Antibody Persistence 1–5 Years Following Vaccination With MenAfriVac in African Children Vaccinated at 12–23 Months of Age

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Background. Following mass vaccination campaigns in the African meningitis belt with group A meningococcal conjugate vaccine, MenAfriVac (PsA-TT), disease due to group A meningococci has nearly disappeared. Antibody persistence in healthy African toddlers was investigated.

Methods. African children vaccinated at 12–23 months of age with PsA-TT were followed for evaluation of antibody persistence up to 5 years after primary vaccination. Antibody persistence was evaluated by measuring group A serum bactericidal antibody (SBA) with rabbit complement and by a group A–specific IgG enzyme-linked immunosorbent assay (ELISA).

Results. Group A antibodies measured by SBA and ELISA were shown to decline in the year following vaccination and plateaued at levels significantly above baseline for up to 5 years following primary vaccination.

Conclusions. A single dose of PsA-TT induces long-term sustained levels of group A meningococcal antibodies for up to 5 years after vaccination.

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Keywords. MenAfriVac; group A meningococcal conjugate vaccine; antibody persistence; African meningitis belt.

The “meningitis belt” of sub-Saharan Africa runs across the continent from Senegal to Ethiopia, and this region is prone to major epidemics of meningococcal meningitis, with a high case fatality rate and serious sequelae. Until recently, most epidemics were due to group A Neisseria meningitidis (MenA). The observed reduction in meningococcal meningitis due to MenA has been due to the development of an affordable group A meningococcal vaccine, PsA-TT (MenAfriVac, Serum Institute of India, Ltd). The Meningitis Vaccine Project, a partnership between the World Health Organization (WHO) and PATH, coordinated the development, testing, licensure, and introduction of this vaccine with the aim of eliminating epidemic meningitis attributable to MenA [1–4].

Since 2010, PsA-TT has been introduced into countries across the meningitis belt through mass campaigns [5, 6]. PsA-TT is expected to confer both longer-lasting individual protection and herd protection than MenA.
polysaccharide vaccines. Ongoing surveillance shows that no cases of MenA meningococcal disease have occurred in vaccinated individuals [6], but the longevity of this protective immune response is not known. Prior to the introduction of PsA-TT into the African countries of the meningitis belt, multiple clinical trials assessed the safety and immunogenicity of PsA-TT. A trial conducted in children aged 12–23 months demonstrated that this vaccine was immunogenic and induced immune memory. However, antibody persistence is key in maintaining direct and indirect protection [7, 8]. We report here on the persistence of MenA-specific antibodies in individuals vaccinated with PsA-TT in early childhood.

METHODS

The study was conducted in accordance with the principles of the Declaration of Helsinki and in compliance with Good Clinical Practice guidelines. The clinical trial was registered (identifier ISRCTN78147026) at www.controlled-trials.com.

The full details of this study have been reported elsewhere by Sow et al [9]; in brief, healthy children (aged 12–23 months) who were fully immunized according to the local Expanded Programme on Immunization schedule were recruited from 2 urban quarters in Bamako, Mali, and from Basse in the Upper River region of The Gambia. Subjects received primary vaccination when aged between 12 and 23 months of either PsA-TT (10 µg), polysaccharide vaccine (PsACWY), or Haemophilus influenzae type b vaccine (Hib-TT) and 10 months later were revaccinated with 1 of these 3 vaccines (the dose of PsACWY administered was one-fifth dose). Blood samples were obtained prior to primary vaccination and revaccination, 4 weeks after primary vaccination, and 1 and 4 weeks after revaccination, the results of which were previously reported [9]. Those subjects who received Hib-TT at the primary and revaccination stages of the initial trial were vaccinated with PsA-TT at the end of the initial trial (3–4 years of age at approximately 2 years following enrollment). The initial trial period followed subjects for 2 years following primary vaccination. Subjects were later approached for enrollment into a follow-on study to assess the persistence of group A-specific antibodies approximately 5 years after primary vaccination. For evaluation of antibody persistence, blood samples were obtained at approximately 1, 2, and 5 years following primary vaccination (initial trial enrollment) in 3 groups who received (1) a single dose of PsA-TT at either primary or revaccination stages, (2) two doses of PsA-TT, and (3) a single dose of PsA-TT at the end of the initial trial period (at 2 years [104 weeks] after primary vaccination) (those who received 2 doses of Hib-TT).

