Effect of ten-valent pneumococcal conjugate vaccine introduction on pneumonia hospital admissions in Fiji: a time-series analysis

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Summary

Background In October, 2012, Fiji introduced routine infant immunisation with a ten-valent pneumococcal conjugate vaccine (PCV10) using three primary doses and no booster dose (3+0 schedule). Data are scarce for the effect of PCV in the Asia and Pacific region. We aimed to evaluate the effect of PCV10 on pneumonia hospital admissions in children younger than 5 years and adults aged 55 years and older in Fiji, 5 years after vaccine introduction.

Methods We did a time-series analysis assessing changes in pneumonia hospital admissions at three public tertiary hospitals in Fiji. Four pneumonia outcomes were evaluated: all-cause pneumonia, severe or very severe pneumonia, hypoxic pneumonia, and radiological pneumonia. Participants aged younger than 2 months, 2–23 months, 24–59 months, and 55 years and older were included. Data were extracted from the national hospital admission database according to International Classification of Diseases-tenth revision codes J10·0-18·9, J21, and J22 for all-cause pneumonia. Medical records and chest radiographs were reviewed for the main tertiary hospital to reclassify hospital admissions in children aged younger than 2 years as severe or very severe, hypoxic, or radiological pneumonia as per WHO definitions. Time-series analyses were done using the synthetic control method and multiple imputation to adjust for changes in hospital usage and missing data.

Findings Between Jan 1, 2007, and Dec 31, 2017, the ratio of observed cases to expected cases for all-cause pneumonia was 0·92 (95% CI 0·70–1·36) for children aged younger than 2 months, 0·86 (0·74–1·00) for children aged 2–23 months, 0·74 (0·62–0·87) for children aged 24–59 months, and 1·90 (1·53–2·31) in adults aged 55 years and older, 5 years after PCV10 introduction. These findings indicate a reduction in all-cause pneumonia among children aged 24–59 months and an increase in adults aged 55 years and older, but no change among children aged younger than 2 months. Among children aged 2–23 months, we observed declines of 21% (95% CI 5–35) for severe or very severe pneumonia, 46% (33–56) for hypoxic pneumonia, and 25% (9–38) for radiological pneumonia. Mortality reduced by 39% (95% CI 5–62) for all-cause pneumonia, bronchiolitis, and asthma admissions in children aged 2–23 months.

Interpretation The introduction of PCV10 was associated with a decrease in pneumonia hospital admissions in children aged 2–59 months. This is the first study in a middle-income country in the Asia and Pacific region to show the effect of PCV on pneumonia, filling gaps in the literature on the effects of PCV10 and 3+0 schedules. These data support decision making on PCV introduction for other low-income and middle-income countries in the region.

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Introduction

Pneumonia is a major cause of illness and death, especially among children younger than 5 years and adults aged 65 years and older in low-income and middle-income countries (LMICs).[1] Pneumococcal pneumonia is a common cause of death from severe pneumonia and is a major contributor to severe illness; however, viral causes, including respiratory syncytial virus and influenza virus contribute to the pneumonia burden.[1] Population-based observational studies post-licensure of the pneumococcal conjugate vaccine (PCV) have shown substantial benefit in reducing pneumonia and invasive pneumococcal disease in young children.[2–4] However, there is considerable heterogeneity in estimates of the effect of PCV on all-cause pneumonia;[5] one study assessing PCV effect in five countries in the Americas found that the decline in all-cause pneumonia hospital admissions ranged from no change to 45% in children younger than 2 years, no change to 23% in children aged 24–48 months, and no decline among adults older than 65 years.[6]

Since 2007, WHO has recommended that PCV be included in all national immunisation schedules.[7] However, in most countries in the Asia and Pacific region, PCV is only available for purchase and is not universally

