Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine compared to a 23-valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naive adults

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A B S T R A C T

Background: Streptococcus pneumoniae is a major cause of morbidity and mortality among adults 50 years of age and older in the United States. Pneumococcal conjugate vaccines are efficacious against pneumococcal disease in children and may also offer advantages in adults.

Methods: We performed a randomized, modified double-blind trial that compared a single dose of 13-valent pneumococcal conjugate vaccine (PCV13) with 23-valent pneumococcal polysaccharide vaccine (PPSV23) in 831 pneumococcal vaccine naive adults 60–64 years of age. An additional group of 403 adults 50–59 years of age received open-label PCV13. Anti-pneumococcal opsonophagocytic activity (OPA) titers were measured at baseline, and at 1 month and 1 year after vaccination.

Results: In the randomized trial, the month 1 post-vaccination OPA geometric mean titers in the PCV13 group were statistically significantly higher than in the PPSV23 group for 8 of the 12 serotypes common to both vaccines and for serotype 6A, a serotype unique to PCV13, and were comparable for the other 4 common serotypes. The immune response to PCV13 was generally greater in adults 50–59 years of age compared to adults 60–64 years of age. OPA titers declined from 1 month to 1 year after PCV13 administration but remained higher than pre-vaccination baseline titers.

Conclusions: PCV13 induces a greater functional immune response than PPSV23 for the majority of serotypes covered by PCV13, suggesting that PCV13 could offer immunological advantages over PPSV23 for prevention of vaccine-type pneumococcal infection.

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1. Introduction

*Streptococcus pneumoniae* is a major cause of morbidity and mortality among older adults in the United States. Currently in the United States the 23-valent pneumococcal polysaccharide vaccine (PPSV23) is recommended for adults 65 years of age and older, as well as for high-risk younger adults, for prevention of invasive pneumococcal disease (IPD) [1,2]. However, PPSV23 has some limitations. While the vaccine is believed to be moderately effective in prevention of IPD in immunocompetent older adults, effectiveness wanes over time, and a protective effect against non-bacteremic pneumococcal pneumonia has not been consistently demonstrated [3]. In contrast, pneumococcal conjugate vaccines (PCVs) are highly effective against vaccine-type IPD in children and have also been shown to reduce the risk of all-cause pneumonia. In addition, a 7-valent PCV (PCV7) has been shown to be effective against vaccine-type IPD in a randomized controlled trial of HIV-infected adults. These data suggest potential advantages for the use of PCVs compared to PPSV23 in older adults [4–8].

We conducted a randomized trial to compare the immunogenicity, tolerability, and safety of a 13-valent PCV (PCV13) with PPSV23 in pneumococcal vaccine-naive adults 60–64 years of age. In addition, a cohort of subjects 50–59 years of age received a single dose of open-label PCV13 to compare immune responses between the younger and older age groups.

![Study design and disposition of subjects](image-url)

**Fig. 1.** Study design and disposition of subjects.
of open-label PCV13 at the enrollment visit with no comparator; PPSV23 is not generally recommended in this age group (Fig. 1).

Non-study medications were permitted. Licensed vaccines, except pneumococcal vaccines, could be given according to local or national recommendations, and could be concomitantly administered. Influenza vaccine was permitted, if given at least 14 days before or after study vaccination.

Clinic visits occurred at enrollment, 1 month (29–43 days) and 1 year (351–379 days) after vaccination with a telephone visit for a safety assessment at 6 months after vaccination. Blood samples were obtained before vaccination and at each clinic visit.

2.2. Vaccines and administration

PCV13 (Prevnar 13/Prevenar 13®, Wyeth Vaccines; Lot Number 7-5095-001A) contains polysaccharides of pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, and 23F individually conjugated to a nontoxic mutant form of diphtheria toxin cross-reactive material 197 (CRM197). Each 0.5 mL dose contains 2.2 μg of each serotype, except type 6B, which is included at 4.4 μg. Each dose is formulated in 5.0 mM succinate and 0.85% sodium chloride at pH 5.8 with 0.125 mg aluminum as aluminum phosphate and 0.02% polysorbate 80. The vaccine is supplied in single-dose syringes without preservatives and stored at 2–8 °C.

PPSV23 (Pneumovax 23®, Merck & Company, Inc; Lot Number 0743F) consists of a purified capsular polysaccharide from 12 of the serotypes included in PCV13 (all except 6A), as well as 11 additional serotypes (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F). The vaccine is formulated to contain 25 μg of each of the 23 purified polysaccharide serotypes per 0.5 mL dose of vaccine and contains phenol as a preservative and stored at 2–8 °C.

