Sinusitis and Pneumonia Hospitalization After Introduction of Pneumococcal Conjugate Vaccine

WHAT'S KNOWN ON THIS SUBJECT: Pneumococcal conjugated vaccines (PCVs) are known to decrease invasive pneumococcal disease in children, but their effect on pneumonia necessitating hospitalization is more variable across study sites, and effects on hospitalization for sinusitis have not been shown previously.

WHAT THIS STUDY ADDS: There was a significant decrease in hospitalizations for sinusitis in children <2 years of age, and hospitalization for pneumonia decreased in children aged <5 years after sequential introduction of PCV7 and PCV13.

abstract

BACKGROUND AND OBJECTIVE: Streptococcus pneumoniae is a major cause of pneumonia and sinusitis. Pneumonia kills >1 million children annually, and sinusitis is a potentially serious pediatric disease that increases the risk of orbital and intracranial complications. Although pneumococcal conjugate vaccine (PCV) is effective against invasive pneumococcal disease, its effectiveness against pneumonia is less consistent, and its effect on sinusitis is not known. We compared hospitalization rates due to sinusitis, pneumonia, and empyema before and after sequential introduction of PCV7 and PCV13.

METHOD: All children 0 to <18 years old hospitalized for sinusitis, pneumonia, or empyema in Stockholm County, Sweden, from 2003 to 2012 were included in a population-based study of hospital registry data on hospitalizations due to sinusitis, pneumonia, or empyema. Trend analysis, incidence rates, and rate ratios (RRs) were calculated comparing July 2003 to June 2007 with July 2008 to June 2012, excluding the year of PCV7 introduction.

RESULTS: Hospitalizations for sinusitis decreased significantly in children aged 0 to <2 years, from 70 to 24 cases per 100 000 population (RR = 0.34, P < .001). Hospitalizations for pneumonia decreased significantly in children aged 0 to <2 years, from 450 to 366 per 100 000 population (RR = 0.81, P < .001) and in those aged 2 to <5 years from 250 to 212 per 100 000 population (RR = 0.85, P = .002). Hospitalization for empyema increased nonsignificantly. Trend analyses showed increasing hospitalization for pneumonia in children 0 to <2 years before intervention and confirmed a decrease in hospitalizations for sinusitis and pneumonia in children aged 0 to <5 years after intervention.

CONCLUSIONS: PCV7 and PCV13 vaccination led to a 66% lower risk of hospitalization for sinusitis and 19% lower risk of hospitalization for pneumonia in children aged 0 to <2 years, in a comparison of 4 years before and 4 years after vaccine introduction. Pediatrics 2014;134:e1528–e1536

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KEY WORDS
Streptococcus pneumoniae, sinusitis, pneumonia, pneumococcal conjugated vaccine

ABBREVIATIONS
CI—confidence interval
ICD-10—International Classification of Diseases, 10th Revision
PCV—pneumococcal conjugate vaccine
RR—rate ratio
RSV—respiratory syncytial virus

Dr Örtqvist and Alfven made equal contributions to this article. Dr Lindstrand conceptualized and designed the study, carried out data collection and analyzed the data, and drafted and revised the manuscript; Dr Bennet conceptualized and designed the study, carried out data collection, and reviewed and revised the manuscript; Dr Galanis performed statistical analysis and reviewed and revised the manuscript; Drs Blennow, Rinder, Erikkson, Henriques-Normark, Örtqvist, and Alfven conceptualized and designed the study and reviewed and revised the manuscript; Drs Ask and Dennison reviewed medical records of the sinusitis patients and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-4177
doi:10.1542/peds.2013-4177

Accepted for publication Sep 2, 2014
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(Continued on last page)
Streptococcus pneumoniae is a common cause of invasive infections in children, such as bacteremic pneumonia, septicemia, and meningitis, but also of noninvasive infections such as nonbacteremic pneumonia, sinusitis, and otitis. Pneumococcal disease is the vaccine-preventable disease that currently causes most child deaths worldwide. Every year 826,000 deaths in children 1 to 59 months old are caused by S. pneumoniae, corresponding to 7% of all deaths in this age group. Pneumonia makes up 90% of these deaths.2–4