Research in context

Evidence before this study

We searched PubMed for evidence of the effect of the introduction of the ten-valent pneumococcal conjugate vaccine (PCV10) on pneumonia using the following terms in combination "pneumococcal", "conjugate vaccine", "pneumonia", "impact", "effectiveness", and "PCV10" between Jan 1, 2010, and Oct 23, 2019, with no language restrictions. We identified eight longitudinal observational studies that assessed the effect of PCV10 on pneumonia morbidity in children or adults or both. We selected seven of the eight studies with data for a minimum of 2 years post-PCV introduction and settings with no previous use of PCV7. All studies used hospital admission data with the period of follow-up post-PCV10 introduction ranging from 2 to 5 years. One study was done in Zambia using a 3+0 schedule; one study was done in Kenya using a 3+0 schedule plus a three-dose catch-up campaign for infants and a two-dose catch-up campaign for children aged 1–4 years; one study was done in Chile using a 3+1 schedule; three studies were done in Brazil using a 3+1 schedule; and one study was done in Finland using a 2+1 schedule. Across all studies, all-cause pneumonia admissions declined by between 8–48% among young children. There were no studies documenting the effect of PCV10 on severe or very severe pneumonia or hypoxic pneumonia in children younger than 5 years. Two studies assessed indirect protection against all-cause pneumonia among older unvaccinated populations: a study from Finland found an 18% reduction among children aged 7–71 months, while a study from Brazil documented a 11–27% reduction among individuals aged 10–49 years with no evidence of change in older people (≥65 years).

Added value of this study

We evaluated the effect of the infant PCV10 vaccination programme on hospital admissions in Fiji on four pneumonia outcomes: all-cause pneumonia, severe or very severe pneumonia, hypoxic pneumonia, and radiological pneumonia in young children. In addition, we have evaluated indirect protection against all-cause pneumonia among children too young to be vaccinated and adults aged 55 years and older. To our knowledge, we report the first published data for the effect of PCV on pneumonia from a low-income or middle-income country (LMIC) in the Asia and Pacific region. Our results showed evidence of protection in the 24–59 month age group 5 years after the introduction of PCV10. There was no evidence of a reduction in infants younger than 2 months and adults aged 55 years and older, and the 2–23 month group showed a non-significant reduction in all-cause pneumonia, but significant reductions in our clinical pneumonia outcomes. These data build on the results from other LMICs in Africa and South America; however, we provide data for the first time from the Asia and Pacific region. A number of countires in this region are yet to implement PCV into their national immunisation schedule.

Implications of all the available evidence

The introduction of PCV10 into routine immunisation schedules using the traditional 3+0 schedule, without catch-up, has the potential to reduce childhood hospital admissions due to pneumonia in LMICs. We have shown little evidence of indirect protection in Fiji, 5 years after PCV10 introduction. However, indirect protection is likely to increase over time. To our knowledge, our results are the first to show the effect of PCV in a LMIC in the Asia and Pacific region and provide the evidence base to support public health decision making regarding PCV introduction in this region. Because the immunogenicity of PCV10 is similar to PCV13, it likely that either vaccine will be effective against childhood pneumonia, including the most severe outcomes.

available in national immunsiation programmes. This issue is common for middle-income countries that are not eligible for support from Gavi, the Vaccine Alliance. Even with external support, governments require evidence of PCV effectiveness, but so far, data are scarce from the Asia and Pacific region on the effect of PCV. There is a particular scarcity of data for the efficacy of the ten-valent PCV (PCV10), and of results from countries using three priming doses and no booster dose (3+0 immunisation schedule),[8] the most commonly used schedule in LMICs.

In October, 2012, Fiji introduced routine infant immunisation with PCV10 using a 3+0 schedule. We aimed to evaluate the effect of the infant PCV10 vaccination programme on hospital admissions in Fiji for all-cause pneumonia in children aged younger than 5 years and adults aged 55 years and older, and severe or very severe pneumonia, hypoxic pneumonia, and radiological pneumonia in children aged younger than 2 years. We used the synthetic control time-series approach to adjust for changes in hospital admissions unrelated to the vaccine.

Methods

Study design and participants

We did a time-series analysis to assess changes in pneumonia hospital admissions at the three public tertiary hospitals that serve the population of Fiji (884 887 people in 2017).[9] Fiji is an upper-middle-income country in the Pacific and has followed the 2005 WHO Integrated Management of Childhood Illnesses guidelines for the assessment and admission of pneumonia cases since 2007.[10]

To identify cases of all-cause pneumonia and controls, hospital admission data for all causes of illness were extracted from the electronic national hospital admission database for children aged 0–59 months and adults aged 55 years and older. This dataset contained admission data for 49% of all admissions in Fiji, excluding obstetrics,

mental health, and conditions related to PCV except pneumonia or rotavirus vaccine. Data were classified according to primary discharge diagnosis by International Classification of Diseases tenth revision (ICD-10)-Australian modification codes. Re-admissions for any cause within 30 days were considered the same episode of illness and the second admission was excluded.

