Pneumonia in Elderly Australians: Reduction in Presumptive Pneumococcal Hospitalizations but No Change in All-Cause Pneumonia Hospitalizations Following 7-Valent Pneumococcal Conjugate Vaccination

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Background. Studies evaluating long-term trends in hospitalizations coded as pneumonia following introduction of the 7-valent pneumococcal vaccine (PCV7) are sparse, especially in adults. We extended our previous analysis to 6.5 years after the “3 + 0” PCV7 schedule was introduced in Australia in 2005.

Methods. We estimated vaccine impact on hospitalizations coded as pneumonia (pneumococcal/lobar, other specified, unspecified, and all-cause) using a multivariate negative binomial regression model of monthly hospitalization rates by age group for the pre-PCV7 (July 1998 to December 2004) and post-PCV7 (January 2005 to June 2011) periods, adjusting for vaccination coverage. Changes in pneumonia hospitalizations were measured as incidence rate ratios.

Results. A total of 791,000 hospitalizations coded as pneumonia were identified; unspecified causes accounted for >85%. Reductions in pneumonia coded as pneumococcal/lobar were statistically significant in all age groups and greatest in children. Significant reductions in all-cause pneumonia were seen only in children aged <2 years (32%; 95% confidence interval [CI], 28%–37%) and 2-4 years (20%; 95% CI, 14%–27%), with no significant changes in other age groups, including adults aged 65–74 (4%; 95% CI, −3% to 10%), 75–84 (2%; 95% CI, −4% to 9%), and ≥85 years (3%; 95% CI, −3% to 10%).

Conclusions. We could not replicate reductions of 23% in all-cause pneumonia 7–9 years post-PCV7 introduction reported for adults aged ≥85 years in the United States. This could be attributable to vaccine program factors, differing proportions of pneumonia due to pneumococci, or data limitations. More data from countries with differing PCV schedules and from the PCV13 era are needed to inform vaccination strategies for elderly adults.

Keywords. Streptococcus pneumoniae; pneumonia; heptavalent pneumococcal conjugate vaccine; immunization schedule.

The 7-valent conjugate pneumococcal vaccine (PCV7) is highly effective against invasive pneumococcal disease (IPD), noninvasive disease, and carriage due to the 7 vaccine serotypes. Reductions in IPD due to vaccine serotypes in unvaccinated age groups have resulted in net decreases in IPD in adults in several settings, although the magnitude has varied [1]. These indirect “herd” benefits have a major impact on cost-effectiveness of PCV7, because of their influence on the total number of cases prevented [2]. In addition to reductions in IPD, reductions in all-cause pneumonia hospitalizations in children following PCV7 introduction have been reported from the United States [3–6],

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Canada [7], the United Kingdom [8, 9], and Australia [10]. However, reductions in pneumonia in adults have been reported only from the United States [4, 6] and Australia [10]. Our original study [10] found significant reductions ranging from 3% to 11% in all-cause pneumonia in the first 2.5 years of the “3+0” Australian infant PCV7 vaccination program (ie, no booster dose after 6 months of age) in persons aged >5 years. Reductions became less marked with increasing age, similar to earlier results from the United States [3]. However, 2 more recent US studies found significant declines in adults aged ≥65 years over longer periods: 6 years [6] and 7–9 years [4] postvaccination. Declines in adults of all ages accounted for 90% [6] and >50% [4] of the overall decline in all-cause pneumonia, respectively. The Australian PCV7 program has a 3-dose primary schedule at 2, 4, and 6 months, but differs from the United States, both in having no booster in the second year of life, and in having achieved high vaccine coverage within 12 months of commencement (>90% received 3 doses in 2005) [11]. In contrast, due to slower uptake exacerbated by a vaccine shortage, coverage took approximately 5 years to reach 90% in the United States [12, 13]. Prior to vaccine introduction, both countries had a high proportion of PCV7-type IPD (Australia: 85% of IPD patients aged <5 years, 67% aged ≥65 years [14]; United States: 83% and 56%, respectively) [15]. We extended our previous study of trends in coded pneumonia hospitalizations to 6.5 years postvaccination, with a particular emphasis on age groups ≥65 years [4].

