

Randomized Clinical Trial To Evaluate the Immunogenicity of Quadrivalent Meningococcal Conjugate and Polysaccharide Vaccines in Adults in the United Kingdom

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Meningococcal conjugate vaccines are today successfully deployed in universal programs for children and adolescents in different geographic regions to control meningitis and septicemia. However, in adults, the advantages of these conjugates over the older polysaccharide vaccines are less clear. In this randomized clinical trial, we demonstrated that both conjugate and polysaccharide quadrivalent meningococcal vaccines elicit protective antibody responses in adults aged 18 to 70. (This study has been registered at www.clinicaltrials.gov under registration no. NCT00901940.)

The primary approach to the control of meningococcal disease remains effective vaccination programs in susceptible populations. Vaccines against serogroups A, C, W, and Y offer the broadest possible protection against meningococci and are available as plain polysaccharide and protein-polysaccharide conjugate vaccines. The conjugate vaccines act as T-dependent antigens and are more immunogenic in infants, children, and adolescents than plain polysaccharide vaccines (1, 2), which are T-independent antigens. In the United Kingdom, both types of quadrivalent vaccines are recommended for travelers to countries with epidemic meningococcal disease and for immunocompromised individuals. In the United States, the conjugate vaccine is used in a routine two-dose adolescent program. However, the immunological advantages of the conjugate in the adults are not well documented. This study was designed to compare the immunogenicity of a quadrivalent conjugate vaccine (MenACWY-CRM) with that of a quadrivalent polysaccharide vaccine (MenACWY-PS) in healthy adults.

MATERIALS AND METHODS

A single-center, phase 3, open-label, randomized, parallel group trial was conducted at the Oxford Vaccine Group, University of Oxford, United Kingdom, between June 2009 and October 2010. Written informed consent was obtained from participants before enrollment. Ethical approval was obtained from the Oxfordshire Research Ethics Committee (09/H0606/20). (This study has been registered at www.clinicaltrials.gov under registration no. NCT00901940.)

Participants and recruitment. Adults aged 18 to 70 years were recruited by mail invitation using the electoral roll. Exclusion criteria were as follows: previous anaphylactic reaction to a vaccine component, previous meningococcal vaccination or disease, HIV or immune dysfunction, recent (<3 months) receipt of blood products, pregnancy, breast-feeding, prolonged bleeding time, and concurrent participation in another clinical trial. Previous meningococcal vaccination status was confirmed with the participant's general practitioner after enrollment.

Interventions. Participants were randomized to receive either a single dose of MenACWY-CRM conjugate vaccine (MenACWY-CRM group) or a single dose of MenACWY-PS polysaccharide vaccine (MenACWY-PS group). All participants subsequently received a second dose of MenACWY-CRM 1 month later, and these data are to be reported separately. Allocation to groups was performed on a 1:1 basis generated by computer ran-

domization, with various block sizes (4, 6, 8, and 10 blocks) concealed in sequentially labeled opaque envelopes. MenACWY-CRM (Menveo; Novartis Vaccines, Bellario-Rosia, Italy) (batch X79P45IIE/V) consisted of *Neisseria meningitidis* serogroup A, C, W, and Y capsular oligosaccharides (10, 5, 5, and 5 μ g, respectively) individually conjugated to CRM₁₉₇ carrier protein and was administered as a 0.5-ml solution intramuscularly with a 21-gauge/25-mm-long needle. MenACWY-PS (ACWYVax; Glaxo-Smith-Kline, Rixensart, Belgium) (batch A83CA066A) consisted of *N. meningitidis* serogroup A, C, W, and Y capsular polysaccharides (50 μ g each serogroup) and was administered as a 0.5-ml solution subcutaneously with a 23-gauge/25-mm-long needle. Blood samples were obtained prevaccination and at 7 and 28 days after vaccination. The study was open labeled, and both clinical staff members and participants were aware of the vaccine received. However, laboratory staff members were blind with respect to the group allocations of the participants to ensure objectivity of analysis. Adverse events were self-reported by participants and recorded at each visit.

