Increased paediatric hospitalizations for empyema in Australia after introduction of the 7-valent pneumococcal conjugate vaccine

Roxanne E Strachan, a Thomas L Snelling b & Adam Jaffe c

Objective To examine rates of paediatric hospitalization for empyema and pneumonia in Australia before and after the introduction of the seven-valent pneumococcal conjugate vaccine (PCV7).

Methods Rates of paediatric hospitalization for empyema and pneumonia (bacterial, viral and all types) were calculated following the codes of the International Classification of Diseases, tenth revision (ICD-10) as a principal diagnosis. The expected number of hospitalizations after the PCV7 was introduced was estimated on the basis of the observed number of hospitalizations before the introduction of the PCV7. Incidence rate differences (IRDs) and incidence rate ratios (IRRs) were calculated. Hospitalization incidence in each study period was expressed as the number of hospitalizations per million (10^6) person–years. The population of children aged 0–19 years in Australia from 1998 to 2004 and from 2005 to 2010, as reported by the Australian Bureau of Statistics, was used to calculate the number of person–years in each period.

Findings In the 5 years following the introduction of the PCV7, hospitalizations for pneumonia were fewer than expected (15 304 fewer; 95% confidence interval, CI: 14 646–15 966; IRR: 0.78 per 10^6 person–years; 95% CI: 0.77–0.78). Hospitalizations for empyema, on the other hand, were more than expected (83 more; 95% CI: 37–128; IRR: 1.35 per 10^6 person–years; 95% CI: 1.14–1.59). Reductions in hospitalizations were observed for all ICD-10 pneumonia codes across all age groups. The increase in empyema hospitalizations was only significant among children aged 1 to 4 years.

Conclusion The introduction of the PCV7 in Australia was associated with a substantial decrease in hospitalizations for childhood pneumonia and a small increase in hospitalizations for empyema.

Introduction

Streptococcus pneumoniae is the leading cause of bacterial infection in children worldwide and the most common cause of bacterial pneumonia in Australia, where it accounts for approximately one third of all cases. 1 In Australia, about 0.7% of all cases of pneumonia in children are complicated by empyema, which requires hospitalization for treatment and possible drainage. 2 S. pneumoniae is also the most common pathogen causing empyema. 3 The 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in Australia’s national immunization programme in two phases: in 2001 for indigenous and immunocompromised children less than 2 years of age, and in January 2005 for all children in this age group. In July 2011 the PCV7 was replaced by a 13-valent conjugate vaccine. The PCV7 was administered as a three-dose series at ages 2, 4 and 6 months, without a booster.

Although pneumococcal conjugate vaccines have reduced invasive pneumococcal disease rates in children and adults throughout the world, 4–12 several studies have reported a concomitant increase in empyema cases, both in the vaccinated and the non-vaccinated population. 13–15 Because up to 90% of these cases have been caused by bacterial serotypes not included in the PCV7, 16–18 some fear that empyema may have emerged as a “replacement disease”, i.e. disease produced by non-vaccine-related serotypes that have become predominant. Although we have reported the rates of childhood empyema in Australia elsewhere, 7 no previous studies have examined how the introduction of PCV7 has affected childhood empyema rates in this country. The objective of this study is to examine the incidence of paediatric hospitalizations for pneumonia and empyema in Australia before and after the introduction of the PCV7.

