Immunogenicity of a reduced schedule of meningococcal group C conjugate vaccine given concomitantly with a 7-valent pneumococcal conjugate vaccine and a combination DTaP/Hib/IPV vaccine in healthy UK infants.

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Abstract

This study investigated the use of 2 doses of 3 different meningococcal group C conjugate (MCC) vaccines when given for primary immunization with 7-valent pneumococcal conjugate (PCV7) vaccine and Pediacel™, a combination product containing 5 acellular pertussis components, diphtheria and tetanus toxoids, *Haemophilus influenzae* type b (Hib) conjugate and inactivated poliovirus vaccine (DTaP/Hib/IPV). 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 (GMTs), Hib-polyribosylribitol phosphate (PRP) 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 ≥ 8) compared with 80% and 53% respectively for Menjugate® and Meningitec™ (both of which are conjugated to CRM197). SBA responses to MCC vaccines were not significantly different when administered at 2, 3 or 2, 4 months of age. Following two doses of each MCC, 98-100% achieved protective levels. Both PRP IgG and tetanus responses were significantly enhanced when Pediacel was coadministered with the NeisVac-C. This study demonstrated 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.

Introduction

In autumn 1999, the United Kingdom (UK) was the first country to introduce meningococcal group C conjugate (MCC) vaccines in the primary immunization schedule [22]. Infants were vaccinated at 2, 3, 4 months of age, receiving a combined diphtheria (D) and tetanus toxoid (TT), whole cell pertussis (wP), and *Haemophilus influenzae* type b (Hib-TT) conjugate vaccine (DTwP/Hib-TT),
concomitantly with a MCC vaccine and oral polio vaccine (OPV). Three different manufacturers’ monovalent MCC vaccines were used, two conjugated to CRM\textsubscript{197}, a non toxigenic natural variant of diphtheria toxin, and one to TT, all of which showed good immunogenicity under a 2, 3, 4 month schedule [26, 27, 17]. In 2004, wP was replaced by an acellular pertussis vaccine (aP) on the grounds of reduced reactogenicity of the latter but subject to the availability of a combined DTaP/Hib-TT vaccine with pertussis efficacy equivalent to that of UK wP [23] and with a satisfactory Hib response [19]. At the same time OPV was replaced with inactivated polio vaccine (IPV) since by then the risk of importation of polio into the UK from Indian or Africa had been greatly reduced by the efforts to achieve global eradication. The combination vaccine of choice was a DTaP\textsubscript{5}/IPV/Hib-TT vaccine (Pediacel\textsuperscript{TM}, Sanofi Pasteur). When given concomitantly with either a MCC-TT or MCC-CRM\textsubscript{197}, Pediacel was shown to give Hib responses within the range seen with DTwP/Hib-TT vaccine [15].

At this time, consideration was also being given to inclusion of a 7-valent pneumococcal conjugate (PCV7) in the UK infant immunization programme as a two dose infant schedule with a booster after 12 months of age. PCV7 vaccine (Prevenar\textsuperscript{TM}, Wyeth Vaccines) was licensed in the UK as 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 US that used a 2, 4, 6 month schedule with a booster at 18 months [3]. However, a recent UK study in which a 9-valent pneumococcal conjugate (PCV9) vaccine was given either at 2, 3, 4 months or at 2, 4 months, with concomitant DTaP\textsubscript{5}/Hib-TT and MCC-CRM\textsubscript{197} vaccines [13], showed pneumococcal serotype-specific responses that were equivalent with the 2 and 3 dose course and similar in magnitude to those reported after the third dose of PCV7 at 6 months in US infants [3, 25, 28].

There are similar data suggesting that a reduced number of doses of MCC are adequate for priming [5, 26, 30] and all three MCC vaccines are now licensed as a 2 dose primary schedule from 2
months of age with at least two months between doses. However, none of the MCC immunogenicity studies using a reduced schedule have included co-administration 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 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 co-administered.