METHODS

Data Sources

The Australian Institute of Health and Welfare National Hospital Morbidity Database is an electronic collection of de-identified records of episodes of care in >99% of public and private hospitals in Australia. A primary diagnosis and up to 31 secondary diagnoses are coded according to the 10th Revision of the International Classification of Diseases, Australian Modification (ICD-10-AM) [16]. All records with a primary diagnosis code for pneumonia were extracted between July 1998 and June 2011 inclusive. Cases were classified into 3 diagnostic groups based on De Wals [7]. The first group was presumptive pneumococcal pneumonia, which included all cases where Streptococcus pneumoniae was identified as the causative pathogen (ICD-10-AM code J13) and lobar pneumonia (J18.1), as S. pneumoniae is more likely to be the causative agent in such cases. The second group, unspecified pneumonia, included all codes for pneumonia for which a cause was not specified (J15.9, J18). The remaining cases, in which a pathogen other than S. pneumoniae was specified, were classified as nonpneumococcal pneumonia (J10.0, J11.0, J12, J14, J15.0–J15.8, J16, J17). Hospitalizations recorded as occurring in Indigenous Australians were excluded from the analysis due to differences in vaccine program implementation and disease etiology [17].

Statistical Analysis

The data were analyzed as a time series. Monthly rates of all-cause pneumonia hospitalizations per 100 000 population were plotted for each of the following age groups: <2 years, 2–4 years, 5–17 years, 18–39 years, 40–64 years, and ≥65 years. A 12-month moving average was then overlaid to smooth out seasonal variation and display underlying trends in the data. For each age group, multivariate negative binomial regression was performed using Stata software, version 9.2 (StataCorp, College Station, Texas) to quantify the change over time in rates of hospitalizations for all cause, and the 3 diagnostic subgroups of pneumonia, associated with introduction of the universal PCV7 program. The number of cases per month was assigned as the dependent variable and the population estimate for that year as the offset variable. Independent variables included in the model were background trend (1/12 increments per month) and seasonality (indicator variables for each calendar month). The vaccine term was modeled as a linear increase per month from January to December 2005 up to a maximum of 91% coverage, and stable from then onward, approximating trends in percentage vaccine uptake. The background trend term was dropped from the model for age groups where it was not a statistically significant component. The vaccine term parameter estimates from the final adjusted analyses were then exponentiated to generate an estimate of the percentage change in pneumonia hospitalization rates associated with vaccine introduction. The model residuals were plotted in a correlogram to check for autocorrelation and ensure the standard errors and P values generated from the model were accurate.

RESULTS

Between July 1998 and June 2011, 791 812 hospitalizations were recorded as due to all-cause pneumonia in Australian hospitals. In 85.7% of cases, coding did not specify a causative organism. Codes for lobar and pneumococcal pneumonia accounted for 4.3%, and the remaining 10.0% were coded as due to other specified causative organisms, with no consistent trend by age group (data not shown). The rate per 100 000 per month varied by age group (Figure 1).

Pneumonia by Diagnostic Subgroup

Decreases were greatest and statistically significant in all age groups except ≥85 years in the pneumococcal and lobar category, consistent with a vaccine effect (Table 1, Figure 2). Decreases in pneumonia coded as unspecified cause were statistically significant only in children aged <5 years. In all age groups, there were significant increases in pneumonia coded as due to other specified causative organisms statistically significant in all except 18–39, 75–84 and ≥85 years (Table 1).
All-Cause Pneumonia

Monthly age-specific rates of hospitalization for all-cause pneumonia per 100,000 population are shown in Figure 1. A strong seasonal pattern is evident in all age groups. For children <5 years of age, the 12-month moving average revealed marked declines in the first 1–2 years after the PCV7 program began in

