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Open-Label Trial of Immunogenicity and Safety of a 13-Valent Pneumococcal Conjugate Vaccine in Adults ≥50 Years of Age in Mexico

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This open-label multicenter clinical trial conducted in Mexico assessed the immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine (PCV13) in adults ≥50 years of age not previously vaccinated with the 23-valent pneumococcal polysaccharide vaccine (PPSV23). The PCV13 elicited a robust immune response in this study population, as reflected by the magnitude of fold rises in functional antibody levels measured by serotype-specific opsonophagocytic activity (OPA) assays before and 1 month after vaccination. Although the prevaccination OPA geometric mean titers (GMTs) for the majority of the serotypes were significantly lower in the 50- to 64-year age group than those in the ≥65-year age group, the postvaccination immune responses were generally similar. The overall immune responses were higher for the majority of the serotypes in the Mexican study population than those in similar adult study populations who received the PCV13 in Europe and the United States. PCV13 was well tolerated, and there were no vaccine-related serious adverse events. In conclusion, PCV13 is safe and immunogenic when administered to adults ≥50 years of age in Mexico and has the potential to protect against vaccine-type pneumococcal disease. (This study has been registered at ClinicalTrials.gov under registration no. NCT01432262.)

Diseases caused by *Streptococcus pneumoniae* are a major worldwide public health problem affecting all age groups, with the highest mortality rates in adults >65 years of age and in individuals with underlying disease (1, 2). In adults ≥50 years of age in Latin American countries, including Mexico, community-acquired pneumonia (CAP) caused mainly by *S. pneumoniae* is associated with high rates of morbidity and mortality, with the incidence increasing substantially with age (3, 4). Worldwide, 20 serotypes account for >70% of invasive pneumococcal disease (IPD) in children <5 years of age, although the prevalence of each varies by region (5). In Latin American and Caribbean countries, the 21 most common serotypes causing IPD in young children, in order of decreasing frequency, are serotypes 14, 6B, 5, 1, 23F, 6A, 18C, 19F, 19A, 9V, 7F, 3, and 4, which are included in the 13-valent pneumococcal conjugate vaccine (PCV13), as well as nonvaccine serotypes 8, 15B, 12F, 2, 12A, 9A, 45, and 46 (5). Castañeda et al. (6) reported similar findings from the Sistema de Redes de Vigilancia de los Agentes Responsables de Neumonias y Meningitis Bacterianas (SIREVA) surveillance data from Latin America and the Caribbean from 2007 to 2009 in children <5 years of age; since the introduction of PCV7, serotype replacement with nonvaccine serotypes, especially 19A, has been observed. The Mexico-specific SIREVA II data from 2011 in children <6 years of age and adults ≥50 years of age reported that the PCV13 serotypes were the most frequently isolated, in particular, serotype 19A (7).

Vaccination is considered an important preventive strategy for adults and children, in part because of the increased prevalence of *S. pneumoniae* strains that are resistant to antibiotics (1). In a study examining the antimicrobial susceptibility patterns of *S. pneumoniae*, Quiñones-Falconi and colleagues (8) concluded that pneumococci isolated from children and adults with community-acquired acute respiratory infections in Mexico City have some of the world's highest rates of penicillin resistance. In addition, these penicillin-nonsusceptible strains were usually resistant to other antimicrobial agents commonly used to treat these infections.

A 23-valent pneumococcal polysaccharide vaccine (PPSV23) is widely available for the prevention of vaccine-type pneumococcal disease for adults ≥50 years of age and for high-risk younger adults; however, PPSV23 has not been widely implemented in Latin American countries (4). PPSV23 is efficacious in preventing IPD, although reports on its efficacy against CAP have been inconsistent, and its duration of protection is limited (1, 9, 10). Recently, a 13-valent PCV (PCV13) was licensed for adults in the United States, Europe, and many other countries, including Mexico, for the prevention of pneumococcal disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. Its licensing was based on immunological and safety comparisons with PPSV23 in clinical studies performed in the United States and in several European countries as part of the PCV13 clinical development program (11). The Community-Acquired

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Pneumonia Immunization Trial in Adults (CAPiTA) ≥65 years of age was recently completed in the Netherlands, with approximately 85,000 subjects; it demonstrated that PCV13 is efficacious against vaccine-type CAP, including nonbacteremic CAP and vaccine-type IPD (12, 13).

