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Acute lower respiratory infections among Indigenous children in the Northern Territory of Australia: A decade of observation spanning three generations of pneumococcal conjugate vaccine.

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Abstract:	Background For Indigenous infants living in Australia's Northern Territory (NT) acute lower respiratory infections (ALRIs) are a leading cause of hospitalisation and preventable mortality. The study describes the burden of ALRI hospitalisation in this population from 2006 to 2015 with contrast between three periods of different pneumococcal conjugate vaccine (PCV) use. Methods We conducted a historical cohort study of NT Indigenous infants born between 1st January 2006 and 31st December 2015 and followed until age 12 months. Data were from administrative hospital and perinatal datasets. International classification of diseases codes were used to identify respiratory hospitalisations of interest: all cause ALRI, all cause pneumonia, bacterial pneumonia, viral pneumonia, influenza-like illness (ILI), respiratory syncytial virus ALRI (RSV-ALRI) and pneumococcal ALRI. Incidence rates were compared between PCV eras (7-valent PCV-PCV7, 2006-2009; PCV10, 2009-2011; PCV13, 2011-2015) using interrupted time trend analysis and negative binomial regression. Findings Over the study period 4138 ALRI episodes (31% of all hospitalisations) occurred among 2888 of the 14594 infants (20% of the cohort). The overall ALRI hospitalisation rate was 29.7 episodes per 100 child-years. Prominent risk factors associated with ALRI hospitalisation were living in a remote community or the Central desert region, being born preterm or with low birth weight. ALRI rates were lowest in the PCV13 era in association with a significant reduction in bacterial pneumonia hospitalisations in the PCV13 relative to the PCV10 (IRR 0•68, 95% CI 0•57-0•81) and PCV7 (IRR 0•70, 95%

	CI 0•60-0•81) eras. In contrast, RSV-ALRI rates were 4•9 episodes per 100 child-years in each era. Interpretation We found a 30% reduction in bacterial-coded pneumonia hospitalisation episodes during the era of PCV13 use. Despite this, one in five NT Indigenous infants continue to be hospitalised with an ALRI in their first year of life. RSV associated ALRI rates were high and remained unchanged over a decade. Funding This work was supported by the National Health and Medical Research Council of Australia (1088733).

Acute lower respiratory infections among Indigenous children in the Northern Territory of Australia: A decade of observation spanning three generations of pneumococcal conjugate vaccine.

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Abstract

Background

For Indigenous infants living in Australia's Northern Territory (NT) acute lower respiratory infections (ALRIs) are a leading cause of hospitalisation and preventable mortality. The study describes the burden of ALRI hospitalisation in this population from 2006 to 2015 with contrast between three periods of different pneumococcal conjugate vaccine (PCV) use.

Methods

We conducted a historical cohort study of NT Indigenous infants born between 1st January 2006 and 31st December 2015 and followed until age 12 months. Data were from administrative hospital and perinatal datasets. International classification of diseases codes were used to identify respiratory hospitalisations of interest: all cause ALRI, all cause pneumonia, bacterial pneumonia, viral pneumonia, influenza-like illness (ILI), respiratory syncytial virus ALRI (RSV-ALRI) and pneumococcal ALRI. Incidence rates were compared between PCV eras (7-valent PCV-PCV7, 2006-2009; PCV10, 2009-2011; PCV13, 2011-2015) using interrupted time trend analysis and negative binomial regression.

Findings

Over the study period 4138 ALRI episodes (31% of all hospitalisations) occurred among 2888 of the 14594 infants (20% of the cohort). The overall ALRI hospitalisation rate was 29.7 episodes per 100 child-years. Prominent risk factors associated with ALRI hospitalisation were living in a remote community or the Central desert region, being born preterm or with low birth weight. ALRI rates were lowest in the PCV13 era in association with a significant reduction in bacterial pneumonia hospitalisations in the PCV13 relative to the PCV10 (IRR 0·68, 95% CI 0·57-0·81) and PCV7 (IRR 0·70, 95% CI 0·60-0·81) eras. In contrast, RSV-ALRI rates were 4·9 episodes per 100 child-years in each era.

Interpretation

We found a 30% reduction in bacterial-coded pneumonia hospitalisation episodes during the era of PCV13 use. Despite this, one in five NT Indigenous infants continue to be hospitalised with an ALRI in their first year of life. RSV associated ALRI rates were high and remained unchanged over a decade.

Funding

This work was supported by the National Health and Medical Research Council of Australia (1088733).

Introduction

Globally, acute lower respiratory infections (ALRIs) remain a leading cause of morbidity and mortality.[1] In 2015, there were 138 million cases of childhood pneumonia resulting in 0·9 million deaths.[1] While ALRI-related mortality is low in Australia, Indigenous infants are hospitalised with ALRIs up to nine times more often than non-Indigenous infants.[2] In the past, the gap has been widest in the Northern Territory (NT)[3] where, despite freely available health care and high rates of vaccination, rates of infant pneumonia (22% hospitalised in first year)[4] were among the highest reported in the world. In this region, Indigenous infants are densely colonised with the major respiratory pathogens *Streptococcus pneumoniae* (pneumococcus) and non-typeable *Haemophilus influenzae* (NTHi) within 6 weeks of birth and nasopharyngeal carriage prevalence reaches 80% by 6 months of age.[5] Further, influenza has a disproportionate impact on Indigenous Australians in the NT[6] which has been linked to a 100-fold higher risk of invasive pneumococcal disease (IPD).[7] To prevent pneumococcal disease, three different pneumococcal conjugate vaccines (PCVs) have been used in the NT since 2001[8] but their impact against ALRI in this setting is unclear.

