

1 **Immunogenicity and Safety of 13-valent Pneumococcal Conjugate Vaccine in Adults**
2 **≥ 50 Years of Age in Mexico: An Open-Label Trial**

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14 **Running Head:** Immunogenicity and Safety of PCV13 in Adults in Mexico

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18 **Abstract:** Current count: 174 words; 250 words allowed

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20 This open-label multicenter clinical trial conducted in Mexico assessed the
21 immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine (PCV13) in
22 adults aged ≥ 50 years not previously vaccinated with the 23-valent pneumococcal
23 polysaccharide vaccine (PPSV23). PCV13 elicited a robust immune response in this
24 study population, as reflected by the magnitude of fold rises in functional antibody levels
25 measured by serotype-specific opsonophagocytic activity (OPA) assays before and one
26 month after vaccination. Although prevaccination OPA GMTs for the majority of
27 serotypes were significantly lower in the 50–64 years age group compared with the
28 ≥ 65 years age group, post vaccination immune responses were generally similar. Overall
29 immune responses were higher for the majority of serotypes in the Mexico study
30 population than in similar adult study populations who received PCV13 in Europe and
31 United States. PCV13 was well tolerated and there were no vaccine-related serious
32 adverse events. In conclusion, PCV13 is safe and immunogenic when administered to
33 adults aged ≥ 50 years in Mexico and has the potential to protect against vaccine-type
34 pneumococcal disease. This trial was registered at www.ClinicalTrials.gov
35 (NCT01432262).

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38 **Word Count:** 3030

39 **Introduction**

40 Diseases caused by *Streptococcus pneumoniae* are a major worldwide public health
41 problem affecting all age groups, with the highest mortality rates in elderly adults aged
42 >65 years and in individuals with underlying disease [1,2]. In adults aged ≥ 50 years in
43 Latin American countries, including Mexico, community acquired pneumonia (CAP)
44 caused mainly by *S. pneumoniae* is associated with a high incidence of morbidity and
45 mortality, with the incidence increasing substantially with age [3,4]. Worldwide, 20
46 serotypes account for more than 70% of invasive pneumococcal disease (IPD) in children
47 <5 years of age, although the prevalence of each varies by region [5]. In Latin America
48 and Caribbean countries, the 21 most common serotypes causing IPD in young children,
49 in order of frequency, were serotypes 14, 6B, 5, 1, 23F, 6A, 18C, 19F, 19A, 9V, 7F, 3,
50 and 4, included in the 13-valent pneumococcal conjugate vaccine (PCV13), and non-
51 vaccine serotypes 8, 15B, 12F, 2, 12A, 9A, 45, and 46 [5]. Castañeda et al reported
52 similar findings from SIREVA surveillance data from Latin America and the Caribbean
53 from 2007–2009 in children <5 years of age; since the introduction of PCV7, serotype
54 replacement with non-vaccine serotypes, especially 19A, has been observed [6]. The
55 Mexico-specific SIREVA II data from 2011 in children aged <6 years and adults aged
56 ≥ 50 years reported that the PCV13 serotypes were the most frequently isolated, in
57 particular serotype 19A[7].

58 Vaccination is considered an important preventive strategy for adults and children, in part
59 because of the increased prevalence of *S. pneumoniae* strains resistant to antibiotics [1].
60 In a study examining antimicrobial susceptibility patterns of *S. pneumoniae*, Quiñones–

61 Falconi and colleagues concluded that pneumococci isolated from children and adults
62 with community-acquired acute respiratory infections in Mexico City have one of the
63 world's highest rates of penicillin resistance. In addition, these penicillin-nonsusceptible
64 strains were usually resistant to other antimicrobial agents commonly used to treat these
65 infections [8].

