Efficacy of Combined Influenza and 23-valent Pneumococcal Polysaccharide Vaccines in Patients with Chronic Illness

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The University of Hong Kong
Outlines

• Study 1: Follow-up study on the efficacy of combined influenza and PPV23 in patients with chronic illness (HK-09-01-16)
• Study 2: Efficacy of combined influenza and PPV23 in patients aged 50-64 years (HK-09-01-16)
• Study 3: Efficacy of combined influenza and PPV23 in smokers (HK-09-01-17) - Poster
Background: Study 1 & 2

• Pneumococcal and influenza infections can cause serious morbidity and mortality, especially in the elderly population

• WHO estimates influenza and pneumococcal disease causes 500,000 and 1.6 millions deaths annually respectively

• In Hong Kong, the overcrowded living conditions facilitate the transmission of both influenza and pneumococcal infection.

http://www.who.int/ith/diseases/pneumococcal/en/
http://www.who.int/topics/influenza/en/
In 2014, 7,431 died from pneumonia:
Average: 20.6 deaths/day

Pneumonia – 2nd Leading Cause of Death in Hong Kong

S. pneumoniae: G+ve diplococci
Polysaccharide capsule: defines serotypes, virulence factors and vaccine targets
29.2% of all-cause CAP

S. pneumoniae: Total 94 serotypes
Varied distribution, pathogenicity
<30 serotypes accounted for 90% isolates

CDC Epidemiology & Prevention of vaccine preventable disease 2009
Streptococcus pneumoniae

ABC SURVEILLANCE REPORT – US DATA – 2009

Streptococcus pneumoniae

Cases
Deaths


Courtesy of Professor Keith Klugman
The overlap between pneumococcal pneumonia and IPD

- **Pneumococcal pneumonia**
  - Bacteremic pneumococcal pneumonia
  - Non-bacteremic pneumococcal pneumonia

- **Invasive pneumococcal diseases**
  - Meningitis
  - Pleuritis, arthritis, etc.
  - Bacteremic pneumococcal pneumonia

- Large circle: Pneumococcal pneumonia
- Small circle: Invasive pneumococcal disease

Fedson, Musher, *Vaccines*, 2004
## Background

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Subgroup</th>
<th>No. of cases of IPD</th>
<th>VE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shapiro and Clemens [2]</td>
<td>Case control</td>
<td>Adults with an indication for pneumococcal vaccination admitted to Yale-New Haven hospital in Connecticut</td>
<td>All Immunocompromised</td>
<td>90</td>
<td>67 (13–87)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>0 (−1228 to 93)</td>
</tr>
<tr>
<td>Sims et al. [4]</td>
<td>Case control</td>
<td>Immuneicompetent persons &gt;55 years of age admitted to 1 of 6 hospitals in Pennsylvania</td>
<td>All</td>
<td>122</td>
<td>70 (36–66)</td>
</tr>
<tr>
<td>Shapiro et al. [5]</td>
<td>Case control</td>
<td>Adults with an indication for pneumococcal vaccination admitted to 1 of 11 hospitals in Connecticut</td>
<td>All Immunocompetent Immunocompromised</td>
<td>983</td>
<td>56 (42–67)</td>
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<tr>
<td></td>
<td>Indirect cohort</td>
<td>Adults with an indication for pneumococcal vaccination admitted to 1 of 11 hospitals in Connecticut</td>
<td>All</td>
<td>808</td>
<td>61 (47–72)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>175</td>
<td>21 (−55 to 60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>932</td>
<td>48 (3–72)</td>
</tr>
</tbody>
</table>

