

Concomitant administration of a fully liquid ready-to-use DTaP-IPV-HB-PRP-T hexavalent vaccine with a meningococcal ACWY conjugate vaccine in toddlers



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ABSTRACT

Invasive meningococcal disease caused by *Neisseria meningitidis* is a life-threatening disease. Several countries now include meningococcal serogroup C (MenC) conjugate and, more recently, a meningococcal serogroup ACWY conjugate (MenACWY) vaccination in their national immunization schedules. DTaP-IPV-HB-PRP-T is a hexavalent vaccine that provides protection against six diseases. The phase III, open-label, randomised, multicentre study enrolled healthy toddlers who received the DTaP-IPV-HB-PRP-T vaccine (at 2, 3 and 4 months) with or without a MenC vaccine (at 2 and 4 months) in the primary series study. At 12 months of age, 312 toddlers were randomised to receive DTaP-IPV-HB-PRP-T co-administered with MenACWY-TT vaccine (Group A; n = 104); DTaP-IPV-HB-PRP-T vaccine alone (Group B; n = 105); or MenACWY-TT vaccine alone (Group C; n = 103). At 12 months of age, there were no notable differences in terms of antibody persistence for any DTaP-IPV-HB-PRP-T vaccine antigen, whether MenC-TT conjugate vaccine was co-administered or not during the primary series. Following booster vaccination, immune responses to DTaP-IPV-HB-PRP-T and MenACWY-TT vaccines were not affected by co-administration. One month after vaccination, the immune responses elicited by both vaccines were high, whether administered concomitantly or separately. The administration of MenC vaccine during infancy did not preclude the use of a MenACWY-TT vaccine for booster vaccination. Even though the reactogenicity after co-administration was somewhat higher, the results of this study support the concomitant administration of the DTaP-IPV-HB-PRP-T vaccine with a MenACWY-TT conjugate vaccine when given from 12 months of age.

The clinical trial registration numbers are: clinicaltrials.gov: NCT01839175; EudraCT: 2012-005547-24.
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1. Introduction

Invasive meningococcal disease is a contagious and life-threatening infection caused by *Neisseria meningitidis*, a Gram-negative endotoxin-producing bacterium known for its ability to cause epidemic disease [1,2]. Meningococcal disease occurs worldwide, with considerable geographical variability in

serogroup distribution [3,4]. Fatality rates for cases of invasive meningococcal disease are between 5% and 15%, with 20% of survivors suffering permanent sequelae including hearing loss, neurological impairment, seizures and intellectual disabilities [5]. Several countries including the UK formerly introduced meningococcal serogroup C conjugate (MenC)³ vaccination and, more recently, a meningococcal serogroup ACWY conjugate

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³ Abbreviations: AE, adverse event; AESI, adverse event of special interest; aP, acellular pertussis; AR, adverse reaction; CI, confidence interval; CRF, case record forms; D, diphtheria; FHA, filamentous haemagglutinin; GMC, geometric mean concentration; GMT, geometric mean titre; HB, hepatitis B; Hib, *Haemophilus influenzae* type b; IPV, inactivated poliovirus; ISR, injection site reactions; LLOQ, lower limit of quantitation; LLT, lowest level term; MedDRA®, Medical Dictionary for Regulatory Activities; Men C, meningococcal serogroup C; MenACWY, meningococcal serogroups A, C, W and Y; NA, not applicable; PPS, per-protocol set; PRP, *Haemophilus influenzae* type b capsular polyribosyl-ribitol-phosphate; PT, pertussis toxoid; SAE, serious adverse event; SAR, serious adverse reaction; SBA, serum bactericidal antibody; T, tetanus; TT, tetanus toxoid.

(MenACWY) vaccination, into their national immunisation schedules [6].

The hexavalent diphtheria (D), tetanus (T), acellular pertussis (aP), inactivated poliovirus (IPV), hepatitis B (HB), *Haemophilus influenzae* type-b (Hib) capsular polyribosyl-ribitol-phosphate (PRP) vaccine (DTaP-IPV-HB-PRP-T; Hexyon[®], Hexacima[®], Hexaxim[®], Sanofi Pasteur; Lyon, France) is a fully liquid ready-to-use combination vaccine that provides protection against six diseases. A primary series vaccination study designed to assess the immunogenicity and safety of DTaP-IPV-HB-PRP-T when administered concomitantly with a MenC vaccine during the first year of life, and whether concomitant administration has any impact on the immunogenicity and safety of either vaccine has already been published [7]. The data presented here report the immunogenicity results and safety findings from the booster part of the previous two–three–four month primary series study that assessed the co-administration of a booster dose of the DTaP-IPV-HB-PRP-T vaccine with a MenACWY-tetanus toxoid (TT) vaccine. In this study a booster dose of a MenACWY vaccine following a childhood MenC vaccination was tested as vaccination with MenACWY is already (or likely to be in the near future) the preferred recommended immunisation schedule against meningococcal diseases.

1.1. Objectives

The primary objective of this booster part of the primary study was to describe the immunogenicity of a booster dose of the DTaP-IPV-HB-PRP-T vaccine and a MenACWY-TT vaccine either co-administered at 12 months of age or given separately.

The secondary objective was to describe the antibody persistence at 12 months of age for the DTaP-IPV-HB-PRP-T vaccine following a three–dose primary vaccination at two, three and four months of age (prior to administration of a booster dose). The secondary objectives included the description of the safety of a booster dose of the DTaP-IPV-HB-PRP-T vaccine and MenACWY-TT vaccine either co-administered at 12 months of age or given separately. The study was descriptive; no formal hypotheses were tested.

2. Materials and methods

2.1. Study population

Healthy toddlers who received three doses of the DTaP-IPV-HB-PRP-T vaccine in the primary series study were eligible for enrolment.

