ORIGINAL ARTICLE

Evaluation of a diphtheria–tetanus–acellular pertussis–inactivated poliovirus–*Haemophilus influenzae* type b vaccine given concurrently with meningococcal group C conjugate vaccine at 2, 3 and 4 months of age

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Background and objective: In view of the possible introduction of diphtheria–tetanus–acellular pertussis–inactivated poliovirus–*Haemophilus influenzae* type b (DTaP-IPV-Hib, eg Pediacel) vaccine in the UK, a study of the immunogenicity of Pediacel when given with one of two different meningococcal group C conjugate (MCC) vaccines at 2, 3 and 4 months of age was conducted.
Methods: Randomised controlled study in 241 infants.
Results: Post vaccination, the proportion of infants with anti-polyribosylribitol phosphate (PRP) levels ⩾0.15 μg/ml was 93.2% (95% confidence interval (CI) 86.6 to 96.7) in the Pediacel group compared with 100% (95% CI 96.4 to 100) in the diphtheria–tetanus–whole-cell pertussis–*Haemophilus influenzae* type b (DTwP-Hib) group. The anti-PRP response was lower in infants receiving either Pediacel or DTwP-Hib when these vaccines were given concomitantly with meningococcal group C conjugate with diphtheria-derived protein CRM_{197} as conjugate protein (MCC-CRM) compared with meningococcal group C conjugate with tetanus toxoid as conjugate protein (MCC-TT). For group C meningococcus, the proportion of infants with serum bactericidal antibody (SBA) titre ⩾1:8 in the Pediacel group was 99.0% compared with 100% in the DTwP-Hib group. The MCC SBA geometric mean titre (GMT) was lower in those receiving Pediacel with MCC-TT than in those receiving DTwP-Hib with MCC-TT, although all titres were well above the protective threshold. The MCC SBA GMT was similar in those receiving Pediacel and DTwP-Hib and MCC-CRM. Responses to all other vaccine components were equivalent in the two groups.
Conclusions: Pediacel is immunogenic when given at 2, 3 and 4 months of age. Coadministration of MCC vaccine can influence the Hib response, and the MCC response to a tetanus conjugate can be influenced by the nature of the coadministered DTP-Hib vaccine.

At the time this study was conducted, the UK infant immunisation programme provided protection against diphtheria (D), tetanus (T), pertussis (P), polio, *Haemophilus influenzae* type b (Hib) and serogroup C meningococcal meningitis. Three doses of all antigens were given at 2, 3 and 4 months of age.

In September 2004, whole-cell pertussis vaccine for infants was replaced with acellular pertussis vaccine. In addition, oral poliomyelitis vaccine (OPV) was replaced with inactivated poliomyelitis vaccine (IPV) throughout the immunisation programme. These changes were facilitated by the availability of new inactivated poliovirus-containing combination vaccines. The meningococcal group C conjugate (MCC) vaccines contain either diphtheria-derived protein CRM_{197} (MCC-CRM) or tetanus toxoid (MCC-TT) as the conjugate protein.

Pediacel is a pentavalent diphtheria–tetanus–acellular pertussis–inactivated poliovirus–*Haemophilus influenzae* type b (DTaP-IPV-Hib) combination containing five-component acellular pertussis. When given at 2, 4 and 6 months of age, Hib-containing combination vaccines based on five-component acellular pertussis have been shown to produce immune responses to the Hib component similar to those when the Hib vaccine is given separately.[1 2]

Hib vaccination has led to dramatic decreases in Hib disease.[3] When added to many acellular pertussis-containing combinations, antibody response to the Hib component is lower compared with the separate administration of Hib vaccine.[4] Use of a three-component acellular pertussis combination vaccine without a booster in the second year of life in the UK seems to have been one of the factors associated with a marked increase in disease, necessitating a national catch-up campaign to be undertaken.[5]

In this study, we assessed the immunogenicity and safety of Pediacel compared with the licensed diphtheria–tetanus–whole-cell pertussis–*Haemophilus influenzae* type b (DTwP-Hib) vaccine under a 2, 3 and 4 month schedule, with concomitant administration of MCC-TT or MCC-CRM. It supported the introduction of Pediacel in the UK.

