Antibody kinetics following vaccination with MenAfriVac and implications for the duration of protection: an analysis of serological data

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Abstract

Background A meningococcal group A conjugate vaccine, PsA-TT (MenAfriVac), was developed with the support of the Meningitis Vaccine Project. Around 280 million individuals aged 1 to 29 years have been immunised across the African meningitis belt. We analysed the kinetics of vaccine-induced antibody response and assessed the possible implications for duration of protection.

Methods We obtained data from longitudinal studies of antibody responses in 193 children aged 12 to 23 months, and 605 participants aged 2 to 29 years following MenAfriVac vaccination. Antibodies were measured using two methods: group A serum bactericidal antibody (SBA) assay and group A-specific IgG ELISA. Data on antibody responses were analysed using a mixed-effects statistical model accounting for the mean response and variation in patterns of antibody kinetics.

Findings In children age 12 to 23 months, the reduction in MenAfriVac-induced antibody levels assessed by SBA titers had two phases; with 97·0% (95% credible interval (CrI): 95·1%, 98·3%) of the response being short-lived and decaying within the first 6 months, and the remainder being long-lived and decaying with a half-life of 7·4 (95% CrI: 2·8, 41·3) years. Antibody levels assessed by SBA titers in participants aged 2 to 29 were more persistent, with 95·0% (95% CrI: 85·7%, 98·1%) of the response being short-lived, and the long-lived phase decaying with a half-life of 16·5 (95% CrI: 7·7, 39·1) years. Greater pre-vaccination antibody levels were associated with greater immunogenicity following vaccination, as well as greater antibody persistence. There is no strong evidence base for a correlate of protection against infection with *Neisseria meningitidis* serogroup A (NmA). Despite rapid antibody declines in the first phase, antibodies in the second phase persisted at SBA titers greater than 128. Based on this assumed relationship between SBA titer and protection, we predict that 20 years after vaccination with a single dose of MenAfriVac, vaccine efficacy will be 52% (95% CrI: 29%, 73%) in children vaccinated at age 12 to 23 months, and 70% (95% CrI: 60%, 79%) in participants vaccinated at age 2 to 29 years.

Interpretation The introduction of MenAfriVac in mass campaigns has been followed by substantial reductions in NmA cases. Routine immunisation with EPI is now being rolled out. Careful monitoring is required to ensure the continued success of MenAfriVac, and future policy can be guided by understanding of the duration of protection provided here.

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Research in context

Evidence before this study

We searched PubMed on July 10, 2018, for studies on the immunogenicity of the MenAfriVac *Neisseria meningitidis* serogroup A vaccine using the MeSH terms ("MenAfriVac" OR "PsA-TT") and ("immunogenicity" OR "antibody"). We identified 18 reports. 11 of these studies investigated the immunogenicity of MenAfriVac within 1-2 years of vaccination. 2 studies demonstrated that antibody responses following MenAfriVac persist for time periods of up to 5 years.

Added value of this study

This study builds on previous data by using a statistical model to predict antibody levels up to 20 years following vaccination and assess the implications for the duration of vaccine-induced protection with robust quantification of uncertainty. The decay of antibody levels after vaccination can be described by a bi-phasic exponential relationship with a phase of rapid decay in the first 6 months, followed by a second slower phase of decay. Importantly, in this second slowly decaying phase, antibody levels are predicted to remain above the assumed threshold for protection for substantial periods of time such that the estimated efficacy in children aged 12 to 23 months is 52% (95% credible interval (CrI): 29%, 73%) after 20 years, and the estimated efficacy in individuals aged 2 to 29 years is 70% (95% CrI: 60%, 79%) after 20 years.

Implications of all the available evidence

MenAfriVac has been developed, tested and licensed on the basis of safety and immunogenicity data. Since 2010 around 280 million individuals have received this vaccine, leading to the widespread disappearance of Group A meningococcal carriage and disease. The estimates of long-term duration of immunity presented here provide an evidence base to assess how ongoing and future vaccination strategies will contribute to the maintenance of population-level immunity over the next 20 years.

Introduction

Countries in the African meningitis belt, a region south of the Sahara stretching from Senegal to Ethiopia, have been subjected to frequent and large epidemics of meningococcal meningitis for more than a century[1]. Incidence rates during epidemics often exceed 500 cases per 100,000 population, with mortality rates of invasive meningococcal disease of 10% to 15%[2]. *Neisseria meningitidis* serogroup A (NmA) has been responsible for the majority of epidemics observed in this region, although epidemics due to other serogroups have been recorded[3].

In response to these public health needs, a group A meningococcal polysaccharide-tetanus toxoid conjugate vaccine (PsA-TT; MenAfriVac) has been developed by the Meningitis Vaccine Project (MVP) and the Serum Institute of India Ltd.[4]. MenAfriVac has been delivered to countries in the African meningitis belt through mass vaccination campaigns of people 1-29 years of age, and countries are now introducing it into their Expanded Programme on Immunization (EPI) schedules targeting children aged 9-18 months[5].

There is limited evidence on the association between antibody levels and vaccine efficacy, with the only established correlate of protection being group A-specific IgG antibodies ≥2 μg/mL[6,7], with no evidence from Africa. Observational studies of natural immunity have not detected associations between antibody levels and NmA meningitis incidence[8], as reported by the classic studies of Goldschneider *et al*[7]. Despite this, MenAfriVac was licensed on the basis of safety and immunogenicity data[9], with data on effectiveness being collected only after largescale MenAfriVac campaigns[3,10]. Ongoing surveillance efforts have not identified cases of NmA meningococcal disease in individuals vaccinated with MenAfriVac[11].

Increased coverage of MenAfriVac vaccination will lead to higher levels of vaccine-induced immunity in target populations[12], however there is an important need to understand how immunity wanes over time, and to assess the implications for future population-level protection. Addressing this key knowledge gap will aid the WHO's Strategic Advisory Group of Experts (SAGE) on Immunization to provide guidance on the implementation of mass vaccination campaigns or routine EPI to ensure the maintenance of population-level immunity. Although it is known that antibody responses induced by MenAfriVac decay over time[13,14], the duration of vaccine-induced immunity has yet to be determined[15]. Immunogenicity data was central to the recommendation for MenAfriVac licensure, and can also play a central role in providing initial estimates of the duration of vaccine-induced immunity. Affordable multivalent meningococcal vaccines are also being developed, to offer broader protection against groups CWYX in addition to A[16]. Investment in these vaccines is currently being considered by Gavi, the Vaccine Alliance and immunogenicity will again be an important factor.

