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Immunogenicity and safety of MenACWY-TT, a meningococcal conjugate vaccine, co-administered with routine childhood vaccine in healthy infants: A phase III, randomized study

Ghassan Dbaibo [a], Juan Carlos Tinoco Favila [b], Magali Traskine [c], Archana Jastorff [c], Marie Van der Wielen [c,*]

[a] Center for Infectious Diseases Research, Department of Pediatrics and Adolescent Medicine, American University of Beirut, Riad El Solh, Beirut 1107-2020, Lebanon
[b] Hospital General de Durango, Durango, Mexico
[c] GSK, Wavre, Avenue Fleming 20 (W23), 1300 Wavre, Belgium

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ABSTRACT

Background: Invasive meningococcal disease has a high burden in young children, particularly during infancy. We investigated the immunogenicity and safety of a quadrivalent meningococcal conjugated vaccine (MenACWY-TT) co-administered with routine vaccines in healthy infants.
Methods: In this phase IIIb study (NCT01340898) conducted in 2 centers in Lebanon and Mexico, 750 infants were randomized (2:1:1) to receive MenACWY-TT according to 3 schedules: 3+1 (at ages 2, 4, 6 and 15–18 months; group ACWY3+1); 1+1 (at 6 and 15–18 months; group ACWY1+1) or single-dose at 15–18 months (group ACWY1). All infants received PHiD-CV and DTPa-IPV/Hib at ages 2, 4, 6, 15–18 months. Immune responses to MenACWY-TT were assessed by rSBA and hSBA at 7 months (groups ACWY3+1, ACWY1+1) and pre- and post-vaccination at 15–18 months of age (all groups). Immune responses to co-administered vaccines, reactogenicity and safety were also evaluated.
Results: Immunogenicity of MenACWY-TT at 1 month post-primary vaccination was demonstrated in group ACWY3+1: the lower limit of the 95% confidence interval for the percentage of infants with rSBA titers ≥8 was >80% for each serogroup. At 7 months of age, ≥93.9% of MenACWY-TT-primed infants had rSBA titers ≥8. Post-MenACWY-TT vaccination at age 15–18 months, ≥96.3% of participants in all groups had rSBA titers ≥8, regardless of the number of doses received previously. The percentage of infants with hSBA titers ≥4 were ≥87.2% and ≥89.7% at post-primary and booster/single-dose vaccination, respectively. Immune responses to PHiD-CV and DTPa-IPV/Hib did not seem impacted by co-administration with MenACWY-TT in infancy. The incidence of all adverse events was similar among groups. Serious adverse events were reported for 63/750 children in all groups; none were considered vaccine-related by investigators.
Conclusion: Primary vaccination with 3 or 1 dose(s) of MenACWY-TT when co-administered with routine pediatric vaccines in infants is immunogenic and well-tolerated.

1. Introduction

Invasive meningococcal disease (IMD) is a life-threatening condition which, if left untreated, can lead to a case fatality ratio of up to 50% [1].

IMD is caused by different serogroups of *Neisseria meningitidis*, 6 of those (MenA, MenB, MenC, MenW, MenX and MenY) being responsible for the majority of IMD cases [1], although epidemiology varies greatly geographically. MenA and MenC are more prominent in Asia, MenB and MenC in Europe, Australia and South America, while in North America, MenB, MenC and MenY prevalence is higher [2–4]. In the African meningitis belt, MenW is the most common serogroup following a decrease in MenA prevalence [1–3], and MenC [5,6] and MenX [7] also emerging as serious causes of meningitis.

The incidence of IMD remains high, with more than 1.2 million cases per year reported worldwide [2]. Children aged <5 years are at particular risk of IMD, and the highest rate of disease is recorded in infants, while a second, lower peak is observed in adolescents [8,9]. While treatment of IMD may be complex, with the choice

* Corresponding author at: GSK Vaccines, Avenue Fleming 20, B-1300 Wavre, Belgium.
E-mail addresses: gdbaibo@aub.edu.lb (G. Dbaibo), jctinoco@prodigy.net.mx (J.C. Tinoco Favila), magali.x.traskine@gsk.com (M. Traskine), archana.m.jastorff@gsk.com (A. Jastorff), marie.x.van-der-wielen@gsk.com (M. Van der Wielen).

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of antibiotics depending on age and local resistance rates [10], the disease is preventable and several vaccines are currently available [11]. Three quadrivalent meningococcal conjugate vaccines using diphtheria toxoid (MenACWY-DT; *Menactra*, Sanofi Pasteur), non-toxic diphtheria cross-reacting mutant CRM_{197} (MenACWY-CRM; *Menveo*, GSK), or tetanus toxoid (MenACWY-TT; *Nimenrix*, Pfizer) as carrier proteins are approved for use in different age groups, including infants [12].

MenACWY-TT was first licensed in 2012 in Europe and Canada for individuals ≥2 years of age followed by an extension of its indication as of 6 weeks of age in Europe [13–15]. Recently, the vaccine was prequalified by the World Health Organization [16]. Co-administration of MenACWY-TT with routine pediatric vaccines at 2, 3, 4 and 12 months of age or 2, 4 and 12 months of age was shown to induce adequate immune responses, as measured by serum bactericidal antibody assays with human (hSBA) and rabbit (rSBA) complement, with an acceptable safety profile in a European population [17].

We studied co-administration of MenACWY-TT with a pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine (PHiD-CV; *Synflorix*, GSK) and a combined diphtheria, tetanus, acellular pertussis, inactivated polio and *H. influenzae* type b vaccine (DTPa-IPV/Hib; *Infanrix-IPV*/Hib, GSK) in healthy infants from Lebanon and Mexico. The 3+1 primary-booster schedule at 2, 4, 6 and 15–18 months of age was designed to align with the priming schedule of other routine infant vaccines used in several countries across the world. This study also evaluates a 1+1 schedule, as well as a single dose in toddlers.

2. Methods

2.1. Study design and participants

This phase IIIb, open, controlled, randomized study was conducted between January 2012 and October 2015 in 2 centers in Lebanon and Mexico.

Infants were randomized (2:1:1) into 3 groups to receive MenACWY-TT according to different schedules. Two groups received a 3-dose (at 2, 4 and 6 months of age; group ACWY3+1) or a 1-dose (6 months of age; group ACWY1+1) primary schedule followed by a booster dose at age 15–18 months. Group ACWY1 received a single dose at 15–18 months of age and served as control. As part of the study, all participants received DTPa-IPV/Hib and PHiD-CV at 2, 4, 6 and 15–18 months of age, according to national immunization programs (NIPs) (Fig. 1). The trial included a primary vaccination phase (up to 7 months of age), a booster phase (14–19 months of age) and a 6-month extended safety follow-up (Fig. 1).

Participants were healthy infants aged 6–12 weeks at enrollment, born after a gestation period of ≥36 weeks. Text S1 presents full inclusion/exclusion criteria.

Treatment allocation was performed at the investigators' site using an internet-based system, using a minimization algorithm accounting for center. All personnel in charge of laboratory testing were blinded to the treatment.

Vaccines were administered intramuscularly, into the upper-left (MenACWY-TT), upper-right (PHiD-CV) or lower-right (DTPa-IPV/Hib) anterolateral thigh; vaccine compositions are detailed in Text S2.

