13-valent Pneumococcal Conjugate Vaccine Given With Meningococcal C–Tetanus Toxoid Conjugate and Other Routine Pediatric Vaccinations: Immunogenicity and Safety

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Background: As multiple vaccines are administered concomitantly during routine pediatric immunizations, it is important to ascertain the potential interference of any new vaccine on the immune response to the concomitantly administered vaccines. Immune responses to meningococcal serogroup C–tetanus toxoid conjugate vaccine (MnCC-TT) and the diphtheria and tetanus antigens in routine pediatric vaccines (diphtheria, tetanus, acellular pertussis–hepatitis B virus–inactivated poliovirus/*Haemophilus influenza* type b [DTaP–HBV–IPV/Hib] and DTaP–IPV+Hib) when given concomitantly with the 13-valent pneumococcal conjugate vaccine (PCV13) were compared with responses when given with PCV7. In addition, the immunogenicity and safety of PCV13 were assessed.

Methods: Healthy infants were randomized to receive PCV13 or PCV7 (ages 2, 4, 6 and 15 months), concomitant with MnCC-TT (2, 4 and 15 months), DTaP–HBV–IPV/Hib (2, 4 and 6 months), and DTaP–IPV+Hib (15 months).

Results: Immune responses to MnCC-TT and to the diphtheria and tetanus antigens administered with PCV13 were noninferior to the responses observed when the vaccines were administered with PCV7; ≥96.6 (postinfant) and ≥99.4% (posttoddler) subjects achieved prespecified immune response levels to each antigen in each group. After the infant series, ≥93.0% of subjects receiving PCV13 achieved pneumococcal anticapsular immunoglobulin G concentrations ≥0.35 μg/mL for all serotypes except serotype 3 (86.2%), increasing to 98.1–100% for most serotypes (serotype 3: 93.6%) after the toddler dose. Local and systemic reactions were similar between groups.

Conclusions: Immune responses to MnCC-TT, and other childhood vaccines (DTaP–HBV–IPV/Hib, DTaP–IPV+Hib) were noninferior when concomitantly administered with PCV13 compared with PCV7. PCV13 does not interfere with MnCC-TT. PCV13 is highly immunogenic with a favorable safety profile.

Key words: *Streptococcus pneumoniae*, pneumococcal vaccination, infants, meningococcal vaccination

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The 7-valent pneumococcal conjugate vaccine (PCV7; Prevnar/Prevenar; Wyeth Pharmaceuticals Inc., Philadelphia, PA) was licensed in 2000 in the United States and in 2001 in the European Union (EU).[1,2] The introduction of PCV7 has led to dramatic reductions in invasive pneumococcal disease (IPD) burden.[3,4]

The 13-valent pneumococcal conjugate vaccine (PCV13; Prevenar 13; Wyeth Pharmaceuticals Inc.), contains the PCV7 serotypes and 6 additional serotypes. The serotypes included in PCV13 are estimated to cause 80–92% of pneumococcal disease in children aged <5 years, globally.[5] PCV13 has been approved for pediatric use in the EU, the United States and other countries worldwide. Noninferiority of PCV13 compared with PCV7 has been demonstrated in previous studies.[6–8]

As multiple vaccines are administered concomitantly during routine pediatric immunizations, it is important to ascertain the potential interference of any new vaccine on the immune response to the concomitantly administered vaccines. In Spain, vaccination against meningococcal serogroup C is part of the routine national immunization schedule. Three different conjugate vaccines are available; this study used the meningococcal serogroup C–tetanus toxoid conjugate vaccine (MnCC-TT; NeisVac-C; Baxter Healthcare, Deerfield, IL).

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The primary objective of this study was to evaluate the noninferiority of the immune responses to MnCC-TT vaccine as well as to the diphtheria and tetanus antigens present in routinely administered vaccines in the Spanish pediatric immunization schedule when these vaccines were administered concomitantly with PCV13 compared with PCV7. The responses to the diphtheria and tetanus antigens were of particular interest given the use of genetically modified diphtheria toxin and tetanus toxoid as immunologic carriers in the PCV and MnCC-TT vaccines. The routine pediatric vaccines containing these antigens included diphtheria, tetanus, acellular pertussis–hepatitis B virus–inactivated poliovirus/*Haemophilus influenza* type b vaccine (DTaP–HBV–IPV/Hib; Infanrix hexa; GlaxoSmithKline Biologicals, Rixensart, Belgium) and DTaP–IPV+Hib vaccine (Infanrix–IPV+Hib, GlaxoSmithKline Biologicals). The immunogenicity and safety of PCV13 were also assessed.