66 A 23-valent pneumococcal polysaccharide vaccine (PPSV23) is widely available for the
67 prevention of vaccine-type pneumococcal disease for adults aged ≥ 50 years and for high-
68 risk younger adults; however, PPSV23 has not been widely implemented in Latin
69 American countries [4]. PPSV23 is efficacious in preventing IPD, although reports on
70 efficacy against CAP have been inconsistent and the duration of protection is limited
71 [1,9,10]. Recently, a 13-valent PCV (PVC13) was licensed for adults in the United States,
72 Europe, and many other countries including Mexico for the prevention of pneumococcal
73 disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F
74 and 23F. Licensing was based on immunological and safety comparisons with PPSV23 in
75 clinical studies performed in the United States and in several European countries as part
76 of the PCV13 clinical development program [11]. The Community-Acquired Pneumonia
77 Immunization Trial in Adults (CAPiTA) 65 years of age and older was recently
78 completed in the Netherlands with approximately 85,000 subjects, demonstrating that
79 PCV13 is efficacious against vaccine-type CAP including non-bacteremic CAP and
80 vaccine-type IPD [12,13].

81 In contrast to PPSV23, PCV13 is manufactured by conjugating the capsular saccharides
82 of *S. pneumoniae* to an immunogenic protein carrier (cross-reacting material 197
83 [CRM₁₉₇], a nontoxic diphtheria toxin cross-reactive material) in order to elicit a T cell-

84 dependent immune response. As T cells provide the signals required for the generation of
85 B cell memory [14], PCV13 has the potential to elicit a memory response on subsequent
86 natural exposure to vaccine type pneumococcal strains and provide protection over a
87 prolonged period of time [15].

88 The aim of the current study was to assess the immunogenicity and safety of PCV13
89 when administered to adults aged ≥ 50 years in Mexico who had not previously been
90 vaccinated with PPSV23. In addition, the immunogenicity data from this study were
91 compared post hoc with those of two other PCV13 studies that assessed similar
92 populations of PPSV23-naïve adults [16-18]. These studies were part of the adult clinical
93 development program for the licensing of PCV13 [11].

94 **Materials and Methods**

95 **Trial design.** This open-label study was conducted at 4 sites in Mexico from 29 July
96 2011 to 5 December 2011. Subjects were stratified into 2 age groups: 50–64 years and
97 ≥ 65 years. The study was conducted in accordance with the International Conference on
98 Harmonization Guideline for Good Clinical Practice and the ethical principles that have
99 their origins in the Declaration of Helsinki.

100 **Study population.** Eligible study participants included male and female subjects ≥ 50
101 years of age, including those with underlying diseases that were stable for ≥ 6 weeks
102 before vaccination (ie, disease not requiring significant change in therapy or
103 hospitalization for worsening disease 6 weeks before vaccination), and had: no history of
104 *S. pneumoniae* infection within the past 5 years; no previous vaccination with any
105 licensed or investigational pneumococcal vaccine; no history of severe vaccine-

106 associated adverse reactions or receipt of plasma products or immunoglobulins within 60
107 days before vaccination; and no immune deficiency or suppression, or severe chronic
108 disease associated with pulmonary, cardiac, or renal failure.

109 **Comparator study populations.** One of the comparator studies enrolled a PPSV23-
110 naive study population aged 50–64 years from the United States to compare the safety
111 and immunogenicity of PCV13 versus PPSV23 [18]. The other comparator study enrolled
112 a PPSV23-naive population aged ≥ 65 years from Europe to compare the safety and
113 immunogenicity of PCV13 administered concomitantly with trivalent inactivated
114 influenza vaccine versus PCV13 administered alone one month after trivalent inactivated
115 influenza vaccine [16,17]; data from the latter group were used for the comparison in this
116 manuscript. Inclusion and exclusion criteria for the study populations in the comparator
117 studies were similar to those described above.

118 **Vaccine and administration.** PCV13 contains capsular polysaccharides from
119 pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (contains
120 2.2 μg of each saccharide, except for 4.4 μg of 6B) individually conjugated to nontoxic
121 diphtheria toxin cross-reactive material 197 (CRM₁₉₇), 5 mM succinate buffer,
122 0.85% sodium chloride, 0.02% polysorbate 80, and 0.125 mg aluminum as aluminum
123 phosphate per 0.5-mL dose. PCV13 was manufactured by Wyeth, a Pfizer Company (Lot
124 number 10-089561). The vaccine was supplied in single-dose syringes without
125 preservatives and stored at 2°C–8°C. All eligible participants received one dose of
126 PCV13 intramuscularly into the deltoid muscle.

