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Pneumococcal Conjugate Vaccines Are Protective Against Respiratory Syncytial Virus Hospitalizations in Infants: A Population-Based Observational Study

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Background. Pneumococcal conjugate vaccines (PCV) reduced the risk of respiratory syncytial virus (RSV) in a randomized clinical trial. We aimed to assess the real-world effectiveness of PCV on RSV-hospitalizations among Western Australian infants.

Methods. We conducted a population-based cohort study of births during 2000–2012, using probabilistically linked individual-level immunization, hospitalization, respiratory microbiology testing, and perinatal data. We performed Cox proportional hazard models with time-varying exposure (receipt of infant PCV doses) against the first RSV-confirmed hospitalization 0–12 months adjusted for perinatal and sociodemographic factors.

Results. From 360 994 children, 3-dose PCV coverage in Aboriginal infants ranged from 29% to 51% in 2001–2004 when PCV was funded for Aboriginal children only. Following universal funding in 2005, coverage increased to 85% for Aboriginal and 73% for non-Aboriginal infants. RSV-hospitalization rates were highest in young infants aged 0–5 months (22.5/1000 child-years) and >2 times higher in Aboriginal infants than in non-Aboriginal infants. Receipt of ≥ 3 PCV doses in the universal funded period was associated with a 30% reduction in RSV-hospitalization in Aboriginal infants (adjusted hazard ratio, aHR 0.70 [95% confidence interval, CI 0.46–1.06]) and 21% reduction in non-Aboriginal infants (aHR 0.79 [95% CI 0.63–0.99]) compared with unvaccinated infants.

Conclusions. Prior to the introduction of RSV vaccines, our study suggests that universal childhood PCV vaccination may result in a reduction in severe RSV infections in children and may be important for countries that are yet to consider PCV programs.

Keywords. infant; off-target vaccine effect; pneumococcal conjugate vaccines; record linkage; respiratory syncytial virus.

Vaccines have health benefits through direct protection of the disease they are designed to target. Evidence has emerged that vaccines also have off-target effects on the burden of disease caused by other pathogens [1]. Respiratory syncytial virus (RSV) is a leading cause of childhood morbidity and mortality, with 2019 estimates of 33.1 million episodes of RSV acute lower respiratory infections in children aged <5 years and 3.6 million hospitalizations globally [2]. RSV rates are highest in young infants aged <12 months, with those born prematurely or with

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underlying conditions such as congenital heart or chronic lung disease also at higher risk of severe disease [3]. First Nations children, including Australian Aboriginal and/or Torres Strait Islander children (herein respectfully referred to "Aboriginal"), also have a disproportionate risk of respiratory infections, including RSV [4]. RSV vaccine development is a World Health Organization (WHO) priority [5], and passive RSV immunization strategies have shown positive results in phase 3 clinical trials [6, 7]. However, despite prevention strategies being close to market [8], there is currently no active vaccine licensed against RSV.

Pneumococcal conjugate vaccines (PCV) have been highly effective in reducing invasive pneumococcal disease [9]. While the target of PCV was to protect against invasive disease caused by *Streptococcus pneumoniae*, introduction of PCV programs have also shown protection against all-cause pneumonia in high-risk populations [10, 11]. In a large randomized controlled trial of young children in South Africa, PCV lowered the risk of pneumonia associated with laboratory-confirmed RSV infection by 22% [12]. In an ecological analysis of hospital admissions in the United States (1992–2009), RSV-coded

hospitalizations in infants were reduced by 18% in the years after PCV introduction [13]. States with greater PCV coverage also had fewer influenza-associated pneumonia hospitalizations [14]. Population-based real-world studies with individually linked PCV immunization data with laboratory-confirmed RSV outcomes are now needed to confirm these findings. We aimed to investigate the off-target impact of PCV on RSV-confirmed hospitalizations in Australian infants and children for a whole-of-population cohort.

METHODS

Study Design and Data Sources

Western Australia (WA) covers the western third of Australia with a total population of 2.7 million as of 2021 [15]. We conducted an individual-level record linkage study using administrative data on a cohort of all WA children born between 2000 and 2012 with health and immunization data observed from birth until the earliest of 7 years of age or December 2013. Data were probabilistically linked through a larger study evaluating immunization coverage and effectiveness across 2 Australian states (WA and New South Wales) as previously described [16, 17]. In brief, probabilistic linkage techniques based on identifying details including full name, date of birth, residential address, and sex were used to link records between databases. While immunization data falls under the jurisdiction of the Commonwealth Government, other health datasets used in this study are state-specific. Linkage of WA specific data occurred at the WA Data Linkage Branch, whereas linkage with immunization data occurred at the Australian Institute of Health and Welfare. We chose a matched linkage rate of >99%, which corresponded to a linkage accuracy of >97% [16]. Data used for this analysis (Figure 1) were limited to WA as linked microbiology testing records for RSV and other nonnotifiable respiratory viruses were only available in WA.

