Vaccine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Incremental effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumonia hospitalisation among Australian Indigenous children: A record linkage study

Alamgir Kabir [a,b,c,d,*], Deborah Randall [b,c], Anthony T. Newall [a], Hannah C. Moore [e,f], Sanjay Jayasinghe [g,h], Parveen Fathima [e,i], Bette Liu [a], Peter McIntyre [g], Heather F. Gidding [a,b,c,g,i]

[a] School of Population Health, Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia
[b] The University of Sydney Northern Clinical School, NSW, Australia
[c] Women and Babies Research, Kolling Institute, Northern Sydney Local Health District, St Leonards, NSW, Australia
[d] Centre for Primary Health Care and Equity, University of New South Wales, Sydney, NSW, Australia
[e] Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, The University of Western Australia, WA, Australia
[f] School of Population Health, Curtin University, Perth, Western, Australia
[g] National Centre for Immunisation Research and Surveillance, Westmead, NSW, Australia
[h] Discipline of Child and Adolescent Health, Children's Hospital Westmead Clinical School, Faculty of Medicine and Health, University of Sydney, Australia
[i] Sydney School of Public Health, Faculty of Medicine and Health, University of Sydney, Australia

ARTICLE INFO

Keywords:
Indigenous
Pneumococcal polysaccharide vaccine
Vaccine effectiveness
Pneumonia
Data linkage

ABSTRACT

Background: The impact of pneumococcal conjugate vaccines (PCVs) on pneumonia in children is well-documented but data on 23-valent pneumococcal polysaccharide vaccine (PPV23) are lacking. Between 2001 and 2011, Indigenous children in Western Australia (WA) were recommended to receive PPV23 at 18–24 months of age following 3 doses of 7-valent PCV. We evaluated the incremental effectiveness of PPV23 against pneumonia hospitalisation.

Methods: Indigenous children born in WA between 2001 and 2012 who received PCV dose 3 by 12 months of age were followed from 18 to 60 months of age for the first episode of pneumonia hospitalisation (all-cause and 3 subgroups: presumptive pneumococcal, other specified causes, and unspecified). We used Cox regression modelling to estimate hazard ratios (HRs) for pneumonia hospitalisation among children who had, versus had not, received PPV23 between 18 and 30 months of age after adjustment for confounders.

Results: 11,120 children had 327 first episodes of all-cause pneumonia hospitalisation, with 15 (4.6%) coded as presumptive pneumococcal, 46 (14.1%) as other specified causes and 266 (81.3%) unspecified. No statistically significant reduction in all-cause pneumonia was seen with PPV23 (HR 1.11; 95% CI: 0.87–1.43), but the direction of the association differed for presumptive pneumococcal (HR 0.47; 95% CI: 0.16–1.35) and specified (HR 0.89; 95% CI: 0.49–1.62) from unspecified causes (HR 1.13; 95% CI: 0.86–1.49). During the baseline period before PPV23 vaccination (12–18 months), all-cause pneumonia risk was higher among PPV23-vaccinated than unvaccinated children (RR: 1.73; 95% CI: 1.30–2.28).

Conclusion: In this high-risk population, no statistically significant incremental effect of a PPV23 booster at 18–30 months was observed against hospitalised all-cause pneumonia or the more specific outcome of presumptive pneumococcal pneumonia. Confounding by indication may explain the slight trend towards an increased risk against all-cause pneumonia. Larger studies with better control of confounding are needed to further inform PPV23 vaccination.

* Corresponding author: Centre for Primary Health Care and Equity, Room-340, Level 3, AGSM Building, University of New South Wales, Sydney, NSW 2052, Australia.
E-mail address: a.kabir@unsw.edu.au (A. Kabir).

https://doi.org/10.1016/j.vaccine.2023.07.042
Received 30 May 2023; Received in revised form 20 July 2023; Accepted 20 July 2023

1. Introduction

While the global burden of pneumonia has declined since 2000, it remains a leading cause of morbidity and mortality in young children, [1,2] especially in developing countries and Indigenous populations in high income countries [3,4]. Given the high burden of childhood pneumonia, WHO and the United Nations Children's Fund (UNICEF) established the Global Action Plan for the Prevention and Control of Pneumonia (GAPP) and set a goal to end childhood pneumonia deaths by 2025 [5]. In Australia, the burden of hospitalisation due to pneumonia is disproportionately high in Aboriginal and Torres Strait Islander (hereafter respectfully referred to as Indigenous) children, especially those living in remote regions [6].

Pneumococcal vaccines have been developed to protect against invasive infections due to *Streptococcus pneumoniae* (pneumococcus) [7–10], which is estimated to account for approximately 10% of all-cause childhood pneumonia globally (4.8% in Australia) [11]. Pneumococcal vaccination programs include various pneumococcal conjugate vaccine (PCV) schedules, with many high-income countries also including the 23-valent pneumococcal polysaccharide vaccine (PPV23) as a booster dose for high-risk populations [12–15]. Between 2001 and 2011, Australian Indigenous children living in regions with the highest incidence of IPD (including Western Australia) were recommended to receive a PPV23 booster at 18–24 months of age following 3 doses of 7-valent PCV (PCV7) at 2, 4 and 6 months of age (details in supplementary material) [16]. Many studies in Australia and internationally have reported a significant impact of PCV7 against pneumonia [6,7,17–20]. However, only two Australian studies have evaluated the impact of a PPV23 booster among Indigenous children, and the findings have been mixed. An early study of lower respiratory tract infection from the Northern Territory (NT), reported that the PPV23 booster was associated with an increased risk of pneumonia hospitalisation [21], but a later study including other regions found some evidence of benefit against invasive pneumococcal disease (IPD) [22].

