EFFICACY OF INACTIVATED QUADRIVALENT INFLUENZA VACCINE (IIV4) IN CHILDREN AND AN HI ANTIBODY CORRELATE OF PROTECTION

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Disclosures and acknowledgements

• I am employed by the GlaxoSmithKline group of companies and I own stocks/options of the GlaxoSmithKline group of companies; my travel to this meeting was funded by GlaxoSmithKline Biologicals SA
• The study I will present was funded by GlaxoSmithKline Biologicals SA

Rationale for a QIV efficacy study in children

IIV efficacy estimates were not robust for children
This study was done to provide direct evidence regarding IIV4’s clinical benefit in children using 2 endpoints:
− The traditional endpoint (any influenza disease)
− A more clinically relevant endpoint (moderate to severe influenza disease)

Study Design (NCT01218308)

- Randomization 1:1
  - Age stratified 1–4 and 5–8 years
- QIV (n = 2,400)
- Havrix™ (n = 1,800)
- Surveillance for ~180 days during the 2010-11 influenza season

<table>
<thead>
<tr>
<th>Visit</th>
<th>Day 0</th>
<th>Day 28</th>
<th>Day 56</th>
<th>Day 180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccination Blood sample</td>
<td>Vaccination Blood sample*</td>
<td>Blood sample</td>
<td>Blood sample</td>
<td></td>
</tr>
<tr>
<td>*Only for primed subjects</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Havrix™ dose 2™ or 3™ for control group

Havrix™ is a trademark of the GlaxoSmithKline group of companies.
Key objectives

- **Confirmatory**
  - Evaluate QIV efficacy for the prevention of:
    - Any RT-PCR confirmed influenza A/B (success criterion: LL 95% CI >30%)
    - Moderate to severe RT-PCR confirmed influenza A/B (success criterion: LL 97.5% CI >0)

- **Descriptive**
  - Descriptive immunogenicity (per strain GMT, SCR, SPR, SCF)
  - Reactogenicity

- **Exploratory**
  - HI correlate of protection

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Case definitions for influenza

**Confirmed by RT-PCR in a nasal/throat swab**

- **Any influenza is:**
  - Temperature ≥37.8°C, and
  - One or more symptoms on the same day (cough, sore throat, runny nose or nasal congestion)

- **Moderate to severe influenza is any influenza plus:**
  - Fever >39°C, or
  - Physician-verified acute otitis media, or
  - Physician-verified lower respiratory tract manifestations (shortness of breath, cough, wheezing, pulmonary congestion, bronchiolitis, bronchitis, pneumonia), or
  - Physician-diagnosed serious extra-pulmonary complication of influenza (including myositis, myocarditis, seizure or encephalitis)

(detects the more clinically relevant outcomes of influenza)

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Countries and enrollment

- Demography similar between groups: mean age 5.4 ± 1.7 years; ~48% female
- Majority of children were vaccine unprimed → received 2 doses

Subtype/lineage distribution

Total vaccinated cohort - from day 0 after vaccination

- **Influenza strains by country**

- **Overall distribution by strain**
  - A/H1N1 (30.8%)
  - A/H3N2 (32.7%)
  - B/Victoria (35.5%)
  - B/Yamagata (0.9%)

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### Vaccine efficacy - cases confirmed by RT-PCR

Total vaccinated cohort for efficacy - from day 0 after vaccination

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Group</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any influenza</td>
<td>QIV</td>
<td>2,584</td>
<td>62</td>
<td>2.40</td>
<td>59.38</td>
<td>45.2</td>
<td>69.7</td>
</tr>
<tr>
<td></td>
<td>HavrixTM</td>
<td>2,584</td>
<td>148</td>
<td>5.37</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Immunogenicity – HI antibodies

Pre, post, & at least 6 month post vaccination

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Group</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate to severe</td>
<td>QIV</td>
<td>2,584</td>
<td>16</td>
<td>0.62</td>
<td>74.2</td>
<td>51.5</td>
<td>86.2</td>
</tr>
<tr>
<td></td>
<td>HavrixTM</td>
<td>2,584</td>
<td>61</td>
<td>2.36</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

N = number of subjects included in each group
n = number of subjects reporting at least 1 event in each group

Vaccine efficacy assessed using Cox Regression model adjusted for age, region and priming status