Study objectives. The primary objective was the comparison of meningococcal serogroup A-specific hSBA (human complement source serum bactericidal activity) titers 7 days after immunization with a single dose of either MenACWY-CRM or MenACWY-PS vaccine. The secondary objective was the comparison of hSBA titers 28 days after vaccination with each vaccine.

Laboratory methods. hSBA assays for detection of meningococcal serogroups A, C, W, and Y were performed at the laboratories of Novartis Vaccines, Marburg, Germany, according to methods described previously (1).

Statistical methods. Statistical analyses were performed using STATA version 11 (StataCorp LP) and Prism version 5 (GraphPad Software). The sample size was calculated to provide 80% power to demonstrate a 30% difference in serogroup A-specific hSBA geometric mean titers (GMTs) at day 7 following administration of MenACWY-CRM or MenACWY-PS at

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TABLE 1 Demographic characteristics of participants in a study comparing the immunogenicities of MenACWY-CRM conjugate and MenACWY-PS polysaccharide vaccines in healthy adult volunteers

Vaccine group	Median age (yrs)	% female participants
MenACWY-CRM	49	64
MenACWY-PS	50	49

a 1% level of significance. Analyses were performed on an intention-to-treat basis, with all data included until participant withdrawal or study conclusion. hSBA titers were skewed in distribution, and data were \log_{10} transformed to approximate a normal distribution prior to analysis. GMTs were therefore presented for description and comparison. Comparisons between groups were carried out using analysis of covariance (ANCOVA), adjusting for prevaccination titers. All statistical tests were 2-sided, and P values < 0.05 were considered significant.

RESULTS

Recruitment. The demographics and flow of participants through the study are shown in Table 1 and Fig. 1, respectively. Although the age range of participants was 18 to 70 years, the majority of volunteers under the age of 35 who expressed interest in the study had received a MenC vaccine as part of the national vaccination campaign in 1999 and were therefore excluded. There were only 10 participants of a total of 150 who were under the age of 35 years.

hSBA responses after a single dose of MenACWY-CRM or MenACWY-PS. A total of 75 participants received a single dose of MenACWY-CRM, and 75 participants received a single dose of MenACWY-PS. hSBA prevaccination GMTs and at days 7 and 28 postvaccination are shown in Table 2. Prevaccination titers (day 0) differed significantly between the study groups for serogroups C and W, with higher titers in the MenACWY-PS group ($P = 0.008$ and $P = 0.007$, respectively [Mann-Whitney U tests]).

Both MenACWY-CRM and MenACWY-PS elicited a rise in hSBA GMTs against all serogroups at day 28 postvaccination. There were no significant differences in meningococcal serogroup-specific hSBA titers at day 7 between MenACWY-CRM and MenACWY-PS recipients (Fig. 2a). At 28 days after immunization, MenACWY-PS generated significantly higher serogroup C titers than MenACWY-CRM ($P = 0.02$), whereas MenACWY-CRM generated higher serogroup W-specific hSBA titers than MenACWY-PS ($P < 0.01$) (Fig. 2b). There were no significant differences observed for serogroup A and Y responses between the vaccine groups at 28 days.

There was a single serious adverse event (SAE), a diagnosis of prostate cancer which was judged unrelated to the study vaccines, during the study.

DISCUSSION

This study, specifically designed to compare MenACWY-CRM with MenACWY-PS in adults, found that both vaccines were immunogenic and elicited hSBA titers above the putative protective threshold. The polysaccharide vaccine generated higher antibody titers than the conjugate vaccine against serogroup C, a major cause of invasive meningococcal disease worldwide.

Both MenACWY-CRM and MenACWY-PS vaccines induced hSBA GMTs ≥ 8 at 28 days postimmunization against all 4 serogroups. hSBA titers ≥ 4 have been established as the correlate of

protection for serogroup C conjugate vaccines (3), indicating that both vaccines are likely to provide protection against serogroup C meningococcal disease. Although there are no validated correlates of protection for serogroups A, W, and Y, a titer value of ≥ 8 has been used as an endpoint in prelicensure immunogenicity studies of conjugate quadrivalent meningococcal vaccines in adults (4).

