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# 1 **Antibody kinetics following vaccination with MenAfriVac and implications for** 2 **the duration of protection: an analysis of serological data**

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41 **Abstract**

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

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

51 **Findings** In children age 12 to 23 months, the reduction in MenAfriVac-induced antibody levels assessed by SBA  
52 titers had two phases; with 97·0% (95% credible interval (CrI): 95·1%, 98·3%) of the response being short-lived and  
53 decaying within the first 6 months, and the remainder being long-lived and decaying with a half-life of 7·4 (95% CrI:  
54 2·8, 41·3) years. Antibody levels assessed by SBA titers in participants aged 2 to 29 were more persistent, with  
55 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  
56 16·5 (95% CrI: 7·7, 39·1) years. Greater pre-vaccination antibody levels were associated with greater  
57 immunogenicity following vaccination, as well as greater antibody persistence. There is no strong evidence base for  
58 a correlate of protection against infection with *Neisseria meningitidis* serogroup A (NmA). Despite rapid antibody  
59 declines in the first phase, antibodies in the second phase persisted at SBA titers greater than 128. Based on this  
60 assumed relationship between SBA titer and protection, we predict that 20 years after vaccination with a single dose  
61 of MenAfriVac, vaccine efficacy will be 52% (95% CrI: 29%, 73%) in children vaccinated at age 12 to 23 months, and  
62 70% (95% CrI: 60%, 79%) in participants vaccinated at age 2 to 29 years.

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

67 **Funding** Meningitis Vaccine Project and Institut Pasteur.

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75 **Research in context**

76 **Evidence before this study**

77 We searched PubMed on July 10, 2018, for studies on the immunogenicity of the MenAfriVac *Neisseria meningitidis*  
78 serogroup A vaccine using the MeSH terms (“MenAfriVac” OR “PsA-TT”) and (“immunogenicity” OR “antibody”). We  
79 identified 18 reports. 11 of these studies investigated the immunogenicity of MenAfriVac within 1-2 years of  
80 vaccination. 2 studies demonstrated that antibody responses following MenAfriVac persist for time periods of up to  
81 5 years.

82 **Added value of this study**

83 This study builds on previous data by using a statistical model to predict antibody levels up to 20 years following  
84 vaccination and assess the implications for the duration of vaccine-induced protection with robust quantification of  
85 uncertainty. The decay of antibody levels after vaccination can be described by a bi-phasic exponential relationship  
86 with a phase of rapid decay in the first 6 months, followed by a second slower phase of decay. Importantly, in this  
87 second slowly decaying phase, antibody levels are predicted to remain above the assumed threshold for protection  
88 for substantial periods of time such that the estimated efficacy in children aged 12 to 23 months is 52% (95%  
89 credible interval (CrI): 29%, 73%) after 20 years, and the estimated efficacy in individuals aged 2 to 29 years is 70%  
90 (95% CrI: 60%, 79%) after 20 years.

91 **Implications of all the available evidence**

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

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108 **Introduction**

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

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

119 There is limited evidence on the association between antibody levels and vaccine efficacy, with the only established  
120 correlate of protection being group A-specific IgG antibodies  $\geq 2 \mu\text{g}/\text{mL}$ <sup>6,7</sup>, with no evidence from Africa.

121 Observational studies of natural immunity have not detected associations between antibody levels and NmA  
122 meningitis incidence<sup>8</sup>, as reported by the classic studies of Goldschneider *et al*<sup>7</sup>. Despite this, MenAfriVac was  
123 licensed on the basis of safety and immunogenicity data<sup>9</sup>, with data on effectiveness being collected only after  
124 largescale MenAfriVac campaigns<sup>3,10</sup>. Ongoing surveillance efforts have not identified cases of NmA meningococcal  
125 disease in individuals vaccinated with MenAfriVac<sup>11</sup>.