Immunogenicity

Blood samples were assayed in the serum bactericidal antibody (SBA) assay using the group A target strain F8238 (phenotype A:4,21:P1.20,9, L10) as previously described [10]. The complement source used in the SBA was pooled serum from 3- to 4-week-old rabbits (Pel Freez Biologicals). Titers were expressed as the reciprocal serum dilutions yielding ≥50% killing after 60 minutes.

Group A–specific immunoglobulin G (IgG) levels were determined using an enzyme-linked immunosorbent assay (ELISA) [11], except that the reference serum CDC1992 and monocolonal-pan antihuman IgG Fc labeled with horseradish peroxidase (Hybbridoma Reagent Laboratory) were used. For the reference serum, CDC1992 was used with the previously assigned group A–specific IgG concentration [12]. The lower limit of quantitation for the ELISA was 0.4 µg/mL; concentrations below this were reported as 0.2 µg/mL.

Statistical Analysis

The SBA geometric mean titers (GMTs) and group A–specific IgG geometric mean concentrations (GMCs) between the vaccine groups at 1 year and 2 years after primary vaccination were compared by mixed-effects modeling adjusted for baseline titers (concentrations), age, sex, study site, time, and interaction effects of interest with log2-transformed titers and log10-transformed concentrations as an outcome. At 5 years after primary vaccination, the comparisons in SBA GMTs and GMCs between the vaccine groups of interest were performed by analysis of covariance adjusted for baseline titers (concentrations), sex, and time. The paired t test was used to compare the GMTs and GMCs between 2 and 5 years after primary vaccination. The percentages of subjects with SBA titers ≥128 and group A–specific IgG concentrations ≥2 µg/mL along with their exact binomial 95% confidence intervals (CIs) were provided. All immunogenicity analyses were conducted in the intention-to-treat population. Missing values were treated as missing at random. All tests were 2-sided with a significance level of .05. Data analysis was performed using SAS software, version 9.1.3.

RESULTS

Study Population

As previously reported [9], 601 Malian and Gambian toddlers were randomized to receive primary vaccination, of whom 589 completed the revaccination stage. Subjects who were recruited into the PsA-TT and Hib-TT groups and received either PsA-TT or Hib-TT at the revaccination phase were followed for antibody persistence at approximately 1, 2, and 5 years after primary vaccination. Figure 1 shows the subjects’ disposition for the initial trial period and for the follow-up study period. All 101 subjects from the Mali site were excluded from the 5-year persistence analysis due to the confirmed and probable receipt of MenAfriVac as part of the national mass vaccination campaign in 2010–2011 or trivalent meningococcal ACW vaccine
during an outbreak of group W meningococcal disease. Long-term persistence was conducted on average 5 years after the initial trial period with a mean duration of 5.1 years following primary vaccination.

**Serum Bactericidal Antibody Titers**

The SBA GMTs and proportion of subjects with SBA titers ≥128 for each study group are shown in Table 1. At 1 year after primary vaccination, the SBA GMTs of the groups that had received PsA-TT were significantly higher than those that had not received any MenA-containing vaccine (Hib-TT/Hib-TT) (P < .0001 for all 3 pairwise comparisons).

The SBA GMTs of those vaccinated with Hib-TT followed by PsA-TT (Hib-TT/PsA-TT) were higher (P < .0001) than the GMTs of those who received PsA-TT followed by Hib-TT (PsA-TT/Hib-TT), with GMTs of 3722.5 (95% CI, 2551.4–5431.3) and 1035.0 (95% CI, 678.4–1578.9), respectively.

The SBA GMT at 1 year after primary vaccination in those who received 2 doses of PsA-TT (PsA-TT/PsA-TT) was statistically significantly higher than that in those who only received 1 dose of PsA-TT at primary vaccination (P < .0001) and similar to those who received 1 dose of PsA-TT at revaccination, with GMTs of 4485.8 (95% CI, 3579.6–5621.4), 3722.5 (2551.4–5431.3), and 1035.0 (95% CI, 678.4–1578.9) in the PsA-TT/PsA-TT, Hib-TT/PsA-TT, and PsA-TT/Hib-TT groups, respectively.

