Safety and Immunogenicity of the Quadrivalent Meningococcal Serogroups A, C, W and Y Tetanus Toxoid Conjugate Vaccine Coadministered With Routine Childhood Vaccines in European Infants

An Open, Randomized Trial

Jose Manuel Merino Arribas, MD, Alfonso Carmona Martínez, MD,† Michael Horn, MD,‡ Xavier Maria Perez Porcuna, MD,§ Maria del Carmen Otero Reigada, MD,¶ Josep Marès Bermúdez, MD,‖ Fernando Centeno Malfaz, MD,** Mariano Miranda, MD,†† Maria Mendez, MD,‡‡ Miguel Angel Garcia Cabezas, MD, PhD,§§ Christoph Wittermann, MD,¶¶ Gerhard Bleckmann, MD,‖‖ Thomas Fischbach, MD,*** Devayani Kolhe, MSc,††† Marie van der Wielen, MD,‡‡‡ and Yaela Baine, PhD§§§*

Background: This was the first study evaluating the immunogenicity and safety of the quadrivalent meningococcal tetanus toxoid conjugate vaccine (MenACWY-TT) coadministered with routine childhood vaccines in young infants.

Methods: In this open, randomized, controlled, phase III study (NCT01144663), 2095 infants (ages 6–12 weeks) were randomized (1:1:1:1) into 4 groups to receive MenACWY-TT at 2, 3, 4 and 12 months of age, or MenACWY-TT, MenC-cross-reactive material (CRM_{197}) or MenC-TT at 2, 4 and 12 months of age. All participants received PHiD-CV and DTPa-HBV-IPV/Hib at 2, 3, 4 and 12 months of age. Immune responses were measured by serum bactericidal activity assays using rabbit (rSBA) and human (hSBA) complement. Solicited and unsolicited symptoms were recorded during 8 and 31 days post-vaccination, respectively, and serious adverse events throughout the study.

Results: Noninferiority of immune responses to MenC induced by 2 or 3 doses of MenACWY-TT versus 2 doses of MenC-TT or MenC-CRM_{197} was demonstrated. Predefined criteria for the immunogenicity of MenACWY-TT to MenA, MenW and MenY were met. One month after 2 or 3 primary MenACWY-TT doses, ≥93.1% and ≥88.5% of infants had rSBA and hSBA titers ≥1:8 for all serogroups. The robust increases in rSBA and hSBA titers observed for all vaccine serogroups postbooster vaccination suggested that MenACWY-TT induced immune memory. MenACWY-TT coadministered with childhood vaccines had a clinically acceptable safety profile.

Conclusions: This study supports the coadministration of MenACWY-TT with routine childhood vaccines as 2 or 3 primary doses during infancy followed by a booster dose in the second year of life.

Key Words: quadrivalent meningococcal conjugate vaccine, coadministration, bactericidal activity, booster, infant

(*Pediatr Infect Dis J* 2017;36:e98–e107)

Infants and toddlers bear the highest burden of invasive meningococcal disease,[1,2] which, although rare, is a severe and life-threatening disease with lasting sequelae. In Europe, in the year 2011, the invasive meningococcal disease notification rate was 0.77 per 100,000 population, with an 8.7% fatality rate among the general population.[3] Meningococcal serogroups B and C (MenB and MenC) are the most common serogroups in this part of the world, but recent European data have indicated an increased incidence of disease caused by serogroups Y (MenY)[2,4] and W (MenW).[5] Although diseases caused by serogroups A (MenA) and W (MenW) are still less common in European countries, these serogroups are

Accepted for publication September 12, 2016.

From the *Pediatrics Department, Hospital Universitario de Burgos, Avenida Islas Baleares, Burgos, Spain; †Instituto Hispalense de Pediatria, C/Jardin de la Isla Nº 6, Edificio Expolocal, Sevilla, Spain; ‡Pediatric Office Dr. Horn, Schoenau, Germany; §Manlleu Primary Care Center, Osona, Spain; ¶Pediatrics Department, Hospital La Fe, Valencia, Spain; ‖Institut Pediàtric Marès – Riera, Pediatría, Blanes, Spain; **Pediatrics Department, Rio Hortega University Hospital, Valladolid, Spain; ††Pediatrics Department, Hospital de Antequera, Antequera, Spain; ‡‡Hospital Universitari Germans Trias i Pujol, Badalona, Spain; §§Hospital General Universitario de Ciudad Real, Ciudad Real, Spain; ¶¶Study Center Weilheim, Pediatric Practice Weilheim, Weilheim in Oberbayern, Germany; ‖‖Private Practice Bleckmann, Baunatal, Germany; ***Private Practice Fischbach, North-Rhine, Solingen, Germany; †††GSK Pharmaceuticals, Bangalore, India; ‡‡‡GSK Vaccines, Vaccine Development and Discovery Department, Wavre, Belgium; and §§§GSK Vaccines, Merion, Pennsylvania.

NIMENRIX, SYNFLORIX, INFANRIX HEXA, MENJUGATE and MENVEO are trademarks of the GSK Group of Companies. NEISVAC-C is a registered trademark of Pfizer. NIMENRIX trademark has been licensed to Pfizer.

GlaxoSmithKline Biologicals SA was the funding source and was involved in all stages of the study conduct and analysis. GlaxoSmithKline Biologicals SA also funded all costs associated with the development and the publishing of the present manuscript. A.C.M. declares financial support from "Fundación Médica Alfonso Carmona." J.M.M.A. received fees for consulting, lectures and expert testimony from the GSK group of companies. X.M.P.P. was a speaker, researcher and consultant for the GSK group of companies. J.M.B. serves on the Board of Sanofi Pasteur MSD and has received fees from Sanofi Pasteur MSD (for lectures including service on speakers bureaus), from the GSK group of companies (for lectures including service on speakers bureaus and as a principal investigator in clinical trials), from Pfizer (as a principal investigator in clinical trials, for lectures including service on speakers bureaus). M.H. received consulting fees from the GSK group of companies and Novartis; support for travel to meetings for the study from the GSK group of companies; payment for board membership from Novartis; payment for lectures including service on speakers bureaus, development of educational presentations, and travel, accommodation and meeting expenses from the GSK group of companies, Sanofi Pasteur MSD and Novartis. D.K. and M.W. are employees of the GSK group of companies. Y.B. was an employee of the GSK group of companies at the time of the study. Y.B. and M.W. declared stock ownership in the GSK group of companies. The other authors have no conflicts of interest to disclose.

Address for correspondence: Yaela Baine, PhD, GSK Vaccines, 216 Edgehill Road, 19066, Merion, PA. E-mail: yaela28c@gmail.com.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.pidj.com).

ISSN: 0891-3668/17/3604-0e98
DOI: 10.1097/INF.0000000000001484

responsible for outbreaks in other parts of the world and may be imported by global travelers.[2,6]

Administration of effective meningococcal vaccines to infants and young children could reduce the burden of invasive meningococcal disease. Since 1999, monovalent conjugate vaccines against MenC have been introduced in the immunization program of most European countries and have contributed to reducing the incidence of meningococcal disease caused by this serogroup.[2] In addition, 2 quadrivalent meningococcal conjugate vaccines are currently licensed in Europe: the MenACWY-CRM_{197} vaccine (*Menveo*, GSK Vaccines, Wavre, Belgium) for use in children from 2 years of age, and the MenACWY-TT vaccine (*Nimenrix*, Pfizer, New York, NY) for children from 1 year of age. Previous studies have shown that MenACWY-TT is immunogenic and well tolerated in toddlers, children, adolescents, and adults.[7–17] Although no quadrivalent meningococcal conjugate vaccine is currently available for infants in Europe, 2 quadrivalent vaccines are recommended in the United States for children as of 2 months (MenACWY-$CRM_{197,}$ *Menveo*, GSK Vaccines) or 9 months (MenACWY-DT, *Menactra*, Sanofi Pasteur, Lyon, France) of age who are at increased risk for meningococcal disease.[18]

This is the first study evaluating the immune response and safety of MenACWY-TT in young infants. MenACWY-TT was coadministered with routine childhood vaccines as 2 or 3 primary doses during infancy followed by a booster dose in the second year of life, and was compared with licensed monovalent MenC vaccines. Because the comparator monovalent MenC vaccines are administered on a 2-dose primary schedule,[19,20] but other licensed quadrivalent meningococcal conjugate vaccines are administered on a 3-dose schedule in this age group,[21] both 2- and 3-dose primary schedules of MenACWY-TT vaccine were investigated in this study.

MATERIALS AND METHODS

Study Design and Participants

This phase III, open, randomized, controlled study was conducted between July 1, 2010 and September 10, 2013 in 44 centers in Estonia, Germany and Spain. Infants were randomized (1:1:1:1) into 4 groups to receive MenACWY-TT as 3 primary doses at 2, 3 and 4 months of age followed by a booster dose at 12 months of age (ACWY-TT_3 group); MenACWY-TT as 2 primary doses at 2 and 4 months of age followed by a booster dose at 12 months of age (ACWY-TT_2 group); MenC-CRM_{197} as 2 primary doses at 2 and 4 months of age followed by a booster dose at 12 months of age (MenC-CRM_{197} group); or MenC-TT as 2 primary doses at 2 and 4 months of age followed by a booster dose at 12 months of age (MenC-TT group). In addition, all participants received the 10-valent pneumococcal nontypeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV; *Synflorix*, GSK Vaccines), and the combined diphtheria-tetanus-acellular pertussis-hepatitis B, inactivated poliomyelitis and *H. influenzae* type b vaccine (DTPa-HBV-IPV/Hib; *Infanrix hexa*, GSK Vaccines) at 2, 3, 4 and 12 months of age.