The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Written informed consent was obtained from each participant's parent/guardian prior to enrollment. The protocol and informed consent forms were reviewed and approved by an Independent Ethics Committee or Institutional Review Board at each center. The study is registered at www.clinicaltrials.gov (NCT01340898) and a protocol summary is available at http://www.gsk-clinicalstudyregister.com/114858.

2.2. Study objectives

The primary objective was to demonstrate that MenACWY-TT is immunogenic in infants after 3 primary doses, in terms of rSBA antibodies to each meningococcal serogroup. The following statistical criterion, which was considered clinically relevant, was used: the lower limit (LL) of the 2-sided 95% confidence interval (CI) for the percentage of infants with rSBA titers ≥8 for each serogroup should be ≥80%.

Secondary objectives evaluated the immune responses to MenACWY-TT vaccination at 1 month post-primary vaccination (groups ACWY3+1 and ACWY1+1) and pre- and 1 month post-booster/single dose (all groups), in terms of percentage of children with titers above pre-specified thresholds, geometric mean titers (GMTs) and booster/vaccine response measured by rSBA and hSBA (subset of participants). The post-primary immunogenicity of co-administered vaccines and post-booster anti-tetanus immune response and immunogenicity of PHiD-CV in subsets of participants, safety and reactogenicity were also assessed.

2.3. Immunogenicity assessment

Approximately 5 mL of blood were collected from all participants, post-primary and pre- and post-booster/single dose vaccination (Fig. 1).

Antibody titers for each meningococcal serogroup were determined by rSBA and hSBA (in a randomized subset), with pre-specified thresholds for seropositivity of 8 and 4, respectively [18–21] (Table S1).

rSBA/hSBA booster and vaccine response to MenACWY-TT in previously-primed groups and group ACWY1, respectively, was defined as a post-vaccination titer of ≥32 (rSBA)/≥8 (hSBA) for initially seronegative participants or as a ≥4-fold increase for initially seropositive participants.

Immune responses to co-administered vaccines was assessed in randomized exclusive subsets of 25% of participants by neutralization (for polio) or enzyme-linked immunosorbent assay (all other antigens), using the thresholds presented in Table S1.

2.4. Safety and reactogenicity assessment

Solicited local and general symptoms (days 0–7) and unsolicited adverse events (AEs) (days 0–30) were recorded by parents on diary cards post-each vaccination and graded by intensity.

Serious AEs (SAEs) and new onset of chronic illnesses were recorded throughout the study.

2.5. Statistical analyses

The target sample size for the evaluation of the primary objective was 300 infants in group ACWY3+1. Assuming a drop-out/non-evaluable rate of 20% post-primary vaccination, a total target sample size of 750 infants was calculated for enrollment. The power to meet the primary confirmatory objective was 99.4%, computed by assuming 90% of evaluable infants will have post-primary vaccination rSBA titers ≥8 for each serogroup.

Analyses were performed separately for the primary and booster phases. Safety was assessed in the primary and booster total vaccinated cohorts, which included all participants with ≥1 primary and booster dose(s) with any of the study vaccines, respectively. Immunogenicity was evaluated in all children or different

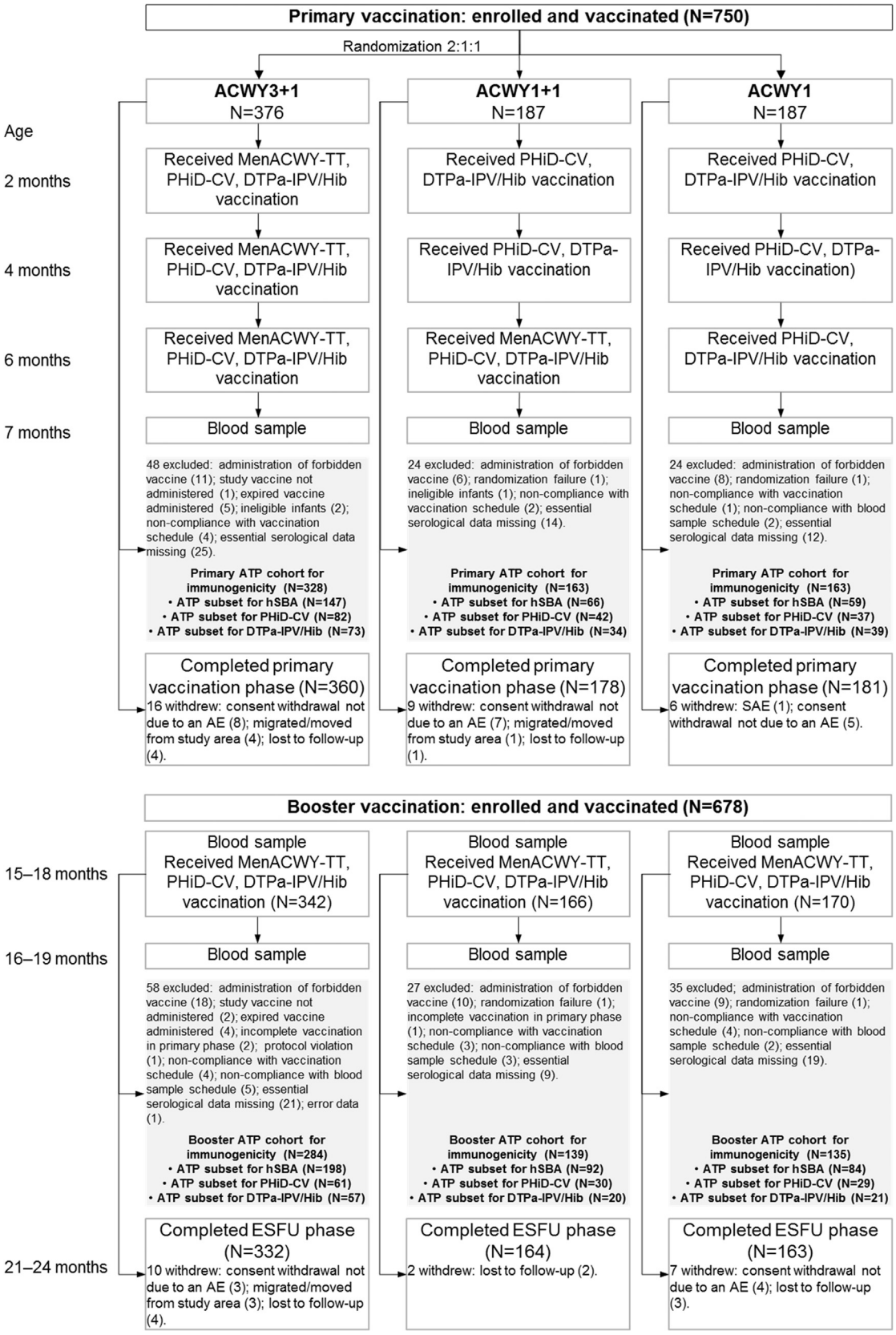

Fig. 1. Study design and participant flow diagram. ACWY3+1, participants who received 4 doses of MenACWY-TT at 2, 4, 6 and 15–18 months of age; ACWY1+1, participants who received 2 doses of MenACWY-TT at 6 and 15–18 months of age; ACWY1, participants who received 1 dose of MenACWY-TT at 15–18 months of age; N, number of participants in each group or maximum number of participants for any of the co-administrated vaccine antigens (for ATP cohorts and subsets); ATP, according-to-protocol; hSBA, serum bactericidal antibody assay using human complement; PHiD-CV, pneumococcal non-typeable H. influenzae protein D conjugate vaccine; DTPa-IPV/Hib, combined diphtheria, tetanus, acellular pertussis, inactivated polio and H. influenzae type b vaccine; AE, adverse event; ESFU, extended safety follow-up.

subsets of the according-to-protocol (ATP) cohorts (Table S1; Fig. 1).

