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ORIGINAL ARTICLE

Effectiveness of 7-Valent Pneumococcal Conjugate Vaccine Against Invasive Pneumococcal Disease in Medically At-Risk Children in Australia: A Record Linkage Study

Alamgir Kabir[1,2,3], Anthony T. Newall[1], Deborah Randall[2,3], Hannah C. Moore[4], Sanjay Jayasinghe[5,6], Parveen Fathima[4,7], Bette Liu[1], Peter McIntyre[5], and Heather F. Gidding[1,2,3,5]

[1]School of Population Health, Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia; [2]The University of Sydney Northern Clinical School, Sydney, New South Wales, Australia; [3]Women and Babies Research, Kolling Institute, Northern Sydney Local Health District, St Leonards, New South Wales, Australia; [4]Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, The University of Western Australia, Perth, Western Australia, Australia; [5]National Centre for Immunisation Research and Surveillance, Westmead, New South Wales, Australia; [6]Discipline of Child and Adolescent Health, Children's Hospital Westmead Clinical School, Faculty of Medicine and Health, University of Sydney, Westmead, New South Wales, Australia; [7]Communicable Disease Control Directorate, Department of Health Western Australia, 189 Royal Street, Perth, Western Australia 6004, Australia

Background: Children with chronic medical conditions are at higher risk of invasive pneumococcal disease (IPD), but little is known about the effectiveness of the primary course of pneumococcal conjugate vaccine (PCV) in these children.

Methods: A cohort born in 2001–2004 from two Australian states and identified as medically at-risk (MAR) of IPD either using ICD-coded hospitalizations (with conditions of interest identified by 6 months of age) or linked perinatal data (for prematurity) were followed to age 5 years for notified IPD by serotype. We categorized fully vaccinated children as either receiving PCV dose 3 by <12 months of age or ≥1 PCV dose at ≥12 months of age. Cox proportional hazard modeling was used to estimate hazard ratios (HRs), adjusted for confounders, and vaccine effectiveness (VE) was estimated as (1-HR) × 100.

Results: A total of 9220 children with MAR conditions had 53 episodes of IPD (43 vaccine-type); 4457 (48.3%) were unvaccinated and 4246 (46.1%) were fully vaccinated, with 1371 (32.3%) receiving dose 3 by 12 months and 2875 (67.7%) having ≥1 dose at ≥12 months. Estimated VE in fully vaccinated children was 85.9% (95% CI: 33.9–97.0) against vaccine-type IPD and 71.5% (95% CI: 26.6–88.9) against all-cause IPD.

Conclusion: This is the first population-based study evaluating the effectiveness of PCV in children with MAR conditions using record linkage. Our study provides evidence that the VE for vaccine-type and all-cause IPD in MAR children in Australia is high and not statistically different from previously reported estimates for the general population. This method can be replicated in other countries to evaluate VE in MAR children.

Key words: invasive pneumococcal disease; medically at-risk condition; pneumococcal conjugate vaccine; record linkage; vaccine effectiveness.

INTRODUCTION

Invasive pneumococcal disease (IPD) due to *Streptococcus pneumoniae* is associated with considerable morbidity and mortality [1]. Introduction of the pneumococcal conjugate vaccine (PCV) has seen a reduction in IPD in many countries including Australia [2, 3]. However, in the post-PCV era, a disproportionately higher burden of IPD persists among children with chronic medical conditions (eg, heart and kidney disease) compared with children without these conditions [4, 5]. A US study reported a 1.8- and 11.2-fold increased risk of IPD in children aged <5 years classified with a moderate and high risk of IPD, respectively, compared with children not in these groups [5]. A recent study in Australia found children with certain medically at-risk (MAR) conditions aged ≤5 years had a 3.3-fold increased risk of IPD before universal PCV introduction and a 5.6-fold increased risk of IPD in the post universal vaccination period compared with non-MAR children [6].

Given the higher risk of IPD in MAR children, additional doses of PCV vaccine are recommend for these children in Australia and in some other countries [7–9]. In Australia, seven-valent PCV (PCV7) was registered for use in infants in 2000, and in 2001 a government funded 3 + 1 (3 primary doses with a booster) PCV7 schedule for MAR children and a 3 + 0 (3 primary PCV7 doses with no booster) schedule for Indigenous children commenced along with a booster dose of 23-valent pneumococcal polysaccharide vaccine (PP23) for all MAR children and

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Corresponding Author: Alamgir Kabir, School of Population Health, University of New South Wales, Sydney New South Wales 2052, Australia. E-mail: a.kabir@unsw.edu.au.

