Epidemiology of *Streptococcus pneumoniae* in the Post-Vaccine Era

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Disclosures
- Received research funding from Wyeth and Pfizer related to pneumococcal work
- Received funding from Roche for research
- Participated in Advisory Boards for: Wyeth, Pfizer, Novartis, Sanofi

History

First isolate by Louis Pasteur in 1881

Originally named "Diplococcus pneumoniae" in 1920 due to its appearance in sputum

Renamed *Streptococcus pneumoniae* in 1974.

Griffiths mouse experiment - 1928

Oswald, Avery and McCarty - 1944

DISEASES

- pneumonia
- bacteremia
- otitis media
- meningitis
- sinusitis
- peritonitis
- arthritis

Transmitted person to person
All-cause pneumonia, which includes pneumococcal pneumonia, is also associated with substantial morbidity and mortality in persons aged ≥65 years.

<table>
<thead>
<tr>
<th>Year</th>
<th>≥65 y</th>
<th>75-94 y</th>
<th>≥85 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>36.4</td>
<td>153.3</td>
<td>730.6</td>
</tr>
<tr>
<td>2000</td>
<td>38.0</td>
<td>156.4</td>
<td>723.9</td>
</tr>
<tr>
<td>2001</td>
<td>36.2</td>
<td>148.1</td>
<td>683.4</td>
</tr>
<tr>
<td>2002</td>
<td>37.2</td>
<td>155.5</td>
<td>687.8</td>
</tr>
<tr>
<td>2003</td>
<td>36.3</td>
<td>147.5</td>
<td>649.1</td>
</tr>
<tr>
<td>2004</td>
<td>34.0</td>
<td>137.0</td>
<td>571.2</td>
</tr>
<tr>
<td>2005</td>
<td>34.8</td>
<td>138.5</td>
<td>574.7</td>
</tr>
</tbody>
</table>


Pneumococcal disease (PD) is caused by the bacterium Streptococcus pneumoniae.

Major Clinical Forms of PD

- **Invasive**
- **Neonatal**
- **Pneumococcal**
- **Acute Otitis Media**
- **Sinusitis**

Serotyping performed by Quellung reaction

Antibodies raised against specific polysaccharide will bind to the capsule. In a positive reaction, microscopically the capsule appears opaque.

Quelling = German word for “swelling”
**Streptococcus pneumoniae**

Capsule major virulence factor

PCV7: 4, 6B, 9V, 14, 18C, 19F, 23F

PCV13: 4, 6B, 9V, 14, 18C, 19F, 23F, 3, 6A, 19A

92 different capsule types (serotypes).

Capsule Main Virulence Factor

Unencapsulated – no disease.

Polysaccharide coating the surface of the pneumococcus

Pneumococcal capsular polysaccharide prevents direct phagocytic uptake of the bacterium

Status of introduction of pneumococcal vaccines into national immunization schedules.

Ruben Lopez. International Microbiology. 10(3). Madrid Sept 2004

"Streptococcus pneumoniae and its bacteriophages: one long argument."

Fitzwater, Sean; Chandran, Aruna; MD, MPH; Santosham, Mathuram; MD, MPH; Johnson, Hope; PhD, MPH


DOI: 10.1097/INF.0b013e31824de9f6

http://www.genome.uab.edu/strep/
CURRENT VACCINES

Conjugated 7-valent (Prevnar 7 - Wyeth)
4, 6B, 9V, 14, 18C, 19F, 23F

Conjugated 10-valent (Synflorix - GSK)
3 and 5, 7F

Conjugated 13-valent (Prevnar 13 - Pfizer)
3, 5, 6A, 7F, 11A, 18C

Polysaccharide only vaccine (Pneumovax 23 - Merck)
1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F.

