Title
The impact of pneumococcal vaccination on bacterial and viral pneumonia in Western Australian children: record linkage cohort study of 469,589 births (1996-2012)

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Key points

- Aboriginal children experience pneumonia hospitalisation rates 7 times higher than non-Aboriginal children
• 73% of all pathogens identified in children hospitalised with pneumonia were viruses; RSV most common

• All-cause pneumonia hospitalisations have declined in the pneumococcal vaccination era including notable declines in viral pneumonia
ABSTRACT

Background

Pneumococcal conjugate vaccine (PCV) was included in Australia’s National Immunisation Program for all children from 2005. We assessed the impact of PCV on all-cause and pathogen-specific pneumonia hospitalisations in Western Australian (WA) children aged ≤16 years.

Methods

All hospitalisations with pneumonia-related ICD-10AM diagnosis codes occurring in WA-born children (1996-2012) were linked to pathology records. Age-specific incidence rate ratios and temporal trends for all-cause and pathogen-specific pneumonia hospitalisations were calculated pre- and post-PCV introduction.

Results

469,589 births had 15,175 pneumonia-related hospitalisations. Hospitalisation rates were 6.7 (95%CI:6.4-6.9) times higher in Aboriginal than in non-Aboriginal children. Following PCV introduction, all-cause pneumonia hospitalisations showed significant declines across all age groups. A pathogen was identified in 2785 (41.6%) of 6693 pneumonia hospitalisations that linked to a pathology record. Respiratory syncytial virus (RSV) was most frequently identified with RSV-associated pneumonia hospitalisation rates of 89.6/100,000 child-years in Aboriginal and 26.6/100,000 child-years in non-Aboriginal children. The most common bacterial pathogen was Streptococcus pneumoniae in Aboriginal children (32.9/100,000) and Mycoplasma pneumoniae in non-Aboriginal children (8.4/100,000). Viral pneumonia rates declined in all children following PCV introduction, with the greatest declines seen in non-Aboriginal children; declines in bacterial pneumonia were observed in non-Aboriginal children.
Conclusions

Based on our ecological analyses, PCV seems to have had an impact on hospitalisations for pneumonia suggesting that the pneumococcus is likely to play a role in both bacterial and viral pneumonia. Respiratory viruses remain an important pathogen in childhood pneumonia. Vaccines targeting respiratory viruses are needed to combat the residual burden of childhood pneumonia.
BACKGROUND

Pneumonia continues to be the leading cause of childhood mortality and morbidity. Approximately 120 million episodes of pneumonia and 1.3 million deaths occur globally in children aged <5 years each year[1]. In Australia and other developed countries, although mortality is low, pneumonia is a common cause of hospital admission in young children[2, 3]. Furthermore, in Australia, pneumonia is a key cause of health inequality, with hospitalisation rates up to 9.9 times higher in Aboriginal and Torres Strait Islander (hereafter referred to as Aboriginal) children than in non-Aboriginal children aged <5 years[4, 5].

A variety of pathogens can cause pneumonia including *Streptococcus pneumoniae*, respiratory syncytial virus (RSV) and influenza virus; however contemporary Australian data on the aetiology of pneumonia are lacking. Before the introduction of pneumococcal conjugate vaccines (PCV), *S. pneumoniae* was the most common bacterial pathogen identified in children hospitalised with pneumonia; RSV was the most common viral pathogen[6-8]. Introduction of PCV programs have reduced invasive pneumococcal disease (IPD) rates in children worldwide with associated significant declines in all-cause pneumonia-related hospitalisation[1, 5, 9]. This reduction has been partly offset by an increase in the incidence of IPD and pneumonia attributed to non-vaccine serotypes[10, 11].

The 7-valent PCV (7vPCV), administered in a 3+0 schedule (2-4-6 months), was nationally funded and included in Australia’s National Immunisation Program from July 2001 for Aboriginal children <2 years and children <5 years with predisposing medical conditions[12]. A booster, initially with 23-valent pneumococcal polysaccharide vaccine (23vPPV) and subsequently with 13vPCV was included in the 2nd year of life for Aboriginal children. From January 2005, 7vPCV in a 3+0 schedule was universally funded for all Australian children aged <2 years and from July 2011, 7vPCV was replaced by 13vPCV.
We previously reported on declining all-cause pneumonia hospitalisation rates between 1996 and 2005 in Aboriginal and non-Aboriginal children in Western Australia (WA) and the pathogens associated with these hospitalisations[5, 13]. Here, we extend this work by examining rates of all-cause pneumonia hospitalisations after implementation of the universal PCV program and identifying the pathogens associated with pneumonia hospitalisations in children prior to and following introduction of the universal PCV program.