While the recommended age for the first PPV23 booster in high-risk children in Australia has changed to 4 years of age, and the PCV schedule to 3 primary doses of 13-valent PCV (PCV13) and a booster at 12 months [23], the evidence gap for incremental effectiveness of PPV23 remains relevant to considerations of PPV23 scheduling and PCVs with additional serotypes including those in PPV23 [23].

2. Methods

2.1. Study population and design

The study population was a sub-cohort of a large population-based data linkage cohort of 1.3 million children born July 2001-December 2012 in two states of Australia – New South Wales (NSW) and Western Australia (WA) [24–26]. Details of the full cohort, datasets, data cleaning and linkage procedures have been described elsewhere [25–27]. As only Indigenous children in WA were eligible for funded PPV23, we restricted the current analysis to WA-born children identified as Indigenous (using an established multi-stage median algorithm) [28] who had received PCV dose 3 by 12 months of age. Children were excluded from the cohort if they were born after June 2012, or if prior to 18 months of age, they died, received PCV dose 4 or PPV23, or had a hospital admission due to all-cause pneumonia.

2.2. Exposure and outcome of interest

Our exposure of interest was the receipt of a PPV23 dose between 18 and 30 months of age. We ascertained vaccination status from the linked Australian Childhood Immunisation Register (ACIR) which records all vaccines given to children <7 years of age by type, dose number and date of administration. A PPV23 dose was considered invalid if it was given within 28 days of a PCV dose 3 or after 30 months of age. Our primary outcome of interest was the first hospital admission due to all-cause pneumonia among children 18–60 months of age in 2001–2013. As in our previous study, [6] all-cause pneumonia hospitalisations were identified by International Classification of Disease 10th Revision Australian Modification (ICD-10-AM) [29] codes (Supplementary Table S1) and included primary and secondary (up to 20) ICD-10-AM diagnosis fields. Our secondary outcomes were three diagnostic subcategories of all-cause pneumonia: presumptive pneumococcal pneumonia (coded as *Streptococcus pneumoniae* or lobar), pneumonia due to other specified causes, and pneumonia due to unspecified causes (Supplementary Table S1).

2.3. Potential confounders

Demographic characteristics, maternal medical and obstetric history, and information on labour and birth were obtained from the perinatal data set and birth registrations (see supplementary material for details). Birth cohort was categorised into pre- (born June 2001-December 2004) and post-universal (born January 2005-December 2012) vaccination periods. Medical conditions associated with increased risk of pneumococcal disease were ascertained from perinatal and hospitalisation data [30,31].

2.4. Statistical analysis

2.4.1. Primary analysis

For the descriptive analysis, numbers and proportions for each category of pneumonia hospitalisation were calculated for the pre- and post-universal PCV birth cohort, and the age distribution of pneumonia hospitalisations among the cohort was presented by their PPV23 vaccination status at the time of becoming a case. Characteristics of the cohort were compared by PPV23 vaccination (at 18–30 months) status using chi-square tests, and the coverage of PPV23 was compared between birth cohorts using the two-sample proportion test. For the study period, incidence rates of pneumonia hospitalisation (all-cause and by category) by PPV23 vaccination status were calculated using person-time-at-risk as the denominator. Person-time started at 18 months of age and was censored at first hospital admission due to pneumonia (if it occurred after 18 months of age), death, PCV dose 4, invalid PPV23 dose, 2nd dose of PPV23, turning 5 years of age or 31st of December 2013, whichever came first. Cox regression modelling, with days of follow-up (beginning at 18 months of age) as the time scale, was used to estimate hazard ratios (HRs) and 95% confidence intervals, comparing the rates of pneumonia hospitalisation according to time-varying PPV23 vaccination status, with exposed time for PPV23 beginning from when the dose was given. Potential confounding variable selection methods are described in the supplementary material. We used SAS Version 9.4 [32] and R3.5.3 [33] statistical software for analysis.

2.4.2. Subgroup analyses

We previously reported a differential effect of PCV on pneumonia hospitalisations by geographical location [6], and thus conducted a stratified analysis by remoteness. We also conducted a stratified analysis by the pre- and post-universal periods [22]. We checked for effect modification by adding an interaction term between each of these two stratifying variables and PPV23 vaccination status into the Cox regression model.

2.4.3. Baseline risk assessment

To explore the potential for confounding by indication we examined the differential baseline risk of pneumonia (i.e. risk prior to entering the study at 18 months of age) by calculating the cumulative incidence and risk ratio (RR) of all-cause pneumonia occurring between 12 and 18 months of age stratified by PPV23 vaccination status by 60 months of age.

Table 1
Hospital admissions for all-cause pneumonia by subcategories in Western Australian Indigenous children born between 2001 and 2012 with follow-up between 18 and 60 months of age.

Subcategories of pneumonia hospitalisation[a]	All children n (%)	Children born Jun 2001-Dec 2004 n (%)	Children born Jan 2005-Dec 2012 n (%)
Presumptive pneumococcal pneumonia	15 (4.6)	4 (4.3)	11 (4.6)
Streptococcus pneumoniae	10 (3.1)	3 (3.2)	7 (3.0)
Lobar pneumonia	5 (1.5)	1 (1.1)	4 (1.7)
Pneumonia due to other specified causes	46 (14.1)	9 (9.8)	37 (15.7)
Pneumonia due to unspecified causes	266 (81.3)	79 (85.9)	187 (79.6)
All-cause pneumonia (Total)	327 (100)	92 (100)	235 (100)

[a] Based on ICD-10-AM codes see Supplementary Table S1 for codes.

2.5. Ethics approvals

Ethics approval was obtained from the Australian Institute of Health and Welfare, the NSW Population & Health Services Research Ethics Committee, Department of Health WA Human Research Ethics Committee, the WA Aboriginal Health Ethics Committee, the NSW Aboriginal Health and Medical Research Council Ethics Committee, and the Australian Government Department of Health and Ageing Departmental Ethics Committee.

