Pneumococcal epidemiology in the conjugate vaccine era - can non-vaccine serotype replacement in carriage predict disease serotypes?

Amanda J. Leach, Peter S. Morris, Gabrielle McCallum, Cate Wilson, Liz Stubbs, Jemima Beissbarth, Susan Jacups, Kim M. Hare, Heidi C. Smith-Vaughan.

Ear & Oral Health Program
Child Health Division
Menzies School of Heath Research.
Carriage studies in the US

Post-PCV7 Changes in Colonizing Pneumococcal Serotypes in 16 Massachusetts Communities, 2001 and 2004

Susan S. Huang, MD, MPH‡; Richard Platt, MD*‡; Sheryl L. Rifas-Shiman, MPH‡; Stephen I. Pelton, MD§; Donald Goldman, MD¶; and Jonathan A. Finkelstein, MD, MPH¶†#

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Carriage (%) by serotype in 2004


* Statistically significant change
IPD in Alaska Native Children < 2 yrs old, by year

Singleton et al. JAMA 2007. 297(16):1784-1792
Serotype 19A colonization among colonized persons in 8 rural Alaska villages

Singleton et al. JAMA 2007. 297(16):1784-1792
Serotype-specific epidemics do occur but should be separately reported in interpretations of replacement.

Figure 1. Cases of invasive pneumococcal disease among patients presenting to St. Paul’s Hospital (Vancouver, Canada), by week of presentation, 1 January 2006–31 July 2007.
“No replacement invasive pneumococcal disease 11 years after introduction of PCV in a population at high risk for IPD: the Navajo experience.”

Weatherholtz, Millar, Moulton, Perilla, Reid, Parkinson, Santosham, O’Brien.
Navajo IPD - at the sero-category level (7PCV vs non-7PCV)

“No evidence of non-7PCV replacement”

Remove serotype 5 outbreak

Weatherholtz et al. ISPPD6 2008
Navajo IPD - at the sero-category level (7PCV vs non-7PCV)

Weatherholtz et al. ISPPD6 2008
IPD in Indigenous people in north Queensland

Jeffrey N Hanna, Jan L Humphreys and Denise M Murphy
MJA 189(1):43-46
2008
Cases of IPD in indigenous children < 5 years in north QLD, 1999-2007, by sero-category

1999-2001 'epidemic' of serotype 1 removed

No evidence of non-7PCV replacement

Hanna et al. MJA 189(1):43-46
Cases of IPD in indigenous children < 5 years in north QLD, 1999-2007, by sero-category

Hanna et al. MJA 189(1):43-46

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Replacement? non-7PCV types in Indigenous children < 5 years in north QLD, 1999-2007

Hanna et al. MJA 189(1):43-46
Rates of IPD due to serotypes 19A, 6A and 7F in Indigenous and non-Indigenous children aged less than five years, 2002 to 2006

Roche et al. CDI 32: 18-30. 2008
Western Australia

Impact of the seven-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in the Western Australian Aboriginal Population.

Willis et al. IIRW, Darwin 2007
IPD in Western Australian Aboriginal children <5 years, by 7PCV or non-7PCV

Incidence rate/100,000

Year


VT
non-7PCV

19A(3), 6A(1), 10F(2), 1, 10A, 13

Willis et al. IIRW, Darwin 2007
IPD in Western Australian adults 30-<50 years, by 7PCV or non-7PCV

Willis et al. IIRW, Darwin 2007
Northern Territory

IPD
Carriage
OM

Krause, Hall et al. 2008
Serotypes and penicillin resistance in NT Indigenous children <5 yrs (cases) – ~6 year comparisons

Pre 7v vaccine period
Mid 1995-2000

Post 7v vaccine period
2002-Mid 2007

NVT

23VT(minus 7V)

7VT

Striped = penicillin reduced susceptibility

Types 1 & 5 not present post-7PCV but not in the vaccine!!

Krause, Hall et al. 2008
Is there replacement IPD in the NT?

All IPD in Indigenous Children <5yrs age, by year

PreV (1994-2000) rates
- 7VT = 184/100,000
- non-7VT = 112/100,000

PostV (2002-2007*) rates
- 7VT = 26/100,000
- non-7VT = 129/100,000

Vaccine introduction

Rate per 100,000

Years

The nasopharynx

....the place to be
..if you’re a pneumococcus
How to predict change that’s important

1, 5…

IPD - Blood, CSF, other normally sterile site

Nasopharynx

Otitis Media – tympanocentesis or TM perforation

4, 6B, 9V, 14, 18C, 19F, 23F

Pneumonia - without bacteraemia
Figure 2: Predominant Spn serotypes isolated from 5 to 16 year olds (n=83)

Figure 3: Predominant Spn serotypes isolated from 2-5 yr olds (n=53)
Monitoring *Antimicrobial Resistance and Serotypes – MARS* - in 2003 to 2005