Methods

Study population

Infants eligible for routine vaccination were recruited from general practices (GPs) in Hertfordshire and Gloucestershire, England. Criteria for study participation included: no contraindication to vaccination as specified in the “Green Book” [11]; written informed consent obtained from the parent or legal guardian; 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 block size 16. Groups 1 to 3 received one of the three licensed MCC vaccines (Meningitec™, Wyeth Vaccines; Menjugate®, Novartis Vaccines; NeisVac-C™, 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 the serum bactericidal antibody (SBA) assay as previously described [18]. The SBA target strain was C11 (C:16:P1.7-1,1) and the
complement source was baby rabbit sera (Pel-Freeze Incorporated, Rodgerson, AZ, USA). SBA titers are expressed as the reciprocal of the final serum dilution giving $\geq 50\%$ killing at 60 minutes. For computational purposes, SBA titers $< 4$ were assigned a value of 2. Hib, diphtheria and tetanus specific antibodies (IgG) were quantified using standardized ELISAs $[20, 21, 24]$. 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, the 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 the PCV7, assessed at the Immunobiology Unit of the Institute of Child Health, London, will be reported separately.

To fulfill a duty of care, a further dose of single antigen Hib vaccine (Hiberix®, GlaxoSmithKline) and/or the MCC vaccine subjects had already been given, was offered to any subject with an antibody response 4-6 weeks after their last dose below the putative protective thresholds of 0.15 $\mu$g/mL $[14]$ and a SBA titer of 8 $[1]$, respectively.

**Analyses**

In all analyses the outcome of interest at the various blood sampling time points, with 95% confidence intervals, were:

- the MCC SBA geometric mean titers (GMTs) and the proportions achieving SBA titers $\geq 8$ or $\geq 128$, the putative protective and more discriminatory antibody levels, respectively $[1]$.
- the Hib antibody geometric mean concentrations (GMCs) and the proportions achieving antibody concentrations $\geq 0.15$ $\mu$g/mL (the putative protective level) or $\geq 1.00$ $\mu$g/mL (considered predictive of longer-term protection $[14]$).
- The diphtheria and tetanus GMCs and the proportions achieving $\geq 0.1$ IU/mL or $\geq 1.0$ IU/mL $[5, 12]$. 
Differences between groups can be assessed by non-overlapping 95% confidence intervals. This gives an approximate level of significance of 1% which is conservative to allow for multiple comparisons. Normal errors regression was used on logged antibody responses to investigate differences in response 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% confidence interval widths of less than +/- 10% (assumed observed proportion >90%) and to estimate geometric means with 95% confidence intervals widths to within +/-1.5 fold (assumed between individual standard deviation <0.65 units on a log_{10} scale). This required a sample size of 55 in each study group, with 65 recruited to allow for drop outs. The study was also powered on the secondary aim of detecting differences in antibody responses between the schedules (groups 1-3 and 4-6) 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 between 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 programme 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, 3 months, achieved comparable protection to that available through routine vaccination outside the trial at 2, 4 months (as given to groups 4 to 6). For the purposes of rapidity this was done using a pneumococcal serotype-specific multiplex assay [16]. 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, 4 month than the 2, 3 month schedule. In view of these results two steps were immediately taken for ethical reasons:
1. Recruitment to groups 1 to 3 was halted and the study was completed by reallocating 10 individuals already randomized to groups 1-3 but not yet vaccinated to groups 4-6 and increasing the total number randomized to groups 4-6 in order to maintain the total target sample size (Table 2).

2. Subjects from groups 1 to 3 in the birth cohort eligible to receive two doses of PCV7 two 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 re-called for a third dose of PCV7 in the first year of life, at least two 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 slightly fewer numbers with serologic results 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 EU Clinical Trial Directive. It was approved by the UK Medicines and Healthcare products Regulatory Authority (MHRA) and the Eastern Multi Center Research Ethics Committee (MREC). The EudraCT number was 2004-001049-14 and the study was registered on the public website, ClinicalTrials.gov 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 randomized group and as treated group. The same infants did not necessarily contribute to sampling at each point due to failed venepuncture or non-attendance. The 10 individuals already randomized to groups 1 to 3 but vaccinated according to the schedule for groups 4 to 6 after the national programme 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 7-9 weeks from the first to third visit.

