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Safety and Immunogenicity of a 13-Valent Pneumococcal Conjugate Vaccine Compared to Those of a 7-Valent Pneumococcal Conjugate Vaccine Given as a Three-Dose Series with Routine Vaccines in Healthy Infants and Toddlers▽†

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A 13-valent pneumococcal conjugate vaccine (PCV13) has been developed to improve protection against pneumococcal disease beyond that possible with the licensed 7-valent vaccine (PCV7). This study compared the safety and immunogenicity of PCV13 with those of PCV7 when given as part of the pediatric vaccination schedule recommended in Italy. A total of 606 subjects were randomly assigned to receive either PCV13 or PCV7 at 3, 5, and 11 months of age; all subjects concomitantly received diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio-*Haemophilus influenzae* type B (DTaP-HBV-IPV/Hib) vaccine. Vaccine reactions were monitored. Antibody responses to DTaP-HBV-IPV/Hib antigens, serotype-specific anticapsular polysaccharide IgG responses, and antipneumococcal opsonophagocytic assay (OPA) activity were measured 1 month after the two-dose primary series and 1 month after the toddler dose. Overall, the safety profile of PCV13 was similar to that of PCV7. The response to DTaP-HBV-IPV/Hib antigens was substantially the same with both PCV13 and PCV7. PCV13 elicited antipneumococcal capsular IgG antibodies to all 13 vaccine serotypes, with notable increases in concentrations seen after the toddler dose. Despite a lower immunogenicity for serotypes 6B and 23F after the primary series of PCV13, responses to the seven common serotypes were comparable between the PCV13 and PCV7 groups when measured after the toddler dose. PCV13 also elicited substantial levels of OPA activity against all 13 serotypes following both the infant series and the toddler dose. In conclusion, PCV13 appeared comparable to PCV7 in safety profile and immunogenicity for common serotypes, demonstrated functional OPA responses for all 13 serotypes, and did not interfere with immune responses to concomitantly administered DTaP-HBV-IPV/Hib vaccine.

The heptavalent pneumococcal conjugate vaccine (PCV7) has been shown to be highly immunogenic, safe, well tolerated, and effective in reducing invasive and noninvasive pneumococcal disease in vaccinated children. This effectiveness has been demonstrated both for a standard vaccination schedule of three doses in the first 6 months of life, followed by a toddler dose at 12 to 15 months of age (5, 8, 14, 32, 38, 45), and for a simplified schedule with a two-dose primary series and a toddler dose at 11 to 12 months (9, 10, 12, 19, 41). Besides the direct benefits for vaccinated infants and children, the administration of PCV7 has a substantial indirect effect in reducing the incidence of pneumococcal disease in unvaccinated adults, especially in those 65 years of age and older (4, 13, 24). Importantly, PCV7 can be administered concurrently with the other vaccines usually recommended in the first year of life without any significant immunologic interference and without any relevant reduction in safety and tolerability (2, 20, 36). For all of these reasons, the World Health Organization (WHO) has recommended the universal use of PCV7 in infants and children (43).

Despite its advantages, the widespread use of PCV7 has been accompanied by a small but statistically significant increase in the incidence of pneumococcal disease due to nonvaccine serotypes in both children and adults, leading to a slightly lower-than-expected vaccination efficacy. After implementation of PCV7 vaccination, serotypes 1, 3, 5, 7F, 19A, 22F, and 33F have been isolated from patients with invasive or noninvasive pneumococcal disease more frequently than before (1, 3, 15, 16, 22, 39). Whereas this finding is considered to be mainly due to a natural phenomenon (26, 29) for serotype 19A, the observed increase in the other serotypes seems to be derived from the direct impact of the vaccine on the carrier state of vaccinated children and the subsequent modification in the circulation of nasopharyngeal colonizing pneumococcal serotypes leading, both in vaccinated children

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and in unvaccinated family members, to the replacement of vaccine serotypes by nonvaccine strains (7, 23, 27).

To address these limitations, different conjugate pneumococcal vaccines have been studied, including the most recently developed 10-valent (40) and 13-valent (PCV13) vaccines. PCV13 is, at the moment, the vaccine with the highest number of serotypes and contains, together with the seven already present in PCV7 (4, 6B, 9V, 14, 18C, 19F, and 23F), six more serotypes chosen from among those emerging as causes of disease (1, 3, 5, 6A, 7F, and 19A) (37). On the basis of known serotype prevalences, 90% or more of the invasive pneumococcal disease in most regions of the world should be preventable with the use of PCV13 vaccine (3, 16, 32, 43). However, in accordance with the guidelines formulated by the WHO and the requirements of national regulatory authorities, the licensing of new pneumococcal vaccines requires randomized clinical trials to show the noninferiority of PCV13 to existing pneumococcal conjugate vaccines (43, 44). Moreover, because in many countries PCV7 is administered concomitantly with other infant vaccinations, including diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio-*Haemophilus influenzae* type B (DTaP-HBV-IPV/Hib) vaccine, it is also important to establish that the concomitant administration of PCV13 and other routine vaccines is safe and well tolerated and that it does not interfere with the immune response to the concomitant vaccine antigens. The present study was planned to (i) evaluate the acceptability of the safety profile of PCV13 as measured by the incidence of local reactions, systemic events, and adverse events (AEs), (ii) demonstrate that the immune response induced by the DTaP-HBV-IPV/Hib vaccine given with PCV13 is not inferior to the immune response induced by the DTaP-HBV-IPV/Hib vaccine given with PCV7, (iii) assess the immune response to PCV13 1 month after the primary series and immediately before the toddler dose, and (iv) assess the pneumococcal immune response induced by PCV13 relative to that induced by PCV7 when measured 1 month after the toddler dose. In accordance with the schedule usually followed in Italy, both pneumococcal and DTaP-HBV-IPV/Hib vaccines were given concomitantly with the simplified scheme of administration at 3, 5, and 11 months of age.

MATERIALS AND METHODS

Study design. This was a phase 3, parallel-group, randomized, active controlled, double-blind, multicenter trial carried out in four Pediatric Departments (Milan, Novara, Rome, Bologna) and five Public Health Departments (Ragusa, Sassari, Genoa, Massafra, Palermo) in Italy. Approval was obtained from the respective Ethics Committees of the participating study sites. Written informed consent for participation in the study was obtained from the subjects' parents/guardians. Subjects were randomly assigned in a 1:1 ratio to one of the two vaccine groups to receive either PCV13 plus DTaP-HBV-IPV/Hib vaccine or PCV7 plus DTaP-HBV-IPV/Hib vaccine at 3, 5, and 11 months of age. The randomization schedule was executed by Wyeth's Clinical Operations Randomization Environment system, which is accessible via the internet and by telephone 24 h a day. Treatment allocation was concealed from all subjects, study staff, and those assessing the outcomes.