A randomization list was used to number the vaccines. The treatment allocation was performed using a central, web-based randomization system, which included a minimization procedure to ensure balanced allocation between groups at individual centers.

Participants were healthy infants between 6 and 12 weeks of age at the time of first vaccination, who were born after at least 36 weeks of gestation. Participants were excluded if they were children in care, were immunosuppressed from any cause, had used any investigational product, had planned administration of a vaccine not foreseen by the protocol between 30 days before the first vaccine dose and 30 days after the last vaccine dose (with the exception of rotavirus vaccine), had history of any reaction or hypersensitivity likely to be exacerbated by any vaccine component, had major congenital defects or a serious chronic illness, had history of any neurologic disorders or seizures, had an acute disease at the time of enrollment, or had received immunoglobulins or other blood products since birth. Participants with a history of disease due to *Neisseria meningitidis*, *Streptococcus pneumoniae*, *H. influenzae* type b, diphtheria, tetanus, pertussis, hepatitis B or poliovirus, or a history of vaccination against any of these diseases performed outside of the study (with the exception of vaccines given within the first 2 weeks of life according to the national recommendations) were also excluded. A measles outbreak impacted 2 study centers in Spain, and local authorities recommended vaccination of individuals from 9 months old onwards against measles. In line with these recommendations, the protocol was amended to allow administration of measles, mumps and rubella, or measles, mumps, rubella and varicella combined vaccines throughout the study.

One 0.5 mL dose of MenACWY-TT contained 5 µg of each meningococcal serogroup polysaccharide conjugated to tetanus toxoid (approximately 44 µg in total). The licensed MenC-CRM_{197} vaccine (*Menjugate*, GSK Vaccines) contained 10 µg of MenC polysaccharide conjugated to CRM_{197} (12.5–25 µg) adsorbed onto aluminum hydroxide (0.3–0.4 mg), and the licensed MenC-TT vaccine (*NeisVac-C*, Pfizer) contained 10 µg of MenC capsular polysaccharide conjugated to 10–20 µg of tetanus toxoid and 500 µg of aluminum hydroxide. The composition of the coadministered vaccines has been previously described.[22,23] MenACWY-TT, MenC-CRM_{197} and MenC-TT were administered intramuscularly into the left anterolateral thigh, PHiD-CV into the upper right anterolateral thigh, and DTPa-HBV-IPV/Hib into the lower right anterolateral thigh.

The study protocol and all study documents were approved by Ethics Committees for each center. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from each participant's parent/guardian before enrollment. This study is registered at www.clinicaltrials.gov NCT01144663. A summary of the protocol is available at http://www.gsk-clinicalstudyregister.com (study ID 113369).

Study Objectives

The following coprimary objectives were based on the rSBA assay results obtained 1 month after completion of the primary vaccination and were evaluated in a hierarchical manner, meaning that a coprimary objective could only be met if the statistical criteria for the objective was met as well as the statistical criteria for all previous coprimary objectives: (1) to demonstrate the noninferiority of the immunogenicity to MenC of 3 MenACWY-TT doses versus 2 MenC-CRM_{197} doses; (2) to demonstrate the noninferiority of the immunogenicity to MenC of 3 MenACWY-TT doses versus 2 MenC-TT doses; (3) to demonstrate the immunogenicity to MenA, MenW and MenY of 3 MenACWY-TT doses; (4) to demonstrate the noninferiority of the immunogenicity to MenC of 2 MenACWY-TT doses versus 2 MenC-CRM_{197} doses; (5) to demonstrate the noninferiority of the immunogenicity to MenC of 2 MenACWY-TT doses versus 2 MenC-TT doses and (6) to demonstrate the immunogenicity to MenA, MenW and MenY of 2 MenACWY-TT doses. The corresponding primary endpoints were described according to the predefined statistical criteria summarized in Table 1.

TABLE 1. Results of the Inferential Analysis for Meningococcal Antigens (Coprimary Objectives: ATP Immunogenicity Cohort)

Coprimary Objective*	Endpoint	Criteria	Serogroup	(*P* Value [95% CI])	Criterion Met?
Noninferiority of 3 MenACWY-TT doses vs 2 MenC-CRM_{197} doses	% of participants with rSBA titers ≥1:8	LL of 2-sided 95% CI for difference (ACWY-TT_3 minus MenC-CRM_{197}) is greater than or equal to −5%	C	(0.01 [**−1.17** to 1.20])	Yes
Noninferiority of 3 MenACWY-TT doses vs 2 MenC-TT doses	% of participants with rSBA titers ≥1:8	LL of 2-sided 95% CI for difference (ACWY-TT_3 minus MenC-TT) is greater than or equal to −5%	C	(−0.43 [**−1.57** to 0.40])	Yes
Immunogenicity of 3 MenACWY-TT doses	% of participants with rSBA titers ≥1:8	LL of 2-sided 95% CI (ACWY-TT_3) is greater than or equal to 80%	A W Y	(99.4 [**98.1**–99.9]) (99.1 [**97.8**–99.8]) (93.1 [**90.3**–95.2])	Yes Yes Yes
Noninferiority of 2 MenACWY-TT doses vs 2 MenC-CRM_{197} doses	% of participants with rSBA titers ≥1:8	LL of 2-sided 95% CI for difference (ACWY-TT_2 minus MenC-CRM_{197}) is greater than or equal to −5%	C	(−0.88 [**−2.45** to 0.43])	Yes
Noninferiority of 2 MenACWY-TT doses vs 2 MenC-TT doses	% of participants with rSBA titers ≥1:8	LL of 2-sided 95% CI for difference (ACWY-TT_2 minus MenC-TT) is greater than or equal to −5%	C	(−1.32 [**−2.84** to −0.48])	Yes
Immunogenicity of 2 MenACWY-TT doses	% of participants with rSBA titers ≥1:8	LL of 2-sided 95% CI (ACWY-TT_2) is greater than or equal to 80%	A W Y	(97.4 [**95.4**–98.6]) (99.1 [**97.8**–99.8]) (98.2 [**96.6**–99.2])	Yes Yes Yes

*The coprimary objectives were concluded in a hierarchical manner.

95% CI indicates 95 percent confidence interval; ACWY-TT_3, participants who received 4 doses of MenACWY-TT at 2, 3, 4 and 12 mo of age; ACWY-TT_2, participants who received 3 doses of MenACWY-TT at 2, 4 and 12 mo of age; ATP, according-to-protocol; LL, lower limit of the 95% CI; MenC-CRM_{197}, participants who received 3 doses of MenC-CRM_{197} at 2, 4 and 12 mo of age; MenC-TT, participants who received 3 doses of MenC-TT at 2, 4 and 12 mo of age.

Based on bold values, it was confirmed whether criterion were met or not.

Secondary objectives included the evaluation of (1) the immunogenicity of the study vaccines (2- and 3-dose priming with MenACWY-TT) at all time-points in terms of rabbit-complement based serum bactericidal assay (rSBA) titers for the 4 serogroups in all participants (except for the prevaccination time-point, when rSBA titers for the 4 serogroups were evaluated in a randomized subset of 50% of infants in the study groups, rSBA titers for MenC in a randomized subset of 50% of infants in the control groups, and rSBA titers for MenA, MenW and MenY in a randomized subset of 25% of participants in the control groups); (2) the immunogenicity of the study vaccines at all time-points in terms of human complement-based serum bactericidal assay (hSBA) titers for the 4 serogroups in a randomized subset of 50% of participants and (3) the safety and reactogenicity of the study vaccines.

The objectives and endpoints related to the immunogenicity of the coadministered vaccines will be reported elsewhere.

Immunogenicity Assessments

Blood samples were collected preprimary vaccination, 1 month postprimary vaccination, prebooster vaccination and 1 month postbooster vaccination.

Functional antibody titers for each serogroup were determined by an rSBA assay (cut-off titer, 1:4) performed at the Public Health England laboratories, and were expressed as the reciprocal of the dilution resulting in 50% killing. An rSBA titer ≥1:8 has been associated with seroprotection against MenC and was extended to the other serogroups.[24–26] The percentage of participants with rSBA titers ≥1:128, the more conservative seroprotection threshold, was also evaluated.[25,26]

Functional antibody responses were also determined by an hSBA assay performed at the GSK Vaccines laboratory.[27] hSBA-MenC titers ≥1:4 correlate with protection,[28] and this threshold was extended to the other serogroups. The more conservative threshold of hSBA titers ≥1:8 was also evaluated.

Safety Assessments

Solicited local reactions (pain, redness and swelling at injection site) or general symptoms (drowsiness, fever, irritability/fussiness and loss of appetite) were recorded by parents on diary cards during an 8-day follow-up period (days 0–7) after each vaccination. Unsolicited adverse events (AEs) were recorded during a 31-day follow-up period (days 0–30) after each vaccination. The intensity of each symptom was graded on a 3-grade scale: pain at the injection site was considered to have a grade 3 intensity if the limb was spontaneously painful or if the child cried when it was moved, redness and swelling at the injection site had a grade 3 intensity if the diameter was >30 mm, fever was rated grade 3 if rectal temperature was >40.0°C and a grade 3 loss of appetite was reported if the child did not eat at all. All other AEs were considered of grade 3 intensity if they prevented normal activity.

The occurrence of serious AEs (SAEs) or new onset of chronic illnesses (eg, autoimmune disorders, asthma, type 1 diabetes and allergies) was recorded from the first vaccine dose through 6 months after the booster vaccination.

Statistical Analyses

With a sample size of 1650 participants evaluable for immunogenicity, the global power to meet all coprimary objectives was ≥82.3%. Assuming that up to 20% of the enrolled participants might be excluded from the according-to-protocol (ATP) cohort for immunogenicity, 2060 participants were planned to be enrolled.

