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Immunogenicity of a Reduced Schedule of Meningococcal Group C Conjugate Vaccine Given Concomitantly with the Prevenar and Pediacel Vaccines in Healthy Infants in the United Kingdom▽

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This study investigated the use of two doses of three different meningococcal group C conjugate (MCC) vaccines when given for primary immunization with a seven-valent pneumococcal conjugate vaccine (PCV7) and Pediacel, a combination product containing five acellular pertussis components, diphtheria and tetanus toxoids, *Haemophilus influenzae* type b (Hib) conjugate, and inactivated-poliovirus vaccine. The immune response after a single dose of MCC is also presented. Infants were randomized to receive two doses of one of the MCC vaccines and PCV7 at 2 and 3 months or at 2 and 4 months of age. Meningococcal group C serum bactericidal antibody (SBA) geometric mean titers, Hib-polyribosylribitol phosphate (PRP) immunoglobulin G (IgG) geometric mean concentrations (GMCs), and diphtheria and tetanus antitoxin GMCs, together with the proportions of infants achieving putative protective levels, were determined. A total of 393 infants were recruited. Following the first dose of NeisVac-C (MCC conjugated to tetanus toxoid), 97% of infants achieved protective levels (SBA titer of ≥8), compared with 80% and 53%, respectively, for Menjugate and Meningitec (both of which are conjugated to CRM_{197}). SBA responses to MCC vaccines were not significantly different when administered at 2 and 3 or 2 and 4 months of age. Following two doses of each MCC, 98 to 100% of infants achieved protective levels. Both PRP IgG and tetanus responses were significantly enhanced when Pediacel was coadministered with NeisVac-C. This study demonstrates that NeisVac-C and Menjugate generate good immunogenicity after the first dose at 2 months of age when coadministered with PCV7 and Pediacel and merit further investigation in single-dose priming strategies.

In autumn 1999, the United Kingdom was the first country to introduce meningococcal group C conjugate (MCC) vaccines in the primary immunization schedule (18). Infants were vaccinated at 2, 3, and 4 months of age, receiving a combined diphtheria (D) and tetanus toxoid (TT), whole-cell pertussis (wP), and *Haemophilus influenzae* type b (Hib) conjugate vaccine (DTwP/Hib-TT) concomitantly with an MCC vaccine and an oral polio vaccine. Three different manufacturers' monovalent MCC vaccines were used, two conjugated to CRM_{197}, a nontoxigenic natural variant of diphtheria toxin, and one conjugated to TT, all of which showed good immunogenicity under a 2-, 3-, and 4-month schedule (13, 22, 23). In 2004, wP was replaced by an acellular pertussis vaccine (aP) on the grounds of the reduced reactogenicity of the latter but subject to the availability of a combined DTaP/Hib-TT vaccine with pertussis efficacy equivalent to that of United Kingdom wP (19) and with a satisfactory Hib response (15). At the same time, the oral polio vaccine was replaced with an inactivated-poliovirus vaccine (IPV) since by then the risk of importation of polio into the United Kingdom from India or Africa had been greatly reduced by the efforts to achieve global eradication. The combination vaccine of choice was a $DTaP_5$/IPV/Hib-TT vaccine (Pediacel; Sanofi Pasteur). When given concomitantly with either MCC-TT or MCC-CRM_{197}, Pediacel was shown to give Hib responses within the range seen with the DTwP/Hib-TT vaccine (11).

At this time, consideration was also being given to the inclusion of a seven-valent pneumococcal conjugate vaccine (PCV7) in the United Kingdom infant immunization program as a two-dose infant schedule with a booster after 12 months of age. PCV7 (Prevenar; Wyeth Vaccines) was licensed in the United Kingdom on a three-dose infant schedule with a booster dose to be given in the second year of life, based on an efficacy study in the United States that used a 2-, 4-, and 6-month schedule with a booster at 18 months (2). However, a recent United Kingdom study in which a nine-valent pneumococcal conjugate vaccine (PCV9) was given either at 2, 3, and 4 months or at 2 and 4 months, with concomitant $DTaP_3$/Hib-TT and MCC-CRM_{197} vaccines (9), showed pneumococcal serotype-specific responses that were equivalent to those

