

# Immunogenicity and safety of 13-valent pneumococcal conjugate vaccine in Mexico

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## ABSTRACT

**Objective.** To assess the safety and immune responses induced by a 13-valent pneumococcal conjugate vaccine (PCV13) after immunization of infants in Mexico.

**Methods.** PCV13 was given with other routine childhood vaccinations to 225 infants in Mexico at ages 2, 4, 6, and 12 months.

**Results.** The proportions of subjects achieving immunoglobulin G (IgG) concentrations  $\geq 0.35$   $\mu\text{g/mL}$  after the infant series and toddler dose were  $\geq 93.1\%$  and  $\geq 96.7\%$ , respectively, for all 13 serotypes. The serotype-specific pneumococcal IgG geometric mean concentrations after the infant series and toddler dose ranged from 1.18 to 9.13  $\mu\text{g/mL}$  and from 1.62 to 15.41  $\mu\text{g/mL}$ , respectively. The most common local reaction and systemic event after each dose were tenderness and irritability, respectively. Most fever was mild; no fever  $> 40.0^\circ\text{C}$  (i.e., severe) was reported. One subject withdrew because of Kawasaki disease 5 days after the first dose of vaccines, but this condition was not considered related to PCV13.

**Conclusions.** Overall, PCV13 administered with routine pediatric vaccines was immunogenic and safe in healthy infants in Mexico.

## Key words

Pneumococcal vaccines; safety; pneumonia; Mexico.

*Streptococcus pneumoniae* causes childhood invasive infections, including pneumonia, meningitis, bacteremia, and acute otitis media. *S. pneumoniae* has become the predominant cause of acute bacterial meningitis in Mexico following introduction of the *Haemophilus influenzae* type b (Hib) vaccine (1). Pneumococcal isolates in Mexico have a high

prevalence of antibiotic resistance (2–6), suggesting that vaccination would be an important preventive strategy.

A 7-valent pneumococcal conjugate vaccine (PCV7) was approved in Mexico in 2007 (7) and was expected to cover 56% to 62% of serotypes causing invasive pneumococcal disease (IPD) (2, 3). With inclusion of 6 additional serotypes, the 13-valent pneumococcal conjugate vaccine (PCV13) potentially could cover 77% of serotypes causing IPD in Latin America and Mexico (2, 3).

This study assessed serotype-specific pneumococcal immune responses induced by PCV13 measured 1 month after doses 2 and 3 of a three-dose infant

series and after a toddler dose in healthy infants in Mexico. The safety objectives were to assess incidence rates of local reactions, systemic events, and adverse events (AEs).

## MATERIALS AND METHODS

### Study design

This phase 3, open-label, single-arm, multicenter trial was conducted at seven sites (Guadalajara, Jalisco; Monterrey, Nuevo León; Puebla, Puebla; Morelia, Michoacán; Mexico City, Distrito Federal; Oaxaca, Oaxaca; and Mérida, Yucatán) to evaluate the safety, toler-

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ability, and immunogenicity of PCV13 administered concomitantly with routine vaccines to healthy infants in Mexico. Study materials, including the protocol and other materials provided to investigators and written materials provided to parent(s)/legal guardian(s), were examined by institutional review boards or independent ethics committees for review and written approval. 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 the parent(s)/legal guardian(s) of every subject before enrollment and before performance of any study-related procedures.

## Subjects

Eligible subjects were healthy infants 2 months of age (42–98 days) who weighed  $\geq 3.5$  kg at enrollment, were available for the entire study period, and had parent(s)/legal guardian(s) who were reachable by telephone and able to complete all relevant study procedures. Subjects were ineligible if they had previously been vaccinated with licensed or investigational pneumococcal, Hib conjugate, diphtheria, tetanus, pertussis, poliovirus, measles, mumps, rubella, or rotavirus vaccines; had shown a previous anaphylactic reaction to any vaccine or vaccine-related component or contra-indication to vaccination with any of the study vaccines; had known or suspected immune deficiency or suppression; had a history of culture-proven invasive disease caused by *S. pneumoniae*; had a major known congenital malformation or serious chronic disorder including a significant neurologic disorder or history of seizure; had received blood products or gamma-globulin (including hepatitis B immunoglobulins and monoclonal antibodies; e.g., palivizumab); or had participated in another investigational or interventional trial other than an observational study.