Sinusitis in preschool children is a potentially serious disease because of anatomic closeness to the orbita and the brain. Complications include periorbital and orbital cellulitis, abscesses, and meningitis. The most commonly isolated pathogens in pediatric sinusitis are S. pneumoniae (30%), Haemophilus influenzae (30%), and Moraxella catarrhalis (10%).5 The disease is more severe in patients infected with pneumococci than in those infected with H. influenzae.6

Pneumococci may be divided into >90 serotypes, depending on the structure of their polysaccharide capsules. Effective pneumococcal conjugate vaccines (PCVs) targeting an increasing number of serotypes (PCV7, PCV10, and PCV13) have been developed for children <2 years of age. Meta-analyses of randomized placebo-controlled clinical trials in children <2 years old show that PCVs have a vaccine efficacy against vaccine-type invasive pneumococcal disease (80% [58%-90%]), radiologically verified pneumonia (27% [15% to 36%]), and clinical pneumonia (6% [2%-9%]).7 Since 2000 global use of PCVs has increased and has consistently led to reductions of 79% to 100% in the incidence of vaccine-type invasive pneumococcal disease. Effectiveness of PCVs in reducing hospitalization rates for pneumonia seems less consistent, with a decrease ranging from 13% to 65% in all-cause pneumonia hospitalizations in children.8,9 However, some studies show decreased risk only in infants and increasing risk in older children.10–12 To our knowledge PCV effectiveness against hospitalizations due to sinusitis in children has not been clarified previously.13–15

In Stockholm County, Sweden, PCV7 was offered on a 2+1 schedule at 3, 5, and 12 months of age to all children born since July 1, 2007. PCV7 was changed to PCV13 in January 2010, even for children who had received 1 or 2 doses of PCV7. No catch-up program was implemented. High coverage with the vaccine was reached early on, and by 2 years of age 96% of children born in 2008 and 98% of those born in 2010 had received 3 doses of PCV.16

The aim of this study was to evaluate the impact of PCV7 and PCV13 on the incidence of hospitalization due to pediatric sinusitis, pneumonia coded as bacterial pneumonia, and empyema. We compared hospital discharge diagnoses during the 4-year periods before and after introduction of PCV7.

METHODS

A retrospective population-based study was performed using International Classification of Diseases, 10th Revision (ICD-10) coded hospital registries to identify all children hospitalized with sinusitis, pneumonia, and empyema in Stockholm County between July 2003 and June 2012. The year of introduction of PCV7, from July 1, 2007 to June 30, 2008, was excluded from the analysis. The study years included cases from July 1 through June 30, to keep winter’s higher infection rates within 1 study year.

Study Population and Data Collection

In 2012 Stockholm County had a population of ~2 million, of whom 22% were <18 years (458,000) and 7% (144,000) were <5 years old.17 Data on hospitalizations were collected from the 3 children’s hospitals in the county. For the diagnosis of sinusitis, data were also included from the only otorhinolaryngologist where children are treated as inpatients in Stockholm. Children 0 to <18 years with the diagnoses being studied were hospitalized exclusively in these 4 places. All children with ICD-10 discharge diagnosis codes J13–J18 (pneumonia coded as bacterial pneumonia, or pneumonia unspecified), J86 (empyema), and J01 (sinusitis) were included. In Sweden children with sinusitis are treated as inpatients only when they have complications, either with orbital or periorbital cellulitis, or are in need of drainage or other surgical procedures.

We used pyelonephritis as a control for the effect of PCV on number of admissions (N10.9). To control for possible changes in diagnosis routines we also recorded the number of children admitted with asthma and obstructive bronchitis (J45.1, J20.9), respiratory syncytial virus (RSV) (J21, J20.5, J12.1), and viral pneumonia (J09–12, except for J12.1 respiratory syncytial pneumonia, J10.1 influenza, and J09 H1N1) during the same time period.

Data on age, gender, and date of admission were recorded for all children. Patients readmitted with the same diagnoses within 30 days of discharge were excluded. The children were divided into the age groups 0 to <2, 2 to <5, and 5 to <18 years for analysis.