MATERIALS AND METHODS

This was an open, randomised, controlled study performed in five study centres in the UK, from November 2001 to December 2002, in accordance with local laws and regulations. Approval was granted by the relevant ethics committees. Written

Abbreviations: DTaP-Hib, diphtheria–tetanus–acellular pertussis; DTaP-IPV-Hib, diphtheria–tetanus–acellular pertussis–inactivated poliovirus–*Haemophilus influenzae* type b; DTwP, diphtheria–tetanus–whole-cell pertussis; DTwP-Hib, diphtheria–tetanus–whole-cell pertussis–*Haemophilus influenzae* type b; GMC, geometric mean concentration; GMT, geometric mean titre; Hib, *Haemophilus influenzae* type b; IPV, inactivated poliomyelitis vaccine; ITT, intention-to-treat; MCC, meningococcal group C conjugate; MenC, meningococcal serogroup C; MCC-CRM, meningococcal group C conjugate with diphtheria-derived protein CRM_{197} as conjugate protein; MCC-TT, meningococcal group C conjugate with tetanus toxoid as conjugate protein; OPV, oral poliomyelitis vaccine; PRP, polyribosylribitol phosphate; SBA, serum bactericidal antibody

Table 1 Study vaccines

	Stratum A	Stratum B
Group 1	DTaP-IPV-Hib (Pediacel) MCC-TT (NeisVac-C, Baxter)	DTaP-IPV-Hib (Pediacel) MCC-CRM (Menjugate, Chiron)
Group 2	DTwP-Hib (Act-Hib DTP, Sanofi Pasteur MSD) MCC-TT (NeisVac-C) OPV	DTwP-Hib (Act-Hib DTP) MCC-CRM (Menjugate) OPV

DTaP-IPV-Hib, diphtheria–tetanus–acellular pertussis–inactivated poliovirus–*Haemophilus influenzae* type b; DTwP-Hib, diphtheria–tetanus–whole-cell pertussis–*Haemophilus influenzae* type b; MCC-CRM, meningococcal group C conjugate with diphtheria-derived protein CRM_{197} as conjugate protein; MCC-TT, meningococcal group C conjugate with tetanus toxoid as conjugate protein; OPV, oral poliomyelitis vaccine.

informed consent was given by the parents of infants or legally acceptable representatives before enrolment.

Participants
Eligible participants were healthy infants aged 7–11 weeks, with birth weight ⩾2000 g. Vaccination was deferred for infants with any acute systemic illness or fever (axillary temperature >37.5°C) on the day of vaccination.

Vaccines
Infants were randomised evenly to one of two groups, each containing two strata (table 1).

Infants were vaccinated at 2, 3 and 4 months of age. Pediacel, DTwP-Hib and MCC vaccines were given intramuscularly into the anterolateral aspect of the thigh through a 16 mm 25 G needle. OPV was given orally.

Pediacel was produced by sanofi pasteur, Canada—a single batch was used. All other vaccines were sourced from commercial stock—more than one batch was used. Pediacel is a 0.5 ml fully liquid DTaP-IPV-Hib vaccine. The five acellular pertussis components are as follows: 20 μg pertussis toxoid, 20 μg filamentous haemagglutinin, 3 μg pertactin and 5 μg fimbrial agglutinins 2 and 3. DTwP-Hib is a 0.5 ml diphtheria, tetanus and whole-cell pertussis vaccine reconstituting Hib vaccine. Both Pediacel and DTwP-Hib contain 10 μg polyribosylribitol phosphate (PRP) conjugated to 20 μg tetanus toxoid (PRP-T).

Safety
Safety is discussed in a separate article.[5a]

Serology
Blood samples were collected before the first vaccination and 4–6 weeks after the third dose. Sera were analysed at the clinical immunology platform, sanofi pasteur for antibodies to the following:

(1). PRP using a Farr-type radioimmunoassay; (2). Pertussis toxin, filamentous haemagglutinin, pertactin, fimbrial agglutinins and tetanus antitoxin by ELISA; (3). Diphtheria antitoxin by a microneutralisation assay; (4). Poliomyelitis viruses types 1, 2 and 3 by a neutralisation assay.

