The Potential Role for Protein-Conjugate Pneumococcal Vaccine in Adults: What Is the Supporting Evidence?

Daniel M. Musher, Rahul Sampath, and Maria C. Rodriguez-Barradas

Vaccination with protein-conjugate pneumococcal vaccine (PCV) provides children with extraordinary protection against pneumococcal disease, although the protective effect may be blunted by the emergence of replacement strains. Studies in adults have compared PCV with pneumococcal polysaccharide vaccine (PPV) using surrogate markers of protection, namely, serum anticapsular IgG antibody and opsonic activity. Results suggest that PCV is at least as effective as PPV for the strains covered, but a definitive and consistent advantage has not been demonstrated. Unfortunately, persons who are most in need of vaccine do not respond as well as otherwise healthy adults to either vaccine. Newer formulations of PCV will protect against the most prevalent of the current replacement strains, but replacement strains will create a moving target for PCVs. Unless an ongoing trial comparing 13-valent PCV with placebo (not to PPV) demonstrates a clearly better effect than that seen in the past with PPV, cost-effectiveness considerations are likely to prevent widespread use of PCV in adults.

Covalent linking of a polysaccharide antigen to a protein yielding a protein-conjugate polysaccharide vaccine represented an extraordinary advancement in vaccinology, although >50 years transpired from the first description of this concept in the 1920s to its first application in the late 1970s [1–3]. The failure of infants and toddlers to respond consistently to polysaccharide antigens greatly limited efforts to vaccinate against infections caused by bacteria that have polysaccharide capsules, including Streptococcus pneumoniae [4] and Haemophilus influenzae type b [5]. In 1985, a vaccine consisting of polyribosylribitol phosphate, the capsular polysaccharide (CPS) of H. influenzae type b, conjugated to diphtheria toxoid was licensed in the United States, followed soon thereafter by a conjugate vaccine using CRM197, a nontoxic protein that differs from diphtheria toxin in 1 amino acid at the 197 position [6]. Widespread use of this vaccine in developed countries has nearly eliminated H. influenzae type b meningitis [7].

In the 1990’s, these same concepts were applied to pneumococcal CPS. In a landmark study [8], 38,000 infants were randomized to receive either 7-valent pneumococcal conjugate protein vaccine (PCV7), a preparation of CPS from 7 serotypes that most frequently infected children, conjugated to CRM197, or a protein-conjugate meningococcal vaccine. In PCV7-vaccinated children, the incidence of invasive pneumococcal disease was reduced by >90%. Not only was the effect in vaccinated children dramatic; with widespread use of this vaccine, invasive pneumococcal disease in children who had not been vaccinated and in adults of all ages also decreased substantially [9]. This phenomenon is called the herd effect [10]: vaccinating a critical number of members of a population, especially with an agent that reduces colonization and infection [11], protects those who are unvaccinated.

Responses to Polysaccharide Vaccines in Adults

Adults respond better than infants and toddlers to polysaccharide antigens. With the exception of a small proportion of genetically determined nonresponders, healthy adults predictably generate IgG antibodies to most CPS after vaccination with pneumococcal polysaccharide vaccine (PPV) [12]. Controversy persists [13–15], but most investigators agree that vaccination with the currently available 23-valent polysaccharide vaccine...
(PPV23) reduces the risk of invasive pneumococcal disease and probably the rate of pneumococcal pneumonia and/or all-cause community-acquired pneumonia by 30%–60% [16–23].

Problems with PPV are essentially 2-fold. First, much of the antibody response after vaccination is transitory. Within 1–2 years after vaccination, antibody levels decrease substantially, although they remain, on average, 2-fold higher than baseline for 5–10 years [24, 25]. It is not known what level of antibody is protective. Second, because adults become more susceptible to pneumococcal infection—with aging, debilitation, or the development of immunosuppressive conditions—their antibody levels after vaccination and/or the opsonic activity of their IgG, as demonstrated in vitro or in vivo in experimental animals, are lower than those of healthy young adults [26, 27]. Perhaps the best placebo-controlled study of PPV in older men with numerous comorbid conditions—the very patients for whom such vaccination is recommended—showed no benefit [28], although this study was underpowered and its generalizability has been questioned [29]. In contrast, persons with successful aging maintain good responses to PPV [30]. However, in an important case-control study [16], protection was demonstrated for >5 years in adults aged <50 years, but it decreased in older persons, such that no demonstrable benefit was observed in older persons >3 years after vaccination.

