Influenza: Virus, vaccines and vaccination strategies

Kathleen Neuzil, MD, MPH
Director, Center for Vaccine Development
University of Maryland School of Medicine
May 31, 2016
Objectives

• To review seasonal and pandemic influenza.
• To review the currently available influenza vaccines, their advantages and limitations.
• To discuss tools and strategies to facilitate influenza prevention through vaccination in low-resource settings.
Influenza: Some Basics

- Influenza A viruses
  - Subtypes based on surface glycoproteins
    - Hemagglutinin (HA) and Neuraminidase (NA)
    - Current human influenza A virus subtypes: H1N1, H3N2
  - Infect multiple species
  - Epidemics and pandemics

- Influenza B
  - Humans only reservoir
  - Less mortality than type A
  - Associated with epidemics, not pandemics
  - Two circulating lineages (Yamagata and Victoria), resulting in expansion of influenza vaccine to include 4 antigens
Genetic Divergence of Influenza HA Over Time

Bedford, T., et al., eLife2014;3:e01914
Reassortment of Influenza A Viruses

Alpha 2,3 receptors in respiratory tract
Non-human virus
Alpha 2,6 receptors
Reassortant virus

Alpha 2,6 & Alpha 2,3 receptors in respiratory tract
## Influenza A HA and NA Subtypes

<table>
<thead>
<tr>
<th>HA Type</th>
<th>Combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>human, swine, fowl</td>
</tr>
<tr>
<td>H2</td>
<td>human, fowl</td>
</tr>
<tr>
<td>H3</td>
<td>human, swine, fowl, equine, canine</td>
</tr>
<tr>
<td>H4</td>
<td>seal, fowl swine</td>
</tr>
<tr>
<td>H5</td>
<td>human, fowl</td>
</tr>
<tr>
<td>H6</td>
<td>fowl</td>
</tr>
<tr>
<td>H7</td>
<td>human, seal, fowl, equine</td>
</tr>
<tr>
<td>H8</td>
<td>fowl</td>
</tr>
<tr>
<td>H9</td>
<td>human, swine, fowl</td>
</tr>
<tr>
<td>H10</td>
<td>fowl</td>
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<tr>
<td>H11</td>
<td>fowl</td>
</tr>
<tr>
<td>H12</td>
<td>fowl</td>
</tr>
<tr>
<td>H13</td>
<td>gulls</td>
</tr>
<tr>
<td>H14</td>
<td>fowl</td>
</tr>
<tr>
<td>H15</td>
<td>gulls</td>
</tr>
<tr>
<td>H16</td>
<td>gulls</td>
</tr>
<tr>
<td>H17</td>
<td>bats</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NA Type</th>
<th>Combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>human, swine, fowl</td>
</tr>
<tr>
<td>N2</td>
<td>human, swine, fowl</td>
</tr>
<tr>
<td>N3</td>
<td>human, swine, fowl</td>
</tr>
<tr>
<td>N4</td>
<td>fowl</td>
</tr>
<tr>
<td>N5</td>
<td>fowl</td>
</tr>
<tr>
<td>N6</td>
<td>fowl</td>
</tr>
<tr>
<td>N7</td>
<td>seal, fowl, equine</td>
</tr>
<tr>
<td>N8</td>
<td>canine, fowl, equine</td>
</tr>
<tr>
<td>N9</td>
<td>fowl, human</td>
</tr>
<tr>
<td>N10</td>
<td>bat</td>
</tr>
</tbody>
</table>
A pandemic can occur if three conditions are met

1. Emergence of novel influenza A subtype
2. Efficient and sustained virus transmission occurs among humans
3. Infection causes disease
WHO Risk Assessment (www.who.int 5/25/16)

- **What is the likelihood that additional human cases of infection with influenza A (H7N9) will occur?**
  - Most human cases are exposed through contact with infected poultry or contaminated environments. Since the virus continues to be detected in animals and environments, further human cases can be expected.