Vaccines were administered by intramuscular injection in the deltotoid using 25 G 1 in. needles.

2.3. Study objectives

The primary objectives for the subjects 60–64 years of age were to demonstrate that PCV13 was at least as immunogenic as PPSV23 for the 12 serotypes common to the 2 vaccines, as measured by opsonophagocytic activity (OPA) titers 1 month after vaccination, and to show that the proportion of subjects with a 4-fold increase in OPA titer to serotype 6A (contained only in PCV13) was significantly greater in the PCV13 group compared to the PPSV23 group. A secondary objective was to show statistically significantly higher responses in PCV13 recipients for at least some of the 12 serotypes in common.

The primary objective for the evaluation of subjects 50–59 years of age was to demonstrate that PCV13 was at least as immunogenic in this age group as in subjects 60–64 years of age.

2.4. Analysis populations

The evaluable immunogenicity population was the primary population for immunogenicity analyses and consisted of eligible subjects who had at least 1 valid and determinate assay result, received the assigned vaccine and no prohibited vaccines, and had no other major protocol violation. The safety population included all subjects vaccinated.

2.5. Immunogenicity assessments

Immunogenicity was assessed by measuring specific functional antibacterial OPA titers using 13 serotype-specific validated OPA assays. Although a specific level of OPA antibody has not been shown to correlate with protection against pneumococcal disease in adults, OPA antibody responses are generally accepted as a correlate of vaccine-induced protection [11,12]. Titers were defined as the interpolated reciprocal serum dilution that resulted in complement-mediated killing of 50% of the assay bacteria. The lowest titer that can be determined in the assay (limit of detection [LOD]), regardless of serotype, is 1:8. However, to quantify functional antibodies with appropriate precision and accuracy, the lower limit of quantitation (LLOQ) was determined for each serotype-specific OPA assay during assay validation. Titers below the LLOQ were set to a value of 1:4 (half of the LOD).

OPA titers were measured in all blood samples obtained at baseline, 1 month after vaccination, and in a randomly selected subset (100 subjects/study group) of blood samples obtained 1 year after vaccination.

2.6. Safety assessments

Participants recorded local reactions (redness, swelling, pain and limitation of arm movement of the injected arm), and systemic events (chills, fatigue, headache, vomiting, decreased appetite, rash, new generalized muscle pain, aggravated generalized muscle pain, new generalized joint pain, and aggravated generalized joint pain), and oral temperature in an electronic diary on the evening of vaccination and for the next 13 days. Adverse events (AEs) were collected from enrollment through the month 1 postvaccination visit, serious adverse events (SAEs) from enrollment through the month 6 follow-up phone contact, and deaths through the end of the study.

2.7. Statistical analysis

2.7.1. Sample size estimation

A sample size of approximately 370 subjects per study group in subjects 60–64 years of age was determined to provide at least 90% overall power to declare noninferiority of PCV13 versus PPSV23 for the 12 common pneumococcal antigens using a 2-fold noninferiority criterion for the OPA geometric mean titer (GMT) ratio (i.e., lower limit of the 2-sided 95% confidence interval [CI] for the ratio GMT PCV13/GMT PPSV23 is greater than 0.5), and assuming a 2-sided type I error rate of 0.05 and a 5% dropout rate. Data from a previous trial was used for computations [13]. This sample size was sufficient to detect a difference of at least 15% in the proportion of subjects achieving a 4-fold rise on the 6A serotype with at least 90% power using a 2-sided type I error rate of 0.05.

A sample size of 370 subjects 50–59 years of age was determined to provide at least 90% overall power to declare noninferiority of the response relative to subjects 60–64 years of age for all 13 pneumococcal antigens using a 2-fold noninferiority criterion and assuming a 5% dropout rate.