## Interventions

All subjects received PCV13 at 2, 4, and 6 months of age (infant series) and at 12 months of age (toddler dose) con-

**TABLE 1. Vaccination schedule**

Visit	Age, months	Vaccines
1	2	PCV13 <sup>a</sup> DTaP-IPV-Hib <sup>b</sup> HBV <sup>c</sup> Rotavirus
2	4	PCV13 DTaP-IPV-Hib Rotavirus
4	6	PCV13 DTaP-IPV-Hib HBV
6	12	PCV13 MMR <sup>d</sup>

<sup>a</sup> 13-valent pneumococcal conjugate vaccine.

<sup>b</sup> Diphtheria, tetanus, acellular pertussis; inactivated poliovirus; *Haemophilus influenzae* type b vaccine.

<sup>c</sup> Hepatitis B virus vaccine.

<sup>d</sup> Measles, mumps, and rubella vaccine.

comitantly with routinely administered pediatric vaccines (Table 1).

PCV13 was administered intramuscularly into the anterolateral muscle of the left thigh. Diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and Hib vaccine was administered intramuscularly into the upper anterolateral muscle of the right thigh. Hepatitis B virus vaccine was administered intramuscularly into the lower anterolateral muscle of the right thigh, away from any other vaccine, according to local practices. Rotavirus vaccine was given as an oral solution. Measles, mumps, and rubella vaccine was administered subcutaneously into the arm.

PCV13 contains saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to CRM<sub>197</sub>, a nontoxic variant of diphtheria toxin. The vaccine is formulated to contain 2.2  $\mu$ g of each saccharide, except for 4.4  $\mu$ g of serotype 6B, per 0.5-mL dose. The final formulation contains 5 mM succinate buffer, 0.02% polysorbate 80, and 0.125 mg of aluminum phosphate per 0.5-mL dose.

## Immunogenicity measurements

Blood samples (3–5 mL) were collected for immunogenicity assessments at 28–42 days after dose 2 and dose 3 of the infant series, and after the toddler dose. Serum concentrations ( $\mu$ g/mL) of anticapsular immunoglobulin G (IgG) were determined by enzyme-linked immunosorbent assay for each of the 13 pneumococcal serotypes (8, 9).

## Safety measurements

Parent(s)/legal guardian(s) of each subject were issued an e-diary and were asked to monitor and record the subject's local reactions, systemic events, and use of antipyretic medication for 4 days after each PCV13 vaccination. Any local reactions or systemic events persisting at day 4 were also recorded in the e-diary until the parent(s)/legal guardian(s) recorded an end date in the e-diary. The e-diary allowed these assessments to be recorded only within a fixed time window, providing an accurate representation of the subjects' experience at that time. Investigators were required to review the e-diary data online at frequent intervals to evaluate e-diary completion compliance and as part of the ongoing safety review.

Local reactions (redness, swelling, and tenderness) on the left leg (site of the PCV13 injection) were monitored. Parent(s)/legal guardian(s) were instructed on how to measure the size of redness or swelling with a caliper and recorded the measurement in caliper units (1–14 or  $> 14$ ; 1 caliper unit represents 0.5 cm) in the e-diary. Measurements were rounded to the nearest whole number. Tenderness was recorded as none, present, or interfered with limb movement. Redness and swelling were categorized as mild (0.5–2.0 cm), moderate (2.5–7.0 cm), or severe ( $> 7.0$  cm). If redness or swelling was  $> 7.0$  cm ( $> 14$  caliper units), the subject was to be seen by study personnel.

Systemic events included decreased appetite, irritability, increased sleep, and decreased sleep. Axillary temperature was recorded daily at bedtime for 4 days and any time fever (axillary temperature  $\geq 38.0^\circ\text{C}$ ) was suspected during the 4 days after vaccination. The highest temperature for each day was recorded in the e-diary. In the event of a fever, temperature was recorded daily until the fever resolved.

The use of antipyretic medication to prevent or treat symptoms was recorded daily during days 1–4 after each vaccination. Antipyretic use beyond day 4 was also recorded in the e-diary.

AEs were monitored from enrollment through the postinfant series 7-month blood draw and from the toddler dose until study conclusion (13-month blood draw) based on clinical observations

during study visits, ancillary information included in the e-diary, or information obtained by asking parent(s)/legal guardian(s) a nonspecific question. Serious AEs (SAEs) were defined as AEs that were life-threatening, required inpatient hospitalization or prolongation of an existing hospitalization, resulted in persistent or significant disability or incapacity, or resulted in cancer or death. SAEs were monitored throughout the study.