Here, we analyse longitudinal data on antibody responses using a statistical model of antibody kinetics to investigate the persistence of antibody responses, and assess the implications for duration of protection.

Methods

Data

Individual-level data on epidemiological covariates and immunological measurements from two randomized controlled trials of the MenAfriVac vaccine[9] were obtained following a request to MVP's Access Program. Data were not available from participants in trial arms receiving the reference polysaccharide vaccine (PsACWY), or from the subset of samples taken greater than 4 years after vaccination.

Full details of the PsA-TT-002 study have been reported elsewhere[9,13]. In brief, healthy Malian and Gambian children aged between 12 and 23 months, fully immunized according to the local EPI schedule, were recruited to receive primary vaccination of either MenAfriVac (10 μg), PsACWY, or *Haemophilus influenzae* type b vaccine (Hib-TT). Children were further randomised to receive a second vaccine dose 10 months later. Blood samples were obtained prior to primary vaccination; 4 weeks after primary vaccination; prior to secondary vaccination; 1 and 4 weeks after secondary vaccination; and approximately 1 and 2 years after primary vaccination. Further samples from a subset of individuals were taken 5 years after primary vaccination. The 5 year follow-up data were not directly incorporated in this analysis, but geometric mean values were used to validate model predictions. The data are summarised in Table 1 and Supplementary Figure 1.

Full details of the PsA-TT-003 study have been reported elsewhere[9,14]. In brief, healthy Malian, Gambian and Senegalese participants aged 2-29 years were recruited and randomized to receive either MenAfriVac or PsACWY. Blood samples were obtained at baseline, 1 month, 6 months and 1 year after primary vaccination. Further samples from a subset of individuals were taken 4 years after primary vaccination. The 4 year follow-up data were not directly incorporated in this analysis, but geometric mean values were used to validate model predictions. The data are summarised in Table 1 and Supplementary Figure 2.

Table 1 here

Immunogenicity

Immunogenicity was assessed using two different assays; firstly, with a serum bactericidal antibody (SBA) assay using the group A target strain F8238 with baby rabbit complement[17]; and secondly with MenA-specific immunoglobulin G (IgG) enzyme-linked immunosorbent assay (ELISA). SBA titers were measured at the Vaccine Evaluation Unit of the Health Protection Agency (now Public Health England), Manchester, UK; and the ELISA was performed at the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia. We refer to antibody levels as measured values from either of these assays.

Statistical analysis

The effects of several covariates on antibody responses, measured in continuous log values, following primary or secondary vaccination with MenAfriVac were assessed using linear regression models. The covariates were age in years, trial, country, sex, height, weight and measurement of antibody response prior to vaccination. The effects of these covariates on the percentage reduction in antibody responses 1 year following vaccination were assessed using logistic regression models. Regression models were applied separately to antibody levels measured using the IgG ELISA and SBA assays.

Antibody kinetics

Exposure of the immune system to vaccine antigens stimulates the generation of memory B cells which subsequently differentiate into antibody secreting cells (ASCs)[18]. ASCs generate IgG molecules responsible for vaccine-induced immunity, and are composed of two populations: one short-lived responsible for the rapid generation of antibodies, and one long-lived responsible for humoral immunity long after vaccination or initial infection[18]. This immunologically based model has been used to describe antibody kinetics following malaria infection[19], pertussis vaccination[20], human papillomavirus vaccination, and hepatitis A vaccination[21]. These mathematical models were adapted to account for the changing antibody response over time following MenAfriVac vaccination. Primary vaccination is assumed to induce proliferation of populations of ASCs of size β in a rapid boost. A proportion ρ of ASCs are assumed to be short-lived with half-life d_s and a proportion $1 - \rho$ long-lived with half-life d_l. ASCs are assumed to generate IgG molecules at a constant rate which decay with half-life d_a. The antibody response at time t after primary vaccination can be modelled as:

$$Ab(t) = Ab_0 e^{-r_l t} + \beta\left(\rho\frac{e^{-r_s t} - e^{-r_a t}}{r_a - r_s} + (1-\rho)\frac{e^{-r_l t} - e^{-r_a t}}{r_a - r_l}\right)$$

This equation is valid for antibody responses measured with either assay. Ab_0 is the baseline antibody response prior to primary vaccination. Decay rates are calculated from half-lives as follows: $r_l = \log_e(2)/d_l$; $r_c = \log_e(2)/d_c$; and $r_a = \log_e(2)/d_a$. Some participants in the PsA-TT-002 study received secondary vaccination with MenAfriVac after 10 months. The antibody response following this second dose are modelled using the same equation as above. The model does not account for the role of natural exposure to NmA.

We refer to the first short-lived phase of the response as the IgG molecules generated by short-lived ASCs, and the second long-lived phase of the response as the IgG molecules generated by long-lived ASCs. There is not a strong evidence base for the dose-response relationship between measured antibody responses following vaccination against *N. meningitidis* and vaccine efficacy[15]. We utilise a flexible functional form[22] to investigate a range of possible relationships:

$$V(t) = 1 - \frac{1}{1 + \left(\frac{Ab(t)}{Ab_{\text{prot}}}\right)^{\alpha}}$$

where Ab_{prot} is the threshold SBA titre required for protection, and α is a shape parameter.

The model for antibody kinetics was fitted separately to data measured from the two assays, and from the two studies. A mixed-effects framework was used allowing for characterisation of the kinetics within each individual, whilst also describing the population-level patterns. Importantly, on the population level both the mean and variation in antibody kinetics are accounted for. The models were fitted in a Bayesian framework utilising Markov Chain Monte Carlo (MCMC) with informative priors (described in Supplementary Table 4).