At approximately 3, 5, and 11 months of age, subjects received a single intramuscular injection of pneumococcal conjugate vaccine (either PCV7 or PCV13) into the left thigh and a single intramuscular injection of DTaP-HBV-IPV/Hib vaccine into the right thigh. Both vaccines were administered with a 22-gauge, 2.5-cm-long needle. A blood sample was collected at approximately 6 months of age or 1 month after the second dose of the primary series. A second blood sample was drawn immediately before the third vaccination (toddler dose), and a third blood sample was drawn 1 month after the toddler dose.

Study population. Subjects eligible to participate in this study were healthy infants, as determined by medical history and physical examination. They were to be 3 months of age (75 to 105 days) at the time of enrollment, to be available for the entire study period, and to be born at more than 32 weeks of gestational age with a birth weight >2,000 g. In addition, the subjects' parents/guardians had to be available to be contacted by telephone and able to complete all of the relevant study procedures.

Excluded were subjects with any of the following: previous vaccination with a licensed or investigational pneumococcal conjugate vaccine or Hib conjugate, diphtheria, tetanus, pertussis, polio, or hepatitis B vaccine; bleeding diathesis or conditions associated with a prolonged bleeding time that would contraindicate intramuscular injection; known or suspected immune deficiency or suppression; a history of culture-proven *Streptococcus pneumoniae* or *H. influenzae* type b invasive disease; major known congenital malformation or serious chronic disorder; or a history of seizures, including febrile seizures, or a significant stable or evolving neurological disorder. Also excluded were children who had received blood products or gamma globulin, who were participating in another investigational study, or who were direct descendants of the study site personnel.

A complete medical history of each child was obtained and a complete physical examination was performed at visit 1, before randomization and administration of any study vaccinations.

Vaccines. PCV7 was equivalent to licensed Prevenar (Wyeth Pharmaceuticals Inc., Philadelphia, PA). PCV13 was formulated in a manner similar to that used for PCV7. It contains serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, as well as serotypes 1, 3, 5, 6A, 7F, and 19A. As with PCV7, each of the polysaccharides is covalently conjugated to a common carrier protein, CRM_{197}, a nontoxic variant of diphtheria toxin. PCV13 contains 2.2 μg of each polysaccharide, except for 4.4 μg of 6B, in 5.0 mM succinate buffer with 0.125 mg of aluminum as aluminum phosphate per 0.5-ml dose. The presentations of PCV13 and PCV7 used identical prefilled syringes.

DTaP-HBV-IPV/Hib vaccine was the commercially available Infanrix hexa (GlaxoSmithKline Biologicals, Rixensart, Belgium). A 0.5-ml dose of the vaccine was prepared for use according to the vaccine's labeling.

Safety assessments. Subjects were observed for 30 min after each vaccination for any immediate reaction. Any AE noted was recorded at this time. After discharge from the vaccination center, local reactions (redness, swelling, and tenderness), systemic events (decreased appetite, irritability, increased or decreased sleep), rectal temperature, and use of antipyretic medication to treat or prevent symptoms were monitored by the parents/guardians for 4 days, including the day of vaccination (day 1), and recorded in an electronic diary (e-diary). Parents/guardians measured the diameter of redness or swelling with a caliper provided for the purpose and recorded the measurement (1 to 14 or 14+) in whole-number increments in the e-diary. Each caliper unit represented 0.5 cm. Tenderness was recorded as none, present, or interfering with limb movement. Rectal temperature was recorded every evening and at any other time during the 4 days a fever was suspected. The highest temperature for each day was recorded in the e-diary.

Other systemic events (decreased appetite, irritability, increased sleep, and decreased sleep), and the use of antipyretic medications to prevent or treat symptoms were also recorded in the e-diary by the parents/guardians for 4 days after each vaccination. AEs (defined as any untoward, undesired, or unplanned signs, symptoms, diseases, or lab test results) were also recorded.

Immunogenicity evaluation. Antibody responses to hepatitis B, Hib antigen polyribosylribitol phosphate (PRP), and pertussis antigens (pertussis toxoid [PT], filamentous hemagglutinin [FHA], and pertactin [PRN]), tetanus toxoid, diphtheria toxoid, and poliovirus (Sabin strains 1, 2, and 3) were measured in the blood drawn 1 month after the primary immunization and 1 month after the toddler dose in all subjects with available sera. Standard enzyme-linked immunosorbent assay (ELISA) techniques were used to measure concentrations of antibodies against tetanus toxoid, PRP, hepatitis B virus, PT, FHA, and PRN (30, 31). Antibodies to poliovirus Sabin strains 1, 2, and 3 were evaluated with a poliovirus *in vitro* plaque neutralization assay (31), and diphtheria toxoid antibodies were evaluated by an anti-diphtheria toxoid ELISA (25).

Serum concentrations of anti-capsular polysaccharide IgG for each of the 13 pneumococcal serotypes were determined for all subjects in the PCV13 group for the 1 month post primary immunization and pre-toddler dose serum samples. They were also determined in all subjects for samples drawn 1 month after the toddler dose. The assay used was a standardized antipolysaccharide ELISA as previously described (6, 33, 34, 35, 42).

Serum opsonophagocytic activity induced by PCV13 was measured using previously described methods (17) on sera obtained 1 month after the primary series and 1 month after the toddler dose in a randomly selected subset of approximately 100 subjects in the PCV13 group.

All of the immunological assays were performed in Wyeth laboratories.

Sample size. Sample size was estimated on the basis of the proportion of immunogenicity responders (see below) in each vaccine group. Data from two earlier Wyeth studies on pneumococcal vaccine and a European Agency for the Evaluation of Medicinal Products scientific discussion document for Infanrix hexa were used in the estimation. A sample size of 85 evaluable subjects per group provided at least 99% power to declare noninferiority of the hepatitis B antigen when administered with PCV13 relative to the hepatitis B antigen administered with PCV7. A sample size of 225 evaluable subjects per group at the toddler dose would provide a 70% power to declare noninferiority for all 13 pneumococcal antigens using a noninferiority criterion of 0.10 (lowest limit of the 95% confidence interval [CI] for the difference between the proportions of responders in the PCV13 and PCV7 groups greater than or equal to −0.1) and a two-sided type 1 error of 0.05. Assuming a dropout rate of, at most, 25%, 600 subjects overall were to be enrolled to ensure that 450 subjects were evaluable at the toddler dose.

