Should 13-Valent Protein-Conjugate Pneumococcal Vaccine Be Used Routinely in Adults?

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In this issue of Clinical Infectious Diseases, Grabenstein and Paradiso present arguments favoring, respectively, continued use of 23-valent pneumococcal polysaccharide vaccine (PPV23) or adoption of 13-valent protein-conjugate pneumococcal vaccine (PCV13) for routine use in adults. These articles are written in a point-counterpoint format rather than as nuanced reviews, and it seems appropriate to examine their arguments side by side in order to place them into proper perspective.

Does PPV23 Protect Recipients Against Pneumococcal Disease?

Citing a 2008 Cochrane analysis by Moberley et al [1], Grabenstein says yes; citing a 2009 Cochrane analysis by Huss et al [2], Paradiso says no.

Moberley’s analysis found that PPV23 reduced the incidence of nonbacteremic pneumococcal pneumonia by 73% and the risk of invasive pneumococcal disease by 87%. Even with that analysis, it is worth noting that some well-done studies (eg, Simberkoff et al [3]) have shown no protection by PPV23 in the population most in need of it, such as middle-aged adults who have a variety of underlying comorbid conditions. However, because of their undue emphasis on statistical criteria, Huss et al [2] retained only a few very few articles in their final analysis of PPV23, at least 2 of which (Koivula et al [4] and Ortwist et al [5]), despite their elegant design and execution, are problematic because the diagnoses of pneumococcal pneumonia were based on methods that have not been validated or have been shown to be nonspecific [6].

Jackson et al [7] found that PPV23 protected against invasive pneumococcal disease, but they were not so certain that protection extended to nonbacteremic pneumococcal pneumonia, and a study from my laboratory [8] actually suggested the same result. But this seems to be biologically implausible. In pneumonia, the initial exudation into alveoli consists of white blood cells and plasma. It is difficult to understand how plasma antibody sufficient to protect against bacteremia would fail to opsonize bacteria within alveoli, thereby protecting the host against pneumonia. My interpretation of the clinical trials of pneumococcal vaccine, supported by a wealth of case-control studies (eg, Bolan et al [9] and Shapiro et al [10], in the finding that pneumococcal polysaccharide vaccine (PPV) effectively prevents pneumococcal pneumonia and invasive pneumococcal disease, although older and sicker persons—the ones most in need of it—are least likely to benefit. In this context, it is important to understand that the conclusions of a recently published cost-effectivity projection by Smith et al [11] relied heavily on a Delphi questionnaire in which the respondents, for whatever reason, largely concluded that PPV23 does not protect against noninvasive pneumococcal disease.

Does PCV Stimulate Better Antibody Responses Than PPV?

Paradiso states, without reference, that persons vaccinated with a conjugate vaccine “have an overall superior antibody response when compared with [those vaccinated with] pneumococcal polysaccharide vaccine.” This is simply not true. Paradiso summarizes one as yet unpublished study that shows higher antibody levels and better opsonic activity against vaccine strains after PCV13 than after PPV23. However, a very thorough recent review [12] of many earlier studies, which Paradiso does not cite, found no compelling or consistent differences in responses to PCV versus PPV. Even if the most recent study, one involving a large number of subjects, shows higher mean antibody levels after PCV than PPV, the clinical relevance of the finding would be unknown, because the protective level of antibody to pneumococcal polysaccharide is unknown.

(See the Vaccines Invited Articles by Grabenstein, on pages 255–8, and Paradiso, on pages 259–64.)
Does PCV Provide Better Protection Than PPV Against Invasive Pneumococcal Disease?
There are no studies in the general population that directly address this question. Rodriguez-Barradas et al [13] reported that PPV23 protected veterans infected with human immunodeficiency virus (HIV), and Klugman et al [14] found that a 9-valent PCV protected HIV-infected African children from pneumococcal infection. Two important studies of AIDS patients, both carried out in Africa under the leadership of Neil French, might provide an indirect comparison. One from Uganda showed no protection by PPV23 [15], whereas a more recent one from Malawi showed a substantial reduction in pneumococcal disease, especially in the first year after vaccination with 7-valent protein-conjugate pneumococcal vaccine (PCV7) [16]. It is difficult to extrapolate from these conditions to conditions in the developed world, but the results suggest that, even in the developed world, patients with AIDS might respond better to PCV than to PPV, a point not addressed by Grabenstein. Although this possibility might extend to immunocompromised hosts in general, in whom protection by PPV23 is thought to be poor, published data on antibody responses do not support it, and there certainly are no clinical data on the subject. A theoretical reason for favoring PCV in compromised hosts is that it is likely to reduce nasopharyngeal colonization by vaccine strains, whereas PPV would have no such effect.

