Pneumococcal vaccination

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Aims of the presentation

• Short overview on risk factors for pneumococcal disease and the two current vaccines, the 23-valent polysaccharide vaccine and the 7-valent conjugate vaccine

• Vaccination of adults – immunogenicity and efficacy/effectiveness

• Vaccination of children – efficacy/effectiveness and herd immunity
S. pneumoniae most common cause of pneumonia – major risk factors

Children < 2yy
Pneumococcal vaccines

- 1881 - *S. pneumoniae* isolated
- 1914 - whole-cell vaccine
- 1930-ies - discovery of serotypes
- 1940-ies - 6-valent capsular polysaccharide vaccine
- 1977 - 14-valent vaccine
- 1983 - 23-valent vaccine (23-PV)
What has happened during the last 25 years since 23-PV was launched?

Concluding remarks made at a meeting in 1995

- **23-PV:**
  - Protective efficacy of about 70% against invasive disease in immunocompetent adults
  - Possible, but non-proven, protection against non-bacteremic pneumococcal pneumonia

- **Future needs**
  - Proof of efficaciousness in pneumonia
  - Increased knowledge concerning revaccination
  - Vaccine efficacious in children - development of protein-conjugates
Pneumococcal vaccines

• 1881 - *S. pneumoniae* isolated
• 1914 - whole-cell vaccine
• 1930-ies - discovery of serotypes
• 1940-ies - 6-valent capsular polysaccharide vaccine
• 1977 - 14-valent vaccine
• 1983 - 23-valent vaccine
• 2000 - 7-valent protein-polysaccharide conjugate vaccine
23-valent pneumococcal polysaccharide vaccine (23-PV)

- Represents about 90% of all serotypes causing invasive pneumococcal disease (IPD)
- T-cell - “independent”
  - no booster-effect
  - children < 2yy - generally poor response,
  - 2-5yy - varying response
- Adults - generally good response with antibody rise $\geq 2x$
- Antibody rise postvaccination decline to baseline over 5 - 10 years
7-valent conjugate vaccine (7-CPV)

- **T-cell dependent immune response**
  - polysaccharide specific B-cells develop to antibody-producing plasma-cells and memory cells

- **Include seven serotypes** – those most common in children (in USA) and commonly associated with reduced sensitivity to penicillin
  - types 4, 6B, 9V, 14, 18C, 19F, 23F

- 10-valent, adding types 1, 5, 7F (GSK) and 13-valent, adding 1, 3, 5, 6A, 7F, 19A (Wyeth) on the market in 1-2 years?
Vaccination of adults
Immunogenicity

• There are no known protective levels of IgG antibodies, neither for absolute concentration, fold increases, or functional capacity

23-PV is “generally” immunogenic
• but, some elderly are “poor responders to one or more serotypes
• A poor antibody rise is often associated with a poor quality of antibodies, as measured by opsonophagocytosis

7-CPV
• In general not more immunogenic than 23-PV and booster response has not been shown in adults (Abraham-Van Parijs B. Vaccine 2004; 22)
Poor responders to the 23-PV

- 53 males, ≥ 65 yy vs. 15 healthy adults < 35yy
- Elderly and young had similar -
  - baseline status
  - magnitude of mean antibody (IgG) rise (both absolute conc. and fold increase) to types 2, 6B, 8, 12F, 14, 19A, 19F
  - avidity (no increase) and opsonization (significant increase) to type 14
- Subset of poor responders among the elderly
  - 11/53 (20.4%) of elderly vs. 0/15 young responded with < 2X FI to ≥ 2 of 7 serotypes
  - 19 elderly vs. 2 young had no increase of opsono-phagocytic activity

Rubins et al, JID 1998;178
Non-response to specific serotypes likely cause for failure to 23-valent pneumococcal polysaccharide vaccine in the elderly (Örtqvist et al. Vaccine 2007; 25: 2445)

• RCT pneumococcal polysaccharide vaccine (PPV) vs placebo (NaCl) 1:1 (Örtqvist et al, Lancet 1998;351:399)