In contrast to PPSV23, PCV13 is manufactured by conjugating the capsular saccharides of *S. pneumoniae* to an immunogenic protein carrier (cross-reacting material 197 [CRM_{197}], a nontoxic diphtheria toxin cross-reactive material) in order to elicit a T-cell-dependent immune response. As T cells provide the signals required for the generation of B-cell memory (14), PCV13 has the potential to elicit a memory response on subsequent natural exposure to vaccine-type pneumococcal strains and to provide protection over a prolonged period of time (15).

The aim of the current study (registered at ClinicalTrials.gov under registration no. NCT01432262) was to assess the immunogenicity and safety of PCV13 when administered to adults ≥50 years of age in Mexico who had not previously been vaccinated with PPSV23. In addition, the immunogenicity data from this study were compared *post hoc* with those of two other PCV13 studies that assessed similar populations of PPSV23-naive adults (16–18). These studies were part of the adult clinical development program for the licensing of PCV13 (11).

MATERIALS AND METHODS

Trial design. This open-label study was conducted at 4 sites in Mexico from 29 July 2011 to 5 December 2011. The subjects were stratified into 2 age groups, 50 to 64 years and ≥65 years. The study was conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and the ethics principles that have their origins in the Declaration of Helsinki.

Study population. Eligible study participants included male and female subjects ≥50 years of age, including those with underlying diseases that were stable for ≥6 weeks before vaccination (i.e., a disease not requiring significant change in therapy or hospitalization for worsening disease within 6 weeks before vaccination), and who had no history of *S. pneumoniae* infection within the past 5 years, no previous vaccination with any licensed or investigational pneumococcal vaccine, no history of severe vaccine-associated adverse reactions or receipt of plasma products or immunoglobulins within 60 days before vaccination, and no immunodeficiency, immunosuppression, or severe chronic disease associated with pulmonary, cardiac, or renal failure.

Comparator study populations. One of the comparator studies enrolled a PPSV23-naive study population 50 to 64 years of age from the United States to compare the safety and immunogenicity of PCV13 versus PPSV23 (18). The second comparator study enrolled a PPSV23-naive population ≥65 years of age from Europe to compare the safety and immunogenicity of PCV13 administered concomitantly with a trivalent inactivated influenza vaccine versus PCV13 administered alone 1 month after a trivalent inactivated influenza vaccine (TIV) (16, 17); the data from the group receiving PCV13 administered alone 1 month after TIV were used for the comparison in this paper. The inclusion and exclusion criteria for the study populations in the comparator studies were similar to those described above.

Vaccine and administration. PCV13 contains capsular polysaccharides from the pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (2.2 μg of each saccharide, except for 4.4 μg of 6B) individually conjugated to nontoxic diphtheria toxin cross-reactive material 197 (CRM_{197}), 5 mM succinate buffer, 0.85% sodium chloride, 0.02% polysorbate 80, and 0.125 mg of aluminum as aluminum phosphate per 0.5-ml dose. PCV13 was manufactured by Wyeth, a Pfizer company (lot no. 10-089561). The vaccine was supplied in single-dose syringes without preservatives and stored at 2°C to 8°C. All eligible participants received one dose of PCV13 administered intramuscularly into the deltoid.

Immunogenicity assessments. Two 15-ml blood samples were taken, one before and one approximately 1 month after vaccination. The functional activity of the antibodies from these samples was measured using serotype-specific validated microcolony opsonophagocytic activity (OPA) assays and expressed as OPA titers. An OPA titer was defined as the interpolated reciprocal serum dilution that resulted in complement-mediated killing of 50% of the assay bacteria. The OPA assay procedures were based on previously described methods (19). The standardized OPA assays from this PCV13 study and the comparator studies were performed in the same central laboratory by the sponsor, thus allowing comparisons to be made.

Safety assessments. The participants recorded local reactions and systemic events on an electronic diary (e-diary) every evening within a fixed time window for 14 days after vaccination. The e-diary prompted the reporting of vaccine-associated signs and symptoms through the use of a standardized questionnaire, providing an accurate representation of each participant's experience. Severity was assessed using the U.S. Food and Drug Administration toxicity grading scale (20). The largest diameter of any redness or swelling was measured using a caliper. Oral temperature was measured using a digital thermometer, and fever was defined as a temperature of ≥38.0°C (100.4°F). The highest daily temperature was recorded. The diary data were transmitted by the participants to the central vendor and could not be altered thereafter. The data were reviewed by the investigator via an Internet-based portal to monitor vaccine reactogenicity and compliance with e-diary completion.