**MARS_RAC**: MARS in Remote Aboriginal Communities  
**MARS_CCC**: MARS in urban Child Care Centres

The MARS study aimed to describe pneumococcal serotype epidemiology and resistance profiles, vaccine uptake & recent antibiotic use.
Pneumococcal vaccination schedule - primary and catch-up – Aboriginal children, & non-Aboriginal children in central Australia

<table>
<thead>
<tr>
<th>Age at first dose (mo)</th>
<th>Primary 7PCV schedule</th>
<th>23PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-6</td>
<td>3 doses</td>
<td>1 dose at 18 mo</td>
</tr>
<tr>
<td></td>
<td>2 mo apart</td>
<td></td>
</tr>
<tr>
<td>7-17</td>
<td>2 doses</td>
<td>1 dose at 18mo or 2 mo after last 7PCV</td>
</tr>
<tr>
<td></td>
<td>2 mo apart</td>
<td></td>
</tr>
<tr>
<td>18-23</td>
<td>1 dose</td>
<td>1 dose ≥ 2 mo later</td>
</tr>
<tr>
<td>24-59** (Central Australia)</td>
<td>1 dose</td>
<td>1 dose ≥ 2 mo later</td>
</tr>
</tbody>
</table>
Major impacts on pneumococcal carriage

- Antimicrobials
  - Azithromycin
    - STIs
    - Trachoma eradication programs – geographic influence
  - Reduces carriage of pneumococci
    - penicillin susceptible & non-susceptible strains
    - macrolide-susceptible pneumococci
  - Allows mac-non-susceptible strains to proliferate and spread – often unusual (non-7PCV) serotypes e.g. 17F

- Pneumococcal vaccines
  - 7PCV
  - 23PV? – impact on carriage not well studied

- Complex interaction
  - Large studies (numbers of isolates) needed to analyse at serotype level.
Eligibility

• Aboriginal children living in 29 participating remote communities in the NT and Central Australia
• Age birth to 6 years
• Parent or caregiver written consent for
  – nasal swabs
  – access to medical records and NT childhood immunisation register
  • Recent antibiotic use (within 5 weeks of swab)
  • Vaccination status
Nasal swabs or nose blowing [see JClinMicro 2008]
One pneumococcal colony selected plus one additional colony if morphologically distinct.
  - Serotype
  - Antimicrobial susceptibility
    • Disc Diffusion (CDS)
      - Etest if CDS annular radius < 6mm
      - Penicillin MIC ≥ 0.12 µg/mL
      - Azithromycin MIC ≥ 2 or ≥ 32 µg/mL
MARS_RAC: MARS in Remote Aboriginal Communities. - results - recruitment

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number communities participating</td>
<td>29</td>
<td>17</td>
</tr>
<tr>
<td>Number children swabbed</td>
<td>902</td>
<td>818</td>
</tr>
<tr>
<td>Mean age</td>
<td>25 months</td>
<td>35 months</td>
</tr>
</tbody>
</table>
### MARS_RAC: MARS in Remote Aboriginal Communities. - results – vaccination status & pneumococcal carriage

<table>
<thead>
<tr>
<th>Children (%)</th>
<th>2003</th>
<th>2005</th>
<th>Risk Difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated (&gt;=1 dose)</td>
<td>87%</td>
<td>96%</td>
<td>9% [7,12]</td>
<td>0.0000</td>
</tr>
<tr>
<td>Vaccinated (primary)</td>
<td>76%</td>
<td>84%</td>
<td>9% [5,12]</td>
<td>0.0000</td>
</tr>
<tr>
<td>Vaccinated (primary+23v)</td>
<td>35%</td>
<td>62%</td>
<td>27% [22,31]</td>
<td>0.0000</td>
</tr>
<tr>
<td>Spn (% children)</td>
<td>82%</td>
<td>76%</td>
<td>-6% [-10,-2]</td>
<td>0.002</td>
</tr>
<tr>
<td>7PCV-type</td>
<td>11%</td>
<td>8%</td>
<td>-4% [-6,-0.1]</td>
<td>0.0105</td>
</tr>
<tr>
<td>23PPV-type</td>
<td>42%</td>
<td>34%</td>
<td>-9% [-13,-4]</td>
<td>0.0003</td>
</tr>
<tr>
<td>23PPV-type, non-7PCV</td>
<td>32%</td>
<td>27%</td>
<td>-5% [-10,-1]</td>
<td>0.0161</td>
</tr>
<tr>
<td>19A</td>
<td>13%</td>
<td>9%</td>
<td>-4% [-7,-1]</td>
<td>0.0150</td>
</tr>
<tr>
<td>Non-23PPV</td>
<td>57%</td>
<td>67%</td>
<td>10% [5,14]</td>
<td>0.0001</td>
</tr>
<tr>
<td>6A</td>
<td>8%</td>
<td>7%</td>
<td>-2% [-4,1]</td>
<td>0.02</td>
</tr>
<tr>
<td>16F</td>
<td>12%</td>
<td>10%</td>
<td>-2% [-5,1]</td>
<td>0.1343</td>
</tr>
</tbody>
</table>
By study_year

