Serotype Replacement in Perspective

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Replacement in carriage

Replacement in disease

- Disease potential (cases for carriage)
- Immunological capability
- Antibiotic pressure

Methodological issues

Secular trends
Replacement in carriage
Pneumococcal Disease Endpoints

Invasive infections
- sepsis
- meningitis
- Bacteremic pneumonia
- Osteomyelitis
- Septic arthritis
- Cellulitis
- Brain abscess
- Pericarditis, endocarditis

Mucosal infections
- otitis media
- sinusitis
- conjunctivitis
- pneumonia

Carriage & spread to other individuals

Antibiotic resistance
## Impact of Pneumococcal Conjugate Vaccines on Pneumococcal Nasopharyngeal Carriage

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<tr>
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</thead>
<tbody>
<tr>
<td>Dagan</td>
<td>Pn$_{OMP}^7$</td>
<td>Israel</td>
<td>12–18</td>
</tr>
<tr>
<td>Dagan</td>
<td>Pn$<em>{D}^4$, Pn$</em>{T}^4$</td>
<td>Israel</td>
<td>2, 4, 6</td>
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<tr>
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<td>1.5, 2.5, 3.5</td>
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**Relationship between Capsule Structure (Carbon per Repeat Unit) and Carriage Prevalence, Children in Massachusetts**

- **PCV7**
- **PCV13**
- **Non-vaccine types**

**Graphs**

- **Prevalence pre-PCV7 (%)**
  - No. of carbons per repeat unit
  - $r = -0.80; p < 0.001$ (excluding type 3)

- **Prevalence post-PCV7 (%)**
  - $r = -0.90; p < 0.05$ (excluding type 3)

**Main Serotypes Before PCV7 Introduction: Relationship to Antibiotic Resistance**

Most global antibiotic resistance is with **“prime league”** serotypes

| 6A, 6B, 9V, 14, 19A, 19F, 23F |

Some important **“2nd league”** players


Some important susceptible serotypes

| 1, 2, 4, 5, 7F, 8, 12F |
% Pnc from NP of Healthy Children that Were VT, Vaccine-Related or Non-VT, By Quarter (2000–2003)

Frequencies of Nasopharyngeal Pneumococcal Carriage in Children and Their Parents Before and 3 Years After PCV7 Program Implementation, the Netherlands

Spijkerman et al, EID, 17:584-591, 2011
Frequency of NP Carriage of Individual Pneumococcal Serotypes in Children at ages 11+24 Months Before and 3 Yrs After PCV7 Implementation, the Netherlands

Pre PCV7
n=640

3 yrs post PCV7
n=659

Replacement in disease

- **Disease potential** *(cases for carriage)*
- **Immunological capability*
- **Antibiotic pressure*
**Pneumococcal Disease Endpoints**

- **Invasive infections**
  - sepsis
  - meningitis
  - Bacteremic pneumonia
  - Osteomyelitis
  - Septic arthritis
  - Cellulitis
  - Brain abscess
  - Pericarditis, endocarditis

- **Mucosal infections**
  - otitis media
  - sinusitis
  - conjunctivitis
  - pneumonia

- **Carriage & spread to other individuals**

- **Antibiotic resistance**

**Otitis media and its complications**

**Pneumonia**

**Infected lung**
# Significant Odds Ratios or Invasive Index Indicating Disease Potential for IPD of Various Commonly Carried Serotypes