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for Indigenous children in selected jurisdictions [10]. PCV7 was recommended for all children in 2003, and a funded 3 + 0 schedule was implemented for children with no MAR conditions in 2005 [10]. However, in 2018, Australia changed the PCV schedule from a 3 + 0 to a 2 + 1 (2 primary doses with a booster) for non-Indigenous children with no MAR conditions [10]. As different PCV vaccination schedules have been implemented for children with and without MAR conditions, it is important to better understand whether the primary course of PCV is as effective in MAR children as in non-MAR children. However, few studies have evaluated the effectiveness of PCV in children with MAR conditions [11–16], and those conducted to date have been underpowered, not population based and mostly in a specific MAR group [11–13, 16]. Linkage of the Australian Immunisation Register with health data has enabled us to identify children with a wide range of MAR conditions at a population level. Our aim was to use these data to evaluate effectiveness of the primary PCV vaccination course in MAR children.

METHODS

Study Population and Design

We extracted our study population from a large retrospective population-based data linkage cohort of 1.3 million children born between July 2001 and December 2012 in two Australian states, New South Wales (NSW) and Western Australia (WA) [17–19]. Details of the full cohort, datasets, linkage procedures and data cleaning are described elsewhere [17–20]. We restricted the cohort to 2001–2004 births because the high vaccine coverage (>90%) achieved following the introduction of the universal PCV program in 2005 [20] meant the number of unvaccinated MAR children born after 2004 was small.

We identified children with MAR conditions using perinatal data for extreme preterm births <28 weeks of gestation and hospital data for the remaining medical conditions. Previously applied lists of ICD-10-AM diagnosis codes identified: (i) respiratory disease, (ii) heart disease, (iii) kidney disease, (iv) liver disease, (v) diabetes, (vi) immunosuppression, (vii) asplenia or dysfunction of the spleen, (viii) breach in CSF barrier, and ix) down syndrome (Supplementary Table 1) [6, 21]. We only included children with an MAR condition identified in the hospital data by 6 months of age to ensure they had an opportunity to receive the recommended primary course of 3 doses before they were age-eligible for the booster dose at 12 months [20]. We excluded children with an IPD notification before the MAR condition was recorded.

Exposure and Outcome Ascertainment

Vaccination status (exposure) was obtained from the linked Australian Childhood Immunisation Register. MAR children were recommended to receive a 3-dose primary course of PCV at 2, 4, and 6 months with a PCV booster at 12 months and a 23-valent pneumococcal polysaccharide vaccine (PPV23) booster at 4–5 years of age [10]. We assumed that if a child received PCV dose 3, they had received the full primary course (ie, doses 1, 2, and 3 using the dose 3 assumption [22]). According to the current catch-up schedule, a child who received their first dose at ≥12 months was also considered to be fully vaccinated with the primary course [21]. We therefore categorized vaccination status as: first dose <12 months, second dose <12 months and fully vaccinated (with the primary course; receipt of either dose 3 at <12 months of age or one or more doses at ≥12 months of age). The study outcomes were: (1) the first recorded episode of IPD due to serotypes contained in PCV7 (vaccine-type IPD); and (2) all-cause IPD. In sensitivity analyses, (i) we censored the follow-up time at the second PCV dose after 12 months of age and (ii) classified vaccination status according to receipt of doses 1, 2, and 3 at any time up to 5 years of age (see Supplementary Appendix for further details).

Potential Confounders

Maternal and child demographic characteristics, maternal medical and obstetric history, and information on labor and birth were obtained from the perinatal data and birth registrations (see Supplementary Appendix and Table 1 for details).

Statistical Analysis

Cumulative prevalence of MAR conditions reported by 6 months of age in surviving children were estimated per 1000 children. For the descriptive analysis, age at receipt of each PCV dose was categorized into "on-time" (14 days before to 30 days after the due date), "on-time to 12 months" (between on-time and <12 months of age), and "given after 12 months", and examined by birth year. The distribution of IPD notifications by serotype group (PCV7, PCV13 non-PCV7, non-PCV13, and unknown) in children with and without MAR conditions was compared between the pre- and the post-universal period based on the notification year. Cohort characteristics were compared by vaccination status using chi-square tests. Incidence rates of vaccine-type and all-cause IPD among vaccinated and unvaccinated children (≤5 years) were calculated using person-time-at-risk as the denominator. Person-time started at birth and was censored at either: the first IPD notification, death, PCV dose 4, first dose of PPV23, invalid dose or turning 5 years of age, whichever came first. VE was estimated as $VE = (1 - HR) \times 100$, where HR is hazard ratio. HRs and 95% confidence intervals were estimated using Cox proportional hazard modeling with age in days as the time scale, comparing the IPD notification rates by time-varying vaccination status (exposed time for each dose began when that dose was given).