Jackson LA. *Clin Infect Dis* 2008;47:1328 38
<table>
<thead>
<tr>
<th>Reference</th>
<th>Vaccine valency</th>
<th>Study population</th>
<th>VE (95% CI)</th>
<th>No. of cases of pneumonia/ no. of vaccinated persons</th>
<th>No. of cases of pneumonia/ no. of nonvaccinated persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austrian [24]</td>
<td>12</td>
<td>Inpatients at the Dorothea Dix psychiatric hospital in Raleigh, North Carolina</td>
<td>$-22 (-49$ to $0)$</td>
<td>154/607</td>
<td>144/693</td>
</tr>
<tr>
<td>Study 1</td>
<td>12</td>
<td>Members of the Kaiser Permanente Health Plan in San Francisco $\geq 45$ years of age</td>
<td>2 (−16 to 7)</td>
<td>268/6782</td>
<td>274/6818</td>
</tr>
<tr>
<td>Study 2</td>
<td>12</td>
<td>Residents of 45 long-term care institutions in France</td>
<td>79 (53 to 91)</td>
<td>7/937</td>
<td>27/749</td>
</tr>
<tr>
<td>Gaillat et al. [25]</td>
<td>14</td>
<td>US veterans, immunocompetent, and either aged $\geq 55$ years or with renal, hepatic, cardiac, or pulmonary disease; alcoholism; or diabetes mellitus</td>
<td>$-39 (-110$ to $8)$</td>
<td>56/1145</td>
<td>41/1150</td>
</tr>
<tr>
<td>Koivula et al. [27]</td>
<td>14</td>
<td>Residents of a small town in Finland $\geq 60$ years</td>
<td>$-17 (-66$ to $17)$</td>
<td>69/1364</td>
<td>64/1473</td>
</tr>
<tr>
<td>Örtqvist et al. [28]</td>
<td>23</td>
<td>Immunocompetent persons 50–95 years of age who had been previously discharged after a hospitalization for community-acquired pneumonia in Sweden</td>
<td>$-20 (-72$ to $11)$</td>
<td>63/339</td>
<td>57/352</td>
</tr>
<tr>
<td>Honkanen et al. [29]</td>
<td>23</td>
<td>Persons $\geq 65$ years of age in Northern Finland</td>
<td>$-20 (-50$ to $10)$</td>
<td>145/13980</td>
<td>116/12945</td>
</tr>
<tr>
<td>Alfageme et al. [30]</td>
<td>23</td>
<td>Immunocompetent patients with COPD 81–73 years of age in Seville, Spain</td>
<td>3 (−52 to 38)</td>
<td>33/298</td>
<td>34/298</td>
</tr>
</tbody>
</table>
Background

- 64 weeks
- Dual vaccinees:
  - Fewer deaths
    - HR 0.65 (0.55-0.77)
  - Fewer pneumonia
    - HR 0.57 (0.51-0.64)
  - Fewer ischemic stroke
    - HR 0.67 (0.54-0.83)
  - Fewer acute MI
    - HR 0.52 (0.38-0.71)

Background: Study 1 & 2

- Long-term effect of dual vaccinations on these subjects and its effect in the 50-64 years age group remained unknown

- To answer these questions, we performed a long-term follow-up study on the elderly subjects we recruited in the initial study and another prospective study on the 50-64 years old with chronic illness.
Study 1: Patients & Methods

- Recruited from the original prospective cohort study
- Between 2007 - 2014
- Single Centre: QMH
- Study protocol approved by the HKU/ HA IRB

**Inclusion**
- Age ≥ 65
- At least one chronic illness: asthma, COPD, CAD, HT, DM, stroke, chronic renal or liver disease, malignancy

**Exclusion**
- Allergy to egg, vaccine components
- Deviation from their initial vaccine group
- All patients in the PPV+TIV or TIV group received TIV annually including the A/H1N1/2009pdm monovalent influenza vaccine
Study 1: Methodology

- Participants to choose their own vaccination
- 4 groups
  - PPV + TIV
  - PPV
  - TIV
  - No vaccination
- PPV23: Pneumovax (Pasteur Merieux) IM
- TIV: Vaxigrip (Sanofi Pasteur) IM

- Diagnosis: ICD-9-CM
- Primary: mortality
- Secondary: hospitalization, ICU admission
Study 1: Methodology

