

Antibody persistence 5 years after vaccination at 2 to 10 years of age with Quadrivalent MenACWY-CRM conjugate vaccine, and responses to a booster vaccination



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ABSTRACT

Background: In a multi-center extension study, children 2–10 years of age, initially vaccinated with one or two doses (2–5 year-olds) or one dose (6–10 year-olds) of quadrivalent meningococcal CRM₁₉₇-conjugate vaccine (MenACWY-CRM), were assessed five years later for antibody persistence and booster response using serum bactericidal assay with human complement (hSBA).

Methods: Children 7–10 and 11–15 years of age, who received MenACWY-CRM in the original study, and age-matched vaccine-naïve children, were enrolled in this extension study. After an initial blood draw, children received one dose of MenACWY-CRM as booster or primary dose, with a second blood draw 28 days later.

Results: hSBA titers decreased five years after primary vaccination, but were higher than in non-vaccinated controls against serogroups C, W and Y, with substantial proportions having titers ≥ 8 : 7–22% for A, 32–57% for C, 74–83% for W, and 48–54% for Y. Previously-vaccinated children demonstrated booster responses to revaccination against all four serogroups. Responses to primary vaccination in vaccine-naïve controls were lower and similar to primary responses observed in the original study. All vaccinations were generally well tolerated, with no safety concern raised.

Conclusions: Approximately half the children vaccinated as 2–10 year-olds maintained protective antibodies against serogroups C, W and Y five years later, but fewer did against serogroup A. Declining titers five years after vaccination and robust booster responses suggest that five years may be an appropriate interval to revaccinate children, subject to epidemiology and delivery considerations.

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1. Background

Invasive meningococcal disease (IMD) due to *Neisseria meningitidis* infection remains a global public health problem, particularly affecting children, adolescents and young adults. IMD is associated with rapid onset and high levels of morbidity and mortality, frequently with severe sequelae in survivors [1]. Two quadrivalent polysaccharide-protein conjugate vaccines (MCV4) have

been developed against four of the major serogroups, A, C, W and Y, responsible for IMD, and are currently licensed in the United States. The Advisory Committee on Immunization Practices (ACIP) currently recommends the use of these vaccines in children at increased risk up to 10 years of age, and routinely for pre-adolescents at 11–12 years of age with a booster dose at 16–18 years [2].

The two conjugate MCV4 vaccines currently licensed in the US differ in their conjugate proteins: MenACWY-D (Menactra[®], Sanofi Pasteur, Swiftwater, PA) uses diphtheria toxoid, and MenACWY-CRM (Menveo[®], Novartis Vaccines and Diagnostics Inc., Cambridge, MA) uses the non-toxic mutant diphtheria toxin, CRM₁₉₇. We have previously reported the results from the original phase 3 study on the safety and immunogenicity of MenACWY-CRM when administered as one or two doses to 2–5 year-old children and one dose

Abbreviations: hSBA, serum bactericidal assay using human complement; CRM₁₉₇, non-toxic mutant of diphtheria toxin; IMD, invasive meningococcal disease; GMT, geometric mean titer.

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to 6–10 year-olds [3]. The original study demonstrated that the tolerability and immune responses to MenACWY-CRM were non-inferior to the licensed MenACWY-D, and statistically superior for serogroups C, W and Y. For MenACWY-CRM in children 2–5 years of age a 2-dose vaccination series induced a higher immune response than a single dose vaccination.

The current study assessed the persistence of bactericidal antibodies to meningococcal serogroups A, C, W and Y in children who participated in the original study [3], five years after their primary vaccinations, compared with age-matched meningococcal vaccine-naïve children. Children vaccinated at 2–5 and 6–10 years in the original study were re-enrolled in this extension study in cohorts of 7–10 and 11–15 year-olds. We also compared the safety, reactogenicity and immune responses to a booster dose of MenACWY-CRM given to previously vaccinated children with that of a first dose in vaccine-naïve children.

2. Methods

This phase 4, open-label, controlled study was performed in 22 sites in the United States from May 2013 to October 2013. The IRB/ECs at each study center approved the protocol, and the study was performed according to current ICH, GCP and US Federal guidelines. The study was registered on ClinicalTrials.gov, identifier NCT01823536.

