Use of Pneumococcal Conjugate Vaccine to Decrease Rates of Bacterial Meningitis

Ron Dagan
Pediatric Infectious Disease Unit, Soroka University Medical Center, Beer-Sheva, Israel

(See the article by Tsai et al. on pages 1664–72)

Bacterial meningitis is a common cause of serious illness and death in both developed and developing countries. Case-fatality rates are high, ranging from 10% to 50% among all ages [1, 2], and the rate of lifelong sequelae exceeds 30% even in countries with a high level of hospital care [3, 4]. The increasing prevalence of antibiotic-resistant pathogens complicates the treatment of meningitis [5]. In the United States, as in other countries that have adopted the use of *Haemophilus influenzae* b vaccine, *Streptococcus pneumoniae* is the leading cause of bacterial meningitis, followed by *Neisseria meningitidis* [2, 6]. The risk of developing pneumococcal meningitis is highest in the extremes of age and in individuals with chronic diseases, including those who are immunocompromised.

After the introduction of a 7-valent pneumococcal conjugate vaccine (PCV7) in national immunization programs in the United States, Canada, Australia, and the United Kingdom, a marked reduction in serious pneumococcal infections occurred in vaccinees and in adult and pediatric contacts (i.e., herd immunity) [7–14]. Despite the impressive decrease in overall invasive pneumococcal disease in all age groups, the effect of PCV7 on the subset of pneumococcal meningitis and, hence, on overall bacterial meningitis was not easy to demonstrate, because pneumococcal meningitis is relatively uncommon and because not all cases are caused by serotypes included in PCV7. Even in the post-PCV7 introduction era in the United States (the first country to introduce PCV7 in a national immunization program in 2000), surveillance was unable to determine unequivocally the magnitude of reduction in meningitis in the country, until now. By the end of 2001, rates of pneumococcal meningitis in children aged <5 years had decreased by 59%, compared with the prevaccine era [7]. A case-control study that looked at children aged 3–59 months from 2001 through 2004 demonstrated an effectiveness of 96% for meningitis cases caused by the serotypes included in PCV7 [15], but the overall reduction in pneumococcal meningitis was not assessed in the study. On the other hand, an article reporting data through 2003 stated that, in the United States, meningitis in adults aged ≥50 years had not changed, compared with the baseline years [11]. In France, PCV7 has been available since 2001 and was recommended in March 2002 for children at high risk (with wide-spectrum definitions that covered up to 89% of all children aged <2 years). A study conducted in all pediatric departments in northern France reported that the pneumococcal meningitis rate in individuals aged <18 years decreased from 1.65 per 100,000 population in 2001 to 0.80 per 100,000 population in 2005 (a 53% reduction) [16], but this was only statistically significant for those aged <2 years (the incidence decreased from 8.9 per 100,000 population to 1.8 per 100,000 population, a 82% reduction). Thus, until now, unequivocal proof of a beneficial effect of PCV7 on pneumococcal meningitis, especially with regard to herd immunity, was missing.

In this issue of *Clinical Infectious Diseases*, Tsai et al. [17] report trends in hospitalization for bacterial meningitis in general and for pneumococcal meningitis in particular in the United States from 1994 through 2004. They used data from the National Inpatient Sample, which contains patient-level clinical resource–utilization data and provides information on 5–8 million hospitalizations annually from ~1000 hospitals (~20% of community hospitals in the United States). Tsai et al. report some very good news: after PCV7 introduction in the United States, pneumococcal meningitis rates decreased by 33%, from a total of 0.8 cases per 100,000 population among all ages in the baseline period (1994–1999) to 0.5 cases per...
100,000 population in the period after PCV7 introduction (2001–2004). This decrease was greatest in children aged <5 years (a decrease of 66% in children aged <2 years and 51.5% in those aged 2–4 years). The trend was in the same direction for all age groups, reaching statistical significance for those aged 18–39 years and those aged ≥65 years. This reduction was expected, in view of previous reports on decreases in invasive pneumococcal disease in general, but had not been established previously. Vaccination coverage with the 23-valent polysaccharide pneumococcal vaccine (PPV23) in individuals aged ≥65 years reached 60% in the elderly population in 2001 and has remained at similar levels since then. However, it is unlikely that PPV23 played a major role in decreasing the incidence among this age group in 2001–2004, because a decrease in invasive pneumococcal disease was seen in this age group for specifically the serotypes included in PCV7, whereas no reduction was observed for the 16 serotypes contained in PPV23 only [13].