### Sample size determination

Sample size estimate was based on the proportion of responders for pneumococcal serotypes measured after the infant series from two previous studies (10, 11). The study was sized to allow estimation of the proportion of responders after the third dose of PCV13 to within  $\pm 6.0\%$  precision and after the second dose of PCV13 to within  $\pm 7.7\%$  precision. These precision estimates were based on the maximum margins of error among all serotypes in the proportion of responders at the relevant time points in the two studies (10, 11). Assuming a dropout rate of  $\leq 25\%$  (estimate based on the maximum dropout rates of the two previous studies), 214 subjects overall were to be enrolled to ensure that 160 subjects were evaluable.

### Enrollment procedure

Although this study was not randomized, eligible subjects received PCV13 and an enrollment number (equivalent to a randomization number for randomized studies). Before enrollment and before any study-related procedures were performed, voluntary written study-specific informed consent was obtained from the parent(s)/legal guardian(s) for each subject. Prior to enrollment, the investigators reviewed the subjects' medical history and medications to ensure that the subjects were in good health and met all the inclusion criteria and none of the exclusion or temporary-delay criteria. Subject numbers were allocated through the sponsor's Clinical Operations Randomization Environment II system.

### Study end points

The primary end point for each of the 13 pneumococcal serotypes was the pro-

portion of subjects achieving a serotype-specific IgG concentration  $\geq 0.35 \mu\text{g/mL}$  (i.e., responders) measured 1 month after the infant series, the reference antibody concentration for assessment of serotype-specific vaccine efficacy against IPD recommended by the World Health Organization (12). Secondary end points for each pneumococcal serotype were the proportion of responders measured 1 month after the second infant dose and the toddler dose, and the serotype-specific IgG geometric mean concentrations (GMCs) after the second and third doses of the infant series and after the toddler dose.

Safety end points were local reactions, systemic events, use of antipyretic medications, and AEs.

### Statistical methods

For each pneumococcal serotype, the proportion of responders was computed for each time point when blood samples were obtained: 28–42 days after dose 2 and dose 3 of the infant series and 28–42 days after the toddler dose. For each serotype, exact, unconditional, two-sided 95% confidence intervals (CIs) on the proportion were calculated. IgG GMCs at each blood draw visit were calculated. Two-sided 95% CIs were constructed by back-transformation of the CIs for the mean of the logarithmically transformed assay results computed using the Student *t* distribution. Geometric mean fold rises (GMFRs) in antibody concentration from after dose 2 to after dose 3 of the infant series, and from after dose 3 of the infant series to after the toddler dose, were summarized by geometric means and 95% CIs, also computed using the logarithmically transformed assay results.

Subjects were considered to have completed the infant series or toddler dose if they completed the blood draw visit after the infant series or toddler dose. Subjects with major protocol deviations were excluded from the evaluable infant immunogenicity population, but minor protocol deviations (i.e., those unlikely to have any marked effect on immune responses) did not result in exclusion from the evaluable immunogenicity population.

All subjects who received  $\geq 1$  dose of study vaccine were included in the safety population.

## RESULTS

### Subjects

The disposition of subjects is shown in Figure 1. A total of 225 subjects were enrolled and assigned to receive PCV13 with other routine childhood vaccinations; 192 (85.3%) completed the infant series, 191 (84.9%) were vaccinated with the toddler dose, and 183 (81.3%) completed the toddler dose (Figure 1).