The birth registry contains parental recorded sociodemographic details of both parents and child. The perinatal details, collected through the Midwives Notification System, include maternal medical history, labor, delivery, and characteristics of infant health at birth. The Australian Childhood Immunisation Register (ACIR), now known as the Australian Immunisation Register, was the world's first purpose-built national immunization register and is one of a limited number of national immunization registers [16, 18]. ACIR included immunization records of all children enrolled in the universal healthcare system (Medicare), which covers 99% of all Australian children [18], and includes vaccination date, vaccine type, and dose number from birth until 7 years of age.

Hospitalization data from the Hospital Morbidity Data Collection includes inpatient hospital admissions to all public and private hospitals with admission and separation dates and up to 21 discharge diagnosis fields using the

International Classification of Diseases, Tenth Revision, Australian Modification (ICD-10-AM). During the study period, RSV was not a notifiable condition; therefore, identification of RSV-confirmed infections relied on routine microbiology testing records from PathWest, the sole statewide public pathology provider [19].

Outcome and Exposure Measures

Our primary outcome of interest was the first RSV-confirmed hospitalization (hereafter "RSV-hospitalization") between January 2000 and December 2013 in the first year of life. We also estimated PCV impact on RSV-hospitalization <2 years of age. An RSV-hospitalization was defined as laboratory detection of RSV where the date of specimen collection was within 48 hours of a hospital admission, as per our previous use of these data [3, 19]. Our primary exposure was receipt of PCV doses between January 2001 and December 2013. In Australia, 7-valent PCV (PCV7) was first funded in 2001 for Aboriginal children and those medically at risk of pneumococcal disease in a 3 + 0 dose schedule at 2, 4, and 6 months of age under the National Immunisation Program. From January 2005, PCV7 was funded for all children. From July 2011, PCV7 was replaced by 13-valent PCV (PCV13) [20]. Invalid PCV doses were those given <39 days after birth, or administered within ≤28 days following a previous PCV dose, as per our previous analyses [10].

Statistical Analysis

RSV-hospitalization rates (per 1000 child-years) were calculated using survival methods for all children and in the following population subgroups <2 years of age: Aboriginal children (derived using a validated algorithm [21]), delivery method, season of birth, sex, markers of infant health at birth (including gestational age, birth weight, and Apgar score), maternal smoking during pregnancy, parental ages, overseas-born mother, geographical remoteness, and socioeconomic status. Socioeconomic status was based on Socioeconomic Indexes for Area (SEIFA) using the residential address of the infant's mother at birth, ranking geographical areas (census collection district, the smallest geographical area for statistical analysis) according to relative socioeconomic advantage and disadvantage in terms of household income, skilled occupation, educational attainment, and access to services [22]. Person-time at risk was used as the denominator for incidence rates commencing at birth and censored at the earliest of first RSV-hospitalization, death, invalid PCV dose, age 24 months, or the end of the study period (31 December 2013), whichever came first. RSV-hospitalization rates by PCV status were calculated for children born in different periods of the PCV funded program (pre-funded for those born in 2000, pre-universal years [2001–2004], and universal period [2005–2012]).
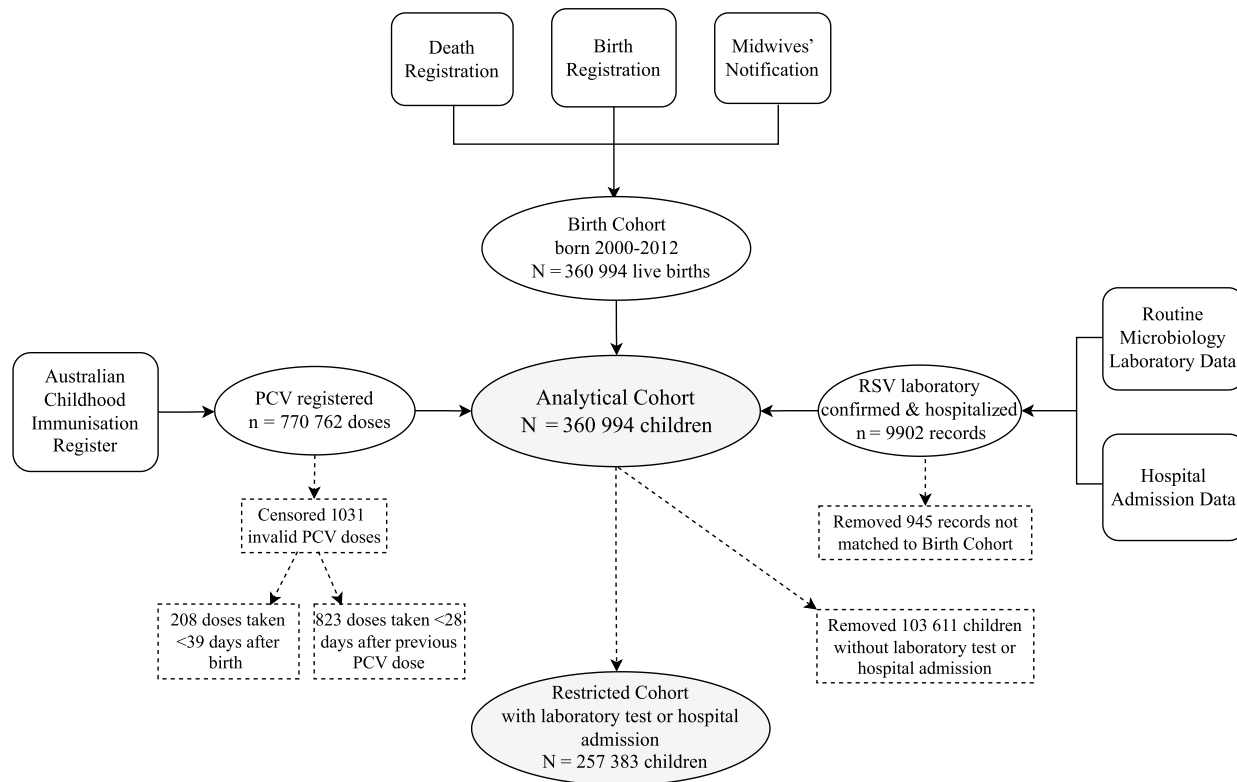
Figure 1. Study flowchart. Abbreviations: PCV, pneumococcal conjugate vaccine; RSV, respiratory syncytial virus.

