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Reduced schedules of 4CMenB vaccine in infants and catch-up series in children: Immunogenicity and safety results from a randomised open-label phase 3b trial

Federico Martinón-Torres [a,*], Marco Aurelio P. Safadi [b], Alfonso Carmona Martinez [c], Pilar Infante Marquez [d], Juan Carlos Tejedor Torres [e], Lily Yin Weckx [f], Edson Duarte Moreira Junior [g], Ilhem Mensi [h], Marco Calabresi [i,1], Daniela Toneatto [i]

[a] Translational Pediatrics and Infectious Diseases, Department of Pediatrics, Hospital Clinico Universitario de Santiago de Compostela, A Choupana, s/n, 15706 Santiago de Compostela, Spain
[b] Santa Casa de São Paulo School of Medical Sciences, Rua Doutor Cesário Motta Júnior, 61 - Vila Buarque, 01221-020 São Paulo, Brazil
[c] Instituto Hispalense de Pediatria de Sevilla, Av. Manuel Siurot, 45, 41013 Sevilla, Spain
[d] Hospital Virgen del Mar, Carretera del Mami a Viator, Almeria, Spain
[e] Hospital Universitario de Mostoles, Río Júcar, s/n, 28935 Móstoles, Madrid, Spain
[f] CRIE UNIFESP, Universidade Federal de Sao Paulo, R. Sena Madureira, 1500 - Vila Clementino, 04021-001São Paulo, Brazil
[g] CPEC-Associação Obras Sociais Irma Dulce and Oswaldo Cruz Foundation, Brazilian Ministry of Health, Salvador, Brazil
[h] GSK, Huis Ter Heideweg 62, 3705 LZ Zeist, Amsterdam, The Netherlands
[i] GSK, Via Fiorentina, 1, 53100 Siena, Italy

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ABSTRACT

Background: This study evaluated the immunogenicity and safety of a licensed meningococcal serogroup B vaccine (4CMenB) administered alone according to reduced schedules in infants or catch-up series in children.
Methods: In this open-label, multicentre, phase 3b study (NCT01339923), infants randomised 1:1:1 received 4CMenB: 2 + 1 doses at 3½–5–11 months or 6–8–11 months of age, 3 + 1 doses at ages 2½–3½–5–11 months. Children aged 2–10 years received 2 catch-up doses administered 2 months apart. Immune responses were measured by hSBA assays against 4 strains specific for vaccine components fHbp, NadA, PorA and NHBA. Sufficiency of immune responses was defined in groups with 2 + 1 doses schedules as a lower limit ≥70% for the 97.5% confidence interval of the percentage of infants with hSBA titres ≥4, 1 month post-dose 2 for fHbp, NadA, PorA. Adverse events were collected for 7 days post-vaccination; serious adverse events (SAEs) throughout the study.
Results: 754 infants and 404 children were enrolled. Post-primary vaccination, 98–100% of infants across all groups developed hSBA titres ≥4 for fHbp, NadA, PorA, and 48–77% for NHBA. Sufficiency of immune responses in infants receiving 2 + 1 schedules was demonstrated for fHbp, NadA, PorA after 2 doses of 4CMenB, as pre-specified criteria were met. Following receipt of 2 catch-up doses, 95–99% of children developed hSBA titres ≥4 for 4CMenB components. Similar safety profiles were observed across groups. A total of 45 SAEs were reported, 3 of which were related to vaccination.
Conclusion: Reduced infant schedules and catch-up series in children were immunogenic and safe, having the potential to widen 4CMenB vaccine coverage.
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Abbreviations: AE, adverse event; CI, confidence interval; 4CMenB, multi-component vaccine against MenB; fHbp, factor H binding protein; GMT, geometric mean titers; hSBA, serum bactericidal assay with human serum; IMD, invasive meningococcal disease; LL, lower limit; MAS, meningococcal antigen typing system; Men, meningococcal serotype; NadA, Neisserial adhesin A; NHBA, *Neisseria* heparin binding antigen; PorA, porin A protein; SAE, serious adverse event.

* Corresponding author.
E-mail addresses: federico.martinon.torres@sergas.es (F. Martinón-Torres), masafadi@uol.com.br (M.A.P. Safadi), alfonsocarmona@ihppediatria.com (A.C. Martinez), InfanteP@vithas.es (P.I. Marquez), JCTEJEDOR@infonegocio.com (J.C.T. Torres), lily.crie@epm.br (L.Y. Weckx), edson@bahia.fiocruz.br (E.D. Moreira Junior), ilhem.z.mensi@gsk.com (I. Mensi), marco.calabresi@gmail.com (M. Calabresi), daniela.x.toneatto@gsk.com (D. Toneatto).
[1] Current affiliation: Covance Inc., Laboratory Corporation of America Holdings, Rome, Italy.

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1. Introduction

Worldwide, invasive meningococcal disease (IMD) represents a significant burden, with a global case fatality rate of 5%–10%, even with antibiotic treatment [1,2]. Six of the 12 serogroups of *Neisseria meningitidis* (MenA, MenB, MenC, MenW, MenX, and MenY) are responsible for virtually all cases of IMD, with MenB, MenC, and MenY being prominent in the Americas and Europe, MenA and MenC in Asia, and MenA, MenC, MenX, and MenW in Africa [3].

Although IMD affects individuals of all age groups, the highest rates of disease are usually found in infants, with secondary peaks seen in adolescents and in adults >65 years of age in some countries [2]. Case fatality ratios of IMD were estimated to 2% during the first year of life, 5–7% in children aged 1–5 years, 4% in children and adolescents aged 5–19 years, 8% in adults aged 20–65 years and 39% in adults over 65 years of age [2,4]. The introduction of meningococcal conjugate vaccines against MenC and MenA in routine paediatric immunisation programmes, with large catch-up campaigns including children, adolescents and young adults, has resulted in a substantial decrease of IMD incidence rates in several countries [5,6].