At 2 years after primary vaccination, the SBA GMT in those who had not received PsA-TT (Hib-TT/Hib-TT) was significantly lower than that of the 3 groups that had received PsA-TT (P = .0001 for Hib-TT/Hib-TT vs Hib-TT/PsA-TT; P = .0279 for Hib-TT/Hib-TT vs PsA-TT/Hib-TT; and P < .0001 for Hib-TT/Hib-TT vs PsA-TT/PsA-TT). The GMTs of the 2 groups that received a dose of PsA-TT at revaccination were similar at 2 years after primary vaccination, with GMTs of 2720.8 (95% CI, 2078.6–3421.0) and 2720.8 (95% CI, 2078.6–3421.0) in the PsA-TT/PsA-TT and Hib-TT/PsA-TT groups, respectively.
Table 1. Summary of Endpoints of Group A Geometric Mean Meningococcal Serum Bactericidal Antibody Titters

| Vaccine Group | SBA GMT | Primary Vaccination | SBA GMT | Primary Vaccination | SBA GMT | Primary Vaccination | SBA GMT | Primary Vaccination | SBA GMT | Primary Vaccination | SBA GMT | Primary Vaccination |
|---------------|---------|---------------------|---------|---------------------|---------|---------------------|---------|---------------------|---------|---------------------|---------|---------------------|
| PsA-TT PsA-TT  | 201     | 14.3 (9.9–20.7)     | 198     | 6234.5 (4947.9–7855.7) | 63      | 1130.6 (666.0–1919.2) | 58      | 10037.4 (7884.5–3776.8) | 26      | 3781.2 (2410.4–5931.4) |
| Hib-TT        | 65      | 801.3 (457.6–1971.9) | 29      | 2363.8 (1256.7–4446.1) | 58      | 9342.9 (7043.8–12392.4) | 58      | 3722.5 (2551.4–5431.3) | 26      | 3681.7 (2325.0–5830.0) |
| Hib-TT PsA-TT | 199     | 12.6 (8.7–18.2)     | 195     | 60.9 (39.8–93.2)      | 63      | 42.6 (20.3–89.4)      | 58      | 9342.9 (7043.8–12392.4) | 58      | 3722.5 (2551.4–5431.3) |

Abbreviations: CI, confidence interval; GMT, geometric mean titer; Hib, Haemophilus influenzae type b; PsA, polyacrotone; SBA, serum bactericidal antibody.

At 1-year postprimary comparison of SBA GMTs: Hib-TT/Hib-TT vs Hib-TT/PsA-TT, P < .0001; Hib-TT/Hib-TT vs PsA-TT/Hib-TT, P < .0001; Hib-TT/PsA-TT vs PsA-TT/Hib-TT, P < .0001; PsA-TT/PsA-TT vs PsA-TT/Hib-TT, P = .0118.

At 2-year postprimary comparison of SBA GMTs: Hib-TT/Hib-TT vs Hib-TT/PsA-TT, P = .0001; Hib-TT/Hib-TT vs PsA-TT/Hib-TT, P < .0001; PsA-TT/Hib-TT vs Hib-TT/PsA-TT, P = .0042.

At all time points, a high percentage (>95%) of subjects in all groups that had received PsA-TT had SBA titers ≥128. In those who had not received PsA-TT (ie, received Hib-TT/Hib-TT), a lower percentage of subjects had SBA titers ≥128, with 72.1% (95% CI, 59.2%–82.9%) and 86.9% (95% CI, 75.8%–94.2%) of subjects achieving this level at 1 year and 2 years after primary vaccination, respectively; the percentage increased to 100% (95% CI, 86.8%–100.0%) at 5 years after primary vaccination (3 years after subjects in the Hib-TT/Hib-TT group received PsA-TT at the end of the initial study period).

**Group A–Specific IgG**

The group A–specific IgG GMCs (µg/mL) and proportion of subjects with group A–specific IgG ≥2 µg/mL of each study group are shown in Table 2.