Potential confounders were included in the Cox models if their univariate relationship with the outcome had a *P*-value <.20. We then removed each variable in a stepwise backward elimination procedure, examining whether the vaccination status

Table 1. Characteristics of Medically At-Risk Children Born in 2001–2004 by Vaccination Status

Characteristics	N[a]	Vaccination status			P-value
		Unvaccinated n (%)	One or two doses received by 12 months n (%)	Fully vaccinated[d] n (%)	
All children	9220	4457 (48.3)	517 (5.6)	4246 (46.1)	
Sex					
Male	5217	2492 (47.8)	303 (5.8)	2422 (46.4)	
Female	4003	1965 (49.1)	214 (5.3)	1824 (45.6)	.366
Birthweight, g					
<1500	1189	574 (48.3)	73 (6.1)	542 (45.6)	
1500–2499	843	392 (46.5)	51 (6.0)	400 (47.4)	
2500–3499	4105	1987 (48.4)	231 (5.6)	1887 (46.0)	
≥3500	3075	1502 (48.8)	162 (5.3)	1411 (45.9)	.836
Gestational age, weeks					
≤31	1259	602 (47.8)	73 (5.8)	584 (46.4)	
32–36	927	453 (48.9)	52 (5.6)	422 (45.5)	
≥37	7034	3402(48.4)	392 (5.6)	3240 (46.1)	.988
Apgar Score					
0–7	1049	572 (54.5)	63 (6.0)	414 (39.5)	
8–10	8143	3870 (47.5)	452 (5.6)	3821 (46.9)	<.001
Season of birth					
Autumn	2014	906 (45.0)	125 (6.2)	983 (48.8)	
Winter	2462	1195 (48.5)	190 (7.7)	1077(43.7)	
Summer	2178	1031 (47.3)	85 (3.9)	1062 (48.8)	
Spring	2566	1325 (51.6)	117 (4.6)	1124 (43.8)	<.001
Year of birth					
2001	1327	1136 (85.6)	19 (1.4)	172 (13.0)	
2002	2665	2135 (80.1)	35 (1.3)	495 (18.6)	
2003	2559	838 (32.7)	110 (4.3)	1611(63.0)	
2004	2669	348 (13.0)	353 (13.2)	1968 (73.7)	<.001
Delivery method					
Vaginal	5034	2506 (49.8)	274 (5.4)	2254 (44.8)	
Instrumentation	850	396 (46.6)	46 (5.4)	408 (48.0)	
Caesarean	3335	1555 (46.6)	197 (5.9)	1583 (47.5)	.051
Indigenous status[b] [30]					
Non-Indigenous	8637	4298 (49.8)	467 (5.4)	3872 (44.8)	
Indigenous	583	159 (27.3)	50 (8.6)	374 (64.2)	<.001
Maternal age, years					
<20	462	233 (50.4)	31 (6.7)	198 (42.9)	
20–24	1387	697 (50.3)	69 (5.0)	621 (44.8)	
25–29	2536	1295(51.1)	134 (5.3)	1107 (43.7)	
30–34	2926	1369 (46.8)	166 (5.7)	1391 (47.5)	
≥35	1909	863 (45.2)	117 (6.1)	929 (48.7)	.005
Parental age difference (father's age – mother's age), years					
≤0	1946	922 (47.4)	103 (5.3)	921 (47.3)	
1–3	2981	1453 (48.7)	173 (5.8)	1355 (45.5)	
4–5	1419	652 (45.9)	91 (6.4)	676 (47.6)	
6–8	1275	634 (49.7)	71 (5.6)	570 (44.7)	
>8	1164	572 (49.1)	59 (5.1)	533 (45.8)	
Missing	435	224 (51.5)	20 (4.6)	191 (43.9)	.442
Parity					
0	3626	1647 (45.4)	217 (6.0)	1762 (48.6)	
1	2939	1442 (49.1)	155 (5.3)	1342 (45.7)	
2	1451	758 (52.2)	73 (5.0)	620 (42.7)	
≥3	1196	605 (50.6)	72 (6.0)	519 (43.4)	<.001
Maternal country of birth					
Australia	5194	2460 (47.4)	277 (5.3)	2457 (47.3)	
Other	4026	1997 (49.6)	240 (6.0)	1789(44.4)	.019

