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Immunogenicity and safety of a quadrivalent meningococcal polysaccharide CRM conjugate vaccine in infants and toddlers☆

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SUMMARY

Objectives: This phase III study assessed the safety and immunogenicity of MenACWY-CRM, a quadrivalent meningococcal conjugate vaccine, administered with routine vaccines starting at 2 months of age.

Methods: Healthy infants received MenACWY-CRM in a two- or three-dose primary infant series plus a single toddler dose. In addition, a two-dose toddler catch-up series was evaluated. Immune responses to MenACWY-CRM were assessed for serum bactericidal activity with human complement (hSBA). Reactogenicity and safety results were collected systematically.

Results: After a full infant/toddler series or two-dose toddler catch-up series, MenACWY-CRM elicited immune responses against the four serogroups in 94–100% of subjects. Noninferiority of the two- versus three-dose MenACWY-CRM infant dosing regimen was established for geometric mean titers for all serogroups. Following the three-dose infant primary series, 89–98% of subjects achieved an hSBA $\geq$8 across all serogroups. Immune responses to concomitant routine vaccines given with MenACWY-CRM were noninferior to responses to routine vaccines alone, except for pertactin after the two-dose infant series. Noninferiority criteria were met for all concomitant antigens after the three-dose infant series.

Conclusions: MenACWY-CRM vaccination regimens in infants and toddlers were immunogenic and well tolerated. No clinically meaningful effects of concomitant administration with routine infant and toddler vaccines were observed.

1. Introduction

Neisseria meningitidis is a leading cause of bacterial meningitis and sepsis that can result in permanent disability or death within hours in otherwise healthy individuals.[1,2] Meningococcal disease occurs globally and is characterized by an epidemiology with fluctuations in the incidence and occurrence of outbreaks and epidemics.[3,4] Six immunologically distinct serogroups (A, B, C, W-135, X, and Y) are associated with significant pathogenic potential for invasive disease.[5] The varied epidemiology of meningococcal disease, its propensity to cause outbreaks, the severity of disease and associated high case fatality rate, and its associated societal impact constitute a uniquely challenging global health concern.

MenACWY-CRM (Menveo®; Novartis Vaccines and Diagnostics) is a polysaccharide–CRM_{197} conjugate vaccine directed against serogroups A, C, W-135, and Y.[6] In early phase studies, MenACWY-CRM was well tolerated and highly immunogenic in infants, a group at high risk for meningococcal disease.[7,8] Results from the US study groups of a large phase III MenACWY-CRM infant study illustrated robust immunogenicity and good tolerability.[9] This report describes results from the Latin American study groups of the same study, in which infants received MenACWY-CRM from 2 months of age. Specific objectives were to assess the safety and immunogenicity of three- and four-dose

☆ Some of the results reported in this manuscript were presented as a poster entitled "Immunogenicity and safety of MenACWY-CRM, a quadrivalent meningococcal conjugate vaccine, in infants" at the 31st Annual European Society for Paediatric Infectious Diseases Meeting in Milan, Italy, May 28–June 1, 2013.

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Table 1
Vaccinations and serum samples, per group, per time point

Cohort	Group	Procedure	Age (months)									
			2	4	6	7	12	13	15	16	17	18
Immunogenicity	LA1A	MenACWY-CRM	X		X		X					
		Routine vaccines	X	X	X		X					
		Serum sample	X			X	X	X				
	LA1B	MenACWY-CRM	X		X			X				
		Routine vaccines	X	X	X		X					
		Serum sample	X			X	X	X				
	LA2	MenACWY-CRM					X		X			
		Routine vaccines	X	X	X		X					
		Serum sample	X			X	X	X				
	LA3A	MenACWY-CRM	X	X	X					X		
		Routine vaccines	X	X	X					X		
		Serum sample	X			X				X	X	
	LA3B	MenACWY-CRM	X	X	X						X	
		Routine vaccines	X	X	X					X		
		Serum sample	X			X				X	X	
	LA4	MenACWY-CRM					X		X			
		Routine vaccines	X	X	X		X		X[a]			
		Serum sample	X			X	X			X		
Safety only	LA5	MenACWY-CRM	X	X	X		X					
		Routine vaccines	X	X	X		X					
	LA6A	MenACWY-CRM					X		X			
		Routine vaccines	X	X	X		X					
	LA6B	MenACWY-CRM						X	X			
		Routine vaccines	X	X	X		X					
	LA6C	MenACWY-CRM										X
		Routine vaccines	X	X	X		X					

DTaP, diphtheria, tetanus, and acellular pertussis; Hib, *Haemophilus influenzae* type b.
[a] MenACWY-CRM concomitant with DTaP and Hib.