• Sera; day 0, 30, 1 and 3 years, and if pneumonia occurred

• 8 patients with pneumococcal pneumonia
  - 4 vacc; 1 bacteremia (23F), 3 pos sputum (6A, 7F, ?)
  - 4 placebo; 2 bacteremias (3 and 8), 2 pos sputum (3, 6A)

• 38 controls
  - matched for vaccination status, sex, age ± 3 years

• IgG anti-PS ab, C-PS and 22F inhibition ELISA (cut-off 0.05 µg/ml) and OPA assay (cut-off 8)
  - response; IgG antibody levels post-vacc > 1 µg/ml
    OPA assay: > 2-fold increase
Antibody levels (μg/ml) in vaccinated patients with pneumococcal pneumonia, serotypes 6A, 7F, and 23F

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<th>5</th>
<th>6A</th>
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<td>&lt;.05</td>
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</tbody>
</table>
Conclusions
(Örtqvist et al. Vaccine 2007; 25: 2445)

23-PV = 23 vaccines, not one!

• Patients with pneumococcal pneumonia after vaccination with 23-PV have
  ➢ equally good Ab response, overall, as controls, but
  ➢ specific deficit for certain type-specific antibodies
Duration of antibodies and immune response to revaccination
Revaccination of middle-aged and elderly persons with PPV

- 61 patients, 56-88yy (mean 69 years)
- Revaccination after 5.3 years (mean), range 4-7 y
- Serotypes 1, 4, 7F, 14, 18C, 19F
- No severe side effects, but 63% mild local reactions
- Post-vacc GM antibody concentration and fold increase (FI) significantly lower than after the primary vaccination, but 37/61 (60%) had antibody fold increase (FI) >2 to >2 serotypes

Combined response to revaccination of 61 middle-aged and elderly persons with 23-PV
Combined GMC in persons <69yy (n=28, black) vs ≥ 69yy (n=33, magenta)
Conclusion

• One revaccination of elderly with PPV after about 5 years;
  - safe
  - results in much lower antibody rise than after primary vaccination, but probably induce an “adequate” immune response in a majority of elderly persons

• But,
  - no data concern protective efficacy
  - duration of antibody response post-revacc?
  - induction of tolerance? More than one revaccination of any use??
Is 23-PV effective? Yes and No!

Yes -
they are effective (?) Possibly (??)

- Invasive pneumococcal dis. in the immunocompetent adult, all age groups
- Pneumococcal pneumonia in young and healthy adults

No -
they are not effective

Pneumococcal pneumonia in the elderly
In the immunocompromised host
23-PV
“recent” RCT’s

Sweden

- 23-PV (n=339) vs. placebo (NaCl) (n=352)
- RCT, 1600 person-years FU, 1991-95
- 50-85 yy, earlier hospital treatment for CAP

Results:
- 120 CAP (6 IPD), 68% hospitalised
- 1 case of IPD in vaccine group vs. 5 in controls, p=0.23

<table>
<thead>
<tr>
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<th>VE, OR (95% CI)</th>
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<tr>
<td>IPD</td>
<td>0.21 (0.02, 1.77)</td>
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<tr>
<td>All-cause CAP</td>
<td>1.18 (0.80, 1.75)</td>
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</tbody>
</table>

Örtqvist et al (Lancet 1998;351)
Cumulative proportion without Pneumonia.

