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Safety of a quadrivalent meningococcal serogroups A, C, W and Y conjugate vaccine (MenACWY-CRM) administered with routine infant vaccinations: Results of an open-label, randomized, phase 3b controlled study in healthy infants

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ABSTRACT

Background: The highest risk for invasive meningococcal disease (IMD) is in infants aged <1 year. Quadrivalent meningococcal conjugate vaccination has the potential to prevent IMD caused by serogroups A, C, W and Y. This phase 3b, multinational, open-label, randomized, parallel-group, multicenter study evaluated the safety of a 4-dose series of MenACWY-CRM, a quadrivalent meningococcal conjugate vaccine, concomitantly administered with routine vaccinations to healthy infants.
Methods: Two-month-old infants were randomized 3:1 to receive MenACWY-CRM with routine vaccines or routine vaccines alone at ages 2, 4, 6 and 12 months. Adverse events (AEs) that were medically attended and serious adverse events (SAEs) were collected from all subjects from enrollment through 18 months of age. In a subset, detailed safety data (local and systemic solicited reactions and all AEs) were collected for 7 days post vaccination. The primary objective was a non-inferiority comparison of the percentages of subjects with ≥1 severe systemic reaction during Days 1–7 after any vaccination of MenACWY-CRM plus routine vaccinations versus routine vaccinations alone (criterion: upper limit of 95% confidence interval [CI] of group difference <6%).
Results: A total of 7744 subjects were randomized with 1898 in the detailed safety arm. The percentage of subjects with severe systemic reactions was 16% after MenACWY-CRM plus routine vaccines and 13% after routine vaccines alone (group difference 3.0% (95% CI −0.8, 6.4%). Although the non-inferiority criterion was not met, post hoc analysis controlling for significant center and group-by-center differences revealed that MenACWY-CRM plus routine vaccinations was non-inferior to routine vaccinations alone (group difference −0.1% [95% CI −4.9%, 4.7%]). Rates of solicited AEs, medically attended AEs, and SAEs were similar across groups.
Conclusion: In a large multinational safety study, a 4-dose series of MenACWY-CRM concomitantly administered with routine vaccines was clinically acceptable with a similar safety profile to routine vaccines given alone.

Abbreviations: AE, adverse event; DTaP, diphtheria, tetanus, pertussis [vaccine]; Hib, *H. influenzae* type b [vaccine]; IM, intramuscular; IMD, invasive meningococcal disease; IPV, inactivated polio vaccine; SAE, serious adverse event.

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1. Introduction

Neisseria meningitidis is a leading cause of bacterial meningitis and septicemia worldwide, with infants, adolescents, and young adults at highest risk [1]. Invasive meningococcal disease (IMD) is associated with high rates of morbidity and mortality even among patients who receive prompt antibiotic treatment, with an overall case fatality rate of 10–15% [2]. Permanent sequelae such as hearing loss, neurological impairment, seizures, and intellectual disabilities can have devastating effects on survivors' quality of life [2]. In developed countries, the risk of IMD is highest among infants aged <12 months [1,3]. Serogroups A, B, C, W and Y are responsible for nearly all cases of IMD, although the incidence and relative distribution of serogroups vary greatly by geographic region and over time [4,5]. The potential availability of quadrivalent glycoconjugate vaccines against serogroups A, C, W and Y for infants offers an opportunity to provide broad protection against IMD in the youngest age group.

MenACWY-CRM (Menveo®, Novartis Vaccines and Diagnostics, Inc.), a quadrivalent (A, C, W and Y) meningococcal vaccine, in which the capsular oligosaccharides are conjugated to CRM_{197}, has been approved for active vaccination against IMD caused by *N. meningitidis* in persons aged ≥2 years in Europe and many other parts of the world, and in persons aged 2–55 years in the US. It is important to ascertain the potential for clinically relevant immunological interference of any new vaccine with current routine infant and toddler vaccinations. Two phase 3 studies have been published that support the immunologic compatibility of concomitant administration of MenACWY-CRM with routine vaccination beginning in early (age 2 months) or late (age 7–9 months) infancy [6,7]. Large-scale infant safety studies of MenACWY-CRM with diverse concomitant infant vaccinations have not been reported.

This multinational study evaluated the safety of a 4-dose series of MenACWY-CRM administered with routine vaccinations in a large cohort of healthy infants. Safety information was collected about medically attended adverse events (AEs), serious AEs (SAEs), and solicited local and systemic reactogenicity.