- **What is the likelihood of human-to-human transmission of avian influenza A (H7N9) viruses?**
  - Even though small clusters of cases have been reported, including those involving HCW, current evidence suggests this virus has not acquired ability for human-to-human transmission.

- **What is the risk of international spread of A (H7N9) by travellers?**
  - Should infected individuals from affected areas travel internationally, their infection may be detected in another country during travel or after arrival. If this were to occur, further community level spread is considered unlikely as this virus has not acquired the ability to transmit easily among humans.
Human Influenza - Clinical

• Acute febrile respiratory illness
  - “Influenza-like illness”
    - Fever or feverish
    - Cough and/or sore throat or other manifestations (otitis)
  - More serious pulmonary manifestations
    - Primary or secondary pneumonia, croup, bronchiolitis

• Non-specific febrile illness

• Extra-pulmonary manifestations
  - Neurologic – Encephalitis, seizures
  - Myositis
  - Cardiac

Absence of data does not equal absence of influenza!
Seasonal Influenza: What do we know?

• WHO Estimates
  • 3-5 million cases of severe illness
  • 250,000 – 500,000 deaths/year globally
  • Highly variable from year-to-year
• Infection rates highest among children; children play an important role in the spread of influenza.
• Severe disease and death most common at extremes of age, pregnant women, those with chronic conditions
• Most data from high resource settings
Influenza Positive Tests Reported to CDC by U.S. Public Health Laboratories, National Summary, 2015-2016 Season

Week

Number of Positive Specimens

- A (subtyping not performed)
- A (H1N1)pdm09
- A (H3N2)
- H3N2v
- B (lineage not performed)
- B (Victoria Lineage)
- B (Yamagata Lineage)
Influenza activity by month, 2010-2013

- **July**
- **August**
- **September**
- **October**
- **November**
- **December**
Pneumonia and Influenza Mortality for 122 U.S. Cities
Week Ending April 16, 2016
Number of Influenza-Associated Pediatric Deaths by Week of Death: 2012-2013 season to present

- **2012-2013**: Number of Deaths Reported = 171
- **2013-2014**: Number of Deaths Reported = 111
- **2014-2015**: Number of Deaths Reported = 148
- **2015-2016**: Number of Deaths Reported = 56
<table>
<thead>
<tr>
<th></th>
<th>Live Attenuated</th>
<th>Standard Inactiv</th>
<th>High dose Inactiv.</th>
<th>Recomb</th>
<th>Inactiv. intradermal</th>
<th>MF59-Adjuvant</th>
</tr>
</thead>
<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>
<td>Annual</td>
<td>Annual</td>
<td>Annual</td>
<td>Annual</td>
</tr>
<tr>
<td><strong>Approved ages</strong></td>
<td>2 - 49 yrs</td>
<td>≥ 6 mos</td>
<td>&gt; 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>
<td>Eggs</td>
<td>Eggs/cell culture</td>
<td>Eggs</td>
<td>Cell culture</td>
<td>Eggs</td>
<td>Eggs</td>
</tr>
<tr>
<td><strong>Common side effects</strong></td>
<td>Sore throat nasal congest.</td>
<td>Injection site rxn</td>
<td>More injection site rxn</td>
<td>Injection site rxns</td>
<td>Erythema at inject site</td>
<td>More injection site rxn</td>
</tr>
<tr>
<td><strong>Pregnant women?</strong></td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>
Current Influenza Vaccines Based on Circulating Viruses

Bedford, T., et al., eLife2014;3:e01914
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
  - GSK
  - CSL Biologics
  - Flublok (Vaccitech)
  - Novartis
  - Isconova

## Phase 1
- **Cell-culture inactivated**
  - GPO
  - MedImmune
  - Virosave
  - Gilead

## Phase 2
- **LAIV**
  - GPO
  - MedImmune
  - Virosave

## Phase 3
- **Recombinant (VLPs)**
  - Novavax
  - Dynavax
  - Vaxxcel
d
## Market Approval
- **Universal**
  - NYU/SSM
  - Dynavax
  - Vaxxcel

## DNA
- **Vicalinnovio**

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**Legend**
- Seasonal
- Pandemic
- Seasonal & Pandemic
- US License

**Date**
16SEPT2013
Preventing influenza with vaccine: What is our goal? What are our options?

- Disease prevention? Severe disease prevention?
- Maintain workforce? Save money?
- Which vaccines?
- Which target populations?
- What vaccination strategies?

