The Expanding Rotavirus Vaccine Landscape: Lessons learned from Influenza Vaccines

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University of Maryland
School of Medicine

September 8, 2016
Can we learn from the influenza experience?

- The number of rotavirus vaccines that are licensed or in development is expanding.
- Multiple products may contribute to a healthy market by keeping prices competitive and ensuring supply.
- Development of new vaccines against a disease for which we have an approved (and recommended) product is challenging – how do we ensure the best return on investment?
Are we talking about influenza? Or rotavirus?

- Segmented RNA virus
- Animal reservoirs
- Multiple strains
- Vaccine efficacy differs in different populations
- Circulation is seasonal in many (but not all) countries
- Safety signals have challenged vaccine development
Unique aspects of influenza vaccines/programs

- Genetic divergence of strains over time and poor cross-protection of current vaccines
- Target groups for vaccination beyond young children (older age groups, pregnant women)
- Periodic pandemics
- Recommendations create sustainable demand in high income countries; no global recommendation for influenza vaccines
Genetic Divergence of Influenza HA Over Time

Bedford, T., et al., eLife 2014; 3:e01914
Current Influenza Vaccines Based on Circulating Viruses

Bedford, T., et al., eLife2014;3:e01914
Routine annual influenza vaccination of all persons aged ≥6 months continues to be recommended.
For countries considering the initiation or expansion of programmes for seasonal influenza vaccination, WHO recommends that pregnant women should have the highest priority”.

SAGE also supported the recommendation, in no particular order of priority, of vaccination of the following targeted populations: Healthcare workers, Children 6 to 59 months of age, the elderly, those with high-risk conditions.
Figure 1. Countries with National Immunization Programs recommending seasonal influenza vaccination, 2015

Data source: WHO/IVB Database, as of 05 March 2015
Map production: Immunization Vaccines and Biologicals (IVB), World Health Organization

- Introduced* to date (78 countries or 40%)
- Introduced* in parts of the country (2 countries or 1%)
- Not Available, Not Introduced/No Plans (114 countries or 59%)

The boundaries and names shown on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. ©WHO 2015. All rights reserved.
What are we looking for in a “better” influenza vaccine?

- More effective at preventing any illness?
- More effective at preventing severe infection?
- More broadly protective?
- Longer lasting immunity?
- Safer?
- Better vaccine presentation (cold chain footprint)?
What are we looking for in a “better” influenza vaccine?

• More effective at preventing any illness?
• More effective at preventing severe infection?
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• Longer lasting immunity?
• Safer?
• Better vaccine presentation (cold chain footprint)?

How much are we willing to pay for these improvements?
What are the major limitations of current nonreplicating influenza vaccines?

• Efficacy
  - Overall efficacy is moderate; varies with virus, vaccine, host
  - Suboptimal, particularly in young children (2 doses), elderly, immunocompromised

• Limited cross-protection

• Annual, seasonal administration

• Cumbersome manufacturing process, twice yearly

• Supply and distribution

• Relatively high cost
# Influenza Vaccine Landscape

## Pre Clinical
- **Egg-based inactivated**
  - Sanofi Pasteur
    - Split w/ SPF-32
  - BIOEFFECT
    - WIV
  - Quadrax
    - WIV
  - Proprietary Avenue
    - WIV

## Phase 1
- **Cell-culture inactivated**
  - EIDV
    - Japan EIDV

## Phase 2
- **LAIV**
  - GPO
    - Egg, Thailand
  - MedImmune
    - EIDV

## Phase 3
- **Recombinant (VLPs)**
  - TechnoVax
    - VLP, Insect cells
  - KBP
    - VLP, ZDO cells
  - BIOEFFECT
    - WIV, Insect Cells

## Universal
- **Vaccines**
  - NYU / MSSM
    - AAV, Oral
  - CANBERA
    - MVA, Plants

## Vectors/Adjuvant
- **DNA**
  - Vical
    - DNA / Viral Vector

## Market Approval
- **Seasonal**
- **Pandemic**
- **Seasonal & Pandemic**
- **US License**

*18SEPT2013*
## Categories of vaccines licensed for prevention of seasonal influenza worldwide

