

FIVE-YEAR PERSISTENCE OF IMMUNE RESPONSES TO TWO LICENSED QUADRIVALENT (MENACWY) CONJUGATE MENINGOCOCCAL VACCINES IN ADOLESCENTS

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BACKGROUND

Meningococcal disease is a major concern in adolescents, particularly in those living in close proximity to each other (e.g. college or military dormitories), or those practising at-risk behaviour (e.g. smoking, kissing, drinking in bars), which may be considered as typical adolescent behaviour. The development and approval of polysaccharide protein conjugate vaccines against four of the five major disease-causing meningococcal serogroups (A, C, W and Y) provided an opportunity to prevent a large proportion of such disease. Current US Advisory Committee on Immunization Practices (ACIP) recommendations are for the vaccination of all adolescents at 11–12 years of age, with a booster dose at 16–18 years using one of the two currently US-licensed vaccines, Menveo[®] (MenACWY-CRM, Novartis Vaccines) and Menactra[®] (MenACWY-D, Sanofi Pasteur). We have previously compared and reported on immune responses to these two vaccines in 11–18 year-old adolescents.^[1] In this report we describe antibody persistence at 5 years post-vaccination (clinicaltrials.gov NCT00856297).

METHODS

In the primary open-label, multi-centre, US-based study 2,180 healthy 11–18 year-old adolescents were enrolled at 44 study centres to receive a single dose of one of the two MenACWY conjugate vaccines.^[1]

Follow-up studies were performed 21 months, 3 years and 5 years after the initial study to assess persistence of the immune response to the primary immunisations, as well as vaccine safety during the long-term follow-up.^[2]

This report describes the levels of bactericidal antibodies directed against meningococcal serogroups A, C, W and Y in five study groups:

- **Groups 1 and 2:** 5 years after vaccination with a single dose of either MenACWY-CRM or MenACWY-D.
- **Groups 3 and 4:** two years after a booster dose of MenACWY-CRM administered three years after primary vaccination with either MenACWY-CRM or MenACWY-D.
- **Group 5:** age-matched subjects were recruited as vaccine-naïve controls for this latest study.

VACCINES

The two US-licensed vaccines both contain polysaccharides from the four meningococcal serogroups, A, C, W and Y, but differ in the carrier protein used:

- **MenACWY-D = Menactra[®]** (Sanofi Pasteur) contains 4 µg of each of the four polysaccharides conjugated to 48 µg of diphtheria toxoid in each dose.
- **MenACWY-CRM = Menveo[®]** (Novartis Vaccines) contains 10 µg of Men A polysaccharide and 5 µg each of the Men C, W and Y polysaccharides conjugated to a total of 32–64 µg of *Corynebacterium diphtheriae* CRM₁₉₇ protein per dose.

Both vaccines were administered as a single intramuscular injection of 0.5 mL in the deltoid.

SEROLOGY

Immune responses were assessed as serum bactericidal activity with human complement (hSBA), and results expressed as:

- percentages of subjects with hSBA titres ≥ 8 (a conservative estimate of seroprotection), and
- geometric mean titres (GMTs) against serogroups A, C, W and Y. Associated two-sided 95% Clopper-Pearson CI were calculated for each serogroup and for each study visit and were presented by vaccine group (follow-on participants). Differences of percentages of subjects with hSBA titres ≥ 8 between vaccine groups and GMTs were tested using a categorical linear model with factors for vaccine group and study centre. P values less than 0.05 (two-sided test of the null hypothesis of no difference) were considered as indicative of statistical significance.

RESULTS

SUMMARY OF THE PRIMARY STUDY

In the primary study 2180 adolescents received one dose of one of the two meningococcal vaccines to assess the non-inferiority of the immune response to MenACWY-CRM compared with the MenACWY-D vaccine. In case of non-inferiority, a test for statistical superiority was performed. This study demonstrated that:

- Responses to serogroups A, W and Y were statistically superior with MenACWY-CRM compared with MenACWY-D.
- Responses to serogroup C were non-inferior with MenACWY-CRM compared with MenACWY-D.
- Reactogenicity of the two vaccines was similar.

5-YEAR FOLLOW-UP STUDY

DEMOGRAPHICS

A total of 389 subjects were enrolled into one of the five groups for this 5-year persistence study (Table 1).

- Mean ages were 18.8–19.7 years across all groups.
- Age, gender and ethnic breakdown were similar in all groups, except the vaccine-naïve subjects had proportionally more female subjects.