The average incidence of MenB disease worldwide is estimated at 0.01–4.26 per 100,000 population, depending on the country [7]; therefore the introduction of a vaccine against MenB was an unmet medical need to reduce the burden of IMD globally. A multicomponent vaccine (4CMenB; *Bexsero*, GSK) is now licensed in 37 countries worldwide, and approved for use in a 3 + 1 dose schedule in young infants, a schedule shown to be immunogenic and to display a clinically acceptable safety profile in clinical trials [8–12]. Combined infant and adolescent vaccination strategies are estimated to have the greatest impact and can be cost-effective [13]. In the United Kingdom, 4CMenB has recently been introduced into the infant vaccination programme as a 2 + 1 dose schedule administered at 2, 4, and 12 months of age [14]. The campaign, monitored by the Public Health England, has already provided important data on both effectiveness and safety of this reduced vaccination schedule [15,16] and will continue to do so.

The current study was designed to investigate different immunisation schedules in infants in whom the 4CMenB vaccine could be administered alone either between or after routine vaccinations. Preliminary study results were already reviewed by the Joint Committee on Vaccination and Immunisation, and supported the recommendation to introduce a routine infant MenB immunisation programme according to a 2 + 1 dose schedule with concomitant routine vaccines [17,18]. The immunogenicity and safety of a 2-dose catch-up series of 4CMenB in healthy 2- to 10-year-old children were also evaluated.

2. Methods

2.1. Study design and participants

This randomised phase 3b, open-label study was conducted in 26 centres (4 in Brazil, 3 in Peru, 10 in Hungary, and 9 in Spain) between April 2011 and December 2014, in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The protocol and its amendments were approved by the institutional review boards and ethics committees for each site, and parents or legal guardians of all study participants provided written informed consent prior to enrolment. The study is registered at clinicaltrials.gov (NCT01339923).

Healthy infants and children were enrolled in 4 study groups, by age at enrolment, without randomisation: approximately 2½ (Group 1), 3½ (Group 2) or 6 months of age (Group 3), and 2–10 years (Group 4). A full list of the inclusion/exclusion criteria is presented in Text S1, Supplementary Material.

Group 1 received primary vaccinations at 2½, 3½, and 5 months of age, Group 2 at 3½ and 5 months of age, and Group 3 at 6 and 8 months of age. All infants received a booster dose at 11 months of age. Children in Group 4 received a 2-dose-catch-up series, administered 2 months apart.

Groups 1–3 were each randomised (1:1) using a web-based randomisation system into 2 sub-groups (a and b), and Group 4 was separated into 2 sub-groups based on age at enrolment (2–5 years [Group 4a] and 6–10 years [Group 4b]). Infants/children in the same group received the same vaccination schedule and results were pooled for analysis.

The study vaccine [19] was administered alone intramuscularly into the outer side of the thigh (Groups 1–3) or deltoid area of the non-dominant arm (Group 4).

2.2. Study outcomes

Immune responses to each of the 4 vaccine components were assessed as the percentage of infants/children with serum bactericidal activity using human complement (hSBA) titres ≥4 (considered as protective [20]) against 4 MenB reference strains. Immune response in infants was defined as sufficient if, in terms of percentages of participants with hSBA titres ≥4 for fHbp, NadA and PorA, the lower limit (LL) of the 97.5% confidence interval [CI] was ≥70% at 1 month post-primary vaccination and the LL of the 95%CI was ≥75% at 1 month following booster vaccination in Groups 1, 2 and 3. Sufficient immune response in children was defined as a LL ≥70% for the 95%CI for the percentage of children achieving hSBA titres ≥4 for the 3 vaccine antigens, at 1 month after administration of the 2-dose catch-up series.

The primary objective of the study was to demonstrate a sufficient immune response to the 3 reference strains specific for fHbp, NadA and PorA at 1 month after the 2-dose primary vaccination series in healthy infants from Groups 2 and 3. Secondary objectives assessed the sufficiency of the immune responses induced by the 3-dose 4CMenB primary vaccination schedule in Group 1, the immune response elicited by a booster dose of 4CMenB in infants, the immunogenicity of the 2-dose catch-up series in children aged 2–10 years, sufficiency of the immune response induced by the fHbp, NadA, PorA vaccine components across all groups and timepoints, and the safety and tolerability of the vaccine.

2.3. Immunogenicity assessments

Blood samples were collected from infants prior to first (Groups 1a to 3a) or second vaccination (Groups 1b to 3b), at 1 month post-primary vaccination, pre-booster vaccination, and 1 month post-booster vaccination. Serum samples from children were taken prior to first dose and 1 month post-second dose. Sera were stored at −20 °C until sent for analysis at GSK Clinical Sciences Laboratory, Marburg, Germany (NHBA) or Public Health England Laboratory, Manchester, United Kingdom (fHbp, NadA, PorA). Antibody responses to vaccine components were measured by hSBA against MenB reference strains: H44/76 for fHbp, 5/99 for NadA, M10713 for NHBA and NZ98/254 for PorA [21]. Geometric mean titres (GMTs) and 95%CIs, estimated using the Clopper-Pearson method, were calculated for each group at each timepoint.

2.4. Safety and reactogenicity assessments

Infants and children were observed for 30 min after each vaccination. Solicited local and systemic adverse reactions were recorded for 7 days (Days 0–7) following each vaccination, by diary cards. Unsolicited adverse events (AEs) were also recorded for

7 days post-vaccination. Any reactions continuing after this time period, AEs leading to study withdrawal, medically attended AEs, or serious AEs (SAEs) were monitored throughout the study. Relatedness to the study vaccine and severity of AEs was determined by the investigator.

2.5. Statistical analysis

No formal statistical hypotheses were tested.

For the primary objective, the following assumptions were made based on results from previous clinical trials: the percentage of infants achieving titres ≥4 was considered to be ≥90% against strains for fHbp and NadA in Group 2 and against strains for fHbp, NadA and PorA in Group 3 [9,22]. Due to lack of prior data for responders in Group 2 for the strain specific to PorA, required responder rate for this strain was calculated to achieve overall power of 85%, 90% and 95% for the primary objective. For a group size of 200 participants, the study had an estimated overall power of 97% for Group 3 and 80% for Group 2 (with an assumed responder rate of at least 79% for PorA) to demonstrate the sufficiency of the immune response against each of the 3 MenB test strains, 1 month post-primary vaccination with 4CMenB (primary objective).