The primary objective was the evaluation of the persistence of bactericidal antibodies at 5 years post-vaccination in subjects who previously received one or two doses of MenACWY-CRM in the original study (NCT00616421) [3], as measured by the percentage of subjects with human serum bactericidal activity (hSBA) titers ≥ 8 directed against *N. meningitidis* serogroups A, C, W, and Y. Secondary objectives were (i) to evaluate the persistence of bactericidal antibodies at 5 years post-vaccination as measured by geometric mean titers (GMTs), (ii) to compare percentages of subjects with hSBA titers ≥ 8 between groups vaccinated 5 years earlier with one or two doses of MenACWY-CRM and the vaccine naive individuals in the same age group, and (iii) to evaluate immunogenicity (hSBA titers ≥ 8 and GMTs) 28 days after vaccination with MenACWY-CRM in children vaccinated 5 years earlier and in age-matched meningococcal vaccine-naïve children. The safety objective was to assess solicited and unsolicited AEs in all subjects following MenACWY-CRM vaccination.

2.1. Participants

Eligible participants were healthy children who had received one or two doses of MenACWY-CRM according to protocol in the original study five years earlier, and who had not received any additional meningococcal vaccination. These subjects were approached according to a randomized list. We also enrolled healthy 7–10 or 11–15 year-old children with no history of meningococcal vaccination as age-matched controls.

Individuals with any history of meningococcal disease or close contact with a case of laboratory-proven meningococcal disease, history of hypersensitivity reactions to prior meningococcal vaccination, known condition leading to immunosuppression, or a chronic health condition were excluded from participation. Sexually active females of childbearing potential were required to have a negative pregnancy test and to have practiced an approved contraceptive method for two months before and during the study.

2.2. Design

A total of five groups of children were enrolled. Three groups of 7–10 year-olds consisted of those vaccinated with either one

dose or two doses of MenACWY-CRM five years earlier, and age-matched vaccine-naïve subjects. The two groups of 11–15 year-olds had either received one dose of MenACWY-CRM five years earlier or were age-matched vaccine-naïve controls. The number of enrolled subjects was driven by the eligibility and availability of the children, and not by sample size considerations.

On Day 1 a 10 mL blood sample was drawn before administration of a single dose of MenACWY-CRM vaccine. Participants or parents/guardians were given a diary card to record solicited local and systemic reactions for 7 days, and any unsolicited adverse events occurring before the second visit on Day 29. On Days 3 and 7 parents/guardians were contacted by telephone to remind them to complete diary cards. On Day 29 a second 10 mL blood sample was drawn, and the investigator site collected the diary card and interviewed the subject/parents regarding unsolicited adverse events to assess the severity and relationship of any event to vaccination.

2.3. Vaccine

MenACWY-CRM (Menveo[®], Novartis Vaccines and Diagnostics, Inc, Cambridge, MA, lot number MI2034) was supplied in two vials: one vial of lyophilized powder containing 10 μg of Men A oligosaccharide conjugated to 12–33 μg CRM₁₉₇, and a second vial containing 5 μg of each of the Men C, W and Y oligosaccharides conjugated to 3.3–12.5 μg CRM₁₉₇ dissolved in buffered saline. Vaccine was prepared by dissolving the MenA component in the liquid MenCWY component, the reconstituted vaccine (0.5 mL) being administered by intramuscular injection in the deltoid of the non-dominant arm.

2.4. Immunogenicity

Sera were prepared immediately after venipuncture and stored at -20°C for transport to the Novartis Vaccines Clinical Laboratory Sciences, Marburg (Germany) to assess functional antibody titers against serogroups A, C, W and Y using a serum bactericidal assay with exogenous human complement (hSBA) [4].

Responses were expressed as percentages of subjects in each study group with hSBA titer ≥ 8 against each of the four serogroups. Although hSBA titer of ≥ 4 was shown to be associated with protection against invasive meningococcal disease caused by serogroups A and C [4], a more conservative titer level (≥ 8) was used to analyze the hSBA data in order not to overestimate protection [5]. In addition, geometric mean titers (GMT) of bactericidal antibodies for the four serogroups at each study visit and geometric mean ratios (GMR) of individual subject titers (Day 29/Day 1) were computed.

2.5. Reactogenicity and safety

Children were monitored for 30 min for any immediate post-vaccination reactions, and parents subsequently recorded the occurrence and severity of solicited local and systemic reactions occurring from day 1 (6 h) to day 7 postvaccination on the supplied diary cards. The intensity of injection-site pain was assessed as mild (transient with no effect on normal daily activity), moderate (some limitation on normal daily activity) or severe (unable to perform normal daily activity), while erythema and induration were measured with a supplied ruler and assessed as mild (25–50 mm), moderate (51–100 mm) or severe (>100 mm).