2. Methods

2.1. Study design

Novartis study V59P23 was a phase 3b, multinational, open-label, randomized, parallel-group, multicenter study to evaluate the safety of MenACWY-CRM concomitantly administered with routine vaccinations in healthy infants. The study was conducted at 153 centers in 6 countries–the US, Guatemala, Peru, Taiwan, Costa Rica, and Panama–between December 2008 and November 2011 (ClinicalTrials.gov identifier, NCT00806195). For number of centers and subjects by country, see Supplemental Table 1.

Subjects were randomized 3:1 into 2 cohorts to receive either MenACWY-CRM plus routine vaccinations or routine vaccinations alone (Fig. 1). From all subjects, medically attended AEs and SAEs were collected after vaccinations at ages 2, 4, 6 and 12 months and through age ≥18 months. This was the extent of the safety data collection in the "non-detailed" safety arm (Groups 1 and 2, enrolled in all countries). Additional safety data were collected in the "detailed" safety arm (Groups 3 and 4), including local and systemic reactions and all AEs for 7 days post vaccination. Subjects in the detailed safety arm were enrolled in the US only.

The primary study objective was a comparison of the percentages of subjects with ≥1 severe systemic reaction during Days 1–7 after any vaccination of MenACWY-CRM plus routine vaccinations (Group 3) versus routine vaccinations alone (Group 4) at ages 2, 4, 6 and 12 months. The key secondary objective was a comparison of the percentages of subjects presenting with ≥1 SAE throughout the entire study period in those who received MenACWY-CRM with routine vaccinations (Groups 1 + 3) versus routine vaccinations alone (Groups 2 + 4).

2.2. Study subjects

Healthy 2-month-old infants (aged 55–89 days), born at ≥37 weeks gestation, with a birth weight ≥2.5 kg were eligible for participation. Exclusion criteria are described in the Supplementary Appendix. Written, informed consent was obtained from the parents or legal guardians of all enrolled subjects. Study approval was obtained from the Ethics Committee or the Institutional Review Board at all participating centers. The study was designed in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice, and applicable regulatory requirements.

2.3. Vaccines

Subjects received 4 doses of MenACWY-CRM vaccine, 1 dose each at 2, 4, 6 and 12 months of age, plus routine vaccinations (Groups 1 and 3) or routine vaccinations alone (Groups 2 and 4). Each 0.5-mL dose of MenACWY-CRM contained 10 μg MenA polysaccharide and 5 μg each of MenC, MenW and MenY conjugated to CRM. Subjects received a minimum core set of routine infant vaccinations including diphtheria, tetanus, pertussis (DTaP), inactivated polio vaccine (IPV), and *H. influenzae* type b (Hib) vaccine at 2, 4 and 6 months of age, 7-valent pneumococcal conjugate vaccine at 2, 4, 6 and 12 months of age, measles, mumps and rubella vaccine at 12 months of age, and an additional dose of DTaP and Hib at 15 months of age. In Groups 1 and 2, other vaccinations were permitted according to local guidelines, excluding other meningococcal vaccines. For concomitant vaccines, see Supplemental Table 2.

Routine vaccinations administered to Groups 3 and 4 included only US-licensed vaccines and were given in accordance with the US Advisory Committee on Immunization Practices. These included the core set of routine vaccinations described above plus varicella and hepatitis A virus vaccines at age 12 months, and hepatitis B vaccine and rotavirus vaccines administered during the first year.

