Antibody kinetics following vaccination with MenAfriVac: an analysis of serological data from randomised trials

Michael White, Olubukola Idoko, Samba Sow, Aldiouma Diallo, Beate Kampmann, Ray Borrow, Caroline Trotter

Summary

Background A meningococcal group A conjugate vaccine, PsA-TT (also known as MenAfriVac), was developed with the support of the Meningitis Vaccine Project. Around 280 million individuals aged 1–29 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 two longitudinal studies done in The Gambia, Mali, and Senegal of antibody responses in 193 children aged 12–23 months and 604 participants aged 2–29 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. Determinants of antibody duration were investigated using regression analysis.

Findings In children age 12–23 months, the reduction in MenAfriVac-induced antibody levels assessed by SBA titres 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 2690 days (95% CrI 1016–15 078). Antibody levels assessed by SBA titres in participants aged 2–29 years were more persistent, with 95·0% (85·7–98·1) of the response being short lived, and the long lived phase decaying with a half-life of 6007 days (95% CrI 2826–14 279). Greater pre-vaccination antibody levels were associated with greater immunogenicity following vaccination, as well as greater antibody persistence. Despite rapid antibody declines in the first phase, antibodies in the second phase persisted at SBA titres greater than 128. Although there is no strong evidence base for a correlate of protection against infection with *Neisseria meningitidis* serogroup A, we use an assumed SBA titre of 128 as a threshold of protection to predict that 20 years after vaccination with a single dose of MenAfriVac, vaccine efficacy will be 52% (29–73) in children vaccinated at age 12–23 months and 70% (60–79) in participants vaccinated at age 2–29 years.

Interpretation Population-level immunity induced by routine vaccination with the Expanded Programme on Immunization is predicted to persist at levels sufficient to confer more than 50% protection over a 20-year time period. Further increases in population-level immunity could be obtained via mass campaigns or by delaying the age of vaccination through the Expanded Programme on Immunization. However, the benefits of such a strategy would need to be weighed against the risks of leaving young children unvaccinated for longer.

Funding Meningitis Vaccine Project and Institut Pasteur.

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 10–15%.[2] *Neisseria meningitidis* serogroup A has been responsible for most epidemics 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; also known as MenAfriVac) has been developed by the Meningitis Vaccine Project and the Serum Institute of India.[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 schedules targeting children aged 9–18 months.[5]

There is little evidence on the association between antibody levels and vaccine efficacy, with the only established correlate of protection being group A-specific IgG antibodies of at least 2 µg/mL,[6,7] with no evidence from Africa. Goldschneider and colleagues noted that higher antibody levels were associated with *N meningitidis* serogroup A meningitis incidence,[7] but subsequent observational studies[8] of natural immunity have not found such associations. Despite this, MenAfriVac was licensed on the basis of safety and immunogenicity data,[9] with data on effectiveness being collected only

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. Two studies showed that antibody responses following MenAfriVac persist for 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. 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 12–23 months is 52% (95% credible interval 29–73) after 20 years and the estimated efficacy in individuals aged 2–29 years is 70% (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. 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.

See **Online** for appendix

after large-scale MenAfriVac campaigns.[3,10] Surveillance programmes have not identified cases of *N meningitidis* serogroup A 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 a 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 Expanded Programme on Immunization 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 were 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 serogroups C, W, X, and Y in addition to A.[16] Investment in these vaccines is 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

Study designs and data collection

We obtained individual-level data for 797 participants on epidemiological covariates and immunological

measurements from two randomised controlled trials of the MenAfriVac vaccine,[9] PsA-TT-002 and PsA-TT-003, following a request to the Meningitis Vaccine Project's Access Program (table 1; appendix). 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[9,13] and PsA-TT-003 study[9,14] have been reported elsewhere. In brief, for the PsA-TT-002 study, healthy Malian and Gambian children aged between 12 and 23 months, fully immunised according to the local Expanded Programme on Immunization schedule, were recruited and randomly assigned to receive primary vaccination of either MenAfriVac (10 µg), PsACWY, or *Haemophilus influenzae* type b vaccine (Hib-TT). Children were further randomly assigned to receive a second vaccine dose 10 months later, independently of the first dose. Blood samples were obtained before primary vaccination, 4 weeks after primary vaccination, before 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 we used geometric mean values from those data to validate model predictions.

For the PsA-TT-003 study, healthy Malian, Gambian, and Senegalese participants aged 2–29 years were recruited and randomly assigned to either MenAfriVac or PsACWY. Blood samples were obtained at baseline and at 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