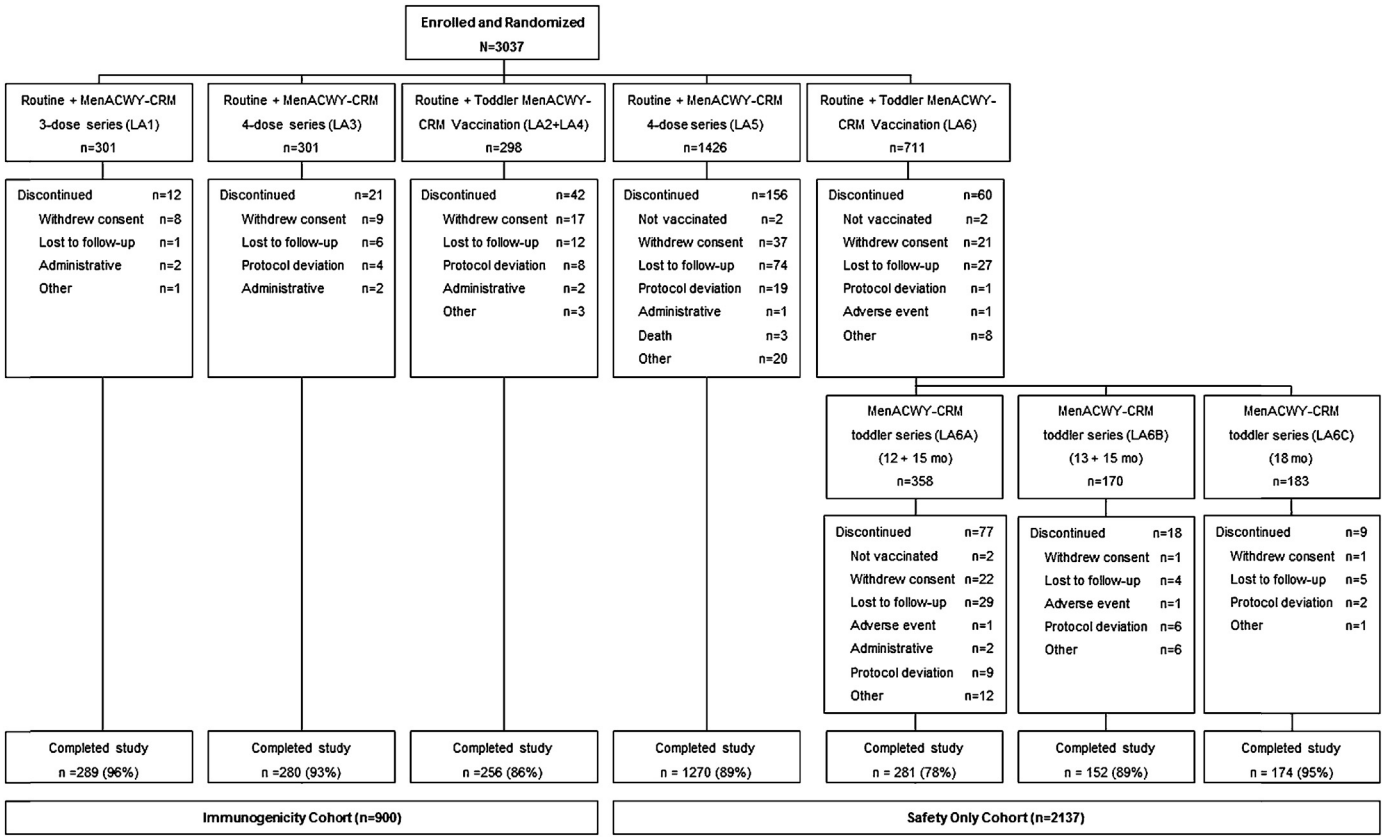

Figure 1. Subject disposition and vaccination schedule. The MenACWY-CRM three-dose series was given at 2, 6, and 12 or 13 months (LA1); the MenACWY-CRM four-dose series was given at 2, 4, 6, and 16 or 17 months (LA3) or at 2, 4, 6, and 12 months (LA5); routine vaccinations only were given before 12 months of age for LA6. Toddler series MenACWY-CRM doses were given at (12 or 13) + 15 months or at 18 months as indicated in the subgroups of LA6. All groups received routine infant vaccinations (DTaP, IPV, Hib, HBV, rotavirus, and PCV7) at months 2, 4, and 6. LA1, LA2, LA4, LA5, and LA6 received concomitant vaccines (MMRV, PCV7, and HAV) at month 12. LA3 received concomitant vaccines (DTaP and Hib) at month 16. (DTaP, diphtheria, tetanus, and acellular pertussis vaccine; HAV, hepatitis A vaccine; HBV, hepatitis B vaccine; Hib, *Haemophilus influenzae* type b vaccine; IPV, inactivated poliovirus vaccine; MMRV, measles, mumps, rubella, varicella vaccine; PCV7, pneumococcal conjugate vaccine; LA, Latin America.).

Table 2
Demographics and other baseline characteristics—all subjects

Group[a]	LA1	LA2	LA3	LA4	LA5	LA6
	Three-dose MenACWY-CRM series (2, 6, and 12 or 13 months) $n=301$	Two MenACWY-CRM toddler doses (12 and 15 months) $n=148$	Four-dose MenACWY-CRM series (2, 4, 6, and 16 or 17 months) $n=301$	Two MenACWY-CRM toddler doses (12 and 15 months) $n=150$	Four-dose MenACWY-CRM series (2, 4, 6, and 12 months) $n=1426$	One or two MenACWY-CRM toddler doses (12 and 15, 13 and 15, or 18 months) $n=711$
Age (days)	68.3 ± 8.3	67.8 ± 8.3	67.7 ± 8.3	67.5 ± 8.0	65.0 ± 9.4	65.1 ± 9.1
Sex						
Male	140 (47%)	76 (51%)	154 (51%)	69 (46%)	744 (52%)	353 (50%)
Female	161 (53%)	72 (49%)	147 (49%)	81 (54%)	682 (48%)	358 (50%)
Weight (kg)	5.3 ± 0.7	5.4 ± 0.7	5.3 ± 0.7	5.3 ± 0.7	5.6 ± 0.7	5.6 ± 0.7
Height (cm)	57.2 ± 3.0	57.4 ± 3.2	57.3 ± 2.8	57.2 ± 2.9	58.7 ± 2.7	58.5 ± 2.7
Met entry criteria						
Yes	297 (99%)	146 (99%)	296 (98%)	148 (99%)	1412 (99%)	703 (99%)
No	4 (1%)	2 (1%)	5 (2%)	2 (1%)	14 (<1%)	8 (1%)

[a] All groups received routine infant vaccinations.

MenACWY-CRM infant/toddler regimens, one- and two-dose toddler regimens, and concomitant administration of MenACWY-CRM with routine infant and toddler vaccines.

2. Methods

2.1. Study design

This phase III, open label, randomized study of healthy infants was conducted in Argentina, Colombia, and the USA (ClinicalTrials.gov identifier NCT00474526). The primary immunogenicity objectives focused on the US study groups and are reported separately.[9] Predefined secondary objectives evaluated in the Latin American study groups are presented here. The protocol and amendments were designed in accordance with the Declaration of Helsinki and approved by the local ethics committees and national regulatory authorities, as appropriate. Informed consent was obtained from a parent or legal guardian. An independent, external data monitoring committee monitored safety during the study.

Healthy infants were randomized 1:2 to receive routine infant vaccines alone or concomitantly with MenACWY-CRM, in various dosing schedules (Table 1). All immunogenicity groups (LA1–LA4) received routine vaccines at 2, 4, and 6 months of age. Subjects in LA1 received a three-dose infant/toddler MenACWY-CRM schedule, consisting of a two-dose infant series (2 and 6 months) and a toddler dose at 12 (LA1A) or 13 months (LA1B). LA3 subjects received a four-dose infant/toddler MenACWY-CRM schedule: a three-dose infant series (2, 4, and 6 months) and a toddler dose at 16 (LA3A) or 17 months (LA3B). Receipt of the toddler dose was delayed in LA1B and LA3B so that the immune response to concomitant vaccines could be compared between the group that received the toddler MenACWY-CRM dose plus routine vaccines to the group that had not yet received the toddler MenACWY-CRM dose but had received routine vaccines (i.e., LA1A vs. LA1B, and LA3A vs. LA3B). LA2 and LA4 received only routine vaccines in the first year of life, followed by a toddler catch-up series of MenACWY-CRM at 12 and 15 months (Table 1).

