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ORIGINAL RESEARCH

Immunogenicity and Safety of a Quadrivalent Meningococcal Conjugate Vaccine (MenACYW-TT) Administered with Routine Pediatric Vaccines: A European Randomized Controlled Trial

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ABSTRACT

Introduction: The immunogenicity and safety of MenACYW-TT (MenQuadfi®) were compared to another quadrivalent meningococcal conjugate vaccine, MCV4-TT (Nimenrix®), when administered in infants alongside routine childhood vaccines in Europe.

Methods: One set of healthy infants was randomized 1:1 to receive MenACYW-TT (group 1; $n=714$) or MCV4-TT (group 2; $n=726$) at age 2, 4, and 12–18 months (2+1 regimen) concomitantly with routine vaccines (including 10-valent pneumococcal conjugate vaccine). Another set was randomized 1:1 to receive MenACYW-TT in a 2+1 regimen (group 3; $n=112$) or a 3+1 regimen at age 2, 4, 6, and 12–18 months (group 4; $n=108$) concomitantly with routine vaccines (including 13-valent pneumococcal conjugate

A list of the MET58 study group members is provided in the supplementary appendix.

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vaccine). Immune responses against meningococcal serogroups A, C, W, and Y were measured by serum bactericidal assay using human complement (hSBA). Non-inferiority of MenACYW-TT versus MCV4-TT was based on hSBA geometric mean titers (GMTs) 30 days post-booster (dose 3; primary endpoint) and rates of seroprotection 30 days post-dose 2 (secondary endpoint) against all vaccine meningococcal serogroups. Immune responses to co-administered vaccines and safety were also assessed. Post hoc, non-inferiority of MenACYW-TT was also assessed based on seroresponse rates 30 days post-booster.

Results: Non-inferiority of MenACYW-TT versus MCV4-TT, based on GMTs post-booster, was demonstrated for serogroups C, W, and Y but not for A. GMTs against serogroups C, W, and Y were 1.5- to 4.5-fold higher with MenACYW-TT than MCV4-TT; those against serogroup A were marginally lower. Antibody responses in groups 3 and 4 against all serogroups were similar to group 1. Non-inferiority of MenACYW-TT based on seroresponse rates post-booster against all serogroups was demonstrated post hoc. No interference with concomitant routine vaccines nor safety concerns were identified.

Conclusions: Consideration of all immunogenicity and safety data generated in this study supports the incorporation of MenACYW-TT into the routine childhood vaccination schedule as a 2 + 1 regimen starting at age 6 weeks.

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PLAIN LANGUAGE SUMMARY

This study compared the immune response and safety of two vaccines that protect against meningococcal disease caused by serogroups A, C, W, and Y. We compared the MenACYW-TT (MenQuadfi®) vaccine to MCV4-TT (Nimenrix®), a vaccine already licensed for infants in Europe. The vaccines were assessed when administered as a three-dose series (2 + 1 regimen) for infants starting vaccination at age 6 weeks, given alongside routine scheduled childhood vaccines. The MenACYW-TT vaccine appeared to trigger a similar or higher immune response as compared with MCV4-TT based on antibody titers that were measured for the different study groups in our main analysis, except against serogroup A. However, a subsequent unplanned analysis, based on increased individual antibody response compared with baseline, found the two vaccines to be similar across all meningococcal serogroups. Thus, the two vaccines would be expected to provide similar protection against the four meningococcal serogroups. The two vaccines had no effect on the immune response to the co-administered routine vaccines, and no new safety concerns were identified. These results support the use of the MenACYW-TT vaccine in infants from 6 weeks of age.

Keywords: Concomitant vaccine administration; Immunogenicity; Infants; Invasive meningococcal disease; MCV4-TT; MenACYW-TT; Meningitis; Quadrivalent meningococcal vaccines; Safety; Toddlers

Key Summary Points

Why carry out this study?

Given the incidence of invasive meningococcal disease is highest in infants aged < 1 year, there is a need to extend the use of MenACYW-TT to include infants from age 6 weeks, particularly in regions where quadrivalent meningococcal vaccine options for this age group are limited (e.g., in Europe) or unavailable.

What was learned from this study?

Non-inferiority of the antibody geometric mean titers (GMTs) induced post-booster by MenACYW-TT compared with MCV4-TT was demonstrated for meningococcal serogroups C, Y, and W in the primary analysis, but not for serogroup A; however, a post hoc analysis demonstrated non-inferiority of MenACYW-TT in terms of seroresponse rates post-booster for all four serogroups.

GMTs against serogroups C, Y, and W were generally higher with MenACYW-TT than MCV4-TT, whereas those against serogroup A were slightly lower.

No interference with responses to the routine vaccines or new safety concerns was identified.

These data confirm the immunogenicity and safety of MenACYW-TT in infants from age 6 weeks when administered alongside routine pediatric vaccines.

INTRODUCTION

Neisseria meningitidis is a commensal human pathogen commonly carried asymptomatically in the oropharynx [1, 2]. Disseminated infection following oropharyngeal colonization can lead to life-threatening invasive meningococcal disease (IMD), which typically manifests as meningitis and/or sepsis [3]. IMD notification rates in EU/EAA countries in 2022 ranged up to 0.3 per 100,000 population, with the highest notification rates observed in infants aged < 1 year (4.3 per 100,000) [3]. Among the meningococcal serogroups identified, six (A, B, C, W, Y, and X) are responsible for the majority of IMD cases worldwide, with the predominant serogroups varying by geographical location [4]. Overall, in 2022, serogroup B was responsible for most (62%) cases of IMD across EU/EAA countries, followed by serogroup Y (16%), serogroup W (10%), serogroup C (6%), and other serogroups (A, X, Z, 29E, and non-groupable; 6%), with case fatality highest with serogroups W (17%) and C (20%) [3]. Recently, a surge in atypical IMD caused by serogroups W and Y has been noted in France [5].

The MenACYW-TT conjugate vaccine (MenQuadfi®) is the result of approximately two decades of clinical development to formulate a vaccine that induces robust immune responses against four meningococcal serogroup antigens (A, C, W, and Y), across all age groups, from infants through to older adults [6]. In the EU, a single dose of MenACYW-TT was approved in November 2020 for immunization of individuals from 12 months of age and older [7]. Between 1 March 2021 and 30 April 2023, an estimated 6,874,713 patients aged ≥ 12 months were expected to have received MenACYW-TT [8].

Recently, a number of studies have been completed in individuals as young as 6 weeks old, to determine the benefit-risk profile of MenACYW-TT in infants ≥ 6 weeks of age (MET33 [NCT03630705], MET39 [NCT01049035] [9], MET42 [NCT03537508] [10], MET52 [NCT03632720] [11], MET61 [NCT03691610] [11, 12]), MET41 [NCT03673462] [13]. As part of the efforts to extend the indication, the phase III study reported herein (MET58) was undertaken to evaluate the immunogenicity and safety of MenACYW-TT compared with those of another quadrivalent meningococcal conjugate vaccine (MCV4-TT; Nimenrix®). MCV4-TT has been approved in Europe for use in infants from 6 weeks of age since 2016 based on demonstrated immunogenicity and safety in this population [14], making it an appropriate comparator. Each vaccine was administered in infants and toddlers as part of the routine childhood vaccination schedule in Europe as a primary series of two doses, with one dose each given at 2 and at 4 months of age, followed by a booster dose at 12–18 months of age (2 + 1 regimen).

METHODS

Study Design and Participants

This was a phase III, partially modified double-blind, randomized, parallel-group, active-controlled, multi-center study in healthy infants and toddlers that compared the immunogenicity and safety profiles of MenACYW-TT and MCV4-TT when administered as a two-dose primary series, with one dose given at 2 and at 4 months of age, followed by a booster dose at 12–18 months of age (2 + 1 regimen) concomitantly with routine pediatric vaccines in Europe. Additionally, MenACYW-TT was also assessed when administered as a three-dose primary series, with one dose given at 2, 4, and 6 months of age, followed by a booster dose at 12–18 months of age (3 + 1 regimen) concomitantly with routine pediatric vaccines.

This study was conducted at 33 centers across seven countries (Czech Republic, Finland, Italy, Spain, Sweden, Poland, and Romania) from 14 December 2018 to 17 May 2023. Study vaccines were coadministered with routinely scheduled vaccines; a hexavalent diphtheria, tetanus, acellular pertussis, inactivated poliovirus, hepatitis B, and *Haemophilus influenzae* type b (DTaP-IPV-HB-Hib) vaccine; a pneumococcal conjugate vaccine (PCV13 or PCV10); and a measles, mumps, and rubella (MMR) vaccine.