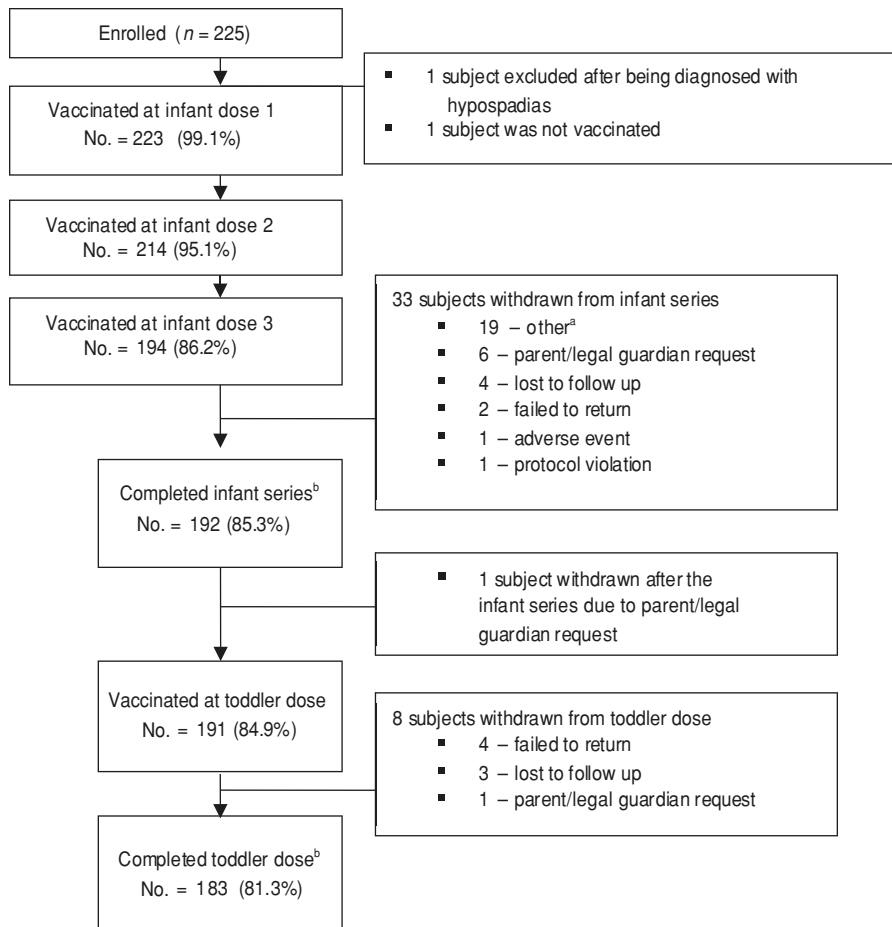
One subject who was diagnosed with hypospadias was not vaccinated because the investigator determined this diagnosis to meet an exclusion criterion. One additional subject was also listed as not receiving study vaccine; however, this subject was re-enrolled later and was vaccinated. All 19 subjects withdrawn from the infant series for the reason "other" were enrolled at the same site and were withdrawn at the request of the site's ethics committee because of vaccination delays caused by problems with vaccine storage at the site.

During the outbreak of the influenza A(H1N1) epidemic in Mexico in May–June 2009, the country was quarantined, with restrictions on nonessential travel, which resulted in subjects being unable to get to the clinic for scheduled vaccinations. PCV13 was administered outside the protocol-specified time frame at  $> 70$  days after the previous study vaccination for 20 subjects (8.9%) after dose 2 and for 42 subjects (18.7%) after dose 3 of the infant series; these were considered minor protocol violations and did not result in exclusion from the evaluable immunogenicity population. In addition, 12 subjects (5.3%) received the toddler dose at  $> 396$  days of age because of the H1N1 influenza outbreak; these subjects were included in the all-available toddler immunogenicity population but were excluded from the evaluable toddler immunogenicity population.

Table 2 presents demographic characteristics for the safety population. All subjects were Mexican, with a mean age of 2.1 months at enrollment.

### Immunogenicity

The proportion of responders after dose 2 of the infant series was  $\geq 93.2\%$  for 11 of the 13 serotypes, 81.4% for serotype 6B, and 77.5% for serotype 23F (Table 3). After dose 3 of the infant

**FIGURE 1. Patient disposition: infants and toddlers immunized with 13-valent pneumococcal conjugate vaccine, Mexico**

<sup>a</sup> These subjects were enrolled at the same site and withdrawn by request of the ethics committee for the site because of delays in vaccine administration caused by vaccine storage problems.

<sup>b</sup> Subjects were considered to have completed the infant series or the toddler dose if they completed the visit for the postinfant series or post-toddler dose blood draws.

**TABLE 2. Demographic characteristics (n = 223)<sup>a</sup> of infants and toddlers immunized with 13-valent pneumococcal conjugate vaccine, Mexico**

Characteristic	No.	Percent
Sex		
Male	114	51.1
Female	109	48.9
Race		
Other <sup>b</sup>	223	100
Ethnicity		
Hispanic or Latino	223	100
Age at enrollment in study (months)		
Mean ± SD <sup>c</sup>	2.1 ± 0.5	
Median	2.1	
Range	1.4–3.3	
Weight at enrollment in study (kg)		
Mean ± SD	5.1 ± 0.8	
Median	5.0	
Range	3.5–7.5	

<sup>a</sup> Safety population, which includes all subjects who received ≥ 1 dose of the study vaccine.

<sup>b</sup> Defined as being not of white, black, or Asian race. All subjects with race reported as “other” were of Mexican ethnicity.