Photo credit: John C. Victor, PATH
Influenza vaccine recommendations, U.S., 2015 - 2016

- Routine annual influenza vaccination of all persons aged ≥6 months continues to be recommended.
- No preferential recommendation is made for one influenza vaccine product over another for persons for whom more than one product is otherwise appropriate.

“For countries considering the initiation or expansion of programmes for seasonal influenza vaccination, WHO recommends that pregnant women should have the highest priority.”

WHO SAGE, April 2012

• The priority accorded to pregnant women was based on “compelling evidence of substantial risk of severe disease in this group and evidence that seasonal influenza vaccine is safe and effective in preventing disease in pregnant women as well as their young infants, in whom disease burden is also high.”

• 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.

Source: WHO. WER 2012; 87: 201-16.
Countries Providing Seasonal Influenza in National Immunization Schedule, 2012

No (116 countries or 60%)
Yes (76 countries or 39%)
Yes (Part of the country) (2 countries or 1%)
Not available
Not applicable

Date of slide: 24 July 2013

The boundaries and names shown and the designations used 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 2013. All rights reserved.
Competition: many new vaccine introductions in strained systems – what will drive uptake?
Review

Influenza vaccine for pregnant women in resource-constrained countries:
A review of the evidence to inform policy decisions

Justin R. Ortiz\textsuperscript{a,b,*}, Janet A. Enlund\textsuperscript{c}, Kathleen M. Neuzil\textsuperscript{a,b,d}

\textsuperscript{a} Vaccine Development Global Program, PATH, Seattle, WA, United States
\textsuperscript{b} Department of Medicine, University of Washington, Seattle, WA, United States
\textsuperscript{c} Department of Pediatrics, Division of Infectious Diseases, Children's Hospital Research Institute, University of Washington, Seattle, WA, United States
\textsuperscript{d} Department of Global Health, University of Washington, Seattle, WA, United States

Table 4
Availability of critical information influencing accelerated introduction of influenza vaccine for pregnant women by low-or high-resource setting, as assessed by the authors.

<table>
<thead>
<tr>
<th>Critical information</th>
<th>Amount of Evidence available</th>
<th>Low-resource setting</th>
<th>High-resource setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease burden, mother</td>
<td>Partial</td>
<td></td>
<td>Substantial</td>
</tr>
<tr>
<td>Disease burden, infant</td>
<td>Partial</td>
<td></td>
<td>Substantial</td>
</tr>
<tr>
<td>Vaccine safety</td>
<td>Partial</td>
<td></td>
<td>Substantial</td>
</tr>
<tr>
<td>Maternal immunogenicity</td>
<td>Partial</td>
<td></td>
<td>Substantial</td>
</tr>
<tr>
<td>Effectiveness in pregnant women</td>
<td>Partial</td>
<td></td>
<td>Partial</td>
</tr>
<tr>
<td>Effectiveness in infants born to vaccinated mother</td>
<td>Partial</td>
<td></td>
<td>Partial</td>
</tr>
<tr>
<td>Knowledge and attitudes of mothers</td>
<td>None or limited</td>
<td></td>
<td>Substantial</td>
</tr>
<tr>
<td>Feasibility</td>
<td>None or limited</td>
<td></td>
<td>Substantial</td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td>None or limited</td>
<td></td>
<td>Partial</td>
</tr>
</tbody>
</table>
Key influenza vaccine benefits:
Uniquely benefits three groups, strengthens maternal immunisation, catalytic market-shaping opportunities

**Key benefits**

- **Potential to uniquely benefit three high-risk groups: pregnant woman, infant, fetus***
  - Pregnant women: highest priority target in WHO position paper; fetus: initial (and limited) data suggests reduction in low birth weight and prematurity*; neonate / infant: highest influenza burden

- **Strengthens maternal immunisation platform and GAVI's contribution to maternal and child health**
  - Pregnant women, fetus, and neonates new target populations for GAVI; strengthens infrastructure for GAVI / countries to leverage antenatal care route in future (e.g., for pertussis, RSV, etc.)