3. Results

3.1. Primary analysis

The study cohort included 11,120 Indigenous children (Supplementary Figure S1). We identified 327 first all-cause pneumonia hospitalisations from 18 to 60 months of age; 92 (28.1%) in the pre- and 235 (71.9%) in the post-universal cohort (Table 1). Starting follow-up at 18 months of age, the number of pneumonia cases generally declined with increasing age for both vaccinated and unvaccinated children (Fig. 1). Pneumonia due to unspecified causes was the most frequent category (81.3%), with presumptive pneumococcal pneumonia accounting for only 4.6% of hospitalisations (Table 1). The greatest variation in vaccine uptake was by remoteness category and socioeconomic status (Table 2). The proportion of children vaccinated with PPV23 was 1.5-fold higher in the pre- (66.7%) than in the post-universal cohort (43.8%). Other significant factors associated with uptake included birth weight, maternal and paternal age, and maternal smoking status.

The overall coverage of PPV23 was 48.0% but was substantially higher among children from remote regions (61.0%; Table 3). In remote regions, coverage was significantly ($p < 0.001$) higher among children born in the pre- than in the post-universal period. However, this was not the case for children born in major cities, leading to a greater difference in coverage between major cities and remote/very remote regions in the pre- versus post-universal cohorts (43.9% versus 20.0%).

Among children not vaccinated with PPV23 post 3 doses of PCV7, the incidence of first all-cause pneumonia hospitalisation episodes was 11.5 per 1000 person-years during follow-up, and for those who received PPV23 was 12.4 per 1000 person-years (Table 4). After adjustment, there was no evidence of incremental protection from PPV23 against all-cause pneumonia (Adjusted HR (aHR): 1.11; 95% CI: 0.87–1.43). Adjusted HRs were similar across remoteness categories (Table 4), with no significant interaction between PPV23 status and area of residence (p-value for interaction = 0.898). When stratifying by birth cohort, vaccination with PPV23 was associated with a significantly increased risk of all-cause pneumonia hospitalisation among the pre-universal cohort (aHR: 1.98, 95% CI: 1.15–3.40), but not among the post-universal cohort (aHR: 0.91, 95% CI: 0.68–1.22), with interaction between PPV23 status and birth period significant (p-value for interaction = 0.030).

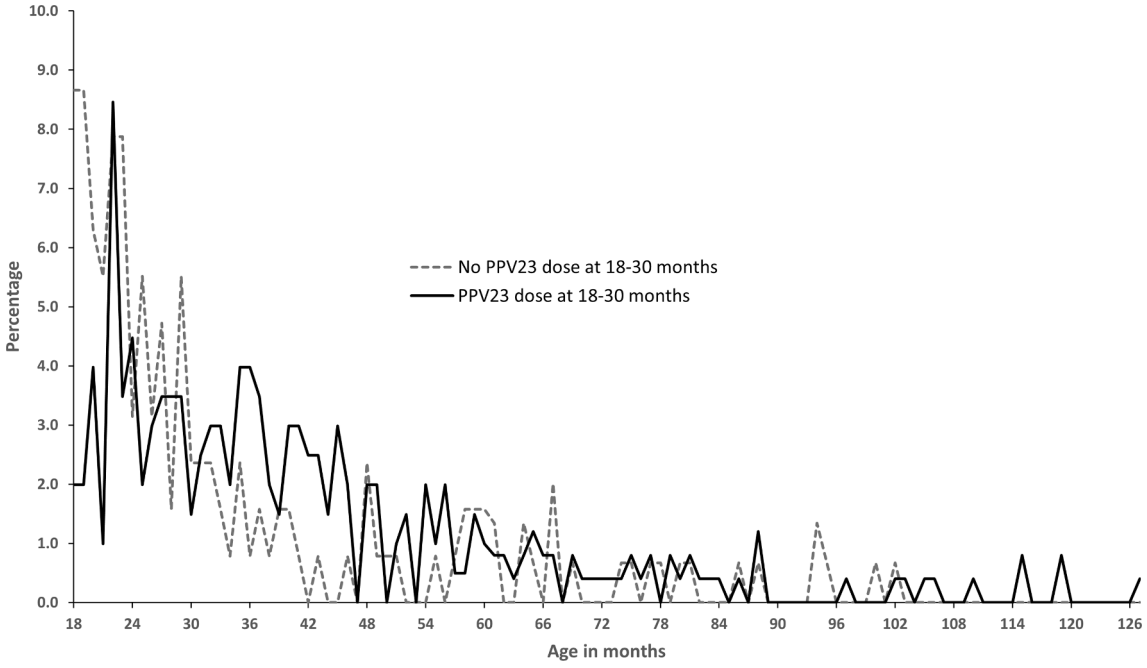

Fig. 1. Distribution[a] of age at pneumonia hospitalisations among children who had received a PCV primary course by 12 months of age by PPV23 vaccination status at the time of becoming a case from 18 months of age to the end of study follow up, December 2013.
Footnote:[a]Distribution of age at pneumonia hospitalisation was calculated by taking the number of pneumonia hospitalisations occurring at a given age and dividing them by the total pneumonia cases for the entire follow-up period by vaccination group.

Table 2
Characteristics of Indigenous children born in Western Australia who received PCV dose 3 by 12 months of age by the status of PPV23 at 18–30 months of age.