• Statistical analysis
  – SPSS 20.0 software
• $X^2$ categorical variables
• Mann-Whitney U test continuous variables
• Cox proportional hazard models
• Log-rank test: vaccine effectiveness
• P values <0.05
Study 1: Results

36636 patients from 2007 Prospective Cohort

- PPV + TIV: 7292 (19.9%)
- TIV: 2076 (5.7%)
- PPV: 1875 (5.1%)
- None: 25393 (69.3%)

PPV + TIV: 6675 (24.8%)
- TIV: 1848 (6.8%)
- PPV: 1676 (6.2%)
- None: 16750 (62.2%)

26949 Follow up till Dec 2014

Mortality, hospitalization, ICU admission
### Study 1: Results

**Baseline characteristics of the 26,949 study subjects**

<table>
<thead>
<tr>
<th></th>
<th>Unvaccinated (n=16,570)</th>
<th>PPV + TIV (n=6,675)</th>
<th>TIV alone (n=1,848)</th>
<th>PPV alone (n=1,676)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range) years</td>
<td>75 (70-80)</td>
<td>77 (71-83)</td>
<td>75 (70-80)</td>
<td>75 (71-80)</td>
<td>0.81</td>
</tr>
<tr>
<td>Male</td>
<td>46.9</td>
<td>40.5</td>
<td>44.3</td>
<td>45.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Asthma</td>
<td>2.1</td>
<td>2.2</td>
<td>2.2</td>
<td>2.8</td>
<td>0.32</td>
</tr>
<tr>
<td>COPD</td>
<td>2.1</td>
<td>4.4</td>
<td>4.6</td>
<td>4.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IHD</td>
<td>7.9</td>
<td>7.5</td>
<td>7.2</td>
<td>7.3</td>
<td>0.55</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.4</td>
<td>1.4</td>
<td>1.3</td>
<td>1.1</td>
<td>0.89</td>
</tr>
<tr>
<td>Heart failure</td>
<td>6.3</td>
<td>6.9</td>
<td>6.8</td>
<td>7.5</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypertension</td>
<td>61.7</td>
<td>60.6</td>
<td>60.6</td>
<td>59.8</td>
<td>0.22</td>
</tr>
<tr>
<td>Diabetes</td>
<td>24.3</td>
<td>25.7</td>
<td>24.6</td>
<td>24.5</td>
<td>0.15</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>7.2</td>
<td>7.9</td>
<td>7.5</td>
<td>7.4</td>
<td>0.28</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
<td>0.3</td>
<td>0.20</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>2.3</td>
<td>2.4</td>
<td>2.5</td>
<td>2.6</td>
<td>0.55</td>
</tr>
<tr>
<td>Cancer</td>
<td>5.4</td>
<td>5.2</td>
<td>5.5</td>
<td>5.9</td>
<td>0.66</td>
</tr>
<tr>
<td>Smoker</td>
<td>13.5</td>
<td>14.2</td>
<td>13.8</td>
<td>14.8</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Note: PPV: pneumococcal polysaccharide vaccine; TIV: trivalent influenza vaccine; COPD: chronic obstructive pulmonary disease, IHD: ischemic heart disease.
Study 1: Results

7 years follow-up:

• Median age: 75 years (IQR: 70-80)
• Mortality rate:
  – PPV+TIV 28% vs. TIV 29.8% vs. PPV 33.1% vs. none 32.9% (p<0.001)

• PPV+TIV vs. none
  – Deaths: HR, 0.80; 95% CI 0.76-0.84; p<0.001
  – CVS events: HR, 0.59; 95% CI 0.55-0.63; p<0.001
  – Pneumonia: HR, 0.53; 95% CI 0.49-0.58; p<0.001
  – Influenza: HR, 0.32; 95% CI 0.22-0.46; p<0.001
  – CVA: HR, 0.68; 95% CI 0.61-0.75; p<0.001
  – ICU admission: HR, 0.58; 95% CI 0.47-0.71; p<0.001
Kaplan-Meier survival of 26,949 patients