- **Opportunity to shape market to serve countries with year-round influenza circulation**
  - Vaccine industry not currently set up to efficiently provide year-round supply; GAVI could help drive regulatory, policy, and logistical changes

* Effects on fetus highly uncertain and not included in VIS impact estimates
Key influenza vaccine challenges:
Uncertainty in impact, complex provision of year-round supply, low awareness / demand

Key challenges

- Health impact
  - Possibility that health impact is not attractive (uncertainty will not be resolved pre GAVI board)
    - Limited number of studies and wide confidence intervals around infant vaccine efficacy and effects on fetus; three studies with 12,000 subjects to provide additional data in 2014

- Epidemic potential

- Impact on vaccine markets

- Cost
  - Logistical challenges with supplying seasonal vaccines
    - To supply year-round, will need to switch formulations mid-year and/or alter label for expiration dates

- Value for money (relative to current portfolio)

- Unique global and country implementation requirements

- Country views
  - Low country awareness and low demand in GAVI-eligible countries
    - Low awareness across multiple groups: pregnant women, health care workers, and decision makers; influenza vaccine ranked as lowest priority for country introduction in 2013 GAVI survey

Source: http://www.gavialliance.org/about/governance/gavi-board/minutes/2013/21-nov/
Effectiveness of Maternal Influenza Vaccination in Dhaka, Bangladesh

• Compared TIV to pneumococcal polysaccharide vaccine in pregnant women
• TIV decreased respiratory illness with fever by 29% among infants and 36% among their mothers.
• Vaccine efficacy against laboratory-confirmed influenza among newborns was 63%
• Three additional RCT’s in South Africa, Nepal and Mali recently completed.

Influenza Vaccination of Pregnant Women and Protection of Their Infants

Shabir A. Madhi, M.D., Ph.D., Clare L. Cutland, M.D., Locadiah Kuwanda, M.Sc., Adriana Weinberg, M.D., Andrea Hugo, M.D., Stephanie Jones, M.D., Peter V. Adrian, Ph.D., Nadia van Niekerk, B.Tech., Florette Treurnicht, Ph.D., Justin R. Ortiz, M.D., Marietjie Venter, Ph.D., Avy Violari, M.D., Kathleen M. Neuzil, M.D., Eric A.F. Simões, M.D., Keith P. Klugman, M.D., Ph.D., and Marta C. Nunes, Ph.D., for the Maternal Flu Trial (Matflu) Team

• Two double-blind, randomized, placebo-controlled trials of IIV3 in South Africa
  • 2011: pregnant women with HIV infection
  • 2011 and 2012: pregnant women who were not HIV-infected.
  • 18-36 years of age, 20 to 36 weeks gestation
• Immunogenicity, safety and efficacy until 24 weeks after birth evaluated
• Influenza diagnosed by RT-PCR assays of respiratory samples

Efficacy of influenza vaccine and influenza episodes prevented per 100 persons, South Africa

Influenza episodes per 100

Women

Infants

HIV-uninfected

HIV-infected

Efficacy

50.4%  
48.8%  
57.7%  
26.7%

(14.5 - 71.2)  
(11.6 - 70.4)  
(0.2 - 82.1)  
(-132.0 - 76.8)

Influenza: Global burden in children < 5 years

- Limited (but increasing) data from low-resource countries.
- 2010 Global burden of disease estimates 2% of all mortality is attributable to influenza virus infection during the first 5 years of life.
- 2011 *Lancet* meta-analysis in children < 5 years estimates:
  - 20 million (95% CI 13-32) acute lower respiratory infections (ALRI).
  - 1 to 2 million severe ALRI.
  - 28,000 to 111,500 deaths.
  - 99% of early childhood influenza deaths occur in low- and middle-income countries.

