Vaccine Efficacy: IPD, Pneumonia and Otitis Media

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Dominican Republic, 2008
Pneumococcal Disease
Clinical Syndromes

Mortality
- Pneumonia
- Bacteremia
- Meningitis

Morbidity
- Otitis
- Sinusitis
## WHO 2002 Estimates on Worldwide Vaccine Preventable Deaths

<table>
<thead>
<tr>
<th>Disease</th>
<th>Age &lt; 5 yrs</th>
<th>Age &gt; 5 yrs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poliomyelitis</td>
<td>&lt;100</td>
<td>1,000</td>
<td>1,000</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1,000</td>
<td>599,000</td>
<td>600,000</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>4,000</td>
<td>1,000</td>
<td>5,000</td>
</tr>
<tr>
<td><em>N. meningitides</em></td>
<td>10,000</td>
<td>16,000</td>
<td>26,000</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>15,000</td>
<td>15,000</td>
<td>30,000</td>
</tr>
<tr>
<td>Tetanus</td>
<td>198,000</td>
<td>15,000</td>
<td>213,000</td>
</tr>
<tr>
<td>Pertussis</td>
<td>294,000</td>
<td>1,000</td>
<td>294,000</td>
</tr>
<tr>
<td><em>H. influenzae</em> B</td>
<td>386,000</td>
<td>0</td>
<td>386,000</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>402,000</td>
<td>47,000</td>
<td>449,000</td>
</tr>
<tr>
<td>Measles</td>
<td>480,000</td>
<td>50,000</td>
<td>530,000</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>716,000</td>
<td>896,000</td>
<td>1,612,000</td>
</tr>
</tbody>
</table>
There is a high burden of pediatric IPD in Latin America

### Latin America Incidence of IPD

<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective and active monitoring:</strong></td>
<td></td>
</tr>
<tr>
<td>Argentina$^1$</td>
<td>3-23 months: 206.8/100,000</td>
</tr>
<tr>
<td></td>
<td>6-11 months: 238/100,000</td>
</tr>
<tr>
<td>Chile$^{2,3}$</td>
<td>0-11 months: 80.8/100,000</td>
</tr>
<tr>
<td></td>
<td>6-11 months: 129/100,000</td>
</tr>
<tr>
<td>Chile$^4$</td>
<td>0-59 months: 179/100,000</td>
</tr>
</tbody>
</table>

Prospective epidemiological studies are ongoing in Costa Rica, Colombia, and Brazil

Epidemiology

- Assess preventable pneumococcal disease
- When country-specific data is not available, use data from epidemiologically similar populations to make estimates
- Technical assistance will be available through WHO and its partners to make such estimates

Considering the burden of disease, the herd immunity and safety, the WHO recently recommended the following:

a-) Countries should consider the implementation of *S. pneumoniae* vaccine into their national immunization program, particularly those countries where mortality among children aged < 5 years is >50/1000 life births or where > 50,000 children die annually.

b-) Countries with high incidence of high risk conditions such as HIV.

Countries are encouraged to conduct appropriate surveillance programs, pre and post-inclusion of pneumococcal vaccination into their national programs.

Countries are also encourage to implement a single catch-up those for children aged 12-24 months and to high risk children aged 2-5 years of age.
• **PCV7**
  - Introduction of PCV7 into NIPs is a priority
  - Introduction of PCV7 into NIPs of developing countries is a high priority
  - PCV7 can be easily integrated into routine vaccination schedules
  - PCV7 should be initiated before 6 months of age and as early as 6 weeks
  - Initiate catch-up vaccination up to 5 years of age with the first year of introduction

NIP=National Immunization Program

Sireva II, 2000 – 2005 in Latin America and Caribbean

### Study Objectives
- Analyze the phenotypical characteristics and susceptibility patterns of invasive *S. pneumoniae*, *H. influenzae* and Meningococos isolates in Latin America and the Caribbean.
- Potential vaccine coverage by conjugate vaccines

### Study Cases and Period
- Neumonia, meningitis, sepsis, bacteremia and other invasive diseases.
- January 1, 2000 – December 31, 2005