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

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

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143 **Methods**

144 **Data**

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

149 Full details of the PsA-TT-002 study have been reported elsewhere<sup>9,13</sup>. In brief, healthy Malian and Gambian children  
150 aged between 12 and 23 months, fully immunized according to the local EPI schedule, were recruited to receive  
151 primary vaccination of either MenAfriVac (10 µg), PsACWY, or *Haemophilus influenzae* type b vaccine (Hib-TT).  
152 Children were further randomised to receive a second vaccine dose 10 months later. Blood samples were obtained  
153 prior to primary vaccination; 4 weeks after primary vaccination; prior to secondary vaccination; 1 and 4 weeks after  
154 secondary vaccination; and approximately 1 and 2 years after primary vaccination. Further samples from a subset of  
155 individuals were taken 5 years after primary vaccination. The 5 year follow-up data were not directly incorporated in  
156 this analysis, but geometric mean values were used to validate model predictions. The data are summarised in Table  
157 1 and Supplementary Figure 1.

158

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

165

166 *Table 1 here*

167

168 **Immunogenicity**

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

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177 **Statistical analysis**

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

184

185 **Antibody kinetics**

186 Exposure of the immune system to vaccine antigens stimulates the generation of memory B cells which subsequently  
187 differentiate into antibody secreting cells (ASCs)<sup>18</sup>. ASCs generate IgG molecules responsible for vaccine-induced  
188 immunity, and are composed of two populations: one short-lived responsible for the rapid generation of antibodies,  
189 and one long-lived responsible for humoral immunity long after vaccination or initial infection<sup>18</sup>. This  
190 immunologically based model has been used to describe antibody kinetics following malaria infection<sup>19</sup>, pertussis  
191 vaccination<sup>20</sup>, human papillomavirus vaccination, and hepatitis A vaccination<sup>21</sup>. These mathematical models were  
192 adapted to account for the changing antibody response over time following MenAfriVac vaccination. Primary  
193 vaccination is assumed to induce proliferation of populations of ASCs of size  $\beta$  in a rapid boost. A proportion  $\rho$  of  
194 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  
195 assumed to generate IgG molecules at a constant rate which decay with half-life  $d_a$ . The antibody response at time  $t$   
196 after primary vaccination can be modelled as:

197

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

198 This equation is valid for antibody responses measured with either assay.  $Ab_0$  is the baseline antibody response prior  
199 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  $r_a =$   
200  $\log_e(2)/d_a$ . Some participants in the PsA-TT-002 study received secondary vaccination with MenAfriVac after 10  
201 months. The antibody response following this second dose are modelled using the same equation as above. The  
202 model does not account for the role of natural exposure to NmA.

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

208

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

209 where  $Ab_{\text{prot}}$  is the threshold SBA titre required for protection, and  $\alpha$  is a shape parameter.

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

215

## 216 **Role of the funding source**

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

221

## 222 **Results**

### 223 **Immunogenicity following vaccination**

224 Antibody levels measured via SBA titer and group A-specific IgG ELISA were significantly correlated (Pearson's  $r =$   
225  $0.58$ ;  $p < 0.0001$ ), with a linear relationship on a log-log scale for measurements from post-vaccination samples, but  
226 not from pre-vaccination samples (Supplementary Figure 3), replicating findings reported elsewhere<sup>15</sup>. Notably,  
227 different relationships were observed for samples from the PsA-TT-002 and PsA-TT-003 studies, with participants in  
228 the PsA-TT-003 study having substantially higher group A-specific IgG ELISA levels at equal SBA titers.

229 The dependence of log antibody responses after vaccination on a number of covariates was assessed using linear  
230 regression (Supplementary Table 3), with univariate relationships shown in Supplementary Figure 4. The results  
231 from this analysis of pooled data were in agreement with findings from the component data sets<sup>23</sup>. In the PsA-TT-  
232 002 study of children aged 12-23 months, for each extra month of age there was a 9% increase in SBA titers ( $p =$   
233  $0.001$ ). However, in the PsA-TT-003 study of participants aged 2-29 years, for each extra year of age there was a 2%  
234 decrease in SBA titers ( $p = 0.0009$ ). High baseline  $\log_{10}$  SBA titers were associated with higher  $\log_{10}$  SBA titers after  
235 vaccination ( $p < 0.0001$ ). When antibody levels were measured by ELISA, there were no significant associations  
236 between age and group A-specific IgG ELISA level following vaccination. Antibody levels in males were 18% lower  
237 than in females ( $p = 0.002$ ). Group A-specific IgG ELISA levels at baseline were significantly associated with higher  
238 levels following primary vaccination ( $p < 0.0001$ ).