Influenza vaccines for young children

- Children younger than 6 months of age: no available influenza vaccines approved
- Children younger than 2 years of age: inactivated, non-adjuvanted vaccines are only approved vaccines
  - Wheezing signal (< 2 years) and excess hospitalizations (< 1 year) associated with LAIV has resulted in approval for use starting at 2 years of age
- Children 2 through 4 years of age
  - Inactivated, non-adjuvanted and live-attenuated vaccines are approved
- Efficacy varies in published studies of inactivated vaccine: 0-83%
Efficacy of MF-59 adjuvanted versus unadjuvanted TIV in 6 to 72 month-old children

<table>
<thead>
<tr>
<th>Analysis*</th>
<th>Cases/ Vaccinated</th>
<th>VE %  (2-sided 95% CI)</th>
<th>Target</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLUAD vs. Non-influenza controls</td>
<td>13/1937 vs. 48/993</td>
<td>86 (74 - 93)</td>
<td>Lower CI ≥40</td>
<td>Met</td>
</tr>
<tr>
<td>TIV vs. Non-influenza control</td>
<td>50/1772 vs. 48/993</td>
<td>43 (15 – 61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FLUAD vs. TIV</td>
<td>13/1937 vs. 50/1772</td>
<td>75 (55 - 87)</td>
<td>Lower CI ≥10</td>
<td>Met</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Efficacy Against Matched Strains</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLUAD vs. Non-influenza controls</td>
</tr>
<tr>
<td>TIV vs. Non-influenza control</td>
</tr>
<tr>
<td>FLUAD vs. TIV</td>
</tr>
</tbody>
</table>

Randomized, controlled trial of quadrivalent IIV in children 3 – 8 years: efficacy by disease severity

<table>
<thead>
<tr>
<th>Table 1. Vaccine Efficacy against rt-PCR–Confirmed and Culture-Confirmed Influenza A or B According to Age and A Subtype and B Lineage.*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort and Influenza Variable</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Total vaccinated cohort</td>
</tr>
<tr>
<td>rt-PCR–confirmed influenza, any severity</td>
</tr>
<tr>
<td>rt-PCR–confirmed influenza, moderate-to-severe</td>
</tr>
<tr>
<td>Culture-confirmed, rt-PCR–confirmed influenza, any severity, any seasonal strain</td>
</tr>
<tr>
<td>Culture-confirmed, rt-PCR–confirmed influenza, any severity, vaccine-matched strain</td>
</tr>
</tbody>
</table>

**Source:** Jain VK, et al. *NEJM* 2013;369 (26):2481-2491
## Effectiveness of influenza vaccine: PICU admission, U.S.

### Table 5. Regression model results and vaccine effectiveness based on comparison of cases and community controls (n=44 cases, 93 community controls)

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
<th>p</th>
<th>Vaccine Effectiveness (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full vaccination</td>
<td>0.18 (0.04 to 0.77)</td>
<td>0.02</td>
<td>82% (23 to 96%)</td>
</tr>
<tr>
<td>Partial vaccination</td>
<td>1.79 (0.50 to 6.41)</td>
<td>0.37</td>
<td>-79% (-541 to 50%)</td>
</tr>
<tr>
<td>No vaccination</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.33 (0.12 to 0.90)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>White race</td>
<td>4.27 (1.22 to 15.0)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>≥3 chronic health conditions</td>
<td>24.6 (3.81 to 158.7)</td>
<td>0.0008</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** From a conditional logistic regression model with cases and controls matched by age group, geographic area, and influenza risk category. Vaccination status was based on parental report for both cases and controls.