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TABLE 1. Treatment schedules for vaccination and blood sampling for the six randomized groups

Group	Treatment[a] given at age			
	2 mo	3 mo	4 mo	5 mo
1	Pediacel, Meningitec, Prevenar	Pediacel, Meningitec, Prevenar	Pediacel, blood sampling	Blood sampling
2	Pediacel, Menjugate, Prevenar	Pediacel, Menjugate, Prevenar	Pediacel, blood sampling	Blood sampling
3	Pediacel, NeisVac-C, Prevenar	Pediacel, NeisVac-C, Prevenar	Pediacel, blood sampling	Blood sampling
4	Pediacel, Meningitec, Prevenar	Pediacel, blood sampling	Pediacel, Meningitec, Prevenar	Blood sampling
5	Pediacel, Menjugate, Prevenar	Pediacel, blood sampling	Pediacel, Menjugate, Prevenar	Blood sampling
6	Pediacel, NeisVac-C, Prevenar	Pediacel, blood sampling	Pediacel, NeisVac-C, Prevenar	Blood sampling

[a] Pediacel, $DTaP_5$/IPV/Hib-TT (Sanofi Pasteur); Meningitec, MCC-CRM_{197} (Wyeth Vaccines); Prevenar, PCV7 (Wyeth Vaccines); Menjugate, MCC-CRM_{197} (Novartis Vaccines); NeisVac-C, MCC-TT (Baxter Bioscience).

reported with the two- and three-dose courses and similar in magnitude to those reported after the third dose of PCV7 at 6 months in U.S. infants (2, 21, 24).

There are similar data suggesting that a reduced number of doses of MCC are adequate for priming (4, 22, 26), and all three MCC vaccines are now licensed on a two-dose primary schedule from 2 months of age, with at least 2 months between doses. However, none of the MCC immunogenicity studies using a reduced schedule have included coadministration of PCV7 and Pediacel. This study was designed to determine whether a two-dose schedule of each of three MCC vaccines is acceptable when given with concomitant PCV7 and Pediacel and to investigate the optimal interval between doses. The study design also permitted the evaluation of the immunogenicity of a single dose of each of the three MCC vaccines in the hope of reducing the need for three injections to be given at the 4-month visit when Pediacel, PCV7, and MCC are coadministered.

MATERIALS AND METHODS

Study population. Infants eligible for routine vaccination were recruited from general practices in Hertfordshire and Gloucestershire, England. Criteria for study participation included no contraindication to vaccination, as specified in the *Green Book* (7); written informed consent obtained from the parent or legal guardian; and the infant aged no less than 7 weeks exactly and no more than 11 weeks 6 days.

Treatment and follow-up schedule. Infants were randomized in order of inclusion to the study to one of six groups by treatment schedule (Table 1), using a computer-generated randomization list with a block size of 16. Groups 1 to 3 received one of the three licensed MCC vaccines (Meningitec [MCC conjugated to CRM_{197}; Wyeth Vaccines], Menjugate [MCC conjugated to CRM_{197}; Novartis Vaccines], or NeisVac-C [MCC conjugated to TT; Baxter Bioscience]) and PCV7 at 2 and 3 months of age and were bled at 4 and 5 months of age. Those in groups 4 to 6 received MCC and PCV7 at 2 and 4 months of age and were bled at 3 and 5 months of age. The booster phase of this study will assess responses to conjugate boosters in the second year of life and will be reported as data become available.

Sera were analyzed for meningococcal group C antibody by a serum bactericidal antibody (SBA) assay as previously described (14). The SBA target strain was C11 (C:16:P1.7-1,1), and the complement source was baby rabbit serum (Pel-Freeze Inc., Rodgerson, AZ). SBA titers are expressed as the reciprocal of the final serum dilution giving ≥50% killing at 60 min. For computational purposes, SBA titers of <4 were assigned a value of 2. Hib-, diphtheria-, and tetanus-specific antibodies (immunoglobulin G [IgG]) were quantified using standardized enzyme-linked immunosorbent assays (ELISAs) (16, 17, 20). For each antigen, sera were titrated against known international standard sera. Standard sera used were the international anti-Hib quality control serum, Center for Biologics and Evaluation Research (CBER) 1983, National Institute for Biological Standards and Control (NIBSC) national diphtheria reference serum 00/496, and the first international tetanus reference serum (26/488). Responses to PCV7, assessed at the Immunobiology Unit of the Institute of Child Health, London, United Kingdom, will be reported separately.