To validate the ICD-10 diagnoses we reviewed the medical records of all children with a discharge diagnosis of sinusitis (N = 678) and 100 children with pneumonia coded as bacterial pneumonia (50 before and 50 after vaccination). Information on signs and symptoms, radiographic findings, treatment, risk factors, and outcome
was collected. Sinusitis cases were considered valid if there was a previous or ongoing respiratory infection, signs of orbital or peri-orbital swelling or redness, or a positive computed tomography scan. Pneumonia cases were considered valid if there was ongoing respiratory infection or radiographic verification, or they were judged by the attending pediatrician to be of bacterial origin and antibiotics were given.

**Ethical Permission**
Ethical approval was obtained from the Stockholm Regional Ethics Committee.

**RESULTS**

Sinusitis
Between July 2003 and June 2012, 678 children <18 years old were discharged from the hospital with a diagnosis of sinusitis. Validation of medical records using preset criteria led to exclusion of 76 cases because of incorrect diagnosis without signs of concomitant sinusitis, such as skin infection, conjunctivitis, or insect bite (n = 46), or because there were no clinical signs of sinusitis (n = 30). Of the 602 remaining validated sinusitis cases, 234 (39%) patients were aged <2 years and 159 (26%) 2 to <5 years. Of the 393 children <5 years of age, 62% were boys.

The incidence of hospitalization for sinusitis in children <2 years of age decreased significantly from the pre-vaccination to the postvaccination period, from 70 to 24 per 100 000 person-years (RR = 0.34; 95% CI, 0.25–0.47, P < .001). A decrease, although not significant, was also seen in children 2 to <5 years of age (RR = 0.72; 95% CI, 0.51–1.02; P = .06), whereas the incidence remained stable in older children (Table 1).

Trend analysis showed that before PCV7 introduction there was no significant increase in month-to-month hospitalizations for pneumonia in children aged 0 to <2 years (P = .001), but there was no significant change in children aged 2 to <5 years. Soon after the first year of vaccination (July 2008) there was a significant decrease in hospitalizations in children aged 0 to <2 years (P = .002). However, a significant month-to-month decrease in the postvaccination period was seen only in those aged 2 to <5 years (P = .02). For the age group 5 to 18 years there was an increasing trend in month-to-month hospitalizations both before and after vaccination, but there was no difference in the incidence RR (Fig 1, Tables 1 and 2).

When we compared the 50 validated pneumonia cases coded as bacterial pneumonia before PCV7 introduction
Table 1: Number of Hospitalizations and Incidence of Pneumonia, Sinusitis, Empyema, Pyelonephritis, Asthma and Obstructive Bronchitis, RSV Infection, and Viral Pneumonia in Children 0 to <18 y Before and After Sequential PCV7 and PCV13 Introduction in Stockholm

