Efficacy of seasonal influenza vaccines in children

Ab Osterhaus

ESWI chair

FACULTY C LUB
UNIVERSITY OF LEUVEN B ELGIUM
14 JUNE 2017
<table>
<thead>
<tr>
<th>Age group, health profile</th>
<th>Vaccine types available</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 6-23 months</td>
<td>QIV, TIV, ATIV</td>
<td>QIV preferred</td>
</tr>
<tr>
<td>Children 2-17 years healthy or with chronic conditions without immune suppression</td>
<td>Q-LAIV, QIV, TIV</td>
<td>Q-LAIV or QIV preferred</td>
</tr>
<tr>
<td>Children 2-17 years, Immune compromising conditions</td>
<td>QIV, TIV</td>
<td>QIV preferred, Q-LAIV contraindicated</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>QIV, TIV</td>
<td>Q-LAIV not recommended</td>
</tr>
</tbody>
</table>

European Scientific Working group on Influenza

ESWI - scientists fighting influenza
Impact of influenza B lineage mismatch and specific pre-season immunity on the effectiveness of influenza vaccines.

A meta-regression study on immunogenicity trials and controlled field trials.

Beyer WEP¹,²*, Palache AM³, Boulfich M⁴, Osterhaus ADME¹,⁵

[5] University of Veterinary Medicine, Hannover, Germany.

Vaccine, resubmitted

European Scientific Working group on Influenza

Beyer et al.: Rationale for two influenza B lineages in seasonal vaccines: meta-regression study on...
Flowchart of literature retrieval
post-vaccination protection rates, for match and B lineage mismatch.

Black lines: regression lines; coloured areas: 95% confidence intervals.

FLUARIX TETRA
GSK - Paediatric efficacy and safety study
A phase III, observer-blind, randomized, multi-country, non-influenza vaccine comparator-controlled study to demonstrate the efficacy of GSK Biologicals’ quadrivalent seasonal influenza candidate vaccine GSK2321138A (FLU D-QIV), administered intramuscularly in children 6 to 35 months of age.

CSR available at: www.gsk-clinicalstudyregister.com/

4 ePosters presented at ESPID 2017 – Madrid Spain

Study was conducted in 13 countries (N=12,018)
Five independent cohorts over five influenza seasons (2011–2014)
Study Design
Phase III observer-blind, randomised, non-influenza vaccine comparator-controlled clinical trial
Vaccine safety and reactogenicity

Solicited adverse events (7-day post-vaccination period) similar to control
**Vaccine safety and reactogenicity**

Solicited adverse events (7-day post-vaccination period) similar to control

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**Local symptoms**

- Pain
- Grade 3 pain
- Redness
- Grade 3 redness
- Swelling
- Grade 3 swelling

- **D-QIV (n=5907)**
- **Control (n=5901)**

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Efficacy objectives

Presented ESPID 2017 http://espid2017.kenes.com/scientific-information/interactive-programme#.WTbbX_IzUid
Study 115345. 2017. Available at: www.gsk-clinicalstudyregister.com/
Prevention of:
• RT-PCR confirmed moderate to severe influenza due to any influenza strain (LL 97.5% CI>25%)
• RT-PCR confirmed influenza of any severity due to any influenza strain (LL 97.5% CI>15%)

**Prevention of:**
1. Lower Respiratory Illness (LRI) associated with RT-PCR confirmed influenza (LL 95% CI>15%)
2. Culture confirmed moderate to severe influenza due to vaccine-matching influenza strains (LL 95% CI>15%)
3. Culture confirmed influenza of any severity due to vaccine-matching influenza strains (LL 95% CI>15%)
4. Culture confirmed moderate to severe influenza due to any influenza strain (LL 95% CI>15%)
5. Culture confirmed influenza of any severity due to any influenza strain (LL 95% CI>10%)
6. Acute Otitis Media (AOM) associated with RT-PCR confirmed influenza (LL 95% CI>10%)
7. RT-PCR confirmed severe influenza (LL 95% CI>15%)