In spite of high-tech medical care and the availability of antibiotics, pneumococcal meningitis remains a deadly disease; 1 in 5 patients with pneumococcal meningitis dies of the infection, and a high percentage have long-term sequelae [18]. The highest mortality rates are found in the extremes of age; thus, it is not surprising that the highest reduction in mortality was found in children aged <2 years (51.1% reduction) and in adults aged ≥65 years (43.9% reduction). Because case-fatality rates did not decrease throughout the study period, the reduction in mortality rates can be attributed to a reduction in the incidence of meningitis.

Those of us who enjoy playing devil’s advocate might speculate that the impressive reduction in hospitalizations and deaths due to pneumococcal meningitis can be attributed to secular trends that are independent of or that have little to do with the introduction of PCV7. However, this position can be refuted easily because Tsai et al. demonstrate clearly that pneumococcal meningitis hospitalizations and the resultant in-hospital deaths were not decreasing gradually throughout the 11 years of the study but, in contrast, a sharp decrease had started to occur already in the first year after PCV7 introduction, and the reduced rates persisted in each of the following years (2001 through 2004). The overall reduction could be translated into a yearly decrease of >800 meningitis hospitalizations (involving ~450 patients aged <5 years) nationwide. Similarly, ~100 fewer deaths occurred annually during the 4 years studied after PCV7 introduction nationwide.

Tsai et al. should be particularly commended for not stopping at the simplistic definition of pneumococcal meningitis and for looking further at the trends in meningitis with use of other definitions—namely, those for “streptococcal meningitis,” “meningococcal meningitis,” “H. influenzae meningitis,” and “other bacterial meningitis.” The type of meningitis with the definition closest to that of pneumococcal meningitis is streptococcal meningitis, because misclassification between these 2 definitions is likely to occur. The authors were correct to add an analysis that excluded cases that occurred within the first month of life, because this is an age at which group B streptococcal meningitis is prevalent (and because such cases could have been reduced significantly by use of interventions for neonatal group B streptococcal disease [19]). Excluding these cases, Tsai et al. found statistically significant reductions of 34.9% and 47.5% in the rates of hospitalization for streptococcal meningitis among children aged 1–23 months and children aged 2–4 years, respectively. The pattern was similar to that for pneumococcal meningitis, showing a sharp decrease soon after PCV7 introduction. Thus, estimates of reductions in disease and deaths attributable to PCV7 that are derived from the diagnosis of pneumococcal meningitis are probably conservative and could be increased by up to 50%, at least for children aged <5 years.

A significant reduction in hospitalizations for H. influenzae, meningococcal, and other bacterial meningitis were observed as well. However, the pattern of this reduction was not similar to that of the reduction in pneumococcal and streptococcal meningitis, because the reduction definitely started before PCV7 introduction, and the trend did not change after PCV7 introduction. The reasons for the reduction in meningococcal meningitis and for the further reduction in H. influenzae meningitis after 2000 are not clear. However, regardless of the reasons, the overall reduction in meningitis in the United States, which was most significant during the first 5 years of life, is impressive and, as the authors state, may lead to the necessity of reevaluating the current age-based empirical treatment recommendations for bacterial meningitis. The epidemiology of meningitis has definitely changed in the United States after the introduction of PCV7.

