Pneumococcal vaccines

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Challenges in establishing the baseline burden of disease, before implementing a vaccination program
S. pneumoniae disease

Endpoints:

- Mucosal infections (AOM, sinusitis, pneumonia)
- Invasive infections (sepsis, meningitis, bacteremic pneumonia)

**Global mortality rates of pneumococcal disease**

Pneumococcal disease caused around 476,000 (333,000–529,000) deaths in children aged 1–59 months in 2008\(^1\)
61% of all deaths in ten countries from Africa and Asia\(^2\)

**Pneumococcal meningitis**

- Incidence rates of 17/100,000 in 2000
- 103,000 cases with 60,500 deaths
  - CFR 59% (27–80%)
- Most cases and deaths in developing countries
- High proportion (up to 50%) of survivors are left with disability

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Incidence of invasive pneumococcal disease - US (meningitis, bacteremia, sepsis, bacteremic pneumonia)

Robinson et al. JAMA 2001;285:1729
Risk Factors for Pneumococcal Diseases or Complications

- Immunocompetent children
  - Chronic heart disease
  - Chronic lung disease
  - Diabetes mellitus
  - Cerebrospinal fluid leaks
  - Cochlear implant

- Children with functional or anatomic asplenia
  - Sickle cell disease and other hemoglobinopathies
  - Congenital or acquired asplenia, or splenic dysfunction

- Children with immunocompromising conditions
  - HIV infection
  - Chronic renal failure and nephrotic syndrome
  - Diseases associated with treatment with immunosuppressive drugs or radiation therapy; or solid organ transplantation
  - Congenital immunodeficiency

What have we learned with the use of pneumococcal conjugate vaccines...
Changes in overall invasive pneumococcal disease, 1998–2007 (US)

PCV7 introduced

Age group       2007 vs baseline
(years)            (% reduction)
<5                76
5–17              43
18–49             40
50–64             18
≥65               37

Cases/100,000 population

Year


PCV7 introduced

Serotype group
- PCV7 type
- Non-PCV7 type
- 19A

*100% reduction in PCV7 serotypes, 2007 vs baseline

Invasive Pneumococcal Disease Among Adults ≥ 65 Years, 1998/99–2007

- PCV7 introduced

*92% reduction in PCV7 serotypes, 2007 vs baseline

Cases/100,000 population

Serotype group
- PCV7 type
- Non-PCV7 type
- 19A

Year


Herd Immunity: Invasive Pneumococcal Disease in Infants 0 to 90 days, 1997–2004

## US Cases Prevented, 2000-2006

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Estimate</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>Nonbacteremic pneumococcal pneumonia (ICD9 481 with no IPD codes)</th>
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<tbody>
<tr>
<td>&lt;2</td>
<td>8440</td>
<td>8101</td>
<td>8752</td>
<td>3399</td>
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<td>2572</td>
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<tr>
<td>2-4</td>
<td>2025</td>
<td>1766</td>
<td>2244</td>
<td>934</td>
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<td>188</td>
</tr>
<tr>
<td>5-17</td>
<td>1528</td>
<td>1257</td>
<td>1772</td>
<td>3977</td>
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</tr>
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<tr>
<td>18-39</td>
<td>8592</td>
<td>7658</td>
<td>9432</td>
<td>21808</td>
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</tr>
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<td></td>
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<td></td>
<td>26976</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>22169</td>
</tr>
<tr>
<td>65+</td>
<td>20046</td>
<td>16851</td>
<td>23014</td>
<td>99415</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>110428</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>87565</td>
</tr>
<tr>
<td>Total</td>
<td>47899</td>
<td>41060</td>
<td>54218</td>
<td><strong>154147</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>171118</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>135893</td>
</tr>
<tr>
<td>% Adults</td>
<td>75%</td>
<td></td>
<td></td>
<td>95%</td>
</tr>
</tbody>
</table>

Incidence rates of pneumococcal meningitis by PCV7 serotype over time in US

- The absolute increase in non-PCV7 serotype disease in this population was smaller than the decrease in PCV7 ST disease

Hsu et al. N Eng J Med 2009;360:244
Estimate reduction in pneumonia episodes according to vaccine efficacy

