Vaccine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Vaccine

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

A retrospective cohort study investigating the comparative effectiveness of pneumococcal vaccines against hospitalisation with otitis media and pneumonia in New Zealand

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ARTICLE INFO

Article history:
Received 15 August 2022
Received in revised form 28 March 2023
Accepted 16 May 2023
Available online xxxx

Keywords:
Pneumococcal vaccine
Effectiveness
Otitis media
Pneumonia
Child health

ABSTRACT

Background: Since 2008 New Zealand has used three different formulations of pneumococcal vaccines on the national infant schedule, PCV7, PCV10 and PCV13, switching between PCV10 and PCV13 twice in 10 years. We have used New Zealand's linkable, administrative health data to examine the comparative risk of otitis media (OM) and pneumonia hospitalisations among children receiving three different pneumococcal conjugate vaccines (PCV).

Methods: This was a retrospective cohort study using linked administrative data. Outcomes were otitis media, all cause pneumonia and bacterial pneumonia related hospitalisation for children in three cohorts representing periods where PCVs transitioned between PCV7, PCV10, PCV13 and back to PCV10 between 2011 and 2017. Cox's proportional hazard regression was used to provide hazard ratio estimates to compare outcomes for children vaccinated with different vaccine formulations and to adjust for different sub population characteristics.

Results: Each observation period, where different vaccine formulations coincided, and therefore comparable with respect to age and the environment, included over fifty-thousand infants and children. PCV10 was associated with a reduced risk for OM compared with PCV7 (Adjusted HR 0.89, 95 %CI 0.82–0.97). There were no significant differences between PCV10 and PCV13 in risk of hospitalisation with either otitis media or all-cause pneumonia amongst the transition 2 cohort. In the 18 -month follow-up, after transition 3, PCV13 was associated with a marginally higher risk of all-cause pneumonia and otitis media compared to PCV10.

Conclusion: These results should offer reassurance about the equivalence of these pneumococcal vaccines against the broader pneumococcal disease outcomes OM and pneumonia.

1. Background

The formulations of pneumococcal conjugate vaccines (PCV7, PCV10, and PCV13) differ. It is hypothesised that the inclusion of non-typeable *Haemophilus influenzae* in PCV10 may offer superior protection against otitis media (OM) [1]. Conversely, the inclusion of three additional serotypes in PCV13 is expected to provide protection against a broader range of pneumococcal serotypes [2]. The few studies that have investigated these questions are 'before-after' studies that compare the incidence of disease before and after a new vaccine is introduced [3]. 'Before-after' studies are inherently biased because they cannot control for changes that occur over time (i.e. fluctuations in the circulation of the pathogen, changes in vaccination coverage, improved disease detection methods). This study was designed to minimise temporal bias by comparing the effectiveness of different vaccine formulations, received by infants in the same birth cohort during periods of transition to a new vaccine; PCV7 to PCV10, PCV10 to PCV13, then from PCV13 to PCV10. In addition to these we have included data on common confounders - gender, ethnicity, deprivation, and locality.

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https://doi.org/10.1016/j.vaccine.2023.05.040
0264-410X/

This provides a 12-month interval of time when both vaccines under study were being administered in the study population.

New Zealand (NZ) is well suited to undertake this comparison due to the implementation phases of different vaccines (Fig. 1), a robust vaccination register and linkable hospital discharge data from a largely public healthcare system. We aimed to compare the effectiveness of PCV7 versus PCV10 and PCV10 versus PCV13 against otitis media (OM) and pneumonia (including bacterial) among cohorts receiving both vaccines during the periods of transition from one vaccine formulation to the next. Invasive pneumococcal disease (IPD) incidence was too low to investigate in these relatively small cohorts and was considered in another companion study (unpublished) along with clinically suspected IPD.

This study was reviewed and approved by the University of Auckland Human Participants Ethics Committee on the 18th May 2018, Reference 021057.