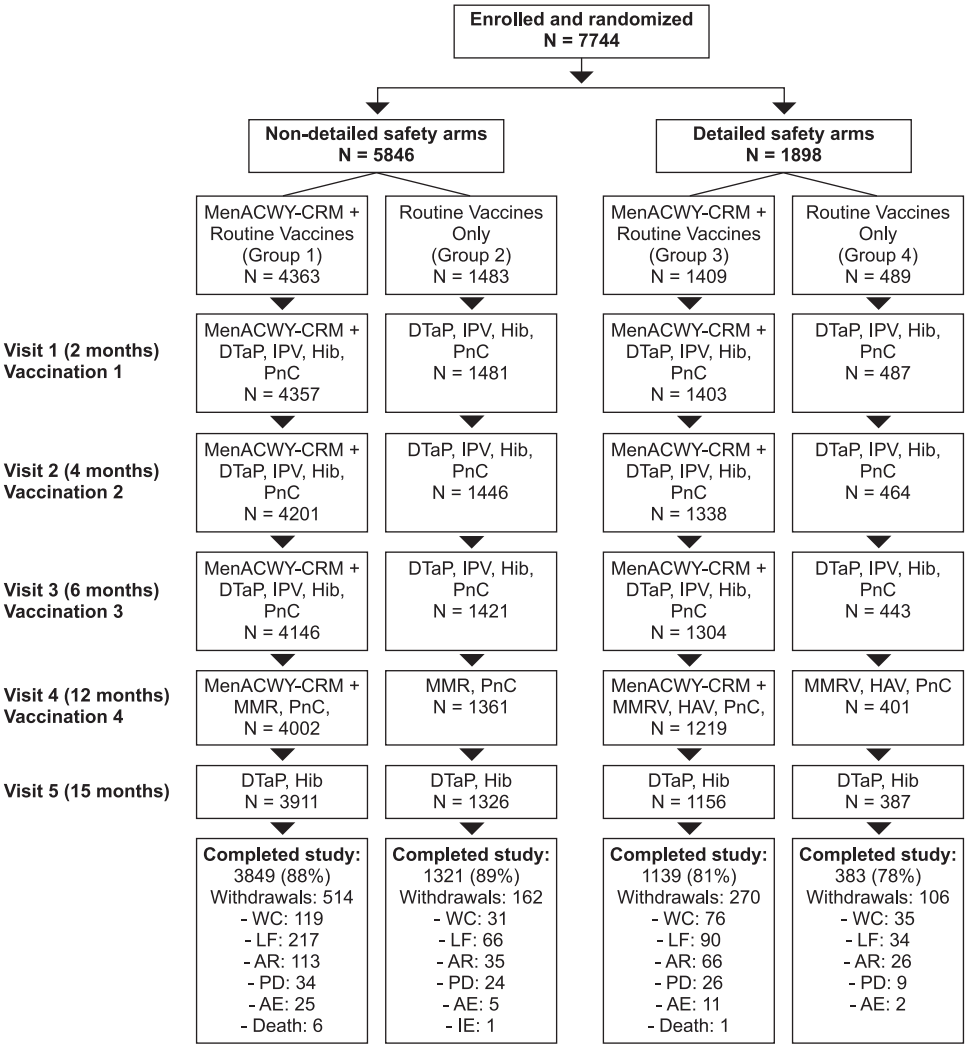
MenACWY-CRM and concomitant routine vaccinations were administered via intramuscular (IM) or subcutaneous injection, as appropriate. In Group 3, MenACWY-CRM and pneumococcal conjugate vaccine were administered IM to the anterolateral area of the right and left thigh, respectively. For Group 4 subjects, pneumococcal conjugate vaccine was administered IM into the anterolateral area of the right thigh, providing a local reactogenicity comparator for the investigational vaccine.

2.4. Safety monitoring

Subjects who received ≥1 study vaccination were evaluated for safety. All subjects were evaluated for SAEs, medically attended AEs and AEs resulting in study discontinuation during the entire study period. In addition, subjects in the detailed safety arm (Groups 3 and 4) were evaluated for solicited local and systemic reactogenicity and any AEs occurring 7 days post vaccination. Temperatures were collected by axillary route. Phone calls were made 2 and 7 days after each vaccination to remind the parent(s)/guardian(s) to complete the diary card. For additional details regarding the recording and collection of safety data, see Supplemental Appendix.

2.5. Statistical analysis

All subjects who received ≥1 dose of study vaccine and provided post-baseline safety data were included in the analyses.



AE: adverse event; AR: administrative reason; DTaP: diphtheria, tetanus, acellular pertussis vaccines; HAV: hepatitis A virus vaccine; Hib: *H. influenzae* type b vaccine; IE: inappropriate enrollment; IPV: inactivated polio vaccine; LF: lost to follow-up; MenACWY-CRM: quadrivalent (A, C, W and Y) meningococcal vaccine, in which the capsular oligosaccharides are conjugated to CRM_{197}; MMR: measles, mumps, and rubella vaccine; MMRV: measles, mumps, rubella, and varicella vaccine; PD: protocol deviation; PnC: pneumococcal conjugate; WC: withdrew consent.

Fig. 1. Study vaccination schedule.

AEs were assessed for their relationship to study treatment only if they occurred in subjects vaccinated with MenACWY-CRM.

The primary endpoint was the percentage of subjects experiencing ≥1 severe systemic reaction during the first 7 days after any vaccination. MenACWY-CRM concomitantly administered with routine vaccinations was considered non-inferior to routine vaccinations alone if the upper limit of the 2-sided 95% confidence interval (UL95%CI) of the difference in the percentages of subjects (Group 3 – Group 4) experiencing ≥1 severe systemic reaction during the first 7 days after any vaccination was <6%. Confidence intervals were calculated using the Miettinen and Nurminen method [8]. A post hoc multivariate categorical linear model analysis [9] adjusting for group, center, and group-by-center interaction was also performed.