The *Haemophilus influenzae* type B vaccine was introduced in 1995. PCV10 was introduced into the national immunisation schedule in October, 2012, without a catch-up campaign to vaccinate older age groups. Both vaccines are provided as a three-dose schedule at 6, 10, and 14 weeks of age. National vaccine coverage estimates for three doses of both PCV10 and *H influenzae* type B vaccine were 87%, 92%, 94%, 93%, and 98% in 2013, 2014, 2015, 2016, and 2017, respectively.[11]

Ethical approval for this study was given by the Fiji National Health Review Ethics Committee (approval number FNRER 2012-28) and The University of Melbourne Human Ethics Research Committee (approval number 1238212.4).

Procedures

To obtain data for clinical pneumonia outcomes (severe or very severe, hypoxic, and radiological), we assessed hospital admissions among children aged 2–23 months admitted at the main tertiary referral hospital Colonial War Memorial Hospital (CWMH; Suva, Fiji), which covers approximately 60% of the Fiji population. Data were ascertained from 2007–17 in the patient admission books (according to discharge diagnosis), the national hospital admissions database (according to ICD-10 code), and autopsy books (according to a pathologist's diagnosis). A list was generated of all cases in which a child aged 2–23 months had a primary discharge diagnosis of pneumonia, bronchiolitis, or asthma. Subsequently, individual patient medical records, including a chest radiograph, were identified by study staff for all cases on the list. Data for patient demographics, clinical information, and deaths were extracted from the medical records and recorded by a paediatrician (ET). Chest radiographs were re-read and re-classified by an independent paediatric radiologist (MdC) on the basis of the WHO 2005 criteria.[12] All clinical forms were monitored by a research coordinator and double-entered into EpiData, version 3.1.

Details on methods to identify laboratory confirmed pneumonia cases are included in the appendix (p 3).

Outcomes

Because there is no gold standard case definition for childhood pneumonia,[13] we used four pneumonia outcomes with varying degrees of sensitivity and specificity: all-cause pneumonia (which is highly sensitive but not specific), and three clinical definitions based on WHO definitions of severe or very severe pneumonia,[10] hypoxic pneumonia (which indicates severe disease and is the main cause for pneumonia-associated death), and radiological pneumonia.[12] These categories are not mutually exclusive. All-cause pneumonia included ICD-10 codes J10·0–18·9, J21, and J22. Bronchiolitis (ICD-10 code J21) was included because clinicians in Fiji code pneumonia according to Integrated Management of Childhood Illnesses definitions (cough and breathing rate, according to age) and this includes bronchiolitis. Severe or very severe pneumonia was based on the WHO 2005 pneumonia case definitions[10] with the addition of oxygen saturation of less than 90% in room air, or death due to pneumonia (confirmed by a pathologist at autopsy). Three Integrated Management of Childhood Illnesses danger signs are included in the WHO 2005 definition for which data were not available in Fiji: inability to drink, persistent vomiting, and stridor in a calm child. However, stridor is most likely to be classified as croup in Fiji and would not be classified as pneumonia when taken alone. Hypoxic pneumonia was defined as any child with pneumonia and oxygen saturation of less than 90% in room air, or death due to pneumonia. Radiological pneumonia was defined as primary endpoint consolidation according to the WHO 2005 standard case definition as re-read by a paediatric radiologist (MdC).[12] Individuals with pneumonia who died from pneumonia before having a chest radiograph taken were also classified as having radiological pneumonia.

Statistical analysis

The pre-PCV10 period was defined as from Jan 1, 2007, to Sept 30, 2012, and the post-PCV10 period was defined as from Oct 1, 2012, to Dec 30, 2017. The annual age-specific incidence for all-cause, severe or very severe, hypoxic, and radiological pneumonia was calculated as the number of cases within the age group divided by 100 000 population of that age group and multiplied by 100 000, with exact Poisson CIs. The annual case fatality rates are reported for all pneumonia, bronchiolitis, and asthma admissions in children aged 2–23 months at CWMH. Case fatality rate was calculated as the number of deaths in hospital divided by the number of hospital cases multiplied by 100, with exact Poisson CIs. The incidence rate ratio in the pre-PCV10 period versus the post-PCV10 period was calculated by dividing the pre-PCV10 rate by the post-PCV10 rate, with exact Poisson CIs.