GMTs/GM concentrations (GMCs) were calculated by taking the anti-log of the mean of the $\log_{10}$ titer/concentration transformations. Antibody concentrations/titers below the assay cut-off (Table S1) were given an arbitrary value of half the cut-off.

Between-group exploratory analyses compared immune responses to MenACWY-TT. Potential group differences were indicated by the exclusion of 1 from the 95% CI on the GMT/GMC ratios (computed using an analysis of variance model on the $\log_{10}$ titers/concentrations transformation) and the exclusion of 0 from the 95% CI on the differences in vaccine response rates/percentage of children with titers/concentrations above pre-established thresholds. However, the results of these analyses should be interpreted with caution, as no adjustment for multiplicity was performed.

Analyses were performed using SAS.

3. Results

3.1. Demographics

From the 753 enrolled infants, 750 and 678 were vaccinated in the primary and booster phase, respectively and 659 completed the study (Fig. 1). Demographic characteristics were balanced between groups (Table S2).

3.2. Immunogenicity

3.2.1. Immune response to MenACWY-TT

One month post-primary vaccination, in the ACWY3+1 group, the LL of the 95% CI for the percentage of infants with rSBA titers ≥8 was ≥97.8%, for each serogroup (Table 1). Thus, the primary confirmatory objective was met.

One month after primary vaccination, for each meningococcal serogroup, ≥99.4% and ≥93.9% of participants had rSBA titers ≥8 in groups ACWY3+1 and ACWY1+1, respectively; at 15–18 months of age, these percentages were ≥68.8% and ≥65.6%, respectively, and at one month post-booster vaccination, ≥99.6% and ≥99.3%, respectively. Post-vaccination with MenACWY-TT, ≥96.3% of children in group ACWY1 had rSBA titers ≥ 8 (Table 1).

Post-primary rSBA GMTs s ranged from 577.5 (MenA) to 1190.3 (MenW) in group ACWY3+1 and from 591.6 (MenC) to 1469.9 (MenY) in group ACWY1+1 (Fig. 2A). Post-booster vaccination, GMTs for each serogroup increased ≥ 33.3- and ≥ 22.0-fold from pre-booster levels in groups ACWY3+1 and ACWY1+1, respectively. After the MenACWY-TT dose, rSBA GMTs ranged between 768.1 (MenC) and 5240.7 (MenW) in group ACWY1 (Fig. 2A).

For each serogroup, rSBA booster responses were observed for ≥90.2% and ≥82.4% of participants in groups ACWY3+1 and ACWY1+1, respectively. Vaccine response rates in group ACWY1 were ≥94.7% for all serogroups (Fig. 2B).

One month post-primary vaccination, in the ATP subsets for hSBA, 100% (ACWY3+1) and ≥87.2% (ACWY1+1) of children had hSBA titers ≥4 for each meningococcal serogroup. One month post-booster dose, these titers were observed for all evaluable participants in groups ACWY3+1 and ACWY1+1. One month post-vaccination, ≥89.7% of the ACWY1 ATP subset for hSBA had hSBA titers ≥ 4 for each meningococcal serogroup (Table 2). For all groups, hSBA GMTs increased compared with pre-booster/pre-vaccination values, with higher GMTs and respective fold increases observed in groups primed with MenACWY-TT (Table 2, Fig. 2A).

For each serogroup, hSBA booster responses rates were ≥94.3% and ≥91.8% in groups ACWY3+1 and ACWY1+1, respectively, and vaccine response rates of ≥87.9% were observed in group ACWY1 (Fig. 2B).

In exploratory analyses, higher rSBA GMTs for MenC were observed in group ACWY3+1 compared to ACWY1+1, post-primary vaccination. Also, GMTs for MenC were higher in the previously-primed groups, post-booster dose compared to group ACWY1, post-vaccination. For each serogroup, hSBA GMTs were higher with increasing number of MenACWY-TT doses received.

Immune responses to MenACWY-TT by country are presented in Text S3.

3.2.2. Immune responses to co-administered vaccines

Post-primary vaccination, all children in the corresponding ATP subsets had antibodies concentrations/titers against DTP/IPV anti-

Table 1
Immune responses to *N. meningitidis* serogroups in terms of percentage of participants with rSBA titers ≥8 and ≥128 (ATP cohort for immunogenicity).

% (95% confidence interval)									
	ACWY3+1			ACWY1+1			ACWY1		
	N	≥8	≥128	N	≥8	≥128	N	≥8	≥128
MenA									
M5	328	100 (**98.9**–100)	97.9 (95.7–99.1)	163	98.8 (95.6–99.9)	95.1 (90.6–97.9)	163	3.7 (1.4–7.8)	3.7 (1.4–7.8)
M13	276	81.5 (76.4–85.9)	52.9 (46.8–58.9)	131	81.7 (74.0–87.9)	67.2 (58.4–75.1)	132	14.4 (8.9–21.6)	12.1 (7.1–18.9)
M14	283	100 (98.7–100)	99.6 (98.0–100)	139	99.3 (96.1–100)	99.3 (96.1–100)	135	98.5 (94.8–99.8)	97.8 (93.6–99.5)
MenC									
M5	328	99.7 (**98.3**–100)	97 (94.5–98.5)	163	99.4 (96.6–100)	92.6 (87.5–96.1)	162	3.7 (1.4–7.9)	3.1 (1.0–7.1)
M13	276	68.8 (63.0–74.3)	33.7 (28.1–39.6)	131	65.6 (56.9–73.7)	29.8 (22.1–38.4)	132	2.3 (0.5–6.5)	0.8 (0.0–4.1)
M14	283	99.6 (98.0–100)	99.6 (98.0–100)	139	99.3 (96.1–100)	98.6 (94.9–99.8)	135	96.3 (91.6–98.8)	94.8 (89.6–97.9)
MenW									
M5	327	99.4 (**97.8**–99.9)	95.7 (92.9–97.6)	163	93.9 (89.0–97.0)	92.6 (87.5–96.1)	163	2.5 (0.7–6.2)	2.5 (0.7–6.2)
M13	275	81.8 (76.7–86.2)	44.4 (38.4–50.5)	131	77.9 (69.8–84.6)	49.6 (40.8–58.5)	132	5.3 (2.2–10.6)	5.3 (2.2–10.6)
M14	284	100 (98.7–100)	100 (98.7–100)	139	100 (97.4–100)	99.3 (96.1–100)	135	97.0 (92.6–99.2)	97.0 (92.6–99.2)
MenY									
M5	328	99.7 (**98.3**–100)	95.1 (92.2–97.2)	163	98.8 (95.6–99.9)	97.5 (93.8–99.3)	162	9.9 (5.8–15.5)	9.9 (5.8–15.5)
M13	275	87.3 (82.7–91.0)	44.0 (38.0–50.1)	131	88.5 (81.8–93.4)	53.4 (44.5–62.2)	132	18.2 (12.0–25.8)	17.4 (11.4–25.0)
M14	284	100 (98.7–100)	99.6 (98.1–100)	139	100 (97.4–100)	98.6 (94.9–99.8)	135	97.0 (92.6–99.2)	97.0 (92.6–99.2)

ACWY3+1, participants who received 4 doses of MenACWY-TT at 2, 4, 6 and 15–18 months of age; ACWY1+1, participants who received 2 doses of MenACWY-TT at 6 and 15–18 months of age; ACWY1, participants who received 1 dose of MenACWY-TT at 15–18 months of age; rSBA, serum bactericidal antibody assay using rabbit complement; ATP, according-to-protocol;%, percentage of participants with titers above the specified cut-off; N, number of participants with available results; M, month.
Note: Analyses were performed on the primary (M5) and booster (M13, M14) ATP cohorts for immunogenicity (M5, 1 month post-primary vaccination; M13, pre-booster/single dose vaccination; M14, 1 month post-booster/single dose vaccination).
Bolded values indicate that the statistical criterion for the confirmatory primary objective was met.