Safety-only groups (LA5 and LA6) received MenACWY-CRM plus routine vaccines (LA5: MenACWY-CRM plus routine vaccines at 2, 4, 6, and 12 months) or routine infant vaccines only followed by routine toddler vaccination and MenACWY-CRM at 12 and 15 months (LA6A). The study design was amended by request of the regulatory authorities; the administration of MenACWY-CRM was delayed to 13 months in a subgroup (LA6B) so that reactogenicity and safety could be compared between subjects who received a first dose of MenACWY-CRM at 12 months of age (LA6A) with subjects who had not yet received MenACWY-CRM (LA6B). A later amendment created another subgroup with delayed administration of MenACWY-CRM until 18 months (LA6C) so that reactogenicity and safety could be compared between subjects who had received the two-dose toddler series (LA6A) with those who were as yet naive for meningococcal vaccine (LA6C) (Table 1).

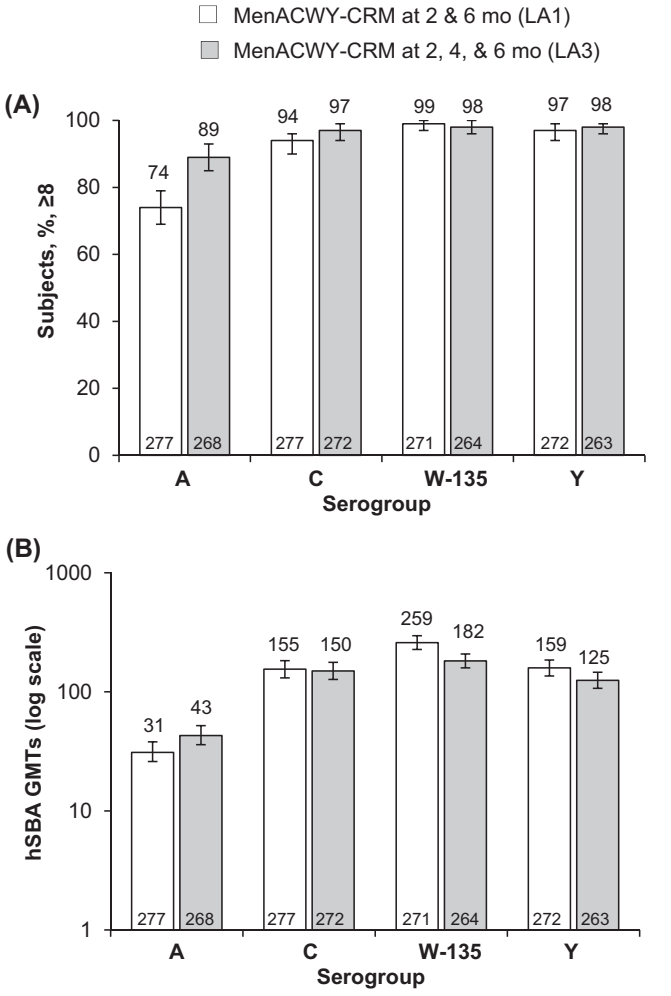

Figure 2. Immunogenicity results for MenACWY-CRM at 7 months. (A) Percentage of subjects with hSBA titers ≥8; values are the percentage of subjects and error bars represent 95% CI. (B) GMTs after MenACWY-CRM; values are hSBA GMTs with 95% CI error bars.