Role of the funding source

Primary data collection was funded by the MVP through a grant from the Bill and Melinda Gates Foundation. Funding for this secondary analysis was provided by Institut Pasteur. The sponsors had no role in the design of the analysis, interpreting the data, or writing this report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Immunogenicity following vaccination

Antibody levels measured via SBA titer and group A-specific IgG ELISA were significantly correlated (Pearson's r = 0·58; p < 0·0001), with a linear relationship on a log-log scale for measurements from post-vaccination samples, but not from pre-vaccination samples (Supplementary Figure 3), replicating findings reported elsewhere[15]. Notably, different relationships were observed for samples from the PsA-TT-002 and PsA-TT-003 studies, with participants in the PsA-TT-003 study having substantially higher group A-specific IgG ELISA levels at equal SBA titers.

The dependence of log antibody responses after vaccination on a number of covariates was assessed using linear regression (Supplementary Table 3), with univariate relationships shown in Supplementary Figure 4. The results from this analysis of pooled data were in agreement with findings from the component data sets[23]. In the PsA-TT-002 study of children aged 12-23 months, for each extra month of age there was a 9% increase in SBA titers (p = 0·001). However, in the PsA-TT-003 study of participants aged 2-29 years, for each extra year of age there was a 2% decrease in SBA titers (p = 0·0009). High baseline $\log_{10}$ SBA titers were associated with higher $\log_{10}$ SBA titers after vaccination (p < 0·0001). When antibody levels were measured by ELISA, there were no significant associations between age and group A-specific IgG ELISA level following vaccination. Antibody levels in males were 18% lower than in females (p = 0·002). Group A-specific IgG ELISA levels at baseline were significantly associated with higher levels following primary vaccination (p < 0·0001).

Antibody kinetics

In both the PsA-TT-002 and PsA-TT-003 studies, the change in antibody response over time was described using a bi-phasic exponential model of decay. Figure 1A-H shows a comparison of the model predicted antibody kinetics with

data on SBA titers and IgG ELISA levels from a representative subset of 8/797 individuals. A number of distinctive patterns are evident: (i) antibody responses induced by MenAfriVac decay rapidly in the first 6 months, after which the remaining antibodies decay at a slower rate; (ii) in most individuals the initial decay of IgG ELISA levels is more rapid than the decay of SBA titers; (iii) Hib-TT vaccination causes boosting in SBA titers but not IgG ELISA levels; (iv) there is substantial variation in the observed antibody kinetics, for example individual G002_3 (Figure 1B) did not sustain a long-lived antibody response as measured by SBA titer. Figure 1I-L shows the geometric mean and range of antibody responses observed in the study population. The model predicted geometric mean antibody responses were in agreement with the data from samples at 4 years follow-up in the PsA-TT-003 study, but slightly under-predict the data at 5 years follow-up in the PsA-TT-002 study. As these data were not used to calibrate the model, this provides some support for the ability of the model to predict long-term antibody responses. Figure 1M-P shows the proportion of individuals predicted to have antibody responses greater than a range of thresholds over the first 5 years of follow-up.

The estimated parameters describing the antibody kinetics are presented in Table 2. In the PsA-TT-002 study, primary vaccination with MenAfriVac is assumed to induce ASCs that generate antibodies causing bactericidal activity. For measurements from the SBA assay all ASCs are assumed to secrete IgG molecules which decay with an estimated half-life of 15·4 (95% Credible Interval (CrI): 12·0, 20·0) days. The short-lived phase is estimated to constitute 97·0% (95% CrI: 95·1%, 98·3%) of the response with a median half-life of short-lived ASCs of 3·5 (95% CrI: 2·1, 5·3) days, with the second long-lived phase having a median half-life of long-lived ASCs of 2690 (95% CrI: 1016, 15078) days. In the PsA-TT-002 study, the key difference between antibody kinetics when investigated using the two assays was the greater proportion of the short-lived phase for the IgG ELISA assay, estimated as 99·1% (95% CrI: 98·5%, 99·5%).

In the PsA-TT-003 study, only data from the first year of longitudinal follow-up was available for model fitting. The posterior estimates of the half-life of long-lived ASCs from the PsA-TT-002 study were therefore used as prior information for the PsA-TT-003 study. For the long-lived phase of the antibody response the half-life of ASCs contributing to bactericidal activity was estimated as 6007 (95% CrI: 2826, 14279) days, and the half-life of ASCs contributing to IgG ELISA measurements was estimated as 2287 (95% CrI: 1380, 4098) days. For both assays, the proportion of the antibody response in the second long-lived phase was estimated to be greater in the PsA-TT-003 study than the PsA-TT-002 study.

Table 2 here

Age dependency of antibody persistence

The immunogenicity following MenAfriVac vaccination has been well characterised, but determinants of antibody persistence remain poorly understood[23]. Figure 2 shows the dependence of antibody persistence 1 year after MenAfriVac vaccination on age, and pre- and post-vaccination antibody responses. The effect of these covariates

are also shown on measured antibody response immediately after vaccination (Supplementary Figure 4), and 1 year after vaccination (Supplementary Figure 14).

Older age was associated with better persistence when antibody response was measured by both SBA titer (Figure 2A) and ELISA (Figure 2D). However, in a multivariate analysis age was not significantly associated with antibody persistence (Table 3). Greater SBA titers before MenAfriVac vaccination were associated with better antibody persistence (Figure 2B), but this was not significant in the multivariate analysis (Table 3). Individuals who had more immunogenic responses to MenAfriVac when measured by SBA titer also experienced greater reduction in the first year (Figure 2C), and this was highly significant ($p < 0{\cdot}0001$). Greater IgG ELISA measurements before MenAfriVac vaccination were associated with better antibody persistence (Figure 2E), and this association was significant ($p < 0{\cdot}0001$). Individuals who had more immunogenic responses to MenAfriVac when measured by IgG ELISA also experienced greater reduction in the first year ($p < 0{\cdot}0001$), although this association was not evident when examined univariately (Figure 2F).