In naive individuals, antibody levels rise from the baseline at about 10 days after vaccination, but the rise is several days earlier in those who have been primed (5). In this study, meningococcal polysaccharide-specific antibody titers started to rise by day 7 (Table 2). However, there were no significant differences in hSBA GMTs at day 7 between participants who received a single dose of MenACWY-CRM and those who received a single dose of MenACWY-PS (Fig. 2a). This early rise in hSBA suggests prior exposure of study participants to meningococcal antigens, probably through nasopharyngeal carriage of meningococci or exposure to cross-reacting antigens from other bacteria. Studies in adults using pneumococcal and *Haemophilus influenzae* vaccines have also demonstrated no difference in early antibody kinetics between polysaccharide and conjugate vaccine recipients (6, 7). These data appear to indicate that the two vaccines act in similar ways to stimulate the preexisting memory cells presumably generated following natural exposure through nasopharyngeal colonization.

Antibody titers following meningococcal vaccination plateau

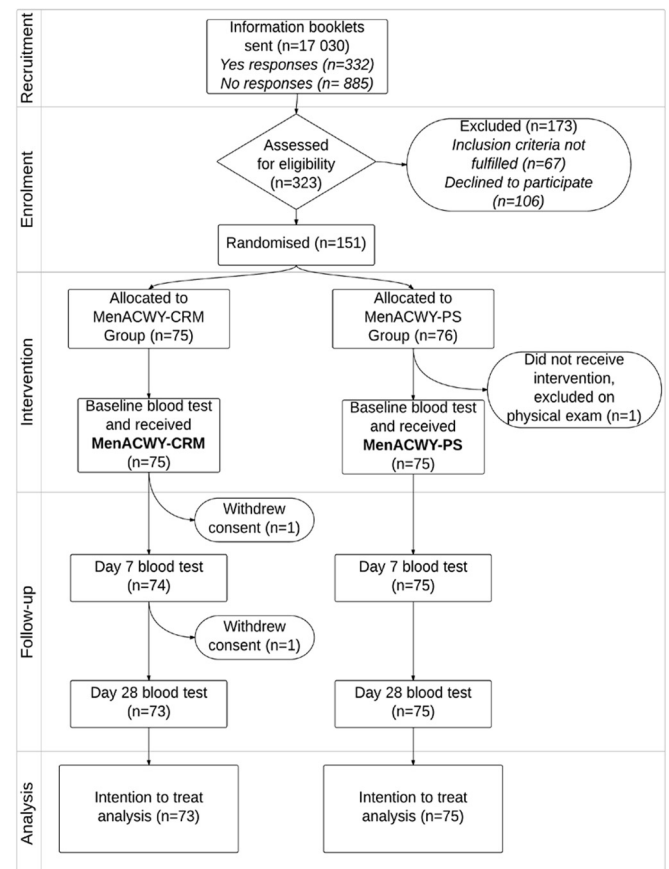


FIG 1 Consolidated Standards of Reporting Trials (CONSORT) diagram indicating disposition of participants in a study, comparing the immunogenicities of MenACWY-CRM conjugate and MenACWY-PS polysaccharide quadrivalent meningococcal vaccines in healthy adult volunteers.

TABLE 2 Unadjusted serum bactericidal activity geometric mean titers against serogroups A, C, W, and Y prevaccination and at 7 and 28 days after a single dose of MenACWY-CRM conjugate or a single dose of MenACWY-PS polysaccharide vaccine^a