Parents graded solicited systemic reactions (chills, malaise, myalgia, arthralgia, headache) as mild (no interference with normal daily activity), moderate (some interference with normal daily activity) or severe (prevents normal daily activity). Nausea was described as mild (present but not interfering with oral intake), moderate (leading to decreased oral intake) or severe (causing minimal or no oral intake). Each day parents measured and recorded

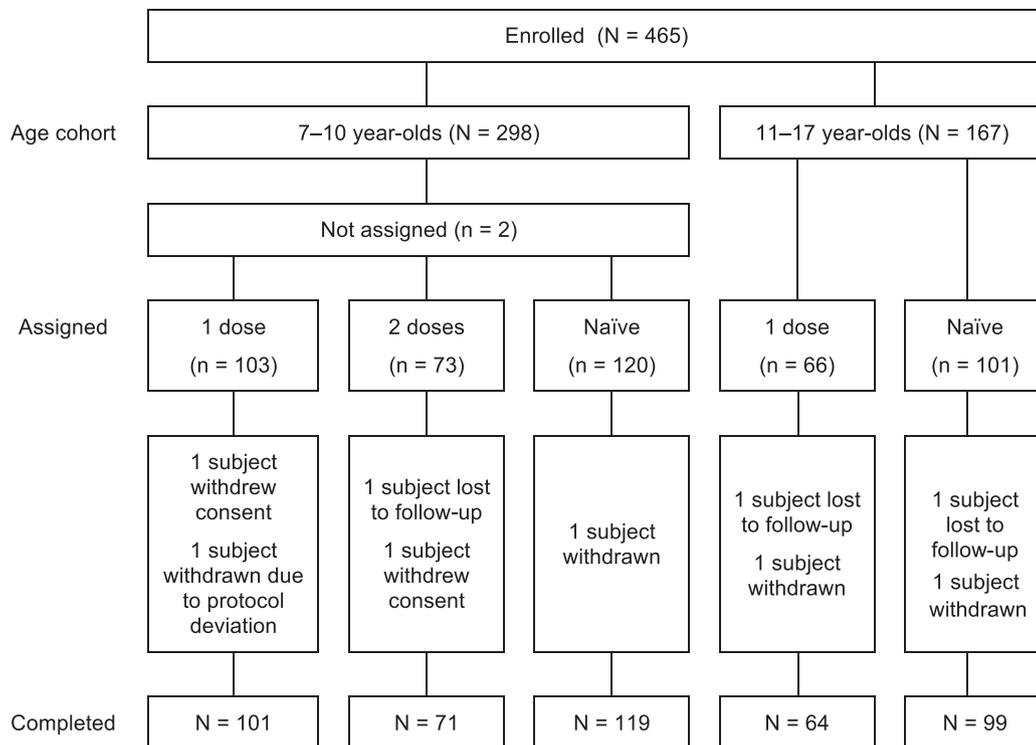


Fig. 1. Study flow chart.

body temperature, preferably orally, with a thermometer issued by the sponsor. Fever was defined as a temperature $\geq 38^{\circ}\text{C}$ irrespective of route of measurement, and described as severe if the temperature was $\geq 40^{\circ}\text{C}$.

Parents also recorded unsolicited adverse events until Day 29, with the investigator assessing the relationship of unsolicited AEs to vaccination. Serious adverse events (SAE) were to be reported during the entire study period.

2.6. Statistics

There was no formal pre-defined statistical hypothesis for testing. Percentages of subjects in each group with hSBA ≥ 8 with 95% Clopper-Pearson CI were calculated, and differences in percentages between groups, calculated by Miettinen and Nurminen [6], were considered significant if two-sided 95% CI for the difference did not contain 0.

3. Results

A total of 465 subjects were enrolled, including 242 subjects previously vaccinated in the original study, together with 221 age-matched vaccine-naïve controls (Fig. 1). Two 7–10 year-old subjects were incorrectly enrolled as they had received MenACWY-D in the original study and therefore were not included in any summaries. Demographic characteristics were similar across the enrolled study groups (Table 1).