2. Methods

2.1. Study population

All children with a live birth record in the National Health Index data set and present in the Immunisation Register; born between 1st Jan 2006 and 31st December 2016. Exclusions from the cohort were those with:

- An inactive, overseas or opt off status indication within the immunisation or national health index data table
- Who died before the start of follow up
- Who had logically inconsistent data (for example birth after receipt of vaccine)

2.2. Study design

This was a retrospective cohort study using administrative data. Data sources include:

- Demographic information from the National Health Index (NHI) database. The National Health Index (NHI) data has demographic information for all people born in NZ and for people born outside of NZ who access the healthcare system; this includes travellers and temporary residents. A person's NHI, date of birth, date of death and sex are not altered over time; however, the remaining data fields such as area of residence, ethnicity may change over time and there is no history kept. Data fields relevant to this study include NHI (encrypted), date of birth, date of death, ethnicity, and geographic area of residence [4].
- Pneumococcal immunisation information from the National Immunisation Register (NIR). The NIR is set up as a comprehensive record of all children born in NZ from 2006 or immigrating to NZ since 2006. All publicly funded vaccinations given in NZ should be recorded as an event in the NIR and when overseas vaccination documentation for a child are available these should also be entered. Relevant data fields include NHI (encrypted), vaccine type, antigen type, vaccination status and vaccination date for all doses.
- OM and all-cause pneumonia hospitalisation data from the National Minimum Dataset (NMDS). The NMDS includes records of all publicly funded hospital discharges in NZ. Data fields relevant to this study include NHI (encrypted), admission event ID, admission date, discharge date, length of stay and ICD-10-AM diagnosis code (the primary plus up to 99 diagnosis codes are available for each admission event). Both primary and secondary diagnosis codes were considered.

3. Outcome measures

Hospitalisation events occurring for the children included in the study population were selected from the NMDS based on the following listed ICD-10-AM codes:

OM – The primary outcome when examining vaccine effectiveness against otitis media was hospitalisation with otitis media. Hospitalisations and elective surgical procedures for otitis media were identified using the codes:

- H65 Nonsuppurative otitis media, H66 Suppurative and unspecified otitis media, H67 Otitis media in disease classified elsewhere, H70 Mastoiditis and related conditions, H74 Other disorder of middle ear and mastoid, H75 Other disorder of middle ear and mastoid in diseases classified elsewhere, H92 Otalgia and effusion of ear; 41632-00 Myringotomy with insertion of tube, unilateral, 41632-01 Myringotomy with insertion of tube, bilateral.

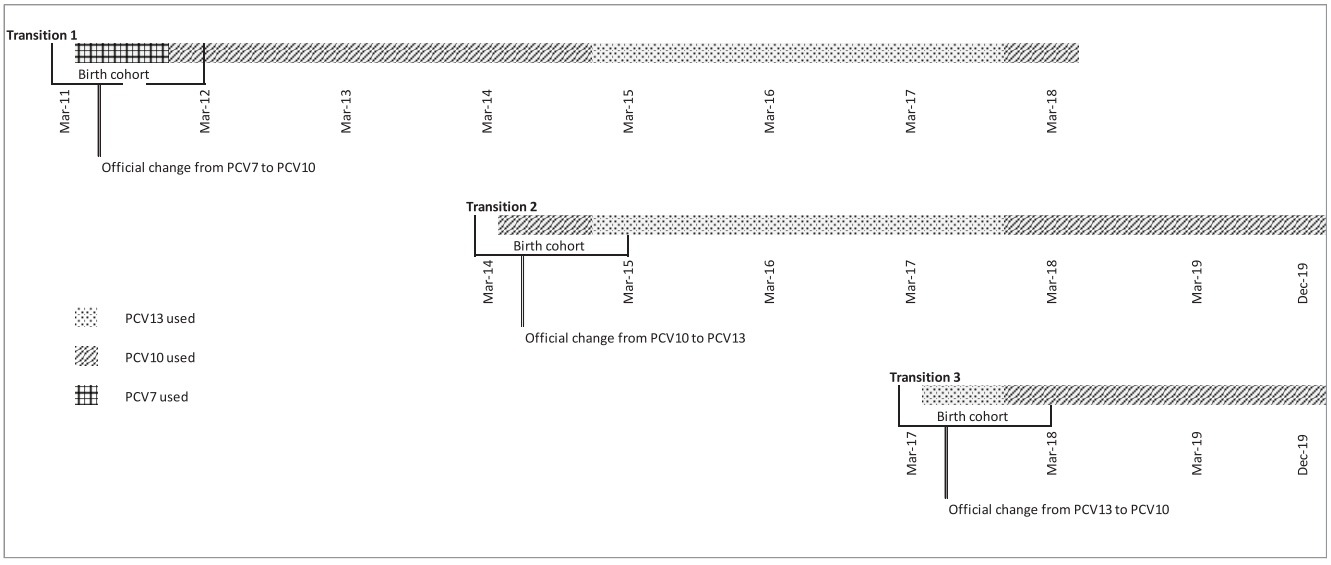

Fig. 1. Birth cohort, follow up time with main vaccine in use indicated throughout and timing of vaccine transitions.

