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.


WHO SAGE recommendation, 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;87:201-216.
Influenza prevention in children in low resource settings: Rationale for LAIV

- Public health need: Young children at high risk for severe influenza outcomes.
- Business case: Pandemic only model not sustainable
- LAIV may be better choice than current, unadjuvanted, inactivated vaccines for seronegative (unprimed) individuals.
- LAIV superior to inactivated influenza vaccine (IV) 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</th>
<th>Attack Rate, LAIV</th>
<th>Relative Effect, % (95% CI)</th>
<th>Attack Rate, TIV</th>
<th>Relative Effect, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-21 (6699)</td>
<td>56 (9.4%)</td>
<td>3.1 (1.9-5.2)</td>
<td>97.7 (95.6-98.9)</td>
<td>1.7 (1.2-2.4)</td>
<td>94.4 (92.5-95.3)</td>
</tr>
<tr>
<td>24-35 (1412)</td>
<td>57 (9.9%)</td>
<td>1.9 (1.3-2.9)</td>
<td>87.7 (84.9-90.4)</td>
<td>1.6 (1.1-2.4)</td>
<td>95.8 (93.2-97.3)</td>
</tr>
<tr>
<td>36-47 (1699)</td>
<td>42 (11.9%)</td>
<td>2.3 (1.7-3.1)</td>
<td>100.0 (99.0-100.0)</td>
<td>1.9 (1.5-2.4)</td>
<td>95.4 (93.1-97.2)</td>
</tr>
<tr>
<td>48-59 (1358)</td>
<td>56 (4.4%)</td>
<td>2.0 (1.1-3.1)</td>
<td>100.0 (97.0-100.0)</td>
<td>1.5 (1.2-2.0)</td>
<td>95.8 (92.2-98.0)</td>
</tr>
</tbody>
</table>

LAIV: live attenuated influenza vaccine; TIV: inactivated influenza vaccine.


Preferential recommendation for LAIV in young children in the United Kingdom, Canada, Germany, Israel.

Russian-derived LAIV in children

- Clinical trials in > 130,000 children in Russia.
- Approved for use in Russia in children at 3 years of age as a single dose in 1986; > 100 million doses to children and adults.
- Prior formulations (monovalent) tested in children down to 1 year of age.
- Most of the studies assessing safety were conducted prior to the pivotal FluMist® studies and did not explicitly report wheezing outcomes.
Russian-derived seasonal LAIV

- Serum Institute of India, Ltd (SIIL) monovalent pandemic H1N1 (Nasovac™) approved for use among healthy children and adults 3+ years by Drugs Controller General of India (2010), and prequalified by WHO (2012).
- Safety of monovalent vaccine supported by:
  - Phase 1 (adults) and Phase 2/3 (pediatric, adults, older adults).
  - Post-marketing surveillance.
- Subsequently, SIIL developed a trivalent seasonal vaccine, recently approved for children 2+ years and adults by DCGI.
  - Safety of trivalent vaccine supported by:
    - Phase 1 (adults) and Phase 2/3 (pediatric, adults, older adults).

PATH-sponsored SIIL trivalent LAIV clinical trials in Bangladesh and Senegal

**Senegal**
- Clinical efficacy
**Site PI**
  - Dr. Aldiouma Diallo,
  - Institut de Recherche pour le Développement
**Funder**
  - CDC (with supplement from BMGF)

**Bangladesh**
- Safety and immunogenicity
- Clinical efficacy
**Site PI**
  - Dr. Abdullah Brooks
  - icddr.b/Johns Hopkins University
**Funder**
  - BMGF

Goal: To provide data to guide policy in low resource countries

Trial objectives

- Assess safety outcomes, including wheezing, in young children.
- Demonstrate efficacy against laboratory-confirmed influenza outcomes.
- Demonstrate burden of illness/risk-benefit ratio in low-resource populations.
- Assess immunogenicity and post-vaccination shedding outcomes.

### 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 Single-dose LAIV</td>
<td>300</td>
<td>24-59 months</td>
<td>Safety</td>
<td>Immunogenicity Shedding/Take Compare</td>
</tr>
<tr>
<td>Bangladesh Clinical Efficacy (Kamalapur and Matlab)</td>
<td>2013</td>
<td>Clinical Efficacy 2:1 randomization Single-dose LAIV</td>
<td>1,761</td>
<td>24-59 months</td>
<td>Clinical efficacy</td>
<td>Safety Outcomes Additional efficacy outcomes</td>
</tr>
<tr>
<td>Senegal Clinical Efficacy (Niakhar)</td>
<td>2013</td>
<td>Clinical Efficacy 2:1 randomization Single-dose LAIV</td>
<td>1,761</td>
<td>24-71 months</td>
<td>Clinical efficacy</td>
<td>Safety Outcomes Shedding/Take Additional efficacy outcomes</td>
</tr>
</tbody>
</table>
Clinical trial design: Key elements

- Children enrolled beginning at 2 years of age (when trials started, approvals were at 3 years of age).
- Age de-escalation a goal of the program from the beginning.
- Children with wheezing illness/asthma were not excluded from the studies.
  - In pivotal FluMist® trial, among children 6 through 23 months of age, 5.9% given LAIV and 3.8% given TIV experienced Medically Significant Wheeze (MSW) (P = 0.002).
  - For children 24 to 59 months of age, rates of MSW were comparable in LAIV and TIV recipients (LAIV, 2.1%; TIV, 2.5%; P = 0.38).

