Impact of 13-Valent Pneumococcal Conjugate Vaccine on Colonisation and Invasive Disease in Cambodian Children

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Summary

Introduction of the 13-valent pneumococcal conjugate vaccine into Cambodia has led to declines in vaccine-type and antimicrobial resistant pneumococcal colonisation and disease in young children. Inclusion of multiple serotype colonisation data did not significantly alter vaccine effectiveness estimates.

Abstract

Background

Cambodia introduced the 13-valent pneumococcal conjugate vaccine (PCV13) in January 2015 using a 3+0 dosing schedule and no catch-up campaign. We investigated the effects of this introduction on pneumococcal colonisation and invasive disease in children aged <5 years**.**

Methods

Six colonisation surveys were done between January 2014 and January 2018 in children attending the outpatient department of a non-governmental paediatric hospital in Siem Reap. Nasopharyngeal swabs were analysed by phenotypic and genotypic methods to detect pneumococcal serotypes and antimicrobial resistance. Invasive pneumococcal disease (IPD) data for January 2012 – December 2018 were retrieved from hospital databases. Pre-PCV IPD data and pre-/post-PCV colonisation data were modelled to estimate vaccine effectiveness (VE).

Results

Comparing 2014 with 2016-2018, and using adjusted prevalence ratios, vaccine effectiveness (VE) estimates for colonisation were 16.6% (95% CI 10.6–21.8) for all pneumococci and 39.2% (26.7–46.1) for vaccine serotype (VT) pneumococci. There was a 26.0% (17.7–33.0) decrease in multi-drug resistant pneumococcal colonisation. IPD incidence was estimated to have declined by 26.4% (14.4–35.8) by 2018, with a decrease of 36.3% (23.8–46.9) for VT IPD and an increase of 101.4% (62.0–145.4) for non-vaccine serotype IPD.

Conclusions

Following PCV13 introduction into the Cambodian immunisation schedule there have been declines in VT pneumococcal colonisation and disease in children aged <5 years. Modelling of dominant serotype colonisation data produced plausible vaccine effectiveness estimates.

Key words

Streptococcus pneumoniae; colonisation; vaccine; children; Cambodia

Introduction

Introduction of pneumococcal conjugate vaccines (PCVs) has significantly reduced the incidence of invasive pneumococcal disease (IPD, *Streptococcus pneumoniae* infection with a positive sterile-site culture [2]) and has led to declines in antimicrobial resistant (AMR) IPD [3]. However, given the large number of serotypes not included in current PCV formulations, initial declines in overall IPD and AMR-IPD incidence have been eroded by increases in non-vaccine serotype IPD [4, 5].

Nasopharyngeal (NP) pneumococcal colonisation is common in childhood and colonisation-based surveillance may be used to predict serotype replacement and IPD incidence changes post-PCV introduction [6-9]. Children may carry multiple serotypes concurrently [11]. A decline in multiple serotype colonisation has been noted following PCV introduction [12], but the effects of multiple serotype colonisation on PCV impact models are unknown.

Uptake of PCV in Asia has been relatively slow [13]. With Gavi support, in January 2015 Cambodia added PCV13 to the national immunisation schedule with a 3+0 dosing schedule (6, 10 14 weeks; no booster) and no catch-up campaign. Following roll out, national PCV13 coverage estimates for the 1st / 3rd doses were 102% (reflecting potential denominator issues) / 77% in 2015, 100% / 96% in 2016, and 93% / 91% in 2017 [13].

To date there are limited pneumococcal disease data for Cambodia. A non-governmental paediatric hospital documented that, between 2007 and 2012, *S. pneumoniae* was responsible for ~10% of bloodstream infections in hospitalised children, with a case fatality rate of 15.6% [14]. Pre-PCV13 introduction surveys at this hospital documented pneumococcal colonisation in 68% of outpatient children aged <5 years [15].

The objective of this study was to estimate PCV13 impact on NP colonisation, invasive disease and AMR in Cambodian children utilising pre- and post-PCV13 introduction data from a well-established sentinel surveillance site.

Methods

Study site

Angkor Hospital for Children (AHC) is a non-governmental paediatric hospital located in the north-western city of Siem Reap. The hospital, and an associated satellite clinic at Sot Nikom district hospital, has ~100 inpatient beds and provides free primary to tertiary level healthcare to children <16 years of age, without geographic restrictions. There are ~180,000 outpatient visits and 6,000 inpatient admissions per year.

Nasopharyngeal colonisation surveys

Six discrete outpatient-based NP colonisation surveys were undertaken between January 2014 and January 2018. Two pre-PCV surveys (January and August 2014) have been described previously [15]. Pre-PCV data from children aged <5 years were further analysed in the current study. For each of four post-PCV surveys (August 2015, January 2016, January 2017, January 2018), the aim was to recruit 450 children aged <5 years presenting to the hospital outpatient department with minor illnesses over a period of a month. Children with suspected pneumonia and/or requiring hospitalisation were excluded and each child could be enrolled only once per survey. Immunisation status was captured by parent/guardian recall or from the immunisation record card, where available. A nasopharyngeal swab was taken from each child.