Inclusion criteria and statistical analysis. The primary objective was to demonstrate noninferiority of the immune response to hepatitis B virus after the toddler dose. Immune responses to all other concomitant vaccine antigens and to PCV13 and PCV7 were also evaluated. The safety profile of PCV13, as measured by the incidence of local reactions, systemic events, and AEs, was also evaluated. The evaluable population in the study consisted of all vaccinated subjects who met all of the eligibility criteria, complied with protocol defined criteria, had follow-up blood drawn 27 to 56 days postvaccination, and had available immunization data for at least one pneumococcal serotype and one DTaP-HBV-IPV/Hib antigen. A separate evaluable toddler population consisted of all subjects who completed the primary immunization on schedule, were immunized at the appropriate age for the toddler dose, had blood samples drawn on schedule (time between toddler dose and blood draw, 27 to 56 days; predose blood drawn <7 days before dose administration), and had available postvaccination data for at least one pneumococcal serotype and for at least one of the DTaP-HBV-IPV/Hib antigens. In both randomized vaccine groups, two subgroups were defined, subjects with at least one valid assay result for a concomitant vaccine antigen and those subjects with at least one valid assay result measuring the immune response to pneumococcal vaccine. Rates of local reactions and systemic events over the study period were calculated for each treatment group, and differences in the incidence of local reactions and systemic events in the PCV13 group relative to the incidence rates in the PCV7 group were reported. Fever was categorized as mild if the rectal temperature was ≥38.0°C but ≤39.0°C, moderate if it was >39.0°C but ≤40.0°C, and severe if it was >40.0°C. Redness and swelling were categorized as absent, mild (0.5 to 2.0 cm), moderate (2.5 to 7.0 cm), or severe (>7.0 cm). The safety population included all subjects who received at least one dose of the study vaccine. Separate populations were defined for each dose, and a two-sided Fisher exact test was used to perform all of the comparisons.

For the concomitantly administered vaccinations, the primary immunological comparison was the hepatitis B antigen immune response in subjects receiving PCV13 relative to the hepatitis B antigen immune response in subjects receiving PCV7. The primary endpoint for each antigen was the proportion of the subjects who achieved a prespecified antibody concentration as follows: hepatitis B antibody level, ≥10 milli-IU/ml; pertussis vaccine (PT, FHA, and PRN), ≥5 EU (ELISA units)/ml; Hib antigen (PRP) antibody level, ≥0.15 μg/ml; diphtheria toxoid antibody level, ≥0.1 IU/ml; tetanus toxoid antibody level, ≥0.1 IU/ml; poliovirus neutralizing antibody titer, >1:8. Alternate levels of ≥7.82 EU/ml for FHA and ≥1.0 μg/ml for PRP were also prespecified. An additional comparison for pertussis compared responders at the antibody level achieved by 95% of the subjects in the PCV7 group; the level was determined for each antigen (pertussis vaccine PT, FHA, and PRN) separately. For concomitant antigens, 95% CIs for the proportion of responders and for the difference in proportions (PCV13 − PCV7 reference) were calculated, with noninferiority declared if the lower bound of the two-sided 95% CI for the difference in proportions was greater than −10%.

The primary immunogenicity endpoints for each of the pneumococcal serotypes were the proportion of the subjects in the PCV13 group attaining serotype-specific antipolysaccharide IgG concentrations of ≥0.35 μg/ml 1 month after the infant series. As recommended by the WHO, this antibody concentration serves as a reference value for the comparison of novel pneumococcal conjugate vaccines with PCV7 to assess the potential for efficacy against invasive disease (44). The geometric mean IgG antibody concentration measured 1 month after the primary series also served as a primary endpoint. The pneumococcal IgG immune responses induced by the PCV13 relative to those of PCV7 1 month after the toddler dose were evaluated as secondary endpoints. Within each vaccine group and for each pneumococcal serotype, the proportion of the subjects with a specific IgG antibody concentration of ≥0.35 μg/ml and 95% CIs on the proportion were calculated. To assess treatment differences, 95% CIs on the difference in proportions (PCV13 − PCV7 reference) were calculated. For each serotype, noninferiority was declared if the lower bound of the two-sided 95% CI for the difference in proportions was greater than −0.10. For the pneumococcal opsonophagocytic assay (OPA) titers, the proportions of the subjects with OPA titers of at least 1:8 were calculated and analyzed in the same way as for IgG responders. According to WHO guidelines, an OPA response above a titer of 1:8 correlates with efficacy for some serotypes (11).

Within each vaccine group and for each antibody concentration or OPA titer, geometric means were also calculated. Each concentration/titer was logarithmically transformed for the analysis. Two-sided 95% CIs were constructed by back transformation of the CIs for the mean of logarithmically transformed assay results computed using the Student *t* distribution. Rises (*n*-fold) in antibody concentrations from before to after the toddler dose were summarized by geometric means and CIs and computed using the logarithmically transformed assay results. To assess differences between the two vaccine groups, two-sided 95% CIs for the ratio of the geometric mean concentrations (GMCs; PCV13/PCV7 reference) were constructed. The noninferiority criterion was met if the lower limit of the 95% CI of the ratio was >0.5 (2-fold criterion). In addition, for the PCV13 group, the ratio of the geometric mean *n*-fold rises (GMFRs) in post- to pretoddler GMCs and the corresponding two-sided 95% CIs were calculated.

TABLE 1. Demographic characteristics of the patients in this study

Characteristic	PCV13 group (*n* = 303)	PCV7 group (*n* = 303)
No. (%) male	164 (54.1)	170 (56.1)
Race		
No. (%) white	285 (94.1)	285 (94.1)
No. (%) Asian	1 (0.3)	2 (0.7)
No. (%) black or African	2 (0.7)	0 (0.0)
No. (%) multiracial Italian	15 (4.9)	16 (5.3)
Ethnicity		
No. (%) non-Hispanic and non-Latino	276 (91.1)	278 (91.7)
No. (%) Hispanic or Latino	27 (8.9)	25 (8.3)
Mean age (mo) at enrollment (SD)	2.9 (0.3)	2.9 (0.3)
Mean wt (kg) at enrollment (SD)	5.7 (0.7)	5.7 (0.7)
No. (%) not vaccinated	1 (0.3)	1 (0.3)
No. (%) vaccinated with dose 1 at age of:		
73 days	1 (0.3)	0 (0.0)
74–106 days	300 (99.0)	302 (99.7)
108 days	1 (0.3)	0 (0.0)
No. (%) vaccinated with dose 2 at:		
Days 42–70	281 (92.7)	279 (92.1)
Days 71–75	15 (5.0)	14 (4.6)
No. (%) who completed infant series	294 (97.0)	291 (96.0)
No. (%) vaccinated with dose 3 at:		
Days 334–381	282 (93.1)	277 (91.4)
Days 382–386	5 (1.7)	5 (1.7)
No. (%) who completed toddler series	285 (94.1)	281 (92.7)

RESULTS

Study population. A total of 606 infants were randomly assigned, 303 to the PCV13 group and 303 to the PCV7 group, both receiving the concomitant DTaP-HBV-IPV/Hib vaccine. The demographic characteristics of the study population are shown in Table 1. The two vaccine groups were similar in terms of sex, race, ethnicity, age, and weight at enrollment. All subjects received study vaccine in the protocol-specified time

TABLE 2. Percentages of subjects with local and systemic reactions within 4 days after each vaccination[a]

