PATH’s LAIV Program
Clinical Trials, Delivery Devices, and Formulation Work

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Overview of Talk

• LAIV clinical trials at PATH.
• Delivery devices.
• Developing stable influenza vaccine formulations.
Part I: LAIV Clinical Trials at PATH
Influenza Vaccine Project (IVP)

**IVP Goal**: Advance the development of promising new influenza vaccines, focusing on novel technologies that can be accessible, affordable, and available to people in low-resource countries.

**Funding from Bill and Melinda Gates Foundation.**
Support the development of live-attenuated influenza vaccines (LAIVs) against influenza subtypes that may emerge as pandemic strains.

Apply recombinant technologies to produce pandemic influenza vaccines.

Explore novel antigen/adjuvant combinations to enhance or broaden immunity to influenza vaccines.

Support innovative development of broadly reactive antigens for influenza vaccines.
LAIVs: Strategy

• LAIV may be better choice than current, unadjuvanted, inactivated vaccines for seronegative (unprimed) individuals.
  - Live vaccine superior to TIV in three comparative trials in children.
  - Relative efficacy less clear in adults; TIV superior to LAIV in 1 RCT in adults, but similar in most studies.
  - Likely better subheterotypic protection as well (drift strains).

• Egg-based production of LAIV can be achieved in higher yield and at lower cost as compared to inactivated vaccines.

• Logistical advantages: Intranasal delivery and single dose.
Vaccine Development Projects
Institute of Experimental Medicine (IEM)

Goal:
Develop prototype pandemic live, attenuated influenza reassortant vaccine, and demonstrate that the A/Leningrad/134/17/57 (H2N2) cold-adapted master donor virus bearing avian or human influenza virus hemagglutinin (HA) and neuraminidase (NA) genes from viruses with pandemic potential will be safe and immunogenic in humans.

Working in close collaboration with WHO.
IEM: Pre-pandemic Vaccines on Leningrad/134/17/57 (H2N2) Backbone

- **H1N1 strain:**
  - Developed in 2009 and transferred to developing-country manufacturers as part of WHO technology-transfer initiative.

- **H7N3 strain:**
  - All preclinical testing complete and approvals received.
  - Clinical trial to begin in April.

- **H5N1 strains:**
  - Three candidates completed preclinical testing.
  - A/17/turkey/Turkey/05/133 strain to be tested in humans in Q312.

- **H2N2 strains:**
  - Preclinical development in progress.
LAIV for Developing-country Manufacturers

**Pandemic only?**
- No correlate of protection for LAIVs.
- No clear licensure pathway for pandemic LAIVs.
- Efficacy trials of pandemic vaccines cannot be performed.
- No business case for exclusive pandemic vaccine manufacture.

**Pandemic and seasonal?**
- Efficacy of seasonal vaccine can be demonstrated.
- Business case?
  - Young children at high risk for severe influenza outcomes.
  - LAIVs perform particularly well in young children.
  - Preventing influenza could prevent a proportion of severe childhood ALRI.
Influenza is a Major Contributor to Childhood Pneumonia in Urban Bangladesh

- April 1, 2004 through December 31, 2007, overall pneumonia incidence of 511 pneumonia episodes/1,000 child-years (0.5 episodes/child/year).
- 102 influenza episodes/1,000 child-years (varied by month/season).
- 28% of children with influenza had pneumonia.
- 10% of all childhood pneumonia was associated with influenza.
A/Leningrad Backbone 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 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.

− 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 in FluMist® trial, rates of MSW were comparable in LAIV and TIV recipients (LAIV, 2.1%; TIV, 2.5%; P = 0.38).
• May 2009, SII signed an agreement with WHO to secure a sub-license for the development, manufacture, and sale of an LAIV using the backbone of A/Leningrad/134/17/57.

• August 2009: SII received A/17/California/2009/38 LAIV reassortant seed strain from IEM for development of monovalent LAIV.

• July 2010: Nasovac approved in India for use in healthy people 3 years of age and above.

• Safety of monovalent vaccine supported by:
  – Phase 1 (adults) and Phase 2 (pediatric, adults, older adults).
  – Post-marketing surveillance.

Seasonal LAIV: Strategy

PVS is supporting clinical trials of the trivalent LAIV produced by SII in children aged 24 through 59 months in Bangladesh.