Pneumonia - The primary outcome was vaccine effectiveness against pneumonia hospitalisation with pneumonia. Hospitalisations with pneumonia were identified using the codes:

- J12-J18 Pneumonia, J10.0 Influenza with pneumonia, virus identified, J11.0 Influenza with pneumonia, virus not identified

A sensitivity analysis was conducted using codes identifying the pneumonia specifically as caused by bacteria – J13, J14, J15 and J16.

3.1. Vaccine profile (exposure variable).

To identify the pneumococcal vaccine types given to each child as accurately as possible within the limitations of the national immunisation register (NIR) we took the following steps using two different variables, vaccine, and batch code. Vaccinators enter the vaccine given e.g., PCV7, PCV10 or PCV13, and the batch code into the NIR. The batch code is usually alphanumeric and accurately entered allows identifying or cross check of the vaccine type given to the child. However, because this variable is a free text field there is a small subset of the data that is ambiguous, invalid or despite one or two errors still enables identification of the probable correct batch code. We assigned vaccine type to erroneous but unambiguous batch using a fuzzy match (SAS). Then we compared 'vaccine type' with 'vaccine type imputed' from batch code. Where there were mismatches, the vaccine type was replaced with imputed vaccine type based on batch code.

Following this we summarised the set of vaccine types and checked that the combination of vaccines made sense in the context of the schedule programme and expected doses at the time.

Table 1
Vaccine dose, formulations and hospitalisations for the three different transition periods.

	Total		*No*		*Yes*	
Vaccination doses received	***N***	***(%)***	***n***	***(%)***	***n***	***(%)***
			Otitis media hospitalisation			
Transition Period 1[1]						
3 doses PCV10	22,271	(41.7)	20,922	(41.9)	1,349	(39.3)
3 doses PCV7	12,422	(23.3)	11,593	(23.2)	829	(24.2)
2 doses PCV7, 1 dose PCV10	9,890	(18.5)	9,237	(18.5)	653	(19.0)
1 dose PCV7, 2 doses PCV10	8,351	(15.6)	7,823	(15.6)	528	(15.4)
Probable high-risk schedule						
1 dose PCV13, 2 doses PCV10	131	(0.2)	120	(0.2)	11	(0.3)
3 doses PCV13	102	(0.1)	81	(0.1)	21	(0.6)
2 doses PCV13, 1 dose PCV10	64	(0.1)	50	(0.1)	14	(0.4)
2 doses PCV7, 1 dose PCV13	37	(0.0)	27	(0.0)	10	(0.2)
1 dose PCV7, 2 doses PCV13	31	(0.0)	21	(0.0)	10	(0.2)
Transition Period 2[2]						
3 doses PCV13	22,461	(43.4)	21,166	(43.6)	1,295	(40.4)
3 doses PCV10	12,471	(24.1)	11,639	(23.9)	832	(25.9)
1 dose PCV13, 2 doses PCV10	9,320	(18.0)	8,719	(17.9)	601	(18.7)
2 doses PCV13, 1 dose PCV10	7,468	(14.4)	6,991	(14.4)	477	(14.8)
2 doses PCV10, 1 dose PCV13	3	(0.0)	3	(0.0)	.	.
Transition Period 3[3]						
3 doses PCV10	29,146	(54.9)	28,662	(55.0)	484	(49.7)
3 doses PCV13	7,078	(13.3)	6,924	(13.3)	154	(15.8)
2 doses PCV13, 1 dose PCV10	9,186	(17.3)	9,013	(17.3)	173	(17.7)
1 dose PCV13, 2 doses PCV10	7,585	(14.3)	7,425	(14.2)	160	(16.4)
2 doses PCV10, 1 dose PCV13	20	(0.0)	19	(0.0)	1	(0.1)
			All cause pneumonia hospitalisation			
Transition Period 1[1]						
3 doses PCV10	22,492	(41.9)	21,766	(41.9)	726	(41.1)
3 doses PCV7	12,419	(23.1)	12,029	(23.1)	390	(22.1)
2 doses PCV7, 1 dose PCV10	9,881	(18.4)	9,551	(18.4)	330	(18.7)
1 dose PCV7, 2 doses PCV10	8,385	(15.6)	8,120	(15.6)	265	(15.0)
Probable High Risk						
1 dose PCV13, 2 doses PCV10	170	(0.3)	156	(0.3)	14	(0.7)
3 doses PCV13	147	(0.2)	127	(0.2)	20	(1.1)
2 doses PCV13, 1 dose PCV10	72	(0.1)	60	(0.1)	12	(0.6)
2 doses PCV7, 1 dose PCV13	36	(0.0)	33	(0.0)	3	(0.1)
1 dose PCV7, 2 doses PCV13	33	(0.0)	30	(0.0)	3	(0.1)
Transition Period 2[2]						
3 doses PCV13	22,446	(43.4)	21,633	(43.4)	813	(44.4)
3 doses PCV10	12,451	(24.1)	12,015	(24.1)	436	(23.8)
1 dose PCV13, 2 doses PCV10	9,303	(18.0)	8,994	(18.0)	309	(16.9)
2 doses PCV13, 1 dose PCV10	7,456	(14.4)	7,186	(14.4)	270	(14.7)
2 doses PCV10, 1 dose PCV13	3	(0.0)	3	(0.0)	.	.
Transition Period 3[3]						
3 doses PCV10	29,154	(55.0)	28,754	(55.1)	400	(49.9)
3 doses PCV13	7,068	(13.3)	6,950	(13.3)	118	(14.7)
2 doses PCV13, 1 dose PCV10	9,161	(17.2)	9,009	(17.2)	152	(18.9)
1 dose PCV13, 2 doses PCV10	7,568	(14.2)	7,437	(14.2)	131	(16.3)
2 doses PCV10, 1 dose PCV13	20	(0.0)	20	(0.0)	.	.