Table 3 here

Predicted vaccine efficacy

Estimates of changing antibody responses over time allow for waning of vaccine efficacy to be estimated, assuming that antibody correlates with protection. There are very limited sources of data on meningococcal surrogates of protection specifically for NmA, however SBA titers ≥ 128 are frequently used as a threshold level[15]. Figure 3 shows an assumed dose-response relationship between SBA titer and vaccine efficacy, corresponding to a profile similar to an all-or-nothing vaccine. Based on model predictions we estimate that 20 years after primary vaccination with a single dose of MenAfriVac, vaccine efficacy will be 70% (95% CrI: 60%, 79%) in the PsA-TT-003 study, and 52% (95% CrI: 29%, 73%) in the PsA-TT-002 study. Secondary vaccination with MenAfriVac 10 months after primary vaccination, was estimated to result in 64% (95% CrI: 40%, 85%) vaccine efficacy after 20 years in the PsA-TT-002 study. This does not account for the potential role that natural exposure may play in boosting immune responses.

Discussion

Vaccination with MenAfriVac causes a rapid increase in antibody responses targeting group A *N meningitidis*, when measured by either SBA titer or group A-specific IgG ELISA. This response is characterised in two phases; after peaking within the first month following vaccination, the first phase of the antibody response decays rapidly within the first 6 months, so that sustained protection is conferred by the second phase of the immune response. In children aged 12-23 months, this long-lived phase of the antibody response is estimated to decay with a half-life of 7·4 (95% CrI: 2·8, 41·3) years when measured by SBA titer, and 4·5 (95% CrI: 2·7, 11·0) years when measured by ELISA. In older individuals aged 2-29 years, the long-lived phase was estimated to be longer with a half-life of 16·5 (95% CrI: 7·7, 39·1) years when measured by SBA titer, and 6·3 (95% CrI: 3·8, 11·2) years when measured by ELISA.

These values are comparable with estimated half-lives for anti-tetanus and anti-diphtheria antibody responses of 11-19 years, but decay more rapidly than anti-measles antibodies which demonstrate little reduction over time[24]. The distinctive pattern of bi-phasic waning is consistent with observations following administration of a combination meningococcal serogroup C and *Haemophilus influenza* type b vaccine[25].

Geometric mean antibody levels in these study populations have been observed to persist above a threshold SBA titer of 128 for up to 4 years[13,14]. However, it is the variation in antibody responses rather than the mean which is the key determinant of how vaccine efficacy wanes over time. A key strength of the statistical methods utilised in this analysis is the ability to characterise the variation in antibody responses in addition to the average behaviour. For example, consider individual G002_3 in Figure 1B whose rapidly decaying SBA titer may be considered atypical of the average antibody response. In some cases in the PsA-TT-002 study, there is an increase in antibody levels between the samples from years 2 and 5 (Figure 1I-L). This may be attributable to natural exposure to NmA or cross-reactivity with antibodies to other serogroups or pathogens. The model does not account for these factors, and the predictions are only valid in the absence of other exposure.

The availability of data from two independent assays is an advantage, as it provides a consistent picture of how antibody responses vary over time. However, some systematic differences between measurements from these assays highlight some of the limitations that arise when analysing antibody data. The ELISA assay provides a specific measurement of IgG molecules that bind to the target antigen, whereas the SBA assay providers a broader measurement of any functional components of the immune response that contribute to bactericidal activity. There were notable differences in the proportion of the antibody response estimated to be long-lived based on measurements from the two assays, with IgG ELISA levels waning much more rapidly than SBA titers. A second point of note is the occurrence of boosting of SBA titers by Hib-TT vaccination (e.g. Figure 1K): this may be attributable to polyclonal activation of other antibody responses that are cross-reactive on the SBA assay, but not measurable on the IgG ELISA assay[26,27]. Another important point is the different relationship between SBA titers and IgG ELISA levels observed in the two studies (Supplementary Figure 3): at equal SBA titers individuals in the PsA-TT-003 study have higher IgG ELISA levels than individuals in the PsA-TT-002 study. This observation may be due to age effects, or the higher proportion of samples at long durations of follow-up in the PsA-TT-002 study when IgG ELISA levels have waned. The group A strain used in the SBA assays was the standard reference strain (F8238), which is more representative of a carrier than disease isolate. It has been argued that assays using strain 3125 provide a more specific measure of vaccine induced immunity[28] but unfortunately, this assay was not used here. This is an important limitation but the data presented here are consistent with the regulatory requirements for licensure.

The key determinants of immunogenicity (measured antibody response after vaccination) were age and pre-vaccination antibody response. For measurements from both assays, high pre-vaccination antibody levels were associated with greater immunogenicity following MenAfriVac. In the PsA-TT-002 study of children aged 12-23 months, older age was associated with greater immunogenicity, however in the PsA-TT-003 study of individuals aged 2-29 years, older age was associated with lower immunogenicity (Supplementary Table 3). This is in contrast to data following meningococcal serogroup C vaccination where immunogenicity increased with age in children 6-15 years[29]. For antibody persistence considered as the percentage of the post-vaccination antibody response remaining after 1

year, there was no significant association with age. The most important determinant of persistence was immunogenicity: individuals with the highest antibody responses following MenAfriVac had the greatest proportional reduction after 1 year. For antibody levels measured by group A-specific IgG ELISA, greater pre-vaccination antibody levels were associated with better persistence. The same trend was evident for antibody levels measured by SBA titer, but was not significant. Comparing the determinants of immunogenicity (magnitude of antibody response) and persistence (duration of antibody response), we see that many covariates affect immunogenicity, notably age and pre-vaccination antibody responses, whereas the key determinant of persistence is immunogenicity.

Mass immunisation campaigns with MenAfriVac targeting individuals aged 1-29 years in countries in the African meningitis belt have been followed by substantial reductions in suspected and confirmed *N meningitidis* group A cases[3,10]. The transition to vaccination of children aged 9-18 months through the routine EPI schedule will lead to a substantially different profile of immunity in a population. In the years immediately after a mass immunisation campaign, most individuals are predicted to still have high levels of vaccine-induced immunogenicity[30]. However, population-level immunity induced via EPI will lead to infants with high levels of immunity due to their recent vaccination, and adults with lower levels of protection because of the elapsed time since childhood vaccination.

