Comparison of Pneumococcal Conjugate Polysaccharide and Free Polysaccharide Vaccines in Elderly Adults: Conjugate Vaccine Elicits Improved Antibacterial Immune Responses and Immunological Memory

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Background. High functional antibody responses, establishment of immunologic memory, and unambiguous efficacy in infants suggest that an initial dose of conjugated pneumococcal polysaccharide (PnC) vaccine may be of value in a comprehensive adult immunization strategy.

Methods. We compared the immunogenicity and safety of 7-valent PnC vaccine (7vPnC) with that of 23-valent pneumococcal polysaccharide vaccine (PPV) in adults ≥70 years of age who had not been previously vaccinated with a pneumococcal vaccine. One year later, 7vPnC recipients received a booster dose of either 7vPnC (the 7vPnC/7vPnC group) or PPV (the 7vPnC/PPV group), and PPV recipients received a booster dose of 7vPnC (the PPV/7vPnC group). Immune responses were compared for each of the 7 serotypes common to both vaccines.

Results. Antipolysaccharide enzyme-linked immunosorbent assay antibody concentrations and opsonophagocytic assay titers to the initial dose of 7vPnC were significantly greater than those to the initial dose of PPV for 6 and 5 of 7 serotypes, respectively (P < 0.01 and P < 0.05, respectively). 7vPnC/7vPnC induced antibody responses that were similar to those after the first 7vPnC inoculation, and 7vPnC/PPV induced antibody responses that were similar to or greater than antibody responses after administration of PPV alone; PPV/7vPnC induced significantly lower antibacterial responses, compared with those induced by 7vPnC alone, for all serotypes (P < 0.05).

Conclusion. In adults, an initial dose of 7vPnC is likely to elicit higher and potentially more effective levels of antipneumococcal antibodies than is PPV. In contrast with PPV, for which the induction of hyporesponsiveness was observed when used as a priming dose, 7vPnC elicits an immunological state that permits subsequent administration of 7vPnC or PPV to maintain functional antipolysaccharide antibody levels.

Infections due to Streptococcus pneumoniae are a major cause of morbidity and mortality worldwide [1, 2]. All age groups may be affected, but the highest rates of invasive pneumococcal disease (IPD) occur among young children and elderly individuals [3]. In the United States and Europe, the risk of IPD remains highest among elderly individuals and high-risk adults, despite years of availability and widespread use of a 23-valent pneumococcal free polysaccharide vaccine (PPV) that is recommended for persons ≥65 years of age and for high-risk individuals 2–64 years of age [4–6].

Certain characteristics of PPV may limit its ability to provide direct protection against IPD over the full duration of the adult risk period. This vaccine is composed of purified free polysaccharides derived from the surface capsule of the bacterium. Such free polysaccharide antigens generally elicit T cell independent immune responses and are, therefore, poor inducers of immunologic memory; these findings are best dem-
onstrated in infants [7]. Vaccine-elicited antibody titers may achieve insufficient levels and, although these levels seem to be maintained for 1–2 years [8, 9], they wane substantially after 5 years [10], as does the clinical effectiveness of the vaccine [11]. This is noted for both antipolysaccharide direct-binding antibodies and functional antibacterial opsonophagocytic titers [8, 10]. Despite the inability of PPV to maintain effective antibody levels, routine reinmunization with PPV has not been recommended because of concerns associated with increased reactogenicity and immunological hyporesponsiveness after repeated dosing [12, 13].

The conjugation of the capsular polysaccharide to a protein carrier converts the polysaccharide to a T cell–dependent antigen. Pneumococcal conjugate vaccines establish a state of immunological priming and memory resulting in substantial enhancement of antibody responses on boosting [14]. In toddlers, bacterial polysaccharide protein-conjugate vaccines elicit functional antibacterial antibody responses that are quantitatively superior to those elicited by free bacterial polysaccharides [15]. Since the licensure in the United States of the 7-valent pneumococcal conjugate vaccine (7vPnC) for infants in 2000, the vaccine’s immunogenicity and effectiveness in preventing IPD have been definitively documented [16–20]. A dramatic decrease in the incidence of IPD among infants and toddlers has been observed [16, 21]. This experience indicates that pneumococcal conjugate vaccines may be of value in a comprehensive program of adult immunization.