The key secondary endpoint was the percentage of infants reporting ≥1 SAE from Day 1 through 6 months post final dose. MenACWY-CRM administered with routine vaccinations was considered non-inferior to routine vaccinations alone if the UL95%CI of the difference in the percentages of subjects experiencing ≥1 SAE was <5% ([Group 1 + Group3] – [Group 2 + Group 4]). The differences in percentages of subjects experiencing SAEs during other study periods (Day 1–12 months of age, Day 1 to ≤Month 7, >Month 7 to ≤Month 12, >Month 13 to study end) were also assessed. Statistical analyses were performed with SAS® version 9.1 or higher (SAS Institute, Cary, NC, USA).

Power calculations were based on the primary study objective: to show that the rate of severe systemic reactions in subjects receiving MenACWY-CRM plus routine vaccines was ≤6% higher than subjects receiving routine vaccines only. Assuming a rate of severe systemic reactions of ~10%, as observed in the pivotal phase 3 MenACWY-CRM infant trial [7], it was estimated that 1250 subjects in the MenACWY-CRM plus routine vaccine group and 417 subjects in the routine vaccines only group would be sufficient to achieve 99% power to detect a group difference in the rate of severe systemic reactions with an UL95%CI <6%. To allow for a potential attrition rate of 10%, the planned sample size was 1380 subjects in Group 3 and 460 in Group 4.

Based on guidance from regulatory agencies for the non-detailed safety arm and assuming an estimated 10% early withdrawal rate, the planned sample sizes for Groups 1 and 2 were 4395 and 1465 subjects, respectively.

Table 1
Summary of results for the key secondary objective analyzing rates of SAEs across vaccine groups within different time intervals.

Study duration	Subjects with SAEs, *n*/N (%)		Group difference, % (95% CI)	Success criterion for secondary safety objective: upper limit 95% CI <5%
	MenACWY-CRM + routine vaccinations (Groups 1 and 3)	Routine vaccinations only (Groups 2 and 4)		
Day 1 to study end (18 months)	354/5757 (6)	114/1967 (6)	0.4 (−0.9, 1.5)	Met
Day 1 to 12 months of age	275/5760 (5)	88/1968 (4)	0.3 (−0.8, 1.3)	Met
Day 1 to <Month 7	158/5760 (3)	42/1968 (2)	–	N/A
>Month 7 to <Month 12	131/5429 (2)	51/1856 (3)	–	N/A
>Month 13 to study end	78/5128 (2)	31/1738 (2)	–	N/A

CI, confidence interval; N/A, not applicable; SAEs, serious adverse events. CI was calculated using the method of Miettinen and Nurminen [8] for the secondary endpoint.

3. Results

3.1. Study population

A total of 7744 subjects were enrolled and randomized to receive MenACWY-CRM plus routine vaccinations ($n = 5772$) or routine vaccinations alone ($n = 1972$). In the non-detailed safety groups, 5846 subjects were enrolled between December 2008 and July 2010 and were randomized to receive MenACWY-CRM plus routine vaccinations (Group 1; $n = 4363$) or routine vaccinations alone (Group 2; $n = 1483$). All subjects in the detailed safety groups were enrolled in the US between April 2009 and September 2009 and were randomized to MenACWY-CRM plus routine vaccinations (Group 3; $n = 1409$) or routine vaccinations alone (Group 4; $n = 489$) (Fig. 1). Overall, 7728 subjects received ≥1 dose of study vaccine and were included in the safety analyses; 16 subjects were randomized but not vaccinated and were therefore excluded from analyses.

Of the 7744 infants enrolled, 6692 (86%) completed the study. Of these, 4988 and 1704 subjects were randomized to MenACWY-CRM plus routine vaccinations and routine vaccinations alone, respectively (Fig. 1). In total, 1052 subjects withdrew from the study, with identical withdrawal rates of 14% for both groups. The most common reasons for withdrawal were "lost to follow-up" ($n = 407$; 5%), "withdrawal of consent" ($n = 261$; 3%) and "administrative reason" ($n = 240$; 3%). Other reasons for early withdrawal were reported for ≤2% of subjects in each group. Seven infants who received MenACWY-CRM plus routine vaccinations were withdrawn from the study due to death: 6 (<1%) in Group 1 (non-detailed safety arm) and 1 (<1%) in Group 3 (detailed safety arm) (see Section 4). One death occurred after a subject who received routine vaccines only (Group 2) was withdrawn from the study 75 days after final vaccination.

Demographic and baseline characteristics were similar between the groups (Supplemental Table 3).