Pneumococcal vaccines induce serotype specific immunity (Table 1). The 7-valent PCV (PCV7) serotypes were selected because they accounted for 50-80% of the global burden of childhood IPD.[9] PCV10 (including *H. influenzae* protein D-HiD) added three serotypes and potential NTHi protection. PCV13 further expanded protection against prominent disease causing pneumococcal serotypes (including replacement serotype 19A) but does not include HiD. A 3+1 schedule of the PCV7 (at 2, 4, 6 months) with 23-valent pneumococcal polysaccharide vaccine booster (PPV23 at 18 months) was introduced for Indigenous infants in the NT in June 2001 under the National Immunisation Program.[8] This was replaced by a 3+1 schedule of PCV10 in October 2009 and then PCV13 in October 2011.[8] PCV coverage has been consistently higher among Indigenous infants in the NT than among those elsewhere (80% in 2008, 88% in 2017).[10] The NT was the only jurisdiction in Australia to utilise PCV10.

Following PCV7 introduction, IPD notifications among Indigenous Australian infants were halved though invasive disease caused by PCV10 or PCV13 serotypes (1, 6A, 7F and 19A) was ongoing.[11] The impact of PCV7 against mucosal infections was less obvious. One ecological study showed a 38% reduction in pneumonia hospitalisations among all Australian children under 2 years of age.[12] Two population-based record-linkage studies across Western Australia and New South Wales showed a 28-49% reduction in pneumonia hospitalisations among Indigenous children under 3 years of age in pre versus post PCV7 periods.[2,13] However, in the NT, ALRI hospitalisation rates remained unchanged after PCV7 introduction[4] and a retrospective cohort study utilising documented vaccination status, blinded radiological assessment of pneumonia (according to World Health Organization guidelines) and controlling for a number of confounding factors, showed no evidence that PCV7 reduced the incidence of pneumonia among Indigenous infants to 18 months of age.[14] There are no published data reporting childhood ALRI hospitalisation rates in the NT beyond 2005 during the PCV10 and PCV13 eras.

Given the importance of early-onset ALRIs in this high-risk population and limited evidence of PCV7 effectiveness, the aim of this study was to describe ALRI hospitalisations among NT Indigenous infants (aged <12 months) between January 2006 and December 2015 over three periods of different PCV formulation use.

Methods

Study design and population

A historical cohort study of NT Indigenous infants born between 1st Jan 2006-31st Dec 2015 and each followed until age 12 months.

Study setting

The NT is sparsely populated with approximately 229000 residents (2018) spread across 1·4 million square kilometres (0·16 people per square kilometre). At the last available census (2016), approximately 30% (74546) of the NT population were Indigenous; 77% lived remotely and 30% lived in the Central desert region. Compared to non-Indigenous Australians, Indigenous Australians were younger in age, lived in more crowded households, had lower income and lower educational attainment.[15]

NT Indigenous children requiring hospital care, including birth, are admitted to one of the five public hospitals; few are born at the sole private hospital. A unique hospital reference number (HRN) is allocated at birth or at first use of public hospital or public health care. The HRN is used as the person identifier for all subsequent episodes of care and for other administrative datasets.

Data sources

Data were sourced from the NT Hospital Inpatient Activity and NT Perinatal datasets. The cohort was defined by births recorded in the hospital dataset (Figure 1). HRNs present in both datasets were deterministically matched by the data custodians. Each dataset was then de-identified with an arbitrary key for final merging and analysis. Where demographic and participant characteristic data present in both datasets were mismatched, perinatal data were considered more accurate and preferred. Geographically, data were categorised by Local Government Areas.[16]

Pneumococcal conjugate vaccine eras

Three different PCVs (7, 10 and 13 valent) were used on the childhood immunisation program in the NT during the study period (Table 1). Each vaccine era was extended by 6 months to best capture the era of protection (during which time the previous generation vaccine provides most protection).

Outcomes

International classification of diseases codes (tenth revision, Australian modification; ICD-10AM) were used to identify the hospital outcomes of interest (Appendix Figure 1, p6). The main outcomes of interest were: all cause ALRI, all cause pneumonia and bacterial pneumonia. Additional outcomes investigated were: viral pneumonia, influenza-like illness (ILI), respiratory syncytial virus ALRI (RSV-ALRI) and pneumococcal ALRI. Respiratory diagnoses occurring within 7 days of birth were excluded. Where multiple consecutive respiratory diagnoses occurred within 14 days of each other only the first episode was included. All coded diagnoses per hospital episode were analysed therefore ALRI subcategories were not always mutually exclusive within an episode.

Analysis

General data are described using proportions (compared using the Chi-square test), means (compared using Student's T-test) and medians (compared using a Wilcoxon Rank Sum test) as appropriate. Crude incidence rates were calculated by dividing the number of episodes per child per calendar period of observation (represented as episodes per 100 child-years). Each individual child contributed approximately 12 months of data (7 days to 12 months of age). Vaccine eras were extended by 6 months to best capture the era of protection. Lead in truncation bias was accounted for by omitting the first 8 months of data in the monthly analysis (at which point rates stabilised) and the first year of data when calculating annual averages. Using Local Government Area borders,[16] geography was categorised as (i) urban/remote and (ii) Top End/Central (Appendix Figure 2, p7). The two cities making up the urban category were Darwin in the north and Alice Springs in the south. All other areas were considered remote. The northern (sub-tropical) region of the NT is known as the 'Top End' while the southern (desert) region is known as 'Central' Australia. Ordinary Least Square regression of monthly rate data (with Newey-West standard error) was used in an interrupted time series framework to estimate and graph the respiratory disease trends by allowing for a change in both slope and level between eras. The error term was modelled as an autoregressive process using plots of the autocorrelation function of the residuals and Akaike Information Criterion (AIC) to choose the autoregressive order. To compare incidence rates between eras, a random-effects negative binomial (RENB) regression model was fitted on the count outcome data. Outcome predictors were selected for our multivariate model based on clinical logic, an imbalance between eras and univariate regression (without imputation for missing data). In the main multivariate RENB models, each respiratory outcome was treated as unique and the most parsimonious model was chosen using stepwise likelihood ratio testing to eliminate covariates without a significant influence. Three standardised multivariate models are also presented for comparison. For all statistical tests significance was set at $p<0{\cdot}05$. Analysis was conducted using STATA 15.