Other adverse events (AEs), which were not prompted by the e-diary, were collected by the investigator on an electronic AE case report form at each visit in response to nonspecific questions.

Statistical methods. (i) Sample size estimation. Sample size estimation was based on pneumococcal OPA geometric mean titers (GMTs) and associated variability observed in two previous Pfizer studies (21, 22). Assuming a dropout rate of ≤7%, a sample size of 150 evaluable subjects in each age group was sufficient to provide adequate precision in the study results for descriptive assessment. Thus, 324 subjects (162 per group) were to be vaccinated.

(ii) Analysis populations. The evaluable immunogenicity population consisted of eligible subjects who adhered to the protocol requirements, received the study vaccine, had valid and determinate assay results, and had no major protocol violations. The all-available immunogenicity population included all subjects who had at least one valid and determinate assay result (data not presented). The safety population included all subjects who received the study vaccine.

(iii) Immunogenicity analysis. The endpoints for the study included measuring the functional antibody OPA titers elicited by the 13 pneumococcal serotypes contained in PCV13 at two time points, before vaccination and at 1 month (28 to 42 days) after vaccination. The serotype-specific OPA titers were logarithmically transformed for the analysis. The OPA GMTs were calculated at each time point. Two-sided 95% confidence intervals (CIs) were constructed by back transforming the CIs based on the Student *t* distribution for the mean logarithm of the titers. For each serotype, the geometric mean fold rises (GMFRs) from before to 1 month after vaccination were computed, and 2-sided 95% CIs were constructed using the logarithmically transformed assay results.

Post hoc analyses included comparisons of the GMT ratios between the age groups within this study and across studies with study populations of comparable ages (16–18). The GMT ratios were calculated by back transforming the mean difference between the groups on the logarithmic scale. The 95% CIs for the ratios are back transformations of a CI based on the Student *t* distribution for the mean difference of the logarithms of the measures. For comparisons between the vaccine groups, the immune responses were statistically significantly lower when the upper limit of the 2-sided 95% CI for the GMT ratio was <1 and were statistically signifi-

TABLE 1 Demographic characteristics for the evaluable immunogenicity population

Characteristic	Age group		
	50–64 yr (n = 161)	≥65 yr (n = 161)	Total (n = 322)
Sex (%)			
Female	59.0	52.2	55.6
Male	41.0	47.8	44.4
Race/ethnicity (%)			
White	100.0	100.0	100.0
Hispanic/Latino	100.0	100.0	100.0
Age at vaccination (yr)			
Mean (SD)	55.8 (4.0)	73.4 (5.8)	64.6 (10.1)
Median	55.1	72.6	64.9
Range	50.0–64.7	65.1–92.2	50.0–92.2

cantly higher when the lower limit of the 2-sided 95% CI for the GMT ratio was >1.

(iv) Safety analysis. AEs were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA). The proportions of subjects with local reactions, systemic events, and AEs were summarized with corresponding exact 2-sided 95% CIs (23). The differences in the proportions in adults 50 to 64 years of age versus those ≥65 years of age were expressed as a percentage with an exact 2-sided 95% CI and corresponding P value (24).

RESULTS

Disposition of subjects and baseline demographics. A total of 324 subjects were enrolled, with 162 subjects in each age group. In the ≥65-year age group, 1 subject withdrew before vaccination. In the 50- to 64-year age group, 1 subject was excluded from the evaluable immunogenicity population because of an eligibility violation. The baseline demographic characteristics of the evaluable immunogenicity population are shown in Table 1. Of note, in the 50- to 64-year age group (mean age, 55.8 years) and in the ≥65-year age group (mean age, 73.4 years), there was a greater percentage of females than males (59% and 52.2%, respectively).