The age at the first, second and third visits was 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 age at the first visit was 48 to 82 days, at the second visit was 76 to 122 days and at the third visit 105 to 161 days. No significant differences were found in responses between males and females for any of the serologic measurements.

**Responses to MCC vaccine**

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

After the second dose there were significant increases in SBA GMTs for Menjugate and Meningitec but only a modest increase for NeisVac-C where a good response had already been achieved after one dose. There were significant differences in the SBA GMTs achieved according to MCC vaccine given, the highest being for Menjugate, 682 (95% CI 546 – 852), followed by NeisVac-C, 437 (95% CI 354 – 539) and then Meningitec, 229 (95% CI 176 – 298). For all three vaccines, 98-99% of subjects achieved SBA titers ≥8, but only the groups receiving Menjugate and NeisVac-C had over 90% with titers ≥ 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 the group that received concomitant NeisVac-C had a significantly higher PRP GMC, 4.29 µg/mL (95% CI 3.27 – 5.62), than either Menjugate, 1.76 µg/mL (95% CI 1.29 - 2.39) or Meningitec recipients, 1.75 µg/mL (95% CI 1.29 – 2.38). The percentage of subjects achieving PRP IgG ≥0.15 µg/mL also rose with each dose, though did not differ between the co-administered MCC products (Table 4). After the third dose, in excess of 85% of subjects had PRP IgG ≥0.15 µg/mL.

For the percentage of subjects achieving PRP IgG ≥1.0 µg/mL, differences were emerging after the second dose according to co-administered MCC vaccine, and after the third dose was significantly higher in the NeisVac-C group at 86% (95% CI 78 - 92) than the groups receiving Menjugate at 66% (95% CI 57 - 74) or Meningitec at 62% (95% CI 53 - 70).

Tetanus and diphtheria

The tetanus GMCs (IU/mL) increased significantly with each dose of vaccine (Table 5). The post third dose GMCs differed significantly with the NeisVac-C group being higher, 1.63 IU/mL (95%CI 1.43 - 1.86), than either the Menjugate, 1.10 IU/mL (95%CI 0.97 - 1.25), or Meningitec, 0.98 IU/mL (95% CI 0.85 - 1.12). All subjects achieved antibody concentrations ≥ 0.1 IU/mL after the third dose, and the proportions ≥ 1.0 IU/mL were 48% (Meningitec), 54% (Menjugate) and 78% (NeisVac-C).

After each dose of Pediacel, the diphtheria IgG GMCs increased significantly and similarly regardless of co-administered MCC product (Table 5). After the third dose, for those in receipt of co-administered Meningitec, Menjugate and NeisVac-C, the percentages of subjects achieving antibody concentrations ≥ 0.1 IU/mL were 100, 100 and 99, respectively and for ≥ 1.0 IU/mL the percentages were 77, 81 and 77, respectively.
**Serious adverse events (SAEs)**

There were nine SAEs during the primary phase of the study, none of these were judged by the investigator to be causally related to vaccination (time since last vaccination 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 admission by parent for irritability – loratidine instead of paracetemol (1 month);
- Bronchiolitis (1 month);
- Repair of nail bed (6 months);
- 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 the three licensed monovalent MCC vaccines when given at 2, 3 or 2, 4 months of age concomitantly with PCV7 and DTaP/IPV/Hib-TT (Pediacel) vaccine. Functional antibody responses to MCC vaccines were not significantly different when administered at 2, 3 or 2, 4 months of age. Differences were seen between the immunogenicity of the three MCC vaccines following one or two doses. Following two doses of MCC, the SBA GMT, but not proportion putatively protected, was higher for Menjugate than NeisVac-C or Meningitec. When coadministered with Pediacel, Menjugate has previously been shown to elicit a higher SBA GMT than NeisVac-C in a 2, 3, 4 month schedule [15].