MATERIALS AND METHODS

This parallel-group, randomized, active-controlled, double-blind study was conducted at 23 sites in Spain from July 4, 2007 to March 23, 2009 (date of last 6-month follow-up telephone contact). An independent ethics committee at each site reviewed and provided written approval of the protocol for this study. The study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki and was designed and performed in compliance with Good Clinical Practice and applicable regulatory requirements. Written informed consent was obtained from parents/legal guardians of every subject before enrollment in the study and before performance of any study-related procedures.

Eligible infants were aged 42–98 days at enrollment and were healthy. Exclusion criteria included previous vaccination with any pneumococcal vaccine antigens required for the study; contraindication to vaccination with study vaccines; history of known or suspected immune deficiency or suppression, culture-proven invasive disease caused by *Streptococcus pneumoniae* or severe chronic disorder; prior receipt of blood products or gamma-globulin (including hepatitis B immunoglobulin and monoclonal antibodies); or prior participation in another investigational trial.

This was a double-blind study, and all participants and study personnel were blind to treatment allocation. Subjects were randomly allocated in a 1:1 ratio to receive PCV13 or PCV7 at ages 2, 4, 6 and 15 months, concomitant with MnCC-TT at 2, 4 and 15 months, DTaP–HBV–IPV/Hib at 2, 4 and 6 months and DTaP–IPV+Hib at 15 months. Combination measles, mumps and rubella vaccine (Priorix; GlaxoSmithKline Biologicals) was administered at 12 months. Vaccine regimens were based on national recommendations for pediatric immunization in Spain.[9] Rotavirus vaccine was permitted at any time during the study. Varicella, hepatitis A and influenza vaccines were permitted, but not concomitantly with PCV7 or PCV13. Antipyretic medications were permitted to treat or prevent symptoms.

PCV13 contains saccharides from pneumococcal serotypes 1, 3, 5, 6A, 7F and 19A, and the PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F and 23F), all individually conjugated to cross-reactive material 197 (CRM_{197}; a nontoxic variant of diphtheria toxin). As with PCV7, PCV13 is formulated to contain 2.2 μg of each saccharide except for 4.4 μg of 6B and 0.125 mg of aluminum phosphate per 0.5-mL dose. The appearance of PCV13 and PCV7 was identical.

Blood samples were collected 1 month after the second, third and toddler doses. Antigroup C meningococcal functional antibody titers were determined for the blood samples collected 1 month after the second dose and 1 month after the toddler dose of MnCC-TT by a standardized serum bactericidal assay (SBA) using rabbit complement.[10] Serum concentrations (IU/mL) of immunoglobulin G (IgG) antibodies to tetanus toxoid and diphtheria toxoid were determined using enzyme-linked immunosorbent assay for the blood samples collected 1 month after the 3-dose DTaP–HBV–IPV/Hib series and 1 month after the DTaP–IPV+Hib toddler dose. For the PCV13 group, serotype-specific IgG serum concentrations were determined for each of the 13 pneumococcal serotypes using the standard pneumococcal enzyme-linked immunosorbent assay.[11,12]

Local reactions (redness, swelling and tenderness), systemic events (decreased appetite, irritability, increased or decreased sleep and fever) and use of antipyretic medications were monitored and recorded by parents/legal guardians in an electronic diary daily for 4 days after each vaccination. Tenderness was recorded as none, present or interfered with limb movement. Redness and swelling were measured with a caliper (1 unit = 0.5 cm). Redness and swelling were categorized as absent, mild (0.5–2.0 cm), moderate (2.5–7.0 cm) or severe (>7.0 cm). Rectal temperature was measured daily at bedtime and whenever fever was suspected for 4 days after each vaccination; the highest temperature of the day was reported. Fever was categorized as absent (,38°C), mild (≥38.0 to ≤39.0°C), moderate (>39.0°C to ≤40.0°C) or severe (>40.0°C). Unsolicited adverse events (AEs) and serious AEs were also recorded.

Statistical Analysis

Sample Size Determination

The study was powered to show immunologic noninferiority of the response to concomitant vaccine antigens when administered with PCV13 relative to administration with PCV7. Assuming a dropout rate of ≤10%, 440 subjects had to be enrolled to ensure 195 evaluable subjects per group. A sample size of 195 per group was required to provide ≥94% overall power to declare noninferiority for all 3 concomitant vaccine antigen comparisons using a noninferiority criterion of 0.10 and a 2-sided, type I error rate of 0.05. In addition, a sample size of 195 evaluable subjects permitted estimation of the proportion of subjects achieving a pneumococcal antibody concentration ≥0.35 μg/mL to within ± 4.5%.

