Third Joint Conference
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Immunological efficacy of a Prime-Boost Strategy Combining the 13-valent conjugate pneumococcal vaccine (PCV13) Followed by the 23-valent polysaccharide pneumococcal vaccine (PPV23) versus PPV23 Alone in HIV-Infected Adults: A stimulus to vaccine review

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Background

• *Strep. pneumoniae* remains one of the most significant causes of morbidity and mortality worldwide

• HIV-infected adults are disproportionately affected\(^1,^2\)

• IPD - associated mortality of 10-50\(^{\%}\)^\(^3,^4\)

Efficacy of vaccine in HIV-infected adults

• Observational studies suggest varying degrees of protection with PPV 23⁵

• Studies have shown a trend towards more cases of IPD in vaccinated patients⁶

• IgG2 levels post pneumococcal vaccination – 17% of HIV infected patients had protective levels⁷

7. Brown A, ECCMID p2;2008
Prime-boost immunisation strategy

- *Strep. pneumoniae* polysaccharides, conjugated with a carrier protein, induce a T-cell dependent immune response (priming)

- Secondary antibody response with revaccination (boosting) may enhance and prolong the period of protection among the vaccine recipients

Aim

• Compare immunological efficacy of a prime boost vaccine strategy combining PCV13 followed by PPV23 versus PPV23 alone in HIV-infected adults
## Study Plan

- HIV-infected adults ≥18 years, pneumococcal vaccine naïve with CD4 count > 200 cells/mm³ were recruited

- Randomised to receive PCV13 + PPV23 at week 4 or PPV23

<table>
<thead>
<tr>
<th>Week 0</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV13 + PPV23 group: Pre-dose blood draw + PCV 13 vaccine</td>
<td>PPV23 group: Pre-dose blood draw</td>
<td>Both Groups: 4 week post vaccine blood draw</td>
<td>Both Groups: 24 weeks post vaccine blood draw</td>
</tr>
</tbody>
</table>

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**Background** | **Aims** | **Methods** | **Results** | **Discussion** | **Conclusion**
Methods

Quantitative measures

• Serotype specific IgG geometric mean titre (GMT) for 12 pneumococcal polysaccharide serotypes shared by PCV13 and PPV23 (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F)
• Fold increase in pneumococcal polysaccharide serotype specific IgG
• Proportion of vaccine responders (≥2-fold increase in AB titre to ≥ 6 serotypes)

Functional measure

• Phagocytic uptake response of neutrophils was measured using an in-house oposonophagocytic flow cytometric assay

Statistical methods

• Wilcoxon and t-tests were used to compare continuous and categorical variables as appropriate
Disposition of subjects

60 subjects recruited

PCV13 + PPV23
- 27 subjects
  - Week 8
    - 26 bloods
  - Week 28
    - 26 bloods

PPV23
- 33 subjects
  - Week 8
    - 28 bloods
  - Week 28
    - 29 bloods

1 subject failed to attend at week 8
1 subject transferred care
5 subject failed to attend at week 8
3 subject failed to attend at week 28, 1 subject transferred care
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>TOTAL COHORT</th>
<th>PPV 23</th>
<th>PCV13+PPV23</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>60</td>
<td>33</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Male n, (%)</td>
<td>55 (92)</td>
<td>29 (88)</td>
<td>26 (96)</td>
<td>0.37</td>
</tr>
<tr>
<td>Age (mean)[SD]</td>
<td>37 [10]</td>
<td>37 [10]</td>
<td>36 [10]</td>
<td>0.70</td>
</tr>
<tr>
<td>Race n, (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>48 (80)</td>
<td>25 (76)</td>
<td>23 (85)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7 (12)</td>
<td>4 (12)</td>
<td>3 (11)</td>
<td>1.0</td>
</tr>
<tr>
<td>Black</td>
<td>5 (8)</td>
<td>4 (12)</td>
<td>1 (4)</td>
<td>0.37</td>
</tr>
<tr>
<td>Risk of Acquisitions n, (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>49 (82)</td>
<td>25 (76)</td>
<td>24 (89)</td>
<td>0.32</td>
</tr>
<tr>
<td>Hetero</td>
<td>8 (13)</td>
<td>6 (18)</td>
<td>2 (8)</td>
<td>0.28</td>
</tr>
<tr>
<td>IDU</td>
<td>3 (5)</td>
<td>2 (6)</td>
<td>0</td>
<td>0.49</td>
</tr>
<tr>
<td>On HAART n, (%)</td>
<td>28 (47)</td>
<td>17 (52)</td>
<td>11 (40)</td>
<td>0.45</td>
</tr>
<tr>
<td>Smoker n, (%)</td>
<td>20 (33)</td>
<td>11 (33)</td>
<td>9 (27)</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Quantitative immunological response
Serotype specific IgG response - week 8

- 88% PB group vs. 86% un-primed group “responders”
- IgG GMT significantly higher in PB group for serotype 23F *
- Fold increase in GMT greater in the PB group
  \[(8.69 [4.61] vs. 4.49 [1.24], p<0.001)\]
Serotype specific IgG response - week 28

• 85% PB group vs. 52% un-primed group (p=0.01) “responders”
• PB IgG GMT significantly higher for 4 serotypes 1 *, 4 *, 19F *, 23F*
• Fold increase in GMT greater in the PB group
  (4.39 [1.77] vs. 2.47 [0.67], p=0.05)
Functional immunological response

- Measurement of total binding IgG includes both functional and non-functional antibodies

- Oposonphagocytic assays are thought to represent the best correlate of protection from pneumococcal infection

- Multiplexed OPA uptake assay to estimate phagocytic activity pre and post-vaccination in a subgroup of 12 patients for serotypes 7F, 14, 19A
Functional neutrophil response

Oposonophagocytic assay titre

Serotype 7F
Serotype 14
Serotype 19A
Correlation between OPA titre and IgG measurement

Number of responders (Total n = 12)
Summary

• The prime boost vaccine strategy resulted in:
  • higher proportion of vaccine responders at week 28;
    (85% vs. 52%, p=0.01)
  • greater fold increase in IgG GMT at week 8 and 28;
    (p<0.001 and p=0.05 respectively)

• Poor correlation between functional and quantitative measures:
  • multiple immune dysregulations associated with HIV
  • antibody formed may have lower functional activity
Limitations

• Study number

• Immunological surrogates as a measure of vaccine response

• Functional assay experimental

• Cannot account for all other factors that may influence vaccine response
Conclusion

• Results of this study indicate that in a HIV-infected cohort immunogenicity and durability of pneumococcal vaccine were enhanced by the prime-boost vaccine strategy

• Adds to evidence supporting recent changes to US pneumococcal vaccination recommendations for immunocompromised hosts
Acknowledgements

Patients who participated in the study

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Dr Alice Coughlan, Immunology research group

Vaccine Evaluation Unit Manchester

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