Cox proportional hazard regression was used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) of RSV-hospitalizations for PCV vaccinated children (with 1, 2, or ≥3 doses) versus PCV unvaccinated children. We estimated a basic model with time-varying exposure for the number of PCV doses as well as fully adjusted models, which additionally controlled for explanatory variables observed at the child, parental, and family level to obtain adjusted HRs (aHRs). Our model controls for sex, infant health at birth (including gestational age at birth, birth weight, Apgar score, season of birth, delivery method), maternal smoking during pregnancy, maternal age when the child was born, overseas-born mother, geographical remoteness, and SEIFA using the residential address of the infant's mother at birth. Inclusion of covariates in the final model was based on likelihood ratio tests comparing models with and without each variable. Where appropriate, we calculated vaccine effectiveness (VE) estimates as (1 – aHR) × 100. All models were estimated separately for Aboriginal and non-Aboriginal children. We present results segregated by PCV funding period as the population receiving PCV in each period was different (ie, pre-universal [2001–2004] PCV was offered to Aboriginal children and those at high risk of pneumococcal disease only, and universal [2005–2012] PCV was offered to all children). To account for health-seeking behavior in that those who are vaccinated are more likely to present to care

and therefore undergo respiratory pathogen testing, we also conducted a sensitivity analysis on a restricted cohort of children who had at least 1 record of respiratory specimen testing or hospitalization for any reason during the study period. Statistical significance was measured at the 5% level ($P \leq 0.05$).

Ethics Approval

Ethics approval was obtained from the WA Department of Health Human Research Ethics Committee, the WA Aboriginal Health Ethics Committee, and the Australian Institute of Health and Welfare Ethics Committee. The ethics committees approved this study and waived individual written patient consent due to the observational characteristic of the study.

RESULTS

There were 360 994 children in the overall cohort born between 2000 and 2012. Of these, 23 107 children (6.4%) identified as Aboriginal (Table 1). Of all respiratory specimens collected between 2000 and 2013 from children who underwent testing for RSV, 12 141 (11.7%) were positive. The majority of RSV detections (93%) were from either polymerase chain reaction or immunofluorescence. Of the positive RSV detections, 9902 (82%) were temporally linked to a hospitalization within 48 hours.

Table 1. Cohort Description and Respiratory Syncytial Virus Hospitalizations in Children Aged <2 Years Born During 2000–2012

Characteristic	No. of Children (%)	RSV Hospitalizations		
		No.	Rate	(95% CI)
Total	360 994 (100)	7023	10.12	(9.88–10.35)
Infant characteristics				
Aboriginal				
Aboriginal	23 107 (6.40)	991	21.35	(21.38–24.19)
Non-Aboriginal	337 887 (93.60)	6032	9.27	(9.04–9.51)
Sex				
Male	184 609 (51.14)	3945	11.13	(10.79–11.48)
Female	176 385 (48.86)	3078	9.06	(8.74–9.38)
Birth weight, grams				
<1500	3305 (0.92)	308	55.19	(49.36–61.71)
1500–2499	18 704 (5.18)	785	22.31	(20.80–23.92)
2500–3499	189 432 (52.48)	3615	9.93	(9.60–10.25)
3500–4499	144 188 (39.94)	2228	8.00	(7.67–8.34)
≥4500	5365 (1.49)	87	8.39	(6.80–10.35)
Gestational age at birth, weeks				
<32	3952 (1.09)	380	56.47	(51.07–62.44)
32–36	26 273 (7.28)	1019	20.52	(19.30–21.82)
≥37	330 700 (91.61)	5621	8.81	(8.59–9.05)
Apgar score				
7–10	356 826 (98.85)	6871	10.00	(9.77–10.24)
0–6	4168 (1.15)	152	20.44	(17.43–23.96)
Season of birth				
Spring	90 524 (25.08)	1159	6.71	(6.33–7.10)
Winter	89 942 (24.92)	2008	11.68	(11.17–12. 19)
Autumn	92 406 (25.60)	2399	13.46	(12.92–14.00)
Summer	88 122 (24.41)	1457	8.52	(8.09–8.97)
Delivery method				
Vaginal	193 588 (53.63)	3881	10.41	(10.00–10.74)
Instrumentation	48 763 (13.51)	626	6.65	(6.15–7.19)
Cesarean	118 643 (32.87)	2516	11.07	(10.64–11.51)
Parental characteristics				
Maternal age, years				
≥35	71 481 (19.80)	1156	8.39	(7.92–8.89)
30–34	114 838 (31.81)	1936	8.75	(8.37–9.15)
25–29	101 243 (28.05)	1920	9.86	(9.43–10.31)
20–24	55 878 (15.48)	1436	13.41	(12.74–14.12)
≤20	17 554 (4.86)	575	17.16	(15.81–18.62)
Paternal age, years				
≥35	122 810 (34.02)	2039	8.62	(8.25–9.00)
30–34	110 838 (30.70)	1912	8.95	(8.56–9.36)
25–29	76 221 (21.11)	1535	10.47	(9.96–11.01)
20–24	33 587 (9.30)	908	14.11	(13.22–15.06)
≤20	6489 (1.80)	213	17.19	(15.03–19.66)
Missing	11 049 (3.06)	416	19.98	(18.15–22.00)
Maternal smoking during pregnancy				
No	304 820 (84.44)	5269	8.98	(8.74–9.23)
Yes	56 174 (15.56)	1754	16.31	(15.56–17.09)
Place of mother's birth				
Australia	221 300 (61.30)	4659	10.96	(10.65–11.28)
Overseas	95 694 (26.51)	1440	7.88	(7.48–8.29)
Missing	44 000 (12.19)	924	10.69	(10.02–11.40)
Socioeconomic Indexes for Area				
91%–100% (most advantaged)	28 674 (7.94)	452	8.16	(7.44–8.95)