Immunogenicity. For all serotypes in both age groups, the OPA GMTs increased significantly from immediately before to 1 month after vaccination, as reflected by the GMFRs (lower limit of the 2-sided 95% CI for the GMFRs, >1). The OPA GMFRs were higher in the 50- to 64-year age group (GMFR range, 5.3 to 63.6) than those in the ≥65-year age group (GMFR range, 3.4 to 35.8; Table 2). The prevaccination OPA GMTs in the 50- to 64-year age group were statistically significantly lower (upper limit of the 2-sided 95% CI for the GMT ratio, <1) than those in the ≥65-year age group for 8 of 13 serotypes and were similar to those in the ≥65-year age group for the 5 other serotypes (1, 4, 6B, 9V, and 14); the postvaccination OPA GMTs in the 50- to 64-year age group were similar to those in the ≥65-year age group for 10 of 13 serotypes but statistically significantly higher for serotypes 4, 7F, and 9V (Table 3).

A *post hoc* analysis comparing the results for adults 50 to 64 years of age from this study in Mexico with those of adults of the same age from the United States comparator study showed that the prevaccination OPA GMTs were statistically significantly higher in the Mexican study for 11 of the 13 serotypes and similar between the studies for serotypes 1 and 3. The postvaccination OPA GMTs were statistically significantly higher in the Mexican study for 8 of the 13 serotypes, similar between the studies for serotypes 3, 5, and 6A, and statistically significantly lower in the Mexican study for serotypes 1 and 3 (Table 4).

Similarly, a *post hoc* analysis comparing the results for adults ≥65 years of age from this Mexican study with those of adults of the same age from the European comparator study showed that the prevaccination OPA GMTs were statistically significantly higher in the Mexican study for the 12 of the 13 serotypes and similar between the studies for serotype 1. The postvaccination OPA GMTs were statistically significantly higher in the Mexican study for 10 of the 13 serotypes and similar between the studies for serotypes 1, 4, and 14 (Table 5).

TABLE 2 Geometric mean fold rises of pneumococcal OPA GMTs for the evaluable immunogenicity population[a]

Serotype	Data by age group (yr)[b]:							
	50–64 (n = 137–153)				≥65 (n = 137–158)			
	Prevaccination GMT	Postvaccination GMT	GMFR	95% CI	Prevaccination GMT	Postvaccination GMT	GMFR	95% CI
1	6	121	21.3	16.17, 28.16	7	84	11.7	8.70, 15.82
3	7	88	12.5	9.77, 16.05	11	89	7.8	6.03, 10.02
4	31	1,767	57.7	36.40, 91.36	58	1,159	19.9	13.23, 29.88
5	8	281	37.3	26.06, 53.47	11	281	26.2	18.74, 36.72
6A	56	3,512	62.3	39.00, 99.36	114	3,273	28.7	19.76, 41.70
6B	237	4,290	18.1	11.61, 28.15	392	3,691	9.4	6.61, 13.45
7F	70	3,025	43.2	26.94, 69.17	124	1,922	15.5	10.05, 23.80
9V	268	2,347	8.8	5.72, 13.43	194	1,396	7.2	4.72, 10.98
14	286	1,518	5.3	3.73, 7.56	382	1,311	3.4	2.58, 4.56
18C	69	3,070	44.3	28.19, 69.51	154	2,152	13.9	9.21, 21.09
19A	51	1,542	30.0	21.19, 42.50	107	1,196	11.2	7.99, 15.69
19F	25	1,078	42.8	28.33, 64.67	54	1,120	20.8	13.38, 32.29
23F	14	881	63.6	43.16, 93.75	26	923	35.8	24.16, 52.95

[a] OPA, opsonophagocytic activity; GMT, geometric mean titer.

[b] n values for the age groups reflect the numbers of subjects with valid and determinate assay results for the specified serotype at both the prevaccination and postvaccination blood draws. The GMTs and geometric mean fold rises (GMFRs) were calculated using all subjects with available data for both the prevaccination and postvaccination blood draws. The 95% confidence intervals (CIs) are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers, or the mean fold rise.

