Hospitalizations and Mortality Greatly Reduced Following Introduction of the Pneumococcal Conjugate Vaccine

Tsai CJ, Griffin MR, Pekka Nuorti J, Grijalva CG. Changing epidemiology of pneumococcal meningitis after the introduction of pneumococcal conjugate vaccine in the United States. Clin Infect Dis 2008;46:1664–72.

Study Overview

Objective. To evaluate the effect of widespread immunization of young children with the 7-valent pneumococcal conjugate vaccine (PCV7) on rates of *Streptococcus pneumoniae* meningitis in the United States.

Design. Ecologic analysis.

Setting and participants. Data were compiled from the Nationwide Inpatient Sample (NIS) survey, which contains information on 5 to 8 million annual hospitalizations from approximately 1000 hospitals in the United States, constituting approximately 20% of the total nonfederal community hospitals. The study analyzed the impact of PCV7 vaccine after its introduction in 2000 by examining trends in incidence and mortality due to pneumococcal meningitis from 1994–2004 in the NIS survey sample. Calendar years were used as markers for vaccine uptake before and after introduction of the vaccine in 2000.

Main outcome measures. Hospitalization and mortality due to pneumococcal meningitis. Hospitalization for pneumococcal meningitis was identified by ICD-9-CM diagnosis code (320.2), and mortality from pneumococcal meningitis was defined as any patient with meningitis who died during hospitalization. Average annual hospitalization and death rates per 100,000 population were calculated using NIS weighted frequencies (numerators) and annual mid-year population estimates from the U.S. census bureau (denominators). Trends were reported by patient age-group (< 2 years, 2–4 years, 5–17 years, 18–39 years, 40–64 years, and ≥ 65 years) as well as time periods (1994–1999 [baseline], 2000 [transition], 2001–2004 [post-PCV7 introduction]). Rates of other causes of bacterial meningitis, including *Haemophilus influenzae*, *Meningococcus*, and other *Streptococcus* species, were also analyzed.

Main results. From 1994–2004, there were a total of 395,917,007 weighted hospitalizations in the United States. Of this total, 21,396 hospitalizations and 2684 deaths (12.5%) were due to pneumococcal meningitis. During this period, the overall average annual hospitalization rates per 100,000 population decreased from 0.8 to 0.5 (change, –33% [95% confidence interval {CI}, –38.9% to –26.5%]). Overall annual mortality rates per 100,000 population decreased from 0.10 to 0.7 (change, –33% [95% CI, –44.7% to –18%]). In subgroup analyses, among children aged < 2 years the hospitalization rate per 100,000 population decreased from 7.7 in 1994–1999 to 2.6 in 2001–2004 (change, –66% [95% CI, –73.5% to –56.3%]). Similarly, among children aged 2 to 4 years the hospitalization rate per 100,000 population decreased from 0.9 in 1994–1999 to 0.5 in 2001–2004 (change, –51.5% [95% CI, –66.9% to –28.9%]). Hospitalization rates per 100,000 population among adults ≥ 65 years decreased from 1.2 to 0.8 (change, –33% [95% CI, –43.3% to –20.9%]). An estimated 3330 hospitalizations and 394 deaths due to pneumococcal meningitis were averted in all age-groups from 2001–2004 after the introduction of the PCV7 vaccine in 2000.

Conclusion. Widespread vaccination with PCV7 during childhood significantly decreased rates of hospitalization and mortality due to pneumococcal meningitis, starting shortly after its introduction in 2000. The effects were most pronounced among children aged < 5 years and adults aged ≥ 65 years.

Commentary

S. pneumoniae is the leading cause of bacterial meningitis in the United States [1]. Case-fatality rates for bacterial meningitis range from 16% to 37% in adults and up to 3% in children, with survivors facing an up to 50% chance of neurologic sequelae [1–4]. In the United States, the PCV7 vaccine was introduced and recommended for routine use in children in 2000. Previous studies have established that invasive pneumococcal disease (defined as *S. pneumoniae* bacteremia and meningitis) in all age-groups declined in the United States after the introduction of PCV7 [5,6]. However, some debate exists as to whether the actual incidence of pneumococcal meningitis declined after PCV7 was introduced.