Despite the lower efficacy against clinical pneumonia, the number of episodes prevented is 12 times higher than the number of severe bacteremic pneumonia cases prevented.
Observational database studies showed that OM visit rates decreased 19% on average following 7vCRM introduction, with estimates ranging widely (+7% to −48%). Before 7vCRM introduction, OM visit rates were already declining in all but one study.
New pneumococcal conjugate vaccines currently in use

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Components</th>
<th>Carrier Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV-10</td>
<td>4, 6B, 9V, 14, 18C, 19F, 23F</td>
<td>1, 5, 7F</td>
</tr>
<tr>
<td></td>
<td>NTHi protein D</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CRM₁₉₇, Diphtheria carrier protein</td>
<td></td>
</tr>
<tr>
<td>PCV-13</td>
<td>4, 6B, 9V, 14, 18C, 19F, 23F</td>
<td>1, 5, 7F</td>
</tr>
<tr>
<td></td>
<td>3, 6A, 19A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NTHi protein D</td>
<td></td>
</tr>
</tbody>
</table>
## Efficacy of PCV10 against IPD. Finland and LA.

<table>
<thead>
<tr>
<th></th>
<th>Number of episodes</th>
<th>Vaccine effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PHiD-CV group</td>
<td>Control group</td>
</tr>
<tr>
<td><strong>FinIP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine-type IPD: 3+1 schedule</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Vaccine-type IPD: 2+1 schedule</td>
<td>1*</td>
<td>12</td>
</tr>
<tr>
<td>Overall IPD: 3+1 &amp; 2+1 combined</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Overall IPD: catch up children 7-18 mo</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td><strong>COMPAS (LA)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine-type IPD: 3+1 schedule</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Overall IPD: 3+1 schedule</td>
<td>7</td>
<td>21</td>
</tr>
</tbody>
</table>

### Notes
- Palmu et al, Lancet 2013
- Tregnaghi ISAAR 2013
Evaluating the impact of a vaccination program:
Brazil: demographic characteristics

- Population: 190 million, with a 3 million children birth cohort
- *PCV10* was introduced into the Brazilian Immunization Program in a 3+1 schedule for children <2 years of age in mid 2010
- Coverage for the primary three doses schedule of the vaccine among infants was 50% in early 2011 and reached 80–85% in late 2011\(^1,2\)

São Paulo is the most populated State with 42 million inhabitants

Invasive pneumococcal disease cases by serotype before PCV10. SIREVA

Children <2 years, Brazil

2007–2009 (Annual average)

80% of the cases were due to PCV10

- Population-based Surveillance Data
Methods

• We analyzed population-based surveillance data to evaluate trends in the burden of PM before and after the introduction of PCV10
• Changes in the incidence of PM in 2011 and 2012 were assessed against baseline values from 2001–2009, considering 2010 as a transition year
• Isolation of *S. pneumoniae* from cerebrospinal fluid or the clinical diagnosis of meningitis with pneumococcus isolated from the blood (culture or PCR)

Adapted from Liphaus et al. ISPPD 8 Iguacu Falls, Brazil from 11-15 March2012. Abstract
The rates of PM in children aged <2 years declined from an average of 10.2/100,000 persons in the pre-vaccination baseline period to 5.4/100,000 in the post-vaccination period.

Reduction of 47% (p<0.01) in incidence rates of children <2 years.
Cumulative number of cases of pneumococcal meningitis in children <2 years, Brazil 2008–2012

N = 1,220 cases reported in children < 2 years

PCV10 introduced in mid 2010 for children <2 y (3 + 1)

Reduction of ~43% in the number of cases reported
Effect of 10-Valent Pneumococcal Vaccine on Pneumonia among Children, Brazil

Elaine Terezinha Afonso, Ruth Minamisawa, Ana Luiza Bierrenbach, Juan Jose Cortez Escalante, Airlane Pereira Alencar, Carla Magda Domingues, Otaliba Libanio Moreira-Neto, Cristiana Maria Toscano, and Ana Lucia Andrade

