Overview

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Influenza Vaccine Project (IVP) at PATH

**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.

**IVP Objectives: Influenza**
- Support the development of live-attenuated influenza vaccines (LAIVs) against influenza subtypes that may emerge as pandemic strains.
  - *Shift in emphasis to seasonal vaccines during the project (2012)*
- 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.

**Funding from Bill & Melinda Gates Foundation.**
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. Approved in India as pandemic vaccine in 2010, and as component of trivalent seasonal vaccine in February 2014.

- **H7N3 strain:**
  - Clinical trial completed. Generally safe and immunogenic (45% seroconversion rate by HAI, 41% by MNT, 41% by nasal IgA, or 86% by any assay after two doses of vaccine).

- **H5N2 strain:**
  - Clinical study completed. Generally safe and immunogenic (38% seroconversion rate by HAI, 48% by MNT, 34% by saliva IgA, 83% by any assay after two doses of vaccine). Currently preparing to evaluate effect of inactivated H5N1 vaccine booster.

- **H2N2 strains:**
  - Study initiated October 2013; results expected May 2014.
<table>
<thead>
<tr>
<th>Design (product)</th>
<th>Location</th>
<th>Number of subjects, age of subjects, randomization ratio</th>
<th>Outcomes measured</th>
<th>Sponsor/ Funder</th>
<th>Completion of study visits</th>
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<tbody>
<tr>
<td>Randomized, double-blind, active-controlled</td>
<td>India</td>
<td>n=110 each; children &gt;2 years of age, adults &gt;18 to &lt;50, adults ≥50, 1:1 (lower dose: higher dose)</td>
<td>Safety, Immunogenicity</td>
<td>SIIL</td>
<td>Completed June 25, 2012</td>
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<tr>
<td>Randomized, double-blind, placebo-controlled</td>
<td>Bangladesh</td>
<td>N=300, children 2-5 years of age, 1:1 (standard dose: placebo)</td>
<td>Safety, Immunogenicity, Shedding</td>
<td>PATH/BMGF</td>
<td>Completed February 2, 2013</td>
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<tr>
<td>Randomized, double-blind, placebo-controlled</td>
<td>Bangladesh</td>
<td>N=1761, children 2-5 years of age, 2:1 (standard dose: placebo)</td>
<td>Safety, Efficacy against laboratory-confirmed influenza</td>
<td>PATH/BMGF</td>
<td>Completed December 2013 Safety follow-up extended 1 year</td>
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<tr>
<td>Randomized, double-blind, placebo-controlled</td>
<td>Senegal</td>
<td>N=1761, children 2-6 years of age, 2:1 (standard dose: placebo)</td>
<td>Safety, Efficacy against laboratory-confirmed influenza, Shedding</td>
<td>PATH /US Centers for Disease Control and Prevention/ BMGF</td>
<td>Completed December 2013</td>
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Novel recombinant and universal flu vaccines

- Evaluated alternative production of HA-based influenza vaccine candidates in fungi, or as VLP in mammalian cells (discontinued).
- Evaluated co-expression of multiple flu proteins in tobacco plants for broader immune response (discontinued).
- Supported approaches to broaden immune response against HA:
  - Computer-optimized consensus sequence (COBRA) for cross-clade response to H5N1.
  - Chimeric HA (exotic HA “head” domain fused to either Group 1 or Group 2 HA stalk domain) for generation of broadly-neutralizing anti-stalk immune response.
PATH Technology Solutions Projects

- Landscape analysis of intranasal delivery devices for use with live attenuated vaccines.
- Assessment of vaccine stabilization technologies
  - **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.
Support for Influenza Vaccine Manufacturers

- **IVAC**
  - Inactivated whole virion H1N1 pandemic vaccine:
    - Phase 1 trial completed at Pasteur Institute HCMC. Generally safe and immunogenic (91% seroresponse rate after 2 doses).
  - Inactivated whole virion H5N1 pandemic vaccine
    - Immunogenic in mice and ferrets and protective from challenge in ferrets.
    - Phase 1 clinical trial planned for 3Q14 in collaboration with PIHCMC and WHO.
  - Seasonal split virion trivalent vaccine
    - Technical support and training – planned for 2014.

- **VABIOTECH**
  - Equipment and training to support manufacturing of inactivated influenza vaccine in cell culture.
  - Sublicense to MDCK cell line commercial license held by PATH (in progress).
  - Technical support to additional manufacturers for CMC and clinical trials.

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