A Pain in the Ear: What Has the 7-Valent Conjugated Pneumococcal Vaccine Done to Reduce the Incidence of Acute Otitis Media?

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(See the article by McEllistrem et al. on pages 1738–44)

Acute otitis media (AOM) remains one of the most common diagnoses in ambulatory pediatric practice. In the United States, cephalosporins and penicillins are frequently prescribed for children with this diagnosis to prevent the short-term suppurative complications of bacterial AOM, because such therapy has been shown to be safe and effective for this indication [1]. Although curative in some of these patients, such antibiotic use selects Streptococcus pneumoniae (and other bacterial) variants that are resistant to these antibiotics. A decrease in the incidence of AOM due to the use of vaccines against relevant bacteria and viruses would be expected to result in decreased use of these antibiotics and decreased selective pressure.

Many of us hoped that the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7 [Prevnar; Wyeth Lederle Vaccines]) to young infants would reduce the incidence of AOM. This hope was tempered by evidence that this reduction would not be large; only 20%–30% of cases of AOM in the United States are associated with middle ear specimens that grow S. pneumoniae on culture [2]. Approximately 70% of children with S. pneumoniae-related AOM had S. pneumoniae serotypes contained in or closely related to serotypes contained in PCV7 [3]. At best, then, we expected an overall risk reduction of ~20% for AOM among US children who completed the PCV7 vaccination course. Among 37,868 infants randomly assigned to receive either PCV7 or meningococcus type C conjugate vaccine in California, those receiving PCV7 experienced a 7.8% relative risk reduction in clinically diagnosed cases of AOM (95% CI, 5.2%–10.5%), and a 20% relative risk reduction in the placement of ventilatory tubes (95% CI, 3.6%–34.1%) [4]. Investigators in Finland found a 6% relative risk reduction in AOM among 831 infants receiving PCV7, compared with 831 receiving hepatitis B vaccine [5]. The 95% CI for the protective efficacy of the vaccine against AOM in this study was −4% to 16%. This has been interpreted as an indication that vaccine use might actually increase the frequency of AOM. This has some biological plausibility, because the increase in the incidence of AOM attributable to S. pneumoniae serotypes or to other otopathogens not contained in the vaccine might be greater than the decrease in the incidence of AOM attributable to S. pneumoniae serotypes contained in PCV7. Thus, these non-PCV7 serotypes would substitute for the eliminated vaccine strains and produce the same or greater incidence of AOM. More likely, the large 95% CI in the Finnish study was directly due to the small sample size, combined with the modest size of the relative risk reduction for AOM attributable to immunization with PCV7 [5]. In the California study, the large sample size narrowed the 95% CI and showed a 97% probability that the relative risk reduction was ≥5.2% [4].

However, probabilities are just that, and concern remains about the overall impact of immunization with PCV7 on AOM as US infants with greater geographic and genetic diversity are vaccinated. Will the incidence of AOM due to S. pneumoniae strains not contained in PCV7 increase because these strains substitute for those reduced in prevalence by the vaccine? Will the net result be no change or even an increase in the incidence of AOM? Alternatively, will these nonvaccine serotypes simply persist? The proportions of nonvaccine serotypes that are cultured from middle ear fluid would predictably increase, compared with the proportion of vaccine serotypes. But, these cultures...
would come from fewer cases of AOM, because the overall incidence of AOM would decrease as more children were protected against AOM caused by PCV7 serotypes. Or would other bacteria, such as *Moraxella catarrhalis*, non–group B *Haemophilus influenzae*, or *Streptococcus pyogenes*, substitute for the *S. pneumoniae* serotypes reduced or eliminated by increased numbers of children with anti-pneumococcal antibodies [6]? On the other hand, widespread immunization with PCV7 might reduce the incidence of AOM more than expected, because it reduces nasopharyngeal carriage of vaccine strains, which would likely reduce transmission of these serotypes to unvaccinated individuals [4, 7].