239

### 240 **Antibody kinetics**

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

243 data on SBA titers and IgG ELISA levels from a representative subset of 8/797 individuals. A number of distinctive  
244 patterns are evident: (i) antibody responses induced by MenAfriVac decay rapidly in the first 6 months, after which  
245 the remaining antibodies decay at a slower rate; (ii) in most individuals the initial decay of IgG ELISA levels is more  
246 rapid than the decay of SBA titers; (iii) Hib-TT vaccination causes boosting in SBA titers but not IgG ELISA levels; (iv)  
247 there is substantial variation in the observed antibody kinetics, for example individual G002\_3 (Figure 1B) did not  
248 sustain a long-lived antibody response as measured by SBA titer. Figure 1I-L shows the geometric mean and range of  
249 antibody responses observed in the study population. The model predicted geometric mean antibody responses  
250 were in agreement with the data from samples at 4 years follow-up in the PsA-TT-003 study, but slightly under-  
251 predict the data at 5 years follow-up in the PsA-TT-002 study. As these data were not used to calibrate the model,  
252 this provides some support for the ability of the model to predict long-term antibody responses. Figure 1M-P  
253 shows the proportion of individuals predicted to have antibody responses greater than a range of thresholds over  
254 the first 5 years of follow-up.

255  
256 The estimated parameters describing the antibody kinetics are presented in Table 2. In the PsA-TT-002 study,  
257 primary vaccination with MenAfriVac is assumed to induce ASCs that generate antibodies causing bactericidal  
258 activity. For measurements from the SBA assay all ASCs are assumed to secrete IgG molecules which decay with an  
259 estimated half-life of 15.4 (95% Credible Interval (CrI): 12.0, 20.0) days. The short-lived phase is estimated to  
260 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:  
261 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,  
262 15078) days. In the PsA-TT-002 study, the key difference between antibody kinetics when investigated using the two  
263 assays was the greater proportion of the short-lived phase for the IgG ELISA assay, estimated as 99.1% (95% CrI:  
264 98.5%, 99.5%).

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

272  
273 *Table 2 here*

### 275 **Age dependency of antibody persistence**

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

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

281 Older age was associated with better persistence when antibody response was measured by both SBA titer (Figure  
282 2A) and ELISA (Figure 2D). However, in a multivariate analysis age was not significantly associated with antibody  
283 persistence (Table 3). Greater SBA titers before MenAfriVac vaccination were associated with better antibody  
284 persistence (Figure 2B), but this was not significant in the multivariate analysis (Table 3). Individuals who had more  
285 immunogenic responses to MenAfriVac when measured by SBA titer also experienced greater reduction in the first  
286 year (Figure 2C), and this was highly significant ( $p < 0.0001$ ). Greater IgG ELISA measurements before MenAfriVac  
287 vaccination were associated with better antibody persistence (Figure 2E), and this association was significant ( $p <$   
288  $0.0001$ ). Individuals who had more immunogenic responses to MenAfriVac when measured by IgG ELISA also  
289 experienced greater reduction in the first year ( $p < 0.0001$ ), although this association was not evident when  
290 examined univariately (Figure 2F).

291

292 *Table 3 here*

293

#### 294 **Predicted vaccine efficacy**

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

304

#### 305 **Discussion**

306 Vaccination with MenAfriVac causes a rapid increase in antibody responses targeting group A *N meningitidis*, when  
307 measured by either SBA titer or group A-specific IgG ELISA. This response is characterised in two phases; after  
308 peaking within the first month following vaccination, the first phase of the antibody response decays rapidly within  
309 the first 6 months, so that sustained protection is conferred by the second phase of the immune response. In  
310 children aged 12-23 months, this long-lived phase of the antibody response is estimated to decay with a half-life of  
311 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  
312 ELISA. In older individuals aged 2-29 years, the long-lived phase was estimated to be longer with a half-life of 16.5  
313 (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.

