Prevention of pneumococcal disease in Canadian adults – Old and New

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Objectives

- Review epidemiology of pneumococcal disease in adults
- Discuss impact of current vaccination programs on the incidence of adult disease
- Ask what the benefit of new vaccines might be
### Annual rates of pneumococcal infection, Adults, developed world

<table>
<thead>
<tr>
<th>Disease</th>
<th>Annual Rate</th>
<th>Case fatality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>15 per 10,000</td>
<td>5%</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>1.5 per 10,000</td>
<td>15%</td>
</tr>
<tr>
<td>Meningitis</td>
<td>0.2 per 10,000</td>
<td>25%</td>
</tr>
</tbody>
</table>
### Most common causes of death, Canada, 1995

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Number of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>56,000</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>19,900</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>5,300</td>
</tr>
<tr>
<td>Heart disease</td>
<td>43,000</td>
</tr>
<tr>
<td>Infections</td>
<td>20,000</td>
</tr>
<tr>
<td>Influenza</td>
<td>4500</td>
</tr>
<tr>
<td>S. aureus</td>
<td>1500</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>1500</td>
</tr>
</tbody>
</table>
Age-Specific Incidence of Invasive Pneumococcal Disease, TIBDN, 1995
Introduction of pneumococcal vaccines

Canada

- 1983 – PPV23 licensed
- 1996-9 – PPV23 programs for adults
Pneumococcal vaccination rates
Eligible adults, Canada

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Percent ever vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Canada 2001</td>
</tr>
<tr>
<td>&gt;=65 years of age</td>
<td>42%</td>
</tr>
<tr>
<td>15-64 years of age with chronic condition</td>
<td>15%</td>
</tr>
</tbody>
</table>

Squires SG, CCDR 2001;27(10), Al-Sukhni, Vaccine 2007; NCS, 2008
How effective is pneumococcal vaccine?

- **Against pneumococcal pneumonia**
  - Effective in young healthy adults
  - In at risk adults, not effective, or effect <20% and not detectable

- **Against invasive pneumococcal disease**
  - CONTROVERSIAL
  - 8 meta-analyses; 2 Cochrane reviews
Preventive effect of pneumococcal vaccine in elderly subjects
(Christenson, Eur Resp J 2004;23:363)

- Prospective cohort of 258,754 Finnish adults >65 years of age
- Offered pneumococcal and influenza vaccines, in 1998, flu again in 1999
- Pneumonia, hospitalization, mortality examined 12/1999 to 11/2000
**Preventive effect of pneumococcal vaccine in elderly subjects**  
*(Christenson, *Eur Resp J* 2004;23:363)*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Effect pneumococcal vaccine</th>
<th>Effect both vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admission for pneumonia</td>
<td>0.91 (.82, 1.0)</td>
<td>0.71 (.65, .75)</td>
</tr>
<tr>
<td>Invasive pneumococcal disease</td>
<td>0.27 (.06, 1.14)</td>
<td>0.56 (.3, 1.05)</td>
</tr>
<tr>
<td>In-hospital mortality due to pneumonia</td>
<td>0.92 (.73, 1.19)</td>
<td>0.65 (.54, .78)</td>
</tr>
</tbody>
</table>
02 i) Adults in low income countries
   Riley 1977 2/2713 14/2660
   Subtotal (95% CI) 2713 2660 100.0 0.14 [0.03, 0.61]
   Total events: 2 (Vaccine), 14 (Control)
   Test for heterogeneity: not applicable
   Test for overall effect z=2.60 p=0.009

03 ii) Adults in high income countries with chronic illness
   Alfageme 2006 0/298 0/298 0.0 Not estimable
   Davis 1987 1/50 0/53 21.5 3.24 [0.13, 81.47]
   Klastersky 1986 1/26 1/21 27.8 0.80 [0.05, 13.60]
   Leech 1987 1/92 0/97 21.6 3.20 [0.13, 79.47]
   Simberkoff 1986 1/1145 1/1150 29.0 1.00 [0.06, 16.08]
   Subtotal (95% CI) 1611 1619 100.0 1.56 [0.35, 6.94]
   Total events: 4 (Vaccine), 2 (Control)
   Test for heterogeneity chi-square=0.70 df=3 p=0.87 P =0.0%
   Test for overall effect z=0.58 p=0.6