P<0.001

Hospitalization for CVS events

P<0.001
Study 1: Discussion

- Sustained protection of PPV + TIV in elderly with chronic illness
- Confirmed long-term efficacy reduced mortality, hospitalization for CVS and respiratory complications, ICU admission
- Highlighted the importance of annual influenza vaccination
- Waning of PPV protection around 5 years
- Limitation: non-randomized, lack of immunological response data
Study 2: Patients & Methods

- **Prospective open label RCT**
- **Between 2010 - 2014**
- **Single Centre: QMH**
- **Study protocol approved by the HKU/ HA IRB**

**Inclusion**
- Age 50-64 years
- At least one chronic illness: asthma, COPD, CAD, HT, DM, stroke, chronic renal or liver disease, malignancy
- Written informed consent (patient or next of kin)

**Exclusion**
- Allergy to egg, vaccine components
- Received chemo or radiation therapy within 12 months
- HIV infection
Study 2: Methodology

- Participants recruited from QMH SOPD
- Oct 2010 to April 2012
- Randomized into 4 groups
  - PPV + TIV
  - PPV
  - TIV
  - No vaccination
- PPV23: Pneumovax (Pasteur Merieux) IM
- TIV: Vaxigrip (Sanofi Pasteur) IM
- Diagnosis: ICD-9-CM
- Primary: mortality
- Secondary: hospitalization, ICU admission
Study 2: Methodology

- Statistical analysis
  - SPSS 20.0 software
- $X^2$ categorical variables
- Mann-Whitney U test continuous variables
- Cox proportional hazard models
- Log-rank test: vaccine effectiveness
- $P$ values <0.05
Study 2: Results

- 2009
  - Prospective Cohort
    - PPV + TIV, 250 (25%)
    - TIV, 250 (25%)
    - PPV, 250 (25%)
    - None, 250 (25%)

Follow up till Dec 2014

Mortality, hospitalization, ICU admission
Study 2: Results

5 years follow-up:
• Median age: 57 years; 485 (48.5%) males
• Well matched baseline demographics

• Significantly fewer hospitalization for respiratory, CVS and cerebrovascular events (p<0.001)
  – PPV+TIV: 17.8% vs. TIV: 22% vs. PPV: 23.3% vs. none: 28%
• Less frequent hospitalization (p<0.001)
• No difference in mortality rate and length of stay
• Both vaccines well tolerated
Study 2: Discussion

- Dual vaccination prevent hospitalization for CVS, pulmonary and cerebrovascular complications in age 50-64 years with chronic illness

- Pneumococcal vaccination justified in age 50-64 chronic illness

- No difference in mortality and LOS

- Limitation: small sample size, no immunological response data
Conclusions for Study 1 & 2

- Dual influenza and PPV vaccination strongly recommended for subjects with chronic illness >50 years
- Importance of annual influenza vaccination
- Protection against pneumococcal disease relied on strong herd immunity from children vaccination
- Clinical efficacy of PCV13 in adults to be determined
- Serotype replacement
- Head to head PCV vs PPV trial undergoing
- When to revaccinate
ACIP vs. JCVI Recommendation

BOX. Recommended intervals for sequential use of PCV13 and PPSV23 for immunocompetent adults aged ≥65 years — Advisory Committee on Immunization Practices, United States

- Pneumococcal vaccine-naive persons aged ≥65 years
  - PCV13 at age ≥65 years
  - PPSV23
  - ≥1 year

- Persons who previously received PPSV23 at age ≥65 years
  - PPSV23 already received at age ≥65 years
  - PCV13
  - ≥1 year

- 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 year
  - ≥1 year
  - ≥5 years

Conclusions

34. The indirect impact of the childhood PCV13 vaccination programme on pneumococcal disease in older adults and those in clinical risk groups means that the additional benefit of the direct protection provided by wider use of PCV13 in older adults and clinical risk groups in the UK is declining and is likely to diminish further over the next few years.