The analysis of safety was performed on the primary and booster total vaccinated cohorts (TVC), which included all participants

who received ≥1 vaccine dose in the respective phases of the study. The analysis of immunogenicity was performed on the primary and booster ATP cohorts for immunogenicity, which included all eligible participants from the corresponding TVCs who met all inclusion criteria and no exclusion criteria, had not received prohibited medications or vaccinations, had no intercurrent medical condition that could have influenced immune responses, complied with the vaccination schedule, and had a blood sample taken 21–48 days after the last primary dose and the booster dose administration, respectively.

Geometric mean titers (GMTs) were calculated by taking the antilog of the mean of the $\log_{10}$ titer transformations. Antibody titers below the assay cut-off were given an arbitrary value of half the cut-off for the purpose of GMT calculations. Percentage of participants with antibody titers above the proposed cut-offs and GMTs were tabulated with 95% confidence intervals (CIs).

Noninferiority of the immunogenicity to MenC of 2 or 3 doses of MenACWY-TT as compared with 2 doses of MenC-CRM_{197} or MenC-TT was to be demonstrated if the lower limit of the asymptotic standardized 95% CI for the difference between groups (ACWY-TT_3 minus MenC-CRM_{197} group; ACWY-TT_3 minus MenC-TT group; ACWY-TT_2 minus MenC-CRM_{197} group and ACWY-TT_2 minus MenC-TT group) in the percentage of participants with rSBA-MenC titers ≥1:8 was greater than or equal to −5% at 1 month postprimary vaccination. The immunogenicity of 2 or 3 doses of MenACWY-TT was to be demonstrated if the lower limit of the 95% CI for the percentage of participants with rSBA-MenA, MenW and MenY titers ≥1:8 was ≥80% at 1 month postprimary vaccination.

Exploratory comparative analyses between groups were also performed for the primary and booster vaccinations. In terms of percentage of participants with antibody titers above a specified cut-off, 2 groups were considered potentially different if the asymptotic standardized 95% CI for the difference in rates between the 2 groups did not contain the value 0. In terms of GMTs, 2 groups were considered potentially different if the 95% CI for the GMT ratio between the 2 groups did not contain the value 1. Because 95% CIs were not adjusted for the multiplicity of endpoints and did not account for clinically relevant differences, these findings have to be interpreted with caution.

The incidence and intensity of solicited local and general symptoms were calculated with exact 95% CIs for each group.

The analyses were performed using the Statistical Analysis System (SAS) software (SAS Institute Inc., Cary, NC).

RESULTS

Demographics

A total of 2095 infants were enrolled in the study and included in the primary TVC; 1559 from Spain, 502 from Germany and 34 from Estonia. Of these, 2017 toddlers received the booster dose of vaccine and were included in the booster TVC. The reasons for withdrawals and exclusions from the primary and booster ATP cohorts for immunogenicity are presented in (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/C644). Five infants withdrew during the primary phase because they had experienced AEs or SAEs (3 in the ACWY-TT_3 group, 1 in the MenC-CRM_{197} group and 1 in the MenC-TT group). None of these AEs or SAEs were considered potentially related to vaccination by the investigator. No withdrawal due to AEs or SAEs was reported in the booster phase.

The 4 study groups were comparable in terms of demographic characteristics in the primary TVC (Table, Supplemental Digital Content 2, http://links.lww.com/INF/C645). In addition, the demographic profile of the toddlers in the booster TVC was consistent with the primary TVC (data not shown).

Immunogenicity of Two or Three Primary Doses of MenACWY-TT

The coprimary objectives in terms of percentage of infants with rSBA titers ≥1:8 at 1 month postprimary vaccination were evaluated in a hierarchical manner (Table 1). All the primary confirmatory objectives were met: the noninferiority of the immune response to MenC induced by 2 or 3 primary doses of MenACWY-TT as compared with 2 primary doses of MenC-CRM_{197} or MenC-TT was demonstrated, and the immunogenicity of 2 or 3 primary doses of MenACWY-TT was also demonstrated for MenA, MenW and MenY.

One month postprimary vaccination, the percentage of infants with rSBA titers ≥1:8 ranged from 93.1% (rSBA-MenY) to 99.6% (rSBA-MenC) in the ACWY-TT_3 group, and from 97.4% (rSBA-MenA) to 99.1% (rSBA-MenW) in the ACWY-TT_2 group (Table 2). For each serogroup, rSBA GMTs in the ACWY-TT_3 and ACWY-TT_2 groups were at least 49-fold higher at 1 month postprimary vaccination compared with prevaccination. At least 98.7% and 92.2% of infants in all groups had rSBA-MenC titers ≥1:8 and ≥1:128, respectively.

For rSBA-MenC, exploratory analyses suggested that the percentage of infants with titers above cut-offs tended to be higher in the MenC-TT compared with the ACWY-TT_2 group at both the ≥1:8 and ≥1:128 thresholds. The same was recorded in the MenC-TT and MenC-CRM_{197} groups compared with the ACWY-TT_3 group at the ≥1:128 threshold. Exploratory analyses also suggested that rSBA-MenC GMTs tended to be higher in the MenC-CRM_{197} and MenC-TT groups compared with the ACWY-TT_2 and ACWY-TT_3 groups (data not shown).

For each serogroup, the percentage of infants with hSBA titers ≥1:8 at 1 month postprimary vaccination ranged from 88.5% (hSBA-MenY) to 99.5% (hSBA-MenC) in the ACWY-TT_3 group, and from 96.5% (hSBA-MenA) to 100% (hSBA-MenW) in the ACWY-TT_2 group (Table 3). For each serogroup, hSBA GMTs in the ACWY-TT_3 and ACWY-TT_2 groups were at least 8-fold higher at 1 month postprimary vaccination compared with prevaccination. At least 98.6% of infants had hSBA-MenC titers ≥1:8 in all groups.

Persistence of Bactericidal Antibodies and Immunogenicity of Booster Doses

Before administration of the booster dose, ≥68.5% of toddlers in the ACWY-TT_3 group and ≥61.3% of toddlers in the ACWY-TT_2 group retained rSBA titers ≥1:8 for each of the 4 vaccine serogroups (Table 2). For rSBA-MenC, 73.5%, 75.8%, 51.9% and 78.9% of toddlers retained titers ≥1:8 in the ACWY-TT_3, ACWY-TT_2, MenC-CRM_{197} and MenC-TT groups, respectively.

Before administration of the booster dose, 73.1% of toddlers in the ACWY-TT_3 group and 58.3% of toddlers in the ACWY-TT_2 group had hSBA-MenA titers ≥1:8, while ≥91.1% of toddlers in both groups had hSBA titers ≥1:8 for the remaining vaccine-serogroups (Table 3). In the MenC-CRM_{197} and MenC-TT groups, 86.5% and 96.6% of toddlers retained hSBA-MenC titers ≥1:8, respectively.

One month postbooster, ≥99.1% of toddlers in the ACWY-TT_3 group and ≥99.4% of toddlers in the ACWY-TT_2 group had rSBA titers ≥1:8 for each serogroup. In both groups, the booster dose of MenACWY-TT induced a robust increase in rSBA GMTs (from 17.8- to 80.1-times). At least 98.4% and 95.5% of toddlers in each group had rSBAMenC titers ≥1:8 and ≥1:128, respectively. When compared with prebooster values, postbooster rSBA-MenC GMTs were 44.9- (ACWY-TT_3), 26.9- (ACWY-TT_2), 65.7- (MenC-CRM_{197}) and 39.8-fold (MenC-TT) higher.

For rSBA-MenC, exploratory analyses at 1 month postbooster suggested that the percentage of toddlers with titers above cut-offs tended to be higher in the ACWY-TT_2 group compared with the MenC-CRM_{197} group at both the ≥1:8 and ≥1:128

TABLE 2. Percentage of Participants With rSBA Antibody Titers ≥1:8 and ≥1:128 and Geometric Mean Titers Prevaccination and One Mo Postprimary Vaccination (Primary ATP Cohort for Immunogenicity) and Prebooster and One Mo Postbooster Vaccination (Booster ATP Cohort for Immunogenicity