Time (days)

Vaccine
n = 339

Placebo
n = 352
23-PV
“recent” RCT’s

Finland

- Influenza + PV (n=13 980) vs. influenza vaccine only (n=12 945), 38 037 person-years FU, 1992-3
- > 65yy, open, quasi-randomised
- **Results**
  - 261 CAP (7 IPD), 83% hospitalised
  - 2 cases of IPD in vaccine group vs. 5 in controls

<table>
<thead>
<tr>
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<th>VE, OR (95% CI)</th>
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<tr>
<td>IPD</td>
<td>0.40 (0.1, 2.5)</td>
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<tr>
<td>All-cause CAP</td>
<td>1.16 (0.9, 1.5)</td>
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</tbody>
</table>

Honkanen et al Vaccine 1999;17
Meta-analyses

- Meta-analyses of RCT’s
  - Fine (94), Hutchinson (99), Moore (00), Cornu (01) and Watson (02):

- Meta-analyses of RCT’s and observational studies
  - Dear (Cochrane, 03), Melegaro (04), Conaty (04)

Not included in the analysis:
Honkanen 1999 2/13980 5/12945 (quasi-randomised) 0.40 (0.1, 2.5)
Invasive pneumococcal disease, non-randomised studies


<table>
<thead>
<tr>
<th>Study</th>
<th>Case</th>
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<th>Odds Ratio (Random)</th>
<th>Weight (%)</th>
<th>Odds Ratio (Random)</th>
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<td>n/N</td>
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<td><strong>01 All studies</strong></td>
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<td>Farr 1995</td>
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<td>Sims 1990</td>
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<td>51/244</td>
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<td>21.4</td>
<td>0.34 [0.17, 0.69]</td>
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<td><strong>Subtotal (94% CI)</strong></td>
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<td>313/1558</td>
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<td>0.43 [0.28, 0.66]</td>
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<td><strong>Test for heterogeneity chi-square = 0.32 df = 1 p = 0.5703</strong></td>
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<td><strong>Test for overall effect = 0.30 p = 0.0001</strong></td>
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<td><strong>02 Immunocompetent subjects</strong></td>
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<td>Shapiro 1964</td>
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<td>Shapiro 1964</td>
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<td>Sims 1998</td>
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Stockholms läns landsting
Smittskyddsenheten
Efficacy of 23-PV against IPD in the elderly – two most recent meta-analyses

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<tr>
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<th>RCT’s</th>
<th>RCT’s + case-control studies</th>
<th>Case-control studies</th>
<th>Cohort studies</th>
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<tr>
<td>Melegaro &amp; Edmunds, 2004</td>
<td>44% (-45 – 79)</td>
<td>47% (30-60)</td>
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<tr>
<td>Conaty et al. (2004)</td>
<td>49% (-23 – 79)</td>
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<td>55% (44-64)</td>
<td>47% (19-65)</td>
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Effects of 23-PV on incidence of IPD

Stockholm, Sweden:

- Prospective cohort 3-year-study of the whole population 65+ years (n=260,000), 1998-2000
- About 100,000 persons in total received pneumococcal vaccine during the three years

<table>
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<tr>
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<th>Vacc</th>
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<th>OR</th>
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<td>0.30, 1.05</td>
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* per 100,000 inhabitants

Total incidence of IPD in Stockholm vs a low vaccinating county

Decline of 9.3/100,000 (-0.13, 18.7)

Serotype distribution stratified by age

IPD in Stockholm all age groups

IPD in Stockholm age 0-18

IPD in Stockholm age 19-64

IPD in Stockholm age >64

Yearly decline of 20%, OR 0.81 (0.72-0.92)
# Clinical Efficacy by Age and Time since Vaccination

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<th>Age</th>
<th>&lt; 3 years % (CI 95)</th>
<th>3-5 years % (CI 95)</th>
<th>&gt; 5 years % (CI 95)</th>
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<td>&gt; 85</td>
<td>46 (-31, 78)</td>
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Shapiro, NEJM 1991;325
Efficacy against pneumonia ??
## All pneumonia - RCTs