Table 1. Continued

Characteristics	N[a]	Vaccination status			P-value
		Unvaccinated n (%)	One or two doses received by 12 months n (%)	Fully vaccinated[d] n (%)	
Maternal smoking					
No	7609	3593 (47.2)	427 (5.6)	3589 (47.2)	
Yes	1609	863 (53.6)	90 (5.6)	656 (40.8)	<.001
Socioeconomic index[c] [31]					
91%–100% (least disadvantaged)	1002	460 (45.9)	72 (7.2)	470 (46.9)	
76%–90%	1243	589 (47.4)	66(5.3)	588 (47.3)	
26%–76%	3992	1931 (48.4)	200 (5.0)	1861 (46.6)	
11%–25%	1566	784 (50.1)	74 (4.7)	708 (45.2)	
0%-10% (most disadvantaged)	1181	586 (49.6)	91 (7.7)	504 (42.7)	
Missing	236	107 (45.3)	14 (5.9)	115 (48.7)	.003
Accessibility or remoteness index of Australia[32]					
Major cities	7043	3445 (48.9)	409 (5.8)	3189 (45.3)	
Inner or outer region	1782	860 (48.3)	88 (4.9)	834 (46.8)	
Remote or very remote	187	57 (30.5)	10 (5.3)	120 (64.2)	
Missing	208	95 (45.7)	10(4.8)	103 (49.5)	<.001
State of residence					
NSW	6949	3343 (48.1)	390 (5.6)	3216 (46.3)	
WA	2058	985 (47.9)	111 (5.4)	962 (46.7)	
Missing	213	129 (60.6)	16 (7.5)	68 (31.9)	.001

[a]Missing values: birthweight, *n* = 8 (0.1%); Apgar score, *n* = 28 (0.3%); delivery method, *n* = 1 (0.0%); parity, *n* = 8 (0.1%); maternal smoking, *n* = 2 (0.0%).

[b]Indigenous status was reported based on an established multi-stage median algorithm using Indigenous status recorded on all linked databases except the deaths data.

[c]State-specific quintiles: 91%–100% = least disadvantaged, 0%–10% = most disadvantaged.

[d]Received either PCV dose 3 at <12 months or ≥1 dose at ≥12 months of age.

β coefficient changed by ≥10% compared with the full model, keeping it if so, and removing it otherwise. The same modeling approach was used to estimate VE in the two sensitivity analyses. We used SAS9.4 [23] and R3.5.3 [24] software for analysis.

RESULTS

Study Cohort

The study cohort included 9220 children (Figure 1) with 42584 person-years of follow-up. The prevalence of MAR conditions reported by age 6 months was 25.2 per 1000 children. Heart disease was the most prevalent MAR condition (11.3/1000) followed by kidney disease (6.1/1000) and respiratory disease (5.3/1000; Supplementary Table 2). Among the study cohort, 53 had IPD by age 5 years; 43 due to PCV7 serotypes (Figure 2). The proportion of non-PCV-type IPD was significantly lower in the pre-universal compared with the post-universal period (13.2% vs. 49.3%; $P < .001$; Figure 2). The proportion of non PCV-type IPD was similar for children with and without MAR conditions during the pre-universal period (~5%) but was higher for MAR compared to non-MAR children during the post-universal period (40.8% vs. 27.3%; *P*-value .005; Supplementary Figure 1).

Overall, 22.7% of dose 1, 28.9% of dose 2, and 41.3% of dose 3 recipients received an on-time dose (Figure 3). These proportions were low for children born in 2001 (6.7% dose 1, 15.4% dose 2, 24.3% dose 3), slightly higher (≤10%) for children born in 2002 and 2003, and substantially higher among children born in 2004 (34.7% dose 1, 34.0% dose 2, 45.0% dose 3). We classified 4246 (46.1%) children as fully vaccinated, 517 (5.6%) as receiving 1 or 2 doses by 12 months of age, and 4457 (48.3%) children as unvaccinated by age 5 (Table 1). Of the fully vaccinated children, 1371 (32.3%) received dose 3 before and 2875 (67.7%) received ≥1 dose after 12 months of age. There were 1970 children who received PCV dose 2 before 12 months of age and, of them, 398 did not have a dose 3 recorded.

Most characteristics (all except sex, birthweight, gestational age, delivery method, and paternal age difference) were significantly ($P < .05$) associated with vaccination status (Table 1). Key differences in full vaccination coverage were between Indigenous (64.2%) and non-Indigenous children (44.8%), and remote or very remote regions (64.2%) and major cities (45.3%). Full vaccination coverage also increased birth year between 2001 (13.0%) and 2004 (73.7%) with the greatest increase from 2003 to 2004.

