Management and Prevention of Pneumococcal diseases

308th and 309th HKDU Afternoon Symposium
16 Aug 2015

Dr Grace Lui
Specialist in Infectious Diseases
About this talk ...
Patient 1

- 54 year-old man
- Fever for 2 days admitted in Jun 2015
- Productive cough

- Hypertension
- Diabetes (HbA1c 10 on last follow-up)
- Sigmoid carcinoma 2008, in remission
Streptococcus pneumoniae antigen: Detected

Date Collected: 08/06/2015 13:07
Date Arrived: 08/06/2015 16:37
Specimen: URINE

Appearance: Mucoid

Microscopy: Large numbers of WBC seen
Epithelial cells seen

Routine culture:

Organism 1: Heavy growth of Streptococcus pneumoniae isolated

Date Collected: 04/06/2015 23:52
Date Arrived: 05/06/2015 01:09
Specimen: BLOOD
Site: peripheral

Gram stain: Broth culture yielded Gram positive cocci in chains (both bottles)

Routine culture:

Organism 1: Streptococcus pneumoniae isolated
Progress

- He received 2 weeks of high dose iv ampicillin
- Insulin was added to improve glycemic control
Patient 2

- 66 year-old man
- Fever for one day
- Mental slowness, reduced verbal response, sudden hearing loss
- Non-Hodgkin lymphoma in remission
- Chronic HBV infection, on entecavir
- GCS E4V4M5, neck rigidity
Lumbar puncture done, opening pressure 30cmH$_2$O

**Appearance**: Turbid

**Gram stain**: Large numbers of Gram positive cocci seen

**Cell count**: WBC : 146 x 10 E6/L  
RBC : 4 x 10 E6/L

**Differential count**: Polymorphs : 90 %  
Lymphocytes : 10 %

**Routine culture**:  
Organism 1 : Heavy growth of Streptococcus pneumoniae isolated  
Sensitive to:  
Cefotaxime (MIC)  
Resistant to:  
Erythromycin  
Penicillin (MIC)

Streptococcus pneumoniae, M.I.C. of Penicillin : 0.25 ug/ml  
Streptococcus pneumoniae, M.I.C. of Cefotaxime : 0.25 ug/ml
Progress

- Given ceftriaxone and dexamethasone
- GCS deteriorated on day 2, required intubation
- CT brain showed generalised cerebral edema
- No neurological recovery
- Complicated by ventilator-associated pneumonia
- Succumbed on day 17 of admission
Spectrum of pneumococcal diseases

- Meningitis
- Bloodstream infection
- Pneumonia
- Sinusitis, otitis media

Invasive pneumococcal disease (IPD)
Mucosal disease

Weekly epidemiological record 2012;87:129-144
Otitis media

- *S. pneumoniae* and nontypable *Hemophilus influenzae* are most common cause of OM in children
  - *S. pneumoniae* is associated with fever and more severe TM findings
  - *H. influenzae* is associated with conjunctivitis and previous OM

- *S. pneumoniae* is the most common cause in adults
Sinusitis

- *S. pneumoniae* and *H. influenzae* predominating bacterial pathogens
- Preceded by obstruction of orifices by viral infection, atmospheric pollutants, or allergens, together with accumulation of fluid in the paranasal sinus cavities
- Differentiated from viral causes
  - *persistent* signs and symptoms (≥10 days),
  - *severe* symptoms and signs (temperature ≥39°C, purulent discharge or pain for greater than 3 days, and
  - *worsening* symptoms (fever, headache, increased nasal discharge) after initial improvement following a viral respiratory tract infection.
Etiologies of pneumonia requiring hospitalization, 2004-2005, n=468

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
<td>23.5%</td>
</tr>
<tr>
<td>Hemophilus influenzae</td>
<td>13.4%</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>17.3%</td>
</tr>
<tr>
<td>Chlamydophila pneumoniae</td>
<td>10.5%</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>22.1%</td>
</tr>
</tbody>
</table>
Pneumonia