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<td>0–&lt;2 y</td>
<td>914</td>
<td>836</td>
<td>450</td>
<td>366</td>
<td>0.81 (0.74–0.89)</td>
<td>&lt;.001</td>
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<td>2–&lt;5 y</td>
<td>687</td>
<td>694</td>
<td>250</td>
<td>212</td>
<td>0.85 (0.76–0.94)</td>
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<td>5–&lt;18 y</td>
<td>604</td>
<td>683</td>
<td>51</td>
<td>56</td>
<td>1.10 (0.99–1.25)</td>
<td>.09</td>
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<td>0–&lt;2 y</td>
<td>142</td>
<td>55</td>
<td>70</td>
<td>24</td>
<td>0.34 (0.25–0.47)</td>
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<td>2–&lt;5 y</td>
<td>70</td>
<td>60</td>
<td>25</td>
<td>18</td>
<td>0.72 (0.51–1.02)</td>
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<td>5–&lt;18 y</td>
<td>62</td>
<td>98</td>
<td>7</td>
<td>6</td>
<td>1.16 (0.87–1.56)</td>
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<td>Empyema</td>
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<td>0–&lt;2 y</td>
<td>5</td>
<td>10</td>
<td>2.5</td>
<td>4.4</td>
<td>1.78 (0.55–6.65)</td>
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<td>2–&lt;5 y</td>
<td>5</td>
<td>10</td>
<td>1.8</td>
<td>3.1</td>
<td>1.68 (0.52–6.26)</td>
<td>.49</td>
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<td>5–&lt;18 y</td>
<td>11</td>
<td>19</td>
<td>0.9</td>
<td>1.6</td>
<td>1.68 (0.80–3.55)</td>
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<td>Pyelonephritis</td>
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<td>0–&lt;2 y</td>
<td>598</td>
<td>757</td>
<td>294</td>
<td>331</td>
<td>1.13 (1.01–1.25)</td>
<td>.03</td>
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<td>2–&lt;5 y</td>
<td>123</td>
<td>156</td>
<td>45</td>
<td>48</td>
<td>1.06 (0.84–1.35)</td>
<td>.61</td>
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<td>5–&lt;18 y</td>
<td>167</td>
<td>233</td>
<td>14</td>
<td>19</td>
<td>1.36 (1.11–1.66)</td>
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<td>Asthma and obstructive bronchitis</td>
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<td>0–&lt;2 y</td>
<td>2136</td>
<td>2493</td>
<td>1051</td>
<td>1080</td>
<td>1.04 (0.98–1.10)</td>
<td>.21</td>
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<td>2–&lt;5 y</td>
<td>709</td>
<td>902</td>
<td>258</td>
<td>275</td>
<td>1.07 (0.97–1.18)</td>
<td>.20</td>
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<td>5–&lt;18 y</td>
<td>334</td>
<td>323</td>
<td>28</td>
<td>27</td>
<td>0.94 (0.81–1.10)</td>
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<td>RSV infection</td>
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<td>0–&lt;2 y</td>
<td>1711</td>
<td>2647</td>
<td>842</td>
<td>1158</td>
<td>1.37 (1.29–1.46)</td>
<td>&lt;.001</td>
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<td>2–&lt;5 y</td>
<td>58</td>
<td>137</td>
<td>21</td>
<td>42</td>
<td>1.98 (1.46–2.69)</td>
<td>&lt;.001</td>
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<td>5–&lt;18 y</td>
<td>7</td>
<td>28</td>
<td>0.6</td>
<td>2.3</td>
<td>3.89 (1.66–10.58)</td>
<td>&lt;.001</td>
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<td>Viral pneumonia</td>
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<td>0–&lt;2 y</td>
<td>70</td>
<td>115</td>
<td>34</td>
<td>50</td>
<td>1.46 (1.08–1.97)</td>
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<tr>
<td>2–&lt;5 y</td>
<td>42</td>
<td>60</td>
<td>15</td>
<td>18</td>
<td>1.20 (0.81–1.78)</td>
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<td>5–&lt;18 y</td>
<td>24</td>
<td>58</td>
<td>2.0</td>
<td>4.8</td>
<td>2.35 (1.46–3.78)</td>
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In (2005) with 50 cases after vaccine introduction (in 2009), no differences were observed in frequency of chest radiographs on admission (100% in 2005, 98% in 2009). Chronic conditions (mainly asthma, prematurity, or neurologic disease) were found in 36% of children in 2005 and 31% in 2009 (P = .82). The clinical severity of pneumonia, measured using mean C-reactive protein, oxygen saturation, and need for oxygen or intensive care, was comparable in 2005 and in 2009 (data not shown).

**Empyema**

For children <2 years old there was a nonsignificant increased incidence of hospitalization for empyema in the period after compared with the period before PCV7 and PCV13 vaccination (4.4 vs 2.5 per 100 000 person-years; RR = 1.78; 95% CI, 0.55–6.63; P = .42) (Table 1).

**Hospitalization for Control Diagnosis**

Pyelonephritis was used as an indicator disease for general hospitalization trends during the study period. There was a slight increase in hospitalizations during the study period in the age group 0 to <2 years but not among children aged 2 to <5 years (Table 1). However, in the time trend analysis (Fig 1) the month-to-month incidence remained stable in the prevaccination and postvaccination period for both age groups (Fig 1 and Table 2).

The incidence of hospitalizations for asthma and obstructive bronchitis remained stable during the study period (Table 1). However, the incidence of hospitalization for RSV infections and viral pneumonia increased significantly in children <2 years old between the prevaccination and postvaccination periods (RR = 1.37; 95% CI, 1.29–1.46; P < .001 and RR = 1.48; 95% CI, 1.08–1.97; P = .01, respectively) (Table 1).