AE	% of subjects with reaction					
	Dose 1 infant series		Dose 2 infant series		Toddler dose	
	PCV13 group (n = 302)	PCV7 group (n = 302)	PCV13 group (n = 296)	PCV7 group (n = 288)	PCV13 group (n = 287)	PCV7 group (n = 282)
Local reactions						
Tenderness						
Any	32.1	30.0	30.4	36.7	47.2	44.1
Significant[b]	2.7	3.5	4.5	5.0	8.5	5.9
Swelling						
Any	19.0	19.6	24.6	28.7	28.6	27.3
Moderate[c]	3.6	3.1	5.6	5.1	7.5	10.2
Redness						
Any	25.8	26.5	31.5	34.4	36.5	36.2
Moderate[c]	2.7	3.0	5.5	3.6	7.5	10.9
Systemic events						
Fever (°C) of:						
≥38–≤39	41.7	38.6	55.5	60.6	63.7[e]	52.3
>39–<40	3.6	4.7	6.9	7.0	9.6	12.5
>40	0.0	0.0	0.0	0.0	0.0	0.7
Decreased appetite	35.4	34.3	47.3	45.4	52.0	57.4
Irritability	72.9[d]	63.7	75.5	75.3	74.7	74.9
Change in sleeping						
Increased	65.8	64.5	57.1	56.5	53.8	54.6
Decreased	39.3	36.4	40.1	41.8	35.6	35.7
Use of medication to:						
Treat symptoms	34.8	30.6	43.4	47.8	53.1	43.7
Prevent symptoms	12.6	18.1	20.2	24.5	27.9	24.3

[a] Percentages of subjects reporting the specific characteristics out of those reporting yes for at least 1 day or no for all days.
[b] Present and interfered with limb movement.
[c] From 2.5 to 7.0 cm.
[d] $P < 0.05$ versus PCV7 at dose 1.
[e] $P < 0.05$ versus PCV7 at toddler dose.

frames, except for 2 subjects at dose 1 (in the PCV13 group), 29 subjects at dose 2 (15 in the PCV13 group, 14 in the PCV7 group), and 10 subjects at the toddler dose (5 in the PCV13 group, 5 in the PCV7 group). Two hundred ninety-four (97.0%) subjects in the PCV13 group and 291 (96.0%) in the PCV7 group completed the infant series (from the first dose at 3 months to infant blood draw at visit 3), and 285 (94.1%) subjects in the PCV13 group and 281 (92.7%) in the PCV7 group completed the entire study. The main reasons for withdrawal were parental request (5 in the PCV13 group, 11 in the PCV7 group) and failure to return (5 in the PCV13 group, 4 in the PCV7 group). The characteristics of the evaluable infant and toddler immunogenicity populations were similar to those of the all-available population.

Safety. Safety data are presented for children vaccinated in the two vaccine groups. For each dose, only subjects whose parents reported information on local reactions or systemic events (yes for at least 1 day or no for all days) were included in the analysis. Overall, the safety profile of PCV13 was similar to that of PCV7. Few statistically significant differences were noted for local reactions and systemic events after any infant or toddler dose. Table 2 shows local reactions and systemic AEs within 4 days after each vaccination. The percentages of children with reports of local reactions or systemic events or antipyretic medication use appeared comparable between the two vaccine groups.

Most of the local reactions in the two vaccine groups were mild in severity and lasted 1 or 2 days. No statistically significant differences between vaccine groups were observed after doses 1 and 2 of the infant series or after the toddler dose. Local reactions, particularly tenderness and redness, were reported slightly more often after the toddler dose than after the infant series. No subject experienced severe swelling or severe redness after any dose. Significant tenderness was reported in ≤5% of the subjects in each vaccine group after each dose in the infant series and in ≤8.5% of the subjects in each vaccine group after the toddler dose.

There were no significant differences between vaccine groups in the incidence of systemic events, with the exception of irritability at dose 1, which was reported more frequently in the PCV13 group than in the PCV7 group ($P < 0.05$). Most cases of fever were mild in severity (≥38.0°C but ≤39.0°C). The incidence of moderate fever did not exceed 7.0% after either infant dose and did not exceed 12.5% after the toddler

dose. Severe fever was reported only once in the study, in one subject in the PCV7 group (0.7%) after the toddler dose. A significant difference between groups was demonstrated only for mild fever, which was more common after the toddler dose in the PCV13 group than in the PCV7 group ($P < 0.05$). The mean duration of individual systemic events did not exceed 4 days in either vaccine group. Use of medication to prevent or treat symptoms was similar between vaccine groups. Use of medication to treat symptoms ranged from 30.6% to 34.8% and from 43.4% to 47.8% after doses 1 and 2 of the primary series, respectively, and from 43.7% to 53.1% after the toddler dose. Use of medication to prevent symptoms ranged from 12.6% to 18.1% and from 20.2% to 24.5% after doses 1 and 2, respectively, and from 24.3% to 27.9% after the toddler dose.

No deaths were reported in this study. No statistically significant differences between vaccine groups were noted for the incidence of serious AEs (SAEs) after any of the doses. Nine SAEs in the PCV13 group and 15 in the PCV7 group were reported after the infant series, among which only 1 (a case of infantile spasms) in the PCV7 group was assessed by the investigator as related to the study vaccine. A total of nine SAEs in the PCV13 group (three cases of vomiting, two cases of diarrhea, two cases of gastroenteritis, one case of pharyngitis, and one case of febrile convulsions) and two in the PCV7 group (one case of diarrhea and one case of pyrexia) were reported after the toddler dose, with none assessed as related to the study vaccine and without any statistically significant difference between the groups ($P = 0.624$).

Concomitant vaccine immunogenicity. The primary series population comprised 554 children. Of these, 275 (90.8%) in the PCV13 group and 279 (92.1%) in the PCV7 group were evaluable for concomitant antigen immunogenicity, whereas 265 (87.5%) in the PCV13 group were evaluable for pneumococcal antigen immunogenicity. The toddler dose population comprised 515 children, with 254 (83.8%) in the PCV13 group and 261 (86.1%) in the PCV7 group evaluable for concomitant antigen immunogenicity and 246 (81.2%) in the PCV13 group and 249 (82.2%) in the PCV7 group evaluable for pneumococcal immunogenicity. The demographic and other baseline characteristics of the evaluable populations were the same as those of the overall randomized population, with no differences between the vaccine groups.

Overall, the immunogenicity data showed that the concomitant vaccine responses in the PCV13 group were not inferior to those in the PCV7 group. Thus, PCV13 did not adversely affect responses to the concomitantly administered DTaP-HBV-IPV/Hib vaccine.

Table 3 summarizes the proportion of subjects who achieved prespecified levels for concomitant vaccine antigens after dose 2 of the infant series and after the toddler dose. For all of the antigens included in the DTaP-HBV-IPV/Hib vaccine, the immune responses observed in the PCV13 recipients after the primary series and toddler doses met noninferiority criteria compared with the recipients of PCV7. In addition, 87% or more of the subjects receiving PCV13 and 90% or more of the subjects receiving PCV7 achieved predefined primary comparison levels of antibody to concomitant vaccine antigen 1 month after dose 2 of the primary series. These percentages were greater after the toddler dose, being 98% and 94% or more, respectively. All of the 95% CI lower limits for the differences between PCV13 and PCV7 responses exceeded −10%, indicating that the responses to concomitant vaccine antigens when given with PCV13 vaccination were not inferior to those when given with PCV7 after both the infant series and the toddler dose.