IMMUNOGENICITY

When assessed as proportions having hSBA titres ≥ 8 , in 128 subjects in the MenACWY-CRM group, 71 subjects in the MenACWY-D group and 105 (106 for serogroup A) age-matched vaccine-naïve subjects:

- MenACWY-CRM (32%, $p < 0.001$) and MenACWY-D (34%, $p < 0.001$) had significantly higher percentage with hSBA $\geq 1:8$ against **serogroup C** than naïve (8%).

Table 1: Summary of Study Participants and Demographics at 5 years After Primary Vaccination

	Number of Subjects (%)				
	Men ACWY-CRM	Men ACWY-D	Men ACWY-CRM / Men ACWY-CRM	Men ACWY-D / Men ACWY-CRM	Naïve
Vaccinated at study start	1631	539			
Persistence at 21 months	278	191			128
Persistence at 3 years	284	178	83	77	108
Persistence at 5 years	131	76	44	31	107
Age (Years):	19.4 ± 2.4	18.8 ± 2.4	19.0 ± 1.9	19.7 ± 2.3	19.3 ± 2.4
Sex:					
Male	66 (50%)	47 (62%)	23 (52%)	18 (58%)	39 (36%)
Female	65 (50%)	29 (38%)	21 (48%)	13 (42%)	68 (64%)
Ethnic Origin:					
Asian	5 (4%)	4 (5%)	1 (2%)	0	4 (4%)
Black	5 (4%)	2 (3%)	3 (7%)	2 (6%)	4 (4%)
Caucasian	103 (79%)	57 (75%)	34 (77%)	24 (77%)	77 (72%)
Hispanic	14 (11%)	10 (13%)	5 (11%)	2 (6%)	21 (20%)
Other	4 (3%)	3 (4%)	1 (2%)	3 (10%)	1 (<1%)
Completed Protocol	129 (98%)	76 (100%)	44 (100%)	31 (100%)	107 (100%)

- MenACWY-CRM (59%, $p = 0.001$) and MenACWY-D (60%, $p = 0.004$) had significantly higher percentage with hSBA $\geq 1:8$ against **serogroup C** than naïve (38%).
- MenACWY-CRM (82%, $p = 0.004$) had a significantly higher percentage with hSBA $\geq 1:8$ against **serogroup W** than naïve (66%), but MenACWY-D was not significantly higher (73%, $p = 0.28$).
- MenACWY-CRM (64%, $p < 0.001$) had a significantly higher percentage with hSBA $\geq 1:8$ against **serogroup Y** than naïve (39%), but MenACWY-D was not significantly higher (54%, $p = 0.057$).

The GMTs (Table 2) showed similar patterns.

Table 2: Geometric Mean hSBA Titres (95%CI) at 5 Years After Primary Vaccination

Serogroup	Study group			
	MenACWY-CRM	p between vaccine groups	MenACWY-D	Naïve
	N = 128		N = 71	N = 105
Serogroup A	4.34 (3.41–5.53) * < 0.001	0.70	4.66 (3.45–6.29) * < 0.001	2.34 ^b (1.73–3.16)
Serogroup C	14 (9.41–20) * < 0.001	0.20	19 ^a (12–31) * < 0.001	4.33 (2.72–6.88)
Serogroup W	32 (23–45) * 0.017	0.24	24 (16–37) * 0.26	18 (12–27)
Serogroup Y	12 (8.49–16) * 0.002	0.19	8.57 (5.73–13) * 0.087	5.4 (3.61–8.1)

* Significance vs. Naïve ^aN = 70 ^bN = 106

- There were no significant differences in GMTs between the MenACWY-CRM and MenACWY-D groups for any serogroup at 5 years after the primary vaccination.
- The MenACWY-CRM group had significantly higher GMTs than vaccine-naïve subjects for all four serogroups.
- Only GMTs for serogroups A and C were significantly higher in the MenACWY-D group than the controls.