Ethics

This project was approved by the Human Research Ethics Committee of the NT Department of Health and Menzies School of Health Research (HREC 2015-2406).

Results

Over the study period, we identified 14594 Indigenous children with both an ICD-10AM coded birth (Z38-Z38·8) and a NT residential postcode. These 14594 children presented a total of 13307 subsequent hospitalisation episodes during observation throughout their first year of life (median of 1 hospitalisation per child, range 1-22). Of the cohort, 51% (n=7490) were male, 70% (n=10,175) lived remotely and 32% (n=4675) were from the Central region (Table 2). Fourteen percent (n=1895) of babies were born preterm (<37 weeks gestation), 13% (n=1779) were low birth weight (<2500g) and 22% (n=2992) were admitted to the special care nursery. Sixty three percent (n=1200) of those born preterm were also low birth weight. Maternal smoking (51%, n=6065) and drinking alcohol (12%, n=1419) during pregnancy, gestational diabetes (11%, n=1455) and anaemia (10%, n=1334) were common. The latter two conditions were reported more frequently with each vaccine era likely due to increased surveillance (Appendix Table 1, p1). The birth rate declined incrementally from 1,526 per year in 2006 to 1,384 per year in 2015 (-9% overall).

There were 4138 ALRI episodes (31% of all non-birth episodes) among 2888 infants (20% of the total infant cohort); 551 (4%) had two episodes and 271 (2%) had three or more episodes including 12 children with more than six episodes. The highest frequency of first ALRI episodes occurred between ages two and five months with little variation by region (Figure 2A). The cumulative proportions of ALRI hospitalised children by region (Figure 2B; Appendix Table 2, p1) were: remote Central (32%), urban Central (24%), remote Top End (19%), urban Top End (7%).

The crude incidence (Table 3) of ALRI hospitalisation per 100 child-years over the entire study period was 29·7 (range 33·8 in 2010, 25·9 in 2013); substantially higher in the Central (47·9) compared to Top End (21·9) region. All cause pneumonia (9·4; comprising bacterial 7·2, viral 3·0) and RSV associated ALRIs (5·0) were the most prominent sub-classifications. Viral pneumonia and influenza-like illness demonstrated predictable peaks in 2009 during the H1N1 pandemic.

In univariate analysis of known potential respiratory disease risk factors (Appendix Table 3, p2), low birth weight, preterm birth, and admission to the special care nursery were significantly associated with a higher risk of ALRI. Infants living in remote Central Australia had the highest rates of ALRI, notably bacterial pneumonia (IRR 4.41 95% CI 3.24-6.00), viral pneumonia (IRR 6.09, 95% CI 3.59-10.34) times) and pneumococcal ALRI (11.14 95% CI 1.5-83.03). There were little differences in ALRI rates by the NT's typical wet and dry season. By classic temperate southern hemisphere seasons (Appendix Table 3), ALRI rates were typically highest in the winter/spring (June-November) related to viral pneumonia and ILI peaks; however, there was a clear difference in the seasonal effects by region (Appendix Figure 3, p8-11). In the Central region, pneumonias and ILI exhibited winter/spring peaks, yet remained relatively stable all year round in the Top End. RSV associated ALRIs had the most contrasting seasonality by region, highest in the Top End in summer/autumn and highest in the Central region in the winter/spring.

By era, the unadjusted incidence of ALRI hospital episodes per 100 child-years (Table 4) was 29·8 in the PCV7 era, 32·3 in the PCV10 era and 27·5 in the PCV13 era; lower in the PCV13 versus the PCV10 era (IRR 0·85, 95% CI 0·78-0·93) and PCV13 versus the PCV7 era (IRR 0·95, 95% CI 0·88-1·03) and higher in the PCV10 versus PCV7 era (IRR 1·11, 95% CI 1·02-1·21).

The between era trends in overall ALRI were dominated by changes in pneumonia hospitalisation rates (Table 4, Figure 3A). ALRI rates were lowest in the PCV13 era in association with the significant reduction in bacterial pneumonia hospitalisations (Table 4, Figure 3B) in the PCV13 relative to the PCV10 (IRR 0·68, 95% CI 0·57-0·81) and PCV7 (IRR 0·70, 95% CI 0·60-0·81) eras. ALRI rates were highest in the PCV10 era due to the peak in viral pneumonia episodes (including ILI; Figure 3B) during the 2009 H1N1 influenza pandemic and increased vigilance thereafter. Viral pneumonias were lowest in the PCV7 era (especially prior to the 2009; Table 4). In the post-pandemic years, viral pneumonia (including ILI) rates were lower in the PCV13 compared to the PCV10 eras (IRR 0·70, 95% CI 0·55-0·90). In contrast to the differences in pneumonia rates across eras, RSV-ALRI rates per 100 child-years (Table 4, Appendix Figure 4, p12) were consistent in each vaccine era (4·9) despite peaks

years in 2009 and 2012. In 84 of the 1006 episodes (8%) where bacterial pneumonia was coded there was a concurrent coding of RSV-ALRI. Only 38 pneumococcal ALRI hospitalisations were recorded over the study period (Table 4). The rate was lower during the PCV13 era than either the PCV10 (IRR 0·56, 95%CI 0·23-1·37) or PCV7 (IRR 0·58, 95%CI 0·26-1·29) eras but the small numbers limited interpretation (Table 4). Adjustment for potential outcome modifiers did not influence the interpretation of ALRI outcomes regardless of the model chosen (Table 4; Appendix Table 4, p4; Appendix Table 5, p5).