The study by McEllistrem et al. [8] in this issue of Clinical Infectious Diseases capitalizes on results of ear cultures done over a 4-year period that straddled the mass introduction of PCV7 in the United States. It provides the first look at the distribution of *S. pneumoniae* serotypes in cohorts of children referred for spontaneously draining AOM or for tympanostomy tube placement to geographically dispersed centers in the United States.

The good news is that the frequency of referral for spontaneously draining ears and for tympanostomy tube placement did not increase after the introduction of PCV7. McEllistrem and colleagues are careful to note that this is not a population-based study, and we cannot really conclude that the incidence of AOM decreased after introduction of the vaccine.

As expected, the proportion of vaccine serotypes recovered from these fluids decreased in the 2 years after the introduction of PCV7, but there was an annoying exception: serotype 19F. This is the serotype most often isolated from children with AOM in the United States. However, these children were selected on the basis of disease severity and referral. Their immune response to the vaccine may not be typical of children their age [9]. However, a persistence of the 19F serotype in spontaneous drainage fluid from infants with AOM in California [4] and in aspirated middle ear fluid from infants with AOM in Finland [5] suggest that this is a typical situation for this *S. pneumoniae* serotype. A better understanding of the circulating anti-capsular antibody concentration and the local immunity to this serotype would be useful [10, 11]. Could an additional oral or nasal vaccine administered to increase mucosal immunity to pneumococcal strains be useful?

Recommendations for empirical treatment of children with AOM rely on estimates of the incidence of AOM due to penicillin-nonsusceptible *S. pneumoniae* and other bacteria. In the United States, practitioners do not routinely tap the tympanic membranes of ears in patients with AOM and culture the contents. The community of pediatric health care professionals must rely on results of cultures of fluid collected from spontaneously ruptured tympanic membranes, during surgical drainage, and from the nasopharynx. These sources may not have the same distribution of bacteria as that of fluids collected from the middle ears of the population of children with AOM. As noted in prior studies, the prevalence of penicillin nonsusceptibility tends to be higher among the PCV7 serotypes.

The study by McEllistrem and colleagues [8] also provides encouraging news about the frequency of penicillin nonsusceptibility, which did not increase over the 4 years of the study period. The highest frequencies were found consistently among the strains included in the vaccine. Thus, increased use of the vaccine might reduce the incidence of strains that are penicillin nonsusceptible. The authors note that, in spontaneously draining ears, the proportion of penicillin-nonsusceptible pneumococci among the PCV7 serotypes increased from 60% before vaccine introduction to 94% after its introduction. There is not sufficient information presented to understand what might be happening here, although this finding is still within the 95% CIs for the reported frequency of penicillin nonsusceptibility among the PCV7 serotypes [12].

The bad news is that penicillin resistance is not a small problem. In the group of referred patients described by McEllistrem et al. [8], 31%–41% of all serotypes were determined to be penicillin resistant by the NCCLS microbroth dilution method (penicillin MIC, ≥2 µg/mL). These children likely represent a population with repeated antibiotic exposure and selection of their microbial flora. Nevertheless, this rate of penicillin nonsusceptibility is quite high.

Such studies as these are likely the best we will have to assess risk and benefit of PCV7 as it pertains to AOM in the United States and to inform our decisions about empirical antibiotic treatment of AOM. Of importance to children and to pediatricians in the United States would be geographically dispersed, sentinel sites that would perform routine population-based surveys of AOM to track the overall impact of vaccines as they are first introduced. This is necessary to assess the impact on the incidence of AOM among recipients of the newer pneumococcal vaccines [13] and the impact of changing immunization practice recommendations. For example, the new recommendation of immunizing infants and children annually against influenza may substantially reduce the overall incidence of AOM [14]. Perhaps sites such as those participating in the Centers for Disease Control and Prevention’s Emerging Infections Consortium would be able to link population-based information about AOM with the microbiologic data from established referral sites, such as those described by McEllistrem et al. [8].

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References