Following a single dose, however, NeisVac-C gave a significantly higher SBA GMT and proportion of infants putatively protected, than Menjugate which was in turn significantly higher than Meningitec. As the proportions protected with NeisVac-C and Menjugate were 97% and 80%, this opens the possibility of immunogenicity studies utilising 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 at 2, 3, 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 275-877) when given at 2 months of age with a DTaP₃-Hib-TT (Infanrix-Hib, GSK) though without concomitant PCV7 [30]. A number of studies have reported good immunogenicity of a single dose of NeisVac-C when given in infancy with wP containing vaccines [6, 26].

The SBA GMTs achieved after 2 doses of NeisVac-C and Menjugate were lower than those reported by Kitchin et al. (2007) [15] when these MCC vaccines were given as a 3 dose schedule with Pediacel but without concomitant PCV7 [15]; in that study GMTs of 690 (95% CI 416-1140) and 2165 (95% CI 1517-3089) were achieved for NeisVac-C and Menjugate, respectively compared with 437 (95% CI 354-539) and 682 (95% CI 546-852), respectively for these MCC vaccines in the current study. Similarly the SBA GMT achieved after two doses of Meningitec (229, 95% CI 176-298) was lower than reported in earlier studies in which three doses were given at 2,3,4 months concomitantly with DTaP₃/Hib-TT [29] or DTwP-HibTT vaccine [7] where GMTs of 380 (95% CI 275-526) and 535 (95% CI 441-649), respectively were achieved. The reasons for these differences are not clear since in all these studies the SBA assays were carried out in the same laboratory (Manchester). They could be related to the use of only 2 doses of MCC vaccine, or concomitant administration of PCV7, or 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 2,3,4 month schedule are not significantly higher than after the second when given without PCV7 [6, 27, 30]. Furthermore, the SBA GMT after 2 doses of Meningitec in the current study was similar to that reported after 3 doses in an earlier UK study in which it was given concomitantly with a DTaP₃/Hib-TT vaccine at 2,3,4 months with 2 or 3 doses of a PCV9 vaccine [13]; in that study SBA GMTs were 291 (95% CI 208 – 407) and 187 (95% CI 127 – 275) for the groups who received 3 and 2 doses of PCV9, respectively. The effect of concomitant PCV7 on the response to Menjugate has been studied in a 2, 4, 6 month schedule [4].
No effect was observed on group C SBA titers when Menjugate was coadministered with DTaP/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 vaccine, at least in a more expanded schedule. It seems likely therefore that the differences seen in SBA GMTs 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 number of doses or concomitant vaccines is to be determined.

As has been previously reported the Hib PRP IgG responses were significantly enhanced when the DTaP/IPV/Hib-TT vaccine was administered with MCC-TT (NeisVac-C) as opposed to either of the MCC-CRM197 vaccines [15, 31]. Likewise, tetanus antitoxin responses were significantly enhanced when the DTaP/IPV/Hib-TT vaccine was administered with the MCC-TT (NeisVac-C) as opposed to either of the MCC-CRM197 vaccines [15]. In the study of Kitchin et al. (2007) [15], which compared 3 doses of either NeisVac-C or Menjugate coadministered with Pediacel at 2, 3, 4 months of age, enhancement was also seen for diphtheria antitoxin IgG GMCs for the Menjugate group 0.1 IU/mL (95% CI 0.07 to 0.13) when compared with the NeisVac-C group 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 in the Kitchin et al (2007) [15] study due to an ELISA being utilized [20], rather than a microneutralization assay as in the Kitchin et al study. A subset of the serum samples (n = 69) from the latter was reassayed in the ELISA and IgG GMCs were 1.40 (95% CI 0.99 – 1.97) and 0.84 (95% CI 0.63 – 1.13) for Menjugate and NeisVac-C groups, respectively, when given with Pediacel [Sanofi Pasteur MSD, Personal communication]. These levels in the present study for the Menjugate and Neisvac-C groups were GMCs of 1.78 (1.54-2.05) and 1.54 (1.32 -1.80), respectively. Thus the addition of another CRM197 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/IPV/Hib-TT and should be investigated further in single dose priming strategies.