Therefore, the present study was designed to investigate whether the apparent shortcomings of the free polysaccharide vaccine in adults can be overcome using a conjugated polysaccharide vaccine, as is used in infants. A comparison of the immunogenicity and safety of 7vPnC and PPV was performed in a population of vaccine-naive elderly adults to assess both the initial immune response against the 7 polysaccharide types common to both vaccines and the ability of the vaccines to suitably prime for booster responses to a second administration of either vaccine.

**METHODS**

The present study was a randomized, open label, phase 2 study that included a comparison of the immunogenicity and safety of a 7vPnC (Prevenar; Wyeth) with a 23-valent pneumococcal free polysaccharide conjugate vaccine (Pneumovax; Aventis Pasteur). The study was conducted from March 2003 through October 2004. Twenty-seven study centers participated. Two centers were the outpatient facilities of German hospitals located in Berlin and Hannover. All other patients were recruited by respiratory and general physicians in private practice. The study protocol was approved by the Ethics Committee of the Free University Berlin (Berlin, Germany).

**Study population.** The focus of this article is a cohort of 219 ambulatory elderly adults $\geq 70$ years of age who had not previously received a pneumococcal vaccine. The study was part of a larger investigation that included a total of 443 individuals. The remaining individuals (224 patients) received 2-fold and 4-fold higher dose formulations of pneumococcal conjugate vaccine, and these data will be reported separately.

Subjects were eligible for inclusion in the study if they were in a stable clinical condition. Subjects were excluded if they were nursing home residents or had severe chronic disorders, impaired immune function, or evidence of dementia or severe cognitive impairment based on Mini Mental Status Examination scores. Other reasons for exclusion included receipt of blood products within 6 months before enrollment, receipt of anticoagulants or bleeding diathesis, documented *S. pneumoniae* infection in the previous 5 years, any previous pneumococcal vaccination, diphtheria vaccination within 6 months, current fever, or current receipt of antibiotic therapy.

**Vaccines.** 7vPnC, which is currently licensed for pediatric use, was used. The vaccine contains polysaccharides of pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. The polysaccharides are conjugated to the protein carrier CRM197, a nontoxic variant of diphtheria toxin. Each serotype is conjugated separately prior to formulation as a multivalent vaccine. The vaccine contains aluminum phosphate as an adjuvant.

The PPV consists of a mixture of purified capsular polysaccharides from 23 types of *S. pneumoniae*: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F. The vaccine does not contain an adjuvant.

**Study design and immunogenicity evaluation.** Subjects immunized at study entry (dose 1) received a second immunization after 1 year (dose 2). For the first dose, all subjects were randomized to receive either PPV or 7vPnC by a single injection in the deltoid muscle. At 1 year, subjects who initially received the conjugate vaccine were rerandomized to receive either another dose of conjugate (the 7vPnC/7vPnC group) or PPV (the 7vPnC/PPV group). All subjects initially vaccinated with PPV were given a dose of conjugate (the PPV/7vPnC group). The vaccination scheme is depicted in figure 1.

Blood samples were obtained immediately before (the pre-dose 1 sample) and approximately 1 month after (the post-dose 1 sample) the first dose of vaccine and again immediately before (the pre-dose 2 sample) and approximately 1 month after (the post-dose 2 sample) the second dose. Prevaccination and postvaccination serotype-specific antipolysaccharide binding IgG antibody levels to all serotypes contained in 7vPnC were measured by ELISA using absorption with cell wall polysaccharide and serotype 22F polysaccharide, as described in Quataert et al. [22]. The mechanism of protection by pneumococcal antibodies relied on opsonophagocytosis [23, 24]. Antibacterial antibody responses were measured by a validated opsonophagocytic assay (OPA), as described elsewhere [25].
Safety. Local and systemic reactions and oral temperature were recorded in a diary card over a 7-day period after each vaccination (i.e., after dose 1 and dose 2). Prompted local reactions included redness, swelling, or pain at the injection site. Prompted systemic events included fatigue, headache, chills, and generalized muscle or joint aches. All subjects were contacted by telephone on or around day 3 after dose administration as a reminder to complete the diary card.