Evaluable Populations

The evaluable concomitant vaccine immunogenicity populations included subjects who received all doses of all assigned study vaccinations for their age group, had a valid and determinate assay result for the planned analysis and had no protocol violations. The evaluable pneumococcal immunogenicity populations included subjects randomly assigned to the PCV13 group who received all expected study vaccinations for their age group, had no protocol violations and had ≥1 valid and determinate infant series pneumococcal assay result after both doses 2 and 3 (evaluable pneumococcal infant immunogenicity population) or after the toddler dose (evaluable pneumococcal toddler immunogenicity population). All subjects who received ≥1 dose of study vaccine were in the safety population. Separate safety populations were defined for each vaccination.

Endpoints

Endpoints for vaccines concomitantly administered with PCV13 or PCV7 included the proportion of subjects who achieved prespecified antibody levels (meningococcal C SBA titer ≥1:8,[13] diphtheria IgG ≥0.10 IU/mL[14] and tetanus IgG ≥0.10 IU/mL[15]) after the infant series and toddler dose. For each concomitant vaccine antigen separately, exact, unconditional, 2-sided 95% confidence intervals (CIs) on the difference (PCV13 − PCV7) in proportions

of subjects achieving a prespecified antibody level were calculated. Noninferiority was declared if the lower bound of the CIs for the difference was >−0.10. Geometric mean concentrations (GMCs) or geometric mean titers were also calculated for antibodies to the concomitant vaccine antigens at each time point, and 2-sided 95% CIs were constructed; the response of the PCV13 group was compared with that of the PCV7 group using a 2-fold criterion, that is, evaluating whether the lower limit of the 95% CI for the ratio of geometric means was >0.5.

Endpoints for PCV13 included the proportion of subjects in the PCV13 group achieving a serotype-specific IgG antibody concentration ≥0.35 μg/mL—a reference antibody concentration for assessment of vaccine efficacy against IPD defined by the World Health Organization.[16] Exact, unconditional, 2-sided 95% CIs on the proportions were calculated for each serotype, and the difference between the proportions 1 month after dose 2 and the proportions 1 month after dose 3 was calculated (2-sided 95% CI for dependent proportions). Serotype-specific IgG GMCs were measured 1 month after doses 2 and 3 of the infant series, and 1 month after the toddler dose; 2-sided 95% CIs were constructed for pneumococcal IgG GMCs for each pneumococcal serotype and time point. Fold rises in antibody concentrations from postdose 2 to postdose 3 were summarized using geometric mean fold rises and CIs.

The incidences of local reactions, systemic events and AEs were summarized separately for each dose of study vaccine. Statistical differences in incidences between PCV13 and PCV7 groups were evaluated using the Fisher exact test.

RESULTS

A total of 449 subjects were randomized: 223 to PCV13 and 226 to PCV7 (Fig. 1, which presents a Consolidated CONSORT diagram of subject disposition; Fig., Supplemental Digital Content 1, http://links.lww.com/INF/B101). The evaluable concomitant vaccine immunogenicity populations comprised 206 and 218 subjects in the PCV13 and PCV7 groups, respectively, after 2 doses; 197 and 212 subjects, respectively, after 3 doses; and 164 and 172 subjects, respectively, after the toddler dose. The evaluable pneumococcal immunogenicity population, which only included subjects in the PCV13 group, comprised 199 subjects postinfant series and 162 subjects posttoddler dose. The sample-size calculations of 195 per vaccine group were for the primary endpoint, which is noninferiority of the concomitant vaccine responses after the infant series. These numbers do not apply after the toddler dose, where antibody concentrations are higher and fewer subjects would be required for the secondary objective. For the concomitant and pneumococcal immunogenicity populations, results were similar for the all-available and evaluable populations both postinfant series and posttoddler dose; therefore, only the results for the evaluable populations are reported.

Demographic characteristics were similar for the 2 vaccine groups (data not shown). For the dose 1 safety population, 50.5% of subjects were male and 99.1% were white. Age at dose 1 was a median of 2.0 months (range, 1.3–3.4 months).

Immunogenicity: Concomitant Vaccine Antigens

The noninferiority criteria were met for the meningococcal C antigen in the PCV13 group compared with the PCV7 postinfant series and posttoddler dose (Table 1). The proportions of responders to meningococcal C antigen were high and similar in both groups after the infant series and after the toddler dose. The meningococcal C antigen geometric mean titers were similar in both groups after the infant series and toddler dose, and increased substantially from postinfant series to posttoddler dose, demonstrating a booster response. Similar results were obtained for the concomitant diphtheria and tetanus antigens (Table 1).