The WHO colonisation detection protocol was used to identify pneumococcal serotype(s) present in the swabs [16]. Antimicrobial susceptibility testing (AST) was performed following Clinical Laboratory and Standards Institute guidelines [17]. Penicillin non-susceptibly was defined as a minimum inhibitory concentration of ≥0.12 μg/mL. Multi-drug resistance (MDR) was defined as resistance to ≥3 drug classes (Supplementary Methods).

Detection of multiple pneumococcal serotype colonisation

To determine characteristics of multiple serotype colonisation pre- and post-PCV introduction, 500 pneumococcus-positive NP swabs were further processed by latex sweep and molecular serotyping microarray methods [11]. One hundred pneumococcus positive swabs were selected randomly from each January survey except for 2018, where the first 100 eligible swabs were selected (Supplementary Methods).

Invasive pneumococcal disease data

Culture-confirmed IPD cases from 1st January 2012 to 31st December 2018 were identified from the hospital laboratory database, which captures data on all clinical specimens submitted for culture. A case of IPD was defined as *S. pneumoniae* isolated from blood, cerebrospinal fluid, or other normally sterile sites in a child aged <5 years of age. Only the first isolate from each infection episode was included. Over this time period, blood and other syndrome appropriate specimens were taken for culture on children requiring hospitalisation with fever and/or signs of sepsis, at the discretion of the treating clinician. Specimen collection guidelines and active diagnostic stewardship were available throughout [18]. Details of specimen processing have been summarised elsewhere [19].

Data analysis

Categorical variables were compared by the chi-squared or Fisher's exact test. Trends were assessed by the Cochran-Armitage test. Non-normally distributed continuous variables were compared by the Wilcoxon rank sum or Kruskal-Wallis test. Analyses were done using R version 3.5.1 [20].

Estimation of PCV13 effect was done by assessment of changes in vaccine-type (VT; serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 23F) pneumococcal colonisation prevalence pre- (2014) and post-PCV (2016-18) introduction, stratified by age. Log-binomial regression was used to determine prevalence ratios (PR) and 95% confidence intervals (CI)

for overall, VT, non-vaccine type (NVT), and non-typeable (NT) pneumococcal colonisation. Models were adjusted for epidemiologic factors associated with variability in colonisation: upper respiratory tract infection (URTI) symptoms, co-habitation with another child aged <5 years, definite recent antibiotic use, and enrolment season (January vs August) [21-23]. Vaccine effectiveness (VE) was calculated as 100 × (one minus the adjusted PR).

IPD detection rates were estimated using total blood cultures processed from children aged <5 years as the denominator, since the hospital catchment area cannot be readily quantified, and this denominator would account for temporal variations in culture practice. Poisson regression was used to determine incidence rate ratios (IRR) for invasive disease.

Modelling of vaccine effect using combined colonisation and disease data was done as specified by Weinberger et al (their Model 1, see Supplementary Methods) [8].

Ethics statement

Colonisation survey protocols were approved by the AHC Institutional Review Board (422/13, 371/14, 0348/15), Cambodia National Ethics Committee for Health Research (210NECHR, 289NECHR, 150NECHR, 137NECHR), WHO Western Pacific Regional Office IRB (2015.6.CAM.1.EPI), and the University of Oxford Tropical Research Ethics Committee (1009-13, 559-15). Analysis of stored swabs by latex sweep and microarray was determined by the US-CDC Center for Global Health Human Subjects Review to be a non-research activity (CGH HSR 2017-532), and CDC IRB review was not required.

Results

Study participants

A total of 1,805 NP swabs were collected in the four post-PCV surveys. Four swabs were removed due to enrolment errors, leaving 1,801 analysable swabs. There were 721 NP swabs

collected from children aged <5 years in the two pre-PCV surveys, giving a combined total of 2,252 NP swabs.

The median age of children was 1.51 (interquartile range (IQR) 0.76 – 2.88) years in the pre-PCV surveys and 1.39 (IQR 0.77 – 2.64) years in the post-PCV surveys (p=0.2). Three children (0.1%) were known to be HIV-positive. Demographic and basic health data on the children contributing swabs are summarised in Table 1. Half (52.7%; 949/1,801) of the children enrolled in post-PCV surveys were age-eligible to have been fully immunised: 86.7% (827/949) of these children were reported to have received ≥2 doses of PCV13. In the 2018 survey, ≥2 doses of PCV13 had been received by 75.4% (342/453) of enrolled children, although this was verified by vaccine record visualisation in only 65 (14.3%).