			ACWY-TT_3		ACWY-TT_2		MenC-CRM$_{197}$		MenC-TT	
Antibody	Estimate	Timing	N	Value (95% CI)	N	Value (95% CI)	N	Value (95% CI)	N	Value (95% CI)
MenA	% ≥1:8	Pre	223	0.9 (0.1–3.2)	219	1.8 (0.5–4.6)	97	2.1 (0.3–7.3)	110	1.8 (0.2–6.4)
		Postprimary	462	99.4 (98.1–99.9)	456	97.4 (95.4–98.6)	455	1.3 (0.5–2.8)	457	0.7 (0.1–1.9)
		Prebooster	438	68.5 (63.9–72.8)	455	61.3 (56.7–65.8)	436	6.0 (3.9–8.6)	453	5.1 (3.2–7.5)
		Postbooster	439	99.5 (98.4–99.9)	462	99.6 (98.4–99.9)	446	4.7 (2.9–7.1)	458	4.1 (2.5–6.4)
	% ≥1:128	Pre	223	0.4 (0.0–2.5)	219	0.0 (0.0–1.7)	97	0.0 (0.0–3.7)	110	0.0 (0.0–3.3)
		Postprimary	462	87.0 (83.6–89.9)	456	82.0 (78.2–85.4)	455	0.7 (0.1–1.9)	457	0.2 (0.0–1.2)
		Prebooster	438	24.4 (20.5–28.7)	455	21.8 (18.1–25.8)	436	2.5 (1.3–4.5)	453	0.7 (0.1–1.9)
		Postbooster	439	98.6 (97.0–99.5)	462	98.7 (97.2–99.5)	446	1.8 (0.8–3.5)	458	2.6 (1.4–4.5)
	GMT	Pre	223	4.1 (4.0–4.2)	219	4.1 (4.0–4.2)	97	4.1 (4.0–4.3)	110	4.1 (3.9–4.3)
		Postprimary	462	250.7 (228.6–274.8)	456	203.5 (182.0–227.5)	455	4.1 (4.0–4.3)	457	4.1 (4.0–4.2)
		Prebooster	438	22.9 (19.8–26.5)	455	19.5 (16.8–22.6)	436	4.7 (4.3–5.0)	453	4.4 (4.2–4.6)
		Postbooster	439	1417.6 (1281.4–1568.3)	462	1561.0 (1412.3–1725.3)	446	4.6 (4.3–4.9)	458	4.7 (4.3–5.0)
MenC	% ≥1:8	Pre	223	5.4 (2.8–9.2)	220	4.5 (2.2–8.2)	207	7.2 (4.1–11.7)	220	6.4 (3.5–10.4)
		Postprimary	461	99.6 (98.4–99.9)	456	98.7 (97.2–99.5)	455	99.6 (98.4–99.9)	457	100 (99.2–100)
		Prebooster	441	73.5 (69.1–77.5)	459	75.8 (71.6–79.7)	441	51.9 (47.2–56.7)	451	78.9 (74.9–82.6)
		Postbooster	439	99.5 (98.4–99.9)	463	99.8 (98.8–100)	446	98.4 (96.8–99.4)	459	100 (99.2–100)
	% ≥1:128	Pre	223	0.9 (0.1–3.2)	220	0.5 (0.0–2.5)	207	2.9 (1.1–6.2)	220	2.3 (0.7–5.2)
		Postprimary	461	92.2 (89.4–94.5)	456	93.9 (91.2–95.9)	455	96.0 (93.8–97.6)	457	99.8 (98.8–100)
		Prebooster	441	24.5 (20.5–28.8)	459	39.9 (35.4–44.5)	441	17.9 (14.4–21.8)	451	43.2 (38.6–48.0)
		Postbooster	439	98.4 (96.7–99.4)	463	98.1 (96.3–99.1)	446	95.5 993.2–97.2)	459	99.6 (98.4–99.9)
	GMT	Pre	223	4.4 (4.1–4.8)	220	4.3 (4.1–4.5)	207	4.9 (4.4–5.5)	220	4.7 (4.3–5.2)
		Postprimary	461	397.7 (358.5–441.2)	456	611.7 (539.9–692.9)	455	957.6 (850.2–1078.6)	457	1188.1 (1080.4–1306.6)
		Prebooster	441	25.7 (22.3–29.6)	459	43.7 (37.4–51.1)	441	16.0 (13.8–18.5)	451	49.3 (42.1–57.7)
		Postbooster	439	1154.6 (1034.1–1289.0)	463	1177.0 (1059.1–1308.0)	446	1051.4 (919.6–1202.1)	459	1960.2 (1776.4–2163.1)
MenW	% ≥1:8	Pre	215	3.7 (1.6–7.2)	217	5.5 (2.9–9.5)	110	4.5 (1.5–10.3)	107	2.8 (0.6–8.0)
		Postprimary	461	99.1 (97.8–99.8)	455	99.1 (97.8–99.8)	453	2.0 (0.9–3.7)	455	1.8 (0.8–3.4)
		Prebooster	441	84.4 (80.6–87.6)	459	90.8 (87.8–93.3)	440	4.1 (2.4–6.4)	453	6.0 (4.0–8.6)
		Postbooster	437	99.1 (97.7–99.8)	462	99.8 (98.8–100)	445	7.6 (5.3–10.5)	459	8.1 (5.7–10.9)
	% ≥1:128	Pre	215	0.0 (0.0–1.7)	217	0.5 (0.0–2.5)	110	0.9 (0.0–5.0)	107	0.9 (0.0–5.1)
		Postprimary	461	94.1 (91.6–96.1)	455	95.6 (93.3–97.3)	453	1.8 (0.8–3.4)	455	0.9 (0.2–2.2)
		Prebooster	441	50.1 (45.3–54.9)	459	55.3 (50.7–59.9)	440	3.6 (2.1–5.8)	453	4.9 (3.1–7.3)
		Postbooster	437	98.4 (96.7–99.4)	462	98.9 (97.5–99.6)	445	7.0 (4.8–9.7)	459	6.8 (4.6–9.4)
	GMT	Pre	215	4.3 (4.1–4.5)	217	4.4 (4.1–4.6)	110	4.3 (3.9–4.8)	107	4.3 (3.9–4.7)
		Postprimary	461	1120.7 (977.9–1284.4)	455	1605.0 (1383.2–1862.3)	453	4.4 (4.1–4.7)	455	4.2 (4.0–4.5)
		Prebooster	441	68.7 (58.3–81.0)	459	97.7 (83.3–114.5)	440	4.7 (4.4–5.1)	453	5.0 (4.6–5.5)
		Postbooster	437	1955.9 (1729.6–2211.9)	462	2777.2 (2485.1–3103.6)	445	5.5 (5.0–6.1)	459	5.6 (5.0–6.2)
MenY	% ≥1:8	Pre	215	2.8 (1.0–6.0)	219	2.7 (1.0–5.9)	111	7.2 (3.2–13.7)	107	2.8 (0.6–8.0)
		Postprimary	461	93.1 (90.3–95.2)	456	98.2 (96.6–99.2)	455	2.4 (1.2–4.3)	457	3.1 (1.7–5.1)
		Prebooster	441	82.5 (78.7–86.0)	459	83.4 (79.7–86.7)	440	12.3 (9.4–15.7)	451	10.4 (7.8–13.6)
		Postbooster	439	99.3 (98.0–99.9)	462	99.4 (98.1–99.9)	445	10.1 (7.5–13.3)	461	8.7 (6.3–11.6)
	% ≥1:128	Pre	215	0.0 (0.0–1.7)	219	1.4 (0.3–4.0)	111	0.9 (0.0–4.9)	107	0.9 (0.0–5.1)
		Postprimary	461	80.5 (76.6–84.0)	456	89.3 (86.0–91.9)	455	2.0 (0.9–3.7)	457	2.8 (1.5–4.8)
		Prebooster	441	28.6 (24.4–33.0)	459	36.6 (32.2–41.2)	440	9.3 (6.8–12.4)	451	8.2 (5.8–11.1)
		Postbooster	439	95.4 (93.1–97.2)	462	96.3 (94.2–97.8)	445	8.3 (5.9–11.3)	461	7.4 (5.2–10.2)
	GMT	Pre	215	4.2 (4.0–4.4)	219	4.2 (4.0–4.5)	111	4.7 (4.2–5.2)	107	4.2 (3.9–4.6)
		Postprimary	461	264.6 (224.6–311.7)	456	483.3 (418.6–558.0)	455	4.4 (4.1–4.6)	457	4.5 (4.2–4.8)
		Prebooster	441	35.4 (30.6–41.0)	459	47.0 (40.3–54.7)	440	6.5 (5.7–7.4)	451	6.0 (5.4–6.8)
		Postbooster	439	630.6 (564.1–705.1)	462	881.3 (787.5–986.4)	445	6.1 (5.4–6.8)	461	5.8 (5.2–6.6)

% indicates percentage of participants with titers at or above the prespecified cut-off; 95% CI; ACWY-TT_3, participants who received 4 doses of MenACWY-TT at 2, 3, 4 and 12 mo of age; ACWY-TT_2, participants who received 3 doses of MenACWY-TT at 2, 4 and 12 mo of age; ATP, according-to-protocol; GMT, geometric mean titer; MenC-CRM$_{197}$, participants who received 3 doses of MenC-CRM$_{197}$ at 2, 4 and 12 mo of age; MenC-TT, participants who received 3 doses of MenC-TT at 2, 4 and 12 mo of age; N, number of participants with available results.

thresholds. The same can be said for the ACWY-TT_3 group compared with the MenC-CRM$_{197}$ group and for the MenC-TT group compared with the ACWY-TT_2 group at the ≥1:128 threshold (Table 2). Exploratory analyses also suggested that rSBA-MenC GMTs tended to be higher in the MenC-TT group compared with the ACWY-TT_3 and ACWY-TT_2 groups (data not shown).

One month postbooster, ≥99.1% of toddlers in the ACWY-TT_3 group and ≥99.5% of toddlers in the ACWY-TT_2 group had hSBA titers ≥1:8 for each vaccine-serogroup. In both groups, postbooster hSBA GMTs were 15.4- to 69.5-fold higher than prebooster hSBA GMTs. In the MenC-CRM$_{197}$ and MenC-TT groups, all toddlers had hSBA-MenC titers ≥ 1:8 at 1 month postbooster. In the 4 groups, a marked increase in hSBA-MenC GMTs was observed after booster vaccination, with values 38.0- (ACWY-TT_3), 27.5- (ACWY-TT_2), 70.8- (MenC-CRM$_{197}$) and 25.9-fold (MenC-TT) higher than before booster administration.

Because more than 5% of the participants were eliminated from both the primary and booster ATP cohorts for immunogenicity, the exploratory and descriptive analyses were also performed on the TVC, and results were consistent with those obtained for the ATP cohorts (data not shown).