<sup>c</sup> Standard deviation.

series, the proportion of responders was ≥ 93.1% for all 13 serotypes (Table 3). After the toddler dose, the proportion of responders was 96.7% to 100% for all 13 serotypes (Table 3).

During the infant series, serotype-specific pneumococcal IgG GMCs were 0.81–5.59 µg/mL after dose 2 and 1.18–9.13 µg/mL after dose 3 (Table 3). After the toddler dose, serotype-specific pneumococcal IgG GMCs were 1.62–15.41 µg/mL (Table 3).

IgG GMC GMFRs were 0.88–6.13 after dose 3 of the infant series (dose 3/dose 2) and 1.14–3.08 after the toddler dose (toddler dose/dose 3) (Table 3). GMCs for all serotypes except serotypes 4 and 19F increased after dose 3 compared with dose 2, and GMCs for all serotypes increased after the toddler dose compared with dose 3.

## Safety

Local reactions were reported for 72.0% of subjects after dose 1, 70.9% after dose 2, and 66.7% after dose 3 of the infant series, and for 47.4% of subjects after the toddler dose (Table 4). The most common local reaction was tenderness. Most local reactions were mild or moderate in severity.

Systemic events were reported for 83.9% of subjects after dose 1, 72.7% after dose 2, and 73.3% after dose 3 of the infant series, and for 59.3% of subjects after the toddler dose (Table 4). The most common systemic event was irritability. Most cases of fever were mild. No cases of fever > 40.0°C were reported.

## Adverse events

During the infant series, 170 AEs were reported in 80 subjects (35.9%), mainly in the categories of infections and infestations (66 subjects; 29.6%) and gastrointestinal disorders (22 subjects; 9.9%). The most common individual AEs reported in ≥ 4% of subjects during the infant series were nasopharyngitis (33 subjects; 14.8%), diarrhea (14 subjects; 6.3%), and viral upper respiratory tract infection (11 subjects; 4.9%). After the infant series, seven AEs were reported in six subjects (2.7%). Seborrheic dermatitis was reported in two subjects; all other AEs occurred in one subject each (pyrexia, allergy to arthropod bite, pneumonia, breath holding, and atopic dermatitis).



**TABLE 3. Immunogenicity assessments after doses 2 and 3 of infant series and after toddler dose of 13-valent pneumococcal conjugate vaccine, Mexico**

Serotype	Infant series postdose 2				Infant series postdose 3				Post-toddler dose					
	Responders		IgG <sup>b</sup> GMC <sup>c</sup>		Responders		IgG GMC		Responders		IgG GMC		GMFR <sup>d</sup>	
	% (No. = 124–162)	95% CI <sup>a</sup>	µg/mL (No. = 160–162)	95% CI	% (No. = 149–162)	95% CI	µg/mL (No. = 160–162)	95% CI	% (No. = 147–155)	95% CI	µg/mL (No. = 134–137)	95% CI	Toddler dose vs. dose 3	95% CI
PCV7 <sup>g</sup> serotype														
4	100.0	97.7–100.0	3.59	3.16–4.08	100.0	97.7–100.0	3.47	3.11–3.89	100.0	97.6–100.0	5.10	4.41–5.89	1.50	1.32–1.72
6B	81.4	74.5–87.1	0.82	0.69–0.97	97.5	93.8–99.3	5.00	4.22–5.93	99.4	96.5–100.0	15.41	12.92–18.38	3.02	2.49–3.67
9V	95.0	90.4–97.8	1.84	1.58–2.14	98.1	94.7–99.6	2.36	2.12–2.63	1.28	1.12–1.47	3.76	3.29–4.29	1.61	1.40–1.84
14	98.8	95.6–99.9	5.59	4.67–6.70	98.8	95.6–99.9	9.13	7.85–10.62	1.63	1.36–1.96	10.62	9.16–12.32	1.14	0.98–1.32
18C	93.2	88.2–96.6	1.80	1.53–2.11	98.8	95.6–99.9	2.53	2.24–2.86	1.41	1.22–1.62	3.93	3.45–4.48	1.58	1.37–1.82
19F	98.1	94.7–99.6	4.19	3.57–4.91	98.1	94.7–99.6	3.70	3.22–4.25	0.88	0.78–1.00	11.33	9.68–13.26	3.08	2.65–3.58
23F	77.5	70.2–83.7	0.81	0.67–0.96	93.1	88.0–96.5	1.83	1.53–2.18	2.27	1.90–2.72	5.70	4.81–6.77	3.07	2.55–3.70
Additional serotypes														
1	98.1	94.7–99.6	3.44	2.98–3.97	99.4	96.6–100.0	4.19	3.69–4.76	1.22	1.06–1.39	5.86	5.08–6.75	1.32	1.14–1.54
3	96.9	92.9–99.0	1.17	1.05–1.30	94.4	89.6–97.4	1.18	1.04–1.35	1.01	0.92–1.12	1.62	1.42–1.84	1.35	1.16–1.57
5	97.5	93.8–99.3	1.88	1.65–2.14	98.1	94.7–99.6	3.13	2.76–3.55	1.66	1.48–1.86	4.75	4.18–5.40	1.51	1.32–1.72
6A	94.4	89.7–97.4	1.82	1.55–2.15	98.8	95.6–99.9	4.09	3.54–4.71	2.25	1.94–2.59	11.64	9.93–13.64	2.89	2.44–3.42
7F	98.8	95.6–99.9	2.97	2.65–3.32	98.8	95.6–99.9	3.78	3.39–4.21	1.27	1.14–1.43	5.81	5.18–6.51	1.55	1.37–1.74
19A	99.4	96.6–100.0	3.53	3.03–4.10	99.4	96.6–100.0	4.19	3.69–4.76	1.19	1.03–1.37	8.95	7.84–10.23	2.21	1.88–2.59