Within each vaccine group, GMCs or geometric mean titers (GMTs) were calculated for each concomitant vaccine antigen after the infant series and after the toddler dose (Table 4). The geometric means of all of the DTaP-HBV-IPV/Hib concomitant vaccine antigens were similar in the two vaccine groups both after the infant series and after the toddler dose. For all concomitant antigens, the geometric means after the toddler dose were significantly higher than those after the infant series ($P < 0.01$). All of the 95% CIs for the ratio of the GMCs had lower limits of >0.5, ranging from 0.78 to 1.03 after the infant series and from 0.65 to 1.25 after the toddler dose, and therefore met the noninferiority criteria. Slight differences ($P > 0.05$) were observed in diphtheria GMCs and poliovirus GMTs. The former were lower in the PCV13 group than in the PCV7 group but rose substantially from after the primary series to after the toddler dose and met the noninferiority criteria at both time points. Although the noninferiority criteria for poliovirus GMTs were met after both the infant series and the toddler dose, the GMTs after the toddler dose were slightly lower in the PCV13 group than in the PCV7 group.

Pneumococcal vaccine immunogenicity. Table 5 shows the proportion of subjects in the PCV13 group who achieved a pneumococcal IgG antibody concentration of ≥0.35 μg/ml after dose 2 of the infant series (PCV13 group only) and after the toddler dose. In children receiving PCV13, for each of the common pneumococcal serotypes, with the exceptions of 6B and 23F, 92.4% or more of the subjects achieved antibody concentrations of ≥0.35 μg/ml after the primary series. The proportions of responders to serotypes 6B and 23F were 58.4% and 68.6%, respectively. The proportion of responders to each of the six additional serotypes in PCV13 was 86.5% or more. After the toddler dose, at least 98.4% of the subjects in the two vaccine groups had antibody concentrations of ≥0.35 μg/ml for each of the common serotypes, including 6B and 23F. The responder proportions for the common serotypes were similar in the PCV13 and PCV7 groups, and comparison of the data indicated that the noninferiority criteria were met for each serotype.

The proportion of responders to each of the six additional serotypes in the PCV13 group ranged from 99.6% to 100%, except for serotype 3, where the proportion of responders was 93.9%. In the PCV7 group, antipolysaccharide antibody responses to serotypes 19A, 6A, and 5 were noted, although these serotypes are not included in PCV7. Reactivity to these non-PCV7 serotypes has been previously reported in studies of PCV7 (28). The cross-reactive antibodies to type 6A mediate some functional antibacterial OPA activity, while those against types 5 and 19A are nonfunctional. This is in contrast to the functional antibody against these serotypes elicited by PCV13 (see below). As expected, PCV7 elicited little to no antipolysaccharide antibody to serotypes 1, 7F, and 3.

The pneumococcal IgG GMCs of the PCV13 group measured after dose 2 of the infant series (before the toddler dose, for both vaccine groups) and after the toddler dose are shown in Table 6. After the infant series, the lowest concentrations among the seven common serotypes were noted for serotypes 6B (0.41 μg/ml) and 23F (0.61 μg/ml). GMCs for the other

TABLE 3. Percentages of subjects who achieved a prespecified level of concomitant vaccine antigens after dose 2 of the infant series and after the toddler dose

Concomitant vaccine antigen	Comparison level	% of total (95% CI[a]), dose 2, infant series		Difference[b] (95% CI[c])	% of total (95% CI[a]), toddler dose		Difference[b] (95% CI[c])
		PCV13 group (n = 155–273)	PCV7 group (n = 214–276)		PCV13 group (n = 125–252)	PCV7 group (n = 96–255)	
Hepatitis B	10.0 milli-IU/ml	93.8 (90.2, 96.3)	93.1 (89.5, 95.8)	0.7 (−3.6, 5.0)	98.4 (96.0, 99.6)	98.8 (96.6, 99.8)	−0.4 (−3.0, 2.0)
Hib (PRP)	0.15 μg/ml	87.0 (82.0, 91.1)	90.3 (86.1, 93.5)	−3.2 (−9.1, 2.4)	99.6 (97.7, 100.0)	98.2 (95.4, 99.5)	1.4 (−0.8, 4.2)
	1.0 μg/ml	49.4 (42.7, 56.0)	48.7 (42.6, 54.9)	0.7 (−8.2, 9.5)	96.2 (92.9, 98.2)	92.2 (87.8, 95.4)	4.0 (−0.4, 8.7)
Pertussis							
PT	≥5 EU/ml	99.6 (97.8, 100.0)	100.0 (98.7, 100.0)	−0.4 (−2.2, 1.0)	100.0 (98.4, 100.0)	100.0 (98.3, 100.0)	0.0 (−1.6, 1.7)
	≥16 EU/ml infant/ ≥21 EU/ml toddler	95.2 (91.8, 97.5)	95.2 (92.0, 97.4)	−0.0 (−4.0, 3.8)	92.8 (88.7, 95.7)	95.4 (91.8, 97.8)	−2.7 (−7.3, 1.8)
FHA	≥5 EU/ml	100.0 (98.5, 100.0)	100.0 (98.7, 100.0)	0.0 (−1.6, 1.4)	100.0 (98.4, 100.0)	100.0 (98.3, 100.0)	0.0 (−1.6, 1.7)
	≥31 EU/ml infant/ ≥162 EU/ml toddler	94.7 (91.0, 97.1)	95.6 (92.4, 97.7)	−0.9 (−5.0, 2.9)	95.2 (91.6, 97.6)	95.3 (91.6, 97.7)	−0.1 (−4.3, 4.1)
PRN	≥5 EU/ml	100.0 (98.5, 100.0)	100.0 (98.6, 100.0)	0.0 (−1.5, 1.4)	100.0 (98.4, 100.0)	100.0 (98.3, 100.0)	0.0 (−1.6, 1.7)
	≥40 EU/ml infant/ ≥106 EU/ml toddler	91.9 (87.8, 95.0)	95.2 (91.9, 97.4)	−3.2 (−7.8, 1.0)	94.9 (91.2, 97.3)	95.4 (91.7, 97.8)	−0.5 (−4.7, 3.7)
Diphtheria	0.01 IU/ml	100.0 (98.2, 100.0)	100.0 (98.5, 100.0)	0.0 (−1.8, 1.6)	100.0 (97.8, 100.0)	100.0 (98.1, 100.0)	0.0 (−2.3, 2.0)
	0.1 IU/ml	92.8 (88.3, 95.9)	96.3 (93.0, 98.3)	−3.5 (−8.3, 0.8)	100.0 (97.8, 100.0)	100.0 (98.1, 100.0)	0.0 (−2.3, 2.0)
Tetanus	0.1 IU/ml	94.2 (89.3, 97.3)	92.5 (88.1, 95.7)	1.7 (−3.9, 7.1)	97.6 (93.1, 99.5)	93.8 (86.9, 97.7)	3.8 (−1.7, 10.9)
Polio							
Type 1	≥1:8	99.5 (97.3, 100.0)	99.6 (97.9, 100.0)	−0.1 (−2.3, 1.7)	100.0 (97.7, 100.0)	100.0 (98.0, 100.0)	0.0 (−2.4, 2.1)
Type 2	≥1:8	95.6 (91.8, 98.0)	96.6 (93.6, 98.4)	−1.0 (−5.0, 2.8)	100.0 (97.6, 100.0)	100.0 (97.9, 100.0)	0.0 (−2.4, 2.1)
Type 3	≥1:8	99.5 (97.3, 100.0)	98.9 (96.7, 99.8)	0.7 (−1.6, 2.9)	100.0 (97.6, 100.0)	100.0 (97.9, 100.0)	0.0 (−2.4, 2.1)