The main exclusion criteria were:

- previous booster vaccination against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, Hib, or meningococcus with either the DTaP-IPV-HB-PRP-T vaccine or another vaccine
- previous (within four weeks) or planned vaccination during study participation,
- any history of diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, Hib or meningococcal serogroup A, C, W or Y infection (s) confirmed either clinically, serologically or microbiologically
- known or suspected contraindication(s) to any of the study vaccines
- hypersensitivity or allergy to components of the study vaccines
- receipt of anticoagulants in the previous three weeks, contraindicating intramuscular injection
- receipt of high doses of systemic corticosteroid therapy or other immunosuppressive therapy in the previous three months
- any recent history of chronic disease or medical condition likely to interfere with the trial assessments.

2.2. Vaccines and vaccinations

All vaccines were administered according to their respective summaries of product characteristics [8–12]. The hexavalent DTaP-IPV-HB-PRP-T vaccine (0.5 mL; batch number: S4370) and/or MenACWY-TT vaccine (0.5 mL; Nimenrix[®] manufactured by GlaxoSmithKline Biologicals SA; batch number: A90CA032A) were administered intramuscularly in the anterolateral aspect of the right thigh. NeisVac-C[®] (Baxter AG; batch number: VNS1M04C) and Prevenar 13[®] (Pfizer; batch number: G40914) with or without measles, mumps and rubella vaccine (live) (M-M-RvaxPro[®]; Merck Sharp & Dohme Corporation; batch number: J011869) were administered 5 cm apart in the left thigh.

Further details of the vaccines used are provided in Supplementary Data 1. The administration of MenACWY-TT was performed either at least one month before (Group C; control group for MenACWY-TT vaccine), or concomitantly with (Group A; test group), a TT-containing DTaP-IPV-HB-PRP-T vaccine. As administration of MenACWY-TT one month after a TT-containing vaccine was not recommended, and as Nimenrix did not have any co-administration labelling claim with Prevenar 13, MenC-TT vaccine was administered instead of MenACWY-TT vaccine to subjects in Group B (control group for the DTaP-IPV-HB-PRP-T vaccine) at approximately 13 months of age to ensure protection against MenC serogroup.

2.3. Study design

This phase III, open-label, randomised, multicentre study (clinicaltrials.gov: NCT01839175; EudraCT: 2012-005547-24) was conducted at 11 vaccine research clinics in Finland.

The randomisation was stratified by groups from the primary series (i.e., Group 1: DTaP-IPV-HB-PRP-T vaccine co-administered with MenC vaccine; Group 2: DTaP-IPV-HB-PRP-T vaccine without MenC-TT vaccine). Participants enrolled in the booster phase were randomly assigned in a 1:1:1 ratio to one of three vaccination groups irrespective of their primary series enrolment group. In Group A, participants received a dose of DTaP-IPV-HB-PRP-T vaccine with a dose of MenACWY-TT vaccine at approximately 12 months of age, and 28–42 days later they received a dose of Prevenar 13 (i.e., at approximately 13 months of age). In Group B, participants received a dose of DTaP-IPV-HB-PRP-T vaccine at approximately 12 months of age, and doses of MenC-TT vaccine and Prevenar 13 at approximately 13 months of age. In Group C, participants received a dose of MenACWY-TT vaccine at approximately 12 months of age, and a dose of the DTaP-IPV-HB-PRP-T vaccine plus a dose of Prevenar 13 at approximately 13 months of age. All participants were offered an optional dose of M-M-RvaxPro at approximately 13 months of age.

The trial was conducted in accordance with applicable local and national requirements and guidelines, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice standards, the Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association, and the Declaration of Helsinki. The parent(s) or legal guardian(s) of the participating children provided written informed consent prior to inclusion in the booster part.

2.4. Immunogenicity measurements

Serology tests for DTaP-IPV-HB-PRP-T vaccine antigens and MenC/MenACWY-TT vaccine antigens were performed by two different laboratories: Public Health England's Vaccine Evaluation Unit (Manchester, UK) for MenC, MenA, MenW and MenY; and the Global Clinical Immunology platform (Sanofi Pasteur Inc.,

Swiftwater, PA, USA) for pertussis, hepatitis B, Hib, diphtheria toxoid, tetanus toxoid, and inactivated poliovirus antigens. Laboratory staff were blinded to the group to which participants were randomised.

The serological analyses were performed as described in the primary series article [7]. The immunogenicity assessments used for the DTaP-IPV-HB-PRP-T vaccine were consistent with those used during the clinical development plan with regards to the assays used, the endpoints analysed, and the timing of the serology assessment. The meningococcal serogroup A, W and Y antibodies were tested by the modified serum bactericidal antibody (SBA) assay with baby rabbit complement, as previously described by Maslanka et al. [13].

Blood samples of approximately 5 mL each were collected before and one month after the booster vaccination (at 13 months of age). The antibody correlates of protection for each vaccine antigen were as described for the primary series, with the addition of meningococcal serogroup A, W and Y endpoints (SBA titre \geq 8).

2.5. Safety assessments

Safety and tolerability for related serious adverse events (SAEs), deaths and adverse events of special interest (AESIs) were monitored between the end of the primary series study and booster vaccination day (at approximately 12 months of age). Within 30 min of booster vaccination, investigators monitored participants for unsolicited (spontaneously reported) systemic adverse events (AEs) or SAEs.