3.1. Immunogenicity—Persistence

When assessed for antibody persistence at 5 years post-vaccination all three groups of previously vaccinated participants, either with one or two doses at 2–5 years of age or one dose at 6–10 years, showed higher proportions with hSBA titers ≥ 8 than the age-matched control groups (Fig. 2). Previous vaccination with 2 doses of MenACWY-CRM resulted in greater proportions of children with hSBA titers ≥ 8 against all 4 serogroups, while prior vaccination

Table 1
Demographics of the study groups.

| MenACWY-CRM vaccination history | 7–10 year-olds | | | 11–15 year-olds | |
|-----------------------------------|----------------------------|-----------------------------|----------------|----------------------------|----------------|
| | Previously received 1 dose | Previously received 2 doses | Naïve controls | Previously received 1 dose | Naïve controls |
| N= | 103 | 73 | 120 | 66 | 101 |
| Mean age \pm SD (years) | 8.1 \pm 1.2 | 8.3 \pm 1.1 | 8.5 \pm 1.1 | 13.0 \pm 1.6 | 11.8 \pm 1.0 |
| Range | 6–10 | 6–10 | 7–10 | 10–16 | 10–15 |
| Male:female (%:%) | 52:48 | 52:48 | 48:53 | 58:42 | 54:46 |
| Race n (%) | | | | | |
| American Indian or Alaskan native | 2(2) | 1(1) | 0 | 0 | 1(<1) |
| Asian | 3(3) | 3(4) | 0 | 0 | 2(2) |
| Black or African American | 13(13) | 9(12) | 33(28) | 6(9) | 14(14) |
| Hawaiian or Pacific Islander | 0 | 0 | 1(<1) | 0 | 0 |
| White | 71(69) | 56(77) | 82(68) | 52(79) | 77(76) |
| Other | 14(14) | 4(5) | 4(3) | 8(12) | 7(7) |

