Trends in Invasive Pneumococcal Disease–Associated Hospitalizations

Samir S. Shah1,2,3,4 and Adam J. Ratner1
Divisions of 1Infectious Diseases and 2General Pediatrics, The Children’s Hospital of Philadelphia, and 3Center for Clinical Epidemiology and Biostatistics and 4Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Background. The heptavalent pneumococcal conjugate vaccine was licensed in the United States in 2000 for use in infants and children. Postlicensure surveillance revealed substantial regional and national decreases in invasive pneumococcal disease. It is not known whether widespread vaccine use has led to a concomitant decrease in invasive pneumococcal disease–associated hospitalization rates.

Objective. We examined national trends in rates of hospitalization among both children and adults with invasive pneumococcal disease.

Methods. Data from the 1998–2003 National Hospital Discharge Survey and population estimates from the National Center for Health Statistics were used to calculate rates of hospital discharge for patients admitted with invasive pneumococcal disease, defined as meningitis or bacteremia caused by Streptococcus pneumoniae.

Results. Rates of hospital discharge for patients admitted with invasive pneumococcal disease decreased during the study period from a peak of 12.03 discharges per 100,000 population in 1999 to 5.60 discharges per 100,000 population in 2003 (P < .001). Rates of hospital discharge for persons admitted with pneumococcal meningitis decreased from 1.60 discharges per 100,000 person-years in the prelicensure period to 0.53 discharges per 100,000 person-years in the postlicensure period. For persons ≥65 years of age but not for those <4 years of age, the rates of hospital discharge for those admitted with pneumococcal bacteremia were significantly lower during the postlicensure period, compared with the prelicensure period.

Conclusions. Hospital discharge rates for persons admitted with invasive pneumococcal disease, including meningitis, have decreased since introduction of the heptavalent pneumococcal conjugate vaccine. The decrease was driven in part by the reduction of invasive pneumococcal disease–associated hospitalizations in the subgroup aged ≥65 years.

Streptococcus pneumoniae is the most commonly identified cause of serious bacterial illness in young children. In 2000, a 7-valent protein-polysaccharide pneumococcal conjugate vaccine (PCV7 [Prevnar; Wyeth Lederle Vaccines]) was licensed in the United States for use in infants and young children. Postlicensure surveillance revealed substantial regional and national decreases in invasive pneumococcal disease [1–6]. Many cases of invasive pneumococcal disease in children occurred in conjunction with occult bacteremia [7], a condition that is managed in the ambulatory setting, with infrequent progression to conditions that require hospitalization [8–10]. Therefore, it is unclear whether this reduction will translate into significantly fewer invasive pneumococcal disease–related hospitalizations.

Few data are available on the impact of PCV7 on hospitalization rates for persons with invasive pneumococcal disease. One study did not find a difference in inpatient hospitalization–related costs between PCV7 recipients and control patients [11]. Ramani et al. [12] examined hospital discharge rates for patients admitted with invasive pneumococcal disease in Michigan 1 year after the introduction of PCV7; hospital discharge rates for invasive pneumococcal disease decreased significantly among children <1 year of age but not among older children. We examine national trends in hospitalization rates for both children and adults admitted with invasive pneumococcal disease by using National Hospital Discharge Survey (NHDS) data from a 6-year...

**METHODS**

**NHDS.** The National Center for Health Statistics created the NHDS to collect annually a nationally representative sample of data on discharges from nonfederally funded, short-stay US hospitals. The design of the NHDS has been described in detail elsewhere [13]. In brief, the 3-stage survey design mandates collection of discharge data from all US hospitals with ≥1000 beds and a representative sample of others that is based on geographic location, size, and specialty. Each year, ~500 hospitals participate in the survey. A random selection of discharges from each of these facilities provides a total sample of ~250,000 entries per year. Discharge records are weighted according to hospital size and region, to allow calculation of national estimates. Each discharge record contains demographic information about the patient and the hospital, as well as up to 7 diagnosis codes that are consistent with the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM).