This study by Tsai et al sought to discern whether the incidence of pneumococcal meningitis declined across different age-groups in the United States after the introduction of PCV7 in 2000. Because of the study's ecologic design and use of data from the NIS, the results are broadly generalizable to a U.S. setting. The authors found an overall reduction of 33% in hospitalization rates due to pneumococcal

meningitis across all age-groups. In children aged younger than 2 years, who have the highest hospitalization rates from pneumococcal meningitis and are the target population for PCV7 vaccination, there was an impressive 66% reduction in hospitalization. This reduction among young children is consistent with previous smaller state and regional population-based studies that have shown decreases of 40% to 69% in rates of pneumococcal meningitis after the introduction of PCV7 [5,6]. Mortality rates due to pneumococcal meningitis were also similarly reduced among all age-groups and specifically among young children (age < 5 years) and adults aged 65 years and older, populations known to be most susceptible to this disease. The reduction in hospitalization rates for those aged 18 to 39 years and 65 years and older suggests indirect effects of the PCV7 on reduced carriage rates in the community, as the vaccine is not recommended for these age-groups.

The authors clearly show that the reduced rates of hospitalization and mortality were temporally related to the introduction of the vaccine in 2000 and not due to other national trends. Prior to that time, pneumococcal meningitis rates were relatively consistent, showing no downward trend, but these rates decreased sharply and consistently starting in 2001. Trends in rates of hospitalization and mortality from other causes of bacterial meningitis, including streptococcal meningitis (often confused with pneumococcal meningitis), were also examined. The pattern of temporal reduction in streptococcal meningitis after the PCV7 vaccine was introduced was similar to that of pneumococcal meningitis, suggesting that the estimates of benefit from PCV7 are conservative. Rates of other causes of bacterial meningitis continued on a steady downward trend seemingly unaffected by the PCV7 introduction.

A few limitations to this study deserve mention. It was not a prospective, blinded, randomized trial. Rather, it used administrative data vulnerable to miscoding and other sources of potential bias. However, the NIS is one of the largest and most widely used nationwide databases, and its size enabled the authors to detect significant decreases in the incidence of a relatively uncommon disease as well as allowed for comparisons across different age-groups [7]. Furthermore, its longitudinal data enabled yearly trends to be established before and after the introduction of PCV7. A key unanswered question is how much of the benefit seen from PCV7, especially among older adults, was actually due to the introduction of PPV23, the 23-valent conjugated pneumococcal polysaccharide vaccine recommended for adults aged 65 years and older [7]. This remains unclear as the national rate of PPV23 coverage increased from 37% in 1995 to 60% in 2001 but has remained steady since then. Finally, given the changing epidemiology of bacterial meningitis in the United States due to the introduction of the PCV7 vaccine as well as the short follow-up time of this study (4 years), it remains to be seen whether the reductions in pneumococcal meningitis will be sustained or whether they will be shifted to serotypes of pneumococcus not covered by the vaccine, leading to a rebound increase in the future [7].

Applications for Clinical Practice

The introduction of the PCV7 vaccine in the United States resulted in large declines in hospitalization and mortality rates due to pneumococcal meningitis. These robust results suggest that vaccine programs can have a significant short-term benefit in the United States, and efforts should be made to expand the coverage of PCV7 and PPV23 among children and older adults, respectively. These findings also should strongly encourage physicians and public health officials to maintain the high rates of PCV7 vaccination in young children and redouble their efforts to improve PPV23 vaccination rates among the elderly. The results suggest that PCV7 should be considered for widespread use among children across the developing world, where pneumococcal meningitis rates are much higher [7].

—Review by Asaf Bitton, MD

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