<sup>a</sup> Confidence interval.

<sup>b</sup> Immunoglobulin G.

<sup>c</sup> Geometric mean concentration.

<sup>d</sup> Geometric mean fold rise.

<sup>e</sup> GMFR values (dose 3/dose 2) were calculated using all subjects with available data from the blood draw after infant dose 2 and after infant dose 3.

<sup>f</sup> Post-toddler GMFR values (toddler dose/dose 3) were calculated using all subjects with available data from the blood draw after infant dose 3 and after the toddler dose.

<sup>g</sup> 7-valent pneumococcal conjugate vaccine.

After the toddler dose, 70 AEs were reported in 51 subjects (26.7%), mainly in the categories of infections and infestations (22 subjects; 11.5%), gastrointestinal disorders (15 subjects; 7.9%), and general disorders and administration-site conditions (15 subjects; 7.9%). The most common individual AEs reported after the toddler dose ( $\geq 3\%$  of subjects) were pyrexia (14 subjects, 7.3%), nasopharyngitis and diarrhea (8 subjects [4.2%] each), and vomiting (7 subjects; 3.7%).

No AEs during or after the infant series were considered related to study vaccines. After the toddler dose, 12 related AEs were reported in 4 subjects (2.1%). Related AEs were most frequently observed in the category of general disorders and administration-site conditions (4 subjects; 2.1%). The most common individual related AEs reported during this period were pyrexia and vaccination-site pain [three subjects (1.6%) each] and erythema and swelling [two subjects (1.0%) each]; one subject reported irritability and one reported decreased appetite. All related AEs were among those expected after vaccination.

A total of six SAEs were reported in three subjects (1.3%) during the infant series. These events included myocarditis, pyrexia, severe diarrhea, and Kawasaki disease in one subject after dose 1; moderate bronchiolitis in one subject after dose 3; and life-threatening angioedema in one subject after dose 1. After the infant series, 3 SAEs were reported in 3 subjects (1.3%)—1 subject with severe pyrexia 115 days after dose 3, 1 subject with severe pneumonia 203 days after dose 3, and 1 subject with severe breath holding 77 days after dose 3. None of these SAEs was life-threatening. After the toddler dose, 2 SAEs were reported in 2 subjects (1.0%)—1 subject with severe acute sinusitis on day 36 and 1 subject with an anoxic seizure on day 6. Neither was life-threatening. One female subject was withdrawn because of the SAE of Kawasaki disease, which occurred 5 days after receipt of dose 1 of the infant series. No SAEs were considered related to study vaccines, and no subjects died during the study.

## DISCUSSION

This open-label, single-arm, multi-center study shows that a 3-dose infant series and toddler dose of PCV13 can be given safely with other routine childhood vaccines to healthy infants at ages

**TABLE 4. Local and systemic reactions reported first 4 days postvaccination of infants and toddlers immunized with 13-valent pneumococcal conjugate vaccine, Mexico**