Characteristics	N	No PPV23 dose between 18 and 30 months of age n (%)	One PPV23 dose between 18 and 30 months of age n (%)	p-value
Sex				
Male	5599	2927 (52.3)	2672 (47.7)	
Female	5521	2853 (51.7)	2668 (48.3)	0.534
Birth weight, grams				
<1500	133	74 (55.6)	59 (44.4)	
1500–2499	922	416 (45.1)	506 (54.9)	
2500–3499	6235	3195 (51.2)	3040 (48.8)	
3500–4499	3672	2009 (54.7)	1663 (45.3)	
>=4500	158	86 (54.4)	72 (45.6)	<0.001
Gestational age, weeks				
18–31	9929	5185 (52.2)	4744 (47.8)	
32–36	1038	506 (48.7)	532 (51.3)	
37–45	150	89 (59.3)	61 (40.7)	0.019
Apgar Score				
0–7	387	210 (54.3)	177 (45.7)	
8–10	10712	5562 (51.9)	5150 (48.1)	0.383
Season of birth				
Spring	2614	1365 (52.2)	1249 (47.8)	
Winter	2705	1413 (52.2)	1292 (47.8)	
Autumn	3037	1612 (53.1)	1425 (46.9)	
Summer	2764	1390 (50.3)	1374 (49.7)	
Birth cohort				
Born Jun 2001-Dec 2004	2035	678 (33.3)	1357 (66.7)	
Born Jan 2005-Dec 2012	9085	5102 (56.2)	3983 (43.8)	<0.001
Delivery method				
Vaginal	7563	3792 (50.1)	3771 (49.9)	
Instrumental	957	564 (58.9)	393 (41.1)	
Caesarean	2600	1424 (54.8)	1176 (45.5)	<0.001
Pneumococcal risk condition identified before 6 months[a] [28]				
No	10819	5619 (51.9)	5200 (48.1)	
Yes	301	161 (53.5)	140 (46.5)	0.594
Maternal age group, years				
<20	2442	1199 (49.1)	1243 (50.9)	
20–24	3622	1780 (49.1)	1842 (50.9)	
25–29	2596	1432 (55.2)	1164 (44.8)	
30–34	1591	875 (55.0)	716 (45.0)	
>=35	869	494 (56.8)	375 (43.2)	<0.001
Parental age difference (Father's age - mother's age), years				
<0	1913	1000 (52.3)	913 (47.7)	
0–3	4707	2515 (53.4)	2192 (46.6)	
4–7	1925	1025 (53.2)	900 (46.8)	
8+	1197	620 (51.8)	577 (48.2)	
Missing	1378	620 (45.0)	758 (55.0)	<0.001
Parity				
0	3067	1582 (51.6)	1485 (48.4)	
1	2640	1422 (53.9)	1218 (46.1)	
2	1812	948 (52.3)	864 (47.7)	
>=3	3601	1828 (50.8)	1773 (49.2)	0.109
Maternal smoking				
No	6514	3568 (54.8)	2946 (45.2)	
Yes	4606	2212 (48.0)	2394 (52.0)	<0.001
Socioeconomic index[b] [33]				
91–100 % (least disadvantaged)	158	98 (62.0)	60 (38.0)	
76–90 %	483	350 (72.5)	133 (27.5)	
26–76 %	3551	2176 (61.3)	1375 (38.7)	
11–25 %	2313	1235 (53.4)	1078 (46.6)	
0–10 % (most disadvantaged)	3093	1306 (42.2)	1787 (57.8)	
Missing	1522	615 (40.4)	907 (59.6)	<0.001
Accessibility or Remoteness Index of Australia [34]				
Major cities	3691	2392 (64.8)	1299 (35.2)	
Inner or outer region	2756	1544 (56.0)	1212 (44.0)	
Remote or very remote	3151	1229 (39.0)	1922 (61.0)	
Missing	1522	615 (40.4)	907 (59.6)	<0.001

[a] If a child had any of the 10 ICD-10-AM-coded conditions by 6 months of age or born preterm.
[b] Socio-economic status was determined using the Socio-economic Indices for Areas (SEIFA) Index of Relative Socio-economic Disadvantage (IRSD) 2006, from the Australian Bureau of Statistics (ABS).

3.2. Subgroup analyses

Vaccination with PPV23 was associated with a trend towards a lower risk of presumptive pneumococcal pneumonia (aHR: 0.47; 95% CI: 0.16–1.35) and pneumonia due to other specified causes (aHR: 0.89; 95% CI: 0.49–1.62), and with higher risk in pneumonia due to unspecified causes (aHR: 1.13; 95% CI: 0.86–1.49), but no associations were statistically significant (Table 5).

3.3. Baseline risk assessment

During the baseline risk assessment period (between 12 and 18 months of age - prior to eligibility for PPV23), 136 pneumonia hospitalisations were recorded among children who later received PPV23 and 75 among children not subsequently vaccinated with PPV23. Cumulative incidence was significantly higher (RR: 1.73; 95% CI: 1.30–2.28) among children vaccinated compared to those who remained unvaccinated with PPV23 (Supplementary Table S2). The baseline RR was higher for children born in the pre- than for those born in the post-universal period (3.17 versus 1.49) but RRs were more similar when stratified by region (1.25 in remote, 1.75 in inner and outer regions, 1.50 in major cities).

4. Discussion

This is the only population-based study in high-risk Australian Indigenous children, mostly living in remote regions, to evaluate the incremental effectiveness of a PPV23 booster dose against pneumonia following the primary course of 3 PCV doses. Our study showed that a PPV23 booster given between 18 and 30 months of age had no incremental protective effect against all-cause pneumonia hospitalisation at 18–60 months of age. Indeed, we found a trend towards a higher rate of pneumonia hospitalisations in vaccinated compared with unvaccinated children, although this association was only statistically significant in the pre-universal cohort. We did find that PPV23 was associated with a non-statistically significant trend towards a lower risk for the more specific presumptive pneumococcal and other specified pneumonias, in contrast to the higher risk (not significant) for all-cause and unspecified pneumonia (which contributed more than 80% of all cases).