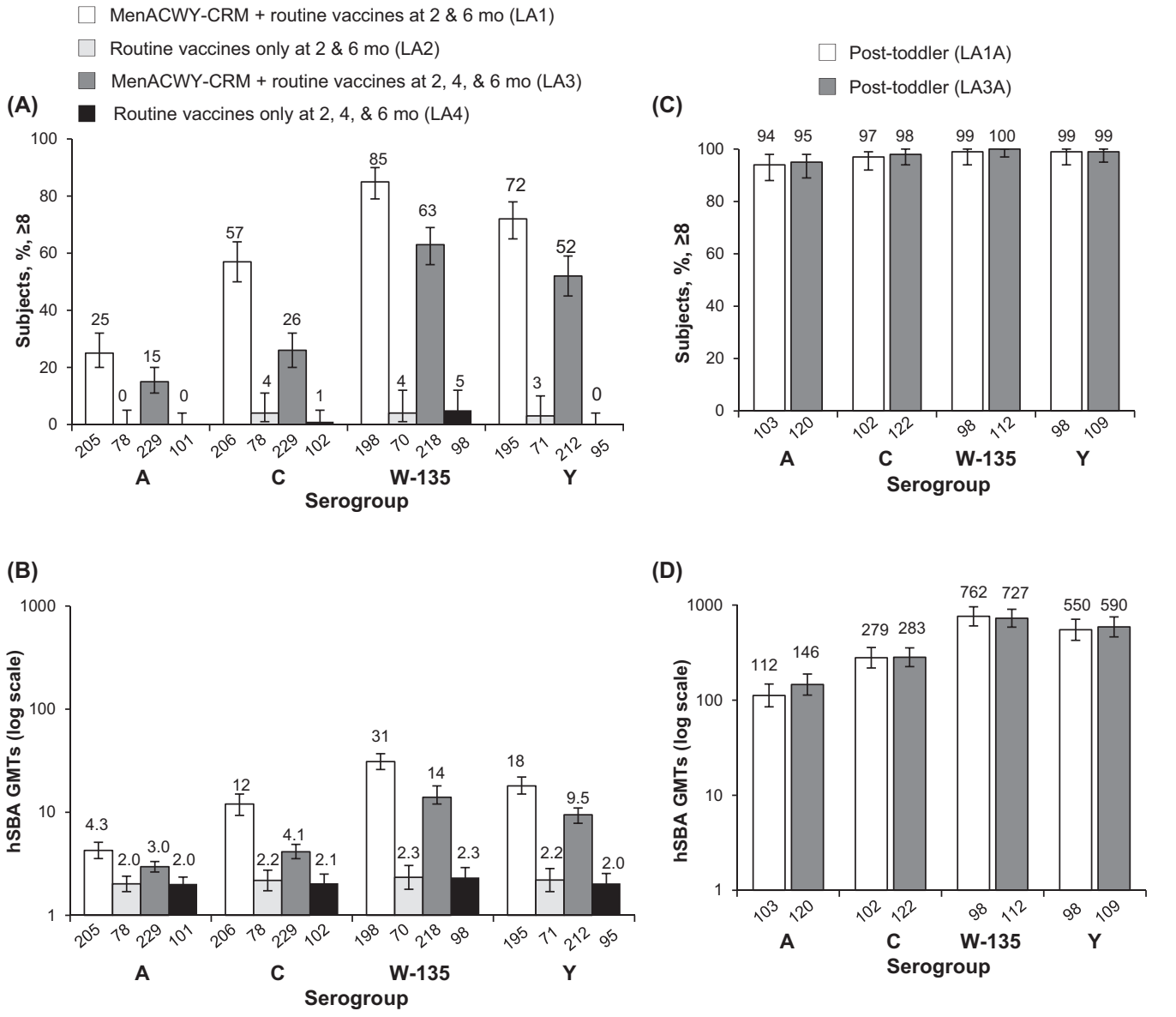

Figure 3. Antibody persistence before the final dose and immune response at 1 month after the final dose of the three- and four-dose MenACWY-CRM infant/toddler series. (A) Percentage of subjects with hSBA titers ≥8 before the final dose. (B) hSBA GMTs before the final dose. (C) Percentage of subjects with hSBA titers ≥8 at 1 month after the final dose. (D) hSBA GMTs at 1 month after the final dose. Error bars represent 95% CI. For the infant series, subjects in the LA1 group received MenACWY-CRM at 2 and 6 months of age, while subjects in the LA3 group received MenACWY-CRM at 2, 4, and 6 months of age. Subjects in the LA2 and LA4 groups did not receive the infant series of MenACWY-CRM vaccination. Antibody persistence was assessed in subjects at 12 (groups LA1 and LA2) or 16 (groups LA3 and LA4) months of age, whereas responses at 1 month after the final dose were assessed in subjects at 13 (LA1A) or 17 (LA3A) months of age.

An interactive voice response system was used to ensure blinding until subject randomization. Subjects were randomized and stratified by study site using two computer-generated lists (for immunogenicity and safety groups) provided by the sponsor. The immunogenicity group was enrolled at pre-selected sites in Argentina.

2.2. Study subjects

Healthy 55–89-day-old infants with birth weight ≥2.5 kg and gestational age ≥37 weeks were eligible. Infants with prior exposure to disease caused by or vaccination against *N. meningitidis*, *Corynebacterium diphtheriae*, *Clostridium tetani*, *Bordetella pertussis*, poliovirus, *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae*, or hepatitis B virus (HBV) were excluded, with the exception that a birth vaccination against HBV was permitted. Infants with contraindications for vaccination, including allergy to vaccine components, or significant infection within 7 days or fever within 3 days of screening, were excluded.

2.3. Vaccines

MenACWY-CRM was prepared by extemporaneous mixing of the lyophilized MenA component with the liquid MenCWY component immediately before intramuscular (IM) injection into the right thigh. Each 0.5-ml dose contained 10 μg of MenA oligosaccharide and 5 μg each of oligosaccharides from MenC, MenW-135, and MenY conjugated to CRM_{197}.[10] Concomitant vaccines were administered either IM or subcutaneously into the left thigh, as appropriate. In subjects receiving only routine vaccines, Hib vaccine was administered IM into the right thigh as the control for local reactogenicity at 2, 4, 6, and 16 months, whereas pneumococcal conjugate vaccine (PCV7) served as the control for the 12-month reactogenicity assessments.

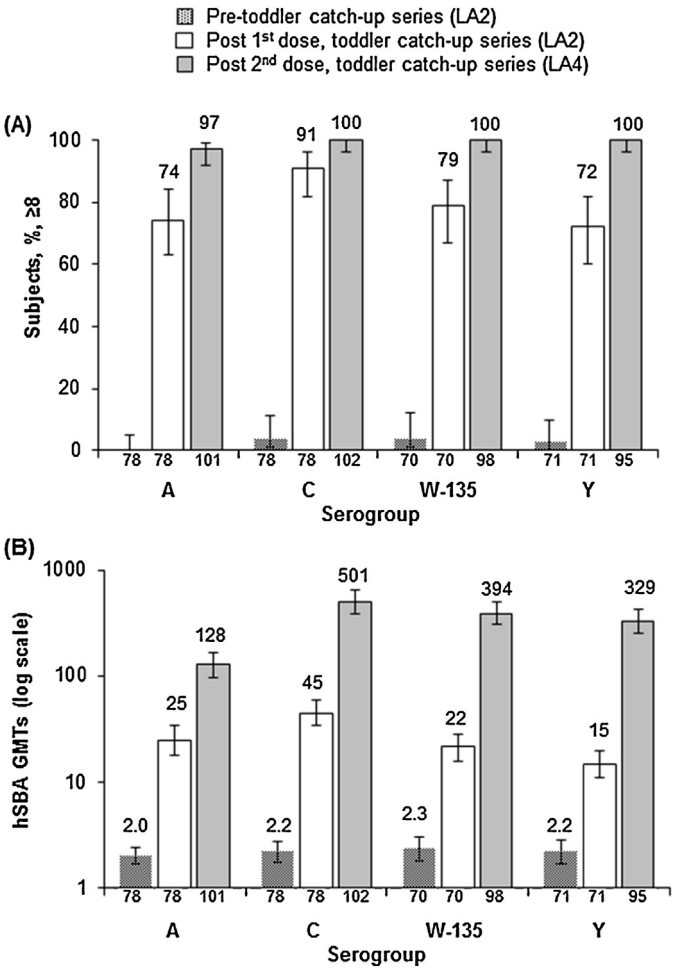

Figure 4. Seroresponse to the toddler catch-up series after one and two doses. Subjects in the LA2 and LA4 groups received the first MenACWY-CRM vaccination at 12 months and the second dose at 15 months. The post-first-dose blood draw was taken at month 13 (LA2), and the post-second-dose blood draw was taken at month 16 (LA4). The pre-toddler vaccine serum samples were collected from both groups at month 12 (before vaccination), but only the results from LA2, the most variable results, are shown.

All subjects received routine vaccines as per the schedule in Figure 1. Concomitant vaccines included combined diphtheria–tetanus–acellular pertussis (DTaP)–hepatitis B virus (HBV)–inactivated polio vaccine (IPV) (Pediarix®; GlaxoSmithKline); DTaP booster (Infanrix®; GlaxoSmithKline); Hib–tetanus toxoid (TT) (ActHIB®; Sanofi Pasteur); PCV7 (Prevnar®; Pfizer, formally Wyeth); rotavirus vaccine (RotaTeq®; Merck & Co.); measles, mumps, rubella and varicella vaccine (MMRV) (ProQuad; Merck & Co.) or measles, mumps and rubella vaccine (M-M-R® II; Merck & Co.); varicella vaccine (Varivax®; Merck & Co.); and hepatitis A vaccine (HAV) (Havrix®; GlaxoSmithKline).