To fulfill a duty of care, a further dose of a single-antigen Hib vaccine (Hiberix; GlaxoSmithKline) or the MCC vaccine that subjects had already been given was offered to any subject with an antibody response below the putative protective threshold of 0.15 μg/ml (10) or an SBA titer of 8 (1), respectively, 4 to 6 weeks after the last dose.

Analyses. In all analyses, the outcomes of interest at the various blood sampling time points, with 95% confidence intervals (CI), were as follows: (i) the MCC SBA geometric mean titers (GMTs) and the proportions of subjects achieving SBA titers of ≥8 or ≥128, the putative protective or more discriminatory antibody level, respectively (1); (ii) the Hib antibody geometric mean concentrations (GMCs) and the proportions of subjects achieving antibody concentrations of ≥0.15 μg/ml (the putative protective level) or ≥1.00 μg/ml (considered predictive of longer-term protection) (10); and (iii) the diphtheria and tetanus GMCs and the proportions of subjects achieving concentrations of ≥0.1 IU/ml or ≥1.0 IU/ml (4, 8). Differences between groups can be assessed by nonoverlapping 95% CI. This gives an approximate level of significance of 1%, which is conservative to allow for multiple comparisons. Normal-error regression was used on logged antibody responses to investigate differences in responses between males and females.

Sample size. The trial aimed to estimate the proportions of subjects achieving protective antibody levels in each treatment group, with 95% CI widths of less than ±10% (assumed observed proportion of >90%), and to estimate geometric means with 95% CI widths to within ±1.5-fold (assumed between individual standard deviations of <0.65 U on a $\log_{10}$ scale). This required a sample size of 55 in each study group, with 65 recruited to allow for dropouts. The study was also powered on the secondary aim of detecting differences in antibody responses between the schedules (groups 1 to 3 and 4 to 6), where a sample size of 165 per schedule gives a detectable difference of 1.8-fold with 80% power at a 1% significance level, and also among the three MCC vaccines, where a sample size of 110 per schedule gives a detectable difference of 2-fold with 80% power at a 1% significance level.

Amendment to the study schedule. During the recruitment phase of the trial, in September 2006, PCV7 was introduced into the national immunization program as a two-dose primary schedule at 2 and 4 months of age. An interim analysis was therefore undertaken to assess whether those in groups 1 to 3, vaccinated with PCV7 at 2 and 3 months, achieved protection comparable to that available through routine vaccination outside the trial at 2 and 4 months (as given to groups 4 to 6). For the purposes of rapidity, this was done using a pneumococcal-serotype-specific multiplex assay (12). The serotype-specific results from this study, as measured by ELISA, will be reported elsewhere. This interim analysis showed that significantly higher pneumococcal IgG concentrations were achieved under the 2- and 4-month schedule than under the 2- and 3-month schedule. In view of these results, two steps were immediately taken for ethical reasons. (i) Recruitment to groups 1 to 3 was halted, and the study was completed by reallocating 10 individuals already randomized to groups 1 to 3 but not yet vaccinated to groups 4 to 6 and increasing the total number randomized to groups 4 to 6 in order to maintain the total target sample size (Table 2). (ii) Subjects from groups 1 to 3 in the birth cohort eligible to receive two doses of PCV7 2 months apart in the first year of life under the new national immunization schedule, who had completed primary immunization but not yet received the booster dose of PCV7 in the second year of life, were recalled for a third dose of PCV7 in the first year of life, at least 2 months before the booster was due. Thus, groups 1 to 3 had smaller sample sizes than groups 4 to 6 and groups 1 to 3 had numbers with serologic results slightly less than the target of 55.

