Increasing Incidence of Empyema Complicating Childhood Community-Acquired Pneumonia in the United States

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Background. The incidence of childhood pneumonia decreased following introduction of 7-valent pneumococcal conjugate vaccine (PCV7) in the United States. Recent regional reports suggest an increase in the incidence of childhood pneumonia complicated by empyema. We assessed whether early decreases in pneumonia hospitalization rates were sustained and trends in such hospitalizations complicated by empyema in United States children aged <5 years.

Methods. Nationwide Inpatient Sample and Census data were used to calculate annual all-cause and pneumococcal pneumonia hospitalization rates for pre-PCV7 (1996–1999) and post-PCV7 years (2001–2007) and to analyze national trends in total and pathogen-specific pneumonia-associated empyema.

Results. Among children aged <2 years, all-cause pneumonia hospitalizations decreased 33% (95% confidence interval, 28%–37%) from 1267 cases per 100,000 children in pre-PCV7 years to 852 cases per 100,000 children in post-PCV7 years. Pneumococcal pneumonia hospitalization rates decreased 61% (95% confidence interval, 55%–67%) post-PCV7, compared with pre-PCV7 years. Pneumonia hospitalizations complicated by empyema increased 2.01-fold from 3.5 cases per 100,000 children in 1996–1998 to 7.0 cases per 100,000 children in 2005–2007. Rates of pneumococcal and streptococcal empyema remained stable, whereas rates of staphylococcal and other or unspecified empyema increased 4.08- and 1.89-fold, respectively. Among children aged 2–4 years, all-cause pneumonia rates remained stable, whereas pneumococcal pneumonia decreased by 26% (95% confidence interval, 16–34). Pneumonia complicated by empyema increased 2.81-fold from 3.7 cases per 100,000 children in 1996–1998 to 7.0 cases per 100,000 children in 2005–2007. In this age group, there were 2.17-, 2.80-, 3.76-, and 3.09-fold increases in rates of pneumococcal, streptococcal, staphylococcal, and other or unspecified empyema, respectively.

Conclusion. Decreases in childhood pneumonia hospitalization rates following PCV7 introduction were sustained. Although empyema complicated only a small fraction of pneumonia hospitalizations, its prevalence increased substantially. This increase was due to several pathogens and warrants continuing monitoring.
studies [12–14] reported increases in childhood pneumonia complicated by empyema due primarily to pneumococcal serotypes not included in PCV7. In those studies, the increases began in the 1990s [13] and continued after PCV7 introduction [14]. Nevertheless, national trends in empyema incidence are unknown.

We assessed whether the previously observed decreases in the incidence of childhood pneumonia hospitalizations continued 7 years after PCV7 introduction. We also evaluated national trends in pneumonia hospitalizations complicated by empyema, including trends in empyema associated with specific pathogens.

**METHODS**

**Nationwide inpatient sample.** The Nationwide Inpatient Sample is the largest source of inpatient data publicly available in the United States. These databases contain information on inpatient stays from states that participate in the Healthcare Cost and Utilization Project. Information recorded includes clinical and resource-utilization data for 5–8 million hospitalizations per year from a sample of 1000 hospitals. These hospitals constitute an estimated 20% sample of community hospitals, including nonfederal short-term, general, and specialty hospitals. Participating hospitals are sampled by stratified probability sampling, with sampling probabilities proportional to the number of community hospitals in each stratum [15].

The Nationwide Inpatient Sample collects data on all hospitalizations regardless of payment source, and sampling variables are provided to calculate national estimates. Up to 15 International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), coded discharge diagnoses and procedures are recorded, with first-listed diagnoses (principal) regarded as the primary reason for hospitalization [16]. Because these data are publicly available and have no personal identifiers, this study was considered to be exempt from review by the institutional review boards of Vanderbilt University and the Centers for Disease Control and Prevention (CDC).

**Outcomes.** Pneumonia hospitalizations were identified using algorithms based on coded discharge diagnoses. All-cause pneumonia hospitalizations were defined by a principal diagnosis of pneumonia or a principal diagnosis of septicemia, meningitis, or empyema and a pneumonia code in another diagnosis field. Pneumococcal pneumonia hospitalizations met the all-cause pneumonia definition but also had either a specific pneumococcal pneumonia code or an unspecified pneumonia code plus another code, indicating pneumococcal infection [8]. Diagnosis and procedure codes identified empyema and thoracentesis-related procedures associated with pneumonia hospitalizations. Diagnosis codes for pneumonia or bacteremia/sepsisemia indicating specific etiologies determined empyema classification into the following mutually exclusive groups: pneumococcal, streptococcal, staphylococcal, and other or unspecified.