Pneumococcal colonisation

Two-thirds (1,629/2,522; 64.6%) of children were colonised by *S. pneumoniae*: 68.0% (490/721) in the pre-PCV surveys and 63.2% (1,139/1,801) in the post-PCV surveys (p=0.03). Comparing pre-PCV with early post-PCV and late post-PCV time periods, overall colonisation prevalence and colonisation by penicillin non-susceptible / MDR pneumococci decreased substantially in the 0-11 month old children (Figure 1 and Table S1). There were declines in colonisation by VT pneumococci, and increases in NVT colonisation, in the 0-11 month, 12-23 month, and 24-35 month age groups. No clear changes in colonisation characteristics were noted in the 36-47 month and 48-59 month age groups, who were not age-eligible for PCV13 (Figure 1; Table S1).

NP swab culture yielded 1,759 pneumococci. Forty five serotypes plus NT isolates were identified: 56.1% of isolates were VT. Serotype 6A or 6B was the most commonly carried serotype in all surveys until January 2018, when serotypes15B/C dominated (Figure S1). VT isolates decreased, NVT increased (notably 15A, 15B/C, 23A, and 34) and NT did not change over time (Figure 2). Penicillin, co-trimoxazole, and tetracycline resistance rates were high

(>60%), with lower rates of resistance to macrolides, ceftriaxone, and chloramphenicol (Table S2). VT isolates were more likely to be MDR than NVT or NT isolates (86.8% vs 47.6%, p<0.001). The proportion of isolates that were penicillin non-susceptible decreased over time (81.0% in 2014 to 65.6% in 2018, p<0.0001), with smaller declines in tetracycline resistance and multi-drug resistance. There were no clear trends in MDR prevalence within serotype categories over time (Figure S2).

Multiple pneumococcal serotype colonisation

In the 500 cases selected for detailed analysis, multiple pneumococcal serotype colonisation was detected in 10.0% (50/500), 12.2% (61/500), 20.8% (104/500) of children by WHO serotyping, latex sweep and microarray, respectively, with no evidence of a temporal trend (Figure S3). Co-colonisation patterns are summarised in Figure S4.

Invasive disease

Between 1st January 2012 and 31st December 2018, there were 81 invasive pneumococcal disease episodes caused by 16 serotypes in hospitalised children aged <5 years (Figure S5). In these episodes, 73 children had a positive blood culture alone, 5 had a positive pleural fluid culture (+positive blood culture in 4), and 3 had a positive CSF culture (+positive blood culture in 2). The median age at presentation was 1.6 years (IQR 0.9 – 2.3), with no difference between pre- and post-PCV periods. Vaccine serotypes accounted for 91.4% (74/81) of infections: 6B (14, 17.3%), 14 (14, 17.3%), 19A (13, 16.0%), 1 (10, 12.3%), 23F (6, 7.4%), 6A (5, 6.2%), 19F (5, 6.2%), 18C (3, 3.7%), 3 (2, 2.5%), 12F (2, 2.5%), 38 (2, 2.5%), 4 (1, 1.2%), 5 (1, 1.2%), 13 (1, 1.3%), 15A (1, 1.2%), 23A (1, 1.2%). In the pre-PCV period 92.9% (39/42) isolates were VT compared with 86.4% (19/22) in the post-PCV period (p=0.4) (Figures S5 and S6). The IPD detection rate fell from 3.76 (95% CI 2.71 – 5.08) / 1,000 blood cultures in the pre-PCV period to 2.33 (95% CI 1.46 – 3.53) / 1,000 blood cultures in the post-PCV period (Table 2; Figure S7).

Overall, 70.4% (57/81) of invasive isolates were penicillin non-susceptible and 67.9% (55/81) were MDR, with no change post-PCV introduction. VT pneumococci were more likely to be MDR than NVT isolates (71.4% vs 28.6%, p=0.03).

Estimates of PCV13 effectiveness

Vaccine effectiveness against colonisation

Comparing pre- and post-PCV periods, the VE estimates for colonisation were 16.6% (95% CI 10.6 – 21.8%) for all pneumococci and 39.2% (95% CI 26.7 – 46.1%) for VT pneumococci, with a 23.3% (95% CI -2.6 – 50.1%) increase in NVT colonisation (Table 3). For colonisation by AMR pneumococci, VE estimates were 22.5% (95% CI 15.0 – 29.0%; penicillin non-susceptible) and 26.0% (95% CI 17.7 – 33.0%; MDR).

Vaccine effectiveness against invasive disease

There was a 37.9% (95% CI 63.6 to -2.9%) decline in overall IPD (p=0.07) and a 42.3% (95% CI 67.3 to -1.5%) decline in VT IPD (p=0.05), between pre- and post-PCV periods. No overall change in NVT IPD was detected (p=0.8) (Table 4).

Combined colonisation-invasive disease model estimates of vaccine effectiveness against invasive disease

In the model including pre-PCV IPD data and the pre- and post-PCV colonisation data, IPD incidence was estimated to have declined by 26.4% (95% CI 14.4 – 35.8) in 2018 (Table S3). VT IPD was estimated to have declined by 36.3% (95% CI 23.8 – 46.9) with a 101.4% (95% CI 62.0 – 145.4) increase in NVT IPD. Repeating the model with a subset of carriage data and sensitive methods to detect multiple serotype colonisation data yielded VE estimates that were very similar to each other (Table S4). The point estimates were all slightly decreased compared with the model including the entire colonisation dataset processed to detect dominant serotype(s) only (Figure 3).