Time-series analyses were done to quantify changes in the rate of the four pneumonia outcomes associated with the introduction of PCV10. For our primary analysis, we used a time-series synthetic control.[6,14] This approach is designed to adjust for changes in pneumonia hospital admissions that are unrelated to the vaccine and that could bias estimates of vaccine effect. With the time-series synthetic control analysis, a Poisson regression model was fitted to the number of pneumonia cases per month. As controls, we included covariates of other disease categories not influenced by the vaccine in the

See Online for appendix

	National admissions for all-cause pneumonia				Colonial War Memorial Hospital admissions*			
	<2 months (n=1763)	2–23 months (n=4815)	24–59 months (n=1205)	≥55 years (n=2696)	All pneumonia, bronchiolitis, and asthma (n=4069†)	Severe or very severe pneumonia (n=2816‡)	Hypoxic pneumonia (n=609§)	Radiological pneumonia (n=518¶)
Annual hospital admissions								
2007	124	458	127	164	396	272/396 (69%)	62/396 (16%)	26/396 (7%)
2008	175	503	146	177	476	329/476 (69%)	65/476 (14%)	31/476 (7%)
2009	150	496	147	154	537	360/537 (67%)	72/537 (13%)	76/537 (14%)
2010	167	416	121	144	395	245/395 (62%)	49/395 (12%)	54/395 (14%)
2011	206	492	94	193	442	323/442 (73%)	89/442 (20%)	78/442 (18%)
2012	176	432	104	198	230	160/230 (70%)	50/230 (22%)	49/230 (21%)
2013	209	399	69	215	231	153/231 (66%)	39/231 (17%)	37/231 (16%)
2014	138	384	88	279	346	265/346 (77%)	64/346 (18%)	55/346 (16%)
2015	143	315	82	297	200	134/200 (67%)	30/200 (15%)	32/200 (16%)
2016	171	568	115	442	489	343/489 (70%)	59/489 (12%)	55/489 (11%)
2017	104	352	112	433	324	232/324 (72%)	30/324 (9%)	23/324 (7%)
Sex								
Female	664 (38%)	1992 (41%)	553 (46%)	1315 (49%)	1726 (43%)	1204 (43%)	265 (44%)	215 (42%)
Male	1099 (62%)	2823 (59%)	650 (54%)	1381 (51%)	2317 (57%)	1605 (57%)	338 (56%)	294 (58%)
Ethnicity								
i-Taukei (Indigenous)	1390 (79%)	4111 (85%)	952 (79%)	1375 (51%)	3590 (88%)	2513 (89%)	482 (94%)	547 (90%)
Fijians of Indian descent	286 (16%)	430 (9%)	179 (15%)	1160 (43%)	313 (8%)	186 (7%)	22 (4%)	36 (6%)
Other‖	87 (5%)	274 (6%)	74 (6%)	161 (6%)	156 (4%)	116 (4%)	11 (2%)	25 (4%)
Median age (IQR), months unless specified	1 (0–2)	9 (6–14)	35 (28–45)	67 years (61–74)	9 (5–14)	9 (5–14)	8 (4–13)	7 (4–11)
Oximetry recorded	NR	NR	NR	NR	2253 (55%)	1833 (65%)	515 (85%)	276 (53%)
Median length of stay (IQR), days	6 (4–8)	4 (2–6)	3 (2–5)	6 (4–8)	4 (2–6)	4 (2–6)	6 (3–10)	5 (3–10)
Deaths	27 (2%)	74 (2%)	7 (1%)	332 (12%)	117 (3%)	117 (4%)	117 (22%)	117 (19%)

Data are n, n/N (%), or n (%) unless otherwise specified. National admissions were based on International Classification of Diseases-tenth revision codes using actual case data for all-cause pneumonia. Colonial War Memorial Hospital admissions were based on discharge diagnosis and clinical data. NR=not recorded. *Case definitions of severe or very severe, hypoxic, and radiological pneumonia are not mutually exclusive—ie, children might be classified as having multiple pneumonia outcomes; therefore the row percentages do not add up to 100% of all pneumonia, bronchiolitis, and asthma admissions. †n varies across variables between 2820 and 4069 due to missing data. ‡n varies across variables between 2174 and 2816 due to missing data. §n varies across variables between 482 and 609 due to missing data. ¶n varies across variables between 356 and 518 due to missing data. ‖Other included ethnicities of Pacific Islands other than Fiji, European, and Chinese.

Table 1: **Characteristics of pneumonia hospital admissions in Fiji, 2007–17**

model. For these controls, we grouped causes of hospital admissions based on ICD-10 categories (appendix p 6).