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<th>Control n/N</th>
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<tr>
<td>Honkanen 1999</td>
<td>145/13980</td>
<td>116/12945</td>
<td></td>
<td>9.0</td>
<td>1.16 [0.91, 1.48]</td>
</tr>
<tr>
<td>Kaufman 1947</td>
<td>99/5750</td>
<td>227/5153</td>
<td></td>
<td>9.1</td>
<td>0.38 [0.30, 0.48]</td>
</tr>
<tr>
<td>Klastersky 1986</td>
<td>2/26</td>
<td>4/21</td>
<td></td>
<td>1.9</td>
<td>0.35 [0.06, 2.16]</td>
</tr>
<tr>
<td>Koivula 1997</td>
<td>73/1364</td>
<td>69/1473</td>
<td></td>
<td>8.5</td>
<td>1.15 [0.82, 1.61]</td>
</tr>
<tr>
<td>Ortvist 1998</td>
<td>63/339</td>
<td>57/352</td>
<td></td>
<td>8.2</td>
<td>1.18 [0.80, 1.75]</td>
</tr>
<tr>
<td>Riley 1977</td>
<td>27/2713</td>
<td>40/2660</td>
<td></td>
<td>7.5</td>
<td>0.60 [0.40, 1.08]</td>
</tr>
<tr>
<td>Simberkoff 1986</td>
<td>48/1175</td>
<td>38/1179</td>
<td></td>
<td>7.9</td>
<td>1.28 [0.83, 1.97]</td>
</tr>
<tr>
<td>Smit 1977, Grp 1</td>
<td>37/993</td>
<td>121/2036</td>
<td></td>
<td>8.3</td>
<td>0.62 [0.42, 0.90]</td>
</tr>
<tr>
<td>Smit 1977, Grp 2</td>
<td>9/540</td>
<td>28/1135</td>
<td></td>
<td>5.7</td>
<td>0.67 [0.31, 1.43]</td>
</tr>
</tbody>
</table>

Total (95% CI): 1017/36739, 1406/38269

Test for heterogeneity chisquare = 108.17 df = 13 p < 0.00001
Test for overall effect = -1.85 p = 0.06
Prevention against pneumonia in the elderly - A question of power?!

- An end-point of “all” pneumonia is used because of the difficulties in establishing the diagnosis of pneumococcal pneumonia
  
  less specific = “dilute” the power

  e.g. 40% efficacy against pneumococcal pneumonia
  40% x 0.90 (serotype coverage) = 36%
  36% x 0.50 (50% other etiologies) = 18%

  18% efficacy against “all” pneumonia, which would require a sample size of 50,000 to 100,000 patients to demonstrate in a RCT!
Prevention against pneumonia
- observational studies goes both ways

**USA:** Retrospective cohort 2-year-study of 1898 elderly COPD patients

23-PV-vaccinated had Risk Ratio 0.55 (0.33-0.95) for need of hospitalization for pneumonia
(Nichol, Arch Intern Med 2000; 160: 1699)

**USA:** Retrospective cohort 3-year-study of 47 365 Group Health Cooperative members 65+ years

23-PV-vaccinated had Hazard Ratio 1.14 (1.02-1.28) for need of hospitalization for pneumonia
(but a significant lower risk for pneumococcal bacteremia (HR 0.56, 0.33-0.93)
(Jackson, NEJM 2003;348:1747)
Hospitalisation for pneumonia / 100.000 inh. during non-influenza season, Stockholm County

<table>
<thead>
<tr>
<th></th>
<th>Vacc</th>
<th>Not vacc</th>
<th>RR</th>
<th>95%CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia 1999</td>
<td>1679</td>
<td>1920</td>
<td>0.88</td>
<td>0.77, 1.00</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pneumonia 2000</td>
<td>1431</td>
<td>1814</td>
<td>0.79</td>
<td>0.73, 0.85</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Stockholm influenza and pneumococcal vaccination study

Hedlund et al, Vaccine 2003;21:3906,
Christenson et al, Eur Respir J 2004;23:363-8
Prevention against pneumonia - recent observational studies indicate protection!