Vaccine efficacy
Confirmatory **primary efficacy objectives** (ATP time to event)
Vaccine efficacy
Secondary confirmatory sequential objectives (ATP time to event)

Outcome
Influenza-associated lower respiratory illness

Influenza A and/or B disease due to matching influenza strains

Thresholds for vaccine efficacy

*Pre-specified statistical success criteria for vaccine efficacy (lower limit of 97.5% CI); ATP, according to protocol; CI, confidence interval

Healthcare resources utilization (1/2)

Exploratory objective, Total vaccinated cohort (TVC)

Among children with confirmed influenza of any severity, compared with controls, D-QIV:

[Graph showing data and statistics related to healthcare resources utilization]
Reduced use of antibiotics

Reduction 50% (3% vs 6% use)

Reduced risk of GP visits

RRR 46% (RR: 0.54, 95% CI: 0.47–0.62)

Reduced risk of ER visits

RRR 79% (RR: 0.21, 95% CI: 0.09–0.51)

Healthcare resources utilization (2/2)

Exploratory objective, Total vaccinated cohort (TVC)

Among children with confirmed **moderate-to-severe influenza**, compared with controls, D-QIV:

Sanofi Pasteur: QIV VaxigripTetra™ Efficacy and Safety in Children 6-35m

INTRAMUSCULAR QUADRIVALENT INFLUENZA VACCINE IS EFFICACIOUS IN NAIVE CHILDREN AGED 6 TO 35 MONTHS: A LARGE-SCALE, PLACEBO-CONTROLLED TRIAL

- A randomized, placebo-controlled clinical efficacy trial in 4 continents during 4 distinct influenza seasons between March 2014 and September 2016

- About 5,500 children 6-35 months of age for efficacy
Primary Objective: To demonstrate the clinical efficacy of QIV for the prevention of at least one of the following endpoints in children aged 6 to 35 months:

- laboratory-confirmed influenza illness caused by any influenza circulating strains (A or B types)
- laboratory-confirmed influenza illness caused by influenza strains similar to those contained in the vaccine

Secondary objective: To assess safety of QIV in children aged 6 to 35 months
Two 0.5 mL doses of QIV VaxigripTetra were well tolerated in naïve children aged 6-35 months

The safety profile of QIV was similar to that of placebo and the TIV
Quadrivalent Influenza Vaccine Efficacy study in previously unvaccinated children from 6 to 35 months

Vaccine and Circulating Strains

<table>
<thead>
<tr>
<th>Season</th>
<th>Vaccine / Circulating</th>
<th>A/H1N1</th>
<th>A/H3N2</th>
<th>B/Victoria</th>
<th>B/Yamagata</th>
</tr>
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<tbody>
<tr>
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<tr>
<td><strong>V</strong></td>
<td>A/California/2009</td>
<td>A/Switzerland/2013</td>
<td>B/Brisbane/2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>A/California/2009-like</td>
<td>A/Switzerland/2013-like</td>
<td>B/Brisbane/2008-like</td>
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</tr>
</tbody>
</table>

* B strain not contained in the licensed TIV
** marketed vaccine

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**Laboratory confirmed* Influenza cases collected by season and country**

![Bar chart showing laboratory confirmed influenza cases by season and country.](chart.png)
Efficacy demonstrated for both primary endpoints

Full Analysis set

<table>
<thead>
<tr>
<th></th>
<th>QIV N=2584 n (%)</th>
<th>Placebo N=2591 n (%)</th>
<th>Efficacy % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory-confirmed influenza illness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Any strain</td>
<td>122 (4.72)</td>
<td>255 (9.84)</td>
<td>52.03 (40.24; 61.66)</td>
</tr>
<tr>
<td>• Vaccine-similar strains (Sanger sequencing method*)</td>
<td>26 (1.01)</td>
<td>85 (3.28)</td>
<td>69.33 (49.79; 81.99)</td>
</tr>
<tr>
<td>• Vaccine-similar strains (Ferret antigenicity method**)</td>
<td>77 (2.98)</td>
<td>188 (7.26)</td>
<td>58.93 (46.19; 68.92)</td>
</tr>
<tr>
<td>PCR-confirmed influenza illness</td>
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Other endpoints of Efficacy (FASE) (1/2)