Table 1. Continued

Characteristic	No. of Children (%)	RSV Hospitalizations		
		No.	Rate	(95% CI)
76%–90%	53 024 (14.69)	939	8.22	(7.68–8.80)
26%–75%	166 708 (46.18)	3030	9.45	(9.12–9.80)
11%–25%	54 627 (15.13)	1387	13.26	(12.58–13.98)
0%–10% (most disadvantaged)	29 824 (8.26)	823	14.45	(13.50–15.47)
Missing	28 137 (7.79)	492	8.98	(8.22–9.81)
Accessibility and remoteness for area				
Major cities	242 443 (67.16)	4817	10.34	(10.05–10.63)
Inner regional	39 469 (10.93)	636	8.40	(7.77–9.08)
Outer regional	29 845 (8.27)	717	12.53	(11.64–13.48)
Remote	14 848 (4.11)	238	8.32	(7.33–9.45)
Very remote	6252 (1.73)	123	10.24	(8.58–12.22)
Missing	28 137 (7.79)	492	8.98	(8.22–9.81)

Overall cohort includes all Western Australian children born during 2000–2012. RSV numbers were from birth to 2 years of age or death. RSV-hospitalization rates were from birth to 2 years of age or death, per 1000 child-years. Column data might not sum up to 100% due to missing observations. All characteristics were assessed at birth unless otherwise noted.

Abbreviations: CI, confidence interval; RSV, respiratory syncytial virus.

From these, 945 RSV-hospitalization records were excluded as they related to children who were living in WA during the observed period but were not born in WA (including children whose parents were interstate or international immigrants and migrants in WA; Figure 1). This left 8957 RSV-hospitalizations in the analytical cohort. The majority occurred in infants aged <12 months (71%) with an additional 19% occurring in those aged 1–2 years.

RSV-hospitalization rates were highest in infants aged <6 months (22.5 per 1000 child-years), declining to 8.79/1000 child-years for children aged 6–11 months, 4.25/1000 child-years for those aged 1–<2 years, and 0.44/1000 child-years for those aged 2–<7 years. Further detail regarding age-specific RSV-hospitalization rates over the years 2000–2012 was described in our previous study using the same data [3]; importantly, rates of RSV-positive detections did not significantly change over this period of study. RSV-hospitalization rates in Aboriginal children were more than twice the rates in non-Aboriginal children (Figure 2). RSV-hospitalization rates were highest in children of low socioeconomic backgrounds, those born preterm, those with low birth weight, those with low Apgar score, or those born to a mother who smoked while pregnant or was aged <20 years (Table 1).