Healthy infants, as determined by medical history, physical examination, and investigator judgement, aged ≥ 42 to ≤ 89 days, with a parent/legally acceptable representative available to attend all scheduled visits and comply with all study procedures and covered by health insurance according to local regulations, were eligible for inclusion. Key exclusion criteria included participation or planned participation (during the present study period or in the 4 weeks preceding the first study vaccination) in another clinical study; prior or planned receipt of any other meningococcal vaccine; high risk of meningococcal infection; previous vaccination against, or infection with, diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, poliovirus, *Streptococcus pneumoniae*, measles, mumps, rubella, or hepatitis B; receipt of immune globulins, blood, or blood-derived products; known/suspected congenital or acquired immunodeficiency, or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks); blood dyscrasias, leukemia, lymphoma of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems; active tuberculosis; history of *Neisseria meningitidis* infection; history of any neurologic disorders, including seizures and progressive neurologic disorders, or history of Guillain–Barré syndrome; and known systemic hypersensitivity to any of the vaccine components. Participants were also excluded if they received any vaccine in the 4 weeks preceding the first study vaccination or planned to receive any vaccine in the 4 weeks before and/or following any study vaccination except for influenza vaccination and rotavirus vaccination, which may be received at a gap of at least 2 weeks before or 2 weeks after any study vaccine; however, in Finland, Sweden, and Poland, participants were allowed to receive the licensed rotavirus vaccine concomitantly with study vaccines at any visit, in line with local standard of care.

Ethical Approval

The study was conducted in compliance with the International Conference on Harmonisation guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. Informed consent was obtained from participants' parents (or legal guardian) before any study procedures were performed. The protocol and any amendments were approved by applicable independent ethics committees or institutional review boards at each participating site and the appropriate regulatory agencies in each country (Supplementary methods).

Randomization

Randomization was performed using a permuted block method with stratification by center and age categories as follows: approximately 6 to 8 weeks (≥ 42 to ≤ 59 days), and 9 to 12 weeks (≥ 60 to ≤ 89 days). Participants were randomized to four groups, depending on the pneumococcal vaccine used for routine vaccination (Table S1). In countries where PCV10 was included as part of routine childhood vaccination (Czech Republic, Romania, Sweden, Finland, and Poland), participants were randomized 1:1 to two groups: group 1: MenACYW-TT vaccine at age 2, 4, and 12–18 months (2 + 1 regimen) + PCV10 + hexavalent vaccine + MMR vaccine and group 2: MCV4-TT (2 + 1 regimen) + PCV10 + hexavalent + MMR vaccine. In countries where PCV13 was included as part of routine childhood vaccination (Italy and Spain), participants were randomized 1:1 to two groups: group 3: Men ACYW-TT vaccine (2 + 1 regimen) + PCV13 + hexavalent vaccine + MMR vaccine and group 4: MenACYW-TT vaccine at age 2, 4, 6, and 12–18 months (3 + 1 regimen) + PCV13 + hexavalent vaccine + MMR vaccine.

Routine pediatric vaccines were given to participants in all groups according to the national immunization schedule, in line with local standard of care [15].

Procedures

The allocated MenACYW-TT (MenQuadfi, Sanofi, Swiftwater, PA, USA) and MCV4-TT (Nimenrix, Pfizer Limited, Sandwich, UK) vaccines were administered by intramuscular (IM) injection into the anterolateral area of the thigh. Each dose of MenACYW-TT consisted of 0.5 ml of saline solution containing 10 µg of each meningococcal capsular polysaccharide serogroups A, C, Y, and W and approximately 55 µg of tetanus toxoid protein carrier. MCV4-TT (Nimenrix) was supplied as a powder and reconstituted in a pre-filled syringe with the provided solvent. Each dose (0.5 ml) contained 5 µg of meningococcal capsular polysaccharide serogroups A, C, W-135, and Y and 44 µg tetanus toxoid protein carrier. The composition of all routine vaccines is listed in the Supplementary methods.

Participants were monitored for 30 min after each vaccination to assess the occurrence of any immediate unsolicited systemic adverse events (AEs). Solicited injection site and systemic reactions were recorded in diary cards for 7 days after each vaccination. Unsolicited AEs were recorded up to 30 days after each vaccination. Serious AEs (SAEs) and AEs of special interest (AESIs) were recorded throughout the study from D0 until the end of the study. AESIs included generalized seizures (febrile and non-febrile), Kawasaki disease, Guillain–Barré syndrome, and idiopathic thrombocytopenic purpura.

The vaccination and blood sampling schedule are shown in Table S1. For groups 1, 2, and 3, blood samples were collected at baseline (day [D] 0, Visit [V] 1), 30 days after the second dose (V3), prior to the third dose (V4), and 30 days after the third dose (V5) to assess vaccine immunogenicity. For group 4, blood samples were collected at baseline (D0, V1), 30 days after the third dose (V4), prior to the fourth dose (V5), and 30 days after the fourth dose (V6).

Immunogenicity Assessment

Antibody titers against meningococcal serogroups A, C, W, and Y were measured by a serum bactericidal antibody assay using human complement (hSBA) by Global Clinical Immunology (GCI), Sanofi, Swiftwater, PA, USA [16]. Antibody titers were also assessed using rabbit complement (rSBA) in a subset of participants, by UKHSA (UK Health Security Agency, Manchester, UK). The lower limit of quantitation (LLOQ) of both the hSBA and rSBA was a titer of 1:4. Antibody titers/concentrations against the antigens included in the concomitant routine pediatric vaccines were evaluated by standard validated methods as previously described [17].

Outcomes

The primary immunogenicity endpoint was antibody titers (geometric mean titers [GMTs]) against meningococcal serogroups A, C, W, and

Y, as measured by hSBA, 30 days after the third dose (booster) of MenACYW-TT (group 1) or MCV4-TT (group 2). Secondary immunogenicity endpoints were rates of seroprotection (hSBA antibody titers ≥ 1:8) against meningococcal serogroups A, C, W, and Y 30 days after the second dose of MenACYW-TT (group 1) or MCV4-TT (group 2); GMTs against meningococcal serogroups A, C, W, and Y in group 3 at D0 (before dose 1), 30 days post-dose 2 of MenACYW-TT, and before and 30 days after the third dose; as well as the proportion of participants with hSBA antibody titers ≥ 1:4 and ≥ 1:8 at the corresponding time points after study vaccination. The same endpoints were assessed in group 4 at baseline, 30 days after the third dose, and before and 30 days after the fourth dose (booster).

Seroresponse, defined as hSBA titers ≥ 1:16 for participants with pre-vaccination titers < 1:8, or at least a fourfold increase for those with pre-vaccination titers ≥ 1:8, was assessed at D30 after the 12–18 month vaccination (dose 3 [booster]) in group 1 and group 2, as well as the proportion of participants with antibody titers ≥ 1:4 and titers ≥ 1:8 before and at D30 after the 12–18 month vaccination (dose 3 [booster]).

Antibody concentrations/titers against DTaP-IPV-HB-Hib vaccine antigens were also assessed in groups 1, 2, and 3 at D0 (only for pertussis toxin [PT] and filamentous hemagglutinin [FHA] antigens), 30 days after the second dose, and before and 30 days after the booster dose (dose 3) (Supplementary methods). Antibody concentrations against the antigens of PCV10 in groups 1 and 2, or against the antigens of PCV13 in group 3, were assessed 30 days after dose 2 and 30 days after the booster dose (dose 3), and those against the antigens of MMR vaccine were assessed 30 days after the MMR vaccine injection. In group 4, antibody titers against the antigens of DTaP-IPV-HB-Hib vaccine and against the antigens of PCV13 vaccine were assessed before and 30 days after the booster dose (dose 4), and antibody concentrations against the antigens of MMR vaccine were assessed 30 days after vaccination.

Antibody titers (GMTs) against meningococcal serogroups A, C, W, and Y were also measured by rSBA in a subset of participants from all groups at D0, 30 days post-dose 2 (groups 1, 2, and 3) or 30 days post-dose 3 (group 4), and before and 30 days after booster dose (all groups). Additionally, the proportion of participants with rSBA antibody titers ≥ 1:8 and ≥ 1:128 and post-vaccination titers ≥ 4 times the pre-vaccination titer were assessed in all groups at the corresponding time points after study vaccination. rSBA seroresponse was defined as a post-vaccination rSBA titer ≥ 1:32 for participants with pre-vaccination titer < 1:8, or a post-vaccination titer ≥ 4 times the pre-vaccination titer for participants with pre-vaccination titer ≥ 1:8.