Effectiveness of PCV7 Against Vaccine-Type IPD

No vaccine-type IPD cases were reported in children who had received PCV dose 1 or PCV dose 2 at <12 months of age (Table 2). Two vaccine-type IPD cases (serotypes 6B and 14) were reported after full vaccination: one was in a child who received dose 1 after 12 months of age (onset 112 days after the PCV

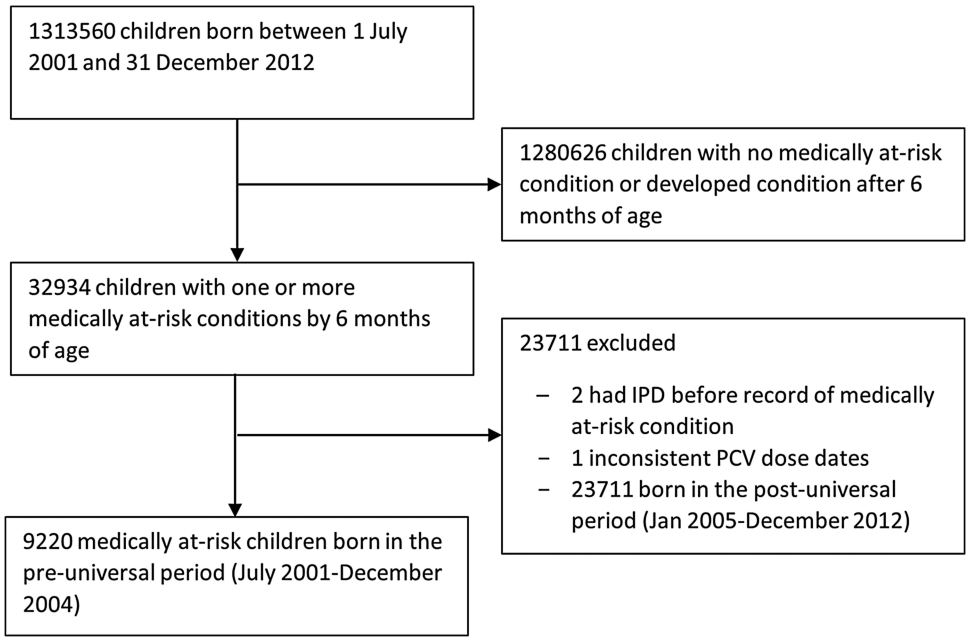

Figure 1. Assembly of analytic cohort [see Gidding et al. [17] for details on initial cleaning and cohort preparation].

dose); and one was in a child who received dose 3 before 12 months of age (onset 2 days after PCV dose3). The vaccine-type IPD incidence rate was 11.6-fold higher in unvaccinated than fully vaccinated children. The adjusted VE for fully vaccinated MAR children was estimated to be 85.9% (95% CI: 33.9–97.0).

Effectiveness of PCV7 Against All-Cause IPD

There was one all-cause IPD case reported after receipt of PCV dose 1 at <12 months of age and 5 all-cause cases reported after full immunization (Table 3). The all-cause IPD incidence rate for unvaccinated children was 1.9-fold higher than dose 1 recipients and 5.3-fold higher than fully vaccinated children. The adjusted VE against all-cause IPD for fully vaccinated MAR children was estimated to be 71.5% (95% CI: 26.6–88.9).

Sensitivity Analyses

The VE estimates for fully vaccinated with censoring and for PCV dose 3 receipt at any time by 5 years of age against both vaccine-type and all-cause IPD were similar to the main analysis but reduction in person-years resulted in wider 95% CIs (Supplementary Tables 3 and 4).

DISCUSSION

To our knowledge, this is the first population-based study to evaluate the effectiveness of PCV in MAR children. Our study found PCV7 was effective in protecting against vaccine-type and all-cause IPD up until 5 years of age in this high-risk group. In fact, the VE estimates were not statistically different from previously reported VE for all children irrespective of MAR status followed to age 2 years (94.2%; 95% CI: 81.9–98.1 for PCV7 dose 3 against vaccine type and 80.1%; 95% CI: 59.4–90.3 against all-cause IPD) [17]. We did not find evidence of waning immunity to age 5 years; among 1371 children vaccinated with dose 3 before 12 months of age, there was only one vaccine-type IPD case and this was within 14 days of dose 3 receipt. Furthermore, our analysis suggests a high degree of protection from a catch-up schedule of one PCV dose after 12 months of age. Among 2750 children who received at least one dose after 12 months of age there was only one IPD case, occurring 112 days after receipt of this dose. Finally, our study provides some evidence to support the use of the new universal 2 + 1 schedule in high-risk children, as is currently recommended for the general population; there were no vaccine-type IPD cases reported up to age 5 years among 2-dose recipients vaccinated by 12 months of age. However, given the small number of cases, larger studies are needed to confirm this finding and to evaluate effectiveness by specific MAR conditions.