Statistical evaluation. Geometric means and 95% CIs for antipolysaccharide binding IgG antibody concentrations and OPA titers were calculated. Comparisons of antibody levels between treatment groups following either primary or booster immunization were performed using Student’s t tests on log-transformed antibody levels. For safety and tolerability evaluations, the frequencies of fever (temperature, ≥38°C or >39°C), and local and systemic reactions for each treatment group following each vaccination were determined with 95% CIs. Comparisons were performed using Fisher’s exact test.

RESULTS

Immunogenicity following the initial vaccine administration. During the first phase of the study, 219 subjects were vaccinated; 110 received 7vPnC, and 109 received PPV. Mean age at enrollment was 75.4 years, and 57% of the subjects were female. Preimmunization antibody levels were similar in both groups. IgG geometric mean concentrations of subjects vaccinated with 7vPnC were statistically significantly higher by 2–3-fold, compared with the geometric mean concentrations of PPV recipients, with the exception of serotype 19F, which was similar in both groups (table 1). Similarly, the geometric mean titers of the OPA in subjects vaccinated with 7vPnC were higher than those in subjects vaccinated with PPV for all serotypes except 6B and 19F, which were similar in both groups (table 2). Statistically significant differences in OPA titers were reached for 5 of 7 serotypes (4, 9V, 14, 18C, and 23F).

Immunogenicity of a subsequent administration of 7vPnC or PPV. One year after the initial vaccination, 159 patients received a second dose of vaccine. The proportion of subjects who did not receive this subsequent dose was similar in both groups: 29 (26%) of 110 in the 7vPnC group and 31 (28%) of 109 in the PPV group. Reasons for withdrawal included protocol violations (in 6 [5%] of the 7vPnC group and 4 [4%] of the PPV group), subject and investigator request (in 9 [8%] of the 7vPnC group and 13 [12%] of the PPV group), loss to follow-up (1 subject in the 7vPnC group and 4 subjects in the PPV group), or death (1 subject in the 7vPnC group and 4 subjects in the PPV group). In addition, subjects with injection site reactions ≥7 cm in diameter (12 subjects in the 7vPnC group and 6 subjects in the PPV group) were excluded according to protocol from receiving a second dose.

Subjects who initially received 7vPnC were rerandomized to receive either another dose of conjugate vaccine (the 7vPnC/7vPnC group; n = 43) or a booster dose of PPV (the 7vPnC/PPV group; n = 38). All subjects who were initially vaccinated with PPV were administered a dose of 7vPnC (the PPV/7vPnC group; n = 78).

The antipolysaccharide and OPA concentrations for the 3 cohorts of subjects who were evaluable after both the first and second doses of vaccine are summarized in figures 2 and 3, respectively. For most serotypes, the highest antipolysaccharide and OPA responses, following 2 doses of vaccine, occurred in the 7vPnC/7vPnC group; for all serotypes, the lowest responses occurred in the PPV/7vPnC group.

Comparison of the immunological priming effect elicited by the initial vaccination. Antibody responses seen after administration of PPV in subjects who received an initial dose of 7vPnC, compared with responses seen after PPV vaccination in vaccine-naive subjects, showed that the ability to respond to PPV was maintained following conjugate vaccine immunization. In fact, the antipolysaccharide antibody geometric mean

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**Figure 1.** Vaccine administration scheme showing the number of subjects, including those who withdrew from the study, in each subgroup. 7vPnC, 7-valent conjugated pneumococcal polysaccharide vaccine; PPV, 23-valent pneumococcal polysaccharide vaccine.
concentrations achieved were higher in the 7vPnC/PPV group, compared with after the initial PPV dose, for all 7 serotypes, and the difference was statistically significant for 19F and 23F ($P < .05$) (table 1). Functional antibody (OPA) geometric mean titers were also higher in the 7vPnC/PPV group, compared with after PPV vaccination alone, for all 7 serotypes, and the difference was statistically significant for all but serotype 6B (table 2).

In addition, the antipolysaccharide and OPA immune responses following a second dose of conjugate vaccine were similar to those achieved after the initial dose (7vPnC/7vPnC vs. 7vPnC alone) (tables 1 and 2), with serotype 9V achieving a significantly lower antibody concentration and serotype 23F achieving a significantly higher functional antibody response following the second dose of 7vPnC (tables 1 and 2).