**DISCUSSION**

To our knowledge this is the first study showing that introduction of PCV7 and PCV13 in the childhood vaccination program significantly reduces hospitalizations for sinusitis in children <5 years of age. We also found a significant reduction in hospitalization rates for pneumonia in children <5 years old. However, there was an increase in empyema in children <2 years of age in the postvaccination compared with the prevaccination period, but this was not statistically significant.
Our finding of a decreased incidence of sinusitis after introduction of PCV7 and PCV13 is supported by a recent study by Peña et al\textsuperscript{20} showing that \textit{S. pneumoniae} was nearly eliminated as an etiological agent of complicated sinusitis in children after PCV introduction in the United States. Moreover, they observed a significant increase in \textit{S. aureus} as a cause of complicated sinusitis. Benninger\textsuperscript{21} described a change in serotype distribution in both acute otitis media and acute rhinosinusitis in children after PCV7 introduction. McNeil et al\textsuperscript{22} showed that in the period when PCV7 was used in the United States, 50% of the pneumococcal isolates recovered from children with chronic sinusitis were serotype 19A, probably because of serotype replacement. So an overall decline in sinusitis after PCV7 and PCV13 vaccination in children may be followed by both serotype replacement and expansion of other bacteria, similar to the experience with invasive pneumococcal disease and otitis media.\textsuperscript{8,23,24}

The effect of PCV on the incidence of pneumonia necessitating hospitalization has varied between studies. A meta-analysis by Fitzwater et al\textsuperscript{8} showed a 13% to 65% reduction in hospitalizations for pneumonia in children. In Norway, Magnus et al\textsuperscript{25} showed a 22% decrease in pneumonia among PCV7-vaccinated children of 12 to 18 months of age. This is comparable to the 19% decrease in hospitalization for pneumonia in children aged <2 years and the 15% decreased risk of pneumonia hospitalization in children 2 to <5 years that we observed in this study.

Nelson et al\textsuperscript{10} observed an effect on pneumonia rates in outpatients in the

*FIGURE 1*  
Trend analysis of hospitalizations by discharge diagnosis per 100,000 population, by age groups 0 to <2 years, 2 to <5 years, and 5 to <18 years in Stockholm County, Sweden, 2003–2012.
United States but only a nonsignificant reduction in confirmed hospitalization events in children aged <1 year. In contrast, a recent study from the United States showed a sustained decrease in hospitalizations for pneumonia in children and a decrease in people >65 years old, possibly a herd effect.26 Our use of a discharge diagnosis of pneumonia coded as bacterial pneumonia as an endpoint was motivated by the difficulty of establishing an etiological diagnosis of pneumonia, especially in small children.

Interestingly, we observed an increasing incidence of admissions to the hospital for pneumonia among children, 2 years and from 5 to 18 years old before vaccine introduction, from 2003 to 2007 (Fig 1). The reason for this increase is unclear, but natural fluctuations caused by expansion of certain pneumococcal serotypes or clones might have contributed. A similar increase in 2004 to 2006 was seen in a national time trend (1997 to 2008) study on hospitalizations for pneumonia among children in England.9 This might have led to an underestimation of the real effect of the PCV vaccination, because we did not calculate expected rates assuming a continued increasing trend and comparing those with the observed rates, as was done in other studies.27

Previous influenza virus infection has been shown to increase the risk of developing pneumococcal pneumonia.28,29 Recent data from the United States showed excess risk of pneumococcal pneumonia during the H1N1 influenza pandemic in 2009.30 In our study we observed only an increase in hospitalizations for pneumonia, coded as bacterial pneumonia, in children aged 2 to <5 years during this pandemic. There was a high coverage rate (50%) of children aged 6 months to 2 years, 70% of children...
aged 3–18 years) of AS03-adjuvanted monovalent vaccine against influenza A(H1N1)pdm09 in Sweden. This vaccine was about 90% effective in preventing the need for hospitalization for pandemic influenza,\textsuperscript{31} which may have lowered the excess risk for pneumococcal pneumonia.

A decrease in RSV infections was seen in South Africa during a PCV trial, and an increase in RSV activity was associated with an increased incidence of pneumonia in children in Israel, indicating mixed infections with RSV and pneumococci.\textsuperscript{32,33} In contrast, we noted an increase in RSV after PCV introduction, which may be explained by 3 consecutive seasons with unusually high circulations of RSV and increasing use of viral respiratory polymerase chain reaction diagnostics on nasopharyngeal samples in the last 10 years. Thus, the higher burden of influenza and RSV after PCV may have lowered the effect of the vaccine on pneumonia, as we found.