Although based on vaccinees in clinical trials, and not the general population, the estimates provided here can guide the optimal design of vaccination strategies. 20 years after vaccination with MenAfriVac in participants aged 2-29 years, vaccine efficacy is estimated to be 70% (95% CrI: 60%, 79%). In children vaccinated at age 12-23 months (representative of the target EPI population aged 9-18 months), efficacy 20 years after vaccination was estimated to be substantially lower at 52% (95% CrI: 29%, 73%). Incorporation of a booster dose of MenAfriVac 10 months after primary vaccination is estimated to increase efficacy at 20 years to 64% (95% CrI: 40%, 85%). However, an alternative strategy would be to delay the primary dose by 10 months until children are older (24-33 months), so that they mount a more immunogenic response, resulted in an estimated efficacy 20 years later of 63% (95% CrI: 37%, 83%). However the benefits of such a strategy would need to be weighed against the risks of leaving young children unvaccinated for longer. To fully understand the population impact of declining individual protection, models that incorporate indirect (herd) protection are required[12], given the effect of MenAfriVac against carriage as well as disease[30].

The introduction of MenAfriVac in 2010 was followed by substantial reductions in *N meningitidis* A cases in the African meningitis belt. Characterisation of the kinetics of MenAfriVac-induced antibody responses in individuals will contribute to understanding the long-term patterns of immunity in populations, enabling us to evaluate and reduce the risk of future epidemics through adaptive vaccination policies.

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Contributors

MTW performed the analysis and wrote the first draft of the report. OI, SS, AD, BK, RB and CT designed the study and collected data. All authors reviewed drafts, and approved the final version of the report.

Conflicts of interest

BK reports grants from PATH for conducting trials at MRC Unit in The Gambia. RB has performed contract research on behalf of Public Health England for GSK, Pfizer and Sanofi Pasteur, outside the scope of the submitted work. CT reports consultancy payment from GSK in 2018, outside the scope of the submitted work. All other authors declare that they have no conflicts of interest.

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Tables

Table 1: Overview of epidemiology and immunogenicity in MenAfriVac (PsA-TT) studies. The PsA-TT-002 data is a subset of that described by Tapia *et al*[13]. The PsA-TT-003 data is a subset of that described by Diallo *et al*[14]. Age and duration of follow-up are presented as medians with 95% ranges. Measurements of immunogenicity are presented as geometric means with 95% ranges. The antibody response measured at baseline is denoted by 'base'; the response following primary vaccine dose by 'prim'; and following secondary vaccine dose by 'sec'.

trial	**PsA-TT-002**						**PsA-TT-003**		
country	**Gambia**	**Gambia**	**Gambia**	**Mali**	**Mali**	**Mali**	**Gambia**	**Mali**	**Senegal**
primary vaccine	Hib-TT	MenAfriVac	MenAfriVac	Hib-TT	MenAfriVac	MenAfriVac	MenAfriVac PsA-TT	MenAfriVac PsA-TT	MenAfriVac PsA-TT
secondary vaccine after 10 months	MenAfriVac	Hib-TT	MenAfriVac	MenAfriVac	Hib-TT	MenAfriVac	–	–	–
N	33	34	30	30	32	34	202	201	201
age (years)	1·5 (1·0, 1·9)	1·4 (1·0, 1·9)	1·6 (1·0, 1·9)	1·3 (1·0, 1·9)	1·3 (1·0,1·9)	1·3 (1·0,1·9)	15 (2, 28)	13 (3, 25)	13 (3, 26)
gender (% female)	16 (48%)	13 (38%)	15 (50%)	11 (37%)	16 (50%)	19 (56%)	84 (42%)	79 (39%)	87 (43%)
follow-up time (days)	779 (777, 807)	779 (777, 789)	780 (777, 799)	786 (770, 805)	785 (771, 801)	783 (770, 799)	371 (366, 380)	371 (369, 384)	391 (380, 428)
SBA_{base}	14 (2, 1024)	45 (2, 3123)	47 (2, 2048)	5 (2, 1331)	3 (2, 659)	4 (2, 1204)	111 (2, 4096)	317 (2, 4096)	318 (2, 4096)
SBA_{prim}	84 (2, 2560)	7375 (1024, 16384)	7625 (1510, 42598)	38 (2, 3738)	4008 (2, 80281)	4724 (2, 65536)	4013 (512, 16384)	4225 (512, 16384)	6187 (1024, 32768)
SBA_{sec}	12299 (1741, 85197)	1961 (256, 32768)	16845 (4096, 91750)	16009 (1766, 65536)	1069 (2, 10035)	26185 (8192, 77004)	–	–	–
$ELISA_{base}$ (µg/mL)	0·13 (0·1, 5·1)	0·15 (0·1, 1·3)	0·13 (0·1, 4·6)	0·13 (0·1, 0·9)	0·11 (0·1, 0·7)	0·13 (0·1, 1·0)	1·9 (0·1, 26·5)	3·5 (0·1, 103·3)	1·4 (0·1, 28·6)
$ELISA_{prim}$ (µg/mL)	0·12 (0·1, 0·5)	17·9 (4·4, 88·6)	16·9 (4·6, 55·5)	0·11 (0·1, 0·6)	18·8 (3·0, 136·9)	20·5 (6·0, 210·6)	48·1 (9·8, 307·2)	76·7 (7·5, 657·5)	76·2 (10·3, 639·8)
$ELISA_{sec}$ (µg/mL)	14·6 (2·1, 241·7)	1·3 (0·1, 24·8)	50·5 (4·3, 316·5)	17·0 (0·6, 180·6)	0·9 (0·1, 10·5)	87·2 (17·7, 420·0)	–	–	–

Table 2: Parameter estimates for the antibody kinetics model. For each parameter, the distribution of values in the population was estimated. The median of this distribution is presented. Parameters are presented as posterior medians with 95% credible intervals. The mean and standard deviation of the parameter distributions are provided in Supplementary Table 1.