Graphs by STUDY_YEAR

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By Region

1. Central Australia n=223
2. Darwin Rural n=696
3. East Arnhem n=538
4. Katherine West n=263

Graphs by REGION

Correct!
By community

Graphs by COMMUNITY

N=95
N=197
N=22
N=4
N=79
<table>
<thead>
<tr>
<th>Children (%)</th>
<th>2003</th>
<th>2005</th>
<th>Risk Difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Vaccinated (primary+23v)</td>
<td>35%</td>
<td>62%</td>
<td>27% [22,31]</td>
<td>0.0000</td>
</tr>
<tr>
<td>Carriage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23PPV-type (non-7PCV) (16 serotypes)</td>
<td>32%</td>
<td>27%</td>
<td>-5% [-10,-1]</td>
<td>0.0161</td>
</tr>
<tr>
<td>Non-23PPV</td>
<td>57%</td>
<td>67%</td>
<td>10% [5,14]</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Does 23PPV reduce carriage of 23PPV types not in 7PCV? – at population level, maybe -5%
Does replacement with non-23PPV types occur? – at population level, maybe +10%
No significant difference in carriage of 23PPV types between 23PPV vaccinated & non-vaccinated

<table>
<thead>
<tr>
<th>Carriage</th>
<th>% children &gt; 18 months of age (%)</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>23PPV (non-7PCV) (16 serotypes)</td>
<td>30%</td>
<td>26%</td>
</tr>
</tbody>
</table>

Leach et al. BMC Infectious Diseases accepted
Proportion of children (mean 2.5 yrs) with nasopharyngeal carriage of pneumococcal serotypes (n=1500), by year.

- 7PCV serotypes: -4%
- 23PPV serotypes not in 7PCV: -5%
- Non-23PPV serotypes: +10%

6C > 6A
Proportion of children with nasopharyngeal carriage of pneumococcal serotypes and penicillin or azithromycin non-susceptibility.

7PCV serotypes  | 23PPV serotypes not in 7PCV  | Non-23PPV serotypes

Serotype by category and order by prevalence in 2003

MacR  | PenR  | Sensitive
Pneumococcal serotypes in ear discharge, by vaccine group: PCV-vaccinated.

- **7PCV serotypes**
- **23PPV serotypes not in 7PCV**
- **Non-23PPV serotypes**

![Bar chart showing ear discharge distribution](image-url)
WA carriage study

Anke Bergmann
Kim Hare
Jacinta Bowman
Deborah Lehmann
Amanda Leach
### Primary culture

<table>
<thead>
<tr>
<th>Carriage rate N=517</th>
<th>Streptococcus pneumoniae</th>
<th>Haemophilus influenzae</th>
<th>Moraxella catarrhalis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children &lt;5years</td>
<td>75%</td>
<td>74%</td>
<td>70%</td>
</tr>
<tr>
<td>Children &gt;5years and adults</td>
<td>35%</td>
<td>25%</td>
<td>25%</td>
</tr>
</tbody>
</table>
Serotype distribution in %

- Age (Categorised) into <5, >5 years

- Percent

- Serotype

- Not types listed

Serotypes

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>&lt;5 years</th>
<th>&gt;= 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>7vPCV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10vPCV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13vPCV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Vaccine %
### Non-capsular *H. influenzae* carriage, 2005

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Indigenous children N=823</th>
<th>Non-Indig (CCC) N=461</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Hi</td>
<td>72%</td>
<td>44%</td>
</tr>
<tr>
<td>Beta-lactamase +ve (%Hi)</td>
<td>7%</td>
<td>13%</td>
</tr>
<tr>
<td>Age &lt; 6mo</td>
<td>82%</td>
<td>0% (n=2)</td>
</tr>
<tr>
<td>Age 6 - 12 mo</td>
<td>70%</td>
<td>65%</td>
</tr>
<tr>
<td>Age 12-18 mo</td>
<td>63%</td>
<td>73%</td>
</tr>
<tr>
<td>Age 18-24</td>
<td>73%</td>
<td>46%</td>
</tr>
</tbody>
</table>
POET – study results: reductions in both NCHi carriage and NCHi OM

-80 -60 -40 -20 0 20 40 60%

Any clinical AOM episode
P<0.001

Vaccine serotype AOM episodes
P<0.001

Non vaccine S.pn AOM episodes
P=0.766

H. influenzae AOM episodes
P=0.03

P-value from Cox regression model

Conclusions

- Carriage is likely to be a useful tool in monitoring pneumococcal epidemiology but large numbers of isolates are needed to provide serotype-specific data over time.

- Possibly only applicable to endemic serotypes.

- NCHi carriage may also be a monitor for NCHi OM.

- Well designed and conducted carriage surveillance can include monitoring other bacterial and viral respiratory pathogens.
ACKNOWLEDGEMENTS

- Families who participated in clinical trials
- Colleagues at Menzies School of Health Research.
- NHMRC, Ch7, CHATA & Wyeth for research funding.