<table>
<thead>
<tr>
<th></th>
<th>Live Attenuated</th>
<th>Standard Inactiv</th>
<th>High dose Inactiv.</th>
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<th>Inactiv. intradermal</th>
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</tr>
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<tbody>
<tr>
<td><strong>Route</strong></td>
<td>Intranasal</td>
<td>IM</td>
<td>IM</td>
<td>IM</td>
<td>ID</td>
<td>IM</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>Annual</td>
<td>Annual</td>
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</tr>
<tr>
<td><strong>Approved ages</strong></td>
<td>2 - 49 yrs</td>
<td>≥ 6 mos</td>
<td>≥65 years</td>
<td>≥ 18 yrs</td>
<td>18 – 64 yrs</td>
<td>6-23mos ≥65 years</td>
</tr>
<tr>
<td><strong>HA (mcg/strain)</strong></td>
<td>15</td>
<td>15</td>
<td>60</td>
<td>45</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td><strong>Substrate</strong></td>
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“Better” influenza vaccines for young children

- Development driven by appreciation for burden of illness, suboptimal efficacy of non-replicating vaccines in young children, and our understanding of immunologic priming.
How have we evaluated new influenza vaccine candidates?

- Placebo-controlled trials
- Head-to-head trials
- Immunogenicity bridge followed by post-approval observational studies
  - Test-negative case-control design
  - Large database studies
- Challenge studies
Study designs evolve over time

### Efficacy of live attenuated influenza vaccine in children 6 months to 17 years of age

Robert B. Belshe, a Seth L. Toback, b Tingting Yi, b Christopher S. Ambrose b

<table>
<thead>
<tr>
<th>Study</th>
<th>Influenza season</th>
<th>Age at enrollment</th>
<th>n</th>
<th>Control</th>
<th>Geographic location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, year 1, Belshe</td>
<td>1996–1997</td>
<td>15–71 months</td>
<td>1602</td>
<td>Placebo</td>
<td>United States</td>
</tr>
<tr>
<td>1, year 2, Belshe</td>
<td>1997–1998</td>
<td>27–83 months</td>
<td>1358</td>
<td>Placebo</td>
<td>United States</td>
</tr>
<tr>
<td>2, Belshe</td>
<td>2004–2005</td>
<td>6–59 months</td>
<td>7852</td>
<td>TIV</td>
<td>Global</td>
</tr>
<tr>
<td>3, Ashkenazi</td>
<td>2002–2003</td>
<td>6–71 months</td>
<td>2085</td>
<td>TIV</td>
<td>Europe/Israel</td>
</tr>
<tr>
<td>4, Fleming</td>
<td>2002–2003</td>
<td>6–17 years</td>
<td>2202</td>
<td>TIV</td>
<td>Europe/Israel</td>
</tr>
</tbody>
</table>

LAIv, live attenuated influenza vaccine; TIV, trivalent inactivated influenza vaccine.
Relative efficacy of LAIV (Ann Arbor) versus trivalent, inactivated influenza vaccine (TIV) by age and strain

<table>
<thead>
<tr>
<th>Age, months (n)</th>
<th>All strains* Relative efficacy, % (95% CI)</th>
<th>H1N1* Attack rate, %</th>
<th>Relative efficacy, % (95% CI)</th>
<th>H3N2* Attack rate, %</th>
<th>Relative efficacy, % (95% CI)</th>
<th>B* Attack rate, %</th>
<th>Relative efficacy, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-23 (3686)</td>
<td>56 (40-68)</td>
<td>0·1</td>
<td>0·3</td>
<td>67 (56 to 95)</td>
<td>0·7</td>
<td>4·1</td>
<td>83 (70-91)</td>
</tr>
<tr>
<td>24-35 (2612)</td>
<td>57 (40-69)</td>
<td>0·1</td>
<td>0·3</td>
<td>78 (79 to 99)</td>
<td>1·0</td>
<td>5·6</td>
<td>82 (68-90)</td>
</tr>
<tr>
<td>36-47 (846)</td>
<td>42 (5-66)</td>
<td>0·0</td>
<td>2·3</td>
<td>100 (63-100)</td>
<td>1·7</td>
<td>3·4</td>
<td>48 (29 to 81)</td>
</tr>
<tr>
<td>48-59 (708)</td>
<td>56 (25-75)</td>
<td>0·0</td>
<td>2·0</td>
<td>100 (47-100)</td>
<td>1·1</td>
<td>4·0</td>
<td>76 (22-95)</td>
</tr>
</tbody>
</table>

LAIV, live attenuated influenza vaccine; TIV, trivalent inactivated influenza vaccine.
*Regardless of antigenic match to vaccine.