		PsA-TT-002		PsA-TT-003	
description	**parameter**	**SBA**	**ELISA**	**SBA**	**ELISA**
ASC boost after primary MenAfriVac vaccination	β_{prim}	2502 (1685, 3984)	4·4 (3·3, 6·2)	1935 (743, 4693)	7·0 (5·3, 12·1)
ASC boost after secondary MenAfriVac vaccination	β_{sec}	3229 (2169, 5033)	12·9 (8·9, 19·0)	–	–
ASC boost after Hib-TT vaccination	β_{Hib}	3·1 (0·9, 9·0)	–	–	–
half-life of short-lived ASCs (days)	d_s	3·5 (2·1, 5·3)	5·5 (3·8, 8·3)	1·5 (0·7, 3·7)	9·9 (5·0, 17·6)
half-life of long-lived ASCs (days)	d_l	2690 (1016, 15078)	1648 (969, 4026)	6007 (2826, 14279)	2287 (1380, 4098)
half-life of IgG molecules (days)	d_a	15·4 (12·0, 20·0)	20·3 (15·3, 24·7)	15·5 (12·4, 20·3)	30·9 (21·7, 38·5)
proportion of short-lived ASCs after primary MenAfriVac vaccination	ρ_{prim}	97·0% (95·1%, 98·3%)	99·1% (98·5%, 99·5%)	95·0% (85·7%, 98·1%)	95·7% (91·9%, 98·0%)
proportion of short-lived ASCs after secondary MenAfriVac vaccination	ρ_{sec}	97·8% (95·9%, 98·8%)	98·8% (98·0%, 99·3%)	–	–
proportion of short-lived ASCs after Hib vaccination	ρ_{Hib}	95·8% (88·2%, 98·4%)	–	–	–

Table 3: Determinants of antibody persistence. The reduction in antibody response is assumed to be the reduction from the peak antibody level 4 weeks after MenAfriVac vaccination to the estimated antibody level 1 year after vaccination. The association between the percentage reduction and the listed covariates was assessed using logistic regression. The association between antibody levels 1 year after MenAfriVac vaccination and the listed covariates was assessed using linear regression. The reference is taken to be a Gambian female in the PsA-TT-002 study.

	Serum bactericidal antibody (SBA)				Group A-specific IgG ELISA			
	1 year reduction		1 year antibody level		1 year reduction		1 year antibody level	
covariate	estimate (95% CI)	p value	estimate (95% CI)	p value	estimate (95% CI)	p value	estimate (95% CI)	p value
study: PsA-TT-002 (reference)	-4·86 (-6·96, -2·76)	<0·0001	-0·80 (-1·39, -0·21)	0·008	1·75 (0·08, 3·42)	0·04	-0·98 (-0·11, -0·86)	<0·0001
study: PsA-TT-003	-1·42 (-2·61, -0·24)	0·019	0·39 (0·06, 0·72)	0·02	-1·34 (-2·90, 0·22)	0·09	0·50 (0·39, 0·60)	<0·0001
country: Mali	-0·16 (-0·54, 0·23)	0·43	0·19 (-0·002, 0·24)	0·054	-0·09 (-0·51, 0·32)	0·64	0·006 (-0·03, 0·045)	0·78
country: Senegal	-0·09 (-0·52, 0·35)	0·70	0·06 (-0·08, 0·20)	0·39	-0·04 (-0·50, 0·41)	0·85	0·02 (-0·03, 0·07)	0·41
age: PsA-TT-002	-0·28 (-0·84, 0·28)	0·32	0·008 (-0·14, 0·16)	0·92	-0·46 (-1·13, 0·22)	0·19	0·14 (0·09, 0·19)	<0·0001
age: PsA-TT-003	0·29 (-0·27, 0·85)	0·31	-0·01 (-0·16, 0·14)	0·90	0·42 (-0·26, 1·10)	0·22	-0·12 (-0·17, -0·07)	<0·0001
$\log_{10}(SBA_{base})$	-0·09 (-0·25, 0·05)	0·20	0·04 (-0·009, 0·09)	0·11	–	–	–	–
$\log_{10}(SBA_{peak})$	1·81 (1·29, 2·33)	< 0·0001	0·93 (0·79, 1·07)	<0·0001	–	–	–	–
$\log_{10}(ELISA_{base})$	–	–	–	–	-0·75 (-1·11, -0·40)	<0·0001	0·23 (0·19, 0·26)	<0·0001
$\log_{10}(ELISA_{peak})$	–	–	–	–	0·73 (0·31, 1·14)	0·0006	0·78 (0·74, 0·82)	<0·0001