Post-vaccine period: ↓ pneumonia hospitalization rates

-40.3%  
P<0.001

-37.6%  
P<0.001

-49.3%  
P<0.001

-23.5%  
P = 0.052

-13.4%  
P = 0.074
- Sentinel Hospital-based Surveillance Data
Hospital-based surveillance in São Paulo (50,000 emergency department consultations and 3,200 admissions/year in children <5 years), including all children <2 years admitted due to pneumococcal invasive disease (2004–2011)

A unique opportunity to assess the impact of the introduction of PCV10 on pneumococcal invasive disease
Average annual number of IPD cases

- Reduction of 95% in the number of annual vaccine-type IPD cases in children < 2 y


N

16
14
12
10
8
6
4
2
0

2004-2009 (Pre-vaccine)

2010-2011 (post-vaccine)

Vaccine-type cases

Non vaccine-type cases

Adapted from Berezin et al. SPPD 8 Iguacu Falls, Brazil on 11–15 March 2012. Abstract
Invasive pneumococcal disease cases by serotype before and after PCV10. São Paulo, Brazil.

Reduction of 80% and 97% in the incidence rates of all IPD and vaccine-type IPD, respectively, in children < 2 years.
No increase in overall non-PCV10 type incidence rates.
- Effectiveness Data
Effectiveness of **PCV10** against invasive pneumococcal disease. Brazil

N = 135 cases of invasive pneumococcal disease (IPD); 66 (49%) meningitis

- **All types IPD**: 71% (48–83)
- **Vaccine-types IPD**: 85% (64–94)

Effectiveness of **PCV10** (≥ one dose)

Domingues C et al. Abstract No 320. ISPPD 2012
Multi-hospital study: early trends for reduction of IPD in children (all ages) after PCV13 introduction

Serotyped IPD isolates (1 July 2007 to 30 June 2011)

All isolates

Isolates by serotype

Early trends indicate 36% reduction in IPD cases among 8 children's hospitals for the 12 months starting 4 months after the introduction of PCV13

19A cases decreased by 45% in the same period

Hospital-based observational study. Children (all ages) with IPD prospectively identified from 8 children's hospitals in the US since 1993. IPD confirmed by a central laboratory. Serotype and antibiotic resistance were identified.

UK: early trend for reduction of IPD in children <2 years after Prevenar13 introduction

Cumulative weekly number of IPD reports in children <2 Years in England and Wales by epidemiological year

PCV7 serotypes

Six additional serotypes in Prevenar 13 but not in PCV7

One year after PCV13 introduced in children <2 years:
- Maintained reduction of PCV7 types IPD
- Decreased number of reported cases of IPD related to 6 additional types included in PCV13 (particularly 19A and 7F types)

Note: The above graph is based on week of isolation, therefore numbers for most recent weeks may not be complete. Numbers of reports of serotyped cases shown in the graph are not adjusted to account for any change that may have occurred over time and between age groups in the proportion of all IPD cases that are serotyped. The 7-valent conjugate vaccine was introduced into the childhood immunization schedule on the 4 September 2006, which corresponds with week 36 above.

Accessed 18th November 2011.
Invasive Pneumococcal Disease (IPD)
Annual Incidence by Serotypes in Children < 2 Years
2003-2011

Presented at the PAHO/WHO Regional Surveillance Meeting on Rotavirus and Bacterial Pneumonia/Meningitis, Nov. 16-17, 2011 Montevideo, Uruguay.
Community Acquired Pneumonia (CAP) Annual Incidence by Age: HP-CHPR

HP-CHPR = Hospital Pediátrico Centro Hospitalario Pereira Rossell

Number of Isolates from IPD in Children per Pneumococcal Season (July Until June of the Following Year)

All serotypes

Start PCV7 vaccination

Start PCV10/PCV13 vaccination

IPD = Invasive Pneumococcal Disease
GNRCS = German National Reference Center for Streptococci