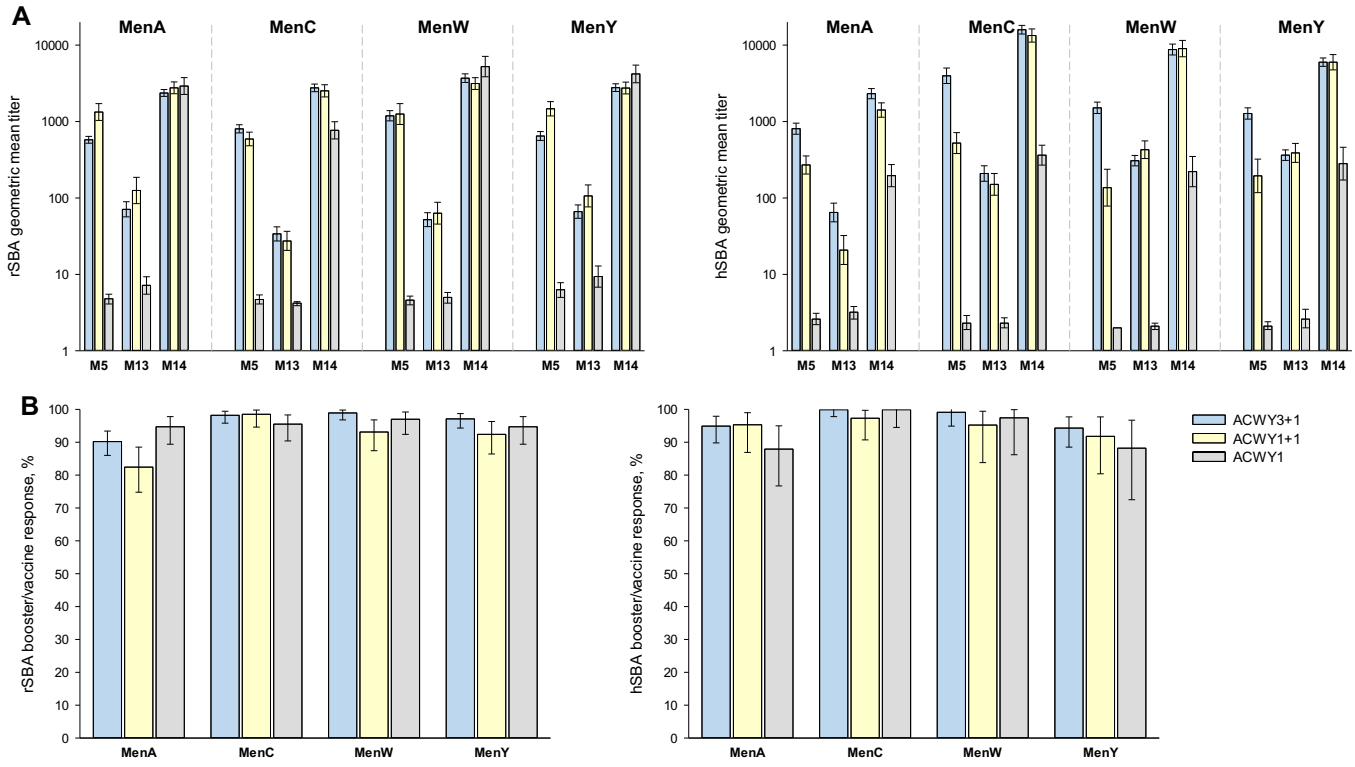

Fig. 2. rSBA and hSBA geometric mean titers (A) and vaccine/booster response (B) for each of the MenA, MenC, MenY and MenW serogroups, by timepoint (ATP cohort for immunogenicity). ATP, according-to-protocol; rSBA/hSBA, serum bactericidal antibody assay using rabbit/human complement; M, study month; ACWY3+1, participants who received 4 doses of MenACWY-TT at 2, 4, 6 and 15–18 months of age; ACWY1+1, participants who received 2 doses of MenACWY-TT at 6 and 15–18 months of age; ACWY1, participants who received 1 dose of MenACWY-TT at 15–18 months of age. Note: Error bars represent 95% confidence intervals; M5, 1 month post-primary vaccination with MenACWY-TT; M13, pre-booster/single dose vaccination with MenACWY-TT; M14, 1 month post-booster/single dose vaccination with MenACWY-TT. Booster/vaccine response for MenACWY-TT was defined as a post-vaccination titer of ≥32 (rSBA) or ≥8 (hSBA) for participants with titers below the 8/4 cut-offs at M13 or as a ≥4-fold increase in the rSBA/hSBA titers for participants with titers ≥8/4 at M13.

Table 2
Immune responses to *N. meningitidis* serogroups in terms of hSBA antibodies (ATP subsets for immunogenicity).

% (95% confidence interval)									
	ACWY3+1			ACWY1+1			ACWY1		
	N	≥4	≥8	N	≥4	≥8	N	≥4	≥8
MenA									
M5	136	100 (97.3–100)	100 (97.3–100)	59	98.3 (90.9–100)	98.3 (90.9–100)	51	17.6 (8.4–30.9)	15.7 (7.0–28.6)
M13	152	86.2 (79.7–91.2)	85.5 (78.9–90.7)	71	67.6 (55.5–78.2)	66.2 (54.0–77.0)	70	25.7 (16.0–37.6)	21.4 (12.5–32.9)
M14	173	100 (97.9–100)	100 (97.9–100)	83	100 (95.7–100)	100 (95.7–100)	73	95.9 (88.5–99.1)	94.5 (86.6–98.5)
MenC									
M5	147	100 (97.5–100)	100 (97.5–100)	66	100 (94.6–100)	100 (94.6–100)	59	5.1 (1.1–14.1)	5.1 (1.1–14.1)
M13	173	97.1 (93.4–99.1)	97.1 (93.4–99.1)	78	97.4 (91.0–99.7)	96.2 (89.2–99.2)	74	5.4 (1.5–13.3)	5.4 (1.5–13.3)
M14	198	100 (98.2–100)	100 (98.2–100)	92	100 (96.1–100)	100 (96.1–100)	84	100 (95.7–100)	100 (95.7–100)
MenW									
M5	107	100 (96.6–100)	100 (96.6–100)	47	87.2 (74.3–95.2)	87.2 (74.3–95.2)	42	0 (0.0–8.4)	0 (0.0–8.4)
M13	123	100 (97.0–100)	100 (97.0–100)	53	100 (93.3–100)	100 (93.3–100)	52	1.9 (0.0–10.3)	1.9 (0.0–10.3)
M14	129	100 (97.2–100)	100 (97.2–100)	59	100 (93.9–100)	100 (93.9–100)	53	92.5 (81.8–97.9)	92.5 (81.8–97.9)
MenY									
M5	127	100 (97.1–100)	100 (97.1–100)	52	92.3 (81.5–97.9)	92.3 (81.5–97.9)	42	2.4 (0.1–12.6)	2.4 (0.1–12.6)
M13	138	99.3 (96.0–100)	99.3 (96.0–100)	61	98.4 (91.2–100)	98.4 (91.2–100)	49	8.2 (2.3–19.6)	8.2 (2.3–19.6)
M14	149	100 (97.6–100)	100 (97.6–100)	69	100 (94.8–100)	100 (94.8–100)	58	89.7 (78.8–96.1)	89.7 (78.8–96.1)