Spain

- Cohort study of elderly persons, n=11241, during 36 months
- 23-PV was associated with lower risk for
  - pneumonia overall, HR 0.79 (0.64-0.98)
  - pneumococcal pneumonia, HR 0.55 (0.34-0.88)
  - death due to pneumonia, HR 0.41 (0.23-0.72)
  - hospitalisation for pneumonia, HR 0.74 (0.59-0.92)

(Vila-Corcoles CID 2006;43:860)
Summary of Efficacy/effectiveness of 23-PV in the elderly

23-PV protects against

- **IPD** 50-80%
  - and with a corresponding decline of the incidence of IPD
  - duration of protection?
- **All-cause pneumonia** 10-20% (?)
  - corresponding to about 25-40% of pneumococcal pneumonia
Efficacy in the immunocompromised
### 23-PV - efficacy against IPD in the immunocompromised

**Protective efficacy, % (95%CI)**

- Anatomic asplenia (n=112) 77 (14, 95)
- Leukemia/Myeloma (n=66 / 56); <0 (NS)
- Hodgkin’s dis (n=51); 11 (-505, 89)
- Non-Hodgkin lymphoma (n=47); 64 (- 58, 92)
- Immunoglobulin def (n=26); 59 (-239, 95)
- Immunocompromised (n=175) 21 (-55, 60)
- HIV, RCT Uganda (n=25) <0 (NS)
- HIV, case -control, USA
  - whites 49 (12 - 70)
  - black 24 (-50 - 67)

(Butler et al JAMA 1993; 270, Shapiro, N Engl J Med 1991; 325,
## Efficacy of 23-PV in HIV Infected Persons

- HIV infected (2/3 female), mean age 31yy, Uganda, RCT, 1995-98
- 23-PV (n=697) vs. placebo (n=695)

<table>
<thead>
<tr>
<th></th>
<th>HR (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPD, all types (n=25)</td>
<td>1.47 (0.7-3.3)</td>
<td>0.34</td>
</tr>
<tr>
<td>- serotype spec. (n=22)</td>
<td>2.10 (0.9-5.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Pneumonia, all (n=61)</td>
<td>1.89 (1.1-3.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Death (n=377)</td>
<td>0.99 (0.8-1.2)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

(French et al, Lancet 2000;355)
Vaccination of children
## RCT with PCV7 in California, USA

Propective, blind, placebo-controlled - meningococcal vaccine
About 18900 children in each group, 4 doses; 2, 4, 6, 14 months age

<table>
<thead>
<tr>
<th></th>
<th>Efficacy, ITT (%), 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Invasive disease</strong></td>
<td></td>
</tr>
<tr>
<td>- all (n=61)</td>
<td>89 (74 - 96)</td>
</tr>
<tr>
<td>- serotype spec. (n=52 )</td>
<td>94 (80 - 99)</td>
</tr>
<tr>
<td><strong>Pneumonia</strong></td>
<td></td>
</tr>
<tr>
<td>- clin. diagnosis (n=1066)</td>
<td>11 (1 - 21)</td>
</tr>
<tr>
<td>- X-ray verified (n=115)</td>
<td>33 (7 - 52)</td>
</tr>
<tr>
<td>- consolidation (n=26)</td>
<td>73 (38 - 88)</td>
</tr>
<tr>
<td><strong>Otitis</strong></td>
<td></td>
</tr>
<tr>
<td>- visits (n=73041)</td>
<td>7.8 (5.2 - 10.5)</td>
</tr>
<tr>
<td>- frequent, ≥ 4/6mo, or 5/year</td>
<td>10.0 (2.4 - 17.0)</td>
</tr>
</tbody>
</table>
# Efficacy of PCV7 against acute otitis media, Finland

<table>
<thead>
<tr>
<th>Type or Cause of Acute Otitis Media</th>
<th>Efficacy (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>6</td>
<td>-4 - 16</td>
</tr>
<tr>
<td>Culture-pos. <em>S. pneumoniae</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>34</td>
<td>21 - 45</td>
</tr>
<tr>
<td>Vaccine-type*</td>
<td>57</td>
<td>44 - 67</td>
</tr>
<tr>
<td>Cross-reactive**</td>
<td>51</td>
<td>27 - 67</td>
</tr>
<tr>
<td>Other types</td>
<td>-33</td>
<td>-80 - 1</td>
</tr>
<tr>
<td>Culture-positive</td>
<td>-11</td>
<td>-34 - 8</td>
</tr>
</tbody>
</table>