	Infant series			Toddler dose
	Dose 1	Dose 2	Dose 3	Dose 4
Local reactions, %	No. = 214 <sup>a</sup>	No. = 196 <sup>a</sup>	No. = 168 <sup>a</sup>	No. = 154 <sup>a</sup>
Tenderness <sup>b</sup>				
Any	63.5	69.4	61.3	43.7
Significant	12.4	12.6	15.4	3.8
Swelling <sup>c</sup>				
Any	31.2	29.9	29.4	21.3
Mild	25.1	20.0	19.0	8.1
Moderate	11.9	13.3	14.6	15.8
Severe	0	0	0	0
Redness <sup>c</sup>				
Any	33.8	28.9	31.8	22.0
Mild	27.9	19.5	20.9	8.8
Moderate	10.6	12.3	13.9	15.7
Severe	0	0	0	0
Systemic events, %	No. = 217 <sup>a</sup>	No. = 198 <sup>a</sup>	No. = 172 <sup>a</sup>	No. = 162 <sup>a</sup>
Fever ≥ 38°C (100.4°F) but ≤ 39°C (102.2°F)	7.0	18.5	18.3	23.0
Fever > 39°C (102.2°F) but ≤ 40°C (104.0°F)	0	0.6	2.2	0
Fever > 40°C (104.0°F)	0	0	0	0
Decreased appetite	31.0	29.3	25.7	33.8
Irritability	69.8	62.2	63.2	46.7
Increased sleep	37.2	24.5	22.9	17.9
Decreased sleep	32.8	35.1	37.3	22.0
Use of medication to treat symptoms	22.9	30.1	34.7	24.5
Use of medication to prevent symptoms	25.4	34.8	37.6	29.7
Use of medication to treat and prevent symptoms	15.5	22.2	23.6	16.4
Use of medication to treat or prevent symptoms	31.7	40.4	45.8	36.1
Any systemic event	83.9	72.7	73.3	59.3

<sup>a</sup> No. = number of subjects reporting yes for ≥ 1 day or no for all days.

<sup>b</sup> Tenderness was recorded as none, present, or interfered with limb movement.

<sup>c</sup> Redness and swelling were categorized as mild (0.5–2.0 cm), moderate (2.5–7.0 cm), or severe (> 7.0 cm) for analysis.

2, 4, 6, and 12 months in Mexico. PCV13 was immunogenic and elicited substantial responses to all 13 vaccine serotypes that met or exceeded those observed in similar phase 3 studies (10, 13–16).

*S. pneumoniae* is a common cause of invasive disease in children. After licensure of PCV7 in the United States of America, overall IPD incidence decreased by 76% and IPD caused by the serotypes in PCV7 declined by 100% among children < 5 years of age (17). However, IPD caused by nonvaccine serotypes has increased, particularly serotype 19A.

Before the introduction of PCV13, IPD caused by the additional serotypes in PCV13 was increasingly prevalent in Mexico. In 2002, an estimated 56% of *S. pneumoniae* serotypes causing IPD in Mexico were covered by PCV7, whereas 77% were covered by PCV13 (3). A study in Mexico in 2002–2003 reported that the most prevalent serotypes in children with acute otitis media were PCV7 serotypes 6B, 14, 19F, and 23F and PCV13-unique serotypes 6A and 19A, with PCV7 providing coverage of 63.9% of cases and PCV13 providing coverage of 83.3% of

cases (18). More recent studies have demonstrated an increased prevalence of IPD caused by non-PCV7 serotypes, including serotypes 3, 7F, and 19A, after introduction of PCV7 into the pediatric immunization schedule in Mexico (19, 20). In addition, studies in Mexico have demonstrated decreased prevalence of PCV7 serotypes and increased prevalence of non-PCV7 serotypes in nasopharyngeal isolates in children after vaccination with PCV7 (21, 22). Interestingly, in a recent study in Peru before the introduction of PCV7, PCV7 serotypes 6B, 14, 19F, and 23F were the most common serotypes in nasopharyngeal isolates from healthy children, with PCV7 covering 50.0% and PCV13 covering 57.2% of the isolated serotypes (23). In addition, in Mexico, many strains of *S. pneumoniae* exhibit antibiotic resistance to penicillin, macrolides, and other antibiotics (2–6). In a regional surveillance study, 69.4% of pneumococcal isolates in Mexico during 2000–2005 were resistant to trimethoprim/sulfamethoxazole, 38.2% were resistant to erythromycin, and 17.2% were resistant to chloramphenicol (5).

