Quadrivalent influenza vaccine developments

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University of Tampere
Tampere, Finland
Burden of disease related to influenza B

Influenza B is responsible for 25 % of laboratory confirmed influenza in the US\(^1\)

Children and young adults affected most, in some epidemics the elderly\(^2\)

Some influenza-related symptoms, such as myositis and leukopenia, more common in children infected with influenza B than A\(^3\)

\(^1\) Thompson et al. JAMA 2003;289:179–86.
Severe influenza B associated diseases in children and adolescents in Taiwan

241 patients hospitalized with influenza B

13 with encephalitis / encephalopathy

28 with influenza-associated myositis

Burden of disease associated with influenza B

Incremental reduction of influenza burden with a potential switch from trivalent to quadrivalent vaccine

Model based on 2007–2008 season, CDC analysis

- 1 million fewer cases
- 7000 fewer hospitalizations
- 320 fewer deaths

Model has numerous limitations (Belshe, Vaccine 2010)

Does not consider that much of morbidity associated with influenza B is in children
The need for quadrivalent influenza vaccine

Two parallel evolutionary pathways of influenza B have existed since at least 1983 (Rota et al. Virology 1990;175:59 – 68)

Continued co-circulation of the Yamagata and Victoria lineages

Annual selection of the influenza B strain for TIV reliant on chance
## Selection of influenza B strain for vaccine

<table>
<thead>
<tr>
<th>Influenza season</th>
<th>Predominant lineage of B in the US</th>
<th>Mismatch with vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000–2001</td>
<td>Yamagata</td>
<td>No</td>
</tr>
<tr>
<td>2001–2002</td>
<td>Victoria</td>
<td>Yes</td>
</tr>
<tr>
<td>2002–2003</td>
<td>Victoria</td>
<td>No</td>
</tr>
<tr>
<td>2003–2004</td>
<td>Yamagata</td>
<td>Yes</td>
</tr>
<tr>
<td>2004–2005</td>
<td>Yamagata</td>
<td>No</td>
</tr>
<tr>
<td>2005–2006</td>
<td>Victoria</td>
<td>Yes</td>
</tr>
<tr>
<td>2006–2007</td>
<td>Victoria</td>
<td>No</td>
</tr>
<tr>
<td>2007–2008</td>
<td>Yamagata</td>
<td>Yes</td>
</tr>
<tr>
<td>2008–2009</td>
<td>Victoria</td>
<td>Yes</td>
</tr>
<tr>
<td>2009–2010</td>
<td>Victoria</td>
<td>No</td>
</tr>
</tbody>
</table>

From Belshe, Vaccine 2010;285:D45–53.
Time to first culture-confirmed modified CDC-ILI influenza caused by any wild-type strains (ATP population)

Relative efficacy of CAIV-T vs. TIV
A/H3N2 79 %
A/H1N1 89 %
(extrapolated efficacy of TIV ~ 50 %)

Efficacy for B strains not different between CAIV-T and TIV and lower than against A strains

Belshe et al, NEJM 2007;356:685-96
Vaccine efficacy for two doses of CAIV-T in children against B-strains

Summary of 9 clinical trials

- Same lineage and matched: 86%
- Same lineage and mismatched: 55%
- Opposite lineage: 31%
Problems of QIV vs. TIV production

- adding one more antigen increases cost
- production capacity is limited and one more antigen may stretch capacity
- adding total antigen content from 45 µg to 60 µg may increase reactogenicity
QIV vs. TIV questions

1. How much incremental benefit exactly there is?
   - in adults
   - in children

2. Does QIV really solve the problem of low(er) protection against B-strains than A-strains?
   - lack of cross-protection by TIV across lineages may not be the only issue
QIV vs. TIV

Other issues related to lower protection against B-strains

1. Inherently lower immunogenicity of B-strains regardless of lineage
   • General order H3 > H1 > B
**Enhanced Immunogenicity of Seasonal Influenza Vaccines in Young Children Using MF59 Adjuvant**

Timo Vesikari, MD,* Michele Pellegrini, MD,† Aino Karvonen, MD,* Nicola Groth, MD,† Astrid Borkowski, MD,‡ Derek T. O’Hagan, PhD,† and Audino Podda, MD†

Proof of Concept Study: unprimed healthy children aged 6 to <36 months, randomized to receive two 0.25 mL doses of MF59-adjuvanted or conventional split influenza vaccines, administered IM, 4 weeks apart

*P<0.001

V70P5 Efficacy trial of FLUAD vs. TIV in 6–72 month-old children

Relative efficacy of Fluad vs. conventional TIV

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Fluad (Efficacy)</th>
<th>Conventional TIV (Efficacy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–&lt;72</td>
<td>86%*</td>
<td>43%</td>
</tr>
<tr>
<td>6–&lt;36</td>
<td>79%*</td>
<td>40%</td>
</tr>
<tr>
<td>36–&lt;72</td>
<td>92%*</td>
<td>45%</td>
</tr>
<tr>
<td>6–&lt;24†</td>
<td>77%*</td>
<td>14%</td>
</tr>
</tbody>
</table>

* Statistically significant result.
† Post hoc analysis.