2.4. Immunogenicity assessments

Immunogenicity was assessed by serum bactericidal activity using human complement (hSBA) with the percentage of subjects with titers ≥8 and geometric mean titers (GMTs) against each serogroup at relevant time points, as described previously.[7] Diphtheria, tetanus, Hib, pneumococcus, and pertussis antigen (pertussis toxin (PT), filamentous hemagglutinin (FHA), and pertactin) antibody concentrations were evaluated using ELISA, and seroresponse to poliovirus was assessed by viral neutralization assay.

2.5. Safety assessments

Local and systemic reactions and all adverse events were solicited for seven days post-vaccination after all vaccination visits. Adverse events (AE) that required a physician's visit, resulted in premature withdrawal, or were considered serious (SAE), were collected during the entire study period. Investigators assigned AE severity and assessed the relationship to vaccination.

2.6. Statistical analyses

Sufficiency of the immune response was prespecified as met if the lower limit of the two-sided 95% confidence interval (LL 95% CI) around the percentage of subjects with hSBA titers ≥8 was ≥80% for serogroup A and ≥85% for serogroups C, W-135, and Y. The noninferiority criterion for the two- versus three-dose infant MenACWY-CRM series required that the LL 95% CI for the ratio of GMTs (LA1/LA3) was >0.5.

Noninferiority of concomitant vaccine response was prespecified as the LL 95% CI for the differences in seroresponse rates >−10%, except for poliovirus for which the threshold was >−5%. For pertussis antigens, noninferiority was defined as a geometric mean concentration (GMC) ratio ($GMC_{MenACWY-CRM+routine}$/$GMC_{routine\ vaccines\ alone}$) >0.67, with pertussis seroresponse as an additional secondary noninferiority endpoint. Noninferiority of the pneumococcal antigens was prespecified as the LL 95% CI for the ratio of the GMCs for all pneumococcal serotypes >0.50.

Sample sizes were based on the response in this age group in previous studies.[7,11] The immunogenicity analysis was based on the per-protocol (PP) population: all subjects without major protocol deviations who received all appropriately timed vaccine doses and provided appropriately timed evaluable serum samples. The safety population included all enrolled subjects who received at least one vaccine dose and provided any safety data.

3. Results

All 900 subjects enrolled in the immunogenicity groups (LA1–LA4) were enrolled in Argentina; the 2137 subjects enrolled in the safety-only groups (LA5 and LA6) were enrolled in Argentina and Colombia (Figure 1). Enrollment began April 19, 2007, and follow-up was completed November 13, 2009. For the immunogenicity analysis, the PP population included 825 subjects after the infant series and 629 subjects after toddler vaccination. Demographic characteristics are shown in Table 2.

3.1. Immunogenicity of the infant/toddler MenACWY-CRM series

Measured at 1 month post-infant series, immune responses to the two-dose (LA1) and three-dose series (LA3) were similar for serogroups C, W-135, and Y: 94–99% and 97–98% of subjects had hSBA titers ≥8 after the two-dose and three-dose series, respectively (Figure 2). Responses for serogroup A were higher in subjects who received the three-dose (89%) than the two-dose infant series (74%) (Figure 2). The percentages of subjects with hSBA titers ≥8 after the two-dose infant series were noninferior to the three-dose series (LL 95% CI >−10%) for all serogroups except A (Figure 2A). Using the GMT endpoint, the two-dose infant series was noninferior for all serogroups (ratios of GMTs >0.5) (Figure 2B).

Antibody persistence prior to the toddler dose is shown in Figure 3. At 12 months of age, 25–85% of subjects who received the two-dose infant series had hSBA ≥8; at 16 months of age, 15–63% of subjects who received the three-dose infant series had hSBA ≥8 (Figure 3A). GMTs were 4.3–31.0 for the two-dose and 3.0–14.0 for the three-dose infant series (Figure 3B). The majority of subjects

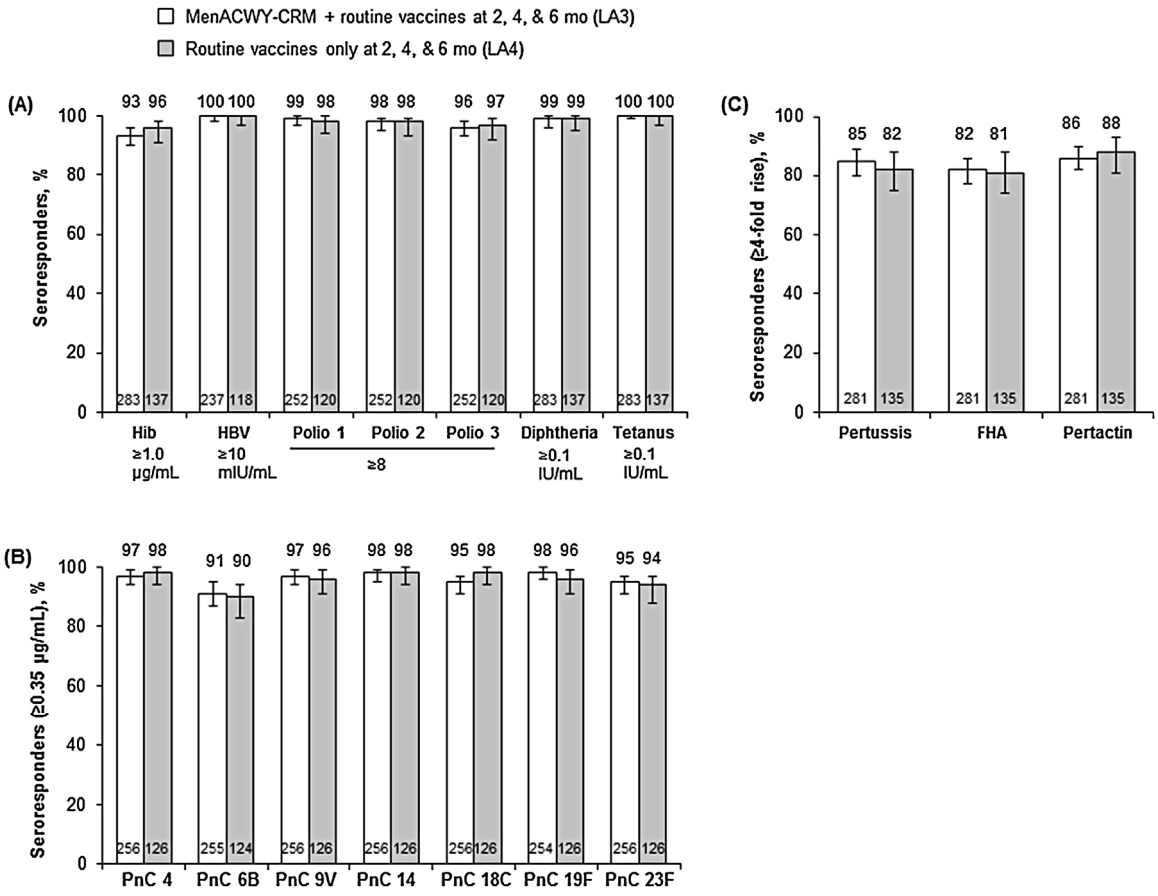

Figure 5. Seroresponses to routine vaccines (DTaP, IPV, HBV, pneumococcal conjugate, Hib) given with (LA3) and without MenACWY-CRM (LA4) were compared at 7 months. Blood was drawn at month 7. Values are the percentage of subjects with 95% CI error bars. (FHA, filamentous hemagglutinin; HBV, hepatitis B virus; Hib, *Haemophilus influenzae* type b; PnC, pneumococcal conjugate vaccine.)

who received only routine vaccines did not have protective antibodies.