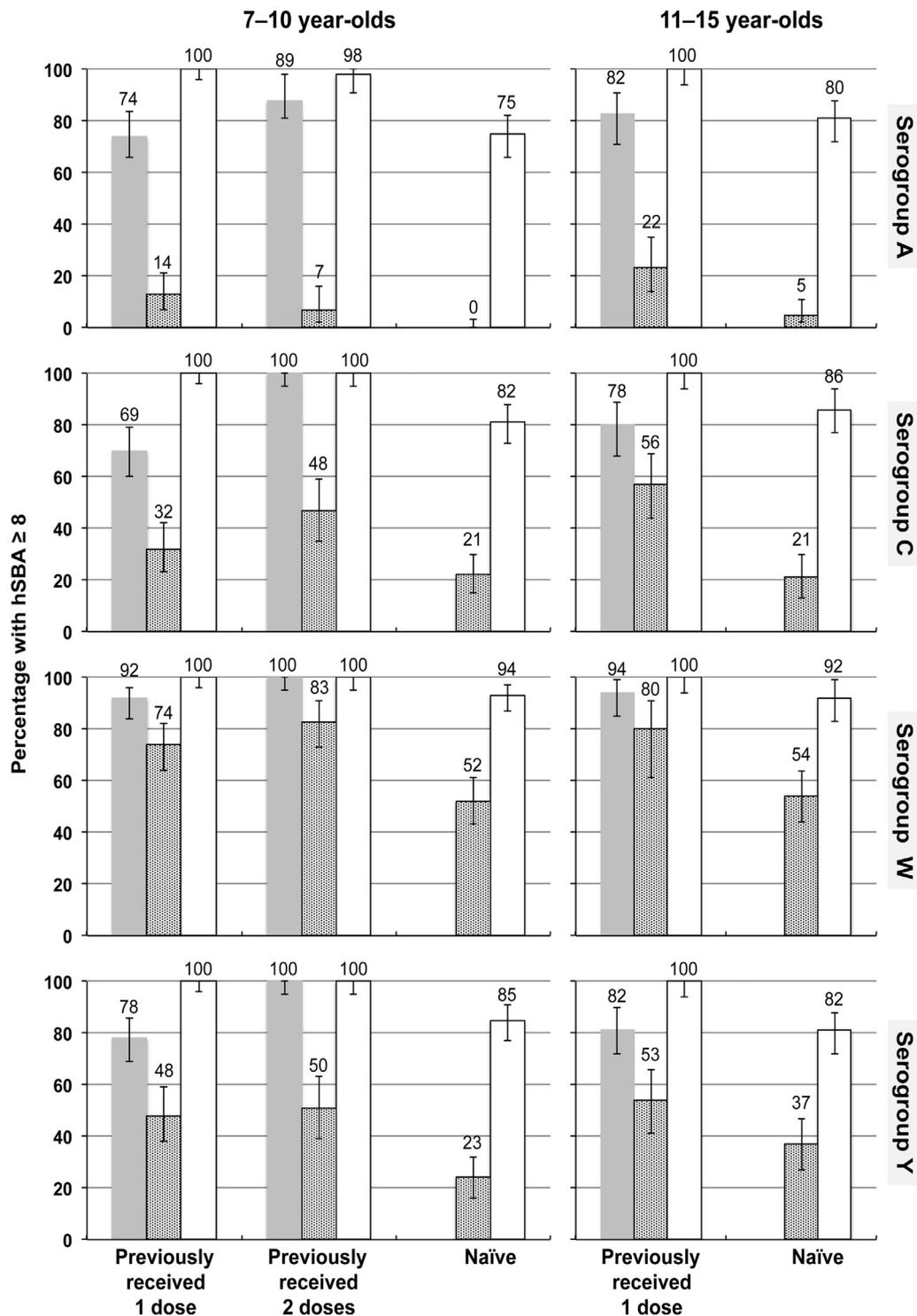


Fig. 2. Percentages (95% CI) of each study group with hSBA titers ≥ 8 against serogroups A, C, W and Y after vaccination in the original study (grey bars), five years later (hatched bars) and after vaccination in this study (open bars). Numbers note actual percentages.

with a single dose resulted in higher immune responses against 3 of 4 serogroups (A, W and Y), when compared with their respective age-matched naïve controls. Similarly, a higher proportion of previously vaccinated 11–15 year-olds had hSBA ≥ 8 for all four serogroups than their age-matched naïve controls. Proportions of subjects with hSBA titers ≥ 8 against serogroups A, C, W and Y were; 7%, 48%, 83% and 50% in 7–10 year olds (2 doses); 14%, 32%, 74% and 48% in 7–10 year olds (1 dose), and 22%, 56%, 80% and 53% in 11–15 year olds (1 dose). Respective proportions in vaccine-naïve subjects

for serogroups A, C, W and Y were 0%, 21%, 52% and 23% in 7–10 year-olds, and 5%, 21%, 54% and 37% in 11–15 year-olds.

Although hSBA titers had waned after the primary vaccinations (Table 2), geometric mean titers (GMT) against serogroups C, W and Y in both age groups remained higher than those observed in age-matched vaccine-naïve controls. Serogroup A GMTs were similar in all groups.

In the original study GMTs were significantly higher in 2–5 year-olds who received two doses of MenACWY-CRM compared with

Table 2
Geometric mean titers (95% CI) against serogroups A, C, W and Y in each of the study groups 1 month after the primary vaccination(s) in the original study, and pre-, (Day 1) and 28 days post-vaccination in the present extension study.

| Group | 7–10 year-olds | | | | | | 11–15 year-olds | | | | | | | | | |
|-------|----------------------------|---------------|------------------|-----------------------------|---------------|------------------|-----------------|------------|------------|----------------------------|-----------------|--------------|----------------|--------------|---------------|--------------|
| | Previously received 1 dose | | | Previously received 2 doses | | | Naïve Controls | | | Previously received 1 dose | | | Naïve Controls | | | |
| | Post-primary | Day 1 | Day 29 | Post-primary | Day 1 | Day 29 | Day 1 | Day 29 | Day 1 | Post-primary | Day 1 | Day 29 | Day 1 | Day 29 | Day 1 | Day 29 |
| N | 96 | 96 | 93–95 | 68–70 | 68–70 | 63–65 | 118 | 109–110 | 64 | 61 | 59–60 | 85 | 99–100 | 85 | 99–100 | 85 |
| A | 27(18–42) | 3.0 (2.4–3.7) | 361 (299–436) | 56(36–85) | 2.4 (2.1–2.8) | 321 (241–428) | 2.0 (2–2) | 28 (20–39) | 42(24–75) | 3.8 (2.8–5.3) | 350(265–463) | 31 (22–45) | 2.4 (2.1–2.7) | 31 (22–45) | 2.4 (2.1–2.7) | 31 (22–45) |
| C | 17(11–27) | 6.7 (4.9–9.3) | 498 (406–610) | 148(112–195) | 7.8 (5.5–11) | 760(545–1059) | 3.6 (3.0–4.3) | 48 (33–70) | 74(40–134) | 13 (8.1–20) | 712 (490–1036) | 102 (63–166) | 3.8 (3.0–4.9) | 102 (63–166) | 3.8 (3.0–4.9) | 102 (63–166) |
| W | 59(42–82) | 19 (14–26) | 1534 (1255–1873) | 147(112–194) | 22 (16–29) | 1571 (1247–1980) | 8.3 (6.3–11) | 55 (42–72) | 94(59–149) | 25 (17–38) | 1556(1083–2237) | 69 (48–99) | 11 (7.8–16) | 69 (48–99) | 11 (7.8–16) | 69 (48–99) |
| Y | 34(22–52) | 8.3 (6.2–11) | 1693 (1360–2107) | 119(86–163) | 8.5 (6.0–12) | 1286(992–1668) | 3.6 (3.0–4.4) | 48 (34–66) | 34(19–61) | 10 (6.3–16) | 1442(1050–1979) | 45 (30–69) | 5.5 (4.1–7.4) | 45 (30–69) | 5.5 (4.1–7.4) | 45 (30–69) |