3.2. Group differences in severe systemic reactions

A similar percentage of subjects experienced ≥1 severe solicited systemic reaction from 15 min to Day 7 after vaccination in Group 3 (16%) and Group 4 (13%). The planned primary statistical comparison assumed no differences between centers in the percentage of subjects experiencing severe solicited reactions and also no center by group interaction. These assumptions did not hold: significant differences were observed in the rates of severe systemic reaction by center ($p < 0.001$) and there was also a significant group by center interaction ($p < 0.001$). Therefore, a post-hoc multivariate categorical linear model analysis [9] was performed to adjust for these factors. This analysis resulted in an estimate of the difference between Group 3 and Group 4 of −0.1% (95% CI −4.9%, 4.7%), which met the primary endpoint criterion for non-inferiority. Using the initially planned primary analysis despite the violation of the underlying assumptions of no vaccine group-by-center interaction, yielded an estimate of the difference between Groups 3 and 4 of 3% with a 2-sided 95% CI of −0.8% to 6.4%, which failed to meet the prespecified non-inferiority criterion (UL95%CI <6%).

3.3. Group difference in SAEs

A key secondary objective involved the percentage of subjects experiencing SAEs from Day 1 to study completion, which did not differ between those administered MenACWY-CRM plus routine vaccinations (Groups 1 and 3; 6%) or routine vaccinations only (Groups 2 and 4, 6%; Table 1). The UL95%CI of the group difference was 1.5%, which met the prespecified criterion (<5%) for non-inferiority.

3.4. Incidence of solicited AEs

The majority of subjects in Groups 3 and 4 experienced ≥1 local or systemic reaction from 15 min to Day 7 after each vaccination (75–89% across groups). All vaccinations were generally well tolerated, with most local or systemic reactions being mild to moderate in severity (Table 2). Rates of solicited local reactions were similar with MenACWY-CRM plus routine vaccinations and routine vaccinations alone. Commonly reported local reactions were tenderness at the injection site, erythema and induration (Table 2). Rates of solicited systemic reactions were similar for MenACWY-CRM with routine vaccinations and routine vaccinations alone. Most systemic reactions occurred after the first vaccination and subsequently declined in both groups. The most commonly reported systemic reactions after any vaccination were irritability, sleepiness and persistent crying (Table 2). Similar rates of fever and treatment with antipyretics after any vaccination were reported in Groups 3 and 4.

3.5. Unsolicited AEs

Overall, 84% of subjects in each group reported ≥1 unsolicited AE during the entire study period (Table 3). The type and incidence of AEs were similar between subjects administered MenACWY-CRM plus routine vaccinations and routine vaccinations alone. The incidence of AEs was higher in the detailed safety arm than in the non-detailed safety arm due to differences in protocol-specified AE reporting. The most commonly reported AEs were upper respiratory tract infection, otitis media, pyrexia, bronchiolitis, and diarrhea (Table 3). SAEs were reported for 354 (6%) and 114 (6%) of subjects who received MenACWY-CRM with routine vaccinations and routine vaccinations alone, respectively. Seven subjects experienced SAEs considered possibly related to MenACWY-CRM, including 2 subjects with Kawasaki disease (12 and 25 days post last vaccination) and 5 with 1 event each of febrile convulsion (38 days post vaccination), epilepsy (77 days post last vaccination), cellulitis with groin abscess (83 days post last vaccination), pyrexia (same day), and acute disseminated encephalomyelitis (35 days post last vaccination). The relationship between (S) AEs and study vaccination was not evaluated in subjects who received routine vaccinations only. In both groups, a low incidence of SAEs (<1%) occurred within

Table 2
Summary of solicited local and systemic reactions experienced by infants from 15 min to 7 days after any vaccination.