METHODS

Setting and cohort

WA covers a total land area of 2.5 million square kilometres with a population of nearly 2.6 million [14], 3.6% of whom identify as being Aboriginal[15]. A cohort of live births between 1996 and 2012 was identified through the Midwives’ Notification System and Birth Register. Data pertaining to children in the birth cohort were then extracted from the Hospital Morbidity Data Collection, PathWest Laboratory Medicine Database (PathWest) and the WA Notifiable Infectious Diseases Database (WANIDD) and probabilistically linked by the WA Data Linkage Branch (WA DLB)[16]. Aboriginal status of the child was derived by the WA DLB[17].

Pathology data

PathWest is the sole public pathology provider in WA and also processes referred samples from private pathology laboratories in WA. Further details on PathWest are provided elsewhere[13]. We extracted pathology data on respiratory specimens collected from children in the birth cohort between January 2000 and December 2012. At PathWest, respiratory samples received for viral testing during the study period were routinely investigated for RSV, influenza viruses A/B, human adenoviruses, and parainfluenza viruses (PIV). Testing for human metapneumovirus (hMPV) was available from 2003 and routinely tested from 2008. Testing for other respiratory viruses, like human picornaviruses, was performed only on request. Culture for bacterial pathogens was routinely
performed following submission of blood cultures and/or other sterile fluids. Culture of lower respiratory specimens including sputa, endotracheal aspirates and bronchoalveolar lavage specimens was performed for respiratory pathogens including *S. pneumoniae* and *Haemophilus influenzae*; and positive culture results were reported only if a predominant or pure growth of a pathogen was identified from high quality or invasive specimen. Testing for fastidious pathogens (e.g. *Bordetella pertussis*; *Mycoplasma pneumoniae*) was performed by culture, polymerase chain reaction (PCR) or serology upon request.

Pathology data from nasal/nasopharyngeal (NP), throat, tracheal, bronchial, sputum, lung, pleural fluid, blood, cerebrospinal fluid (CSF) or serum specimens were extracted from PathWest laboratory information systems. Nasal/NP specimens (for viruses) included combined nose and throat, nasopharyngeal, per- and post-nasal swabs and aspirates. For respiratory bacterial pathogens, any positive bacterial culture or positive PCR result from normally sterile sites (blood, pleural fluid, lung biopsy and CSF) or significant growth from lower respiratory tract samples (as described above) were considered to be the causative pathogen for that episode of infection. For atypical bacterial pathogens, positive PCR or culture identifications from nasal/NP and throat swabs were also considered valid. For viral pathogens, positive results from any specimens (excluding CSF) on which respiratory virus testing was conducted (including using antigen detection [e.g. immunofluorescent antibodies], PCR, viral culture and serology) were considered to be the aetiological cause. If multiple pathogens (bacterial, viral or in combination) were identified in the same specimen (co-detection), the episode of infection was considered to be caused by more than one pathogen (i.e. co-infection).

**Notifiable infectious disease data**

WANIDD is an intranet-based real-time database storing information on notifiable infectious diseases in WA. It relies on mandatory reporting by doctors and laboratories, and is curated by the
WA Department of Health. We extracted WANIDD records pertaining to children in the birth cohort, with notifications for influenza, pertussis and invasive pneumococcal disease.

**Hospital morbidity data**

We identified hospital records (hereafter referred to as hospital admissions) with an admission and separation date between January 1996 and December 2012 and having a pneumonia-related diagnosis code (International Statistical Classification of Diseases and Related Health Problems, Ninth/Tenth Revision, Clinical/Australian Modification (ICD-9-CM or ICD-10-AM)) (Supplementary Table 1) listed in the principal diagnosis field or in any of the 20 additional diagnosis fields. Inter-hospital transfers and transfers within the same hospital, with the same principal diagnosis, were merged into a single admission. Pneumonia-related admissions within 14 days of a previous pneumonia-related separation were merged and classified as a single episode. ICD codes for admissions relating to skin infections (Supplementary Table 1) were assessed as a negative control to investigate trends in hospitalisations unrelated to vaccination.

**Linking of records relating to same episode of hospitalisation**

WANIDD records were first combined with a PathWest record and if the date of onset on WANIDD matched the reporting date (± 48 hours) on PathWest for the same disease/pathogen, it was considered to be the same episode of infection. As pathology data were available only from 2000, we restricted the hospitalisation data to those pneumonia-related hospital admissions with an admission and separation date between January 2000 and December 2012. The combined pathology and WANIDD records were linked to a pneumonia-related hospital admission record if a specimen was collected 48 hours before or after the date of admission (Figure 1). If the same person had multiple pathology and/or WANIDD records within the 48 hour period, results were merged onto the same admission record.
Statistical analyses