Preferential recommendation for LAIV in young children in the U.S.* (one year), United Kingdom, Canada (withdrawn), Germany, Israel.
Correlates of Immune Protection Induced by Live, Attenuated, Cold-Adapted, Trivalent, Intranasal Influenza Virus Vaccine

Robert B. Belshe,1 William C. Gruber,2 Paul M. Mendelman,3 Harshvardhan B. Mehta,3 Kutubuddin Mahmood,3 Keith Reisinger,5 John Treanor,6 Ken Zangwill,4 Frederick G. Hayden,7 David I. Bernstein,8 Karen Kotloff,10 James King,11 Pedro A. Piedra,9 Stan L. Block,10 Lihan Yan,12 and Mark Wolff12

1Department of Medicine, Saint Louis University, St. Louis, Missouri; 2Department of Pediatrics, Vanderbilt University, Nashville, Tennessee; 3Aviron, Mountain View, and 4Kaiser-UCLA Vaccine Program/Harbor-UCLA Medical Center, Department of Pediatrics, Los Angeles, California; 5Pittsburgh Pediatric Research, Pittsburgh, Pennsylvania; 6Department of Medicine, University of Rochester, Rochester, New York; 7Departments of Internal Medicine and Pathology, University of Virginia, Charlottesville; 8Department of Pediatrics, Children’s Hospital Medical Center, Cincinnati, Ohio; 9Department of Microbiology and Immunology, Baylor College of Medicine, Houston, Texas; 10Kentucky Pediatric Research, Bardstown; 11Department of Pediatrics, University of Maryland at Baltimore, Baltimore; 12EMMES Corporation, Potomac, Maryland

# Table 1.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. challenged</th>
<th>No. shedding (%)</th>
<th>No. shedding/no. tested, according to prechallenge HAI antibody status</th>
<th>No. shedding/no. tested, according to prechallenge nasal IgA antibody status</th>
<th>No. shedding/no. without either serum HAI or nasal IgA (no. with serum microneutralizing antibody)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>144</td>
<td>6 (4)</td>
<td>Seronegative (HAI≤1 : 4) 4/46, Seropositive (HAI≥1 : 8) 2/97</td>
<td>IgA negative 5/41, IgA positive 1/90</td>
<td>4/16 (12)</td>
</tr>
<tr>
<td>Placebo</td>
<td>78</td>
<td>19 (24)</td>
<td>19/51, 0/25</td>
<td>16/45, 3/23</td>
<td>16/35 (1)</td>
</tr>
<tr>
<td>All</td>
<td>222</td>
<td>25</td>
<td>23/97, 2/122</td>
<td>21/86, 4/113</td>
<td></td>
</tr>
</tbody>
</table>

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9/29/2016
No correlate of protection for LAIV: Immunogenicity bridging allowed for formulation changes
A randomized, double-blind noninferiority study of quadrivalent live attenuated influenza vaccine in adults

Stan L. Block\textsuperscript{a,}\textsuperscript{*}, Tingting Yi\textsuperscript{b}, Eric Sheldon\textsuperscript{c}, Filip Dubovsky\textsuperscript{b}, Judith Falloon\textsuperscript{b}
US Flu VE Network: LAIV and IIV VE age 2-17 yrs
Any Influenza A or B

http://www.cdc.gov/vaccines/acip/meetings/slides-2016-06.html
Oil-in-Water Emulsion Adjuvant with Influenza Vaccine in Young Children

Timo Vesikari, M.D., Markus Knuf, M.D., Peter Wutzler, M.D.,
Aino Karvonen, M.D., Dorothee Kieninger-Baum, M.D.,
Heinz-Josef Schmitt, M.D., Frank Baehner, M.D., Astrid Borkowski, M.D.,
Theodore F. Tsai, M.D., and Ralf Clemens, M.D.
Efficacy of MF-59 adjuvanted versus non-adjuvanted TIV in 6 to 72 month-old children, any disease severity

