Pneumococcal Conjugate Vaccine, Polysaccharide Vaccine, or Both for Adults? We’re Not There Yet

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(See the article by Goldblatt et al, on pages 1318–25.)

There is wide acceptance that Streptococcus pneumoniae (pneumococcus) is a major cause of morbidity and mortality. With the declaration of an influenza pandemic from novel H1N1, optimizing strategies to prevent pneumococcal pneumonia and invasive disease takes on added meaning and urgency. Currently, the 23-valent pneumococcal polysaccharide vaccine (PPV23), which is licensed for use among adults and children aged ≥2 years, is recommended in some countries for universal use among elderly persons (defined variably) and in a larger number of countries for targeted use among nonelderly persons with specified underlying medical conditions. By contrast, the pneumococcal polysaccharide-protein conjugate vaccines (PCV)—of which 3 are now available (PCV7 [Prev(e)nar; Wyeth Vaccines], which is licensed in >100 countries, including the United States; PCV10 [Synflorix; GlaxoSmithKline], which is licensed in Canada and Europe but not in the United States; and PCV13 [Wyeth Vaccines], which is licensed in Chile—are labeled for use only in children. Their potential to overcome limitations of PPV23 and contribute to adult pneumococcal disease prevention remains unclear.

The article by Goldblatt et al [1] in this issue of Clinical Infectious Diseases provides comparative immunogenicity data on PCV7 and PPV23, alone or in combination, among otherwise healthy adults aged 50–80 years. Although other studies have reported similar data among mostly elderly adults with and without underlying medical conditions, this study provides results that both challenge and add to our expectations of PCV. This study has several design elements that strengthen our confidence in the immunologic findings and the policy inferences that emerge from those findings. Specifically, the study evaluated single or combined PCV and PPV23 schedules (1) across a range of age strata from 50 through 80 years, each of which was powered to detect meaningful differences in antibody responses; (2) among pneumococcal vaccine–naive healthy adults, thereby removing confounding by preceding vaccination status; (3) with follow-up through 12 months after administration of the initial vaccine dose, allowing for an understanding of vaccine effect duration. Directly comparing the findings from this study with those already published is confounded by between-study differences in study participant baseline characteristics, follow-up time, intervals of dosing, doses of vaccine administered, and comparator schedules. In spite of the mosaic of variables within and between studies, this study helps us more clearly frame the potential role, or lack thereof, of PCV alone or in combination with PPV23.

Does giving a single dose of PCV result in a “better” antibody response than giving a single dose of PPV23? Regardless of age strata, the study by Goldblatt et al [1] finds that immunoglobulin G (IgG) concentrations were greater among the PCV recipients than among the PPV23 recipients for only 3 of 7 serotypes common to the 2 products—a finding similar to other studies using either a standard [2–4] or enhanced dose of PCV [5]. By contrast, some studies have found PCV regimens to be clearly superior to PPV23, inducing higher antibody concentrations to virtually all common serotypes [2, 6]. Of these 3 comparator studies, only the study by deRoux et al [6] included subjects without previous PPV23 vaccine experience or pneumococcal disease, as in the study by Goldblatt and colleagues. Both used the licensed PCV7 formulation, so why one showed decidedly improved IgG concentrations after receipt of PCV7 while the other had less impressive results is not clear. Study design and population variations aside, we should not overinterpret the differences but instead appreciate where the findings converge. In all studies, there are at least some serotypes for
which PCV induced a greater IgG response than did PPV23, whereas the converse was true for only a very limited number of serotypes. But is this the essential issue? Apart from outbreaks or epidemic settings in which rapid achievement of the highest antibody concentration possible is desirable, the absolute height of the immediate postdose antibody concentrations is not the essential failing of PPV23. More essential is the long-term effect of PCV on the immune response to subsequent pneumococcal antigen exposure, either naturally or through PPV23. The hope has been that PCV would overcome limitations of PPV23, which include limited antibody duration, lack of immune memory induction, immunologic tolerance with repeated vaccine doses, and limited efficacy against pneumococcal pneumonia.

