Pneumococcal Conjugate Vaccine: Are 3 Doses Equal to 4 Doses?

After the introduction of routine infant immunization with 7-valent pneumococcal conjugate vaccine (PCV-7), the United States has witnessed a 74% decline in the number of children <5 years of age diagnosed with invasive pneumococcal disease (IPD) and a 30% decline among all age groups.1 Likewise, rates of pneumonia- and otitis media-related medical visits among children, hospitalizations for pneumonia among children and young adults, and procedures for insertion of tympanostomy tubes also decreased.2 Because of increases in IPD owing to pneumococcal serotypes not included in the vaccine, 13-valent pneumococcal conjugate vaccine replaced PCV-7 10 years later.3,4 Although a major public health accomplishment, the current 4-dose 13-valent pneumococcal conjugate vaccine series administered at 2, 4, 6, and 12 to 15 months of age is now the most expensive vaccine series in the routinely recommended immunization schedule for persons 0 through 18 years of age.5

In this issue, Stoecker et al describe the cost savings if the United States adopted a reduced 3-dose pneumococcal conjugate vaccine (PCV) (2 + 1) schedule, as is recommended in many other countries.6 They suggest that possible increases in observed morbidity and mortality resulting from adoption of a reduced schedule could be mitigated by increasing vaccine coverage. Another option for a reduced schedule is 3 + 0; this regimen gives greater early protection but without the benefit of a booster dose (although the booster dose greatly enhances antibody response, there are no clinical differences documented to date). The 3 + 0 vaccine schedule is found in a few countries where vaccination after 9 months becomes less reliable.7

There have been 2 recent reviews of reduced immunization schedules for PCV. Both reviews note the variation by serotype in the immune response after the first 2 versus the first 3 doses.8,9 For most serotypes there are only modest reductions in the immune response after 2 doses; however, for serotypes 6B and 23F the diminution in immune responses is more significant. The World Health Organization estimated that an antibody concentration of 0.35 μg/mL for all PCV-associated serotypes correlates with clinical efficacy against IPDs related to that specific vaccine serotype.10 Although believed true for IPD, the antibody concentration correlating to protection from pneumonia or otitis media remains unknown. Interestingly, in a prelicensure immunogenicity study for PCV-7, responses to serotypes 6B and 23F did not achieve the 0.35 μg/mL concentration after 2 doses but did after 3, thus providing the rationale for the 4-dose series.11 These data further suggest that children receiving only 2 primary doses would remain vulnerable to infection owing to these serotypes and hence would need to rely on herd immunity for protection until receiving a boosting dose at 12 months of age.
Despite somewhat reduced immunogenicity, in observational studies reduced-dose regimens have been shown to be effective at preventing otitis media, pneumonia, and IPD. However, in 1 study examining effectiveness of a reduced-dose regimen at preventing lower respiratory tract infections, there was some suggestion that a reduced-dose regimen may confer less protection during the first year of life. Furthermore, in the study assessing effectiveness of vaccine at preventing IPD, there were 2 cases of IPD reported after 2 doses, whereas there were none reported after 2 doses plus a booster. Additional randomized controlled trials comparing the effectiveness of the 3- versus 4-dose regimens are lacking.

Lastly, Stoecker et al argue that modest increases in vaccine coverage could prevent the potential increase in the number of disease cases. Although true, achieving these increases may be difficult. Whereas coverage for 4 or more doses of PCV for children aged 19 to 35 months increased during the period between 2007 and 2011, the 84.4% coverage reported for 2011 is now comparable to the 4-dose coverage level for diphtheria, tetanus, and acellular pertussis vaccine. Diphtheria, tetanus, and acellular pertussis vaccine coverage remained stable during the same time period, suggesting that improving coverage rates for PCV may be a challenge.

In looking back, the driving force behind the recommendation for PCV-7 was its remarkable efficacy at preventing IPD and devastating sequelae such as meningoitis, neurologic complications after meningitis, and death. Efficacy estimates with respect to the prevention of less serious infections such as pneumonia and otitis media were realized to be more modest. Ironically, as the authors point out, the majority of cost savings for PCV are related to reductions in costs for treating very frequently occurring infections, such as otitis media, rather than less commonly occurring but more serious life-threatening IPD. Before contemplating a switch to a 3-dose series, it is important to remember the most serious diseases that PCV prevents and assure that the dosing schedule ultimately chosen is up to the challenge of preventing these infections.
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