Immunogenicity: PCV13

Immunogenicity to pneumococcal serotypes was only determined for the PCV13 group (Tables 2 and 3). After dose 2, >80% of subjects achieved a pneumococcal serotype-specific IgG antibody concentration ≥0.35 μg/mL for most PCV13 serotypes; the most notable exceptions were serotypes 6B (27.9%) and 23F (55.8%) (Table 2). The proportion of responders increased from dose 2 to dose 3 for most serotypes; the response increased to 94.9% for serotype 6B and to 93.0% for serotype 23F. Similar increases in serotype-specific IgG GMCs were also seen when comparing the postdose 2 and postdose 3 responses (Table 3).

The proportion of subjects with pneumococcal IgG antibody concentration ≥0.35 μg/mL increased after the toddler dose to >98% for all serotypes except serotype 3, which increased to 93.6% (Table 2). IgG GMCs were substantially higher after the toddler dose compared with after the infant series, for all serotypes (Table 3).

Safety

Local reactions were similar for the PCV13 and PCV7 groups (Table 4). Most local reactions were mild in severity. Significant tenderness that interfered with leg movement was reported in ≤4% of subjects in either vaccine group after each infant and toddler dose. There were no reports of severe swelling with any infant or toddler dose. Severe redness was reported for only 1 infant vaccinated with PCV13, after dose 3.

The frequency of most systemic events was similar for the PCV13 and PCV7 groups, with the exception of irritability, which had a higher frequency in the PCV7 group than the PCV13 group after the toddler dose (53.6 versus 41.5%; $P = 0.025$) (Table 4). Fever >40°C was reported in 1 infant in the PCV7 group after dose 1 and in 1 toddler in the PCV13 group. Antipyretic medication use was similar in both groups.

Most AEs were of the types expected for infants and toddlers. No subjects died, and none withdrew due to AEs. During the infant series, the frequency of AEs was significantly higher in the PCV7 group (57.3%) than in the PCV13 group (46.3%; $P = 0.023$). The most frequent AEs were infections and infestations, which were reported more frequently in the PCV7 group than in the PCV13 group (48.9 versus 39.4%; $P = 0.056$). In both vaccine groups, most of these events were infections and infestations, and there were no clear trends between groups within this or other AE categories. Among individual AEs, the only significant difference between groups was noted for rash, which occurred in 2.7% of infants in the PCV7 group and no infants in the PCV13 group ($P = 0.030$). After toddler vaccination, the frequency of AEs did not differ significantly between groups.

DISCUSSION

This study demonstrates that immune responses to MnCC-TT and to the diphtheria and tetanus antigens in routine pediatric vaccines (DTaP–HBV–IPV/Hib or DTaP–IPV+Hib) were noninferior in the PCV13 group compared with the responses in the PCV7 group. PCV13 does not interfere with MnCC-TT.

These results are consistent with those of other studies of routine childhood vaccinations administered concomitantly with PCV13.[8,17–20] In particular, 2 studies in which MnCC-TT vaccine was administered concomitantly with PCV13 and 1 study in Spain in which MnCC-CRM_{197} vaccine was administered concomitantly with PCV13 demonstrated no interference with

TABLE 1. Concomitant Vaccine Antigen Levels and Proportion of Subjects Achieving Predefined Concomitant Meningococcal Antigen Levels