Discussion

In accordance with previous findings,[4] we show that one in five Indigenous infants in the NT continue to be hospitalised with an ALRI during their first year of life. Key risk factors associated with ALRI hospitalisation were living in a remote community, living in Central Australia, being born preterm or with low birth weight. The prevalence of infant ALRI hospitalisation in remote central Australia was one in three. Despite the ongoing burden, we demonstrated a 30% decline in bacterial coded pneumonia hospitalisations following the introduction of PCV13 (2012-2015). Given that RSV-ALRI hospitalisations remained stable across eras, the specific reductions in pneumonia hospitalisations are suggestive of a PCV13 impact.

Pneumococcal pneumonia is the leading cause of lower respiratory infection among children and adults worldwide.[17] In many high-risk settings PCVs have effectively reduced pneumonia[13,18] and otitis media[19,20] but until now these findings have not previously been replicated in the NT.[14,21,22] Pre-2012 surveillance among NT Indigenous children shows that serotypes 19A and 6A/C (exclusive to PCV13) comprised up to 20% of nasopharyngeal carriage types and were associated with up to 20% of IPD cases.[21-24] Serotypes 3, 6A/C and 19A also have a demonstrably higher potential to cause both invasive and mucosal disease than most other types and serotype 19A is commonly non-susceptible to antibiotics such as penicillin.[25,26] Given this local prominence and virulence of the exclusive PCV13 serotypes, it is plausible the reduction in pneumonia hospitalisations seen during the PCV13 era is vaccine related.

Trends in viral pneumonias (including ILI) and therefore all cause ALRI and all cause pneumonia and were confounded by shifts in the surveillance trends associated with the H1N1 epidemic in 2009. Viral pneumonia and ILI rates increased in 2009 and remained higher thereafter; however, rates were noticeably highest from 2009 through to 2011 almost certainly due to enhanced surveillance programs in the immediate wake of the pandemic. However, as other studies have demonstrated a PCV impact against viral respiratory infections[27] (postulated to be associated with the viral-bacterial synergy) it is possible some of the viral pneumonia reduction was more than an artefact of surveillance tendencies.

Though the prevalence of ALRI hospitalisation was high, the overall incidence of ALRI hospitalisations per 100 child-years (2006-2015; 29·7) was lower than that shown previously (1999-2004: 42·7[4]). Subtle differences in case ascertainment (we excluded episodes within 7 days of birth and within 14 days of a previous episode) will explain some of the difference but PCVs and temporal improvements in health care are likely contributors. Whilst it is difficult to make direct comparisons between studies, rates of pneumonia and RSV-ALRI hospitalisation among NT Indigenous infants in our study rank among the highest in the world. All cause pneumonia

hospitalisations per 100 child-years were substantially higher in our cohort (2006-2015; 9.4) than among Indigenous children in Western Australia (2001-2005: 4·2[2]) and children in developing nations globally (children under 5 years of age in 2015: 2-3[1]). Bacterial pneumonia hospitalisations (2006-2015: 7·2) were akin to those previously reported in the NT using ICD codes (1997-2005: 7·4[4]) but were higher than the rates of WHO defined pneumonia in the NT (1997-2005: 5·8[28]). Likewise, the rate of RSV-ALRI hospitalisations per 100 child-years in Central Australia (7·5) was exceeded by only five of 76 studies examined in a recent global review;[29] South Africa (9·2), Thailand (10·5) and First Nations populations of the United States (19·4-29·2) and Alaska (16·4).

Our study has several limitations. Individual level hospital notes, primary health care, pathology, notification and vaccination data were not included. Health and demographic data were exclusively from two sources (Hospital Inpatient Activity and Perinatal datasets) and we assumed complete follow up of each child to 12 months. While ICD-10AM codes are internationally consistent and simple to interrogate, they have inherent diagnostic imprecision because accurate coding relies on definitive diagnoses that are not always available, particularly with single admissions. This is reflected in our data where several dominant codes relate to 'unspecified' diagnoses or where bacterial and viral diagnoses overlap. Few pneumococcal pneumonias (n=38) were reported in our hospital data. Given the global prominence of pneumococcal associated ALRIs and endemicity of pneumococcal carriage among NT Indigenous children (~80%[3,26,28]) the proportion of ALRIs with pneumococcal aetiology is undoubtedly underestimated. It is unclear whether this relates to pre-admission antibiotics, inadequate testing, the poorly sensitive blood cultures, or ICD-10AM coding practices. A further limitation is the temporal assessment of intervention strategies and outcome measurements. We were not able to account for progressive changes such as shifts in ICD10 coding practices, diagnostic definitions, surveillance, antibiotic prescribing preferences and other health care initiatives. We are currently working with the NT Centre for Disease Control to obtain individual immunisation status for further analysis.

Due to early, dense and diverse colonisation by respiratory pathogens,[5] targeted vaccination strategies[14,21,30] and antibiotic therapy[31] have been less effective among infants in the NT than elsewhere. In this study we provide evidence of reduced ALRIs among NT Indigenous infants contemporary with the introduction of PCV13. Unfortunately, the burden of ALRI remains excessive. High rates of maternal smoking (51%), alcohol use in pregnancy (10%), gestational diabetes (15%), and preeclampsia (13%) link to preterm (14%) and low birth weight babies (13%). These factors coupled with early life malnutrition, overcrowding, lack of culturally appropriate antenatal and child health care and inadequate health-related housing infrastructure contribute to the high ALRI burden.[32] While broader vaccine protection (such as maternal RSV vaccination and higher valency infant PCVs), improvements in nutrition (such as improved vitamin D at birth[33]) and smoking cessation programs are key strategies for the future, in these and other challenging settings, fundamental socioeconomic and other improvements are essential.