Governance. The study was conducted in accordance with the 1996 ICH GCP guidelines, the 2000 Declaration of Helsinki, and the 2004 European Union

TABLE 2. Number of subjects randomized to each group and reassignment following the protocol amendment (as treated group)

Randomized group (no. of subjects)	No. of subjects assigned to treated group:						No. of subjects excluded
	1	2	3	4	5	6	
1 (54)	49			2			3
2 (54)		49			4		1
3 (56)			48			4	4
4 (81)				78			3
5 (77)					76		1
6 (71)						68	3
Total	49	49	48	80	80	72	15[a]

[a] Fifteen subjects were excluded from analyses for the following reasons: the interval between doses 1 and 2 was greater than 6 weeks or that between doses 1 and 3 was greater than 12 weeks ($n = 6$); three doses of MCC vaccine were given at 2, 3, and 4 months ($n = 1$); three doses of PCV7 were given at 2, 3, and 4 months ($n = 1$); subject left the trial by vaccine 2 ($n = 2$); subject left the trial by vaccine 3 ($n = 3$); and subject received two different MCC vaccines ($n = 2$).

Clinical Trial Directive. It was approved by the United Kingdom Medicines and Healthcare Products Regulatory Authority (MHRA) and the Eastern Multi Center Research Ethics Committee (MREC). The EudraCT number is 2004-001049-14, and the study was registered on the public website www.ClinicalTrials.gov under identifier NCT00197808.

RESULTS

Study population. A total of 393 infants were recruited. The distribution across the treatment groups is shown in Table 2 according to both randomized groups and treated groups. The same infants did not necessarily contribute to sampling at each point due to failed venipuncture or nonattendance. The 10 individuals already randomized to groups 1 to 3 but vaccinated according to the schedule for groups 4 to 6 after the national program for PCV7 was introduced were included in the analysis, as their group was deliberately changed. With this exception, the analysis was per protocol, with individuals included until they departed from the protocol. The tolerance allowed for the interval between vaccinations was 3 to 5 weeks from the first to second visit and 7 to 9 weeks from the first to third visit.

The ages at the first, second, and third visits were similar across the groups, with a median of 60 or 61 days for the first visit, 90 to 93 days for the second visit, and 121 to 125 days for the third visit. The range for the ages at the first visit was 48 to 82 days, that at the second visit was 76 to 122 days, and that at the third visit was 105 to 161 days. No significant differences in responses between males and females were found for any of the serologic measurements.

Responses to MCC vaccine. Table 3 shows the meningococcal group C SBA GMTs and percentages of subjects with titers of ≥8 and 128 for each of the three MCC vaccines 1 month after the first dose at 2 months of age or after two doses at either 2 and 3 or 2 and 4 months of age. The SBA GMTs and proportions of subjects achieving the given antibody titers after two doses of MCC vaccine at 2 and 3 or 2 and 4 months were combined for each MCC vaccine (i.e., groups 1 and 4, 2 and 5, and 3 and 6), as there were no significant differences between them. After the first dose, 97% (95% CI, 88 to 100) of infants receiving NeisVac-C achieved the putative correlate of protection, an SBA titer of ≥8, with a GMT of 295 (95% CI, 199 to 438). Responses were lower for Menjugate, with 80% (95% CI, 69 to 89) with a titer of ≥8 and a GMT of 48 (95% CI, 31 to 74), and lower again for Meningitec, with 53% (95% CI, 41 to 65) with a titer of ≥8 and a GMT of 10 (95% CI, 7 to 14).

After the second dose, there were significant increases in SBA GMTs for subjects given Menjugate and Meningitec but only a modest increase for subjects given NeisVac-C, where a good response had already been achieved after one dose. There were significant differences in the SBA GMTs achieved according to the MCC vaccine given, the highest being for Menjugate, at 682 (95% CI, 546 to 852), followed by NeisVac-C, at 437 (95% CI, 354 to 539), and then Meningitec, at 229 (95% CI, 176 to 298). For all three vaccines, 98 to 99% of subjects achieved SBA titers of ≥8 but only the groups receiving Menjugate and NeisVac-C had over 90% with titers of ≥128.