Will PCV13 Remain Effective in Adults in Countries That Have Implemented a Vaccine Program in Children?
In my opinion, this is the most important question of them all and, like the proverbial elephant in the room, it is overlooked by Paradiso. Widespread vaccination of infants and toddlers with PCV7 has reduced the rate of pneumococcal disease due to vaccine strains in the United States by a staggering 95% [17]. Because PCV also stimulates mucosal antibody, it also is likely to prevent nasopharyngeal carriage of pneumococci. Since small children are the usual source of spread of nasopharyngeal bacteria to adults, vaccination of young children with PCV reduces the spread of these organisms to other members of the population. Thus, vaccination of young children has also been associated with a >90% decline in pneumococcal disease due to vaccine serotypes in older children and adults, the so-called indirect or “herd” effect (Figure 1) [17]. The same phenomenon will very likely by observed for serotypes in PCV13 now that this vaccine has been adopted for routine use. As a result, vaccination of adults with PCV13 may already, or soon, be irrelevant. This is the strongest argument against the routine use of PCV13 in adults, whether they be healthy or immunocompromised.

What Are Replacement Strains?
When PCV7 was adopted for widespread use, other serotypes not contained in that vaccine emerged to fill the ecological niche created by the loss of vaccine strains; these have been termed “replacement strains.” Not surprisingly, these strains also cause disease. In the United States in the past few years, Streptococcus pneumoniae types 6A, 7A, and 19A, not contained in PCV7, have emerged as common causes of disease. These types are included in PCV13 and PPV23. Although it is possible, as assumed by Grabenstein, that with widespread use of PCV13, new replacement strains will be those contained in PPV23, it is also possible that altogether new strains may emerge, not covered by any current vaccine.

Will the Forthcoming Study in The Netherlands Answer the Question of Whether PCV13 Provides Better Protection Than PPV23 in Adults?
Although this study is already being heralded with enthusiasm [18], the answer is a resounding no. Eighty-three thousand Dutch adults have been randomized to receive placebo or PCV13. I have no doubts that recipients of PCV13 will be shown to be protected against pneumococcal disease. But this study does not include a group of subjects who received PPV23, so it will not answer the question of whether PPV23 might be as effective. More importantly, the study began at a time when PCV was not recommended in children, so there will have been no suppression of PCV13 serotypes by the herd effect. Thus, even when the results are finally tabulated, they will not answer the question of

Figure 1. The rate of invasive pneumococcal disease in the United States in persons >5 years of age, showing a striking reduction in the rate of disease caused by strains contained in the 7-valent protein-conjugate pneumococcal vaccine [17]. Abbreviation: PCV7, 7-valent protein-conjugate pneumococcal vaccine.
whether PCV13 should be used routinely for adults in a country where PCV13 is widely used in children.

**Should We Look for an Altogether Different Approach to Vaccination?**

The principal advantage of the conjugate vaccine appears to be that it primes for a better immunological response with revaccination, but a multiple-vaccine approach greatly increases the cost of vaccination, and one is still left with the issue of replacement strains now that PCV13 has been adopted. With all the concerns over indirect effects and replacement strains following the use of polysaccharide vaccines, it seems appropriate to direct efforts toward developing vaccines that use highly conserved pneumococcal proteins, such as pneumolysin, surface protein A, or other surface-expressed proteins as their basis; several such vaccines are currently under study, and any discussion of new paradigms should directly address their use.

**Conclusions**

Given the choice between (1) PCV, which may be more effective than PPV23 but is directed against strains that are likely to be greatly reduced in the population; and (2) PPV23, which may be less effective than PCV13 but will provide protection against 10 other pneumococcal serotypes, I prefer to continue to administer PPV23 as part of routine vaccination policy, albeit with less enthusiasm than I did 10 years ago. I cannot see making a priority for vaccinating adults with PCV13 because the data do not show this vaccine to be that much better of an immunogen, even in compromised hosts and, more importantly, the strains contained in that vaccine are likely on their way to becoming uncommon isolates.

**References**