those who received only one dose (56 vs. 27 for serogroup A, 148 vs. 17 for C, 147 vs. 59 for W and 119 vs. 34 for Y) [3]. Proportions of subjects with titers ≥ 8 were also higher after two doses than one dose (see Fig. 2). These differences did not persist when both groups were assessed five years later.

3.2. Vaccination as a booster or first dose of MenACWY-CRM

Following administration of a booster dose of MenACWY-CRM five years after their primary vaccination, proportions of subjects with hSBA titer ≥ 8 increased substantially in all 3 study groups, and reached 98–100% against each of the four serogroups (Fig. 2). After a first vaccination with MenACWY-CRM in the age-matched vaccine-naïve controls, 75–94% of 7–10 year-olds and 80–92% of 11–15 year-olds achieved titers ≥ 8 against the four serogroups (Fig. 2).

In previously vaccinated subjects hSBA GMTs (Table 2) were increased dramatically at one month after the booster and were similar across age groups, irrespective of the number of previous doses. These GMTs were also many-fold higher than those observed one month after the last vaccination in the original study, demonstrating priming by the original vaccinations and a booster response to the revaccination. The GMTs following a first dose of MenACWY-CRM in the vaccine-naïve participants were consistent with those reported in the original study, despite the five-year age difference. There were no age-dependent differences in these responses in vaccine-naïve subjects, except for serogroup C, for which the observed GMTs were twice as high in 11–15 year-olds than in 7–10 year-olds.

Higher GMRs (post/prevaccination) were observed in previously vaccinated children (Table 3). GMRs across all serogroups ranged from 74–207 and 55–142 in 7–10 and 11–15 year-olds, respectively, compared with 6.6–14 and 6.6–27 in the respective age-matched vaccine-naïve groups.

3.3. Reactogenicity and safety

Vaccination was generally well tolerated in all groups and no safety issues were identified. The majority of solicited reactions were mild to moderate in severity, transient, occurred between 6 h and 4 days after vaccination, and resolved spontaneously without sequelae within 7 days.

3.4. Solicited reactions

Comparable proportions of 7–10 year-old children previously vaccinated with one or two doses reported solicited local (56% and 57%, respectively) and systemic (27% and 33%, respectively) reactions, compared with 39% and 29% in vaccine-naïve controls. A similar pattern was observed in the older children, with solicited local and systemic reactions, respectively, being reported by 53% and 30% of previously vaccinated children, and 50% and 36% of vaccine-naïve controls.

Pain was the most frequent solicited reaction, reported in 36–57% of children (Table 4), but most cases were mild to moderate, and transient, with <1% described as severe. Other reactions were much less frequent and few were described as severe. Only five children had fever ($\geq 38^\circ\text{C}$) and none reported high fever. Reactogenicity profiles were similar across age groups, and in vaccine-naïve and previously vaccinated groups.

3.5. Unsolicited reactions

Reporting rates of unsolicited AEs were similar in the two previously vaccinated 7–10 year-old groups (23% and 25%), and slightly lower in vaccine-naïve controls (16%). Only 3–5% of children had

Table 3
Geometric Mean Ratios (95% CI) of hSBA titers at Day 29 to Day 1 following vaccination with MenACWY-CRM.

| Serogroup | N | 7–10 year-olds | | | 11–15 year-olds | |
|-----------|--------------|----------------------------|-----------------------------|----------------|----------------------------|----------------|
| | | Previously received 1 dose | Previously received 2 doses | Naïve controls | Previously received 1 dose | Naïve controls |
| A | 92–93 | 123 (95–160) | 63–65 | 109–110 | 59–60 | 84–85 |
| | GMR (95% CI) | | 131 (97–178) | 14 (10–20) | 94 (64–137) | 14 (9.7–19) |
| C | 74 (52–105) | | 98 (61–158) | 13 (9.3–19) | 55 (34–90) | 27 (17–43) |
| W | GMR (95% CI) | 78 (58–105) | 75 (50–112) | 6.6 (4.8–9.1) | 61 (37–100) | 6.6 (4.8–9.0) |
| Y | GMR (95% CI) | 207 (156–275) | 153 (106–222) | 13 (9.1–19) | 142 (86–233) | 8.5 (5.8–12) |

