13-valent pneumococcal conjugate vaccine efficacy is declining with old age: results from an exploratory analysis of the CAPiTA trial

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Objective
To assess the effect of age on 13-valent pneumococcal conjugate vaccine (PCV13) efficacy in immunocompetent 65+ adults

Methods
This is a post-hoc analysis of data from the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA), a randomized comparison of PCV13 to placebo in 84,496 immunocompetent subjects aged 65 and older.1

Data collection
• Identification of vaccine-type community-acquired pneumonia (VT-CAP) and invasive pneumococcal disease (VT-IPD) (see Box)
• Urine collection within 48 hours for serotype-specific urinary antigen detection (UAD)2
• Cultures as part of routine clinical care
• Serotyping of isolated Streptococcus pneumoniae strains in a central laboratory

Data analysis
• Cox proportional hazards model - PCV13 allocation, age and interaction term - Outcome: first episode of VT-CAP or VT-IPD - Vaccine efficacy (VE): 1 – hazard ratio (HR)
• Primary analysis: modified intention-to-treat analysis
• Sensitivity analyses: - VT-CAP and VT-IPD separately - Per protocol population (subjects still immunocompetent at time of event) - Adjusted analyses

Results
The vaccine group consisted of 42,240 and the placebo group of 42,256 subjects, both with a median follow-up duration of 3.9 years (IQR 3.8-4.8 years).

• Age was similarly distributed in the vaccine and placebo group with a median of 71.6 years (IQR 68.1-76.5). A total of 10,657 (12.6%) were 80+ years and 2,942 (3.5%) were 85+.

• The interaction effect of age on VE is given in the Table and Figure.

Discussion
• PCV13 efficacy was highest among 65 year old subjects and declined with increasing age
• Previous studies found reduced antibody responses to PCV7 in subjects > 75 years,3 although this was not seen in PCV13
• Similar age-vaccine interactions have been observed in meningococcal vaccines and hepatitis B vaccine5-6
• Our findings are relevant for cost effectiveness analyses: differences in VE for age groups can be based on empirical data
• Limited number events in subjects > 85 years. Point estimate suggests no VE in this age group, but a relevant effect could not be excluded given the small numbers
• This is a post-hoc hypothesis generating analysis. Yet, there was a statistically significant decline in VE by increasing age in the primary analysis with similar effect estimates in sensitivity analyses.

Conclusion
In immunocompetent subjects aged 65 years and older, vaccine efficacy of PCV13 declined with increasing age

Table: Vaccine-age interaction effects

<table>
<thead>
<tr>
<th>Vaccine-age interaction</th>
<th>N events</th>
<th>Crude HR (95% CI)</th>
<th>P-value</th>
<th>Adjusted HR *</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified intention-to-treat analysis</td>
<td></td>
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<tr>
<td>VT-CAP or VT-IPD</td>
<td>184</td>
<td>1.058 (1.008-1.110)</td>
<td>0.022</td>
<td>1.058 (1.008-1.111)</td>
<td>0.023</td>
</tr>
<tr>
<td>VT-CAP</td>
<td>172</td>
<td>1.050 (1.000-1.102)</td>
<td>0.052</td>
<td>1.050 (0.999-1.104)</td>
<td>0.053</td>
</tr>
<tr>
<td>VT-IPD</td>
<td>41</td>
<td>1.087 (0.965-1.224)</td>
<td>0.171</td>
<td>1.079 (0.950-1.225)</td>
<td>0.240</td>
</tr>
<tr>
<td>Per protocol analysis</td>
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</tr>
<tr>
<td>VT-CAP or VT-IPD</td>
<td>149</td>
<td>1.067 (1.011-1.126)</td>
<td>0.019</td>
<td>1.067 (1.010-1.128)</td>
<td>0.021</td>
</tr>
<tr>
<td>VT-CAP</td>
<td>139</td>
<td>1.061 (1.004-1.122)</td>
<td>0.035</td>
<td>1.062 (1.003-1.124)</td>
<td>0.038</td>
</tr>
<tr>
<td>VT-IPD</td>
<td>35</td>
<td>1.090 (0.963-1.235)</td>
<td>0.174</td>
<td>1.086 (0.949-1.241)</td>
<td>0.230</td>
</tr>
</tbody>
</table>

* Adjusted for gender, pulmonary disease, cardiac disease, diabetes and smoking. HR: hazard ratio; CI: confidence interval. HR represents increase of HR for the outcome of vaccinated subjects, for every year increase of age. HR above 1 means decreasing VE by increasing age.

References
1. Bonten et al. ID Week 2014, abstract no. 47346
4. van Deuren et al. ID Week 2014, abstract no. 47279

Box: case definitions

VT-CAP:
• 2 or more clinical criteria (cough, sputum production or change in sputum character, temperature >38°C or <36.1°C, auscultatory findings of pneumonia, leucocyte count >1010/L, CRP >30 mmol/L, arterial pO2 <8 kPa)
• Abnormalities on chest X-ray consistent with CAP
• Detection of vaccine-type S. pneumoniae in blood culture, other sterile cultures, and/or serotype specific UAD

VT-IPD:
• Vaccine-type S. pneumoniae strain isolated from sterile site
• Or, non-typable S. pneumoniae strain isolated from sterile site and detection of vaccine-type S. pneumoniae by serotype specific UAD
• Sterile site: blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, surgical aspirate, bone, or joint fluid

Legend: Modified intention-to-treat analysis for combined endpoint. Solid lines represent model derived VE and 95%CI. Triangles represent crude estimates of age groups of 2.5 years each.

Figure: Model derived vaccine efficacy by age

In immunocompetent subjects aged 65 years and older, vaccine efficacy of PCV13 declined with increasing age