Safety was evaluated descriptively.

All statistical analyses were performed using SAS v9.1 or higher.

3. Results

3.1. Demographics

A total of 754 infants and 404 children were enrolled; 94%–98% of participants across all groups completed the study (Fig. 1). Demographic characteristics (ethnicity, gender) were similar across groups, while baseline characteristics such as height and weight varied across groups due to the age differences (Table S1, Supplementary Material).

3.2. Immunogenicity

hSBA titres ≥4 against the reference strains specific to fHbp and NadA antigens were measured in all infants in Groups 1–3 at one month after completion of the primary series and in 99% of children in Group 4 after the 2-dose catch-up series (Table 1). Across all groups, 98%–99% of participants had hSBA titres ≥4 against the PorA test strain. Bactericidal response to NHBA reference strain varied across the groups, with 59%, 49% and 77% of infants in Groups 1, 2, and 3, respectively, and 95% of children in Group 4 achieving hSBA titres ≥4. Of note, early responses were observed after the first vaccination in infants from subgroups 1b to 3b, when percentages of infants achieving hSBA titres ≥4 against reference strains were 62%–82% for fHbp, 91%–95% for NadA, 39%–43% for PorA, and 21%–36% for NHBA. hSBA GMTs against the 4 test strains seemed similar across all groups at each time point, except for NHBA GMTs in Group 4, which were higher at baseline and after completion of the catch-up series (Fig. 2).

Antibody GMTs against all strains declined between the primary series and the booster vaccination (Fig. 2). One month post-booster booster vaccination, all infants (95%CI: 98%–100%) in Groups 1 to 3 had hSBA titres ≥4 against fHbp and NadA reference strains. All infants (95%CI: 98%–100%) in Groups 1 and 3, and 99% (95%CI: 96%–100%) of infants in Group 2 had hSBA titres ≥4 against PorA reference strain, while 83%–87% of infants in Groups 1–3 had hSBA titres ≥4 against NHBA reference strain.

The criteria for sufficient immune response against the 3 reference strains for fHbp, NadA, and PorA were met in Groups 1–3 after receipt of both the primary series and the booster dose, and in Group 4 after receipt of the catch-up series (Tables S2 and 1).

3.3. Safety

At least 1 solicited reaction was reported by 84%–97% of infants and children after any of the study vaccinations. In Groups 1–3, the most commonly reported local reactions following vaccinations were tenderness (41%–53% of infants) and erythema (33%–42% of infants) (Fig. 3). Rates of systemic adverse reactions in infants were similar across the 3 groups and highest after the first vaccination. The most commonly reported local reaction in Group 4 was pain (85%–93% of children) (Fig. 4). Across all groups, no increased reactogenicity was observed following subsequent vaccinations.

The most frequent systemic reactions in infants were fever (rectal temperature ≥38 °C) reported in 36%–55% of infants across all groups, unusual crying (34%–60%), sleepiness (25%–58%), and irritability (31%–52%) (Fig. 5). Fever ≥40 °C was reported by less than 1% of infants and lasted for a maximum of 1 day, except for 1 infant in Group 1 who reported fever ≥40 °C on Day 6 after the second vaccination that resolved after 2 days. One infant in Group 3 with fever ≥40 °C was diagnosed with influenza 2 days post- booster vaccination.

Irritability (in 31%–37% of children following both doses), sleepiness (20%–28%), and arthralgia (19%–27%) were the most common systemic reactions in children aged 2–5 years, and myalgia (27%–29%) and malaise (23%–28%) in children aged 6–10 years (Fig. 4). Most cases of fever were considered mild or moderate in severity. One child in the 6–10 years subgroup reported fever ≥40 °C on Day 7 following vaccination and was diagnosed with influenza, which resolved after 3 days.

Unsolicited AEs were reported in 75%–79% of infants across the Groups 1–3, and 16%–25% were considered at least possibly related to vaccination (Table S2). For infants, the most commonly reported unsolicited AEs were induration lasting more than 7 days, reported in 23% of infants in Group 1, and upper respiratory tract infection, reported in 22% of infants in Groups 2 and 3.

In Group 4, fewer AEs were reported in children aged 6–10 years (34%) than in children aged 2–5 years (56%). Induration (7% of children aged 2–5 years) and pyrexia (4% of children aged 6–10 years) were the most commonly reported unsolicited AEs.

Most unsolicited AEs were reported in less than 2% of participants, were mild to moderate, and resolved by the time of study termination. Two infants withdrew from the study following AEs: a congenital central nervous anomaly and muscle spasms were reported for 1 infant in Group 1, and 1 infant in Group 2 was withdrawn due to allergic colitis. Neither AE was considered related to vaccination.

Three out of the 45 recorded SAEs were considered at least possibly related to vaccination (Table S2). Pyrexia, which resolved within 3 days of onset, was reported in 2 infants from Groups 1 and 2. One infant in Group 3 developed juvenile idiopathic arthritis, which was reported after the study (110 days after the third vaccination) and was unresolved by study end. There were no deaths in the study.

4. Discussion

This is the first study assessing the immunogenicity and safety of the 4CMenB vaccine administered alone according to a reduced 2 + 1 dose schedule in infants, and the first trial primarily designed to investigate administration of 4CMenB to children aged 2–10 years. The immune responses and safety profile of 4CMenB administered to infants in our study were similar to those previously reported following a 3 + 1 dose schedule in young infants