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Invasive index</th>
<th>OR</th>
<th>OR</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lagos¹</td>
<td>Hanage²</td>
<td>Shouval³</td>
<td>Brueggemann⁴</td>
</tr>
<tr>
<td>4</td>
<td>5.5</td>
<td>1.7</td>
<td>ND</td>
<td>12.1</td>
</tr>
<tr>
<td>6B</td>
<td>1.2</td>
<td>1.6</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>9V</td>
<td>1.5</td>
<td>1.6</td>
<td>1.7</td>
<td>1.5</td>
</tr>
<tr>
<td>14</td>
<td>4.1</td>
<td>4.1</td>
<td>0.7</td>
<td>8.8</td>
</tr>
<tr>
<td>18C</td>
<td>4.1</td>
<td>3.3</td>
<td>2.3</td>
<td>5.8</td>
</tr>
<tr>
<td>19F</td>
<td>0.6</td>
<td>0.7</td>
<td>1.2</td>
<td>0.6</td>
</tr>
<tr>
<td>23F</td>
<td>0.3</td>
<td>0.6</td>
<td>0.9</td>
<td>0.4</td>
</tr>
<tr>
<td>6A</td>
<td>0.5</td>
<td>0.5</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>11A</td>
<td>ND</td>
<td>0.1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>15 (A, B, C)</td>
<td>ND</td>
<td>0.4</td>
<td>0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>19A</td>
<td>2.6</td>
<td>2.9</td>
<td>1.3</td>
<td>1.1</td>
</tr>
<tr>
<td>33F</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>0.5</td>
</tr>
<tr>
<td>35B</td>
<td>ND</td>
<td>ND</td>
<td>0.4</td>
<td>0.0</td>
</tr>
</tbody>
</table>

ND = no data


<table>
<thead>
<tr>
<th>Serotype group</th>
<th>Comorbidity, no./total (%)</th>
<th>aOR† (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All PCV7-IPD cases‡</td>
<td>44/248 (17.7)</td>
<td>0.24 (0.13–0.45) against PCV7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 extra PCV10 serotypes (1, 5, 7F) §</td>
<td>15/299 (5.0)</td>
<td>0.72 (0.46–1.13) against PCV7</td>
<td>0.15</td>
</tr>
<tr>
<td>3 extra PCV13 serotypes (3, 6A, 19A) §</td>
<td>45/336 (13.4)</td>
<td>3.58 (1.93–6.66) against PCV10‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>11 extra PPV23 serotypes</td>
<td>39/186 (21.0)</td>
<td>1.23 (0.76–1.99) against PCV7</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.02 (3.16–11.5) against PCV10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.68 (1.04–2.71) against PCV13</td>
<td>0.033</td>
</tr>
<tr>
<td>Remaining non-PPV23 serotypes</td>
<td>38/138 (27.5)</td>
<td>1.76 (1.07–2.89) against PCV7</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.57 (4.46–16.5) against PCV10</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td></td>
<td>2.39 (1.46–3.93) against PCV13</td>
<td>0.001</td>
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<tr>
<td></td>
<td></td>
<td>1.42 (0.85–2.40) against PPV23</td>
<td>0.18</td>
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* aOR, adjusted odds ratio; PCV7, 7-valent pneumococcal conjugate vaccine; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPV23, 23-valent polysaccharide vaccine.
† Odds ratio adjusted for age, vaccination status, and time since PCV7 introduction by using a multinomial logistic regression with serotype group as the outcome.
‡ Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F.
§ Comorbidity was lower for each of the 3 extra PCV10 serotypes, 1 (7/129, 5.4%), 5 (1/17, 5.9%), and 7F (7/153, 4.6%), compared with the additional 3 serotypes in PCV13, 3 (13/98, 13.3%), 6A (12/47, 25.5%), and 19A (20/191, 10.5%).
Rates of IPD, by Age, Serotype, Race, and Presence of Indications for PPV23

Rates of IPD, by Age, Serotype, Race, and Presence of Indications for PPV23

Although IPD rates have declined among adults, adults with underlying conditions remain at increased risk of IPD and compared with 2000.
Main Serotypes Before PCV7 Introduction: Relationship to Antibiotic Resistance

Most global antibiotic resistance is with “prime league” serotypes

6A, 6B, 9V, 14, 19A, 19F, 23F

Some important “2nd league” players


Some important susceptible serotypes

1, 2, 4, 5, 7F, 8, 12F
Antibiotics + PCV7
Overall Serotype 19A IPD Rates and Proportion of Disease due to Pen-S, Pen-I and Pen-R in 1999-2008,

Based upon ABC Surveillance Data
After 1999, the surveillance areas were expanded; only the years 2004–2008 reflect the same catchment populations