314 These values are comparable with estimated half-lives for anti-tetanus and anti-diphtheria antibody responses of 11-  
315 19 years, but decay more rapidly than anti-measles antibodies which demonstrate little reduction over time<sup>24</sup>. The  
316 distinctive pattern of bi-phasic waning is consistent with observations following administration of a combination  
317 meningococcal serogroup C and *Haemophilus influenzae* type b vaccine<sup>25</sup>.

318 Geometric mean antibody levels in these study populations have been observed to persist above a threshold SBA  
319 titer of 128 for up to 4 years<sup>13,14</sup>. However, it is the variation in antibody responses rather than the mean which is  
320 the key determinant of how vaccine efficacy wanes over time. A key strength of the statistical methods utilised in  
321 this analysis is the ability to characterise the variation in antibody responses in addition to the average behaviour.  
322 For example, consider individual G002\_3 in Figure 1B whose rapidly decaying SBA titer may be considered atypical of  
323 the average antibody response. In some cases in the PsA-TT-002 study, there is an increase in antibody levels  
324 between the samples from years 2 and 5 (Figure 1I-L). This may be attributable to natural exposure to NmA or cross-  
325 reactivity with antibodies to other serogroups or pathogens. The model does not account for these factors, and the  
326 predictions are only valid in the absence of other exposure.

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

344 The key determinants of immunogenicity (measured antibody response after vaccination) were age and pre-  
345 vaccination antibody response. For measurements from both assays, high pre-vaccination antibody levels were  
346 associated with greater immunogenicity following MenAfriVac. In the PsA-TT-002 study of children aged 12-23  
347 months, older age was associated with greater immunogenicity, however in the PsA-TT-003 study of individuals aged  
348 2-29 years, older age was associated with lower immunogenicity (Supplementary Table 3). This is in contrast to data  
349 following meningococcal serogroup C vaccination where immunogenicity increased with age in children 6-15 years<sup>29</sup>.  
350 For antibody persistence considered as the percentage of the post-vaccination antibody response remaining after 1

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

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

366 Although based on vaccinees in clinical trials, and not the general population, the estimates provided here can guide  
367 the optimal design of vaccination strategies. 20 years after vaccination with MenAfriVac in participants aged 2-29  
368 years, vaccine efficacy is estimated to be 70% (95% CrI: 60%, 79%). In children vaccinated at age 12-23 months  
369 (representative of the target EPI population aged 9-18 months), efficacy 20 years after vaccination was estimated to  
370 be substantially lower at 52% (95% CrI: 29%, 73%). Incorporation of a booster dose of MenAfriVac 10 months after  
371 primary vaccination is estimated to increase efficacy at 20 years to 64% (95% CrI: 40%, 85%). However, an  
372 alternative strategy would be to delay the primary dose by 10 months until children are older (24-33 months), so  
373 that they mount a more immunogenic response, resulted in an estimated efficacy 20 years later of 63% (95% CrI:  
374 37%, 83%). However the benefits of such a strategy would need to be weighed against the risks of leaving young  
375 children unvaccinated for longer. To fully understand the population impact of declining individual protection,  
376 models that incorporate indirect (herd) protection are required<sup>12</sup>, given the effect of MenAfriVac against carriage as  
377 well as disease<sup>30</sup>.

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

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390 this publication.

391

392 **Contributors**

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

395

396 **Conflicts of interest**

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

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481 MenAfriVac, on carriage and herd immunity. *Clin Inf Dis* 2013; **56**: 354-363

