Essential Criteria for Evaluation of Pneumococcal Conjugate Vaccine (PCV) Candidates

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Wyeth Vaccines
The Impact of PCV7

- The direct effects
  - Invasive disease
  - Otitis media
  - Pneumonia

- The indirect effects
  - Invasive disease
  - Pneumonia
Since the Licensure of PCV7

- Launched in 90 countries
- More than 170M doses have been distributed
- Capacity has been expanded to meet global demand
Pneumococcal Conjugate Vaccines and Serotype Coverage

- PCV7 was designed to cover the most prevalent serotypes.

- At the time of licensure, it was hoped that serogroup protection would be achieved, especially for 6A and 19A.

- Next-generation products should expand serogroup coverage.
Issues With Expanding Vaccine Coverage

1. The potential for interference in combinations\(^1\)
   
   - Experience with CRM\(_{197}\)-based pneumococcal conjugate\(^2\)

2. The inability to do efficacy trials\(^3\)
   
   - The need for a reference value associated with clinical efficacy\(^3\) (correlate of protection)

Pneumococcal Conjugate Vaccines: Correlates of Immunity

- **2003** - WHO working group estimated the protective concentration of anticapsular antibodies by correlating the anticapsular antibody levels of children with the clinical efficacy against IPD in three efficacy trials (PCV7 or 9v-PnC)
  - Northern California Kaiser Permanente
  - South Africa
  - Navajo

- **WHO working group concluded**
  - 0.35 µg/mL of IgG class anticapsular antibodies to be the best estimate of the protective concentration applicable on a global level
  - The primary end point for comparing future PnC vaccines with PCV7 will be the proportion of infants achieving this concentration 1 month after primary immunization

**A. NCKP**
- NCKP PP VE: 97.4%
- Predicted VE with 0.2 μg/mL cut-off: 97.3%
- VE = 97.4%
- \([C]_{prot} = 0.20 \mu g/mL\)

**B. American Indian**
- American Indian Trial VE: 76.8%
- Predicted VE with 0.99 μg/mL cut-off: 76.7%
- VE = 76.8%
- \([C]_{prot} = 0.99 \mu g/mL\)

**C. South African**
- South African Trial PP VE: 90%
- Predicted VE with 0.68 μg/mL cut-off: 89.9%
- VE = 90%
- \([C]_{prot} = 0.68 \mu g/mL\)

**D. Pool of 3 Studies (Weighted)**
- Pooled VE: 93%
- Predicted VE with 0.35 μg/mL cut-off: 92.5%
- VE = 93%
- \([C]_{prot} = 0.35 \mu g/mL\)
RCDC for Antibody to All 7 Vaccine Types (Pooled) With and Without 22F Absorption and Effect on the Estimate of the Protective Concentration

Effect of Additional 22F Absorption on the 89-SF Reference Serum

- Pneumococcal reference standard 89-SF, with assigned serotype-specific IgG levels, allows consistent quantitation of serotype-specific IgG levels in both adult and pediatric sera
  - Serotype-specific IgG assignments were developed using a single C-Ps absorption to remove nonspecific antibody
  - 22F absorption of the reference standard is not currently recommended
- Reference standard 89-SF was derived from a pool of adult donors immunized with 23-valent PnPS vaccine
- It has been shown previously that absorption of adult sera with 22F removes additional nonspecific antibodies
- 22F absorption of the reference standard 89-SF would, therefore, reduce the serotype-specific IgG levels detected for each of the serotypes
- This was tested by treating the reference standard 89-SF as an unknown sample in the standard ELISA and the titers measured for the 13 serotypes