Statistical Analyses

The primary objective was to demonstrate the non-inferiority of MenACYW-TT (group 1) to MCV4-TT (group 2) in terms of hSBA GMTs against meningococcal serogroups A, C, W, and Y at day 30 post-dose 3 (the booster). Approximately 1652 participants were planned for enrollment, with 716 in both group 1 and group 2. Considering a potential attrition rate of 26.2% in group 1 and group 2, the study would have 96.2% power to declare the non-inferiority of MenACYW-TT (group 1) vs MCV4-TT (group 2), assuming a one-sided alpha level of 2.5%, a non-inferiority margin of 1.5 (GMT ratio), and a standard deviation (SD) of log10-transformed titers of 0.7 for serogroups A and C, 0.5 for serogroup Y, and 0.6 for serogroup W. No formal sample size calculations were performed for groups 3 and 4; however, the sample size was arbitrarily set to 110 participants in each group to achieve > 95% probability to observe an AE with an incidence of 2.7%.

The non-inferiority of MenACYW-TT (group 1) compared with MCV4-TT (group 2) was demonstrated if the lower limit of the two-sided 95% confidence interval (CI) of the GMT ratio for group 1/group 2 for all four serogroups was above 1/1.5. A secondary objective of non-inferiority of MenACYW-TT (group 1) compared with MCV4-TT (group 2) in terms of the percentage of infants with hSBA antibody titers ≥ 1:8 post-dose 2 would be tested if the primary non-inferiority objective was met. Non-inferiority of MenACYW-TT compared with MCV4-TT would be demonstrated if the lower limit of the two-sided 95% CI of the difference between the two percentages was greater than – 10% for all four serogroups.

Categorical variables, including safety outcomes, were summarized and presented by frequency counts, percentages, and CIs. The 95% CIs of point estimates were calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper–Pearson method) for proportions. For GMTs and geometric mean concentrations (GMCs), 95% CIs of point estimates were calculated using a normal approximation, assuming log-normal distribution.

Immunogenicity assessments were performed on the per-protocol analysis set (PPAS), which included all participants who met all protocol-specified inclusion criteria and did not meet any protocol-specified exclusion criteria, received the primary (PPAS1) or booster (PPAS2) vaccine they were randomized to receive, and provided blood samples within specified time windows. Immunogenicity analyses were confirmed on the full analysis set (FAS), which consisted of all participants who received at least one dose of the primary vaccination (FAS1) or one booster dose (FAS2) and had a valid post-vaccination blood sample result. Safety analyses were performed on the safety analysis set (SafAS), which comprised all participants who received at least one dose of the study vaccine and had safety data available.

Since clinical trials to assess vaccine efficacy are not feasible due to the low incidence of IMD, the efficacy of meningococcal vaccines has been inferred from SBA data alone [18]. Although several factors including variations in assay performance can affect the number of individuals achieving a specific hSBA titer threshold (such as ≥ 1:4), these factors have limited impact on response measures like fold increases, which are based on self-referenced comparisons to each individual's own pre-vaccination titer. As such, vaccine seroresponse may be considered the most informative measure to estimate how well a vaccine induces a protective immune response [18]. In a post hoc analysis, we assessed the non-inferiority of MenACYW-TT (group 1) to MCV4-TT (group 2) based on hSBA seroresponse rates at D30 post-booster dose. Non-inferiority was demonstrated if the lower limit of the two-sided 95% CI for the difference in seroresponse rates between MenACYW-TT (group 1) and MCV4-TT (group 2) was > – 10% for all four serogroups.

Statistical analyses were done using SAS® Version 9.4 software or later (SAS Institute Inc, Cary, NC, USA).

RESULTS

Study Populations

A total of 1660 participants were enrolled and randomized to group 1 (n = 714), group 2 (n = 726), group 3 (n = 112) and group 4 (n = 108). Of these, 681 (95.4%) participants in group 1, 691 (95.2%) participants in group 2, 106 (94.6%) participants in group 3, and 104 (96.3%) participants in group 4 completed the study (Fig. 1). The reasons for not completing the study included withdrawal by parent/guardian (n = 54), protocol deviation (n = 15), loss to follow-up (n = 7), and AEs (n = 2). Of the AEs that led to study discontinuation, one was reported in group 1 (poor weight gain) and one in group 2 (food allergy); both AEs were considered not related to the study vaccine (Fig. 1).

For analysis of the primary vaccination series, 1548 (93.3%) participants were included in FAS1 (group 1, n = 669; group 2, n = 670; group 3, n = 107; group 4, n = 102), and 1232 (74.2%) participants were included in PPAS1 (group 1, n = 522; group 2, n = 524; group 3, n = 96; group 4, n = 90). For analysis of the booster series, 1556 (93.7%) participants were included in FAS2 (group 1, n = 668; group 2, n = 680; group 3, n = 106; group 4, n = 102), and 1328 (80.0%) participants were included in PPAS2 (group 1, n = 560; group 2, n = 584; group 3, n = 94; group 4, n = 90). The overall SafAS comprised 1623 (100%) participants (group 1, n = 696; group 2, n = 706; group 3, n = 112; group 4, n = 108). The number of participants included in these analysis populations does not exactly match the number of participants present at corresponding visits in Fig. 1, since the definitions used (see methods) do not necessarily reflect the numbers assessed at the corresponding visits.

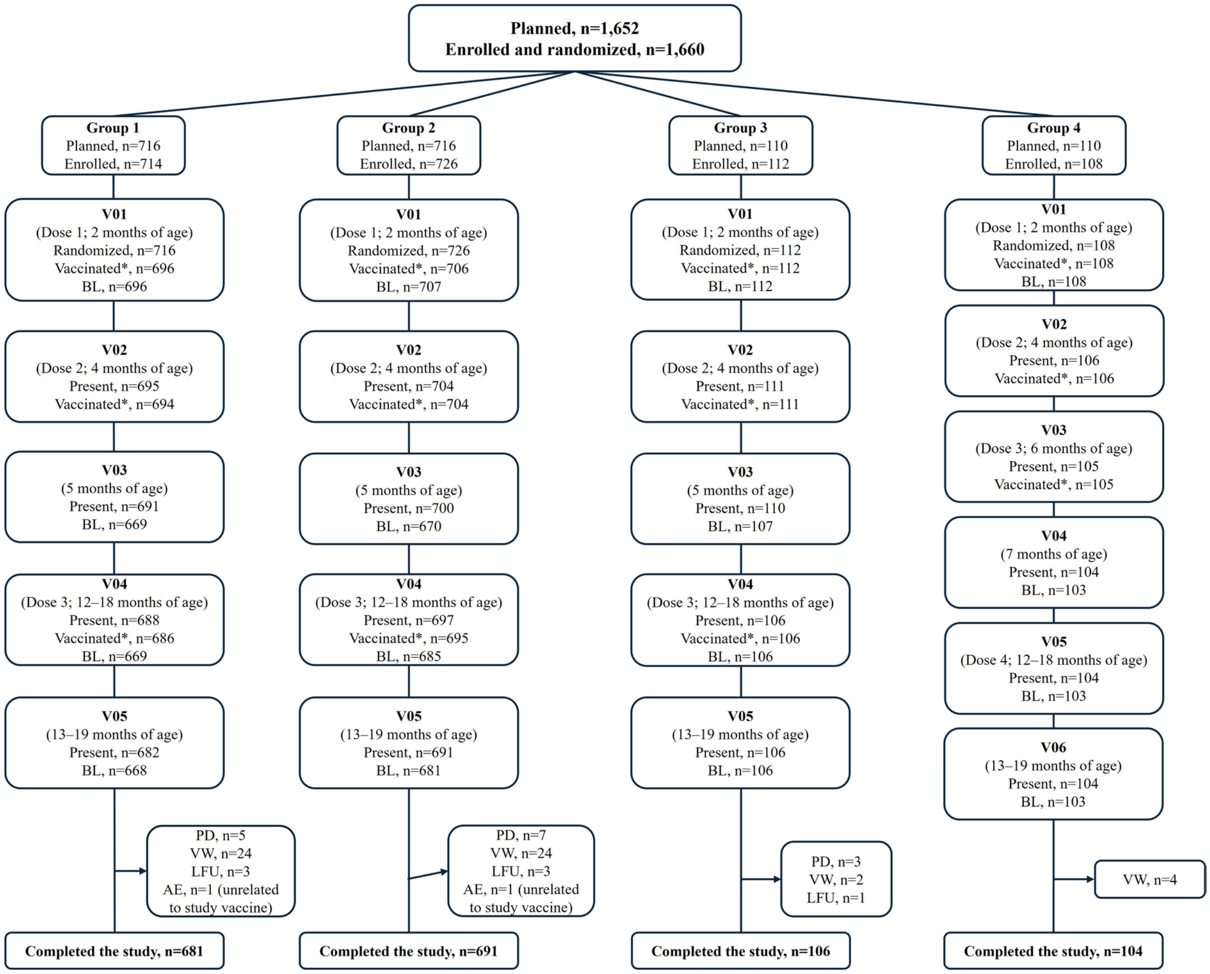

Fig. 1 Flow of participants through the study. *AE* adverse event, *BL* blood sample, *LFU* lost to follow-up, *MCV4-TT* quadrivalent meningococcal conjugate vaccine, *MenACYW-TT* quadrivalent meningococcal polysaccharide tetanus toxoid-conjugate vaccine, *PD* protocol deviation, *V* visit, *VW* voluntary withdrawal by parent(s)/legally acceptable representative(s). *The numbers of participants who received MenACYW-TT (groups 1, 3, and 4) or MCV4-TT (group 2)

The baseline characteristics of the participants in the study groups are summarized in Table 1.