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References


Immunogenicity of one, two or three doses of a meningococcal C conjugate vaccine conjugated to tetanus toxoid, given as a three-dose primary vaccination course in UK infants at 2, 3 and 4 months of age with acellular pertussis-containing DTP/Hib vaccine. Vaccine. 24:215-219.

Table 1. Treatment schedule for vaccination and blood sampling for the six randomized groups

<table>
<thead>
<tr>
<th>GROUP</th>
<th>2 months</th>
<th>3 months</th>
<th>4 months</th>
<th>5 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pediacelea&lt;br&gt;Meningitecb&lt;br&gt;Prevenarc</td>
<td>Pediacelea&lt;br&gt;Meningitec&lt;br&gt;Prevenarc</td>
<td>Pediacelea</td>
<td>Blood&lt;br&gt;Blood</td>
</tr>
<tr>
<td>2</td>
<td>Pediacelex&lt;br&gt;Menjugate&lt;br&gt;Prevenar</td>
<td>Pediacelex&lt;br&gt;Menjugate&lt;br&gt;Prevenar</td>
<td>Pediacelex</td>
<td>Blood&lt;br&gt;Blood</td>
</tr>
<tr>
<td>3</td>
<td>Pediacelex&lt;br&gt;NeisVac-C&lt;br&gt;Prevenar</td>
<td>Pediacelex&lt;br&gt;NeisVac-C&lt;br&gt;Prevenar</td>
<td>Pediacelex</td>
<td>Blood&lt;br&gt;Blood</td>
</tr>
<tr>
<td>4</td>
<td>Pediacelex&lt;br&gt;Meningitec&lt;br&gt;Prevenar</td>
<td>Pediacelex</td>
<td>Pediacelex&lt;br&gt;Meningitec&lt;br&gt;Prevenar</td>
<td>Blood&lt;br&gt;Blood</td>
</tr>
<tr>
<td>5</td>
<td>Pediacelex&lt;br&gt;Menjugate&lt;br&gt;Prevenar</td>
<td>Pediacelex</td>
<td>Pediacelex&lt;br&gt;Menjugate&lt;br&gt;Prevenar</td>
<td>Blood&lt;br&gt;Blood</td>
</tr>
<tr>
<td>6</td>
<td>Pediacelex&lt;br&gt;NeisVac-C&lt;br&gt;Prevenar</td>
<td>Pediacelex</td>
<td>Pediacelex&lt;br&gt;NeisVac-C&lt;br&gt;Prevenar</td>
<td>Blood&lt;br&gt;Blood</td>
</tr>
</tbody>
</table>

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a Pediacelex, DTaP3/Hib/IPV, Sanofi Pasteur.
b Meningitec, MCC-CRM197, Wyeth Vaccines
c Prevenar, PCV7, Wyeth Vaccines
d Menjugate, MCC-CRM197, Novartis Vaccines
e NeisVac-C, MCC-TT, Baxter Bioscience
Table 2. Number of subjects randomized to each group and the reassignment following the protocol amendment (as treated group)

<table>
<thead>
<tr>
<th>Randomized group (n)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>Excluded</th>
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<tbody>
<tr>
<td>1 (54)</td>
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<td>2</td>
<td></td>
<td></td>
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<td>4</td>
<td></td>
<td></td>
<td>1</td>
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<td>3 (56)</td>
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<td>48</td>
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<td>4</td>
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<tr>
<td>4 (81)</td>
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<td></td>
<td></td>
<td>78</td>
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<td>5 (77)</td>
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<td></td>
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<td>76</td>
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<td>1</td>
</tr>
<tr>
<td>6 (71)</td>
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<td></td>
<td>68</td>
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<td>48</td>
<td>80</td>
<td>80</td>
<td>72</td>
<td>15*</td>
</tr>
</tbody>
</table>