### Participant regions
- Latin America
- Caribbean

### Sireva II, 2000 – 2005

*S. pneumoniae* in Latin America

#### Number of Isolates
- 17,303 isolates
- 9,963 (57.6%) children < 6 years of age
- 1,683 (9.7%) children between 6 and 14 years of age

#### Isolation sites
- Blood culture: 47.0%
- CSF: 37.1%
- Others: 15.9%

#### Most Common Diagnosis
- Neumonia 5,475 cases (31.6%)
- Meningitis 6,753 (39.0%)
- Sepsis/Bacteremia: 3,783 (21.9%)
- Other Invasive cases: 1,292 (7.5%)

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Sireva II, 2000 – 2005
Most common S. pneumoniae in children < 6 year of age
Latin America

15,953 isolates

PCV7

Non-PCV7

Penicillin Susceptible: 63.3%
Penicillin Intermediate: 21.3%
Penicillin Resistant: 15.4%

Otitis Media: Bacterial Pathogens
## AOM
### Incidence Different Locations

<table>
<thead>
<tr>
<th>Author</th>
<th>Location</th>
<th>Population</th>
<th>Episodes/child/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teele et al. (^a)</td>
<td>Boston</td>
<td>877</td>
<td>1.2</td>
</tr>
<tr>
<td>Fireman et al. (^b)</td>
<td>California</td>
<td>16,152</td>
<td>1.8</td>
</tr>
<tr>
<td>Eskola et al. (^c)</td>
<td>Finland</td>
<td>832</td>
<td>1.2</td>
</tr>
</tbody>
</table>

\(^a\) J Infect Dis 1989;160:83-94  
\(^b\) Pediatr Infect Dis J 2003;22:10-16  
\(^c\) N Engl J Med 2001;344:403-9  

**1.4 episodes / child / year**
Community-Wide Vaccination with the PCV7 Significantly Alters the Microbiology of AOM

Proportion of the various pathogens causing AOM

1992 - 1998
n = 336
- Hi: 41%
- Pnc: 48%
- GAS: 9%
- Mc: 2%

2000 - 2003
n = 83
- Hi: 56%
- Pnc: 31%
- GAS: 11%
- Mc: 2%

Pre-PCV-7 AOM

Post-PCV-7 AOM

Pediatr Infect Dis J 2004;23:829-33

Courtesy Professor Dagan
Otitis Media History and Bacterial Pathogens

- Pneumococcal OM is less likely to resolve spontaneously\(^1\)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Spontaneous Resolution Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>20%</td>
</tr>
<tr>
<td>Nontypable <em>Haemophilus influenzae</em></td>
<td>60%</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>80%</td>
</tr>
</tbody>
</table>

- Pneumococcal OM is more likely to be complicated OM:
  - Spontaneous TM perforation\(^2\)
  - Requirement of PET insertion\(^3\)
  - Serious supportive complications\(^3,4\) (meningitis, brain abscess, mastoiditis)
  - Hearing loss\(^3\)

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\(^1\) Klein JO. *Pediatric Infect Dis J* 1993;12:973-5.
\(^2\) Leibowitz E. Presented at ICAAC 2007
\(^3\) Bluestone C. *Pediatric Infect Dis J* 2000;19:S37-46
Acute Otitis Media: Beta Lactamase +ve *H. influenzae*

S. pneumoniae Serotypes in Costa Rica

- Establish the most common S. pneumoniae serotypes and clones from Costa Rican Children with OM.
- **Samples:** MEF, NP and OP.
- **Antimicrobial susceptibility to:** Penicillin, TMP/SMX, cephalosporins, macrolides and quinolones.

S. pneumoniae Serotypes in Costa Rica

- 110 MEF and 207 NP / OP Samples.
- Median age: 15 months (range: 3 – 47).
- Patients < 24 months: 65 %.