The Health Protection Agency assessed anti-PRP antibodies using an ELISA[6] at the Immunoassay Laboratory, Porton, UK, and meningococcal serogroup C (MenC) serum bactericidal antibodies (SBAs) and immunoglobulin (Ig)G antibodies (by ELISA)[7] at the Meningococcal Reference Laboratory, Manchester, UK.

Statistical analysis
Statistical analyses were performed by Chiltern International Limited, Berkshire, UK using SAS V.6.12. The main immunogenicity analysis was a Per Protocol analysis, excluding data from non-compliant infants. An intention-to-treat analysis was also performed. For the primary objectives, comparisons between groups were made using 90% confidence intervals (CIs) of the difference of anti-PRP and MenC proportions above protective antibody levels.[8 9] The upper limit of the 90% CI of the difference of <10% was an indication that the antibody responses in the Pediacel group were non-inferior to those in the DTwP-Hib group. All other analyses were descriptive. Antibody responses were expressed as geometric mean concentrations (GMCs) or titres (GMTs), or proportions achieving known seroconversion or seroprotection rates. A direct comparison of the two groups within the MenC stratum was added after availability of the results because of its importance in interpreting the study results.

Sample size
The sample size calculation was based on the assumption that the proportion of infants achieving protective levels (antibody level ⩾0.15 μg/ml for Hib and SBA ⩾1:8 for MenC) would be 95% for both Hib and MenC. Non-inferiority was defined as an upper confidence limit of the absolute difference between groups at <10%. In all, 103 evaluable infants were required to achieve 95% power for each antigen, with a 5% one-sided type I error rate. A minimum of 90% power for this study could be achieved when multiple comparisons were taken into consideration.

RESULTS
Study population
A total of 241 infants were enrolled to the study and received at least one study vaccine (table 2).

The mean duration between doses 1 and 2 was 32 days, between doses 2 and 3 was 31 days and between dose 3 and the post-vaccination blood sample was 33 days, with no significant differences between the groups. No subject withdrew due to an adverse event.

Table 2 Study demographics

	Pediacel (n = 121)	DTwP-Hib + OPV (n = 120)
Age, weeks		
Mean (SD)	8.62 (0.76)	8.63 (0.81)
Range	7.0–11.1	7.1–10.7
Sex, n (%)		
Male	68 (56.2)	60 (50)
Female	53 (43.8)	60 (50)
Temperature (°C) before dose 1	36.67 (0.34)	36.68 (0.28)
Number of infants withdrawn from the study	2	3

DTwP-Hib, diphtheria–tetanus–whole-cell pertussis–*Haemophilus influenzae* type b; OPV, oral poliomyelitis vaccine.

Immunogenicity

A total of 105 (85.1%) infants from group 1 and 102 (85.0%) from group 2 were included in the Per Protocol population analysis of immunogenicity. Exclusions were primarily due to study visits outside of the time windows allowed (these infants were included in the ITT analysis), whereas nine infants did not have a post-vaccination blood sample. Similar results were seen in the Per Protocol and ITT populations and so results from only the Per Protocol analysis are presented.

Anti-PRP response (RIA)

The anti-PRP GMCs before vaccination were 0.07 μg/ml in group 1 and 0.08 μg/ml in group 2. The proportion of group 1 infants with an anti-PRP level ⩾0.15 μg/ml 4 weeks after the third dose of vaccine was 93.2% (95% CI 86.6 to 96.7) compared with 100% (95% CI 96.4 to 100) in group 2 infants (table 3). The difference was 6.8% (90% CI 2.8 to 12.1). As the upper bound of the 90% CI was >10%, non-inferiority of Pediacel, compared with DTwP-Hib+OPV, was not shown.