**Source:** Ferdinands et al JID 2014
Seasonal influenza vaccination of children in Senegal: a cluster-randomized trial

U.S. CDC Co-operative agreement; Partners: Institut de Recherch pour la Developpement; Institut Pasteur of Dakar; Presented by JC Victor, PATH, at Options for the Control of Influenza VIII September 6, 2013.
Group-randomized trials: measures of vaccine effectiveness in the population

**Effectiveness Measure:**
- Population or Overall:
- **Total:**
- Indirect:
- Direct:

**Group Incidence Compared:**
- Population or Overall: vs Total:
  - vs Indirect:
    - vs Direct:

**Vaccine Village**
- Received flu vaccine
- Did not receive flu vaccine

**Control Village**
- Received control vaccine
- Did not receive control vaccine
Results: incidence of A/H3N2 influenza among children participating in vaccinations

![Graph showing cumulative incidence of A/H3N2 influenza among different age groups, comparing TIV and IPV.](image_url)
Results: effectiveness against A/H3N2 among participating children (total effectiveness)
Influenza prevention in children in low resource settings: Rationale for LAIV

- Public health need: Young children at high risk for severe influenza outcomes.
- Is LAIV a better choice than current, unadjuvanted, inactivated vaccines for seronegative (unprimed) individuals?
  - LAIV superior to inactivated influenza vaccine (IIV) in RCTs in young children
  - Potentially better cross-protection (antigenic drift variants).
- Egg-based production of LAIV can be achieved in higher yield and at lower cost as compared to inactivated vaccines.
- Enhanced feasibility: Intranasal delivery and potentially single dose for all ages.
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, % LAIV</th>
<th>TIV</th>
<th>Relative efficacy, % (95% CI)</th>
<th>H3N2* Attack rate, % LAIV</th>
<th>TIV</th>
<th>Relative efficacy, % (95% CI)</th>
<th>B* Attack rate, % LAIV</th>
<th>TIV</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>
<td>2·3</td>
<td>2·7</td>
<td>15 (–29 to 43)</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>
<td>2·8</td>
<td>3·0</td>
<td>10 (–42 to 43)</td>
</tr>
<tr>
<td>36–47 (846)</td>
<td>42 (5–66)</td>
<td>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>
<td>4·1</td>
<td>4·8</td>
<td>12 (–69 to 55)</td>
</tr>
<tr>
<td>48–59 (708)</td>
<td>56 (25–75)</td>
<td>0</td>
<td>2·0</td>
<td>100 (47–100)</td>
<td>1·1</td>
<td>4·0</td>
<td>76 (22–95)</td>
<td>5·0</td>
<td>7·5</td>
<td>25 (–37 to 60)</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, Germany, Israel.
A pandemic influenza vaccine in India: From strain to sale within 12 months

Rajeev Dhere*, Leena Yeolekar, Prasad Kulkarni, Ravi Menon, Vivek Vaidya, Milan Ganguly, Parikshit Tyagi, Prajakt Barde, Suresh Jadhav

Serum Institute of India Limited, 212/2 Off Soli Poonawalla Road, Hadapsar, Pune 411 028, Maharashtra, India

Fig. 2. Intranasal spray device for administration of H1N1 pandemic vaccine.
## SIIL Trivalent LAIV clinical trials in Bangladesh and Senegal

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>N</th>
<th>Ages</th>
<th>Primary Objective</th>
<th>Secondary Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh (Kamalapur)</td>
<td>2012</td>
<td>Safety &amp; Immunogenicity 1:1 randomization</td>
<td>300</td>
<td>24-59 months</td>
<td>Safety</td>
<td>Immunogenicity, Shedding/Take Compare</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Single dose LAIV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangladesh Clinical Efficacy</td>
<td>2013</td>
<td>Clinical Efficacy 2:1 randomization</td>
<td>1,761</td>
<td>24-59 months</td>
<td>Clinical efficacy</td>
<td>Safety Outcomes</td>
</tr>
<tr>
<td>(Kamalapur and Matlab)</td>
<td></td>
<td>Single dose LAIV</td>
<td></td>
<td></td>
<td></td>
<td>Additional efficacy outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Senegal Clinical Efficacy (Niakhar)</td>
<td>2013</td>
<td>Clinical Efficacy 2:1 randomization</td>
<td>1,761</td>
<td>24-71 months</td>
<td>Clinical efficacy</td>
<td>Safety Outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Single dose LAIV</td>
<td></td>
<td></td>
<td></td>
<td>Additional efficacy outcomes</td>
</tr>
</tbody>
</table>
What have we learned?