Using person-time-at-risk from pneumonia-related hospital episodes as denominator, annual age-specific incidence rates of all-cause pneumonia hospitalisations were calculated for Aboriginal and non-Aboriginal children. We estimated incidence rate ratios (IRRs) with 95% confidence intervals (CI), across different age groups, between the pre-PCV period (1996-2000) and universal PCV period (2005-2012). Yearly incidence trends were analysed by log-linear modelling using negative binomial regression (nbreg) in STATA and presented graphically as log-transformed rates. Interrupted time trend models were used to examine differences in trend between the pre- and universal PCV periods. To test the impact of the universal vaccine program on population-based trends of pneumonia and to investigate the annual changes in incidence from 1996 to 2012, interrupted linear time trend modelling was conducted with a break point in the year 2001 for Aboriginal children and 2005 for non-aboriginal children. For comparisons with the negative control, we compared linear trends in the pre-PCV and universal PCV periods only. Fitted trends from these models are presented graphically.

To investigate the aetiology of pneumonia, pneumonia-related hospital admissions were used. Pathogen-specific pneumonia hospitalisation rates in children aged <5 years were calculated for Aboriginal and non-Aboriginal children, comparing the pre-universal PCV period (2000-2004) to the universal PCV period (2005-2012). Data cleaning and analysis were performed using SPSS (version 23), EpiBasic (version 3) and STATA (version 13.1).

Ethical approvals

This study was approved by the WA Department of Health Human Research Ethics Committee, the WA Aboriginal Health Ethics Committee and the University of Western Australia Human Research Ethics Committee.
RESULTS

The birth cohort comprised 469,589 children born in WA between 1996 and 2012, 6.7% of whom identified as being Aboriginal. 2428 children (0.5%) had died by 2012. The total person-years at risk available for the study was 3,753,975. There were 541,207 hospital admissions relating to the children in the birth cohort, 2.9% (n=15,809) of which were identified as pneumonia-related. These admissions were further collapsed into 15,175 pneumonia-related episodes. Aboriginal children accounted for 32.4% (n=4,914) of these episodes.

Pneumonia-related hospital episodes

Overall, pneumonia hospitalisation rates in children aged ≤16 years were 6.7 times higher (95% CI: 6.4, 6.9) in Aboriginal than in non-Aboriginal children (19.4 vs 2.9 per 1000 child-years). Pneumonia hospitalisation rates were highest in Aboriginal children aged 6-11 months (64.0/1000 child-years) and in non-Aboriginal children aged 12-23 months (7.3/1000 child-years).

For all children, pneumonia hospitalisation rates declined over the study period (1996-2012). Comparing the pre-PCV with universal PCV periods, the age groups with the greatest declines were children aged 6-11 months (50-63% decline Aboriginal; 39-46% decline non-Aboriginal) and 2-4 years (54-66% decline Aboriginal; 32-44% decline non-Aboriginal; Table 1). The disparity between Aboriginal and non-Aboriginal children for all-cause pneumonia-related hospital episodes declined significantly from the pre-PCV period to the universal PCV period by 35% in children aged 2-4 years, by 30% in those aged 6-11 months and by 27% in those aged 12-23 months (Table 1).

Log-linear modelling showed significant declines (p<0.001) in the annual incidence of all-cause pneumonia hospitalisations in both Aboriginal and non-Aboriginal children in all age groups over the study period, with the largest decline (by 8.1% per year) seen in Aboriginal children aged 2-4 years. A significant (p=0.007) step-down trend was observed in the annual reduction rates in Aboriginal
children aged 12-23 months (Figure 2). In non-Aboriginal children, a decline was observed in annual trends from 2002 to 2008 in all age groups; hospitalisation rates remained steady thereafter. There was no significant step-down trend in the universal PCV period for non-Aboriginal children. In contrast there were increases in skin infection hospitalisations in the universal PCV period in most age groups in both Aboriginal and non-Aboriginal children (Figure 3).

**Aetiology of pneumonia hospitalisations in children ≤16 years**

Nearly half (49.4% (n=6693)) of all pneumonia hospitalisations linked to a PathWest and/or WANIDD record for respiratory pathogen testing and of those 41.6% (n=2785) had ≥1 respiratory pathogen identified (Figure 1). More than 1 pathogen was co-detected in 339 (12.2%) of admissions.

The frequency and admission rates of pathogens identified in children hospitalised with pneumonia who had a linked pathology record with one or more pathogens identified (hereafter known as pathology-confirmed pneumonia hospitalisations) are presented in Table 2. In both Aboriginal and non-Aboriginal children, RSV was the most commonly identified viral respiratory pathogen with RSV-confirmed pneumonia hospitalisation rate of 89.6/100,000 child-years in Aboriginal and 26.6/100,000 child-years in non-Aboriginal children (Table 2). Influenza A, human adenovirus and picornavirus were the next most common viral pathogens identified in Aboriginal children with pathology-confirmed pneumonia hospitalisations. *S.pneumoniae* (9.7%; 32.9/100,000 child-years) was the most common bacterial pathogen identified in Aboriginal children followed by *H.influenzae* (3.9%; 13.3/100,000 child-years). In non-Aboriginal children, the most commonly identified bacterial pathogen was *M.pneumoniae* (11.7%; 8.4/100,000 child-years) followed by *S.pneumoniae* and among non-RSV viral pathogens, PIV and hMPV were most common (Table 2).