	PsA-TT-002						PsA-TT-003		
	Gambia	Gambia	Gambia	Mali	Mali	Mali	Gambia	Mali	Senegal
Primary vaccine	Hib-TT	MenAfriVac	MenAfriVac	Hib-TT	MenAfriVac	MenAfriVac	MenAfriVac	MenAfriVac	MenAfriVac
Secondary vaccine after 10 months	MenAfriVac	Hib-TT	MenAfriVac	MenAfriVac	Hib-TT	MenAfriVac	..	..	..
Number of participants	33	34	30	30	32	34	202	201	201
Age									
Months	18 (4)	17 (4)	18 (4)	17 (4)	16 (3)	17 (4)	166 (85)	164 (78)	163 (75)
Years	1·5 (0·3)	1·4 (0·3)	1·6 (0·3)	1·3 (0·3)	1·3 (0·3)	1·3 (0·3)	13·6 (7·1)	13·7 (6·5)	13·6 (6·3)
Sex									
Female	16 (48%)	13 (38%)	15 (50%)	11 (37%)	16 (50%)	19 (56%)	84 (42%)	79 (39%)	87 (43%)
Male	17 (52%)	21 (62%)	15 (50%)	19 (63%)	16 (50%)	15 (44%)	118 (58%)	122 (61%)	114 (57%)
Follow-up time (days)	782 (11)	781 (4)	782 (7)	787 (10)	785 (10)	784 (9)	371 (4)	373 (5)	401 (16)
SBA$_{base}$ (titres)	14 (288)	45 (1449)	47 (15)	5 (455)	3 (363)	4 (267)	111 (1343)	317 (1789)	318 (1334)
SBA$_{prim}$ (titres)	84 (860)	7375 (5901)	7625 (13129)	38 (1531)	4008 (25077)	4724 (15729)	4013 (10146)	4225 (5787)	6187 (15210)
SBA$_{sec}$ (titres)	12299 (26405)	1961 (7735)	16845 (27451)	16009 (17334)	1069 (3530)	26185 (26246)	..	..	..
ELISA$_{base}$ (µg/mL)	0·13 (4·0)	0·15 (0·4)	0·13 (2·7)	0·13 (0·3)	0·11 (0·2)	0·13 (0·3)	1·9 (6·7)	3·5 (34·4)	1·4 (8·3)
ELISA$_{prim}$ (µg/mL)	0·12 (0·13)	17·9 (31·5)	16·9 (13·6)	0·11 (0·2)	18·8 (41·8)	20·5 (53·2)	48·1 (88·5)	76·7 (192·4)	76·2 (182·3)
ELISA$_{sec}$ (µg/mL)	14·6 (121·8)	1·3 (13·8)	50·5 (92·3)	17·0 (51·2)	0·9 (3·0)	87·2 (130·3)	..	..	..

Data are n, n (%), or geometric mean (SD). 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] 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". Hib-TT=*Haemophilus influenzae* type b vaccine. MenAfriVac=group A meningococcal polysaccharide-tetanus toxoid conjugate vaccine. SBA=serum bactericidal antibody.

Table 1: Overview of epidemiology and immunogenicity in MenAfriVac studies

analysis but the geometric mean values were used to validate model predictions.

Immunogenicity

Immunogenicity was assessed using two different assays: first, with a serum bactericidal antibody (SBA) assay using the group A target strain F8238 with baby rabbit complement,[17] and second, with *N meningitidis* serogroup A-specific IgG ELISA. SBA titres were measured at the Vaccine Evaluation Unit of the Health Protection Agency (now Public Health England; Manchester, UK) and the ELISA was done at the Centers for Disease Control and Prevention (CDC; Atlanta, GA, USA). We refer to antibody levels as measured values from either of these assays.

Statistical analysis

We assessed the effects of several covariates on antibody responses, measured in continuous log values, following primary or secondary vaccination with MenAfriVac using linear regression models. The covariates were age in years, trial, country, sex, height, weight, and measurement of antibody response before 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. Statistical analyses were implemented in C++ using Microsoft Visual Studio and using R version 3.5.1.

Antibody kinetics

Exposure of the immune system to vaccine antigens stimulates the generation of memory B cells that subsequently differentiate into antibody-secreting cells.[18] Antibody-secreting cells 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 antibody-secreting cells of size β in a rapid boost. A proportion ρ of antibody-secreting cells are assumed to be short lived with half-life d_s and a proportion 1–ρ are assumed to be long lived with half-life d_l. Antibody-secreting cells are assumed to generate IgG molecules at a constant rate that 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 before primary vaccination. Decay rates are calculated from half-lives as follows: $r_i=\log(2)/d_i$, $r_c=\log(2)/d_c$, and $r_a=\log(2)/d_a$. Some participants in the PsA-TT-002 study received a secondary vaccination with MenAfriVac after 10 months. The antibody response following this second dose is modelled using the same equation as above. The model does not account for the role of natural exposure to *N meningitidis* serogroup A.

We refer to the first short-lived phase of the response as the IgG molecules generated by short-lived antibody-secreting cells and the second long-lived phase of the response as the IgG molecules generated by long-lived antibody-secreting cells. 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 use a flexible functional form[22] to investigate a range of possible relationships:

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

where Ab_{prot} is the threshold SBA titre required for protection and α is a shape parameter. There are very few sources of data on meningococcal surrogates of protection specifically for *N meningitidis* serogroup A; however, SBA titres of $Ab_{prot}=128$ are frequently used as a threshold level.[15]

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 while also describing the population-level patterns. On the population level, both the mean and variation in antibody kinetics are accounted for. The models were fitted in a Bayesian framework using Markov chain Monte Carlo methods with informative priors (appendix p 14). Posterior parameter estimates are presented as medians with 95% credible intervals (CrIs).

Role of the funding source

The sponsors had no role in the design of the analysis, collecting or analysing the data, 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

Data were analysed from 193 participants in the PsA-TT-002 study, who were aged 11–23 months and followed up for a mean of 784 days, and from 604 participants in the PsA-TT-003 study, who were aged 2–29 years and followed up for a mean of 382 days (table 1). Antibody levels measured via SBA titre 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 (appendix p 5), replicating findings reported elsewhere.[15] Different relationships were observed for samples from the PsA-TT-002 and PsA-TT-003 studies: participants in the PsA-TT-003 study had substantially higher group A-specific IgG ELISA levels at equal SBA titres, with these differences being most pronounced at low SBA titres (appendix p 5).

