Effectiveness and Serotype Coverage: Key Criteria for Pneumococcal Vaccines for Adults

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(Please see the Vaccines Invited Article by Paradiso, on pages 259–64, and the Editorial Commentary by Musher, on pages 265–7.)

Pneumococcal polysaccharide vaccines (PPSVs) received their proof-of-principle affirmation over 65 years ago, in the pivotal trial led by Colin MacLeod and Michael Heidelberger at a military technical school in the 1940s [1]. Four cases of vaccine-type pneumococcal pneumonia developed among 8586 vaccine recipients, in contrast to 26 cases among 8449 controls injected with saline as placebo. All 4 cases among vaccinees developed within 2 weeks of vaccination. Cases of non-vaccine-type pneumococcal pneumonia occurred at comparable rates in each group of young, working adults. Interestingly, the pneumococcal carriage rate in vaccine recipients was significantly lower than in the control group, similar to findings from South Africa in the 1970s [2]. Robert Austrian cited the MacLeod-Heidelberger study, among others, in concluding that PPSVs prevent non-bacteremic pneumococcal pneumonia [3].

Subsequent randomized clinical trials and observational studies, overall and in strata of older populations (discussed below), provide further evidence for PPSV efficacy in preventing invasive pneumococcal disease (IPD) and pneumococcal pneumonia [4–6]. The 14-valent PPSV14 was licensed in 1977 for people 50 years and older or those 2 years and older with certain underlying health conditions, targeting 70%–80% of IPD cases [7–9]. Expansion to 23 serotypes (PPSV23) was based on a broader global survey of invasive pneumococcal isolates coordinated by multiple national governments and the World Health Organization. Thus, PPSV23 was introduced in 1983 with serotypes covering about 87% of bacteremic pneumococcal disease in the United States [9, 10].

Although the technology for conjugate vaccines dates back to the 1920s [11, 12], that technique was applied to useful pneumococcal conjugate vaccines (PCVs) only since 2000. The most recent development has been licensing of PCV13 for adults in industrialized countries since late 2011. Now that 2 forms of pneumococcal vaccine are available for adults, how should clinicians choose between them? Clinical efficacy measures (eg, reduction in disease incidence, safety) are obvious choices, as is the proportion of disease burden a vaccine can target.

Except for a 2-dose PCV7 study among adults infected with human immunodeficiency virus (HIV) in Malawi [13], the randomized clinical trial results for preventing pneumococcal disease in adults currently available assess the performance of PPSVs against clinical endpoints [4–6]. As discussed at the February 2012 meeting of the US Advisory Committee on Immunization Practices (ACIP), the recent licensure of PCV13 for adults is based on noninferiority of antibody concentrations (typically at day 30 after vaccination) in relation to PPSV23 serotypes in common. Until now, clinical-outcome studies with PCVs have been conducted in infants and young children, whose response to vaccination varies substantially from that of adults (who respond robustly to both PPSVs and PCVs). PCV13 is the subject of a randomized clinical trial in Netherlands adults that eventually will compare its clinical performance to a saline placebo; key endpoints are not expected until the latter part of 2013 [14, 15].

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Meta-analyses serially conducted for the Cochrane Collaboration, assessing randomized clinical trials and observational studies, conclude that PPSVs are effective against definitive pneumococcal pneumonia (vaccine-type), with an odds ratio of 0.13 (95% confidence interval [CI], 0.05–0.38; N = 30,561), and presumptive pneumococcal pneumonia (vaccine-type), with an odds ratio of 0.27 (95% CI, 0.18–0.38; N = 18,568) [4]. The odds ratio computed for efficacy against IPD (vaccine-type) was 0.18 (95% CI, 0.10–0.31; N = 31,223), corresponding to estimated vaccine efficacy of 82%. Of the randomized clinical trials in these analyses, the majority involved populations with mean or median ages ≥60 years. The study populations generating these results included community-living and institutionalized adults (with and without health conditions elevating their risk of pneumococcal infection) in Belgium, Finland, France, Sweden, and the United States, as well as South African miners and Papua New Guinea villagers in settings with remarkably high incidence rates [4, 16].

Analyzing vaccine effect against IPD (all types) measured in observational studies among older adults, the odds ratio was 0.32 (95% CI, 0.22–0.47; N = 59,748). The various contributing studies reflect both formal efficacy trials and studies of effectiveness in the course of clinical practice [16]. Consistent with the 2008 Cochrane meta-analysis, a subsequent placebo-controlled trial among elderly Japanese nursing home residents showed 64% efficacy (95% CI, 32%–81%) for PPSV23 against pneumococcal pneumonia diagnosed by urinary antigen assay [6]. The randomized clinical trial data for PPSVs are reinforced by similar findings in nonrandomized (case control and other observational) studies for IPD as a clinical endpoint (both all types and vaccine-types) [4].