- Acute onset of cough, fatigue, shortness of breath, and dyspnea with documented or subjective fever, chills, sweats, purulent sputum, and pleuritic chest pain
- Elderly less well defined clinical syndrome, slight or no elevation of temperature, but more likely tachypnea
- Dullness to percussion, bronchial breath sounds, crackles
Lobar consolidation with pleural effusion

Multilobar airspace consolidation
Necrotizing pneumonia: extensive consolidation with necrotic changes with multiple small cavitation
Diagnosis

• Sputum
  – Polymorphs >25/HPF
  – Epithelial cells <10/HPF
  – Gram positive cocci in pairs or chains

• Blood culture
  – Positive in up to 20-25% of pneumococcal pneumonia
Diagnosis

• Urine for *S. pneumoniae* antigen
  – In 22 studies of more than 4600 patients with pneumococcal pneumonia:
    • sensitivity of 75% (range, 58% to 93%)
    • specificity of 95% (range, 58% to 93%)
    • positive predictive value of 79% (range, 25% to 100%)
    • negative predictive value of 93% (74% to 100%)
  – Rapid point-of-care test
  – can remain positive for weeks
  – not useful in children because of positive results with pharyngeal colonization
Complication

- Pleural effusion (parapneumonic)
- Empyema
  - 2-8% of pneumococcal pneumonia
  - Suspected when persistent fever, leukocytosis, or pleural effusion despite treatment
  - Treatment: adequate drainage by chest drain, pleuroscopy or thoracotomy
- Noninfectious: cardiac complications in ~20%
Long-term survival after pneumococcal pneumonia

Average 63-year-old American male


Published by Oxford University Press on behalf of the Infectious Diseases Society of America

2013.

Survived pneumococcal pneumonia
Etiologies of bacterial meningitis in adults in Hong Kong, 1992-2001

- M tuberculosis: 46%
- S pneumoniae: 11%
- S suis: 9%
- S agalactiae: 6%
- K pneumoniae: 8%
- S aureus: 5%
- L monocytogenes: 3%
- other streptococci: 3%
- others: 9%
Meningitis

- Hematogenous spread or direct extension from sinusitis/otitis media
- Fever, headache, meningism, confusion, obtundation
- CSF: Gram stain, bacterial culture
- Treatment: high dose iv penicillin / ceftriaxone or cefotaxime / vancomycin (depending on susceptibility) + dexamethasone
- Significant morbidity and mortality
## Community-acquired pneumonia (CAP)

1. **CAP, not hospitalized**


   - P.O. amoxicillin-clavulanate (e.g., 1 g b.i.d.) ± a macrolide or
   - P.O. high dose amoxicillin (at least 1.5 g/day) + a newer macrolide

   **Levofloxacin**

   **Penicillin allergy:** Levofloxacin

   Meta-analysis of 127 studies (n=33,148): *S. pneumoniae* (73%); *H. influenzae* (14%); *S. aureus* (3%); Gram-negative rods (2%). In Hong Kong, macrolide/azalide, tetracycline or cotrimoxazole should not be used alone for empiric treatment of CAP. Locally, 50–70% pen-S and pen-R *S. pneumoniae* isolates (both community and hospital isolates) are multi-resistant to these agents [1, 204, 205].
### Streptococcus pneumoniae

**Drug of choice**

For infections outside the central nervous system:
- Penicillin-sensitive: I.V. penicillin G (4 to 8 MU / day, q6h)
- Penicillin-intermediate: I.V. penicillin G (high dose, 12 to 18 MU / day, q4h)\(^a\)
- Penicillin-resistant: I.V. cefotaxime or ceftriaxone

**Alternatives**

- Beta-lactam / beta-lactamase inhibitor combination with the exception of cefoperazone-sulbactam (for mixed infections).
- Erythromycin or clindamycin (if allergic to penicillin).

**Remarks**

- Most pneumococcal pneumonia can be treated with high dose amoxicillin-clavulanate.
- For pure pneumococcal infection, penicillin G instead of amoxicillin-clavulanate is preferred, switch therefore recommended.
- >70% resistant to erythromycin. Cross-resistance to clindamycin very common.
- Resistance to erythromycin = resistance to other newer macrolides (clarithromycin, azithromycin, roxithromycin).