2.7.2. Immunogenicity analyses

For the comparison of OPA GMTs elicited by PCV13 relative to PPSV23, the 2-sided 95% CI on the geometric mean ratio (GMR) (GMT PCV13/GMT PPSV23) for each of the 12 common serotypes was calculated (back-transformed 95% CI for mean difference on the logarithmic scale computed using the Student t distribution). Noninferiority of PCV13 relative to PPSV23 was declared if the lower limit of the 2-sided 95% CI for the GMR was greater than 0.5 (2-fold criterion). This value was selected based on matching immunogenicity to efficacy results from several infant PCV7 or 9-valent PCV efficacy trials [14]. A secondary analysis assessed statistically significantly greater responses elicited for at least some serotypes. Statistical significance was declared if the lower limit of the 95% CI for the GMR was >1.0 (>2.0 for serotype 6A).
For evaluation of the response to serotype 6A (only in PCV13), the proportions of subjects achieving a 4-fold rise in OPA titer 1 month after vaccination were compared between the 2 groups. Superiority of response for the PCV13 group was declared if the lower limit of the 2-sided 95% CI computed using Chan and Zhang methodology for the difference in proportions (PCV13–PPSV23) was greater than zero (0) [15].

Analyses comparing responses to PCV13 serotypes in subjects 50–59 years of age relative to subjects 60–64 years of age were performed in the same manner as those comparing responses to PCV13 relative to PPSV23.

All analyses were performed using the SAS software package. No imputations were done for missing data.

2.7.3. Safety analyses

Differences in the frequency of local reactions and systemic events between PCV13 and PPSV23 were determined and corresponding 95% CIs and p-values generated based on Chan and Zhang [15].

3. Results

3.1. Baseline characteristics and disposition of subjects

A total of 831 subjects 60–64 years of age received PCV13 (N = 417; mean age 61.8 years) or PPSV23 (N = 414; mean age 61.7 years) and 403 subjects 50–59 years of age (mean age 54.4 years) received open-label PCV13 and included in the safety population (Table 1, Fig. 1). In the older group, distribution of age, race, and ethnicity were similar in the PCV13 and PPSV23 groups. The large majority of the population was white, and in the evaluable population, gender distribution was significantly different between the PPSV23 group (female: 61.2%, male: 38.8%) and the PCV13 group (female: 53.5%, male: 46.5%) (p = 0.027). In the older and younger age group 20.1% and 17.1% respectively, who received PCV13 had 1 or more chronic underlying diseases including cardiovascular disease, liver disease (including alcoholic liver disease and alcoholism), pulmonary disease, renal or urinary tract disease, or diabetes mellitus. 48.7% of older adults and 37.9% of younger adults had a history of smoking (Supplemental Table S1).

3.2. Immune responses

3.2.1. PCV13 compared to PPSV23 at 1 month after vaccination

The evaluable immunogenicity population of subjects 60–64 years of age consisted of 818 subjects (411 received PCV13 and 407 received PPSV23).

OPA GMTs at baseline were similar in the 2 vaccine groups. PCV13 OPA GMTs were noninferior to PPSV23 for all 12 common serotypes and statistically significantly greater in PCV13 recipients for 8 of the 12 common serotypes (1, 4, 6B, 7F, 9V, 18C, 19A, 23F). For serotype 6A, contained only in PCV13, the OPA GMT was substantially greater in PCV13 recipients than in PPSV23 recipients (Table 2). In addition, the proportion of subjects achieving a 4-fold increase in OPA titer for serotype 6A was statistically significantly

<table>
<thead>
<tr>
<th>Serotype</th>
<th>60–64 Year age group</th>
<th>Vaccine comparison (PCV13 vs PPSV23)</th>
<th>50–59 Year age group</th>
<th>Group comparison (50–59 yr/60–64 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GMT^b</td>
<td>GMT^b</td>
<td>GMT^b</td>
<td></td>
</tr>
</tbody>
</table>

^a Number of subjects with a determinant OPA titer to the given serotype.
^b GMTs were calculated using all evaluable subjects with available data for the specified blood draw.
^c Ratio of GMTs PCV13 to PPSV23 is calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
^d 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 (PCV13–PPSV23).
^e Ratio of GMTs, 50–59 years to 60–64 years, is calculated by back transforming the mean difference between vaccine cohorts on the logarithmic scale.
^f 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 (50–59 years–60–64 years).
Fig. 2. Reverse cumulative distribution curves for OPA titers measured before vaccination and 1 month after PCV13 or PPSV23 administration in subjects 60–64 years of age and 50–59 years of age. One (1) serotype (as noted) is displayed per panel. Solid lines depict the prevaccination titers and dotted lines depict the postvaccination titers. (–) PCV13, 60–64 yr; (–) PPSV23, 60–64 yr; (–) PCV13, 50–59 yr. Abbreviations: OPA, opsonophagocytic activity; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.
Table 3
Local reactions and systemic events reported up to day 14 after vaccination.