Between 2001 and 2004, PCV coverage (percentage of children with at least 3 doses assessed at 12 months of age) in Aboriginal children ranged from 29% in 2001 to 51% in 2004. In the universal funded period, coverage of at least 3 doses of PCV assessed at age 12 months increased to 85%–87% in non-Aboriginal children and 73%–79% in Aboriginal children (Supplementary Figure 1). PCV coverage of at least 3 doses at age 2 years increased to approximately 90% for all infants by
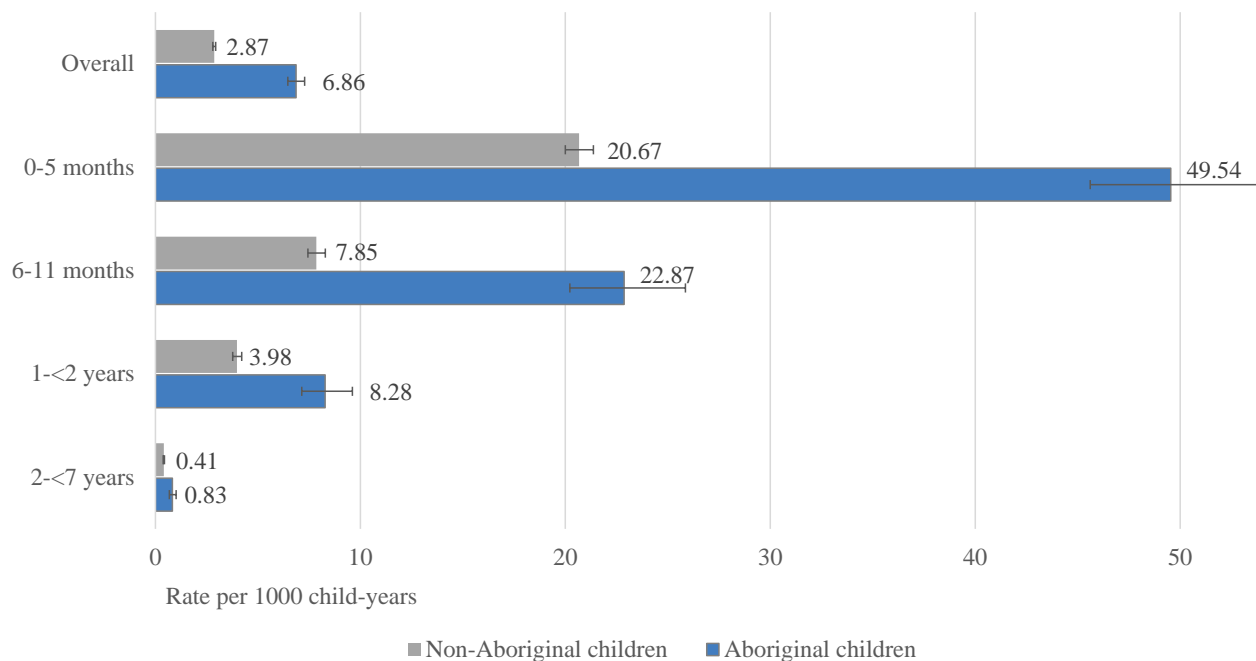
Figure 2. Respiratory syncytial virus hospitalization rates per 1000 child-years by age group, 2000–2013. Error bars are 95% confidence intervals.

2012 (Supplementary Figure 2). Figure 3 shows crude RSV-hospitalization rates in those aged <12 months by PCV funded periods. For Aboriginal infants, rates increased from the pre-funded to the pre-universal period, which closely approximated the rate in the universal period. Crude RSV-hospitalization rates for non-Aboriginal infants were similar in the pre-funded and pre-universal periods (around 16/1000 child-years), before reducing by 20% to 13/1000 child-years in the PCV universal period (Figure 3).

Compared with unvaccinated children, Aboriginal and non-Aboriginal children who had received ≥1 dose of PCV had lower RSV-hospitalization rates in the first year of life across both PCV funding periods (Table 2). For example, in the pre-universal period, the RSV-hospitalization rate for unvaccinated Aboriginal children was 47.49/1000 child-years compared with 14.48/1000 child-years in those with ≥3 PCV doses (Table 2). After controlling for perinatal and sociodemographic factors, we found weak evidence that receipt of at least 3 doses of PCV was associated with a reduced risk of RSV-hospitalization (aHR, 0.91 [95% CI, 0.43–1.90]) in Aboriginal infants compared with unvaccinated Aboriginal infants in the pre-universal period, with a high degree of uncertainty. In the pre-universal period when PCV was available for non-Aboriginal children at higher risk of severe pneumococcal disease, those with ≥2 PCV doses had a higher RSV-hospitalization risk than those who were unvaccinated after adjustment (ie, aHR, 1.53 [95% CI, 1.08–2.16] for 2 doses; Table 2). In the universal PCV period, receipt of at least 3 PCV doses was

associated with a decreased risk in both Aboriginal infants (aHR, 0.70 [95% CI, 0.46–1.06]) and non-Aboriginal infants (aHR, 0.79 [95% CI, 0.63–0.99]), equating to a VE point estimate of 30% (95% CI, −6% to 54%) for Aboriginal infants and 21% (95% CI, 1%–37%) for non-Aboriginal infants (Table 2). In the universal period, we found weak evidence with a high level of uncertainty that both Aboriginal and non-Aboriginal infants receiving 1 or 2 PCV doses had a lower risk of RSV-hospitalization compared with unvaccinated infants (Table 2).

In the restricted cohort of 257 383 births (18 761 Aboriginal and 238 622 non-Aboriginal) to adjust for health-seeking behavior, the risk of RSV-hospitalization was significantly reduced in both Aboriginal and non-Aboriginal infants who received ≥3 PCV doses in the universal PCV period (Table 3). This equated to a VE of 41% (95% CI, 5%–63%) in Aboriginal children and 28% (95% CI, 9%–42%) in non-Aboriginal infants. Results were similar when the outcome was extended to RSV-hospitalizations <2 years in the full cohort (Supplementary Table 1) and restricted cohort (Supplementary Table 2).