Effect of Additional 22F Absorption on the 89-SF Reference Serum

<table>
<thead>
<tr>
<th>Type</th>
<th>89-SF Assigned Ab Concentrations&lt;sup&gt;a&lt;/sup&gt;</th>
<th>89-SF Calculated Ab Concentration&lt;sup&gt;b&lt;/sup&gt;</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.30</td>
<td>4.07</td>
<td>35.4%</td>
</tr>
<tr>
<td>3</td>
<td>2.40</td>
<td>1.24</td>
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<td>4</td>
<td>4.10</td>
<td>2.94</td>
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<tr>
<td>5</td>
<td>5.80</td>
<td>2.88</td>
<td>50.3%</td>
</tr>
<tr>
<td>6B</td>
<td>16.9</td>
<td>13.50</td>
<td>20.1%</td>
</tr>
<tr>
<td>6A</td>
<td>6.10</td>
<td>3.34</td>
<td>45.2%</td>
</tr>
<tr>
<td>7F</td>
<td>5.20</td>
<td>3.37</td>
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<td>9V</td>
<td>6.90</td>
<td>5.13</td>
<td>25.7%</td>
</tr>
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<td>14</td>
<td>27.8</td>
<td>23.83</td>
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</tr>
<tr>
<td>18C</td>
<td>4.50</td>
<td>3.14</td>
<td>30.2%</td>
</tr>
<tr>
<td>19A</td>
<td>18.57</td>
<td>13.46</td>
<td>27.5%</td>
</tr>
<tr>
<td>19F</td>
<td>13.0</td>
<td>9.18</td>
<td>29.4%</td>
</tr>
<tr>
<td>23F</td>
<td>8.10</td>
<td>5.89</td>
<td>27.3%</td>
</tr>
</tbody>
</table>

<sup>a</sup>C-PS absorption alone

<sup>b</sup>C-PS plus 22F absorption


Effect of Additional 22F Absorption on the 89-SF Reference Serum

- Addition of 22F absorption to the reference standard 89-SF removes antibodies to common nonspecific pneumococcal antigens.
- The serotype-specific IgG detected by the ELISA was reduced for each serotype.
- Consequently, if the reference standard 89-SF is absorbed with 22F in addition to C-Ps, and the original single absorbent-derived serotype-specific IgG assignments are retained, all serotype-specific IgG assignments for test sera will be incorrectly inflated.

Summary

- PCV7 was licensed based on placebo-controlled clinical trials
- Such trials are no longer practical or ethical
- Efficacy of new pneumococcal conjugate vaccines can be assessed using an immunologic correlate\(^1\)
- In 2003, WHO recommended a concentration of ELISA IgG anticapsular antibody of 0.35 µg/mL as a reference value against which new vaccines should be measured\(^1\)
- ELISA specificity improved with additional 22F absorption of tested sera\(^2\)
- Wyeth reevaluated the protective threshold using double-absorption assay of sera from the pivotal efficacy trial with no significant change in the correlate\(^3\)

Summary

- All pneumococcal conjugate vaccines should meet the same rigorous standards.
- The key principles for bridging to new assays must be followed, including:
  - Bridge to a vaccine of demonstrated efficacy.
  - Sufficient sample size in appropriate populations.
  - Controlled experiments with only one variable.
  - Statistical methodology consistent with original assessment.
- Failure to meet the prevailing standard for licensure could set an inappropriately low standard for noninferiority comparisons and potentially result in the licensure of a vaccine with inferior efficacy.
- This correlate of immunity applies only to invasive disease.
  - There is currently no correlate for pneumonia.
Using the Correlate of Immunity to Develop a New Vaccine Candidate

*Investigational vaccine in late-stage development.
The Correlate of Protection Used for Assessing PCV13

- WHO recommended reference value of 0.35 μg/mL

- For 7 serotypes in PCV7
  - Noninferiority to PCV7

- For additional 6 serotypes
  - Immune response comparable to the PCV7 serotypes
  - Evidence of priming

Proof-of-Concept Trial

- Randomized, placebo-controlled trial comparing PCV13 with PCV7
  - 1:1 randomization
  - 249 subjects
- Schedule: 3 doses—at 2, 4, and 6 months of age
- Primary end point: percentage of subjects achieving ≥0.35 μg/mL anticapsular antibody after 3 doses in infants

Percentage of Subjects Achieving a Postinfant Series Pneumococcal IgG Antibody Concentration $\geq 0.35 \, \mu g/mL$

Percentage of Subjects Achieving a Postinfant Series Pneumococcal Serotype-Specific OPA Antibody Titer ≥1:8 (6096A1-003)

Postinfant Series Pneumococcal Antibody Serum IgG Geometric Mean Concentrations (μg/mL) (6096A1-003)

Conclusions

- PCV7 has had a significant impact on public health where it has been introduced\(^1\)

- WHO recommended reference value of 0.35 \(\mu g/mL\) based on efficacy of PCV7

- PCV13 coverage when compared with PCV7 includes newly emerging serotypes (eg, 19A) and serotypes prevalent in developing countries (eg, 1 and 5)

- All PCVs should meet the 0.35 \(\mu g/mL\) standard