Immunogenicity of Meningococcal Vaccines (Primary Objective)

The hSBA GMTs at D30 post-dose 3 (after the 12 to 18-month vaccination) for MenACYW-TT recipients (group 1) and MCV4-TT recipients (group 2) are presented in Table 2. At D30 post-dose 3, the lower limit of the two-sided 95% CI of the ratio of hSBA GMTs between group 1 and group 2 was greater than 1/1.5 for serogroups C, W, and Y but not for serogroup A (Table 2). Thus, the non-inferiority of MenACYW-TT (group 1) compared with MCV4-TT (group 2) was demonstrated for meningococcal serogroups C, W, and Y but not for serogroup A. Accordingly, the primary objective was not met. Similar results were observed in the FAS.

Since the primary objective was not met, non-inferiority of the percentage of participants with hSBA antibody titers ≥ 1:8 at D30 post-dose 2 (after 4-month vaccination) in MenACYW-TT recipients (group 1) versus MCV4-TT recipients

Table 1 Summary of participants demographic characteristics at baseline (all randomized participants)

	MenACYW-TT+MMR+PCV10 (2+1 regimen; group 1) (*N*=714)	**MCV4-TT+MMR+PCV10 (2+1 regimen; group 2) (*N*=726)**	**MenACYW-TT+MMR+PCV13 (2+1 regimen; group 3) (*N*=112)**	**MenACYW-TT+MMR+PCV13 (3+1 regimen; group 4) (*N*=108)**
Sex: *n* (%)				
Male	359 (50.3)	348 (47.9)	67 (59.8)	50 (46.3)
Female	355 (49.7)	378 (52.1)	45 (40.2)	58 (53.7)
Sex ratio: M/F	1.01	0.92	1.49	0.86
Age: (days) M				
Mean (SD)	72.6 (12.2)	72.4 (12.1)	62.5 (7.12)	63.3 (7.9)
Min; max	42.0; 89.0	42.0; 89.0	43.0; 84.0	43.0; 86.0
Median	76.0	75.5	63.0	63.5
Q1; Q3	64.0; 83.0	65.0; 82.0	59.0; 65.5	59.5; 67.0
Age group: *n* (%)				
≥ 42 to ≤ 59 days	114 (16.0)	115 (15.8)	29 (25.9)	27 (25.0)
≥ 60 to ≤ 89 days	600 (84.0)	611 (84.2)	83 (74.1)	81 (75.0)
Racial origin: *n* (%)				
American Indian or Alaska Native	0	0	1 (0.9)	0
Asian	2 (0.3)	1 (0.1)	4 (3.6)	2 (1.9)
Black or African American	0	0	1 (0.9)	3 (2.8)
Native Hawaiian or Other Pacific Islander	0	1 (0.1)	0	0
White	693 (97.1)	699 (96.3)	106 (94.6)	101 (93.5)
Not Reported	13 (1.8)	16 (2.2)	0	1 (0.9)
Unknown	2 (0.3)	3 (0.4)	0	0
Multiple origin	4 (0.6)	6 (0.8)	0	1 (0.9)
Ethnicity: *n* (%)				
Hispanic or Latino	17 (2.4)	12 (1.7)	77 (68.8)	75 (69.4)
Not Hispanic/Latino	642 (89.9)	660 (90.9)	35 (31.3)	33 (30.6)
Not Reported	51 (7.1)	52 (7.2)	0	0

Table 1 continued

	MenACYW-TT+MMR+PCV10 (2+1 regimen; group 1) (N=714)	MCV4-TT+MMR+PCV10 (2+1 regimen; group 2) (N=726)	MenACYW-TT+MMR+PCV13 (2+1 regimen; group 3) (N=112)	MenACYW-TT+MMR+PCV13 (3+1 regimen; group 4) (N=108)
Unknown	4 (0.6)	2 (0.3)	0	0
Gestational age: n (%)				
Preterm birth[a]	15 (2.1)	14 (1.9)	0	0
Full-term birth[b]	698 (97.8)	710 (97.8)	112 (100)	108 (100)
Missing	1 (0.1)	2 (0.3)	0	0

Group 1: MenACYW-TT and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12–18 months of age

Group 2: MCV4-TT and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12–18 months of age

Group 3: MenACYW-TT and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12–18 months of age

Group 4: MenACYW-TT administered at 2, 4, 6, and 12–18 months of age. Routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12–18 months of age

MCV4-TT, quadrivalent meningococcal conjugate vaccine; MenACYW-TT, quadrivalent meningococcal polysaccharide tetanus toxoid-conjugate vaccine; MMR, measles-mumps-rubella; M, number of participants with available data for the endpoint; n, number of participants fulfilling the item listed in the first column; N, number of participants randomized in each study group; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; Q1; first quartile; Q3, third quartile; SD, standard deviation

[a]Preterm infant born at gestational age < 37 weeks

[b]Full-term infant born at gestational age ≥ 37 weeks

(group 2) was assessed only for information purposes (Fig. 2a). Non-inferiority was also met for all serogroups except serogroup A (Fig. 2b).

Post hoc Immunogenicity Analyses

Over 90% of participants who received MenACYW-TT (group 1) achieved vaccine seroresponse against all meningococcal serogroups, including serogroup A, similar to those in the MCV4-TT group (group 2) (Fig. 3a). Post hoc non-inferiority, based on hSBA vaccine seroresponse post-dose 3, was met for all four meningococcal serogroups, including serogroup A; the lower limit of the 95% CI of the difference in the proportion of participants with an hSBA vaccine seroresponse rate was greater than the non-inferiority margin of − 10% for all meningococcal serogroups (Fig. 3b).

Immunogenicity of Meningococcal Vaccines (Secondary Objectives)

We also descriptively assessed the percentage of participants with hSBA titers ≥ 1:4 and ≥ 1:8 before the first dose, post-dose 2, and before and after dose 3 with MenACYW-TT (group 1) and MCV4-TT (group 2). Regardless of vaccine, hSBA titers increased post-dose 2 using the ≥ 1:4 seroprotection threshold (Fig. 4a). Seroprotection rates decreased between doses 2 and 3 across both groups but was higher in MenACYW-TT recipients (group 1) than MCV4-TT

Table 2 Non-inferiority of hSBA titers 30 days after the booster dose of MenACYW-TT (group 1) versus MCV4-TT (group 2) at 12–18 months of age (PPAS2)

Serogroup	MenACYW-TT + MMR + PCV10 (2 + 1 regimen; group 1) (*N* = 560)		MCV4-TT + MMR + PCV10 (2 + 1 regimen; group 2) (*N* = 584)		Group 1/Group 2	
	M	GMT (95% CI)	M	GMT (95% CI)	Ratio (95% CI)	Non-inferiority
A	543	131 (113; 151)	567	189 (165; 218)	0.7 (0.6; 0.8)	No
C	550	565 (505; 632)	578	120 (106; 135)	4.7 (4.0; 5.6)	Yes
Y	554	285 (260; 313)	579	160 (145; 177)	1.8 (1.6; 2.0)	Yes
W	547	423 (382; 468)	575	275 (247; 305)	1.5 (1.3; 1.8)	Yes

CI, confidence interval; GMT, geometric mean titer; hSBA, serum bactericidal antibody assay using human complement; M, number of participants with available data for the endpoint; MCV4-TT, quadrivalent meningococcal conjugate vaccine; MenACYW-TT, quadrivalent meningococcal polysaccharide tetanus toxoid-conjugate vaccine; MMR, measles-mumps-rubella; *N*: number of participants in PPAS2 for the booster series; PCV10, 10-valent pneumococcal conjugate vaccine; PPAS2, per-protocol analysis set 2

95% CI of the geometric mean calculated on Log10 titers using the usual calculation for normal distribution, then antilog transformations were applied to the results of the calculations

95% CI of the ratio calculated using a normal approximation of log-transformed titers

Non-inferiority was demonstrated if the lower limit of the two-sided 95% CI was > 1/1.5 for all four serogroups

Group 1: MenACYW-TT and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12–18 months of age

Group 2: MCV4-TT and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12–18 months of age

recipients (group 2) for serogroups C, W, and Y before the booster dose (pre-dose 3); seroprotection rates remained well above those noted at baseline across both groups (Fig. 4a). A similar pattern was observed using the more stringent 1:8 seroprotection threshold, with the difference between the two groups pre-dose 3 more pronounced (Fig. 4b). Seroprotection rates post-dose 2 with the stringent definition of ≥ 1:8 appeared to be slightly higher against serogroups C, W, and Y in MenACYW-TT recipients (group 1) than MCV4-TT recipients (group 2) but not against serogroup A, for which the rate was higher in MCV4-TT recipients (group 2; Fig. 4b). Of note, the seroprotection rates against serogroups C, W, and Y pre-dose 3 remained higher in MenACYW-TT recipients (group 1) than MCV4-TT recipients (group 2). Regardless of the hSBA threshold, seroprotection rates post-dose 3 (booster) were approximately 95–100% for all serogroups across the different vaccine groups.

