SERUM BACTERICIDAL ANTIBODY LEVELS FOLLOWING QUADRIVALENT CONJUGATE (MenACWY-CRM) OR SEROGROUP B (4CMenB) MENINGOCOCCAL VACCINES IN A PHASE 3 STUDY TO EVALUATE THE EFFECT OF VACCINATION ON PHARYNGEAL CARRIAGE OF *N. MENINGITIDIS* IN YOUNG ADULTS.

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BACKGROUND

The highest incidence of invasive meningococcal disease (IMD) is observed among infants and adolescents, the latter group frequently suffering from higher case fatality rates than younger children. This age group represents a target for meningococcal vaccination as carriage rates are highest and the potential to impact disease through herd protection is most likely to be successful through high coverage rates in this group; this is provided that the vaccine is capable of impacting acquisition of carriage.
There are five major serogroups responsible for meningococcal disease, A, B, C, W and Y. Two types of meningococcal vaccine, manufactured by Novartis Vaccines, are now licensed for use in Europe to provide protection against all of these serogroups – a quadrivalent polysaccharide-protein conjugate vaccine against A, C, W and Y, MenACWY (Menveo®), and the recently licensed multicomponent, recombinant protein vaccine against serogroup B, 4CMenB (Bexsero®).
In the course of a carriage study performed in students at ten sites in England incorporating 13 universities, reported elsewhere at this congress, in which participants received vaccination with either MenACWY, 4CMenB, or a control vaccine, we analysed the immunogenicity of the meningococcal vaccines in a subset of subjects (NCT01214850). This was in order to assess the immunogenicity of the vaccines in a UK population and explore interactions between systemic immunogenicity and pharyngeal carriage. In addition, as UK university students would have been expected to have received MenC conjugate vaccination during the catch-up vaccination campaigns in the early 2000s, the setting offered an opportunity to assess safety and immunogenicity of MenACWY among a MenC conjugate vaccinated cohort.

METHODS

There were 2968 subjects enrolled in the carriage study. Subjects were randomly allocated to three equal groups to receive two injections, one month apart, of either:

- MenACWY-CRM and then placebo,
- Two doses of 4CMenB, or
- Two doses of Japanese encephalitis vaccine (JEV, Ixiaro®).

VACCINES

- 4CMenB (Bexsero®), is a serogroup B vaccine composed of a recombinant protein component (rMenB) with OMV from the New Zealand strain. The three principal antigens in rMenB are factor H binding protein (fHbp), *Neisserial* adhesin A (NadA) and *Neisseria* heparin binding antigen (NHBA).
- MenACWY-CRM (Menveo®) is a quadrivalent polysaccharide-protein conjugate vaccine. Each dose 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* CRM_{197} protein per dose.
- JEV, the Japanese encephalitis vaccine (Ixiaro®) contains inactivated JEV proteins.

Vaccines were supplied by Novartis Vaccines; meningococcal vaccines were manufactured by Novartis Vaccines and JEV by Intercell. All vaccines were administered as 0.5 mL doses by intramuscular injection in the deltoid – two doses for 4CMenB and JEV, one dose for MenACWY (followed by a placebo injection of aluminium hydroxide in saline).

SEROLOGY

At one study site, Sheffield University, subsets of participants (n~200 per group) provided blood samples immediately before the first vaccination, and at 2, 4, 6 and 12 months (1, 3, 5 and 11 months after the second vaccination, respectively). Sera were analysed for serum bactericidal antibodies using human complement (hSBA) responses.
Further subsets of subjects were randomly selected to test by hSBA the three most frequently occurring serogroups in the UK, serogroups B, C and Y. Thus, not all subjects were tested for all time points for all strains.

- For serogroups C and Y the hSBA was performed at Novartis Vaccines, Clinical Serology Laboratory, Marburg, Germany.
- For Men B strains hSBA was measured at Public Health England, Public Health Laboratory, Manchester, against three Men B indicator strains for vaccine antigens:
  fHbp (44/76-SL),
  NadA (5/99), and
  PorA/NZ OMV (NZ98/254)

STATISTICS

- hSBA responses were calculated as geometric mean titres (GMTs), and
- Percentages of subjects with hSBA titres ≥ 8 against serogroups C and Y, and
- Percentages of subjects with hSBA titres ≥ 4 against serogroup B strains.