Overall rates of acute respiratory tract illness (ARTI) and nonpneumonia ARTI hospitalizations were examined to assess whether changes occurred in coding practices from pneumonia to nonpneumonia ARTI (See Table 1 for ICD-9-CM codes).

**Statistical analyses.** Annual hospitalization rates for all-cause and pneumococcal pneumonia were computed using weighted frequencies as numerators and annual, mid-year census population estimates as denominators to estimate person-time. Annual rates were calculated per 100,000 population and age-stratified by <2 and 2–4 year age groups. To estimate the effect attributable to the PCV7 vaccination program, we compared the average annual weighted hospitalization rates for post-PCV7 years (2001–2007) with pre-PCV7 years (1996–1999). Year 2000 was considered to be a transition year and was excluded from these analyses [17].

Rates and rate ratios were estimated by fitting outcome-specific Poisson regression models that included parameters for age group, study period, and their interaction, while accounting for the data sampling design. Population estimates for each age group and calendar year represented the offset term for the models. Comparisons of rates before and after PCV7 introduction were obtained through linear combinations of model coefficients [18, 19].

Annual rates of all-cause pneumonia complicated by empyema and procedures associated with these complicated pneumonias were analyzed separately. Because of an increasing trend in empyema incidence from 1996 through 1999 among children aged <2 years (P = .001, by test for trend), all pre-PCV7 years were not combined. Among children aged 2–4 years, a nonsignificant increasing trend pre-PCV7 was also observed (P = .157). The slopes for trends in empyema rates pre- and post-PCV7 decreased among children aged <2 years (P = .029) but were not significantly different among children aged 2–4 years (P = .695). Therefore, these secular trends were assessed and described over the whole 12-year study period. Per Healthcare Cost and Utilization Project recommendations, estimates based on <10 unweighted observations were considered unreliable and were not reported. To obtain reliable pathogen-specific empyema rate estimates, we combined annual data in 3-year periods. To perform parallel analyses of total and pathogen-specific empyema and to quantify secular trends, we compared rates in combined years 2005–2007 with those in 1996–1998. All reported P values were 2-tailed and accounted for the

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**Table 1. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Codes**

This table is available in its entirety in the online version of *Clinical Infectious Diseases*.
sampling design. A P value of <.05 or the exclusion of 1 from the rate ratio 95% confidence intervals (CIs) indicated statistical significance. Statistical analyses used the survey applications of SAS, version 9.1.3 (SAS Institute), and Stata, version 10.0 (StataCorp).

**RESULTS**

**Characteristics of pneumonia hospitalizations.** During the 12-year study period, there were an estimated 1.5 million all-cause pneumonia hospitalizations among US children aged <5 years. In 2007, a total of 59,980 children aged <2 and 42,356 children aged 2–4 years were hospitalized for all-cause pneumonia. There were more boys (56.0%) than girls; 35.3% were white, 17.5% Hispanic, 14.2% African American, 5.9% other race, and 27.1% were missing race information.

Among children aged <2 years, the overall proportion of all-cause pneumonia hospitalizations complicated by empyema and with a thoracentesis-related procedure performed was 0.51% (95% CI, 0.45%–0.58%) and 0.67% (95% CI, 0.59%–0.76%), respectively. Similarly, among children aged 2–4 years empyema and thoracentesis procedures were recorded in 1.59% (95% CI, 1.41%–1.80%) and 1.86% (95% CI, 1.66%–2.08%) of all-cause pneumonia hospitalizations, respectively. The overall proportion of in-hospital deaths during all-cause pneumonia hospitalizations was 0.20% (95% CI, 0.17%–0.23%) and 0.17% (95% CI, 0.14%–0.20%) for children aged <2 and 2–4 years, respectively.

Among children aged <2 years hospitalized due to all-cause pneumonia, the mean number of discharge diagnoses recorded increased from 2.71 (95% CI, 2.62–2.81) in 1996 to 3.29 (95% CI, 3.11–3.48) in 2007 (P < .001), and the mean number of procedures recorded was 0.33 (95% CI, 0.24–0.42) in 1996 and 0.31 (95% CI, 0.25–0.37) in 2007 (P = .656). Among children aged 2–4 years, the mean number of discharge diagnoses recorded increased from 2.96 (95% CI, 2.91–3.02) in 1996 to 3.41 (95% CI, 3.21–3.60) in 2007 (P < .001), and the mean number of procedures was 0.29 (95% CI, 0.25–0.32) in 1996 and 0.30 (95% CI, 0.24–0.36) in 2007 (P = .881).