As a measure of vaccine effect, we compared observed cases with the estimated number of cases that would be expected if PCV10 had not been introduced, extrapolated from the model. To estimate the cases expected in the absence of vaccine introduction, we fitted models to the pneumonia data from the pre-PCV10 period, along with observed values of the control time-series, and we extrapolated the number of pneumonia hospital admissions in the post-PCV10 period. The ratio gave an estimate of the relative effect of the vaccine and the difference between the observed and extrapolated values gave an estimate of the absolute effect of the vaccine. The number of cumulative cases prevented was estimated by summing the observed and expected cases between the date of vaccine introduction and the indicated date. As a sensitivity analysis, a time-trend analysis was done (appendix p 4). Details on the model fitting, Bayesian priors, and analysis code have been published previously.[6] Several steps were taken to account for incomplete data. Firstly, we audited the electronic national hospital admission database between 2007–11 and 2014–15 and found that 89% of all-cause admissions were captured compared with the ward admission registers.[15] We assumed that these missing admissions were not specific to a pneumonia admission but instead related to logistical factors pertaining to any hospital admission. For the clinical pneumonia outcomes, there were missing data for severe or very severe, hypoxic, and radiological pneumonia outcomes due to the patient medical records, chest radiograph, or oxygen saturation data being unavailable for review. We investigated differences between cases with and without missing clinical outcomes by comparing them for demographic and clinical characteristics (appendix p 7). The missing data for these clinical outcomes were handled using multiple imputation (appendix p 2).

Data were analysed using STATA, version 14 and R, version 3.3.

Role of the funding source

The Fiji Health Sector Support Program, which implemented the bilateral health programme on behalf of the Australian Government (a study funder), contributed to the conception and design of the study. The funders of the study had no role in data collection, data analysis, data interpretation, or in the decision to submit for publication. KJ was an employee of the funder and had a role in the writing of the report. RR had full access to all the data in the study and FMR had final responsibility for the decision to submit for publication.

Results

Between Jan 1, 2007, and Dec 31, 2017, there were 14 386 national hospital admissions due to all-cause pneumonia and 10 479 of these occurred within the age groups relevant for this study (<2 months, 2–23 months, 24–59 months, and ≥55 years). Summary data for national and CWMH admissions are shown in table 1, monthly case numbers are shown in appendix p 8, and annual incidence is shown in appendix p 11. Among the 2–23 month age group admitted to CWMH, there were 4069 hospital admissions due to pneumonia, bronchiolitis, or asthma. Of these, 494 (12%) were missing clinical data required to assign severity status, 1816 (45%) were missing hypoxia status, and 1765 (43%) were missing radiological pneumonia status (appendix p 7). After adjustments for the missing data, the mean number of cases classified as severe or very severe pneumonia was 3181, as hypoxic pneumonia was 937, and as radiological pneumonia was 846.

We observed a 39% reduction in case fatality rates for all pneumonia, bronchiolitis, and asthma admissions in children aged 2–23 months at CWMH between the pre-PCV10 and the post-PCV10 period (incidence rate ratio 0·61, 95% CI 0·38–0·95; p=0·021; appendix p 12).

Our analysis on all-cause pneumonia associated with the introduction of PCV10 is shown in the figure and table 2. The ratio of observed cases to expected cases for all-cause pneumonia was 0·86 (95% CI 0·74–1·00) 5 years post-PCV10 introduction among children aged 2–23 months and 0·74 (0·62–0·87) among children aged 24–59 months (table 2). There was no evidence of a reduction in pneumonia hospital admissions among the children aged younger than 2 months and adults aged 55 years and older post-PCV10. For the 55 years and older age group, there was an increase 5 years post-PCV10 (ratio of observed to expected 1·90 [95% CI 1·53–2·31]; table 2).

The estimated cumulative number of cases prevented following PCV10 introduction is shown in the appendix (pp 14, 17). The largest numbers of all-cause pneumonia hospital admissions were prevented in the 2–23 month age group. In this age group, 315 (95% CI –22 to 686) hospital admissions were estimated to have been prevented for all-cause pneumonia within 5 years of vaccine introduction. Among all three age groups of children younger than 5 years, we found substantial uncertainty around the estimates of cases prevented. More details on the relationship between the control variables and pneumonia are described in the appendix (p 4).