Concomitant Vaccine Antigen	Endpoint	Time Point	PCV13 Group	PCV7 Group	Comparison
Meningococcal C			% (95% CI*) n†/N‡	% (95% CI*) n†/N‡	Difference§ (95% CI¶)
	Proportion of subjects with MnCC SBA titer ≥1:8	Infant postdose 2	98.5 (95.8 to 99.7) 203/206	99.1 (96.7 to 99.9) 216/218	−0.5 (−3.3 to 2.0)
		Posttoddler dose	100 (97.8 to 100) 164/164	99.4 (96.8 to 100) 171/172	0.6 (−1.7 to 3.2)
			GMT‖ (95% CI#) N‡	GMT‖ (95% CI#) N‡	Ratio** (95% CI††)
	MnCC SBA GMT	Infant postdose 2	654.55 (557.75 to 768.16) 206	757.04 (648.45 to 883.81) 218	0.86 (0.69 to 1.08)
		Posttoddler dose	2573.06 (2176.29 to 3042.16) 164	2098.12 (1779.65 to 2473.58) 172	1.23 (0.97 to 1.55)
Diphtheria			% (95% CI*) n†/N‡	% (95% CI*) n†/N‡	Difference§ (95% CI¶)
	Proportion of subjects with diphtheria concentration ≥0.10 IU/mL	Infant postdose 3	98.5 (95.6 to 99.7) 193/196	99.1 (96.6 to 99.9) 210/212	−0.6 (−3.5 to 2.0)
		Posttoddler dose	100 (97.8 to 100) 163/163	100 (97.9 to 100) 170/170	0 (−2.2 to 2.2)
			GMC‖ (95% CI#) N‡	GMC‖ (95% CI#) N‡	Ratio** (95% CI††)
	Diphtheria GMC (IU/mL)	Infant postdose 3	0.79 (0.69 to 0.90) 196	0.92 (0.81 to 1.04) 212	0.86 (0.72 to 1.03)
		Posttoddler dose	3.00 (2.63 to 3.41) 163	3.23 (2.88 to 3.63) 170	0.93 (0.78 to 1.10)
Tetanus			% (95% CI*) n†/N‡	% (95% CI*) n†/N‡	Difference§ (95% CI¶)
	Proportion of subjects with tetanus concentration ≥0.10 IU/mL	Infant postdose 3	96.6 (92.6 to 98.7) 168/174	96.7 (93.0 to 98.8) 177/183	−0.2 (−4.4 to 4.0)
		Posttoddler dose	100 (97.8 to 100) 163/163	100 (97.9 to 100) 170/170	0 (−2.3 to 2.2)
			GMC‖ (95% CI#) N‡	GMC‖ (95% CI#) N‡	Ratio** (95% CI††)
	Tetanus GMC (IU/mL)	Infant postdose 3	1.10 (0.94 to 1.27) 174	1.20 (1.04 to 1.39) 183	0.91 (0.74 to 1.12)
		Postoddler dose	3.29 (2.83 to 3.83) 164	3.28 (2.83 to 3.79) 170	1.00 (0.81 to 1.24)

*Exact 2-sided CI based on the observed proportion of subjects.
†n = number of subjects with an antibody concentration/titer of at least the prespecified level for the given concomitant vaccine antigen.
‡N = number of subjects with a determinate antibody concentration for the specified concomitant vaccine component.
§Difference in proportions, expressed as a percentage.
¶Exact 2-sided CI for the difference in proportions (PCV13 – PCV7) expressed as a percentage.
‖GMTs and GMCs were calculated using all subjects with available data for the specified blood draw.
#CIs are back-transformations of a CI based on the Student *t* distribution for the mean logarithm of the concentrations.
**Ratio of GMTs or GMCs: PCV13 to PCV7.
††CIs for the ratio are back-transformations of the CIs based on the Student *t* distribution for the mean difference of the logarithms of the measures (PCV13 – PCV7).
SBA, serum bactericidal assay; GMTs, geometric mean titers.

TABLE 2. Proportion of Subjects in the PCV13 Group Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 μg/mL, % (95% CI)*

	Postdose 2	Postdose 3	Difference†	Posttoddler dose
Seven common serotypes				
4	92.5 (87.9 to 95.7)	98.5 (95.7 to 99.7)	6.0 (2.6 to 9.4)	100 (97.7 to 100)
6B	27.9 (21.8 to 34.7)	94.9 (90.9 to 97.5)	67.0 (59.7 to 73.0)	100 (97.7 to100)
9V	89.9 (84.8 to 93.7)	97.0 (93.5 to 98.9)	7.1 (3.3 to 10.7)	99.3 (96.3 to 100)
14	91.0 (86.1 to 94.6)	97.0 (93.6 to 98.9)	6.0 (1.8 to 10.1)	99.4 (96.6 to 100)
18C	88.9 (83.7 to 92.9)	99.0 (96.4 to 99.9)	10.1 (5.5 to 14.4)	98.8 (95.6 to 99.8)
19F	100 (98.2 to 100.0)	99.0 (96.4 to 99.9)	−1.0 (−2.7 to 0.7)	98.7 (95.5 to 99.8)
23F	55.8 (48.6 to 62.8)	93.0 (88.5 to 96.1)	37.2 (29.5 to 44.1)	98.1 (94.7 to 99.6)
Six additional serotypes				
1	96.0 (92.2 to 98.2)	98.5 (95.7 to 99.7)	2.5 (−0.6 to 5.6)	98.8 (95.6 to 99.8)
3	73.8 (67.1 to 79.9)	86.2 (80.5 to 90.7)	12.3 (5.6 to 18.8)	93.6 (88.6 to 96.9)
5	86.4 (80.8 to 90.8)	96.0 (92.2 to 98.2)	9.6 (4.9 to 14.1)	100 (97.6 to 100)
6A	80.8 (74.6 to 86.0)	99.0 (96.4 to 99.9)	18.2 (12.6 to 23.4)	99.4 (96.5 to 100)
7F	94.5 (90.3 to 97.2)	100 (98.2 to 100)	5.5 (2.2 to 8.8)	99.4 (96.5 to 100)
19A	92.9 (88.4 to 96.1)	99.5 (97.2 to 100)	6.6 (2.7 to 10.4)	100 (97.5 to 100)

*CIs are exact, unconditional 2-sided 95% CIs.
†Difference in proportions (postdose 3 – postdose 2) expressed as a percentage, with 95% CIs for difference in dependent proportions.