The dependence of log antibody responses after vaccination on several covariates was assessed using linear regression, with univariate relationships shown in the appendix. The results from this analysis of pooled data were in agreement with findings from separate analyses of the PsA-TT-002 and PsA-TT-003 studies.[23] In the PsA-TT-002 study of children aged 12–23 months, for each extra month of age there was a 9% (95% CrI 4–15) increase in SBA titres ($p=0.0012$). However, in the PsA-TT-003 study of participants aged 2–29 years, there was no significant association between age and SBA titres ($p=0.29$; appendix p 9). High baseline $\log_{10}$ SBA titres were associated with higher $\log_{10}$ SBA titres 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 (appendix p 9). After adjusting for other covariates, antibody levels in males were 18% lower than in females (30·3 µg/mL in males *vs* 36·4 µg/mL in females, $p=0.0021$). Group A-specific IgG ELISA levels at baseline were significantly associated with higher levels following primary vaccination ($p<0.0001$).

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. We randomly selected eight individuals (two from each of the four vaccination regimens studied) of the 797 included for presentation purposes to give an overview of the patterns of model-predicted antibody kinetics with data on SBA titres and IgG ELISA levels (figure 1). Several distinctive patterns are evident: (1) antibody responses induced by MenAfriVac decay rapidly in the first 6 months, after which the remaining antibodies decay at a slower rate; (2) in most individuals, the initial decay of IgG ELISA levels is more rapid than the decay of SBA titres; (3) Hib-TT vaccination causes boosting in SBA titres but not IgG ELISA levels (appendix p 9); and (4) 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 titre. The model-predicted geometric mean antibody responses observed in the study population were in agreement with the data from samples at 4-year follow-up in the PsA-TT-003 study but slightly underestimate the data at 5-year follow-up in the
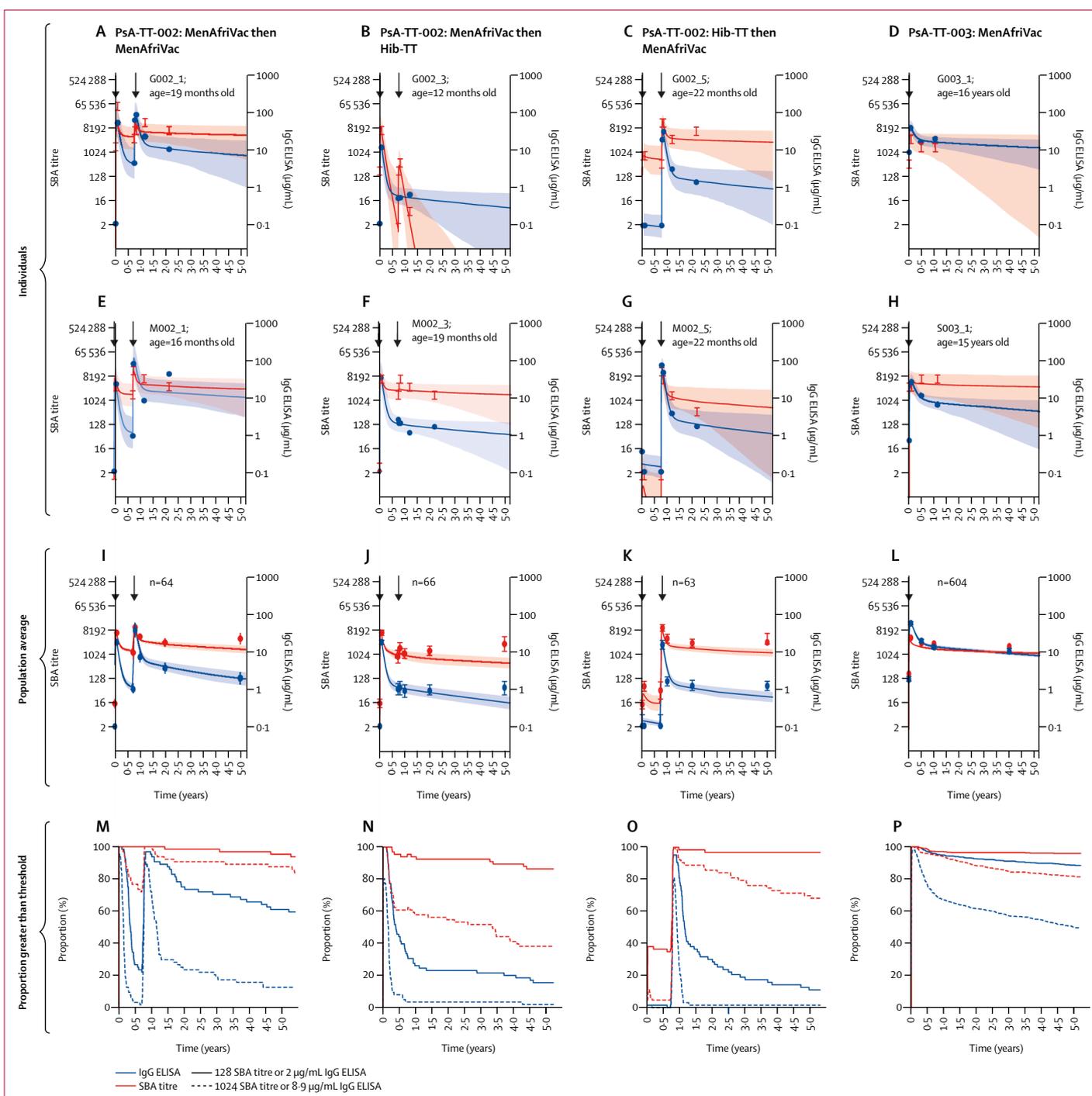
Figure 1: Antibody kinetics following MenAfriVac vaccination
Vertical arrows indicate the time of first and second vaccination (if applicable). Panels A–H show antibody kinetics in a subset of eight of 797 individuals selected for illustrative purposes. Data on measured IgG ELISA levels are represented using points and SBA titres are represented using intervals, with y-axes presented on log scales. Solid lines denote the median model predicted antibody level over time, and the shaded regions denote the 95% credible intervals of the model predictions. Panels I–L show the geometric mean antibody levels in the population. Shaded regions represent the 95% CIs of the model-predicted levels, calculated using a Student's t test. Datapoints represent geometric mean antibody level as reported in Tapia et al[13] and Diallo et al.[14] Panels M–P show the proportion of individuals with antibody levels greater than specified thresholds. Solid lines represent a threshold SBA titre of 128, which corresponds to IgG ELISA level of 2 μg/mL. Dashed lines represent a threshold SBA titre of 1024, which corresponds to IgG ELISA level of 8·9 μg/mL. Hib-TT=*Haemophilus influenzae* type b vaccine. MenAfriVac=group A meningococcal polysaccharide-tetanus toxoid conjugate vaccine. SBA=serum bactericidal antibody.