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\(^a\) CLSI (NCCLS) MIC (\(\mu g/mL\)) breakpoints for penicillin G: sensitive, \(\leq 0.06\); intermediate 0.12-1; resistant \(\geq 2\).

These breakpoints were decided mainly for the relevance on meningitis. For pneumococcal pneumonia, pharmacokinetic/dynamic data indicates that isolates with MIC of up to 1-2 \(\mu g/mL\) should be considered ‘sensitive’ to appropriate dose of penicillin, ampicillin and amoxicillin.
Susceptibility of *S. pneumoniae* in HK

<table>
<thead>
<tr>
<th>Site, year</th>
<th>Penicillin</th>
<th>Erythromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Meningitis breakpoint</td>
<td>Non-meningitis breakpoint</td>
</tr>
<tr>
<td>Hong Kong West cluster, 2013</td>
<td>33.1%</td>
<td>91.0%</td>
</tr>
<tr>
<td>Kowloon East cluster, 2012</td>
<td></td>
<td>92%</td>
</tr>
<tr>
<td>Kowloon West cluster, 2012</td>
<td>52%</td>
<td>99%</td>
</tr>
<tr>
<td>NT East Cluster, 2012</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>NT West Cluster, 2012</td>
<td>41%</td>
<td>99%</td>
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<tr>
<td>Public Health Laboratory, 2013</td>
<td></td>
<td>62.5%</td>
</tr>
<tr>
<td>Private hospitals, 2012-2014</td>
<td>39%</td>
<td>100%</td>
</tr>
</tbody>
</table>
Streptococcus pneumoniae

- Gram-positive
- diplococcus
- encapsulated
Polysaccharide capsule

• an essential virulence factor
• Determines serotype (>92 identified)
  – Immunity is serotype-specific
  – Virulence/”invasiveness”
  – Antimicrobial resistance
Colonization, transmission, disease

Main reservoir in children
Transmission via respiratory droplets
Epidemiology

• Leading cause of bacterial death in children $\leq 5$ years old worldwide
• Leading cause of bacterial pneumonia in older adults in developed countries
• Most cases are sporadic, but outbreaks (certain serotypes) may occur in institutions
• Associations with respiratory viruses, e.g. influenza and RSV
Figure 2 - Number of IPD cases by month, 2007 to June.
IPD = notifiable disease in HK since Jan 2015

Figure 1 - Age-specific incidence of IPD in Hong Kong, PHLSB lab surveillance, 2007 to June 2014.
Age-specific incidence (per 100,000) and case-fatality ratio (percent) of invasive pneumococcal disease, Active Bacterial Core surveillance, 1998.
Incidence of invasive pneumococcal disease in older adults by age group and illness

![Graph showing incidence of invasive pneumococcal disease by age group and illness](chart.png)