DISCUSSION

Our population-based study provided an estimate of the real-world off-target impact of PCV on RSV-hospitalization in young children. In our population, RSV-hospitalizations were high in young infants, with rates in Aboriginal infants twice
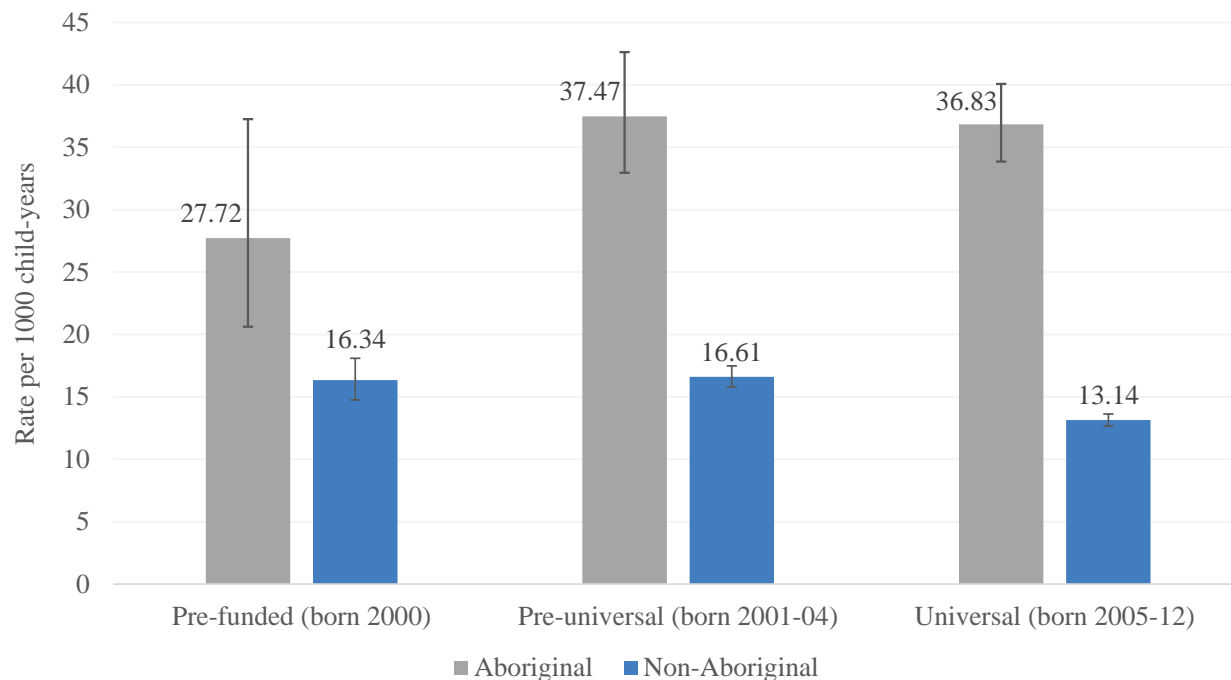
Figure 3. Respiratory syncytial virus hospitalization rates per 1000 child-years by vaccination periods in infants aged <12 months. Error bars are 95% confidence intervals.

as high as those in non-Aboriginal children. We showed that receipt of 3 PCV doses was associated with a protective effect on RSV hospitalizations in all infants. This was particularly noted in the universal period when PCV coverage rates were high, and ≥3 doses was associated with a 41% reduction of RSV-hospitalizations in Aboriginal infants and 28% reduction in non-Aboriginal infants, as shown in the results for the restricted cohort, which adjust for health-seeking behavior. The stronger risk reduction found in Aboriginal children in the universal PCV period compared with the pre-universal period suggests protective indirect effects, as we have observed in this cohort for invasive pneumococcal disease [9].

RSV continues to be a significant pathogen for young children [2] and has been shown to be the predominant cause of childhood pneumonia [23, 24]. The RSV vaccine landscape is rapidly changing with multiple vaccine targets and monoclonal antibodies undergoing clinical trials [8]. However, it is likely to be some years before RSV immunization strategies are available to low- and middle-income countries (LMICs) that suffer the highest RSV burden. Therefore, alternative prevention strategies, such as the potential beneficial impact of preexisting vaccines to reduce RSV burden, as well as extended cost-benefit analyses for preexisting vaccines, are worthy of investigation.

Our findings of a such a beneficial impact are consistent with those of a previous randomized controlled trial in South Africa [12] and ecological analyses using hospital admission data in the United States [13]. Viral–bacterial interactions involving RSV have previously been noted, with *Streptococcus*

pneumoniae, *Haemophilus influenzae*, and *Moraxella catarrhalis* detected more frequently in RSV-infected children than in healthy controls [25]. Additionally, viral bronchiolitis has been found to be more severe when infants were colonized with *S pneumoniae* [25]. Our findings support this notion that vaccinating against *S pneumoniae* reduces severe RSV disease as the outcome measured in our analysis was RSV-confirmed hospitalization. Indeed, recent data from the coronavirus disease 2019 pandemic era has shown further relationships between pneumococcal disease and RSV, with the concomitant decline in pneumococcal disease following the abrupt disappearance of RSV [26, 27]. The role of vaccination with PCV in reducing RSV infection or milder disease might now warrant further investigation to understand the immunological mechanisms of off-target vaccine effects.

