Persistence of the immune response two years after vaccination with quadrivalent meningococcal ACWY-tetanus toxoid conjugate vaccine (MenACWY-TT) in Asian adolescents

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ABSTRACT
Invasive meningococcal disease is a serious infection that is most often vaccine-preventable. Long-term protection relies on antibody persistence. Here we report the persistence of the immune response 2 y post-vaccination with a quadrivalent meningococcal serogroups A, C, W, Y tetanus toxoid conjugate vaccine (MenACWY-TT) compared with a MenACWY polysaccharide vaccine (Men-PS), in Asian adolescents aged 11–17 y. We also report a re-analysis of data from the primary vaccination study. This persistence study (NCT00974363) conducted in India and the Philippines included subjects who previously (study NCT00464815) received a single dose of MenACWY-TT or Men-PS. Persistence of functional antibodies was measured in 407 MenACWY-TT recipients and 132 Men-PS recipients (according-to-protocol cohort) using a rabbit complement serum bactericidal assay (rSBA, cut-off 1:8). Vaccine-related serious adverse events (SAEs) occurring since the end of the initial vaccination study were retrospectively recorded. Two y post-vaccination ≥99.3% of adolescents who received MenACWY-TT had persisting antibody titers ≥1:8 against each vaccine serogroup. Antibody persistence was higher (exploratory analysis) in the MenACWY-TT group than the Men-PS group in terms of rSBA titers ≥1:8 for serogroups W and Y; rSBA titers ≥1:128 for serogroups A, W and Y; and was lower in the MenACWY-TT group for rSBA GMTs for serogroups A, W and Y; and was lower in the MenACWY-TT group for rSBA GMTs for serogroup C. No vaccine-related SAEs were reported. The results of this study indicated that antibodies persisted for at least 2 y in the majority of adolescents after vaccination with a single dose of MenACWY-TT.

Adolescents are at high risk of invasive meningococcal disease because of environmental and social behaviors that results in close contact, such as dormitory living and night club attendance, that promote transmission and increased carriage of Neisseria meningitidis. Invasive meningococcal infection can be prevented through vaccination. Meningococcal polysaccharide vaccines have been available for several decades but their effectiveness is limited because they do not stimulate T-cell dependent immune responses; therefore protection is not long-lasting, immune memory does not develop and repeated administration may result in hyporesponsiveness. These limitations are avoided by meningococcal conjugate vaccines, which, through the coupling of a carrier protein to the meningococcal capsular polysaccharide, induce T-cell dependent responses with improved immunogenicity and development of immune memory. Three quadrivalent meningococcal conjugate vaccines are available for use in adolescents as a single dose: MenACWY-diphtheria toxoid (DT) conjugate vaccine (Menactra™, Sanofi Pasteur, Lyon, France), MenACWY-CRM197 (non-toxic mutant diphtheria toxin) conjugate vaccine (Menvax™, GSK Vaccines, Wavre, Belgium) and MenACWY-tetanus toxoid conjugate vaccine (MenACWY-TT: Nimenrix™, Pfizer, New York, USA). In addition, 2 new N. meningitidis serogroup B vaccines that target non-capsular proteins are licensed for use in adolescents: Bexsero™ (GSK Vaccines, 2-dose schedule), and Trumenba™ (Pfizer; 3-dose schedule).

MenACWY-TT vaccine is licensed for use as a single dose from 12 months of age in more than 50 countries, including the European Union, Australia, Canada, India and the Philippines. Clinical trials have demonstrated that one dose of MenACWY-TT is immunogenic and well tolerated in children as of 12 months of age, and in adolescents and in adults.

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Long-term protection against meningococcal disease is thought to rely on the presence of circulating antibodies. As yet, the duration of clinical protection following vaccination with meningococcal conjugate vaccines is not known and booster recommendations continue to evolve. Although 3 Men-ACWY conjugate vaccines are available for use as a single dose in adolescents, data from the United States (US) indicate that immunity begins to wane 3 to 5 years after immunization. In 2010, a booster dose of MenACWY conjugate vaccine was recommended in the US due to evidence of waning immunity and concerns about ongoing protection. Reporting on long-term persistence adds important information to the understanding of the kinetics of the antibody response to MenACWY-TT as compared to licensed quadrivalent meningococcal polysaccharide vaccines (Men-PS), and will assist in understanding whether booster doses are needed.