Figure 1. Age-specific monthly rates of hospitalization for all-cause pneumonia per 100,000 population in Australia, July 1998–June 2011 (gray line). Solid black line indicates annual moving average for the previous 12 months. Vertical lines represent pneumococcal conjugate vaccine program introduction. Note the variation in the scale on the y-axis between age groups. Abbreviation: PCV7, 7-valent pneumococcal conjugate vaccine.
January 2005. Two to 3 years after program commencement, decreases in ages 5–39 years were less marked, but still evident, whereas there was no clear impact in age groups ≥40 years.

After adjusting for background trends in the prevaccine period and seasonality, statistically significant decreases following PCV7 introduction were found in age-specific hospitalization rates for all-cause pneumonia of 32% (95% confidence interval [CI], 28%–37%) in children aged <2 years and 20% (95% CI, 14%–27%) in children 2–4 years (Table 2). In older age groups, the corresponding point estimates for percentage of change ranged from −5% to 7%, and 95% CIs for the post- to prevaccination incidence rate ratios (IRRs) overlapped 1.0. Overall, the model estimated that for the 1.43 million Australian children aged ≤4 years, PCV7 prevented 2070 hospitalizations for pneumonia per year in the period 2005–2011.

**DISCUSSION**

In this updated analysis, our point estimates of vaccine impact on all-cause pneumonia were lower at 6.5 years postvaccination compared with our previous analysis at 2.5 years, but 95% CIs overlapped in all age groups [10]. As in our previous analysis, we found statistically significant reductions in pneumonia hospitalizations coded as pneumococcal or lobar in all age groups (except ≥85 years). However, these represented only a small proportion of all-cause pneumonia hospitalizations.

In vaccinated age groups (children aged <2 years and 20% aged 2–4 years), statistically significant decreases of approximately 30% in all-cause pneumonia hospitalizations were seen in the 6.5-year period following introduction of universal childhood PCV7 vaccination (Table 2), similar to findings from a number of countries using both 3 + 1 (United States, Uruguay) and 2 + 1 (Quebec, England, and Wales) schedules [3, 4, 6–8, 18, 19]. However, no net decreases were seen in those aged ≥5 years, in contrast to 2 US studies, both of which found significant decreases in adults aged ≥65 years [4, 6]. A comparison of our results with the US study for which comparable age groups and time periods were available is presented in Table 2. There is no suggestion of the late emergence of any decreasing trend in the elderly in Australian data, as occurred in the United States, where decreases were evident at 6 years after introduction of PCV7.

The reasons for differing findings in ours and the US studies are unclear, but there are several potential reasons for varying trends in ecological studies. They include the possibility of vaccine program differences, including vaccination schedules (lack of a routine booster in the second year of life in Australia) or childhood conjugate vaccine coverage, and differing epidemiologic settings such as prevaccine distributions of pneumococcal serotypes and/or the proportion of pneumonia attributable to pneumococci. It is also possible that other population characteristics unrelated to causative agents or vaccination, such as prevalence of smoking, polysaccharide pneumococcal, and influenza vaccination may be responsible, or that undetected study biases, such as differing coding practices or treatment guidelines, could be responsible.

It is unlikely that herd immunity was limited by low coverage in our study. Data on the rapid uptake are presented in the introduction to this article, and high coverage was maintained at >90% every year since then [20]. In addition there was a catch-up program in 2005–2006, in which approximately 60% of children aged <2 years received the recommended number of doses (data not shown).