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488 **Tables**

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

trial	PsA-TT-002						PsA-TT-003		
	Gambia	Gambia	Gambia	Mali	Mali	Mali	Gambia	Mali	Senegal
<b>primary vaccine</b>	Hib-TT	MenAfriV ac	MenAfriV ac	Hib-TT	MenAfriV ac	MenAfriV ac	MenAfriV ac PsA-TT	MenAfriV ac PsA-TT	MenAfriV ac PsA-TT
<b>secondary vaccine after 10 months</b>	MenAfriVac	Hib-TT	MenAfriV ac	MenAfriV ac	Hib-TT	MenAfriV ac	–	–	–
<b>N</b>	33	34	30	30	32	34	202	201	201
<b>age (years)</b>	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)
<b>gender (% female)</b>	16 (48%)	13 (38%)	15 (50%)	11 (37%)	16 (50%)	19 (56%)	84 (42%)	79 (39%)	87 (43%)
<b>follow-up time (days)</b>	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)
<b>SBA<sub>base</sub></b>	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)
<b>SBA<sub>prim</sub></b>	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)
<b>SBA<sub>sec</sub></b>	12299 (1741, 85197)	1961 (256, 32768)	16845 (4096, 91750)	16009 (1766, 65536)	1069 (2, 10035)	26185 (8192, 77004)	–	–	–
<b>ELISA<sub>base</sub> (µg/mL)</b>	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)
<b>ELISA<sub>prim</sub> (µg/mL)</b>	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)
<b>ELISA<sub>sec</sub> (µg/mL)</b>	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)	–	–	–

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

description	parameter	PsA-TT-002		PsA-TT-003	
		SBA	ELISA	SBA	ELISA
ASC boost after primary MenAfriVac vaccination	$\beta_{\text{prim}}$	2502 (1685, 3984)	4.4 (3.3, 6.2)	1935 (743, 4693)	7.0 (5.3, 12.1)
ASC boost after secondary MenAfriVac vaccination	$\beta_{\text{sec}}$	3229 (2169, 5033)	12.9 (8.9, 19.0)	–	–
ASC boost after Hib-TT vaccination	$\beta_{\text{Hib}}$	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	$\rho_{\text{prim}}$	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	$\rho_{\text{sec}}$	97.8% (95.9%, 98.8%)	98.8% (98.0%, 99.3%)	–	–
proportion of short-lived ASCs after Hib vaccination	$\rho_{\text{Hib}}$	95.8% (88.2%, 98.4%)	–	–	–

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

covariate	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
<b>study: PsA-TT-002 (reference)</b>	-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
<b>study: PsA-TT-003</b>	-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
<b>country: Mali</b>	-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
<b>country: Senegal</b>	-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
<b>age: PsA-TT-002</b>	-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
<b>age: PsA-TT-003</b>	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
<b>log<sub>10</sub>(SBA<sub>base</sub>)</b>	-0.09 (-0.25, 0.05)	0.20	0.04 (-0.009, 0.09)	0.11	–	–	–	–
<b>log<sub>10</sub>(SBA<sub>peak</sub>)</b>	1.81 (1.29, 2.33)	<0.0001	0.93 (0.79, 1.07)	<0.0001	–	–	–	–
<b>log<sub>10</sub>(ELISA<sub>base</sub>)</b>	–	–	–	–	-0.75 (-1.11, -0.40)	<0.0001	0.23 (0.19, 0.26)	<0.0001
<b>log<sub>10</sub>(ELISA<sub>peak</sub>)</b>	–	–	–	–	0.73 (0.31, 1.14)	0.0006	0.78 (0.74, 0.82)	<0.0001

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## 552 **Figure legends**

553 **Figure 1: Antibody kinetics following MenAfriVac vaccination. (A-H)** Antibody kinetics in a subset of 8/797  
554 individuals selected for illustrative purposes. Data on measured IgG ELISA levels are represented using points, and  
555 SBA titers are represented using intervals. Solid lines denote the median model predicted antibody level over time,  
556 and the shaded regions denote the 95% credible intervals of the model predictions. **(I-L)** Geometric mean antibody  
557 levels in the population. Shaded regions represent the 95% confidence intervals of the model predicted geometric  
558 mean antibody levels, calculated using a Student's *t*-test. Data points represent geometric mean antibody level as  
559 reported in Tapia *et al*<sup>13</sup> and Diallo *et al*<sup>14</sup>. **(M-P)** Proportion of individuals with antibody levels greater than specified  
560 thresholds. Solid lines represent a threshold SBA titer of 128, which corresponds to IgG ELISA level of 2 µg/mL.  
561 Dashed lines represent a threshold SBA titer of 1024, which corresponds to IgG ELISA level of 8.9 µg/mL.