The breadth of serotype coverage for each vaccine is another important criterion. As shown in Table 1, PCV13 features 1 unique serotype, whereas PPSV23 features 11 unique serotypes (where unique refers to a serotype present in one formulation but not in the other). Differential breadth of coverage results from the difference in proportions of disease accounted for by these unique serotypes. Are the coverage differentials meaningful from an individual or public health perspective? The differentials vary somewhat from country to country and will vary further over time. On the basis of published literature, subtracting the proportion of IPD cases in adults corresponding to the PCV13 serotypes from the proportion corresponding to the PPSV23 serotypes yields differentials ranging from 14% to 28% in 8 out of 9 studies with at least 400 isolates (Table 2) [17–25].

What will happen to the differential serotype coverage in adults between PPSV23 and PCV13 in the future? As PCV10 and PCV13 are increasingly adopted around the world among infants and young children, the ability of children to serve as reservoirs and infect adults can be expected to diminish, as happened after widespread use of PCV7 [17]. If this expectation is realized, wholly or partially, then this incidence of disease due to the 6 additional serotypes can be expected to fall, even in unvaccinated adults. At the same time, the differential proportion of IPD and pneumonia cases between PPSV23 and PCV13 would increase. If so, then PPSV23 would offer even broader advantage in coverage for adult cohorts.

The increasing incidence of serotype 19A has been well documented [17, 26, 27]. Could other serotypes emerge in similar fashion, in standard periods or during influenza pandemics? If so, breadth of serotype coverage would be expected to continue to play a pivotal role in offering more extensive protection in circumstances that arise after widespread childhood vaccination. Even with licensing of 2 pneumococcal vaccine options for adults, a full research agenda awaits us. We need to better discern duration and correlates of protection, and how these formulations (or their successors) can best be used (alone or in tandem) to advance the public health.

PPSV23 is a vaccine that evokes antibodies persisting up to 10 years after first, second, third, or fourth doses in adults [28–32], which is important for an aging population. When the 1997 recommendations of the ACIP were adopted [33], only a handful of studies of revaccination in several dozen recipients each had been published. Today, data from many studies each with several hundreds to more than a thousand participants have been published, showing robust and durable antibody responses to PPSV23, including functional (opsonophagocytic) antibody responses, even after third or fourth doses with appropriate intervals [28–32]. An assessment of the degree of comparability between PPSV23 and PCV7 in adults in published studies appears elsewhere [27]. In brief, among 10 published studies, antibody responses were comparable for the 2 vaccine types in 70%–100% of serotype-specific assays performed (both immunoglobulin G and opsonophagocytic assays), based on specimens collected 6–12 months after vaccination [27]. This held true for both single-dose and sequential-regimen studies. Optimal regimens for PCV13 and PPSV23 must take into account the consistent

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**Table 1. Pneumococcal Serotypes Contained in Pneumococcal Vaccines for Adults**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Serotypes Included</th>
<th>Serotypes Unique to Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV13</td>
<td>1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, and 23F</td>
<td>6A</td>
</tr>
<tr>
<td>PPSV23</td>
<td>1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F</td>
<td>8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F</td>
</tr>
</tbody>
</table>

Abbreviations: PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine.
finding of a clear inverse association between circulating antibody level at time of pneumococcal vaccination and antibody increase [28–31, 34].

The continuing clinical relevance of PPSV23 centers on its established record of clinical effectiveness and safety and its broad serotype coverage in the face of evolving serotype epidemiology. Over 160 million doses of PPSV23 have been distributed worldwide since 1983. Even so, tens of millions of adults in the United States recommended for vaccination have never been vaccinated and remain vulnerable; additional tens of millions of vulnerable adults are unvaccinated in other countries. Rates of pneumococcal vaccination are especially low in people younger than 65 who have chronic diseases.

As important as the vaccines chosen to protect adults from pneumococcal disease is the vigor and thoroughness of adult vaccination programs, whether viewed from the perspective of a clinical practice or a nation. Adults cannot be protected from serious infectious diseases unless vaccination is offered conveniently, with a clinician’s strong recommendation to be vaccinated.

### Notes

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**Potential conflicts of interest.** The author is an employee of Merck and Co, Whitehouse Station, New Jersey, manufacturer of 23-valent pneumococcal polysaccharide vaccine and developer of 15-valent pneumococcal conjugate vaccine.

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### References


and dose responses, safety, persistence of antibody, revaccination, and simultaneous administration of pneumococcal and influenza vaccines. Rev Infect Dis 1981; 3(suppl):s31–42.