Contributors

MJB conceived the project, led the data extraction, performed the data linkage, cleaning, analysis and prepared the manuscript. VO provided expert statistical advice. AC edited the first and subsequent drafts of the manuscript. All other authors contributed intellectual input to the design, and preparation of the manuscript.

Declarations of interest

None exist.

Role of the funding source

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Data sharing

All summary statistics are available upon request. De-identified individual level data can only be released with approval from the data custodians in the NT Department of Health.

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Table 1. Pneumococcal vaccination for Indigenous infants in Australia's Northern Territory.

Vaccine	Vaccine delivery	Vaccine protection*	Schedule (months)	Serotypes
PCV7	Jan2006-Sep2009	Jan2006-Mar2010	3+1 (2,4,6,18)[#]	4, 6B, 9V, 14, 18C, 19F, 23F
PCV10	Oct2009-Sep2011	Apr2010-Mar2012	3+1 (2,4,6,12-18)	+1, 5, 7F, HiD[^]
PCV13	Oct2011-Dec2015	Apr2011-Dec2015	3+1 (2,4,6,12)	+1, 5, 7F, 3, 6A, 19A

*We assumed vaccine protection extended for 6 months beyond the cessation of program delivery. [#]The 23-valent pneumococcal polysaccharide vaccine was used as the booster during the PCV7 era. [^]HiD (*H. influenzae* protein D) is a highly conserved surface protein from Non-Typeable *H. influenzae* used as a carrier in the vaccine.

Table 2. Characteristics of Indigenous Australian children born within each vaccine era.

Participant Characteristics, n (%)		PCV7 Jan 2006-Mar 2010 N=6441	PCV10 Apr 2010-Mar 2012 N=2954	PCV13 Mar 2012-Dec 2015 N=5199	PCV10 vs PCV7	PCV13 vs PCV10	PCV13 vs PCV7
Male		3333 (52)	1511 (51)	2646 (51)	0·592	0·824	0·360
Region							
Top End	Urban	1318 (20)	569 (19)	1133 (22)	0.177	0.007	0.080
	Remote	3086 (48)	1425 (48)	2388 (46)	0.768	0.045	0.033
Central	Urban	619 (10)	284 (10)	496 (10)	0.995	0.913	0.898
	Remote	1418 (22)	676 (23)	1182 (23)	0.347	0.877	0.354
Gestational age (weeks)*							
20-31		135 (2)	63 (2)	116 (2)	0.945	0.689	0.563
32-36		663 (11)	327 (12)	591 (12)	0.301	0.503	0.040
≥37		5133 (87)	2349 (86)	4034 (85)	0.324	0.428	0.032
Birthweight (grams)*							
<1500		112 (2)	52 (2)	96 (2)	0.974	0.705	0.611
1500-2499		644 (11)	325 (12)	550 (12)	0.166	0.731	0.225
2500-3999		4743 (80)	2149 (78)	3765 (79)	0.109	0.328	0.489
≥4000		433 (7)	213 (8)	330 (7)	0.432	0.190	0.500
Admission to the special care nursery*		1282 (22)	626 (23)	1084 (23)	0·144	0·843	0·136
Maternal smoking during pregnancy*		2,494 (53)	1276 (51)	2295 (49)	0·057	0·395	0·001
Maternal alcohol use during pregnancy*		675 (14)	298 (12)	446 (10)	0·127	0·006	<0·001

Data are n (%) or median (range). Smoking and alcohol use during pregnancy were considered positive if reported at any antenatal visit. *Incomplete era denominators due to missing data (PCV7, PCV10, PCV13): birthweight and gestational age (n=5930, 2739, 4741); special care nursery (n=5908, 2709, 4732); smoking during pregnancy (n=4716, 2525, 4638); alcohol during pregnancy (n=4910, 2393, 4355). p-values were calculated using the Chi-square (proportions) or Wilcoxon ranksum test (continuous data) accordingly.

Table 3. Annual ALRI hospitalisation rates among Indigenous infants in Australia's Northern Territory.

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Overall*
	Rate per 100 child-years (n)										
ALRI	16·2 (247)	30·9 (474)	27·0 (389)	29·9 (461)	33·8 (506)	32·2 (468)	27·3 (400)	27·0 (366)	25·9 (362)	33·6 (465)	**29·7 (4138)**
Pneumonia											
All cause	4·1 (62)	9·4 (144)	9·1 (131)	11·0 (170)	10·9 (163)	12·2 (178)	8·6 (126)	7·4 (100)	7·1 (99)	8·6 (119)	**9·4 (1292)**
Bacterial	3·7 (57)	8·0 (123)	7·6 (110)	7·9 (122)	8·8 (131)	9·0 (131)	6·6 (97)	5·5 (75)	4·6 (65)	6·9 (95)	**7·2 (1006)**
Viral	0·5 (7)	1·8 (27)	1·7 (25)	4·1 (64)	2·8 (42)	4·8 (70)	3·5 (52)	2·4 (33)	3·3 (46)	2·0 (28)	**3·0 (394)**
ILI	0·1 (1)	0·8 (12)	1·0 (15)	2·9 (45)	1·1 (17)	2·8 (40)	1·3 (19)	1·4 (19)	2·2 (31)	1·2 (17)	**1·6 (216)**
Pathogen specific											
RSV-ALRI	2·6 (39)	4·2 (65)	4·7 (68)	6·7 (104)	4·3 (65)	4·8 (70)	6·7 (98)	4·2 (57)	5·5 (77)	3·9 (54)	**5·0 (697)**
Pneumococcal ALRI	0·1 (2)	0·3 (5)	0·3 (5)	0·3 (4)	0·4 (6)	0·4 (6)	0·1 (2)	0·3 (4)	0·2 (3)	0·1 (1)	**0·3 (38)**

*Overall rate excludes 2006 data to avoid lead-in bias. ALRI subcategories are not mutually exclusive within a hospital episode. **ALRI:** Acute lower respiratory infection. **ILI**: Influenza-like illness. **RSV**: Respiratory syncytial virus.