Serogroup	Study group	Prevaccination hSBA GMT (95% CI)	Day 7 hSBA GMT (95% CI)	Day 28 hSBA GMT (95% CI)
A	MenACWY-CRM	3.2 (2.6, 4.0) [<i>n</i> = 75]	4.3 (3.2, 5.7) [<i>n</i> = 72]	16.7 (10.9, 26.1) [<i>n</i> = 71]
	MenACWY-PS	3.9 (3.0, 5.1) [<i>n</i> = 75]	5.9 (4.2, 8.3) [<i>n</i> = 73]	26.5 (16.1, 43.5) [<i>n</i> = 75]
C	MenACWY-CRM	6.3 (4.6, 8.5) [<i>n</i> = 73]	14.3 (9.7, 21.3) [<i>n</i> = 71]	32.7 (20.1, 53.2) [<i>n</i> = 68]
	MenACWY-PS	11.1 (8.2, 15.0) [<i>n</i> = 75]	27.0 (18.8, 38.6) [<i>n</i> = 74]	98.9 (64.9, 150.6) [<i>n</i> = 75]
W	MenACWY-CRM	12.0 (8.0, 18.0) [<i>n</i> = 75]	20.67 (13.4, 31.8) [<i>n</i> = 68]	64.1 (40.7, 100.8) [<i>n</i> = 66]
	MenACWY-PS	26.2 (17.5, 39.3) [<i>n</i> = 74]	34.5 (23.4, 50.7) [<i>n</i> = 73]	53.1 (35.6, 79.0) [<i>n</i> = 74]
Y	MenACWY-CRM	3.8 (3.0, 4.7) [<i>n</i> = 75]	5.5 (4.1, 7.5) [<i>n</i> = 70]	15.4 (10.1, 23.5) [<i>n</i> = 71]
	MenACWY-PS	5.6 (4.2, 7.5) [<i>n</i> = 75]	9.8 (7.1, 13.7) [<i>n</i> = 74]	21.7 (13.9, 33.8) [<i>n</i> = 75]

^a Abbreviations: hSBA, human complement source serum bactericidal activity; GMT, geometric mean titers; CI, confidence intervals. 95% confidence intervals are shown in parentheses, and numbers of samples are shown in square brackets. The numbers of samples at each time point differed due to missed visits, participant dropout, insufficient serum for assays, or failed assays.

by day 28 (8), and this time point is therefore used as the standard outcome in vaccine immunogenicity trials. In this study, 28 days after vaccination, significantly higher serogroup C antibody titers were seen in MenACWY-PS recipients than in MenACWY-CRM recipients (Fig. 2b). We suggest two potential reasons for this observation. First, in this study, MenACWY-PS recipients had higher baseline MenC-specific hSBA titers than MenACWY-CRM recipients by chance and may therefore have experienced a greater degree of natural priming by nasopharyngeal carriage. Capsular polysaccharide on intact organisms at the nasopharyngeal mucosa in association with subcapsular proteins may be seen by the immune system as conjugate-like T dependent antigens, which could

therefore induce immune memory (9). Thus, in adult populations previously primed by carriage, antibody responses to a single vaccination with conjugate or polysaccharide may reflect the effect of a booster on preexisting memory B cells rather than true primary T-dependent or T-independent responses.

Second, the higher serogroup C-specific antibody response evoked by the polysaccharide vaccine may reflect a dose response. Results of dose-ranging studies suggest that larger doses of MenC polysaccharide evoke greater immune responses (10, 11). Thus, MenACWY-PS (containing 50 µg of each serogroup polysaccharide) may elicit greater MenC hSBA responses than MenACWY-CRM (containing 10 µg of MenA and 5 µg each of MenC, MenW,