Responses to Hib vaccine. The Hib-polyribosylribitol phosphate (PRP) IgG GMCs rose significantly after each of the three doses of Pediacel at 2, 3, and 4 months, regardless of the concomitant MCC vaccine (Table 4). After the third dose,

TABLE 3. Percentages of subjects achieving an SBA titer of ≥8 or ≥128 and SBA GMTs 1 month following either one dose at 2 months of age or two doses at 2 and 3 months of age or 2 and 4 months of age, differentiated by MCC vaccine manufacturer

Group(s)	Point measured	MCC vaccine	Total no. of subjects	% of subjects with SBA titer of ≥8 (95% CI)	% of subjects with SBA titer of ≥128 (95% CI)	GMT (95% CI)
4	After one dose at 2 mo	Meningitec	70	53 (41–65)	10 (4–20)	10 (7–14)
5	After one dose at 2 mo	Menjugate	66	80 (69–89)	44 (32–57)	48 (31–74)
6	After one dose at 2 mo	NeisVac-C	59	97 (88–100)	85 (73–93)	295 (199–438)
1	After two doses at 2 and 3 mo	Meningitec	43	100 (92–100)	84 (69–93)	277 (189–408)
2	After two doses at 2 and 3 mo	Menjugate	44	98 (88–100)	89 (75–96)	648 (397–1,060)
3	After two doses at 2 and 3 mo	NeisVac-C	44	100 (92–100)	93 (81–99)	451 (324–629)
4	After two doses at 2 and 4 mo	Meningitec	76	96 (89–99)	78 (67–86)	206 (144–293)
5	After two doses at 2 and 4 mo	Menjugate	77	100 (95–100)	99 (93–100)	702 (563–875)
6	After two doses at 2 and 4 mo	NeisVac-C	65	98 (92–100)	92 (83–98)	427 (323–564)
1 and 4	After two doses	Meningitec	119	98 (93–99)	80 (72–87)	229 (176–298)
2 and 5	After two doses	Menjugate	121	99 (96–100)	95 (90–98)	682 (546–852)
3 and 6	After two doses	NeisVac-C	109	99 (95–100)	93 (86–97)	437 (354–539)

TABLE 4. PRP IgG GMCs and percentages of subjects achieving a PRP IgG of ≥0.15 μg/ml or ≥1.0 μg/ml 1 month following one dose at 2 months of age, two doses at 2 and 3 months of age, or three doses at 2, 3, and 4 months of age, differentiated by MCC vaccine manufacturer

Group(s)	Point measured	MCC vaccine	Total no. of subjects	% of subjects with PRP IgG GMC of ≥0.15 μg/ml (95% CI)	% of subjects with PRP IgG GMC of ≥1.0 μg/ml (95% CI)	GMC (95% CI)
4	After one dose at 2 mo	Meningitec	76	25 (16–36)	3 (0–9)	0.13 (0.10–0.15)
5	After one dose at 2 mo	Menjugate	74	26 (16–37)	4 (0–11)	0.12 (0.10–0.15)
6	After one dose at 2 mo	NeisVac-C	64	31 (20–44)	3 (0–11)	0.14 (0.11–0.18)
1	After two doses at 2 and 3 mo	Meningitec	47	51 (36–66)	15 (6–28)	0.23 (0.16–0.33)
2	After two doses at 2 and 3 mo	Menjugate	48	54 (39–69)	21 (10–35)	0.30 (0.20–0.47)
3	After two doses at 2 and 3 mo	NeisVac-C	45	67 (51–80)	27 (15–42)	0.47 (0.26–0.85)
1 and 4	After three doses at 2, 3, and 4 mo	Meningitec	126	89 (82–94)	62 (53–70)	1.75 (1.29–2.38)
2 and 5	After three doses at 2, 3, and 4 mo	Menjugate	126	85 (77–91)	66 (57–74)	1.76 (1.29–2.39)
3 and 6	After three doses at 2, 3, and 4 mo	NeisVac-C	115	96 (90–99)	86 (78–92)	4.29 (3.27–5.62)