[a] Exact two-sided CI based on the observed proportion of subjects.
[b] Difference in proportions, PCV13 minus PCV7, expressed as a percentage.
[c] Exact two-sided CI for the difference in proportions, PCV13 minus PCV7, expressed as a percentage.

common serotypes ranged from 1.68 μg/ml to 3.42 μg/ml. For the additional serotypes, the concentrations ranged from 1.15 μg/ml to 2.87 μg/ml. All of the pneumococcal GMCs before the toddler dose decreased from the levels attained after dose 2 of the infant series, except for serotype 6B, which demonstrated a modest increase. After the toddler dose, GMCs for the common serotypes ranged from 2.83 μg/ml to 10.30 μg/ml in the PCV13 group and from 4.10 μg/ml to 11.99 μg/ml in the PCV7 group. For the additional six serotypes, the lowest GMC in the PCV13 group after the toddler dose was for serotype 3 (1.22 μg/ml); GMCs for the other five serotypes ranged from 3.59 μg/ml to 9.81 μg/ml. For each of the common serotypes, the GMC ratios ranged from 0.67 to 1.12 and the lower bounds of the CIs were all 0.58 or higher. For the additional six serotypes, the GMC ratios ranged from 2.31 (serotype 19A) to 173 (serotype 1). The GMCs before and after the toddler dose can be summarized as GMFRs, which show a rise in titers for all of the serotypes. In the PCV13 group, the GMFRs ranged from 5.19 to 16.59 for the common serotypes and from 4.13 to 8.52 for the additional serotypes. The GMCs after the toddler dose were higher for 12 of 13 serotypes than the levels observed after the infant series. For serotype 3, there was no booster response and antibody concentrations reached a level comparable to that seen after the infant series.

Table 7 shows the OPA responder proportions (subjects who achieved OPA antibody titers of ≥1:8) and OPA GMTs in a randomly selected subset of 100 subjects in the PCV13 group determined 1 month after dose 2 of the infant series and 1 month after the toddler dose. The proportion of responders to the seven common serotypes was 90.0% or more after dose 2 of the infant series and 97.9% or more after the toddler dose. The proportion of responders to the six additional serotypes was 94.8% or more after dose 2 of the infant series and 100% after the toddler dose. OPA GMTs following the toddler dose were higher than the levels observed after the infant series for all of the serotypes, including serotype 3.

DISCUSSION

To overcome the worldwide problem of severe disease caused by serotypes not represented in PCV7, pneumococcal conjugate vaccines containing a greater number of serotypes

have been developed, including the most recently developed 10- and 13-valent vaccines (1, 3, 7, 15, 16, 21–23, 27, 40). Such vaccines need to be suitable for concomitant administration with other vaccines because of the large number of required vaccines specified in pediatric vaccination schedules in industrialized countries. For this reason, an evaluation of safety, as well as of the possible immunologic interference between concomitantly administered vaccine antigens and pneumococcal antigens, has become a mandatory part of vaccine testing. This study reports the immunogenicity and safety data for the concomitant administration of an investigational vaccine (PCV13) given at the same time as DTaP-HBV-IPV/Hib vaccine. The currently indicated PCV7 vaccine in combination with DTaP-HBV-IPV/Hib vaccine served as the control treatment. This study was designed taking into account the schedule for the administration of pediatric vaccines used in Italy and in Scandinavian countries, i.e., two doses comprising a primary series at 3 and 5 months of age and a toddler dose at 11 to 12 months.

The safety results of this study demonstrated a satisfactory safety profile for PCV13, comparable to that of PCV7. For both vaccines, most of the local reactions and systemic AEs, including fever, were mild in severity.

The immunogenicity results from this study showed no significant differences between PCV13 and PCV7 in the responses to concomitantly administered DTaP-HBV-IPV/Hib vaccine. Findings of other studies have demonstrated a lack of interference between PCV7 and DTaP-HBV-IPV/Hib vaccine (20, 28). Similar results have been obtained with a 10-valent pneumococcal vaccine containing different carrier proteins (21). Our study extends these data and shows that pneumococcal conjugate polysaccharides can be administered concomitantly with other vaccines without any reduction in the immune response to all of the antigens, independently of the type and number of carrier proteins. Taking into account also the data regarding the safety profile, it can be concluded that PCV13, despite containing more antigens, can be included in vaccination schedules with DTaP-HBV-IPV/Hib vaccine without any increase in the incidence of AEs and any immunologic interference.

In this study, both pneumococcal vaccines were highly immunogenic for all of their serotypes represented. Importantly, the immune response to the seven common serotypes evoked by PCV13 after the toddler dose was demonstrated not to be inferior to that evoked by PCV7. In addition, the response to the additional serotypes suggests that the new vaccine will be effective at providing extended protection against pneumococcal infections.

The immunogenicity data in the current study for the pneumococcal antigens common to PCV13 and PCV7 are consistent with those in previous studies of PCV7 given as a simplified two-dose infant series and suggest that PCV13 can be administered with a primary series of only two doses in the first 6 months of life, followed by a toddler dose at about 1 year of age, without any reduction in theoretical protection (10, 19). As in those PCV7 studies, 6B and 23F IgG levels were low after the infant series but boosted well after the third dose. In addition, surveillance data for two-plus-one regimens show that they are effective (41).

Functional activity was also shown in this study for the common serotypes, with over 90% and 97.9% of the subjects achieving an OPA titer of 1:8 or above after the infant series and the toddler dose, respectively.