TABLE 3. Percentage of Participants With hSBA Antibody Titers ≥1:4 and ≥1:8 and Geometric Mean Titers Prevaccination and One Mo Postprimary Vaccination (Primary ATP Cohort for Immunogenicity) and Prebooster and One Mo PostBooster Vaccination (Booster ATP Cohort for Immunogenicity)

			ACWY-TT_3		ACWY-TT_2		MenC-CRM$_{197}$		MenC-TT	
Antibody	Estimate	Timing	N	Value (95% CI)	N	Value (95% CI)	N	Value (95% CI)	N	Value (95% CI)
MenA	% ≥1:4	Pre	164	20.7 (14.8–27.7)	166	18.7 (13.1–25.4)	161	25.5 (18.9–32.9)	166	20.5 (14.6–27.4)
		Postprimary	200	98.5 (95.7–99.7)	202	96.5 (93.0–98.6)	172	12.2 (7.7–18.1)	205	8.8 (5.3–13.5)
		Prebooster	193	73.6 (66.8–79.6)	204	58.3 (51.2–65.2)	188	14.9 (10.1–20.8)	202	12.9 (8.6–18.3)
		Postbooster	212	99.1 (96.6–99.9)	214	99.5 (97.4–100)	204	24.5 (18.8–31.0)	205	26.8 (20.9–33.4)
	% ≥1:8	Pre	164	17.1 (11.7–23.7)	166	11.4 (7.0–17.3)	161	16.8 (11.4–23.5)	166	16.3 (11.0–22.8)
		Postprimary	200	98.0 (95.0–99.5)	202	96.5 (93.0–98.6)	172	8.7 (5.0–14.0)	205	6.8 (3.8–11.2)
		Prebooster	193	73.1 (66.2–79.2)	204	58.3 (51.2–65.2)	188	13.8 (9.2–19.6)	202	12.9 (8.6–18.3)
		Postbooster	212	99.1 (96.6–99.9)	214	99.5 (97.4–100)	204	24.5 (18.8–31.0)	205	26.8 (20.9–33.4)
	GMT	Pre	164	2.8 (2.5–3.2)	166	2.7 (2.4–3.0)	161	3.0 (2.7–3.4)	166	2.9 (2.6–3.3)
		Postprimary	200	240.9 (207.8–279.3)	202	157.2 (131.4–188.1)	172	2.5 (2.2–2.7)	205	2.3 (2.2–2.5)
		Prebooster	193	32.0 (24.2–42.2)	204	14.5 (11.2–18.7)	188	2.7 (2.4–3.0)	202	2.7 (2.4–3.1)
		Postbooster	212	1192.7 (978.4–1453.9)	214	1007.2 (835.7–1213.8)	204	3.9 (3.3–4.6)	205	4.2 (3.5–5.0)
MenC	% ≥1:4	Pre	181	23.8 (17.8–30.6)	178	19.7 (14.1–26.3)	168	29.8 (23.0–37.3)	185	23.8 (17.8–30.6)
		Postprimary	214	99.5 (97.4–100)	218	98.6 (96.0–99.7)	202	100 (98.2–100)	226	100 (98.4–100)
		Prebooster	193	95.3 (91.3–97.8)	208	95.2 (91.3–97.7)	185	86.5 (80.7–91.1)	203	96.6 (93.0–98.6)
		Postbooster	213	99.5 (97.4–100)	221	99.5 (97.5–100)	216	100 (98.3–100)	219	100 (98.3–100)
	% ≥1:8	Pre	181	23.8 (17.8–30.6)	178	19.7 (14.1–26.3)	168	29.2 (22.4–36.7)	185	22.7 (16.9–29.4)
		Postprimary	214	99.5 (97.4–100)	218	98.6 (96.0–99.7)	202	100 (98.2–100)	226	100 (98.4–100)
		Prebooster	193	95.3 (91.3–97.8)	208	95.2 (91.3–97.7)	185	86.5 (80.7–91.1)	203	96.6 (93.0–98.6)
		Postbooster	213	99.5 (97.4–100)	221	99.5 (97.5–100)	216	100 (98.3–100)	219	100 (98.3–100)
	GMT	Pre	181	3.9 (3.2–4.7)	178	3.6 (3.0–4.4)	168	4.9 (3.9–6.2)	185	3.9 (3.2–4.7)
		Postprimary	214	765.6 (647.4–905.3)	218	1308.3 (1051.7–1627.4)	202	3188.1 (2645.8–3841.5)	226	2626.5 (2218.9–3109.0)
		Prebooster	193	116.1 (94.2–143.0)	208	181.4 (147.3–223.4)	185	76.8 (58.5–100.8)	203	213.7 (174.6–261.7)
		Postbooster	213	4411.2 (3654.5–5324.6)	221	4992.3 (4085.7–6100.0)	216	5438.2 (4412.4–6702.3)	219	5542.3 (4765.2–6446.2)
MenW	% ≥1:8	Pre	182	27.5 (21.1–34.6)	184	25.0 (18.9–31.9)	190	28.4 (22.1–35.4)	187	19.8 (14.3–26.2)
		Postprimary	201	98.0 (95.0–99.5)	217	100 (98.3–100)	205	2.9 (1.1–6.3)	204	1.5 (0.3–4.2)
		Prebooster	198	99.0 (96.4–99.9)	203	99.0 (96.5–99.9)	201	0.5 (0.0–2.7)	210	2.9 (1.1–6.1)
		Postbooster	207	100 (98.2–100)	218	100 (98.3–100)	204	1.5 (0.3–4.2)	206	2.9 (1.1–6.2)
	% ≥1:128	Pre	182	26.9 (20.6–34.0)	184	23.9 (17.9–30.7)	190	27.4 (21.2–34.3)	187	19.3 (13.9–25.6)
		Postprimary	201	98.0 (95.0–99.5)	217	100 (98.3–100)	205	2.0 (0.5–4.9)	204	1.5 (0.3–4.2)
		Prebooster	198	99.0 (96.4–99.9)	203	99.0 (96.5–99.9)	201	0.5 (0.0–2.7)	210	2.9 (1.1–6.1)
		Postbooster	207	100 (98.2–100)	218	100 (98.3–100)	204	1.5 (0.3–4.2)	206	2.9 (1.1–6.2)
	GMT	Pre	182	5.0 (3.9–6.3)	184	4.7 (3.8–6.0)	190	5.0 (4.0–6.3)	187	3.7 (3.1–4.6)
		Postprimary	201	190.9 (160.0–227.8)	217	753.5 (643.8–881.8)	205	2.1 (2.0–2.3)	204	2.1 (2.0–2.3)
		Prebooster	198	248.1 (210.4–292.6)	203	332.4 (287.3–384.5)	201	2.0 (2.0–2.1)	210	2.3 (2.0–2.6)
		Postbooster	207	3944.9 (3419.1–4551.7)	218	5122.7 (4504.2–5826.1)	204	2.1 (2.0–2.2)	206	2.3 (2.1–2.7)
MenY	% ≥1:8	Pre	191	38.2 (31.3–45.5)	192	38.0 (31.1–45.3)	204	34.8 (28.3–41.8)	192	40.6 (33.6–47.9)
		Postprimary	209	89.5 (84.5–93.3)	214	97.7 (94.6–99.2)	204	5.4 (2.7–9.4)	196	2.6 (0.8–5.9)
		Prebooster	203	91.1 (86.3–94.7)	216	94.4 (90.5–97.1)	219	2.7 (1.0–5.9)	213	4.7 (2.3–8.5)
		Postbooster	206	100 (98.2–100)	217	100 (98.3–100)	213	3.3 (1.3–6.7)	217	5.5 (2.9–9.5)
	% ≥1:128	Pre	191	38.2 (31.3–45.5)	192	37.5 (30.6–44.8)	204	34.8 (28.3–41.8)	192	40.1 (33.1–47.4)
		Postprimary	209	88.5 (83.4–92.5)	214	97.7 (94.6–99.2)	204	5.4 (2.7–9.4)	196	2.0 (0.6–5.1)
		Prebooster	203	91.1 (86.3–94.7)	216	94.4 (90.5–97.1)	219	2.7 (1.0–5.9)	213	4.7 (2.3–8.5)
		Postbooster	206	100 (98.2–100)	217	100 (98.3–100)	213	3.3 (1.3–6.7)	217	5.5 (2.9–9.5)
	GMT	Pre	191	8.0 (6.1–10.5)	192	8.0 (6.1–10.5)	204	7.1 (5.5–9.2)	192	8.1 (6.3–10.4)
		Postprimary	209	66.5 (53.7–82.2)	214	328.1 (275.8–390.2)	204	2.4 (2.1–2.7)	196	2.1 (2.0–2.2)
		Prebooster	203	99.8 (80.7–123.5)	216	140.2 (116.2–169.2)	219	2.2 (2.0–2.4)	213	2.4 (2.1–2.7)
		Postbooster	206	2491.5 (2125.8–2920.1)	217	2954.0 (2497.9–3493.3)	213	2.3 (2.1–2.6)	217	2.4 (2.2–2.7)

% indicates percentage of participants with titers at or above the prespecified cut-off; 95% CI, 95% confidence interval; ACWY-TT_3, participants who received 4 doses of MenACWY-TT at 2, 3, 4 and 12 mo of age; ACWY-TT_2, participants who received 3 doses of MenACWY-TT at 2, 4 and 12 mo of age; ATP, according-to-protocol; GMT, geometric mean titer; MenC-CRM$_{197}$, participants who received 3 doses of MenC-CRM$_{197}$ at 2, 4 and 12 mo of age; MenC-TT, participants who received 3 doses of MenC-TT at 2, 4 and 12 mo of age; N, number of participants with available results.

Safety

During the 8-day post-vaccination period, the percentages of participants reporting local and general symptoms were similar in the 4 groups (Fig. 1).