While there have been several randomised control trials (RCTs) evaluating the immunogenic response of a PPV23 booster against PPV23 serotypes [34–38], few studies have evaluated the incremental effectiveness of PPV23 booster against clinical end points [21,22]. A retrospective cohort study of 5482 Indigenous children born in 2000–2004 from the NT, Australia, reported that PPV23 given after the primary course of PCV7 was associated with a 43% (HR: 1.43, 95% CI: 1.04–1.98) increased risk of pneumonia hospitalisation by 2 years of age compared with those unvaccinated with either PCV7 or PPV23 [21]. This is the most comparable study to ours, although their comparison

Table 3
Coverage of PPV23 at 18–30 months of age among Western Australian Indigenous children who received PCV dose 3 by 12 months of age by area of residence and period of birth.

Area of residence	Overall		Children born Jun 2001 - Dec 2004		Children born Jan 2005 - Dec 2012		p-value[b]
	N	Vaccinated with PPV23 n (%)	N	Vaccinated with PPV23 n (%)	N	Vaccinated with PPV23 n (%)	
All[a]	11120	5340 (48.0)	2035	1357 (66.7)	9085	3983 (43.8)	<0.001
Major cities	3691	1299 (35.2)	390	147 (37.7)	3301	1152 (34.9)	0.300
Inner or outer regional	2756	1212 (44.0)	480	289 (60.2)	2276	923 (40.6)	<0.001
Remote or very remote	3151	1922 (61.0)	722	589 (81.6)	2429	1333 (54.9)	<0.001

[a] Missing values for area of residence: n = 1522 (n = 443 in children born in Jun 2001-Dec 2004 and n = 1079 in children born in Jan 2005-Dec 2012).
[b] p-values for comparing coverage of PPV23 between children born in Jun 2001-Dec 2004 and in Jan 2005-Dec 2012.

Table 4
Rate of hospitalisation for all-cause pneumonia in children with 3 doses of PCV7 by 12 months of age by PPV23 status in Western Australian Indigenous children born between 2001 and 2012 followed up from 18 to 60 months of age.

Population sub-group	PPV23 status	Person-years (PYs)	Cases	Rate per 1000 PY (95 % CI)	HR (95 % CI)	aHR[d] (95 % CI)
Overall	Unvaccinated	10998	126	11.5 (9.5, 13.6)	Ref	Ref
	Vaccinated	16237	201	12.4 (10.7, 14.2)	1.50 (1.19, 1.91)	1.11 (0.87, 1.43)
By area of residence[a,b]						
Major cities	Unvaccinated	5117	29	5.7 (3.9, 8.1)	Ref	Ref
	Vaccinated	3928	23	5.9 (3.7, 8.8)	1.19 (0.68, 2.09)	1.19 (0.18, 7.90)
Inner or outer regions	Unvaccinated	3016	29	9.6 (6.4, 13.8)	Ref	Ref
	Vaccinated	3710	34	9.2 (6.3, 12.8)	1.35 (0.79, 2.29)	1.20 (0.72, 1.99)
Remote or very remote	Unvaccinated	1733	40	23.1 (16.5, 31.4)	Ref	Ref
	Vaccinated	5854	94	16.1 (13.0, 19.7)	1.14 (0.75, 1.73)	1.14 (0.65, 2.00)
By year of birth[c]						
Children born Jun 2001-Dec 2004	Unvaccinated	2270	21	9.2 (5.7, 14.1)	Ref	Ref
	Vaccinated	4341	71	16.4 (12.8, 20.6)	2.53 (1.50, 4.26)	1.98 (1.15, 3.40)
Children born Jan 2005-Dec 2012	Unvaccinated	8727	105	12.0 (9.8, 14.6)	Ref	Ref
	Vaccinated	11896	130	10.9 (9.1, 13.0)	1.24 (0.94, 1.63)	0.91 (0.68, 1.22)

[a] There were 78 pneumonia cases in 1522 children whose area of residence was missing.
[b] Interaction between PPV23 status and area of residence was not statistically significant (p = 0.818).
[c] Interaction between PPV23 status and pre/post-universal period was statistically significant (p = 0.030).
[d] HR for combined data was adjusted for SEIFA and ARIA; HR for children living in major cities was adjusted for medically at-risk conditions by 6 months of age and parental age difference; HR for children living in regional areas was adjusted for parental age difference and SEIFA and birth cohort (born in the pre-/post-universal period); HR for children living in remote regions was adjusted for birth weight, birth cohort (born in the pre-/post-universal period), medically at-risk conditions by 6 months of age, parental age difference, parity, smoking status and SEIFA; VE for children who were born in the pre-universal period was adjusted for ARIA, and HR for children born in the post-universal period was adjusted for SEIFA and ARIA.

Table 5
Rate of hospitalisation for different sub-categories of pneumonia by PPV23 status and effect of PPV23 against hospitalisation for different sub-categories of pneumonia in Western Australian Indigenous children born between 2001 and 2012 and followed up from 18 to 60 months of age.