Approximately 1.65% (95% CI, 1.53%–1.79%) and 2.61% (95% CI, 2.43%–2.79%) of all-cause pneumonia hospitalizations met the definition of pneumococcal pneumonia among children aged <2 years and 2–4 years, respectively. In 2007, a total of 834 children aged <2 years and 1062 children aged 2–4 years had hospitalizations coded as pneumococcal pneumonia. During the study years, empyema was recorded in 7.92% (95% CI, 6.75%–9.27%) and 16.87% (95% CI, 14.95%–18.99%) of pneumococcal pneumonia hospitalizations in children aged <2 and 2–4 years, respectively. For both age groups, ~83% of all-cause pneumonia hospitalizations complicated by empyema had a thoracentesis procedure performed throughout the study years.

**Pneumonia hospitalization trends.** Among children aged <2 years, annual rates of all-cause pneumonia hospitalizations decreased by 33%, from 1267 hospitalizations per 100,000 children in pre-PCV7 years to 852 hospitalizations per 100,000 children during post-PCV7 years. Among children aged 2–4 years, the rates of all-cause pneumonia did not change (Table 2). After the initial decrease, pneumonia hospitalizations remained relatively stable after PCV7 introduction with the exception of a transient increase in 2005 (Figure 1).

Among children aged <2 years, annual rates of pneumococcal pneumonia hospitalizations decreased by 61%, from 27 hospitalizations per 100,000 children in 1996 to 10 (95% CI, 7.92%–2.43%–2.79%) of pneumococcal pneumonia hospitalizations in children aged <2 and 2–4 years, respectively. For both age groups, ~83% of all-cause pneumonia hospitalizations complicated by empyema had a thoracentesis procedure performed throughout the study years.

### Table 2. Rates of Acute Respiratory Tract Illness (ARTI), All-Cause Pneumonia, and Pneumococcal Pneumonia Hospitalizations, United States Children Aged <5 Years, 1996–2007

<table>
<thead>
<tr>
<th>Hospitalizations per 100,000 children</th>
<th>Pre-PCV7 period (1996–1999)</th>
<th>Post-PCV7 period (2001–2007)</th>
<th>Rate difference (95% CI)</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ARTI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>3984</td>
<td>3272</td>
<td>−712 (−935 to −474)</td>
<td>0.82 (0.77–0.88)</td>
</tr>
<tr>
<td>2–4 years</td>
<td>969</td>
<td>1011</td>
<td>43 (−1 to 88)</td>
<td>1.04 (1.00–1.09)</td>
</tr>
<tr>
<td>Nonpneumonia ARTI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>2718</td>
<td>2419</td>
<td>−298 (−479 to −104)</td>
<td>0.89 (0.82–0.96)</td>
</tr>
<tr>
<td>2–4 years</td>
<td>567</td>
<td>607</td>
<td>40 (11–71)</td>
<td>1.07 (1.02–1.12)</td>
</tr>
<tr>
<td>Pneumonia (all-cause)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>1267</td>
<td>852</td>
<td>−414 (−471 to −353)</td>
<td>0.67 (0.63–0.72)</td>
</tr>
<tr>
<td>2–4 years</td>
<td>402</td>
<td>404</td>
<td>2 (−21 to 27)</td>
<td>1.01 (0.95–1.07)</td>
</tr>
<tr>
<td>Pneumococcal pneumonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>27</td>
<td>11</td>
<td>−17 (−18 to −15)</td>
<td>0.39 (0.33–0.45)</td>
</tr>
<tr>
<td>2–4 years</td>
<td>12</td>
<td>9</td>
<td>−3 (−4 to −2)</td>
<td>0.74 (0.66–0.84)</td>
</tr>
</tbody>
</table>

NOTE. ARTI, acute respiratory tract illness; CI, confidence interval; PCV7, 7-valent pneumococcal conjugate vaccine.

* All-cause pneumonia includes pneumococcal pneumonia.
Figure 1. Annual hospitalization rates for all-cause (A) and pneumococcal (B) pneumonia among children aged <5 years, United States, 1996–2007. Error bars indicate 95% confidence intervals. Vertical lines indicate the year of 7-valent pneumococcal conjugate vaccine (PCV7) introduction.

