A Tale of 2 Pneumococcal Vaccines

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(See the Major Article by Ochoa-Gondar et al on pages 909–17 and Angoulvant et al on pages 918–24.)

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Pneumonia is the leading infectious cause of death in all age groups. After 4 decades with just a single bacterial vaccine to prevent the disease, we now have conjugate pneumococcal vaccines licensed across most age groups to complement the 23-valent pneumococcal polysaccharide vaccine (PPV23), which has been the mainstay of efforts to protect persons aged >2 years from pneumococcal infections.

Two articles in the current issue of Clinical Infectious Diseases from authors in adjacent European countries advance our knowledge on the effectiveness of these vaccines, although the clarity of their messages are starkly different.

From Angoulvant et al in France [1], we see the extraordinary effectiveness of the 13-valent pneumococcal conjugate vaccine (PCV13) just a year after introduction when given to infants without any catch-up program for older children. In an observational effectiveness study dedicated to the late Edouard Bingen, a giant in pediatric microbiology in France, his colleagues used PCV13 introduction to illustrate vaccine effectiveness and to provide insight into the pneumococcal etiology of community-acquired pneumonia (CAP) and empyema in children. Their article contains at least 5 interesting messages.

First, they observed a rapid (within a year) reduction of 31% among nearly 2000 radiographically-confirmed pneumonias in the target age group of children <2 years seen in the emergency rooms of 8 hospitals across France. This study illustrates that surveillance of radiographically-confirmed pneumonia in a limited number of hospitals is a useful measure of PCV effectiveness, beyond surveillance for invasive pneumococcal disease (IPD) alone. The impact of PCV13 on IPD was recently demonstrated in a similar study in 8 US hospitals [2]. The observed reduction of several hundred episodes of radiographically-confirmed pneumonia in the French study contrasts with the small (4%) yield of pneumococcal cultures from blood from these patients and makes the argument that the evaluation of PCV impact may be possible in developing countries without microbiology facilities if radiography can be provided and performed in an adequate fashion with surveillance in place at emergency rooms of large urban hospitals.

Second, the data on empyema provide considerable insight into the etiology of empyema in children. Not only were polymerase chain reaction–based diagnostics useful to diagnose pneumococcal empyema, but a >50% reduction in empyema was seen within a year of PCV13 introduction. As the vaccine adds just 6 (albeit important) additional serotypes, with population coverage estimated at 92% and individual protection not complete (a case of vaccine failure leading to CAP with pleural effusion is described in the paper), their observed percentage reduction is consistent with a pneumococcal etiology in a significant majority of cases of pediatric empyema.

The age of children presenting with radiographically-confirmed pneumonia increased during the study. This observation is not discussed in the article but represents an interesting possibility that PCV given to infants will shift the age of admission for pneumonia in children to higher ages, hopefully reducing morbidity.

The data suggest herd protection in children 2–5 years of age who were not vaccinated. This would be a very quick herd effect given the lack of catch-up, but it is biologically plausible given the high rates of vaccination among children <2 years of age.

Finally, it is worth noting that only 2 isolates were 7-valent pneumococcal conjugate vaccine (PCV7) strains, suggesting that these strains may be close to elimination among children in France.

As an observational study without a control group, the French study has significant limitations, but the excellent microbiology and serotype-specific
reductions seen in the invasive disease surveillance are indicative of a causal effect. However, it should be remembered that the baseline pre-PCV13 year was 2009, which coincided with the H1N1 influenza pandemic, so the reductions seen in just a year after PCV introduction may have been influenced by a particularly high baseline and by rather less influenza activity in the subsequent years. There are both randomized efficacy trial [3] and observational effectiveness data [4] to indicate that influenza activity will increase pneumococcal CAP hospitalization in children.

The second article, from Ochoa-Gondar et al in Spain [5], on the surface represents a more robust observational study in that all persons were followed prospectively in a health system from which considerable health and risk factor data are available. In addition, the authors also made an admirable attempt to document the microbiological etiology of pneumonia, this time among adults aged >60 years of age. Unfortunately, the take-home messages are fewer, as the initial multivariate analysis failed to find any benefit of PPV23 in this population. In a sensitivity analysis, it appears that recent administration of PPV23 (<5 years before the start of the study) did provide benefit, if not against mortality (not listed in this analysis), then against all forms of pneumonia, including a 25% reduction in all-cause pneumonia. This reduction was not apparent if individuals who received PPV23 >5 years before the start of the study were included in the immunized group; indeed, they were included in the unimmunized group. These data are hard to interpret because there were so many differences in risk factors between those immunized and unimmunized (including a massive difference in influenza immunization). In fact, another recent and similar observational study from Europe (this time in Germany) concluded that influenza vaccination rather than PPV23 reduced presumed bacterial CAP severity and mortality [6]. Nonetheless, the stratification of PPV efficacy by time since vaccination makes sense for a T-cell-independent vaccine that lacks a mechanism for long-term boosting of the immune response; indirect cohort data for this vaccine also suggest rapid waning of protection in older age groups [7]. The authors suggest 5 yearly repeat vaccinations, but given that efficacy and antibody responses reduce with age, there are no recommendations, at least in the United States, for multiple doses in individuals aged >65 years.

So we have a tale of 2 vaccines, one demonstrating increasing evidence of effectiveness, including herd protection, and the other providing at best limited protection in a subset of vaccinees for <5 years. This leads to a discussion of duration of protection of pneumococcal vaccines. The duration of individual protection from disease and impact on carriage of PCV can best be assessed from randomized trials in countries in which the vaccine was not immediately introduced so that individual protection could be measured in a setting in which vaccine serotypes were not disappearing. One such study from South Africa suggested that protection may wane after 5 years, particularly in children infected with human immunodeficiency virus [8, 9]. The key to long-term population effects of these vaccines is that conjugates, by interruption of carriage, if given to the key transmitters of infection can induce long-term population-based protection. This almost certainly will apply to other infections for which there are both conjugate and polysaccharide vaccines, such as vaccines for meningococcal and Haemophilus influenzae type b disease prevention and Vi capsular vaccines for typhoid fever.

Long-term protection in all age groups from hospitalized pneumonia has recently been confirmed after PCV7 introduction in the United States [10]. The study from Spain, in its most optimistic interpretation, does not suggest that we can rely on unconjugated polysaccharides for long-term immunity. The days of such unconjugated polysaccharide vaccines as a public health tool to reduce the burden of pneumococcal pneumonia in populations, are, in my view, numbered, and their utility is confined to individual protection for some at-risk populations.

**Note**

_Potential conflicts of interest._ Author certifies no potential conflicts of interest.

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