In group 3, the antibody responses against meningococcal serogroups A, C, W, and Y, characterized by the hSBA GMTs (Table S2) and the percentages of participants with hSBA titers ≥ 1:4 and ≥ 1:8 (Fig. 4), were similar to those achieved in group 1 (Table 3). The antibody responses observed after the four-dose series (3 + 1 regimen) of MenACYW-TT (group 4) (Tables S3 and S4) were also generally similar to those observed after the three-dose series (2 + 1 regimen) (group 3) at the respective time points (Fig. 4).

The trends in antibody responses measured by rSBA were similar to those measured by hSBA, confirming the reliability of the study results (Supplementary Tables 5–8).

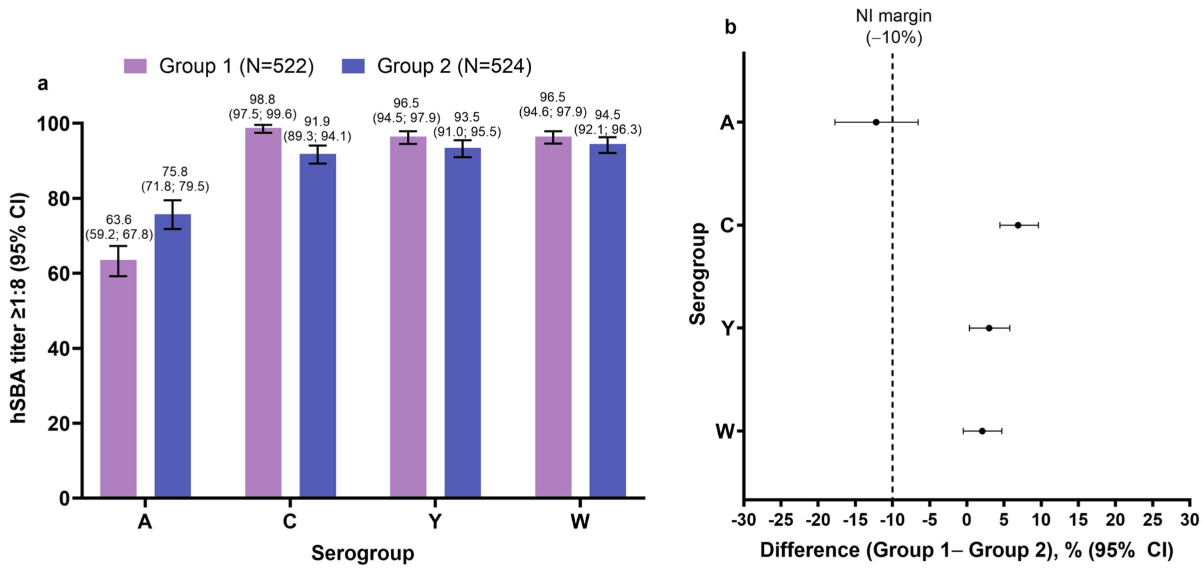

Fig. 2 hSBA vaccine seroprotection (antibody titers ≥ 1:8) 30 days after the second dose of MenACYW-TT (group 1) versus MCV4-TT (group 2) at 4 months of age (**a**) seroprotection rates and (**b**) non-inferiority analysis in PPAS. *CI* confidence interval, *hSBA* serum bactericidal antibody assay using human complement, *MCV4-TT* quadrivalent meningococcal conjugate vaccine, *MenACYW-TT* quadrivalent meningococcal polysaccharide tetanus toxoid-conjugate vaccine, *N* number of participants, *NI* non-inferiority, *PCV10* 10-valent pneumococcal conjugate vaccine. 95% CI of the single proportion calculated from the exact binomial method. 95% CI of the difference calculated from the Wilson score method without continuity correction. The overall non-inferiority was demonstrated if the lower limit of the two-sided 95% CI was > − 10% for all four serogroups. Group 1: MenACYW-TT and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12–18 months of age. Group 2: MCV4-TT and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12–18 months of age

Immunogenicity of Concomitant Routine Vaccines

The immune responses to the routine pediatric vaccines administered concomitantly with MenACYW-TT did not appear to differ from those administered concomitantly with MCV4-TT, irrespective of the MenACYW-TT regimen (Supplementary tables 9–13).

Responses to PCV10 were similar between those who received MenACYW-TT (group 1) and MCV4-TT (group 2), and responses to PCV13 in group 3 (2 + 1 regiment) and group 4 (3 + 1 regimen) were comparable to those observed in groups 1 and 2 for the shared vaccine serotypes (Supplementary tables 14–18).

Safety Analyses

A summary of the safety data from D0 to D30 is presented in Table 4. Overall, the safety profile and tolerance of MenACYW-TT was comparable to those of MCV4-TT, with no new safety concerns identified following the administration of MenACYW-TT as a three- or four-dose series in healthy infants and toddlers. Two immediate unsolicited AEs were reported, one following the 4-month vaccination (contusion in group 1; unrelated to MenACYW-TT) and one following the 6-month vaccination (syncope in group 4; related to MenACYW-TT). Across all groups, the most common solicited site injection reaction was tenderness (group 1, 57.8%; group 2, 58.3%; group 3, 60.7%; and group 4, 64.2%) and the most common solicited systemic reaction was irritability (group 1, 86.1%; group 2, 86.1%;

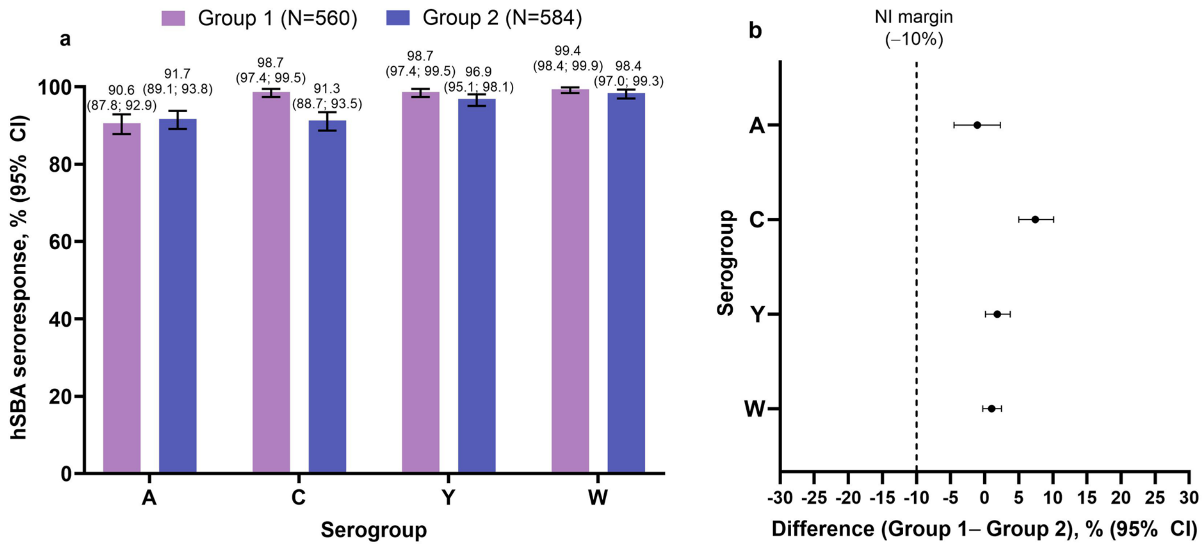

Fig. 3 hSBA seroresponse 30 days after booster dose of MenACYW-TT (group 1) versus MCV4-TT (group 2) at 12–18 months of age; (**a**) hSBA seroresponse rate and (**b**) post hoc non-inferiority analysis in PPAS. *CI* confidence interval, *hSBA* serum bactericidal antibody assay using human complement, *MCV4-TT* quadrivalent meningococcal conjugate vaccine, *MenACYW-TT* quadrivalent meningococcal polysaccharide tetanus toxoid-conjugate vaccine, *N* number of participants, *NI* non-inferiority, *PCV10* 10-valent pneumococcal conjugate vaccine, *PPAS* per-protocol analysis set. hSBA vaccine seroresponse was defined as a post-vaccination titer ≥ 1:16 for participants with a pre-vaccination hSBA titer < 1:8, or a post-vaccination titer ≥ fourfold increase from baseline for participants with a pre-vaccination hSBA titer ≥ 1:8. Post hoc non-inferiority assessment: lower limit of the two-sided 95% CI of the difference in hSBA seroresponse rates > − 10% for all four serogroups. Group 1: MenACYW-TT and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12–18 months of age. Group 2: MCV4-TT and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12–18 months of age.

group 3, 81.3%; and group 4, 81.1%). Most solicited reactions started within 3 days of vaccination and resolved spontaneously after 1–3 days (data not shown). Additionally, no AEs that led to study discontinuation were reported within 30 days of any vaccination in any group. A total of 37 SAEs were reported within 30 days of vaccination (group 1, 2.6%; group 2, 2.3%; group 3, 1.8%; group 4, 0.9%); however, no SAEs or AESIs were considered related to study vaccine, and no deaths were reported during the study.