TABLE 3. Pneumococcal Serotype-specific Antipolysaccharide IgG GMC*, μg/mL, (95% CI)† and GMFR‡ for Subjects Receiving PCV13

	Postdose 2	Postdose 3	GMFR‡	Posttoddler dose
Seven common serotypes				
4	1.55 (1.35–1.78)	2.32 (2.08–2.60)	1.50 (1.34–1.67)	3.88 (3.42–4.40)
6B	0.21 (0.18–0.25)	2.59 (2.20–3.05)	12.40 (10.74–14.32)	12.25 (10.78–13.92)
9V	1.15 (1.01–1.32)	1.51 (1.35–1.68)	1.31 (1.19–1.44)	2.67 (2.34–3.05)
14	1.94 (1.64–2.29)	4.51 (3.89–5.22)	2.33 (2.00–2.70)	9.82 (8.54–11.30)
18C	1.30 (1.11–1.51)	1.86 (1.68–2.07)	1.44 (1.25–1.65)	2.29 (2.01–2.61)
19F	2.98 (2.60–3.41)	2.46 (2.21–2.74)	0.83 (0.74–0.92)	6.11 (5.21–7.16)
23F	0.40 (0.34–0.48)	1.67 (1.44–1.94)	4.15 (3.53–4.87)	3.96 (3.43–4.59)
Six additional serotypes				
1	1.87 (1.61–2.16)	2.95 (2.61–3.33)	1.58 (1.39–1.80)	4.60 (3.94–5.37)
3	0.54 (0.48–0.61)	0.85 (0.76–0.95)	1.57 (1.39–1.76)	1.04 (0.91–1.19)
5	0.88 (0.77–1.00)	1.83 (1.62–2.06)	2.08 (1.87–2.31)	3.69 (3.26–4.18)
6A	0.81 (0.70–0.95)	3.08 (2.76–3.44)	3.78 (3.30–4.32)	7.71 (6.75–8.80)
7F	1.51 (1.33–1.71)	3.41 (3.11–3.74)	2.26 (2.00–2.56)	5.66 (4.90–6.53)
19A	1.52 (1.31–1.76)	2.50 (2.27–2.75)	1.64 (1.46–1.85)	10.21 (8.92–11.68)

GMFR, geometric mean fold rise.
*GMCs were calculated using all subjects with available data for the specified blood draw.
†CIs are back-transformations of the CIs based on the Student *t* distribution for the mean of the logarithmically transformed assay results.
‡GMFRs were calculated using all subjects with available data from both postdose 3 and postdose 2.

the antimeningococcal C response.[17–19] In addition, a study of PCV7 given with or without MnCC-CRM_{197} showed no interference with meningococcal, diphtheria or pneumococcal responses when the vaccines were given together compared with separate administration.[21]

Immune responses to diphtheria and tetanus antigens were specifically assessed in this study to evaluate the potential for interference arising from the genetically modified diphtheria toxin CRM_{197} and the tetanus toxoid conjugate proteins in the pneumococcal and meningococcal conjugate vaccines, respectively. The conjugate proteins had no differential impact on immune responses to the relevant antigens included in the DTaP vaccines, consistent with previous studies with PCV13.[8,17–20] In addition, other studies have shown no interference with antigens included in the DTaP–HBV–IPV/Hib vaccine after vaccination with PCVs such as PCV7,[22,23] or a 10-valent PCV that uses nontypeable *Haemophilus influenzae* protein D, tetanus toxoid and diphtheria toxoid carrier proteins (Synflorix; GlaxoSmithKline Biologicals).[24] In contrast, interference with an Hib tetanus toxoid conjugate vaccine was observed when it was coadministered with an experimental combination 9-valent pneumococcal meningococcal C–CRM_{197} conjugate vaccine.[25] This indicates the potential for interference with coadministration of polysaccharide protein conjugate vaccines, despite a difference in carriers.