- Other immunocompromising conditions: asplenia/splenic dysfunction, antibody defects, complement deficiencies, neutropenia
<table>
<thead>
<tr>
<th>ABNORMALITY</th>
<th>PRIMARY</th>
<th>SECONDARY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomic</td>
<td>Congenital CSF leak</td>
<td>Poor eustachian tube drainage</td>
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<td></td>
<td></td>
<td>Traumatic CSF leak</td>
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<td></td>
<td></td>
<td>Cochlear implants</td>
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<td></td>
<td></td>
<td>COPD</td>
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<td></td>
<td></td>
<td>Asthma</td>
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<td></td>
<td></td>
<td>Preceding viral/influenza infection</td>
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<tr>
<td>Antibody defects</td>
<td>Congenital agammaglobulinemia</td>
<td>CLL</td>
</tr>
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<td></td>
<td>Common variable immunodeficiency</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td></td>
<td>IgG2 subclass deficiency (± selective low IgA)</td>
<td>HIV infection</td>
</tr>
<tr>
<td></td>
<td>Selective hyporesponsiveness to polysaccharides</td>
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<tr>
<td></td>
<td>Hyper-IgM syndrome</td>
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<tr>
<td></td>
<td>Hyper-IgE syndrome</td>
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<tr>
<td>Low complement</td>
<td>Classical pathway (low C2, C1, C4)</td>
<td>Nephrotic syndrome</td>
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<tr>
<td></td>
<td>Alternative pathway (low factors I, H, and B)</td>
<td>Complement consumption</td>
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<tr>
<td></td>
<td>Low C3 (all pathways)</td>
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<td></td>
<td>MBL deficiency and polymorphisms</td>
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<tr>
<td>Neutropenia</td>
<td>Cyclic neutropenia</td>
<td>Drug-induced neutropenia</td>
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<td></td>
<td></td>
<td>Aplastic anemia</td>
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<tr>
<td>ABNORMALITY</td>
<td>PRIMARY</td>
<td>SECONDARY</td>
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<td>--------------------------</td>
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<td>------------------------------------------------</td>
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<tr>
<td>Neutrophil dysfunction</td>
<td>Fcγ receptor IIa (R131 allele) (low avidity for IgG2)</td>
<td>Diabetes</td>
</tr>
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<td></td>
<td>Chédiak-Higashi syndrome</td>
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<tr>
<td>Reticuloendothelial cell defects</td>
<td>Congenital asplenia</td>
<td>Splenectomy</td>
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<tr>
<td></td>
<td>Hyposplenia</td>
<td>Sickle cell disease</td>
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<td></td>
<td></td>
<td>Portal hypertension</td>
</tr>
<tr>
<td>Combined/other</td>
<td>IRAK4 deficiency (decreased cytokines)</td>
<td>Extremes of age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HIV/AIDS</td>
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<tr>
<td></td>
<td></td>
<td>Sickle cell disease</td>
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<tr>
<td></td>
<td></td>
<td>Chronic organ dysfunction (lung, liver, kidney, heart)</td>
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<td></td>
<td></td>
<td>Chronic alcohol use</td>
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<tr>
<td></td>
<td></td>
<td>Solid-organ and bone marrow transplantation</td>
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<tr>
<td></td>
<td></td>
<td>Lymphoma</td>
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<tr>
<td>Environmental</td>
<td></td>
<td>Environmental smoke</td>
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<td></td>
<td></td>
<td>Smoking (tobacco)</td>
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<td></td>
<td></td>
<td>Crowding (daycare, homeless shelters, prison, military training)</td>
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<tr>
<td></td>
<td></td>
<td>Stress (military training)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cold season</td>
</tr>
</tbody>
</table>
Prevention of pneumococcal disease

Lancet 2013; 381: pp. 1417-1429
J Infect Dis 2013; 207: pp. 1144-1147
Pneumococcal vaccines

PPV23
Plain Polysaccharide Vaccine

PCV13
Polysaccharide Conjugate Vaccine

Antigen is different

Polysaccharide

Polysaccharide + Carrier protein
What is the difference in the body?

**PPV23**

Plain Polysaccharide Vaccine

- Polysaccharide
- No activation
- No involvement in immune response
- Not formed
- B Lymphocytes → Plasma Cells → Secreted IgM Antibodies → Memory B Lymphocytes
- Weaker immune response
- Poor memory

**PCV13**

Polysaccharide Conjugate Vaccine

- Polysaccharide + Carrier protein
- Activated
- Involved in immune response
- Formed from activated B Lymphocytes
- B Lymphocytes → Plasma Cells → Secreted IgG Antibodies → Memory B Lymphocytes
- Powerful immune response
- Long term memory
# Efficacy of pneumococcal vaccination in adults: a meta-analysis

(PPV 23)

Anke Huss PhD, Pippa Scott MSc, Andreas E. Stuck MD, Caroline Trotter PhD, Matthias Egger MD MSc