Overall, coverage with ≥1 PCV dose was low in this pre-universal vaccination cohort but increased considerably over time. Initially, there may have been a lack of awareness of the recommended schedule [25]. Children born in 2003–2004 were eligible for a catch-up program, targeting all children aged <2 years in 2005 alongside the introduction of the universal vaccination.

As the majority of children in our study did not receive their vaccinations according to the recommended schedule (approximately three quarters of dose 1 recipients born in 2001–2003 received this dose after 12 months of age), we focused on

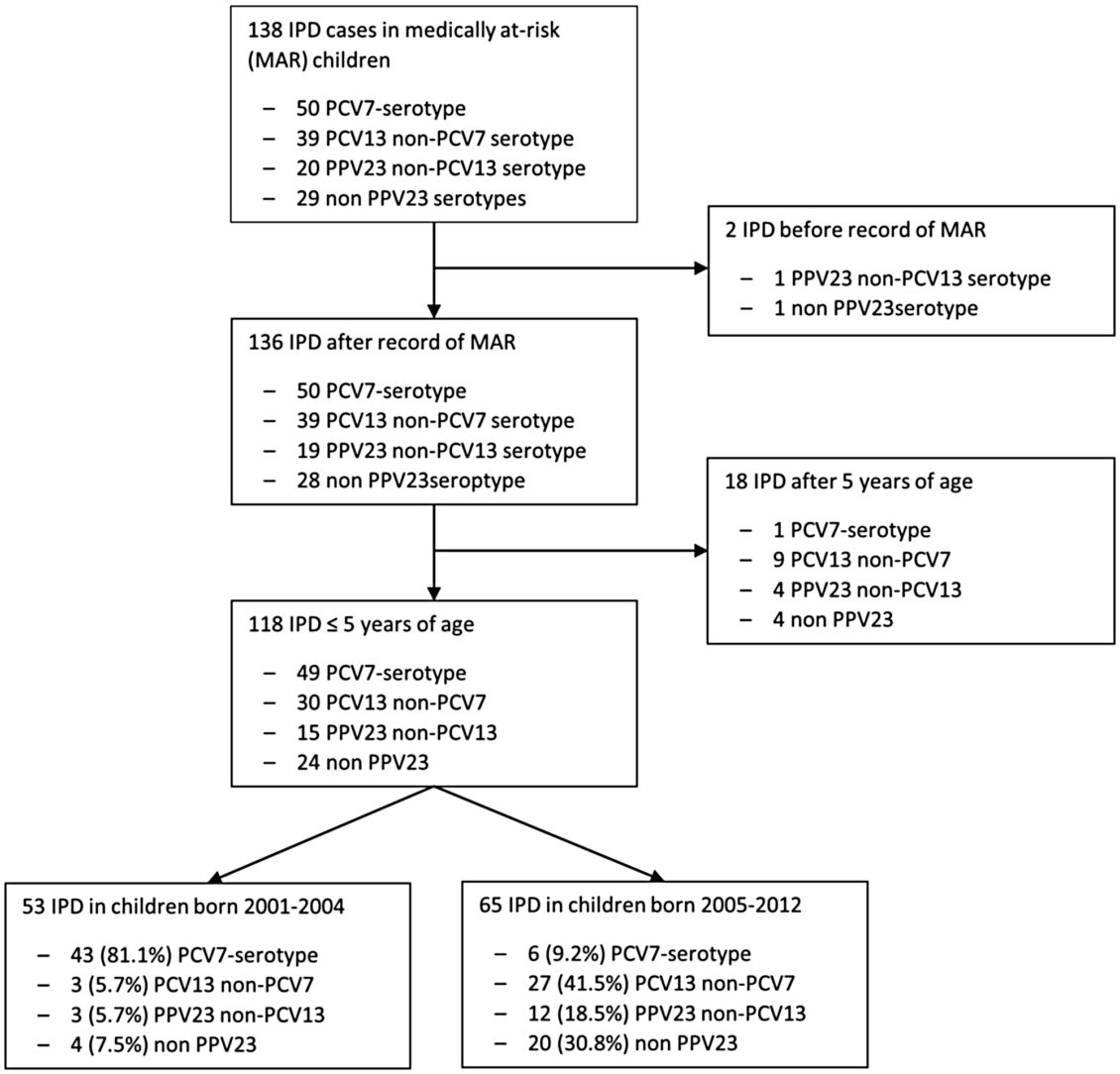

Figure 2. Flow diagram for identifying invasive pneumococcal disease (IPD) cases from the analytic cohort of medically at-risk children with serotype distribution.

measuring VE for the fully vaccinated, and defined "fully vaccinated" as receipt of either the 3-dose primary course before 12 months of age or at least one dose at ≥12 months of age as per current recommendations [7]. However, we estimated VE for receipt of each PCV dose at any time by age 5 years, as used previously in the general population [17], and found similar results in this sensitivity analysis to the main analysis.