Additional pre-defined complementary analysis

<table>
<thead>
<tr>
<th></th>
<th>QIV N=2584 n (%)</th>
<th>Placebo N=2591 n (%)</th>
<th>Relative Risk % (95% CI)</th>
<th>Efficacy %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe laboratory-confirmed influenza illnesses, due to</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>· Any strain</td>
<td>42 (1.6)</td>
<td>97 (3.7)</td>
<td>43.42 (29.48; 62.97)</td>
<td>57%</td>
</tr>
<tr>
<td>· Vaccine-similar strains</td>
<td>11 (0.4)</td>
<td>39 (1.5)</td>
<td>28.28 (13.06; 56.31)</td>
<td>72%</td>
</tr>
<tr>
<td>Moderate or Severe laboratory-confirmed influenza illnesses, due to</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>· Any strain</td>
<td>136 (5.2)</td>
<td>228 (8.8)</td>
<td>19 (16.51)</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Any strain</td>
<td>Vaccine-similar strains</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>101 (3.9)</td>
<td>239 (9.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>23 (0.8)</td>
<td>79 (3.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associated with health care medical visit due to</td>
<td>59 (2.3)</td>
<td>145 (5.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>40.80 (29.62; 55.59)</td>
<td>59%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 (0.3)</td>
<td>38 (1.5)</td>
<td></td>
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<tr>
<td></td>
<td>23.75 (10.10; 49.97)</td>
<td>76%</td>
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Source: Tables 10.44, 10.61 & 10.59 of CSR

Efficacy column computed based on risk ratio available in stat analysis

15/05/2017 | 25

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**Global Circulation of Seasonal Influenza A (H3N2) Viruses**

*Science 2008, Russell et al.*
Recent findings show that Asia is the epicenter for both influenza A/H1N1 and A/H3N2 subtypes, but not for influenza B viruses. van der Vries et al., in preparation

Substitutions near the receptor binding site determine major antigenic change during influenza virus evolution

BF Koel et al, Science. 2013

Fig. 2. Positions of the cluster-transition amino acid substitutions indicated on an A/Aichi/2/1968 HA trimer. The three monomers are shown in black, white, and gray; the RBS is in yellow. (A and B) The positions responsible for A/H3N2 cluster transitions are shown in red. An asterisk indicates an amino acid substitution that has been dropped in recent virus strains.
An asterisk indicates accessory substitutions (fig. S10). Position 193 is both a cluster-transition substitution and an accessory substitution (Fig. 1B). (C) Positions of amino acid substitutions responsible for antigenic change of influenza A/H1N1 and B virus are shown in green and magenta, respectively. The positions responsible for cluster transitions of A/H3N2 virus are shown in light brown.

Creating an antibody landscape

A) Antigenic map of A/H3N2 showing virus strains color-coded by antigenic cluster.

B) An additional dimension indicates the measured antibody titers as vertical impulses, and a smooth surface is fitted using locally weighted multiple linear regression.

C) The height of the landscape along the path in (A) shows a slice through the landscape.
Conclusions QIV’s for children

(recent GSK & Sanofi trials)

- Influenza B lineage mismatch for vaccine efficacy most relevant for children
- Safety profiles QIV’s similar to those previously observed for TIV’s
- Efficacy in reducing laboratory-confirmed influenza ranging from 50 to 75%
- Higher level of protection dependent on
  - matching of vaccine strains versus circulating strains
  - severity of disease
NB: reduction antibiotics usage / GP visits / ER hospitalisation