Vesikari et al., NEJM 2011;365:1406-1416
V70P5 Efficacy trial of MF59 adjuvanted influenza vaccine FLUAD in 6 to 72 month-old children

Point estimates suggested that Fluad could be efficacious against mismatched influenza B

<table>
<thead>
<tr>
<th>B (all lineage mismatched)</th>
<th>VE % (2-sided 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluad vs. non-influenza controls*</td>
<td>79% (-5–96)</td>
</tr>
<tr>
<td>Conventional TIV† vs. non-influenza control*</td>
<td>36% (-162–84)</td>
</tr>
<tr>
<td>Fluad vs. conventional TIV†</td>
<td>66% (-103–94)</td>
</tr>
</tbody>
</table>

Influenza cases: Year 1, 5 B cases lineage all mismatched or unknown; Year 2, 94 A(H3N2) cases, all matched to vaccine, 4 subtype unknown, and 5 B cases lineage all mismatched or unknown. TIV, trivalent influenza vaccine.
Vesikari et al., NEJM 2011;365:1406-1416
Interpretation of V70P5 study: a mismatched TIV can induce protection across lineages of influenza B, if the (adjuvanted) vaccine is highly immunogenic

Likewise, hyperimmunization (in sheep) can induce cross-lineage antibodies

Cross-reactive antibodies induced by a monovalent influenza B virus vaccine.

R A Levandowski, P A Gross, M Weksler, E Staton, M S Williams and J Bonelli
<table>
<thead>
<tr>
<th>Vaccine(^a)</th>
<th>HI antibody titers for(^b):</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Yam</td>
</tr>
<tr>
<td>B/Yamagata/16/88</td>
<td>640</td>
</tr>
<tr>
<td>B/Victoria/2/87</td>
<td>&lt;20</td>
</tr>
<tr>
<td>B/Ann Arbor/1/86</td>
<td>&lt;20</td>
</tr>
<tr>
<td>B/USSR/100/83</td>
<td>&lt;20</td>
</tr>
<tr>
<td>B/Singapore/222/79</td>
<td>&lt;20</td>
</tr>
</tbody>
</table>

\(^a\) Detergent-split subunit vaccine.

\(^b\) Values shown are the reciprocals of the titer. Yam, sheep antiserum to B/Yamagata/16/88; Vic, sheep antiserum to B/Victoria/2/87; Ann, sheep antiserum to B/Ann Arbor/1/86; USSR, ferret antiserum to B/USSR/100/83; Sing, sheep antiserum to B/Singapore/222/79.
QIV vs. TIV

Decline of antibodies in relation to exposure (time of epidemic)

- Influenza B may happen late in the season
Persistence of antibodies 6 months after FLUAD vaccination

Proof of Concept Study: unprimed healthy children aged 6 to <36 months, randomized to receive two 0.25 mL doses of MF59-adjuvanted or conventional split influenza vaccines, administered IM, 4 weeks apart

Timing of influenza B epidemic in relation to influenza A
Laboratory confirmed influenza in Finland 2008–2009

Source: Niina Jokinen, THL
Timing of influenza B epidemic in relation to influenza A
Laboratory confirmed influenza in Finland 2010–2011

Source: Niina Jokinen, THL
A randomized, double-blind noninferiority study of quadrivalent live attenuated influenza vaccine in adults

Stan L. Block\textsuperscript{a,*}, Tingting Yi\textsuperscript{b}, Eric Sheldon\textsuperscript{c}, Filip Dubovsky\textsuperscript{b}, Judith Falloon\textsuperscript{b}

\textsuperscript{a} Kentucky Pediatric and Adult Research, 201 South 5th Street, Bardstown, KY 40004-1142, USA
\textsuperscript{b} MedImmune, LLC, One MedImmune Way, Gaithersburg, MD 20878, USA
\textsuperscript{c} Miami Research Associates, 6141 Sunset Drive Suite 501, Miami, FL 33143, USA
Q/LAIV vs. T/LAIV GMT response in all adult subjects