127 **Immunogenicity assessments.** Two 15-mL blood samples were taken: one before and
128 one approximately 1 month after vaccination. Functional activity of the antibodies was
129 measured using serotype-specific validated microcolony opsonophagocytic activity
130 (OPA) assays and expressed as OPA titres. OPA titers were defined as the interpolated
131 reciprocal serum dilution that resulted in complement-mediated killing of 50% of the
132 assay bacteria. OPA assay procedures were based on previously described methods [19].
133 Standardized OPA assays from this PCV13 study and the comparator studies were
134 performed in the same central laboratory by the sponsor, thus allowing comparisons.

135 **Safety assessments.** Participants recorded local reactions and systemic events on an
136 electronic (e)-diary every evening within a fixed time window for 14 days after
137 vaccination. The e-diary prompted reporting of vaccine-associated signs and symptoms
138 through a checklist, providing an accurate representation of each participant's experience.
139 Severity was assessed using the US Food and Drug Administration's "Toxicity Grading
140 Scale" [20]. The largest diameter of any redness or swelling was measured using a
141 caliper. Oral temperature was measured using a digital thermometer, and fever was
142 defined as a temperature of ≥ 38.0 °C (100.4 °F). The highest daily temperature was
143 recorded. Diary data were transmitted by the participants to the central vendor and
144 thereafter could not be altered. The data were reviewed by the investigator via an
145 internet-based portal to monitor vaccine reactogenicity and compliance with e-diary
146 completion.

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

150 **Statistical methods**

151 **Sample size estimation.** Sample size estimation was based on pneumococcal OPA
152 GMTs and associated variability observed in two previous Pfizer studies [21,22].
153 Assuming a dropout rate of no more than 7%, a sample size of 150 evaluable subjects in
154 each age group was sufficient to provide adequate precision in the study results for
155 descriptive assessment. Thus, 324 subjects (162 per group) were to be vaccinated.

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

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

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

180 **Safety analysis.** AEs were categorized according to the Medical Dictionary for
181 Regulatory Activities (MedDRA). The proportion of subjects with local reactions,
182 systemic events, and AEs were summarized with corresponding exact 2-sided 95% CI
183 [23]. Difference in proportions of adults 50–64 years of age versus ≥65 years of age were
184 expressed as a percentage with exact 2-sided CI and corresponding *P*-value [24].

185 **Results**

186 **Disposition of subjects and baseline demographics.** A total of 324 subjects were
187 enrolled, with 162 subjects in each age group. In the ≥65 years group, 1 subject was
188 withdrawn before vaccination. In the 50–64 years age group, 1 subject was excluded
189 from the evaluable immunogenicity population because of an eligibility violation. The
190 baseline demographic characteristics of the evaluable immunogenicity populations are
191 shown in Table 1. Of note, in the 50–64 years age group (mean age, 55.8 years) and in

192 the ≥ 65 years age group (mean age, 73.4 years), there was a greater percentage of females
193 (59% and 52.2%, respectively).

194 **Immunogenicity.** For all serotypes in both age groups, OPA GMTs increased
195 significantly from immediately before to one month after vaccination, as reflected by the
196 GMFRs (lower limit of the 2-sided, 95% CI for the GMFRs >1). OPA GMFRs were
197 higher in the 50–64 years age group (GMFR range, 5.3–63.6) compared with the ≥ 65
198 years age group (GMFR range, 3.4–35.8; Table 2). Prevacination OPA GMTs in the
199 50–64 year age group were statistically significantly lower (upper limit of the 2-sided,
200 95% CI for the GMT ratio <1) than those in the ≥ 65 year age group for 8 of 13 serotypes
201 and were similar to those in the ≥ 65 year age group for the 5 other serotypes (1, 4, 6B,
202 9V, and 14), whereas post vaccination OPA GMTs in the 50–64 year age group were
203 similar to those in the ≥ 65 year age group for 10 of 13 serotypes but statistically
204 significantly higher for serotypes 4, 7F and 9V (Table 3).

205 Post hoc analysis comparing adults 50–64 years of age from this Mexico study with same
206 aged adults from the United States comparator study showed prevaccination OPA GMTs
207 were statistically significantly higher in the Mexico study for 11 of 13 serotypes and
208 similar between studies for serotypes 1 and 3. Post vaccination OPA GMTs were
209 statistically significantly higher in the Mexico study for 8 of 13 serotypes, similar
210 between studies for serotypes 3, 5, and 6A, and statistically significantly lower in the
211 Mexico study for serotypes 1 and 3 (Table 4).

