Emergence of Nonvaccine Serotypes following Introduction of Pneumococcal Conjugate Vaccine: Cause and Effect?

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(See the article by Muñoz-Almagro et al. on pages 174–82)

Since the 7-valent pneumococcal conjugate vaccine (PCV7) was first introduced in the United States in 2000, there has been great interest in understanding its clinical and public health impact. Early reports after the introduction of PCV7 revealed striking reductions in the incidence of invasive pneumococcal disease (IPD) throughout the United States, not only among the population targeted for vaccination, but also among persons too young or too old to receive the vaccine [1–3]. These changes were so dramatic that long-standing disparities in the incidence of IPD among certain racial and ethnic groups were substantially reduced [4, 5]. The incidence of more-common manifestations of pneumococcal disease, such as otitis media [6] and hospitalizations for pneumonia [7], has also decreased, providing evidence of a much broader public health impact. Epidemiological studies have shown the vaccine to be highly effective in practice [8, 9], with efficacy similar to that measured in clinical trials [10, 11]. Over the past few years, more countries have adopted PCV7 as part of their routine vaccination programs, and the demand for information from these populations has grown.

Determining which trends in disease incidence are attributable to vaccine introduction and which are unrelated is not simple. In contrast to interpreting the results of randomized, controlled clinical trials, in which potential confounders are (ideally) randomly distributed between 2 study groups, the evaluation of PCV7 impact on pneumococcal disease following routine introduction is prone to ecological bias [12]. In other words, although changes in disease patterns occur after vaccine introduction, vaccine introduction is not necessarily responsible. Pneumococcal disease incidence varies somewhat from year to year, and the distribution of pneumococcal serotypes can change as different strains pass through a community. Such natural fluctuations can appear large if the population studied is relatively small or is limited to 1 area. In addition, changes in the workings of a surveillance program or changes in provider practices, such as the use of blood cultures to detect pneumococcal bacteremia, can greatly affect measured disease incidence.

It is against this backdrop that studies like the one published in this issue of Clinical Infectious Diseases [13] attempt to describe the population-level effects of introducing PCV7. Muñoz-Almagro et al. [13] document their experience at Sant Joan de Deu Hospital, a pediatric hospital in Barcelona, Spain, by comparing rates of IPD during the pre-PCV7 period (1997–2001) with those during the period after the introduction of PCV7 (2002–2006). PCV7 became available in Spain in June 2001 and was recommended for children at the ages of 2, 4, and 6 months, with a booster in the second year of life. However, the vaccine was not subsidized by the Spanish Health Service, and vaccine uptake was relatively slow. Muñoz-Almagro and colleagues used data from children enrolled in a nasopharyngeal colonization study to estimate a coverage of 36% in 2005 [13]; other Barcelona investigators estimated that 22%–34% of children received at least 2 doses of vaccine during the period 2004–2005 [14]. Because no children were vaccinated until the second half of 2001, vaccine coverage for the reported period of observation was low—perhaps too low to show substantial effect in the population.

One way to strengthen the argument that observed trends may be related to vaccine introduction is to look for effects on disease caused by the 7 serotypes included in the vaccine, especially among the target age group—young children. One reason that the findings of Muñoz-Almagro et al.
[13] do not support a direct effect of PCV7 is that rates of IPD caused by PCV7 serotypes decreased relatively little among children targeted for vaccination. Another, perhaps more important, reason is that they observed a phenomenon not seen in any other setting where PCV7 has been introduced, including elsewhere in Spain: after vaccine introduction, the overall rate of IPD among children aged <2 years was almost 60% higher than the prevaccine rate. Other investigators in Spain have shown either no change [14, 15] or modest reductions [16] in the overall incidence of IPD among children in the targeted age group. How might these differing observations be explained?

Early trials of pneumococcal conjugate vaccines documented rapid changes in the serotypes colonizing the nasopharynx in children receiving study vaccine but not in those receiving control vaccines [17, 18]. This phenomenon, known as serotype replacement, raised concern that similar changes in the serotypes causing invasive disease could occur following routine vaccine introduction. Recent data from Alaska Native children showed that increases in the incidence of IPD caused by non-PCV7 serotypes during the PCV7 period drove overall rates of IPD toward—but not beyond—pre-PCV7 levels, and rates of IPD among the non-Native Alaskan population remained persistently low [19]. Among the general US population, the increase in the rate of IPD caused by non-PCV7 serotypes following PCV7 introduction has been small, relative to the reduction in disease caused by vaccine serotypes [20]. On the basis of the unique experience among Alaska Natives, the more modest increases in non-PCV7 serotypes seen elsewhere, and the small reduction in vaccine-type disease reported by Muñoz-Almagro et al. [13], rapid serotype replacement is an unlikely explanation for the dramatic increases in overall rates of IPD.

If PCV7 is not primarily responsible for the observations of Muñoz-Almagro et al. [13], what are some alternative explanations? Changes in clinical practices may be one explanation. In the absence of vaccine introduction, increases or decreases in blood culturing practices can artificially inflate or reduce the apparent incidence of invasive disease [21]. Muñoz-Almagro et al. [13] evaluated this possibility by comparing the total number of blood cultures performed at their hospital and the proportion of cultures yielding pneumococcus before PCV7 introduction with that after PCV7 introduction. Although the increases observed were not statistically significant, the investigation may have lacked sufficient power to show such a difference. Indeed, the incidence of occult bacteremia among children aged <2 years—with occult bacteremia being the syndrome most likely to be detected by expanded diagnostic testing—increased from 14.5 episodes per 100,000 population to 21.4 episodes per 100,000 population; the increase accounted for a substantial proportion of the overall increase in IPD. Changes in surveillance methodology (e.g., reporting patterns) can also dramatically affect reported trends in pneumococcal disease.

Secular trends in pneumococcal disease may, in part, explain the reported findings. The distribution of pneumococcal serotypes is known to change over time [22]. The authors noted an increase in the incidence of empyema from 2.2 episodes per 100,000 population to 9.2 episodes per 100,000 population. Although not stated in the article, the increase in the incidence of empyema might be related to the emergence of serotype 1, a common cause of childhood empyema in communities with [23] and without [24–29] conjugate vaccine introduction. Other secular trends have been observed in various geographic locations [30, 31], including Spain [32]. Because such trends tend to occur relatively slowly, a paradoxical weakness of long-term ecological studies is that they increase the likelihood of capturing such events, irrespective of vaccine introduction. These changes would be even more pronounced in small populations, in which the overall burden of pneumococcal disease is relatively small at baseline.

The findings of Muñoz-Almagro et al. [13] are intriguing and useful, because they provide further insight into the epidemiology of IPD in Spain at a time when PCV7 was first being introduced; these data will form an important baseline against which to measure future trends. The article also highlights some of the challenges in measuring vaccine impact. With time and more data from Spain and elsewhere, we will gain a greater understanding of the benefits and limitations of PCV7 use and of the optimal methods for tracking vaccine impact.

Acknowledgments


References

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