[1] 6 year follow up period.
[2] 4.5 year follow up period.
[3] 18 month follow up period.

For example, those children given PCV13 vaccine during the period 2008–2010 are highly likely to be children with specific underlying health conditions (high-risk children). PCV7 given in 2013 or later was likely to have been an error.

The NZ primary immunisation 3-dose schedule across the period of this study was delivered at 6-weeks, 3-months, 5-months and then there was a booster at 15 months. We excluded children who had a recorded dose of vaccine prior to 38 days of age (4 days leeway on first dose recommended at 6 weeks of age), only one dose in total, or had a second dose of vaccine <22 days following the first dose of vaccine. Finally, we also excluded children if any of the vaccine types they had been given were ambiguous - i.e., we were unsure if they had had PCV7, PCV10 or PCV13 or did not receive three doses of the primary series. Follow- up begins for each child two weeks after the receipt of their second dose. Because the booster is given about 10 months after the primary schedule the boosters of most of the children in the transition period will receive the same booster (the one NZ is transitioning to at the time), so this design can only robustly evaluate the different combinations of primary series.

3.2. Definition of transition period

Children from the study population that were included in the analysis specifically examining the transition from PCV7 to PCV10 (Transition 1, Fig. 1) were all children born between the 5th of March 2011 and the 5th of March 2012. The official date for change was the 1st of July 2011. Children from the study population that were included in the analysis specifically examining the transition from PCV10 to PCV13 (Transition 2, Fig. 1) were all children born between the 1st of March 2014 and the 1st of March 2015. The official date for change was the 1st of July 2014. The final transition period (Transition 3, Fig. 1) examined the shift from PCV13 back to PCV10 included all children born 1st of March 2017 through to the 1st of March 2018. The official date for this change was the 1st of July 2017, and most children did not start receiving PCV13 until September 2017, enabling 18-month or shorter follow up only for data relating to this cohort.

3.3. Follow up period

Follow up begins from the earliest possible time that a child can be considered appropriately vaccinated. This means a first dose at 6-weeks, at least 21 days between dose 1 and dose 2, and 2-weeks following the second dose to allow for development of an immune response. Then they were either followed up until 6 years of age after transition 1, 4.5 years of age after transition 2 and to 18 months following transition 3.

3.4. Statistical analysis

Demographic characteristics were summarised for each outcome (OM or all-cause pneumonia) and period of interest (74-days of age up to 18-months or 74-days of age up to 6-years of age for children born during Transition 1 and up to 4.5 years for transition 2). Cox's proportional hazard regression was used to provide hazard ratio estimates to compare outcomes for children vaccinated with different vaccine formulations and to adjust for different sub population characteristics, gender, ethnicity, and area deprivation level.

4. Results

Three doses of the same vaccine type (40–50 % of the cohort) was most common pattern for babies during transition periods. However, combinations of the vaccine formulations comprised the remaining 50–60 % of the cohort (Table 1). The total cohort size for **Transition Period 1,** 6-year OM follow-up was 53,299 individuals with 3425 OM related first hospitalisations. For the all-cause

Table 2
Demographics and otitis media or pneumonia hospitalisations of babies vaccinated during Transition Period 1, 6-year follow-up.