At 1 year and 2 years after primary vaccination, the group A–specific IgG GMC in all 3 groups that received PsA-TT was significantly higher than that of those who had not received PsA-TT (Hib-TT/Hib-TT) (P < .0001 for all 3 pairwise comparisons at 1 year and 2 years after primary vaccination).

The group A–specific IgG GMC of the Hib-TT/PsA-TT group was significantly higher than that of the PsA-TT/Hib-TT group at 1 year after primary vaccination, with GMCs of 1.6 (95% CI, 1.2–2.1) and 0.9 (95% CI, 0.6–1.3) (P = .0037).

This effect was not found at 2 years after vaccination, though, with GMCs of 1.2 (95% CI, 0.9–1.7) and 0.9 (95% CI, 0.7–1.3) in the Hib-TT/PsA-TT and PsA-TT/Hib-TT groups, respectively. At 1 year postvaccination, the group that received 2 doses of PsA-TT had higher group A–specific IgG GMCs (7.3 [95% CI, 5.4–9.8]) than the Hib-TT/PsA-TT group (1.6 [95% CI, 1.2–2.1]) (P < .0001). The GMC of the 2-dose PsA-TT group was also higher than that of Hib-TT/PsA-TT at 2 years following vaccination (P < .0001), with GMCs of 3.7 (95% CI, 2.7–5.0) and 1.2 (95% CI, 0.9–1.7), respectively.
### Table 2. Summary of Endpoints of Meningococcal Geometric Mean Group A–Specific IgG Concentrations

| Vaccine Group | Group A–Specific IgG GMCs | Long-term Follow-up Study (5 y Postprimary) |
|---------------|---------------------------|--------------------------------------------|
|               | Week 0 (Preprimary) | Week 4 (28 d Postprimary) | Week 40 (Prebooster) | Week 44 (28 d Postbooster) | Week 52 (1 y Postprimary) | Week 104 (2 y Postprimary) |
| PsA-TT        | 3/200 1.5 (3.4–4.3) | 198/199 99.5 (97.2–100.0) | 166/3 25.4 (15.3–37.9) | 55/68 94.8 (85.6–98.9) | 55/61 90.2 (79.8–98.0) | 44/81 72.1 (59.6–82.6) |
| Hib-TT        | 2/65 3.1 (4.0–10.7) | 260 3.3 (4–11.3) | 761 11.5 (4.7–22.2) | 142/6 53.8 (33.4–73.4) |

Abbreviations: C, confidence interval; GMC, geometric mean concentration; Hib, Haemophilus influenzae type b; IgG, immunoglobulin G; PsA, polysaccharide; SBA, serum bactericidal antibody; TT, tetanus toxoid.

a At 1-year postprimary comparison of IgG GMCs: Hib-TT/Hib-TT vs Hib-TT/PsA-TT, \( P < .0001 \); Hib-TT/Hib-TT vs PsA-TT/Hib-TT, \( P < .0001 \); Hib-TT/PsA-TT vs PsA-TT/Hib-TT, \( P = .0037 \); PsA-TT/PsA-TT vs Hib-TT/PsA-TT, \( P = .0149 \).
b At 2-year postprimary comparison of IgG GMCs: Hib-TT/Hib-TT vs PsA-TT/Hib-TT, \( P < .0001 \); Hib-TT/PsA-TT vs PsA-TT/Hib-TT, \( P = .0483 \); PsA-TT/PsA-TT vs PsA-TT/Hib-TT, \( P = .0386 \).
c At 5-year postprimary comparison of IgG GMCs: PsA-TT/PsA-TT vs PsA-TT/Hib-TT, \( P = .0089 \); PsA-TT/PsA-TT vs Hib-TT/PsA-TT, \( P = .0483 \); Hib-TT/Hib-TT vs Hib-TT/PsA-TT, \( P = .0149 \); and Hib/T-TT (PsA-TT/PsA-TT) vs Hib-TT (PsA-TT/PsA-TT), \( P = .0009 \).