Percentages of seroresponders to *N. meningitidis* serogroups C and Y were calculated, defined as those with pre-vaccination hSBA titres < 4 having hSBA ≥ 8 titres, or those with pre-vaccination hSBA ≥ 4 titres demonstrating at least a four-fold increase at 2 months.
Pre-specified analyses were also performed among subjects given MenACWY conjugate vaccine who had documented evidence of a prior dose of MenC vaccine; evidence of prior MenC vaccination required paper documentation from the subject's physician.

RESULTS

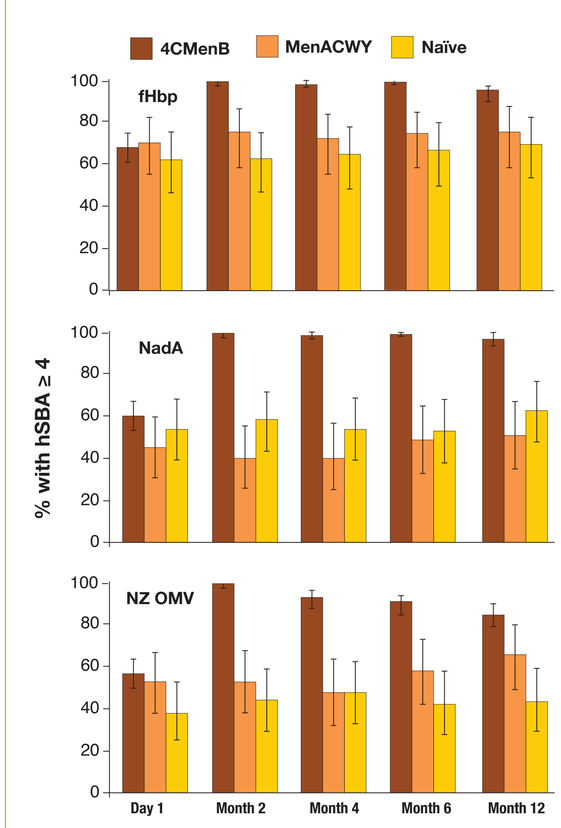
A total of 581 subjects were included in the analyses in the three study groups (Table 1).

Table 1: Demographic of subjects analysed for immunogenicity

	4CMenB N = 192	MenACWY N = 192	Control N = 197
Age (Years):	20.2 ± 1.7	20.2 ± 1.5	20.2 ± 1.7
Sex:			
Male	47%	51%	44%
Female	53%	49%	56%
Ethnic Origin:			
Asian	10 (5%)	11 (6%)	11 (6%)
Black	3 (2%)	5 (3%)	2 (1%)
Caucasian	177 (92%)	165 (86%)	170 (86%)
Hispanic	1 (<1%)	2 (1%)	1 (<1%)
Other	1 (<1%)	9 (5%)	13 (7%)

Figure 1 shows the proportions of subjects in each group with hSBA titres ≥ 4 against the three Men B indicator strains.

Figure 1. Percentages of subjects in each study group with hSBA titres ≥ 4 against the three Men B indicator strains over the course of the study.



At baseline across all vaccine groups:

- 62–71% of subjects had hSBA titres ≥ 4 against 44/76-SL (fHbp),
- 45–60% of subjects had hSBA titres ≥ 4 against 5/99 (NadA), and
- 38–57% of subjects had hSBA titres ≥ 4 against NZ98/254 (NZ OMV).
- One month after the second dose of 4CMenB (Month 2), 99–100% of subjects had hSBA titres ≥ 4 against each of the Men B strains.
- At Month 12, 11 months after the second vaccination, 85–97% of these subjects maintained hSBA titres ≥ 4.
- The MenACWY-CRM and Control groups showed no substantial increase in hSBA titres ≥ 4 against Men B strains over the 12-month study period.