TABLE 4. Comparison of concomitant vaccine antigen geometric means after dose 2 of the infant series and after the toddler dose

Concomitant vaccine antigen	GM[a] (95% CI[b]), dose 2, infant series		Ratio[c] (95% CI[d])	GM[a] (95% CI[b]), toddler dose		Ratio[c] (95% CI[d])
	PCV13 group (n = 155–273)	PCV7 group (n = 214–276)		PCV13 group (n = 125–252)	PCV7 group (n = 96–255)	
Hepatitis B, milli-IU/ml	260.46 (214.47, 316.31)	272.67 (220.83, 336.68)	0.96 (0.72, 1.27)	1,655.30 (1,343.30, 2,039.77)	2,284.95 (1,878.82, 2,778.88)	0.72 (0.54, 0.96)
Hib (PRP), μg/ml	0.99 (0.80, 1.21)	1.00 (0.83, 1.20)	0.99 (0.75, 1.30)	9.09 (7.80, 10.60)	8.85 (7.37, 10.62)	1.03 (0.81, 1.30)
Pertussis						
PT, EU/ml	50.01 (45.82, 54.58)	48.44 (44.71, 52.49)	1.03 (0.92, 1.16)	60.89 (55.61, 66.67)	64.53 (59.13, 70.42)	0.94 (0.83, 1.07)
FHA, EU/ml	102.87 (94.35, 112.16)	105.17 (97.25, 113.73)	0.98 (0.87, 1.10)	463.23 (425.19, 504.67)	456.55 (415.06, 502.18)	1.01 (0.89, 1.15)
PRN, EU/ml	167.76 (149.54, 188.18)	166.19 (150.28, 183.78)	1.01 (0.87, 1.17)	339.30 (309.16, 372.38)	361.70 (328.59, 398.14)	0.94 (0.82, 1.07)
Diphtheria, IU/ml	0.52 (0.46, 0.60)	0.67 (0.59, 0.76)	0.78 (0.65, 0.94)	2.77 (2.45, 3.13)	3.71 (3.28, 4.20)	0.75 (0.63, 0.89)
Tetanus, IU/ml	0.53 (0.45, 0.63)	0.63 (0.53, 0.74)	0.85 (0.67, 1.08)	2.62 (2.12, 3.25)	2.09 (1.56, 2.81)	1.25 (0.88, 1.79)
Polio						
Type 1, titer	180.72 (154.31, 211.64)	207.17 (178.64, 240.25)	0.87 (0.70, 1.08)	924.52 (782.71, 1,092.03)	1,348.04 (1,163.56, 1,561.77)	0.69 (0.55, 0.86)
Type 2, titer	123.74 (102.68, 149.13)	130.39 (109.96, 154.63)	0.95 (0.74, 1.22)	1,141.62 (958.68, 1,359.47)	1,340.51 (1,147.88, 1,565.48)	0.85 (0.68, 1.07)
Type 3, titer	397.32 (327.00, 482.76)	452.14 (382.57, 534.35)	0.88 (0.68, 1.13)	1,567.64 (1,289.72, 1,905.45)	2,421.31 (2072.82, 2,828.39)	0.65 (0.51, 0.83)

[a] Geometric means (GMs) were calculated using all subjects with available data for the specified blood draw.
[b] CIs are back transformations of a CI based on the Student t distribution of the mean logarithm of the concentrations/titers.
[c] Ratio of GMs (PCV13 to PCV7).
[d] CIs for the ratio are back transformations of a CI based on the Student t distribution of the mean difference between the logarithms of the measurements (PCV13 − PCV7).

TABLE 5. Subjects who achieved a pneumococcal IgG antibody concentration of ≥0.35 μg/ml in the PCV13 group after dose 2 of the infant series, in the PCV13 group before the toddler dose, and in both the PCV13 and PCV7 groups after the toddler dose

Vaccine serotype	% of total (95% CI[a])			Difference[b] (95% CI[c])
	PCV13 group (n = 258–264) after dose 2	After toddler dose		
		PCV13 group (n = 235–245)	PCV7 group (n = 218–248)	
PCV7				
4	96.6 (93.6, 98.4)	100.0 (98.5, 100.0)	100.0 (98.5, 100.0)	0.0 (−1.5, 1.5)
6B	58.4 (52.2, 64.4)	100.0 (98.5, 100.0)	100.0 (98.5, 100.0)	0.0 (−1.6, 1.5)
9V	94.7 (91.2, 97.1)	100.0 (98.4, 100.0)	100.0 (98.5, 100.0)	0.0 (−1.6, 1.5)
14	94.2 (90.6, 96.7)	99.6 (97.7, 100.0)	99.6 (97.7, 100.0)	0.0 (−2.0, 1.9)
18C	92.4 (88.5, 95.3)	99.2 (97.1, 99.9)	99.6 (97.8, 100.0)	−0.4 (−2.6, 1.5)
19F	95.1 (91.7, 97.3)	98.8 (96.4, 99.7)	98.4 (95.9, 99.6)	0.4 (−2.1, 3.0)
23F	68.6 (62.6, 74.1)	99.2 (97.0, 99.9)	98.8 (96.4, 99.7)	0.4 (−1.9, 2.8)
Additional				
1	96.6 (93.6, 98.4)	99.6 (97.7, 100.0)	3.3 (1.4, 6.5)	96.3 (93.0, 98.3)
3	92.8 (89.0, 95.6)	93.9 (90.1, 96.5)	6.7 (3.9, 10.6)	87.2 (82.1, 91.2)
5	91.6 (87.5, 94.6)	100.0 (98.5, 100.0)	70.2 (63.6, 76.2)	29.8 (23.8, 36.4)
6A	86.5 (81.8, 90.4)	99.6 (97.7, 100.0)	86.4 (81.5, 90.5)	13.2 (9.1, 18.1)
7F	98.5 (96.2, 99.6)	99.6 (97.7, 100.0)	4.9 (2.6, 8.5)	94.6 (91.0, 97.1)
19A	98.5 (96.1, 99.6)	100.0 (98.5, 100.0)	99.6 (97.7, 100.0)	0.4 (−1.1, 2.3)

[a] Exact two-sided CI based on the observed proportion of subjects.
[b] Difference in proportions, PCV13 − PCV7, expressed as a percentage.
[c] Exact two-sided CI for the difference in proportions, PCV13 − PCV7, expressed as a percentage.

The current study demonstrated that the six additional pneumococcal serotypes included in PCV13 elicited substantial immune responses, demonstrated by the fact that an antipolysaccharide antibody concentration of ≥0.35 μg/ml, the WHO reference value used for comparison, was reached in at least 93.9% of the subjects. It is notable that the antipolysaccharide GMCs after the toddler dose increased for six of seven additional serotypes in comparison with the infant series GMCs, whether after the second dose or before the toddler dose. The GMC for serotype 3 increased from before the toddler dose to a level comparable to that seen after the infant series. There were a high proportion of OPA responders to the six additional serotypes, with at least 94.8% achieving an OPA titer of 1:8 or above after the infant series and 100% after the toddler dose. The OPA GMTs for all six of the additional serotypes, including serotype 3, increased significantly after the toddler dose compared to the titers seen after the infant series. As with the PCV7 serotypes, the OPA GMTs varied between serotypes but there is no external reference standard, so it is not possible to compare between serotypes. The presence of

TABLE 6. Pneumococcal IgG GMCs in the PCV13 group after dose 2 of the infant series, in the PCV13 group before the toddler dose, and in both the PCV13 and PCV7 groups after the toddler dose