TABLE 3 Effect of age on pneumococcal OPA GMTs in the evaluable immunogenicity population[a]

Serotype	OPA GMTs at[b]: Prevaccination 50–64 yr (n = 142–159)	Prevaccination ≥65 yr (n = 146–161)	Comparison[c] Ratio	Comparison[c] 95% CI	Postvaccination 50–64 yr (n = 148–155)	Postvaccination ≥65 yr (n = 150–159)	Comparison[c] Ratio	Comparison[c] 95% CI
1	6	7	0.8	0.64, 1.00	120	84	1.4	0.96, 2.10
3	7	11	0.6	0.48, **0.86**	88	89	1.0	0.74, 1.33
4	30	53	0.6	0.32, 1.06	1,729	1,209	1.4	**1.05**, 1.95
5	7	10	0.7	0.51, **0.99**	288	285	1.0	0.65, 1.58
6A	57	110	0.5	0.30, **0.91**	3,380	3,343	1.0	0.73, 1.39
6B	235	388	0.6	0.33, 1.10	3,982	3,384	1.2	0.88, 1.58
7F	66	125	0.5	0.29, **0.98**	3,130	1,929	1.6	**1.25**, 2.11
9V	264	173	1.5	0.81, 2.88	2,416	1,402	1.7	**1.17**, 2.54
14	291	361	0.8	0.50, 1.30	1,569	1,316	1.2	0.89, 1.60
18C	70	155	0.4	0.24, **0.83**	3,063	2,197	1.4	0.99, 1.96
19A	52	105	0.5	0.32, **0.77**	1,542	1,196	1.3	0.98, 1.70
19F	26	53	0.5	0.29, **0.85**	1104	1,188	0.9	0.63, 1.38
23F	13	25	0.5	0.34, **0.82**	879	930	0.9	0.60, 1.48

[a] OPA, opsonophagocytic activity; GMT, geometric mean titer.
[b] n values are the numbers of subjects with a valid and determinate OPA titer to the given serotype. The GMTs were calculated using all subjects with available data for the specified blood draw.
[c] The ratio of GMTs (50 to 64 years GMT/≥65 years GMT) was calculated by back transforming the mean difference between the age groups on the logarithmic scale. The 95% confidence intervals (CIs) for the ratios are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (50 to 64 years data − ≥65 years data). The statistically significant differences are in bold type.

Safety. In both age groups, the majority of the local and systemic reactions occurred within 14 days after PCV13 administration and were mild or moderate in intensity. Pain at the injection site was the most common local reaction. Muscle and joint pain, fatigue, and headache were the most common systemic reactions. A significantly higher proportion of subjects in the 50- to 64-year age group compared with that in the ≥65 years group reported any local reaction ($P = 0.008$) or any systemic reaction ($P = 0.003$; Table 6). These differences were mainly driven by pain at the injection site ($P = 0.007$) for the local reactions and by headache ($P = 0.049$), diarrhea ($P = 0.030$), and muscle pain ($P = 0.006$) for the systemic reactions. The exception was fever of ≥38°C, which was more frequent in the ≥65 years group ($P = 0.012$). Of note, fever of >40°C in 5 subjects aged ≥65 years was reported by the investigator as data entry errors. Other local (redness and swelling) and systemic (fatigue, vomiting, and joint pain) reac-

TABLE 4 Comparison of pneumococcal OPA GMTs in subjects 50 to 64 years of age in Mexican study versus U.S. comparator study in the evaluable immunogenicity populations[a]

Serotype	OPA GMTs at[b]: Prevaccination Mexican study (n = 142–159)	Prevaccination U.S. study (n = 672–795)	Comparison[c] Ratio	Comparison[c] 95% CI	Postvaccination Mexican study (n = 148–155)	Postvaccination U.S. study (n = 709–786)	Comparison[c] Ratio	Comparison[c] 95% CI
1	6	5	1.1	0.94, 1.24	120	171	0.7	0.53, **0.94**
3	7	7	1.0	0.84, 1.24	88	92	1.0	0.76, 1.20
4	30	16	2.0	**1.23**, 3.09	1,729	2,412	0.7	0.53, **0.96**
5	7	6	1.3	**1.05**, 1.52	288	231	1.2	0.88, 1.78
6A	57	16	3.5	**2.35**, 5.32	3,380	3,331	1.0	0.75, 1.37
6B	235	38	6.1	**3.68**, 10.26	3,982	2,516	1.6	**1.16**, 2.15
7F	66	7	9.2	**6.55**, 12.82	3,130	1,301	2.4	**1.75**, 3.30
9V	264	24	11.0	**6.81**, 17.86	2,416	1,416	1.7	**1.22**, 2.38
14	291	35	8.2	**5.30**, 12.78	1,569	765	2.1	**1.45**, 2.91
18C	70	23	3.0	**1.95**, 4.60	3,063	1,828	1.7	**1.22**, 2.30
19A	52	25	2.1	**1.51**, 2.85	1,542	805	1.9	**1.52**, 2.41
19F	26	17	1.5	**1.07**, 2.21	1,104	556	2.0	**1.41**, 2.80
23F	13	8	1.6	**1.20**, 2.14	879	430	2.0	**1.38**, 3.03