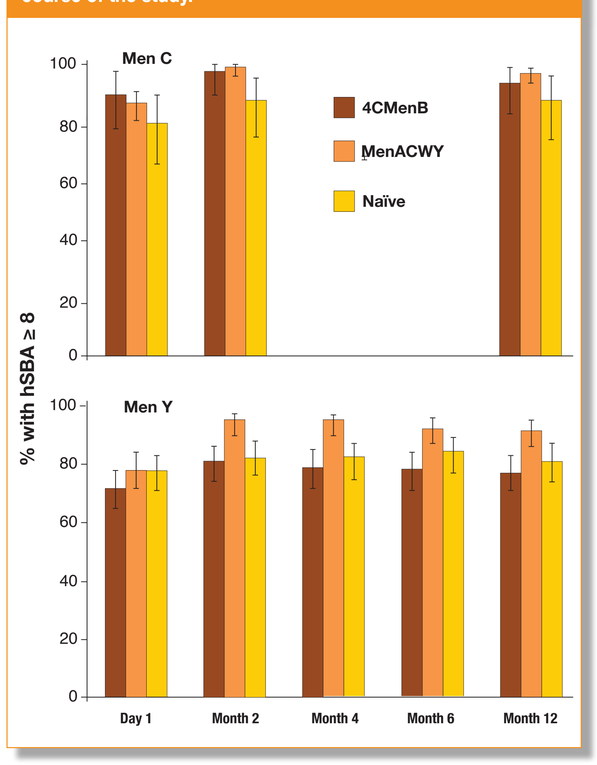
- The GMTs for each group (Table 2) show the increase and subsequent waning of hSBA titres in the 4CMenB group, and the stability of hSBA levels in the MenACWY and Control groups over the study period.

Table 2. hSBA GMTs (95% CI) against the serogroup B indicator strains in the three study groups over the 12 month study period.

Strain (Antigen)		4CMenB	MenACWY	Control
44/76-SL (fHbp)	Day 1	11 (8.74–14) N = 193	11 (6.59–18) N = 49	9.42 (5.73–15) N = 50
	Month 2	229 (192–274) N = 189	11 (7.92–16) N = 45	10 (7.18–15) N = 48
	Month 4	144 (116–178) N = 173	9.07 (5.79–14) N = 40	11 (7.07–16) N = 46
	Month 6	111 (89–138) N = 169	12 (7.57–18) N = 43	12 (7.62–18) N = 45
	Month 12	68 (54–84) N = 177	14 (8.84–22) N = 40	14 (8.97–21) N = 46
5/99 (NadA)	Day 1	6.44 (5.1–8.13) N = 193	3.12 (1.97–4.95) N = 49	5.49 (3.47–8.67) N = 50
	Month 2	424 (355–507) N = 189	2.63 (1.83–3.79) N = 45	5.62 (3.95–8.01) N = 48
	Month 4	169 (139–207) N = 173	2.95 (1.94–4.47) N = 40	5.6 (3.8–8.26) N = 46
	Month 6	105 (87–128) N = 169	3.36 (2.27–4.97) N = 43	5.32 (3.63–7.79) N = 45
	Month 12	55 (45–67) N = 177	3.58 (2.37–5.4) N = 41	5.98 (4.05–8.82) N =4 6
NZ98/254 (NZ OMV)	Day 1	6.15 (4.82–7.84) N = 193	4.32 (2.66–7) N = 49	4.16 (2.58–6.72) N = 50
	Month 2	99 (80–122) N = 188	4.82 (3.11–7.47) N = 45	3.88 (2.54–5.93) N = 48
	Month 4	56 (44–73) N = 172	4.93 (2.89–8.4) N = 40	4.72 (2.87–7.76) N = 46
	Month 6	50 (38–66) N = 169	6.5 (3.73–11) N = 43	4.67 (2.72–8.03) N = 45
	Month 12	34 (26–45) N = 176	7.77 (4.38–14) N = 41	6.93 (3.99–12) N = 44

Figure 2 shows the proportions of subjects in each group with hSBA titres ≥ 8 against Men C and Men Y serogroups at the time-points tested.

Figure 2. Percentages of subjects in each study group with hSBA titres ≥ 8 against Men C and Men Y at the tested time-points (Men C was not tested at Months 4 and 6) over the course of the study.