Surveillance

- Characterization of national and local trends
- Detection of geographic and temporal changes in the incidence of drug resistant S. pneumoniae
- Monitoring impact of vaccines on disease
- Informing future vaccine development

Impact of 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease

Impact of introduction of PCV-7 on incidence of Hospitalizations due to IPD

The Worldwide Impact of the Seven-valent Pneumococcal Conjugate Vaccine.
Fitzwater, Sean; Chandran, Aruna; MD, MPH; Santosham, Mathuram; MD, MPH; Johnson, Hope; PhD, MPH
DOI: 10.1097/INF.0b013e31824de9f6
Impact of Introduction of PCV-7 on Incidence of Hospitalizations due to IPD

<table>
<thead>
<tr>
<th>Country</th>
<th>Age Group</th>
<th>Vaccination Date</th>
<th>Infection Date</th>
<th>Reduction in Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>0-11 mos.</td>
<td>2000-2000</td>
<td>2000</td>
<td>75.3%</td>
</tr>
<tr>
<td>Mexico</td>
<td>0-11 mos.</td>
<td>2000-2000</td>
<td>2000</td>
<td>75.3%</td>
</tr>
<tr>
<td>United States</td>
<td>2-4 yrs.</td>
<td>2000-2000</td>
<td>2000</td>
<td>75.3%</td>
</tr>
<tr>
<td>Canada</td>
<td>0-11 mos.</td>
<td>2000-2000</td>
<td>2000</td>
<td>75.3%</td>
</tr>
<tr>
<td>Denmark</td>
<td>0-11 mos.</td>
<td>2000-2000</td>
<td>2000</td>
<td>75.3%</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>0-11 mos.</td>
<td>2000-2000</td>
<td>2000</td>
<td>75.3%</td>
</tr>
<tr>
<td>France</td>
<td>0-11 mos.</td>
<td>2000-2000</td>
<td>2000</td>
<td>75.3%</td>
</tr>
</tbody>
</table>

Impact of 7-valent pneumococcal conjugate vaccine on all-cause otitis media.

- Canada: <5 yr, 2000-2000
- U.S.: <1 yr
- Italy: <1 yr
- Senegal: <1 yr
- U.S.: <2 yr

Reduction in all-cause otitis media

PATHOGEN-SPECIFIC CAUSES OF SEVERE PNEUMONIA CASES

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Distribution of severe pneumonia cases by cause</th>
<th>Discussion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus pneumonia (bacterium)</td>
<td>Leading cause</td>
<td></td>
</tr>
<tr>
<td>Hemophilus influenzae (bacterium)</td>
<td>Major cause</td>
<td></td>
</tr>
<tr>
<td>Other respiratory pathogens</td>
<td>Less common</td>
<td></td>
</tr>
</tbody>
</table>

These pathogens include respiratory viruses such as respiratory syncytial virus (RSV) and influenza, other bacteria such as Staphylococcus aureus and hemolytic streptococci, and fungi. Pneumococcal disease (PDS), which is particularly important in young children with ACS, is also a major risk factor for severe pneumonia and death.
Regional Proportion of Invasive Isolates Covered in of Currently Licensed Pneumococcal Conjugate Vaccines

| Region                      | PCV-7 (95% CI) | PCV-10 (95% CI) | PCV-13 (95% CI) |
|-----------------------------|----------------|----------------|----------------|---|
| Africa                      | 49% (41–57)    | 72% (67–76)    | 77% (71–82)    |   |
| Asia                        | 52% (43–61)    | 70% (64–75)    | 74% (67–79)    |   |
| Europe                      | 72% (69–74)    | 81% (78–82)    | 88% (87–89)    |   |
| Latin America, and Caribbean| 58% (55–61)    | 77% (74–80)    | 82% (79–85)    |   |
| North America               | 82% (78–84)    | 84% (81–87)    | 88% (85–91)    |   |
| Oceania                     | 68% (53–80)    | 75% (63–83)    | 79% (67–87)    |   |

Adapted from Johnson et al.*

UNITED STATES

Changes in invasive pneumococcal disease incidence (1998 to 2007) by serotype among U.S. children aged <5 years (top) and adults aged ≥65 years (bottom).