PCV programs are continuously monitored, with schedules and vaccines altered in response to current trends of pneumococcal disease and product development. For example, PCV7 was used in Australia for the majority of our observed period, from 2000 until May 2011 when PCV13 became universal [9]. Our study therefore predominately reflects the protective effect of PCV7. The protective effect against RSV-hospitalization could be even greater for PCVs with a higher serotype coverage. Australia recently changed from a 3 + 0 PCV schedule to a 2 + 1 schedule (primary dose at 2 and 4 months with a 12-month booster) to combat the increase in vaccine failures in fully vaccinated children aged >12 months [20]. In the United Kingdom, PCV13 has been recommended since 2020 as a 1

Table 2. Respiratory Syncytial Virus Hospitalization Rates and Hazard Ratios by Pneumococcal Vaccination Status in Infants Aged <12 Months

Vaccination Status	Pre-universal Period[a] (2001–2004)				Universal Period[b] (2005–2012)			
	Cases, No.	Rate[c] (95% CI)	HR (95% CI)	aHR[d] (95% CI)	Cases, No.	Rate[c] (95% CI)	HR (95% CI)	aHR[d] (95% CI)
Aboriginal								
Unvaccinated	158	47.49 (40.63–55.51)	1 (ref)	1 (ref)	228	54.79 (48.12–62.38)	1 (ref)	1 (ref)
1 dose	41	39.07 (28.76–53.06)	0.82 (.57–1.18)	0.98 (.59–1.63)	148	45.85 (39.03–53.87)	0.88 (.67–1.15)	0.97 (.73–1.30)
2 doses	19	22.40 (14.28–35.11)	0.56[e] (.33–.93)	0.95 (.48–1.87)	88	29.74 (24.13–36.66)	0.67[e] (.48–.93)	0.77 (.53–1.11)
≥3 doses	14	14.48 (8.57–24.45)	0.39[e] (.21–.71)	0.91 (.43–1.90)	76	17.61 (14.07–22.06)	0.59[e] (.40–.87)	0.70 (.46–1.06)
Non-Aboriginal								
Unvaccinated	1393	17.12 (16.24–18.04)	1 (ref)	1 (ref)	1101	22.23 (20.95–23.58)	1 (ref)	1 (ref)
1 dose	33	9.98 (7.09–14.04)	0.71[e] (.50–1.00)	0.73 (.51–1.06)	785	18.57 (17.32–19.92)	0.92 (.79–1.06)	0.91 (.77–1.06)
2 doses	40	14.77 (10.83–20.13)	1.33 (.96–1.83)	1.53[e] (1.08–2.16)	484	11.05 (10.11–12.08)	0.85 (.71–1.02)	0.92 (.75–1.12)
≥3 doses	27	10.82 (7.42–15.77)	1.18 (.79–1.76)	1.42 (.92–2.18)	539	6.28 (5.77–6.83)	0.67[e] (.55–.82)	0.79[e] (.63–.99)

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; ref, reference.

[a]Birth in pre-universal period.

[b]Birth in universal period.

[c]RSV-hospitalization rates were from birth to 1 year of age or death, per 1000 child-years.

[d]Adjusted model additionally controls for sex, birth weight, gestational age at birth, Apgar score, season of birth, delivery method, parental age group, Socioeconomic Indexes for Area, and remoteness indexes.

[e]$P \leq 0.05$.

+ 1 schedule for infants, with dose 1 at 12 weeks, followed by a booster at 12–13 months, a replacement of a previous PCV schedule given to infants at 8 and 16 weeks, with a booster at 12–13 months of age [28]. With these changes resulting in infants only receiving 1 or 2 PCV doses at <12 months of age, in whom the majority of RSV burden occurs, the demonstrated protective effect of PCV on RSV-hospitalization will need to be reassessed. Indeed, in our analysis where the PCV schedule in Australia at the time was a 3 + 0 schedule, the only statistically significant protective effects against RSV-hospitalization were achieved with receipt of 3 or more PCV doses. Continued monitoring of real-world effectiveness and off-target effects of childhood vaccines including PCV vaccines is needed.

Our study has several strengths. First, we believe these data to be internationally novel in the use of real-world individually linked immunization, microbiological, clinical, and perinatal data to assess off-target vaccine effects. Second, the use of population-based data avoided possible biases, including sample selection when analyzing data of hospital admissions in the absence of linked laboratory data to confirm the RSV-specific outcome measure, nongeneralizability in the study design, or low statistical power due to small sample sizes. Third, compared with other studies [12–14, 29], we were able to control for a broader set of explanatory perinatal and sociodemographic variables due to the breadth of data available in our population-linked dataset. Fourth, we used a sensitivity analysis on a restricted cohort to account for health-seeking behavior in that vaccinated children might be more likely than unvaccinated children to access medical care for illness (and therefore laboratory testing to detect RSV), as we have done in previous analyses [10]. The restricted cohort analysis increased the beneficial impact of PCV on risk of RSV-hospitalization in all children, suggesting that health-seeking behavior is an important factor to control for.