212 Similarly, a post hoc analysis comparing adults ≥ 65 years of age from this Mexico study
213 with same aged adults from the European comparator study showed prevaccination OPA

214 GMTs were statistically significantly higher in the Mexico study for the 12 of 13
215 serotypes and similar between studies for serotype 1. Post vaccination OPA GMTs were
216 statistically significantly higher in the Mexico study for 10 of 13 serotypes and similar
217 between studies for serotypes 1, 4, and 14 (Table 5).

218 **Safety.** In both age groups, the majority of local and systemic reactions occurred within
219 14 days after PCV13 administration and were mild or moderate in intensity. Pain at the
220 injection site was the most common local reaction. Muscle and joint pain, fatigue, and
221 headache were the most common systemic reactions. A significantly higher proportion of
222 subjects in the 50–64 years age group compared with the ≥ 65 years group reported any
223 local reaction ($P=0.008$) or any systemic reaction ($P=0.003$; Table 6). These differences
224 were mainly driven by pain at the injection site ($P=0.007$) for local reactions and by
225 headache ($P=0.049$), diarrhea ($P=0.030$), and muscle pain ($P=0.006$) for systemic
226 reactions. The exception was fever $\geq 38^{\circ}\text{C}$, which was more frequent in the ≥ 65 years
227 group ($P=0.012$). Of note, fever $>40^{\circ}\text{C}$ in 5 subjects aged ≥ 65 years was reported as data
228 entry errors by the investigator. Other local (redness, swelling) and systemic reactions
229 (fatigue, vomiting, joint pain) did not differ significantly between age groups. The mean
230 durations of events were similar between the age groups and did not exceed 4.5 days for
231 local events, 2.0 days for fever, and 6.6 days for other systemic events

232 The percentage of subjects reporting any AEs within approximately 1 month after
233 vaccination was 11.1% in the 50–64 years age group and 6.2% in the ≥ 65 years age
234 group; infections were the most common AE reported (5.6% and 1.9%, respectively).
235 Serious adverse events (SAEs) were only reported in the ≥ 65 years group (2 subjects

236 [1.2%]; benign prostatic hyperplasia; gastric ulcer and gastritis). Both were considered to
237 be unrelated to the study vaccine. No deaths were reported during the study. No subjects
238 were withdrawn from the study for safety-related reasons.

239 **Discussion**

240 PCV13 elicited a robust immune response in adults aged ≥ 50 years in Mexico who had
241 not been previously vaccinated with PPSV23, as reflected by the magnitude of the fold
242 rises in functional antibody levels measured by OPA immediately before to one month
243 after vaccination. Postvaccination OPA GMTs were generally similar between the 50–64
244 years age group and the ≥ 65 years age group for most serotypes. Of interest, although the
245 OPA GMFRs were numerically higher in the 50–64 years age group, this was due to the
246 lower prevaccination OPA GMTs in the 50–64 years age group. As discussed previously,
247 numerically higher GMFRs do not always indicate a superior immune response [25].

248 Generally similar immune responses in the ≥ 65 years age group compared with the 50–64
249 years age group was unanticipated. Younger age groups generally have significantly higher
250 immune responses than older age groups [26]

251 Immune responses elicited in this Mexico study were statistically significantly higher for
252 most serotypes when compared with immune responses elicited by a similar study
253 population aged 50–64 years in the United States (for serotypes 6B, 7F, 9V, 14, 18C,
254 19A, 19F, and 23F) and aged ≥ 65 years in Europe (for serotypes 3, 5, 6A, 6B, 7F, 9V,
255 18C, 19A, 19F, and 23F) [16-18]. In the Mexico study, the baseline OPA GMTs for these
256 serotypes were generally also significantly higher than baseline OPA GMTs observed in
257 the two comparator studies [16-18]. High baseline pneumococcal GMTs of antibody may

258 be due to exposure to *S. pneumoniae* in the environment and may reflect the high burden
259 of disease in Mexico [3]. Higher antibody responses after PCV13 in subjects in Mexico
260 compared with those seen in other study populations may reflect a memory response
261 commensurate with this greater degree of exposure.