- Assess safety outcomes, including wheezing, in young children.
- Demonstrate efficacy against laboratory-confirmed influenza outcomes in a population with high pneumonia burden.
- Demonstrate burden of illness/risk-benefit ratio in a low-resource population.
- Phase 2 to begin in Q2, 2012, with Phase 3 in 2013.
Assessment of the Safety and Immunogenicity of a Single Dose of Intranasal Seasonal Trivalent Live-Attenuated Influenza Vaccine among Children 24 through 59 Months of Age in Bangladesh

- **Trial Design:** Phase 2, double-blind, placebo-controlled, clinical vaccine trial
- **PI:** Abdullah Brooks, ICDDR,B and Johns Hopkins
- **Vaccine Manufacturer:** Serum Institute of India, Ltd
- **Sponsor:** PATH
- **Co-investigators:** ICDDR,B, Johns Hopkins, CDC
What This Study Will Add

• Additional safety and immunogenicity data in the youngest age group.
• First prospectively collected data on wheezing with this LAIV formulation.
• First data on children between 2 and 3 years of age with this LAIV formulation (depending on timing of SIIL Phase 2).
• Important background data to inform next steps:
  • Phase 3 study design.
  • Potential age-de-escalation
Part II: Delivery Devices
Part II: Delivery devices

- In 2010, IVP commissioned Working in Tandem, Ltd. (Julian Hickling, MBA, PhD, and Rebecca Jones, PhD) and the Vaccine Delivery Technologies Group, PATH to perform a landscape analysis of intranasal delivery devices for use with live attenuated vaccines.

- PATH Vaccine Delivery Technologies Team: Emily Griswold, Erica Jacoby, Courtney Jarrahian, Neeti Nundy, Gene Saxon, Darin Zehrung

- PATH IVP Team: Rick Bright, Jorge Flores, Kathy Neuzil, George Robertson, Vadim Tsvetnitsky

- Landscape analysis shared with WHO and limited partners, but not meant for public distribution due to confidential nature of effort
Factors Influencing Delivery Device Design and Selection

- Product formulation (lyophilized versus liquid).
- Primary indication (seasonal versus pandemic).
- Mode of use (single versus multiple).
- Form of administration (drops versus sprays).
Parameters to be considered for IN delivery devices

- Performance (e.g. dropper vs spray)
- Safety (are multi-dose devices acceptable?)
- Cost
- Compatibility with a lyophilized formulation
- Ease of Use
- Number of steps required to administer each dose
- Manufacturing status and capacity
- Regulatory status of the device
- Vaccine wastage
- Device disposal
Example 1: BD AccuSpray™

- FluMist™ is supplied in a prefilled BD AccuSpray™ device, a syringe-based device with a spray-generating nozzle.

- Each sprayer contains 0.2 ml. One half of the total dose is delivered to each nostril. A flange is fitted to the plunger of the device to stop administration after delivery of half of the contents. The flange is snapped off and remaining vaccine delivered to second nostril.

- Challenges: Cost, scalability, not compatible with lyophilized formulation,
Example 2: Lindal Device (Ultravac)

- Uses a single-use spray nozzle with Luer lock to fit on end of a syringe.
- Half of the total dose is delivered to each nostril. The dose for each nostril is drawn separately from the vial (either liquid or lyophilized formulation).
- Challenges: Single manufacturer, broad-based tip, number of administration steps.
Example 3: Wolfe-Tory Device (SII)

- Atomization tip with Luer lock to fit on end of syringe. Vaccine’s dose volume is 0.5ml, which is administered 0.25 ml in each nostril. A dose divider is fitted to the plunger of the device to stop administration after delivery of half of the contents.

- Challenges: Number of administration steps, cost (related to scale).
Drops vs sprays: The MedImmune experience

- Conflicting data from earlier studies that used different formulations and vaccine volumes
- Recent comparison in 1800 adults aged 18 through 49 years, randomized 4:1:1 to receive:
  - 1 intranasal dose of Q/LAI V delivered using a blow-fill-seal device (Q/LAI V-BFS; n=1202) or
  - 1 of 2 trivalent live attenuated influenza vaccines (T/LAI V) containing 1 of the corresponding B strains (total T/LAI V, n=598).
- Primary endpoints were the postvaccination strain-specific serum hemagglutination inhibition antibody geometric mean titers for each strain.
- Secondary immunogenicity endpoints, safety, and acceptability of the BFS device were also assessed.
Q/LAIV (BFS) vs. T/LAIV (spray)

- Vaccines delivered intranasally using:
  - BFS delivery system (Q/LAIV-BFS; 0.2 mL, one nostril) or
  - Accuspray device (T/LAIV; 0.1 mL per nostril, 0.2 mL total).
- Blood samples for HAI analysis collected on day 0 prevaccination and once 28–35 days postvaccination
- The HAI GMT ratio was selected as the primary endpoint for the study, based on consultation with US FDA
- GMT previously used to:
  - Bridge frozen/refrigerator formulations of T/LAIV
  - Determine manufacturing/lot consistency
  - Evaluate concomitant administration of T/LAIV with other live virus vaccines