the group that received concomitant NeisVac-C had a significantly higher PRP GMC, 4.29 μg/ml (95% CI, 3.27 to 5.62), than recipients of either Menjugate, 1.76 μg/ml (95% CI, 1.29 to 2.39), or Meningitec, 1.75 μg/ml (95% CI, 1.29 to 2.38). The percentages of subjects achieving a PRP IgG of ≥0.15 μg/ml also rose with each dose, though they did not differ between the coadministered MCC products (Table 4). After the third dose, in excess of 85% of subjects had a PRP IgG of ≥0.15 μg/ml. For the percentage of subjects achieving a PRP IgG of ≥1.0 μg/ml, differences according to coadministered MCC vaccine were emerging after the second dose, and after the third dose the percentage was significantly higher for the NeisVac-C group, at 86% (95% CI, 78 to 92), than for the group receiving Menjugate, at 66% (95% CI, 57 to 74), or Meningitec, at 62% (95% CI, 53 to 70).

Tetanus and diphtheria. The tetanus GMCs (IU/ml) increased significantly with each dose of vaccine (Table 5). The GMCs after the third dose differed significantly, with those for the NeisVac-C group being higher, at 1.63 IU/ml (95% CI, 1.43 to 1.86), than those for the Menjugate group, at 1.10 IU/ml (95% CI, 0.97 to 1.25), or the Meningitec group, at 0.98 IU/ml (95% CI, 0.85 to 1.12). All subjects achieved antibody concentrations of ≥0.1 IU/ml after the third dose, and the proportions were 48% for the Meningitec group, 54% for the Menjugate group, and 78% for the NeisVac-C group.

After each dose of Pediacel, the diphtheria IgG GMCs in-

TABLE 5. Tetanus and diphtheria GMCs 1 month following one dose at 2 months of age, two doses at 2 and 3 months of age, or three doses at 2, 3, and 4 months of age, differentiated by MCC vaccine manufacturer

Group(s)	Point measured	MCC vaccine	Tetanus GMC, in IU/ml (95% CI) [total no. of subjects tested]	% of subjects with tetanus GMC of ≥0.1 IU/ml (95% CI)	% of subjects with tetanus GMC of ≥1.0 IU/ml (95% CI)	Diphtheria GMC, in IU/ml (95% CI) [total no. of subjects tested]	% of subjects with diphtheria GMC of ≥0.1 IU/ml (95% CI)	% of subjects with diphtheria GMC of ≥1.0 IU/ml (95% CI)
4	After one dose at 2 mo	Meningitec	0.30 (0.25–0.36) [75]	92 (83–97)	7 (2–15)	0.12 (0.10–0.14) [76]	62 (50–73)	0 (0–5)
5	After one dose at 2 mo	Menjugate	0.29 (0.25–0.34) [74]	95 (87–99)	4 (1–11)	0.12 (0.10–0.14) [74]	55 (43–67)	0 (0–5)
6	After one dose at 2 mo	NeisVac-C	0.30 (0.25–0.36) [64]	89 (79–95)	3 (0–11)	0.11 (0.09–0.14) [64]	52 (39–64)	0 (0–6)
1	After two doses at 2 and 3 mo	Meningitec	0.42 (0.34–0.52) [47]	100 (92–100)	17 (8–31)	0.83 (0.67–1.02) [47]	100 (92–100)	47 (32–62)
2	After two doses at 2 and 3 mo	Menjugate	0.47 (0.38–0.59) [48]	100 (93–100)	13 (5–25)	0.73 (0.55–0.98) [48]	98 (89–100)	35 (22–51)
3	After two doses at 2 and 3 mo	NeisVac-C	0.62 (0.50–0.78) [45]	100 (92–1.00)	18 (8–32)	0.61 (0.44–0.85) [45]	93 (82–99)	33 (20–49)
1 and 4	After three doses at 2, 3, and 4 mo	Meningitec	0.98 (0.85–1.12) [126]	100 (97–100)	48 (37–57)	1.69 (1.47–1.95) [126]	100 (97–100)	77 (69–84)
2 and 5	After three doses at 2, 3, and 4 mo	Menjugate	1.10 (0.97–1.25) [126]	100 (97–100)	54 (45–63)	1.78 (1.54–2.05) [125]	100 (97–100)	81 (73–87)
3 and 6	After three doses at 2, 3, and 4 mo	NeisVac-C	1.63 (1.43–1.86) [115]	100 (97–100)	78 (70–85)	1.54 (1.32–1.80) [113]	99 (95–100)	77 (68–84)