	Parameter	PsA-TT-002		PsA-TT-003	
		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 (1016–15 078)	1648 (969–4026)	6007 (2826–14 279)	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-TT vaccination	ρ_{Hib}	95·8% (88·2–98·4)	..	..	..

For each parameter, the distribution of values in the population was estimated and the median of this distribution is presented. Parameters are presented as posterior medians with 95% credible intervals. The mean and SD of the parameter distributions are provided in the appendix. SBA=serum bactericidal antibody. ASC=antibody-secreting cell. MenAfriVac=group A meningococcal polysaccharide-tetanus toxoid conjugate vaccine. Hib-TT=*Haemophilus influenzae* type b vaccine.

Table 2: Parameter estimates for the antibody kinetics model
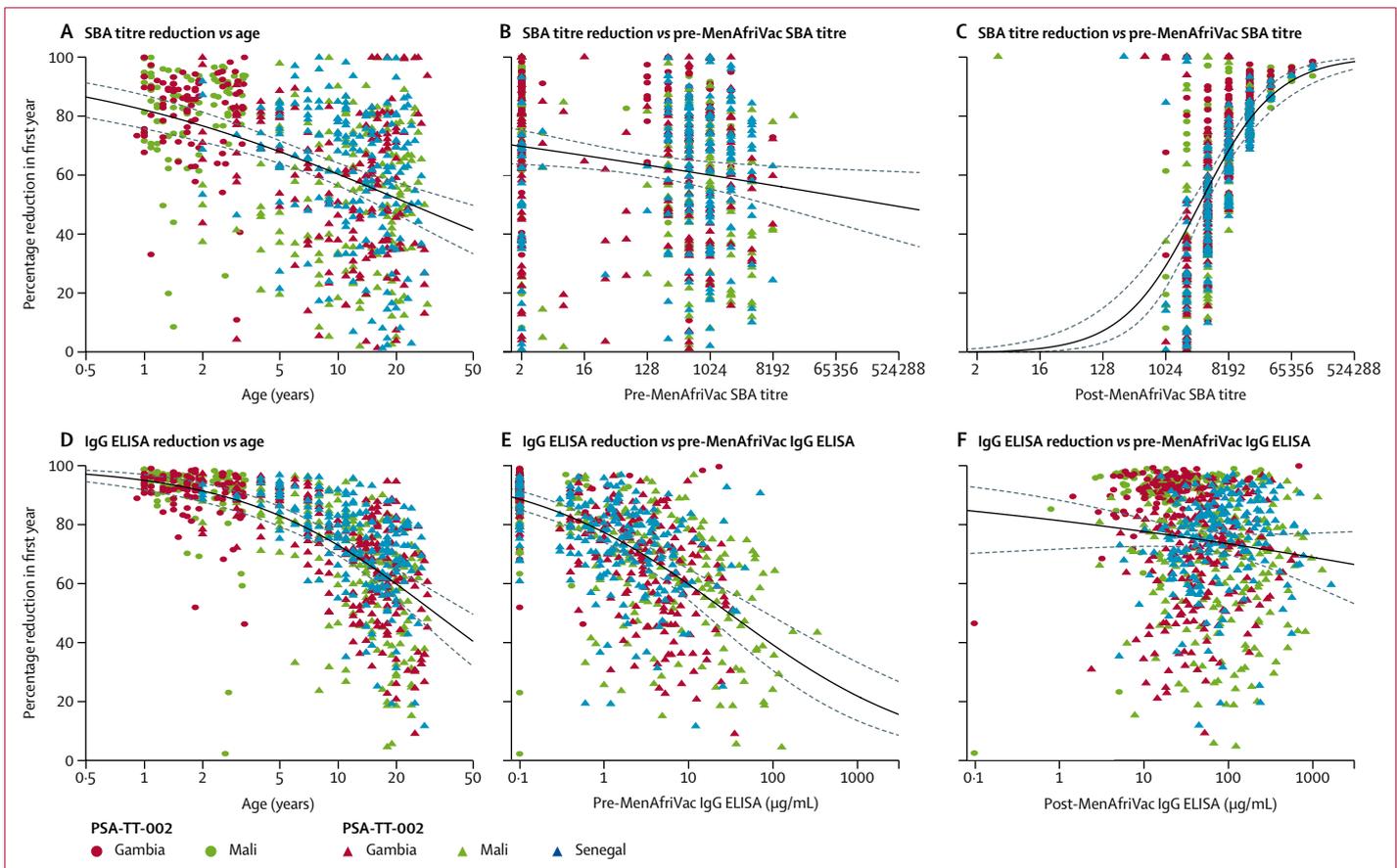