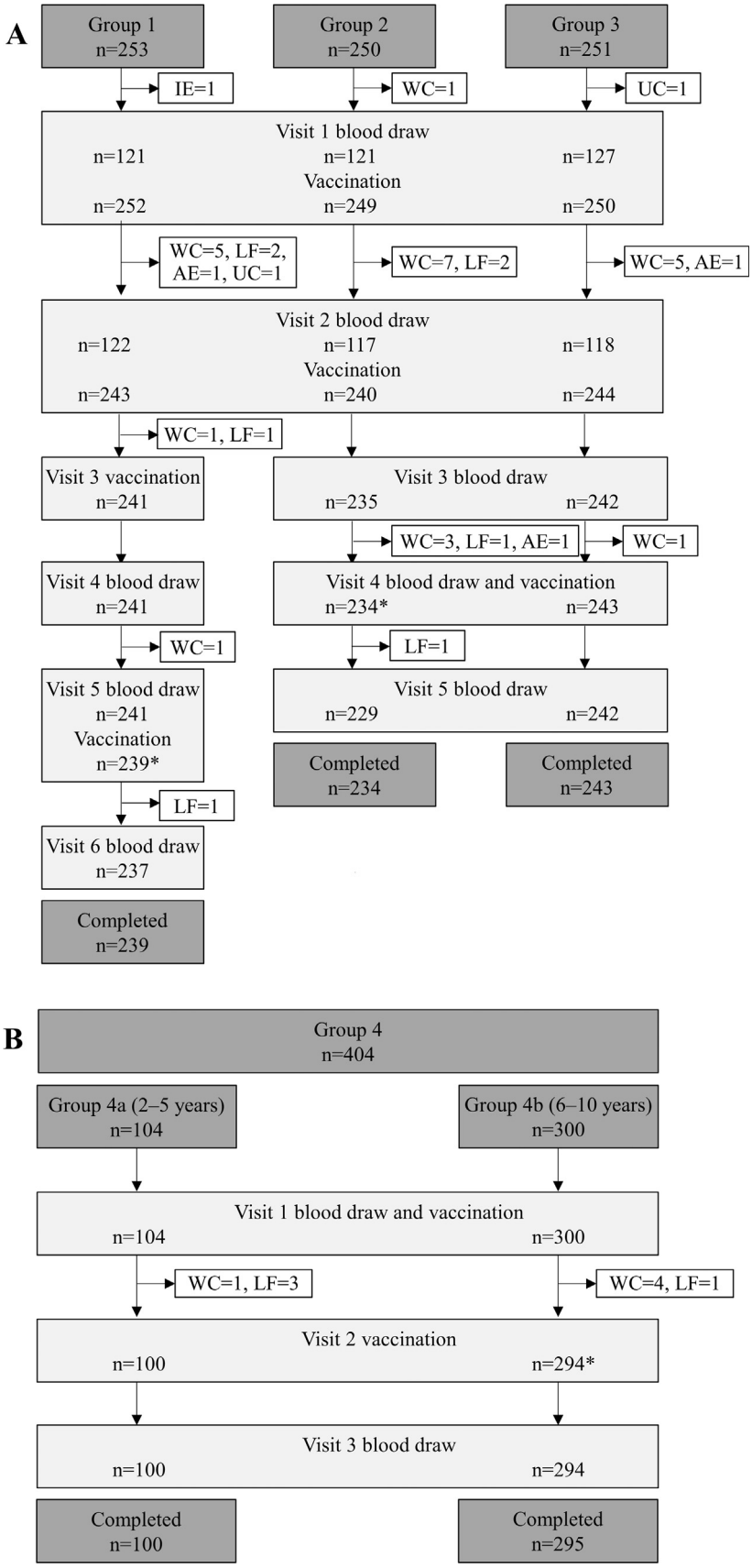

Fig. 1. Study design and subject disposition flowchart for (A) infants and (B) children. Footnote: Group 1, infants receiving 4CMenB vaccine at 2½–3½–5–11 months; Group 2, infants receiving 4CMenB vaccine at 3½–5–11 months of age; Group 3, infants receiving 4CMenB vaccine at 6–8–11 months of age; Group 4, children receiving 2 catch-up doses of 4CMenB vaccine at least 2 months apart; n, number of infants/children; IE, inappropriate enrolment; WC, withdrew consent; UC, unable to classify; LF, lost to follow-up; AE, adverse event; *One participant did not receive the study vaccine at this visit, but complied with all other procedures up to study end.

Table 1
Percentage of infants/children with hSBA titres ≥4 against strains specific for vaccine components, by timepoint.

	Group 1		Group 2		Group 3		Group 4	
	N	*% (95% CI)*	*N*	*% (95% CI)*	*N*	*% (95% CI)*	*N*	*% (95% CI)*
fHbp (strain H44/76)								
Pre-vaccination	112	13% (8%–21%)	114	15% (8%–22%)	120	19% (13%–27%)	385	18% (14%–22%)
1 month after primary/catch-up series	237	100% (98%–100%)	228	100% (98%–100%)	234	100% (98%–100%)	386	99% (97%–100%)
1 month post-booster dose	233	100% (98%–100%)	227	100% (98%–100%)	238	100% (98%–100%)		–
NadA (strain 5/99)								
Pre-vaccination	114	4% (1%–10%)	115	6% (2%–12%)	123	1% (0.02%–4%)	388	6% (4%–9%)
1 month after primary/catch-up series	238	100% (98%–100%)	230	100% (98%–100%)	238	100% (98%–100%)	390	99% (98%–100%)
1 month post-booster dose	233	100% (98%–100%)	228	100% (98%–100%)	239	100% (98%–100%)		–
PorA (strain NZ98/254)								
Pre-vaccination	115	2% (0%–6%)	114	3% (1%–7%)	119	0% (0%–3%)	387	6% (4%–8%)
1 month after primary/catch-up series	238	99% (96%–100%)	230	98% (95%–99%)	233	99% (97%–100%)	389	99% (97%–100%)
1 month post-booster dose	231	100% (98%–100%)	226	99% (96%–100%)	236	100% (98%–100%)		–
NHBA (strain M10713)								
Pre-vaccination	72	35% (24%–47%)	66	26% (16%–38%)	69	17% (9%–28%)	352	62% (57%–67%)
1 month after primary/catch-up series	171	59% (52%–66%)	166	49% (41%–65%)	148	77% (70%–83%)	370	95% (92%–97%)
1 month post-booster dose	203	84% (78%–89%)	181	88% (83%–93%)	193	87% (81%–91%)		–

Group 1, infants receiving 4CMenB vaccine at 2½–3½–5–11 months; Group 2, infants receiving 4CMenB vaccine at 3½–5–11 months of age; Group 3, infants receiving 4CMenB vaccine at 6–8–11 months of age; Group 4, children receiving 2 catch-up doses of 4CMenB vaccine at least 2 months apart; hSBA, human complement serum bactericidal activity; N, number of infants/children in each group for which analyses were carried out; CI, confidence interval; fHbp, factor H binding protein; NadA, Neisserial adhesin A; PorA, porin A protein; NHBA, *Neisseria* heparin binding antigen.