The most frequently reported solicited local symptom at the injection sites of each of the meningococcal vaccines was redness, which was reported after 27.7%–34.6% of doses after primary vaccination (overall per dose) and after 37.9%–45.3% of booster doses. Grade 3 local symptoms were reported after 0.1%–3.5% and 0.2%–7.9% of primary and booster doses, respectively. The most frequently reported solicited general symptom was irritability, which was reported after 59.7%–62.1% (with grade 3 intensity after 6.8%–9.3%) of doses after primary vaccination (overall per dose), and 57.3%–58.9% (with grade 3 intensity after 7.3%–8.9%) of doses after booster vaccination.

During the 31-day follow-up period after primary vaccination, the percentage of infants with unsolicited AEs (52.1%–56.4%) and grade 3 unsolicited AEs (3.2%–5.3%) were similar in the 4 study groups. After booster vaccination, unsolicited AEs were reported in 32.6%–36.4% of toddlers, and grade 3 unsolicited AEs in 2.8%–3.6% of toddlers. The most frequent grade 3 AEs were bronchiolitis, bronchitis, upper respiratory tract

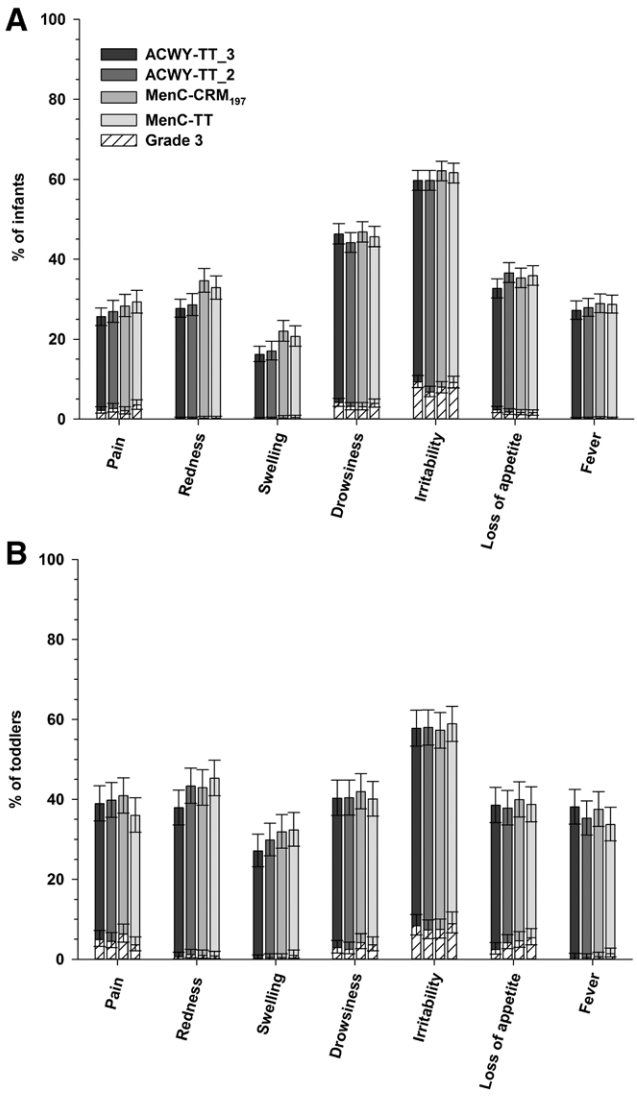

FIGURE 1. Local symptoms reported at the meningococcal vaccine injection site and general solicited symptoms within 8 days after (A) primary and (B) booster vaccination (overall per dose; primary and booster total vaccinated cohort). For all groups, local symptoms refer to the percentage of participants with ≥1 local symptom at the MenACWY-TT, MenC-CRM_{197} or MenC-TT injection site. Any fever (rectal temperature) ≥38.0°C; Grade 3: redness and swelling >30 mm; pain: cried when limb was touched/spontaneously painful; fever (rectal temperature) >40°C; irritability/fussiness and drowsiness: prevented normal activity; loss of appetite: not eating at all.

infection and gastroenteritis after primary vaccination and gastroenteritis and upper respiratory tract infection after booster vaccination.

SAEs occurring from the first vaccine dose through the end of the extended safety follow-up period (ie, 6 months after the booster vaccination) were reported by 54 (10.2%), 56 (10.7%), 45 (8.7%) and 52 (9.9%) participants in the ACWY-TT_3, ACWY-TT_2, MenC-CRM_{197} and MenC-TT groups, respectively. One SAE was considered potentially related to vaccination (epilepsy at 7 days postdose 3 in an infant of the ACWY-TT_3 group). No fatal SAEs were reported. New onsets of chronic illnesses were reported in 2.1%–2.9% of participants during the entire study period.

DISCUSSION

This was the first study evaluating the immunogenicity and safety of MenACWY-TT coadministered with routine childhood vaccines during infancy. Two or 3 primary doses of MenACWY-TT induced a robust immune response, with ≥93.1% of infants having rSBA titers ≥1:8 against each serogroup 1 month after completion of the primary vaccination series. While exploratory analyses indicated some differences in the response to MenC between MenACWY-TT and control vaccine groups, all noninferiority objectives of the study related to this serogroup were achieved. Eight months postprimary vaccination, the percentage of infants retaining protective rSBA titers against MenC in MenACWY-TT groups (73.5%–75.8%) were similar to those in groups receiving the licensed MenC vaccines (51.9%–78.9%). Administration of a booster dose of MenACWY-TT during the second year of life further strengthened the immune response, with >99% of toddlers acquiring protective levels to each vaccine serogroup, regardless of the number of priming doses. Of note, immune responses assessed as either rSBA or hSBA titers were generally similar for all serogroups across all study groups. Moreover, MenACWY-TT had a clinically acceptable safety profile when coadministered with routine childhood vaccines in the infants and toddlers.

All prespecified criteria for noninferiority of the immune response to MenC induced by 2 or 3 primary doses of MenACWY-TT versus 2 primary doses of MenC-CRM_{197} or MenC-TT were met. These results suggest that MenACWY-TT would provide similar protection levels against MenC as the monovalent vaccines that are currently licensed for use during infancy. However, postprimary exploratory analyses suggested that rSBA-MenC antibody GMTs tended to be lower in infants primed with MenACWY-TT compared with MenC-CRM_{197} or MenC-TT. The difference of immunogenicity between the quadrivalent and the monovalent vaccine could be related to the different concentrations of MenC antigen (5 vs 10 µg). Similar findings were observed in previous studies conducted in toddlers vaccinated with MenACWY-TT or infants vaccinated with another quadrivalent conjugated vaccine (MenACWY-CRM_{197}) compared with MenC-CRM_{197}.[29,30] However, these results are in contrast with other studies showing that a single dose of MenACWY-TT tended to induce higher functional antibody titers against MenC than MenC-CRM_{197} in toddlers or children.[13,31,32] The clinical significance of the lower rSBA-MenC GMTs induced by MenACWY-TT in the present study is unclear, because 98.7% and 99.6% of children primed with 2 and 3 doses of MenACWY-TT were seroprotected against this serogroup at 1 month postprimary vaccination.

All prespecified criteria related to the immunogenicity of 2 or 3 primary doses of MenACWY-TT were successfully met for MenA, MenW and MenY. The expansion of immunity to these serogroups is a major benefit of MenACWY-TT over monovalent MenC vaccines. One month after primary vaccination with 2 or 3 MenACWY-TT doses, ≥93.1% of infants had rSBA titers ≥1:8 and ≥88.5% of infants had hSBA titers ≥1:8 for each of the 4 vaccine serogroups. Moreover, a robust increase in rSBA and hSBA GMTs was observed for each serogroup compared with prevaccination. The fact that the immune response was not compromised for any of the 4 vaccine serogroups was in line with findings of previous studies evaluating the immunogenicity of a single dose of MenACWY-TT in terms of rSBA and hSBA functional antibodies in toddlers,[8,13,14,31–33] children,[12,34] adolescents[35,36] and adults.[7,9,10,37–39]

The findings in the current study are consistent with previous studies on MenACWY-CRM_{197} coadministered with routine childhood vaccines in the same age group, in which 67%–89% of infants had protective hSBA titers for MenA, and 94%–98% had protective hSBA titers for MenC, MenW and MenY at 1 month after completion of a 3-dose infant series.[40–42]

Before the booster dose administration, ≥61.3% and ≥58.3% of toddlers primed with either 2 or 3 MenACWY-TT doses retained rSBA and hSBA titers ≥1:8 for each vaccine serogroup. Although functional antibody GMTs had decreased compared with 1 month postprimary vaccination, they were still higher than those observed at prevaccination. In contrast to observations made at 1 month postprimary vaccination, percentage of toddlers with rSBA-MenC titers above cut-offs and rSBA-MenC GMTs were higher in infants primed with MenACWY-TT compared with MenC-CRM_{197}. Moreover, rSBA- and hSBA-MenC GMTs were markedly lower before the booster administration compared with 1 month postprimary vaccination for infants primed with MenC-CRM_{197} group (59.8- and 41.5-fold, respectively), while these differences were less pronounced and ranged from 6.6- to 24.1-fold for the ACWY-TT_3, ACWY-TT_2 and MenC-TT recipients. This observation is in line with a previous study showing a 74.67-fold decrease in rSBA-MenC GMT levels between 1 and 8 months after 2-dose primary vaccination of infants with MenC-CRM_{197}.[43] The higher levels of persisting antibodies to MenC in the ACWY-TT_3, ACWY-TT_2 and MenC-TT groups as compared with the MenC-CRM_{197} group could be due to the different carrier protein, as has been previously reported in the literature.[44,45] As expected because the waning of antibodies is known to be more pronounced when children are vaccinated at a younger age, less steep declines were observed in other studies conducted in toddlers between 1 and 12 months after administration of 1 dose of either MenACWY-TT or Men-CRM_{197} in terms of rSBA-MenC GMTs (4.49- and 5.38-fold decrease, respectively) and hSBA-MenC GMTs (2.14- and 1.73-fold decrease, respectively),[13] and between 1 and 7 months after the administration of 1 dose of MenC-TT in terms of rSBA-MenC GMTs (6.45-fold decrease).[46,47]