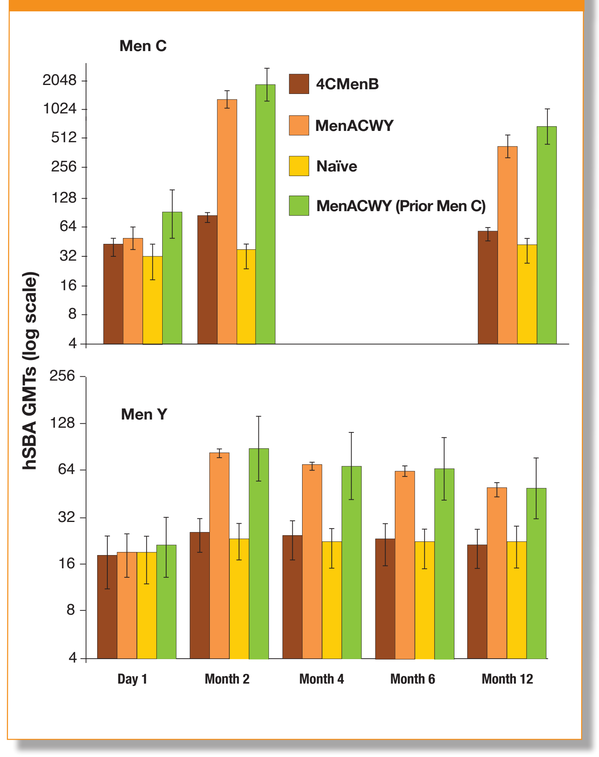
At baseline across all vaccine groups:

- 80–90% of subjects had hSBA titres ≥ 8 against Men C,
- 72–78% of subjects had hSBA titres ≥ 8 against Men Y.

By Month 2, the rate against Men C increased to 98% in the 4CMenB group, and 99% in the MenACWY group, and these groups maintained rates of 94% and 97%, respectively, at Month 12. The Control group showed a smaller change, 80% to 88%, over this period.
The GMTs for hSBA against Men C and Y (Figure 3) show the large response in the MenACWY group, with subsequent waning, and the stability of these values in the Control group. Also evident is the much lower increase in Men C titres in the 4CMenB group compared with the MenACWY group.

This pattern of responses was similar in those subjects with a documented history of Men C vaccination. Despite the higher baseline level of Men C hSBA titres than in controls, (91 vs. 32) in the control group, MenACWY vaccination markedly increased the level at month 2 while controls were unchanged (1905 vs. 37). Men Y levels were not affected in Controls and increased to a similar extent in the MenACWY group (Figure 3).

Figure 3. GMTs against serogroups C and Y (log scale) at the tested time-points (Men C was not tested at Months 4 and 6) over the course of the study, and in those subjects with documented prior Men C vaccination before receiving MenACWY vaccine.



Comparing seroresponse rates to serogroups C and Y in the groups revealed a high response to C (81%) and moderate response to Y (44%) in the MenACWY group, with little change in the 4CMenB or Control groups (Table 3).

Table 3: Numbers (%) of subjects with seroresponse (95% CI) against serogroups C and Y at 2 months (1 month after the second 4CMenB vaccination and 2 months after the single MenACWY vaccination).

		4CMenB	MenACWY	Control
Men C	n/N % (95% CI)	4/48 8% (2–20)	147/181 81% (75-87)	2/48 4% (1–14)
Men Y	n/N % (95% CI)	22/187 12% (8–17)	80/181 44% (37-52)	14/188 7% (4–12)

Carriage rates for serogroups B, C, or Y strains were generally higher in seropositive subjects than in seronegative subjects at baseline, but there was no clear association between carriage rates and post-vaccination hSBA levels for serogroups B or C (data not shown). In contrast, serogroup-specific immune responses were different ($p < 0.001$) among MenACWY-CRM recipients in accordance with whether or not they were carrying a serogroup Y strain at baseline. After vaccination, 76 of 144 non-carriers (44% [95% CI: 36–51%]) achieved a seroresponse (either a seroconversion from seronegative to seropositive, or 4-fold increase in hSBA titre in seropositive subjects) versus 0 of 7 carriers (0% [95% CI: 0–41%]).

CONCLUSION

Two doses of 4CMenB, or one dose of MenACWY elicited strong immune responses against their constituent antigens in English university students. MenACWY recipients demonstrated the expected anamnestic response among those with documented prior Men C conjugate vaccination as well as among the overall population of enrolled subjects.
High percentages of 4CMenB and MenACWY recipients maintained respective bactericidal antibodies 11–12 months post-vaccination.
No clear association between carriage rates and post-vaccination hSBA levels was observed, although some evidence of decreased immune response was observed among subjects with baseline carriage of serogroup Y.

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