On the basis of all these results, clinicians and researchers agree that there is need for a better vaccine to protect older and sicker adults against pneumococcal infection. This agreement has led to consideration of the routine use of PCV in adults. A comprehensive review of PCV in adults published in 2004 [31] concluded that there was no obvious superiority of conjugate vaccine over polysaccharides vaccines in adults. In this review, we examine the available data as of 2010.

**MATERIAL AND METHODS**

We searched medical literature databases for studies of pneumococcal conjugate vaccine in adults from 1996 to the present, focusing on studies that (1) were prospective and randomized; (2) contained >2 study groups, including one that received a currently US Food and Drug Administration–approved PCV (7-valent or 13-valent) and a PPV comparator group; (3) focused on adults, including HIV-infected persons and other immunosuppressed populations; (4) measured pre- and postvaccination IgG antibody levels to CPS and/or in vitro opsonic activity (OPA) against *S. pneumoniae* surrogates for protection, no studies of protection having been reported); and (5) were published in refereed journals (Table 1).

**RESULTS**

**PCV Versus PPV in Nonimmunosuppressed Adults**

In the short term, antibody responses in adults are generally better to PCV than to PPV; IgG levels are as high or higher after PCV than after PPV, and opsonic activity is also greater. Jackson et al [32] studied healthy persons aged 70–79 years, excluding those with immunocompromised conditions. All had received PPV >5 years previously. The investigators randomized persons to receive PPV23 or PCV7 and included a dose-response study of PCV7, using .1 mL, .5 mL (the recommended pediatric dose), 1 mL, or 2 mL. In the dose-response study, 1 mL was more immunogenic than the 2 lower doses and was as effective as the 2-mL dose. Four weeks after vaccination with PPV23 or 1 mL of PCV7, IgG levels to 4 of 7 polysaccharides were significantly greater in recipients of PCV7. One year later, IgG levels had decreased substantially but still exceeded baseline for most CPS; for 2 CPS, levels after PCV were significantly higher than those after PPV. Opsonic activity, measured only at 4 weeks, was greater after PCV than after PPV for all CPS, and differences were significant for 5 of 7 CPS. The investigators concluded that “these results lend support to the concept that PCV may offer some advantages over PPV in older adults.”

In similar studies, de Roux et al [33] confirmed the findings of Jackson et al [32], and Scott et al [34] showed similar results in younger adults with a 13-valent PCV. Most recently, Goldblatt et al [35] found that results slightly favored PCV7 over PPV23 in successfully aging adults 50–80 years of age. Responses to either vaccine decreased by ~10% with each decade of life.

Dransfield et al [36] undertook a short-term study of persons aged >40 years who had chronic obstructive pulmonary disease. Fifty-two percent were vaccine naive (the rest had received PPV >5 years previously), and approximately one-half had previously documented pneumonia; relatively few had other important comorbid conditions. The results showed superiority of PCV7 over PPV23, in IgG levels and opsonic activity and in both for vaccine-naive and previously vaccinated persons. In multivariate analysis, younger age, vaccine naiveté, and receipt of PCV were associated with higher antibody levels and better fold responses.

It was not unexpected that vaccine-naive patients have higher post- to prevaccination fold increases in antibody responses. Previously vaccinated patients have higher baseline levels of IgG than do those who are vaccine naive, consistent with persistence of antibody in many individuals for >5 years after vaccination [24]. As was shown in classical studies by Heidelberger et al [37], if the peak antibody level after revaccination is no greater than the original peak and if the baseline antibody level in previously...
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vaccinated persons is higher, then, of necessity, the fold increase will be lower in previously vaccinated persons. This lower fold increase has been used to suggest that revaccinated persons are less responsive to vaccine than are vaccine-naive persons, a concept that might be misleading if, after revaccination, they were to achieve antibody levels similar to those in first-time vaccinees.