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563 **Figure 2: Determinants of antibody persistence.** The percentage reduction from the peak antibody level measured  
564 4 weeks after vaccination to the estimated antibody level 1 year after vaccination is shown. **(A)** Association between  
565 age and percentage reduction in SBA titer 1 year after MenAfriVac. **(B)** Association between pre-vaccination SBA  
566 titer and percentage reduction in SBA titer 1 year after MenAfriVac. **(C)** Association between post-vaccination SBA  
567 titer and percentage reduction in SBA titer 1 year after MenAfriVac. **(D)** Association between age and percentage  
568 reduction in IgG ELISA 1 year after MenAfriVac. **(E)** Association between pre-vaccination IgG ELISA and percentage  
569 reduction in IgG ELISA 1 year after MenAfriVac. **(F)** Association between post-vaccination IgG ELISA and percentage  
570 reduction in SBA titer 1 year after MenAfriVac. The black lines show univariate associations estimated from logistic  
571 regression models.

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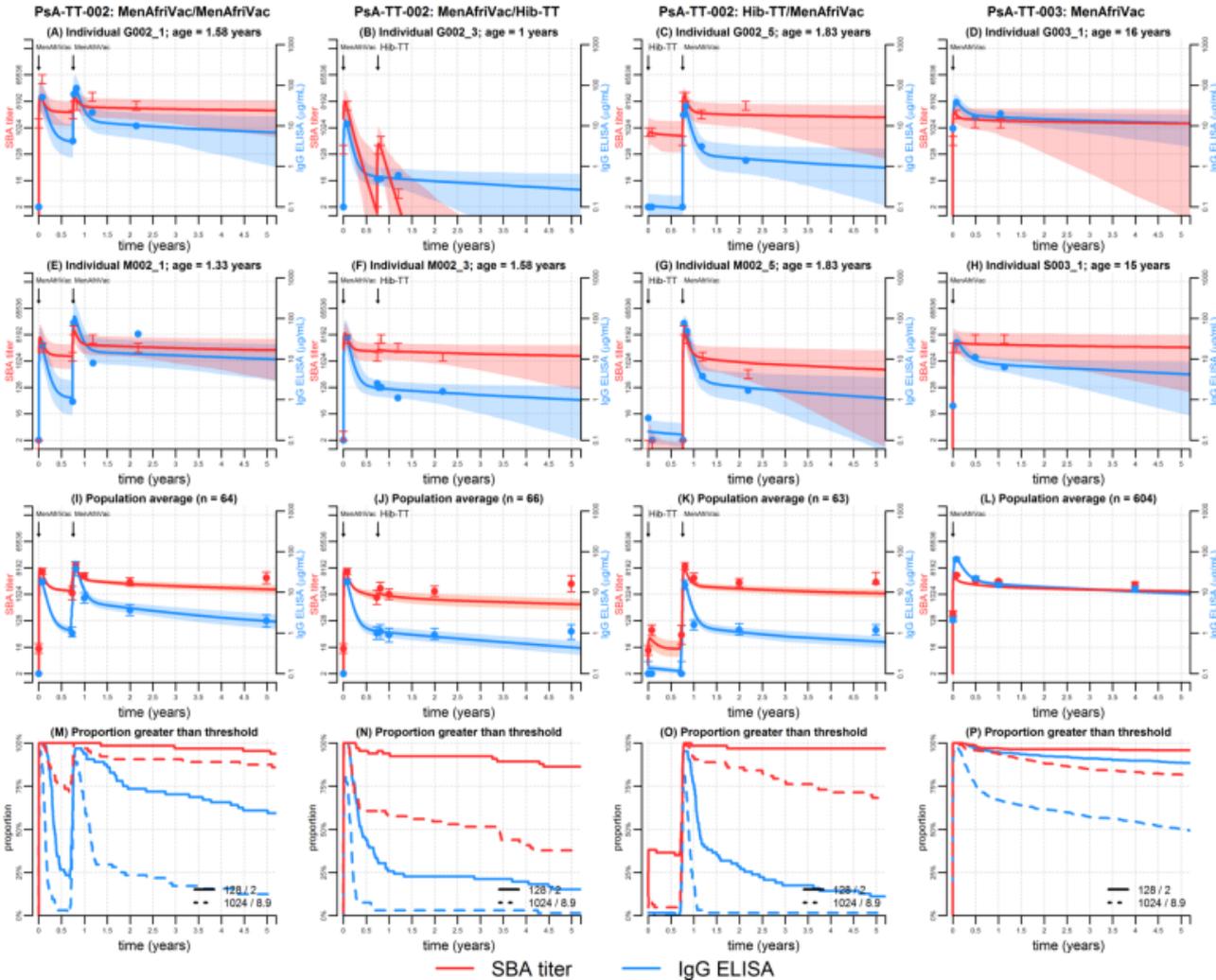
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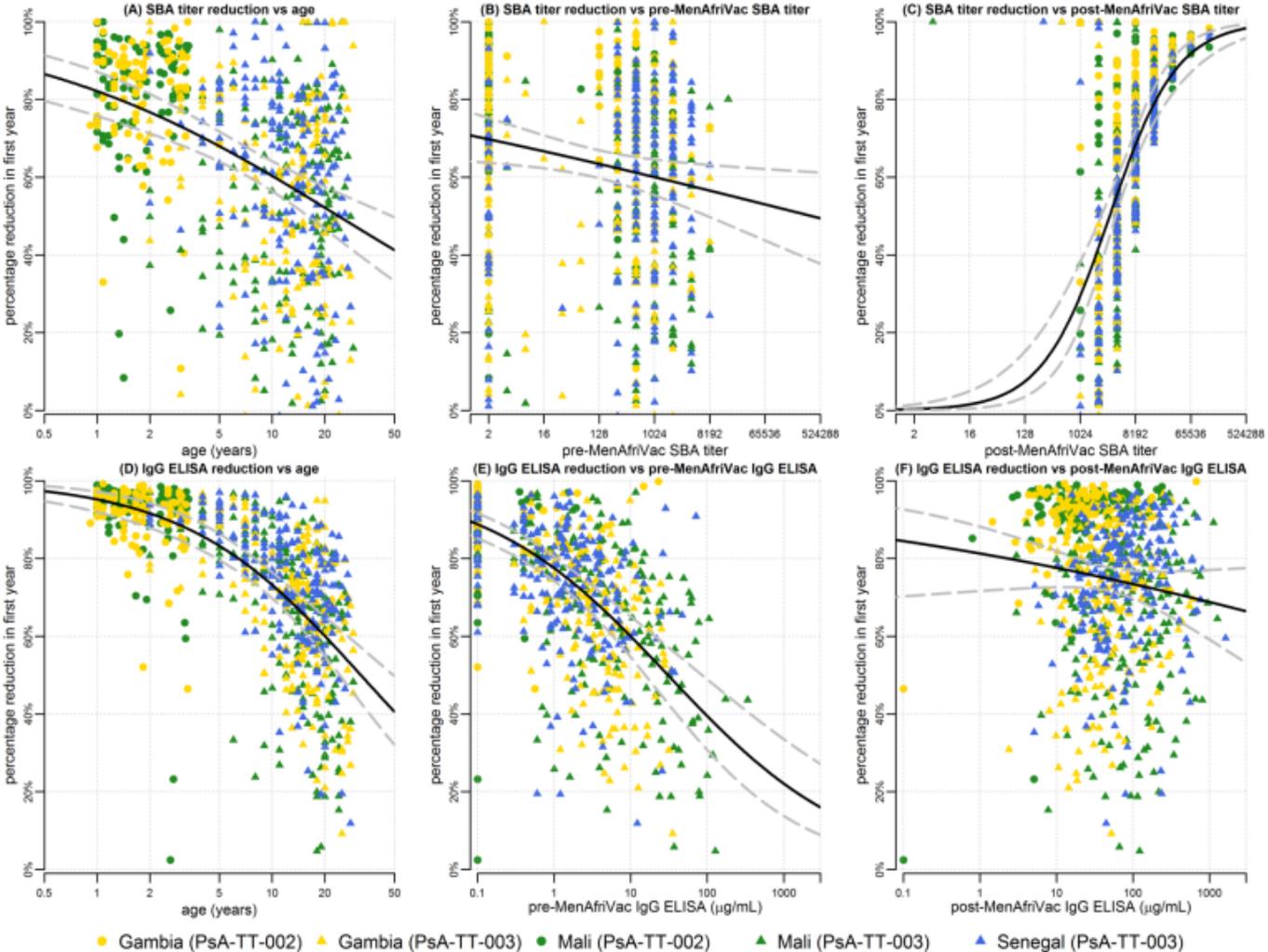
## 582 **Supplementary files**