Methods

We reviewed the annual incidence in Australia of paediatric hospitalizations for empyema and pneumonia (viral and bacterial) before and after the introduction of PCV7 among children in the following age groups: < 1 year, 1–4 years, 5–9 years, 10–14 years and 15–19 years. The pre-vaccine period extended from July 1998 to June 2004; the post-vaccine period, from July 2005 to June 2010. We included all hospitalizations from July 2004 to June 2005 because the PCV7 was introduced midway through this period. In Australia, hospital discharges are coded for the principal diagnosis (primary cause) in accordance with the coding system of the International Classification of Diseases, tenth revision. The Australian Institute of Health and Welfare collated the national hospital discharge codes supplied by state and territory authorities per financial year, from July to June, and introduced them into the National Hospital Morbidity Database, which is publicly available. From this database we obtained data on the hospitalizations in the age groups already indicated. Although a “child” is generally defined as a person under the age of 18 years, data cubes were only available for these age groups. We included codes for bacterial pneumonia (J13–J15.9, J16.8, J18.0, J18.1, J18.8–J20.0) and viral pneumonia (J10.0, J11.0, J12.0–J12.2, J12.8, J12.9), as well as codes for empyema (J86–J86.9). We expressed hospitalization incidence as hospitalizations per 10^6 person–years following the introduction of the PCV7, hospitalizations for pneumonia were fewer than expected (15 304 fewer; 95% confidence interval, CI: 14 646–15 966; IRR: 0.78 per 10^6 person–years; 95% CI: 0.77–0.78). Hospitalizations for empyema, on the other hand, were more than expected (83 more; 95% CI: 37–128; IRR: 1.35 per 10^6 person–years; 95% CI: 1.14–1.59). Reductions in hospitalizations were observed for all ICD-10 pneumonia codes across all age groups. The increase in empyema hospitalizations was only significant among children aged 1 to 4 years. Conclusion The introduction of the PCV7 in Australia was associated with a substantial decrease in hospitalizations for childhood pneumonia and a small increase in hospitalizations for empyema.

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person–years and used census data for the population less than 20 years of age from the Australian Bureau of Statistics to calculate the number of person–years in each study period. There were 31,846,901 and 27,713,068 person–years in the pre- and post-vaccine periods, respectively.

We compared the incidence of hospitalization for all pneumonias, as well as for bacterial and viral pneumonia separately and for empyema, in the pre-and post-vaccine periods. We estimated the expected number of hospitalizations in the post-vaccine period by multiplying the hospitalization incidence rate in the pre-vaccine period by the number of person–years in the post-vaccine period. We also calculated incidence rate differences (IRD = incidence rate in pre-vaccine period minus incidence rate in post-vaccine period) and incidence rate ratios (IRR = incidence rate in post-vaccine period divided by incidence rate in pre-vaccine period) with their exact 95% confidence intervals (CIs), assuming a Poisson distribution.

**Results**

Overall, 78,552 and 53,052 pneumonia-coded hospitalizations took place in the periods before and after the introduction of the PCV7, respectively. The incidence of hospitalizations was 22% lower in the post-vaccine period than in the pre-vaccine period (IRR: 0.78; 95% CI: 0.77–0.78) (Fig. 1, Table 1). This reduction in hospitalization incidence was greatest among children whose age made them eligible for vaccination (i.e. <1 year and 1 to 4 years in age) but was observed in all age groups. Most of the decrease in the incidence of hospitalizations was noted among children hospitalized for pneumonia with a bacteria-specific code (Table 1). In contrast, the incidence of hospitalizations coded as being for empyema was 35% higher (IRR: 1.35; 95% CI: 1.14–1.59) in the post-vaccine period than in the pre-vaccine period (Fig. 2, Table 1); the incidence of hospitalizations coded for viral pneumonia was 31% higher (IRR: 1.31; 95% CI: 1.27–1.35) (Table 1). However, the absolute increase in the incidence of hospitalizations for empyema and for viral pneumonia (3 and 70 hospitalizations more per 10^6 person–years, respectively) was much smaller than the absolute decrease in the incidence of hospitalization for bacterial pneumonia (623 hospitalizations fewer per 10^6 person–years). On subgroup analysis, the increase in empyema was only significant among children aged 1 to 4 years, which was the age group with the largest number of hospitalizations. There was little evidence of an increase in empyema among children born before the PCV7 became routinely available in Australia (i.e. those aged 5–9, 10–14 and 15–19 years).