Symptom	Dose	Type	Group 3, *n*/*N* (%)	Group 4, *n*/*N* (%)
Local				
Tenderness[a]	1	Any	602/1301 (46)	218/446 (49)
		Severe	40/1301 (3)	23/446 (5)
	2	Any	464/1255 (37)	177/418 (42)
		Severe	24/1255 (2)	11/418 (3)
	3	Any	329/1106 (30)	136/372 (37)
		Severe	15/1106 (1)	9/372 (2)
	4	Any	433/1098 (39)	175/353 (50)
		Severe	19/1098 (2)	9/353 (3)
	After any vaccination	Any	913/1348 (68)	336/461 (73)
		Severe	90/1348 (7)	44/461 (10)
Erythema[b]	1	Any	216/1297 (17)	93/445 (21)
		Severe	2/1297 (<1)	2/445 (<1)
	2	Any	236/1255 (19)	122/417 (29)
		Severe	1/1255 (<1)	0/417 (0)
	3	Any	240/1104 (22)	122/1417 (29)
		Severe	0/1104 (0)	0/1417 (0)
	4	Any	232/1095 (21)	106/349 (30)
		Severe	0/1095 (0)	0/349 (0)
	After any vaccination	Any	509/1346 (38)	236/460 (51)
		Severe	3/1346 (<1)	2/460 (<1)
Induration[b]	1	Any	108/1297 (8)	73/446 (16)
		Severe	0/1297 (0)	1/446 (<1)
	2	Any	116/1257 (9)	72/417 (17)
		Severe	0/1257 (0)	0/417 (0)
	3	Any	98/1107 (9)	70/370 (19)
		Severe	0/1107 (0)	0/370 (0)
	4	Any	114/1095 (10)	80/351 (23)
		Severe	0/1095 (0)	0/351 (0)
	After any vaccination	Any	281/1346 (21)	178/460 (39)
		Severe	0/1346 (0)	1/460 (<1)
Systemic				
Rash				
	1	Any	38/1296 (3)	12/446 (3)
		Urticarial	7/1296 (1)	2/446 (<1)
	2	Any	36/1253 (3)	15/416 (4)
		Urticarial	8/1253 (1)	4/416 (1)
	3	Any	31/1101 (3)	10/367 (3)
		Urticarial	10/1101 (1)	5/367 (1)
	4	Any	44/1093 (4)	16/353 (5)
		Urticarial	19/1093 (2)	6/353 (2)
	After any vaccination	Any	121/1346 (9)	44/460 (10)
		Urticarial	40/1346 (3)	14/460 (3)
Change in eating habits[c]	1	Any	301/1289 (23)	105/446 (24)
		Severe	12/1289 (1)	6/446 (1)
	2	Any	229/1245 (18)	71/414 (17)
		Severe	15/1245 (1)	4/414 (1)
	3	Any	188/1094 (17)	50/367 (14)
		Severe	8/1094 (1)	1/367 (<1)
	4	Any	201/1089 (18)	56/348 (16)
		Severe	13/1089 (1)	1/348 (<1)
	After any vaccination	Any	593/1343 (44)	187/461 (41)
		Severe	46/1343 (3)	12/461 (3)
Sleepiness[d]	1	Any	671/1297 (52)	231/447 (52)
		Severe	30/1297 (2)	7/447 (2)
	2	Any	479/1253 (38)	152/416 (37)
		Severe	16/1253 (1)	5/416 (1)
	3	Any	347/1104 (31)	107/367 (29)
		Severe	6/1104 (1)	1/367 (<1)
	4	Any	334/1096 (30)	103/353 (29)
		Severe	7/1096 (1)	0/353 (0)
	After any vaccination	Any	927/1348 (69)	306/460 (67)
		Severe	55/1348 (4)	12/460 (3)
Persistent crying[e]	1	Any	543/1299 (42)	177/446 (40)
		Severe	22/1299 (2)	8/446 (2)
	2	Any	395/1254 (31)	116/417 (28)
		Severe	21/1254 (2)	8/417 (2)
	3	Any	284/1103 (26)	73/368 (20)
		Severe	11/1103 (1)	3/368 (1)
	4	Any	306/1094 (28)	85/353 (24)
		Severe	16/1094 (1)	6/353 (2)

Table 2 (*Continued*)