262 A limitation of this study was the absence of a comparison of PCV13 with PPSV23, a
263 pneumococcal vaccine for which efficacy against pneumococcal disease has been in part
264 confirmed [1,10]. However this comparison has been made in other similar PCV13
265 studies, which showed that PCV13 elicited noninferior responses for all PCV13 vaccine
266 serotypes and superior immune responses for the majority of PCV13 vaccine serotypes
267 when compared with PPSV23 [18,27]. IgG immune responses measured by ELISA were
268 not performed in this study. While ELISAs quantify IgG levels, OPA assays assesses
269 antibody function rather than just quantity. This difference is important because a
270 proportion of antibodies measured by ELISA may have no functional activity. For this
271 reason, particularly in the elderly, OPA assays are recommended as the primary measure
272 of immune response because ELISA may have limited relevance due to the presence of
273 nonfunctional antibodies in older adults [28]. OPAs are considered the best correlate of
274 protection [28,29].

275 Overall, PCV13 was well tolerated in both age groups. Some local (pain) and systemic
276 (headache, diarrhea, muscle pain) reactions were significantly more frequent among the
277 50–64 years age group than in the ≥ 65 years age group, but were mainly mild to
278 moderate in intensity. Because postvaccination immune responses were generally similar
279 between age groups, no conclusions could be drawn regarding higher immune responses

280 and associations with increased reactogenicity. There were no deaths, no SAEs
281 considered related to PCV13, and no safety related withdrawals from the study.

282 In conclusion, PCV13 was safe and well tolerated, and elicited robust immune responses
283 in adults aged ≥ 50 years in Mexico. Taking into consideration the significantly higher
284 immune responses observed in this population compared with PCV13 and PPSV23
285 responses observed in other studies [16-18], and the efficacy data from the CAPITA
286 study [12,13], PCV13 has the potential to protect adults in Mexico against vaccine-type
287 pneumococcal disease.

288 **Acknowledgments**

289 We would like to thank the B1851048 study group and the participants of the study.

290 This study was funded by Wyeth, which was acquired by Pfizer Inc in October 2009.

291 Editorial support was provided by Nicole Gudleski O'Regan and Deborah M. Campoli-

292 Richards of Complete Healthcare Communications, Inc. and was funded by Pfizer Inc.

293 Each author participated in the preparation of this article, and were involved in: (1)

294 collection and interpretation of data; (2) drafting the article, or revising it critically for

295 important intellectual content, and (3) final approval of the version to be submitted. In

296 addition WCG, DAD, BS-T, CJ contributed to the design of the study, VS to the analysis.

297

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389 **Table 1.** Demographic Characteristics — Evaluable Immunogenicity Population

	Age Group, %		Total, % N =322
	50–64 yr	≥65 yr	
	N =161	N=161	
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

390 **Table 2.** Geometric Mean Fold Rises of Pneumococcal OPA GMTs — Evaluable Immunogenicity Population

Serotype	Age Group							
	50–64 yr				≥65 yr			
	N ^a =137–153				N ^a =137–158			
	Pre- vaccination	Post vaccination	GMFR ^b	(95% CI ^c)	Pre- vaccination	Post vaccination	GMFR ^b	(95% CI ^c)
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	1767	57.7	(36.40, 91.36)	58	1159	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	3512	62.3	(39.00, 99.36)	114	3273	28.7	(19.76, 41.70)
6B	237	4290	18.1	(11.61, 28.15)	392	3691	9.4	(6.61, 13.45)
7F	70	3025	43.2	(26.94, 69.17)	124	1922	15.5	(10.05, 23.80)
9V	268	2347	8.8	(5.72, 13.43)	194	1396	7.2	(4.72, 10.98)

14	286	1518	5.3	(3.73, 7.56)	382	1311	3.4	(2.58, 4.56)
18C	69	3070	44.3	(28.19, 69.51)	154	2152	13.9	(9.21, 21.09)
19A	51	1542	30.0	(21.19, 42.50)	107	1196	11.2	(7.99, 15.69)
19F	25	1078	42.8	(28.33, 64.67)	54	1120	20.8	(13.38, 32.29)
23F	14	881	63.6	(43.16, 93.75)	26	923	35.8	(24.16, 52.95)

CI, confidence interval; GMT, geometric mean titer; GMFR, geometric mean fold rise; OPA, opsonophagocytic activity.