Pneumonia type	PPV23 status	Person-years (PYs)	Cases	Rate per 1000 PY (95 % CI)	HR (95 % CI)	aHR[a] (95 % CI)
Presumptive pneumococcal pneumonia	Unvaccinated	14000	7	0.5 (0.2, 1.0)	Ref	Ref
	Vaccinated	19356	8	0.4 (0.2, 0.8)	0.70 (0.25, 1.93)	0.47 (0.16, 1.35)
Pneumonia due to other specified causes	Unvaccinated	13982	20	1.4 (0.9, 2.2)	Ref	
	Vaccinated	19310	26	1.3 (0.9, 2.0)	0.94 (0.52, 1.69)	0.89 (0.49, 1.62)
Pneumonia due to unspecified causes	Unvaccinated	13925	79	5.7 (4.5, 7.1)	Ref	Ref
	Vaccinated	18982	187	9.9 (8.5, 11.4)	1.64 (1.26, 2.13)	1.13 (0.86, 1.49)

[a] HR for presumptive pneumococcal pneumonia was adjusted for parental age difference and ARIA; HR for pneumonia due to other specified causes was adjusted for gestational age, birth cohort (born in the pre-/post-universal period), parity, and SEIFA; HR for pneumonia due to other specified causes was adjusted for SEIFA and ARIA.

group was children unvaccinated with PCV7 and follow-up was only until 2 years of age. Our study finding for all-cause pneumonia was in the same direction, but our point estimate was lower and non-significant (HR: 1.11; 95% CI: 0.87–1.43). However, we believe the trend towards a slightly higher risk among PPV23 vaccinated children may be explained by confounding by indication, which is discussed in more detail below. In contrast, a nationally representative ecological study in Australia evaluating the impact of a PPV23 booster against PPV23-non-PCV7 type IPD, reported a 'possible effect'; they found that the incidence rate ratio (IRR) for PPV23-non-PCV7 type IPD in the post- relative to the pre-PCV introduction period was lower for Indigenous (IRR: 1.2, 95% CI: 0.8–1.8) than for non-Indigenous children (IRR: 3.1, 95% CI: 2.5–3.7) [22]. Furthermore, studies evaluating the immunogenicity of PPV23 provided after the primary PCV course against PPV23-serotypes reported a significant increase in immunogenicity against the PPV23-serotypes [34–38]. Given the mixed findings to date regarding the incremental effectiveness of PPV23, further research is required.

There are several potential biological reasons that might explain why we did not find a direct effect of PPV23 against pneumonia hospitalisation in this high-risk population. First, our study population was a

highly selected group; they had received PCV dose 3 prior to 12 months of age and had not been hospitalised with pneumonia before 18 months of age. However, we wanted to evaluate the recommended schedule at the time. Second, childhood pneumonia is predominantly caused by pathogens other than *Streptococcus pneumoniae;* an estimated >90% of all-cause pneumonias are caused by other pathogens [11,19,39]. Finally, while vaccine-type serotypes declined significantly as a cause of IPD in both Indigenous and non-Indigenous children after the introduction of PCV7, nasopharyngeal carriage of non-vaccine type serotypes (especially non PPV23 serotypes) was found to have increased to a greater extent among Indigenous children than non-Indigenous children in WA [40].

Our study has the following strengths. First, we analysed data from a large population-based cohort with a longer follow up time than other published studies. Second, we measured only the added effect of PPV23 against pneumonia in those who had received a full primary PCV schedule. Third, we included a comprehensive range of potential confounders in our analysis, birth weight, area-level socioeconomic status, maternal smoking status, and parental age difference, reducing the potential for residual confounding.

One potential limitation with our study is that there may have been confounding by indication, which could have biased our vaccine effectiveness estimates. We found that children subsequently vaccinated with PPV23 had a higher underlying risk of pneumonia than the PPV23 unvaccinated cohort (RR: 1.73; 95% CI: 1.30–2.28), and coverage of PPV23 among children at the highest risk of pneumonia (low socioeconomic status and/or living in remote regions) was higher than among children living in areas of high-socio-economic status and/or more urban areas. Therefore, the association of PPV23 vaccination with a higher risk of pneumonia might be due to our inability to fully control for differences in underlying risk. For example, we used area-level socioeconomic status not household-level socioeconomic status, and maternal smoking status during pregnancy without knowing pre/post-pregnancy smoking status and did not have data on possibly important unmeasured cofounding variables, such as household size and breast-feeding status.

Our study findings could potentially be affected by several other limitations. First, even though our study showed a non-significant trend towards an increased risk of all-cause pneumonia and a trend towards a reduced risk of presumptive pneumococcal pneumonia among the PPV23 vaccinated compared with the unvaccinated cohort, the estimates were imprecise due to the small number of cases, particularly for the subgroup analyses. Therefore, a larger study on the incremental effectiveness of PPV23 in high-risk populations would be helpful. Second, pneumonia hospitalisations were identified using ICD diagnosis codes without any clinical or pathological validation, and thus the effect of the vaccine might be underestimated due to non-differential misclassification bias. Third, as we only considered severe pneumonia cases, our study findings may not be generalisable to milder cases not requiring hospitalisation. Finally, the vaccinated children may also have more access to health care than the unvaccinated children, and thus pneumonia hospitalisation might be under-reported among the unvaccinated. However, this potential bias was reduced because the comparator was PCV dose 3 recipients. Limitations related to cohort assembly are described elsewhere [25].

Differential confounding by indication between the pre- and post-universal cohort could potentially explain the higher rate of pneumonia hospitalisation in children vaccinated with PPV23 compared to the unvaccinated children in the pre-universal cohort. During the pre-universal period, only Indigenous children and children who were at higher risk of IPD were targeted for pneumococcal vaccination. Therefore, it may be the case that Indigenous children who were at higher risk of pneumonia hospitalisation were more likely to be selectively vaccinated with PPV23 in the pre- than in the post-universal period, and thus the HR was higher in the pre-universal period.