After vaccination, significant differences in the anti-PRP response between the strata were observed. The anti-PRP response was lower in infants receiving either Pediacel or DTwP-Hib+OPV when these vaccines were given concomitantly with MCC-CRM than when given with MCC-TT.

Anti-PRP response (ELISA)

After vaccination, the anti-PRP response was also measured on an ongoing basis by ELISA, as a clinical precaution to determine any requirement for an additional dose of Hib vaccine for infants with anti-PRP concentration below the protective threshold (0.15 μg/ml).

Two infants from group 1 with post-vaccination anti-PRP concentrations below the protective threshold received an additional dose of the Hib vaccine, after which they achieved concentrations of 16.9 and 58.1 μg/ml, respectively.

MenC response (SBA)

The MenC SBA GMTs before vaccination were 2.3 in both groups. After vaccination, the seroprotection rate in group 1 was 99.0% compared with 100% in group 2. This difference of 1.0% (90% CI −1.7 to 4.3) showed that the MenC SBA response was non-inferior comparing MCC vaccination given with Pediacel or DTwP-Hib+OPV. After vaccination, we found no significant differences in the GMTs or in the proportions of infants achieving protective titres, between those receiving Pediacel with MCC-CRM or those receiving DTwP-Hib+OPV either with MCC-CRM or with MCC-TT. However, the MenC SBA GMT was significantly lower in those receiving Pediacel with MCC-TT. This resulted in the MenC SBA GMT for the whole Pediacel group being lower than that for the DTwP-Hib+OPV group. All titres were well above the protective threshold in all groups (table 3).

Pertussis response (ELISA)

Before vaccination, pertussis GMCs were similar in both groups. After vaccination, the pertussis toxoid response was similar in the two groups. The filamentous haemagglutinin response was higher in group 1, whereas the pertactin and fimbrial agglutinogen responses were higher in group 2 (table 4).

Polio responses (neutralisation)

Before vaccination, polio GMTs were similar in both groups. After vaccination, the proportion of infants having a titre ⩾1:8 was 100% in both groups for types 1 and 2, and 97.9% and 99%, respectively for type 3 (table 4).

Table 3 Anti-polyribosylribitol phosphate (radioimmunoassay v ELISA) and MenC (serum bactericidal antibody) responses by group and stratum (Per Protocol population)

	Anti-PRP (RIA)				Anti-PRP (ELISA)				Anti-MenC (SBA)			
	n	GMC (μg/ml)	⩾0.15 μg/ml (%)	⩾1.0 μg/ml (%)	n	GMC (μg/ml)	⩾0.15 μg/ml (%)	⩾1.0 μg/ml (%)	n	GMT	⩾1:8 (%)
Pediacel											
Overall	103	2.19 (1.58 to 3.03)	93.2 (86.6 to 96.7)	72.8 (63.5 to 80.5)	101	3.40 (2.47 to 4.66)	91.1 (83.9 to 95.2)	80.2 (71.4 to 86.8)	101	1216 (880 to 1680)	99.0 (94.6 to 99.8)
MCC-TT	53	3.67 (2.56 to 5.26)	98.1 (90.1 to 99.7)	83 (70.8 to 90.8)	52	5.17 (3.53 to 7.58)	94.2 (84.4 to 98)	90.4 (79.4 to 95.8)	51	690 (418 to 1140)	98 (89.7 to 99.7)
MCC-CRM	50	1.26 (0.75 to 2.13)	88 (76.2 to 94.4)	62 (48.2 to 74.1)	49	2.17 (1.34 to 3.53)	87.8 (75.8 to 94.3)	69.4 (55.5 to 80.5)	50	2165 (1517 to 3089)	100 (92.9 to 100)
DTwP-Hib											
Overall	102	3.18 (2.57 to 3.93)	100 (96.4 to 100)	82.4 (73.8 to 88.5)	100	5.7 (4.5 to 7.24)	99 (94.6 to 99.8)	90 (82.6 to 94.5)	101	3178 (2416 to 4180)	100 (96.3 to 100)
MCC-TT	49	4.01 (2.97 to 5.42)	100 (92.7 to 100)	87.8 (75.8 to 94.3)	49	7.51 (5.54 to 10.19)	100 (92.7 to 100)	91.8 (80.8 to 96.8)	49	3816 (2583 to 5638)	100 (92.7 to 100)
MCC-CRM	53	2.57 (1.91 to 3.45)	100 (93.2 to 100)	77.4 (64.5 to 86.5)	51	4.38 (3.08 to 6.22)	98 (89.7 to 99.7)	88.2 (76.6 to 94.5)	52	2674 (1807 to 3956)	100 (93.1 to 100)