^aNumber of subjects with valid and determinate assay results for the specified serotype at both the prevaccination and post vaccination blood draws.

^bGMTs and GMFRs were calculated using all subjects with available data for both the prevaccination and post vaccination blood draws.

^cCIIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers, or the mean fold rise.

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393 **Table 3.** Effect of Age on Pneumococcal OPA GMTs — Evaluable Immunogenicity Population

Serotype	OPA GMTs Prevaccination				OPA GMTs Post Vaccination			
	50–64 yr		≥65 yr		50–64 yr		≥65 yr	
	N ^a =142–159		N ^a =146–161		N ^a =148–155		N ^a =150–159	
	GMT ^b	GMT ^b	Ratio ^c	(95% CI ^d)	GMT ^b	GMT ^b	Ratio ^c	(95% CI ^d)
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)	1729	1209	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)	3380	3343	1.0	(0.73, 1.39)
6B	235	388	0.6	(0.33, 1.10)	3982	3384	1.2	(0.88, 1.58)
7F	66	125	0.5	(0.29, 0.98)	3130	1929	1.6	(1.25, 2.11)
9V	264	173	1.5	(0.81, 2.88)	2416	1402	1.7	(1.17, 2.54)
14	291	361	0.8	(0.50, 1.30)	1569	1316	1.2	(0.89, 1.60)
18C	70	155	0.4	(0.24, 0.83)	3063	2197	1.4	(0.99, 1.96)

19A	52	105	0.5	(0.32, 0.77)	1542	1196	1.3	(0.98, 1.70)
19F	26	53	0.5	(0.29, 0.85)	1104	1188	0.9	(0.63, 1.38)
23F	13	25	0.5	(0.34, 0.82)	879	930	0.9	(0.60, 1.48)

CI, confidence interval; GMT, geometric mean titer; OPA, opsonophagocytic activity.

^aNumber of subjects with a valid and determinate OPA titer to the given serotype.

^bGMTs were calculated using all subjects with available data for the specified blood draw.

^cRatio of GMTs (50–64 yr / \geq 65 yr) is calculated by back transforming the mean difference between the age groups on the logarithmic scale.

^dCI 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 (50–64 years – \geq 65 years). Statistically significant differences are bolded.

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396 **Table 4.** Comparison of Pneumococcal OPA GMTs in Subjects Aged 50–64 Years, Mexico Study Versus US Comparator Study —
 397 Evaluable Immunogenicity Populations

Serotype	OPA GMTs Prevaccination				OPA GMTs Post Vaccination			
	Mexico Study	US Study	Comparison		Mexico Study	US Study	Comparison	
	N ^a =142–159	N ^a =672–795		(95% CI ^d)	N ^a =148–155	N ^a =709–786		(95% CI ^d)
	GMT ^b	GMT ^b	Ratio ^c		GMT ^b	GMT ^b	Ratio ^c	
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)	1729	2412	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)	3380	3331	1.0	(0.75, 1.37)
6B	235	38	6.1	(3.68, 10.26)	3982	2516	1.6	(1.16, 2.15)
7F	66	7	9.2	(6.55, 12.82)	3130	1301	2.4	(1.75, 3.30)
9V	264	24	11.0	(6.81, 17.86)	2416	1416	1.7	(1.22, 2.38)
14	291	35	8.2	(5.30, 12.78)	1569	765	2.1	(1.45, 2.91)

18C	70	23	3.0	(1.95, 4.60)	3063	1828	1.7	(1.22, 2.30)
19A	52	25	2.1	(1.51, 2.85)	1542	805	1.9	(1.52, 2.41)
19F	26	17	1.5	(1.07, 2.21)	1104	556	2.0	(1.41, 2.80)
23F	13	8	1.6	(1.20, 2.14)	879	430	2.0	(1.38, 3.03)

CI, confidence interval; GMT, geometric mean titer; OPA, opsonophagocytic activity.

^aNumber of subjects with a valid and determinate OPA titer to the given serotype.

^bGMTs were calculated using all subjects with available data for the specified blood draw.

^cRatio of GMTs (Mexico study to US study) is calculated by back transforming the mean difference between the studies on the logarithmic scale.