Discussion

This study describes the effects of PCV13 on pneumococcal colonisation, invasive disease, and AMR in Cambodian children three years after its introduction into the routine immunisation schedule.

PCV13 was introduced without a catch-up campaign. However, coverage of target children was reported to be high nationally and, by the 2018 colonisation survey, around three-quarters of enrolled children <5 years were reported to have received ≥2 doses. Three years following introduction, there was a 39% decline in VT colonisation and a 23% increase in NVT colonisation. Despite declines, the prevalence of VT colonization among children age-eligible to have received PCV13 continues to be high (~29%), which may explain the lack of indirect effects observed in children >36 months, i.e. those too old to have received PVC13. In comparison, two years after introduction of PCV10 in Kilifi, Kenya (with catch-up campaign), VT colonisation prevalence had declined by 64% and NVT colonisation increased by 37% in children aged <5 years [23]. Reductions in VT colonisation of 44-66% and increases in NVT colonisation of 5-72% were reported recently in young children, three years after PCV10 introduction in Fiji, an Asia-Pacific region upper middle-income country [24]. A recent model-based study estimated that it would take approximately 10 years to eliminate VT colonisation, with almost complete replacement by NVT colonisation, if PCV13 were introduced in Vietnam without a catch up campaign [25]. In due course, it will be important to compare findings from our study to ongoing colonisation-based PCV impact studies in Lao People's Democratic Republic and Papua New Guinea [26].

Antimicrobial resistance rates were high in VT pneumococci and a reduction in colonisation by MDR (VE 26%) and penicillin non-susceptible pneumococci (VE 23%) was seen following PCV13 introduction. At the isolate level, there was a decline in the proportion of pneumococci that were penicillin non-susceptible, from 81% in 2014 to 66% in 2018.

The nature of the study site meant that estimation of population IPD rates was not possible. However, comparing post-PCV (January 2016 to December 2018) with pre-PCV (January 2012 to December 2014) blood culture data, a 38% decline in overall IPD, with a 42% decline in VT IPD, was detected. Unfortunately, the small number of positive cultures and wide confidence intervals limit the interpretability of these results. This is a frequent problem when attempting to estimate the impact of PCVs in low- and middle income countries (LMICs), where microbiology and epidemiologic surveillance resources are scarce and pre-hospital treatment may reduce blood culture yields [10]. However, it has been shown that reasonable estimates of PCV impact could be obtained by modelling pre-PCV IPD data with changes in colonisation before and after PCV7 introduction [8]. Using the data from the current study, this approach estimated that there would have been a 26% decrease in overall IPD, a 36% decrease in VT IPD and a 101% increase in NVT IPD incidence in 2018, compared to baseline (2012-2014). These point estimates are somewhat more modest than the post-PCV declines in IPD observed in large population-based IPD surveillance in other LMICs [27, 28], perhaps as a result of the known limitations of the model which will tend to underestimate declines in VT disease as a result of the requirement for inclusion of continuity corrections for non-carried serotypes. Weinberger and colleagues were cautiously optimistic that their PCV7-validated model would produce reasonable results when applied to PCV13 data, but stressed that validation would be important using datasets where temporally variable and highly invasive serotypes, such as 1 and 5, are found in NP specimens [8]. We identified forty-three colonising serotypes and 16 serotypes from IPD cases. Serotype 1 was responsible for 13% of IPD cases, and disappeared rapidly after PCV13 introduction, but was not detected in NP specimens. Whilst we cannot formally validate the model results, the findings demonstrate comparable trends to those from population–based surveillance, and the modelled confidence intervals overlap with those from population-based studies in other

locations. However, given the heterogeneity in invasiveness between serotypes, ongoing IPD surveillance remains a critically important activity to monitor vaccine impact [29].

The impact of inclusion of multiple pneumococcal serotype colonisation data on disease model estimates was unknown and at least one study has demonstrated a decline in multiple serotype colonisation following PCV introduction [12]. In Cambodian children, multiple serotype colonisation was detected in up to 24% of NP swabs using sensitive methodologies but did not vary significantly over time. Inclusion of multiple serotype data did not impact on modelled VE estimates, suggesting that dominant serotype data generated from studies using the standard WHO methodology for pneumococcal colonisation detection is adequate for determination of VE in such models [16].