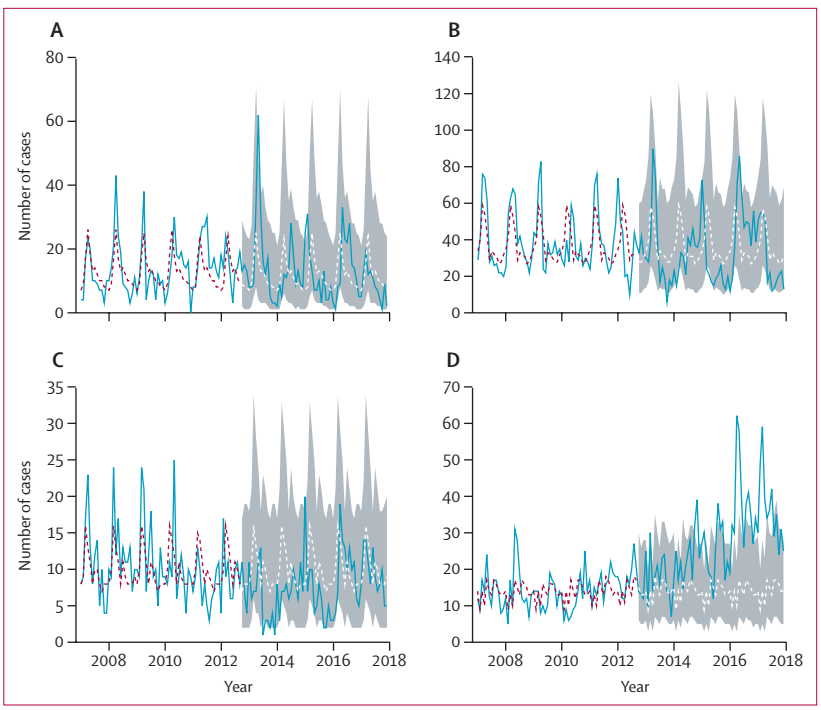

Figure: **Times-series plots for all-cause pneumonia, by age group**
The blue line indicates actual cases. The red dotted line indicates the fitted model. The white dotted line indicates extrapolated values based on synthetic control model. Grey shading indicates the 95% CI at timepoints after introduction of the ten-valent pneumococcal conjugate vaccine in October, 2012. <2 months (A), 2–23 months (B), 24–59 months (C), and ≥55 years (D).

Regarding our clinical pneumonia outcomes associated with introduction of PCV10, we found a 21% (95% CI 5–35) reduction in severe or very severe pneumonia, 46% (33–56) reduction in hypoxic pneumonia, and 25% (9–38) reduction in radiological pneumonia among children aged 2–23 months, relative to control diseases and using pneumonia data imputed to correct for missing data for case definitions (figure, table 2, appendix pp 15–16). Credible intervals for these estimates were wide due to the small numbers of cases (monthly case numbers are shown on appendix p 8) and unexplained variability in the data. The rolling rate ratio decreased to less than 1 before the vaccine was introduced, which indicates that some of the reduction might be due to other factors (appendix p 16). How well the control variables correlated with outcome variable pneumonia is described in the appendix (p 4).

There was a 75% decrease (95% CI 18–94; p=0·0041) in bacteraemic pneumococcal pneumonia among children younger than 5 years and no change among adults aged 55 years and older (ratio of observed to expected 1·26

	All-cause pneumonia				Severe or very severe pneumonia (2–23 months)	Hypoxic pneumonia	Radiological pneumonia
	<2 months	2–23 months	24–59 months	≥55 years			
Synthetic control	0·92 (0·70–1·36)	0·86 (0·74–1·00)	0·74 (0·62–0·87)	1·90 (1·53–2·31)	0·79 (0·65–0·95)	0·54 (0·44–0·67)	0·75 (0·62–0·91)
Time trend	0·83 (0·53–1·27)	0·94 (0·76–1·16)	0·98 (0·70–1·36)	2·51 (1·66–3·54)	1·20 (0·78–1·84)	0·80 (0·51–1·25)	0·89 (0·56–1·42)

Data are the ratio of observed to expected cases (95% CI). Expected cases were those projected to occur if time trends were to continue; thus, a ratio of less than 1 indicates a decrease, and a ratio of more than 1 indicates an increase. Data were estimated using the synthetic control and time-trend method with imputed data (multiple imputation was only done for severe or very severe, hypoxic, and radiological pneumonia outcomes) in Fiji by PCV period. The pre-PCV10 period was defined as Jan 1, 2007, to Sept 30, 2012, and the post-PCV10 was defined as Oct 1, 2012, to Dec 31, 2017. PCV=pneumococcal conjugate vaccine.

Table 2: **Ratio of the observed cases to the expected cases in pneumonia hospital admissions by age group**

[95% CI 0·40–4·63]; p=0·69) in the post-PCV10 period (2013–17) versus pre-PCV10 period (2007–11; appendix p 13). Full results are in the appendix (p 6).