A. All-cause pneumonia

B. Pneumococcal pneumonia

Hospitalizations per 100,000 children during pre-PCV7 years to 11 hospitalizations per 100,000 children during post-PCV7 years. Similarly, rates of pneumococcal pneumonia decreased by 26% among children aged 2–4 years (Table 2). Rates of pneumococcal pneumonia hospitalizations remained relatively stable during post-PCV7 years in both age groups (Figure 1).

ARTI hospitalization trends. Among children aged <2 years, overall annual rates of ARTI (including all-cause pneumonia) decreased by 18%, from 3984 cases per 100,000 children during pre-PCV7 years to 3272 cases per 100,000 children during post-PCV7 years. In this age group, rates of nonpneumonia ARTI decreased by 11% from 2718 cases per 100,000 children during pre-PCV7 years to 2419 cases per 100,000 children during post-PCV7 years. Among children aged 2–4 years, overall rates of ARTI remained stable. However, rates of nonpneumonia ARTI increased by 7% from pre- to post-PCV7 years (Table 2).

Empyema trends. Among children aged <2 years, annual rates of pneumonia complicated by empyema increased 2.01-fold from 3.5 cases per 100,000 children in 1996–1998 to 7.0 cases per 100,000 children in 2005–2007 (441 cases in 2007). Similarly, empyema hospitalization rates increased 2.81-fold among children aged 2–4 years, from 3.7 hospitalizations per 100,000 children to 10.3 hospitalizations per 100,000 children (1088 cases in 2007). Among children aged <2 years, annual rates of thoracentesis performed during pneumonia hospitalizations increased 1.48-fold. Among children aged 2–4 years, rates of thoracentesis increased 2.18-fold (Table 3 and Figure 2).

Pathogen-specific empyema trends. Among children aged <2 years, annual rates of pneumococcal empyema per 100,000 children were 1.1 cases in 1996–1998 and 1.3 cases in 2005–2007 (rate ratio, 1.13 cases; 95% CI, 0.68–1.88 cases). Among children aged 2–4 years, pneumococcal empyema increased from 1.1 cases per 100,000 children in 1996–1998 to 2.5 cases per 100,000 children in 2005–2007, a 2.17-fold increase.

Among children aged <2 years, rates of streptococcal empyema per 100,000 children were 0.4 cases in 1996–1998 and 0.7 cases in 2005–2007 (rate ratio, 1.74 cases; 95% CI, 0.98–3.07 cases). The incidence of staphylococcal empyema increased 4.08-fold from 0.6 cases per 100,000 children in 1996–1998 to 2.5 cases per 100,000 children in 2005–2007. Empyema rates due to other or unspecified pathogens increased 1.89-fold during the study years. Among children aged 2–4 years, streptococcal empyema rates increased 2.80-fold, whereas staphylococcal empyema rates increased 3.76-fold. Empyema due to other or unspecified pathogens increased 3.09-fold (Table 3 and Figure 3).

During the study period, there were some years with strong...
Table 3. Rates of Overall and Pathogen-Specific Pneumonia Hospitalizations Complicated by Empyema, United States Children Aged <5 years, 1996–2007

<table>
<thead>
<tr>
<th>Cause of hospitalization, age group</th>
<th>Hospitalizations per 100,000 children</th>
<th>Rate difference (95% CI)</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empyema</td>
<td></td>
<td></td>
<td>3.5 (1.5–6.3)</td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>3.5</td>
<td>7.0</td>
<td>3.5 (1.5–6.3)</td>
</tr>
<tr>
<td>2–4 years</td>
<td>3.7</td>
<td>10.3</td>
<td>6.6 (4.5–9.3)</td>
</tr>
<tr>
<td>Thoracentesis</td>
<td></td>
<td></td>
<td>2.6 (0.6–5.5)</td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>5.6</td>
<td>8.2</td>
<td>2.6 (0.6–5.5)</td>
</tr>
<tr>
<td>2–4 years</td>
<td>4.8</td>
<td>10.5</td>
<td>5.7 (3.6–8.2)</td>
</tr>
<tr>
<td>Pneumococcal empyema</td>
<td></td>
<td></td>
<td>0.3 (0–0.8)</td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>0.4</td>
<td>0.7</td>
<td>0.3 (0–0.8)</td>
</tr>
<tr>
<td>2–4 years</td>
<td>0.4</td>
<td>1.0</td>
<td>0.7 (0.3–1.3)</td>
</tr>
<tr>
<td>Streptococcal empyema</td>
<td></td>
<td></td>
<td>1.9 (0.9–3.5)</td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>0.6</td>
<td>2.5</td>
<td>1.9 (0.9–3.5)</td>
</tr>
<tr>
<td>2–4 years</td>
<td>0.2</td>
<td>0.8</td>
<td>0.6 (0.2–1.4)</td>
</tr>
<tr>
<td>Staphylococcal empyema</td>
<td></td>
<td></td>
<td>1.2 (0.3–2.5)</td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>1.3</td>
<td>2.5</td>
<td>1.2 (0.3–2.5)</td>
</tr>
<tr>
<td>2–4 years</td>
<td>1.9</td>
<td>6.0</td>
<td>4.0 (2.6–6.0)</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval.