It is plausible that the lack of a booster in Australia results in a less robust herd immunity impact. A recent systematic review found that evidence of a net decrease in all-cause pneumonia

### Table 1. Estimates of the 7-Valent Pneumococcal Conjugate Vaccine Impact on Pneumonia Hospitalizations, Australia, July 1998–June 2011

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>Pneumococcal and Lobar (95% CI)</th>
<th>Other Specified Cause (95% CI)</th>
<th>Unspecified Cause (95% CI)</th>
<th>All-Cause Pneumonia (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>0.26 (0.21–0.33)</td>
<td>1.28 (1.11–1.47)</td>
<td>0.57 (0.53–0.61)</td>
<td>0.68 (0.63–0.72)</td>
</tr>
<tr>
<td>2–4</td>
<td>0.40 (0.32–0.48)</td>
<td>1.48 (1.29–1.69)</td>
<td>0.69 (0.64–0.75)</td>
<td>0.80 (0.73–0.87)</td>
</tr>
<tr>
<td>5–17</td>
<td>0.46 (0.38–0.55)</td>
<td>1.15 (1.00–1.33)</td>
<td>0.91 (0.84–1.00)</td>
<td>0.94 (0.86–1.03)</td>
</tr>
<tr>
<td>18–39</td>
<td>0.66 (0.59–0.73)</td>
<td>1.11 (0.97–1.27)</td>
<td>0.99 (0.92–1.06)</td>
<td>0.98 (0.92–1.06)</td>
</tr>
<tr>
<td>40–64</td>
<td>0.77 (0.70–0.84)</td>
<td>1.17 (1.06–1.29)</td>
<td>1.05 (1.00–1.10)</td>
<td>1.05 (1.00–1.10)</td>
</tr>
<tr>
<td>65–74</td>
<td>0.86 (0.74–0.99)</td>
<td>1.21 (1.04–1.40)</td>
<td>0.95 (0.88–1.01)</td>
<td>0.96 (0.90–1.03)</td>
</tr>
<tr>
<td>75–84</td>
<td>0.86 (0.76–0.98)</td>
<td>1.13 (0.99–1.29)</td>
<td>0.96 (0.90–1.03)</td>
<td>0.98 (0.91–1.04)</td>
</tr>
<tr>
<td>≥85</td>
<td>0.91 (0.77–1.09)</td>
<td>1.07 (0.89–1.27)</td>
<td>0.96 (0.89–1.02)</td>
<td>0.97 (0.90–1.03)</td>
</tr>
</tbody>
</table>


Abbreviation: CI, confidence interval.

a Using multivariate negative binomial regression modeling, adjusting for background and seasonal trends.

in adults was found only from the United States (3 + 1 schedule), but there was no evidence either way from countries with 2 + 1, and only our preliminary study from a 3 + 0 schedule [18]. However, although there is evidence that a 3 + 1 schedule produces a superior immunologic response compared with 3 + 0 [21], differences in vaccine effectiveness and herd
immunity have not been clearly established. Another recent re-
view concluded that boosters following 2 primary doses were
clearly beneficial in preventing carriage, but the benefit of a boost-
er remained uncertain for 3 + 0 schedules that achieve high cov-
erage [22]. In fact, a comparison of IPD trends in a wide range of
settings found that post- to prevaccination IRRs of vaccine-type
IPD were similar in Australia and the United States for children
aged <5 years at 5 years postvaccination (0.03 [95% CI, .02–.08]
and 0.04 [95% CI, .02–.08]). However, in those aged ≥65 years,
IRRs were actually lower in Australia (0.12 [95% CI, 0.08–.17]
vs 0.20 [0.17–.23]), suggesting a greater herd immunity impact. The
smaller overall decrease in total IPD in those aged ≥65 years in
Australia compared to the United States was due to a greater in-
crease in non-vaccine-type IPD (IRR for Australia: 2.74 [95% CI,
2.22–3.39]; United States: 1.38 [95% CI, 1.22–1.56]) [1]. Statisti-
cally significant decreases in pneumonia hospitalizations coded
classified as pneumococcal or lobar were seen in all age groups in
our study, consistent with a herd effect on vaccine-type pneumonia
from infant vaccination, which in adults did not translate into
a decrease in all-cause pneumonia.