Rates of overall invasive pneumococcal disease (IPD) (A), PCV7-type IPD (B), serotype 19A IPD (C), and all other IPD (D), by site and year.


Absolute changes in rates in invasive pneumococcal disease (IPD), by age group and site, for 2009, compared with the mean of 2 baseline years (1998 and 1999) before vaccine introduction for overall IPD (A), PCV7-type IPD (B), serotype 19A (C), and all other type IPD (D).


Distribution of pneumococcal serotypes by age group before and after introduction of 7-valent pneumococcal conjugate vaccine (PCV7).


Children less than 5 years

Adults ≥ 65 years

OUTBREAK

Geography and Populations

<table>
<thead>
<tr>
<th>Province</th>
<th>Population</th>
<th>Comox Valley</th>
<th>Victoria</th>
<th>Edmonton</th>
<th>Calgary</th>
<th>Saskatoon</th>
<th>Regina</th>
<th>Winnipeg</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Columbia</td>
<td>4,308,349</td>
<td>337,400</td>
<td>3,474,000</td>
<td>2,285,900</td>
<td>712,700</td>
<td>241,400</td>
<td>201,500</td>
<td>1,081,300</td>
<td>10,037,900</td>
</tr>
<tr>
<td>Alberta</td>
<td>5,705,849</td>
<td>1,091,300</td>
<td>1,126,100</td>
<td>643,400</td>
<td>283,800</td>
<td>215,500</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>1,885,868</td>
<td>341,400</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manitoba</td>
<td>1,186,700</td>
<td>712,700</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>12,794,820</td>
<td>4,308,349</td>
<td>5,705,849</td>
<td>2,285,900</td>
<td>712,700</td>
<td>241,400</td>
<td>201,500</td>
<td>1,081,300</td>
<td>10,037,900</td>
</tr>
</tbody>
</table>
MLST pattern of serotype 5

<table>
<thead>
<tr>
<th>Gene</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>arcE</td>
<td>16</td>
</tr>
<tr>
<td>gdh</td>
<td>12</td>
</tr>
<tr>
<td>gki</td>
<td>9</td>
</tr>
<tr>
<td>recp</td>
<td>1</td>
</tr>
<tr>
<td>spl</td>
<td>41</td>
</tr>
<tr>
<td>xpt</td>
<td>33</td>
</tr>
<tr>
<td>ddl</td>
<td>33</td>
</tr>
</tbody>
</table>

Sequence type (ST): 289


Seen in Brazil, Niger, Italy, Poland, United Kingdom and Switzerland.

Where did it start???

Earliest clone we have yet identified by PFGE.

Dates back to March 2004.

This is one of the 4 serotype 5’s from 2004.

Recall:
- 2000 - 0
- 2001 - 1
- 2002 - 1
- 2003 - 1
- 2004 - 4
- 2005 - 8
- 2006 - 92
- 2007 - 452
- 2008 - 56

Came through Medicine Hat Regional Hospital.

42 yo

March 2004
Recommendations for use of PPV23

*All ages* at high risk of IPD

**Co-morbid conditions:**
- sickle cell anemia
- other sickle cell hemoglobinopathies
- functional or anatomic asplenia
- HIV infection
- immunocompromising conditions
- pulmonary disease
- diabetes
- liver cirrhosis
- chronic renal disease
- CSF leaks or cochlear implants

**Risk factors:**
- alcoholism
- smoking

In: Canadian Immunization guide 2006

Other recommendations in Canada for provision of PPV23

**Homeless**

**Individuals who use illicit drugs**

Serotypes in PPV23

Summary

1. *S. pneumoniae* is important historically
2. Causes a variety of diseases (otitis media to IPD)
3. Main virulence factor: capsule
4. Vaccines
   - 2 main: conjugated PCV13, polysaccharide 23
5. Good vaccine uptake in industrialized nations, developing countries: poor—disease rates high
6. PCV7: very effective in target population, older population
7. For developing countries: PCV13 would be effective
8. Coverage of PCV13 in >50 yo: 50-60%
9. Problem serotypes: 19A, 5