**Discussion**

Hospitalizations for childhood empyema in Australia appear to have increased after the introduction of the PCV7, despite a significant decrease in hospitalizations for pneumonia as a whole over the same period. The reduction in the incidence of hospitalizations for pneumonia was greatest among children whose age made them eligible for vaccination (i.e. <1 year and 1–4 years in age), but more modest reductions were also observed among older children. Although the increase in the incidence of hospitalizations for empyema (which is present in fewer than 1% of pneumonia hospitalizations) was greatly outweighed by the reduction in the incidence of hospitalizations for pneumonia, empyema accounts for an important fraction of the cases of severe, complicated pneumonia. We assume that the IRDs we report here are primarily the result of vaccine-attributable changes in the epidemiology of childhood pneumonia in Australia, although they could also be reflecting other factors, including underlying secular trends. Our method is analogous to the method used in studies in England and Scotland on trends in childhood pneumonia and empyema.16,19

We based this analysis on publicly available hospitalization and population data. A limitation of the study is that we used hospital discharge data coded for the primary diagnosis. Bacterial pneumonias in children are difficult to distinguish from viral pneumonias because bacterial culture has a low positive yield. Furthermore, as many as 33% of the children with pneumonia are infected by mixed pathogens.20 Hence, the coding data may be inaccurate. To avoid this problem, we chose to compare the hospitalization rates for pneumonia as a whole rather than for bacteria-specific pneumonias. The reduction in hospitalizations for bacterial pneumonia was accompanied by a smaller absolute increase in pneumonias coded as viral (Table 1). This might reflect changes in coding practices or perhaps improvements in molecular diagnostics and a greater availability of viral antigens over time. Pneumonias coded as viral decreased among infants. This was also seen in a field trial of conjugate vaccine that demonstrated a reduction in viral pneumonia, presumably because viral pneumonia in young children is

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**Table 1.** Incidence of hospital admissions for pneumonia, Australia, 1998–2004 and 2005–2010

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Incidence (per 10^6 person–years)</th>
</tr>
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<tbody>
<tr>
<td>&lt;1 year</td>
<td>1000</td>
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<tr>
<td>1–4 years</td>
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<td>5–9 years</td>
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<td>4000</td>
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<td>15–19 years</td>
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* Number of hospitalizations per million (10^6) person–years. There were 31,846,901 person–years in the period from July 1998 to June 2004 and 27,713,068 person–years in the period from July 2005 to June 2010.

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**Fig. 1.** Incidence of hospital admissions for pneumonia, Australia, 1998–2004 and 2005–2010
Table 1. Incidence rate differences (IRDs) and incidence rate ratios (IRRs) for paediatric hospitalizations for pneumonia and empyema before and after the introduction of the 7-valent pneumococcal conjugate vaccine, Australia

<table>
<thead>
<tr>
<th>Age group (years), by disease category</th>
<th>July 1998 to June 2004</th>
<th>July 2005 to June 2010</th>
<th>IRD&lt;sup&gt;c&lt;/sup&gt; (95% CI)</th>
<th>IRR&lt;sup&gt;d&lt;/sup&gt; (95% CI)</th>
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<tr>
<td></td>
<td>PY Hospitalizations</td>
<td>Incidence&lt;sup&gt;a&lt;/sup&gt;</td>
<td>PY Hospitalizations (no.)</td>
<td>Incidence&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td>Expected&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Observed</td>
<td></td>
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<td>Bacterial pneumonia</td>
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<td>15–19</td>
<td>8012134</td>
<td>71</td>
<td>9</td>
<td>7240822</td>
</tr>
</tbody>
</table>

CI, confidence interval; PY, person–years.

<sup>a</sup> Hospitalizations per million (10<sup>6</sup>) person–years.

<sup>b</sup> The number of hospitalizations expected in the post-vaccine period was derived by multiplying the hospitalization incidence rate in the pre-vaccine period by the number of person–years in the post-vaccine period.

<sup>c</sup> IRD is the incidence rate in pre-vaccine period minus incidence rate in post-vaccine period.

<sup>d</sup> IRR is the incidence rate in post-vaccine period divided by incidence rate in pre-vaccine period.
often complicated by co-infection with pneumococcus.21 Another limitation of our study is that we only included hospitalizations for which pneumonia and empyema were the primary diagnosis. Hence, our findings probably represent minimum estimates of disease incidence. Furthermore, we were unable to perform subgroup analysis by ethnic group and place of residence because these data are not publicly available.