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of trials</th>
<th>No. of study participants</th>
<th>No. of cases</th>
<th>Combined RR (95% CI)</th>
<th>Test for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definitive pneumococcal</td>
<td>2</td>
<td>794</td>
<td>7</td>
<td>0.62 (0.05–8.61)</td>
<td>( I^2 = 49%, p = 0.16 )</td>
</tr>
<tr>
<td>Presumptive pneumococcal</td>
<td>11</td>
<td>56 564</td>
<td>589</td>
<td>0.64 (0.43–0.96)</td>
<td>( I^2 = 74%, p &lt; 0.001 )</td>
</tr>
<tr>
<td>All causes</td>
<td>19</td>
<td>82 665</td>
<td>2 722</td>
<td>0.73 (0.56–0.94)</td>
<td>( I^2 = 90%, p &lt; 0.001 )</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>6</td>
<td>32 770</td>
<td>44</td>
<td>0.90 (0.46–1.77)</td>
<td>( I^2 = 5%, p = 0.48 )</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>4</td>
<td>20 589</td>
<td>1 698</td>
<td>0.92 (0.76–1.12)</td>
<td>( I^2 = 54%, p = 0.09 )</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal infection</td>
<td>3</td>
<td>15 942</td>
<td>18</td>
<td>0.93 (0.29–3.05)</td>
<td>( I^2 = 14%, p = 0.31 )</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8</td>
<td>33 384</td>
<td>214</td>
<td>0.88 (0.62–1.25)</td>
<td>( I^2 = 26%, p = 0.22 )</td>
</tr>
<tr>
<td>All causes</td>
<td>12</td>
<td>45 365</td>
<td>2 246</td>
<td>0.97 (0.87–1.09)</td>
<td>( I^2 = 44%, p = 0.053 )</td>
</tr>
</tbody>
</table>
A total of 470,070 individuals aged ≥65 years

<table>
<thead>
<tr>
<th>Disease outcomes</th>
<th>Adjusted odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive pneumococcal disease</td>
<td>0.58</td>
<td>0.41-0.81</td>
</tr>
<tr>
<td>Hospitalized pneumonia</td>
<td>1.01</td>
<td>0.97-1.04</td>
</tr>
</tbody>
</table>
Efficacy of PPV23: current evidence

- Protective effect against IPD and all-cause pneumonia among generally healthy young adults
- Protection against IPD in the general population of elderly people to a lesser extent
- Not demonstrated efficacy against either IPD or all-cause pneumonia in populations at higher risk, (adults and children with underlying conditions that increase their risk of pneumococcal disease or highly immunosuppressed individuals of any age)
## PCV in children

<table>
<thead>
<tr>
<th>Condition</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otitis media</td>
<td>Reduction in out-patient clinic visits in children ≤2yo</td>
<td>246 fewer otitis media visits per 1000 annually (=20% reduction)</td>
</tr>
<tr>
<td>Hospitalized pneumonia</td>
<td>Decline in hospitalization rate in children ≤2yo in USA</td>
<td>↓551.1 per 100,000 children (95% confidence interval, 445.1 to 657.1), (=47,000 fewer hospitalizations annually than expected)</td>
</tr>
<tr>
<td>Invasive pneumococcal disease</td>
<td>Vaccine efficacy for vaccine serotypes</td>
<td>97.4% (95% confidence interval, 82.7 to 99.9%)</td>
</tr>
</tbody>
</table>

Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance


US routine infant immunization programme: 2000 - PCV7; 2010 - PCV13

Lancet Infect Dis 2015;15: 301–09
Average OPA for 12 Serotypes by Regimen in older adults

Cohort 1: 60–64 year olds

Cohort 2: 50–59 year olds

Polysaccharide Conjugate Vaccine against Pneumococcal Pneumonia in Adults


Randomized, double-blind, placebo-controlled trial in the Netherlands

Community Acquired Pneumonia Immunization Trial in Adults (CAPiTA)

84,496 volunteers Aged ≥ 65 years

Screening and recruitment

Placebo

Prevenar 13

Accrual of VT-CAP Cases

Regulatory Review of Primary and Secondary Outcome Data

Sept 2008 Jan 2010 3Q13 2014

mean follow up: 3.97 years
# Community Acquired Pneumonia Immunization Trial In Adults (CAPiTA)

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Male or female</td>
<td>• Previous pneumococcal vaccination</td>
</tr>
<tr>
<td>• Male or female ≥65 years of age</td>
<td>• Use of investigational vaccine or medication in past 30 days</td>
</tr>
<tr>
<td>• Registered with the GP referring subjects to study</td>
<td>• Resident in nursing home/long-term care facility</td>
</tr>
<tr>
<td>• Able to fulfill study requirements</td>
<td>• Immune deficiency or suppression†</td>
</tr>
<tr>
<td>• Able to fulfill study requirements</td>
<td>• History of severe adverse reaction to a vaccine or component</td>
</tr>
<tr>
<td></td>
<td>• Contraindication to influenza vaccination if influenza vaccine is to be administered at same time</td>
</tr>
<tr>
<td></td>
<td>• Contraindication to Prevenar 13</td>
</tr>
</tbody>
</table>