**Study definitions.** We examined data from the NHDS for the period from 1 January 1998 through 31 December 2003. Extraction of records was based on the appearance of specific ICD-9-CM codes in any of the 7 discharge diagnosis fields. Bacteremia of any cause (“any bacteremia”) was defined as a record containing a code for septicemia (038) or bacteremia (790.7). Bacterial meningitis of any cause (“any bacterial meningitis”) was defined as a record containing a code for bacterial meningitis (320). Pneumococcal bacteremia was defined as a record containing a code for either pneumococcal septicemia (038.2) or bacteremia and pneumococcus (790.7 and 041.2, respectively). Pneumococcal meningitis was defined as a record containing a code for pneumococcal meningitis (320.1). Invasive pneumococcal disease was defined as a diagnosis of either pneumococcal meningitis or pneumococcal bacteremia.

**Data extraction and analysis.** Record extraction was performed using MacPython 2.3 (Python Software Foundation; available at http://www.python.org) and Epi Info, version 3.3.2 (Centers for Disease Control and Prevention). Population estimates used in the calculation of rates, including age-specific rates, were supplied by the National Center for Health Statistics and were consistent with census estimates. Because racial data were missing for ~20% of records in the NHDS, records were not subdivided by race.

Published guidelines were used to calculate relative SEs of NHDS-derived estimates, as well as 95% CIs [13]. According to these procedures, estimates derived from the NHDS that are based on <30 actual discharges should not be reported, because these often have unacceptably large relative SEs. Projected values based on 30–60 discharges should not be assumed to be reliable, and the same is true of any estimate with a calculated relative SE of >30%, regardless of sample size. Potentially unreliable data points are noted when presented in this report.

Data were analyzed using GraphPad Prism (GraphPad software). Unpaired *t* tests were used to compare rates of bacteremia and meningitis in the prelicensure period (1998–2000) and postlicensure period (2001–2003). One-way analysis of variance with posttest for linear trend was used to analyze trends in overall invasive disease and in bacteremia. A 2-tailed *P* value of <.05 was considered to be statistically significant.

**RESULTS**

Of a data set of 3,796,376 entries in the NHDS for the period of 1998–2003, a total of 44,934 entries (1.2%) contained a code for bacteremia, septicemia, or meningitis, corresponding to a national estimate of 4,744,596 hospital discharges related to invasive bacterial disease during the 6-year period. Of these, 1257 records (2.8%) had a code for invasive pneumococcal disease, leading to an estimate of 141,426 hospital discharges related to invasive pneumococcal disease during the same period. Using census-derived data, we calculated the annual discharge rates per 100,000 population. These estimates revealed a decrease in the number of hospitalizations of patients with invasive pneumococcal disease, starting in 2000–2001 (table 1). Hospital discharge rates for patients with pneumococcal bacteremia or meningitis were also examined separately. Stratification of hospital discharge rates for patients admitted with *S. pneumoniae* bacteremia by year revealed a statistically significant decreasing trend (figure 1).

The rates in the prelicensure and postlicensure periods varied with age (table 2). Differences in discharge rates for patients admitted with *S. pneumoniae* bacteremia were significantly lower in the postlicensure period, compared with the prelicensure period, for patients ≥65 years of age, with a decrease of 36%. However, the difference in hospital discharge rates among children <4 years of age who were hospitalized with pneumococcal disease was not significant.

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of discharges</th>
<th>Discharge rate per 100,000 population (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>33,142</td>
<td>12.03 (9.09–14.97)</td>
</tr>
<tr>
<td>2000</td>
<td>28,417</td>
<td>10.22 (7.96–12.47)</td>
</tr>
<tr>
<td>2001</td>
<td>20,318</td>
<td>7.16 (5.25–9.08)</td>
</tr>
<tr>
<td>2002</td>
<td>18,443</td>
<td>6.42 (4.51–8.34)</td>
</tr>
<tr>
<td>2003</td>
<td>16,205</td>
<td>5.60 (3.63–7.57)</td>
</tr>
</tbody>
</table>

**NOTE.** *P*<.001, by analysis of variance posttest for linear trend, for the comparison between the rates in 1999 and 2003.
Figure 1. Hospital discharge rates per 100,000 population (± SE) for patients admitted with bacteremia of any cause (square) or with pneumococcal bacteremia only (triangle). Statistical analysis using the analysis of variance posttest for linear trend demonstrated a statistically significant decrease in the rate of hospital discharges during the study period for patients admitted with *Streptococcus pneumoniae* bacteremia (*P* ≤ .005) but not for those admitted with bacteremia of any cause (*P* > .133).