The study has limitations. All data come from a single sentinel surveillance site, which may limit generalisability. However, given the sample size, location and unrestricted catchment area (where approximately one-third of patients reside outside of Siem Reap province), the study population is likely to be representative of many children in Cambodia. Selection of children with minor illnesses only was done to minimise potential biases of recruiting hospital attendees into the colonisation surveys. The small number of children in whom PCV immunisation status could be verified from their personal immunisation record card meant that planned analyses of PCV impact on colonisation at the individual level were not possible. The lack of a population denominator limits the utility of IPD data. However, this has been compensated by estimating VE using a combined colonisation–invasive disease data approach, which was previously well validated for estimation of VE for PCV7 [8]. The frequency of blood culture collection in the AHC outpatient department decreased significantly in late 2015 following introduction of updated laboratory guidelines, which may have reduced IPD case detection rates, although there were no changes in culture practices for patients requiring hospitalisation. This change in diagnostic practice will not have

impacted on modelled VE estimates. Finally, only three years of post-PCV data were collected. Future surveillance efforts should ideally include older children and adults to capture indirect effects of immunisation.

In conclusion, introduction of PCV13 into the childhood immunisation schedule in Cambodia has resulted in declines in VT pneumococcal colonisation and disease in children aged <5 years. Ongoing surveillance will be critical to determine further changes as the PCV13 immunisation programme matures.

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CDC Disclaimer

The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centres for Disease Control and Prevention (CDC).

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Conflict of interests

Potential conflicts of interest: **(JH):** St George's, University of London, UK (SGUL), but not JH, have received funding from GSK, Sanofi Pasteur and Pfizer for research conducted by JH as an SGUL employee. JH is co-founder, board member and shareholder of BUGS Bioscience, a not-for-profit spin-out company of SGUL, but JH receives no personal income from this activity. **(KAG):** SGUL sub-contract KAG to BUGS Bioscience as an SGUL employee, but KAG receives no personal income from this activity. **(JDH):** owns stock in Pfizer (managed by an investment advisor). All other authors have no potential conflicts.

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Tables

Table 1. Demographic, health and PCV13 immunisation summary data for children included in the pre- and post-PCV colonisation surveys

Variable	Pre-PCV		Post-PCV				P-value
	Jan-2014	Aug-2014	Aug-2015	Jan-2016	Jan-2017	Jan-2018	
Children, n	373	348	450	449	449	453	-
Demographic / health							
Age (y), median (IQR)	1.35 (0.73-2.78)	1.46 (0.79-2.95)	1.51 (0.82-2.79)	1.26 (0.75-2.40)	1.49 (0.77-2.90)	1.36 (0.76-2.38)	0.1
Gender, n (% female)	165 (44.2)	171 (49.1)	222 (49.3)	218 (48.6)	215 (47.9)	215 (47.5)	0.7
URTI symptoms, n (%)	352 (94.4)	265 (76.1)	426 (94.7)	422 (94.0)	402 (89.5)	404 (89.2)	0.5
Co-habiting with other children <5y, n (%)	107 (28.8)	102 (29.3)	162 (36.0)	134 (29.9)	156 (34.7)	156 (34.4)	0.06
Definite recent antibiotic use, n (%)	13/371 (3.5)	24/346[a] (6.9)	27 (6.0)	11/447[a] (2.5)	12 (2.7)	15 (3.3)	0.03
PCV immunisation							
PCV13 (≥1 dose) - verified[b], n (%)	0 (0.0)	0 (0.0)	25 (5.6)	49 (10.9)	51 (11.4)	72 (15.9)	-
PCV13 (≥1 dose) - parent recall, n (%)	0 (0.0)	0 (0.0)	41 (9.1)	133 (29.6)	222 (49.7)	291 (64.2)	-
PCV13 (≥2 doses) - verified[b], n (%)	0 (0.0)	0 (0.0)	24 (5.3)	42 (9.4)	46 (10.3)	65 (14.3)	-
PCV13 (≥2 doses) - parent recall, n (%)	0 (0.0)	0 (0.0)	40 (8.9)	130 (29.0)	204 (45.6)	277 (61.1)	-

[a] Data missing for two cases in Aug-2014 and Jan-2016 surveys.
[b] Immunisation status verified by visualisation of the child's personal immunisation record
IQR: inter-quartile range; URTI: upper respiratory tract infection.

Table 2. Summary of invasive pneumococcal disease (IPD) episodes per 1,000 blood cultures in hospitalized children aged <5 years, by time period

	Blood cultures (n)	IPD (n)	IPD detection rate (95% CI)	VT (n)	VT detection rate (95% CI)	NVT (n)	NVT detection rate (95% CI)
Pre-PCV (2012-2014)	11,170	42	3.76 (2.71 - 5.08)	39	3.49 (2.48 - 4.77)	3	0.27 (0.05 - 0.78)
Post-PCV (2016-2018)	9,425	22	2.33 (1.46 - 3.53)	19	2.01 (1.21 - 3.15)	3	0.32 (0.07 - 0.09)
Early post-PCV (2016-2017)	6,556	16	2.44 (1.40 - 3.96)	15	2.29 (1.28 - 3.77)	1	0.15 (0.04 - 0.85)
Late post-PCV (2018)	2,869	6	2.09 (0.77 - 4.55)	4	1.39 (0.38 - 3.57)	2	0.70 (0.08 - 2.51)

CI: confidence interval; VT: vaccine type; NVT: non-vaccine type.