Q/LAIV vs. T/LAIV seroresponse in all adult subjects

Q/LAIV vs. T/LAIV seroresponse in serosusceptible adults

Q/LAIV vs. T/LAIV reactogenicity in adults

Immunogenicity and Safety of a Quadrivalent Live Attenuated Influenza Vaccine in Children

Stan L. Block, MD,* Judith Falloon, MD,† Jeffrey A. Hirschfield, MD,‡ Leonard R. Krilov, MD,§ Filip Dubovsky, MD,† Tingting Yi, PhD† and Robert B. Belshe, MD¶

The Pediatric Infectious Disease Journal • Volume 31, Number 7, July 2012
Seroconversion in all children

Block et al. PIDJ 2012;31:745–751
Seroconversion in serosusceptible children

Block et al. PIDJ 2012;31:745–751
Q/LAIV vs. T/LAIV reactogenicity in children

Immunogenicity and Safety of a Quadrivalent Live Attenuated Influenza Vaccine in Children

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The Pediatric Infectious Disease Journal • Volume 31, Number 7, July 2012
Conclusions from immunogenicity and safety studies of Q/LAIV vs. T/LAIV

- No advantage in adults for immunogenicity
- Some advantage in children, especially seronegative ones
- No difference in safety in adults or children
QIV vs. TIV in adults

Safety and immunogenicity of a quadrivalent inactivated influenza vaccine compared to licensed trivalent inactivated influenza vaccines in adults

David P. Greenberg\textsuperscript{a,*}, Corwin A. Robertson\textsuperscript{a}, Michael J. Noss\textsuperscript{b}, Mark M. Blatter\textsuperscript{c}, Rex Biedenbender\textsuperscript{d}, Michael D. Decker\textsuperscript{a}

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\textsuperscript{b} Radiant Research, 11500 Northlake Drive, Cincinnati, OH 45249, USA  
\textsuperscript{c} Primary Physicians Research, 1580 McLaughlin Run Road, Pittsburgh, PA 15241, USA  
\textsuperscript{d} Eastern Virginia Medical School, 825 Fairfax Avenue, Hafheimer Hall Suite 201, Norfolk, VA 23507, USA

QIV vs. TIV
Post-immunization seroprotection rates in subjects >61 years (N=97)

<table>
<thead>
<tr>
<th></th>
<th>TIV “Victoria”</th>
<th>TIV “Yamagata”</th>
<th>QIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>B/Brisbane (Victoria)</td>
<td>79 %</td>
<td>56 %</td>
<td>78 %</td>
</tr>
<tr>
<td>B/Florida (Yamagata)</td>
<td>67 %</td>
<td>83 %</td>
<td>86 %</td>
</tr>
</tbody>
</table>

# QIV vs. TIV

**Post-immunization HI GMTs in adults**

<table>
<thead>
<tr>
<th></th>
<th>TIV &quot;Victoria&quot;</th>
<th>TIV &quot;Yamagata&quot;</th>
<th>QIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>B/Brisbane (Victoria)</td>
<td>114 (97.8,134)</td>
<td>44 (37.8,51.3)</td>
<td>101 (85.6,120)</td>
</tr>
<tr>
<td>B/Florida (Yamagata)</td>
<td>78.1 (65.5,93.1)</td>
<td>135 (117,156)</td>
<td>155 (133,180)</td>
</tr>
</tbody>
</table>

QIV vs. TIV in adults
Reactogenicity

Conclusions from immunogenicity and safety studies in adults

QIV vs. TIV

- marginally more immunogenic
- safe
Conclusions on quadrivalent influenza vaccines

No evidence of incremental clinical benefit over trivalent vaccines at present

Both QIV and CAIV-Q are safe compared with TIV and CAIV-T, respectively

→ Quadrivalent vaccines may be used instead of the equivalent trivalent ones
Flumist Quadrivalent
(MedImmune, AstraZeneca)
Licenced by FDA 29 February 2012
for people ages 2 to 49 years

Quadrivalent inactivated influenza vaccine
based on the approved trivalent Fluzone®
(SanofiPasteur)
Filed for licensure in the US

Fluarix® quadrivalent
(GSK)
Approved by FDA 14 December 2012
Quadrivalent influenza vaccine(s)

To do

Efficacy trials in children

Quadrivalent vs. trivalent (vs. placebo)

QIV vs. TIV
  with or without adjuvant

Q/LAIV vs. T/LAIV
Thank you!