	Otitis media hospitalisation			**Pneumonia hospitalisation**		
	Total	*Yes*		*Total*	*Yes*	
	N	*n*	*(%)*	*N*	*n*	*(%)*
	53,299			53,635	1,763	(100.0)
Total	53,299	3,425	(6.4)	53,635	1,763	(3.3)
	53,299			53,635	1,763	(100.0)
Sex						
Male	27,201	2,087	(60.9)	27,373	977	(55.4)
Female	26,097	1,338	(39.0)	26,261	786	(44.5)
missing	1	0	(0)	1	0	(0)
	53,299			53,635	1,763	(100.0)
Ethnicity						
Māori	13,202	1,030	(30.0)	13,375	550	(31.1)
Pacific Peoples	5,814	358	(10.4)	5,845	473	(26.8)
Asian	6,021	167	(4.8)	6,045	178	(10.0)
Other	871	44	(1.2)	883	26	(1.4)
European	27,289	1,823	(53.2)	27,385	536	(30.4)
missing	102	3	(0.0)	102	0	(0)
	53,299			53,635	1,763	(100.0)
Area deprivation level						
high	19,986	1,389	(40.5)	20,176	946	(53.6)
medium	19,054	1,255	(36.6)	19,172	507	(28.7)
low	14,205	775	(22.6)	14,233	309	(17.5)
missing	54	6	(0.1)	54	1	(0.0)
	53,299			53,635	1,763	(100.0)
DHB Region						
Northern	20,713	1,156	(33.7)	20,851	946	(53.6)
Midland	11,148	922	(26.9)	11,254	335	(19.0)
Central	10,309	514	(15.0)	10,351	299	(16.9)
South Island	11,085	827	(24.1)	11,135	183	(10.3)
missing	44	6	(0.1)	44	0	(0)

pneumonia, 6-year follow-up there were 53,635 children and 1763 first hospitalisations, 92 of these were bacterial pneumonia.

The total cohort size for **Transition Period 2**, 6-year follow-up for OM was 51,723 individuals. During this period there were 3205 OM hospitalisations. For all-cause pneumonia there were 51,659 children and 1828 hospitalisations, 63 of these were bacterial pneumonia.

The total cohort size for **Transition Period 3**, 18-month follow up for OM was 53,015 individuals. During this period there were 972 OM hospitalisations. For all-cause pneumonia there were 52,971 children and 801 hospitalisations. There were no bacterial pneumonia hospitalisations.

The demographic profiles of the transition cohorts and associations between demographic characteristics and hospitalisation were consistent (Tables 2-4) across transitions. Males were more likely to be hospitalised with OM or pneumonia than females. Higher deprivation was associated with higher risk of hospitalisation. Māori and Pacific infants were more likely to be hospitalised than European and other ethnic groups.

5. Comparative risk

PCV10 was significantly associated with a lower risk of OM hospitalisation than PCV7 over the 6-years of follow-up (Table 5) of

Table 3
Demographics and otitis media or pneumonia hospitalisations of babies vaccinated during Transition Period 2, 4.5 years follow-up.

	Otitis media hospitalisation			**Pneumonia hospitalisation**		
	Total	*Yes*		*Total*	*Yes*	
	N	*n*	*(%)*	*N*	*n*	*(%)*
Total	51,723	3,205	(100.0)	51,659	1,828	(100.0)
Sex						
Male	26,886	1,979	(61.7)	26,857	999	(54.6)
Female	24,836	1,226	(38.2)	24,801	829	(45.3)
missing	1	0	(0.0)	1	0	(0.0)
Ethnicity						
Māori	14,496	1,135	(35.4)	14,473	648	(35.4)
Pacific Peoples	5,266	350	(10.9)	5,242	414	(22.6)
Asian	8,017	189	(5.8)	8,017	223	(12.1)
Other	1,042	55	(1.7)	1,041	31	(1.6)
European	22,889	1,475	(46.0)	22,873	512	(28.0)
missing	13	1	(0.0)	13	0	(0.0)
Area deprivation level						
high	18,739	1,297	(40.4)	18,690	898	(49.1)
medium	18,777	1,181	(36.8)	18,771	577	(31.5)
low	14,183	726	(22.6)	14,174	352	(19.2)
missing	24	1	(0.0)	24	1	(0.0)
DHB Region						
Northern	20,030	1,029	(32.1)	19,983	937	(51.2)
Midland	11,027	849	(26.4)	11,019	432	(23.6)
Central	9,818	529	(16.5)	10,831	183	(10.0)
South Island	10,831	797	(24.8)	9,809	275	(15.0)
missing	17	1	(0.0)	17	1	(0.0)

Table 4
Demographics and otitis media or pneumonia hospitalisations of babies vaccinated during Transition Period 3, 18 months follow-up.