DTwP-Hib, diphtheria–tetanus–whole-cell pertussis–*Haemophilus influenzae* type b; GMC, geometric mean concentration; GMT, geometric mean titre; MenC, meningococcal serogroup C; MCC-CRM, meningococcal group C conjugate with diphtheria-derived protein CRM_{197} as conjugate protein; MCC-TT, meningococcal group C conjugate with tetanus toxoid as conjugate protein; PRP, polyribosylribitol phosphate; RIA, radio immunoassay; SBA, serum bactericidal antibody.
Values are mean (95% CI).

Table 4 Pertussis (ELISA) and polio (neutralisation) responses by group (Per Protocol population)

	Pediacel			DTwP-Hib+OPV		
Pertussis	GMC (EU/ml), n = 105			GMC (EU/ml), n = 102		
PT	78.7 (67.7 to 91.5)			98.5 (77.6 to 125)		
FHA	51.9 (45.2 to 59.7)			25.7 (21.8 to 30.3)		
FIM	278.7 (232.3 to 334.3)			591.4 (479.1 to 730)		
PRN	32.7 (26.3 to 40.6)			68.9 (57.9 to 82)		
Poliomyelitis	n	GMT	⩾1:8 (%)	n	GMT	⩾1:8 (%)
Type 1	98	372 (270 to 514)	100 (96.2 to 100)	98	670 (456 to 983)	100 (96.2 to 100)
Type 2	96	735 (510 to 1058)	100 (96.2 to 100)	98	2776 (2174 to 3545)	100 (96.2 to 100)
Type 3	96	1077 (788 to 1472)	97.9 (92.7 to 99.4)	98	805 (579 to 1120)	99 (94.4 to 99.8)

DTwP-Hib, diphtheria–tetanus–whole-cell pertussis–*Haemophilus influenzae* type b; FHA, filamentous haemagglutinin; FIM, fimbrial agglutinins; GMT, geometric mean titres; OPV, oral poliomyelitis vaccine; PRN, pertactin; PT, pertussis toxin.
Values are mean (95% CI).

Diphtheria response (microneutralisation)

The diphtheria antitoxin GMCs before vaccination were 0.02 IU/ml in both groups (table 5). After vaccination, the responses were similar in both groups, 99.0% in group 1 and 97.0% in group 2 achieving concentrations ⩾0.01 IU/ml. In both groups the GMC was higher in the stratum receiving concomitant MCC-CRM than in the stratum receiving MCC-TT.

Tetanus response (ELISA)

The tetanus antitoxin GMCs before vaccination were 0.39 EU/ml in group 1 and 0.53 EU/ml in group 2. After vaccination, the proportion of infants with concentrations ⩾0.01 EU/ml was 100% in both groups. In both groups, the GMC was higher in infants given MCC-TT than in those given MCC-CRM.

DISCUSSION

In developed countries, acellular pertussis vaccines are increasingly replacing the older whole-cell vaccines. Five-component DTaP vaccines have been shown to be equally efficacious as DTwP, but with an improved reactogenicity profile[10] when given in schedules at 2, 4 and 6, or 3, 5 and 12 months. Although safety data are not presented here, this was confirmed in the present study, with Pediacel being associated with fewer local and systemic reactions than the whole-cell comparator.[5a]

Some DTaP-Hib combination vaccines elicit anti-PRP antibody responses lower than those when Hib is given separately.[4] The assumption that this has no clinical relevance is being re-examined following the recent experience in the UK, where a marked increase in the incidence of Hib disease was partly associated with the lower immunogenicity of the Hib component of a three-component DTaP-Hib combination vaccine, when compared with whole-cell DTP-Hib combinations.[5]