ACWY3+1, participants who received 4 doses of MenACWY-TT at 2, 4, 6 and 15–18 months of age; ACWY1+1, participants who received 2 doses of MenACWY-TT at 6 and 15–18 months of age; ACWY1, participants who received 1 dose of MenACWY-TT at 15–18 months of age; hSBA, serum bactericidal antibody assay using human complement; ATP, according-to-protocol;%, percentage of participants with titers above the specified cut-off; N, number of evaluable participants; M, month.
Note: The ATP subsets for immunogenicity consisted of randomized subsets of 50% of the participants in the primary (M5) and 75% of participants in the booster (M13, M14) ATP cohorts for immunogenicity, respectively (M5, 1 month post-primary vaccination with MenACWY-TT; M13, pre-booster/single dose vaccination with MenACWY-TT; M14, 1 month post-booster/single dose vaccination with MenACWY-TT).

Table 3
Immune responses to co-administrated vaccines in each group (ATP subsets for immunogenicity).

			ACWY3+1			ACWY1+1			ACWY1		
Antigen	Time point	Threshold	N	% of participants (95% CI)	GMC/GMT (95% CI)	N	% of participants (95% CI)	GMC/GMT (95% CI)	N	% of participants (95% CI)	GMC/GMT (95% CI)
PHiD-CV vaccination											
1	M5	0.35 μg/mL	82	92.7 (84.8–97.3)	1.3 (1.1–1.6)	42	97.6 (87.4–99.9)	1.4 (1.1–1.8)	37	91.9 (78.1–98.3)	1.5 (1.1–2.1)
	M13		57	21.1 (11.4–33.9)	0.2 (0.1–0.2)	32	15.6 (5.3–32.8)	0.2 (0.1–0.2)	27	29.6 (13.8–50.2)	0.2 (0.2–0.3)
	M14		61	100 (94.1–100)	2.1 (1.6–2.6)	30	96.7 (82.8–99.9)	1.7 (1.2–2.5)	29	96.6 (82.2–99.9)	2.2 (1.5–3.2)
4	M5		82	98.8 (93.4–100)	1.7 (1.5–2.0)	42	97.6 (87.4–99.9)	1.8 (1.4–2.2)	37	100 (90.5–100)	2.0 (1.6–2.5)
	M13		57	29.8 (18.4–43.4)	0.2 (0.2–0.3)	33	15.2 (5.1–31.9)	0.2 (0.1–0.2)	27	37 (19.4–57.6)	0.3 (0.2–0.4)
	M14		61	95.1 (86.3–99.0)	2.4 (1.8–3.1)	30	96.7 (82.8–99.9)	1.8 (1.3–2.5)	29	100 (88.1–100)	3.1 (2.3–4.2)
5	M5		82	87.8 (78.7–94.0)	0.6 (0.6–0.7)	42	76.2 (60.5–87.9)	0.6 (0.5–0.7)	37	75.7 (58.8–88.2)	0.7 (0.5–0.9)
	M13		57	17.5 (8.7–29.9)	0.2 (0.1–0.2)	33	15.2 (5.1–31.9)	0.2 (0.1–0.2)	27	18.5 (6.3–38.1)	0.2 (0.1–0.2)
	M14		61	80.3 (68.2–89.4)	0.7 (0.6–0.9)	30	76.7 (57.7–90.1)	0.5 (0.4–0.7)	29	89.7 (72.6–97.8)	0.7 (0.5–1.0)
6A	M5		69	52.2 (39.8–64.4)	0.3 (0.3–0.4)	37	54.1 (36.9–70.5)	0.4 (0.3–0.6)	28	46.4 (27.5–66.1)	0.3 (0.2–0.4)
	M13		56	46.4 (33.0–60.3)	0.3 (0.2–0.4)	32	31.3 (16.1–50.0)	0.3 (0.2–0.4)	26	42.3 (23.4–63.1)	0.2 (0.2–0.4)
	M14		51	92.2 (81.1–97.8)	1.7 (1.3–2.3)	25	88.0 (68.8–97.5)	1.4 (0.9–2.1)	25	92.0 (74.0–99.0)	1.6 (1.0–2.5)
6B	M5		81	90.1 (81.5–95.6)	1.8 (1.4–2.3)	42	95.2 (83.8–99.4)	1.7 (1.3–2.4)	37	94.6 (81.8–99.3)	1.8 (1.3–2.5)
	M13		57	64.9 (51.1–77.1)	0.6 (0.4–0.7)	33	69.7 (51.3–84.4)	0.5 (0.4–0.7)	27	55.6 (35.3–74.5)	0.4 (0.3–0.7)
	M14		61	100 (94.1–100)	3.8 (3.1–4.8)	30	93.3 (77.9–99.2)	2.4 (1.7–3.5)	29	96.6 (82.2–99.9)	3.4 (2.2–5.2)
7F	M5		82	98.8 (93.4–100)	2.5 (2.2–3.0)	42	100 (91.6–100)	2.2 (1.8–2.7)	37	100 (90.5–100)	2.8 (2.1–3.7)
	M13		57	66.7 (52.9–78.6)	0.4 (0.4–0.5)	33	51.5 (33.5–69.2)	0.4 (0.3–0.5)	27	51.9 (31.9–71.3)	0.4 (0.3–0.6)
	M14		61	100 (94.1–100)	3.5 (2.9–4.2)	30	96.7 (82.8–99.9)	2.2 (1.6–3.1)	29	96.6 (82.2–99.9)	3.4 (2.4–4.9)
9 V	M5		82	96.3 (89.7–99.2)	1.2 (1.0–1.4)	42	95.2 (83.8–99.4)	1.2 (1.0–1.5)	37	97.3 (85.8–99.9)	1.3 (1.0–1.7)
	M13		57	33.3 (21.4–47.1)	0.3 (0.2–0.4)	33	30.3 (15.6–48.7)	0.3 (0.2–0.4)	27	33.3 (16.5–54.0)	0.2 (0.1–0.3)
	M14		61	96.7 (88.7–99.6)	1.6 (1.3–2.0)	30	93.3 (77.9–99.2)	1.0 (0.8–1.4)	29	96.6 (82.2–99.9)	1.6 (1.2–2.2)
14	M5		82	97.6 (91.5–99.7)	5.2 (4.1–6.5)	42	97.6 (87.4–99.9)	6.0 (4.4–8.0)	36	100 (90.3–100)	7.0 (4.9–10.0)
	M13		57	77.2 (64.2–87.3)	1.0 (0.7–1.3)	33	84.8 (68.1–94.9)	0.8 (0.6–1.0)	27	77.8 (57.7–91.4)	0.9 (0.5–1.4)
	M14		61	100 (94.1–100)	8.4 (6.8–10.4)	30	96.7 (82.8–99.9)	6.8 (4.8–9.7)	29	96.6 (82.2–99.9)	9.0 (6.0–13.5)
18C	M5		82	96.3 (89.7–99.2)	2.3 (1.9–2.8)	42	97.6 (87.4–99.9)	2.0 (1.5–2.5)	37	97.3 (85.8–99.9)	2.9 (2.2–3.8)
	M13		57	31.6 (19.9–45.2)	0.2 (0.2–0.3)	33	27.3 (13.3–45.5)	0.2 (0.1–0.3)	27	40.7 (22.4–61.2)	0.3 (0.2–0.4)
	M14		61	100 (94.1–100)	3.6 (3.0–4.4)	30	90.0 (73.5–97.9)	2.3 (1.5–3.6)	29	100 (88.1–100)	3.4 (2.6–4.6)
19A	M5		82	34.1 (24.0–45.4)	0.2 (0.2–0.3)	42	33.3 (19.6–49.5)	0.2 (0.2–0.4)	37	35.1 (20.2–52.5)	0.2 (0.2–0.3)
	M13		57	43.9 (30.7–57.6)	0.3 (0.2–0.4)	33	45.5 (28.1–63.6)	0.3 (0.2–0.4)	27	18.5 (6.3–38.1)	0.2 (0.1–0.3)
	M14		61	85.2 (73.8–93.0)	1.2 (0.8–1.7)	29	72.4 (52.8–87.3)	1.1 (0.6–1.9)	29	75.9 (56.5–89.7)	0.8 (0.5–1.2)
19F	M5		81	98.8 (93.3–100)	3.7 (3.0–4.6)	42	100 (91.6–100)	3.8 (2.7–5.3)	37	97.3 (85.8–99.9)	4.7 (3.3–6.6)
	M13		57	91.2 (80.7–97.1)	0.9 (0.7–1.2)	33	90.9 (75.7–98.1)	0.9 (0.7–1.3)	27	74.1 (53.7–88.9)	0.9 (0.5–1.5)
	M14		61	100 (94.1–100)	8.0 (6.2–10.2)	30	100 (88.4–100)	6.9 (4.5–10.6)	29	100 (88.1–100)	9.8 (6.8–14.2)
23F	M5		71	87.3 (77.3–94.0)	1.4 (1.0–1.9)	42	100 (91.6–100)	1.8 (1.4–2.4)	36	88.9 (73.9–96.9)	1.5 (1.0–2.2)
	M13		57	49.1 (35.6–62.7)	0.3 (0.2–0.4)	33	42.4 (25.5–60.8)	0.3 (0.2–0.4)	26	46.2 (26.6–66.6)	0.2 (0.2–0.4)
	M14		45	100 (92.1–100)	3.4 (2.6–4.5)	24	95.8 (78.9–99.9)	2.1 (1.3–3.4)	21	95.2 (76.2–99.9)	2.9 (1.8–4.7)
DTPa-IPV/Hib vaccination											
D	M5	≥0.1 IU/mL	72	100 (95.0–100)	2.259 (1.820–2.804)	34	100 (89.7–100)	3.028 (2.177–4.213)	38	100 (90.7–100)	2.462 (1.700–3.565)
T	M5	≥0.1 IU/mL	73	100 (95.1–100)	5.798 (4.998–6.726)	34	100 (89.7–100)	7.246 (5.305–9.897)	39	100 (91.0–100)	5.973 (4.818–7.406)
	M13		49	98.0 (89.1–99.9)	0.479 (0.398–0.576)	24	95.8 (78.9–99.9)	0.659 (0.427–1.018)	21	95.2 (76.2–99.9)	0.461 (0.297–0.716)
	M14		57	100 (93.7–100)	18.977 (16.013–22.489)	20	100 (83.2–100)	16.813 (12.386–22.821)	21	100 (83.9–100)	35.835 (23.802–53.951)
PT	M5	assay cut-off[a]	73	100 (95.1–100)	49.9 (43.3–57.6)	34	100 (89.7–100)	51.9 (40.8–66.0)	39	100 (91.0–100)	47.8 (38.3–59.7)
FHA	M5	assay cut-off[a]	73	100 (95.1–100)	126.2 (108.8–146.3)	34	100 (89.7–100)	134.2 (108.3–166.4)	39	100 (91.0–100)	132.6 (107.8–163.1)
PRN	M5	assay cut-off[a]	73	100 (95.1–100)	108.6 (88.8–132.9)	34	100 (89.7–100)	167.5 (117.6–238.7)	39	100 (91.0–100)	158.2 (106.5–235.1)
Polio1	M5	8ED50	69	100 (94.8–100)	788.8 (584.1–1065.2)	28	100 (87.7–100)	1102.9 (725.2–1677.2)	29	100 (88.1–100)	908.6 (549.1–1503.4)
Polio2	M5	8ED50	69	100 (94.8–100)	850.4 (647.3–1117.3)	29	100 (88.1–100)	953.3 (579.0–1569.5)	33	100 (89.4–100)	1079.2 (704.9–1652.1)
Polio3	M5	8ED50	68	100 (94.7–100)	1678.8 (1211.2–2326.9)	26	100 (86.8–100)	1676.7 (1011.1–2780.5)	30	100 (88.4–100)	1261.3 (720.8–2207.1)