A diary card was provided at approximately 12 months of age (booster vaccination day, day 0) that participants' parents or legal guardians used on days 0–7 to record solicited injection-site adverse reactions (injection-site erythema, injection-site pain, injection-site swelling) and solicited systemic adverse reactions (pyrexia, vomiting, crying, somnolence, anorexia and irritability). Unsolicited injection-site reactions and systemic AEs were recorded on days 0–30. Parents or legal guardians recorded the start, end and intensity of any unsolicited events; the investigator assessed the relationship of these events to the vaccination. Serious AEs, including deaths, and AESIs were recorded from approximately 12 to 13 months of age. For children randomised to Group C, a telephone contact was made at approximately 14 months of age to collect any relevant safety information.

2.6. Statistical methods

2.6.1. Sample size

Sample size for the primary series was determined as previously reported [7]. The maximum number of participants in the primary series was expected to be 350; all children who received three doses of the DTaP-IPV-HB-PRP-T vaccine were to be invited to participate in the booster study. We estimated that a participation rate in the booster phase of 70–85% would result in 245–298 participants being evaluable for the primary analysis. With a sample size of 80 evaluable participants per group, the half-width of the two-sided 95% confidence interval (CI) should not exceed 10% for observed response rates above 80%.

2.6.2. Analyses

Descriptive statistics were used for the immunogenicity and safety analyses. The randomised set was defined as all randomised subjects in the booster part of the study. The persistence analysis was performed on the persistence analysis set (all children randomised and who provided a blood sample on booster vaccination day).

The post-booster immunogenicity primary analyses were performed on the per-protocol set (PPS; randomised participants

excluding those with protocol deviation(s) that could interfere with the immunogenicity evaluation).

The full analysis sets (all randomised participants who received at least one dose of the study vaccines and who had any post-vaccination immunogenicity data) were used for supportive analyses.

Safety analyses were described for all participants with safety follow-up data who received at least one dose of study vaccine(s) (safety analysis set).

Statistical analyses were performed using SAS[®] software version 9.1.3 (SAS[®] Institute Inc., Cary, NC, USA).

3. Results

3.1. Demographic and other baseline characteristics

At 12 months of age, 312 toddlers (mean age 376.5 days; range: 366–415 days) previously primed at two, three and four months of age with DTaP-IPV-HB-PRP-T vaccine with or without MenC-TT vaccine were randomised as follows:

- 104 toddlers received DTaP-IPV-HB-PRP-T co-administered with MenACWY-TT (Group A)
- 105 toddlers received DTaP-IPV-HB-PRP-T alone (Group B)
- 103 toddlers received MenACWY-TT alone (Group C).

Demographic and baseline characteristics were similar across the three groups in terms of age, ethnic origin and temperature in the overall randomised set (Table 1). The participant disposition is summarised in Fig. 1. In the PPS, demographic and baseline characteristics were similar across the groups.

3.2. Pre-booster antibody persistence to DTaP-IPV-HB-PRP-T vaccine antigens (persistence analysis set)

Following the three-dose primary vaccination series at two, three and four months of age, no notable differences were observed at 12 months of age between Group 1 (DTaP-IPV-HB-PRP-T vaccine co-administered with the MenC-TT vaccine) and Group 2 (DTaP-IPV-HB-PRP-T vaccine without MenC-TT vaccine) in terms of antibody levels to the different DTaP-IPV-HB-PRP-T vaccine antigens, with the exception of the proportion of participants with an anti-T concentration \geq 0.10 IU/mL, which was higher in Group 1 versus Group 2 (100%, 95% CI: 97.6; 100.0, and 92.0%, 95% CI: 86.4; 95.8, respectively) (Table 2).

At 12 months of age, there were no notable differences in geometric mean concentrations (GMCs) or titres (GMTs) between Group 1 and Group 2 for any DTaP-IPV-HB-PRP-T vaccine antigen with the exception of anti-T GMC, which was significantly higher in Group 1 versus Group 2 (0.61, 95%CI: 0.55; 0.68, and 0.34, 95% CI: 0.29; 0.39, respectively) (Supplementary Data 2).

3.3. Post-booster antibody response to DTaP-IPV-HB-PRP-T vaccine antigens (PPS)

One month after the booster dose, no notable differences were observed between Group A (DTaP-IPV-HB-PRP-T with MenACWY-TT) and Group B (DTaP-IPV-HB-PRP-T alone) in terms of seroprotection rates (Group A: 97.7–100%; Group B: 98.9–100%) for any DTaP-IPV-HB-PRP-T vaccine antigen (PPS) (Table 3).

The proportions of participants with anti-D concentration \geq 1.0 IU/mL and anti-T concentration \geq 1.0 IU/mL were also high and comparable in both groups. For pertussis antigens, the proportion of participants with vaccine response (from pre-vaccination [pre-dose 1] to post-booster) for pertussis toxoid

Table 1
Demography and other baseline characteristics (randomised set).

	Group A DTaP-IPV-HB-PRP-T with MenACWY (N = 104)	Group B DTaP-IPV-HB-PRP-T alone (N = 105)	Group C MenACWY-TT alone (N = 103)	Total (N = 312)
Age (days) at vaccination				
n	104	105	103	312
Mean (SD)	375.8 (8.8)	376.8 (9.4)	376.8 (9.2)	376.5 (9.1)
Median	373.0	374.0	374.0	373.0
Min; max	366; 406	366; 415	366; 410	366; 415
Sex				
n	104	105	103	312
Female, n (%)	49 (47.1) [‡]	54 (51.4) [‡]	46 (44.7) [‡]	149 (47.8) [‡]
Male, n (%)	55 (52.9) [‡]	51 (48.6) [‡]	57 (55.3) [‡]	163 (52.2) [‡]
Ethnic origin				
n	104	105	103	312
Asian, n (%)	0	1 (1.0) [‡]	0	1 (0.3) [‡]
Black, n (%)	1 (1.0) [‡]	0	0	1 (0.3) [‡]
Caucasian, n (%)	96 (92.3) [‡]	100 (95.2) [‡]	95 (92.2) [‡]	291 (93.3) [‡]
Other, n (%)	7 (6.7) [‡]	4 (3.8) [‡]	8 (7.8)	19 (6.1) [‡]
Temperature (°C)				
n	104	105	103	312
Mean (SD)	36.6 (0.6)	36.6 (0.6)	36.6 (0.6)	36.6 (0.6)
Median	36.6	36.6	36.6	36.6
Min; max	35.3; 37.9	35.4; 37.8	35.1; 37.7	35.1; 37.9
Disposition of subjects according to groups in the primary series [†]				
Hexavalent co-administered with MenC (Group 1), n (%)	53 (51.0) [‡]	52 (49.5) [‡]	51 (49.5) [‡]	156 (50.0) [‡]
Hexavalent without MenC (Group 2), n (%)	51 (49.0) [‡]	53 (50.5) [‡]	52 (50.5) [‡]	156 (50.0) [‡]