Latin America: Characteristic of Costa Rican Patients with Middle Ear Fluid Serotype 3 Otitis Media

- Mean Age: 27 months (60% > 24 month of age) (< vs. > 24 month; $P = 0.031$)

- Season: Dry > Rainy Season ($P = 0.02$)

- Presence in the NP a risk factor

- Strains: 100% mucoid
  94% Penicillin susceptible (Type 3 vs. others; $P = 0.003$)
Mucoid and Non-Mucoid Middle Ear Fluid S. pneumoniae

Mucoid Serotype 3

Non-Mucoide 19F
Site-Specific Disease Potential of Individual *Streptococcus pneumoniae* Serotypes in Pediatric Invasive Disease, Acute Otitis Media and Acute Conjunctivitis

Dror S. Shouval, MD, David Greenberg, MD, Noga Givon-Lavi, PhD, Nurith Porat, PhD, and Ron Dagan, MD

**Study Period:** 2000 – 2004
**AOM:** 3200 Children
**NP:** 1763

**AOM:** 8th
**OR:** 18.8
Otitis Media
Seasonality in Costa Rica

S. pneumoniae Resistance Pattern

# PCV7 Impact: OM

<table>
<thead>
<tr>
<th>Clinical Parameter</th>
<th>Efficacy</th>
<th></th>
<th>Navajo/ Apache</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Finnish OM and F/U</td>
<td>NCKP and F/U</td>
<td></td>
</tr>
<tr>
<td>All AOM/ OM Episodes</td>
<td>6%</td>
<td>7%</td>
<td>-0.1 to -0.4%</td>
</tr>
<tr>
<td>All pneumococcal AOM</td>
<td>34%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Vaccine Serotype Disease</td>
<td>57%</td>
<td>--</td>
<td>64%</td>
</tr>
<tr>
<td>Recurrent OM</td>
<td>9-26%</td>
<td>16-18%</td>
<td>--</td>
</tr>
<tr>
<td>OM visits</td>
<td>--</td>
<td>8.9%</td>
<td>5.1%</td>
</tr>
</tbody>
</table>

**References:**
**IMPACT OF PCV7 VACCINE IN TYMPANOSTOMY TUBE PLACEMENT IN CHILDREN**

Finnish follow up study: 756 children (403 PCV-7 vaccinated / 353 controls)
Single Visit: 4-5 years old

Real World

Study Period: 4 %

39%
REDUCCION IN TYMPANOSTOMY TUBE PLACEMENT
Pneumococcal Conjugate Vaccines

**PCV7**
- Serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F
- Composition: 2 Tg of each serotype except 6B has 4 Tg
- Cross-reactive: 6A
- Carrier Protein: CRM₁₉₇

**10-valent - GSK**
- Serotypes: 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F
- Composition: 1 Ug of each serotype
- Carrier Protein: Protein D of *H. influenzae* - cell surface lipoprotein
  Tetanus and Diphtheria toxoid

**13-valent - Wyeth**
- Serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F
- Carrier Protein: CRM₁₉₇
**PCV7 Impact in OM / 1997-2004**

- **Objective:** Estimate the population effect of PCV-7 on rates of OM in children < 2 years of age.
- **Methods:** Retrospective database (MarketScan) analysis of a defined population that included an average of > 500,000 person-years of observation in children < 2 years of age.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Period 1997-1999</th>
<th>Period 2004</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOM related visits a</td>
<td>2,173</td>
<td>1,244</td>
<td>42.7% (42.4-43.1)</td>
</tr>
<tr>
<td>Antibiotic prescriptions attributable to AOM a</td>
<td>1,244</td>
<td>722</td>
<td>41.9%</td>
</tr>
<tr>
<td>Direct AOM costs (visits and antibiotics)</td>
<td>$ 1.41 billion</td>
<td>$ 0.95 billion</td>
<td>32.3%</td>
</tr>
</tbody>
</table>

a per 100 person-y

Zhou F Pediatrics 2008;121;253-260

1-) PCV7 introduction
2-) Watch and wait approach
3-) Less Atb for AOM tx
Otitis Media