Table 3. Estimates of PCV13 effectiveness against colonisation in Cambodian children aged <5 years

	Colonisation prevalence (95% CI)	Crude prevalence ratio (95% CI)	Adjusted[a] prevalence ratio (95% CI)	P-value
All pneumococci				
Pre-PCV (2014)[b]	68.0 (64.4 - 71.4)	-	-	-
Post-PCV (2016-2018)	64.2 (61.5 - 66.7)	0.944 (0.866 - 1.008)	0.834 (0.782 - 0.894)	<0.0001
Early post-PCV (2016-2017)	62.1 (58.9 - 65.3)	0.914 (0.851 - 0.982)	0.806 (0.750 - 0.869)	<0.0001
Late post-PCV (2018)	68.2 (63.7 - 72.5)	1.004 (0.925 - 1.087)	0.890 (0.820 - 0.966)	0.006
VT pneumococci				
Pre-PCV (2014)	47.6 (43.9 - 51.3)	-	-	-
Post-PCV (2016-2018)	32.3 (29.8 - 34.8)	0.678 (0.609 - 0.757)	0.608 (0.539 - 0.689)	<0.0001
Early post-PCV (2016-2017)	34.1 (31.0 - 37.3)	0.716 (0.636 - 0.806)	0.642 (0.563 - 0.733)	<0.0001
Late post-PCV (2018)	28.7 (24.6 - 33.1)	0.603 (0.510 - 0.708)	0.543 (0.455 - 0.644)	<0.0001
NVT pneumococci				
Pre-PCV (2014)	19.6 (16.7 - 22.6)	-	-	-
Post-PCV (2016-2018)	31.5 (29.1 - 34.1)	1.612 (1.369 - 1.914)	1.233 (1.026 - 1.501)	0.03
Early post-PCV (2016-2017)	27.1 (24.2 - 30.1)	1.384 (1.155 - 1.666)	1.056 (0.865 - 1.302)	0.6
Late post-PCV (2018)	40.4 (35.8 - 45.1)	2.066 (1.718 - 2.492)	1.587 (1.297 - 1.961)	<0.0001
NT pneumococci				
Pre-PCV (2014)	4.9 (3.4 - 6.7)	-	-	-
Post-PCV (2016-2018)	4.1 (3.1 - 5.3)	0.839 (0.557 - 1.280)	0.970 (0.577 - 1.731)	0.9
Early post-PCV (2016-2017)	3.5 (2.4 - 4.9)	0.711 (0.441 - 1.142)	0.819 (0.460 - 1.517)	0.5
Late post-PCV (2018)	5.3 (3.4 - 7.8)	1.091 (0.650 - 1.800)	1.275 (0.693 - 2.4414)	0.4
Pen-NS pneumococci				
Pre-PCV (2014)	57.3 (53.6 - 60.9)	-	-	-
Post-PCV (2016-2018)	50.7 (48.0 - 53.4)	0.885 (0.816 - 0.961)	0.775 (0.710 - 0.850)	<0.0001
Early post-PCV (2016-2017)	51.8 (48.5 - 55.1)	0.904 (0.827 - 0.989)	0.791 (0.719 - 0.872)	<0.0001
Late post-PCV (2018)	48.6 (43.9 - 53.3)	0.848 (0.755 - 0.948)	0.744 (0.660 - 0.838)	<0.0001
MDR pneumococci				
Pre-PCV (2014)	51.0 (47.3 - 54.7)	-	-	-
Post-PCV (2016-2018)	44.3 (41.7 - 47.0)	0.867 (0.792 - 0.954)	0.740 (0.670 - 0.823)	<0.0001
Early post-PCV (2016-2017)	44.1 (40.8 - 47.4)	0.864 (0.780 - 0.958)	0.735 (0.659 - 0.823)	<0.0001
Late post-PCV (2018)	44.8 (40.2 - 49.5)	0.878 (0.773 - 0.993)	0.751 (0.658 - 0.856)	<0.0001

[a] Adjusting for presence of upper respiratory tract infection symptoms, co-habitation with a child <5 years, definite recent antibiotic use, enrolment season (January vs August).

[b] Pre-PCV data consists of two colonisation surveys from January and August 2014.

CI: confidence interval; VT: vaccine type; NVT: non-vaccine type; NT: non-typeable; NS: non-susceptible; MDR: Multi-drug resistant.