Immune responses to PCV13 were substantial after the infant series and the toddler dose. After dose 2, the proportion of responders was lower for serotypes 6B (27.9%) and 23F (55.8%) than for the other 11 serotypes (73.8–100%), consistent with previous studies of PCV7[26–28] and PCV13.[8,18,20] The proportion of responders increased notably after the third infant dose and after the toddler dose. Previous studies of the immunogenicity of PCV13 in children receiving concomitant routine childhood vaccinations have shown similar results.[6–8,18,29,30] Thus, the majority of infants may have

Table 4. Percentages of Subjects Reporting Local Reactions or Systemic Events Within 4 Days of Each Dose

	Dose 1, % (n*/N†)		Dose 2, % (n*/N†)		Dose 3, % (n*/N†)		Toddler Dose, % (n*/N†)	
	PCV13	PCV7	PCV13	PCV7	PCV13	PCV7	PCV13	PCV7
Local reactions								
Tenderness								
Any	21.1 (42/199)	18.5 (38/205)	21.4 (39/182)	16.1 (29/180)	10.6 (18/170)	14.3 (25/175)	28.7 (47/164)	26.7 (46/172)
Significant‡	3.0 (6/199)	4.0 (8/200)	1.1 (2/177)	4.0 (7/177)	1.2 (2/167)	1.2 (2/169)	2.6 (4/154)	3.8 (6/160)
Swelling								
Any	13.3 (26/196)	14.5 (29/200)	22.0 (40/182)	14.7 (26/177)	23.4 (40/171)	20.0 (34/170)	26.6 (45/169)	18.5 (31/168)
Mild§	12.2 (24/196)	13.0 (26/200)	20.3 (37/182)	13.0 (23/177)	20.5 (35/171)	17.1 (29/170)	22.9 (38/166)	16.0 (26/163)
Moderate§	2.6 (5/196)	2.0 (4/196)	2.3 (4/177)	2.3 (4/175)	6.6 (11/166)	6.0 (10/168)	9.0 (14/156)	5.5 (9/163)
Severe§	0 (0/196)	0 (0/196)	0 (0/177)	0 (0/175)	0 (0/166)	0 (0/168)	0 (0/152)	0 (0/156)
Redness								
Any	15.2 (30/197)	15.1 (30/199)	23.8 (43/181)	20.0 (36/180)	26.7 (46/172)	22.7 (39/172)	30.0 (51/170)	23.1 (39/169)
Mild§	14.7 (29/197)	14.1 (28/198)	22.2 (40/180)	19.4 (35/180)	24.4 (42/172)	21.1 (36/171)	28.1 (47/167)	21.2 (35/165)
Moderate§	0.5 (1/196)	1.0 (2/197)	2.2 (4/178)	1.1 (2/175)	3.6 (6/166)	3.6 (6/169)	9.6 (15/157)	6.7 (11/163)
Severe§	0 (0/196)	0 (0/196)	0 (0/177)	0 (0/175)	0.6 (1/166)	0 (0/168)	0 (0/152)	0 (0/156)
Systemic events								
Fever								
≥38°C but ≤39°C	22.9 (46/201)	19.6 (40/204)	32.6 (59/181)	41.8 (79/189)	20.9 (36/172)	29.0 (51/176)	31.4 (49/156)	34.3 (58/169)
>39°C but ≤40°C	1.0 (2/196)	0.5 (1/196)	1.7 (3/177)	1.1 (2/176)	3.6 (6/166)	3.0 (5/168)	4.5 (7/154)	2.6 (4/156)
>40°C	0 (0/196)	0.5 (1/197)	0 (0/177)	0 (0/175)	0 (0/166)	0 (0/168)	0.7 (1/152)	0 (0/156)
Decreased appetite	31.4 (64/204)	35.7 (74/207)	46.6 (88/189)	44.0 (84/191)	37.1 (66/178)	36.0 (64/178)	31.9 (52/163)	41.0 (73/178)
Irritability	46.5 (94/202)	49.8 (105/211)	57.3 (110/192)	60.0 (114/190)	43.0 (77/179)	39.4 (74/188)	41.5 (71/171)	53.6¶ (96/179)
Increased sleep	38.7 (79/204)	39.3 (81/206)	39.2 (74/189)	36.4 (68/187)	21.1 (37/175)	27.0 (47/174)	16.7 (27/162)	24.8 (41/165)
Decreased sleep	19.4 (38/196)	27.5 (56/204)	27.3 (50/183)	27.8 (52/187)	22.9 (40/175)	25.3 (45/178)	19.8 (32/162)	18.7 (31/166)
Use of antipyretic medication								
To treat symptoms	41.0 (84/205)	44.5 (93/209)	54.4 (105/193)	57.9 (114/197)	39.4 (69/175)	42.9 (81/189)	50.3 (83/165)	46.9 (83/177)
To prevent symptoms	41.3 (83/201)	45.7 (96/210)	47.9 (93/194)	49.5 (97/196)	44.6 (79/177)	40.5 (75/185)	43.5 (73/168)	41.8 (74/177)