The annual direct medical costs of *S. pneumoniae* and nontypeable *H. influenzae*-associated diseases in children aged < 10 years in Mexico are considerable, estimated at U.S. \$277–\$432 million (\$2.59–\$4.05 per capita) in a study based on 2008 data (7). Vaccination with a pneumococcal conjugate vaccine is cost-saving compared with no vaccination, with the greatest estimated savings realized with PCV13 (24). Comparable results suggesting greater cost-effectiveness of PCV13 compared with lower-valent pneumococcal conjugate vaccines, or no vaccination, have been reported for other countries as well (25, 26). Thus, vaccination is an increasingly important preventive strategy.

PCV13 was well-tolerated in this study. The rates of local reactions, systemic events, and AEs observed were similar to those reported in previous trials comparing PCV13 with PCV7 given as a 3 + 1 series with routine pediatric vaccines (10, 14, 16). Although significant tenderness was reported during the infant series, all local reactions of redness and swelling were mild or moderate in severity. Fever

was uncommon, and mostly mild in severity, and no subject reported severe fever after any dose. Irritability was the most frequently reported systemic event and it occurred in about two-thirds of subjects after each dose.

AEs were generally consistent with those common or expected in children of this age. The most common categories of AEs were infections and infestations, gastrointestinal disorders, and general disorders and administration-site conditions. No life-threatening AEs or deaths were reported, and no SAEs were considered related to study vaccines. One case of Kawasaki disease presented in a female child 5 days after receiving the first dose of vaccines. This subject also reported myocarditis, pyrexia, and severe diarrhea; all resolved within a few weeks, and none was considered to be related to PCV13. Kawasaki disease is an acute, self-limiting vasculitis of unknown etiology (27). Based on clinical and epidemiologic features, an infectious cause is suspected but no organism has been determined as the causative agent. An alternative hypothesis is that the disease is triggered by an immunologic response to any of several antigens. A nonsignificant higher rate of Kawasaki

disease has been noted in association with some rotavirus vaccines (28). In a phase 4, observational, database safety study of PCV7, Kawasaki disease was not significantly more frequent than in a historic control group after adjustment for race, sex, and other factors (29).

This study has limitations that should be mentioned. First, it was an open-label study with no comparator arm. However, the antibody responses and safety profile observed in this trial are similar to those observed in other trials comparing PCV13 with PCV7 (10, 12–16). Second, the safety follow-up for adverse events was 1 month after the toddler dose. Other studies have performed safety evaluations of PCV13 in comparison with PCV7, including 6 months of follow-up after the toddler dose, and have demonstrated a comparable safety profile (16, 30).

In conclusion, PCV13 was immunogenic and had an acceptable safety profile in infants in Mexico when administered with routine pediatric vaccines. Because of the prevalence of IPD and pneumococcal antibiotic resistance, vaccination with pneumococcal conjugate vaccine is an important strategy in Mexico. PCV13 provides increased protec-

tion against pneumococcal serotypes not included in PCV7.

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## RESUMEN

### Inmunogenia y seguridad de la vacuna antineumocócica conjugada 13 valente en México

**Objetivo.** Evaluar la seguridad y la respuesta inmunitaria inducida por una vacuna antineumocócica conjugada 13 valente (PCV13) tras la vacunación de lactantes en México.

**Métodos.** Se administró la PCV13, junto con otras vacunas habituales de la niñez, a 225 lactantes a los 2, 4, 6 y 12 meses de edad en México.

**Resultados.** Las proporciones de lactantes que alcanzaron concentraciones de inmunoglobulina G (IgG) iguales o superiores a 0,35 µg/ml después de las tres primeras dosis (serie del lactante) y tras la cuarta (dosis del inicio de la deambulación) fueron de ≥ 93,1% y ≥ 96,7%, respectivamente, para los 13 serotipos. Las medias geométricas de las concentraciones de IgG antineumocócica específica de serotipo después de las tres primeras dosis y tras la cuarta variaron de 1,18 a 9,13 µg/ml, y de 1,62 a 15,41 µg/ml, respectivamente. Las reacciones local y sistémica más frecuentes después de cada dosis fueron respectivamente el dolor en el punto de inyección y la irritabilidad. En la mayor parte de los casos, la fiebre fue de carácter leve; no se notificó ningún caso de fiebre de más de 40,0 °C (fiebre grave). Un lactante fue excluido del estudio como consecuencia de la aparición de una enfermedad de Kawasaki cinco días después de la primera dosis de la vacuna, aunque se consideró que este proceso no estaba relacionado con la PCV13.

**Conclusiones.** En términos generales, la PCV13, administrada conjuntamente con las vacunas pediátricas habituales, se mostró inmunógena e inocua en lactantes sanos de México.

## Palabras clave

Vacunas neumocócicas; seguridad; neumonía; México.