	Otitis media hospitalisation			**Pneumonia hospitalisation**		
	Total	*Yes*		*Total*	*Yes*	
	N	*n*	*(%)*	*N*	*n*	*(%)*
Total	53,015	972	(100.0)	52,971	801	(100.0)
Sex						
Male	27,147	565	(58.1)	27,125	423	(52.8)
Female	25,868	407	(41.8)	25,846	378	(47.1)
Ethnicity						
Māori	14,472	377	(38.7)	14,449	300	(37.4)
Pacific Peoples	5,388	125	(12.8)	5,375	229	(28.5)
Asian	9,051	66	(6.7)	9,050	79	(9.8)
Other	1,261	17	(1.7)	1,259	18	(2.2)
European	22,834	387	(39.8)	22,829	175	(21.8)
missing	9	0	(0.0)	9	0	(0.0)
Area deprivation level						
high	20,108	421	(43.3)	20,071	448	(55.9)
medium	19,584	346	(35.5)	19,581	248	(30.9)
low	13,307	205	(21.0)	13,303	105	(13.1)
missing	16	.	.	16	.	.
DHB Region						
Northern	20,409	301	(30.9)	20,371	435	(54.3)
Midland	11,107	326	(33.5)	11,102	198	(24.7)
Central	10,045	166	(17.0)	10,046	113	(14.1)
South Island	11,442	179	(18.4)	11,440	55	(6.8)
missing	12	0	(0.0)	12	0	(0.0)

Table 5
Cox's proportional hazards regression modelling estimates for the three different transition periods with otitis media and all-cause pneumonia hospitalisations as outcomes.

Primary Doses	P-value	Hazard Ratio	95 % CI	Adjusted[1] P-value	Adjusted Hazard Ratio	Adjusted 95 % CI
Transition Period 1, 6 years follow up, Otitis media						
3 doses PCV10	0.7561	1.01	(0.93–1.10)	0.0106	0.89	(0.82–0.97)
3 doses PCV7		ref			ref	
2 doses PCV7, 1 dose PCV10	0.8867	1.01	(0.91–1.12)	0.6710	0.98	(0.88–1.08)
1 dose PCV7, 2 doses PCV10	0.9106	1.02	(0.90–1.12)	0.1823	0.93	(0.83–1.04)
Probable high risk						
1 dose PCV13, 2 doses PCV10	0.7788	1.09	(0.60–1.97)	0.8693	0.95	(0.53–1.73)
3 doses PCV13	<0.0001	2.82	(1.83–4.35)	<0.0001	2.97	(1.94–4.54)
2 doses PCV13, 1 dose PCV10	<0.0001	3.51	(2.11–5.84)	<0.0001	3.47	(2.04–5.88)
2 doses PCV7, 1 dose PCV13	<0.0001	4.473	(2.47–8.11)	<0.0001	4.51	(2.42–8.41)
1 dose PCV7, 2 doses PCV13	<0.0001	5.464	(2.93–10.19)	<0.0001	5.10	(2.73–9.51)
Transition Period 1, 6 years follow up, All-cause Pneumonia						
3 doses PCV10	0.2228	1.079	(0.96–1.22)	0.5684	0.97	(0.85–1.09)
3 doses PCV7		ref			ref	
2 doses PCV7, 1 dose PCV10	0.4808	1.054	(0.91–1.22)	0.9642	1.00	(0.87–1.16)
1 dose PCV7, 2 doses PCV10	0.6259	1.039	(0.89–1.21)	0.2739	0.92	(0.78–1.07)
Probable high risk						
1 dose PCV13, 2 doses PCV10	0.0002	2.826	(1.63–4.91)	0.0016	2.36	(1.39–4.03)
3 doses PCV13	<0.0001	5.265	(3.32–8.34)	<0.0001	5.25	(3.35–8.23)
2 doses PCV13, 1 dose PCV10	<0.0001	6.356	(3.66–11.05)	<0.0001	5.56	(3.13–9.87)
2 doses PCV7, 1 dose PCV13	0.1316	2.394	(0.77–7.45)	0.0408	3.27	(1.05–10.2)
1 dose PCV7, 2 doses PCV13	0.0491	3.124	(1.01–9.72)	0.0522	3.08	(0.99–9.61)
Transition Period 2, 4.5 years follow up, Otitis media						
3 doses PCV13	0.0557	0.92	(0.84–1.00)	0.0565	0.92	(0.84–1.00)
2 doses PCV13, 1 dose PCV10	0.7793	0.98	(0.88–1.10)	0.6252	0.97	(0.87–1.09)
1 dose PCV13, 2 doses PCV10	0.6713	0.98	(0.88–1.09)	0.5235	0.97	(0.87–1.07)
3 doses PCV10	ref					
Transition Period 2, 4.5 years follow up, All-cause pneumonia						
3 doses PCV13	0.2526	1.07	(0.95–1.20)	0.3865	1.05	(0.94–1.18)
2 doses PCV13, 1 dose PCV10	0.5153	1.05	(0.90–1.22)	0.8323	1.02	(0.87–1.18)
1 dose PCV13, 2 doses PCV10	0.5135	0.95	(0.82–1.10)	0.2874	0.92	(0.80–1.07)
3 doses PCV10	ref					
Transition Period 2, 4.5 years follow up, Bacterial pneumonia						
3 doses PCV13	0.0530	1.68	(0.99–2.85)	0.0537	1.68	(0.99–2.85)
2 doses PCV13, 1 dose PCV10	0.6153	1.20	(0.58–2.48)	0.6222	1.20	(0.58–2.47)
1 dose PCV13, 2 doses PCV10	0.3899	1.33	(0.70–2.53)	0.4292	1.30	(0.68–2.47)
3 doses PCV10	ref					
Transition Period 3, 18 month follow up, Otitis media						
3 doses PCV13	0.0059	1.29	(1.08–1.55)	0.0033	1.31	(1.09–1.57)
2 doses PCV13, 1 dose PCV10	0.2031	1.12	(0.94–1.33)	0.1921	1.12	(0.94–1.34)
1 dose PCV13, 2 doses PCV10	0.0070	1.28	(1.07–1.53)	0.0168	1.24	(1.04–1.49)
3 doses PCV10	ref					
Transition Period 3, 18 month follow up, All-cause pneumonia						
3 doses PCV13	0.0816	1.20	(0.98–1.47)	0.0337	1.25	(1.02–1.53)
2 doses PCV13, 1 dose PCV10	0.0603	1.20	(0.99–1.44)	0.0566	1.20	(0.99–1.45)
1 dose PCV13, 2 doses PCV10	0.0192	1.27	(1.04–1.54)	0.0826	1.19	(0.98–1.45)
3 doses PCV10	ref					