<table>
<thead>
<tr>
<th></th>
<th>60–64 Year age group</th>
<th>50–59 Year age group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCV13%</td>
<td>PPSV23%</td>
</tr>
<tr>
<td>Local reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rednessb</td>
<td>Any</td>
<td>20.2</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>15.9</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>1.7</td>
</tr>
<tr>
<td>Swellingb</td>
<td>Any</td>
<td>19.3</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>15.5</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0.6</td>
</tr>
<tr>
<td>Pain</td>
<td>Any</td>
<td>80.1</td>
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<tr>
<td></td>
<td>Mild</td>
<td>78.6</td>
</tr>
<tr>
<td></td>
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<td>23.3</td>
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<tr>
<td></td>
<td>Severe</td>
<td>1.7</td>
</tr>
<tr>
<td>Limitation of arm movementd</td>
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<td>28.5</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>26.9</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>1.7</td>
</tr>
<tr>
<td>Any local reactione</td>
<td></td>
<td>82.2</td>
</tr>
<tr>
<td>Systemic events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any (≥38°C)</td>
<td>4.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Mild (≥38°C but &lt;38.5°C)</td>
<td>4.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Moderate (≥38.5°C but &lt;39°C)</td>
<td>0.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Severe (≥39°C but ≤40°C)</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>&gt;40°C</td>
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<td>0.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>63.2</td>
<td>61.5</td>
</tr>
<tr>
<td>Headache</td>
<td>54.0</td>
<td>54.4</td>
</tr>
<tr>
<td>Chills</td>
<td>23.5</td>
<td>24.1</td>
</tr>
<tr>
<td>Rash</td>
<td>16.5</td>
<td>13.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3.9</td>
<td>5.4</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>21.3</td>
<td>21.7</td>
</tr>
<tr>
<td>New generalized muscle pain</td>
<td>56.2</td>
<td>57.8</td>
</tr>
<tr>
<td>Aggravated generalized muscle pain</td>
<td>32.6</td>
<td>37.3</td>
</tr>
<tr>
<td>New generalized joint pain</td>
<td>24.4</td>
<td>30.1</td>
</tr>
<tr>
<td>Aggravated generalized joint pain</td>
<td>24.9</td>
<td>21.4</td>
</tr>
<tr>
<td>Any systemic evente</td>
<td>82.6</td>
<td>82.1</td>
</tr>
</tbody>
</table>

*Exact 2-sided confidence interval and corresponding p-value (based on Chan and Zhang) for the difference in proportions, [13vPnC]:[23vPS], expressed as a percentage.

b Redness and swelling were categorized as absent if <2.5 cm, mild if ≥2.5 cm and ≤5.0 cm, moderate if >5.0 cm and ≤10.0 cm, and severe if >10.0 cm.

c If pain at the injection site was present, subjects were asked to enter the severity as mild if the symptom was easily tolerated, moderate if there was discomfort sufficient to interfere with usual activity, and severe if the pain was incapacitating.

d If limitation of arm movement was present, subjects were asked to enter the severity as mild if there was some limitation of arm movement, moderate if the subject was unable to move his or her arm above the head but able to move it above the shoulder, and severe if the subject was unable to move the arm above the shoulder.

e Any local reaction = any pain, any swelling, any redness, or any limitation of arm movement.

f Any systemic event = any fever ≥38°C, any fatigue, any headache, any chills, any rash, any vomiting, any decreased appetite, any new or aggravated generalized muscle pain, and any new or aggravated joint pain.

Higher after PCV13 (88.5%) compared to PPSV23 (49.3%) with a difference in proportions of 39.2% (95% CI, 33.0%–45.1%).

Because of the higher percentage of females in the PPSV23 group, an analysis of OPA responses by sex was performed. In these sex-stratified analyses of OPA GMTs, the magnitude of the serotype-specific effects among females and males was generally similar to that among all subjects (data not shown).

A post hoc analysis assessing immune response in subjects with chronic underlying conditions showed no differences when compared to healthy subjects.

Reverse cumulative distribution curves (RCDCs) showed that for the 9 serotypes for which PCV13 OPA GMTs were significantly greater than those of PPSV23, the PCV13 curves were generally higher across the full range of antibody titers (Fig. 2). Serotypes 6A and 23F displayed the greatest differences between the PCV13 and PPSV23 curves.