- Vaccine is safe and well-tolerated in both populations
- Influenza was common in both populations
- Attack rate for LCI in control group 24.5% in Bangladesh and 18.0% in Senegal

<table>
<thead>
<tr>
<th>Strain</th>
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<th>Senegal</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1N1</td>
<td>50.0% (9.2 - 72.5)</td>
<td></td>
</tr>
<tr>
<td>H3N2</td>
<td>60.4% (44.8 - 71.6)</td>
<td></td>
</tr>
<tr>
<td>B lineage match</td>
<td>0.0* (&lt;0 - 90.9)</td>
<td></td>
</tr>
<tr>
<td>B lineage mismatch</td>
<td>8.1% (-40.8 - 40.0)</td>
<td></td>
</tr>
</tbody>
</table>

*2 LAIV and 1 placebo
What have we learned?

- Vaccine is safe and well-tolerated in both populations
- Influenza was common in both populations
  - Attack rate for LCI in control group 24.5% in Bangladesh and 18.0% in Senegal
- Efficacy estimates for H1N1 strain differed between populations

<table>
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<tr>
<th>Strain</th>
<th>Bangladesh</th>
<th>Senegal</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1N1</td>
<td>50.0% (9.2 - 72.5)</td>
<td>-9.7% (-62.6 - 26.1)</td>
</tr>
<tr>
<td>H3N2</td>
<td>60.4% (44.8 - 71.6)</td>
<td>--------</td>
</tr>
<tr>
<td>B lineage match</td>
<td>0.0* (&lt;0 - 90.9)</td>
<td>9.5% (-88.9 - 56.6)</td>
</tr>
<tr>
<td>B lineage mismatch</td>
<td>8.1% (-40.8 - 40.0)</td>
<td>7.3% (-26.3 - 31.9)</td>
</tr>
</tbody>
</table>

*2 LAIV and 1 placebo
What could account for differences in efficacy for H1N1 strain?

- **Vaccine?**
  - Single dose of SIIL’s lyophilized trivalent LAIV of 2012-13 NH formulation, same lot
  - Storage conditions monitored and appropriate
  - Environmental conditions at two sites differed?
    - Diluent temperature at time of reconstitution?

- **Virus?**
  - Any drift in circulating strains at either site?

- **Population?**
  - Prior history of influenza infection or vaccine use?
  - Nutritional differences?
  - Ecology of the nasopharynx?
LAIV effectiveness against medically-attended influenza, by season and age category

Adjusted Vaccine Effectiveness (%)

<table>
<thead>
<tr>
<th>Year</th>
<th>2–8 years</th>
<th>9–18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-12</td>
<td>64</td>
<td>60</td>
</tr>
<tr>
<td>2012-13</td>
<td>57</td>
<td>32</td>
</tr>
<tr>
<td>2013-14</td>
<td>-31</td>
<td>43</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Total, Flu +</th>
<th>LAIV, Flu +</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-12</td>
<td>168</td>
<td>6</td>
</tr>
<tr>
<td>2012-13</td>
<td>391</td>
<td>35</td>
</tr>
<tr>
<td>2013-14</td>
<td>127</td>
<td>22</td>
</tr>
<tr>
<td>2011-12</td>
<td>100</td>
<td>6</td>
</tr>
<tr>
<td>2012-13</td>
<td>347</td>
<td>26</td>
</tr>
<tr>
<td>2013-14</td>
<td>99</td>
<td>12</td>
</tr>
</tbody>
</table>
Vaccines as a tool to estimate the burden of severe influenza in children of low-resourced areas (November 30–December 1, 2012, Les Pensieres, Veyrier-du-Lac, France)