Pneumococcal bacteremia was not statistically significant between the 2 periods (table 2). Hospital discharge rates for patients admitted with *S. pneumoniae* meningitis were significantly lower in the postlicensure period, compared with the prelicensure period, across all age groups (table 2); small numbers of hospitalizations prevented calculation of age-specific rates of hospital discharge for patients admitted with *S. pneumoniae* meningitis. The rates of any bacteremia and any bacterial meningitis did not decrease in the postlicensure period, compared with the prelicensure period (table 2).

### DISCUSSION

We documented a significant national decrease in rates of discharge after hospitalization with invasive pneumococcal disease during the postlicensure period. The overall rate of hospital discharge for patients admitted with pneumococcal meningitis decreased significantly in the postlicensure period, compared with the prelicensure period. Although rates of hospital discharge for patients admitted with pneumococcal bacteremia decreased significantly among patients ≥ 65 years of age, this same decrease was not observed among patients < 4 years of age.

In the only previous study to examine trends in hospital discharge rates for patients admitted with invasive pneumococcal disease, the discharge rates among children < 1 year of age in Michigan decreased from 40.0 to 23.9 discharges per 100,000 population between 1994–2000 and 2000–2001 (*P* < .005); however, there was no difference in rates of hospital discharge among children 2–5 years of age admitted with invasive pneumococcal disease [12]. Our study reveals a national decrease in hospital discharges after introduction of PCV7 for patients admitted with invasive pneumococcal disease. The decrease was driven in part by the reduction of invasive pneumococcal disease–associated hospitalizations in the subgroup of patients aged ≥ 65 years.

Several studies have documented regional and national decreases in the incidence of pneumococcal bacteremia among young children following licensure of PCV7. However, in our study, the decrease in hospital discharges associated with pneumococcal bacteremia was not statistically significant among children < 4 years of age. The phenomenon of occult bacteremia

### Table 2. Hospital discharge rates before and after licensure of the 7-valent protein-polysaccharide pneumococcal conjugate vaccine for patients admitted with bacteremia or meningitis.

<table>
<thead>
<tr>
<th>Disease, age</th>
<th>Discharge rate per 100,000 person-years (95% CI)</th>
<th>Prelicensure period</th>
<th>Postlicensure period</th>
<th><em>P</em>&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any bacteremia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>269.46 (237.77–301.15)</td>
<td>283.38 (250.05–316.70)</td>
<td>.555</td>
<td></td>
</tr>
<tr>
<td>0–4 years</td>
<td>373.02 (182.9–563.11)</td>
<td>304.16 (143.20–465.12)</td>
<td>.592</td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>1235.03 (605.66–1864.40)</td>
<td>1278.07 (576.67–1979.48)</td>
<td>.929</td>
<td></td>
</tr>
<tr>
<td>Pneumococcal bacteremia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>8.86 (6.43–11.29)</td>
<td>5.86 (3.79–7.93)</td>
<td>.085</td>
<td></td>
</tr>
<tr>
<td>0–4 years</td>
<td>18.43 (10.85–26.02)</td>
<td>9.19 (4.15–14.23)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>.147</td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>30.05 (22.98–37.12)</td>
<td>19.29 (13.62–24.96)</td>
<td>.029</td>
<td></td>
</tr>
<tr>
<td>Any bacterial meningitis, all ages</td>
<td>4.75 (3.08–6.43)</td>
<td>4.61 (2.62–6.59)</td>
<td>.916</td>
<td></td>
</tr>
<tr>
<td>Pneumococcal meningitis, all ages</td>
<td>1.60 (1.01–2.20)</td>
<td>0.53 (0.19–0.87)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>.007</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> By the 2-tailed unpaired *t* test.

<sup>b</sup> Based on 40–60 actual records from the National Hospital Discharge Survey.
may, in part, explain this discrepancy. Before introduction of PCV7, occult pneumococcal bacteremia occurred in 1.5%–2.1% of febrile children 2–36 months of age [8, 9]. Most of these children did not require hospitalization, and progression to suppurative disease was uncommon [8]. In a randomized, controlled trial, use of PCV7 resulted in an 89% reduction in invasive pneumococcal disease; occult bacteremia was the most common clinical manifestation of disease [7]. After licensure of PCV7, the prevalence of occult bacteremia decreased to 0.9% [10]. Therefore, because occult pneumococcal bacteremia is frequently managed in the ambulatory setting, the dramatic reduction in the prevalence of pneumococcal bacteremia may correlate with a smaller decrease in hospital discharges for patients with pneumococcal bacteremia. Unfortunately, because of sample size limitations, we were unable to further subdivide the 0–4-year age group to better assess these hypotheses.