DISCUSSION

Overall, data from this study are consistent with those from previous studies, with MenACYW-TT providing young infants seroprotection against IMD caused by serogroups A, C, W, and Y. High seroprotection (hSBA titer ≥ 1:8) rates (≥ 95%) and seroresponse rates (> 90%) against all four meningococcal serogroups were observed upon completion of the 2 + 1 regimen. However, based on the EMA-recommended endpoints, which include both GMTs post-booster dose (at 12–18 months of age) and seroprotection (hSBA titer ≥ 1:8) 30 days after completion of primary vaccination (at 2 and 4 months of age), formal non-inferiority of MenACYW-TT (group 1) vs MCV4-TT (group 2) was missed for serogroup A but met for serogroups C, Y, and W. Nonetheless, for all four serogroups, MenACYW-TT elicited hSBA protective titers after the first two doses (2 and 4 months) that persisted well above those observed at baseline through 12–18 months and were substantially enhanced with a booster dose. The non-inferiority of MenACYW-TT versus

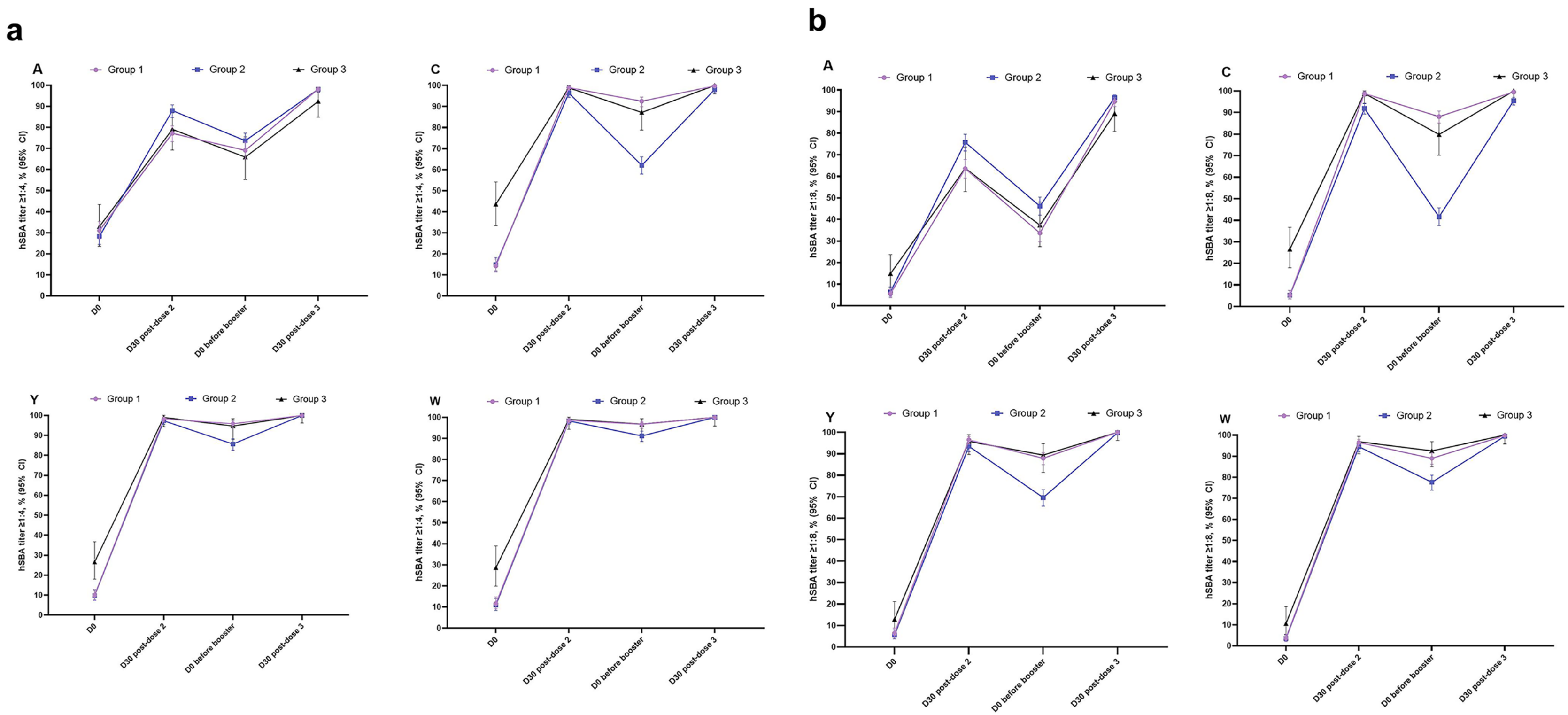

Fig. 4 Percentage of participants with hSBA titer (**a**) ≥ 1:4 and (**b**) ≥ 1:8 at D0 before dose 1 at 2 months of age, D30 post-dose 2 at 4 months of age, and at D0 before and D30 after the booster at 12–18 months of age for groups 1, 2 and 3. *CI* confidence interval, *D* day, *hSBA* serum bactericidal antibody assay using human complement, *MCV4-TT* quadrivalent meningococcal conjugate vaccine, *MenACYW-TT* quadrivalent meningococcal polysaccharide tetanus toxoid-conjugate vaccine, *PCV10* 10-valent pneumococcal conjugate vaccine, *PCV13* 13-valent pneumococcal conjugate vaccine. 95% CI of the single proportion calculated from the exact binomial method. group 1: MenACYW-TT and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12–18 months of age. Group 2: MCV4-TT and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12–18 months of age. Group 3: MenACYW-TT and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12–18 months of age

MCV4-TT was also evaluated—and met—post hoc based on seroresponse rates post-booster (Fig. 3) (where seroresponse was defined as the post-vaccination titer ≥ 1:16 for those with pre-vaccination hSBA titer < 1:8 or ≥ fourfold increase from baseline for those with pre-vaccination hSBA titer ≥ 1:8). It is important to note that seroresponse, which assesses individual antibody level change from baseline, may be considered a more meaningful endpoint for evaluating vaccine performance than seroprotection, which refers to a pre-defined cut-off that does not take into account an individual's baseline antibody levels [18].

While antibody responses against meningococcal serogroup A were marginally lower with MenACYW-TT, those against serogroups C, W, and Y were generally more robust than those with MCV4-TT, with responses against serogroup C markedly higher with MenACYW-TT. Although non-inferiority based on seroprotection (hSBA titer ≥ 1:8) was not met at D30 after completion of the primary infant series for serogroup A, 64% of infants were seroprotected with MenACYW-TT. Additionally, hSBA titers ≥ 1:4 can also infer vaccine-mediated protection, although a threshold of ≥ 1:8 is usually used to account for assay variability [19–21]. As an example of such variability, in this study, GMTs observed with MCV4-TT varied between 120 and 275 post-booster with the hSBA assay conducted in-house; however, in another study, GMTs for MCV4-TT were up to 40 times higher for the same time point if the hSBA assay was conducted in a different laboratory [22]. Of note, the majority (77%) of participants achieved hSBA titers ≥ 1:4 for serogroup A at D30 after the infant series (two doses) with MenACYW-TT and the majority (69%) retained this level of seroprotection through 12–18 months of age; similar results were observed for serogroup A in the MCV4-TT group (88% and 74%). The proportion of participants with hSBA titers ≥ 1:4 for serogroup A at D30 post-booster dose increased to 98% with both MenACYW-TT and MCV4-TT. These findings were consistent with immune responses that were measured using rSBA.

Marginally lower hSBA GMTs against serogroup A were observed with MenACYW-TT vs MCV4-TT in this study (131 vs. 189, respectively, 30 days after the booster dose). These data are in line with a previous study in toddlers that also reported similar or marginally lower (depending on whether they were meningococcal vaccine naïve and/or meningococcal vaccine primed) hSBA GMTs against serogroup A 30 days post-vaccination with a single dose of MenACYW-TT compared with MCV4-TT [23]. However, another study in toddlers (≥ 12 months of age) reported marginally higher hSBA GMTs with MenACYW-TT versus MCV4-TT for serogroup A after a single dose [24]. This variability supports use of immune measures beyond GMTs to fully assess immunogenicity and perhaps, use of a less stringent threshold (e.g., 0.5 [previously used for assessing lot-to-lot consistency of MenACYW-TT] instead of 0.667) when assessing non-inferiority of MenACWY vaccines based on GMT ratios [25].