POET Study vs. Zhou Study

**Poet Study**
- 11 valent + Protein D
- Prospective Clinical Trial
- Low incidence of OM (0.12 episodes/person-year)

**Zhou Study**
- PCV7
- Retrospective database analysis

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Any clinical AOM episode

P-value from Cox regression model

Poet Study

- Any clinical AOM episode 34%

Zhou Study

- Any clinical AOM episode 42.7%

Lancet 2006; 367:740-48

Zhou F Pediatrics 2008;121;253-260
**PCV7 DIRECT impact / 2008**

**Importance of a S. pneumoniae Vaccine**

- Invasive disease.
- Chest-X-ray confirmed pneumonia.
- Otitis Media.
- Ambulatory visits.
- Antimicrobial usage / resistant rates.
- Herd immunity.
## PCV7 evolution in the USA: IPD

<table>
<thead>
<tr>
<th>Clinical Parameter</th>
<th>Efficacy</th>
<th>Post-Introduction Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IPD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCKP:</td>
<td></td>
<td>CDC’s Active Bacterial Core Surveillance 1998-1999 vs 2005 (Children &lt; 5 years of age)</td>
</tr>
<tr>
<td>&gt;18,000 children immunized at 2,4,6 &amp; 12-15m</td>
<td>97.4%</td>
<td>98%</td>
</tr>
<tr>
<td>%Vaccine Serotype IPD</td>
<td>89.1%</td>
<td>77%</td>
</tr>
<tr>
<td>%All Serotype IPD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>--</td>
<td>50% decrease in mortality in children under 2 after 1 year of vaccination</td>
</tr>
</tbody>
</table>

**Increase in non-PCV7 IPD**
- Children < 1 year: 10.8/100,000
- 2005: 19A represented 40% of all IPD in < 5 years old

*PIDJ 2000;19:187-95*
*MMWR 2008;57:144-8*
*Arch Pediatr Adolesc Med. 2005; 159:195-6*
PCV7 Efficacy: CXR + Pneumonia

Pediatr Infect Dis J. 2006 25:779-81
Lancet 2005;365:1139-46
Penicillin-resistant *S. pneumoniae* Post-introduction of PCV7 in the USA

Children < 2 years of age

Indirect Effect - Herd Immunity: Invasive Pneumococcal Disease in Adults

MMWR 2005;54:893-97
Current Situation 8 years Post-Introduction of PCV7

- Increase in the proportion of OM caused by non-typeable *H. influenzae* but NOT in the total number of OM cases or in the appearance of this agent as cause of invasive infections in children.

- Need to improve *S. pneumoniae* vaccine coverage in developing countries (serotypes 1 and 5).

- Emergence of new serotypes in invasive and non-invasive infections.

19 A, 6 A and 3 (among others)
Streptococcus pneumoniae

- Recently there has been an increase in the number of infections caused by serotype 19A in countries that have incorporated Prevenar into national schedules as well as those that have not.

- Globally serotype 19A represents ~5% of all isolates and in the USA represents the most common non-vaccine serotype:
  
  **IPD infections:** 301% increase in children < 5 years of age  
  173% increase in adults > 80 years of age  
  **OM infections:** Reports of multi-drug resistant cases

- Usually serotype 19A is penicillin resistant.

PneumoADIP, GSP Summary Report for SAGE 2007  
*JAMA* 2007;297:1784-92  
*J Infect Dis* 2005;192:1988-95  
Dagan R. ICAAC 2007  
*JAMA* 2007: 1772-8
**6A Streptococcus pneumoniae**

- Poor cross-protection with PCV-7

**Nasopharyngeal colonization**

<table>
<thead>
<tr>
<th></th>
<th>2000-2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>6A</td>
<td>6%</td>
</tr>
<tr>
<td>19A</td>
<td>7%</td>
</tr>
<tr>
<td>23A</td>
<td>8%</td>
</tr>
<tr>
<td>9a</td>
<td>5%</td>
</tr>
<tr>
<td>18</td>
<td>3%</td>
</tr>
</tbody>
</table>