Table 4. ALRI hospitalisation rates among Indigenous infants in Australia's Northern Territory by vaccine era.

	PCV7 N=6441	PCV10 N=2954	PCV13 N=5199	PCV10 vs PCV7		PCV13 vs PCV10		PCV13 vs PCV7	
	Rate (n)	Rate (n)	Rate (n)	IRR (95%CI)	Adjusted IRR (95%CI)	IRR (95%CI)	Adjusted IRR (95%CI)	IRR (95%CI)	Adjusted IRR (95%CI)
ALRI	29·8 (1710)	32·3 (963)	27·8 (1465)	1·11 (1·02,1·21)	1·11 (1.02,1·22)	0·85 (0·78,0·93)	0·85 (0·78,0.93)	0·95 (0·88,1·03)	0·95 (0·88,1·03)
Pneumonia									
All cause	9·9 (554)	11·3 (337)	7·6 (401)	1·13 (0·98,1·30)	1·13 (0·98,1·31)	0·68 (0·58,0·79)	0·68 (0·58,0·79)	0·77 (0·67,0·88)	0·77 (0·67,0·88)
Bacterial	8·2 (456)	8·4 (252)	5·6 (298)	1·02 (0·86,1·20)	1·02 (0·86,1·20)	0·68 (0·57,0·81)	0·68 (0·57,0·82)	0·70 (0·60,0·81)	0·70 (0·60,0·81)
Viral	2·3 (128)	4 (119)	2·8 (147)	1·71 (1·32,2·20)	1·70 (1·31,2·21)	0·70 (0·55,0·90)	0·68 (0·53,0·87)	1·19 (0·94,1·52)	1·16 (0·90,1·49)
Viral (excl. 2009)	1·5 (64)			2·49 (1·82,3·42)	2·51 (1·83,3·46)			1·75 (1·29,2·37)	1·73 (1·27,2·36)
ILI	1·3 (73)	2·0 (60)	1·6 (83)	1·45 (1·03,2·04)	1·43 (1·01,2·03)	0·79 (0·57,1·10)	0·78 (0·55,1·09)	1·14 (0·83,1·57)	1·11 (0·80,1·53)
ILI (excl. 2009)	0·7 (28)			2·68 (1·70,4·20)	2·65 (1·68,4·18)			2·11 (1·37,3·25)	2·10 (1·36,3·22)
Pathogen specific									
RSV-ALRI	4·9 (292)	4·9 (147)	4·9 (258)	0·99 (0·81,1·21)	0·95 (0·77,1·17)	0·99 (0·81,1·21)	1·01 (0·82,1·24)	0·98 (0·83,1·17)	0·96 (0·80,1·14)
Pneumococcal ALRI	0·3 (18)	0·3 (10)	0·2 (10)	1·03 (0·47,2·29)	1·04 (0·47,2·32)	0·56 (0·23,1·37)	0·55 (0·23,1·34)	0·58 (0·26,1·29)	0·58 (0·26,1·27)

Data are: **Rate** in episodes per 100 child-years (excludes first 8 months of 2006 to limit truncation bias), episode count **(n)** and incidence rate ratio (**IRR**) calculated using random effects negative binomial regression of count episode data. Characteristics selected for multivariate model are listed in Appendix Table 4. PCV7 era data for *viral* pneumonia and ILI are also shown with the exclusion the 2009 H1N1 pandemic year. **PCV7**: Jan 2006-Mar 2010. **PCV10**: Apr 2010-Mar 2012. **PCV13**: Apr 2012-Dec 2015. **95%CI**: 95% confidence interval. **ALRI:** Acute lower respiratory infection. **ILI**: Influenza-like illness. **RSV**: Respiratory syncytial virus.

Research in context

Evidence before the study

In most settings, pneumococcal conjugate vaccines (PCVs) have effectively reduced the risk of invasive pneumococcal disease, pneumonia, and otitis media in children, both directly and via herd protection. A PubMed search using terms "pneumococcal conjugate vaccine" or "acute lower respiratory infection" or "pneumonia" and "Northern Territory" or "Australia" revealed few studies reporting rates of acute lower respiratory infection (ALRI) among high-risk Indigenous children in the Northern Territory (NT). With the introduction of the 7-valent PCV (PCV7) in Australia, a national decline (38%) in pneumonia hospitalisations (all children aged <2 years) and invasive pneumococcal disease notifications (Indigenous children aged <5 years) were reported. Also, two population-based record-linkage studies across Western Australia and New South Wales showed a decline in all cause pneumonia hospitalisation rates (28-49%) among Indigenous children aged <3 years and most recently, a 17% reduction in pneumococcal pneumonia hospitalisations was seen among Indigenous and non-Indigenous infants (aged <1 year) nationally between an early PCV7 era (2005-2007) and post PCV13 era (>2011). However, despite the success elsewhere, in the Northern Territory (NT) of Australia which has the highest proportion of Indigenous peoples and reported burden of pneumococcal diseases, population-based hospital surveillance and a retrospective cohort study utilising documented vaccination status and blinded radiological assessment of pneumonia showed no evidence that PCV7 reduced the incidence of pneumonia among Indigenous infants aged <18 months. In the NTs challenging setting, despite high PCV coverage and breastfeeding rates, Indigenous infants are densely colonised with a diversity of respiratory pathogens within 6-weeks of birth and rates of pneumonia (22% hospitalised in first year), otitis media (90% at age 6 months) and chronic suppurative lung disease (1 in 68 in Central Australia) are among the highest reported in the world.