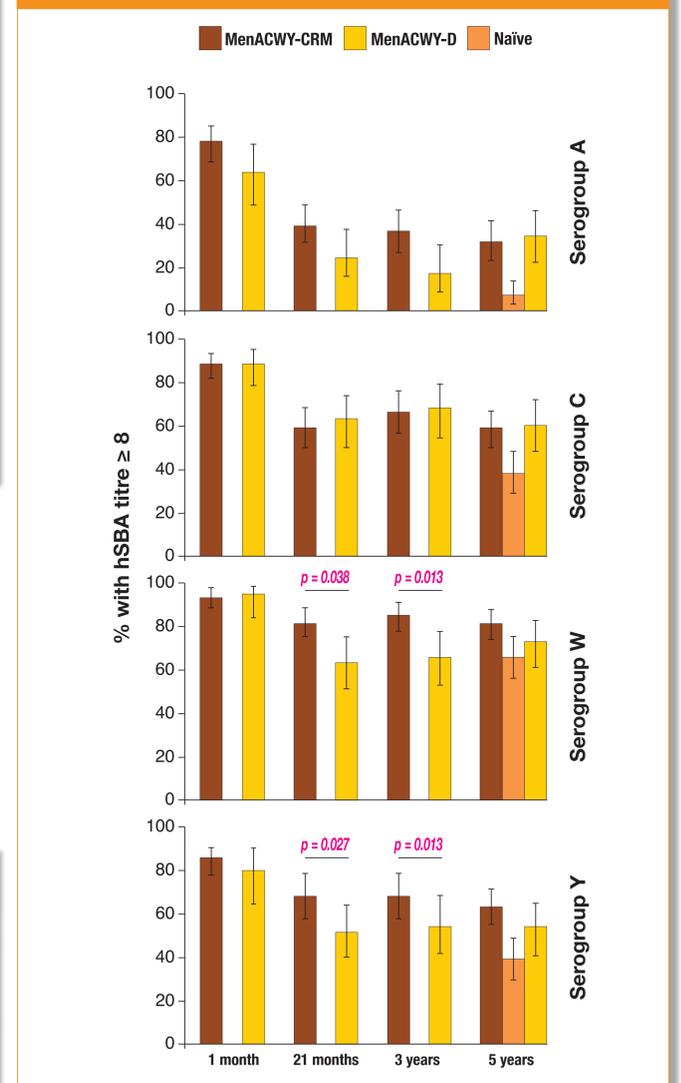
Table 3: Geometric mean hSBA titres (95%CI) and proportions of subjects with hSBA titres ≥ 8 at 5 years, 2 years after a booster vaccination with MenACWY-CRM*

Serogroup	Vaccine Groups	Primary dose Booster dose	MenACWY-CRM	
			MenACWY-CRM N = 44	MenACWY-D N = 31
Serogroup A	GMT		21 (11–38)	19 (9.8–38)
	% ≥ 8		77% (62–89)	77% (59–90)
Serogroup C	GMT		133 (67–261)	61 (29–131)
	% ≥ 8		95% (85–99)	87% (70–96)
Serogroup W	GMT		95 (60–151)	114 (68–191)
	% ≥ 8		100% (92–100)	93% (87–100)
Serogroup Y	GMT		61 (34–109)	46 (24–87)
	% ≥ 8		95% (85–99)	94% (79–99)

* Booster was administered at 3 years after primary vaccination

Responses assessed as proportions remaining seropositive for the two vaccine groups at each time-point over the course of the five-year study are shown in Figure 1, with any significant differences between the two vaccinated groups shown.

Figure 1. Proportions of subjects in the MenACWY-CRM and MenACWY-D groups with hSBA titres (95% CI) ≥ 8 at 1 month, 21 months, 3 years and 5 years after the primary vaccination. Vaccine-naïve group enrolled at 5 years post-vaccination served as a control. N = 102-128 for MenACWY-CRM, 41-71 for MenACWY-D, and 105 for Controls.



Those subjects, who received a booster dose of MenACWY-CRM at three years after the primary vaccination, showed a robust immune response at 1 month after the booster which largely persisted through 2 years after booster dose with seropositivity rates in the two groups:

- 77% against serogroup A,
- 87–95% against serogroup C,
- 97–100% against serogroup W, and
- 94–95% against serogroup Y.

High GMTs were also observed two years after the booster dose (Table 3). There were no significant differences between the groups who received primary vaccination with MenACWY-CRM (n = 44) or MenACWY-D (n = 31).

CONCLUSIONS

- Bactericidal antibodies against serogroups A, C, W and Y decreased as measured by hSBA GMTs over the 5-year period relative to levels observed 1 month following vaccination, but a significant proportion maintained an hSBA titres ≥ 8 against serogroups C, W and Y.
- Subjects maintained levels higher than naïve controls for all serogroups after MenACWY-CRM; after MenACWY-D, levels remained statistically significantly different than controls only for serogroups A and C.
- Booster vaccination with MenACWY-CRM elicited a robust immune response that maintained higher levels of hSBA over the 2-year period.
- Overall, these findings support the use of MenACWY-CRM for the routine boosting of adolescents after primary vaccination with either MenACWY-CRM or MenACWY-D, in accordance with the recent recommendation by the US ACIP.

REFERENCES

1. Jackson LA, Baxter R, Reisinger K, et al. Phase III comparison of an investigational quadrivalent meningococcal conjugate vaccine with the licensed meningococcal ACWY conjugate vaccine in adolescents. Clin Infect Dis 2009;49:e1–e10.
2. Gill C, Baxter R et al, Human Vaccines 2010.