Previous studies of Hib-containing five-component acellular pertussis combination vaccines, given at 2, 4 and 6 months of age, have shown Hib responses similar to those seen when the Hib vaccine was given separately,[1 2] even if MCC-CRM was given concomitantly.[11] In our study, where infants were vaccinated at 2, 3 and 4 months, and MCC vaccine was given concomitantly, interesting influences on both the Hib and MenC responses were observed, depending on which type of MCC vaccine was coadministered, irrespective of whether DTaP or DTwP was used in the combination.

One month after the third dose, 93.2% of infants who received Pediacel achieved anti-PRP titres ⩾0.15 μg/ml (radioimmunoassay) compared with 100% of those who received DTwP-Hib. This significant reduction was entirely because of the response was lower in those receiving concomitant MCC-CRM (88.0%) than in those receiving MCC-TT (98.1%). This was also reflected in the GMCs, which were 1.26 and 3.67 μg/ml, respectively. A similar pattern was also observed in the DTwP-Hib group: the GMC in those receiving MCC-CRM was 2.57 μg/ml compared with 4.01 μg/ml in those receiving MCC-TT. This compares with a GMC of 4.86 μg/ml when Pediacel was given without concomitant MCC vaccine at 2, 4 and 6 months of age (sanofi pasteur; personal communication, Peter Lashley, 2005). The type of MCC conjugate also had an influence on the response to the MCC vaccine itself. The GMT response to MCC-TT when given with Pediacel (694) was significantly lower than the GMT response to MCC-TT when given with DTwP-Hib (3816) and MCC-CRM when given with Pediacel (2165).

It is not clear whether these differences have any clinical relevance. Influences on antibody titres that are well above the protective threshold may be less important than those on titres that are closer to such a threshold. In the UK, childhood vaccines are procured and distributed centrally, and purchasing

Table 5 Diphtheria (microneutralisation) and tetanus (ELISA) antitoxin responses by group and stratum (Per Protocol population)

	Diphtheria antitoxin			Tetanus antitoxin		
	n	GMC (IU/ml)	⩾0.01 IU/ml (%)	n	GMC (EU/ml)	⩾0.01 EU/ml (%)
Pediacel						
Overall	103	0.06 (0.05 to 0.07)	99 (94.7 to 99.8)	100	1.61 (1.32 to 1.95)	100 (96.3 to 100)
MCC-TT	53	0.04 (0.03 to 0.05)	98.1 (90.1 to 99.7)	52	1.96 (1.47 to 2.61)	100 (93.1 to 100)
MCC-CRM	50	0.1 (0.07 to 0.13)	100 (92.9 to 100)	48	1.30 (1 to 1.68)	100 (92.6 to 100)
DTwP-Hib						
Overall	99	0.05 (0.04 to 0.06)	97 (91.5 to 99)	96	3.62 (3.02 to 4.35)	100 (96.2 to 100)
MCC-TT	47	0.04 (0.02 to 0.05)	95.7 (85.8 to 98.8)	47	5.29 (4.18 to 6.71)	100 (92.4 to 100)
MCC-CRM	52	0.07 (0.05 to 0.08)	98.1 (89.9 to 99.7)	49	2.52 (1.97 to 3.21)	100 (92.7 to 100)

DTwP-Hib, diphtheria–tetanus–whole-cell pertussis–*Haemophilus influenzae* type b; GMC, geometric mean concentration; MCC-CRM, meningococcal group C conjugate with diphtheria-derived protein CRM_{197} as conjugate protein; MCC-TT, meningococcal group C conjugate with tetanus toxoid as conjugate protein.
Values are mean (95% CI).

decisions are made by decision makers rather than prescribers. It is usual for MCC vaccines with different conjugate proteins to be used widely across the country and interchangeably. The observed immune interferences between the conjugate vaccines are therefore not expected to have an effect on population effectiveness or safety of the vaccines studied. In addition, data from routine usage of Hib and MCC vaccines, even when coadministered with DTwP in infants, indicate that their efficacy wanes markedly after 1 year.[12 13] Booster doses in the second year of life of conjugate vaccines first administered in infancy seem to be necessary to provide long-term protection.