†Immunocompetent subjects with comorbid conditions were included (eg, chronic heart disease, diabetes mellitus, chronic pulmonary disease). Immune–deficient or suppressed individuals were not eligible for study entry. However, if study subjects became immune–deficient or suppressed after receipt of study vaccine (ie, during the case accrual period) and experienced an episode of CAP or IPD, these events were included in the mITT analyses.

CAP=community-acquired pneumonia; GP=general practitioner; IPD=invasive pneumococcal disease; mITT=modified intent-to-treat.
Study Objectives
Primary and Secondary Efficacy Objectives

Demonstrate the Efficacy of Prevenar 13 in the Prevention of a First Episode of:

1° VT pneumococcal CAP
   - Invasive or noninvasive

2° VT nonbacteremic/noninvasive pneumococcal CAP

2° VT invasive pneumococcal disease
   - With or without pneumonia

CAP=community-acquired pneumonia; VT=vaccine type.
### Study Subjects—Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Prevenar 13 n=42,237</th>
<th>Placebo n=42,255</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years (mean, SD, range)</strong></td>
<td>72.8 (5.7) (61.9–101.1)†</td>
<td>72.8 (5.6) (63.3–99.5)†</td>
</tr>
<tr>
<td><strong>Male (% n)</strong></td>
<td>55.5 (23,447)</td>
<td>56.3 (23,801)</td>
</tr>
<tr>
<td><strong>Female (% n)</strong></td>
<td>44.5 (18,790)</td>
<td>43.7 (18,454)</td>
</tr>
<tr>
<td><strong>Patient-reported comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Any (%)</strong></td>
<td>42.3</td>
<td>42.4</td>
</tr>
<tr>
<td><strong>Asthma (%)‡</strong></td>
<td>4.8</td>
<td>5.0</td>
</tr>
<tr>
<td><strong>Diabetes mellitus: insulin use (%)‡</strong></td>
<td>3.3</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>Diabetes mellitus: no insulin use (%)‡</strong></td>
<td>9.1</td>
<td>9.4</td>
</tr>
<tr>
<td><strong>Heart disease (%)‡</strong></td>
<td>25.3</td>
<td>25.4</td>
</tr>
<tr>
<td><strong>Liver disease (%)‡</strong></td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Lung disease (%)‡</strong></td>
<td>10.1</td>
<td>10.3</td>
</tr>
<tr>
<td><strong>Splenectomy (%)‡</strong></td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td><strong>Smoking (%)</strong></td>
<td>12.3</td>
<td>12.2</td>
</tr>
</tbody>
</table>

*Subjects <65 years of age were excluded from efficacy analyses.

†Not mutually exclusive.

SD=standard deviation.

## Primary and Secondary Objectives, Per-Protocol Population

<table>
<thead>
<tr>
<th>Efficacy end point</th>
<th>Vaccine group</th>
<th>VE (%)</th>
<th>95.2% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevenar 13 (n=42,240)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo (n=42,256)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1°: First episode of confirmed VT pneumococcal CAP</strong></td>
<td>49</td>
<td>90</td>
<td>45.6</td>
<td>(21.8, 62.5)</td>
</tr>
<tr>
<td><strong>2°: First episode of confirmed NB/NI VT pneumococcal CAP</strong></td>
<td>33</td>
<td>60</td>
<td>45.00</td>
<td>(14.2, 65.3)</td>
</tr>
<tr>
<td><strong>2°: First episode of VT-IPD</strong></td>
<td>7</td>
<td>28</td>
<td>75.00</td>
<td>(41.4, 90.8)†</td>
</tr>
</tbody>
</table>

†95% CI.