clustering of empyema cases in relatively few hospitals. For instance, in 2005, 20% of hospitals reporting empyema in children aged <2 years accounted for one-half of the reported cases. For the same year, 10% of hospitals reporting empyema in children aged 2–4 years accounted for one-half of the reported cases. This clustering of empyema resulted in wide confidence intervals around some estimates (Figure 2).

DISCUSSION

The decreases observed in all-cause and pneumococcal pneumonia hospitalizations following introduction of PCV7 in the United States were sustained through 2007. Despite the major impact of PCV7 on pneumonia, rates of pneumonia complicated by empyema increased gradually throughout the study period. Our findings indicate that these increases began before PCV7 introduction and that several pathogens contributed to these changes. Among young children aged <2 years, empyema caused by *Staphylococcus aureus* accounted for most of the increase, whereas among children aged 2–4 years, most of the increase in empyema was recorded as due to unspecified pathogens.

By the end of 2007, the estimated coverage with 3 and 4 doses of PCV7 among US children aged 19–35 months was 90% and 75.3%, respectively [20]. Although invasive pneumococcal disease caused by vaccine serotypes has been virtually eliminated in young children, invasive pneumococcal disease caused by nonvaccine serotypes increased. However, invasive pneumococcal disease incidence due to these nonvaccine serotypes remains small [11]. After the initial decreases, the overall incidence of invasive pneumococcal disease has remained relatively constant and well below historical values through the end of 2007 [21]. Consistent with these changes, decreases in pneumonia hospitalizations were sustained and pneumonia hospitalization rates remained relatively stable after the initial decreases [8].

Our findings indicate that the observed decreases in pneumonia incidence were not the result of changes in coding practices from pneumonia to other nonpneumonia diagnoses [22]. Changes in hospital admission practices do not appear to account for the reduction in pneumonia hospitalizations, because no compensatory increases in rates of pneumonia ambulatory visits have been observed after PCV7 introduction [23]. On the contrary, the incidence of ambulatory visits for pneumonia have also decreased, further supporting the beneficial effects of the vaccination program [9].

We also considered whether the increase in empyema may have been attributable at least in part to changes in coding practices. We observed an overall trend of increasing number of diagnoses recorded for all hospitalizations (data not shown). Both the overall increase in the number of recorded diagnoses and thoracentesis procedures suggests that some of the observed increase in empyema may be associated with enhanced coding.
and improved diagnosis. However, the magnitude of the increase was consistent with other local and regional reports of an increase in this complication. An increasing number of empyemas was reported in Utah before PCV7 introduction, from 1993 through 1999 [13], and similar increases were documented in Texas [24]. Moreover, a multistate surveillance initiative documented an increase in complicated pneumococcal pneumonia (mainly empyema) from 1996 through 1999 [12]. Similar increases have also been observed in other countries [25–29].

Nationally, empyema was a relatively rare occurrence, complicating <1% of all-cause pneumonia hospitalizations among children aged <5 years. In 2007, an estimated 1500 US children aged <5 years were hospitalized for pneumonia complicated by empyema. Nevertheless, our analysis of 12 years of national data allowed the assessment of trends in this rare outcome. The increasing incidence of pneumonia complicated by empyema during the study years is intriguing. Other reports suggest that pneumococcal serotype 1 (not covered by PCV7) was a leading cause of this complication, even before PCV7 introduction [12, 13, 24]. Although no serotype information was available in our study database, a recent surveillance report suggested that serotype 1 accounted for <1% of invasive pneumococcal diseases among US children aged <5 years in 2007 [30]. The serotypes most commonly reported to be associated with empyema (1, 3, and 19A) are included in the new 13-valent conjugate vaccine. Peaks of empyema hospitalizations were observed during some years (eg, 1999 and 2005), possibly associated with epidemic patterns of disease caused by certain serotypes. Although overall rates of empyema increased over time, pneumococcal empyema rates remained stable in children aged <2 years but increased among children aged 2–4 years. Rates of staphylococcal empyema increased substantially in children aged <5 years. These findings are consistent with results of a study performed in Texas (1993–2002) that documented a gradual increase in staphylococcal empyema, especially among young children [24].