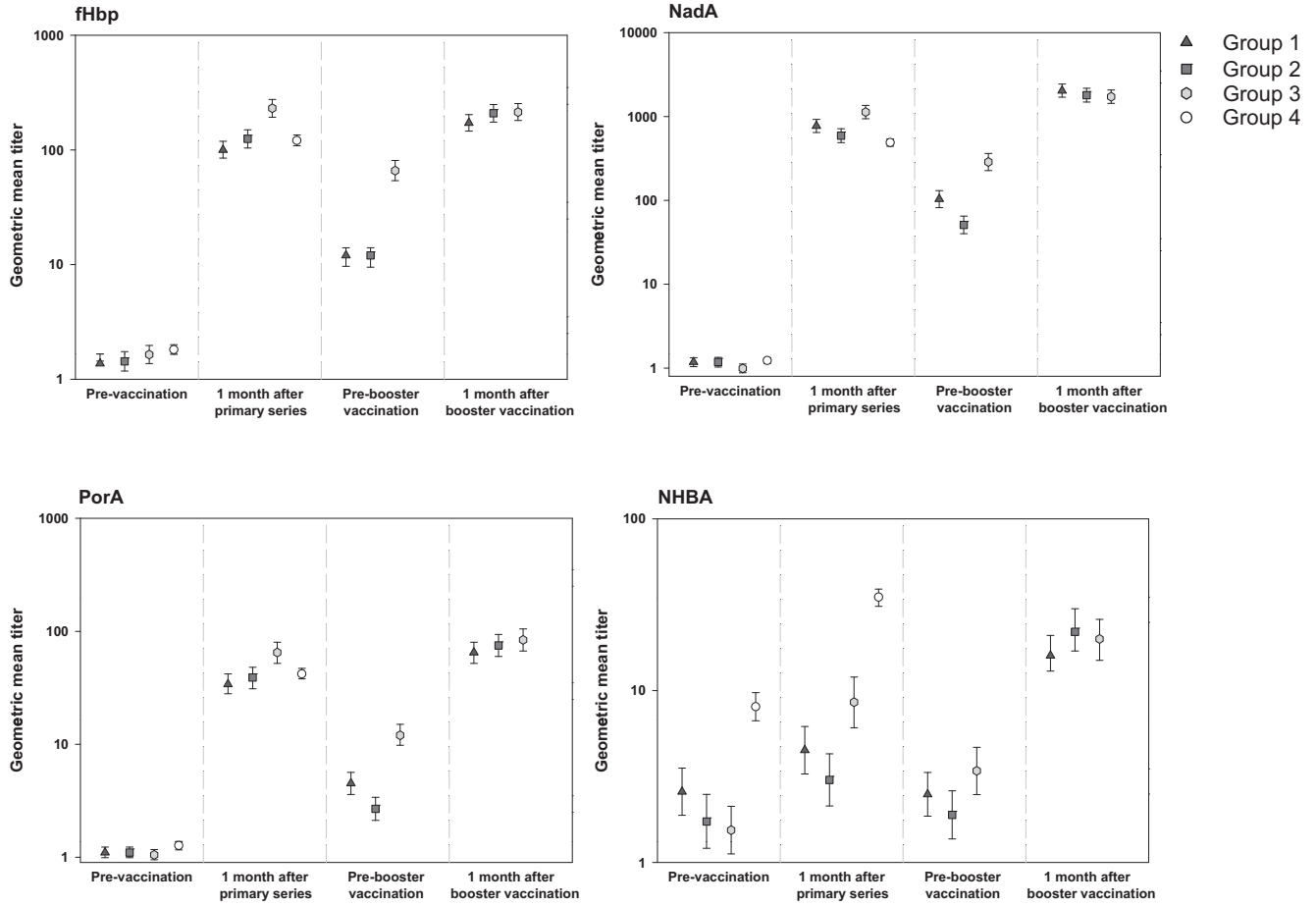

Fig. 2. Geometric mean titres (95% confidence intervals) against the four MenB test strains for each of the study groups at baseline, 1 month after completion of the primary vaccination series, pre-booster, and 1 month after the booster dose. Footnote: Group 1, infants receiving 4CMenB vaccine at 2½–3½–5–11 months; Group 2, infants receiving 4CMenB vaccine at 3½–5–11 months of age; Group 3, infants receiving 4CMenB vaccine at 6–8–11 months of age; Group 4, children receiving 2 catch-up doses of 4CMenB vaccine at least 2 months apart; fHbp, factor H binding protein; NadA, Neisserial adhesin A; PorA, porin A protein; NHBA, *Neisseria* heparin binding antigen.