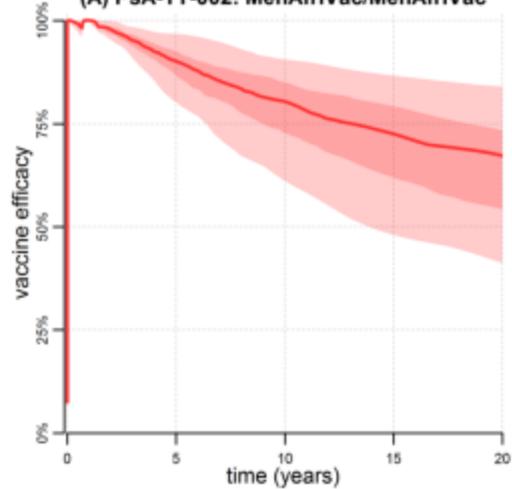
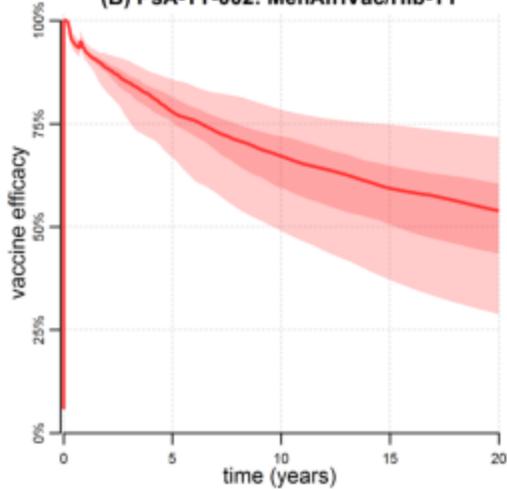
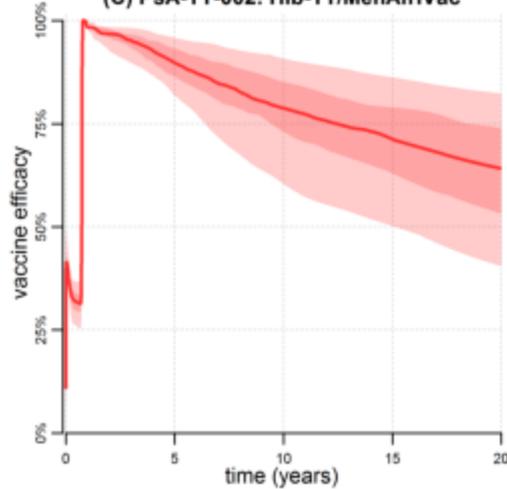
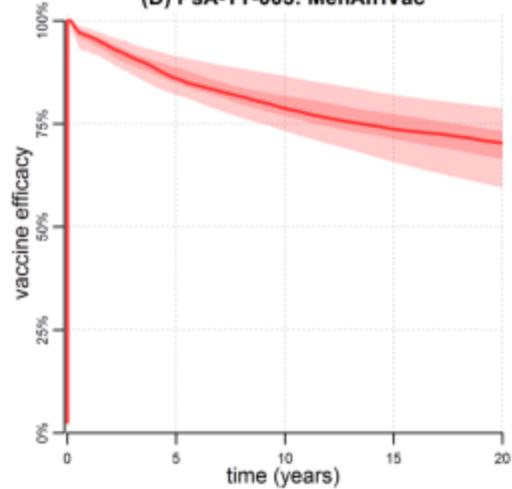
583 **Supplementary methods file:** Details of statistical model of antibody kinetics.

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**(A) PsA-TT-002: MenAfriVac/MenAfriVac****(B) PsA-TT-002: MenAfriVac/Hib-TT****(C) PsA-TT-002: Hib-TT/MenAfriVac****(D) PsA-TT-003: MenAfriVac****(E) Assumed dose-response relationship**