Figure 2: Determinants of antibody persistence
The percentage reduction from the peak antibody level measured 4 weeks after vaccination to the estimated antibody level 1 year after vaccination with MenAfriVac is shown. Associations are shown between age and percentage reduction in SBA titre (A), between pre-vaccination SBA titre and percentage reduction in SBA titre (B), between post-vaccination SBA titre and percentage reduction in SBA titre (C), between age and percentage reduction in IgG ELISA (D), between pre-vaccination IgG ELISA and percentage reduction in IgG ELISA (E), and between post-vaccination IgG ELISA and percentage reduction in SBA titre (F). The black lines show univariate associations estimated from logistic regression models. All x-axes are presented on log scales. MenAfriVac=group A meningococcal polysaccharide-tetanus toxoid conjugate vaccine. SBA=serum bactericidal antibody.

	SBA				Group A-specific IgG ELISA			
	1-year reduction		1-year antibody level		1-year reduction		1-year antibody level	
	Estimate (95% CI)	p value	Estimate (95% CI)	p value	Estimate (95% CI)	p value	Estimate (95% CI)	p value
Study								
PsA-TT-002	–4·86 (–6·96 to –2·76)	<0·0001	–0·80 (–1·39 to –0·21)	0·0078	1·75 (0·08 to 3·42)	0·040	–0·98 (–0·11 to –0·86)	<0·0001
PsA-TT-003	–1·42 (–2·61 to –0·24)	0·019	0·39 (0·06 to 0·72)	0·019	–1·34 (–2·90 to 0·22)	0·092	0·50 (0·39 to 0·60)	<0·0001
Country								
Mali	–0·16 (–0·54 to 0·23)	0·43	0·19 (–0·002 to 0·24)	0·054	–0·09 (–0·51 to 0·32)	0·64	0·006 (–0·03 to 0·045)	0·78
Senegal	–0·09 (–0·52 to 0·35)	0·70	0·06 (–0·08 to 0·20)	0·39	–0·04 (–0·50 to 0·41)	0·85	0·02 (–0·03 to 0·07)	0·41
Age								
PsA-TT-002	–0·28 (–0·84 to 0·28)	0·32	0·008 (–0·14 to 0·16)	0·92	–0·46 (–1·13 to 0·22)	0·19	0·14 (0·09 to 0·19)	<0·0001
PsA-TT-003	0·29 (–0·27 to 0·85)	0·31	–0·01 (–0·16 to 0·14)	0·90	0·42 (–0·26 to 1·10)	0·22	–0·12 (–0·17 to –0·07)	<0·0001
$\log_{10}(SBA_{base})$	–0·09 (–0·25 to 0·05)	0·20	0·04 (–0·009 to 0·09)	0·11	..	..	..	..
$\log_{10}(SBA_{peak})$	1·81 (1·29 to 2·33)	<0·0001	0·93 (0·79 to 1·07)	<0·0001	..	..	..	..
$\log_{10}(ELISA_{base})$	..	..	..	..	–0·75 (–1·11 to –0·40)	<0·0001	0·23 (0·19 to 0·26)	<0·0001
$\log_{10}(ELISA_{peak})$	..	..	..	..	0·73 (0·31 to 1·14)	0·0006	0·78 (0·74 to 0·82)	<0·0001

Table shows estimates from regression analyses of the effects of covariates on the percentage reduction in antibody levels after 1 year and on antibody levels after 1 year. 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 woman in the PsA-TT-002 study. SBA=serum bactericidal antibody. MenAfriVac=MenAfriVac=group A meningococcal polysaccharide-tetanus toxoid conjugate vaccine.

Table 3: **Determinants of antibody persistence**

PsA-TT-002 study (figure 1I–L). Because 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. The proportion of individuals with SBA titres in excess of 128 after 5 years was greater than 85% for all vaccination regimens tested. This proportion dropped to 68% for the higher threshold SBA titre of 1024, with the exception of individuals in the PsA-TT-002 study given MenAfriVac and then Hib-TT, where this proportion was 38% (figure 1M–P).