Symptom	Dose	Type	Group 3, *n*/*N* (%)	Group 4, *n*/*N* (%)
	After any vaccination	Any	851/1346 (63)	273/460 (59)
		Severe	61/1346 (5)	20/460 (4)
Irritability[f]	1	Any	764/1300 (59)	263/446 (59)
		Severe	26/1300 (2)	8/446 (2)
	2	Any	633/1254 (50)	199/416 (48)
		Severe	21/1254 (2)	11/416 (3)
	3	Any	503/1104 (46)	151/369 (41)
		Severe	16/1104 (1)	5/369 (1)
	4	Any	544/1094 (50)	172/354 (49)
		Severe	24/1094 (2)	5/354 (1)
	After any vaccination	Any	1032/1346 (77)	358/460 (78)
		Severe	79/1346 (6)	27/460 (6)
Vomiting[g]	1	Any	136/1298 (10)	42/446 (9)
		Severe	4/1298 (<1)	0/446 (0)
	2	Any	95/1254 (8)	25/416 (6)
		Severe	1/1254 (<1)	0/416 (0)
	3	Any	70/1106 (6)	15/369 (4)
		Severe	3/1106 (<1)	0/369 (0)
	4	Any	51/1094 (5)	13/353 (4)
		Severe	2/1094 (<1)	0/353 (0)
	After any vaccination	Any	283/1346 (21)	78/460 (17)
		Severe	10/1346 (1)	0/460 (0)
Diarrhea[h]	1	Any	214/1299 (16)	47/446 (11)
		Severe	7/1299 (1)	1/446 (<1)
	2	Any	140/1255 (11)	34/416 (8)
		Severe	6/1255 (<1)	1/416 (<1)
	3	Any	90/1102 (8)	21/369 (6)
		Severe	7/1102 (1)	1/369 (<1)
	4	Any	135/1094 (12)	33/353 (9)
		Severe	10/1094 (1)	4/353 (1)
	After any vaccination	Any	414/1346 (31)	104/460 (23)
		Severe	28/1346 (2)	7/460 (2)
Other indicators of reactogenicity				
Fever[i]	1	Any	35/1297 (3)	8/446 (2)
		Severe	0/1297 (0)	1/446 (<1)
	2	Any	56/1251 (4)	25/416 (6)
		Severe	0/1251 (0)	1/416 (<1)
	3	Any	82/1101 (7)	21/368 (6)
		Severe	0/1101 (0)	0/368 (0)
	4	Any	100/1092 (9)	28/353 (8)
		Severe	4/1092 (<1)	1/353 (<1)
Analgesic and antipyretic medicines used	1	–	865/1302 (66)	269/448 (60)
	2	–	729/1254 (58)	229/416 (55)
	3	–	584/1103 (53)	181/370 (49)
	4	–	542/1095 (49)	176/354 (50)
	After any vaccination	–	1110/1347 (82)	368/460 (80)

n = number of subjects with local or systemic reactions.
[a] Severe if subject cried when injection limb was moved.
[b] Classified as >50 mm.
[c] Change in eating habits, severe = missed >2 feeds.
[d] Sleepiness, severe = sleeps most of the time, hard to arouse.
[e] Persistent crying, severe = ≥3 h.
[f] Irritability, severe = unable to console.
[g] Vomiting, severe = little/no intake for more prolonged time.
[h] Diarrhea, severe = ≥6 liquid stools, no solid consistency.
[i] Fever, ≥38 °C; severe fever, ≥38.9 °C (axillary route).

14 days of any study vaccination. The rate of AEs leading to study discontinuation was similar in both groups, with 44/5760 (1%) and 8/1968 (<1%) subjects withdrawn in the MenACWY-CRM plus routine vaccinations and routine vaccinations alone groups, respectively.

Among the 52 cases of AEs leading to premature withdrawal from the study, there were 5 cases of febrile convulsions (range, 9–178 days after study vaccination), 4 cases of epilepsy (range, 22–128 days after study vaccination) and 4 cases of convulsion (range, 41–192 days after study vaccination), 2 cases of atopic dermatitis, 2 cases of Kawasaki disease, 2 cases of hypotension, and 2 cases of diarrhea.

Some AEs resulting in withdrawal were congenital disorders such as hydrocephalus, vascular angiopathy, mitochondrial enzyme deficiency, congenital bile duct absence and IgA immunodeficiency. These were clearly pre-existing conditions that had not been diagnosed at the time of the study entry.

A total of 7 subjects (6 in Group 1; 1 in Group 3) died between 3 and 67 days following the last vaccination, for highly diverse causes, none of which were considered to be related to MenACWY-CRM. The primary cause of death was unknown for 1 subject (seizure-like activity and fever), 1 experienced sudden death due to pulmonary edema and pneumonitis, and the remaining deaths were attributed to a congenital cardiac condition, brain stem dysfunction, head

Table 3
Summary of AEs reported by ≥10% of subjects after any vaccination (as-treated safety population).