For convenience, we examined the period preceding and the period following the introduction of the PCV7. Since the vaccine was introduced in January 2005, we excluded from the analysis all data for the period from July 2004 to June 2005 (Table 1). Nonetheless, the post-vaccine period included some children whose age would not have made them eligible for vaccination, and this could have resulted in an underestimation of the vaccine’s effect except in the youngest age group (<1 year). In addition, targeted vaccination of indigenous children occurred during part of the pre-vaccine period. However, this probably affected our estimates only minimally since indigenous people account for only 3% of the Australian population.22

Although the PCV7 has substantially reduced the rates of invasive pneumococcal disease, reports from around the world suggest that the incidence of empyema in children has increased following the introduction of the PCV7.10,11 The reasons for this are not entirely clear, but virulent serotypes not covered by the PCV7 may have emerged as a result of the selective pressure applied by the vaccine. Most cases of empyema among Australian children are caused by serotypes 1, 3 and 19A,23 which are believed to be particularly virulent and more likely to invade the pleural cavity.24,25 The reported increase in serotypes 1, 3 and 19A among invasive isolates might explain the increase in empyema but not in pneumonia per se.10–12 On the other hand, an increase in the incidence of empyema was observed in some studies before the introduction of the PCV7.26–28 This suggests that the observed association between the introduction of the PCV7 and the rise in empyema incidence may be coincidental.

Irrespective of its cause, the observed increase in empyema adds to health system costs. In a clinical study in the United Kingdom of Great Britain and Northern Ireland, we calculated that the cost per admission for a child with empyema was between 7600 and 11 700 United States dollars (US$).29 A study in the United States yielded similar estimates.30 Thus, the 35% increase in empyema admissions observed in Australia following the introduction of the PCV7 has brought an additional expenditure of US$ 126 160–194 220 per year to the Australian health-care system. On the other hand, the reduction in pneumonia admissions has saved the health system US$ 3.8 million–6.1 million annually (based on United Kingdom cost-analysis data for pneumonia admissions).31 Although modest, the additional costs owing to the increase in cases of empyema among children would be reduced by the use of a vaccine with broader pneumococcal serotype coverage.3

In July 2011 (October 2011 in Australia’s Northern Territory), Australia’s 13-valent pneumococcal conjugate vaccine was introduced into the national immunization programme. This vaccine includes six serotypes that the PCV7 does not contain, including serotypes 1, 3 and 19A. Despite this, the large number of pneumococcal serotypes that have been identified makes it likely that other virulent pneumococcal strains will emerge. This underscores the need for on-going, enhanced molecular surveillance of invasive pneumococcal strains, including those that cause empyema in children. The results of such surveillance, which is already being practised in the United Kingdom, will directly affect future policy decisions regarding the adoption of newer vaccines as part of the national immunization schedule in Australia. ■

Competing interests: AJ previously received an unrestricted grant from GlaxoSmithKline, Belgium.
Empyema following pneumococcal vaccine in Australia

Research

Z. Strachan et al.

Objective

Examine the incidence of hospitalization for pneumonia in children aged 0-19 years in Australia before and after the introduction of the pneumococcal heptavalent conjugate vaccine, PCV7.

Methods

Assess the incidence of hospitalization for pneumonia in children aged 0-19 years in Australia before and after the introduction of PCV7. The incidence was calculated using the International Classification of Diseases-10 (ICD-10) codes.

Results

There was a significant increase in the incidence of hospitalization for pneumonia after the introduction of PCV7 in children aged 0-19 years in Australia. This increase was observed in both the current and previous years.

Discussion

The increase in hospitalization for pneumonia after the introduction of PCV7 is consistent with the expected increase in cases of pneumonia in children aged 0-19 years in Australia. However, the increase is small compared to the overall decrease in hospitalization for pneumonia in children aged 0-19 years in Australia.

Conclusion

The introduction of PCV7 has led to a significant increase in the incidence of hospitalization for pneumonia in children aged 0-19 years in Australia. The increase is small compared to the overall decrease in hospitalization for pneumonia in children aged 0-19 years in Australia.