ACWY3+1, participants who received 4 doses of MenACWY-TT at 2, 4, 6 and 15–18 months of age; ACWY1+1, participants who received 2 doses of MenACWY-TT at 6 and 15–18 months of age; ACWY1, participants who received 1 dose of MenACWY-TT at 15–18 months of age; ATP, according-to-protocol; N, number of children with available results in each group;% percentage of children with antibody concentration above specified threshold; CI, confidence interval; GMC, geometric mean concentrations; GMT, geometric mean titer; M, study month; PHiD-CV, pneumococcal non-typeable *H. influenzae* protein D conjugate vaccine; DTPa-IPV/Hib, combined diphtheria, tetanus, acellular pertussis, inactivated polio and *H. influenzae* type b vaccine; D, diphtheria; T, tetanus; IU, International Units; PT, pertussis toxoid; FHA, filamentous hemagglutinin; PRN, pertactin; ED50, endpoint dilution 50%.
Note: The ATP subsets for immunogenicity consisted of randomized subsets of 25% of the participants from the primary (M5) and booster (M13, M14) ATP cohorts for immunogenicity, respectively (M5, 1 month post-primary vaccination with DTPa-IPV/Hib and PHiD-CV; M13, pre-booster vaccination with DTPa-IPV/Hib and PHiD-CV; M14, 1 month post-booster vaccination with DTPa-IPV/Hib and PHiD-CV).
[a] Assay cut-off for anti-PT, anti-PRN, and anti-FHA were 2.693 IU/mL, 2.046 IU/ml and 2.187 IU/ml respectively.

gens above pre-specified thresholds (Table 3). The proportion of participants with pneumococcal antibody concentrations ≥ 0.35 μg/mL for each of the PHiD-CV vaccine serotypes was 75.2–87.3% and 76.7–89.7% after primary and booster vaccination, respectively (Table 3); Table S3 presents results for the 0.15 μg/mL threshold. Post-primary GMCs did not differ between the ACWY3+1 and ACWY1 groups (Table 3).

Post-booster vaccination, higher anti-TT antibody GMCs were observed in group ACWY1 than in groups ACWY3+1 and ACWY1+1 (Table 3).