*Fifteen subjects were excluded from analyses for the following reasons:

- Interval between dose 1 and 2 greater than 6 weeks or dose 1 and 3 greater than 12 weeks: N = 6
- Three doses of MCC vaccine given 2, 3, 4 months: N = 1
- Three doses of PCV7 given 2, 3, 4 months: N = 1
- Left the trial by vaccine 2: N = 2
- Left the trial by vaccine 3: N = 3
- Received two different MCC vaccines: N = 2
Table 3. Meningococcal group C percentages of subjects achieving SBA titers $\geq 8$ or $\geq 128$ and SBA GMTs one month following either 1 dose at 2 months of age, 2 doses at 2, 3 months of age or 2, 4 months of age by MCC vaccine manufacturer

<table>
<thead>
<tr>
<th>Group</th>
<th>measure</th>
<th>MCC vaccine</th>
<th>n</th>
<th>% $\geq 8$ (95% CI)</th>
<th>% $\geq 128$ (95% CI)</th>
<th>Geometric mean titer (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>post 1 dose at 2 months</td>
<td>Meningitec</td>
<td>70</td>
<td>53 (41 - 65)</td>
<td>10 (4 – 20)</td>
<td>10 (7-14)</td>
</tr>
<tr>
<td>5</td>
<td>post 2 doses at 2, 3 months</td>
<td>Menjugate</td>
<td>66</td>
<td>80 (69 - 89)</td>
<td>44 (32 – 57)</td>
<td>48 (31-74)</td>
</tr>
<tr>
<td>6</td>
<td>post 2 doses at 2, 3 months</td>
<td>NeisVac-C</td>
<td>59</td>
<td>97 (88 - 100)</td>
<td>85 (73 – 93)</td>
<td>295 (199-438)</td>
</tr>
<tr>
<td>1</td>
<td>post 2 doses at 2, 3 months</td>
<td>Meningitec</td>
<td>43</td>
<td>100 (92 - 100)</td>
<td>84 (69 – 93)</td>
<td>277 (189-408)</td>
</tr>
<tr>
<td>2</td>
<td>post 2 doses at 2, 3 months</td>
<td>Menjugate</td>
<td>44</td>
<td>98 (88 – 100)</td>
<td>89 (75 – 96)</td>
<td>648 (397-1060)</td>
</tr>
<tr>
<td>3</td>
<td>post 2 doses at 2, 3 months</td>
<td>NeisVac-C</td>
<td>44</td>
<td>100 (92 - 100)</td>
<td>93 (81 – 99)</td>
<td>451 (324-629)</td>
</tr>
<tr>
<td>4</td>
<td>post 2 doses at 2, 4 months</td>
<td>Meningitec</td>
<td>76</td>
<td>96 (89 - 99)</td>
<td>78 (67 – 86)</td>
<td>206 (144-293)</td>
</tr>
<tr>
<td>5</td>
<td>post 2 doses at 2, 4 months</td>
<td>Menjugate</td>
<td>77</td>
<td>100 (95 - 100)</td>
<td>99 (93 - 100)</td>
<td>702 (563-875)</td>
</tr>
<tr>
<td>6</td>
<td>post 2 doses at 2, 4 months</td>
<td>NeisVac-C</td>
<td>65</td>
<td>98 (92 - 100)</td>
<td>92 (83 – 98)</td>
<td>427 (323-564)</td>
</tr>
<tr>
<td>1 and 4</td>
<td>post 2 doses</td>
<td>Meningitec</td>
<td>119</td>
<td>98 (93-99)</td>
<td>80 (72-87)</td>
<td>229 (176-298)</td>
</tr>
<tr>
<td>1 and 5</td>
<td>post 2 doses</td>
<td>Menjugate</td>
<td>121</td>
<td>99 (96-100)</td>
<td>95 (90-98)</td>
<td>682 (546-852)</td>
</tr>
<tr>
<td>3 and 6</td>
<td>post 2 doses</td>
<td>NeisVac-C</td>
<td>109</td>
<td>99 (95-100)</td>
<td>93 (86-97)</td>
<td>437 (354-539)</td>
</tr>
</tbody>
</table>
Table 4. Hib-polyribosylribitol phosphate (PRP) IgG geometric mean concentrations (GMCs) and percentages of subjects achieving PRP IgG of $\geq 0.15$ µg/mL or $\geq 1.0$ µg/mL one month following either 1 dose at 2 months of age, 2 doses at 2, 3 months of age or three doses at 2, 3, 4 months of age by MCC vaccine manufacturer.