However, our observational study is not without limitations. First, despite high PCV coverage, receipt of PCV is likely not to be random in that children who were vaccinated may differ from those who were not, and these differential characteristics may simultaneously affect both vaccination status and RSV-hospitalization risk. In particular, non-Aboriginal children were offered PCV in the pre-universal period if they were high risk for pneumococcal disease, which may also be seen as high risk for RSV. Therefore, this nonrandomness in PCV vaccination status will likely bias our estimation result. Indeed, we noted an increased risk of RSV-hospitalization for non-Aboriginal children in the non-universal period. Second, RSV-hospitalizations are highest in infants aged <6 months (eg, up to 21% RSV-hospitalizations occurred <2 months of age when the first PCV dose is recommended, and 13% before 6 weeks of age—the earliest age to be eligible for PCV); hence, PCV is likely to not offer any direct protection against early RSV infection. The role of maternal vaccination, especially with influenza in the off-target protection of early-life RSV, needs to be explored. A recent study in WA showed that maternally vaccinated infants aged <6 months had a significantly lower risk of acute respiratory infection–associated hospitalization compared with maternally unvaccinated infants [30]. Although this study did not assess laboratory-confirmed outcomes, one would assume that the vast majority of acute respiratory infection hospitalizations in that age group are caused by RSV. Indeed, we are in the process of obtaining contemporary population-based data to investigate the impact of maternal vaccines on laboratory-confirmed outcomes in young children.

Table 3. Respiratory Syncytial Virus Hospitalization Rates and Hazard Ratios by Pneumococcal Vaccination Status in Restricted Cohort of Infants Aged <12 Months With PathWest or Hospital Admissions

Vaccination Status	Pre-universal Period[a] (2001–2004)				Universal Period[b] (2005–2012)			
	Cases, No.	Rate[c] (95% CI)	HR (95% CI)	aHR[d] (95% CI)	Cases, No.	Rate[c] (95% CI)	HR (95% CI)	aHR[d] (95% CI)
Aboriginal								
Unvaccinated	158	54.91 (46.98–64.17)	1 (ref)	1 (ref)	228	70.79 (62.17–80.60)	1 (ref)	1 (ref)
1 dose	41	44.35 (32.65–60.23)	0.80 (.56–1.16)	0.98 (.59–1.64)	148	59.55 (50.69–69.96)	0.89 (.67–1.16)	0.93 (.67–1.28)
2 doses	19	25.31 (16.14–39.68)	0.54[e] (.32–.89)	0.95 (.48–1.88)	88	38.80 (31.48–47.81)	0.68[e] (.49–.95)	0.77 (.52–1.15)
≥3 doses	14	16.17 (9.58–27.31)	0.37[e] (.20–.67)	0.90 (.43–1.90)	76	23.06 (18.42–28.87)	0.60[e] (.41–.89)	0.59[e] (.37–.95)
Total	232	42.82 (37.65–48.70)	…	…	540	47.91 (44.04–52.13)	…	…
Non-Aboriginal								
Unvaccinated	1393	22.29 (21.15–23.49)	1 (ref)	1 (ref)	1101	33.95 (32.00–36.01)	1 (ref)	1 (ref)
1 dose	33	12.95 (9.21–18.22)	0.71 (.50–1.00)	0.74 (.51–1.07)	785	27.70 (25.83–29.71)	0.87 (.75–1.01)	0.87 (.74–1.02)
2 doses	40	19.35 (14.19–26.38)	1.34 (.97–1.84)	1.54[e] (1.09–2.17)	484	16.43 (15.03–17.97)	0.78[e] (.65–.93)	0.86 (.70–1.05)
≥3 doses	27	14.22 (9.75–20.74)	1.19 (.80–1.78)	1.43 (.93–2.20)	539	9.33 (8.57–10.15)	0.60[e] (.49–.74)	0.72[e] (.58–.91)
Total	1493	21.63 (20.56–22.76)	…	…	2909	19.66 (18.96–20.38)	…	…

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; ref, reference.

[a]Birth in pre-universal period.

[b]Birth in universal period.

[c]RSV-hospitalization rates were from birth to 1 year of age or death, per 1000 child-years.

[d]Adjusted model additionally controls for sex, birth weight, gestational age at birth, Apgar score, season of birth, delivery method, parental age group, Socioeconomic Indexes for Area, and remoteness indexes.

[e]$P \leq 0.05$.

Finally, there are other covariates, such as duration of breast-feeding, that were not available in our linked datasets that may be important to control for in the relationship between vaccination and protection of early childhood infection.

In conclusion, we have provided real-world evidence of an off-target benefit of PCV vaccination on infant RSV-hospitalizations. PCV has been introduced in 154 of 194 countries worldwide and global coverage of a third dose in children was 51% as of July 2021 [31]. While PCV coverage is high in developed countries, PCV coverage is low in LMICs (eg, 19% in countries within the WHO Western Pacific Region and 29% within the WHO South-East Asia region [32]). More than 95% of RSV-associated acute lower respiratory infections in young children occur in LMICs [2]. Our results here showing an off-target benefit of PCV on reducing RSV-hospitalizations in young children suggest that improving PCV uptake, especially in these jurisdictions, will reduce the global burden of RSV, prior to the introduction of RSV vaccination programs.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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