MenACYW-TT (group 1) and MCV4-TT (group 2) administered concomitantly with routine scheduled childhood vaccines displayed similar safety profiles, with no new safety concerns identified with any of the study vaccines. Overall, this study adds to the accumulating safety data of the use MenACYW-TT during the first year of life from six Phase III studies (MET33, MET41, MET42, MET52, MET58, and MET61), which to date includes over 6000 participants who received one dose, over 4800 participants who received two doses (primary series), and over 3590 participants who received three doses (primary series plus booster dose).

Considering that vaccination programs differ among countries, this study also assessed both a 2 + 1 and a 3 + 1 regimen. We found that an additional dose had limited impact on immune responses to serogroups C, W, and Y, with only a marginally increased response to serogroup A noted, and a comparable safety profile.

In general, there was no evidence to suggest any interference with immune responses to the scheduled routine pediatric vaccines administered alongside MenACYW-TT or MCV4-TT, consistent with other studies in which these vaccines were administered with similar routine pediatric vaccines in other infant populations (MET39 [9] and MET42) [22, 26, 27].

A strength of this study was the reliability of the antibody titer data, as all hSBA and rSBA

Table 3 Number and percentage of participants with ≥ fourfold rise in hSBA titer in groups 1, 2, and 3 (PPAS)

Serogroup	MenACYW-TT + MMR + PCV10 (2 + 1 regimen; group 1)				MCV4-TT + MMR + PCV10 (2 + 1 regimen; group 2)				MenACYW-TT + MMR + PCV13 (2 + 1 regimen; group 3)			
	D0 to 30 days post 4-month vaccination (N = 522)[a]		D0 to 30 days post 12 to 18-month vaccination N = 560)[b]		D0 to 30 days post 4-month vaccination (N = 524)[a]		D0 to 30 days post 12 to 18-month vaccination (N = 584)[b]		D0 to 30 days post 4-month vaccination (N = 96)[a]		D0 to 30 days post 12 to 18-month vaccination (N = 94)[b]	
	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)
A	290/507	57.2 (52.8; 61.6)	508/542	93.7 (91.3; 95.6)	355/504	70.4 (66.2; 74.4)	534/564	94.7 (92.5; 96.4)	51/89	57.3 (46.4; 67.7)	74/90	82.2 (72.7; 89.5)
C	496/508	97.6 (95.9; 98.8)	539/545	98.9 (97.6; 99.6)	459/514	89.3 (86.3; 91.8)	540/573	94.2 (92.0; 96.0)	86/93	92.5 (85.1; 96.9)	91/91	100 (96.0; 100)
Y	481/513	93.8 (91.3; 95.7)	545/551	98.9 (97.6; 99.6)	467/517	90.3 (87.4; 92.7)	568/575	98.8 (97.5; 99.5)	87/94	92.6 (85.3; 97.0)	92/92	100 (96.1; 100)
W	494/516	95.7 (93.6; 97.3)	544/545	99.8 (99.0; 100)	484/519	93.3 (90.7; 95.3)	567/572	99.1 (98.0; 99.7)	91/94	96.8 (91.0; 99.3)	85/85	100 (95.8; 100)

Group 1: MenACYW-TT and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12–18 months of age

Group 2: MCV4-TT and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12–18 months of age

Group 3: MenACYW-TT and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12–18 months of age

CI, confidence interval; D, day; hSBA, serum bactericidal antibody assay using human complement; M, number of participants with valid serology results for the particular serogroup; MCV4-TT, quadrivalent meningococcal conjugate vaccine; MenACYW-TT, quadrivalent meningococcal polysaccharide tetanus toxoid-conjugate vaccine; MMR, measles-mumps-rubella; n, number of participants with valid serology results for the particular serogroup and who met the criterion; N, number of participants in PPAS for the booster series; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPAS, per-protocol analysis set

Percentages are based on M

95% CI of the single proportion calculated from the exact binomial method

[a]PPAS1

[b]PPAS2

Table 4 Safety overview after any study vaccine (Overall Safety Analysis Set for Any Dose)

Subjects experiencing at least one	**MenACYW-TT + MMR + PCV10 (2 + 1 regimen; group 1) (*N* = 696)**			**MCV4-TT + MMR + PCV10 (2 + 1 regimen; group 2) (*N* = 706)**			**MenACYW-TT + MMR + PCV13 (2 + 1 regimen; group 3) (*N* = 112)**			**MenACYW-TT + MMR + PCV13 (3 + 1 regimen; group 4) (*N* = 108)**		
	n*/*M	%	**(95% CI)**	***n*/*M***	%	**(95% CI)**	***n*/*M***	%	**(95% CI)**	***n*/*M***	%	**(95% CI)**
Within 30 min after any vaccine injections												
Immediate unsolicited AE	1/696	0.1	(0; 0.8)	0/706	0	(0; 0.5)	0/112	0	(0; 3.2)	1/108	0.9	(0; 5.1)
Immediate unsolicited AR	0/696	0	(0; 0.5)	0/706	0	(0; 0.5)	0/112	0	(0; 3.2)	1/108	0.9	(0; 5.1)
D0 to D7 after any vaccine injections	677/696	97.3	(95.8; 98.3)	680/705	96.5	(94.8; 97.7)	104/112	92.9	(86.4; 96.9)	103/106	97.2	(92.0; 99.4)
Solicited injection-site reaction	628/696	90.2	(87.8; 92.3)	632/705	89.6	(87.2; 91.8)	95/112	84.8	(76.8; 90.9)	86/106	81.1	(72.4; 88.1)
Solicited injection-site reaction after injection of MenACYW-TT or MCV4-TT	494/696	71.0	(67.4; 74.3)	476/705	67.5	(63.9; 71.0)	72/112	64.3	(54.7; 73.1)	74/106	69.8	(60.1; 78.3)
Solicited injection-site reaction after injection of DTaP-IPV-HB-Hib	584/696	83.9	(81.0; 86.6)	577/705	81.8	(78.8; 84.6)	81/112	72.3	(63.1; 80.4)	71/106	67.0	(57.2; 75.8)
Solicited injection-site reaction after injection of PCV13 or PCV10	596/696	85.6	(82.8; 88.2)	592/705	84.0	(81.1; 86.6)	86/112	76.8	(67.9; 84.2)	72/106	67.9	(58.2; 76.7)
Solicited injection-site reaction after injection of MMR vaccine	291/643	45.3	(41.4; 49.2)	303/651	46.5	(42.7; 50.5)	39/105	37.1	(27.9; 47.1)	38/103	36.9	(27.6; 47.0)
Solicited systemic reaction	661/696	95.0	(93.1; 96.5)	659/705	93.5	(91.4; 95.2)	100/112	89.3	(82.0; 94.3)	96/106	90.6	(83.3; 95.4)
D0 to D30 after any vaccine injections												
Unsolicited AE	458/696	65.8	(62.1; 69.3)	480/706	68.0	(64.4; 71.4)	80/112	71.4	(62.1; 79.6)	79/108	73.1	(63.8; 81.2)
Unsolicited AR	128/696	18.4	(15.6; 21.5)	128/706	18.1	(15.4; 21.2)	10/112	8.9	(4.4; 15.8)	17/108	15.7	(9.4; 24.0)
Unsolicited non-serious AE	453/696	65.1	(61.4; 68.6)	477/706	67.6	(64.0; 71.0)	79/112	70.5	(61.2; 78.8)	79/108	73.1	(63.8; 81.2)