Studies cited thus far suggest that, up to 6 months after vaccination, antibody responses to PCV are at least as good as or better than those to PPV. Two other studies, however, found no differences between PCV7 and PPV23 [36, 38]. In Alaskan natives [38], a population at high risk for invasive pneumococcal disease [39], persons aged 55–70 years who had virtually identical antibody levels and opsonic activity 2 months after vaccination with PPV23 or PCV7. A PCV7 booster dose 6 months (but not 2 months) after initial vaccination stimulated a further antibody increase. Two months after final vaccination, however, levels were equivalent in those who had received and those who had not received a booster. This study suggested that revaccination at close intervals is followed by diminished antibody responses, whereas responses are better when a longer interval has elapsed. There appeared to be no lasting benefit from 6-month revaccination with PCV7. In another study involving frail older persons, Ridda et al [40] reported similar IgG antibody levels 6 months after PPV23 or PCV7 that were inversely proportional to age and frailty, as assessed by a standardized measurement.

**PCV Versus PPV in HIV-Infected Adults**

Only 2 studies comparing PPV and PCV in HIV-infected persons met our inclusion criteria. In a complex 4-arm study involving HIV-infected persons that included 2 vaccinations 8 weeks apart (PCV7-placebo, PCV7-PCV7, PCV7-PPV23, and placebo-placebo groups) [41], IgG levels and opsonic activity were similar 8 weeks after participants received an initial dose of PCV7 or PPV23. A second dose of either PCV7 or PPV23 8 weeks after PCV7 vaccination caused no further response. Persistence of antibody >2 months after the second dose was not reported. Another study involving HIV-infected adults found no difference between PCV7 and PPV23, but suggested that an initial dose of PCV7 followed by PPV23 caused a distinct booster effect [42].

**PPV and PCV in Survivors of Pneumococcal Pneumonia**

We [43] studied hospitalized patients who survived pneumococcal pneumonia, randomizing them at discharge to receive either PPV23 or PCV7. Six months later, in a cross-over design, they received the alternative vaccine. IgG and opsonic activity to the 7 PCV CPS were measured before and 1–2 and 6 months after each vaccination.

IgG levels increased significantly in response to either vaccine, and both groups achieved similar levels. Six months after PPV23, IgG antibody levels returned to baseline, whereas 6 months after PCV7, they remained significantly elevated for all 7 CPS (Figure 1), suggesting an advantage of PCV7 over PPV23.

Revaccination at 6 months, however, showed more complex results. Patients who received PPV23 followed by PCV7 had an increase in IgG level at 1–2 months that approached but did not surpass the initial peak. In contrast, those who received PCV7 followed by PPV23 appeared to exhibit a booster response, with a further increase in IgG level above the original peak [44]. However, 6 months after revaccination, mean IgG levels in both groups had returned to the original baseline. Opsonic activity closely followed IgG levels at each time point and for all CPS studied. The observed effect of revaccination was consistent with initial antigenic stimulation followed by induction of suppression because of activity of long-lived regulatory
cells. This study failed to include a group that simply received PCV7 without subsequent vaccination, which might have been the best approach [32].

Our study also stratified IgG responses based on prior vaccine status (Figure 2). Persons who had received PPV23 within the previous year had almost no response to vaccination. Those who had received PPV23 within 1–5 years responded less well than those with histories of more remote or no vaccination. Dagan et al [45] found that recent exposure to a pneumococcal serotype by simple colonization was associated with serotype-specific vaccine hyporesponsiveness. Although some investigators [32, 46] found that prior vaccination with PPV23 did not inhibit short-term responses to PCV, most of their study participants had been vaccinated >5 years previously.