It is possible that there were differing distributions of the
causes of pneumonia prior to vaccine use between the 2 coun-
tries. The proportions of total IPD caused by PCV7 serotypes
were high and not substantially different between Australia
and the United States, as mentioned earlier. However, studies
on the proportions of total pneumonia due to S. pneumoniae
by age group are too few to permit a comparison between the
2 countries [23]. Differences in the diagnostic codes used in
our study and that by Griffin et al [4] are also unlikely to
have been influential. Griffin et al [4] included all-cause septi-
cemia and meningitis as a principal diagnosis, with pneumonia
as a secondary cause, whereas we did not. Testing for sensitivity
to this in our study, these codes constituted an extra 4.6% to the
primary, and time trends were similar to those for pneumonia as
a secondary cause, in all age groups (data not shown).

Influenza vaccination coverage in persons ≥65 years was stable
at 79% in 2004 to 75% in 2009, as was pneumococcal polysaccha-
ride coverage at 51% vaccinated within the previous 5 years in 2004
to 54% in 2009 [24, 25]. Smoking rates declined from 19% of the
adult population in 2001 to 16% in 2011, declining in all age groups
[26]. The results could have been influenced by changes in admis-
sion, diagnostic or coding practices, patterns in other causes of
pneumonia, or other factors. However, there have been no changes
to ICD-10-AM recommendations for pneumonia coding over this
study period [27]. Although Indigenous Australians have high rates
of pneumonia hospitalization, and hospitalizations reported in In-
digenous people have been excluded from this analysis, variations
in reporting of Indigenous status are unlikely to have influenced
the results. Indigenous status reporting in hospitalization data has been
assessed [28]. In 4 jurisdictions that include 60% of the total In-
digenous population and >90% of areas classified as remote, re-
porting has been verified as complete and suitable for analyzing
time trends from 1999 onward. In the other jurisdictions where
reporting has increased over the study period, which comprise
mostly urbanized populations, Indigenous people constitute
only 0.4% of the population aged ≥65 years [29, 30].

This study is consistent with many others that have shown a
decrease in all-cause pneumonia hospitalizations in children
following introduction of a PCV7 infant vaccination program.
However in the elderly, despite showing evidence of herd im-
munity impacts on presumptive pneumococcal pneumonia,
this did not translate to a net decrease in all-cause pneumonia,
unlike recent US studies. Our data show that decreases in all-
main of the studies. More studies are

Table 2. Comparison of Trends in All-Cause Pneumonia Hospitalizations Following Introduction of 7-Valent Pneumococcal Conjugate Vaccine—Australia and the United States

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Prevaccine Ratea</th>
<th>Percentage of Decline 0–6.5 y Postvaccination (95% CI)</th>
<th>Australia</th>
<th>Prevaccine Ratea</th>
<th>Percentage of Decline 7–9 y Postvaccination (95% CI)</th>
<th>United States [4]</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>738</td>
<td>32 (28–37)</td>
<td>1274</td>
<td>43 (34–52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–4</td>
<td>480</td>
<td>20 (13–27)</td>
<td>411</td>
<td>13 (2–23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–17</td>
<td>98</td>
<td>6 (–3 to 14)</td>
<td>97</td>
<td>5 (–6 to 16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–39</td>
<td>90</td>
<td>2 (–6 to 8)</td>
<td>107</td>
<td>8 (0–16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–64</td>
<td>191</td>
<td>–5 (–10 to 0)</td>
<td>336</td>
<td>–10 (–18 to –3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–74</td>
<td>719</td>
<td>4 (–3 to 11)</td>
<td>1293</td>
<td>7 (0–13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75–84</td>
<td>1600</td>
<td>2 (–5 to 9)</td>
<td>2758</td>
<td>13 (7–19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥85</td>
<td>3224</td>
<td>4 (–3 to 11)</td>
<td>5697</td>
<td>23 (7–14)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

* Hospitalizations per 100 000 population per year.
Notes

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