AEs considered possibly related to the vaccination. The majority of these were injection site reactions continuing beyond the 7 day post-vaccination window for solicited reactions. Previously vaccinated 11–15 year-olds reported more vaccine-related unsolicited AEs (11%) than age-matched controls (5%).

Two subjects reported SAEs, unrelated to vaccination during the study (a viral infection 18 days after vaccination, and gastroenteritis 4 days after vaccination).

4. Discussion

We have previously demonstrated that MenACWY-CRM has a robust safety profile and is well tolerated and effective in inducing bactericidal antibodies in children from 2–10 years of age, whether administered as one or two doses in 2–5 years olds, or as one dose in 6–10 year-olds. A single dose vaccination was also immunologically non-inferior to MenACWY-D in these respects [3]. This extension study showed decreases in bactericidal antibody titers 5 years after initial vaccination with MenACWY-CRM. While antibodies in previously vaccinated subjects persisted at higher levels than in age-matched vaccine-naïve controls for serogroups C, W and Y, the decline was more pronounced in serogroup A antibody titers, especially in children vaccinated at 2–5 years of age.

In the original study, 2–5 year-old children initially produced higher antibody responses to two doses of MenACWY-CRM than those who only received one dose [3]. However, this difference did not persist 5 years later, as levels of residual antibodies were

similar in both groups of children, now aged 7–10 years. Similar patterns of antibody persistence have been observed in other studies in older adolescents [7,8], and five year-olds vaccinated as infants or toddlers [9].

When previously vaccinated children were revaccinated with a single dose of MenACWY-CRM 5 years later the fold-increases in GMTs were characteristic of booster responses, indicating that immune priming had occurred. The magnitude of antibody GMTs and ratio of GMTs post- to pre-vaccination were significantly higher in previously vaccinated subjects than in the vaccine-naïve controls of the same age. All children revaccinated at 5 years had hSBA titers ≥ 8 , the commonly accepted surrogate marker for protection [4,10], against each of the four serogroups, except one subject who did not respond to serogroup A. Responses to the booster vaccination were similar regardless of the number of previous doses in younger children, or the age group when the primary vaccinations were administered.

Antibody levels in controls were consistent with previously published data in this age group [3], which were lower than those of previously vaccinated children. hSBA GMTs in these age-matched controls after a first dose were similar to those in 2–5 year-olds or 6–10 year-olds when they were originally vaccinated with either one or two doses of MenACWY-CRM five years earlier.

Vaccination with MenACWY-CRM was well tolerated in each age group studied. No vaccine-related SAEs occurred and rates of vaccine-related unsolicited adverse events were low. Injection site pain, reported by approximately half of the recipients, was mainly

Table 4
Rates of Local and Systemic reactions in the study groups in the 7 days after MenACWY-CRM vaccination.

| | N | 7–10 year-olds | | | 11–15 year-olds | |
|--------------------|-----------------------------|----------------------------|-----------------------------|----------------|----------------------------|----------------|
| | | Previously received 1 dose | Previously received 2 doses | Naïve controls | Previously received 1 dose | Naïve controls |
| Local reactions | | | | | | |
| Pain | Any(severe) | 52 (53) | 39 (57) | 42 (36) | 31 (48) | 47 (48) |
| | | 1 (1) | 3 (4) | 0 | 0 | 0 |
| Erythema | Any(severe) | 13 (13) | 10 (15) | 10 (9) | 10 (16) | 6 (6) |
| | | 1 (1) | 0 | 2 (2) | 4 (6) | 1 (1) |
| Induration | Any(severe) | 12 (12) | 12 (18) | 7 (6) | 7 (11) | 8 (8) |
| | | 1 (1) | 1 (1) | 2 (2) | 1 (2) | 0 |
| Systemic reactions | | | | | | |
| Chills | Any(severe) | 3 (3) | 5 (7)* | 6 (5) | 1 (2) | 2 (2) |
| | | 1 (1) | 0 | 0 | 0 | 0 |
| Malaise | Any(severe) | 14 (14) | 15 (22) | 13 (11) | 11 (17) | 19 (19) |
| | | 1 (1) | 0 | 1 (1) | 0 | 0 |
| Myalgia | Any(severe) | 8 (8) | 9 (13) | 8 (7) | 4 (6) | 8 (8) |
| | | 0 | 1 (1) | 0 | 0 | 0 |
| Arthralgia | Any(severe) | 4 (4) | 8 (12) | 5 (4) | 4 (6) | 8 (8) |
| | | 0 | 1 (1) | 0 | 0 | 0 |
| Headache | Any(severe) | 9 (9) | 13 (19) | 22 (19) | 12 (19) | 21 (22)* |
| | | 0 | 2 (3) | 1 (1) | 2 (3) | 0 |
| Nausea | Any(severe) | 11 (11) | 10 (15)* | 12 (10) | 7 (11) | 8 (8)* |
| | | 0 | 0 | 1 (1) | 0 | 0 |
| Fever | ($\geq 38^\circ\text{C}$) | 0 | 1 (2)** | 3 (3)** | 1 (2) | 0 |
| | ($\geq 40^\circ\text{C}$) | 0 | 0 | 0 | 0 | 0 |