Abbreviations: aP, acellular pertussis; D, diphtheria; HB, hepatitis B; IPV, inactivated poliovirus; MenACWY, meningococcal serogroups A, C, W and Y; PRP, *Haemophilus influenzae* type-b capsular polyribosyl-ribitol-phosphate; SD, standard deviation; T, tetanus; TT, tetanus toxoid.

[‡] Percentages are based on the number of randomised subjects.

[†] Vaccines actually received during the primary series part.

and filamentous haemagglutinin were 98.8% and 100%, respectively, in both Group A and Group B. The proportion of participants with a four-fold-rise from pre-vaccination (pre-dose 1) to post-booster for pertussis toxoid and filamentous haemagglutinin were respectively 83.5% and 96.5% in Group A, and 88.4% and 92.1% in Group B.

There were no notable differences in GMCs/GMTs for any DTaP-IPV-HB-PRP-T vaccine antigen between Group A and Group B except for anti-IPV3 GMT and anti-PRP GMC, which tended to be higher in Group B but deemed not to be clinically significant (Table 3). Comparable results for seroprotection rates/response rates and GMCs/GMTs were observed in the full analysis set DTaP-IPV-HB-PRP-T.

3.3.1. Antibody response to MenACWY-TT vaccine antigens (PPS)

In the PPS, one month after vaccination no notable differences were observed between Group A (DTaP-IPV-HB-PRP-T with MenACWY-TT) and Group C (MenACWY-TT alone) in terms of seroprotection rates for any meningococcal serogroup. The proportion of participants with an antibody titre ≥ 8 (1/dil) was high in both groups, ranging from 98.9 to 100% in Group A, and 95.7 to 100% in Group C (Table 4).

There were no notable differences in GMTs between Group A and Group C for any meningococcal antigen except for MenA SBA GMT, which tended to be higher in Group C (Table 4). For both Group A and Group C, the subgroup of participants who had previously received the MenC vaccine during the primary series part (Group 1) displayed higher anti-MenC GMTs versus the subgroup of participants who did not (Group 2) (data not shown).

3.4. Safety

The safety profile of the DTaP-IPV-HB-PRP-T vaccine was generally comparable whether co-administered with MenACWY-TT vaccine or not (Table 5). Overall, most of the participants reported AEs

occurring within 30 days after vaccination: 94.2% in Group A (DTaP-IPV-HB-PRP-T with MenACWY-TT), 92.4% in Group B (DTaP-IPV-HB-PRP-T alone), and 87.4% in Group C (MenACWY-TT alone). Two participants (0.6% of all participants), one in Group A (1.0%) and one in Group B (1.0%), experienced an immediate unsolicited AE after the booster – grade 1 urticaria and grade 2 diarrhoea, respectively – both considered by the investigator to be related to the study vaccines.

Solicited injection site reactions within seven days after DTaP-IPV-HB-PRP-T vaccination were reported by 66.0% of subjects in Group A, and 60.0% of subjects in Group B.

Solicited injection site reactions within seven days after MenACWY-TT vaccination were reported by 47.6% of subjects in Group A, and 32.0% of subjects in Group C, and injection site pain was reported more frequently in Group A (46.6% versus 17.5%). Grade 3 intensity reactions were observed in 11% in Group A and 1% in Group C.

Nearly all solicited injection site reactions occurred between day 0 and day 3 following vaccination, and lasted no more than three days (Table 5). The details of the intensity scales used for safety parameters are shown in Supplementary Data 3.

The frequency of solicited systemic reactions was higher in Group A versus Group C for crying, irritability, pyrexia and somnolence (respectively: 50.5% versus 30.1%; 76.7% versus 48.5%; 30.1% versus 10.7%; and 52.4% versus 32.0%). No notable differences were observed between Group A and Group C in frequencies of reactions of Grade 3 intensity. Pyrexia of grade 3 intensity (>39.5 °C) was reported by four participants: two who received DTaP-IPV-HB-PRP-T and MenACWY-TT vaccine concomitantly; one who received DTaP-IPV-HB-PRP-T vaccine alone; and one who received MenACWY-TT vaccine alone.