*4, 6B, 9V, 14, 18C, 19F, 23F.  ** 6A, 9N, 18B, 19A, 23A

---

*Eskola et al, NEJM 2001;344*
Meta-analysis of efficacy of 7-9 valent conjugate vaccines

- **Efficacy against**
  - vaccine-type IPD; 88% (73% - 94%)
  - all types IPD; 66% (46% - 79%)
  - x-ray verified pneumonia; 22% (11% - 31%)

Effect in Target Age Group
Invasive Pneumococcal Disease Rates in Children <5 Years, ABCs, 1998-2005

PCV7

2005 vs baseline
- 77% (<1 yr)
- 82% (1 yr)
- 75% (2 yr)
- 61% (3 yr)
- 26% (4 yr)

CDC unpublished data and MMWR Sep 16, 2005
Vaccine-Type Invasive Disease in Children <5 Years
ABCs 1998-2005

Cases per 100,000

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998/99</td>
<td>81</td>
</tr>
<tr>
<td>2000</td>
<td>63</td>
</tr>
<tr>
<td>2001</td>
<td>27</td>
</tr>
<tr>
<td>2002</td>
<td>9.4</td>
</tr>
<tr>
<td>2003</td>
<td>4.8</td>
</tr>
<tr>
<td>2004</td>
<td>2.4</td>
</tr>
<tr>
<td>2005</td>
<td>1.5</td>
</tr>
</tbody>
</table>

PCV7

98% reduction

CDC unpublished data and MMWR Sep 16, 2005

Stockholms läns landsting
Smittskyddsenheten
Effects on herd immunity in the US

Decline 1999 to 2001

-18% (-11 to -24)

-8% (-1 to -15)

-40% (-29 to -49)

Asterisks * indicate p<0.05 for 2000-2001 vs. 1998-1999.

Whitney NEJM 2003;348:1737, ”
IPD in the US -% reductions 1998-1999 to 2002-2003:

- ≥85 years, –28%
- 75-84 years, –35%
- 65-74 years, –29%
- 50-64 years, –17%

P<.001 in each age group

Lexau JAMA 2005; 294
Decline of IPD caused by PNSP

Decline 1999 to 2004

-49% (-46 to -51), ≥ 65yy

-36% (-33 to -40), 40-64 yy

-51% (-46 to -55), 20-39 yy

Kyaw NEJM 2006; 354:1455
Decline of hospital admissions due to all-cause pneumonia in the US, 1997-2004

- Decline in admission rates

<table>
<thead>
<tr>
<th>Age group</th>
<th>% decline (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 years</td>
<td>39 (22-52)</td>
</tr>
<tr>
<td>18-39 years</td>
<td>26 (4 - 43)</td>
</tr>
<tr>
<td>&gt; 65 years</td>
<td>15 (-2- 30)</td>
</tr>
</tbody>
</table>

Grijalva et al Lancet 2007;369
Conjugate vaccines
– ”a moving target”

• Serotype coverage too low, especially in many developing countries
  - 13 serotypes would probably cover 80-90%, today

• ”Replacement” may reduce effectiveness of the vaccine
In conclusion – some new knowledge, but not enough, has evolved during the last 12 years

Concluding remarks today

• **23-PV**
  - efficacy of ≈70% against IPD in immunocompetent adults - OK
  - Still only possible, and non-proven, protection against pneumococcal pneumonia

• **Conjugate vaccines have been developed:**
  - highly efficacious against vaccine type IPD in children
  - induce herd immunity also protects adults

• **Future needs and questions to be answered**
  - Proof of efficaciousness of 23-PV in pneumonia – still there
  - Increased knowledge concerning revaccination – still there
  - Usefulness of conjugate vaccines in adults
  - Will 13-valent conjugates be enough to compensate for serotype replacement (most likely not in the long run)

→ need for a (protein) vaccine common for all pneumococci!
Thank you