<table>
<thead>
<tr>
<th>Group</th>
<th>measure</th>
<th>MCC vaccine</th>
<th>n</th>
<th>% $\geq 0.15$ µg/mL (95% CI)</th>
<th>% $\geq 1.0$ µg/mL (95% CI)</th>
<th>Geometric mean concentration (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>post 1 dose at 2 months</td>
<td>Meningitec</td>
<td>76</td>
<td>25 (16 - 36)</td>
<td>3 (0 - 9)</td>
<td>0.13 (0.10-0.15)</td>
</tr>
<tr>
<td>5</td>
<td>post 1 dose at 2 months</td>
<td>Menjugate</td>
<td>74</td>
<td>26 (16 - 37)</td>
<td>4 (0 - 11)</td>
<td>0.12 (0.10-0.15)</td>
</tr>
<tr>
<td>6</td>
<td>post 1 dose at 2 months</td>
<td>NeisVac-C</td>
<td>64</td>
<td>31 (20 - 44)</td>
<td>3 (0 - 11)</td>
<td>0.14 (0.11-0.18)</td>
</tr>
<tr>
<td>1</td>
<td>post 2 doses at 2, 3 months</td>
<td>Meningitec</td>
<td>47</td>
<td>51 (36-66)</td>
<td>15 (6-28)</td>
<td>0.23 (0.16-0.33)</td>
</tr>
<tr>
<td>2</td>
<td>post 2 doses at 2, 3 months</td>
<td>Menjugate</td>
<td>48</td>
<td>54 (39-69)</td>
<td>21 (10-35)</td>
<td>0.30 (0.20-0.47)</td>
</tr>
<tr>
<td>3</td>
<td>post 2 doses at 2, 3 months</td>
<td>NeisVac-C</td>
<td>45</td>
<td>67 (51-80)</td>
<td>27 (15-42)</td>
<td>0.47 (0.26-0.85)</td>
</tr>
<tr>
<td>1,4</td>
<td>post 3 doses at 2,3,4 months</td>
<td>Meningitec</td>
<td>126</td>
<td>89 (82-94)</td>
<td>62 (53-70)</td>
<td>1.75 (1.29-2.38)</td>
</tr>
<tr>
<td>2,5</td>
<td>post 3 doses at 2,3,4 months</td>
<td>Menjugate</td>
<td>126</td>
<td>85 (77-91)</td>
<td>66 (57-74)</td>
<td>1.76 (1.29-2.39)</td>
</tr>
<tr>
<td>3,6</td>
<td>post 3 doses at 2,3,4 months</td>
<td>NeisVac-C</td>
<td>115</td>
<td>96 (90-99)</td>
<td>86 (78-92)</td>
<td>4.29 (3.27-5.62)</td>
</tr>
</tbody>
</table>
Table 5. Tetanus and diphtheria GMCs one month following either 1 dose at 2 months of age, 2 doses at 2, 3 months of age or three doses of Pediacel at 2, 3, 4 months of age by MCC vaccine manufacturer