Compared to the pre-universal PCV period, there was an overall decline in the rate of RSV-specific pneumonia hospitalisations (from 145.1 to 73.1 per 100,000 child-years in Aboriginal and from 42.6
to 21.9 per 100,000 child-years in non-Aboriginal children; p<0.05) in children aged <16 years in the universal PCV period, but the level of decline varied in the different age groups (Tables 2, Table 3a and 3b). Other changes observed over the study period included a significant reduction (p=0.008) in influenza-A-specific pneumonia rates in non-Aboriginal children aged 12-23 months and 2-4 years, although declines in Aboriginal children did not reach statistical significance (Tables 3a and 3b).

Compared to pre-universal period, *S.pneumoniae*-specific pneumonia rates showed a 60% reduction in non-Aboriginal children aged 12-23 months in the universal PCV period, whereas the rates were 4.3 times higher (p=0.52) in Aboriginal children aged 12-23 months.

**DISCUSSION**

We previously showed declining trends in pneumonia hospitalisations from 1996-2005[5]. Using extended population-based data, we have shown sustained declines in all-cause pneumonia hospitalisation rates in WA in both Aboriginal and non-Aboriginal children in all age groups after the implementation of the universal PCV program. In contrast, skin infection-related hospitalisations showed similar declines in the pre-PCV period but rates increased across almost all age groups in the universal PCV period, suggesting a positive impact of PCV on pneumonia-related hospitalisations.

We observed a 40% reduction in pneumonia-related hospitalisations in WA children aged <2 years in the universal PCV period. Several clinical trials have demonstrated the efficacy of PCV in preventing IPD and all-cause pneumonia in young children[18]. Our estimates are within the range reported by these clinical trials and are similar to the findings of a national study conducted in the United States showing a decline of 39% in all-cause pneumonia hospitalisation rates in children aged <2 years[19]. An estimated 32% decline in pneumonia hospitalisations in this age group was observed in a national study in Australia[20]. Elsewhere, studies have reported modest declines in pneumonia hospitalisations in the post-PCV period, ranging from 15-30%[21-24].
To our knowledge, the aetiology of childhood pneumonia hospitalisations in the pre- and post-PCV periods has never been reported in Australia. At least one viral pathogen was identified in 73% of children with pathology-confirmed pneumonia hospitalisations (Figure 1). Over the study period, RSV was the most commonly identified pathogen in both Aboriginal and non-Aboriginal children hospitalised with pneumonia, accounting for nearly 34% of all pathogens identified. Studies have shown that RSV is the most frequently identified pathogen in children diagnosed with pneumonia, especially in younger children [1, 25, 26]. *S. pneumoniae* was the most common bacterial pathogen identified in Aboriginal children with hospitalisation rates 8 times higher than in non-Aboriginal children. *M. pneumoniae* was the most commonly identified pathogen in non-Aboriginal children. This was not due to differential testing based on Indigeneity: the rate of *M. pneumoniae*-specific hospitalisation was similar for Aboriginal and non-Aboriginal children (Table 2) and the rate of *M. pneumoniae* tests was lower in non-Aboriginal children (4.3/10,000 child-years) as compared to Aboriginal children (10.0/10,000 child-years). *M. pneumoniae*-specific hospitalisation rates appeared to rise with increasing age in both Aboriginal and non-Aboriginal children as documented elsewhere[26, 27].

Our data show marked declines in RSV-, influenza A- and PIV-specific pneumonia hospitalisation rates from the pre-universal PCV to universal PCV periods, especially in young non-Aboriginal children. Studies have documented the role of infecting viruses in facilitating bacterial spread in the pathogenesis pathway of pneumonia, whereby a favourable environment for bacterial growth is created by the cytopathic effect of the virus on the mucociliary barrier in the bronchial epithelium[25, 28]. Furthermore, the broader impact of PCV in preventing hospitalisation for viral pneumonia, most likely by prevention of superimposed bacterial co-infections, has been shown in a randomised trial[29]. Despite overall declines in pneumonia hospitalisations in Aboriginal children, relative contribution of *S. pneumoniae* hospitalisations increased over the study period. This is likely a reflection of small numbers and potentially increased testing in Aboriginal children.[30] Also, the
earlier implementation of the PCV program in Aboriginal children in mid-2001 may possibly have impacted on pathogen rates in the pre-universal PCV period itself.