CAP=community-acquired pneumonia; IPD=invasive pneumococcal disease; NB=nonbacteremic; NI=noninvasive; VE=vaccine efficacy; VT=vaccine type.

First Episodes VT-CAP Cumulative Case Counts, Per-Protocol Population


Mean duration of follow-up = 3.97 years

VT-CAP=vaccine-type community-acquired pneumonia.
Cumulative Case Counts, Secondary End Points, Per-Protocol Population

Mean duration of follow-up=3.97 years

1st episodes NB/NI VT-CAP
- Prevenar 13
- Placebo

1st episodes VT-IPD
- Prevenar 13
- Placebo

45.0%
75.0%

CAP=community-acquired pneumonia; IPD=invasive pneumococcal disease; NB=nonbacteremic; NI=noninvasive; VT=vaccine type.

### Table 3. Safety Outcomes.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Safety Subgroup</th>
<th>P Value†</th>
<th>All Participants</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCV13 (N = 1006)</td>
<td>Placebo (N = 1005)</td>
<td>PCV13 (N = 42,237)</td>
<td>Placebo (N = 42,255)</td>
</tr>
<tr>
<td>Adverse event within 1 mo after vaccination</td>
<td>188 (18.7)</td>
<td>144 (14.3)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Chronic medical condition diagnosed 1–6 mo after vaccination‡</td>
<td>17 (1.7)</td>
<td>12 (1.2)</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>Serious adverse event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 6 mo after vaccination</td>
<td>70 (7.0)</td>
<td>60 (6.0)</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>327 (0.8)</td>
<td>314 (0.7)</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3006 (7.1)</td>
<td>3005 (7.1)</td>
<td>0.98</td>
<td></td>
</tr>
</tbody>
</table>

*Injection site reaction
Muscular pain
Summary

• Prevenar 13 demonstrated efficacy in adults aged 65 years and older
  – 45.6% (95.2% CI, 21.8%–62.5%; \( P<0.001 \)) for preventing the first episode of VT-CAP
  – 45.00% (95.2% CI, 14.2%–65.3%; \( P=0.007 \)) for preventing the first episode of NB/NI VT-CAP
  – 75.00% (95% CI, 41.4%–90.8%; \( P<0.001 \)) for preventing VT-IPD

• All 13 vaccine serotypes were circulating
  – PCV7 in Dutch children from 2006 (3+1), PCV10 introduced in March 2011 (3+1)

• Durability of vaccine efficacy through 4 years of follow-up
  – Mean duration of follow-up was 3.97 years

• The safety profile of Prevenar 13 in this study was consistent with that observed in previous studies of Prevenar 13 in adults
( ) PCV13/PPSV23; ( ) PCV13/PCV13; and ( ) PPSV23/PCV13.
ACIP Recommendations (Sep 2014)

- 2010: PPSV23 for age ≥65 years
- 2012: PCV13 and PPSV23 for adults aged ≥19 years with immunocompromising conditions
- Sept 2014:
  - PCV13 was approved by FDA in late 2011 for use among adults aged ≥50 years.
  - In June 2014, results of CAPiTA trial presented to ACIP
  - The recommendation was designated as a Category A recommendation

- What are the new recommendations?
  - Both PCV13 and PPSV23 should be routinely administered in series to all adults aged ≥65 years.
  - ACIP recommendations for routine use of PCV13 in adults aged ≥19 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leak, or cochlear implants remain unchanged.
Pneumococcal vaccine-naïve persons aged ≥65 years

PCV13 at age ≥65 years → PPSV23

≥1 years

Persons who previously received PPSV23 at age ≥65 years

PPSV23 already received at age ≥65 years → PCV13

≥1 years

Persons who previously received PPSV23 before age 65 years who are now aged ≥65 years

PPSV23 already received at age <65 years → PCV13 at age ≥65 years → PPSV23

≥1 years

≥5 years

Abbreviations: PCV13 = 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine.