[a] OPA, opsonophagocytic activity; GMT, geometric mean titer.
[b] n values are the numbers of subjects with a valid and determinate OPA titer to the given serotype. The GMTs were calculated using all subjects with available data for the specified blood draw.
[c] The ratio of GMTs (Mexican study to U.S. study) was calculated by back transforming the mean difference between the studies on the logarithmic scale. The 95% confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Mexican study to U.S. study). The statistically significant differences are in bold type.

TABLE 5 Comparison of pneumococcal OPA GMTs in subjects ≥65 years of age in the Mexican study versus the European Union comparator study in the evaluable immunogenicity populations[a]

Serotype	OPA GMTs at[b]: Prevaccination: Mexican study (n = 146–161)	Prevaccination: EU study (n = 212–254)	Prevaccination: Comparison[c] Ratio	Prevaccination: Comparison[c] 95% CI	Postvaccination: Mexican study (n = 150–159)	Postvaccination: EU study (n = 234–255)	Postvaccination: Comparison[c] Ratio	Postvaccination: Comparison[c] 95% CI
1	7	6	1.2	0.95, 1.47	84	95	0.9	0.62, 1.26
3	11	6	1.9	**1.50**, 2.45	89	51	1.8	**1.29**, 2.37
4	53	14	3.7	**2.18**, 6.20	1,209	1,486	0.8	0.58, 1.15
5	10	6	1.8	**1.38**, 2.36	285	112	2.6	**1.68**, 3.88
6A	110	17	6.4	**3.99**, 10.11	3,343	1,597	2.1	**1.46**, 2.99
6B	388	53	7.4	**4.26**, 12.73	3,384	2,017	1.7	**1.17**, 2.41
7F	125	9	13.5	**8.53**, 21.27	1,929	835	2.3	**1.54**, 3.47
9V	173	21	8.1	**4.69**, 14.16	1,402	723	1.9	**1.22**, 3.08
14	361	80	4.5	**2.77**, 7.38	1,316	1,088	1.2	0.86, 1.69
18C	155	22	6.9	**4.21**, 11.39	2,197	1,415	1.6	**1.10**, 2.20
19A	105	21	5.1	**3.50**, 7.51	1,196	539	2.2	**1.60**, 3.07
19F	53	15	3.6	**2.33**, 5.60	1,188	467	2.5	**1.72**, 3.76
23F	25	9	2.7	**1.83**, 4.01	930	295	3.1	**1.98**, 5.00

[a] OPA, opsonophagocytic activity; GMT, geometric mean titer.

[b] n values are the numbers of subjects with a valid and determinate OPA titer to the given serotype. The GMTs were calculated using all subjects with available data for the specified blood draw.

[c] The ratio of GMTs (Mexican study to EU study) was calculated by back transforming the mean difference between the studies on the logarithmic scale. The 95% confidence intervals (CIs) for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (Mexican study to EU study). The statistically significant differences are in bold type.

tions did not differ significantly between the age groups. The mean durations of events were similar between the age groups and did not exceed 4.5 days for local events, 2.0 days for fever, and 6.6 days for other systemic events.

The percentages of subjects reporting any AEs within approximately 1 month after vaccination were 11.1% in the 50- to 64-year age group and 6.2% in the ≥65-year age group; infections were the most common AE reported (5.6% and 1.9%, respectively). Serious adverse events (SAEs) were reported in the ≥65-year age group only (2 subjects [1.2%], benign prostatic hyperplasia in one, and gastric ulcer and gastritis in the other). Both were considered to be unrelated to the study vaccine. No deaths were reported during the study. No subjects were withdrawn from the study for safety-related reasons.

DISCUSSION

PCV13 elicited a robust immune response in adults ≥50 years of age in Mexico who had not been previously vaccinated with PPSV23, as reflected by the magnitude of the fold rises in the functional antibody levels measured by OPA immediately before to 1 month after vaccination. The postvaccination OPA GMTs were generally similar between the 50- to 64-year and ≥65-year age groups for most serotypes. Of interest, although the OPA GMFRs were numerically higher in the 50- to 64-year age group, this was due to the lower prevaccination OPA GMTs in that age group. As discussed previously, numerically higher GMFRs do not always indicate a superior immune response (25). The generally similar immune responses in the ≥65-year age group compared with those in the 50- to 64-year age group were unanticipated, as younger age groups generally have significantly higher immune responses than do older age groups (26).

