Fallah[10] PhD, Marie-Alix Fauvel[1] MSc, Sylvain Faye[14] PhD, John Fayiah[10] MSc, Suzanne Fleck[3] PhD, Vemy Fofana[6] BComp, Karine Fouth Tchos[2] MD, MPH, Kokulo Franklin[10] MPhil, MSc, Daniela Fusco[1] PhD, Auguste Gaddah[13] PhD, Marylène Gaignet[1] MSc, Katherine Gallagher[3] PhD, Julie Gardner[12], BS, Harrison Gichini[28] MSc, Julia Garcia Gozalbes[1] MD, Greg Grandits[5] MS, Maima Gray[10] BPharm, Brian Greenwood[3] MD, Nico Grobler[13] PhD, Robin Gross[28] MSc, Louis Grue[17] RN, BS, BSN, Birgit Grund[27] PhD, Oumar Guindo[20] MSc, PharmD, Swati Gupta[12] DrPH, MPH, Fadima Haidara[19] MD, Benjamin Hamzé[1] PharmD, Emma Hancox[3] MSc, Jean-Christophe Hébert[1] MSL, Jenny Hendriks[13] PhD, Patricia Hensley[3] MPh, Lisa E Hensley[28] PhD, MSPH, Betsey Herpin[2], MSN, Elisabeth Higgs[2] MD, DTMH, MIA, Trudi Hilton[3] BPharm, MSc, Mickael Hneino[1], PhD, Tracey-Ann Höeltermann[28], BSc, MPH, Horace Preston Holley[17] MD, Marie Hoover[16] PhD, Natasha Howard[3] PhD, Melissa Hughes[12] BA, MBA, CPM, PMP, Dicko Ilo[20] MD, MPH, Skip Irvine[12] BS, David Ishola[3] MD, PhD, Yvonne Jato[2] MPH, Madison Joe[10] MSc, Melvin Johnson[10] MSc, Aboubacar Sidiki Kaba[6] MD, Jonathan Kagan[2] PhD, Kade Kallon[17] MSc, Michael Kamara[3] MBChB, MSc, Myriam Kante[4] BS, Judith Katoudi[6] MD, MPH, Cheick Mohamed Keita[6] MD, Sakoba Keita[15] MD, Seykou Keita[22] MD, Stephen B. Kennedy[10] MD, MSc, Babajide Keshinro[13] MBBS, FWACP, Hassan Kiawu[10] MSc, Mark Kieh[10] MD, MSMHC, Brent Killinger[12] BA, Moumouni Kinda[6] MD, MBA, Matthew Kirchoff[2] PharmD, MSc, MBA, Gregory Kocher[28] MSc, Mamoudou Kodio[19] PharmD, Brian Kohn[3] BSc, Lamine Koivogui[23] PharmD, PhD, Richard Kojan[6] MD, Cece Francis Kolié[6] PharmD, Jacques Seraphin Kolié[6] MD, David Kollie[10] BSc, Stacy Kopka[17] MS, Bockarie Koroma[11] BPharm, Dickens Kowuor[3] BSc, MSc, PhD, Catherine Kpayieli-Freeman[10] MSc, Liane Kwast[13] MSc, Christine Lacabaratz[1,18] PhD, Boris Lacarra[1] MD, Laurie Lambert[17]