[1] Adjusted for sex, ethnicity and deprivation.

the **Transition Period 1**. There were no significant measurable differences between PCV10 and PCV7 in preventing all-cause pneumonia hospitalizations over the 7 years of follow-up. Children who received PCV13 were significantly more likely to be hospitalised with all-cause pneumonia, however this group are likely to have a higher proportion of high-risk children because PCV13 was only funded/supplied free of charge based on the presence of a high-risk condition.

There were no significant differences between PCV13 and PCV10 in either OM, all cause pneumonia or bacterial pneumonia hospitalisations over the 6-years of follow-up after **Transition Period 2** (Table 5). PCV10 was significantly more effective than PCV13 in reducing OM and all-cause pneumonia hospitalisations in the 18-months of follow-up after **Transition Period 3** (Table 5).

6. Discussion

We were able to study the comparative risk of hospitalisation for OM and pneumonia among infants and children who received PCV7, PCV10 or PCV13 head-to-head using three periods of observation where the immunisation programme transitioned from one formulation to another. Each observation period included greater than fifty-thousand infants and children receiving different vaccine formulations at the same time.

During the first transition period the schedule changed from PCV7 to PCV10. After six-years follow up PCV10 was associated with a reduced risk for OM related hospitalisations compared with PCV7.

For the second transition from PCV10 to PCV13 we found both vaccines to be equivalent in their protective effect against both OM and pneumonia after six-years follow up, this included equivalent reduced risk against bacterial pneumonia.

For the transition from PCV13 back to PCV10 we found a higher risk for both OM and pneumonia in children who received three-doses of PCV13 compared with one or two doses of PCV10 by 18-months of age. It is estimated that around 1 % of children receiving PCV13 were children with conditions putting them at higher risk of pneumococcal disease. However, a small (up to15 %, unpublished data), proportion of children at higher risk of pneumococcal dis-

ease will also be contributing to the observed risk of hospitalisation for PCV10, because they have received PCV10 as per routine schedule rather than the recommended PCV13 combined with 23PPV schedule. Therefore, the data suggests that neither PCV13 nor PCV10 offer markedly superior protection for children at high risk of pneumococcal disease.