Table 4. Observed estimates of PCV13 effectiveness based on pre- and post-PCV invasive pneumococcal disease (IPD) data in hospitalised children aged <5 years, 1st January 2012 to 31st December 2018

	IRR (95% CI)	Change in disease rate, % (95% CI)
All IPD		
Post-PCV (2016-2018)	0.621 (0.364 - 1.029)	-37.9 (-63.6 to +2.9)
Early (2016-2017)	0.649 (0.354 - 1.131)	-35.1 (-64.6 to +13.1)
Late (2018)	0.556 (0.212 - 1.211)	-44.4 (-78.8 to +21.1)
VT IPD		
Post-PCV (2016-2018)	0.577 (0.327 - 0.985)	-42.3 (-67.3 to +1.5)
Early (2016-2017)	0.655 (0.350 - 1.163)	-34.5 (-64.9 to +16.3)
Late (2018)	0.399 (0.120 - 0.992)	-60.1 (-88.0 to +0.8)
NVT IPD		
Post-PCV (2016-2018)	1.185 (0.219 - 6.404)	+18.5 (-78.1 to +540.4)
Early (2016-2017)	0.568 (0.028 - 4.435)	-43.2 (-97.2 to +343.5)
Late (2018)	2.596 (0.342 - 15.666)	+159.6 (-65.8 to +1,466.6)

IRR: Incidence rate ratio; VT: vaccine type; NVT: non-vaccine type.

Figure legends

Figure 1. Pneumococcal colonisation stratified by age category, pneumococcal serotype category, and time period

VT; vaccine type; NVT: non-vaccine type; NT: non-typeable. Results for 2014 are the combined data from January and August surveys.

Figure 2. Pneumococcal serotype colonisation, by proportion of total isolates in each time period

Light grey lines show detected serotypes as a proportion of all isolates from that year, with a single serotype highlighted in colour (green = vaccine type; blue = non-vaccine type; red = non-typeable). The vertical black dashed line represents PCV13 introduction.

Figure 3. Observed and modelled IPD incidence rate ratios (IRR), late post-PCV (2018) compared to pre-PCV (2012-2014) time period

VT: vaccine type; NVT: non-vaccine type. For clarity, the upper bound of the confidence interval for the observed NVT IRR has been truncated at 8 (actual value 15.6). The dashed horizontal line indicates an IRR of 1.