The immune responses elicited in this Mexican study were statistically significantly higher for most serotypes compared with the immune responses elicited by a similar study population 50 to 64 years of age in the United States (for serotypes 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) and ≥65 years of age in Europe (for serotypes 3, 5, 6A, 6B, 7F, 9V, 18C, 19A, 19F, and 23F) (16–18). In the Mexican study, the baseline OPA GMTs for these serotypes were generally also significantly higher than the baseline OPA GMTs observed in the two comparator studies (16–18). High baseline pneumococcal GMTs of antibody may be caused by exposure to *S. pneumoniae* in the environment and may reflect the high burden of disease in Mexico (3). The higher antibody responses after PCV13 in subjects in Mexico than those seen in other study populations may reflect a memory response commensurate with this greater degree of exposure.

A limitation of this study was the absence of a comparison of PCV13 with PPSV23, a pneumococcal vaccine for which efficacy against pneumococcal disease has been confirmed in part (1, 10). However, this comparison has been made in other similar PCV13 studies, which showed that PCV13 elicited noninferior responses for all PCV13 vaccine serotypes and superior immune responses for the majority of the PCV13 vaccine serotypes compared with those of the PPSV23 (18, 27). IgG immune responses measured by enzyme-linked immunosorbent assay (ELISA) were not performed in this study. While ELISAs quantify IgG levels, OPA assays assess antibody function rather than just their quantity. This difference is important, because a proportion of the antibodies measured by ELISA may have no functional activity. For this reason, particularly in the elderly, OPA assays are recommended as the primary measure of immune response because ELISA may have limited relevance due to the presence of nonfunctional antibodies in older adults (28). OPAs are considered the best correlate of protection (28, 29).

Overall, PCV13 was well tolerated in both age groups. Some local (pain) and systemic (headache, diarrhea, and muscle pain)

TABLE 6 Subjects reporting local and systemic reactions within 14 days postvaccination in the safety population

Reactions by type	Age group (yr)[a]						
	50–64 (n = 124–155)		≥65 (n = 112–145)				
	No. reporting	%	No. reporting	%	Difference[b]	95% CI[c]	P value[c]
Local							
Any	117	77.0	87	62.6	14.4	3.7, 24.9	**0.008**
Redness[d]							
Any	18	14.4	19	15.8	−1.4	−10.7, 7.7	0.832
Mild	12	9.7	16	13.3	−3.7	−12.1, 4.5	0.444
Moderate	11	8.8	8	7.0	1.8	−5.4, 9.2	0.619
Severe	3	2.4	0	0.0	2.4	−0.9, 6.9	0.117
Swelling[d]							
Any	28	21.5	16	13.3	8.2	−1.4, 17.8	0.091
Mild	23	18.1	14	11.7	6.4	−2.6, 15.7	0.167
Moderate	11	8.7	5	4.4	4.3	−2.3, 11.2	0.242
Severe	3	2.4	1	0.9	1.5	−2.6, 6.0	0.572
Injection site pain[e]							
Any	114	75.5	83	60.6	14.9	3.8, 25.6	**0.007**
Mild	112	74.2	82	60.3	13.9	2.8, 24.7	**0.014**
Moderate	28	21.5	10	8.5	13.0	3.5, 22.2	**0.005**
Severe	4	3.2	4	3.5	−0.3	−6.0, 4.9	0.958
Systemic							
Any	119	76.8	88	60.7	16.1	5.5, 26.4	**0.003**
Fever							
≥38°C	3	2.4	12	10.2	−7.8	−14.8, −1.5	**0.012**
≥38°C to <38.5°C	2	1.6	4	3.5	−2.0	−7.3, 2.5	0.488
≥38.5°C to 39°C	1	0.8	2	1.8	−1.0	−5.5, 2.8	0.625
≥39°C to ≤40°C	1	0.8	2	1.8	−1.0	−5.5, 2.8	0.629
>40°C[f]	0	0.0	5	4.3	−4.3	−9.8, −0.9	**0.019**
Fatigue[e]							
Any	68	47.2	51	38.6	8.6	−3.3, 20.2	0.155
Mild	56	39.4	47	36.2	3.3	−8.3, 14.9	0.583
Moderate	36	26.9	25	20.0	6.9	−3.6, 17.2	0.199
Severe	8	6.3	6	5.3	1.0	−5.5, 7.6	0.766
Headache[e]							
Any	62	44.3	42	32.6	11.7	0.0, 23.3	**0.049**
Mild	55	39.3	39	30.5	8.8	−2.7, 20.3	0.134
Moderate	24	18.6	19	16.0	2.6	−7.0, 12.3	0.594
Severe	5	4.0	6	5.2	−1.2	−7.4, 4.5	0.744
Vomiting[g]							
Any	5	4.0	2	1.8	2.2	−2.7, 7.6	0.341
Mild	4	3.2	2	1.8	1.4	−3.3, 6.5	0.576
Moderate	2	1.6	1	0.9	0.7	−3.3, 4.9	0.739
Severe	0	0.0	0	0.0	0.0	−3.3, 3.0	>0.99
Diarrhea[h]							
Any	35	26.1	18	15.0	11.1	1.1, 21.1	**0.030**
Mild	30	23.3	17	14.2	9.1	−0.7, 19.0	0.068
Moderate	8	6.2	2	1.8	4.4	−0.9, 10.4	0.100
Severe	1	0.8	1	0.9	−0.1	−4.1, 3.6	>0.99
Muscle pain[e]							
Any	89	60.5	58	43.9	16.6	4.8, 28.3	**0.006**
Mild	87	59.6	52	40.3	19.3	7.3, 30.8	**0.001**
Moderate	31	23.5	24	19.5	4.0	−6.3, 14.3	0.448
Severe	7	5.6	7	6.0	−0.4	−7.1, 6.0	0.945