We have relied upon ICD codes to identify pneumonia-related hospitalisations. Though the use of ICD codes in identifying pneumonia diagnosis has been validated, an element of error due to misclassification or changes in coding practices remains[31]. As with most ecological studies, the main limitation is the lack of individual immunisation data to accurately assess the impact of PCV on the incidence of all-cause pneumonia and our results might be confounded by other factors such as changes in clinical and diagnostic practices. We are currently assessing the impact of PCV programs in children through a cross jurisdictional record linkage study with individual immunisation data from WA and New South Wales[32].

A strength of our study is the inclusion of pathology data to assess pathology-confirmed pneumonia but, only half of all hospital admissions for pneumonia linked to any pathology record. This is likely because the diagnosis of pneumonia is based on clinical and/or radiological evidence and hence a significant proportion of children hospitalised for pneumonia will not undergo testing. This, in addition to the limited sensitivity of current diagnostics particularly for bacterial pneumonia, will lead to underestimation of the pathogen-specific pneumonia hospitalisation rates. Also, there have been changes in respiratory pathogen testing patterns in WA over the study period [30]. For example, hMPV testing at PathWest was conducted only upon request from 2003-2007 and switched to routine testing from 2008. These changes coupled with temporal changes in the sensitivity and specificity of current tests could also affect pathogen estimates. As increased use of more sensitive molecular diagnostic methods occurred later in the study, it is possible that the decreasing incidence of viral pneumonia is underestimated due to artificially low rates in earlier years.
CONCLUSION

The burden of pneumonia hospitalisations remains high in children aged <5 years. PCV has had a significant impact in reducing pneumonia-related hospitalisations in WA, especially in the Aboriginal population. Though the disparity in pneumonia hospitalisation rates between the Aboriginal and non-Aboriginal population has decreased after the implementation of the universal PCV program, young Aboriginal children are still hospitalised with pneumonia at 7 times the rate of their non-Aboriginal counterparts. A multitude of pathogens were identified with respiratory viruses being most common. In addition to all-cause pneumonia, the incidence of viral pneumonia has also declined with PCV vaccination. The high burden of RSV- and PIV-related pneumonia hospitalisations highlights the need for acceleration of development and/or roll-out of vaccines targeting these pathogens.
FUNDING

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CONFLICTS OF INTEREST

None to declare.

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REFERENCES


Table 1. All-cause pneumonia hospitalisation rates per 1000 child years and rate ratios before and after the introduction of PCV in Aboriginal and non-Aboriginal children aged ≤16 years (1996-2012)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Aboriginal</th>
<th>Non-Aboriginal</th>
<th>IRRb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>96–00 pre-PCV</td>
<td>01–04 PCV - only Aboriginal</td>
<td>05–12 universal PCV</td>
</tr>
<tr>
<td>&lt; 6 months</td>
<td>60.2</td>
<td>53.4</td>
<td>33.3</td>
</tr>
<tr>
<td>6-11 months</td>
<td>97.9</td>
<td>77.8</td>
<td>42.1</td>
</tr>
<tr>
<td>12-23 months</td>
<td>72.3</td>
<td>47.4</td>
<td>36.5</td>
</tr>
<tr>
<td>2-4 years</td>
<td>33.3</td>
<td>20.1</td>
<td>13.2</td>
</tr>
<tr>
<td>5-9 years</td>
<td>-</td>
<td>7.8</td>
<td>6.1</td>
</tr>
<tr>
<td>≥10 years</td>
<td>-</td>
<td>-</td>
<td>5.1</td>
</tr>
</tbody>
</table>

a IRR – Incidence rate ratio of non-Aboriginal to Aboriginal hospitalisation rate
b IRR – Incidence rate ratio of universal PCV period to pre-PCV period hospitalisation rate
c Data for 12-23 month age group available only from 1997 onwards
d Data for 2-4 years age group available from 1998 onward
e Data for 5-9 years age group available from 2001 onward. IRR for this group is universal PCV period to PCV-only Aboriginal period hospitalisation rate
f Data for ≥10 years age group available from 2006 onward.
Table 2. Frequency of detection and pathogen-specific pneumonia hospitalisation rates per 100,000 child-years in Aboriginal and non-Aboriginal children aged ≤16 years (2000-2012)