Figure 1

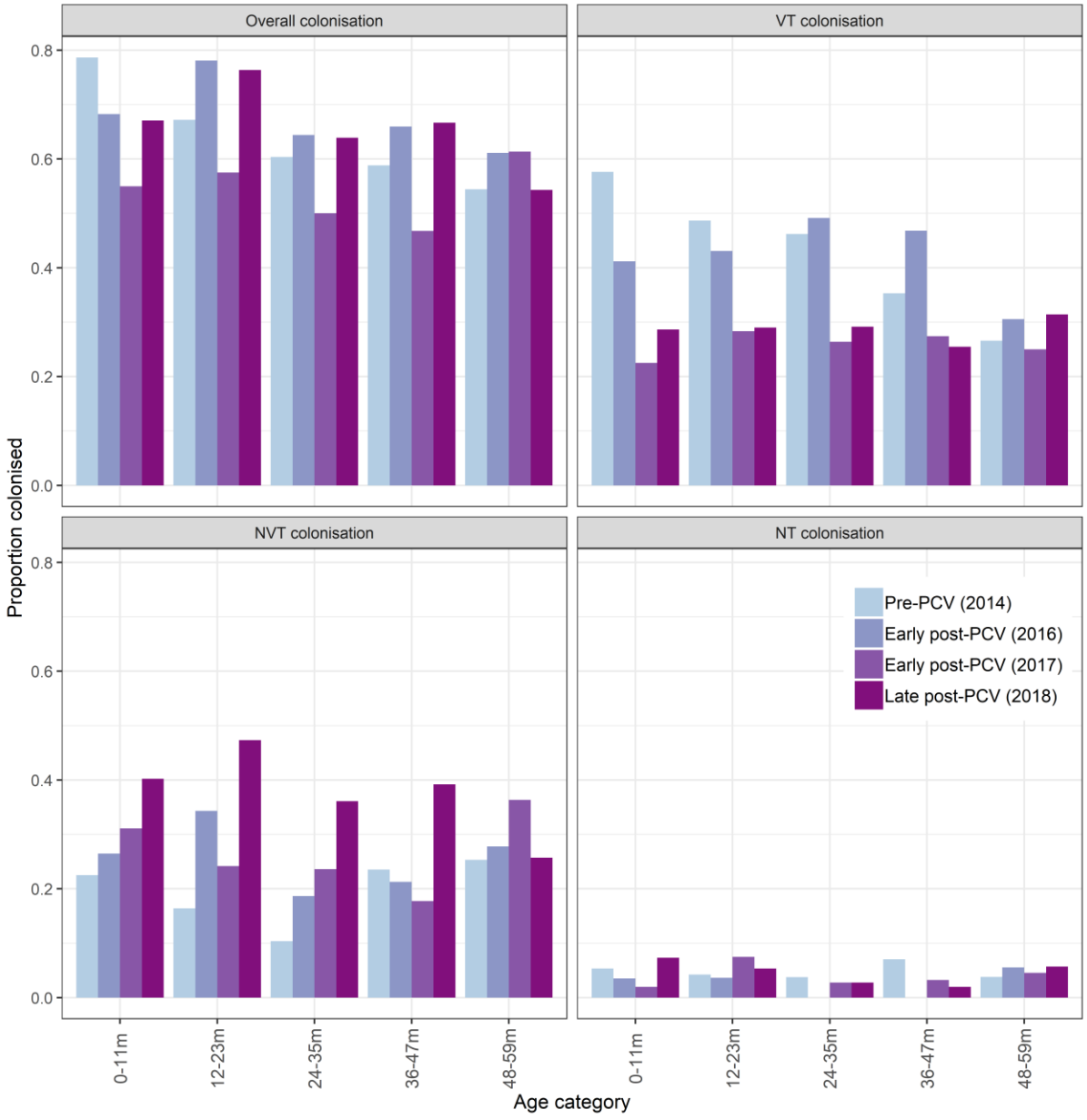

Figure 2

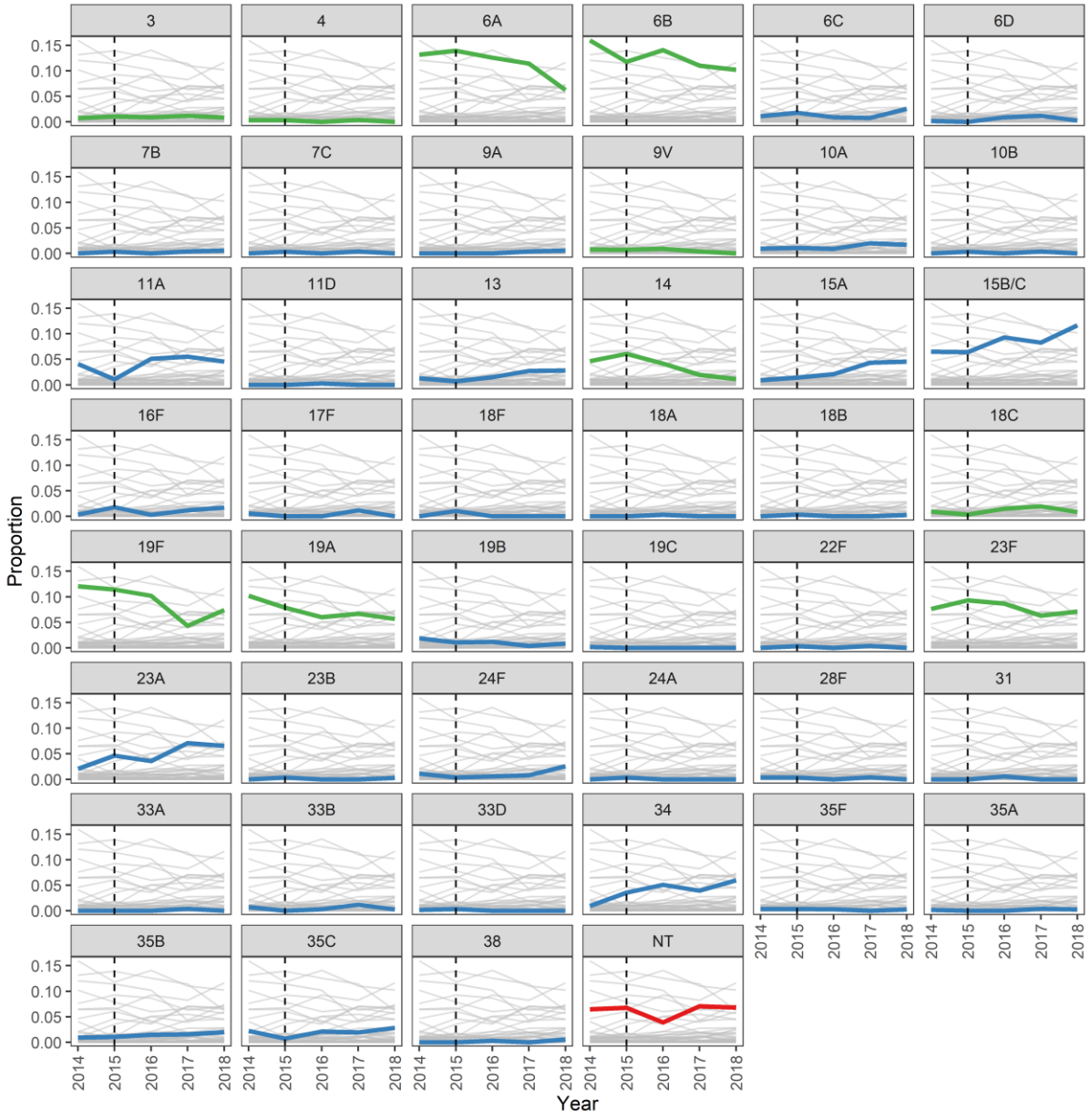

Figure 3