Table 4 continued

Subjects experiencing at least one	**MenACYW-TT + MMR + PCV10 (2 + 1 regimen; group 1) (*N* = 696)**			**MCV4-TT + MMR + PCV10 (2 + 1 regimen; group 2) (*N* = 706)**			**MenACYW-TT + MMR + PCV13 (2 + 1 regimen; group 3) (*N* = 112)**			**MenACYW-TT + MMR + PCV13 (3 + 1 regimen; group 4) (*N* = 108)**		
	n*/*M	%	**(95% CI)**	***n*/*M***	%	**(95% CI)**	***n*/*M***	%	**(95% CI)**	***n*/*M***	%	**(95% CI)**
Unsolicited non-serious AR	128/696	18.4	(15.6; 21.5)	128/706	18.1	(15.4; 21.2)	10/112	8.9	(4.4; 15.8)	17/108	15.7	(9.4; 24.0)
Unsolicited non-serious injection-site AR related to MenACYW-TT or MCV4-TT	84/696	12.1	(9.7; 14.7)	74/706	10.5	(8.3; 13.0)	6/112	5.4	(2.0; 11.3)	13/108	12.0	(6.6; 19.7)
Unsolicited non-serious injection-site AR related to DTaP-IPV-HB-Hib	158/696	22.7	(19.6; 26.0)	142/706	20.1	(17.2; 23.3)	5/112	4.5	(1.5; 10.1)	4/108	3.7	(1.0; 9.2)
Unsolicited non-serious injection-site AR related to PCV13 or PCV10	156/696	22.4	(19.4; 25.7)	152/706	21.5	(18.6; 24.7)	9/112	8.0	(3.7; 14.7)	10/108	9.3	(4.5; 16.4)
Unsolicited non-serious injection-site AR related to MMR vaccine	29/696	4.2	(2.8; 5.9)	32/706	4.5	(3.1; 6.3)	4/112	3.6	(1.0; 8.9)	5/108	4.6	(1.5; 10.5)
Unsolicited non-serious systemic AE	406/696	58.3	(54.6; 62.0)	428/706	60.6	(56.9; 64.2)	74/112	66.1	(56.5; 74.7)	77/108	71.3	(61.8; 79.6)
Unsolicited non-serious systemic AR	56/696	8.0	(6.1; 10.3)	63/706	8.9	(6.9; 11.3)	4/112	3.6	(1.0; 8.9)	4/108	3.7	(1.0; 9.2)
AE leading to study discontinuation	0/696	0	(0; 0.5)	0/706	0	(0; 0.5)	0/112	0	(0; 3.2)	0/108	0	(0; 3.4)
SAE	18/696	2.6	(1.5; 4.1)	16/706	2.3	(1.3; 3.7)	2/112	1.8	(0.2; 6.3)	1/108	0.9	(0; 5.1)
Related SAE	0/696	0	(0; 0.5)	0/706	0	(0; 0.5)	0/112	0	(0; 3.2)	0/108	0	(0; 3.4)
Death	0/696	0	(0; 0.5)	0/706	0	(0; 0.5)	0/112	0	(0; 3.2)	0/108	0	(0; 3.4)
AESI	1/696	0.1	(0; 0.8)	0/706	0	(0; 0.5)	0/112	0	(0; 3.2)	0/108	0	(0; 3.4)
During the study												
SAE	51/696	7.3	(5.5; 9.5)	57/706	8.1	(6.2; 10.3)	8/112	7.1	(3.1; 13.6)	3/108	2.8	(0.6; 7.9)
Related SAE	0/696	0	(0; 0.5)	0/706	0	(0; 0.5)	0/112	0	(0; 3.2)	0/108	0	(0; 3.4)

Table 4 continued

Subjects experiencing at least one	**MenACYW-TT + MMR + PCV10 (2 + 1 regimen; group 1) (*N* = 696)**			**MCV4-TT + MMR + PCV10 (2 + 1 regimen; group 2) (*N* = 706)**			**MenACYW-TT + MMR + PCV13 (2 + 1 regimen; group 3) (*N* = 112)**			**MenACYW-TT + MMR + PCV13 (3 + 1 regimen; group 4) (*N* = 108)**		
	n*/*M	**%**	**(95% CI)**	***n*/*M***	**%**	**(95% CI)**	***n*/*M***	**%**	**(95% CI)**	***n*/*M***	**%**	**(95% CI)**
Death	0/696	0	(0; 0.5)	0/706	0	(0; 0.5)	0/112	0	(0; 3.2)	0/108	0	(0; 3.4)
AESI	3/696	0.4	(0.1; 1.3)	3/706	0.4	(0.1; 1.2)	0/112	0	(0; 3.2)	0/108	0	(0; 3.4)

AE, adverse event; AESI, adverse events of special interest; AR, adverse reaction; CI, confidence interval; D, day; DTaP-IPV-HB-Hib, hexavalent diphtheria, tetanus, acellular pertussis, inactivated poliovirus, hepatitis B and *Haemophilus influenzae* type b; *M*, number of participants with available data for the relevant endpoint; MCV4-TT, quadrivalent meningococcal conjugate vaccine; MenACYW-TT, quadrivalent meningococcal polysaccharide tetanus toxoid-conjugate vaccine; MMR, measles-mumps-rubella; n, number of participants experiencing the endpoint listed in the first column; N, number of participants in overall safety analysis set for any dose; NIMP, National Immunization Program; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; SAE, serious adverse event

Percentages are based on *M*

“Immediate unsolicited AE” were collected only for immediate unsolicited systemic AEs

"Unsolicited non-serious AE" includes any unsolicited AE that is non-serious

"Unsolicited AE" also includes immediate and serious unsolicited AEs

AR: Reactions related to study vaccine (MenACYW-TT/MCV4-TT); Unsolicited injection-site reactions related to NIMP (routine vaccines) are reported separately

Group 1: MenACYW-TT and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12–18 months of age

Group 2: MCV4-TT and routine pediatric vaccines (including hexavalent and PCV10) administered at 2, 4, and 12–18 months of age

Group 3: MenACYW-TT and routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12–18 months of age

Group 4: MenACYW-TT administered at 2, 4, 6, and 12–18 months of age. Routine pediatric vaccines (including hexavalent and PCV13) administered at 2, 4, and 12–18 months of age assays, respectively, were undertaken at the same laboratories (GCI Sanofi and UKHSA, respectively) as with other clinical studies conducted with MenACYW-TT. Additionally, the study had a large sample size, and a high proportion of participants completed the study across all study groups, decreasing the potential for bias. This study also had limitations that warrant discussion. For example, while both study vaccines induced robust hSBA titers that were maintained well above those observed at baseline, post-licensure studies and real-world surveillance are still required to fully assess effectiveness against infection, severe disease, or transmission. Furthermore, while hSBA titers of ≥ 1:8 and ≥ 1:4 are widely recognized as serological correlates of protection against meningococcal disease, the clinical significance of these protective titers has not been fully determined [19–21, 28, 29].

CONCLUSIONS

MenACYW-TT induced robust immune responses to all four meningococcal serogroups after the primary series (two doses) and after completion of the booster dose (dose 3/4). Although formal non-inferiority criteria were not met for serogroup A, the available immunogenicity data suggest that MenACYW-TT would provide protection against serogroup A. This is supported also by post hoc analysis of vaccine seroresponse post-booster, where MenACYW-TT achieved non-inferiority for all four serogroups, including serogroup A. Overall, this study reaffirms that MenACYW-TT should provide sufficient protection against IMD caused by serogroups A, C, W, and Y in infants from age 6 weeks.

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Data Availability. Qualified researchers may request access to patient-level data and related documents, including, for example, the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://vivli.org/.

Declarations

Conflict of Interest. Betzana Zambrano, Mandeep Singh Dhingra, Siham B'Chir, Olga Syrkina, Olga Lyabis, Christine Rehm, and Gustavo Vasquez are employees of Sanofi and may hold shares and/or stock options in the company. Federico Martinon-Torres has acted as principal investigator in this trial and also in other randomized controlled trials of Ablynx, Abbot, Seqirus, Sanofi Pasteur MSD, Sanofi Pasteur, Cubist, Wyeth, Merck, Pfizer, Roche, Regeneron, Jansen, Medimmune, Moderna, Novavax, Novartis, and GSK, with honoraria paid to his institution. He also reports consulting or advisory relationship with AstraZeneca, GSK Vaccines SRL, BioNet, Biofabri, Pfizer Inc, Sanofi Pasteur Inc, Seqirus Janssen Pharmaceuticals Inc, and MSD. Susanna Koski acted as a principal investigator for the study reported in this manuscript, which was sponsored by Sanofi. She is an employee of Finnish Vaccine Research (FVR), which conducts clinical vaccine studies for many major vaccine manufacturers, including Sanofi. Henryk T Szymanski reports personal fees and trial fees paid to his institution from MSD, Seqirus, Pfizer, Janssen, and Sanofi Pasteur. Miia Virta, Ignacio Salamanca de la Cueva and Samantha Bosis have no conflicts of interest to declare. Anca Cristina Drăgănescu acted as a principal investigator for the study reported in this manuscript, which was sponsored by Sanofi. Sven-Arne Silfverdal acted as a principal investigator for the study reported in this manuscript, which was funded by Sanofi, and also for other trials sponsored by GSK, Jansen, Medimmune, MSD, and Pfizer. He has been a member of advisory boards for Astra, GSK, MSD, Pfizer, and Sanofi Pasteur, with honoraria to his institution or personal.

Ethical Approval. The study was conducted in compliance with the International Conference on Harmonisation guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. Informed consent was obtained from participants' parents (or legal guardian) before any study procedures were performed. The protocol and any amendments were approved by applicable independent ethics committees or institutional review boards at each participating site and the appropriate regulatory agencies in each country (Supplementary methods).

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