In the PsA-TT-002 study, primary vaccination with MenAfriVac is assumed to induce antibody-secreting cells that generate antibodies causing bactericidal activity (table 2). For measurements from the SBA assay, all antibody-secreting cells are assumed to secrete IgG molecules that decay with an estimated half-life of 15·4 days (95% credible interval [CrI] 12·0–20·0). 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 antibody-secreting cells of 3·5 days (2·1–5·3), with the second long-lived phase having a median half-life of long-lived antibody-secreting cells of 2690 days (1016–15 078). 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 (table 2).

In the PsA-TT-003 study, only data from the first year of longitudinal follow-up were available for model fitting. The posterior estimates of the half-life of long-lived antibody-secreting cells 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 antibody-secreting cells contributing to bactericidal activity was estimated as 6007 days (95% CrI 2826–14 279) and the half-life of antibody-secreting cells contributing to IgG ELISA measurements was estimated as 2287 days (1380–4098). 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).

When exploring the dependence of antibody persistence 1 year after MenAfriVac vaccination on age and pre-vaccination and post-vaccination antibody responses, we found that older age was associated with better persistence when antibody response was measured by both SBA titre and ELISA (figure 2). However, in a multivariate analysis, age was not significantly associated with antibody persistence (table 3). Greater SBA titres before MenAfriVac vaccination were associated with better antibody persistence (figure 2) but this was not significant in the multivariate analysis (table 3). Individuals who had more immunogenic responses to MenAfriVac when measured by SBA titre also experienced greater reduction in the first year (figure 2) and this was significant (p<0·0001). Greater IgG ELISA measurements before MenAfriVac vaccination were associated with better antibody persistence (figure 2) and this association was also significant (p<0·0001). Individuals who had more immunogenic responses to MenAfriVac when measured by IgG ELISA also experienced greater reduction in the first year (p<0·0001), although this association was not evident when examined univariately (figure 2). The effect of these covariates is also shown on measured antibody response immediately after vaccination and 1 year after vaccination in the appendix.
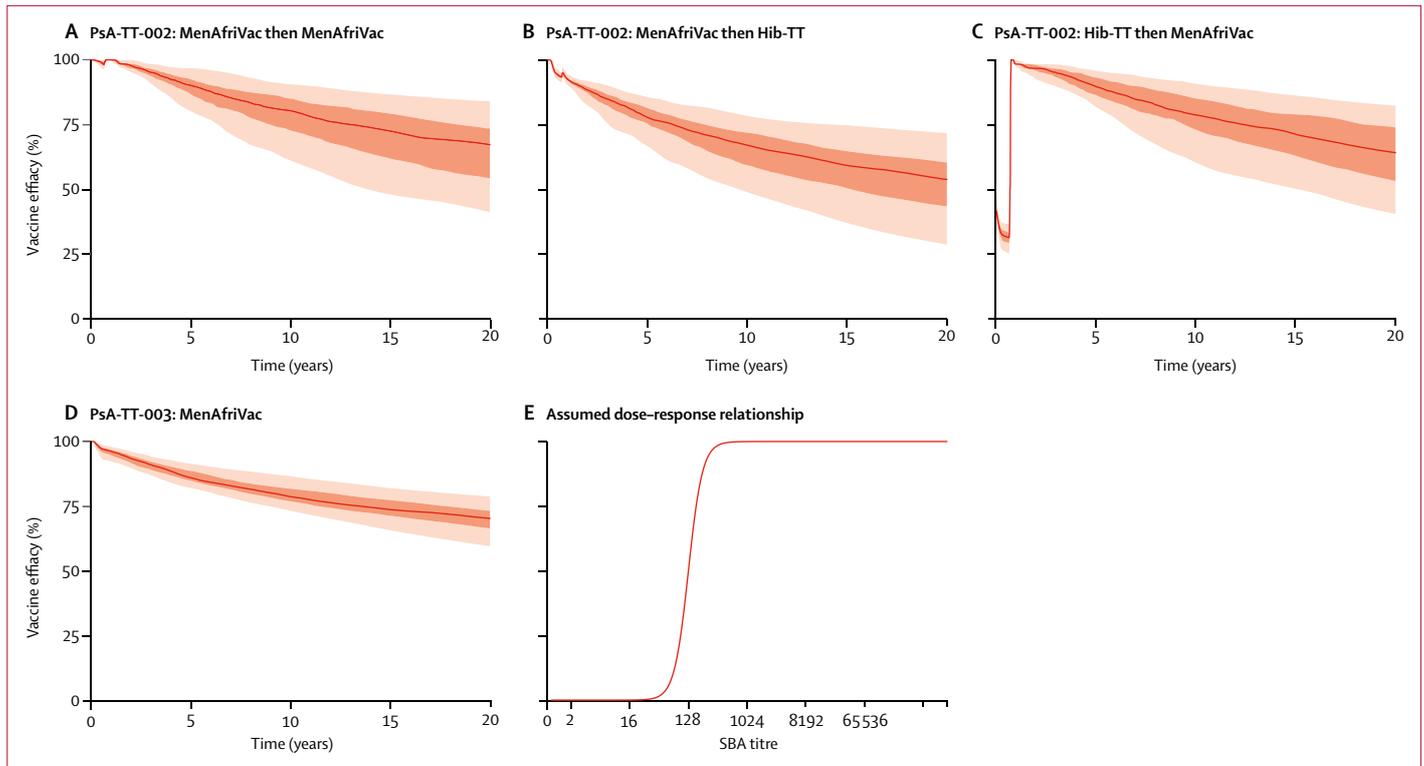
Figure 3: Predicted vaccine efficacy based on modelled SBA titres

Panels A–C show model-predicted efficacy against infection over a 20-year time horizon for different vaccination schedules in the PsA-TT-002 study whereas panel D shows model-predicted efficacy against infection in the PsA-TT-003 study. Solid lines denote the median model prediction and the dark and light shaded regions represent the 50% and 95% credible intervals of the model prediction. Panel E shows the assumed dose–response relationship corresponding to a threshold SBA titre for protection of Ab_{prot}=128 and shape parameter α=4, with SBA titres presented on a log scale. Hib-TT=*Haemophilus influenzae* type b vaccine. MenAfriVac=group A meningococcal polysaccharide-tetanus toxoid conjugate vaccine. SBA=serum bactericidal antibody.