### Immunogenicity

<table>
<thead>
<tr>
<th></th>
<th>Endpoint</th>
<th>Baseline</th>
<th>1 Month</th>
<th>End of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/H1N1</td>
<td>QIV</td>
<td>22.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>18.6</td>
<td>92.0</td>
<td>92.0</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>QIV</td>
<td>20.7</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>18.9</td>
<td>61.2</td>
<td>61.2</td>
</tr>
<tr>
<td>B/Victoria</td>
<td>QIV</td>
<td>21.9</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>19.6</td>
<td>84.3</td>
<td>84.3</td>
</tr>
<tr>
<td>B/Yamagata</td>
<td>QIV</td>
<td>21.9</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>19.6</td>
<td>84.3</td>
<td>84.3</td>
</tr>
</tbody>
</table>

**Geometric Mean Titer**


### Methodology

Case distribution, variables predicting outcome by logistic regression

- 67 cases of H3N2 disease occurred 36 to 202 days after last vaccination
  - 4 matched controls per case, by age, gender, center
- Logistic regression w/ HI titer and treatment group as independent predictors of H3N2 disease → HI titer was statistically significant independent predictor

Preliminary Analysis of Correlate of Protection

(unpublished data)
Methodology

Dunning’s scaled logit model

- Dunning’s model used to quantify the relationship between an HI titer and the probability of developing disease (any & mod-severe) associated with a disease prevalence and an individual’s chance of exposure to H3N2

\[ P(\text{Disease}) = P(\text{Exposed}) \times (1 - P(\text{Protected})) = A \times \left( 1 - \frac{1}{1 + \exp(-\alpha - \beta \times t)} \right) \]

- \(A\) represent the probability that a susceptible individual develops disease and is estimated by the standard maximum likelihood method;
- \(\alpha\) and \(\beta\) are parameters of the probability that an individual with titer \(t\) is protected and are estimated by the standard maximum likelihood method

- For cases, a linear decay model was assumed to estimate the HI titer at disease onset.
- For controls, the post-vacc HI titer was used unless the case occurred after D180, when a D180 titer was used.
- The Dunning model was used to estimate the HI titer associated with the probability of occurrence of influenza → output was used to derive a plot of probability of protection \(\text{P(protection)}\) as a function of H3N2 HI titer

Summary

- The QIV evaluated was 74% protective against moderate to severe influenza and 59% protective against any influenza
- HI titer in children 3-8 YOA, whether elicited by IIV or not, is predictive of probability of H3N2 influenza illness if exposed
- Immunity, correlated with HI antibody, prevents or attenuates illness, i.e. low levels of HI antibody reflect immunity sufficient to prevent “mod-severe” illness but higher levels of HI antibody (reflecting more complete immunity) are required to prevent “mild” illness
- Using the GSK HI assay:
  - titer of 1:45 is predictive of 50% protection against “any” H3N2 illness
  - titer of 1:53 is predictive of 80% protection against “mod to severe” H3N2 illness
- IVs may have greater benefit for children age 3 and older than appreciated

Protection against H3N2 disease predicted by HI Titer

Model predicts more protection per unit HI ab against mod to severe disease

Data limitations and next steps

- Data limitations
  - Case definition of moderate to severe influenza illness needs to be clinically validated in other studies
  - CoP model needs validation with another data set
  - Relevance of CoP for children younger than age 3 needs to be established
- Next steps
  - Extend analysis to H1N1
  - Extend analysis to B-Victoria
  - Repeat analysis with N ab in place of HI ab
  - Validate with an independent dataset down to 6 mos of age
### Incidence of adverse events

#### Total vaccinated cohort

<table>
<thead>
<tr>
<th></th>
<th>QIV (N=2,584)</th>
<th>Havrix™ (N=2,584)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td><strong>Within 7 days of vaccination:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AE (solicited and unsolicited)</td>
<td>1467</td>
<td>56.8</td>
</tr>
<tr>
<td>Any general AE (solicited and unsolicited)</td>
<td>880</td>
<td>34.1</td>
</tr>
<tr>
<td>Any local AE (solicited and unsolicited)</td>
<td>1219</td>
<td>47.2</td>
</tr>
<tr>
<td><strong>During entire study:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>36</td>
<td>1.4</td>
</tr>
<tr>
<td>Medically attended events</td>
<td>792</td>
<td>30.7</td>
</tr>
<tr>
<td>Grade 3 medically attended events</td>
<td>26</td>
<td>1.0</td>
</tr>
<tr>
<td>Medically attended events with causal relationship to vaccination</td>
<td>6</td>
<td>0.2</td>
</tr>
</tbody>
</table>

n/% = number/percentage of subjects reporting at least 1 event in each group

### Influenza severity by subtype/lineage

#### Total vaccinated cohort – from 14 days after vaccination

- [Graph showing influenza severity by subtype/lineage]