The methodology used in the study could be regarded by some as deficient, because it was not a prospective, randomized, blind clinical trial. In addition, the vaccination status of the patients is unknown, and risk factors among patients (i.e., smoking, attendance at a day-care center, and underlying diseases) are missing data. Furthermore, the serotypes causing the disease and the antibiotic-resistance patterns of the pathogens are missing as well. However, the study, based on analysis of administrative data, has invaluable advantages, especially in the evaluation of the effect of PCV7 on meningitis. First, it used databases large enough to detect statistically significant decreases in this relatively uncommon disease and to show the similarity of decreases in meningitis to those of invasive pneumococcal disease overall [7, 13, 20]. Second, it permitted comparison of hospitalizations and deaths between different age groups in the same population. Third, it allowed comparison of trends in pneumococcal men-
ingitis with trends in other types of meningitis, and, by the plotting of annual values, the methodology showed that the reduction in pneumococcal meningitis (and related streptococcal meningitis) dropped sharply after PCV7 introduction, unlike the trends for other causes of meningitis, which makes it unlikely that the reduction is attributable to naturally occurring, secular trends. Fourth, and perhaps most important, the methodology allowed evaluation of the overall effect of PCV7 (including both direct effect and herd immunity) in a real-life situation.

Randomized placebo-controlled trials are, and always will be, the optimum approach to evaluate a new intervention, because they are best able to minimize selection and information bias and to control confounding. However, for policy makers, the field effectiveness of an intervention under routine program conditions may be a more relevant measure [21]. A recent study conducted by the same group using similar methodology [14] demonstrated that hospitalization rates for all-cause pneumonia were reduced by 39% for children aged <2 years, which can be translated to 506 fewer hospitalizations per 100,000 children or an annual nationwide reduction of 41,000 admissions for this age group. Furthermore, as in the present study, the impressive reduction in pneumonia was not confined to the vaccinated age groups but included all age groups, reaching statistical significance for those aged 18–39 years and those aged ≥65 years. Other studies with similar methodologies showed a reduction in otitis media burden after PCV7 introduction [22, 23]. This series of articles helps put into place some pieces of the puzzle with regard to the overall effect of PCV7 and raises optimistic expectations for PCV7 introduction worldwide.

This rosy picture, although derived from massive evidence, is nevertheless based on a short follow-up period (mainly from 2000 through 2004). Evidence from the United States and other countries clearly demonstrates that, in parallel to the sharp and impressive decrease in invasive disease caused by the pneumococcal serotypes included in PCV7, there has been a definitive although relatively small increase in disease caused by a few serotypes not included in PCV7 (i.e., the replacement phenomenon) [24–26]. To date, there is no evidence derived from well-designed studies that such replacement disease considerably reduces the beneficial effect of PCV7. The figures in the article by Tsai et al. [17] show a sustained reduction in meningitis hospitalizations among children aged <5 years, the age group to which PCV7 is targeted. A similar picture also emerged with regard to pneumonia hospitalizations [14] and overall invasive pediatric infections [24]. However, because the rates of disease caused by some serotypes not included in PCV7 are still increasing and have not yet reached a plateau [24], we need to wait an additional few years before we know that the observed benefit of PCV7 is definitively sustained.

The enormous success of PCV7 in the United States suggests but does not guarantee its success in other populations. Although evidence from other developed countries has started to accumulate and largely follows the patterns observed in the United States [8, 9, 16], virtually no data exist for developing countries, where PCV7 has not yet been introduced in routine practice [21]. Although data from 2 clinical trials in Africa showed high efficacy of a conjugate vaccine in prevention of invasive disease, pneumonia, and death [27, 28], a reduction in morbidity and mortality after PCV7 introduction needs to be demonstrated in Africa, as well as in other developing countries.

PCV7 seems to be one of the most powerful health-promoting tools introduced in the past few decades. New beneficial effects are being continually revealed. There is no doubt that this wonderful tool is not used sufficiently worldwide. The expansion of PCV7 to include additional serotypes is under way [29, 30]. However, despite the limitation of serotype coverage and the potential that some replacement disease will occur, the immediate benefit, as demonstrated in the article by Tsai et al., should encourage the global expansion of PCV7 use.

Acknowledgments

Potential conflicts of interest. R.D. has received grants and consultancy fees from GlaxoSmithKline and Wyeth.

References