One month after the full three-dose and four-dose infant/toddler series (at 13 and 17 months, respectively), the percentages of subjects with hSBA titers ≥8 were 94–99% for the three-dose series (LA1A) and 95–100% for the four-dose series (LA3A) (Figure 3C). Both schedules achieved the pre-defined immunogenicity criteria for sufficiency; the LL 95% CI was ≥80% for serogroup A and ≥85% for serogroups C, W-135, and Y. GMTs were similar for both schedules (Figure 3D).

3.2. Immunogenicity of the two-dose toddler catch-up series

Two groups (LA2 and LA4) received only routine vaccines during their first year, followed by MenACWY-CRM toddler 'catch-up' vaccinations at 12 and 15 months. Serum samples were collected from LA2 at 1 month after the first dose (at 13 months of age) and from LA4 at 1 month after the second dose (at 16 months of age). One month after the first toddler vaccination, 72–91% of subjects achieved hSBA titers ≥8 and GMTs were 15–45. One month after the second toddler vaccination, 97–100% of subjects achieved hSBA titers ≥8 and GMTs were 128–501 (Figure 4).

3.3. Response to routine vaccines

Seroresponses to routine vaccines (DTaP, IPV, HBV, pneumococcal conjugate, Hib) given with (LA3) and without MenACWY-CRM (LA4) were compared at 7 months (Figure 5). The difference in seroresponse rates ($P_{LA3} - P_{LA4}$) for poliovirus antigens ranged from −1% to 0 with the LL 95% CI >−5% for each, achieving noninferiority (Figure 5A). Noninferiority was also achieved for each pneumococcal antigen, with the LL 95% CI around the difference in seroresponse rates ($P_{LA3} - P_{LA4}$) >−10% for each (Figure 5B). The LL 95% CI for the difference in seroresponse rates ($P_{LA3} - P_{LA4}$) for diphtheria, tetanus, hepatitis B, Hib, and pertussis antigens PT and FHA was >−10%, achieving noninferiority (Figure 5A and C).

The ratio of GMCs (GMC_{LA3}/GMC_{LA4}) for pertussis antigens ranged from 0.80 to 0.93, with the LL 95% CI >0.67 for PT and FHA (noninferiority achieved) and 0.66 for pertactin (noninferiority not achieved). The ratio of GMCs or GMTs (poliovirus only) for the other antigens ranged from 0.75 to 1.07 (LL 95% CI >0.50, for each).

The immune response (GMCs) to PCV7 administered concomitantly with MenACWY-CRM at 12 months of age (LA1A) was noninferior to responses in subjects who received PCV7 alone (LA1B) (LL 95% CI >0.50, for each).

Immune responses to DTaP and Hib given with a fourth dose of MenACWY-CRM or alone at 16 months were examined at 17 months (Figure 6). The LL 95% CI around the difference in percentages of seroresponders ($P_{LA3A} - P_{LA3B}$) against diphtheria, tetanus, Hib, PT, and pertactin (≥4-fold rise) were >−10%, achieving noninferiority. Noninferiority was not achieved for FHA, for which the LL 95% CI was −10.2%. The ratio of GMCs (GMC_{LA3A}/GMC_{LA3B}) for Hib, diphtheria, and tetanus antigens ranged from 0.86 to 1.05 with the LL 95% CI >0.50 (noninferiority achieved) for each antigen. The ratio of GMCs for PT, FHA, and pertactin antigens ranged from 1.11 to 1.21 with LL 95% CI >0.67 for all pertussis antigens (noninferiority achieved).