The data from this study are not encouraging that PCV provides a clear benefit, as measured by priming for immune memory or improved antibody duration over PPV23. The IgG antibody concentrations for all PCV7 serotypes were similar after receipt of PPV23 alone, compared with its administration 6 months after a PCV dose. This lack of booster response—and, by inference, failure of PCV to induce an immune memory response—is consistent with studies of elderly PPV23-vaccinated subjects who have been immunized with conventional and double PCV doses [2], of PCV among healthy adults aged ≥50 years [6, 7], and among persons with human immunodeficiency virus (HIV) infection [8]. By contrast, a booster response to PPV23 has been found in studies of adults immunized with a double dose of PCV following a pneumococcal disease episode [5] or with conventional doses of PCV among those with Hodgkin disease [9] or HIV infection [10, 11]. In the only study (to my knowledge) to have evaluated the booster response after administration of a range of PCV doses, only a fractional dose of PCV set up for a boost to PPV23 [2]. Not only is there inconsistency in the ability of PCV to induce memory, PCV also failed to induce persistence of antibody over time among the subjects in this study.

How can these disparate results of immune memory following PCV be reconciled? We must recognize the lack of comparability of the study populations; the studies where boosting was seen have generally been among immunologically compromised populations, whereas those where boosting has not been observed have more commonly been among otherwise immunologically intact subjects. Furthermore, the findings of this study are based on IgG antibody concentrations alone; the functional measures of antibody among adults do not always correlate well with IgG concentrations. Nevertheless, in the studies of generally healthy adults, the preponderant failure to see an antibody boost or persistence of antibody following combined PCV-PPV23 may reveal the limits of the adult immune system. A lifetime of pneumococcal exposure, through colonization and illness, may mean that no further maturation of the B cells and T cells typically induced by PCV, as seen in vaccine-naive infants and toddlers, is possible among adults. Although the adults in the study by Goldblatt and colleagues were naïve to pneumococcal vaccine, they are certainly not naïve to pneumococcal antigen.

This study and the comparative findings from other studies of PCV-PPV23 vaccine combinations illustrate the importance of disease end points in adult pneumococcal vaccine studies, because immunologic data do not provide a fully consistent, compelling, or clear story. Nasopharyngeal colonization is one biological, culture-confirmed end point that should be considered for adult studies, because it is both a functional measure of vaccine effect and a culture-confirmed end point, in contrast with most episodes of pneumococcal pneumonia.

As we consider the potential role for PCV in an adult immunization strategy, especially for pneumonia, we must consider the context in which the vaccine might be used, given the lack of clear benefit over PPV23 from a purely immunologic perspective. Assuming that adult PCV administration would only occur in a setting in which PCV is routinely used among children, what disease burden from PCV serotypes will exist given the stunning herd effects already observed? PCV7 has resulted in the virtual elimination of vaccine-serotype disease among both children and adults through its protective effect on nasopharyngeal acquisition among immunized infants and consequent reduced transmission among adults throughout the community. The additional 6 serotypes in the 13-valent PCV, whose licensure is expected in the near future, may not all behave in a similar fashion to the PCV7 types. In particular, serotype 1 is known to be rarely identified in asymptomatic colonization, yet is a significant cause of disease, particularly pneumonia; its propagation in a community may more likely be from ill persons rather than from those with asymptomatic colonization. Thus, PCV use in children may not result in reduced adult disease for those serotypes that cause little community-based carriage. For these serotypes, an argument could be made regarding the benefit of adult PCV immunization even in the context of routine pediatric PCV use, assuming that PCV was associated with some immunologic benefit beyond PPV23.

Furthermore, determining the efficacy of PCV against pneumonia in adults is critically important, and it is especially relevant in the face of the H1N1 influenza pandemic, because PPV23 is poorly protective against non-bacteremic pneumococcal pneumonia. It is disappointing that the PCV immunogenicity data do not raise great hopes for improved efficacy of PCV compared with PPV23, although our limited understanding of the intricacies in the adult immune response to PCV should give us pause. The role of PCV for adults with compromised immune systems is yet
to be adequately addressed as there are few immunogenicity studies and conflicting results. To date, the data on PCV among adults is not cause for sounding the trumpets of success, but neither is it yet sufficient to draw the curtains of failure. We should await with calm anticipation more detailed information on the functionality of the antibodies following PCV and results of the PCV impact on pneumonia to fully understand its potential for disease prevention among adults.

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References