One AESI was reported during the booster phase, a serious febrile convulsion related to pneumonia caused by respiratory syncytial viral infection reported 24 days after administration of MenACWY-TT vaccine alone. The number of SAEs reported was

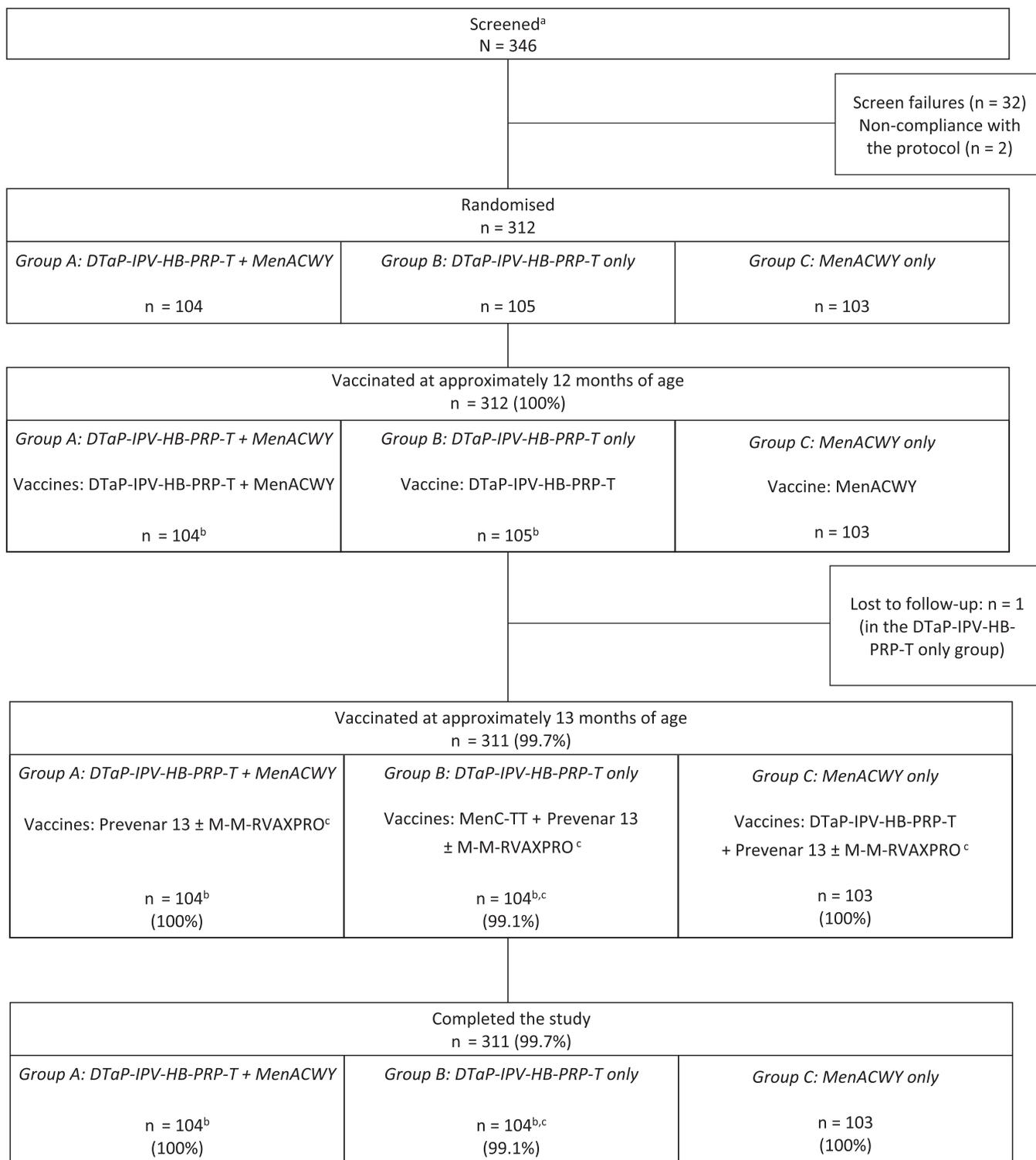


Fig. 1. Disposition of patients through the study. ^aParticipants who received three doses of the DTaP-IPV-HB-PRP-T vaccine during the primary series part. ^bOne participant randomised to Group A (DTaP-IPV-HB-PRP-T vaccine co-administered with MenACWY-TT vaccine) had received the DTaP-IPV-HB-PRP-T vaccine prior to randomisation (and received the MenC vaccine at approximately 13 months of age). ^cOne participant was lost to follow-up after vaccination at approximately 12 months of age, with no safety data available.

low and none was considered to be related to the study vaccines by the investigator. No AE leading to study discontinuation during the booster phase of the study were reported during the course of that part of the study.

4. Discussion

The results demonstrate that, one month after vaccination with a booster dose, the immune responses elicited by the DTaP-IPV-HB-PRP-T vaccine and the meningococcal serogroup ACWY

Table 2
Summary of antibody levels at 12 months of age for all DTaP-IPV-HB-PRP-T antigens following the three-dose primary vaccination (pre-booster) (persistence analysis set).

Component	Endpoint	Group 1 (primary series part) DTaP-IPV-HB-PRP-T co-administered with MenC (N = 152)			Group 2 (primary series part) DTaP-IPV-HB-PRP-T without MenC (N = 151)		
		M [*]	n (%)	95% CI	M [*]	n (%)	95% CI
Anti-D	≥0.01 IU/mL	151	148 (98.0)	94.3; 99.6	150	149 (99.3)	96.3; 100.0
	≥0.10 IU/mL	151	62 (41.1)	33.1; 49.3	150	71 (47.3)	39.1; 55.6
Anti-T	≥0.01 IU/mL	151	151 (100.0)	97.6; 100.0	150	150 (100.0)	97.6; 100.0
	≥0.10 IU/mL	151	151 (100.0)	97.6; 100.0	150	138 (92.0)	86.4; 95.8
Anti-IPV1	≥8 1/dil	151	122 (80.8)	73.6; 86.7	150	127 (84.7)	77.9; 90.0
Anti-IPV2	≥8 1/dil	151	98 (64.9)	56.7; 72.5	150	114 (76.0)	68.4; 82.6
Anti-IPV3	≥8 1/dil	150	123 (82.0)	74.9; 87.8	148	131 (88.5)	82.2; 93.2
Anti-HB	≥10 mIU/mL	152	137 (90.1)	84.2; 94.4	151	138 (91.4)	85.7; 95.3
	≥100 mIU/mL	152	72 (47.4)	39.2; 55.6	151	77 (51.0)	42.7; 59.2
Anti-PRP	≥0.15 µg/mL	151	131 (86.8)	80.3; 91.7	150	116 (77.3)	69.8; 83.8
	≥1.0 µg/mL	151	70 (46.4)	38.2; 54.6	150	71 (47.3)	39.1; 55.6
Anti-PT	≥LLOQ [†]	151	151 (100.0)	97.6; 100.0	148	147 (99.3)	96.3; 100.0
	≥2 × LLOQ [†]	151	150 (99.3)	96.4; 100.0	148	147 (99.3)	96.3; 100.0
Anti-FHA	≥LLOQ [†]	151	151 (100.0)	97.6; 100.0	149	149 (100.0)	97.6; 100.0
	≥2 × LLOQ [†]	151	151 (100.0)	97.6; 100.0	149	149 (100.0)	97.6; 100.0