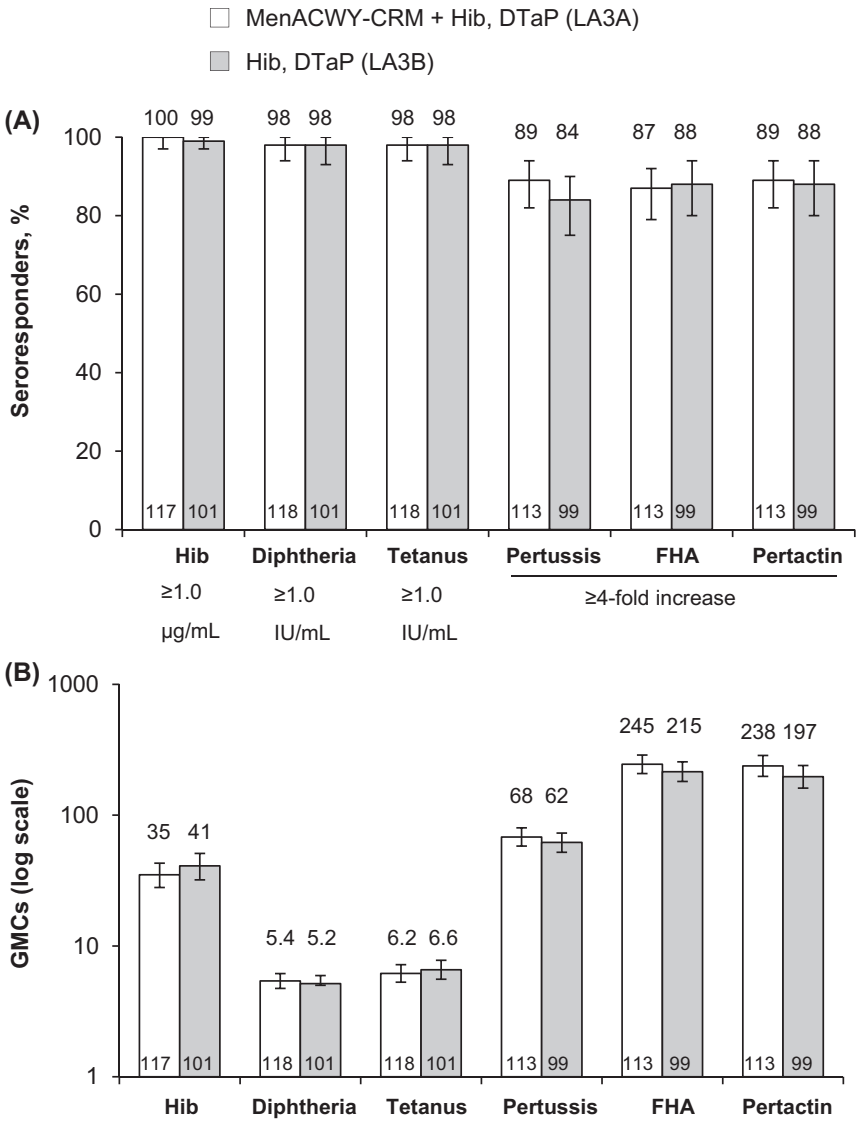

Figure 6. Seroresponse after the fourth dose of MenACWY-CRM at 16 months of age. Subjects in the LA3A group received Hib and DTaP vaccines concomitantly with a fourth dose of MenACWY-CRM at 16 months of age. Subjects in the LA3B group received the Hib and DTaP vaccines without a concomitant dose of MenACWY-CRM at 16 months of age. Serum samples were collected at 17 months. (A) Percentage of subjects with a seroresponse; values are the percentage of subjects with 95% CI error bars. (B) GMTs; values are the geometric mean concentrations/titers with 95% CI error bars. (FHA, filamentous hemagglutinin; Hib, *Haemophilus influenzae* type b vaccine.)

3.4. Safety

The incidence of local and systemic reactions within seven days after the first (at 2 months) vaccination was similar in groups that received routine vaccines with (LA1, LA3, LA5) or without MenACWY-CRM (LA2, LA4, LA6) (Table 3). The most common systemic reactions were sleepiness (31–54%) and irritability (33–42%), with ≤5% of subjects reporting severe reactions. Fever of ≥38 °C was reported for 3–15% of subjects. Analgesic and/or antipyretic medications were used in 51–72% of subjects.

AEs were summarized for the infant series, between the infant series and toddler dose, and from 12 to 18 months of age (Table 4). For the infant series, AE rates were similar in groups that received the three-dose infant MenACWY-CRM series plus routine vaccines (LA3 + LA5, 59%) and those that received routine vaccines only (LA2 + LA4 + LA6, 55%). The lower AE rate reported after the two-dose infant MenACWY-CRM series (LA1, 34%) is likely due to the lower number of infant series visits where all adverse events were collected for LA1 (two visits) than LA3 and LA5 (three visits). AE rates were similar across groups between the infant series and toddler dose (20–30%), and from 12 to 18 months of age (25–27%). SAEs occurred in ≤4% of subjects across all groups. Three deaths occurred, none of which were considered related to MenACWY-CRM vaccination: one due to a lung infection, one due to a car accident trauma, and one due to sepsis with a history of tetralogy of Fallot.

4. Discussion

This study demonstrates that at the completion of a three-dose (2, 6, and 12 months) or four-dose (2, 4, 6, and 16 months) MenACWY-CRM infant/toddler regimen, a robust immune response is produced against all four serogroups. An improved early response at 7 months of age against serogroup A was demonstrated by the additional dose in the first year of life. Based on the percentage of subjects with an hSBA titer ≥8, noninferiority of the two- versus three-dose infant series was established for serogroups C, W, and Y, but not for serogroup A. However, based on GMTs, noninferiority was established for the two-dose infant

Table 3
Local and systemic reactions during the 7-day period after the first infant series vaccination at 2 months

Vaccinations received at 2 months		LA1 Routine[a] + MenACWY-CRM $n=301$	LA2 Routine $n=148$	LA3 Routine + MenACWY-CRM $n=301$	LA4 Routine $n=150$	LA5 Routine + MenACWY-CRM $n=1424$	LA6 Routine $n=709$
Local[b]							
Tenderness	Any	154 (51%)	96 (65%)	170 (56%)	95 (63%)	916/1423 (64%)	501 (71%)
	Cried when injured limb moved	30 (10%)	19 (13%)	22 (7%)	20 (13%)	92/1423 (6%)	74 (10%)
Erythema (mm)	Any	86 (29%)	62 (42%)	86 (29%)	65 (43%)	542/1423 (38%)	273 (39%)
	>50 mm	0	0	1 (<1%)	1 (1%)	1/1423 (<1%)	4 (1%)
Induration (mm)	Any	74 (25%)	56 (38%)	72 (24%)	53 (35%)	249/1423 (17%)	126 (18%)
	>50 mm	1 (<1%)	0	0	0	2/1423 (<1%)	0
Systemic							
Rash	Any	11 (4%)	6 (4%)	12 (4%)	4 (3%)	98/1423 (7%)	55 (8%)
	Urticarial	7 (2%)	2 (1%)	4 (1%)	1 (1%)	54/1423 (4%)	26 (4%)
Change in eating habits	Any	37 (12%)	30 (20%)	44 (15%)	16 (11%)	250/1423 (18%)	127 (18%)
	Severe	2 (1%)	0	0	1 (1%)	6/1423 (<1%)	4 (1%)
Sleepiness	Any	106 (35%)	53 (36%)	93 (31%)	52 (35%)	727/1423 (51%)	381 (54%)
	Severe	8 (3%)	2 (1%)	6 (2%)	4 (3%)	21/1423 (1%)	14 (2%)
Persistent crying	Any	95 (32%)	53 (36%)	87 (29%)	43 (29%)	479/1423 (34%)	258 (36%)
	Severe	5 (2%)	3 (2%)	11 (4%)	8 (5%)	29/1423 (2%)	21 (3%)
Irritability	Any	121 (40%)	62 (42%)	99 (33%)	59 (39%)	508/1423 (36%)	240 (34%)
	Severe	7 (2%)	2 (1%)	4 (1%)	2 (1%)	22/1423 (2%)	2 (<1%)
Vomiting	Any	25 (8%)	9 (6%)	29 (10%)	17 (11%)	215/1423 (15%)	100 (14%)
	Severe	0	0	1 (<1%)	1 (1%)	2/1423 (<1%)	1 (<1%)
Diarrhea	Any	42 (14%)	20 (14%)	44 (15%)	22 (15%)	222/1423 (16%)	96 (14%)
	Severe	1 (<1%)	0	1 (<1%)	0	2/1423 (<1%)	2 (<1%)
Fever (≥38 °C)	Yes	15 (5%)	12 (8%)	18 (6%)	5 (3%)	211/1422 (15%)	97/708 (14%)
Other							
Temperature (°C)	<38.0 °C	286 (95%)	136 (92%)	283 (94%)	145 (97%)	1211/1422 (85%)	611/708 (86%)
	≥40.0 °C	0	0	0	0	1/1422 (<1%)	0
Analgesic/antipyretic medications used	Yes	155 (51%)	75 (51%)	159 (53%)	80 (53%)	996 (70%)	510 (72%)

[a] Routine vaccinations given at 2 months were: tetanus, diphtheria, and acellular pertussis (DTaP), inactivated poliovirus vaccine (IPV), hepatitis B vaccine (as Pediarix®), *Haemophilus influenzae* type b vaccine (as ActHIB®), rotavirus vaccine (RotaTeq®), and pneumococcal conjugate vaccine (Prevnar®).
[b] Local reactions evaluated in the control group at the pneumococcal vaccine injection site.

series compared with the three-dose infant series for all serogroups.