35. Analyses indicate that it would not be cost-effective to extend the PCV13 vaccination programme to those aged 65 years and over or to additional clinical risk groups, and it is likely to become less cost-effective over time. Use of PPSV23 vaccine in those aged 65 years and over is likely to remain cost-effective.

36. JCVI has therefore concluded that there should be no changes to the advice on adult pneumococcal vaccination in the UK at this time. PPSV23 should continue to be offered to those aged 65 years and over and the indicated risk groups. PCV13 should continue to be offered to those risk groups previously identified as being at particularly high risk of, and high mortality from, IPD, but should not be offered more widely to other risk groups or older adults.

The advice of JCVI is made with reference to the UK immunisation programme and may not necessarily transfer to other epidemiological circumstances.

JCVI

Joint Committee on Vaccination and Immunisation

November 2016
Acknowledgements

• Health and Medical Research Fund
• Department of Microbiology, LKS Faculty of Medicine, HKU
• Department of Medicine, LKS Faculty of Medicine, HKU
• School of Nursing, LKS Faculty of Medicine, HKU
• Hospital Authority
Thank you!
Background: Study 3

- Chronic smokers are at risk of acquiring severe pneumococcal and influenza infections
- Risk of pneumococcal pneumonia x 2 for 1 cigarette a day, x 4 for 15 to 24 cigarettes a day
- Higher chance of upper respiratory viral infection as well as nasopharyngeal pneumococcal carriage.
- Smoking affect the mucociliary function, as well as reducing the clearance of mucus, thereby compromising the local airway defences
- At risk populations not covered by the HA/ DH vaccination program
- To investigate the effect of dual influenza and PPV vaccination in chronic smokers

http://www.who.int/ith/diseases/pneumococcal/en/
http://www.who.int/topics/influenza/en/
Study 3: Patients & Methods

- Prospective open label RCT
- Between 2009 - 2014
- Single Centre: QMH
- Study protocol approved by the HKU/ HA IRB

Inclusion
- Age \( \leq 50 \) years
- Chronic smokers: at least 1 cigarette per day
- Chronic illness allowed
- Written informed consent (patient or next of kin)

Exclusion
- Allergy to egg, vaccine components
- Received chemo or radiation therapy within 12 months
- HIV infection
Study 3: Methodology

- Participants randomized
- 4 groups
  - PPV + TIV
  - PPV
  - TIV
  - No vaccination
- PPV23: Pneumovax (Pasteur Merieux) IM
- TIV: Vaxigrip (Sanofi Pasteur) IM

- TIV 2010-11 and 2011-12: A/California/7/2009 H1N1, A/Perth/16/2009 H3N2, B/Brisbane/60/2008
- Diagnosis: ICD-9-CM
- Primary: mortality
- Secondary: hospitalization, ICU admission
Study 3: Methodology

• Statistical analysis
  – SPSS 20.0 software
• $X^2$ categorical variables
• Mann-Whitney U test continuous variables
• Cox proportional hazard models
• Log-rank test: vaccine effectiveness
• P values <0.05
Study 3: Results