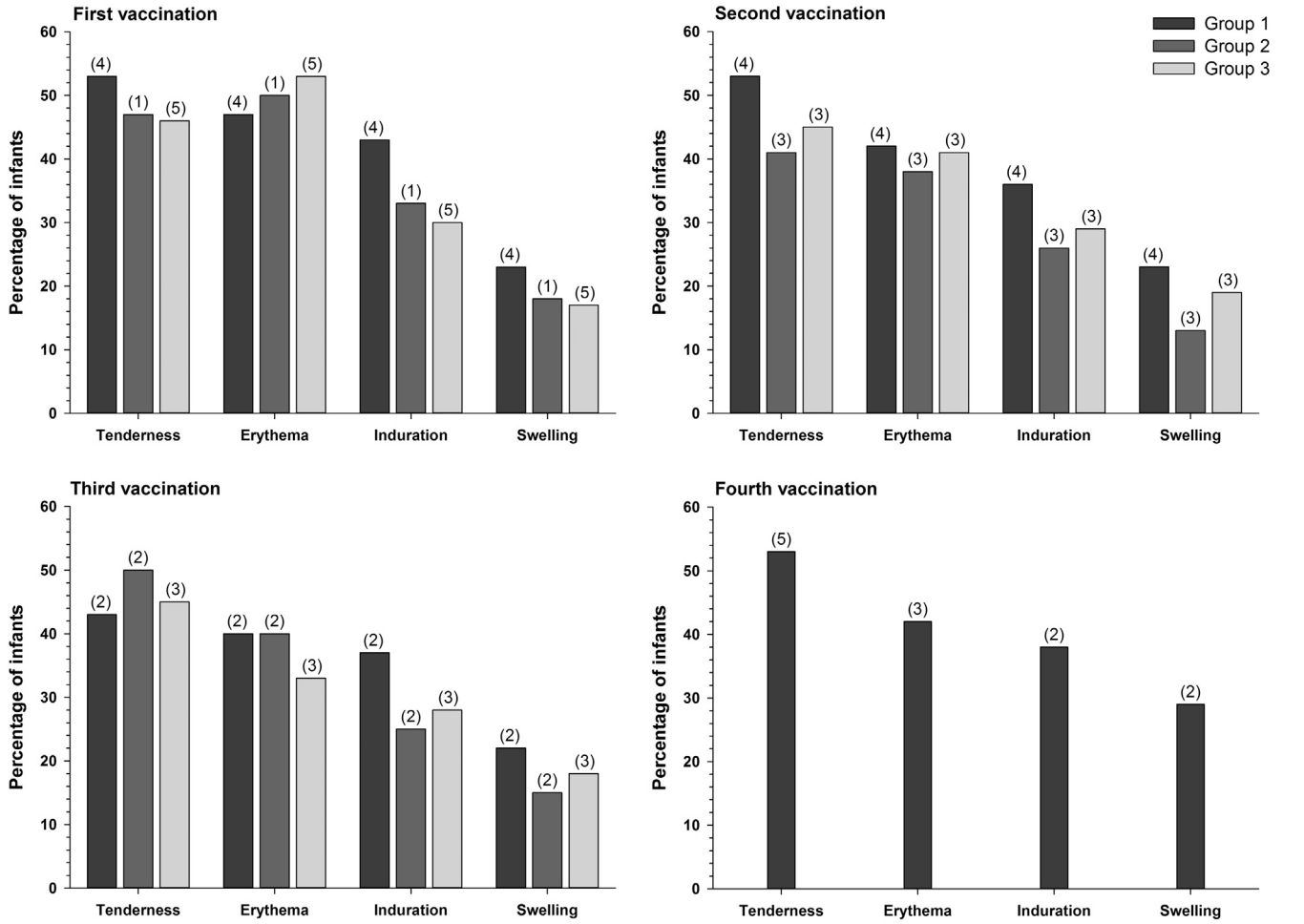

Fig. 3. Percentage of infants reporting solicited local adverse reactions after each vaccination in Groups 1–3. The percentage of reactions classified as severe is given in brackets. Footnote: Group 1, infants receiving 4CMenB vaccine at 2½–3½–5–11 months; Group 2, infants receiving 4CMenB vaccine at 3½–5–11 months of age; Group 3, infants receiving 4CMenB vaccine at 6–8–11 months of age. Severe reactions were defined as "infant cried when the limb was moved" for tenderness, and "diameter > 50 mm" for the others.

[8,10–12], or a 3-dose schedule in older infants (6–8 months of age at first vaccination) [22]. Regardless of the schedule used nearly all infants and children in our study achieved seroprotective titres (hSBA titres ≥4) [23] against 3 MenB test strains following each vaccination.

hSBA GMTs against the MenB test strains for the 4 vaccine components were similar across groups, except for NHBA GMTs that were higher in children than in infants both before and after vaccination. As NHBA is conserved in nearly all strains of pathogenic MenB the higher baseline titres in children may be due to exposure to circulating strains [24].

Studies assessing the persistence of immune responses to 4CMenB showed that immunogenicity declines by 5 years of age [25], suggesting the need for further immunisations during childhood, but a booster dose at 40 months of age, following vaccination according to a 3 + 1 doses schedule (administered at 2, 4, 6, and 12 months) induces an anamnestic response [26]. Waning of antibodies by the age of 4 years was also observed in children having received other 3 + 1 schedules, with antibody levels for each of the 4 vaccine components declining differently in time [27]. In several studies, the administration of additional doses of 4CMenB at the age of 5 years was shown to be immunogenic and well tolerated in previously vaccinated children [25,28]. Since the direct protection of infants through vaccination should remain a priority especially in Europe where the incidence of serogroup B meningococcal disease is the highest in this age category, an infant immunisation schedule followed by boosting in childhood and adolescence is needed to ensure continuous protection against the disease and may even increase the potential for herd immunity.

Safety profiles were similar in all groups, with the highest reactogenicity observed after the first dose, and no associated safety signals were detected. Of note, the open-label design of the study might have biased the reporting of AEs towards higher reported incidences, and this could potentially impact any interpretation of the safety results. A higher reactogenicity of 4CMenB than expected was linked to the inclusion of outer membrane vesicles in the vaccine formulation [8], but the vaccine is still considered well tolerated in infants [8–10], even when co-administered with routine paediatric vaccines [10,12] and reducing the content in outer membrane vesicles was found to impact negatively the immunogenicity profile [8]. As expected, the highest rates of fever were observed in infants, but most cases were mild to moderate and transient. Fever rates observed in our study were similar to those reported in previous trials [9,10,12]. Previous studies have shown that co-administration of the vaccine with paracetamol can significantly reduce the incidence of fever and other local and systemic reactions without impacting the immunogenicity of