In this high-risk population, we did not find a statistically significant incremental effect of PPV23 given between 18 and 30 months of age against all-cause pneumonia hospitalisation or against the more specific outcome of presumptive pneumococcal pneumonia. We believe our study shows evidence of confounding by indication, which may explain the slight trend towards an increased risk against all-cause pneumonia. In contrast, the trend towards a lower risk for presumptive pneumococcal pneumonia is promising, but there were too few cases to reliably interpret the effect. Therefore, larger studies with better control of confounding are needed to further inform PPV23 vaccination in this population.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

Acknowledgements

Authors acknowledge the staff at the Population Health Research Network (PHRN) and participating PHRN data linkage and infrastructure nodes (the Western Australian Data Linkage Branch, the NSW Centre for Health Record Linkage, and the Australian Institute for Health and Welfare), and the WA and Commonwealth Departments of Health and NSW Ministry of Health who provided advice and data from the following collections: inpatient hospitalisations, registries of births, deaths and marriages, midwives/perinatal datasets, disease notification registers, and Australian Childhood Immunisation Register (ACIR). The Authors also acknowledge the people of New South Wales and Western Australia whose data were used for this project. The Aboriginal and Torres Strait Islander community and members of the Aboriginal Immunisation Research Group are acknowledged for their contribution to this research project.

Authors contributions

AK, DR, ATN, HM, SJ, PM and HG conceptualised and designed the study, and reviewed and revised the manuscript. AK conducted the analysis and drafted the initial manuscript. All authors provided expert advice on the study design, critically reviewed the study results, analysis methods and the initial draft of manuscript. As the final manuscript has not been submitted, all authors have not reviewed the final manuscript.

Sources of funding

This project was funded by the Population Health Research Network (PHRN), a capability of the Commonwealth Government National Collaborative Research Infrastructure Strategy and Education Investment Fund Super Science Initiative, and a National Health and Medical Research Council (NHMRC) project grant (APP1082342). A. Kabir is supported by a University International Postgraduate Scholarship (UIPA) from UNSW. H. Gidding is supported by an NHMRC Fellowship.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.07.042.

References

[1] McAllister DA, Liu L, Shi T, Chu Y, Reed C, Burrows J, et al. Global, regional, and national estimates of pneumonia morbidity and mortality in children younger than