(Continued on following page)

TABLE 6 (Continued)

Reactions by type	Age group (yr)[a]				Difference[b]	95% CI[c]	*P* value[c]
	50–64 (n = 124–155)		≥65 (n = 112–145)				
	No. reporting	%	No. reporting	%			
Joint pain[e]							
Any	49	35.3	43	33.3	1.9	−9.5, 13.5	0.750
Mild	42	30.7	38	29.9	0.7	−10.5, 12.0	0.913
Moderate	17	13.1	21	17.1	−4.0	−13.1, 5.0	0.415
Severe	5	4.0	6	5.2	−1.2	−7.3, 4.6	0.760

[a] n values in each group are the numbers of subjects reporting "yes" for ≥1 day or "no" for all days. These values are used as the denominators for the percentages.
[b] Difference in proportions, calculated by 50 to 64 years value − ≥65 years value, expressed as a percentage.
[c] Exact 2-sided 95% confidence intervals (CIs) and corresponding *P* value for the difference in proportions, calculated by 50 to 64 years value − ≥65 years value, expressed as a percentage. The statistically significant differences are in bold type.
[d] Mild, 2.5 to 5.0 cm; moderate, 5.1 to 10.0 cm; severe, >10.0 cm.
[e] Mild, does not interfere with activity; moderate, some interference with activity; severe, prevents daily routine activity.
[f] Fever of >40°C reported in 5 subjects were data entry errors, as confirmed by the investigator.
[g] Mild, 1 to 2 times in 24 h; moderate, >2 times in 24 h; severe, requires intravenous hydration.
[h] Mild, 2 to 3 loose stools in 24 h; moderate, 4 to 5 loose stools in 24 h; severe ≥6 loose stools in 24 h.

reactions were significantly more frequent among those in the 50- to 64-year age group than in the ≥65-year age group but were mainly mild to moderate in intensity. Because the postvaccination immune responses were generally similar between the age groups, no conclusions could be drawn regarding higher immune responses and associations with increased reactogenicity. There were no deaths, no SAEs considered related to PCV13, and no safety-related withdrawals from the study.

In conclusion, PCV13 was safe and well tolerated and elicited robust immune responses in adults ≥50 years of age in Mexico. Taking into consideration the significantly higher immune responses observed in this population compared with the PCV13 and PPSV23 responses observed in other studies (16–18), as well as the efficacy data from the CAPiTA study (12, 13), PCV13 has the potential to protect adults in Mexico against vaccine-type pneumococcal disease.

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