<table>
<thead>
<tr>
<th>Analysis*</th>
<th>Efficacy Against All Strains</th>
<th>Efficacy Against Matched Strains</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases/ Vaccinated</td>
<td>VE % (2-sided 95% CI)</td>
</tr>
<tr>
<td>FLUAD vs. Non-influenza controls</td>
<td>13/1937 vs. 48/993</td>
<td>86 (74 - 93)</td>
</tr>
<tr>
<td>TIV vs. Non-influenza control</td>
<td>50/1772 vs. 48/993</td>
<td>43 (15 – 61)</td>
</tr>
<tr>
<td>FLUAD vs. TIV</td>
<td>13/1937 vs. 50/1772</td>
<td>75 (55 - 87)</td>
</tr>
<tr>
<td>FLUAD vs. Non-influenza controls</td>
<td>9/1937 vs. 41/993</td>
<td>89 (78 - 95)</td>
</tr>
<tr>
<td>TIV vs. Non-influenza control</td>
<td>44/1772 vs. 41/993</td>
<td>45 (16 - 64)</td>
</tr>
<tr>
<td>FLUAD vs. TIV</td>
<td>9/1937 vs. 44/1772</td>
<td>80 (59 - 90)</td>
</tr>
</tbody>
</table>

What about improved non-replicating vaccines?

- Better vaccines for older adults: market-driven
- Accepted relative correlate of protection: Hemagglutination-inhibition (HAI) assay

Figure 1: Number of Persons 65+, 1900 to 2060 (numbers in millions)

Note: Increments in years are uneven. Source: U.S. Census Bureau, Population Estimates and Projections.
Table 2. Comparison of responses to high-dose (HD) and standard-dose (SD) influenza vaccine.

<table>
<thead>
<tr>
<th>Response, by antigen</th>
<th>HD vaccine recipients&lt;sup&gt;a&lt;/sup&gt; (n = 2576)</th>
<th>SD vaccine recipients&lt;sup&gt;a&lt;/sup&gt; (n = 1275)</th>
<th>HAI GMT ratio for HD and SD vaccine, (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subjects with valid serologic result, no.</td>
<td>HAI GMT (95% CI)</td>
<td>Subjects with valid serologic result, no.</td>
</tr>
<tr>
<td>GMT</td>
<td>Day 0 2553 28.5 (27.4–29.7)</td>
<td>1267 29.4 (27.7–31.1)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Day 28 2543 115.8 (111.4–120.3)</td>
<td>1252 57.3 (63.7–71.1)</td>
<td>1.7 (1.6–1.8)</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>Day 0 2552 74.6 (70.3–78.2)</td>
<td>1268 74.7 (68.6–81.4)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Day 28 2544 608.9 (583.5–635.3)</td>
<td>1252 332.5 (310.4–356.1)</td>
<td>1.8 (1.7–2.0)</td>
</tr>
<tr>
<td>B</td>
<td>Day 0 2551 19.3 (18.6–20.1)</td>
<td>1267 19.0 (17.9–20.0)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Day 28 2542 69.1 (66.6–71.6)</td>
<td>1252 52.3 (49.5–55.3)</td>
<td>1.3 (1.2–1.4)</td>
</tr>
<tr>
<td>Seroconversion&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Subjects, % (95% CI)</td>
<td>Subjects, % (95% CI)</td>
<td>Percentage difference in rate (95% CI)</td>
</tr>
<tr>
<td>A/H1N1</td>
<td>2531 48.6 (46.6–50.5)</td>
<td>2549 23.1 (20.2–25.6)</td>
<td>25.4 (22.4–28.5)</td>
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<td>A/H3N2</td>
<td>2531 69.1 (67.3–70.9)</td>
<td>2548 50.7 (47.9–53.5)</td>
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<td>2529 41.8 (39.8–43.7)</td>
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<td>2543 69.9 (68.7–71.0)</td>
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<tr>
<td>A/H3N2</td>
<td>2544 99.3 (88.9–99.6)</td>
<td>1252 96.5 (95.3–97.4)</td>
<td>2.8 (1.7–3.9)</td>
</tr>
<tr>
<td>B</td>
<td>2542 79.3 (77.6–80.3)</td>
<td>1252 67.6 (64.9–70.2)</td>
<td>11.7 (8.7–14.7)</td>
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NOTE. Superiority was demonstrated if the lower limit of the 95% confidence interval for the difference in seroconversion rates (i.e., HD vaccine minus SD vaccine) was >10%, and noninferiority was shown if the lower limit was ≥-10%. The ratios of the hemagglutination inhibition (HAI) geometric mean titers (GMT) for HD vaccine and SD vaccine were assessed for all vaccine strains. Superiority was demonstrated if the lower limit of the 95% confidence interval for the ratio was >1.5, and noninferiority was defined as an HAI GMT ratio value >0.67. For HD vaccine to be considered superior to SD vaccine overall, for each measure it was required to demonstrate superiority for at least 2 of the 3 vaccine strains without demonstrating inferiority for any strain. CI, confidence interval.