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>All 2000-12</th>
<th>Aboriginal 2000-04</th>
<th>Aboriginal 2005-12</th>
<th>Non-Aboriginal 2000-04</th>
<th>Non-Aboriginal 2005-12</th>
<th>IRR* (95% CI) 2000-12</th>
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<tr>
<td></td>
<td>n (%) rate</td>
<td>Pre-universal PCV n (%) rate</td>
<td>Universal PCV n (%) rate</td>
<td>Pre-universal PCV n (%) rate</td>
<td>Universal PCV n (%) rate</td>
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<td>RSV</td>
<td>1097 (34.4) 30.9</td>
<td>215 (26.5) 89.6</td>
<td>80 (35.1) 145.1</td>
<td>135 (23.1) 73.1</td>
<td>882 (37.2) 26.6</td>
<td>324 (39.8) 42.6</td>
</tr>
<tr>
<td>PIV (1-4)</td>
<td>243 (7.6) 6.8</td>
<td>54 (6.6) 22.5</td>
<td>25 (11.0) 45.3</td>
<td>29 (5.0) 15.7</td>
<td>189 (8.0) 5.7</td>
<td>68 (8.4) 8.9</td>
</tr>
<tr>
<td>Influenza A</td>
<td>228 (7.2) 6.4</td>
<td>78 (9.6) 32.5</td>
<td>31 (13.6) 56.2</td>
<td>47 (8.0) 25.4</td>
<td>150 (6.3) 4.5</td>
<td>68 (8.4) 8.9</td>
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<tr>
<td>hMPVb</td>
<td>192 (6.0) 6.1</td>
<td>33 (4.1) 15.6</td>
<td>&lt;5 (1.8) 14.7</td>
<td>29 (5.0) 15.7</td>
<td>159 (6.7) 5.4</td>
<td>22 (2.7) 5.9</td>
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<td>Picornavirus</td>
<td>195 (6.1) 5.5</td>
<td>66 (8.1) 27.5</td>
<td>19 (8.3) 34.5</td>
<td>47 (8.0) 25.4</td>
<td>129 (5.4) 3.9</td>
<td>35 (4.3) 4.6</td>
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<td>157 (4.9) 4.4</td>
<td>66 (8.1) 27.5</td>
<td>13 (5.7) 23.6</td>
<td>53 (9.1) 28.7</td>
<td>91 (3.8) 2.8</td>
<td>36 (4.4) 4.7</td>
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<td>24 (3.0) 10.3</td>
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<td>21 (3.6) 11.4</td>
<td>30 (1.3) 0.9</td>
<td>&lt;5 (0.5) 0.6</td>
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<td>M.pneumoniae</td>
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<td>23 (2.8) 9.6</td>
<td>&lt;5 (0.4) 1.8</td>
<td>22 (3.8) 11.9</td>
<td>278 (11.7) 8.4</td>
<td>98 (12.0) 12.9</td>
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<td>215 (6.8) 6.1</td>
<td>79 (9.7) 32.9</td>
<td>13 (5.7) 23.6</td>
<td>66 (11.3) 35.7</td>
<td>136 (5.7) 4.1</td>
<td>58 (7.1) 7.6</td>
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<td>B.pertussisd</td>
<td>108 (3.4) 3.3</td>
<td>20 (2.5) 9.0</td>
<td>6 (2.6) 15.7</td>
<td>14 (2.4) 7.6</td>
<td>88 (3.7) 2.9</td>
<td>25 (3.1) 4.8</td>
</tr>
<tr>
<td>H.influenzae</td>
<td>64 (2.0) 1.8</td>
<td>32 (3.9) 13.3</td>
<td>&lt;5 (1.3) 5.4</td>
<td>29 (5.0) 15.7</td>
<td>32 (1.4) 1.0</td>
<td>11 (1.4) 1.4</td>
</tr>
<tr>
<td>Other pathogens*</td>
<td>333 (10.5) 9.4</td>
<td>123 (15.1) 51.3</td>
<td>30 (13.2) 54.4</td>
<td>93 (15.9) 50.3</td>
<td>210 (8.9) 6.3</td>
<td>65 (8.0) 8.5</td>
</tr>
</tbody>
</table>

Note: Frequency (n) includes pathogens that were co-detected
*IRR – Incidence rate ratio of Aboriginal to non-Aboriginal (2000-2012)
*bMPV data available only from 2003 onwards
*cInfluenza B data available only from 2001 onwards
*dB.pertussis data available only from 2002 onwards
*Includes other bacteria and viruses like parvovirus, herpes simplex virus, klebsiella species, morcata species, pseudomonas, chlamydia species and other streptococci species
Table 3a. Frequency of detection and pathogen-specific pneumonia hospitalisation rates (per 100,000 child-years) by age in Aboriginal children (2000-2012)