5 years between 2000 and 2015: a systematic analysis. Lancet Glob Health 2019;7:e47–57.
[2] World Health Organization. Pneumonia.World Health Organization, https://www.who.int/news-room/fact-sheets/detail/pneumonia. 2019; [Accessed March 12, 2021].
[3] Gracey M, King M. Indigenous health part 1: determinants and disease patterns. Lancet 2009;374:65–75.
[4] Anderson I, Crengle S, Kamaka ML, Chen T-H, Palafox N, Jackson-Pulver L. Indigenous health in Australia, New Zealand, and the Pacific. Lancet 2006;367:1775–85.
[5] World Health Organization & United Nations Children's Fund (UNICEF). Ending preventable child deaths from pneumonia and diarrhoea by 2025 : the integrated global action plan for pneumonia and diarrhoea (GAPPD). Geneva: World Health Organization; 2013.
[6] Fathima P, Gidding HF, McIntyre PB, Snelling TL, McCallum L, de Klerk N, et al. Effectiveness of pneumococcal conjugate vaccine against hospital admissions for pneumonia in Australian children: a retrospective, population-based, record-linked cohort study. Lancet Child Adolesc Health 2019;3:713–24.
[7] Loo JD, Conklin L, Fleming-Dutra KE, Knoll MD, Park DE, Kirk J, et al. Systematic review of the effect of pneumococcal conjugate vaccine dosing schedules on prevention of pneumonia. Pediatr Infect Dis J 2014;33:S140–51.
[8] Wasserman M, Chapman R, Lapidot R, Sutton K, Dillon-Murphy D, Patel S, et al. Twenty-year public health impact of 7-and 13-valent pneumococcal conjugate vaccines in US children. Emerg Infect Dis 2021;27:1627.
[9] Shiri T, McCarthy ND, Petrou S. The impact of childhood pneumococcal vaccination on hospital admissions in England: a whole population observational study. BMC Infect Dis 2019;19:1–8.
[10] Binks MJ, Beissbarth J, Oguoma VM, Pizzutto SJ, Leach AJ, Smith-Vaughan HC, et al. Acute lower respiratory infections in Indigenous infants in Australia's Northern Territory across three eras of pneumococcal conjugate vaccine use (2006–15): a population-based cohort study. Lancet Child Adolesc Health 2020;4:425–34.
[11] Rudan I, O'Brien KL, Nair H, Liu L, Theodoratou E, Qazi S, et al. Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. J Glob Health 2013;3:010401.
[12] Public Health England. Pneumococcal polysaccharide vaccine (PPV23) Patient Group Direction (PGD). https://www.england.nhs.uk/north-east-yorkshire/wp-content/uploads/sites/49/2020/08/PPV23.pdf. 2020; [Accessed 14 October 2021].
[13] Centers for Disease Control and Prevention. Pneumococcal vaccination: what everyone should know. https://www.cdc.gov/vaccines/vpd/pneumo/public/index.html. 2020; [Accessed 14 October 2021].
[14] National Advisory Committee on Immunization (NACI). Re-immunization with polysaccharide 23-valent pneumococcal vaccine (Pneu-P-23). https://www.canada.ca/en/public-health/services/publications/healthy-living/re-immunization-with-polysaccharide-23-valent-pneumococcal-vaccine-pneu-p-23.html. 2016; [Accessed 14 October 2021].
[15] New Zealand Ministry of Health. Immunisation handbook 2020. 16. Pneumococcal disease. https://www.health.govt.nz/our-work/immunisation-handbook-2020/16-pneumococcal-disease#_ENREF_21_72. 2020; [Accessed 14 October 2021].
[16] Australian Technical Advisory Group on Immunisation. The Australian immunisation handbook. Canberra: Australian Government Department of Health; 2018.
[17] Kolditz M, Schmitt J, Pletz MW, Tesch F. Impact of the 13-valent pneumococcal conjugate vaccine on the incidence of all-cause pneumonia in adults aged ≥60 years: a population-based, retrospective cohort study. Clin Infect Dis 2019;68:2117–9.
[18] Moore HC, Lehmann D, De Klerk N, Jacoby P, Richmond PC. Reduction in disparity for pneumonia hospitalisations between Australian Indigenous and non-Indigenous children. J Epidemiol Community Health 2012;66:489–94.
[19] Fathima P, Blyth CC, Lehmann D, Lim FJ, Abdalla T, De Klerk N, et al. The impact of pneumococcal vaccination on bacterial and viral pneumonia in Western Australian children: record linkage cohort study of 469589 births, 1996–2012. Clin Infect Dis 2018;66:1075–85.
[20] Menzies RI, Jardine A, McIntyre PB. Pneumonia in elderly Australians: reduction in presumptive pneumococcal hospitalizations but no change in all-cause pneumonia hospitalizations following 7-valent pneumococcal conjugate vaccination. Clin Infect Dis 2015;61:927–33.
[21] O'Grady K-A-F, Lee KJ, Carlin JB, Torzillo PJ, Chang AB, Mulholland EK, et al. Increased risk of hospitalization for acute lower respiratory tract infection among Australian indigenous infants 5–23 months of age following pneumococcal vaccination: a cohort study. Clin Infect Dis 2010;50:970–8.
[22] Jayasinghe S, Chiu C, Menzies R, Lehmann D, Cook H, Giele C, et al. Evaluation of impact of 23 valent pneumococcal polysaccharide vaccine following 7 valent pneumococcal conjugate vaccine in Australian Indigenous children. Vaccine 2015;33:6666–74.
[23] National Center for Immunisation Research and Surveillance. History of vaccination in Australia.NCIRS, https://www.ncirs.org.au/health-professionals/history-immunisation-australia. 2020; [Accessed 16 May 2020].
[24] Gidding H, McCallum L, Fathima P, Moore H, Snelling T, Blyth C, et al. Effectiveness of a 3+0 pneumococcal conjugate vaccine schedule against invasive pneumococcal disease among a birth cohort of 1.4 million children in Australia. Vaccine 2018;36:2650–6.
[25] Gidding H, McCallum L, Fathima P, Snelling T, Liu B, de Klerk N, et al. Probabilistic linkage of national immunisation and state-based health records for a cohort of 1.9 million births to evaluate Australia's childhood immunisation program. Int J Popul Data Sci 2017;2:1–13.
[26] Moore HC, Guiver T, Woollacott A, De Klerk N, Gidding HF. Establishing a process for conducting cross-jurisdictional record linkage in Australia. Aust N Z J Public Health 2016;40:159–64.
[27] Kabir A, Newall AT, Randall D, Menzies R, Sheridan S, Jayasinghe S, et al. Estimating pneumococcal vaccine coverage among Australian Indigenous children and children with medically at-risk conditions using record linkage. Vaccine 2021;39:1727–35.
[28] Christensen D, Davis G, Draper G, Mitrou F, McKeown S, Lawrence D, et al. Evidence for the use of an algorithm in resolving inconsistent and missing Indigenous status in administrative data collections. Aust J Soc Issues 2014;49:423–43.
[29] Roberts RF, Innes KC, Walker SM. Introducing ICD-10-AM in Australian hospitals. Med J Aust 1998;169:S32–5.
[30] Australian Technical Advisory Group on Immunisation. The Australian immunisation handbook. Canberra: Australian Government Department of Health; 2022.
[31] Jayasinghe S, Liu B, Gidding H, Gibson A, Chiu C, McIntyre P. Long-term vaccine impact on invasive pneumococcal disease among children with significant comorbidities in a large Australian birth cohort. Pediatr Infect Dis J 2019;38:967–73.
[32] SAS Institute Inc. SAS 9.4 [Computer software]. Author Cary, NC; 2013.
[33] R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020.
[34] Knuf M, Pankow-Culot H, Grunert D, Rapp M, Panzer F, Köllges R, et al. Induction of immunologic memory following primary vaccination with the 10-valent pneumococcal nontypeable *Haemophilus influenzae* protein D conjugate vaccine in infants. Pediatr Infect Dis J 2012;31:e31–6.
[35] Orami T, Ford R, Kirkham L-A, Thornton R, Corscadden K, Richmond PC, et al. Pneumococcal conjugate vaccine primes mucosal immune responses to pneumococcal polysaccharide vaccine booster in Papua New Guinean children. Vaccine 2020;38:7977–88.
[36] Leach AJ, Morris PS, Mackenzie G, McDonnell J, Balloch A, Carapetis J, et al. Immunogenicity for 16 serotypes of a unique schedule of pneumococcal vaccines in a high-risk population. Vaccine 2008;26:3885–91.
[37] Russell F, Balloch A, Licciardi PV, Carapetis JR, Tikoduadua L, Waqatakirewa L, et al. Serotype-specific avidity is achieved following a single dose of the 7-valent pneumococcal conjugate vaccine, and is enhanced by 23-valent pneumococcal polysaccharide booster at 12 months. Vaccine 2011;29:4499–506.
[38] Borrow R, Heath PT, Siegrist C-A. Use of pneumococcal polysaccharide vaccine in children: what is the evidence? Curr Opin Infect Dis 2012;25:292–303.
[39] Collins DA, Hoskins A, Bowman J, Jones J, Stemberger NA, Richmond PC, et al. High nasopharyngeal carriage of non-vaccine serotypes in Western Australian aboriginal people following 10 years of pneumococcal conjugate vaccination. PLoS One 2013;8:e82280.
[40] Dunne EM, Carville K, Riley TV, Bowman J, Leach AJ, Cripps AW, et al. Aboriginal and non-Aboriginal children in Western Australia carry different serotypes of pneumococci with different antimicrobial susceptibility profiles. Pneumonia 2016;8:1–9.