Empyema due to other or unspecified pathogens also increased among children aged <5 years. Defining the etiology of empyema is difficult [12, 13], and whether these increases in empyema due to other or unspecified pathogens indicate true emerging trends, reduced or delayed laboratory testing, or increased use of antibiotics prior to hospitalization [31] is unclear. Interestingly, several studies that used molecular diagnostic techniques found that a sizable proportion of culture-negative empyema in children was caused by pneumococci, mainly serotype 1 [26, 32–35]. Even though those studies sug-
Figure 3. Rates of pneumonia hospitalizations complicated by empyema by associated pathogens, United States children aged <5 years (1996–2007). Error bars indicate 95% confidence intervals.

gest that pneumococcus remains the leading cause of empyema in children, our data also suggest that the etiology of empyema is changing and that the monitoring of empyema trends is warranted.

The observed reductions in pneumonia hospitalization rates preceded the formal recommendations for influenza vaccination of young children that started in 2004 [36]. The national estimated coverage of influenza vaccine among children aged 6–23 months (fully vaccinated) was 17.8%, 20.6%, and 21.3% for the 2004–2005, 2005–2006, and 2006–2007 influenza seasons, respectively [37]. We considered that this low influenza vaccine coverage was an unlikely explanation for the substantial pneumonia incidence decreases observed. Of interest, the national incidence of empyema associated with S. aureus infections was highest during 2005–2007, coinciding temporally with increases in mortality attributable to coinfection of influenza
and *S. aureus* in young children [38]. Continuous surveillance will be necessary to explore the effects of increasing coverage with influenza vaccine on pneumonia and its complications.

Several caveats in the interpretation of our results must be considered. First, in this ecologic study we assessed the population effects of the PCV7 vaccination program regardless of the individual’s vaccination status, thus reflecting direct and indirect vaccine effects as well as effects unrelated to vaccination. Second, because our main analyses focused on children aged <2 years, our estimates included vaccine effects on young infants who were not yet eligible for vaccination but likely benefited from reduced exposure to the pneumococcus [39]. Third, our databases do not contain information on pneumococcal serotypes or patterns of antibiotic resistance. Because serotyping is not part of routine diagnostic work-up and this information is not recorded in medical charts, our estimates represent changes in disease caused by both vaccine and non-vaccine serotypes. Similarly, the available information did not allow the distinction between empyema due to methicillin-resistant and non–methicillin-resistant *S. aureus*. Finally, the accuracy of our approach to identify pneumonia and empyema cannot be determined with the information available, and changes in coding and recording practices could affect our estimates (ie, artificially increasing the number of empyema during recent years). Nevertheless, ~83% of empyema hospitalizations had thoracentesis procedures recorded, suggesting high specificity of the discharge diagnosis codes. Nationwide Inpatient Sample data are deidentified before public release; thus, chart reviews cannot be performed to confirm diagnoses. The identification of pneumonia with use of any listed discharge diagnosis in administrative databases can be suboptimal in identifying pneumonia as the main reason for hospitalization [10]. That approach would include nosocomial pneumonia that developed during a hospital stay. In this study, we attempted to exclude nosocomial pneumonia or empyema by focusing our outcome definitions on the principal discharge diagnosis (first listed). Discharge diagnoses are recorded at the end of the hospitalization episode, and principal discharge diagnoses are considered to represent the main reason for hospitalization in the Nationwide Inpatient Sample data [16].

For the analyses of pneumonia hospitalizations, our study averaged the annual incidence rates observed before and after PCV7 introduction. This approach ignored secular trends and provided conservative estimates, compared with those obtained by modeling monthly disease rates [8]. However, hospitalization monthly data were not consistently available for all study years, and empyema was a rare outcome, necessitating pooling data in 3-year time periods.

Our findings indicate that the initial decreases observed in rates of all-cause and pneumococcal pneumonia hospitalizations were sustained. Routine vaccination with PCV7 has substantially reduced the burden of childhood pneumonia hospitalizations in the United States. The increasing trend in empyema preceded PCV7 introduction, suggesting that a direct association with the PCV7 vaccination program is unlikely. Although empyema was associated with only a small fraction of pneumonias, the observed increase is of concern and warrants monitoring.

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