Added value of the study

Prior to this study there were no published data reporting childhood ALRI rates in Australia's NT beyond 2005 and no evaluation of the impact of the expanded valency PCVs against ALRI. This study of all NT Indigenous children born between 2006-2015 (n=14594) highlights the ongoing respiratory health crisis in the region. One in five Indigenous infants were hospitalised with an ALRI in their first year of life as was the case 15 years earlier and rates of maternal smoking and alcohol use in pregnancy, gestational diabetes, anaemia, preterm birth and low birth weight babies remain high. Living in a remote community or the Central desert region were the strongest predictors of ALRI hospitalisation. Despite the ongoing burden, we demonstrated a reduction in pneumonia hospitalisations associated with the introduction of PCV13, supporting its ongoing use in this high-risk region.

Implications of the evidence

To our knowledge this the first suggestion of a PCV related reduction in pneumonia hospital admissions seen exclusively in the NT. These data are important to inform future vaccine strategies. Future gains however, given the high burden of ALRIs and its consequences in the NT, will require alternative strategies including broader valency (a 20-valent vaccine is in Phase 2 clinical trials), protein or whole cell pneumococcal vaccines, maternal vaccination (respiratory syncytial virus and PCVs), nutritional supplementation, smoking cessation and improved housing.

Figure

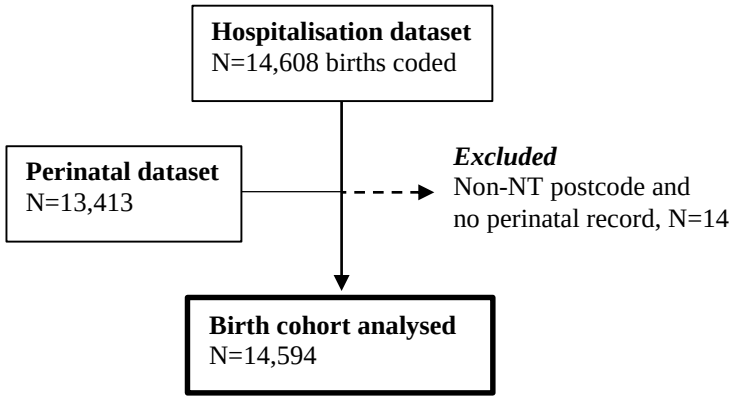


Figure 1. The birth cohort.

Deidentified hospitalisation and perinatal data were sourced from the NT Department of Health (Hospital Inpatient Activity Dataset and Midwives Collection Dataset respectively).

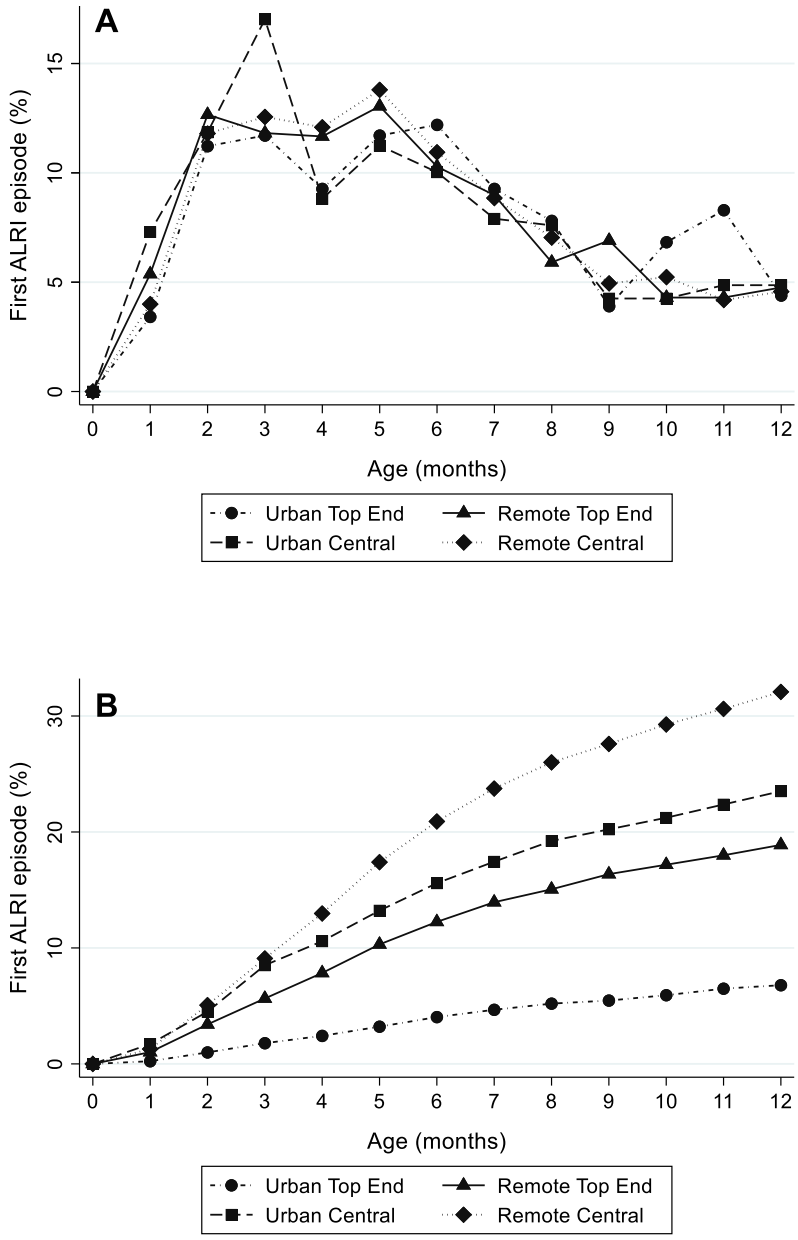
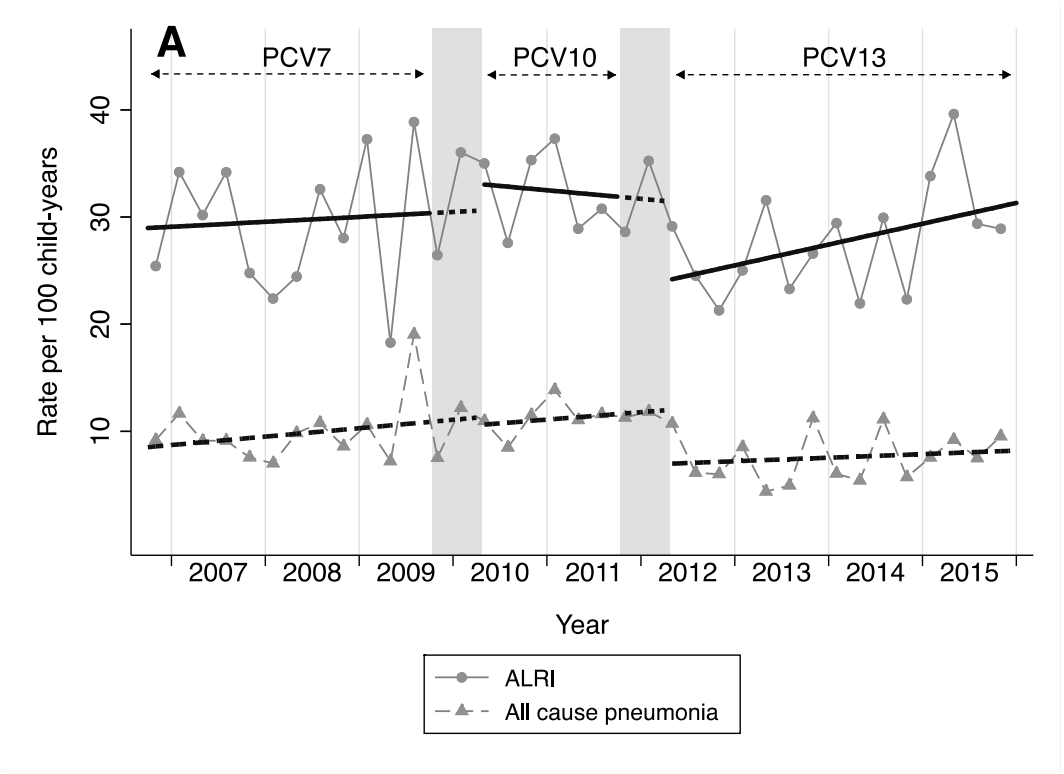