**Q/LAIV (BFS) vs. T/LAIV (spray)**

<table>
<thead>
<tr>
<th>Strain</th>
<th>T/LAIV</th>
<th>Q/LAIV-BFS</th>
<th>GMT Ratio</th>
<th>Met non-infer. criteria?*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>GMT</td>
<td>N</td>
<td>GMT</td>
</tr>
<tr>
<td>A/H1N1</td>
<td>586</td>
<td>7.7</td>
<td>1176</td>
<td>8.1</td>
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<tr>
<td>A/H3N2</td>
<td>586</td>
<td>7.7</td>
<td>1176</td>
<td>8.3</td>
</tr>
<tr>
<td>B/Yamagata</td>
<td>294</td>
<td>54.1</td>
<td>1176</td>
<td>60.3</td>
</tr>
<tr>
<td>B/Victoria</td>
<td>292</td>
<td>26.7</td>
<td>1176</td>
<td>27.4</td>
</tr>
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</table>

*The immune response of Q/LAIV-BFS was declared noninferior to that of T/LAIV if the upper bound for each of the four 95% CIs for postvaccination strain-specific GMT ratios (T/LAIV divided by Q/LAIV) was ≤1.5.*

Q/LAIV (BFS) vs. T/LAIV (spray)

- Immunogenicity profile of Q/LAIV and T/LAIV are comparable
  - Studies met primary non-inferiority endpoints
  - Secondary endpoints consistent with primary endpoint
- Solicited symptoms and adverse events were comparable in Q/LAIV-BFS and T/LAIV groups
- Overall satisfaction with delivery devices comparable
  - 86% among Q/LAIV-BFS recipients
  - 90% among T/LAIV recipients

Potential next steps: Evaluation of simple dropper delivery methods (e.g. Tuberculin syringe) that could be affordable and scalable for LAIV administration.
Part III: Developing Stable Influenza Vaccine Formulations
Project Background

- HHS/BARDA “manages Project BioShield, which includes … countermeasures for pandemic influenza and other emerging infectious diseases …”

- Influenza Pandemic Countermeasures (2005):
  - Stockpile pre-pandemic vaccines (20 million doses).
  - Develop US manufacturing capacity to produce 300 million doses within 6 months.

- **Problem**: A vaccine stockpiling strategy is limited by the relatively short shelf-life of influenza vaccines.
Project Goals

• Significantly improve stability of subunit and LAIV influenza vaccines.

• Formulation process must be relatively easy to implement into existing production process.

• Work with vaccine manufacturer for pilot scale production, toxicology, and Phase 1 testing.

• Critical factors:
  • Safety—Use GRAS excipients previously approved for indicated administration route.
  • Cost—Low-cost excipients; improved stability offsets increased manufacturing cost.
## LAIV Vaccine Stability

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<tr>
<th>Current LAIV Vaccines</th>
<th>Stability</th>
<th>Target Stability</th>
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| **Liquid**            | • 6 months at 2-8°C  
                       | • Less than 1 week at 37°C  | **Preferred:**  
                       |                       | 5-10 years at 2-8°C  
                       |                       | **Or**  
                       |                       | 3-5 years at controlled 25°C + 1 month at 37°C |
| **Freeze-dried**      | • 1 year at 2-8°C  
                       | • 1 week at 37°C  | **Acceptable:**  
                       |                       | 3-5 years at 2-8°C + 3 months at controlled 25°C |
Live-Attenuated Influenza Virus Vaccine

• Manufactured by Serum Institute of India (SIIL):
  • A/California(H1N1)
  • Bulk frozen liquid

• LAIV Drying Processes:
  • Freeze-Drying
  • Spray-Drying
  • Foam-Drying
Three Drying Processes

- Product stability unique to the manufacturing process.
- Best process for a product is empirically determined.

- **Freeze-drying:**
  - Pro: Industry-standard method to prepare dried, sterile, product.
  - Pro: Commonly used for parenteral products, including vaccines.
  - Con: Throughput—Batch process.

- **Spray-drying:**
  - Pro: Throughput—Continuous process; common in food industry (few lbs. to 100s lbs. per hour).
  - Pro: Control of particle size—ideal for inhaled/pulmonary delivery; aseptic.
  - Con: Limited availability; capital investment.

- **Foam-drying:**
  - Pro: Excellent stability, rapid cycle, uses existing freeze-dryer infrastructure.
  - Con: No precedent for parenteral; batch process.
Summary

Foam drying >> Spray-drying > Freeze-drying

- **Foam Drying**
  - Stability improved up to 10-fold compared to freeze-drying and spray-drying.
  - Up to 6 months stability at 37°C can be achieved (process not optimized).
  - No loss observed at 2-8°C to date (3 months so far).

- **Spray-drying**
  - Stability at 37°C ~ 2-3 weeks; greatly improved at 2-8°C (0.5 - 1 yrs.).
  - Consistently better than freeze-drying, but not as good as foam-drying.
  - Process loss can be reduced to 0.3 log or less.

- **Freeze-drying**
  - Stability at 37°C less than 2 weeks.
  - Least stable of the three processes.
Acknowledgments

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• WHO

• Serum Institute of India, Ltd.

• Aridis Pharmaceuticals