Beall et al, J Infect Dis, 203:1360–8, 2011
Serotypes in IPD After PCV7 Introduction

USA, 2005 - 2010

Vodzak et al et al, IDSA, Oct 2010, Vancouver

Australia, 2007

Clonal Distribution of Pn19A Isolated from MEF of Bedouin Children with AOM in Southern Israel, 1998*-2006

Yearly clonal distribution (%)

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

Dagan et al, J Infect Dis, 199:776-85, 2009
Methodological issues
Cumulative Weekly Number of Reports of IPD by VT and Non-VT Serotypes All Age in England and Wales Epidemiological Year: July-June (2003 to Date)

* The 7-valent conjugate vaccine was introduced into the childhood immunisation schedule on the 4th September 2006, which corresponds with week 36.

Downloaded Dec 2007

http://www.hpa.org.uk/infections/topics_az/pneumococcal/IPD5WMA.htm
Epidemiology of IPD in the Pre-PCV7 Era: England and Wales, 1996-2006

Number of reported cases

Trotter et al, J Infect, 60:200-8, 2010
Epidemiology of IPD in the Pre-PCV7 Era: England and Wales, 1996-2006


Number of reported cases

PCV7
Epidemiology of IPD in the Pre-PCV7 Era: England and Wales, 1996-2006

Total reported number of IPD cases

Number of reported cases

98/99 99/00 00/01 01/02 02/03 03/04 04/05 05/06 06/07 07/08 09/10

Trotter et al., J Infect, 60:200-8, 2010
Epidemiology of IPD in the Pre-PCV7 Era: England and Wales, 1996-2006

Total reported number of IPD cases

Disease reduced

Number of reported cases

Trotter et al, J Infect, 60:200-8, 2010
**Trends in IPD in England and Wales (2000–10), by Age Group**

Data are adjusted for missing serotype or age and for changes in population denominators

Secular trends
Age Group Related Incidences of IPD Caused by Predominant NVTs in Denmark Before and After Introduction of PCV in October 2007

Age Group Related Incidences of IPD Caused by Predominant NVTs in Denmark Before and After Introduction of PCV in October 2007

The Effect of PCV7 Vaccination on the Prevalence of Specific S. pneumoniae Serotypes, by Age Group

**Absolute Changes in the Rate of Admissions to Hospital for IPD, by Age Group in England and Wales and in the USA**

(A) Rate differences for England and Wales compare data from 2009–10 and 2000–06, and were calculated from Miller and colleagues’ study.³

(B) Rate differences for the USA compare data from 2004 and 1998–99, and were calculated with unpublished data from the Active Bacterial Core surveillance programme.

Admission rates in the USA were estimated with the methods described by Pillishvili and colleagues³ and rate differences were calculated by subtracting age-specific average rates in 1998–99 from age-specific rates in 2004.
Replacement in non-IPD pneumococcal disease was not discussed
Impact of PCVs on Serotype Replacement – WHO Position
(Pneumococcal Vaccines - WHO Position Paper – 2012)

• “A review of available surveillance data from Australia, Canada, England and Wales, South Africa and the USA collected during the period 1998–2009 showed rapid and substantial reductions of IPD caused by PCV-serotypes of the target group for vaccination (children aged <5 years) in all settings, although the magnitude of reductions from the pre-vaccine baseline varied

• Reduction in IPD was evident also in individuals older than the targeted age group for vaccination (reflecting herd protection)

• For IPD caused by non-PCV serotypes, increases were evident among hospitalized cases aged <5 years in some settings and also for some age groups in the non-targeted population

• For IPD caused by any serotype the incidence was reduced among those aged <5 years in all settings whereas for older age groups some settings experienced decreases, some no change, and one setting experienced an increase in some age strata

• Non-vaccine factors may influence recorded rates of serotype-specific disease and thereby confound interpretation of the relationship between PCV introduction and serotype changes…Thus there is a need for caution in interpreting pneumococcal disease surveillance data
Picasso; The kiss; 1969