04 iii) Adults in high income countries
   Austrian 1980b 0/6782 4/6818 5.5 0.11 [0.01, 2.07]
   Gaillat 1985 0/937 1/749 4.6 0.27 [0.01, 6.54]
   Kaufman 1947 8/5750 34/5153 79.6 0.21 [0.10, 0.45]
   Ortvist 1998 1/339 5/352 10.2 0.21 [0.02, 1.77]
   Subtotal (95% CI) 13808 13072 100.0 0.20 [0.10, 0.41]
   Total events: 9 (Vaccine), 44 (Control)
   Test for heterogeneity chi-square=0.20 df=3 p=0.98 P =0.0%
   Test for overall effect z=4.52 p<0.00001
02 Immunocompetent
Dominguez 2005  -1.43 (0.35)  10.3  0.24 [0.12, 0.48]
Jackson 2003  -1.05 (0.46)  6.5  0.35 [0.14, 0.56]
Shapiro 1984  -1.20 (0.60)  3.9  0.30 [0.09, 0.97]
Shapiro 1991  -0.76 (0.04)  64.6  0.47 [0.43, 0.51]
Sims 1988  -1.20 (0.38)  9.2  0.30 [0.14, 0.63]
Vila-Corcoles 2006  -0.51 (0.50)  5.4  0.60 [0.22, 1.61]

Subtotal (95% CI)
Test for heterogeneity chi-square=6.10 df=5 p=0.30 P=18.0%
Test for overall effect z=7.27 p<0.000001

03 Immunocompetent older adults
Dominguez 2005  -1.43 (0.35)  30.3  0.24 [0.12, 0.48]
Jackson 2003  -1.05 (0.46)  18.0  0.35 [0.14, 0.66]
Shapiro 1984  -1.20 (0.60)  10.4  0.30 [0.09, 0.97]
Sims 1988  -1.20 (0.38)  26.5  0.30 [0.14, 0.63]
Vila-Corcoles 2006  -0.51 (0.50)  14.8  0.60 [0.22, 1.61]

Subtotal (95% CI)
Test for heterogeneity chi-square=2.31 df=4 p=0.68 P=0.0%
Test for overall effect z=5.90 p<0.000001

04 Cohort studies
Jackson 2003  -0.58 (0.26)  79.1  0.56 [0.34, 0.93]
Vila-Corcoles 2006  -0.51 (0.50)  20.9  0.60 [0.22, 1.61]

Subtotal (95% CI)
Test for heterogeneity chi-square=0.01 df=1 p=0.90 P=0.0%
Test for overall effect z=2.45 p=0.01

05 Case control studies
Benin 2003  -0.30 (0.28)  23.7  0.74 [0.43, 1.28]
Dominguez 2005  -1.20 (0.27)  25.1  0.30 [0.18, 0.50]
Shapiro 1984  -1.11 (0.48)  12.2  0.33 [0.13, 0.74]
Shapiro 1991  -0.63 (0.13)  39.0  0.53 [0.41, 0.69]

Subtotal (95% CI)
Test for heterogeneity chi-square=6.61 df=3 p=0.09 P=54.6%
Test for overall effect z=3.94 p=0.000008
### PPV23 efficacy against IPD
**Indirect cohort analyses**

<table>
<thead>
<tr>
<th>Location</th>
<th>Vaccine efficacy, eligible adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>US 1978-1992 (1)</td>
<td>57% (45,66)</td>
</tr>
<tr>
<td>Australia 1995-2002 (2)</td>
<td>79% (-14, 96)</td>
</tr>
<tr>
<td>Scotland 2003-4 (3)</td>
<td>51% (-278,94)</td>
</tr>
<tr>
<td>Ontario 1995-2006 (4)</td>
<td>49% (34,60)</td>
</tr>
</tbody>
</table>

## Rates of invasive pneumococcal disease, persons >=65 years of age

<table>
<thead>
<tr>
<th>Pre PPV program</th>
<th>Initial year of PPV program</th>
<th>Average post-PPV, pre PCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIBDN</td>
<td>58</td>
<td>44</td>
</tr>
<tr>
<td>Casper</td>
<td>-</td>
<td>53</td>
</tr>
</tbody>
</table>
Invasive pneumococcal disease, elderly
Metropolitan Toronto, 1995-2007

Rate per 100,000 per year

110
100
90
80
70
60
50
40
30
20
10
0


65-74yrs
>75 yrs

- 65-74yrs
- >75 yrs
But

- How is it possible that PPV prevents invasive pneumococcal disease, but not pneumonia?
- What is the duration of protection?
- Is hyporesponsiveness a clinically significant issue?
## PPV23 efficacy against IPD

**Indirect cohort analysis, TIBDN**

<table>
<thead>
<tr>
<th>Vaccine efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy adults &gt;=65 years</td>
</tr>
<tr>
<td>Immunocompromised patients</td>
</tr>
<tr>
<td>Against lab-confirmed pneumococcal pneumonia</td>
</tr>
</tbody>
</table>

# Duration of Effect

<table>
<thead>
<tr>
<th>Interval since vaccine:</th>
<th>Butler et al.</th>
<th>Liu et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 yrs</td>
<td>51%</td>
<td>52%</td>
</tr>
<tr>
<td>2-4 yrs</td>
<td>54%</td>
<td>47%</td>
</tr>
<tr>
<td>5-8 yrs</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>9+ yrs</td>
<td>80%</td>
<td>46%</td>
</tr>
</tbody>
</table>
Is hyporesponsiveness clinically significant?