After administration of the booster dose of MenACWY-TT in the second year of life, a robust increase in functional immune response was observed for each vaccine serogroup. Higher rSBA and hSBA antibody levels were observed postbooster compared with postprimary vaccination, suggesting that 2 or 3 primary doses of MenACWY-TT administered during infancy were able to induce immune memory. Immune memory after a polysaccharide challenge had been also previously observed after priming of toddlers with a single dose of MenACWY-TT.[48] In our study, marked increases in terms of rSBA- and hSBA-MenC GMTs were observed after the booster doses of MenACWY-TT, MenC-CRM_{197} and MenC-TT, with values 25.9- to 70.8-fold higher than before booster administration. Exploratory analyses suggested that the percentage of toddlers with postbooster rSBA-MenC titers ≥1:128 tended to be higher in MenACWY-TT compared with MenC-CRM_{197} recipients, but that rSBA-MenC GMTs tended to be higher in MenC-TT compared with MenACWY-TT recipients. The clinical significance of this observation is not clear, because ≥99.5% of toddlers receiving MenACWY-TT had titers ≥1:8, and ≥98.1% of them also had titers ≥1:128. The findings in the current study are similar to those of a previous study evaluating the immune response to a booster dose of MenACWY-CRM_{197}, in which the percentage of children with hSBA titers ≥1:8 for the four serogroups were 94%–99% for the children who received 2 + 1 doses and 95%–100% for children who received 3 + 1 doses.[42]

In the present study, MenACWY-TT was coadministered with DTPa-HBV-IPV/Hib and PHiD-CV. Because the primary and booster doses of MenACWY-TT induced robust immune responses to all meningococcal vaccine serogroups, our results confirmed that this vaccine is immunogenic when coadministered with routine childhood vaccines.[8,32,33,36] So far, there is limited information on the effect of MenACWY-TT on the immune response to other vaccines administered concomitantly in young children,[8,32,33] so the current study also assessed the immunogenicity of the coadministered routine childhood vaccines after primary and booster vaccination. Available data indicate that there was little or no impact of MenACWY-TT on the immune response to the coadministered vaccine components, and further details will be reported in a separate manuscript.

The coadministration of 2 or 3 primary doses of MenACWY-TT with routine childhood vaccines had a clinically acceptable safety profile in infants. No increase in reactogenicity was observed in infants who received 3 doses of MenACWY-TT. However, a SAE considered as potentially related to vaccination was reported in an infant 7 days after administration of the third primary dose of MenACWY-TT. The safety profile of MenACWY-TT remained clinically acceptable after administration of the booster dose and was similar to the licensed comparators. However, the local reactogenicity at the meningococcal vaccine injection sites appeared to slightly increase in the 4 study groups compared with the postprimary time-point.

The limitations of this study included the lack of a quadrivalent meningococcal conjugate control vaccine, because none of these vaccines are currently licensed for use during infancy in Europe. The study was also limited by its open design, which is unlikely to have influenced the immunogenicity assessments but may have biased the safety assessment toward increased reporting of AEs in the toddlers who received the MenACWY-TT vaccine. Another potential bias was the fact that, in line with the recommendation of the local authorities, administration of measles-containing vaccines was allowed in individuals from 9 months old onwards throughout the study. The fact that some participants received this vaccine had probably no or a limited impact on our results because a previous study has shown that ACWY-TT can be coadministered with measles, mumps, rubella and varicella combined vaccine without affecting the immunogenicity or safety profiles of either vaccine.[32] The current study was only powered for the coprimary objectives; the exploratory comparisons were performed without adjustment for multiplicity and should be interpreted cautiously. In addition, while 2 and 3 primary doses of MenACWY-TT followed by a booster appeared to be clinically similar with respect to immunogenicity and reactogenicity, the study was not designed to compare both schedules. The study also lacked persistence data after the booster dose administration.

In conclusion, this study showed that 2 or 3 primary doses of MenACWY-TT, when coadministered with routine childhood vaccines during infancy, were noninferior to 2 doses of either the MenC-CRM_{197} or MenC-TT vaccine in terms of immunogenicity to MenC, and induced immune responses to MenA, MenW and MenY that met the prespecified immunogenicity criteria. A booster dose of MenACWY-TT administered in the second year of life induced a robust memory response to the 4 meningococcal vaccine serogroups. Use of MenACWY-TT might prove to be a viable alternative to MenC vaccination in infants, by offering a broader protection against MenA, MenW and MenY without compromising the MenC response. This study also showed that the safety profile of MenACWY-TT was clinically acceptable in infants and toddlers.

ACKNOWLEDGMENTS

The authors thank the study participants and their parents, clinicians, nurses and laboratory technicians at the study site, as

well as to clinical investigators for their contribution to this study. The authors are grateful to the Vaccine Evaluation Unit, Public Health England, Manchester, United Kingdom for performing the serum bactericidal antibody assays. The authors also thank Régis Azizieh (XPE Pharma & Science, Belgium) for publication management and Claire Verbelen (XPE Pharma & Science, Belgium) for medical writing services.

All authors had full access to the data and had final responsibility to submit for publication. Drafts were developed by a professional publication writer according to the recommendations, documentation and outline provided by the lead author. A.C.M., F.C.M., M.Mi., M.Me., M.A.G., C.W., T.F., J.M.M.A., X.M.P.P. and M.C.O.R. participated in the recruitment of subjects, in the collection of data and in center coordination. J.M.M.A., X.M.P.P. and M.C.O.R. also provided interpretation of results. M.H., J.M.B. and G.B. participated in the recruitment of subjects and in the collection of data. D.K. provided the statistical expertise and interpretation of results. M.V.D.W. participated in the conception, design and planning of the study, supervised the analysis and participated in the interpretation of results. Y.B. provided quality check, supervised the analyses and participated in the interpretation of results and the review of the clinical study report.