**PCV Versus PPV in Transplant Recipients.**

Kumar et al [47] compared PCV7 with PPV23 in patients >3 years after renal transplantation who had stable renal function and were receiving immunosuppressive drugs. IgG responses to each capsular polysaccharide, defined as a 2-fold increase in titer and a post vaccine level of $>1 \mu g/mL$, were poor for both groups (13%–40% for PPV and 17%–50% for PCV); similar numbers of persons had a response to any serotype (80%–83%). The rate of response to PCV7 exceeded that for PPV23 only for CPS 23F. OPA results (fold increases or response rates) were not different between the groups. Three years later, IgG levels remained similar in the 2 groups of patients [48]. Similarly, in liver transplant recipients [49], there were no differences in IgG levels or OPA between recipients of PPV23 or PCV7, and there was no additional benefit of administering PPV23 after PCV7. These 2 studies suggest that recipients of solid organ transplants respond similarly to PPV or PCV and that there is no benefit to the sequential use of PCV followed by PPV. In a single study [50] involving allogeneic stem cell transplant recipients, antibody responses 6 months after vaccination with PPV23 or PCV7 were low, but they tended to be somewhat better among patients vaccinated with PCV7; in

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**Figure 1.** A, IgG to 2 representative pneumococcal capsular polysaccharides (types 6B and 19F) after patients received 23-valent pneumococcal polysaccharide vaccine (PPV23), followed 6 months later by 7-valent protein-conjugate pneumococcal vaccine (PCV7; dashed line), or PCV7, followed 6 months later by PPV23 (solid line). B, Opsonophagocytosis of *Streptococcus pneumoniae* type 6B after patients received PPV23, followed 6 months later by PCV7 (dashed line), or PCV7, followed 6 months later by PPV23 (solid line). Similar responses were observed with 6 other capsular polysaccharides studied. Reprinted with permission from Musher DM, Rueda AM, Nahm MH, Graviss EA, Rodriguez-Barradas MC. Initial and subsequent response to pneumococcal polysaccharide and protein-conjugate vaccines administered sequentially to adults who have recovered from pneumococcal pneumonia. J Infect Dis 2008;198(7):1019-27 [43]. © 2008 by the Infectious Diseases Society of America. All rights reserved.

**Figure 2.** IgG after patients received 23-valent pneumococcal polysaccharide vaccine (PPV23), followed 6 months later by 7-valent protein-conjugate pneumococcal vaccine (PCV7; A), or PCV7, followed 6 months later by PPV23 (B), with patients stratified according to prior vaccination status. The dotted line represents those who had received PPV23 within the previous year; the dashed line represents those vaccinated with PPV23 1–5 years previously; and the solid line represents those vaccinated with PPV23 >5 years previously or never vaccinated. Representative data are shown for capsular polysaccharide 6B; similar responses were observed with 6 other capsular polysaccharides studied. Reprinted with permission from Musher DM, Rueda AM, Nahm MH, Graviss EA, Rodriguez-Barradas MC. Initial and subsequent response to pneumococcal polysaccharide and protein-conjugate vaccines administered sequentially to adults who have recovered from pneumococcal pneumonia. J Infect Dis 2008;198(7):1019-27 [43]. © 2008 by the Infectious Diseases Society of America. All rights reserved.
the context of the present report, this study is difficult to interpret because stem cell donors had also been previously vaccinated with PPV23 or PCV7.

Effectiveness of PCV Versus PPV

No studies have compared the effectiveness of PCV with that of PPV in adults. However, 2 studies in HIV-infected patients, one comparing PPV23 with placebo and the other comparing PCV7 with placebo, have had similar clinical end points [51, 52]. An initial study involving Ugandan adults [51] showed no benefit and, perhaps, a deleterious effect of PPV23. In contrast, a subsequent clinical trial in Malawi documented significant protection from PCV7. In this study, survivors of pneumococcal pneumonia (mean age, 32 years) were randomized to receive PCV7 or placebo [52] and were followed up thereafter for a mean of 1.2 years. Nearly 90% of the participants were HIV infected. The rates of protection were 74% in HIV-infected persons and 73% in the entire group. Protection decreased dramatically with time, from 85% in the first year after vaccination to 25% thereafter. The reason(s) for discrepant results in these 2 studies remain(s) unknown, and it is further uncertain whether such results could be extrapolated to populations in developed countries where combination antiretroviral therapy is more readily available and the rate of pneumococcal pneumonia in the population is lower.