* Minimum interval between sequential administration of PCV13 and PPSV23 is 8 weeks; PPSV23 can be given later than 6–12 months after PCV13 if this window is missed.
ACIP recommendations for persons 19-64 years old with immunocompromising conditions

**19 years old**
- PCV 13
- ≥8 weeks
- PSV 23
- ≥5 years
- PSV 23*
- ≥5 years
- PSV 23

**65 years old**
- PCV 13
- ≥8 weeks
- PSV 23
- ≥5 years
- PSV 23

**19 years old**
- PSV 23
- ≥1 year
- PCV 13
- ≥8 weeks
- PSV 23*
- ≥5 years
- PSV 23

**65 years old**
- PCV 13
- ≥8 weeks
- PSV 23*
- ≥5 years
- PSV 23

*MMWR, October 12, 2012, Vol 61, #40*
### HK CHP Recommendations (Dec 2014)

<table>
<thead>
<tr>
<th>Risk Groups</th>
<th>Pneumococcal Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk individuals aged 2 to 64 years who have not received any pneumococcal vaccines</td>
<td>One dose of PCV13 followed by one dose of 23vPPV at least 2 months after the previous PCV13 vaccination.</td>
</tr>
<tr>
<td>High risk individuals aged 2 to 64 years who have received 23vPPV</td>
<td>Single dose of PCV13 at least one year after previous 23vPPV vaccination. Additional dose of 23vPPV is not recommended.</td>
</tr>
<tr>
<td>High risk individuals aged 2 to 64 years who have received PCV13</td>
<td>Single dose of 23vPPV at least 2 months after previous PCV13 vaccination. Additional dose of PCV13 is not recommended.</td>
</tr>
<tr>
<td>Elders aged 65 years and above</td>
<td>Either a single dose of PCV13 or a single dose of 23vPPV. For those with additional high risk conditions, one-time revaccination may be considered 5 years after the first dose, depending on clinical judgment.</td>
</tr>
</tbody>
</table>

High Risk Groups

Box 1: High Risk groups in which pneumococcal vaccination is recommended for personal protection
1. Persons age 65 years or above, with or without additional high risk conditions
2. Persons age between 2 to 64 years and with the following high risk conditions:
   (a) History of invasive pneumococcal disease
   (b) Immunocompromised states:
      . Asplenia, HIV/AIDS, primary immunodeficiency
      . Immunodeficiencies related to malignancies and transplantation
      . Immunodeficiencies related to use of immunosuppressive drugs / systemic steroid
   (c) Chronic disease
      . Chronic cardiac, pulmonary, liver or renal disease
      . Diabetes mellitus or CSF leakage
   (d) With cochlear implants
Practical tips

• Both PCV10 and PCV13 are preservative-free, their recommended storage temperature is 2–8 °C, and the vaccines must **not** be frozen.
• The vaccines are given by injection into the anterolateral aspect of the thigh in infants and into the deltoid muscle in older age groups.
• The immunogenicity and reactogenicity of the involved vaccines have been shown **not** to be significantly altered when PCVs are given concomitantly with monovalent or combination vaccines against diphtheria, tetanus, pertussis (acellular and whole-cell vaccines), hepatitis B, polio (inactivated and live oral vaccines), Hib, measles, mumps, rubella, varicella, meningococcus serogroup C (conjugate vaccine), and rotavirus.
Thank you
Back-up slides
HK IPD Serotype Distribution (2014, all ages)

## Pneumococcal Serotypes in the 7-Valent, 10-Valent, and 13-Valent Pneumococcal Conjugate Vaccines

<table>
<thead>
<tr>
<th>7-valent*</th>
<th>Carrier: CRM\textsubscript{197}</th>
<th>4</th>
<th>6B</th>
<th>9V</th>
<th>14</th>
<th>18C</th>
<th>19F</th>
<th>23F</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-valent†</td>
<td><em>H. influenzae</em> protein D, tetanus, and diphtheria toxoid</td>
<td>4</td>
<td>6B</td>
<td>9V</td>
<td>14</td>
<td>18C</td>
<td>19F</td>
<td>23F</td>
</tr>
<tr>
<td>13-valent‡</td>
<td>Carrier: CRM\textsubscript{197}</td>
<td>4</td>
<td>6B</td>
<td>9V</td>
<td>14</td>
<td>18C</td>
<td>19F</td>
<td>23F</td>
</tr>
<tr>
<td>23-valent§</td>
<td>1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>