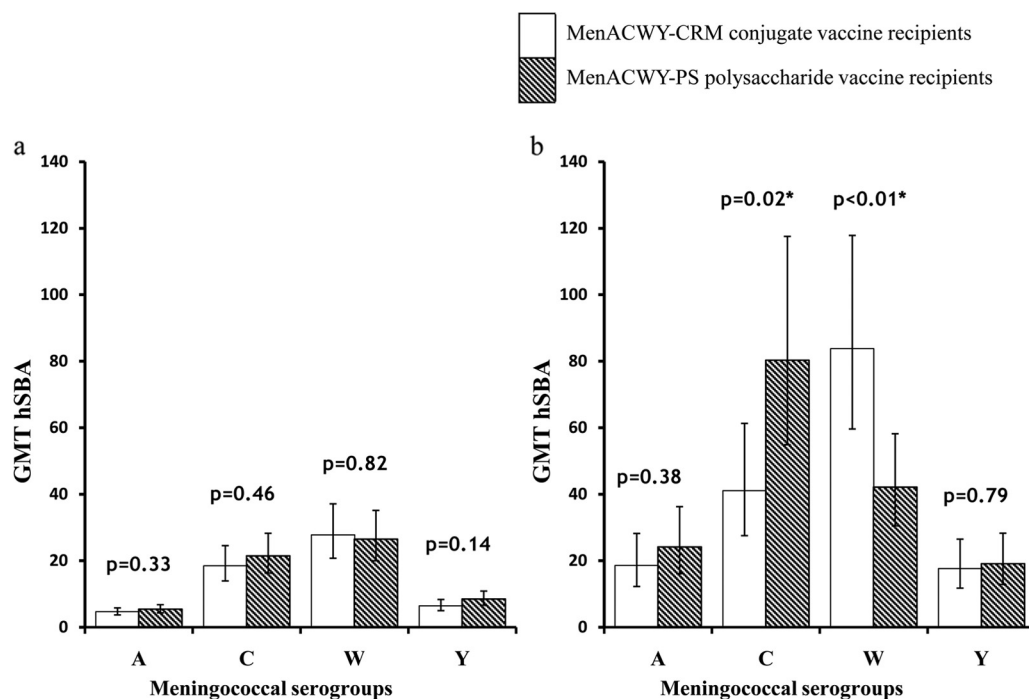


FIG 2 (a) Serum bactericidal activity (hSBA) geometric mean titers (GMT) and 95% confidence intervals (CI) at 7 days after vaccination with a single dose of MenACWY-CRM conjugate vaccine (*n* = 68 to 72) or a single dose of MenACWY-PS polysaccharide vaccine (*n* = 73 to 74). (b) hSBA GMTs and 95% CI at 28 days after vaccination with a single dose of MenACWY-CRM (*n* = 66 to 71) or MenACWY-PS (*n* = 71 to 75). All comparisons used analysis of covariance (ANCOVA) with adjustment for baseline hSBA values prevaccination.

and MenY capsular oligosaccharides). By extrapolation, dose responses may also explain the trend to higher MenA- and MenY-specific hSBA titers in the MenACWY-PS group.

Surprisingly, MenACWY-CRM elicited higher serogroup W-specific hSBA titers at 28 days than MenACWY-PS (Fig. 2b), and the explanation for this is not clear. Prevacination titers were higher than expected given the infrequent serogroup W carriage demonstrated in the United Kingdom (12) and were higher in the MenACWY-PS group than in the MenACWY-CRM group. It is possible that high prevaccination titers inhibited further rises in antibody levels in MenACWY-PS recipients by negative feedback, as has been described for protein vaccines (13, 14). The mechanism for this may be competition for antigen between preexisting antibody and membrane-bound B cell receptor molecules, thus reducing the stimulus to *de novo* antigen-specific B cell proliferation.

Results of studies in South American and North American adults (2, 4, 15) comparing MenACWY-CRM with an alternative quadrivalent polysaccharide vaccine (also containing 50 µg of each serogroup polysaccharide) suggest that higher day 28 hSBA titers are elicited by the conjugate vaccine. Similar results have also been demonstrated in studies conducted in Asia and continental Europe which compared a quadrivalent tetanus toxoid conjugate meningococcal vaccine and MenACWY-PS (16–18). The differences seen in the current study may relate to geographical variations in meningococcal nasopharyngeal carriage between the United Kingdom study population and those from previous studies leading to differential degrees of natural priming or may be due to differences in the comparator polysaccharide vaccine used.

Meningococcal carriage is less prevalent in children, leading to lower natural priming levels than in adults (19). Furthermore, children cannot mount immune responses against T-independent antigens due to an immature splenic marginal zone (20). Thus, in the young, conjugate meningococcal vaccines are more immunogenic than polysaccharide vaccines (1). In this report, we show that in an adult population with prior natural exposure to meningococcal antigens, there is remarkable similarity between the early bactericidal responses to conjugate and polysaccharide vaccines, though more-robust serogroup C meningococcal responses were noted with the plain polysaccharide vaccine used in this study.

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