Here we report antibody persistence 2 years after vaccination of adolescents with MenACWY-TT or Men-PS (Mencevax™ ACWY, GSK Vaccines) (www.clinicaltrials.gov NCT00974363). A protocol summary is available at www.gsk-clinicalstudyregistry.com (study ID: 112148). We also report results of a re-analysis of clinical trial data from the original vaccination study (NCT00464815) which was performed after identification of deviations in Good Clinical Practice (GCP) procedures that occurred during the study conduct.

Healthy adolescents randomized to receive a single dose of MenACWY-TT or Men-PS in the previous vaccination study were invited to return for the evaluation of antibody persistence 2 years after vaccination (y 2), and yearly thereafter until y 5. Here we report persistence data until y 2, after which time the sBA assay used to test persistence samples was changed. Results from the 3 subsequent time points (y 3 to 5), which were generated with this different SBA assay, will be reported elsewhere. Subjects were not allowed to participate in the extension study if they had developed meningococcal disease or received any meningococcal vaccination since the primary vaccination study. The primary vaccination study was conducted in the Philippines, India and Taiwan. Based on the enrollment in the primary study, participation of the Indian and Filipino sites was deemed sufficient in terms of the sample size to be followed for antibody persistence. The persistence study was conducted from 08 September 2009 to 01 May 2010 and was open in design.

The studies were to be conducted in accordance with GCP and the Declaration of Helsinki. After publication of the initial vaccination study, GSK Vaccines became aware of deviations from GCP procedures that had occurred during the study conduct. The identified issues included the following: the assent form was not signed by some subjects at one Indian site, and documentation confirming the appropriate storage of serum samples was lacking at one Indian site. In total 55 participants (8.0%) were excluded from the According-to-protocol persistence cohort due to GCP deviations. These findings necessitated a re-analysis of the persistence data.

A single blood sample was collected at y 2 for the assessment of antibody persistence. Serum bactericidal activity antibody dilution titers against each polysaccharide (A, C, W and Y) were measured by a serum bactericidal activity assay using baby rabbit complement (rSBA). The cut-off of the assay was a 1:8 dilution. An antibody titer ≥1:8 is considered indicative of seroprotection for rSBA-MenC and was also applied to the other serogroups.

In addition, data were analyzed according to a more conservative estimate using a threshold of 1:128.

The primary study objective was to assess persistence in terms of percentage of subjects with rSBA titers ≥1:8 for each of the 4 serogroups at y 2. The secondary objective was to assess persistence in terms of rSBA geometric mean titers (GMTs) for each serogroup at y 2.

For each vaccine serogroup, an exploratory evaluation of the difference in the immune response at each time point was performed in terms of the percentage of subjects with rSBA antibody titers ≥1:8 and ≥1:128 (with standardized asymptotic 95% confidence intervals [CIs]) and the ratio of the GMTs (with 95% CIs) between the MenACWY-TT and Men-PS groups. A potential difference was indicated if the value ‘1’ was excluded from the 95% CI on the GMT ratios, or, if the value ‘0%’ was excluded from the 95% CI on differences in proportions of subjects above an antibody threshold between groups. Note that potential differences should be interpreted with caution considering that there was no adjustment for multiplicity for these comparisons and that potentially significant findings may have occurred by chance alone.

Serious adverse events considered by the investigator to be related to study procedures were captured retrospectively at the y 2 study visit. To comply with worldwide safety reporting requirements, all serious adverse events considered to be related to any GSK medicine were also recorded.

Statistical analyses were performed using SAS® software version 9.22 for Windows (SAS Institute Inc., Cary, NC, US).

