Impact of conjugate pneumococcal vaccine on nasopharyngeal *S.pneumoniae* serotypes and antibiotic susceptibility over 7 years

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Introduction

- *Streptococcus pneumoniae* (pneumococcus, *S. pneumoniae*) is a major childhood pathogen implicated in mucosal infections and invasive disease (IPD)
- Colonisation of the nasopharynx (NP) by *S. pneumoniae* is a key event prior to development of disease[1]
- Children <2yrs have high rates of NP colonisation (10-70%); higher rates in disadvantaged populations
- South Auckland is an area with a large Maori and Pacific population and areas of socioeconomic deprivation. Children from this area have high rates of IPD[2]
- NZ introduced the 7-valent pneumococcal conjugate vaccine (PCV7) to the national immunisation schedule, switched to PCV10 in 2011 and PCV13 in 2014.
- Internationally, introduction of PCV has led to a decline in IPD and reduction of NP carriage of vaccine serotypes. Alteration in antimicrobial resistance of pneumococcus is also seen in both NP and invasive *S. pneumoniae* isolates following PCV[3]
- We aimed to document the changing NP pneumococcal serotypes and antimicrobial resistance with our changing PCV schedule in an area of disproportionately high IPD.

Methods

- Nasopharyngeal aspirates (NPA) from children aged ≤2 years presenting to Kidz First with acute respiratory infection (ARI) between Aug 2007 - Aug 2008 (**pre-PCV7**); between Aug 2009 - Aug 2010 (**post-PCV7**); and Aug to Nov 2014 (**post-PCV10**) were collected
- NPA samples were either immediately cultured[4] or stored at -70°C. NPA were cultured for *S. pneumoniae* on both colistin, nalidixic acid agar and horse blood agar. Colonial variants were detected visually in only 4 instances and isolated as separate pure growths for susceptibility and serotyping. This demonstrated 2 distinct serotypes within 1 sample (co-colonising serotypes)
- *S. pneumoniae* susceptibility testing was done by Kirby-Bauer disc diffusion method and serotyping by Quellung reaction at the national reference laboratory (Institute of Environmental Science and Research)

Definitions: *Clinical Laboratory Standards Institute oral penicillin treatment criteria used*
Penicillin intermediate (PEN-I) = MIC 0.12-1µg/mL; Penicillin resistance (PEN-R) = MIC≥2µg/mL;
Penicillin non susceptibility (PEN-NS) = MIC≥0.12µg/mL (PEN-I and PEN-R)
Ceftriaxone intermediate (CEFT-I) = MIC 1µg/mL; Ceftriaxone resistance (CEFT-R) = MIC≥2µg/mL;
Ceftriaxone non susceptibility (CEFT-NS) = MIC≥1µg/mL (CEFT-I and CEFT-R).

Discussion

- Isolation of *S. pneumoniae* from the NP of young children provides a "snapshot" into patterns of common circulating serotypes and antibiotic resistance. PCV give mucosal immunity against vaccine serotypes but colonisation rates are maintained by serotype replacement
- Prior to PCV7 Pen NS and Ceft-NS rates were significantly higher amongst NP *S.pneumoniae* when compared with isolates from IPD national surveillance of IPD (Pen-NS 22% amongst IPD isolates for children aged <2 years in 2008)[5]
- Significantly decreased Pen-R, Pen- NS and multidrug resistance was seen following implementation of PCV. This is in the face of rising community antimicrobial consumption reported in NZ over the last ten years[6,7]
- Pre-PCV7 antibiotic resistance was predominantly related to high carriage of serotypes 19F and other PCV7 serotypes. Currently resistance observed with serotype 19A reflects international and national IPD trends.
- Although emergent serotype 19A is covered by recently introduced PCV13, serotypes 15 subtypes may be emergent and future vaccine serotype candidate[8]

Limitations

- Small numbers in post-PCV10 cohort as this collection is ongoing
- Observed carriage rates slightly declined over our 3 cohort time periods (30% to24%). Overall carriage rates are low compared with the only other NZ data which showed *S. pneumoniae* carriage in children with established ear disease aged <3 years was 43%; and 29% amongst healthy controls[9]
- Our lower carriage rates may be due to storage of NPA (pre and post PCV7) or younger age in later cohort (post PCV10)

Results

Nasopharyngeal carriage rates

Over the 3 time periods proportions of NPA which isolated *S. pneumoniae* were

Pre PCV7 218/732 (30%)

Post-PCV7 233/927 (25%)

Post-PCV10 50/206 (24%)

Table 1: Age and Immunisation status of cohorts with nasopharyngeal samples cultured for *S.pneumonaie*

NPA cultured for *S. pneumoniae* from children aged <2 with respiratory illness	Age < 6 months	6 - <12 months	12 - < 24 months
Pre PCV7 (n =732) Post PCV7 (n =927)	50%	26%	24%
Immunisation status at year end 2010[1]	Fully immunised by 6 months = 65%	Fully immunised by 12 months = 89%	Fully immunised by 24 months = 87%
Post PCV10 (n= 206)	65%	22%	13%
Immunisation status at year end 2014[1]	Fully immunised by 6 months= 77%	Fully immunised by 12 months = 95%	Fully immunised by 24 months = 96%

[1]Immunisation coverage data by quarter and DHB accessed at http://www.health.govt.nz/our-work/preventative-health-wellness/immunisation/immunisation-coverage/national-and-dhb-immunisation-data

The post-PCV10 cohort was younger and had more complete vaccination status compared with the pre-PCV10 cohorts.