REFERENCES

1. Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. *Vaccine*. 2009;27(suppl 2):B51–B63.
2. Jafri RZ, Ali A, Messonnier NE, et al. Global epidemiology of invasive meningococcal disease. *Popul Health Metr*. 2013;11:17.
3. European Centre for Disease Prevention and Control. Surveillance of invasive bacterial diseases in Europe, 2011. 2013:38–41.
4. Bröker M, Emonet S, Fazio C, et al. Meningococcal serogroup Y disease in Europe: continuation of high importance in some European regions in 2013. *Hum Vaccin Immunother*. 2015;11:2281–2286.
5. Ladhani SN, Waight PA, Ribeiro S, et al. Invasive meningococcal disease in England: assessing disease burden through linkage of multiple national data sources. *BMC Infect Dis*. 2015;15:551.
6. Gautret P, Botelho-Nevers E, Brouqui P, et al. The spread of vaccine-preventable diseases by international travellers: a public-health concern. *Clin Microbiol Infect*. 2012;18 suppl 5:77–84.
7. Baxter R, Baine Y, Ensor K, et al. Immunogenicity and safety of an investigational quadrivalent meningococcal ACWY tetanus toxoid conjugate vaccine in healthy adolescents and young adults 10 to 25 years of age. *Pediatr Infect Dis J*. 2011;30:e41–e48.
8. Knuf M, Pantazi-Chatzikonstantinou A, Pfletschinger U, et al. An investigational tetravalent meningococcal serogroups A, C, W-135 and Y-tetanus toxoid conjugate vaccine co-administered with Infanrix™ hexa is immunogenic, with an acceptable safety profile in 12-23-month-old children. *Vaccine*. 2011;29:4264–4273.
9. Borja-Tabora C, Montalban C, Memish ZA, et al. Immune response, antibody persistence, and safety of a single dose of the quadrivalent meningococcal serogroups A, C, W-135, and Y tetanus toxoid conjugate vaccine in adolescents and adults: results of an open, randomised, controlled study. *BMC Infect Dis*. 2013;13:116.
10. Dbaibo G, Macalalad N, Aplasca-De Los Reyes MR, et al. The immunogenicity and safety of an investigational meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate vaccine (ACWY-TT) compared with a licensed meningococcal tetravalent polysaccharide vaccine: a randomized, controlled non-inferiority study. *Hum Vaccin Immunother*. 2012;8:873–880.
11. Østergaard L, Van der Wielen M, Bianco V, et al. Persistence of antibodies for 42 months following vaccination of adolescents with a meningococcal serogroups A, C, W-135, and Y tetanus toxoid conjugate vaccine (MenACWY-TT). *Int J Infect Dis*. 2013;17:e173–e176.
12. Vesikari T, Forstén A, Boutriau D, et al. A randomized study to assess the immunogenicity, antibody persistence and safety of a tetravalent meningococcal serogroups A, C, W-135 and Y tetanus toxoid conjugate vaccine in children aged 2-10 years. *Hum Vaccin Immunother*. 2012;8:1882–1891.
13. Vesikari T, Forstén A, Boutriau D, et al. Randomized trial to assess the immunogenicity, safety and antibody persistence up to three years after a single dose of a tetravalent meningococcal serogroups A, C, W-135 and Y tetanus toxoid conjugate vaccine in toddlers. *Hum Vaccin Immunother*. 2012;8:1892–1903.
14. Klein NP, Baine Y, Bianco V, et al. One or two doses of quadrivalent meningococcal serogroups A, C, W-135 and Y tetanus toxoid conjugate vaccine is immunogenic in 9- to 12-month-old children. *Pediatr Infect Dis J*. 2013;32:760–767.
15. Baxter R, Baine Y, Kolhe D, et al. Five-year antibody persistence and booster response to a single dose of meningococcal A, C, W and Y tetanus toxoid conjugate vaccine in adolescents and young adults: an open, randomized trial. *Pediatr Infect Dis J*. 2015;34:1236–1243.
16. Vesikari T, Forsten A, Bianco V, et al. Immunogenicity, safety and antibody persistence of a booster dose of quadrivalent meningococcal ACWY-tetanus toxoid conjugate vaccine compared with monovalent meningococcal serogroup C vaccine administered four years after primary vaccination using the same vaccines. *Pediatr Infect Dis J*. 2015;34:e298–e307.
17. Vesikari T, Forsten A, Bianco V, et al. Antibody persistence up to 5 years after vaccination of toddlers and children between 12 months and 10 years of age with a quadrivalent meningococcal ACWY-tetanus toxoid conjugate vaccine. *Hum Vaccin Immunother*. 2016;12:132–139.
18. MacNeil JR, Rubin L, McNamara L, et al; Meningitis and Vaccine Preventable Diseases Branch, Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, CDC. Use of MenACWY-CRM vaccine in children aged 2 through 23 months at increased risk for meningococcal disease: recommendations of the Advisory Committee on Immunization Practices, 2013. *MMWR Morb Mortal Wkly Rep*. 2014;63:527–530.
19. Electronic Medicines Compendium. MENJUGATE 10 micrograms suspension for injection: summary of product characterisitcs. 2015. Available at: https://www.medicines.org.uk/emc/medicine/31302. Accessed June 29, 2016.
20. Electronic Medicines Compendium. NeisVac-C 0.5ml Suspension for injection in pre-filled syringe: summary of product characteristics. 2015. Available at: https://www.medicines.org.uk/emc/medicine/30325. Accessed June 29, 2016.
21. GSK Vaccines. Highlights of prescribing information: Menveo®. Available at: https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Menveo/pdf/MENVEO.PDF. Accessed July 22, 2016.
22. Tichmann-Schumann I, Soemantri P, Behre U, et al. Immunogenicity and reactogenicity of four doses of diphtheria-tetanus-three-component acellular pertussis-hepatitis B-inactivated polio virus-Haemophilus influenzae type b vaccine coadministered with 7-valent pneumococcal conjugate vaccine. *Pediatr Infect Dis J*. 2005;24:70–77.
23. Vesikari T, Wysocki J, Chevallier B, et al. Immunogenicity of the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) compared to the licensed 7vCRM vaccine. *Pediatr Infect Dis J*. 2009;28(4 suppl):S66–S76.
24. Andrews N, Borrow R, Miller E. Validation of serological correlate of protection for meningococcal C conjugate vaccine by using efficacy estimates from postlicensure surveillance in England. *Clin Diagn Lab Immunol*. 2003;10:780–786.
25. Borrow R, Balmer P, Miller E. Meningococcal surrogates of protection–serum bactericidal antibody activity. *Vaccine*. 2005;23:2222–2227.
26. Campbell H, Andrews N, Borrow R, et al. Updated postlicensure surveillance of the meningococcal C conjugate vaccine in England and Wales: effectiveness, validation of serological correlates of protection, and modeling predictions of the duration of herd immunity. *Clin Vaccine Immunol*. 2010;17:840–847.
27. Maslanka SE, Gheesling LL, Libutti DE, et al. Standardization and a multilaboratory comparison of Neisseria meningitidis serogroup A and C serum bactericidal assays. The Multilaboratory Study Group. *Clin Diagn Lab Immunol*. 1997;4:156–167.
28. Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the Meningococcus. *J Exp Med*. 1969;129:1307–1326.
29. Knuf M, Romain O, Kindler K, et al. Immunogenicity and safety of the quadrivalent meningococcal serogroups A, C, W-135 and Y tetanus toxoid conjugate vaccine (MenACWY-TT) in 2-10-year-old children: results of an open, randomised, controlled study. *Eur J Pediatr*. 2013;172:601–612.
30. Snape MD, Perrett KP, Ford KJ, et al. Immunogenicity of a tetravalent meningococcal glycoconjugate vaccine in infants: a randomized controlled trial. *JAMA*. 2008;299:173–184.
31. Knuf M, Kieninger-Baum D, Habermehl P, et al. A dose-range study assessing immunogenicity and safety of one dose of a new candidate meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate (MenACWY-TT) vaccine administered in the second year of life and in young children. *Vaccine*. 2010;28:744–753.

32. Vesikari T, Karvonen A, Bianco V, et al. Tetravalent meningococcal serogroups A, C, W-135 and Y conjugate vaccine is well tolerated and immunogenic when co-administered with measles-mumps-rubella-varicella vaccine during the second year of life: an open, randomized controlled trial. *Vaccine*. 2011;29:4274–4284.
33. Ruiz-Palacios GM, Huang LM, Lin TY, et al. Immunogenicity and safety of a booster dose of the 10-valent pneumococcal Haemophilus influenzae protein D conjugate vaccine coadministered with the tetravalent meningococcal serogroups A, C, W-135 and Y tetanus toxoid conjugate vaccine in toddlers: a randomized trial. *Pediatr Infect Dis J*. 2013;32:62–71.
34. Memish ZA, Dbaibo G, Montellano M, et al. Immunogenicity of a single dose of tetravalent meningococcal serogroups A, C, W-135, and Y conjugate vaccine administered to 2- to 10-year-olds is noninferior to a licensed-ACWY polysaccharide vaccine with an acceptable safety profile. *Pediatr Infect Dis J*. 2011;30:e56–e62.
35. Bermal N, Huang LM, Dubey AP, et al. Safety and immunogenicity of a tetravalent meningococcal serogroups A, C, W-135 and Y conjugate vaccine in adolescents and adults. *Hum Vaccin*. 2011;7:239–247.
36. Østergaard L, Silfverdal SA, Berglund J, et al. A tetravalent meningococcal serogroups A, C, W-135, and Y tetanus toxoid conjugate vaccine is immunogenic and well-tolerated when co-administered with Twinrix(®) in subjects aged 11-17 years: an open, randomised, controlled trial. *Vaccine*. 2012;30:774–783.
37. Ostergaard L, Lebacq E, Poolman J, et al. Immunogenicity, reactogenicity and persistence of meningococcal A, C, W-135 and Y-tetanus toxoid candidate conjugate (MenACWY-TT) vaccine formulations in adolescents aged 15-25 years. *Vaccine*. 2009;27:161–168.
38. Dbaibo G, El-Ayoubi N, Ghanem S, et al. Immunogenicity and safety of a quadrivalent meningococcal serogroups A, C, W-135 and Y tetanus toxoid conjugate vaccine (MenACWY-TT) administered to adults aged 56 Years and older: results of an open-label, randomized, controlled trial. *Drugs Aging*. 2013;30:309–319.
39. Dbaibo G, Van der Wielen M, Reda M, et al. The tetravalent meningococcal serogroups A, C, W-135, and Y tetanus toxoid conjugate vaccine is immunogenic with a clinically acceptable safety profile in subjects previously vaccinated with a tetravalent polysaccharide vaccine. *Int J Infect Dis*. 2012;16:e608–e615.
40. Klein NP, Reisinger KS, Johnston W, et al. Safety and immunogenicity of a novel quadrivalent meningococcal CRM-conjugate vaccine given concomitantly with routine vaccinations in infants. *Pediatr Infect Dis J*. 2012;31:64–71.
41. Nolan TM, Nissen MD, Naz A, et al. Immunogenicity and safety of a CRM-conjugated meningococcal ACWY vaccine administered concomitantly with routine vaccines starting at 2 months of age. *Hum Vaccin Immunother*. 2014;10:280–289.
42. Tregnaghi M, Lopez P, Stamboulian D, et al. Immunogenicity and safety of a quadrivalent meningococcal polysaccharide CRM conjugate vaccine in infants and toddlers. *Int J Infect Dis*. 2014;26:22–30.
43. Pace D, Khatami A, McKenna J, et al. Immunogenicity of reduced dose priming schedules of serogroup C meningococcal conjugate vaccine followed by booster at 12 months in infants: open label randomised controlled trial. *BMJ*. 2015;350:h1554.
44. Borrow R, Andrews N, Findlow H, et al. Kinetics of antibody persistence following administration of a combination meningococcal serogroup C and haemophilus influenzae type b conjugate vaccine in healthy infants in the United Kingdom primed with a monovalent meningococcal serogroup C vaccine. *Clin Vaccine Immunol*. 2010;17:154–159.
45. Lee LH, Blake MS. Effect of increased CRM_{197} carrier protein dose on meningococcal C bactericidal antibody response. *Clin Vaccine Immunol*. 2012;19:551–556.
46. Noya F, McCormack D, Reynolds DL, et al. Safety and immunogenicity of two doses of quadrivalent meningococcal conjugate vaccine or one dose of meningococcal group C conjugate vaccine, both administered concomitantly with routine immunization to 12- to 18-month-old children. *Can J Infect Dis Med Microbiol*. 2014;25:211–216.
47. Trotter CL, Andrews NJ, Kaczmarski EB, et al. Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. *Lancet*. 2004;364:365–367.
48. Knuf M, Baine Y, Bianco V, et al. Antibody persistence and immune memory 15 months after priming with an investigational tetravalent meningococcal tetanus toxoid conjugate vaccine (MenACWY-TT) in toddlers and young children. *Hum Vaccin Immunother*. 2012;8:866–872.