The results of the updated immunogenicity analysis for the previously published study time points are included in this report (Table 1). The composition of the according-to-protocol cohort for the re-analysis is provided in Figure 1. The conclusions of the initial vaccination study were not impacted by the re-analysis: the statistical criteria for the non-inferiority of the vaccine response induced by the MenACWY-TT conjugate vaccine as compared to Men-PS 1 month after vaccination were met (Table 2).
Table 1. rSBA antibody persistence 1 month and 2 y after vaccination with MenACWY-TT or Men-PS at 11–17 y of age (According to protocol cohort as defined for each time point).

| Sero group | Time point | N | n | % ≥ 1:8 [95% CI] | n | % ≥ 1:128 [95% CI] | GMT [95% CI] |
|------------|------------|---|---|-----------------|---|-------------------|------------|
| A Pre°     |            | 557| 463| 83.1 [79.7; 86.1] | 427| 76.7 [72.9; 80.1] | 208.1 [176.4; 245.5] |
| M1°        |            | 674| 674| 100 [99.5; 100]  | 674| 100 [99.5; 100]  | 5928.5 [5557.4; 6324.3] |
| Y2         |            | 405| 404| 99.8 [98.6; 100] | 403| 99.5 [98.2; 99.9] | 1493.4 [1369.0; 1629.0] |
| C Pre°     |            | 648| 381| 58.8 [54.9; 62.6] | 277| 42.7 [38.9; 46.7] | 1137.5 [1006.1; 1286.0] |
| M1°        |            | 673| 673| 100 [99.5; 100]  | 672| 99.9 [99.2; 100]  | 13109.8 [11939.1; 14395.2] |
| Y2         |            | 407| 404| 99.3 [97.9; 99.8] | 396| 97.3 [95.2; 98.6] | 5246.6 [4738.8; 5793.4] |
| W Pre°     |            | 640| 519| 81.1 [77.8; 84.1] | 373| 58.3 [54.4; 62.1] | 109.4 [94.6; 126.6] |
| M1°        |            | 678| 677| 99.9 [99.2; 100] | 677| 99.9 [99.2; 100] | 8246.6 [7638.8; 8902.7] |
| Y2         |            | 407| 405| 99.5 [98.2; 99.9] | 403| 99.0 [97.5; 99.7] | 1977.6 [1775.0; 2203.4] |
| Y Pre°     |            | 659| 597| 90.6 [88.1; 92.7] | 538| 81.6 [78.5; 84.5] | 348.3 [303.5; 399.7] |
| M1°        |            | 677| 677| 100 [99.5; 100]  | 677| 100 [99.5; 100]  | 14086.5 [13168.0; 15069.0] |
| Y2         |            | 407| 407| 100 [99.1; 100]  | 407| 100 [99.1; 100]  | 3502.5 [3203.2; 3829.7] |

Pre = prior to vaccination at 11–17 y of age; M1 = 1 month after vaccination; Y2 = 2 y after vaccination; N = number of subjects with available results; n/\% = number/percentage of subjects with titer equal to or above specified value; 95% CI = 95% confidence interval; GMT = geometric mean antibody titer; rSBA = serum bactericidal activity against N. meningitidis using rabbit complement, performed at GSK Vaccines' laboratories; bold = statistically higher proportion of subjects reaching the indicated threshold, or higher GMT value (adjusted for pre-vaccination measurements and age strata for M1 results) in the indicated group (exploratory analysis). This table reports the results of the re-analysis of data after elimination of subjects due to GCP violations. Note: the discrepancy in the numbers of subjects in pre and post-vaccination samples is mainly due to a high number of 'invalid results' at pre-vaccination time point. A result was considered invalid when an irregular pattern of the killing curve was observed between 60% and 40% of killing. During this study, process changes in the testing laboratory meant that samples were automatically repeat-tested. However numerous invalid results occurred in the low range of titres affecting repeat tested pre-vaccination samples more than post-vaccination samples. As indicated in this table, the results provided at each time point are from the "According to protocol cohort as defined for each time point." N for Pre and M1 includes subjects from the ATP immunogenicity cohort from the vaccination study, and N for Y2 includes ATP persistence cohort subjects who returned at y 2. Fewer subjects returned for follow-up 2 y after the initial study, resulting a lower N at y 2.
Based on review of the source documents, 2 previously unreported unsolicited adverse events (non-serious episodes of grade 1 headache and grade 1 vertigo) that occurred in the 31-days follow-up after vaccination were identified in 2 subjects in India. GSK’s study database was updated to include these reports. No re-analysis of safety was conducted as neither event was considered by the investigator to be vaccine related and there would be no impact of these data on the study co-primary safety objective or on the Prescribing Information if they were considered as part of a re-analysis.