Prospective Cohort: 1006 recruited

- PPV + TIV 250
- TIV 254
- PPV 250
- None 252

Follow up till Dec 2014

Mortality, hospitalization, ICU admission
# Demographics and Outcomes

<table>
<thead>
<tr>
<th></th>
<th>PPV+TIV (n=250)</th>
<th>TIV (n=254)</th>
<th>PPV (n=250)</th>
<th>None (n=252)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Median; IQR)</td>
<td>48 (47.48)</td>
<td>48 (46.48)</td>
<td>48 (46.48)</td>
<td>48 (46.48)</td>
<td>0.221</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>222</td>
<td>213</td>
<td>212</td>
<td>217</td>
<td>0.363</td>
</tr>
<tr>
<td>Mean Charlson’s comorbidity index</td>
<td>0.150</td>
<td>0.40</td>
<td>0.43</td>
<td>0.37</td>
<td>0.980</td>
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<tr>
<td>Cardiovascular disease</td>
<td>120</td>
<td>143</td>
<td>139</td>
<td>132</td>
<td>0.326</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>29</td>
<td>26</td>
<td>33</td>
<td>37</td>
<td>0.307</td>
</tr>
<tr>
<td>Neurological disease</td>
<td>10</td>
<td>13</td>
<td>16</td>
<td>6</td>
<td>0.302</td>
</tr>
<tr>
<td>Metabolic disease</td>
<td>24</td>
<td>13</td>
<td>19</td>
<td>20</td>
<td>0.510</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>35</td>
<td>30</td>
<td>20</td>
<td>28</td>
<td>0.329</td>
</tr>
<tr>
<td>Hematological disease</td>
<td>8</td>
<td>6</td>
<td>3</td>
<td>5</td>
<td>0.391</td>
</tr>
<tr>
<td>Dermatological disease</td>
<td>10</td>
<td>11</td>
<td>13</td>
<td>14</td>
<td>0.414</td>
</tr>
<tr>
<td>Rheumatological disease</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>0.550</td>
</tr>
<tr>
<td>Renal disease</td>
<td>7</td>
<td>5</td>
<td>9</td>
<td>5</td>
<td>0.550</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>PPV+TIV (n=250)</th>
<th>TIV (n=254)</th>
<th>PPV (n=250)</th>
<th>None (n=252)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall hospitalization</td>
<td>23 (9.2%)</td>
<td>66 (26%)</td>
<td>74 (29.6%)</td>
<td>84 (33%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean length of stay in hospital (days)</td>
<td>2.69</td>
<td>6.65</td>
<td>7.05</td>
<td>4.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequency of hospitalization</td>
<td>0.19</td>
<td>0.49</td>
<td>0.60</td>
<td>0.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>11 (4.4%)</td>
<td>29 (11%)</td>
<td>41 (16.4%)</td>
<td>36 (14%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>12 (4.8%)</td>
<td>32 (13%)</td>
<td>31 (12.4%)</td>
<td>45 (18%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Neurological disease</td>
<td>0 (0%)</td>
<td>5 (2%)</td>
<td>2 (0.8%)</td>
<td>3 (1%)</td>
<td>0.026</td>
</tr>
<tr>
<td>Mortality</td>
<td>10 (4%)</td>
<td>14 (6%)</td>
<td>10 (4%)</td>
<td>15 (6%)</td>
<td>0.320</td>
</tr>
</tbody>
</table>

Overall hospitalization: from vaccination to first episode of hospitalization
Frequency of hospitalization: total number of admissions
Study 3: Results

2 years follow-up:
• Median age: 48 years; 816 male (81.1%)
• Well matched baseline demographics

• Significantly fewer hospitalization for respiratory, CVS and cerebrovascular events (p<0.001)
  – PPV+TIV: 9.2% vs. TIV: 26% vs. PPV: 29.6% vs. none: 33.3%
• Less frequent hospitalization (p<0.001)
• No difference in mortality rate and length of stay
• Both vaccines well tolerated
Study 3: Discussion

- Dual PPV + TIV effectively prevent *S. pneumonia* and influenza infection in chronic smokers
- Reduces risk of exacerbating underlying CVS and respiratory disease
- Such reduction of hospitalization of smokers can greatly reduce the government expenses.
- Role of PCV13 to be determined
- Limitations in the study
  - Only recruited aged ≤50, therefore, the efficacy of dual vaccination on chronic smoker aged >50 remained unknown. Secondly, a
  - All participants recruited were from Queen Mary hospital and might not represent the population in Hong Kong as a whole
  - Dose effect of number of cigarettes smoked and smoking years not available for analysis
  - Effect on ‘healthy’ smokers unknown