creased significantly and similarly regardless of coadministered MCC product (Table 5). After the third dose, for those in receipt of coadministered Meningitec, Menjugate, and NeisVac-C, the percentages achieving antibody concentrations of ≥0.1 IU/ml were 100, 100, and 99, respectively, and the percentages achieving antibody concentrations of ≥1.0 IU/ml were 77, 81, and 77, respectively.

Serious adverse events. There were nine serious adverse events during the primary phase of the study, none of which were judged by the investigator to be causally related to vaccination (the times since the last vaccination are shown in parentheses): red/purple rash on legs (1 week); bullous impetigo (1 week); cataract operation (2 weeks); urine infection and dehydration (3 weeks); drainage of abscess (1 month); error of drug administration by parent for irritability, i.e., loratadine instead of paracetamol (1 month); bronchiolitis (1 month); repair of nail bed (6 months); and allergic reaction to ingestion of lemon pavlova (6 months).

DISCUSSION

This is the first report of a randomized study of the immunogenicity of each of three licensed monovalent MCC vaccines when given at 2 and 3 or 2 and 4 months of age concomitantly with PCV7 and the $DTaP_5$/IPV/Hib-TT vaccine (Pediacel). Functional antibody responses to MCC vaccines were not significantly different when the vaccines were administered at 2 and 3 or 2 and 4 months of age. Differences among the immunogenicities of the three MCC vaccines were seen following one or two doses. Following two doses of MCC, the SBA GMT, but not the proportion of infants putatively protected, was higher for Menjugate than for NeisVac-C or Meningitec. Menjugate has previously been shown to elicit a higher SBA GMT than NeisVac-C when coadministered with Pediacel on a 2-, 3-, and 4-month schedule (11).

Following a single dose, however, NeisVac-C gave a significantly higher SBA GMT and proportion of infants putatively protected than Menjugate, which in turn gave significantly higher results than Meningitec. As the proportions of infants protected with NeisVac-C and Menjugate were 97% and 80%, respectively, this opens the possibility of immunogenicity studies utilizing a single dose of either of these two MCC vaccines to prime in infancy but at an immunologically less demanding age, for example, 3 months. PCV7 could be administered at 2 and 4 months of age and an appropriate DTaP/IPV/Hib vaccine at 2, 3, and 4 months of age. Under such a schedule, no more than two injections would be required at any visit, hopefully improving acceptability. NeisVac-C has also been reported to induce putative levels of protection in 92% of infants, with a GMT of 491 (95% CI, 275 to 877), when given at 2 months of age with a $DTaP_3$/Hib-TT vaccine (Infanrix-Hib; GSK) though without concomitant PCV7 (26). A number of studies have reported good immunogenicity of a single dose of NeisVac-C when given in infancy with wP-containing vaccines (5, 22).