ARTICLE INFO

Keywords:
- Clinical trial
- Conference report
- Disease burden
- Immunization
- Influenza
- Vaccine

ABSTRACT

There is an increasing focus on influenza in low-resourced areas as a vaccine-preventable cause of severe lower respiratory disease in young children, especially among those under two years of age. The extent of the disease burden is unclear; current etiologic studies may underestimate the impact of influenza if recognized or unrecognized infection occurs some time before severe disease manifestations prompt specimen collection for diagnosis.

Because of various methodological challenges, a vaccine probe approach was used to estimate vaccine preventable disease incidence (VPDI) for Streptococcus pneumoniae and Haemophilus influenzae type b, particularly for pneumonia outcomes among young children. A similar approach could be used to determine VPDI for influenza. A highly effective vaccine would facilitate this approach; however, with appropriate design, a less than ideal vaccine also could be used to estimate VPDI. Because influenza vaccine efficacy against severe disease may be greater than against all symptomatic influenza disease, a vaccine probe approach could provide a better measure than etiologic studies of the public health utility of influenza vaccine.

The first 6 months of life is a time of particularly increased influenza risk among young children, and an age group for which current vaccines are not approved. Previous studies have found that maternal influenza immunization can reduce acute respiratory infection in the infant during this vulnerable period. Additional randomized, controlled trials are currently underway using a vaccine probe approach to estimate VPDI among mothers and their infants following maternal influenza immunization. The World Health Organization now identifies pregnant women as the highest priority target group for influenza vaccination. Should countries implement this strategy, infants age 6–23 months likely would remain at increased risk; vaccine probe approaches could quantify the public health benefit of immunizing this group.

1. Background

While vaccine probe studies can use a variety of designs, ideally complications, such as secondary bacterial respiratory infection [1], but the virus may be absent by the time a patient presents with severe disease; alternatively, influenza may cause mild and asym-
Influenza Vaccine: Research questions remain

- Why the variable effectiveness with LAIV, and how will we judge future vaccines (no correlate of protection)?
- What is the effect of priming (original antigenic sin?) on future vaccine responses?
- What is the effect of vaccination over multiple years?
- What is the duration of vaccine protection?
- Will effects differ by type of vaccine (non-replicating vs live attenuated?)
- How do we best measure indirect protection in different settings/environments?
Influenza - Summary

- Common respiratory illness accounting for substantial morbidity, mortality, lost productivity annually
- Influenza vaccines are safe and effective—how effective varies by year and influenced by virus, vaccine, host
- HA-based non-replicating vaccines and live-attenuated vaccines will be our primary options in the near-term.
- Vaccination schedules in high resource countries will become more nuanced in regard to the use of specific vaccines for specific age and risk groups.
Influenza Vaccines in Low-resource Settings

- Demonstrating burden of severe disease is critical
  - Large, multicenter probe center
- Focus on distinct target populations
  - Pregnant women
  - Young children
- Unique logistical/feasibility challenges
  - Demonstration projects
  - Year-round vaccination may be needed in many places
- Financing
How does data from US contribute to our understanding of the data in Bangladesh/Senegal?

• Vaccine?
  • No effectiveness shown for Medimmune vaccine against H1N1 strain; effectiveness shown for other strains
  • LAIV H1N1pdm09 may be less stable than seasonal H1N1 LAIV viruses (Cotter et al, 2014)
    • Sequence in HA stalk confers higher susceptibility to thermal degradation
    • Potentially could affect stability and/or replicative fitness of the vaccine virus

• Virus antigenic mismatch?
  • IIV effectiveness demonstrated in US studies

• Population?
  • Prior history of influenza infection or vaccine use – higher effectiveness in older children in US argues against this hypothesis