Finally, reduced antipolysaccharide and OPA responses were observed when conjugate vaccine was administered after PPV, compared with after the administration of conjugate vaccine alone (PPV/7vPnC vs. 7vPnC). Both antibody responses were statistically significantly lower for all serotypes, with the exception of functional antibodies for 19F, which were similar in both groups (tables 1 and 2; figure 3).

### Safety

Local reactions are summarized in figure 4. Overall, there were no vaccine-related serious adverse events in the study. Five subjects died of unrelated causes in the 1-year interval between the 2 vaccination periods (1 subject in the 7vPnC group and 4 subjects in the PPV group).

After the first dose, injection site reactions were reported by 57 (53.8%) of 106 subjects receiving 7vPnC and 43 (43%) of 100 subjects receiving PPV. This difference was not significant ($P = .13$). In both groups, the most frequently reported local reaction was pain at the injection site, followed by redness and swelling. Most of these reactions were mild or moderate and of short duration. Systemic symptoms were reported by 39.6% of subjects after administration of 7vPnC and 38.2% after administration of PPV (not significant).

### Table 1. Antipneumococcal polysaccharide binding antibody concentrations following the first and second doses of vaccine.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of subjects</th>
<th>4</th>
<th>6B</th>
<th>9V</th>
<th>14</th>
<th>18C</th>
<th>19F</th>
<th>23F</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dose, by initial vaccine</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>7vPnC</td>
<td>110</td>
<td>3.1 b (2.2–4.3)</td>
<td>8.0 b (6.0–10.8)</td>
<td>9.8 b (7.5–12.8)</td>
<td>17.1 b (12.3–24.0)</td>
<td>13.0 b (10.1–16.7)</td>
<td>5.3 (4.1–7.4)</td>
<td>12.4 b (9.0–17.0)</td>
</tr>
<tr>
<td>PPV</td>
<td>107</td>
<td>1.4 a (1.1–2.0)</td>
<td>4.4 a (3.4–5.6)</td>
<td>3.8 a (2.9–4.6)</td>
<td>8.3 a (6.0–12.1)</td>
<td>6.8 a (5.2–8.9)</td>
<td>4.4 (3.4–5.6)</td>
<td>3.8 a (2.9–5.0)</td>
</tr>
<tr>
<td>Second dose, by vaccine combination</td>
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<td></td>
</tr>
<tr>
<td>7vPnC/7vPnC</td>
<td>43</td>
<td>3.1 (1.9–5.1)</td>
<td>10.0 (5.8–17.4)</td>
<td>5.7 (4.0–8.1)</td>
<td>16.5 (10.6–26.6)</td>
<td>8.6 (6.2–11.9)</td>
<td>5.4 (3.5–8.5)</td>
<td>15.2 (10.9–21.2)</td>
</tr>
<tr>
<td>7vPnC/PPV</td>
<td>36</td>
<td>2.0 (1.2–3.5)</td>
<td>5.4 (3.3–9.0)</td>
<td>5.7 (3.6–8.9)</td>
<td>14.5 (8.9–23.9)</td>
<td>7.6 (5.2–11.1)</td>
<td>8.4 a (5.3–13.1)</td>
<td>7.4 a (4.0–13.6)</td>
</tr>
<tr>
<td>PPV/7vPnC</td>
<td>78</td>
<td>0.9 a (0.6–1.3)</td>
<td>2.2 a (1.5–3.2)</td>
<td>3.0 a (2.2–4.0)</td>
<td>6.7 a (4.5–9.9)</td>
<td>5.1 a (3.7–6.8)</td>
<td>2.1 a (1.5–3.0)</td>
<td>3.0 a (1.9–4.8)</td>
</tr>
</tbody>
</table>