Figure 3 shows an assumed dose–response relationship between SBA titre 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; figure 3D) in the PsA-TT-003 study and 52% (29–73; figure 3B) in the PsA-TT-002 study. Secondary vaccination with MenAfriVac 10 months after primary vaccination with MenAfriVac was estimated to result in 64% (40–85) vaccine efficacy after 20 years (figure 3A). For the arm with primary vaccination with Hib-TT, the first dose of MenAfriVac was delayed by 10 months until children were older (ie, aged 24–33 months), resulting in a more immunogenic response and an estimated efficacy 20 years later of 63% (37–83; figure 3C). This does not account for the potential role that natural exposure might 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 titre or group A-specific IgG ELISA. This response is characterised by 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 years (95% CrI 2·8–41·3) when measured by SBA titre and 4·5 years (2·7–11·0) 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 years (7·7–39·1) when measured by SBA titre, and 6·3 years (3·8–11·2) 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 show 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 *H influenza* type b vaccine.[25]

Geometric mean antibody levels in these study populations have been observed to persist above a threshold SBA titre of 128 for up to 4 years.[13,14] However, it is the variation in antibody responses rather than the mean that is the key determinant of how vaccine efficacy wanes over time. A key strength of the statistical methods

used in this analysis is the ability to characterise the variation in antibody responses as well as the average behaviour. For example, consider individual G002_3 (figure 1) whose rapidly decaying SBA titre might 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 1). This might be attributable to natural exposure to *N meningitidis* serogroup A 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 because 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 on the basis of measurements from the two assays, with IgG ELISA levels waning much more rapidly than SBA titres. A second point of note is the occurrence of boosting of SBA titres by Hib-TT vaccination: 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] We observed a different relationship between SBA titres and IgG ELISA levels in the two studies: at equal SBA titres, individuals in the PsA-TT-003 study have higher IgG ELISA levels than individuals in the PsA-TT-002 study. This observation might be due to age effects or the higher proportion of samples taken after 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, there was no significant association between age and immunogenicity. This

contrasts with 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, we found 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 relationship was suggested for antibody levels measured by SBA titre 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 cases of *N meningitidis* serogroup A.[3,10] The transition to vaccination of children aged 9–18 months through the routine Expanded Programme on Immunization 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 immuno-genicity.[30] However, population-level immunity induced via Expanded Programme on Immunization 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 (and thus representative of the target Expanded Programme on Immunization population), efficacy 20 years after vaccination was estimated to be substantially lower at 52% (29–73). Incorporation of a booster dose of MenAfriVac 10 months after primary vaccination is estimated to increase efficacy at 20 years to 64% (40–85). However, an alternative strategy would be to delay the primary dose by 10 months until children are older (ie, aged 24–33 months) so that they mount a more immunogenic response; this resulted in an estimated efficacy 20 years later of 63% (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

(ie, herd) protection are required,[12] given the effect of MenAfriVac against carriage as well as disease.[30]

The key limitation of this study is the lack of a strong evidence base for the association between vaccine-induced antibody level and protection against infection with *N meningitidis* serogroup A. Nonetheless, characterisation of the kinetics of MenAfriVac-induced antibody responses in individuals will contribute to understanding the long-term patterns of immunity in populations, enabling researchers to evaluate and reduce the risk of future epidemics through adaptive vaccination policies.

References

1   Greenwood B. Editorial: 100 years of epidemic meningitis in West Africa—has anything changed? *Trop Med Int Health* 2006; **11:** 773–80.

2   Rouphael NG, Stephens DS. *Neisseria meningitidis*: biology, microbiology, and epidemiology. *Methods Mol Biol* 2012; **799:** 1–20.

3   Trotter CL, Lingani C, Fernandez K, et al. Impact of MenAfriVac in nine countries of the African meningitis belt, 2010–15: an analysis of surveillance data. *Lancet Infect Dis* 2017; **17:** 867–72.

4   LaForce FM, Djingarey M, Viviani S, Preziosi MO. Lessons from the Meningitis Vaccine Project. *Viral Immunol* 2018; **31:** 109–13.

5   WHO. Meeting of the Strategic Advisory Group of Experts on immunization, October 2014—conclusions and recommendations. *Wkly Epidemiol Rec* 2014; **50:** 561–76.

6   Peltola H, Makela H, Kayhty H, et al. Clinical efficacy of meningococcus group A capsular polysaccharide vaccine in children three months to five years of age. *N Engl J Med* 1977; **297:** 686–91.

7   Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. *J Exp Med* 1969; **129:** 1307–26.