Reduction in IPD from US ABC Surveillance Post PCV13

<table>
<thead>
<tr>
<th>Age, yrs</th>
<th>Jan-Mar</th>
<th>Apr-Jun</th>
<th>Jul-Sep</th>
<th>Oct-Dec</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>2011</td>
<td>% Change</td>
<td>Baseline</td>
</tr>
<tr>
<td>&lt;5</td>
<td>16.5</td>
<td>5.7</td>
<td>-65*</td>
<td>12.8</td>
</tr>
<tr>
<td>5-17</td>
<td>2.1</td>
<td>1.5</td>
<td>-29</td>
<td>1.7</td>
</tr>
<tr>
<td>18-49</td>
<td>5.2</td>
<td>3.7</td>
<td>-29</td>
<td>3.1</td>
</tr>
<tr>
<td>50-64</td>
<td>10.8</td>
<td>11.9</td>
<td>10</td>
<td>7.4</td>
</tr>
<tr>
<td>≥65</td>
<td>19.4</td>
<td>13.7</td>
<td>-29</td>
<td>11.9</td>
</tr>
</tbody>
</table>

*P<0.0025

Moore et al, IDSA oral abstract 1219, Oct 2012
## Year of PCV introduction in Latin-American Countries

<table>
<thead>
<tr>
<th>Año</th>
<th>Antineumocócica conjugada: 26 países y territorios</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>USA</td>
</tr>
</tbody>
</table>
| 2002 / 2003 | CAN 2002  
              | BER 2003                                         |
| 2007    | COR                                               |
| 2008    | MEX, URU, GUY FRA                                 |
| 2009    | PER, BAR, CAYMAN ISL                              |
| 2010    | ARU, BRA, ECU, ELS, PAN, NIC                      |
| 2011    | HON, GUY, CHI, COL, CUR                           |
| 2012    | ARG, BAH, GUT, PAR, TRT                           |
Routine conjugate vaccination for adults?
Efficacy against Invasive Pneumococcal Disease (IPD)

- Double-blind, randomized, placebo-controlled
- Efficacy trial among HIV-Infected Adults in Malawi (N=496)
- All enrolled subjects had recovered from documented IPD
- 2 doses of PCV7 given 4 weeks apart

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vaccine Efficacy (95% CI)</th>
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<tbody>
<tr>
<td>PCV7-serotype IPD</td>
<td>74% (30%, 90%)</td>
</tr>
</tbody>
</table>

## Indications for PCV13 and PPSV23

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Underlying medical condition</th>
<th>PCV13</th>
<th>PPSV23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunocompetent persons</td>
<td>Chronic heart disease†</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Chronic lung disease§</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Cerebrospinal fluid leak</td>
<td></td>
<td>✓</td>
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<tr>
<td></td>
<td>Cochlear implant</td>
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<tr>
<td></td>
<td>Alcoholism</td>
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<tr>
<td></td>
<td>Chronic liver disease, cirrhosis</td>
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<tr>
<td></td>
<td>Cigarette smoking</td>
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<tr>
<td>Persons with functional or anatomic asplenia</td>
<td>Sickle cell disease/other hemoglobinopathy</td>
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<td>✓</td>
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<tr>
<td></td>
<td>Congenital or acquired asplenia</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Immunocompromised persons</td>
<td>Congenital or acquired immunodeficiency§</td>
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<tr>
<td></td>
<td>Human Immunodeficiency virus infection</td>
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<tr>
<td></td>
<td>Chronic renal failure</td>
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<td>Nephrotic syndrome</td>
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<td>Lymphoma</td>
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<td>Hodgkin disease</td>
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<td>Generalized malignancy</td>
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<tr>
<td></td>
<td>Iatrogenic Immunosuppression**</td>
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<tr>
<td></td>
<td>Solid organ transplant</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Multiple myeloma</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

* All adults aged ≥65 years should receive a dose of PPSV23, regardless of previous history of vaccination with pneumococcal vaccine.
† Including congestive heart failure and cardiomyopathies, excluding hypertension.
§ Including chronic obstructive pulmonary disease, emphysema, and asthma.
¶ Includes B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease).
** Diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy.

Advisory Committee on Immunization Practices, MMWR 2012
Future

• 15-valent pneumococcal conjugate vaccine (PCV)
  • Continue to further expand valency of PCVs
• Protein-based vaccines (protection independent of serotype)
  • Addition of pneumococcal proteins to conjugate vaccines
  • Innovative whole-cell killed pneumococci as a vaccine