Résumé

Augmentation des hospitalisations pédiatriques dues à un empystème en Australie, après l’introduction du vaccin pneumococcique heptavalent conjugué

Objectif

Évaluer l'incidence des hospitalisations pour pneumonie en Australie avant et après l'introduction du vaccin pneumococcique heptavalent conjugué, PCV7.

Méthodes

Les taux d'hospitalisation pédiatrique pour pneumonie ont été calculés à partir des données de l'Annuaire Australien des Hospitalisations (Australian Hospital Morbidity Database) pour les années 2005 et 2010. Les taux d'hospitalisation ont été comparés entre les deux périodes.

Résultats

L'incidence des hospitalisations pour pneumonie a augmenté après l'introduction du PCV7 en Australie. Cependant, l'augmentation est mineure par rapport à la diminution globale des hospitalisations pour pneumonie en Australie.

Discussion

L'augmentation des hospitalisations pour pneumonie après l'introduction du PCV7 est cohérente avec l'augmentation attendue des cas de pneumonie en Australie. Cependant, l'augmentation est faible par rapport à la diminution générale des hospitalisations pour pneumonie en Australie.

Conclusion

L'introduction du PCV7 a entraîné une augmentation significative des hospitalisations pour pneumonie en Australie. Cependant, l'augmentation est faible par rapport à la diminution générale des hospitalisations pour pneumonie en Australie.
Aumento de las hospitalizaciones pediátricas por empiema en Australia tras la introducción de la vacuna conjugada antineumocócica heptavalente

Objetivo Examinar las tasas de hospitalización pediátrica por empiema y neumonía en Australia antes y después de la introducción de la vacuna conjugada antineumocócica heptavalente (PCV7).

Métodos Se calcularon las tasas de hospitalización pediátrica por empiema y neumonía (bacteriana, viral o de todos los tipos) siguiendo los códigos de la Clasificación Internacional de Enfermedades, Tercera Revisión (CIE-10) como forma de diagnóstico principal. El número esperado de hospitalizaciones tras la PCV7 se calculó en base al número de hospitalizaciones observado antes de la introducción de la vacuna. Se calcularon las diferencias en la tasa de incidencia (ITI) y las proporciones de la tasa de incidencia (PTI). La frecuencia de las hospitalizaciones en cada periodo de estudio se expresó como el número de hospitalizaciones por millón (10⁶) de años-persona. Para calcular el número de años-persona en cada periodo, se utilizó la población de niños entre 0 y 19 años en Australia desde 1998 hasta 2004 y desde 2005 hasta 2010, de acuerdo con las informaciones de la Oficina de Estadística Australiana.

Resultados En los cinco años siguientes a la introducción de la PCV7, las hospitalizaciones por neumonía fueron inferiores a lo esperado (15,304 menos; intervalo de confianza del 95%, IC del 95%: 14,646–15,960; DIT: 0,78; IC del 95%: 0,77–0,78). Por el contrario, las hospitalizaciones por empiema fueron más numerosas de lo esperado (83 más; IC del 95%: 14,15–1,59). Se observó una disminución de las hospitalizaciones para todos los códigos CIE-10 de neumonía en todos los grupos de edades. El aumento de las hospitalizaciones por empiema fue significativo únicamente entre los niños con edades comprendidas entre uno y cuatro años.

Conclusión La introducción de la PCV7 en Australia estuvo asociada con un descenso notable en las hospitalizaciones por neumonía infantil, así como con un pequeño aumento de las hospitalizaciones por empiema.
empyema in Spanish children using multilocus sequence typing directly on
PMID:16288412
PMID:11797168
Clin Infect Dis
2002;34:434–40. PMID:12724479
Arch Pediatr
inf.0000202137.37642.ab PMID:16511389
Pediatr Infect Dis J
the pneumococcal conjugate vaccine on pneumococcal parapneumonic
disease among children in a health district of Barcelona: early impact of
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disease in children: changing epidemiology of invasive pneumococcal
disease in Canada, 1998–2007. update from the Calgary-area Streptococcus pneumoniae
PMID:19508165
21.
Obando I, Arroyo LA, Sanchez-Tatay D, Tarrago D, Moreno D, Hausdorff WP et
al. Oral versus i.v. antibiotics for community-acquired pneumonia
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