8   Trotter CL, Yaro S, Njanpop-Lafourcade BM, et al. Seroprevalence of bactericidal, specific IgG antibodies and incidence of meningitis due to group A *Neisseria meningitidis* by age in Burkina Faso 2008. *PLoS One* 2013; **8:** e55486.

9   Sow SO, Okoko BJ, Diallo A, et al. Immunogenicity and safety of a meningococcal A conjugate vaccine in Africans. *N Eng J Med* 2011; **364:** 2293–304.

10   Daugla DM, Gami JP, Gamougam K, et al. Effect of a serogroup A meningococcal conjugate vaccine (PsA-TT) on serogroup A meningococcal meningitis and carriage in Chad: a community study. *Lancet* 2014; **383:** 40–47.

11   WHO. Meningococcal disease control in countries of the African meningitis belt, 2014. *Wkly Epidemiol Rec* 2015; **90:** 123–31.

12   Karachaliou A, Conlan AK, Preziosi MP, Trotter CL. Modeling long-term vaccination strategies with MenAfriVac in the African Meningitis Belt. *Clin Infect Dis* 2015; **61:** S594–600.

13   Tapia MD, Findlow H, Idoko OT, et al. Antibody persistence 1–5 years following vaccination with MenAfriVac in African children vaccinated at 12–23 months of age. *Clin Infect Dis* 2015; **61:** S514–20.

14   Diallo A, Sow SO, Idoko OT, et al. Antibody persistence at 1 and 4 years following a single dose of MenAfriVac or quadrivalent polysaccharide vaccine in healthy subjects aged 2–29 years. *Clin Infect Dis* 2015; **61:** S521–30.

15   Keiser PB, Gill CJ. Defining efficacy in meningococcal vaccine trials. *Clin Invest* 2012; **2:** 589–601.

16   Chen WH, Neuzil KM, Boyce CR, et al. Safety and immunogenicity of a pentavalent meningococcal conjugate vaccine containing serogroups A, C, Y, W and X in health adults: a phase 1, single-centre, double-blind, randomised, controlled study. *Lancet Infect Dis* 2018; **1088–96.**

17   Maslanka SE, Gheesling LL, Libutti DE, et al. Standardisation and a multilaboratory comparison of *Neisseria meningitidis* serogroup A and C serum bactericidal assays. *Clin Diagn Lab Immunol* 1997; **4:** 156–67.

18   Slifka MK, Antia R, Whitmire JK, Ahmed R. Humoral immunity due to long-lived plasma cells. *Immunity* 1998; **8:** 363–72.

19   White MT, Griffin JT, Akpogheneta O, et al. Dynamics of the antibody response to *Plasmodium falciparum* infection in African children. *J Infect Dis* 2014; **210:** 1115–22.

20   Teunis PF, van Eijkeren JC, de Graaf WF, Marinović AB, Kretzschmar ME. Linking the seroresponse to infection to within-host heterogeneity in antibody production. *Epidemics* 2016; **16:** 33–39.

21   Andraud M, Lejeune O, Musoro et al. Living on three time scales: the dynamics of plasma cell and antibody populations illustrated for hepatitis A virus. *PLoS Comput Biol* 2012; **8:** e1002418.

22   White MT, Verity R, Griffin JT, et al. Immunogenicity of the RTS,S/AS01 malaria vaccine and implications for duration of vaccine efficacy: secondary analysis of data from a phase 3 randomised controlled trial. *Lancet Infect Dis* 2015; **15:** 1450–58.

23   Tang Y, Plikaytis BD, Preziosi MP, Borrow R. Influence of age on antibody response and persistence following immunization with MenAfriVac. *Clin Infect Dis* 2015; **61:** S531–39.

24   Amanna IJ, Carlson NE, Slifka MK. Duration of humoral immunity to common viral and vaccine antigens. *N Eng J Med* 2007; **357:** 1903–15.

25   Borrow R, Andrews N, Findlow H, et al. Kinetics of antibody persistence following administration of a combination meningococcal serogroup C and *Haemophilus influenza* type b conjugate vaccine in healthy infants in the United Kingdom primed with a monovalent meningococcal serogroup C vaccine. *Clin Vac Immunol* 2010; **17:** 154–59.

26   Bernasconi NL, Traggiai E, Lanzavecchia A. Maintenance of serological memory by polyclonal activation of human memory B cells. *Science* 2002; **298:** 2199–202.

27   Guirguis N, Schneerson R, Bax A, et al. *Escherichia coli* K51 and K93 capsular polysaccharides are crossreactive with the group A capsular polysaccharide of *Neisseria meningitidis*. Immunochemical, biological, and epidemiological studies. *J Exp Med* 1985; **162:** 1837–51.

28   Poolman JT, De Vleeschauwer I, Durant N, et al. Measurement of functional anti-meningococcal serogroup A activity using strain 3125 as the target strain for serum bactericidal assay. *Clin Vac Immunol* 2011; **18:** 1108–17.

29   Snape MD, Kelly DF, Lewis S, et al. Seroprotection against serogroup C meningococcal disease in adolescents in the United Kingdom: observational study. *BMJ* 2008; **336:** 1487–91.

30   Kristiansen PA, Diomande F, Ba AK, et al. Impact of the serogroup A meningococcal conjugate vaccine, MenAfriVac, on carriage and herd immunity. *Clin Infect Dis* 2013; **56:** 354–63.