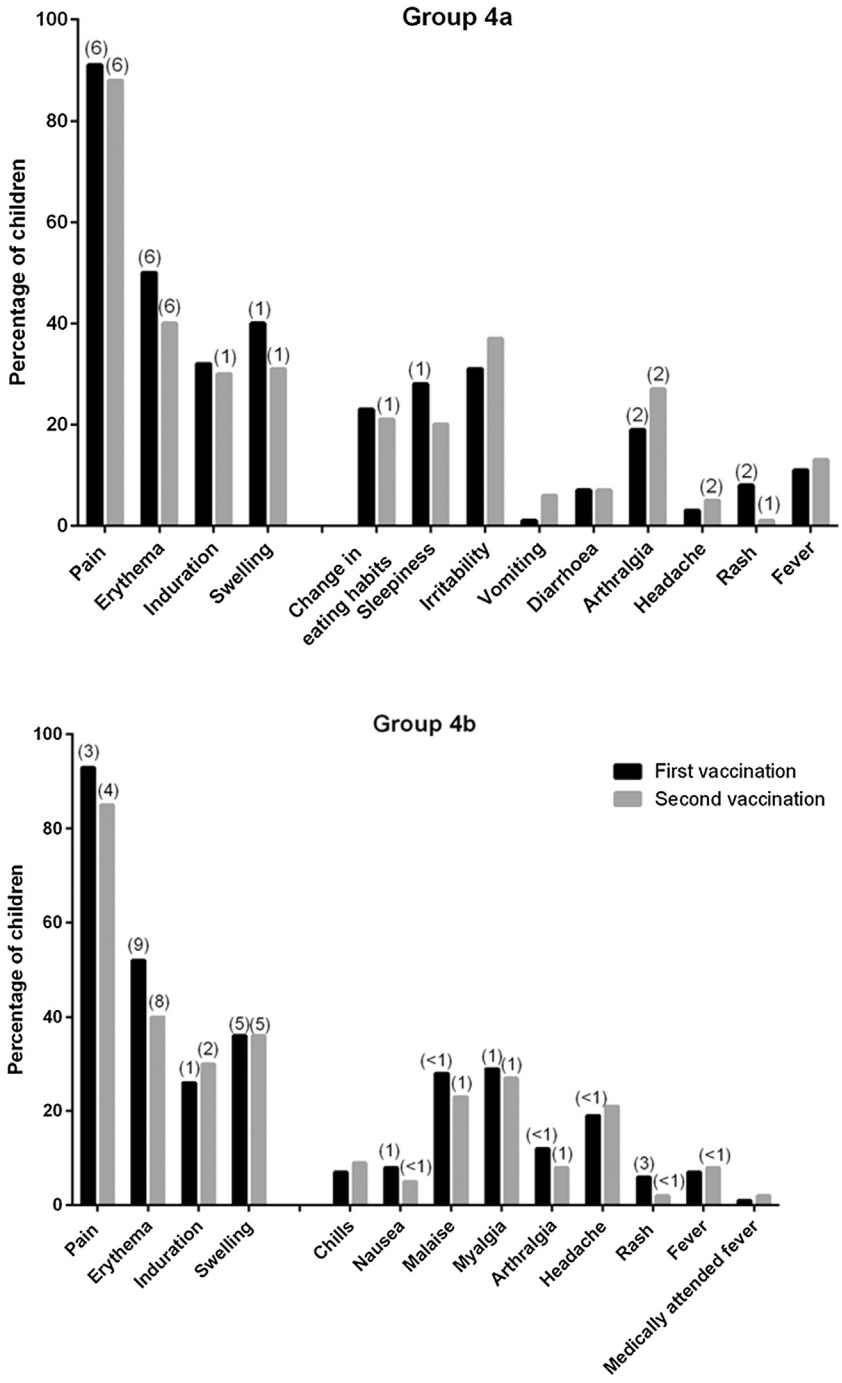

Fig. 4. Percentages of children in Groups 4a and 4b reporting solicited local or systemic reactions after each vaccination. The percentage of reactions classified as severe is given in brackets. Footnote: Group 4a, children aged 2–5 years receiving 2 catch-up doses of 4CMenB vaccine at least 2 months apart; Group 4b, children aged 6–10 years receiving 2 catch-up doses of 4CMenB vaccine at least 2 months apart. Severe reactions were defined as "no meals all day" for change in eating habits, "requiring intravenous hydration" for vomiting, "temperature $\geq$ 40 °C" for fever, "urticarial" for rash and "preventing normal daily activity" for the others.

4CMenB or co-administered routine paediatric vaccines [11]. Moreover, rates of fever in real life experience are lower than those reported in trials [29].

As the 4CMenB vaccine targets genetically diverse meningococcal antigens, its effectiveness may vary depending on the level of expression and on the sequence identity of these particular proteins by each MenB strain. The potential global coverage of MenB strains by the 4CMenB vaccine has been assessed by the meningococcal antigen typing system (MATS) assay that evaluates the potential strain killing of vaccine-induced antibodies. The mean coverage was estimated to range from 66% to 91% in 13 countries worldwide [30]. However, MATS might underestimate the true neutralising capability of the vaccine-induced immune response [31]. The 4CMenB vaccine has also the potential to offer some cross-protection against non-B meningococcal serogroups [32], including against other bacteria of the same genus [33], with shared protein antigens.

Although vaccine efficacy was not measured in this study, the high percentages of infants and children with hSBA titres $\geq$4, together with the global estimates for strain coverages, indicate