Abbreviations: aP, acellular pertussis; CI, confidence interval; D, diphtheria; FHA, filamentous haemagglutinin; HB, hepatitis B; IPV, inactivated poliovirus; LLOQ, lower limit of quantitation; MenC, meningococcal serogroup C; PRP, *Haemophilus influenzae* type b capsular polyribosyl-ribitol-phosphate; PT, pertussis toxin; T, tetanus.

^{*} M: number of subjects with available data.

[†] LLOQ = 2 EU/mL for PT and FHA.

Table 3
Summary of post-booster antibody levels (A) and geometric means of antibody concentrations or titres (B) to DTaP-IPV-HB-PRP-T vaccine antigens (PPS).

Component	Endpoint	Group A Hexavalent co-administered with MenACWY (N = 87)			Group B Hexavalent alone (N = 91)		
		M [*]	n (%)	95% CI	M [*]	n (%)	95% CI
A. Post-booster antibody levels							
Anti-D	≥0.10 IU/mL	87	87 (100.0)	95.8; 100.0	91	91 (100.0)	96.0; 100.0
	≥1.0 IU/mL	87	78 (89.7)	81.3; 95.2	91	88 (96.7)	90.7; 99.3
Anti-T	≥0.10 IU/mL	87	87 (100.0)	95.8; 100.0	91	91 (100.0)	96.0; 100.0
	≥1.0 IU/mL	87	84 (96.6)	90.3; 99.3	91	88 (96.7)	90.7; 99.3
Anti-IPV1	≥8 1/dil	87	86 (98.9)	93.8; 100.0	91	90 (98.9)	94.0; 100.0
Anti-IPV2	≥8 1/dil	87	87 (100.0)	95.8; 100.0	91	91 (100.0)	96.0; 100.0
Anti-IPV3	≥8 1/dil	87	87 (100.0)	95.8; 100.0	90	90 (100.0)	96.0; 100.0
Anti-HBs	≥10 mIU/mL	87	86 (98.9)	93.8; 100.0	91	90 (98.9)	94.0; 100.0
	≥100 mIU/mL	85	85 (97.7)	91.9; 99.7	91	87 (95.6)	89.1; 98.8
Anti-PRP	≥0.15 µg/mL	87	87 (100.0)	95.8; 100.0	91	91 (100.0)	96.0; 100.0
	≥1.0 µg/mL	87	85 (97.7)	91.9; 99.7	91	91 (100.0)	96.0; 100.0
Anti-PT	Vaccine response [†]	85	84 (98.8)	93.6; 100.0	86	85 (98.8)	93.7; 100.0
	4-fold increase [‡]	85	71 (83.5)	73.9; 90.7	86	76 (88.4)	79.7; 94.3
Anti-FHA	Vaccine response [†]	85	85 (100.0)	95.8; 100.0	89	89 (100.0)	95.9; 100.0
	4-fold increase [‡]	85	82 (96.5)	90.0; 99.3	89	82 (92.1)	84.5; 96.8
B. Post-booster GMTs/GMCs							
Component	M	Geometric mean (GMC/GMT) [§]	95% CI	M	Geometric mean (GMC/GMT) [§]	95% CI	
Anti-D (IU/mL)	87	3.07	2.49; 3.79	91	3.24	2.69; 3.91	
Anti-T (IU/mL)	87	6.89	5.78; 8.21	91	6.25	5.30; 7.37	
Anti-IPV1 (1/dil)	87	2174.05	1606.18; 2942.70	91	2040.21	1522.96; 2733.14	
Anti-IPV2 (1/dil)	87	1678.14	1203.60; 2339.77	91	1738.58	1242.59; 2432.56	
Anti-IPV3 (1/dil)	87	3086.91	2278.10; 4182.89	90	4127.67	3175.40; 5365.53	
Anti-HBs (mIU/mL)	87	2230.68	1597.48; 3114.87	91	2233.15	1597.30; 3122.13	
Anti-PRP (µg/mL)	87	22.70	17.20; 29.96	91	27.82	21.89; 35.35	
Anti-PT (EU/mL)	87	111.78	97.90; 127.63	91	114.72	102.68; 128.16	
Anti-FHA (EU/mL)	87	174.98	153.98; 198.86	91	184.57	162.43; 209.72	

Abbreviations: CI, confidence interval; D, diphtheria; FHA, filamentous haemagglutinin; GMC, geometric mean concentration; GMT, geometric mean titre; HBs, hepatitis B; IPV, inactivated poliovirus; LLOQ, lower limit of quantitation; MenACWY, meningococcal serogroups A, C, W and Y; PRP, *Haemophilus influenzae* type b capsular polyribosyl-ribitol-phosphate; PPS, per-protocol set; PT, pertussis toxin; T, tetanus.

^{*} M: number of subjects with available data.