Serotype

- Elimination of PCV7 serotypes from NP is seen over the 3 time periods. Increased 19A carriage along with persisting non-vaccine serotypes 35 nontypable/ nontypable and increasing 15 and 11A serotypes were seen post-PCV10 (Figure 1 and Figure 2).

Antibiotic susceptibility

- PEN-NS was found in 94/209 (45%) of isolates pre-PCV7; declined to 58/191 (30%) after PCV7 introduction and 10/50 (20%) in post PCV10 era (Figure 3)
- CEFT-NS was found in 76/209 (36%)of isolates pre-PCV7; declined to 19/191 (10%) post-PCV7 and 4/50 (8%) post-PCV10 (Figure 4)
- Overall a decrease in cotrimoxazole and tetracycline resistance between study periods was observed with erythromycin and clindamycin resistance remaining the same

Multi-drug resistance (MDR)

- MDR: defined as resistance to 3 antibiotics in addition to PEN-R (MIC >2).

Pre PCV7 2007-08: 23/209 (11%) MDR

Post PCV7 2009-10: 2/191 (1%) MDR

Post PCV10 2014: 0/50 MDR

Serotypes and antibiotic resistance

- Pre- PCV7, serotypes 19F, 6B, 14, 9V, 23F accounted for vast majority of PEN-R (plus non-typable serotypes).
- Along with non-typable serotypes these serotypes continued to be associated with PEN-R post PCV7 (9V, 19F and to a lesser extent 6B, 14, 23F)
- In 2014, post PCV10, PEN-NS isolates were either nontypable or 19A with 6B and 15B representing one each of non-susceptible isolates. PEN-NS plus resistance in >3 other antibiotics were all serotype 19A (5/10 isolates)

Table 2: Antimicrobial resistance among nasopharyngeal *S. pneumoniae* pre and post conjugate vaccines from children aged<2years, South Auckland

	Penicillin		Cefotaxime		Erythromycin		Cotrimoxazole		Tetracycline		Clindamycin (constitutive)	
	R	NS	R	NS	R	NS	R	NS	R	NS	R	NS
PrePCV7 2007-08 n = 209	56 (27%)	94 (45%)	11 (5%)	76 (36%)	31 (15%)	35 (17%)	95 (45%)	95 (45%)	43 (21%)	48 (23%)	21 (10%)	22 (10%)
Post PCV7 2009-10 n = 191	2 (1%)	58 (30%)	8 (4%)	19 (10%)	24 (12%)	25 (13%)	62 (33%)	65 (34%)	26 (14%)	29 (15%)	17 (9%)	18 (9%)
Post PCV10 2014 n=50	0	10 (20%)	1 (2%)	4 (8%)	8 (16%)	8 (16%)	5 (10%)	6 (12%)	7 (14%)	7 (14%)	7 (14%)	7 (14%)
IPD (all ages) 2013 n=454*	27 (6%)	73 (16%)	2 0.4%	17 (4%)	26 (6%)	26 (6%)	98 (22%)	111 (24%)	34 (7%)	34 (7%)	16 (4%)	16 (4%)
IPD <2 years 2013 n=23 *	1 (4%)	4 (17%)	0 (-)	1 (4%)	3 (13%)	3 (13%)	4 (17%)	4 (17%)	4 (17%)	4 (17%)	2 (9%)	2 (9%)

IPD data provided by ESR report and on personal communication with Helen Heffernan

Figure 1: Nasopharyngeal S. pneumoniae serotypes pre and post conjugate vaccines from children admitted with respiratory illness, South Auckland

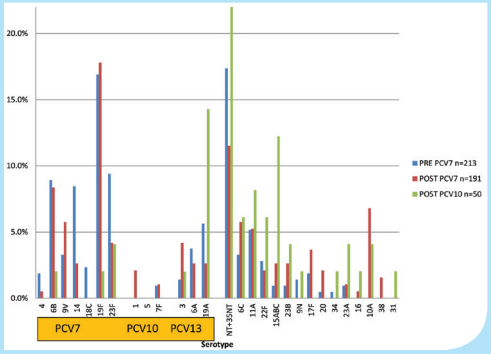


Figure 2: Figure 2: Proportion of nasopharyngeal *S.pneumoniae* serotypes covered by conjugate vaccines

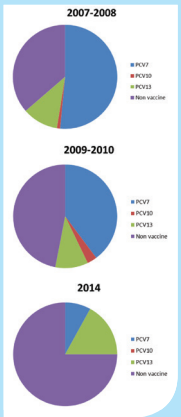


Figure 3: Penicillin non-susceptibility in nasopharyngeal *S. pneumoniae* from children aged < 2 years in eras of pre and post conjugate vaccine

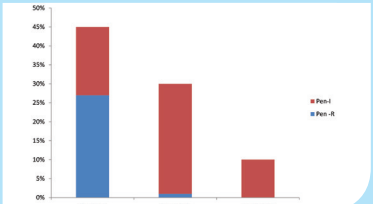
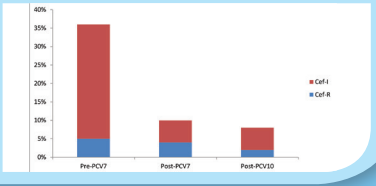


Figure 4: Ceftriaxone non-susceptibility in nasopharyngeal *S. pneumoniae* from children aged < 2 years in eras pre and post conjugate vaccines



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