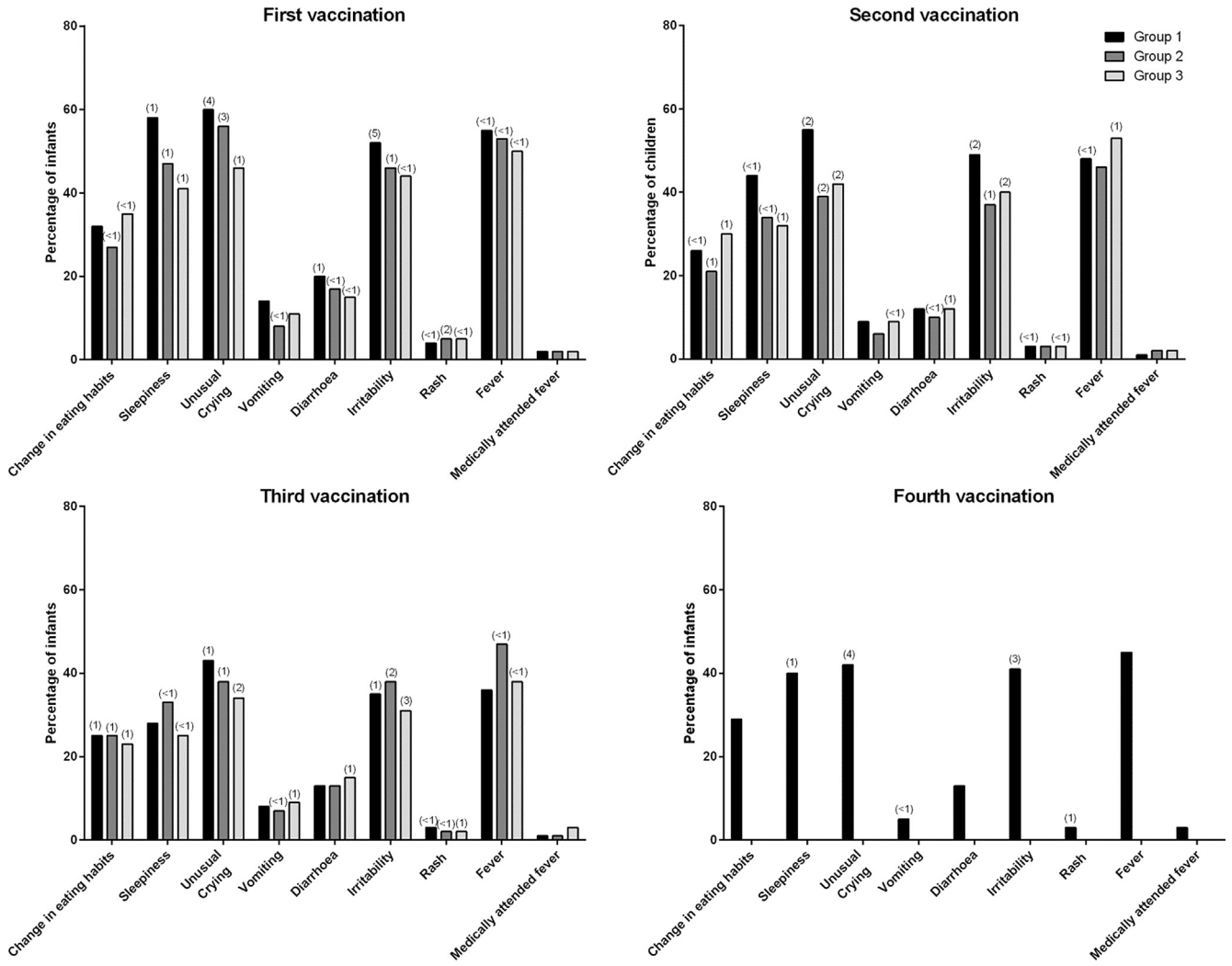

Fig. 5. Percentage of infants reporting solicited systemic adverse reactions after each vaccination in Groups 1–3. The percentage of reactions classified as severe is given in brackets. Footnote: Group 1, infants receiving 4CMenB vaccine at 2½–3½–5–11 months; Group 2, infants receiving 4CMenB vaccine at 3½–5–11 months of age; Group 3, infants receiving 4CMenB vaccine at 6–8–11 months of age. Severe reactions were defined as "no meals all day" for change in eating habits, "persisting for ≥3 h" for unusual crying, "little/no intake for more prolonged time due to vomiting" for vomiting, "≥6 liquid stools" for diarrhoea, " unable to console" for irritability, "urticarial" for rash, and "temperature ≥40 °C" for fever.

that the 4CMenB vaccine may be a powerful tool to reduce the burden of MenB IMD in these age groups. However, as there is currently no clinical efficacy correlate for MenB and the impact on carriage/herd immunity of the different schedules has not been estimated, the potential impact of the vaccine is still unknown. The reduced number of doses offers greater flexibility to fit the administration of the 4CMenB vaccine into an already crowded infant immunisation schedule.

5. Conclusions

Almost all infants and children in our study achieved seroprotective antibody levels, following any vaccine schedule, including the reduced dose schedules in young infants, and no safety signals were identified. These results support the potential protective benefit of the reduced and catch-up schedules in these age groups.

Our study may have important public health implications, as both the reduced vaccine schedule in young infants and the administration of catch-up series in children up to 10 years of age have the potential to widen the use of the 4CMenB vaccine, diminish the costs of immunisation programmes, as well as improve vaccination schedule compliance.

Trademark statement

Bexsero is a trademark of the GSK group of companies.

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Declaration of interest

MC was and, DT and IM are employees of the GSK group of companies. DT owns stock/stock options in the GSK group of companies. MAPS reported a grant from the GSK group of companies during the conduct of the study. MAPS received research grant from the GSK group of companies, Pfizer and Takeda and speaker's honoraria from the GSK group of companies, Pfizer and Sanofi-Pasteur outside the submitted work. The institution of LYW received a grant from Novartis during the conduct of this study and from the GSK group of companies outside the submitted work. LYW reported personal fees as member of advisory board for the GSK group of companies, Novartis and MSD outside the submitted

work. The institution of FMT received clinical trial fees from Novartis during the conduct of this study, and he received personal fees/non-financial support/grants/other from Pfizer, SPMSD and/or GSK, outside the submitted work. FMT's research activities have been supported by grants from Instituto Carlos III (Contrato de intensificación de la actividad investigadora) from National Plan I+D+I and FEDER funds. EDM reported a grant from Novartis during the conduct of the study. JCTT, PIM and ACM declare no conflict of interest.

Authors' contributions

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed and commented critically drafts of the manuscript for important intellectual content and gave final approval to submit for publication. DT contributed to the study conception and design. FMT, MAPS, ACM, PIM, JCTT, LYW, and EDMJ contributed to the acquisition of data. IM, MC, and DT contributed to the analysis and interpretation of data. IM provided statistical expertise.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2017.05.023.

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