^dCI 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 (Mexico study to US study). Statistically significant differences are bolded.

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400 **Table 5.** Comparison of Pneumococcal OPA GMTs in Subjects Aged ≥ 65 Years, Mexico Study Versus European Union Comparator
 401 Study — Evaluable Immunogenicity Populations

Serotype	OPA GMTs Prevaccination				OPA GMTs Post Vaccination			
	Mexico Study	EU Study	Comparison		Mexico Study	EU Study	Comparison	
	N ^a =146–161	N ^a =212–254	Ratio ^c	(95% CI ^d)	N ^a =150–159	N ^a =234–255	Ratio ^c	(95% CI ^d)
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)	1209	1486	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)	3343	1597	2.1	(1.46, 2.99)
6B	388	53	7.4	(4.26, 12.73)	3384	2017	1.7	(1.17, 2.41)
7F	125	9	13.5	(8.53, 21.27)	1929	835	2.3	(1.54, 3.47)
9V	173	21	8.1	(4.69, 14.16)	1402	723	1.9	(1.22, 3.08)
14	361	80	4.5	(2.77, 7.38)	1316	1088	1.2	(0.86, 1.69)

18C	155	22	6.9	(4.21, 11.39)	2197	1415	1.6	(1.10, 2.20)
19A	105	21	5.1	(3.50, 7.51)	1196	539	2.2	(1.60, 3.07)
19F	53	15	3.6	(2.33, 5.60)	1188	467	2.5	(1.72, 3.76)
23F	25	9	2.7	(1.83, 4.01)	930	295	3.1	(1.98, 5.00)

CI, confidence interval; GMT, geometric mean titer; OPA, opsonophagocytic activity.

^aNumber of subjects with a valid and determinate OPA titer to the given serotype.

^bGMTs were calculated using all subjects with available data for the specified blood draw.

^cRatio of GMTs (Mexico study to EU study) is calculated by back transforming the mean difference between the studies on the logarithmic scale.

^dCI 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 (Mexico study to EU study). Statistically significant differences are bolded.

403 **Table 6.** Subjects Reporting Local and Systemic Reactions Within 14 Days Post

404 Vaccination — Safety Population

	Age Group				Difference ^c	(95% CI ^d)	p-value ^d
	50–64 yr		≥65 yr				
	n ^b	%	n ^b	%			
	N ^a =124–155		N ^a =112–145				
Local							
Any	117	77.0	87	62.6	14.4	(3.7, 24.9)	0.008
Redness ^e							
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 ^e							
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 ^f							
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 – <38.5°C	2	1.6	4	3.5	-2.0	(-7.3, 2.5)	0.488
≥38.5°C – 39°C	1	0.8	2	1.8	-1.0	(-5.5, 2.8)	0.625
≥39°C – ≤40°C	1	0.8	2	1.8	-1.0	(-5.5, 2.8)	0.629
>40°C ^g	0	0.0	5	4.3	-4.3	(-9.8, -0.9)	0.019
Fatigue ^f							
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 ^f							
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 ^h							
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)	>.99
Diarrhea ⁱ							
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)	>.99
Muscle pain ^f							
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
Joint pain ^f							
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

CI, confidence interval.

^aNumber of subjects reporting “yes” for ≥ 1 day or “no” for all days. These values are

used as the denominators for percentages.

^bn = Number of subjects reporting the specified event.

^cDifference in proportions, 50–64 years – \geq 65 years, expressed as a percentage.

^dExact 2-sided CI and corresponding p-value for the difference in proportions, 50–64 years – \geq 65 years, expressed as a percentage. Statistically significant differences are bolded.

^eMild = 2.5–5.0 cm, moderate = 5.1–10.0 cm, and severe = $>$ 10.0 cm.

^fMild = does not interfere with activity, moderate = some interference with activity, severe = prevents daily routine activity.

^gFever $>$ 40°C reported in 5 subjects were data entry errors as confirmed by the investigator.

^hMild = 1–2 times in 24 hours, moderate = $>$ 2 times in 24 hours, severe = requires IV hydration.

ⁱMild = 2–3 loose stools in 24 hours, moderate = 4–5 loose stools in 24 hours, severe \geq 6 loose stools in 24 hours.

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