- Polysaccharide antigens can induce tolerance
  - Good evidence for meningococcal polysaccharide, some evidence for pneumococcal polysaccharide
- BUT
  - Data not as convincing in adults
  - Some evidence that hyporesponsiveness may be time-limited
  - Likely to be different for different serotypes

Introduction of conjugate pneumococcal vaccines, Canada

- 1983 – PPV23 licensed
- 1996-9 – PPV23 programs for adults
- Dec 2001 – PCV7 licensed
- Sep 2002-Jan 2005 – PCV7 programs
- Dec 2008 - PCV10 licensed
- ?2009 – PCV13 to be licensed
Serotype composition of pneumococcal conjugate vaccines

<table>
<thead>
<tr>
<th>7-valent</th>
<th>10-valent</th>
<th>13-valent</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>6B</td>
<td>6B</td>
<td>6B</td>
</tr>
<tr>
<td>9V</td>
<td>9V</td>
<td>9V</td>
</tr>
<tr>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>18C</td>
<td>18C</td>
<td>18C</td>
</tr>
<tr>
<td>19F</td>
<td>19F</td>
<td>19F</td>
</tr>
<tr>
<td>23F</td>
<td>23F</td>
<td>23F</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>6A</td>
</tr>
<tr>
<td>7F</td>
<td>7F</td>
<td>19A</td>
</tr>
</tbody>
</table>
### Serotype coverage

#### Conjugate vs. polysaccharide vaccines

<table>
<thead>
<tr>
<th>PCV</th>
<th>4</th>
<th>6B</th>
<th>9V</th>
<th>14</th>
<th>18C</th>
<th>19F</th>
<th>23F</th>
<th>1</th>
<th>5</th>
<th>7F</th>
<th>3</th>
<th>19A</th>
<th>6A</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV</td>
<td>4</td>
<td>6B</td>
<td>9V</td>
<td>14</td>
<td>18C</td>
<td>19F</td>
<td>23F</td>
<td>1</td>
<td>5</td>
<td>7F</td>
<td>3</td>
<td>19A</td>
<td></td>
</tr>
</tbody>
</table>

| 2   | 8  | 9N | 10A | 11A | 12F | 15B | 17F | 20  | 22F | 33F |    |    |
So, why not conjugate vaccines for adults?

- PC7 not great coverage in adults
  - 87% of pediatric IPD, but only 62% of adult IPD due to PCV7 serotypes (vs. >90% for PPV)
- PCV7 is more expensive, so perhaps not cost-effectiveness
- Adults are not large children
  - In immunogenicity studies, little difference between antibody response to PPV23 and PCV7 in adults
  - EIA titers are (a bit) higher, but OPA not different
1. Attachment
   - bacteria

2. Engulfment
   - Phagosome

3. Degranulation:
   - fusion of granules to phagosome

4. Respiratory Burst Stimulation of NADPH oxidase

- Phagocyte
- Lysosomes
- Microvilli
Opsonophagocytic antibodies

Without Ab and C’

Pnc are not being engulfed

With Ab and C’

Notice engulfed diplococci
Herd immunity from pediatric PCV7 programs
### Decline in pneumonia admissions after routine childhood immunization with PCV7, USA


<table>
<thead>
<tr>
<th>Age group</th>
<th>Decline in rate of hospital admission for pneumonia (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 years</td>
<td>39% (22,52)</td>
</tr>
<tr>
<td>18-39 years</td>
<td>28% (4, 43)</td>
</tr>
<tr>
<td>40-64 years</td>
<td>19% (-3, 35)</td>
</tr>
<tr>
<td>&gt;=65 years</td>
<td>15% (-2, 30)</td>
</tr>
</tbody>
</table>
Will PCV13 make a difference? – I
PCV13 vs. PPV coverage of adult IPD

Toronto, 2008

Neither: 21%
PPV: 52%
PCV13: 7%
Both: 20%

Calgary, 2007

Neither: 11%
PPV: 22%
PCV13: 3%
Both: 64%
What about pneumococcal pneumonia?

- Now occurs at a rate ~15-20 x higher than IPD, CFR 5% vs. 15% for IPD

- Will PCV13 protect adults against pneumococcal pneumonia?
  - EIA titers are higher……..
Questions - I

- Will the extended spectrum conjugate vaccines deliver?
- Can we really eradicate serotypes included in conjugate vaccines?
  - By pediatric vaccination alone?
  - More rapid effect with catch-up? Adult? four doses?
- Does PCV13 prevent pneumococcal pneumonia in adults?
Questions - II

1. How extensive will serotype replacement be in adults?
   - Will it be with PPV23 serotypes or non-vaccine types?

2. Is hyporesponsiveness with PPV23 a clinically significant issue?
Invasive pneumococcal disease
Adults
TIBDN, 2002-2008

Rate per 100,000 per year

- PCV7 type
- PPV-PCV7 type
- Non-vaccine type
What are the issues for Canadian adults?

- What is the interaction between influenza and pneumococcal pneumonia/invasive pneumococcal disease?