### Table 2. Geometric mean titers (GMTs) of antipneumococcal opsonophagocytic antibody (OPA) following the first and second doses of vaccine.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of subjects</th>
<th>4</th>
<th>6B</th>
<th>9V</th>
<th>14</th>
<th>18C</th>
<th>19F</th>
<th>23F</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dose, by initial vaccine</td>
<td></td>
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<tr>
<td>7vPnC</td>
<td>110</td>
<td>1457 a,b (997–2130)</td>
<td>1351 b (938–1946)</td>
<td>2915 a,b (2142–3967)</td>
<td>2397 a,b (1606–3579)</td>
<td>1318 a,b (919–1889)</td>
<td>182 (121–273)</td>
<td>1309 a,b (862–1990)</td>
</tr>
<tr>
<td>PPV</td>
<td>107</td>
<td>78 (52–144)</td>
<td>396 b (202–775)</td>
<td>1129 b (721–1769)</td>
<td>1006 b (661–1532)</td>
<td>282 b (179–446)</td>
<td>87 (52–144)</td>
<td>396 b (202–775)</td>
</tr>
<tr>
<td>Second dose, by vaccine combination</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>7vPnC/7vPnC</td>
<td>43</td>
<td>1505 e (863–2625)</td>
<td>1172 (678–2375)</td>
<td>2255 e (1187–4285)</td>
<td>2436 e (1355–4378)</td>
<td>985 e (619–1569)</td>
<td>522 e (308–884)</td>
<td>1476 e (771–2828)</td>
</tr>
<tr>
<td>7vPnC/PPV</td>
<td>36</td>
<td>2.0 (1.2–3.5)</td>
<td>5.4 (3.3–9.0)</td>
<td>5.7 (3.6–8.9)</td>
<td>14.5 (8.9–23.9)</td>
<td>7.6 (5.2–11.1)</td>
<td>8.4 a (5.3–13.1)</td>
<td>7.4 a (4.0–13.6)</td>
</tr>
<tr>
<td>PPV/7vPnC</td>
<td>78</td>
<td>0.9 a (0.6–1.3)</td>
<td>2.2 a (1.5–3.2)</td>
<td>3.0 a (2.2–4.0)</td>
<td>6.7 a (4.5–9.9)</td>
<td>5.1 a (3.7–6.8)</td>
<td>2.1 a (1.5–3.0)</td>
<td>3.0 a (1.9–4.8)</td>
</tr>
</tbody>
</table>

### Notes

7vPnC, 7-valent conjugated pneumococcal polysaccharide vaccine; PPV, 23-valent pneumococcal polysaccharide vaccine.

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Figure 2. Antipneumococcal polysaccharide binding antibody responses elicited during the immunization series. Titers are presented as geometric mean concentrations (GMCs) as determined by individual antipneumococcal ELISA (see Methods). 7vPnC, 7-valent conjugated pneumococcal polysaccharide vaccine; PPV, 23-valent pneumococcal polysaccharide vaccine.

DISCUSSION

One major finding in this study was that healthy elderly subjects who had not previously received pneumococcal PPV responded significantly better to 7vPnC than to PPV for serotypes that both vaccines had in common. The improved antibody responses were observed for both binding antipolysaccharide antibodies and for functional OPA titers and were noted for all serotypes except 19F, which was similar between the 2 vaccines (tables 1 and 2). Previous studies have shown indeterminate results when conjugate vaccines were compared with PPV, but their comparability with this study is questionable for various reasons, such as different investigational conjugate formulations used, small sample sizes, preimmunization status, and comorbidity conditions [26–34].

Furthermore, the comparison of conjugate and free polysaccharide vaccine in the study revealed important results regarding the sequential use of both vaccines. A dose of 7vPnC followed by PPV at 1 year increased both antipolysaccharide antibody and OPA responses after the second vaccination for
all 7 serotypes, with statistically significant increases in OPA titers to all serotypes except 6B (tables 1 and 2). In contrast, in subjects who received PPV followed by 7vPnC at 1 year, the antibody responses were ∼3-fold lower, compared with the antibody responses of individuals who were vaccinated with 7vPnC who had not previously received PPV (table 1). This immunological hyporesponsiveness was observed for both antipolysaccharide binding antibodies and OPA titers and for all serotypes. These observations may suggest that an initial dose of PPV depleted—whereas a dose of 7vPnC increased—the number of polysaccharide-specific memory B cells, affecting the response to the subsequent vaccine, compared with the response of unprimed individuals.

Immunologic hyporesponsiveness after immunization with polysaccharide vaccines has been observed with a variety of different polysaccharide antigens. Serogroup C meningococcal polysaccharide vaccine has been reported to produce the most profound hyporesponsiveness in infants and adults as measured by decreased antibody responses to a second dose of polysaccharide vaccine [35–37]. Meningococcal C conjugate vaccines do not induce hyporesponsiveness and, in fact, partially restore responsiveness induced by polysaccharide immunization [36, 37].