[†] Pertussis vaccine response was defined as:

- if pre-vaccination (pre-dose 1) antibody concentration < 4 × LLOQ, then post-booster antibody concentration ≥ 4 × LLOQ
- if pre-vaccination (pre-dose 1) antibody concentration ≥ 4 × LLOQ, then post-booster antibody concentration > pre-vaccination antibody concentration.

[‡] Increase from pre-vaccination (pre-dose 1) to post-booster.

[§] GMCs for anti-D, anti-T, anti-HBs, anti-PRP, anti-PT, and anti-FHA; GMTs for anti-IPV1, anti-IPV2 and anti-IPV3.

Table 4

Summary of post-vaccination antibody levels (A) and geometric means of antibody titres (B) for MenACWY-TT vaccine antigens (PPS).

		Group A Hexavalent co-administered with MenACWY (N = 87)		Group C MenACWY alone (N = 94)			
A. Post-vaccination antibody levels							
Component	Endpoint (1/dil)	M*	n (%)	95% CI	M*	n (%)	95% CI
Anti-MenA	≥8	87	87 (100.0)	95.8; 100.0	94	94 (100.0)	96.2; 100.0
Anti-MenC	≥8	All subjects		93.8; 100.0	94	90 (95.7)	89.5; 98.8
		Subjects who received the MenC vaccine in primary series part [†]		91.8; 100.0	47	46 (97.9)	88.7; 99.9
		Subjects who did not receive any MenC vaccine in primary series part [‡]		88.0; 99.9	47	44 (93.6)	82.5; 98.7
		All subjects		91.9; 99.7	94	85 (90.4)	82.6; 95.5
	≥128	Subjects who received the MenC vaccine in primary series part [†]		91.8; 100.0	47	46 (97.9)	88.7; 99.9
		Subjects who did not receive any MenC vaccine in primary series part [‡]		84.5; 99.4	47	39 (83.0)	69.2; 92.4
		All subjects		87	85 (97.7)	91.9; 99.7	94
Anti-MenW	≥8	87	87 (100.0)	95.8; 100.0	94	93 (98.9)	94.2; 100.0
Anti-MenY	≥8	87	87 (100.0)	95.8; 100.0	94	94 (100.0)	96.2; 100.0
B. Post-booster GMTs							
Component		M	Geometric mean (GMT)	95% CI	M	Geometric mean (GMT)	95% CI
Anti-MenA		87	4096.00	3335.98; 5029.17	94	5302.07	4249.49; 6615.38
Anti-MenC	All subjects	87	693.03	524.15; 916.33	94	620.20	425.53; 903.94
	Subjects who received the MenC vaccine in primary series part [†]	43	1262.73	901.11; 1769.46	47	1617.53	1083.22; 2415.39
	Subjects who did not receive any MenC vaccine in primary series part [‡]	44	385.59	264.11; 562.93	47	237.80	141.85; 398.66
Anti-MenW		87	2148.28	1650.66; 2795.91	94	2555.07	1930.58; 3381.58
Anti-MenY		87	1952.40	1538.58; 2477.53	94	2003.19	1592.49; 2519.81

Abbreviations: CI, confidence interval; GMT, geometric mean titre; MenACWY, meningococcal serogroups A, C, W and Y; PPS, per-protocol set; TT, tetanus toxoid.

* M: number of subjects with available data.

[†] Subjects from Group 1 in primary series: hexavalent vaccine co-administered with MenC vaccine.[‡] Subjects from Group 2 in primary series: hexavalent vaccine without MenC vaccine.

conjugate vaccine, either co-administered at 12 months of age, or when administration is staggered at different time points, are high for any vaccine antigen.

Overall, concomitant administration of the DTaP-IPV-HB-PRP-T and MenACWY-TT vaccines did not affect the immune response to either vaccine: the similar response rates and antibody GMCs/GMTs between the groups are supportive of concomitant administration of the two vaccines when given at 12 months of age in healthy toddlers. The seroprotection rates/response rates and the antibody GMCs/GMTs reported for the different antigens contained in the DTaP-IPV-HB-PRP-T vaccine in the present study were consistent with those previously reported and/or summarised for the vaccine used in booster vaccination, irrespective of the primary immunisation schedule for DTaP-IPV-HB-PRP-T (including a two-, three-, four-month schedule) [7,8,14–17]. Similarly, the seroprotection rates/response rates and the antibody GMTs reported for the meningococcal serogroup A, C, W and Y conjugate vaccine antigens were consistent with those previously reported with the MenACWY-TT vaccine for the toddler population [9], and when co-administered with the DTaP-IPV-HB-PRP-T vaccine Infanrix[®]-hexa [18].

The immunogenicity assessment used for the MenACWY-TT vaccine (rabbit SBA) was consistent with that generally used for this type of vaccine (including Nimenrix) [9,18–20]. Furthermore, the use of MenC vaccine in the primary series schedule did not pre-

clude the use of MenACWY-TT for co-administration with a DTaP-IPV-HB-Hib booster dose post-booster, and response rates/antibody GMTs were high for all MenACWY antigens whether MenC-TT vaccine was used in the primary series schedule or not. Prior receipt of MenC-TT vaccine in the current study led to a higher GMT for MenC antigen, as previously documented [21].

Antibody persistence at 12 months of age against the DTaP-IPV-HB-PRP-T vaccine antigens was similar between primary series groups except for higher anti-T antibody level in subjects who had received both TT-containing vaccines (DTaP-IPV-HB-PRP-T and MenC). At 12 months of age, a high proportion of subjects retained antibody levels associated with short-term protection that are consistent with those previously observed after a 2, 3 and 4 months priming [17] and equal to or higher than those observed in a similar population receiving two-dose priming at 3 and 5 months of age [22]. This finding supports the administration of a booster dose, as confirmed by the subsequent robust post-booster response in all booster groups.