Figure 2. ALRI in the first year of life: Northern Territory Indigenous infants, 2006-2015.
A: Frequency distribution of first episodes occurring in each age in month by region (as a proportion of total first episodes) during the decade: 2006-2015. **B**: Cumulative proportion of acute lower respiratory infection (ALRI) hospitalised children by age month and region.



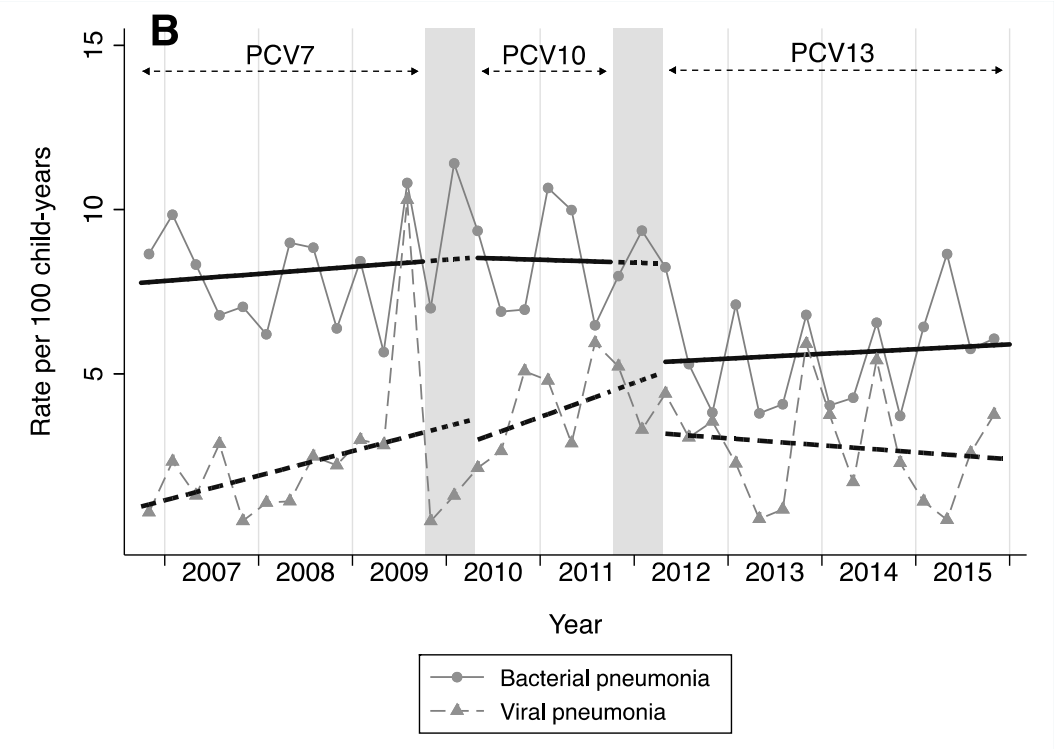


Figure 3. ALRI hospitalisation rates by pneumococcal vaccine era.
Interrupted time series plot of ALRI rates during spanning three eras of pneumococcal conjugate vaccine eras. Predicted trends allowed for both level and slope shift between eras. Vaccine eras were extended by 6 months to best capture the era of protection. Data are episodes per 100 child-years (resolution quarterly). **A**: All acute lower respiratory infections (ALRI) and All cause pneumonia. **B**: Bacterial pneumonia and viral pneumonia.