Definition of Wheeze and Protocol-Defined Wheezing Illness (PDWI)

- Definition of Wheeze
  - Long high-pitched whistling or musical sound on expiration heard by auscultation over the lung fields.
  - Can occur in the presence or absence of pneumonia or other medical diagnoses.

- Definition of PDWI
  - Meets protocol evaluation criteria (acute respiratory or febrile illness).
  - Seeks care in the study clinic or participating hospital.
  - Is found to have a wheeze by a study physician.
  - Not all PDWI will be serious adverse events (SAEs), although moderate and severe PDWI will be SAEs.

Efficacy of 1 or 2 doses of LAIV (Ann Arbor) vs. placebo in children 2 to 6 years of age

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Year, Location, Age Group</th>
<th>Efficacy* (% [95% CI] [n])</th>
<th>Study Year, Location, Age Group</th>
<th>Efficacy* (% [95% CI] [n])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bracco Neto et al1</td>
<td>2005, South Africa and South America, 24–35 mos</td>
<td>71.5 (52.9–86.4) [818]</td>
<td>2006, South Africa and South America, 24–35 mos</td>
<td>81.8 (64.8–93.8) [322]</td>
</tr>
<tr>
<td>Behle et al1</td>
<td>1996–1997, United States, 24–35 mos</td>
<td>87.3 (58.2–96.3) [61]</td>
<td>1998–1999, United States, 24–35 mos</td>
<td>94.6 (66.6–97.4) [53]</td>
</tr>
<tr>
<td>Tave et al1</td>
<td>2002–2003, Southeast Asia, 24–35 mos</td>
<td>59.9 (35.0–77.4)</td>
<td>2002–2003, Southeast Asia, 24–35 mos</td>
<td>69.9 (35.0–77.4)</td>
</tr>
</tbody>
</table>

*Not applicable.
*The primary efficacy end point was the incidence of the first episode of culture-confirmed influenza illness caused by a virus subtype antigenically similar to that in the vaccine in the per-protocol population.
**All trials were randomized, double-blind, placebo-controlled 2-dose studies.

In 6–35 month-old children, efficacy was 57.7% for one dose and 73.5% for 2 doses, Bracco Neto study.

Clinical trial design: Key elements

- Children enrolled beginning at 2 years of age (when trials started, approvals were at 3 years of age).
  - Age de-escalation a goal of the program from the beginning.
- Children with wheezing illness/asthma were not excluded from the studies.
- One-dose regimen was chosen for all age groups.
- **Clinical illness definition**
  - Moderate to Severe Influenza Disease, defined as presence of any of the following:
    - Measured temperature ≥39°C
    - Physician diagnosis with clinical illness criteria (pneumonia, acute otitis media, meningitis, or sepsis).

Randomized, controlled trial of quadrivalent IIV in children: efficacy by disease severity

<table>
<thead>
<tr>
<th>Cohort and Influenza Variable</th>
<th>QIV Group</th>
<th>Control Group</th>
<th>QIV Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Attack Rate</td>
<td>Cases</td>
</tr>
<tr>
<td>Total vaccinated cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rIVR-confirmed influenza, any severity</td>
<td>62</td>
<td>3.49</td>
<td>140</td>
</tr>
<tr>
<td>rIVR-confirmed influenza, moderate to severe</td>
<td>16</td>
<td>8.62</td>
<td>61</td>
</tr>
<tr>
<td>Culture confirmed, rIVR-confirmed influenza, any severity, any season</td>
<td>54</td>
<td>2.08</td>
<td>129</td>
</tr>
<tr>
<td>Culture confirmed, rIVR-confirmed influenza, any severity, seasonal strain</td>
<td>15</td>
<td>1.55</td>
<td>66</td>
</tr>
</tbody>
</table>

**Evaluation timelines**

<table>
<thead>
<tr>
<th>Study</th>
<th>Enrollment Start</th>
<th>Outcomes Evaluation</th>
<th>Independent Safety Review</th>
<th>Results Timelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh Safety &amp; Immunogenicity (Kamalapur)</td>
<td>June 2012</td>
<td>Completed January 2013</td>
<td>Final DSMB meeting completed June 2013</td>
<td>Immunogenicity analysis ongoing–May 2014</td>
</tr>
<tr>
<td>Bangladesh Clinical Efficacy (Kamalapur and Matlab)</td>
<td>Feb 2013</td>
<td>First season completed December 2013</td>
<td>Second season follow-up through July 2014</td>
<td>Statistical analysis ongoing, initial results available in May/June 2014</td>
</tr>
<tr>
<td>Senegal Clinical Efficacy (Niakhar)</td>
<td>May 2013</td>
<td>Completed December 2013</td>
<td>Final DSMB meeting in August 2014</td>
<td>Data entry and cleaning ongoing, initial results available in July 2014</td>
</tr>
</tbody>
</table>
Summary

- PATH, SIIL, and partners in Bangladesh and Senegal have recently completed efficacy trials through a single season with one dose of the Russian-derived SIIL trivalent LAIV among children 2 through 5/6 years of age in Bangladesh/Senegal.
- Important study design parameters that differ from other clinical trials of LAIV
- Second year of follow-up ongoing in Bangladesh
- If the SIIL seasonal LAIV is safe and efficacious in 2 through 5 year olds, additional age de-escalation studies are planned.

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