In the initial study on the safety and immunogenicity of MenACWY-TT in adolescents, 1025 subjects were enrolled in the Total vaccinated cohort (768 in the MenACWY-TT group and 257 in the Men-PS group). Among these, 689 subjects returned at y 2 (521 in the MenACWY-TT group and 168 in the Men-PS group). The median time since the primary vaccination dose was 25 months (range 22 –25 months). There were 150 subjects eliminated from the According-to-protocol persistence cohort (Fig. 1). The mean age of subjects (According-to-protocol persistence cohort) in each study group and overall was 16.4 y (range 13–20 y) and 53.4% of subjects were female.

Results from a post hoc analysis on the According-to-protocol persistence cohort showed that 2 y after primary vaccination, at least 99.26% of subjects in the MenACWY-TT group

| Serogroup | MenACWY-TT N | n | %VR [95% CI] | Men-PS N | n | %VR [95% CI] | Difference in %VR |
|-----------|---------------|---|-------------|----------|---|-------------|------------------|
| A         | 553           | 472 | 85.4[82.1; 88.2] | 191     | 148 | 77.5[70.9; 83.2] | 7.87[1.63; 14.87] |
| C         | 642           | 625 | 97.4[95.8; 98.5] | 211     | 204 | 96.7[93.3; 98.7] | 0.67[−1.65; 4.18] |
| W         | 639           | 616 | 96.4[94.6; 97.7] | 216     | 189 | 87.5[82.3; 91.6] | 8.90[4.78; 14.14] |
| Y         | 657           | 616 | 93.8[91.6; 95.5] | 219     | 172 | 78.5[72.5; 83.8] | 15.22[9.89; 21.37] |

ATP = According-to-Protocol
VR = vaccine response defined as:
For initially seronegative subjects: antibody titer ≥1:32 post-vaccination
For initially seropositive subjects: antibody titer post-vaccination that is ≥4-fold the pre-vaccination antibody titer
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of subjects with a vaccine response
95% CI = exact 95% confidence interval
*Lower limit of 95% CI was above pre-specified clinical non-inferiority limit of −10%
**statistically higher value in ACWY-TT group than in Men-PS group (exploratory analysis)
and at least 93.02% in the Men-PS group had persisting antibody titers \( \geq 1:8 \) for each vaccine serogroup, and hence were seroprotected to all 4 serogroups (Table S1). The percentage of subjects with titers \( \geq 1:128 \) for each vaccine serogroup was at least 96.79% in the MenACWY-TT group and at least 79.84% in the Men-PS group.

For each serogroup, rSBA GMTs were reduced by year 2 but remained higher than pre-vaccination levels (Table 1).

Exploratory analyses indicated that antibody persistence was higher in the MenACWY-TT group than in the Men-PS group in terms of the percentage of subjects with rSBA titers \( \geq 1:8 \) for serogroups W and Y, the percentage with rSBA titers \( \geq 1:128 \) for serogroups A, W and Y, and in terms of rSBA GMTs for serogroups A, W and Y (Table 1). The rSBA GMT for serogroup C was higher in the Men-PS group than the MenACWY-TT group at y 2. A similar trend was observed in another study of MenACWY-TT conducted in adolescents and adults,\(^{16,26} \) although the study was not designed or powered to detect differences in persistence so the data should be interpreted cautiously – particularly since there are other studies where the same trend has not been observed.\(^{27} \) Despite the lower GMT, seroprotection rates in both groups were similar in our study. Of note, some countries, such as the United States, now recommend a booster dose approximately 5 y after primary vaccination for those at continued increased risk for meningococcal disease.