There have been several ecological studies evaluating vaccine impact in MAR populations [11, 26, 27] including one population-based study in Australia [6]. However, only a few studies have evaluated vaccine effectiveness, and none were population-based. One small cohort study in the US evaluated VE of ≥1 PCV7 dose against all-cause IPD among 1247 children with sickle cell disease and estimated a similar VE to our study (81.4%) [11]. A sub-analysis of two case–control studies in the US evaluating VE for ≥1 PCV7 or PCV13 dose restricted to children up to age 5 years with a range of underlying conditions also found similar VE point estimates to ours for both vaccine type (81%; both studies [14, 15]) and all-cause IPD (77%; only evaluated in [14]). The vaccine-type VE for healthy children in these two studies was higher than for children with underlying conditions for PCV7 (96% vs. 81%) [14] but not for PCV13 (85% vs. 81%) [15], although the PCV13 study included only a small number of vaccine-discordant child pairs with underlying conditions. Case–control studies in South Africa did not demonstrate protection in HIV-infected children for ≥2 doses of PCV7 or PCV13, unlike for their uninfected counterparts [12, 16]. Compared with these studies, the main strength of our study is that the use of data linkage has enabled us to assemble a large cohort of children with a wide range of MAR conditions at the population level, representative of MAR children nationally, as described elsewhere [20]. To the best of our knowledge, no other studies nationally or internationally have used linked data for

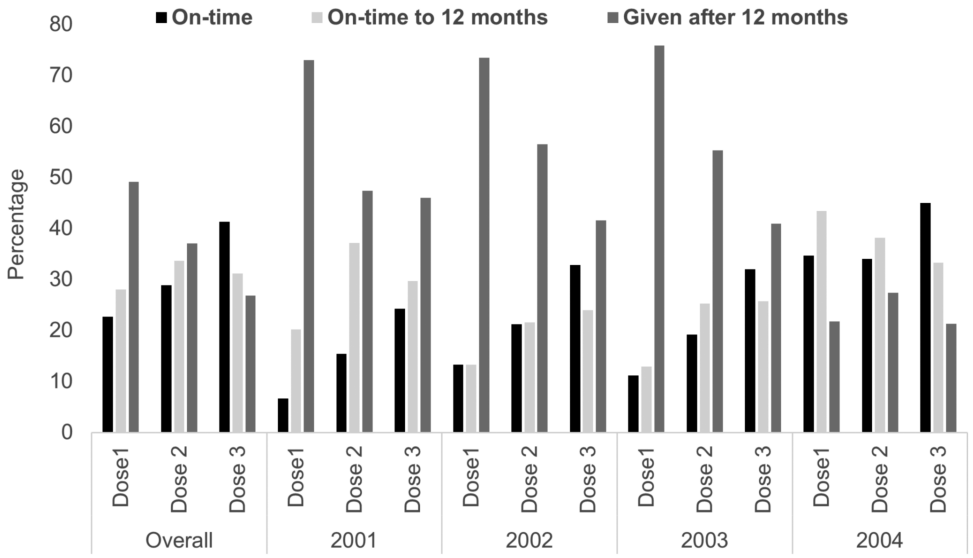

Figure 3. Distribution of age at PCV7 vaccination in medically at-risk children.

evaluating VE in MAR children. Despite this, our wide confidence intervals indicate that larger studies with longer follow-up are needed.