Effects of MenACWY-CRM on immune responses to routine infant vaccinations were minimal. Noninferiority of the immune responses to routine vaccines administered concomitantly with the two-dose MenACWY-CRM infant series compared with responses to routine vaccines only was demonstrated for pneumococcal, Hib, HBV, IPV, diphtheria, tetanus, and all pertussis

Table 4
Overview of adverse events; number (%) of subjects with adverse events

Infant series	MenACWY-CRM Two-dose infant series (LA1) $n=301$	MenACWY-CRM Three-dose infant series (LA3 + LA5) $n=1725$	Routine only (LA2 + LA4 + LA6) $n=1007$
Any AEs	103 (34%)	1020 (59%)	557 (55%)
SAEs	6 (2%)	65 (4%)	41 (4%)
AEs leading to premature withdrawals	0	0	0
Deaths	0	0	0
Between infant series and toddler dose	MenACWY-CRM Three-dose infant/toddler series (LA1) $n=301$	MenACWY-CRM Four-dose infant/toddler series (LA3 + LA5) $n=1620$	MenACWY-CRM Toddler (LA2 + LA4 + LA6) $n=945$
Any AEs	90 (30%)	329 (20%)	219 (23%)
SAEs	9 (3%)	60 (4%)	35 (4%)
AEs leading to premature withdrawals	0	1 (<1%)	1 (<1%)
Deaths	0	1 (<1%)	0
12–18 months (subjects who completed the trial)		MenACWY-CRM Four-dose infant/toddler (LA5) $n=1270$	Routine only 18 months (LA6C) $n=174$
Any AEs		338 (27%)	44 (25%)
SAEs		35 (3%)	0
AEs leading to premature withdrawals		2 (<1%)	1 (<1%)
Deaths		2 (<1%)	0

AE, adverse event; SAE, serious adverse event.

antigen comparisons, with the exception of the seroresponse rate comparison for pertactin (data not shown). Noninferiority to all concomitant vaccine antigens was established after the three-dose MenACWY-CRM infant series, with the exception of the GMC ratio comparison of pertactin.

Antibody persistence after the MenACWY-CRM infant series was evident at 12 and 16 months. At 12 or 16 months of age, subjects who had received the two- or three-dose infant series, respectively, had higher antibody levels than control subjects, particularly for serogroups W-135 and Y. However, the noticeable drop in protective antibodies from 1 month post-infant series, especially for serogroups A and C, highlights the importance of a toddler dose to ensure adequate protection in this vulnerable group.

One month after the toddler dose of the full three- and four-dose infant/toddler MenACWY-CRM series (13 or 17 months, respectively), robust immune responses were evident to each of the four serogroups, with hSBA titers $\geq$8 in 94–100% of subjects.

Subjects who received routine vaccinations only in the first year, received two toddler catch-up doses of MenACWY-CRM at 12 and 15 months of age. Sufficiency of the immune response to MenACWY-CRM was demonstrated after the two-dose toddler regimen, with protective antibodies to each of the four serogroups in 97–100% of subjects. Although the three- and four-dose infant/toddler regimens induce protective antibodies at an earlier age, the current data show that the two-dose toddler regimen can be used to induce protective antibodies in toddlers who have not been vaccinated previously against meningococcal disease.

Responses to concomitant toddler vaccines (DTaP and Hib) given with MenACWY-CRM were noninferior, except for the percentage of subjects with seroresponses to FHA. GMCs for pneumococcal antibodies in response to a fourth dose of pneumococcal vaccine were noninferior to responses produced when administered concomitantly with MenACWY-CRM at 12 months. Taken together, we conclude that MenACWY-CRM may be administered concomitantly with routine infant and toddler vaccines without clinically relevant immunological interference.

Rates of reactogenicity and safety events for groups receiving MenACWY-CRM were similar to those who received routine vaccinations only. The most commonly reported local reaction was tenderness, and the most common systemic reactions were irritability and sleepiness. Most reactions were mild to moderate in severity. After each infant vaccination, the percentages of subjects with local reactions were slightly lower than after the previous vaccination. Systemic reactions were similar in subjects who received MenACWY-CRM plus routine vaccination compared with those who received routine vaccinations only.

During the study, the most commonly reported AEs were nasopharyngitis, bronchiolitis, pyrexia, and bronchitis. Fewer than 6% of subjects reported AEs that were at least possibly related to MenACWY-CRM, and no deaths were associated with MenACWY-CRM vaccination.

The results of this analysis are consistent with results reported for the US groups of the study,[9] in which a three-dose infant series (at 2, 4, and 6 months) was followed by a fourth (toddler) vaccination at 12 or 13 months of age. Across both geographic regions, the two- or three-dose infant regimens, the full three- or four-dose infant/toddler regimens, and a two-dose toddler regimen of MenACWY-CRM, all produced adequate immunogenicity with little effect on routine concomitant vaccinations.

In conclusion, MenACWY-CRM was shown to be highly immunogenic in infants when given as a three- or four-dose infant/toddler series with concomitant infant and toddler vaccinations. Administration of MenACWY-CRM to infants did not affect responses to concomitantly administered vaccines in a clinically meaningful way. Given the high risk of invasive meningococcal disease during infancy, earlier vaccination is optimal; however, the robust immune response elicited by the two-dose MenACWY-CRM toddler catch-up series demonstrates that this regimen can be offered to unimmunized toddlers. Reactogenicity and adverse events were generally similar in the MenACWY-CRM and control groups, and the most frequently observed events were expected. The results from various dosing regimens assessed in infants and toddlers consistently illustrated that MenACWY-CRM effectively induces antibody protection to serogroups A, C, W-135, and Y; these results confirm that MenACWY-CRM is a valuable tool for reducing the burden of invasive meningococcal disease in very young children, and will also assist local decisions about vaccine administration.

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