Before introduction of PCV7, the risk of invasive pneumococcal disease caused by pneumococcal serotypes commonly found in pediatric patients was significantly elevated among persons aged 65–74 years, compared with those aged 35–49 years (relative risk, 1.68; 95% CI, 1.29–2.20). This risk increased progressively among persons aged 75–84 years and >85 years [14]. After introduction of PCV7, several investigators demonstrated decreases in rates of invasive pneumococcal disease among older adults [1, 2]. Whitney et al. [1] reported an 18% decrease (from 60.1 to 49.5 cases per 100,000 population in the areas covered by active surveillance) in invasive pneumococcal disease among patients ≥65 years of age. In northern California, Black et al. [2] documented a 27% decrease in invasive pneumococcal disease among adults ≥60 years of age. In our study, the overall rates of hospital discharge for patients admitted with invasive pneumococcal disease decreased by 36% for those ≥65 years of age, lending support to the notion that older adults may also benefit from the use of PCV7 in children. Cost-benefit analyses of PCV7 use have generally focused on the pediatric population, but the potential reduction of disease among older adults may prove to be an additional benefit of PCV7 use [15].

This study has several limitations. We were only able to indirectly measure the effect of PCV7 on hospital discharge rates for patients admitted with invasive pneumococcal disease, because individual-level data on vaccination status were not available. Similarly, information on specific pneumococcal serotypes responsible for invasive pneumococcal disease is not coded in the NHDS and, thus, is not measurable using these techniques. Unmeasured factors other than PCV7 use may also potentially affect hospital discharge rates for patients with invasive pneumococcal disease. For example, efforts to increase pneumococcal polysaccharide and influenza vaccine use among older adults may have contributed to this trend. Furthermore, the inability to consider age-specific rates of bacteremia other than for patients aged 0–4 years and patients aged ≥65 years also limits our ability to conclude whether the decrease in pneumococcal bacteremia among older adults is related to a herd effect or to other factors. Likewise, we were unable to meaningfully subdivide the population of patients with invasive pneumococcal disease on the basis of comorbid factors, because of the relatively small sample size of the database. Information regarding changes within groups with specific risks for invasive pneumococcal disease (e.g., patients with HIV infection or asthma) will likely require active surveillance strategies. Interpretation of decreasing rates of hospital discharge could be confounded by changes in clinical strategies for assessment of febrile infants after introduction of PCV7 [16]. We believe that this latter effect is unlikely for 2 reasons. First, even if blood specimens are now obtained for culture less frequently from children at risk for occult bacteremia, these children are more commonly treated in the ambulatory rather than the hospital setting and, therefore, would not have been counted in the NHDS during either the prelicensure and postlicensure periods we evaluated. Second, the decision to obtain blood or CSF specimens for culture from children who were sufficiently ill to require hospitalization is unlikely to be affected by the introduction of PCV7. Finally, discharge diagnosis coding may be unreliable for specific diseases or pathogens. However, because a large number of hospitals are included in the NHDS, systematic coding errors at a particular hospital would not be expected to impact our overall findings. Likewise, we would not expect coding accuracy to vary from year to year in a way that would substantially affect trends in invasive pneumococcal disease–associated hospitalizations.

In summary, we document a national decrease in rates of hospital discharge rates for both children and adults admitted with invasive pneumococcal disease. For persons ≥65 years of age but not for those <4 years of age, the rates of hospital discharge for pneumococcal bacteremia were significantly lower during the postlicensure period, compared with the prelicensure period.

Acknowledgments

We thank Paul A. Offit for his careful reading of the manuscript.

Financial support: National Institute of Allergy and Infectious Diseases, National Institutes of Health (AI065450) and the Pediatric Infectious Disease Society–St. Jude Children’s Research Hospital Fellowship (to A.J.R.)


References