BS, Courtney Lambeth[12] BS, Solange Lancrey-javal[1,8] PharmD, H. Clifford Lane[2] MD, Shadrach Langba[10] BSc, Bolarinde Lawal[3] MSc, Andrew Wen-Tseng Lee[12] MD, Shona Lee[3] PhD, Shelley Lees[3] PhD, Annabelle Lefevre[1] MD, Bailah Leigh[11] MD, MSc, Frederic Lemarcis[1] PhD, Yves Lévy[1,18] MD, PhD, Claire Levy-Marchal[1] MD, Maarten Leyssen[13] MD, PhD, Edouard Lhomme[26] MD, PhD, Janie Liang[28] MSc, Mameni Linga[10] MSc, Ken Liu[12] PhD, Brett Lowe[3] MPhil, Julia Lysander[10] MSc, Ibrah Mahamadou[6] PharmD, Irina Maljkovic-Berry[28] PhD, Marvington Mambiah[10] ASc, Daniela Manno[3] MD, PhD, Jonathan Marchand[2,17] MS, Lindsay Marron[28] MSc, Moses B.F. Massaquoi[10] MD, MSc, Laure Masson[1] MIBL, Charly Matard[4] BS, Steven Mazur[28] BS, John McCullough[16] BS, Katherine McFadyen[13] MPH, Chelsea McLean[13] PhD, Noémie Mercier[1] PharmD, Pauline Michavila[6] BBus, Tracey Miller[17] RN, BSN, Niouma Pascal Millimouno[6] MD, Alejandra Miranda[17] MS, Soumaya Mohamed[6] BJ, Tom Mooney[3] BA, Dally Muamba[6] MD, James Mulbah[11] BPharm, Rita Lukoo Ndamenyaa[6] MD, MSc, James Neaton[5] PhD, Désiré Neboua[1] MD, Micki Nelson[12] BSN, MS, Kevin Newell[17] MPH, MEd, Vinh-kim Nguyen[24] MD, Yusupha Njie[3] BSc, Wissedi Njoh[17] MSN, Anna Novotney-Barry[13] MSC, Matthew Onorato[12] BS, Uma Onwuchekwa[22] BSc, Susan Orsega[2] MSN, FNP-BC, Inmaculada Ortega-Perez[1,8] PhD, MPH, Cynthia Osborne[17] BS, Tuda Otieno[3] MSC, Davy Oulaï[4] MD, Sushma Patel[12] MS, PMP, Danielle Peart[2] BS, Martine Peeters[30] PhD, James Pettitt[28] MSc, Nathan Peiffer-Smadja[1] MD, PhD, Robert Phillips[3] MSc, Jerome Pierson[2] PhD, Peter Piot[3] MD, PhD, Micheal Piziali[2] JD, MSc, Stéphany Pong[1,8] PharmD, Elena Postnikova[2] PhD, Calvin Proffitt[17] MA, Alexandre Quach[1] MD, Sinead Quigley[1] MSSc, Nadeeka Randunu[2,17] BSc, MBA, Laura Richert[26] MD, PhD, Priscille Rivière[1] MSc, Cynthia Robinson[13] MD, Céline Roy[4,29], PhD, Amy Falk Russell[12] MS, Philip Sahr[10] MD, Katy Saliba[2] MSc, PhD, Mohamed Samai[11] MBBS, PhD, Sibiry Samake[20] PharmD, MSc, Jen Sandrus[17] AA, Ibrahim Sanogo[20] MsP, MD, Yeya Sadio Sarro[20] PharmD, PhD, Serge Sawadogo[6] MD, MSc, Sani Sayadi[6] MD, MPH, Maxime Schvartz[1] MD, Christine Schwimmer[4] PhD, Fatou Secka[3] BSc, MSc, MBChB, Heema Sharma[28] MSc, Denise Shelley[17] MS, Bode Shobayo[10] MSc, Sophia Siddiqui[2] MD, MPH, Jakub Simon[12] MD, Shelly Simpson[17] MS, Billy Muyisa Sivahera[6] MD, Karen Slater[3], Mary Smolskis[2] BSN, MA, Elizabeth Smout[3] MD, MSc, Emily Snowden[3] MA, Anne-Aygline Southiphong[4,29] MSc, Amadou Sow[6] MSc, Samba O. Sow[22] MD, MSc, Ydrissa Sow[2] MD, MPH, Michael Stirratt[25] PhD, Jeroen Stoop[13] PhD, Guna Subramaniam[13] MSc, Léa Surugue[1] MJ, Nathalie Swales[13] MSc, Sienneh Tamba[10] RN, BSN, Chan Tang[13] BSc, Cheick Tangara[20] MSc, Milagritos D. Tapia[22] MD, Julius Teahton[10] MSc, Jemee Tegli[10] MSc, Monique Termote[4] MSc, Guillaume Thaurignac[30] MSC, Rodolphe Thiebaut[4] MD, PhD, Greg Thompson[5] BS, John Tierney[2] BSN, MPM, Daniel Tindanbil[3] MSc, Abdoulaye Touré[23] PharmD, MPH, PhD, Elvis Towalid[10] BPharm, Stacey Traina[12] BS, Awa Traore[19] PharmD, Tijili Tyee[10] PharmD, David Vallée[1] PharmD, Renaud Vatrinet[1] PhD, Corine Vincent[4] MSc, Susan Vogel[2] RN, BSN, Cedrick Wallet[4] MSc, Travis Warren[2] PhD, Deborah Watson-Jones[3] MD, PhD, Wade Weaver[28] MSc, Deborah Wentworth[5] MPH, Cecelia Wesseh[10] BSc, Hilary Whitworth[3] PhD, Jimmy Whitworth[3] PhD, Aurelie Wiedemann[1,18] PhD, Wouter Willems[13] PhD, Barthalomew Wilson[10] MSc, Jayanthi Wolf[12] PhD, Alie Wurie[11] MD, MSc, Delphine Yamadjako[17] MS, Marcel Yaradouno[6] MSc, Quiawiah Yarmie[10] MSc, Yazdan Yazdanpanah[1,7,8] MD, PhD, Shuiqing Yu[28] BS, Zara Zeggani[6] MSc, Huanying Zhou[28] BS.

Affiliations

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

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

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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.

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