**Herd Immunity**

<table>
<thead>
<tr>
<th>Age, serotype</th>
<th>Total no. cases</th>
<th>No. of cases/100,000 population</th>
<th>Relative risk (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 years</td>
<td>Overall</td>
<td>1219</td>
<td>72</td>
<td>61.7</td>
</tr>
<tr>
<td></td>
<td>PCV7</td>
<td>381</td>
<td>171</td>
<td>71.5</td>
</tr>
<tr>
<td>Nonvaccine</td>
<td>Overall</td>
<td>502</td>
<td>502</td>
<td>27.0</td>
</tr>
<tr>
<td></td>
<td>6A</td>
<td>17</td>
<td>17</td>
<td>71.5</td>
</tr>
<tr>
<td></td>
<td>19A</td>
<td>14</td>
<td>14</td>
<td>71.5</td>
</tr>
<tr>
<td></td>
<td>23A</td>
<td>30</td>
<td>30</td>
<td>71.5</td>
</tr>
<tr>
<td></td>
<td>9A</td>
<td>20</td>
<td>20</td>
<td>71.5</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>71.5</td>
</tr>
</tbody>
</table>

**Pediatric Infections (Protek US study)**

- Low / Unknown protection with PCV-10
- Limitation in number of patients (OM only)
- No immunogenicity data for 6A

**Vaccine-related cross reactive pneumococcal serotypes**

- **Serotype 6A**: 4, 11 (65.7, 139 to 886)
- **Serotype 3N**: 5, 4 (25.5, 23 to 832)
- **Serotype 18A**: 0, 1 (1000, 283 to 1000)
- **Serotype 18B**: 0, 1 (1000, 283 to 1000)
- **Serotype 18F**: 0, 1 (1000, 283 to 1000)
- **Serotype 19A**: 2, 3 (67.4, 2087 to 966)
- **Serotype 23A**: 0, 2 (100.0, 91.8 to 100.0)

### Emerging Serotypes – Trends

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Issue</th>
</tr>
</thead>
</table>
| **Serotype 3**<sup>1-7</sup> | • Statistically increase in complicated pneumonia and empyema  
• Associated with a high invasiveness rate and high mortality  
• Important cause of otitis media “replacement”. |
| **Serotypes 1 and 5** | • Although present in all countries to varying degrees  
  - Usually cause IPD in children > 2 yrs of age  
  - Not associated with antibiotic resistance  
  - Not seen to be increasing in frequency |
| **Serotype 7F**<sup>6</sup> | • Increases in serotype 7F have been documented after the introduction of Prevenar in the US |
| **Others**<sup>9,10</sup> | • Other emerging serotypes include 15, 33F and 35 |

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<sup>1</sup> Clin Infect Dis 2005;41:21-9  
<sup>2</sup> Pediatric Infect Dis J 2006;25:602-7  
<sup>4</sup> J Clin Microbiol 1998;36:3447-54  
<sup>5</sup> Kansenshogaku Zasshi 2007;81:59-66  
<sup>6</sup> Arguedas A. ICAAC 2006  
<sup>7</sup> FEMS Immunol Med Micro 2006;48:179-82  
<sup>8</sup> JAMA 2007;297:1784-92  
<sup>9</sup> Pediatr 2004;113:443-9  
<sup>10</sup> Pediat Infect Dis J 2005;24:17-23
The value of an Extended Pneumococcal Serotype Vaccine / Summary 2008

- Worldwide *S. pneumoniae* continues to be the most important bacterial pathogen in infectious diseases in children.

- PCV7 have proven to be extremely effective in the prevention of invasive and non-invasive vaccine type *S. pneumoniae* infections.

- In the case of otitis media, PCV7 have modify the proportion of MEF pathogens and currently non-typeable *H. influenzae* is the most frequent agent; however, this pathogen rarely produce invasive disease and in 60% of the OM episodes the disease is self limited. Also, *S. pneumoniae* is usually associated with a more severe and complicated disease (-/+/ 40% reduction in PTE).

- There is a need to enhance the potential *S. pneumoniae* serotype coverage to include other serotypes that are more prevalent in developing countries (1 and 5) and the emerging types (19A, 6A and 3, primarily).

- Based on all the above evidence, a *S. pneumoniae* vaccine with extended coverage against emerging serotypes should be preferred.