No vaccine-related serious adverse events were reported from the end of the primary vaccination study until y 2.

Evaluation of antibody persistence in a large cohort of adolescents vaccinated with a single dose of quadrivalent MenACWY-TT showed that vaccine serogroup-specific antibodies persist in almost all subjects until y 2 after vaccination. Exploratory analyses conducted after the primary vaccination dose indicated that the post-vaccination rSBA GMTs, adjusted for pre-vaccination measurements and age strata, were higher for all serogroups in the MenACWY-TT group compared to the Men-PS group (Table 2). Consistent with these results, antibody GMTs at y 2 were observed to be higher in the MenACWY-TT group than the Men-PS group in an exploratory analysis, for 3 out of 4 serogroups (A, W and Y).

The results of our study using the GSK rSBA are in-line with other studies of MenACWY-TT persistence in adolescents and children that employed the same assay.\(^{16,27,28,26} \) Antibody persistence in the majority of MenACWY-TT recipients up until 42 months after vaccination of adolescents with MenACWY-TT has been demonstrated, with persisting antibody levels \( \geq 1:8 \) that were similar or higher than after vaccination with licensed Men-PS vaccine.\(^{27} \)

While limited comparisons can be made with other studies using different rSBA assays, our results suggest that antibody persistence after a single dose of MenACWY-TT in adolescents is at least as good as that of other licensed MenACWY conjugate vaccines after 2 y follow-up.\(^{29} \) Two y after vaccination of 11–18 y olds with Menactra\(^{TM} \) or Menvio\(^{TM} \), the percentage of adolescents with rSBA \( \geq 1:8 \) for each vaccine serogroup was 25%–74% and 36%–84%, respectively.\(^{29} \) In a study of antibody persistence 3 y after vaccination with Menactra\(^{TM} \), the percentage of adolescents with rSBA \( \geq 1:128 \) for serogroup C, W and Y was 75%–89%.\(^{30} \)

In conclusion, 2 y after vaccination with MenACWY-TT, the majority of subjects retained rSBA titers \( \geq 1:8 \) for all vaccine serogroups, indicating that immunogenicity following a single dose in adolescents persists for at least 2 y.

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**Abbreviations**

CI confidence interval  
GCP Good Clinical Practice guidelines  
GMT geometric mean antibody titer  
MenACWY-TT quadrivalent meningococcal serogroups A, C, W and Y vaccine conjugated to tetanus toxoid  
Men-PS Quadrivalent meningococcal serogroups A, C, W and Y polysaccharide vaccine  
rSBA serum bactericidal assay using rabbit complement 
TT tetanus toxoid

**Disclosure of potential conflicts of interest**

BPQ declares personal consulting fees, support for meetings, travel or accommodation expenses for the study from GSK group of companies; BPQ reports also personal consulting fees from Sanofi Pasteur for speaker’s bureau.

APD and AB declare personal support for traveling to investigator meetings from GSK group of companies; AB declares personal support for congress, travel or accommodation expenses from GSK group of companies.

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DK, VB, MVdW and JMM are employees of GSK group of companies. MVdW and JMM declare stock ownership in GSK group of companies.

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Authors’ contributions

BPQ, APD, AB and HJ were investigators involved in the supervision of the study, administrative, logistic and technical supports, the recruitment and the medical evaluation of subjects, the evaluation of any reported AEs/SAEs for severity and causality, the collection and interpretation of the data, and the drafting and approval of the manuscript. JMM, MVW (clinical development scientists) and VB (biostatistician) were involved in all stages of the study (study design, data analyses and interpretations, drafting and approval of the manuscript). DK (biostatistician) was involved in re-analysis of the data excluding all subjects with improper consent, data interpretation, drafting and approval of the manuscript.

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