*n = number of subjects reporting the specific characteristic.
†N = number of subjects reporting yes for ≥ 1 day or no for all days.
‡Significant = present and interfered with limb movement.
§Mild, 0.5–2.0 cm; moderate, 2.5–7.0 cm; and severe, >7.0 cm.
¶Statistically significant difference, $P < 0.05$ (Fisher exact test, 2-sided).

protection against vaccine-serotype pneumococcal disease after a 2-dose infant PCV13 series for most serotypes, but completion of a 3-dose series followed by a toddler dose maximizes the immune response. Consistent with the clinical experience of PCV7, a booster dose of PCV13 between ages 11 and 15 months induces a substantial enhancement of the immune response against serotypes 6B and 23F. It can be anticipated that PCV13 will be as effective as PCV7 when given in a 2 + 1 schedule. This conclusion is based on the comparable vaccine response patterns seen between recipients of PCV13 and PCV7, and on the high levels of effectiveness of PCV7 against vaccine serotype disease, including serotypes 6B and 23F, following PCV7 introduction in England and Wales[31,32] and other countries or regions that have adopted a 2 + 1 schedule (eg, Norway, Quebec, the Liguria region of Italy).[33–35] In addition, a study in England and Wales 1 year after the introduction of PCV13 reported a 50% reduction of IPD caused by the 6 additional serotypes in PCV13 (including serotypes 3 and 6A), demonstrating the effectiveness of PCV13 in reducing incidence of IPD caused by the 6 additional serotypes.[36] In countries in which the recommended schedule is 2 infant doses followed by a toddler dose (ie, a 2 + 1 schedule), a national pediatric immunization program with high levels of uptake and adherence to vaccine schedules will be important to ensure protection, and active surveillance should continue to be conducted to monitor disease caused by serotypes 3, 6A, 6B and 23F.

PCV13 and PCV7 were well tolerated, and no new safety concerns were identified. Safety outcomes were in general similar between groups, with the exception that irritability after the toddler dose and AEs during the infant series occurred at higher frequencies in the PCV7 group compared with the PCV13 group. Most AEs were conditions and symptoms commonly expected for children in this age group, and with the exception of rash, AE categories generally showed no clear trends for differences between groups.

After the introduction of PCV7 in Spain in 2001, incidence of IPD caused by PCV7 serotypes decreased concurrently with an increase in incidence of disease caused by non-PCV7 serotypes, with most of this increase caused by the 6 additional serotypes in PCV13.[4,37,38] PCV13 covers approximately 78–87% of IPD in children aged <5 years in Spain,[4] similar to the worldwide estimate of 80–92% reported by the Global Serotypes Project.[5] The immunogenicity data from the present study are promising and reassuring but active surveillance of disease incidence and serotypes will continue to be needed, and correlation of immune response and clinical efficacy for each serotype will need to be ascertained.

A limitation to this study was that immune responses for the PCV7 serotypes were not measured in the subjects who received PCV7, and thus noninferiority of PCV13 as compared with PCV7 for these serotypes could not be evaluated. In previous studies, IgG antibody responses to PCV13 have been demonstrated to be noninferior as compared with PCV7 when administered in a 3 + 1[6,7] or 2 + 1 schedule.[8] In addition, functional opsonophagocytic activity (OPA) responses were not obtained in this study. In other studies, OPA responses for the 7 common serotypes were noninferior for PCV13 compared with PCV7, and OPA responses to the 6 additional serotypes were substantial after the infant series and toddler dose of PCV13 administered in a 3 + 1[6,7,29] or 2 + 1 schedule.[8,20]

In conclusion, immune responses to MnCC-TT and other routine childhood vaccines (DTaP–HBV–IPV/Hib and DTaP-–IPV+Hib) were noninferior when concomitantly administered with PCV13 compared with PCV7. PCV13 does not interfere with MnCC-TT or other routine childhood vaccines. PCV13 produces a strong immune response against all vaccine serotypes with a favorable safety profile in both infants and toddlers. PCV13 can be given safely at ages 2, 4 and 6 months (infant series) and 15 months (toddler dose) with concomitant MnCC-TT, DTaP–HBV–IPV/Hib and DTaP–IPV+Hib.

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