3.2.3. Safety and reactogenicity

Post-primary vaccination, the most frequently reported solicited local symptom was pain, after 41.4% and 33.0% of MenACWY-TT doses, 46.0% and 48.0% of PHiD-CV doses, and 45.7% and 48.1% of DTPa-IPV/Hib doses, in groups ACWY3+1 and ACWY1+1, respectively. In the ACWY1 group, pain was reported by 53.0% (DTPa-IPV/Hib) and 52.1% (PHiD-CV) of participants. In the booster phase, pain was also most frequently reported following vaccination, in 33.1%, 38.2% and 37.7% (MenACWY-TT), 38.3%, 40.6% and 43.1% (PHiD-CV), and 40.2%, 41.8% and 41.3% (DTPa-IPV/Hib) of participants in groups ACWY3+1, ACWY1+1, and ACWY1, respectively (Fig. 3).

The most frequently reported solicited general symptom was irritability/fussiness, after 46.1%, 48.5% and 48.1% of doses post-primary vaccination and 33.1%, 32.7% and 36.5% of participants post-booster vaccination, in groups ACWY3+1, ACWY1+1 and ACWY1, respectively (Fig. 3).

At least one unsolicited AE was reported after ≤45.7% of primary doses, and in ≤55.4% of participants, post-booster vaccination, in the 3 groups. For all groups and timepoints, grade 3 and vaccination-related unsolicited AEs were reported after ≤7.0% and ≤3.5% of doses, respectively (Table S4).

At least one new onset of chronic illnesses was reported for 4.3% of participants in each of the ACWY3+1 and ACWY1+1 groups and 2.1% of participants in group ACWY1 (Table S4).

At least one SAE was reported for 9.3% of participants in group ACWY3+1, and 7.5% of participants in each of the ACWY1+1 and ACWY1 groups. None of the events were considered vaccination-related by the investigator and all recovered/resolved by study end (Table S4). No infections due to pathogens targeted by MenACWY-TT or co-administered vaccines were reported throughout the study. One fatal SAE (sudden infant death syndrome, not-related to vaccination) was reported in group ACWY1, 39 days after the second dose of PHiD-CV and DTPa-IPV/Hib.

4. Discussion

This study demonstrated that primary vaccination with 3 doses of MenACWY-TT was immunogenic when co-administered with PHiD-CV and DTPa-IPV/Hib in healthy infants. Following 3 doses of MenACWY-TT at 2, 4 and 6 months or 1 dose at 6 months of

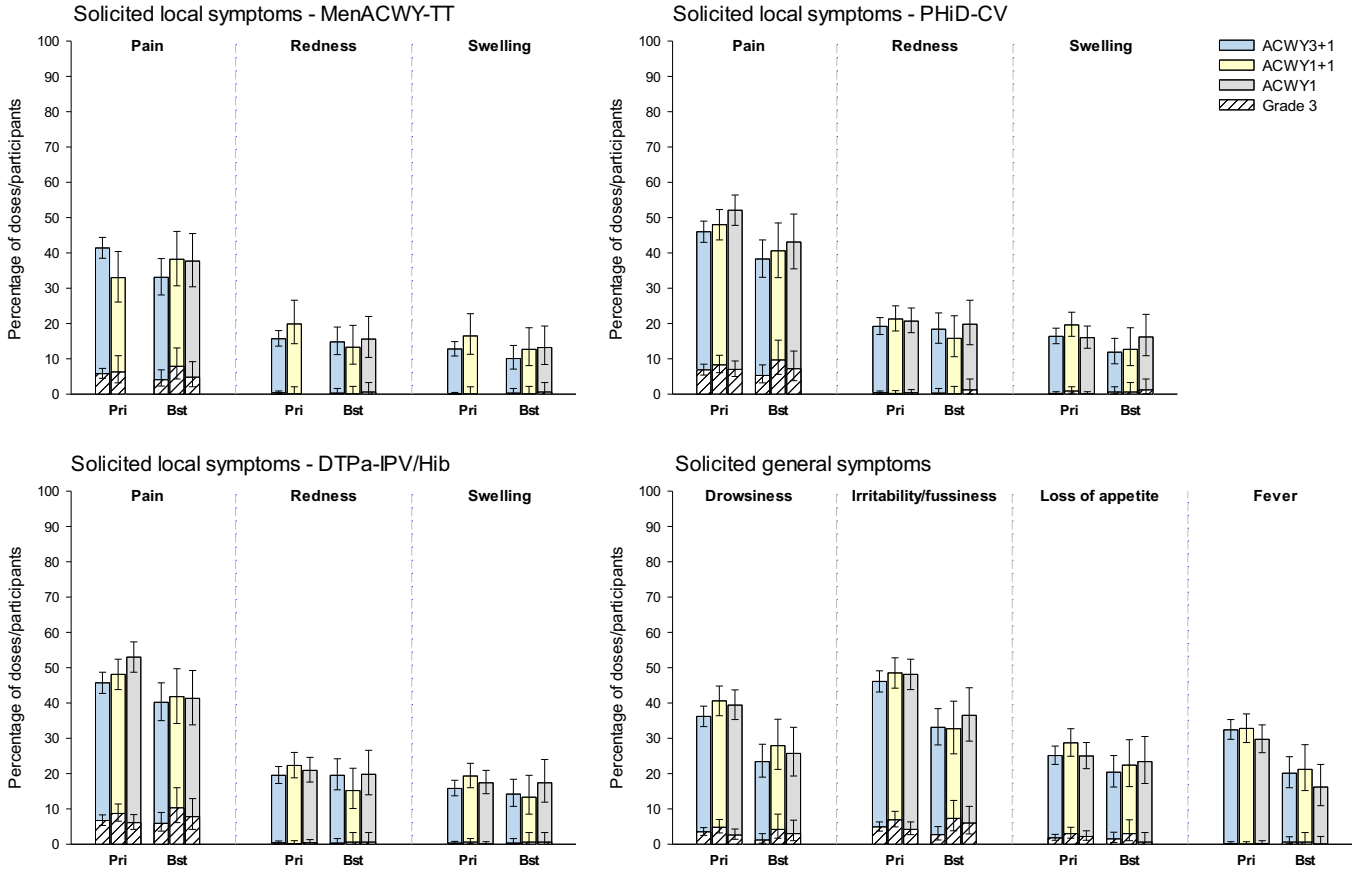

Fig. 3. Incidence of solicited local and general symptoms during the 7-day period following administration of study vaccines in the primary (overall/dose) and booster (percentage of participants) vaccination phase (total vaccinated cohort). Pri, primary vaccination phase; Bst, booster vaccination phase; ACWY3+1, participants who received 4 doses of MenACWY-TT at 2, 4, 6 and 15–18 months of age; ACWY1+1, participants who received 2 doses of MenACWY-TT at 6 and 15–18 months of age; ACWY1, participants who received 1 dose of MenACWY-TT at 15–18 months of age; PHiD-CV, pneumococcal non-typeable H. influenzae protein D conjugate vaccine; DTPa-IPV/Hib, combined diphtheria, tetanus, acellular pertussis, inactivated polio and H. influenzae type b vaccine. Grade 3 events were defined as "diameter >30 mm" for redness and swelling, "child did not eat at all" for loss of appetite, "rectal temperature >38.0 °C" for fever, and "preventing normal every day activity" for all other events. Note: Error bars represent 95% confidence intervals. All solicited symptoms were considered related to vaccination.

age, ≥93% of infants achieved rSBA titers ≥8 for each meningococcal serogroup, which is an adequate basis to assume clinical protection. These results further support previous findings in infants; either 3 or 2 primary doses of MenACWY-TT were immunogenic in healthy European infants, when co-administered with PHiD-CV and DTPa-HBV-IPV/Hib, with ≥93% of children achieving rSBA titers ≥ 8 for all serogroups, at 5 months of age [17].