We evaluated the sensitivity of the results to the modelling approach, by comparing simple trend adjustments with the synthetic control model and by evaluating the estimated effect when different control variables were used (appendix p 4). The results were robust for those aged 55 years and older whereas, for the 24–59 month age group, the results were sensitive to the modelling approach used, and alternative models gave different estimates: in the time-trend analysis, the estimates of the rate ratio were closer to 1 among the 2–23 month age group for all outcomes, and none of the clinical pneumonia outcomes showed a significant change over time (table 2).

Discussion

To our knowledge, this study represents the first evaluation of the effect of PCV10 on pneumonia from a LMIC in the Asia and Pacific region, and provides data for the effect of PCV10 on pneumonia hospital admissions, of which there is a paucity, in particular with use of a 3+0 schedule. We evaluated several clinically relevant pneumonia outcomes. We found evidence of protection in the 24–59 month age groups with all-cause pneumonia and in the 2–23 month age groups with severe or very severe, hypoxic, or radioligical pnuemonia. The ratio of observed cases to expected cases for all-cause pneumonia was 0·86 (95% CI 0·74–1·00) among children aged 2–23 months and we found no evidence of indirect effects in the infants too young to be vaccinated (<2 months) or older people (≥55 years). Mortality reduced by 39% among children aged 2–23 months who were admitted to CWMH with all-cause pneumonia, bronchiolitis, and asthma.

Our results showed that hospital admissions for severe or very severe, hypoxic, and radiological pneumonia in children aged 2–23 months reduced by 14–46% after introduction of PCV10 in Fiji. Bacteraemic pneumococcal pneumonia also reduced, although total cases were few. Hospital admissions for non-pneumonia causes did not change suggesting that the decrease was unlikely to be due to changes in clinical practice or health-seeking behaviour. These findings are largely in line with patterns observed in a study of five countries in the Americas.[6] Observational studies in The Gambia and Brazil estimated a 23–29% decline in radiological pneumonia among children younger than 2 years.[3,16] An inherent problem with undertaking PCV effect studies on pneumonia is the absence of a gold standard case definition to capture all cases of pneumococcal pneumonia. Because pneumococcal pneumonia has been estimated to account for 50% of all child pneumonia deaths,[17] the effect of PCV is expected to be higher for the more severe outcomes, including hypoxic pneumonia, which is more likely to be pneumococcal, compared with the less specific outcomes of all-cause and severe or very severe pneumonia. Our results support this assumption, finding greater decreases in the incidence of hypoxic pneumonia than severe or very severe pneumonia and all-cause pneumonia.

In the 2–23 month age group, we found the ratio of observed cases to expected cases was 0·86 (95% CI 0·74–1·00) in all-cause pneumonia, but we had less certainty regarding this finding as the lower band of the 95% CI was one, and the variability in the data made it difficult to accurately assess changes associated with the vaccine. This variability is due in part to epidemic variability in pneumonia hospital admissions during the post-PCV10 period, which was not well explained by the model. An epidemic of pneumonia of unknown cause in 2014–15 and 2016–2017 particularly challenged the analysis in this age group. However, for many age groups, the control variables did not adequately adjust for the epidemic variations in the data, so the analyses were effectively comparing incidence before and after vaccine introduction. Other studies have found similar estimates of effect to ours. Two studies from Brazil and one from Zambia found that changes in all-cause pneumonia hospital admissions among children younger than 5 years varied between a 2% increase and 38% decrease following the introduction of PCV10.[16,18,19]

Mortality reduced by 39% among children aged 2–23 months who were admitted to CWMH with all-cause pneumonia, bronchiolitis, and asthma. Few studies have

documented the effect of PCV on pneumonia mortality, but the effect on hypoxia (a potential precursor to mortality) provides supportive evidence of mortality risk. Previous studies showed that, following PCV13 introduction, hypoxic pneumonia decreased by 47% among Malawian children younger than 5 years and 57–72% among Gambian children aged 2–23 months.[3,4] All-cause mortality reduced by 16–36% in studies from Chile, The Gambia, Malawi, and Nicaragua.[20–22] Among Moroccan children younger than 5 years, mortality from respiratory causes decreased by 28% and in those younger than 1 year, it decreased by 30% after the introduction of PCV13.[23]

