Serotype Replacement in Perspective

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Pneumococcal Disease Endpoints

Invasive infections
- sepsis
- meningitis

Spread to other individuals

Antibiotic resistance

Mucosal infections
- otitis media
- sinusitis
- conjunctivitis
- pneumonia
## Impact of Pneumococcal Conjugate Vaccines Against Pneumococcal Nasopharyngeal Carriage

<table>
<thead>
<tr>
<th>Author</th>
<th>Conjugate</th>
<th>Country</th>
<th>Age at vaccination (m)</th>
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<tbody>
<tr>
<td>Dagan</td>
<td>Pn(_{OMP})(_7)</td>
<td>Israel</td>
<td>12–18</td>
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</tr>
<tr>
<td>Dagan</td>
<td>Pn(_D)(_4), Pn(_T)(_4)</td>
<td>Israel</td>
<td>2, 4, 6</td>
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</tr>
<tr>
<td>Obaro</td>
<td>Pn(_{CRM})(_7)</td>
<td>Gambia</td>
<td>2, 3, 4</td>
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<td>Kristinsson</td>
<td>Pn(_D)(_8), Pn(_T)(_8)</td>
<td>Iceland</td>
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<tr>
<td>Mbelle</td>
<td>Pn(_{CRM})(_9)</td>
<td>S. Africa</td>
<td>1.5, 2.5, 3.5</td>
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<td>Edwards</td>
<td>Pn(_{CRM})(_9)</td>
<td>USA</td>
<td>2, 4, 6, 12</td>
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<td>Dagan</td>
<td>Pn(_D/T)(_11)</td>
<td>Israel</td>
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Evidence for NP replacement after PCV is universal and beyond doubt

How does this relate to replacement disease?

There is increasing evidence that replacement disease occurs mostly in compromised hosts or situations
AOM

IPD – HIV (+) Adults

Contacts

IPD – Elderly
VIRUS
Eustachian tube
Nasopharynx
Middle ear
VIRUS

Eustachian tube

Middle ear

Nasopharynx
Effect of 7-valent PCVs on AOM by Organism

Overall efficacy

\[
\begin{align*}
\text{PCV}_{\text{CRM}} &= 6\% \ ( -4\% \text{ to } 16\%) \\
\text{PCV}_{\text{OMP}} &= -1\% \ (-12 \text{ to } 10\%)
\end{align*}
\]

Kilpi et al *Clin Infect Dis* 37:1155-64, 2003
Otitis Media: Efficacy of Prevenar™ in Preventing Ventilation Tube Insertion

<table>
<thead>
<tr>
<th>Country</th>
<th>Rate</th>
<th>Range</th>
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<tbody>
<tr>
<td>US</td>
<td>20.1%</td>
<td>(1.5-35.2)</td>
</tr>
<tr>
<td>Finland</td>
<td>39%</td>
<td>(4-61)</td>
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</table>


Rates of Ambulatory Visits and Antibiotic Prescriptions for AOM and non-AOM ARIs, 1997-2004

Overall decrease 42.7% (95% CI 42.7 – 43.1)

Replacement Disease in Children <5 Yrs

Children <5 yrs

- PCV7 serotypes
- Nonvaccine serotypes

Cases/100,000 population

Baseline
PCV7 introduced
Year

1998 1999 2000 2001 2002 2003 2004

Effect in Target Age Group IPD Rates in Children <5 Years, ABCs, 1998-2005

Slide Courtesy Cindy Whitney, CDC
Changes of Admissions for All Cause Pneumonia by December 2004 Compared to Expected Rates (Pre-Vaccination Rates) in the US

Decline 39%
(95% CI 22 to 52)

Changes in Rates of Hospitalizations and Ambulatory Visits for All-Cause Pneumonias among Children <2 Years: 2004 vs 1997-9

This retrospective, population-based study was conducted to estimate the effect of PCV7 on rates of pneumonia-related health care utilization and costs in children < 2 years.

Data were derived from approximately 40 large employers each year, from 1997 to 2004.

Error bars indicate 95% confidence intervals. Rates are given for the period of 1997 to 1999 and 2004, respectively.


Tsai et al, Clin Infect Dis 2008 (In press)
Effect of PCVs on Pneumococcal Transmission

Replacement carriage

Replacement in contacts
Replacement Disease in Children <5 Yrs vs Elderly (65+ Yrs)


Tsai et al, *Clin Infect Dis* 2008 (In press)

<table>
<thead>
<tr>
<th>Serotype</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
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<tbody>
<tr>
<td>4</td>
<td>6B</td>
<td>9V</td>
<td>14</td>
</tr>
<tr>
<td>18C</td>
<td>19F</td>
<td>23F</td>
<td>6A</td>
</tr>
<tr>
<td>19A</td>
<td>9N</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>7F</td>
<td>11A</td>
<td>12F</td>
</tr>
<tr>
<td>15B</td>
<td>22F</td>
<td>33F</td>
<td></td>
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</table>

Non-vaccine serotype disease, Adults 18-64 years with vs without HIV/AIDS

Source: 7 ABCs sites, preliminary data slide by Cindy Whitney

Flannery et al, Ann Internal Med, 144:1-9, 2006
Replacement Disease in Children <5 Yrs vs Elderly (65+ Yrs)

Replacement Disease in Children <5 Yrs vs Elderly (≥65 Yrs)

Replacement Disease in Children <5 Yrs vs Elderly (65+ Yrs)

Age-Specific Incidence of 19A IPD, 1998-2005

Relative changes in rates represent results of the $\chi^2$ test comparing rates in 2005 to pre-PCV7 average rates during 1998-1999

Moore et al, JID, (In press)
Proportion of all IPD isolates of Serotype 19A with Intermediate or Full Pen-R and Nonsusceptibility to ≥ 3 Antibiotic Classes in Children <5 years old, Active Bacterial Core Surveillance Sites, July 1999–June 2004

CDC; Hicks et al, IDSA 2005

Pai et al, JID 192:1988–95, 2005
Single Clonal Expansion of *S. pneumoniae* Serotype 19A in Korean Children Before PCV7 Introduction

- All 19A isolates were MDR
- All isolates from 2001 exhibited Sequence Type (ST) 320

A dramatic increase in rates of IPD caused by antibiotic-resistant serotype 19A can occur without vaccination

Choi et al, 45th IDSA abstract #202, 2007
Serotype 19A AOM in Bedouin Children in Southern Israel 1999-2006 (Pre-PCV7 Era)

Dagani et al, 47th ICAAC abstract #1001, 2007
Clonal Distribution of Pn19A Isolated from MEF of Bedouin Children with AOM in Southern Israel, 1998*-2006

Yearly clonal distribution (%)

Year


n=13* n=35 n=26 n=31 n=39 n=34 n=26 n=16 n=13

* Isolates from 1998 were obtained before the initiation of the prospective surveillance.

Dagani et al, 47th ICAAC abstract #1001, 2007
Conclusions

• Evidence for NP replacement after PCV is universal and beyond doubt

• In contrast to the NP situation, there is increasing evidence that replacement disease occurs mostly in compromised hosts or situations
  – AOM
  – Elderly
  – HIV (+) young adults
  – Children with underlying conditions?

• The effect of replacement on overall IPD and pneumonia has been so far small

• The dramatic increase in serotype 19A is universally related to antibiotic use and resistance and is seen also in non-vaccinating countries

• PCV7 is ineffective against serotype 19A, but the extent of its contribution to the expansion of this serotype is unclear