<table>
<thead>
<tr>
<th></th>
<th>&lt;6 months</th>
<th>6-11 months</th>
<th>12-23 months</th>
<th>2-4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate/100,000</td>
<td>IRR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Rate/100,000</td>
<td>IRR&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>VIRUSES</strong></td>
<td></td>
<td>'00 - '04</td>
<td>'05 - '12</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>RSV</td>
<td>479.5</td>
<td>488.3</td>
<td>1.0 (0.6, 1.7)</td>
<td>480.3</td>
</tr>
<tr>
<td>PIV(1-4)</td>
<td>137.0</td>
<td>90.0</td>
<td>0.7 (0.2, 1.9)</td>
<td>182.9</td>
</tr>
<tr>
<td>Influenza A</td>
<td>68.5</td>
<td>25.7</td>
<td>0.4 (0.1, 2.3)</td>
<td>205.8</td>
</tr>
<tr>
<td>Influenza B&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.0</td>
<td>38.6</td>
<td>-</td>
<td>57.2</td>
</tr>
<tr>
<td>hMPV&lt;sup&gt;c&lt;/sup&gt;</td>
<td>57.8</td>
<td>77.1</td>
<td>1.3 (0.2, 11.1)</td>
<td>0.0</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>45.7</td>
<td>179.9</td>
<td>3.9 (0.9, 17.3)</td>
<td>91.5</td>
</tr>
<tr>
<td>Picornavirus</td>
<td>182.7</td>
<td>295.6</td>
<td>1.6 (0.7, 3.6)</td>
<td>114.4</td>
</tr>
<tr>
<td><strong>BACTERIA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.pneumoniae</td>
<td>22.9</td>
<td>12.9</td>
<td>0.6 (0.1, 9.0)</td>
<td>0.0</td>
</tr>
<tr>
<td>M.pneumoniae</td>
<td>0.0</td>
<td>0.0</td>
<td>-</td>
<td>0.0</td>
</tr>
<tr>
<td>B.pertussis&lt;sup&gt;d&lt;/sup&gt;</td>
<td>114.2</td>
<td>51.4</td>
<td>0.5 (0.1, 2.0)</td>
<td>113.8</td>
</tr>
<tr>
<td>H.influenzae</td>
<td>0.0</td>
<td>12.9</td>
<td>-</td>
<td>0.0</td>
</tr>
</tbody>
</table>

<sup>a</sup>IRR – Incidence rate ratio of universal PCV period (2005-2012) to pre-universal PCV period (2000-2004) hospitalisation rate

<sup>b</sup>Influenza B data available only from 2001 onwards

<sup>c</sup>hMPV data available only from 2003 onwards

<sup>d</sup>B.pertussis data available only from 2002 onwards
**Table 3b. Frequency of detection and pathogen-specific pneumonia hospitalisation rates (per 100,000 child-years) by age in non-Aboriginal children (2000-2012)**

<table>
<thead>
<tr>
<th>Age</th>
<th>VIRUSES</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate/100,000</td>
<td>IRR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>'00 - '04</td>
<td>'05 - '12</td>
<td>(95% CI)</td>
<td>Rate/100,000</td>
<td>IRR&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>&lt;6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV</td>
<td>121.4</td>
<td>80.1</td>
<td>0.7</td>
<td>(0.5, 0.9)</td>
<td></td>
<td>91.8</td>
<td>60.7</td>
</tr>
<tr>
<td>PIV(1-4)</td>
<td>13.9</td>
<td>4.5</td>
<td>0.3</td>
<td>(0.1, 0.9)</td>
<td></td>
<td>20.8</td>
<td>10.9</td>
</tr>
<tr>
<td>Influenza A</td>
<td>8.7</td>
<td>1.8</td>
<td>0.2</td>
<td>(0.1, 1.1)</td>
<td></td>
<td>12.1</td>
<td>5.4</td>
</tr>
<tr>
<td>Influenza B&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.0</td>
<td>0.0</td>
<td>-</td>
<td></td>
<td></td>
<td>0.0</td>
<td>3.6</td>
</tr>
<tr>
<td>hMPV&lt;sup&gt;c&lt;/sup&gt;</td>
<td>25.9</td>
<td>9.8</td>
<td>0.4</td>
<td>(0.1, 1.0)</td>
<td></td>
<td>21.9</td>
<td>19.0</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>0.0</td>
<td>3.6</td>
<td>-</td>
<td></td>
<td></td>
<td>17.3</td>
<td>16.3</td>
</tr>
<tr>
<td>Picornavirus</td>
<td>10.4</td>
<td>12.5</td>
<td>1.2</td>
<td>(0.5, 3.1)</td>
<td></td>
<td>12.1</td>
<td>8.2</td>
</tr>
<tr>
<td>BACTERIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.pneumoniae</td>
<td>6.9</td>
<td>1.8</td>
<td>0.3</td>
<td>(0.1, 1.4)</td>
<td></td>
<td>8.7</td>
<td>7.3</td>
</tr>
<tr>
<td>M.pneumoniae</td>
<td>1.7</td>
<td>0.0</td>
<td>-</td>
<td></td>
<td></td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>B.pertussis&lt;sup&gt;d&lt;/sup&gt;</td>
<td>8.7</td>
<td>8.0</td>
<td>0.9</td>
<td>(0.3, 3.4)</td>
<td></td>
<td>2.9</td>
<td>6.3</td>
</tr>
<tr>
<td>H.influenzae</td>
<td>3.5</td>
<td>0.9</td>
<td>0.3</td>
<td>(0.1, 2.8)</td>
<td></td>
<td>1.7</td>
<td>2.7</td>
</tr>
</tbody>
</table>