Our estimates on the effect of PCV10 on severe or very severe pneumonia, hypoxic pneumonia, and radiological pneumonia show a variance according to whether results were adjusted for missing data by imputation. The sensitivity analyses without imputed data assumed that if the data were missing, then the outcome was not present. This method is likely to have underestimated case numbers, with a possible bias towards the null in estimating PCV10 effect because a substantial proportion of cases were missing classification data (13% were missing severity results, 54% were missing hypoxia results, and 23% were missing radiology results), with a greater proportion of missing data in the pre-PCV10 period compared with the post-PCV10 period. Multiple imputation addresses this potential bias by replacing missing data with imputed values modelled using clinical information, thus including all cases in the analysis. Because the missing data were associated with severity, we adjusted for missing data by including clinical variables in the multiple imputation model. Therefore, we consider the multiple imputation results to be a more valid estimate of the true vaccine effect.

Indirect effects were not evident in infants aged younger than 2 months and adults aged 55 years and older. The exact contribution of pneumococci to pneumonia in very young infants is unknown; however, studies suggest that *Streptococcus pneumoniae* probably causes about 25% of neonatal pneumonia cases in LMICs[24] and 66% of acute lower respiratory infections in children younger than 5 years globally.[25] In a separate study in Fiji looking at pneumococcal carriage in infants aged 5–8 weeks pre-PCV10 introduction, we found that 10% of serotypes carried were PCV10 types.[26] Since pneumococcal carriage is a precursor for invasive disease, PCV10 serotypes might contribute little to very young infant pneumococcal infection in this setting.

The reason for the increase in cases of pneumonia in the 55 years and older age group is unknown. Other studies show heterogeneous results for indirect effect on pneumonia among older people (≥65 years), with the majority documenting no effect.[27] In Scotland, the rates of pneumonia hospital admissions were also found to have increased among older people after the introduction of PCV13.[28] In Fiji, we found no change in bacteraemic pneumococcal pneumonia, suggesting the increase was due to another cause and not serotype replacement. We also found that rates of all-cause hospital admissions increased for the 55 years and older age group, which suggests this change was not specific to pneumonia. In a separate analysis on the effect of PCV10 on invasive disease, we found an increase in ICD-10 coded all-cause sepsis in this age group in the post-PCV10 period (unpublished). Further virological and microbiological data are required to understand this finding, but *Staphylococcus aureus* might contribute to this increase in pneumonia hospital admissions in this age group and needs further investigation.

In addition to the weaknesses already highlighted, our study has limitations that are common to other retrospective observational studies that evaluate vaccine effects. First, the use of hospital admission data is likely to be subject to incomplete reporting that might vary during the period of the study. We quantified the degree of under-reporting of pneumonia cases through an audit of the national hospital admission database and found that 89% of admissions at the tertiary hospitals were captured when compared with the hospital ward registers.[15] Second, the decrease in childhood pneumonia hospital admissions might also be due to other factors unrelated to PCV10, including changes in access to care, admission practice, population changes, and other health interventions. This limitation is inherent to all observational studies and therefore causation cannot be implied generally. In this study, we used the novel synthetic control method to adjust for changes in admissions (eg, due to changes in reporting, access to care, among others) that are unrelated to PCV10 introduction, and therefore used the time-trend method as a sensitivity analysis. Variation in the interpretation of chest radiographs is a possibility that we minimised by using a single senior consultant radiologist.

In conclusion, we found a temporal association of PCV10's effects on hospitalised pneumonia in children aged 24–59 months, and decreases in clinical pneumonia outcomes in children aged 2–23 months. These results were consistent with our previous findings showing a reduction in vaccine-type pneumococcal carriage in young children 3 years after the introduction of PCV10 in Fiji.[26] These results provide supportive evidence of the probable benefits of PCV10 in reducing pneumonia in children in Fiji. Our findings are likely to be helpful for decision making regarding PCV introduction for other LMICs in the Asia and Pacific region. In addition, the quantification of the PCV effect could provide an opportunity for economic studies to compare relative benefits of PCV with other interventions to reduce child mortality.

Contributors

FMR designed, conceived, and initiated the study and led editing of the manuscript. ET collected data and drafted the manuscript. RR analysed data and drafted the manuscript. RR, CDN, and DMW led the statistical methods and did the statistical analysis. EKM reviewed the methods and manuscript. LT and JK were Colonial War Memorial Hospital (Suva, Fiji) leads in accessing data. ER, RD, LT, JK, DN, and MK coordinated

ministry facilities. ET, FTR, and RR coordinated study staff, in particular data collection. MdC classified radiological pneumonia cases. All authors approved the manuscript for submission.

Declaration of interests

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