This is the first study where a DTaP-IPV-Hib vaccine has been given concomitantly with different MCC vaccines according to a 2, 3 and 4 month schedule. A previous study suggested that coadministering MCC-TT with DTaP-Hib-TT vaccine has a positive influence on the Hib response, with an accompanying reduction in the SBA GMT response to MCC-TT.[14]

Interactions between conjugate vaccines have been described previously.[15] Various potential immunological mechanisms have been proposed to explain such interactions. These include carrier-induced epitopic suppression, modulation of antigen presentation and inadequate T helper cell activity. However, our observations are somewhat different from previous ones: concomitant PRP-T and MCC-TT had a positive influence on the response to one (PRP) but a negative influence on the response to the other (MCC). In addition, no negative influence on the tetanus response was seen. The dose–response curve may therefore be U-shaped and different for the two antigens. Differences between the Pediacel and DTwP-Hib groups may also relate to the ability of DTwP to enhance the concomitant MCC-TT response because of the effects on tetanus-specific T cell priming, as DTwP favours a T helper cell 1 response to constituent antigens.

As expected, responses to all other vaccine components were equivalent. Diphtheria and tetanus responses were higher in the infant groups given MCC-CRM and MCC-TT conjugates, respectively, but all infants developed protective antibody titres. The different MCC vaccines did not affect the other antigens.

Diphtheria antitoxin levels were assessed with a microneutralisation assay. All infants developed titres ⩾0.01 IU/ml (widely accepted as indicative of immunity), with a similar GMC in both groups (0.06 and 0.05 IU/ml in groups 1 and 2, respectively). This compares to a GMC of 0.03 observed in 49 3–3½-year-old children who had been primed with DTwP-Hib and MCC-CRM as infants (measured using the same assay).[16] A subset of samples with remaining serum was retested using an ELISA at the Immunoassay Laboratory, Porton. As expected with an ELISA, this showed GMCs of 1.08 (n = 69) and 1.38 IU/ml (n = 56) in groups 1 and 2, respectively. The values are in the same range as those observed with a different DTaP-Hib vaccine given according to the UK schedule, measured by the same laboratory using the same method.[17]

Pediacel contains five-component acellular pertussis, which is as effective as whole-cell pertusis in protecting against pertussis disease (in schedules of 2, 4 and 6, or 3, 5 and 12 months), and is also considerably better tolerated. In addition, it includes IPV, permitting the replacement of OPV in infant immunisation schedules. Our study has shown that Pediacel is immunogenic when administered at 2, 3 and 4 months of age. Coadministration with MCC-CRM or MCC-TT vaccine influenced the Hib and MCC responses, respectively.

What is already known on this topic

- The *Haemophilus influenzae* type b (Hib)-containing combination vaccine containing five-component acellular pertussis produces Hib immune responses similar to those when the Hib vaccine is given separately.
- Concomitant administration of polysaccharide–protein conjugate vaccines can result in unpredictable immunological interactions even when the vaccines are given at separate sites.

What this study adds

- Pediacel, a diphtheria–tetanus–acellular pertussis–inactivated poliovirus–*Haemophilus influenzae* type b vaccine containing five-component acellular pertussis, is immunogenic when given at 2, 3 and 4 months of age.
- Concomitant administration of the Hib and meningococcal group C conjugate (MCC) vaccines conjugated to tetanus toxoid had a positive influence on the response to polyribosylribitol phosphate but a negative influence on the response to MCC, which are not expected to have an effect on population effectiveness or safety of the vaccines studied.

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Competing interests: NREK, FH, ST and MWW are employees of Sanofi Pasteur MSD, which markets Pediacel and Act-HIB DTP.

Partial immunological data were presented at the 21st Annual Meeting of the European Society for Paediatric Infectious Diseases, Sicily, 9–11 April 2003 (abstract number 272).

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