<sup>a</sup> n values are the number of subjects used for the immunogenicity analysis (i.e., the counts of subjects as randomized rather than as actually vaccinated; see figure 1A).

<sup>b</sup> Paired samples with prevaccination (day 0) HAI titer <1.10 and postvaccination (day 28) titer ≥1.40 or a ≥4-fold increase from day 0 to day 28.

<sup>c</sup> Postvaccination samples with HAI GMT ≥1:40
Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults

Trial Design (FIM12)

RCT
126 centers
US & Canada

Adults ≥ 65 years of age
N = 32,000

Time
DO (Sep-Oct)

Intervention / Control

Fluzone High-Dose
16,000
1:1 ratio
16,000
Fluzone

Endpoint

Influenza
No Influenza
Influenza
No Influenza

April 30

6-8 months

Study conducted over two influenza seasons
Primary endpoint based on influenza caused by any influenza strain associated with a protocol-defined ILI

DOI: 10.1056/NEJMoa1315727
Primary Analysis: Superior Relative Efficacy Achieved (FIM12)

Laboratory-confirmed influenza caused by any viral type or subtype (regardless of similarity)\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Fluzone High-Dose N=15,892 n (%)</th>
<th>Fluzone N=15,911 n (%)</th>
<th>Relative Efficacy % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated with PD ILI(^b)</td>
<td>227 (1.43)</td>
<td>300 (1.89)</td>
<td>24.2 (9.7; 36.5)</td>
</tr>
</tbody>
</table>

Lower limit of the 95% CI of relative efficacy = 9.7%

Pre-specified lower limit required by FDA to demonstrate superior clinical benefit > 9.1%

\(^a\) Per-protocol analysis set
\(^b\) Protocol-defined influenza-like illness
Cost-effectiveness of high-dose versus standard-dose inactivated influenza vaccine in adults aged 65 years and older: an economic evaluation of data from a randomised controlled trial

Ayman Chit, Debbie L. Becker, Carlos A. DiazGranados, Michael Maschio, Eddy Yau, Michael Drummond

- Used data from the FIM12 head-to-head randomized controlled trial
- High dose cost US $31.82, standard dose $12.04
- HD more cost-effective, primarily driven by avoiding hospitalization costs
Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis

Hector S Izurieta*, Nicole Thadani*, David K Shay, Yun Lu, Aaron Maurer, Ivo M Foppa, Riley Franks, Douglas Pratt, Richard A Forshee, Thomas Macurdy, Chris Worrall, Andrew E Howery, Jeffrey Kelman

Comparative Effectiveness of High-Dose Versus Standard-Dose Influenza Vaccination in Community-Dwelling Veterans

Diane M. Richardson,1 Elina L. Medvedeva,1 Christopher B. Roberts,1 and Darren R. Linkin2,3; for the Centers for Disease Control and Prevention Epicenter Program

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Clinical Infectious Diseases® 2015; 15:293-300
Licensure of MF-59 adjuvanted influenza vaccine for persons 65 years and older, US

- Multicenter safety and immunogenicity trial in US
- 7,082 people aged 65+ randomized to aTIV or TIV
- Antibody endpoints met non-inferiority criteria
  - aTIV elicited higher antibody responses; did not meet pre-defined superiority criteria
- 27,000 additional followed for safety
  - No safety concerns
  - Higher frequency of mild and moderate local and systemic reactions
- Supportive data from immunogenicity and observational studies in Europe, Canada
- Confirmatory study required to show clinical benefit
What are the potential advantages or challenges of “new” rotavirus vaccines?

- Will they be more effective at preventing severe rotavirus gastroenteritis? If so, how much “more effective”
- Will non-replicating vaccines provide cross-protection?
- Will they have longer lasting immunity (second year of life)?
- Will they be safe? IS?
- What will be the mode of administration and acceptability?
- How many doses will be required?
- Could they be combined with other vaccines?
- What will be their logistics/cold chain requirements?
- Will they be lower cost and have/ensure more stable supply?
How do we evaluate new rotavirus vaccines?

• The need for better vaccines is in low resource countries
  • Market AND public health driven decisions
  • Likely requires shared investment
• Each candidate will require an individual assessment by regulators – immunogenicity bridge/challenge/head-to-head/post-licensure assessments/combination
• Head-to-head comparisons, severe disease outcomes will provide strongest policy evidence
  • Feasibility, cost
  • Minor differences can have negative effects on market, as multiple manufacturers preferred
• Need to consider how we will prioritize “improvements”