### DISCUSSION

Children vaccinated with PsA-TT demonstrated sustained SBA levels from 1 year to 5 years following vaccination that were significantly above baseline levels, with the majority of subjects having SBA titers ≥ 230. Direct protection from meningococcal disease and vaccine effectiveness against susceptibility to disease have been shown to be associated with high vaccine coverage inducing herd protection in the population and persistence of circulating antibodies. The assessment of the vaccine’s ability to prime for immunologic memory and their persistence over time has become an essential component of the evaluation of new meningococcal vaccines to better understand their safety, immunogenicity, and potential for herd immunity. Previous studies have shown that a single dose of the meningococcal C conjugate vaccine is not sufficient to ensure protection against serogroup C meningococcal disease; however, a booster dose administered at 12–24 months was associated with an increase in geometric mean antibody levels, which was maintained until 5 years after the primary vaccination [15, 17]. The ability to generate a booster response on direct exposure was found not to be sufficient to protect against disease, as antibody levels in subjects with vaccine failure showed evidence of an anamnestic immune response [16]. However, the presence of circulating bactericidal antibodies in adequate quantities, along with interruption of carriage, is critical to prevent meningococcal disease in the population and persistence of circulating antibodies [16].

Higher than expected increases of antibodies following 5 years postprimary vaccination were observed in the Hib-TT groups (PsA-TT/PsA-TT vs Hib-TT/PsA-TT, \( P = .0009 \); PsA-TT/PsA-TT vs PsA-TT/Hib-TT, \( P = .0149 \); and Hib-TT (PsA-TT/PsA-TT) vs Hib-TT (PsA-TT/PsA-TT), \( P = .0009 \)) groups from 2 years following primary vaccination.
with a quadrivalent meningococcal ACWY conjugate vaccine (ACWY-TT, Nimenrix, GlaxoSmithKline) in which an SBA GMT of 967 (95% CI, 843–1109.3) at 1 year postvaccination was observed [18]. However, at the later persistence time points of 2 and 3 years following vaccination, a decline in GMTs was observed in the trial of Vesikari et al [18], whereas similar GMTs were measured at 1, 2, and 5 years postvaccination in this trial. Despite the decline in GMTs, the majority of subjects in the trial of Vesikari et al had SBA titers ≥128 at all persistence time points; this was also true of the results reported here. It is of note that the baseline immunogenicity characteristics of the Finnish child population [18] were very different to those of our trial reported here and may contribute to the differences observed.

Difference in the SBA GMTs was observed at 1 and 2 years postvaccination between those who received 1 dose of PsA-TT at primary vaccination and those who received 2 doses. However, the same difference was not observed when a single dose of PsA-TT was administered at an older age of 22–33 months, at the revaccination visit. Differences between the groups that received 1 and 2 doses were also evident with the IgG GMCs, with those who received 2 doses having higher IgG GMCs at 2 and 5 years after primary vaccination. This is in contrast to the results observed by Klein et al [19], which showed no difference in the group A meningococcal SBA GMTs 1 year following vaccination with 1 dose of quadrivalent meningococcal ACWY vaccine at 12 months of age or 2 doses at 9 and 12 months of age, with group A meningococcal SBA GMTs of 259.7 (95% CI, 191.4–352.3) and 257.2 (95% CI, 187.0–301.0) in those who received 1 or 2 doses, respectively. The SBA GMTs and IgG GMCs of the Hib-TT/Hib-TT group that received PsA-TT at the end of the initial trial period at an older age of 3–4 years were similar to those of the group that received 2 doses of PsA-TT. Despite observed differences in the persisting antibody levels in those who received 1 or 2 doses of PsA-TT, both the SBA GMTs and IgG GMCs at 5 years after primary vaccination were significantly above baseline for all groups in which subjects received PsA-TT during the initial study or at the end of the initial study.

PsA-TT has been introduced into several countries of the African meningitis belt via mass vaccination campaigns in which individuals aged 1–29 years received 1 dose. PsA-TT has been shown to have had a major impact on MenA disease and carriage in Chad [20]. This study and others [21] have demonstrated the persistence of antibodies following PsA-TT; however, ongoing active surveillance is needed to establish the longer-term duration of protection provided by PsA-TT. In conclusion, we have demonstrated that 5 years following a single dose of PsA-TT in African children aged 12–23 months, the majority are still protected.

**Notes**

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