The SBA GMTs achieved after two doses of NeisVac-C and Menjugate were lower than those reported by Kitchin et al. (11) when these MCC vaccines were given on a three-dose schedule with Pediacel but without concomitant PCV7 (11); in that study, GMTs of 690 (95% CI, 416 to 1,140) and 2,165 (95% CI, 1,517 to 3,089) were achieved for NeisVac-C and Menjugate, respectively, compared with 437 (95% CI, 354 to 539) and 682 (95% CI, 546 to 852), respectively, for these MCC vaccines in the current study. Similarly, the SBA GMT of 229 (95% CI, 176 to 298) achieved after two doses of Meningitec was lower than that reported in earlier studies in which three doses were given at 2, 3, and 4 months concomitantly with the $DTaP_3$/Hib-TT vaccine (25) or the DTwP/Hib-TT vaccine (6), where GMTs of 380 (95% CI, 275 to 526) and 535 (95% CI, 441 to 649), respectively, were achieved. The reasons for these differences are not clear since in all of these studies the SBA assays were carried out in the same laboratory (Manchester, United Kingdom). They could be related to the use of only two doses of MCC vaccine, the concomitant administration of PCV7, or the declining immunogenicity of subsequent batches for all three MCC vaccines. The first of these possible explanations seems unlikely as GMTs after the third dose of MCC vaccine under the 2-, 3-, and 4-month schedule are not significantly higher than those after the second dose when given without PCV7 (5, 23, 26). Furthermore, the SBA GMT after two doses of Meningitec in the current study was similar to that reported after three doses in an earlier United Kingdom study in which Menegitec was given concomitantly with a $DTaP_3$/Hib-TT vaccine at 2, 3, and 4 months with two or three doses of PCV9 (9); in that study, SBA GMTs were 291 (95% CI, 208 to 407) and 187 (95% CI, 127 to 275) for the groups who received three and two doses of PCV9, respectively. The effect of concomitant PCV7 on the response to Menjugate under a 2-, 4-, and 6-month schedule has been studied previously (3). No effect on group C SBA titers was observed when Menjugate was coadministered with $DTaP_3$/IPV/HepB/Hib-TT (Infanrix hexa; GSK), whether given with or without PCV7. This suggests that concomitant PCV does not impair the response to a concomitant MCC-CRM_{197} vaccine, at least under a more expanded schedule. It seems likely, therefore, that the differences in SBA GMTs seen between studies largely reflect batch-to-batch variation and emphasize the importance of conducting randomized studies with the same batches of MCC vaccine if the effect of the number of doses or concomitant vaccines is to be determined.

As has been reported previously, the PRP IgG responses were significantly enhanced when the $DTaP_5$/IPV/Hib-TT vaccine was administered with MCC-TT (NeisVac-C) as opposed to either of the MCC-CRM_{197} vaccines (11, 27). Likewise, tetanus antitoxin responses were significantly enhanced when the $DTaP_5$/IPV/Hib-TT vaccine was administered with MCC-TT (NeisVac-C) as opposed to either of the MCC-CRM_{197} vaccines (11). In the study of Kitchin et al. (11), which compared three doses of either NeisVac-C or Menjugate coadministered with Pediacel at 2, 3, and 4 months of age, enhancement was also seen for diphtheria antitoxin IgG GMCs for the Menjugate group, at 0.1 IU/ml (95% CI, 0.07 to 0.13), compared with results for the NeisVac-C group, at 0.04 IU/ml (95% CI, 0.03 to 0.05). The diphtheria antitoxin IgG GMCs in the current study showed no difference by coadministered MCC vaccine but were significantly higher than those from the Kitchin et al. study (11) due to the use of an ELISA (16) rather than a microneutralization assay as in the Kitchin et al. study. A subset of the serum samples ($n = 69$) from the latter study was reassayed by ELISA, and the IgG GMCs were 1.40 (95% CI, 0.99 to 1.97) and 0.84 (95% CI, 0.63 to 1.13) for the

Menjugate and NeisVac-C groups, respectively, when given with Pediacel (Sanofi Pasteur MSD, personal communication). These levels for the Menjugate and Neisvac-C groups in the present study were GMCs of 1.78 (95% CI, 1.54 to 2.05) and 1.54 (95% CI, 1.32 to 1.80), respectively. Thus, the addition of another CRM_{197} conjugate (PCV7) appeared to enhance the diphtheria response such that the concomitant MCC vaccine no longer had an effect on the magnitude of the diphtheria response to Pediacel.

In conclusion, this study has demonstrated that two of the MCC vaccines, NeisVac-C and Menjugate, showed good immunogenicity after a single dose at 2 months of age when coadministered with PCV7 and $DTaP_5$/IPV/Hib-TT and should be investigated further in single-dose priming strategies.

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