3.2.2. Immune responses to PCV13 at 1 month after vaccination in subjects 50–59 years of age compared to subjects 60–64 years of age

OPA GMTs in 50–59 year olds were noninferior to 60–64 year olds for all 13 serotypes, and statistically significantly greater in the younger cohort for 9 serotypes (Table 2). RCDCs showed that the 9 serotypes for which PCV13 OPA GMTs were significantly greater in the 50–59 year old subjects than those in the 60–64 year old group, the PCV13 curves were generally higher across the full range of antibody titers (Fig. 2).
and redness were similar in the 2 groups. No notable differences in systemic events were observed between the PCV13 and PPSV23 groups (Table 3).

The incidence of AEs was similar between PCV13 (17.0%) and PPSV23 (16.7%) recipients and was somewhat lower in the younger age cohort (11.4%). Most of the AEs included diseases and conditions commonly observed among older adults, and infectious disorders were the most frequently occurring types of AEs in all groups. One (1) subject died but the event leading to death was not considered related to the study vaccine, and there were no vaccine related SAEs.

4. Discussion

In pneumococcal conjugate vaccines the conjugation of the capsular polysaccharide to a protein carrier converts the polysaccharide from a T cell-independent to a T cell-dependent antigen, with the potential to elicit more robust and longer-lasting immune responses and to establish immune memory. In infants, PCVs are highly effective against IPD and also reduce the risk of all-cause pneumonia [6–8]. In older adults PCV7 has been shown to elicit vaccine serotype-specific OPA responses at levels that have been associated with protection in children and that are greater than those measured after adult PPSV23 administration [13,16–18].

In addition, PCV7 significantly reduced the risk of vaccine-type IPD in a randomized, placebo-controlled trial conducted among HIV-infected adults in Malawi, while a reduction was not seen in a study of PPSV23 in a similar population of HIV-infected adults [8,19]. Overall, these observations suggest that PCV immunization may reduce the burden of IPD and potentially non-bacteremic pneumococcal pneumonia in adults.

The present study was performed to determine if PCV13, in comparison to PPSV23, could elicit quantitatively greater anti-pneumococcal functional immune responses, as a result of its T cell-dependent nature. This is the first study comparing safety and immunogenicity of PCV13 with PPSV23 in pneumococcal vaccine-naive older adults 60–64 years of age. The study included adults with stable non-immunocompromising chronic diseases which nonetheless increase the risk for pneumococcal disease. Approximately 20% of adults in both age groups had 1 or more of these conditions. Vaccine serotype-specific OPA responses to PCV13 were noninferior to PPSV23 for all 12 serotypes common to both vaccines, and were statistically significantly higher after PCV13 relative to PPSV23 for 8 of those serotypes. Similar findings have been observed in other studies for two of the four serotypes (serotypes 3 and 14) for which immune responses were not higher in PCV13 recipients compared to PPSV23 recipients. The biological basis for this finding is not known. In addition, PCV13 elicited a statistically superior response to serotype 6A which is contained only in PCV13. Of note, the functional OPA response against type 6A has been shown to be cross-reactive with serotype 6C, a serotype that was recently demonstrated to cause IPD [11,20]. An OPA titer that correlates with protection has not been defined; however, RCDCs showed that for the 9 serotypes for which PCV13 OPA GMTs were significantly greater than those of PPSV23, the PCV13 curves were generally higher across the full range of antibody titers.

Responses in 50–59 year olds were noninferior to the older age group and statistically significantly greater for 9 serotypes, demonstrating a not unexpected greater response in younger compared with older adults. This higher level of response in the younger age group notably persisted over the year following vaccination, suggesting that vaccination of younger adults may result in greater antibody persistence.

PCV13 had an acceptable safety and reactogenicity profile in both the younger and older age groups. In the older age group, mild pain at the injection site was significantly higher after PCV13 and severe pain significantly higher after PPSV23. Other local reactions did not differ significantly between the two vaccine groups. There were no vaccine related AEs or SAEs at the 6 months follow up contact. Previous studies comparing PCV7 and PPSV23 in vaccine naive older adults have also found generally comparable safety and reactogenicity profiles [13,17,18].

5. Conclusion

The generally greater functional antibody response to PCV13 compared to PPSV23 in adults confirms the enhanced immunogenicity previously seen with T cell-dependent conjugate vaccines, and supports the perspective that PCV13 has the potential for improved clinical efficacy against pneumococcal disease. A large, randomized, placebo-controlled clinical trial to assess the efficacy of PCV13 against bacteremic and nonbacteremic vaccine type community acquired pneumonia and IPD is in progress [21].

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2013.04.085.

References