6.1. Strengths

The strengths of this study are the large, nationally-representative, multi-cultural cohort, robust measure of vaccine exposure provided by our National Immunisation Register and concurrent use of different PCV vaccine types within a short timeframe. Our study is generalisable to the NZ ethnically diverse paediatric population and thus also relevant to our Pacific neighbouring nations.

6.2. Limitations

The risk estimates applied to the general population may be an underestimate because we are not able to effectively identify and separate children who are at elevated risk of pneumococcal disease due to underlying conditions. In addition, the identification of outcomes, except for notified invasive pneumococcal disease, relies on non-specific ICD10-AM codes for pneumonia and will include causes of pneumonia not linked to *S. pneumoniae*. This will also lead to an underestimate of vaccine effectiveness overall but should not influence the relative effectiveness ratios comparing different vaccines. Finally, the measurement of comparative effectiveness here may be influenced indirectly by reductions in circulating serotypes by the vaccines given to slightly older birth cohorts. However, equivalence of effectiveness is consistent in both transition 2 and transition 3. This study did not seek to capture all otitis media and pneumonia cases in New Zealand. The focus was public hospitalisations. A proportion of otitis media are treated in private hospitals and pneumonia may be treated in ED or primary care settings. However, this is unlikely to influence the robustness of the comparative estimates of vaccine effectiveness in preventing public hospital cases of pneumonia or otitis media because there is unlikely to be bias in type of vaccine received by treatment location.

6.3. Context

PCV vaccines were originally developed to address the burden of invasive pneumococcal disease (IPD) among infants and young children. Since introduction they have demonstrated an impact beyond invasive disease both directly and indirectly [5–7]. However, recent data suggests the currently available PCV10 and PCV13 formulations may have reached a plateau in terms of overall reduction in IPD due to serotype replacement [2,8]. These replacement trends are apparent in countries using either formulation despite different serotype distribution, where 19A generally makes a larger contribution in PCV10 settings [2,8,9]. It is likely that this observation would also hold true for OM and pneumonia, which represent much larger non-invasive or mucosal related pneumococcal disease burden.

The inclusion of carrier protein D from non-typeable *Haemophilus influenzae* in PCV10 may offer superior protection against otitis media (OM) in view of *H. influenzae* being a major OM pathogen along with *S. pneumoniae*. However, the inclusion of three additional pneumococcal serotypes in PCV13 is expected to provide protection against a broader range of serotypes, particularly 19A. Of interest we did observe a trend towards reduced risk in children receiving combination schedules which could be examined further. Since implementation both vaccines have demonstrated they provide protection against OM, although comparative studies are few and limited in generalisability and by biases such as missing data [10–16]. Evaluations of the evidence for comparative effectiveness of these vaccines are hampered by significant heterogeneity [3] and generally restricted to IPD as an outcome.

Types of *S. pneumoniae* circulating are likely to influence vaccine impact. Across the period the proportion of vaccine serotypes of *S. pneumoniae* has reduced. A trend toward an increase in non-PCV related and non-typeable associated with IPD is evident [17] which could impact on vaccine performance against OM and pneumonia.

We previously reported on the dramatic impact of PCVs in NZ on IPD, OM and all cause pneumonia between 2006 and 2015, along with a significant reduction in ethnic and socioeconomic disparities for these diseases [18]. This study indicates that these gains have been sustained through 2018. IPD decreased across the study period to 2020 however more recently 19A has been increasing [19]. Our data demonstrate the effectiveness of the PCV programme on OM and pneumonia.

7. Conclusion

These results should offer reassurance about the equivalence of these pneumococcal vaccines against the broader pneumococcal disease outcomes OM and pneumonia.

Funding

This work was supported by GlaxoSmithKline (GSK) as an investigator-led study. GSK were not involved in study design, nor in the collection, analysis and interpretation of data, in the writing of this manuscript, or in the decision to submit the manuscript for publication.

CRediT authorship contribution statement

Janine Paynter: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – original draft. **Anna S. Howe:** Validation, Writing – review & editing. **Emma Best:** Methodology, Writing – review & editing. **Helen Petousis-Harris:** Conceptualization, Methodology, Investigation, Resources, Data curation, Writing – original draft.

Data availability

The authors do not have permission to share data.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Helen Petousis-Harris reports financial support was provided by GSK Vaccines. Janine Paynter reports a relationship with GSK Vaccines that includes: consulting or advisory.].

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