Serotype Replacement in Invasive Pneumococcal Disease: Where Do We Go from Here?

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(See the article by Hicks et al., on pages 1346–54.)

Conjugate vaccines have been an impressive addition to our arsenal of weapons against infection. Polysaccharide antigens alone are not good at eliciting a long-lasting immune response, particularly in infants as maternally derived immunity wanes. By coupling or conjugating polysaccharide antigens to protein antigens, we can effectively draw them to the immune system’s attention, allowing us to target bacterial pathogens expressing polysaccharide capsules, such as Neisseria meningitidis and Haemophilus influenzae, and, just as importantly, to do so in the vulnerable pediatric host population [1]. In 2000, a pneumococcal conjugate vaccine (PCV7) was introduced against Streptococcus pneumoniae, the pneumococcus, covering 7 of the serotypes most commonly recovered from patients with invasive disease in the United States. In early trials, PCV7 demonstrated >95% efficacy against invasive disease due to vaccine serotypes [2]. Given the leading role of the pneumococcus in infant meningitis and other life-threatening diseases, not to mention its contribution as a cause of less severe but common conditions, such as otitis media (for which the efficacy of PCV7 was significant but much lower than that for more-severe conditions), it was all but inevitable that the new advance would be greeted with wild enthusiasm. The vaccine has been such a turning point in preventing pneumococcal disease that it is now commonplace to refer to the prevaccine and postvaccine “eras” [3–6].

Despite its undoubted success, PCV7 covers only 7 of 91 pneumococcal serotypes (including the recently discovered 6C [7]) and conspicuously does not include highly invasive serotypes common in developing and some industrialized countries (e.g., serotype 1 [8]). By targeting a small subset of serotypes, we have begun a vast ecological experiment. In short, we have created a vacant niche, which may be filled by pneumococcal serotypes not included in PCV7. This phenomenon of “serotype replacement” is clearly occurring in pneumococcal carriage and can be observed in some types of pneumococcal disease [9, 10]. An important issue is the extent to which this replacement phenomenon will be carried over into invasive disease.

In this issue of the journal, Hicks et al. [5] use data from the Centers for Disease Control and Prevention’s Active Bacterial Core surveillance program to report from the front line, showing evidence that replacement is indeed occurring but that, for the moment at least, it is having little effect on overall levels of invasive disease.

With good reason, Hicks et al. [5] chose to concentrate on the vulnerable patient populations of children aged <5 years and adults aged ≥65 years. The study period (1998–2004) conveniently straddles the interval over which the vaccine has come into widespread use since its introduction in 2000. The effect of PCV7 has been dramatic: for children <5 years old, the rate of invasive pneumococcal disease due to vaccine serotypes decreased from 78.9 to 2.7 cases/100,000 population between the prevaccine years and 2004. A similar though less striking decrease occurred in older adults, which has been hypothesized to be due to a herd effect [6].

This success is not particularly surprising. We already know that PCV7 is highly effective. The issue of pressing interest is the effect of the vaccine on nonvaccine serotypes in invasive disease. Are they increasing? Indeed it is, but the increase (though significant) is puny in comparison to the decrease in the incidence of disease due to vaccine serotypes. For children aged <5 years, the rate increased from 16.3 to 19.9 cases per 100,000 persons during the study period; for adults aged ≥65 years, the rate increased from 27 to 29.8 cases per 100,000 persons.

Nevertheless, the outlook is not quite...
as rosy as it might initially appear. Hicks et al. [5] report a significant, incremental year-to-year increase in the incidence of invasive disease due to several nonvaccine serotypes. More serotypes are identified as expanding among older adults, and Hicks and colleagues report rather tenuous evidence that this age group may be benefiting from additional protection due to the 23-valent polysaccharide vaccine, which was used prior to the conjugate-vaccine era. However, we have identified a core group of organisms—serogroup 15 and serotypes 19A and 33F—common to both age groups. It is becoming clear from the work of Hicks et al. [5] and others that these serotypes will be among the major players in the postvaccine era. Another, serotype 3, was identified as causing an increasing incidence of invasive disease in children but not older adults (possibly because of the additional protection mentioned above). In both age groups, serotype 19A is a particularly prominent cause of disease and becoming more so.