Similar observations have been previously reported in adults who received a second dose of PPV. Torling et al. [12] reported that antibody titers achieved after a second dose of PPV were lower than those achieved after an initial dose, and Jackson et al. [13] demonstrated a trend to lower antibody titers in the 3 measured serotypes following revaccination with PPV, compared with after the initial PPV immunization. In addition, Jackson et al. [13] evaluated antibody responses to either PPV or 7vPnC in adults (mean age, 75 years) who had been vaccinated with PPV at least 5 years earlier. Antibody responses were consistent with reduced levels seen in the PPV/7vPnC group in the current study, and support diminished immunologic response to subsequent pneumococcal antigen exposure after immunization with pneumococcal polysaccharide vaccine [34].
In contrast, subjects in this study who received 7vPnC followed by 7vPnC had antipolysaccharide antibody and OPA responses that were comparable to responses after the first vaccine dose (tables 1 and 2), demonstrating a lack of hyporesponsiveness to a second dose of 7vPnC.

Approximately 30% of subjects in both groups did not receive a subsequent dose. The older age of the study population may have contributed to the fairly high withdrawal rate, and a cautiously chosen limit for local reactions (diameter, ≥7 cm) may have encouraged subjects not to receive a subsequent dose (11% of those who received a first dose of 7vPnC and 6% of those who received a first dose of PPV did not receive a subsequent dose).

Local reactions were more frequent when 7vPnC was followed by PPV than vice versa. When 7vPnC was given twice, the incidence of local reactions was slightly higher after the second dose; however, it was significantly less than the incidence of local reactions after a subsequent dose of PPV (7vPnC/PPV).

Jackson et al. [38] studied reactogenicity of PPV and conjugate vaccines in subjects who had all received PPV at least 5 years previously. In these subjects who had been previously vaccinated with PPV, receipt of a second dose of 7vPnC was associated with a significantly lower rate and severity of local reactions, compared with receipt of a second dose of PPV. Our data, together with those of Jackson et al. [38], suggest that revaccination with conjugate vaccine may be better tolerated than repeated doses of PPV.

To our knowledge, no previous study involving healthy adults has directly compared the sequence of vaccination when both 7vPnC and PPV are used. The present study did not include a vaccination sequence with PPV followed by PPV that would have allowed a direct comparison of different revaccination schedules. This study arm was not included because of concern over potential local reactions with a short 1-year interval between vaccinations. Nonetheless, the study data clearly demonstrated an immunological benefit when 7vPnC was given prior to PPV, compared with when PPV was administered first.

If conjugate vaccines are confirmed to be safe and immunogenic with repeated administration in adults, they provide the potential to extend the duration of protection throughout the period of highest risk. The issue of serotype coverage is a challenge, especially because serotypes that affect adults and children differ, and the serotype distribution has started to change since the introduction of 7vPnC [39]. Next-generation conjugate vaccines containing up to 13 serotypes are in development to improve coverage in adults and in children on a global basis. An enhanced immunization strategy for protection of the elderly population against pneumococcal disease will

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Figure 4. Injection site reactions within 7 days after vaccination. 7vPnC, 7-valent conjugated pneumococcal polysaccharide vaccine; PPV, 23-valent pneumococcal polysaccharide vaccine.
become increasingly important; the older adult age group is expected to grow by >30 million people by the year 2030 [40] in the United States alone, with each individual experiencing an extended period of disease risk as the result of increasing life expectancy.

Acknowledgments


Potential conflicts of interest. A.D.R. and A.K. have received travel grants for attending conferences where the data of the study were presented. T.W. has received travel grants for attending conferences, research grants, and honoraria for lectures from Wyeth and is member of the international advisory board of Wyeth. H.L. has served as consultant for Astellas, Bayer, Johnson and Johnson, Pfizer, Sanofi-Aventis, and Wyeth, has received research grants from Bayer, Pfizer, Sanofi-Aventis, and Wyeth, and has been a member of the speakers bureau for Bayer, Johnson and Johnson, Pfizer, and Wyeth. All other authors: no conflicts.

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