There are some limitations with our study. First, while we restricted our analysis to children born during the pre-universal vaccination period, a portion of their follow-up time was in the post universal period when herd immunity (indirect effects of vaccination) was established. However, the indirect effects of vaccination should impact equally on vaccinated and unvaccinated children (as long as exposure is assumed to be similar in the two groups) yielding direct VE estimates that exclude herd immunity effects [28, 29]. To control for differences in exposure, we intrinsically adjusted for age and included calendar time in models where required. Another limitation was that the majority of children did not follow the recommended vaccination schedule and thus our estimate is not a VE for on-time vaccine coverage. Also, we only identified children whose condition was severe enough to be hospitalized and was identified by 6 months of age. However, these children are probably at a greater risk of IPD, and we found that the vaccine was highly effective for them, although our findings may not represent the mix of conditions seen for older ages, which includes a greater proportion of children with respiratory diseases [6]. Furthermore, our results may not be generalizable to countries with a different mix of MAR conditions (eg, some low-income counties). PCV13 was introduced in 2011, but we only had data until 2013, and while PPV23 was introduced in 2001, uptake in our cohort was 3% [20], so we were not able to evaluate VE of PCV13 or PPV23 in this high-risk group due to insufficient numbers. Our study cohort could have experienced loss to follow-up from overseas or inter-state migration, but this is estimated to be ~3% in 2011 [18] and is unlikely to have made an impact. Finally, despite being population based, the numbers of MAR children, especially with both vaccination and IPD were low and we were unable to provide VE estimates for specific MAR conditions.

Table 2. Incidence rate of vaccine-type (serotypes contained in 7-valent pneumococcal conjugate vaccine, PCV7) invasive pneumococcal disease (IPD) by vaccination status and estimated effectiveness of PCV7 against vaccine-type IPD in medically at-risk children less than 5 years of age in New South Wales or Western Australia born in the pre-universal vaccination period (2001–2004)

PCV dose status	Person-years	Vaccine-type IPD	Incidence rate/1000 py	Crude VE (95% CI)	Adj. VE[d] (95% CI)
Unvaccinated	25 293	41	1.62 (1.16, 2.20)	Ref	Ref
First dose <12 months[a]	10 36	0	0.0	—	—
Second dose <12 months[b]	19 68	0	0.0	—	—
Fully vaccinated[c]	14 160	2	0.14 (0.02, 0.51)	87.2 (45.9, 96.9)	85.9 (33.9, 97.0)

[a]Received first PCV dose at <12 months of age (additional doses may also have been received at <12 months of age).

[b]Received second PCV dose at <12 months of age (additional doses may also have been received at <12 months of age).

[c]Fully vaccinated with the primary course was defined as received either 3 PCV doses at <12 months or ≥1 dose at ≥12 months of age.

[d]Adjusted for year of birth.

Table 3. Incidence Rate of All-Cause Invasive Pneumococcal Disease (IPD) by 7-Valent Pneumococcal Conjugate Vaccination (PCV7) Status and Estimated Effectiveness of PCV7 Against All-Cause IPD in Medically At-Risk Children Less Than 5 Years of Age in New South Wales or Western Australia Born in the Pre-Universal Vaccination Period (2001–2004)

PCV7 dose status	Person-year	All-cause IPD	Incidence rate/1000 py	Unadj. VE (95% CI)	Adj. VE[d] (95% CI)
Unvaccinated	25 271	47	1.86 (1.37, 2.47)	Ref	Ref
First dose <12 months[a]	1036	1	0.97 (0.02, 5.38)	60.2 (−190.0, 94.5)	62.5 (−173.1, 94.9)
Second dose <12 months[b]	1968	0	0.00	–	–
Fully vaccinated[c]	14 147	5	0.35 (0.11, 0.82)	70.9 (25.1, 88.7)	71.5 (26.6, 88.9)

[a]Received first PCV dose at <12 months of age (additional doses may also have been received at <12 months of age).

[b]Received second PCV dose at <12 months of age (additional doses may also have been received at <12 months of age).

[c]Fully vaccinated with the primary course was defined as received either 3 PCV doses at <12 months or ≥1 dose at ≥12 months of age.

[d]Adjusted for birthweight.

In conclusion, our population-based cohort study provides evidence of the effectiveness of PCV7 up until age 5 years in MAR children. The increased risk of all-cause IPD in MAR children may therefore not be due to the suboptimal VE of PCV, rather it might be due to the higher proportion of non-vaccine-type IPD in MAR children compared with the general child population. It also suggests that a 2 + 1 schedule and the catch-up schedule with 1 primary PCV dose after 12 months of age may be effective in this high-risk group. However, further studies are needed to confirm the VE for specific MAR conditions and for the current PCV13 schedule. The methods reported in this study can be replicated in other countries and studies to help inform MAR vaccination programs elsewhere.

Supplementary Data

Supplementary materials are available at the *Journal of The Pediatric Infectious Diseases Society* online (http://jpids.oxfordjournals.org).

Notes

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Authors' contributions. A. K., D. R., A. T. N., H. M., S. J., P. M., and H. G. conceptualized and designed the study, and reviewed and revised the manuscript. A. K. 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 manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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