Figures

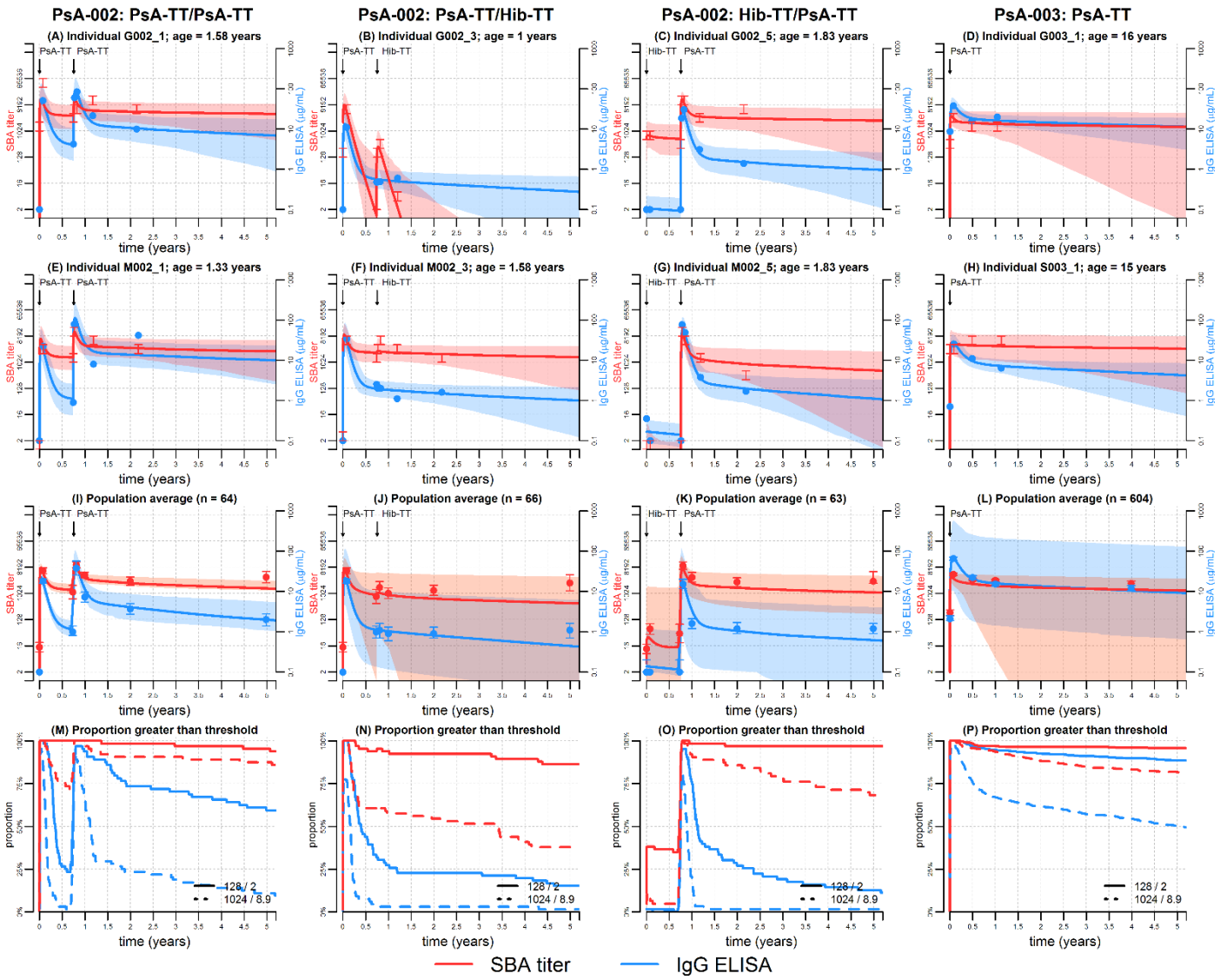


Figure 1: Antibody kinetics following MenAfriVac vaccination. (A-H) Antibody kinetics in a subset of 8/797 individuals selected for illustrative purposes. Data on measured IgG ELISA levels are represented using points, and SBA titers are represented using intervals. Solid lines denote the median model predicted antibody level over time, and the shaded regions denote the 95% credible intervals of the model predictions. **(I-L)** Geometric mean antibody levels in the population. Shaded regions represent the 95% confidence intervals of the model predicted geometric mean antibody levels, calculated using a Student's *t*-test. Data points represent geometric mean antibody level as reported in Tapia *et al*[13] and Diallo *et al*[14]. **(M-P)** Proportion of individuals with antibody levels greater than specified thresholds. Solid lines represent a threshold SBA titer of 128, which corresponds to IgG ELISA level of 2 µg/mL. Dashed lines represent a threshold SBA titer of 1024, which corresponds to IgG ELISA level of 8·9 µg/mL.