The co-administration of the hexavalent DTaP-IPV-HB-PRP-T vaccine and of the MenACWY-TT conjugate vaccine resulted in higher reactogenicity for many systemic signs. The frequency of injection site adverse reactions reported in this present study for the MenACWY-TT vaccine was consistent with clinical trials data reported in the Nimenrix summary of product characteristics [9].

Table 5
Safety overview from approximately 12 to 13 months of age (safety analysis set).

Period/participants with at least one of the following:	Group A DTaP-IPV-HB-PRP-T co-administered with MenACWY (N = 103)		Group B DTaP-IPV-HB-PRP-T alone (N = 105)		Group C MenACWY-TT alone (N = 103)	
	n (%)	95% CI (participants) [†]	n (%)	95% CI (participants) [†]	n (%)	95% CI (participants) [†]
AE within 30 days after any injection at approximately 12 months of age	97 (94.2)	87.8; 97.8	97 (92.4)	85.5; 96.7	90 (87.4)	79.4; 93.1
Immediate unsolicited AE	1 (1.0)	<0.1; 5.3	1 (1.0)	<0.1; 5.2	0	–
Solicited reactions within 7 days after booster vaccination	96 (93.2)	86.5; 97.2	96 (91.4)	84.4; 96.0	80 (77.7)	68.4; 85.3
Grade 3 solicited reaction	14 (13.6)	7.6; 21.8	11 (10.5)	5.3; 18.0	5 (4.9)	1.6; 11.0
Solicited injection site reaction	71 (68.9)	59.1; 77.7	63 (60.0)	50.0; 69.4	33 (32.0)	23.2; 42.0
Grade 3 ISR	11 (10.7)	5.5; 18.3	5 (4.8)	1.6; 10.8	1 (1.0)	<0.1; 5.3
After Hexavalent vaccine	68 (66.0)	56.0; 75.1	63 (60.0)	50.0; 69.4	NA	–
Grade 3 ISR	10 (9.7)	4.8; 17.1	5 (4.8)	1.6; 10.8	NA	–
After MenACWY vaccine	49 (47.6)	37.6; 57.6	NA	–	33 (32.0)	23.2; 42.0
Grade 3 ISR	1 (1.0)	<0.1; 5.3	NA	–	1 (1.0)	<0.1; 5.3
Solicited systemic reaction	91 (88.3)	80.5; 93.8	90 (85.7)	77.5; 91.8	75 (72.8)	63.2; 81.1
Grade 3 solicited systemic reaction	5 (4.9)	1.6; 11.0	6 (5.7)	2.1; 12.0	4 (3.9)	1.1; 9.6
Unsolicited non-serious systemic AE	53 (51.5)	41.4; 61.4	50 (47.6)	37.8; 57.6	60 (58.3)	48.1; 67.9
Unsolicited non-serious systemic AR	5 (4.9)	1.6; 11.0	4 (3.8)	1.0; 9.5	1 (1.0)	<0.1; 5.3
AE leading to study discontinuation	0	–	0	–	0	–
SAE	1 (1.0)	<0.1; 5.3	0	–	1 (1.0)	<0.1; 5.3
SAR	0	–	0	–	0	–
Death	0	–	0	–	0	–
AESI/SAE from approximately 12–13 months of age	97 (94.2)	87.8; 97.8	97 (92.4)	85.5; 96.7	90 (87.4)	79.4; 93.1
AESI	0	–	0	–	1 (1.0)	<0.1; 5.3
SAEs	1 (1.0)	<0.1; 5.3	1 (1.0) [‡]	<0.1; 5.2	1 (1.0)	<0.1; 5.3
Related to Hexyon	0	–	0	–	0	–
Death	0	–	0	–	0	–

Abbreviations: AE, adverse event; AESI, adverse event of special interest; aP, acellular pertussis; AR, adverse reaction; CI, confidence interval; D, diphtheria; HB, hepatitis B; IPV, inactivated poliovirus; ISR, injection site reactions; MenACWY, meningococcal serogroups A, C, W and Y; NA, not applicable; PRP, *Haemophilus influenzae* type b capsular polyribosyl-ribitol-phosphate; SAE, serious adverse event; SAR, serious adverse reaction; T, tetanus; TT, tetanus toxoid.

[†] Two-sided 95% CIs of the percentage of participants presenting the specified event at least once were calculated using the exact binomial method.

[‡] This event occurred 64 days after vaccination at approximately 12 months of age (visit 5); consequently, the visit at 13 months of age was delayed and performed 85 days after visit 5.

5. Conclusions

Co-administration of DTaP-IPV-HB-PRP-T vaccine with MenACWY-TT vaccine did not affect the immune response to either vaccine. Prior receipt of MenC-TT conjugate vaccine during infancy did not preclude the use of a MenACWY-TT vaccine for booster vaccination and resulted in higher responses to MenC after booster.

The immunogenicity and safety findings of this study support the concomitant administration of the DTaP-IPV-HB-PRP-T vaccine with a MenACWY-TT conjugate vaccine when given from 12 months of age, but a higher systemic reaction rate after concomitant vaccination should be noted.

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Contributions

TV contributed to the protocol review, participants' enrolment, participants' data collection/acquisition, and data interpretation. RB and XDC contributed to the laboratory analysis and data interpretation. FB, ST and SL contributed to the study design and development, and data analysis and interpretation. CE contributed to the writing of the manuscript drafts. All authors critically reviewed and revised the manuscript drafts, and approved the final version of the manuscript. All authors take responsibility for the integrity of the data and accuracy of the data analysis. All authors were involved in the decision to submit the manuscript to *Vaccine* for publication.

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Appendix A. Supplementary material

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