Serotype 19A strains were relatively common inhabitants of the nasopharynx before the introduction of PCV7 and were not an especially infrequent cause of disease. In fact, it was initially hoped that cross-protection by the vaccine, as a result of the inclusion of serotype 19F, would offer additional benefits against serotype 19A. Although disease due to the other major “vaccine-related serotype” (serotype 6A) has decreased precipitately since the introduction of PCV7 (at least among children), such hopes have been clearly misplaced for serotype 19A. Hicks et al. [5] explain the success of serotype 19A as follows: the high frequency of carriage during the prevaccine era means that this serotype was in an excellent position to benefit from the niche unveiled by PCV7 introduction. Moreover, because serotype 19A shows a significant association with invasive disease, in contrast to serotype 23F (which is less invasive [11] but included in the vaccine), any increase in serotype 19A carriage would be expected to result in increased representation among patients with invasive disease. This serotype is also found in association with several distinct antibiotic-nonsusceptible clones, which are now expanding [4]. Moreover, clones previously associated with vaccine serotypes are now reappearing, having acquired serotype 19A capsular loci [12]. These seem to be quite rare, for the moment, but you would have to be brave to wager that this will remain the case.

The factors governing serotype replacement are beginning to become clear. First, the frequency of carriage of the replacing serotype must increase. If the serotype in question is readily able to cause disease, then replacement in disease will occur. This explains why replacement is particularly evident in contexts such as otitis media [10, 13] and in invasive disease in adults with HIV/AIDS [3], for which there are relatively small differences in the tendency of different serotypes to cause disease. This is in marked contrast with the characteristics of invasive disease in the host populations studied by Hicks et al. [5].

Given our improved understanding of how the pneumococcus is responding to vaccine pressure, can we speculate about future trends? One important question is how quickly after vaccination the pneumococcal population reaches a new equilibrium. The incremental changes over time could be explained by the bacterium responding to vaccine pressure relatively slowly, or they could be due to an increasing rate of vaccination. If it is the latter, then we might predict relatively few changes once the rate of vaccination reaches a plateau. If it is the former and there are ongoing changes in the pneumococcal population that have yet to run their course, then we must prepare for further increases in the prevalence of these and possibly other serotypes. Disentangling these 2 factors will require a robust mathematical model of serotype replacement along with good data from continued surveillance. Although pneumococcal disease, particularly invasive disease, is what we are most interested in, carriage should not be neglected. For example, we have evidence that the increases in serotype 19A and serogroup 15 disease may be largely explained by increases in the prevalence of carriage of these organisms. What of the other serotypes? In the main, we know little of how likely these are to cause disease—they were just too rare in the prevaccine era to appear much in surveys of carriage or disease. If any of these serotypes are highly invasive, then any increase in carriage would be worrying.

A final and sobering comment on the postvaccine era is that, at least in this study [5], although there was a dramatic decrease in hospitalizations for invasive pneumococcal disease, this did not result in a lower overall mortality rate among children under 5 (7 deaths in 1998, compared with 8 deaths in 2004). The numbers are naturally small but are still surprising, given how good the vaccine is. They are explained by a higher case-fatality rate for disease due to vaccine and non-vaccine serotypes. The reasons for this are obscure. Hicks and colleagues speculate that it could be due to a higher rate of comorbid conditions in 2004, but since they do not present these data for 1998, this possibility is hard to assess.

Although there are reasons to be less than sanguine about the continued effectiveness of PCV7, this is no reason for failing to urge its use. Even in 2004, with serotype replacement at its most advanced, the overall rate of disease was a fraction of that prior to the introduction of the vaccine. There is no evidence that these benefits will be overturned in the near future. Although new conjugate vaccines are in development that will incorporate additional serotypes, including some prominent causes of replacement as discussed here, as well as those causing disease in developing countries, this is no long-term solution. It addresses the immediate problem with another ecological experiment. But it will buy us time to develop a vaccine based on an antigen (or antigens) common to all serotypes. For now, the present
vaccine is the best one we have. What seems certain is that the postvaccine era will be an interesting one.

Acknowledgments

I thank Christophe Fraser and Brian Spratt for discussions and comments on the manuscript.

References