Empyema is a rare complication of pneumonia. Grijalva et al\textsuperscript{34,35} showed a twofold increase in hospitalizations for parapneumonic empyema after vaccine introduction in children in the United States. Serotypes 1 and 3 have been associated with empyema, and because they are not included in PCV7, serotype replacement may cause increased rates of empyema after vaccine introduction.\textsuperscript{36} An increase in staphylococcal empyema or empyema of unknown etiology has been described, as well as an increase in pneumonia complicated by empyema, from 3.7 cases per 100 000 children to 10.3 after vaccine introduction in the United States.\textsuperscript{35–37} As was found in earlier studies, we found a nearly twofold increase in hospitalizations for empyema in children aged <2 years; this was nonsignificant, probably because of low numbers. The highest incidence of empyema was observed in 2007 to 2009, immediately after introduction of PCV7, indicating that factors other than the vaccine may have contributed.

A major strength of this population-based study is inclusion of 100% of the relevant hospitalizations registered in the area. This is also the main weakness, because the result depends on doctors assigning the correct ICD diagnosis and not changing coding practices over time. However, we validated all cases of sinusitis and a selection of cases of pneumonia, finding no major changes in ICD coding. Another weakness is that we could not link clinical cases to bacterial strains or serotypes of pneumococci with this study design. However, in prospective studies it is also difficult to isolate the causative microbe in children with pneumonia, sinusitis, or empyema.

Except for introduction of PCV in the vaccination programs, there were no changes or interventions that should have affected pneumonia or sinusitis case management or hospital care or that could have explained the decrease in hospitalizations for sinusitis and pneumonia. This finding is supported by the fact that the hospitalization rates for asthma or obstructive bronchitis and pyelonephritis were stable during the postvaccination period. However, a clear limitation is that data on outpatient care are not available.

Our data come from Sweden, a country with 98% PCV coverage, >80% day care attendance, very low levels of HIV infection and tuberculosis, and low antibiotic consumption compared with most countries, all of which play a role in the results. Therefore, it is not only pneumococcal vaccines that affect the rate of hospitalization for pneumonia and sinusitis in children; fluctuations in other bacterial and viral pathogens, socioeconomic status, hygiene in day care centers, and antibiotic pressure in society may also affect pneumococcal transmission.

**CONCLUSIONS**

Pneumococcal disease is the most important vaccine-preventable disease in children, because it causes most child deaths. Many low- and middle-income countries are implementing PCV vaccination programs. This study adds evidence that PCV vaccine (PCV7 and PCV13) prevents severe sinusitis and pneumonia, with implications for global child survival.\textsuperscript{38–40} Specifically, we are the first to show great effectiveness against sinusitis in children aged <5 years.

**ACKNOWLEDGMENTS**

We gratefully acknowledge Anna Granath for her scientific contribution to the sinusitis part of the study.

**REFERENCES**


FINANCIAL DISCLOSURE: In the tender for buying pneumococcal vaccine, Stockholm County Council included a demand that the company chosen to supply the vaccine was to give the county a 5% discount off the vaccine price for enabling an epidemiological follow-up. Money from this discount has been used for the current study. The money was not paid to an institution but directly to the Stockholm County Council.

FUNDING: Supported by Stockholm County Council research funds, Foundation Samariten, Sachs’ Children’s Hospital, Swedish Research Council, Swedish Foundation for Strategic Research, Knut and Alice Wallenberg Foundation, and Sven Jerrings Foundation.

POTENTIAL CONFLICT OF INTEREST: Dr Lindstrand received financial contributions for participation in 2 scientific conferences from GSK and Pfizer, and her employer financed the equivalent amount according to the national rules for pharmaceutical sponsorship for medical education, and she has participated in 1 clinical vaccine trial in collaboration with GSK.
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Pediatrics 2014;134;e1528
DOI: 10.1542/peds.2013-4177 originally published online November 10, 2014;

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*Pediatrics* 2014;134;e1528
DOI: 10.1542/peds.2013-4177 originally published online November 10, 2014;

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