Safety and Tolerability

Both PPV23 and PCV7 appear to be safe in adults [19, 24, 53]. Although there is a moderately high rate of local discomfort at the injection site (redness, pain, and swelling), the discomfort is tolerable, rarely discouraging individuals from continuing to participate in ongoing studies. Younger age, healthier status, and revaccination at <1 year are associated with increased rate of local reactions.

DISCUSSION

All these data, based on measurements of IgG levels and/or opsonic activity, suggest that PCV7 is at least as good as and very likely to be somewhat better than PPV23 in inducing immunity to pneumococcal infection. Limited data on PCV13 suggest that similar results might be expected [34, 54, 55]. For either PPV23 or PCV7, persons at greatest risk of infection exhibit the poorest responses. Favoring the use of PCV is the potentially better persistence of antibody, especially because it appears that hyporesponsiveness will limit the effectiveness of a strategy based on repeated pneumococcal vaccination at close intervals. We have shown that persons who, on a genetic basis, do not respond to PPV may develop IgG to CPS in PCV [56]. A large study of PCV13 is underway in the Netherlands [57], and in the absence of any results, the manufacturer is already positioning this vaccine to replace PPV23 [58]. However, this study will not answer the essential question of which vaccine is better in adults because it compares PCV13 with placebo.

On the basis of these observations, should PCV replace PPV in adults? The principal disadvantages of PCVs are their lesser breadth of coverage and the appearance of replacement strains, non-vaccine serotypes that, with widespread use of a vaccine, emerge as common causes of pneumococcal disease [59, 60]. Although newer formulations of PCV contain up to 15 serotypes and include some that have emerged as replacement strains after PCV7 (for example type 19A), they do not include others (such as 6C). Furthermore, the widespread use of a new PCV is likely to lead to newer replacement strains, rendering the formulation of conjugate pneumococcal vaccine a moving target [61, 62]. The idea of PCV13 vaccination followed closely by vaccination with PPV23 raises all the aforementioned issues of hyporesponsiveness.

What is the cost-effectiveness of pneumococcal vaccination of adults? Studies relying on data obtained in the United States and published before 2002 estimated the incremental cost-effectiveness of PPV23 vaccination at about $3500 per quality-adjusted life year (QALY) [63]. The cost-effectiveness of PPV23 was lower in western Europe [64]. As a result of widespread vaccination of children, the incidence of pneumococcal disease in adults in the United States and Europe has decreased. A more recent study [65] using data from 2003–2004 calculated the incremental cost-effectiveness ratio of a single dose of PPV at age 65 years at $26,000 per QALY, and at age 75–80 years at >$71,000 per QALY. Vaccination at age 65 years and again at age 75 years would cost $88,000 per QALY. Since 2003, the price of PPV23 has more than doubled. At present, the price of PPV23 (Pneumovax) is $43 per dose, the price of PCV7 (Prevnar) is $84 per dose, and that of PCV13 (Prevnar13) is $103 per dose [66]. The cost of using PCV13 would double if the recommended dose for adults is twice the pediatric dose [32, 43] and would be 5 times that of the PPV23. On balance, it is likely that the cost-effectiveness of pneumococcal vaccination in general will decrease in developed countries and that the cost of routine PCV13 in adults would be prohibitive, whereas a potential benefit over PPV23 will not have been demonstrated.

CONCLUSION

With the decreased rates of pneumococcal disease in adults in developed countries, the potential for emergence of new replacement strains with conjugate vaccines; the higher cost for PCV13, compared with PPV23; and a possible preference for administering double the pediatric dose of PCV13 in adults, it is doubtful that widespread use of PCV13 in adults would be cost-effective. Although an ongoing field trial of PCV13 in adults [57] does not
include a PPV23 arm, a stunning result might provide indirect evidence to favor use of conjugate vaccine. The distinctly better outcome with PCV7 [67], compared with PPV23 [51], in separate studies and different populations of HIV-infected adults in Africa leave open to question an option favoring PCV in that population.

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