<table>
<thead>
<tr>
<th>Group</th>
<th>measure</th>
<th>MCC vaccine</th>
<th>Tetanus GMC (IU/mL) (95% CI) [N]</th>
<th>% ≥ 0.1 IU/mL (95% CI)</th>
<th>% ≥ 1.0 IU/mL (95% CI)</th>
<th>Diphtheria GMC (IU/mL) (95% CI) [N]</th>
<th>% ≥ 0.1 IU/mL (95% CI)</th>
<th>% ≥ 1.0 IU/mL (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>post 1 dose at 2 months</td>
<td>Meningitec</td>
<td>0.30 (0.25-0.36) [75]</td>
<td>92 (83-97)</td>
<td>7 (2-15)</td>
<td>0.12 (0.10-0.14) [76]</td>
<td>62 (50-73)</td>
<td>0 (0-5)</td>
</tr>
<tr>
<td>5</td>
<td>post 2 doses at 2, 3 months</td>
<td>Menjugate</td>
<td>0.29 (0.25-0.34) [74]</td>
<td>95 (87-99)</td>
<td>4 (1-11)</td>
<td>0.12 (0.10-0.14) [74]</td>
<td>55 (43-67)</td>
<td>0 (0-5)</td>
</tr>
<tr>
<td>6</td>
<td>post 3 doses at 2, 3, 4 months</td>
<td>NeisVac-C</td>
<td>0.30 (0.25-0.36) [64]</td>
<td>89 (79-95)</td>
<td>3 (0-11)</td>
<td>0.11 (0.09-0.14) [64]</td>
<td>52 (39-64)</td>
<td>0 (0-6)</td>
</tr>
<tr>
<td>1</td>
<td>post 1 dose at 2 months</td>
<td>Meningitec</td>
<td>0.42 (0.34-0.52) [47]</td>
<td>100 (92-100)</td>
<td>17 (8-31)</td>
<td>0.83 (0.67-1.02) [47]</td>
<td>100 (92-100)</td>
<td>47 (32-62)</td>
</tr>
<tr>
<td>2</td>
<td>post 2 doses at 2, 3 months</td>
<td>Menjugate</td>
<td>0.47 (0.38-0.59) [48]</td>
<td>100 (93-100)</td>
<td>13 (5-25)</td>
<td>0.73 (0.55-0.98) [48]</td>
<td>98 (89-100)</td>
<td>35 (22-51)</td>
</tr>
<tr>
<td>3</td>
<td>post 3 doses at 2, 3, 4 months</td>
<td>NeisVac-C</td>
<td>0.62 (0.50-0.78) [45]</td>
<td>100 (92-1.00)</td>
<td>18 (8-32)</td>
<td>0.61 (0.44-0.85) [45]</td>
<td>93 (82-99)</td>
<td>33 (20-49)</td>
</tr>
<tr>
<td>1,4</td>
<td>post 1 dose at 2 months</td>
<td>Meningitec</td>
<td>0.98 (0.85-1.12) [126]</td>
<td>100 (97-100)</td>
<td>48 (37-57)</td>
<td>1.69 (1.47-1.95) [126]</td>
<td>100 (97-100)</td>
<td>77 (69-84)</td>
</tr>
<tr>
<td>2,5</td>
<td>post 2 doses at 2, 3 months</td>
<td>Menjugate</td>
<td>1.10 (0.97-1.25) [126]</td>
<td>100 (97-100)</td>
<td>54 (45-63)</td>
<td>1.78 (1.54-2.05) [125]</td>
<td>100 (97-100)</td>
<td>81 (73-87)</td>
</tr>
<tr>
<td>3,6</td>
<td>post 3 doses at 2, 3, 4 months</td>
<td>NeisVac-C</td>
<td>1.63 (1.43-1.86) [115]</td>
<td>100 (97-100)</td>
<td>78 (70-85)</td>
<td>1.54 (1.32-1.80) [113]</td>
<td>99 (95-100)</td>
<td>77 (68-84)</td>
</tr>
</tbody>
</table>