<sup>a</sup>IRR – Incidence rate ratio of universal PCV period (2005-2012) to pre-universal PCV period (2000-2004) hospitalisation rate
<sup>b</sup>Influenza B data available only from 2001 onwards
<sup>c</sup>hMPV data available only from 2003 onwards
<sup>d</sup>B.pertussis data available only from 2002 onwards
FIGURE LEGENDS

Figure 1. Flowchart of record linkage and frequency of pathogen detection

Note: PathWest=PathWest Laboratory Medicine WA; WANIDD=Western Australian Notifiable Infectious Diseases Database
Hospital Morbidity Database System
Pneumonia hospitalisations N=13544 (2000-2012)

- Did not link to PathWest/WANIDD
  - 6851 (50.6%)

- Linked to PathWest/WANIDD
  - 6693 (49.4%)
    - ≥ 1 pathogen identified
      - 2785 (41.6%)
        - Single pathogen
          - 2445 (87.8%)
            - Viral
              - 1776 (72.6%)
            - Bacterial
              - 669 (27.4%)
        - > 1 pathogen
          - 339 (12.2%)
            - >1 Virus
              - 132 (38.9%)
            - >1 Bacteria
              - 72 (21.2%)
            - Mixed
              - 136 (39.8%)
    - No pathogen identified
      - 3909 (58.4%)
Figure 2. Annual age-specific incidence rates for all-cause pneumonia hospitalisations in Aboriginal and non-Aboriginal children 1996-2012. Note the difference in scale on the y-axis.
Fitted trend lines from interrupted linear time series model, with a break point in 2001, showing a 'step down' trend post-PCV for 12-23 month age group.
Figure 3. Trends in annual age-specific incidence rates for hospitalisations relating to all-cause pneumonia and skin infections in Aboriginal and non-Aboriginal children in the pre-PCV and universal PCV periods. Dashed blue lines show trend for all-cause pneumonia and solid purple lines show trend for skin infections. Note the difference in scale on the y-axis.
The graphs illustrate hospitalisation rates per 1000 child-years for pneumonia and skin infections in Aboriginal and non-Aboriginal children, categorized by age groups: pre-PCV and Universal-PCV periods, and 6-11, 12-23, and 24 months.

- **Pre-PCV**: The hospitalisation rates show a decline in both groups, with percentages and confidence intervals indicated for each age group.
- **Universal-PCV**: The rates increase in both groups, with percentages and confidence intervals also provided.

The graphs are labeled with the age categories and the hospitalisation rates for each period, with the confidence intervals in parentheses. The labels for the graphs indicate the groups being compared:

- **All-cause pneumonia**
- **Skin infection**

The key points are:

- **6-11 months**:
  - Aboriginal: 4.1% (95% CI -2.4 to 10.9) increase
  - Non-Aboriginal: 6.6% (95% CI 2.5 to 10.9) increase

- **12-23 months**:
  - Aboriginal: 1.4% (95% CI -2.1 to 5.1) increase
  - Non-Aboriginal: 2.0% (95% CI -0.7 to 4.5) decline

- **24 years**:
  - Aboriginal: 2.4% (95% CI -0.2 to 5.1) increase
  - Non-Aboriginal: 0.3% (95% CI -3.6 to 4.3) increase

The lines in the graphs represent the hospitalisation rates for different causes, with specific notes on the introduction of PCV for certain groups.
**Supplementary Table.** International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM) diagnosis codes used to identify hospital admissions for all-cause pneumonia and skin infections

<table>
<thead>
<tr>
<th></th>
<th>ICD-9-CM codes</th>
<th>ICD-10-AM codes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pneumonia</strong></td>
<td>003.22, 031.0, 052.1, 055.1, 112.4, 115.05, 115.15, 115.25, 136.3, 480-486</td>
<td>J10-J11, J12-J18, B01.2, B05.2, B37.1, B59</td>
</tr>
<tr>
<td><strong>Skin infection</strong></td>
<td>035, 110, 111, 112.3, 132-133, 134.1, 134.8, 134.9, 380.1, 680-682, 684-686</td>
<td>A46, B35-36, B37.2, B85-86, B88.0, B88.9, L00-03, L05, L08, L30.3, L30.4, L60.3</td>
</tr>
</tbody>
</table>