Adverse event	Incidence of adverse events, *n* (%)					
	Non-detailed safety arm[a]		Detailed safety arm[b]		Overall	
	Group 1[c] *n* = 4357	Group 2[d] *n* = 1481	Group 3[c] *n* = 1403	Group 4[d] *n* = 487	MenACWY – CRM + routine vaccines *n* = 5760	Routine vaccines only *n* = 1968
Any AE	3567(82)	1216(82)	1281(91)	443(91)	4848(84)	1659(84)
Upper respiratory tract infection	1568(36)	570(38)	791(56)	273(56)	2359(41)	843(43)
Otitis media	896(21)	317(21)	684(49)	236(48)	1580(27)	553(28)
Pyrexia	813(19)	240(16)	282(20)	94(19)	1095(19)	334(17)
Bronchiolitis	608(14)	221(15)	256(18)	85(17)	864(15)	306(16)
Diarrhea	681(16)	222(15)	178(13)	52(11)	859(15)	274(14)
Nasopharyngitis	719(17)	227(15)	32(2)	12(2)	751(13)	239(12)
Conjunctivitis	462(11)	150(10)	270(19)	84(17)	732(13)	234(12)
Dermatitis diaper	416(10)	134(9)	212(15)	67(14)	628(11)	201(10)
Pharyngitis	447(10)	150(10)	163(12)	58(12)	610(11)	208(11)
Viral infection	327(8)	102(7)	265(19)	73(15)	592(10)	175(9)
Gastroenteritis	379(9)	134(9)	153(11)	48(10)	532(9)	182(9)
Cough	333(8)	115(8)	171(12)	56(11)	504(9)	171(9)
Otitis media acute	253(6)	85(6)	160(11)	72(15)	413(7)	157(8)
Eczema	242(6)	91(6)	157(11)	54(11)	399(7)	145(7)
Teething	121(3)	43(3)	173(12)	63(13)	294(5)	106(5)

AE, adverse event; SAE, serious adverse event.
[a] SAEs and medically attended AEs throughout the study for the non-detailed safety arm.
[b] All AEs for 7 days post-vaccination and SAEs and medically attended AEs throughout the study in the detailed safety arm.
[c] MenACWY-CRM + routine vaccinations.
[d] Routine vaccinations only.

injury due to a fall, septic shock or acute bronchopneumonia. One additional death due to nosocomial pneumonia occurred in an infant randomized to routine vaccines alone. In this case, the subject had a late-identified congenital cardiac anomaly and death occurred after the subject was withdrawn from the study, 75 days after final vaccination.

4. Discussion

Infants and children receive multiple routine childhood vaccinations, protecting them against a wide variety of pathogens, many of which are recommended for simultaneous administration [10]. The introduction of new vaccines targeting diseases early in life, such as meningococcal vaccines, requires concomitant use studies in infants. Previous studies have demonstrated that MenACWY-CRM was well tolerated and highly immunogenic when administered concomitantly with routine US vaccines as either a 4-dose series administered from 2 months of age or a 2-dose series administered from 7 to 9 months of age [6,7]. This current study provides additional data that MenACWY-CRM is well-tolerated and does not impact the safety profile of routine infant vaccines, when administered as a 4-dose vaccination series.

Although the planned primary analysis of group difference in the percentages of subjects reporting severe systemic reactions during the first 7 days after vaccination was not met, overall reported rates of severe systemic reactions were similar in the MenACWY-CRM plus routine vaccination and routine vaccinations only groups. Retrospectively, significant center differences and a group-by-center interaction were identified that were not taken into account in the prespecified primary analysis. An analysis adjusting for these factors showed the groups to be very similar with a group difference of −0.1% (95% CI −4.9%, 4.7%). The exact cause of center and center by group differences is unknown, but may be due, in part, to reporting bias. The strong center differences may also be partially explained by differences in sample size per center and these center differences may largely be due to random variation. The fact that differences tend to be larger in centers with smaller sample sizes reflects the well-known phenomenon that statistics computed from larger samples provide a better representation of the population parameter. However, even centers with the greatest sample sizes (35–77 subjects) exhibited large differences, both positive and negative between the two vaccine groups (range −11% to +13%). There appeared to be no single systemic reaction that accounted for the apparent difference between the groups in frequency of any severe systemic reaction. Overall, the profile of systemic reactions as well as the rates and characteristics of unsolicited AEs and SAEs during the course of the study confirm that MenACWY-CRM is safe and well tolerated when administered concomitantly with routine infant vaccinations.

In conclusion, the 4-dose infant/toddler series of MenACWY-CRM administered in conjunction with routine vaccines was safe and well tolerated. The rates of solicited local and systemic reactions were consistent with those previously reported for this dosing schedule [7]. No new safety concerns with MenACWY-CRM were identified. Taken together with immunogenicity and safety data from previous studies [6,7,11–13], these findings further support the use of MenACWY-CRM vaccination to protect infants, thereby reducing the burden of IMD.

Conflict of interest statement

Peter E. Silas has research relationships with numerous pharmaceutical companies including Novartis, Merck, Sanofi, and GSK. Allen Izu, Tatjana Odrljin, Igor Smolenov, Matthew Hohenboken and Peter Dull are employed by Novartis Vaccines and Diagnostics. Arturo Abdelnour, Marta Raquel Valdés Lamas, Nan-Chang Chiu, Cheng-Hsun Chiu, Carlos Fernándo Grazioso Aragón, Tirza de León Castrejón and Teobaldo Herrera Acuña declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2013.12.034.

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