Pneumococcal Vaccination and Revaccination in the Elderly Population

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(See the article by Musher et al, on pages 516–524 and the article by Manoff et al, on pages 525–533, both of which are in the 15 February 2010 issue of the Journal.)

Pneumococcal disease remains a major cause of morbidity and mortality among elderly persons. Invasive infections including bacteremic pneumonia and meningitis are responsible for tens of thousands of hospitalizations and thousands of deaths in this age group each year. According to estimates from the Centers for Disease Control and Prevention, in the United States in 2008 approximately one-third of the 44,000 cases of invasive pneumococcal disease occurred among elderly persons, whereas more than one-half of the 4500 deaths were in this age group [1]. Vaccination with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) is recommended as a critical component of efforts to reduce this burden of invasive pneumococcal disease (IPD) among elderly persons [2].

PPSV23 induces a significant, serotype-specific antibody response in most elderly persons receiving the vaccine for the first time, although certain subgroups (including those with very advanced age and those with serious comorbidities or higher frailty scores) may have diminished immune responses to the vaccine [3]. Vaccination has also been found to be safe and efficacious. In a recent update to a Cochrane Collaboration systematic review, overall pneumococcal polysaccharide vaccine efficacy against invasive pneumococcal disease among adults from the 10 randomized, controlled trials included in the study was found to be 74% (95% confidence interval [CI], 56%–85%). For the subgroup of otherwise healthy adults in high-income countries (most of whom were older or institutionalized adults), vaccine efficacy was 80% (95% CI, 59%–90%). The authors also conducted an analysis of 5 observational studies that assessed pneumococcal vaccine effectiveness among immunocompetent older adults, with a pooled vaccine efficacy estimate of 68% (95% CI, 53%–78%) [4].

Although PPSV23 can protect against invasive pneumococcal disease, the duration of this protection may not be long-lasting. Antibody levels following initial vaccination in the elderly decline over time [3] and may approach prevaccination levels after ~5 years [3, 5]. Furthermore, results from a large observational study suggested that clinical protection also declines over time. In this study of 1054 persons with laboratory documented IPD and 1054 matched controls, polyvalent pneumococcal vaccine effectiveness tended to vary both by increasing age and time since vaccination. For the 64–74-year age group, vaccine efficacy was 80% (95% CI, 51%–92%) for <5 years since vaccination but only 58% (95% CI, −2% to 83%) for >3 years since vaccination. For persons aged ≥85 years, vaccine efficacy was 46% (95% CI, −31% to 78%) for <3 years since vaccination and −13% (95% CI, −174% to 54%) for >3 years since vaccination [6]. Taken together, these findings have been used to support vaccination guidelines that include a recommendation to revaccinate several groups, including persons aged ≥65 years if they were first vaccinated before the age of 65 years and if it has been ≥5 years since their initial vaccination [2].

Among elderly persons who have been revaccinated, significant antibody responses to most serotypes studied are generally observed [3]. However, the magnitude of the antibody response in some studies has been lower than after initial vaccination, raising questions about whether these adults may experience hyporesponsiveness or immune tolerance to repeated doses of these polysaccharide antigens [7]. Furthermore, few previous studies have assessed the duration of the immune response following revaccination. In one recently published study de-
signed to assess the dose response to 7-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV7) in 220 elderly persons previously vaccinated with PPSV23, among the participants who received PPSV23 (ie, those who were revaccinated with PPSV23), immunoglobulin (Ig) G antibody levels were significantly higher 1 month after revaccination for the serotypes tested but decreased toward the baseline after 1 year. Functional antibody activity levels—which are thought to be as important, if not even more important, in predicting clinical protection against pneumococcal disease—were also significantly higher 1 month after revaccination versus prevaccination levels but were not assessed thereafter. Longer-term assessments of the immune response were not conducted [8].

The study by Musher et al [9] in the 15 February issue of the Journal provides important new information about the magnitude and duration of the antibody response after vaccination with PPSV23 among middle-aged and elderly adults. One thousand eight adults aged 50–64 or ≥65 years received PPSV23 either as a primary vaccination if they were vaccine naïve or as revaccination 3–5 years after initial vaccination. IgG levels to 8 representative pneumococcal serotypes were measured at baseline, 30 and 60 days after vaccination, and then annually for years 2–5 following vaccination. The investigators found that PPSV23 was associated with significant increases in IgG levels at days 30 and 60 in all groups, compared with baseline levels. After day 60, antibody levels decreased but remained significantly higher than the baseline levels for vaccine-naive persons for years 2–5 for 7 of the 8 serotypes studied. These findings were seen among elderly persons and among younger persons, as well as for primary vaccination and revaccination groups.

A companion article by Manoff et al [10] in the same issue of the Journal provides even more detailed information about the immune response to PPSV23 revaccination versus primary vaccination in elderly study participants from the study by Musher and colleagues. In 120 randomly selected subjects aged ≥65 years, representing a subset of the larger study, the immune responses to serotypes 4, 14, and 23F (the most common serotypes causing invasive pneumococcal disease in adults at the time of study initiation) were assessed by measuring total IgG antibody levels and as functional (opsonic) antibody activity levels at baseline, 30 days following vaccination and 5 years following vaccination. Importantly, the researchers used modern, standardized assays for their measures. One-half of the subjects received PPSV23 as a primary vaccination, and one-half received it as revaccination 3–5 years after their initial vaccination. The results demonstrated significant increases in total IgG and opsonic antibody activity levels at 1 month in both the primary and revaccination groups. The year 5 antibody levels were nearly identical between the primary vaccination and revaccination groups, and the levels remained significantly higher than the baseline levels for subjects who were vaccine naïve.

These studies provide strong evidence that both primary vaccination and revaccination with PPSV23 in elderly persons result in significant and sustained increases in total IgG and functional antibody activity levels without evidence of significant hyporesponsiveness with revaccination. Despite the fact that immune correlates of clinical protection against invasive pneumococcal disease have yet to be defined, the findings of Manoff et al [10] relating to functional antibody activity levels are especially important, because it is likely that these kinds of immune responses are even more closely associated with clinical protection than total IgG levels achieved.

When the study by Manoff et al [10] was initiated in 1997–1998, serotypes 4,14, and 23F were important causes of IPD in adults. However, the epidemiology of IPD in adults has changed dramatically with the introduction of PCV7 into pediatric populations in 2000. Herd immunity effects have resulted in a dramatic decline in PCV7 serotypes, including 4, 14, and 23F in adults. Recent data suggest that replacement serotypes not included in PCV7, such as 19A, are now much more common and important causes of IPD in adults [11]. Because immune responses to the PPSV23 antigens are serotype specific, some caution must therefore be used in concluding that functional antibody responses to other PSV23 vaccine antigens would be similar to the responses to serotypes 4, 14, and 23F that were evaluated in this study.

In 2008, only 60% of elderly persons in the United States had received at least 1 pneumococcal vaccination [12], a level well below the national goal of 90%. Limited data suggest that rates of revaccination according to national guidelines are much lower [13]. The present studies demonstrate a robust and durable immune response not only with primary PPSV23 vaccination but also revaccination. These findings, along with previous studies demonstrating that PPSV23 clearly prevents IPD, should encourage providers to enhance efforts to ensure that their elderly patients are fully immunized against pneumococcal disease.

References

5. Torling J, Hedlund J, Konradsen H, Ortvist A. Revaccination with the 23-valent pneumococcal polysaccharide vaccine in middle-