* One subject less.

** Two subjects less.

mild or moderate and resolved within a few days of vaccination. The rates of solicited reactions were generally similar whether the vaccine was given as a booster dose or a first dose. We observed no safety concerns with repeat vaccination five years after primary vaccination.

This study was limited by the small sample size and non-randomized design as it relied on enrolment of children from the original study. The use of serum bactericidal assay with human complement is considered the gold standard for assessment of functional antibodies following vaccination and associated protection against serogroups-specific IMD, but may underestimate persisting immunity, especially for serogroup A [5].

Recent studies with conjugated serogroup A vaccine (PsA-TT) in Africa showed a sustained effectiveness against serogroup-specific invasive meningococcal diseases and oropharyngeal carriage during at least 2 years after vaccination [11,12,13] despite of rapid decline of hSBA titers [14]. Alternative assays (e.g. measurement of serogroup-specific IgG concentrations or rSBA activity) have been investigated [14] and might be more appropriate for assessment of antibody persistence for serogroup A [5,14].

Immune protection against IMD probably relies on the presence of circulating bactericidal antibodies [10]. In the United States the main age groups at risk are infants, children younger than 5 years of age, and adolescents, particularly those in institutional settings such as dormitory-dwelling college students or the military [15]. The rapidity of onset, notable treatment failure rate, and mortality rate of 10–14% [1,16], suggest that vaccination offers the best protection against the consequences of the disease. Currently ACIP recommends a single dose vaccination to children 2–10 years of age at increased risk for meningococcal disease; however limited data are available regarding duration of protection and a need of a booster dose in this age group.

Although 2 doses of MenACWY-CRM could provide an immediate benefit for children 2–5 years of age at higher risk for IMD (e.g., those with an immunocompromised status or living in an endemic area), this schedule may not be associated with greater lasting protection compared with a single dose. The extent of antibody waning following the primary vaccination series suggests that a five-year booster may be beneficial. Given the robust and anamnestic responses to a booster vaccination at 5 years demonstrated in this study, we believe that introducing a larger interval between the 2 doses of MenACWY-CRM in high-risk children may constitute a viable option, and the timing of the second dose may need to be decided based on epidemiologic conditions and the health status of the child.

MenACWY-CRM has been shown to have a robust safety profile and be immunogenic and generally well tolerated in all age ranges [17]. Specifically, previous studies have confirmed the acceptability and immunogenicity of three- and four-dose MenACWY-CRM vaccination series in infants [18–20], a two-dose series in toddlers [16,21], as well as the induction of immune priming in infants [20].

5. Conclusions

This study shows persistence of bactericidal antibodies against vaccine serogroups C, W and Y for up to five years after vaccination with MenACWY-CRM in about half of 2–10 year-old children. Minimal differences in antibody persistence between one- or two-dose primary series in children 2–5 years of age were observed after 5 years. Both schedules induced immune priming demonstrated by anamnestic responses to revaccination after five years. Revaccination was well tolerated, with no apparent safety concerns, and induced booster responses against all four serogroups in virtually all subjects.

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Conflict of interest statement

BV, PK, PMD and IS are full-time employees of Novartis Group companies with associated financial interests. FX is a contract employee of Novartis Vaccines and Diagnostics Inc., Cambridge, USA. SLB and SC were provided research grants as investigators to perform the study but have no other financial interest.

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