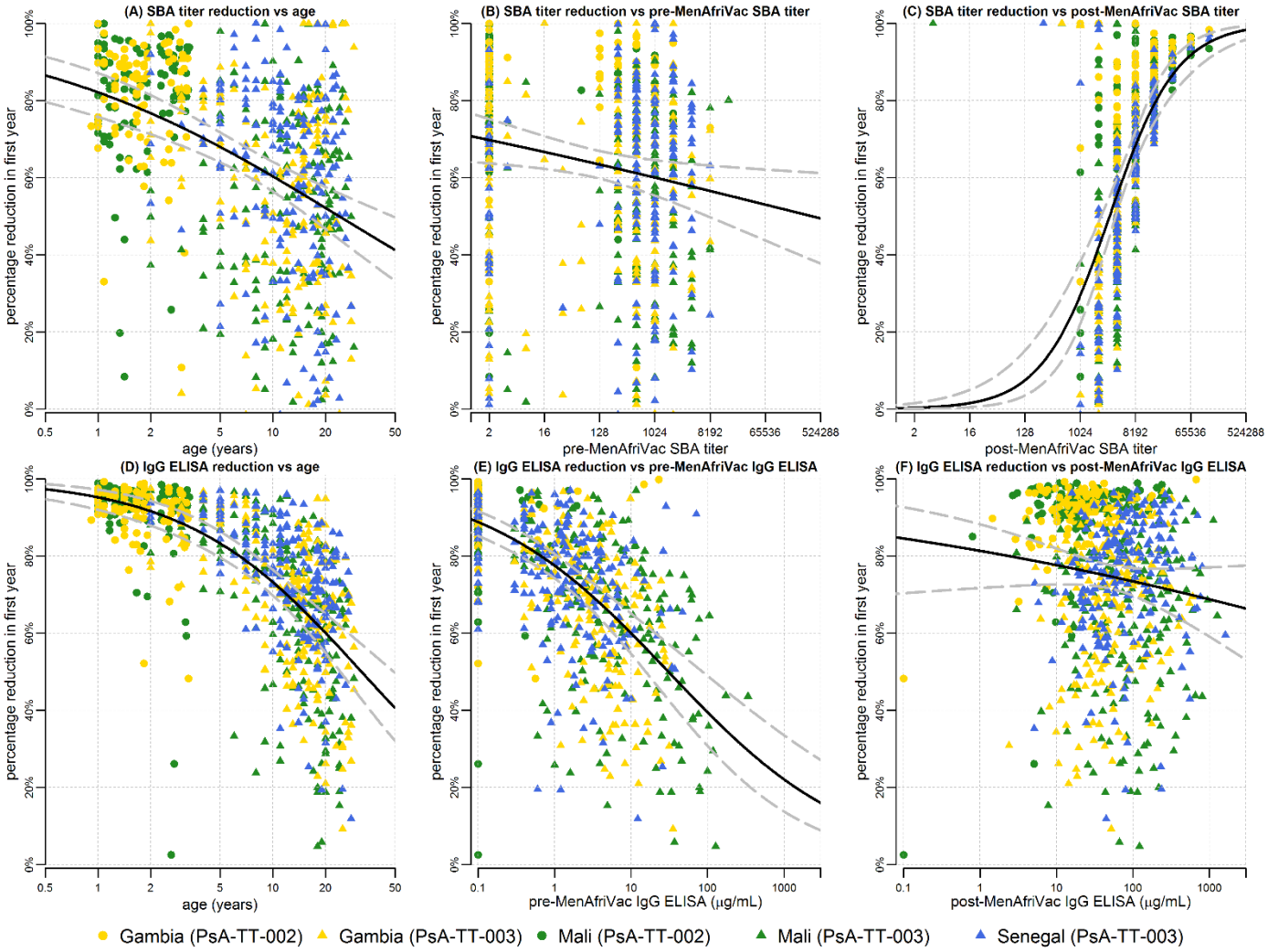
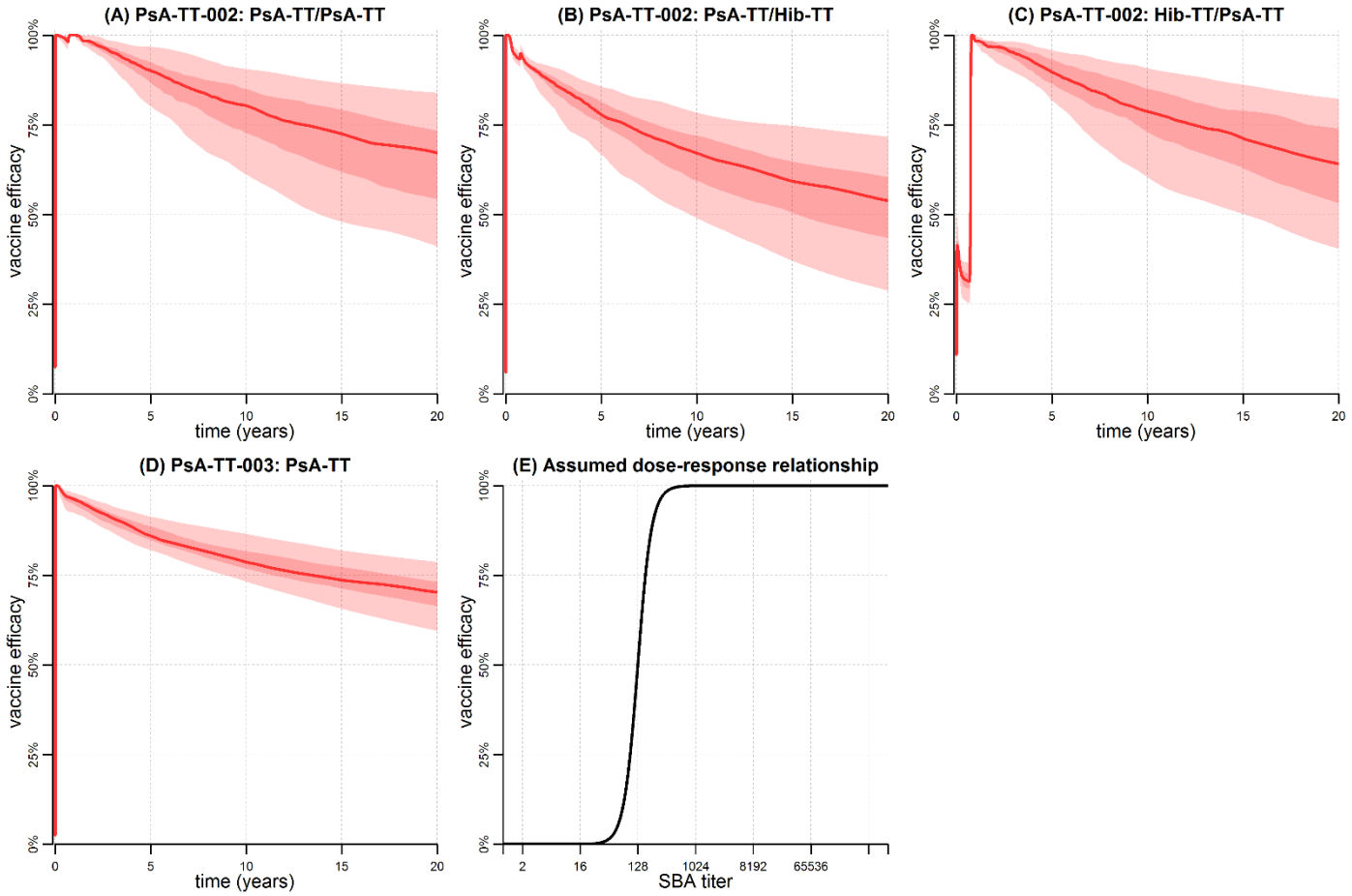


Figure 2: Determinants of antibody persistence. The percentage reduction from the peak antibody level measured 4 weeks after vaccination to the estimated antibody level 1 year after vaccination is shown. **(A)** Association between age and percentage reduction in SBA titer 1 year after MenAfriVac. **(B)** Association between pre-vaccination SBA titer and percentage reduction in SBA titer 1 year after MenAfriVac. **(C)** Association between post-vaccination SBA titer and percentage reduction in SBA titer 1 year after MenAfriVac. **(D)** Association between age and percentage reduction in IgG ELISA 1 year after MenAfriVac. **(E)** Association between pre-vaccination IgG ELISA and percentage reduction in IgG ELISA 1 year after MenAfriVac. **(F)** Association between post-vaccination IgG ELISA and percentage reduction in SBA titer 1 year after MenAfriVac. The black lines show univariate associations estimated from logistic regression models.



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584 **Figure 3: Predicted vaccine efficacy based on modelled SBA titers. (A-C)** Model predicted efficacy against infection
585 over a 20 year time horizon for different vaccination schedules in the PsA-TT-002 study. **(D)** Model predicted
586 efficacy against infection in the PsA-TT-003 study. Solid lines denote the median model prediction and the dark and
587 light shaded regions represent the 50% and 95% credible intervals of the model prediction. **(E)** Assumed dose-
588 response relationship corresponding to a threshold SBA titer for protection of Ab_{prot} = 128, and shape parameter α =
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Supplementary files

Supplementary methods file: Details of statistical model of antibody kinetics.