At 15–18 months of age, rSBA titers ≥8 were maintained in ≥65% of participants previously primed with MenACWY-TT. Following MenACWY-TT vaccination at this age, ≥96% of children had rSBA titers ≥8, regardless of primary vaccination. Moreover, immunogenicity of MenACWY-TT did not seem impacted by co-administration with other pediatric vaccines, as previously shown for toddlers [22–24].

Overall, the percentage of children with rSBA titers ≥8 at 7 or 15–18 months of age was not affected by the number of doses of MenACWY-TT, nor was there a significant difference in the booster/vaccine response. However, post-primary rSBA GMTs for MenC appeared to increase with the number of primary doses and post-booster MenC GMTs were higher in the primed groups compared to the naïve group. A more pronounced effect of cumulative doses was observed for hSBA GMTs, with increasing GMTs with the number of primary doses received. Intriguingly, MenC rSBA GMTs were lower compared to other serogroups in the ACWY1 group, an observation that was made in other studies, after a single dose of MenACWY-TT at 12–15 [25] or 12–23 months [26] of age. Immune responses to MenACWY-TT vaccination within the same group were similar between countries, as expected from previous data obtained in different geographic locations in infants and toddlers [12–15].

Immunogenicity of DTP/IPV components was not impacted by its co-administration with MenACWY-TT, as evidenced by the high seroprotection/seropositivity rates. Our results also compare well with those observed for co-administration of MenACWY-CRM_{197} with routine pediatric vaccines according to the same 3+1 schedule [27] and confirm that co-administration of MenACWY-TT with PHiD-CV during the first years of life does not affect the immunogenicity of the pneumococcal vaccine [17].

Although all children had protective anti-TT antibody concentrations after vaccination at age 15–18 months, antibody GMCs tended to be lower in MenACWY-TT-primed groups. The effect of high anti-TT antibody levels due to conjugated meningococcal vaccines on the immune response to subsequent TT administration was discussed by others, noting a potential negative impact on tetanus immunity [28]. A lower immune response to pneumococcal serotype 18C (conjugated to TT in PHiD-CV), although not evidenced in our study, was previously observed following co-administration of MenACWY-TT with PHiD-CV at 12–23 months of age and attributed to the effect of high TT dosage on the response to co-administrated TT-conjugated vaccines [23].

The reactogenicity profile of MenACWY-TT was similar between groups. For both PHiD-CV and DTPa-IPV/Hib, the most frequently reported solicited symptom was pain, in contrast with other studies where redness was more frequent [29,30]. Nevertheless, pain and redness were found to have similar incidence in a review on safety data of PHiD-CV co-administration with routine vaccines [31]. No SAEs were assessed as related to vaccination. Moreover, safety results in our study are also similar to those for separate administration of MenACWY-TT in infants and toddlers [14].

Meningococcal vaccination is not currently included in the NIPs of either Lebanon or Mexico. Although data regarding the burden of IMD in Lebanon is scarce [2,32,33], the reported incidence was 0.14 per 100,000 inhabitants in 2013 [34]. MenA is the major cause of disease in the Middle East and North Africa, while outbreaks due to MenW were also recorded [2]. In Mexico, IMD incidence is <0.1 cases per 100,000 inhabitants of all ages, but is likely to be underreported [35], with the most prominent serogroup being MenC, followed by MenW [35,36], similar to serogroup prevalence in Latin America. Despite the risk of IMD, meningococcal vaccination with quadrivalent vaccines is currently included in the NIPs of very few countries in these regions [37]. While MenA vaccination was successfully implemented in the African meningitis belt [38] and MenC/MenACWY vaccination is used as outbreak response in some countries in Latin America [37], there is an unmet need in adapting current meningococcal vaccination recommendations to serogroup prevalence specific to each geographic location. Our results support expanding the use of MenACWY-TT to predominantly non-European populations, and as part of NIPs worldwide. The 3+1 schedule would ensure immunization against IMD from an early age, while the 1+1 schedule might be used to offer a similar level of protection in children not likely to be exposed to IMD in the first 6 months of life.

Our trial was designed with sufficient power to assess the primary confirmatory objective, and with a non-inferiority criterion that complied with guidelines imposed by regulatory organizations. Moreover, the ACWY1 group was used as a control for the post-primary and pre-booster timepoints.

The study had several potential limitations. Immunogenicity endpoints were not assessed post-each dose in the ACWY3+1 group. Therefore, only the cumulative effect of the 3 primary doses was demonstrated, and the immunogenicity of one or 2 MenACWY-TT doses in early infancy is not answered. A quadrivalent control group could not be used, as no quadrivalent vaccines were licensed in the participating countries. When assessing immune responses to PHiD-CV, no functional assay testing was done, due to the limited volume of sera available. The study was not designed to include a long-term follow-up to evaluate the persistence of the immune response to MenACWY-TT vaccination. Previous reports showed that rSBA titers ≥8 were maintained up to 3 years post-vaccination in 90.8% of toddlers who had received MenACWY-TT at 12–23 months of age [26], although hSBA antibody levels are known to decline more rapidly following vaccination during the first 2 years of life, especially for MenA [26,39]. Also, the sample size for immunogenicity assessments of co-administered vaccines was relatively low.

5. Conclusions

MenACWY-TT was immunogenic in healthy infants after 3 primary doses at 2, 4 and 6 months or after 1 dose at 6 months of age. Regardless of the primary vaccination schedule received, ≥96.3% of children had rSBA titers ≥ 8 after 1 dose of MenACWY-TT at 15–18 months of age, showing that immune response to MenACWY-TT vaccination in toddlers is not affected by the number of previously-administered doses. Co-administration of MenACWY-TT with DTPa-IPV/Hib and PHiD-CV during the first years of life was immunogenic, well-tolerated and no safety concerns were identified.

Our results support the potential use of MenACWY-TT in routine pediatric vaccination programs worldwide to ensure protection against IMD caused by 4 meningococcal serogroups at a very young age. However, the need for vaccinating infants, the age at vaccination and the number of administered doses should be dictated by geographic and epidemiological factors.

Trademark statement

Menveo, *Synflorix* and *Infanrix*-IPV/Hib are trademarks owned by the GSK group of companies. *Menactra* is a trademark of Sanofi

Pasteur. *Nimenrix* is a trademark of the GSK group of companies, licensed to Pfizer.

Authors' contribution

All authors had full access to the data and corresponding author 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.

GD and JCFT were the principal investigators at the participating sites, responsible for the administrative, logistic and technical support, the recruitment and the medical evaluation of subjects, the collection of data and the conduct of the study and participated in the analysis of the data. MT and AJ participated in the analyses and interpretation of data, MW participated in the conception, design and planning of the study, supervised the analysis, participated in the interpretation of results. All authors participated in the drafting and approval of the manuscript.

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Conflict of interest

MT and MW are employees of the GSK group of companies. AJ was consultant of XPE Pharma and Science for GSK at the time the study was conducted. MW declared stock ownership in the GSK group of companies. GD reports that his institution received funding for the conduct of the study. JCTF has no conflict of interest to disclose.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.05.046.

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