Vaccine serotype	IgG GMC[a] (95% CI[b])				Ratio[c] (95% CI[d])
	PCV13 group		After toddler dose		
	After dose 2	Before toddler dose	PCV13 group	PCV7 group	
PCV7					
4	2.38 (2.11, 2.67)	0.53 (0.48, 0.59)	4.77 (4.29, 5.30)	7.08 (6.41, 7.83)	0.67 (0.58, 0.78)
6B	0.41 (0.36, 0.47)	0.61 (0.54, 0.69)	10.00 (8.79, 11.38)	10.39 (9.14, 11.82)	0.96 (0.80, 1.15)
9V	1.68 (1.51, 1.86)	0.48 (0.43, 0.52)	3.02 (2.74, 3.32)	4.10 (3.72, 4.51)	0.74 (0.64, 0.84)
14	2.84 (2.44, 3.31)	2.03 (1.79, 2.30)	10.30 (9.26, 11.47)	11.99 (10.77, 13.35)	0.86 (0.74, 1.00)
18C	1.72 (1.54, 1.93)	0.35 (0.32, 0.39)	2.83 (2.55, 3.14)	4.26 (3.85, 4.70)	0.67 (0.58, 0.77)
19F	3.42 (2.95, 3.97)	0.94 (0.83, 1.06)	9.01 (7.84, 10.36)	8.06 (7.06, 9.21)	1.12 (0.92, 1.35)
23F	0.61 (0.53, 0.71)	0.26 (0.23, 0.29)	3.43 (3.02, 3.88)	4.87 (4.30, 5.51)	0.70 (0.59, 0.84)
Additional					
1	2.30 (2.03, 2.60)	0.68 (0.61, 0.75)	5.76 (5.12, 6.47)	0.03 (0.03, 0.04)	173.22 (145.34, 206.45)
3	1.15 (1.04, 1.28)	0.25 (0.22, 0.27)	1.22 (1.09, 1.35)	0.07 (0.06, 0.08)	16.83 (13.93, 20.35)
5	1.27 (1.14, 1.41)	0.88 (0.80, 0.97)	3.59 (3.25, 3.96)	0.56 (0.49, 0.64)	6.44 (5.47, 7.57)
6A	1.17 (1.02, 1.33)	0.81 (0.72, 0.92)	6.78 (6.04, 7.61)	1.42 (1.21, 1.66)	4.77 (3.93, 5.79)
7F	2.06 (1.88, 2.26)	0.76 (0.70, 0.82)	4.31 (3.94, 4.72)	0.04 (0.04, 0.05)	97.88 (83.60, 114.60)
19A	2.87 (2.55, 3.24)	1.20 (1.06, 1.35)	9.81 (8.82, 10.92)	4.24 (3.85, 4.67)	2.31 (2.00, 2.67)

[a] GMCs (μg/ml) were calculated using all subjects with available data for the specified blood draw.
[b] CIs are back transformations of a CI based on the Student t distribution of the mean logarithm of the concentrations.
[c] Ratio of GMCs, PCV13 to PCV7.
[d] CIs are back transformations of a CI based on the Student t distribution of the mean difference between the logarithms of the measurements (PCV13 − PCV7).

TABLE 7. Percentages of subjects who achieved a pneumococcal OPA antibody titer of ≥1:8 and pneumococcal OPA GMTs in the PCV13 group after dose 2 of the infant series and after the toddler dose in a subset of 100 subjects

Vaccine serotype	After dose 2		After toddler dose	
	% of subjects with ≥1:8 titers (95% CI[a])	GMT[b] (95% CI[c])	% of subjects with ≥1:8 titers (95% CI[a])	GMT[b] (95% CI[c])
PCV7				
4	100.0 (96.3, 100.0)	526.69 (431.88, 642.32)	100.0 (95.8, 100.0)	1,276.21 (1,025.09, 1,588.85)
6B	90.0 (82.4, 95.1)	191.34 (133.35, 274.55)	99.0 (94.3, 100.0)	2,383.31 (1,850.47, 3,069.57)
9V	100.0 (96.3, 100.0)	3,585.80 (2,787.34, 4,612.99)	100.0 (96.1, 100.0)	16,384.00 (13,066.97, 20,543.06)
14	100.0 (96.3, 100.0)	1,882.96 (1,446.51, 2,451.10)	100.0 (96.2, 100.0)	1,903.89 (1,580.90, 2,292.88)
18C	97.0 (91.4, 99.4)	294.48 (221.80, 390.98)	100.0 (96.3, 100.0)	1,324.41 (1,063.57, 1,649.22)
19F	96.0 (90.1, 98.9)	222.86 (170.46, 291.37)	97.9 (92.7, 99.7)	391.97 (296.34, 518.46)
23F	97.0 (91.4, 99.4)	487.51 (356.25, 667.13)	100.0 (96.3, 100.0)	3,679.67 (2,971.61, 4,556.44)
Additional				
1	94.8 (88.3, 98.3)	62.63 (47.59, 82.41)	100.0 (96.2, 100.0)	294.07 (226.88, 381.15)
3	99.0 (94.6, 100.0)	176.07 (144.89, 213.96)	100.0 (96.2, 100.0)	504.66 (435.71, 584.53)
5	96.0 (90.0, 98.9)	127.11 (99.36, 162.60)	100.0 (96.1, 100.0)	333.24 (274.24, 404.94)
6A	95.9 (89.9, 98.9)	541.81 (392.09, 748.68)	100.0 (96.2, 100.0)	2,217.29 (1,821.95, 2,698.42)
7F	100.0 (96.4, 100.0)	5,914.33 (4,710.83, 7,425.30)	100.0 (96.2, 100.0)	14,886.35 (12,560.25, 17,643.22)
19A	95.6 (89.0, 98.8)	157.59 (118.91, 208.94)	100.0 (96.0, 100.0)	1,415.08 (1,140.56, 1,755.66)

[a] Exact two-sided CI based on the observed proportion of subjects.
[b] GMTs were calculated using all subjects with available data for the specified blood draw.
[c] CIs were back transformations of a CI based on the Student *t* distribution for the mean logarithm of the titers.

high levels of functional activity against the additional serotypes suggests that PCV13 may be effective in preventing disease caused by these serotypes.

One limitation of this study is that it was not designed to compare the antipneumococcal response evoked by PCV13 and PCV7 after the primary series. The WHO recommends that comparisons with existing pneumococcal vaccines be made using a three-dose rather than a two-dose infant series, which has been done in two separate trials (44). For a two-plus-one schedule, the important comparison is that done after completion of the regimen. However, to compare responses after a two-dose infant series, the PCV7 responses were compared to those for PCV13 in a two-plus-one schedule (2, 4, and 12 months) in a study performed in the United Kingdom (18). Those data show that after the infant series, responses to the common serotypes, as measured by IgG and OPA, were comparable in PCV7 and PCV13 recipients.

The percentage of responders in the PCV13 group (those who attained antibody concentrations of ≥0.35 μg/ml) after the primary series in this study was, for common antigens, quite similar to that found in our previous study, in which PCV7 was administered at 3, 5, and 11 months of age to preterm and full-term subjects (10). On the basis of these data, although a direct comparison was not performed in this study, it is reasonable to suppose that the responses evoked by the two vaccines are also similar after the first two doses and that the addition of six new serotypes does not modify the global response to the pneumococcal antigens.

In conclusion, the observations from the study reported here suggest that PCV13 has, even when given with a simplified scheme of administration, the potential to significantly extend protection against serious pneumococcal disease.

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