Bangladesh Vaccine Trials

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International Meeting on Influenza Vaccine Effectiveness
Geneva, 03 – 04 December 2012
Overview

• Past studies on influenza
• Data on disease burden
• Current studies
• Next steps
• Where we hope to be in next 1 – 5 y
Bangladesh
Dhaka: Kamalapur Field Site
Research Infrastructure

- Demographic surveillance
- Active morbidity surveillance
- Clinical services
- Training
- Monitoring and evaluation
Active Surveillance: FRA examining child on home visit to screen for illness
Standardised physical exam and data collection
Specimen Collection
Laboratory analysis

- Respiratory specimens transported to icddr,b clinical microbiology & virology laboratory twice daily
- Respiratory specimens (NPW, blood, serum) tested by RT-PCR and/or culture for:
  - **Bacterial pathogens**
    - Pneumococcus, Hib, others
  - **Viruses**
    - Influenza
    - Respiratory syncytial virus
    - Human metapneumovirus
    - Human parainfluenza viruses
    - Adenoviruses
- **Quantitative PCR**
- **Microneutralisation tests**
Vaccination
Types of Studies in Kamalapur

• Disease burden
  – Active population-based surveillance
  – Clinical evaluation
  – Laboratory-based aetiological detection
Types of Studies in Kamalapur

• Interventions
  – GCP Clinical trials
    • Therapeutics or preventives (Oseltamivir, Zn)
    • Rapid diagnostics (POC Reader – MesoScale)
    • Vaccines (Phases I – III)
Past Influenza Vaccine Trials

- Vaccine trials (Wyeth)
  - CAIV-T P511 (Flumist – Medimmune)
    - Wyeth
    - Phase II
    - Co-administration with OPV
    - 2000 – 2001
  - CAIV-T P522 (Flumist – Medimmune)
    - Wyeth
    - Phase II
    - Co-administration with measles vaccine
    - 2001 – 2002

Past Trials: Matlab
Maternal immunisation study

- Dr K Zaman: PI (Zaman et al. NEJM 2008; 359)
- 340 mothers:
  - Trivalent inactivated vaccine
  - 23-valent pneumococcal vaccine
- Followed weekly until 24 wk post partum
- Vaccine effectiveness 63% against lab-confirmed influenza
- 29% reduction in febrile respiratory illness
340 Pregnant women randomized

- 85 mothers PPS vaccine
- 83 mothers PPS vaccine
- 85 mothers PPS vaccine
- 87 mothers Influenza vaccine

24 weeks mothers and infants followed up

Zaman et al, NEJM 2008
Maternal immunization with Flu vaccine showed 63% reduction in lab proven influenzae and 29% reduction in respiratory illness with fever (RIF) in infants and 36% reduction of RIF in mothers.

Zaman et al, 2008
Flu Vaccine study, 3-8 years- Completed

- To evaluate the safety, immunogenicity and efficacy of FLU Q- QIV vaccine in the prevention of influenza A and/or B disease
- Vaccine – H1N1, H3N2 and two B strain Victoria and Yamagata lineage
- Study site- Matlab, 1,000 children 12 to 35 months

Flu Vaccine study, 1-3 years- Ongoing

- To evaluate the safety, immunogenicity and efficacy of FLU D QIV vaccine in the prevention of influenza A and/or B disease
- Vaccine – H1N1, H3N2 and two B strain (Brisbane 60/2008, Brisbane 3/2007)
- Study site- Matlab, 819 children 12 to 35 months already enrolled
Seasonality pneumonia, influenza and invasive pneumococcal disease:
Kamalapur APR 2004 - DEC 2008

Incidence 0.5 episodes/child/year < 5y/o
- Leading cause mortality
  - 63% < 2y/o
  - 28% < 5y/o
- Major contributors:
  - S. pneumoniae
  - Influenza
  - Other viruses
What proportion is severe and very severe?

Pneumonia Diagnoses < 5y: Kamalapur (N = 12,632)

Clinical pneumonia incidence:
0.5 episodes/child-year
CXR Findings Pneumonia Kamalapur 2004 - 2011

CXR Findings Pneumonia <5y: Kamalapur (N=12,632)
2004 - 2011

- Normal: 48%
- Interstitial: 14%
- Aleolar: 26%
- Lobar Consolidation: 4%
- Other: 4%
- Missing: 31%

2/25/2013
Influenza key findings among children < 5y

- Influenza incidence 102 e/1000 cy
- Influenza pneumonia incidence: 28.6 e/1000 cy
- Influenza associated with 10% all pneumonia (attributable fraction by Cx)
- Among flu-positives: age pneumonia-positive vs pneumonia-negative 23.4m < 29.7m (p<0.001)
- Pneumonia associated viruses: A (H3N2) 3X > A (H1N1) or B

Final Diagnoses Influenza Children < 5y: N = 321

Based on tissue culture isolates
Pneumonia vs. Non-Pneumonia Influenza

KM failure (diagnosis) pneumonia vs non-pneumonia in childhood influenza
Kamalapur APR 2004 - DEC 2007
Influenza Pneumonia Probe Study
Influenza Pneumonia Probe Study

• Rationale
  – Pneumonia leading cause of child death
  – Influenza associated with pneumonia
  – Two-thirds of pneumonia in kids < 2y

• Vaccine Qualifications
  – Needs to be available to young children <2y
  – Should be trivalent

• Concept
  – Does not need to be optimally efficacious against influenza
  – If it blunts infection severity, it may prevent pneumonia
  – It might prevent both flu-related and non-flu-related pneumonia
Influenza Pneumonia Probe Study

- Design: double-blind, randomised, vaccine-controlled (IPV)
- Children 6mo – 24mo at first dose
- Partners: US CDC (Influenza Division)
- Sponsor: Bill & Melinda Gates Foundation
Influenza Pneumonia Probe Study

• **Primary Outcome:**
  - Clinical pneumonia incidence (3600 child-years)
    • Total
    • Influenza-associated

• **Secondary outcomes:**
  - Radiographic pneumonia
  - Effect on influenza infection
  - Effect on other pathogen-specific pneumonia and invasive disease (e.g. IPD)
  - Rates of complication/severe illness
  - Household transmission
  - Immune responsiveness
Influenza Pneumonia Probe Study

- **Vaccine:**
  - Trivalent inactivated vaccine (Sanofi-Pasteur donation)
- **Three seasons – now extended to fourth season**
- **Total target 3600 child-years**
  - 1200/year
- **Began vaccination 30 AUG 2010**
- **Fourth season vaccination JAN – FEB 2013**
- **Ongoing through December 2013**
Phase II Live Attenuated Influenza Vaccine Trial
Phase II LAIV Trial

- Live attenuated vaccine using Leningrad backbone
- Serum Institute of India, Ltd (SIIL)
- Sponsor: PATH
- Non-licensed vaccine
- Phases
  - Phase II just completed
  - Phase III to begin 2013
LAIV Phase II Study

• Primary Objectives: Safety
  – To determine the incidence of solicited and unsolicited local and systemic reactions among children receiving Trivalent LAIV and placebo
  – To determine the incidence of safety outcomes of special concern, including serious adverse events (SAEs), all-cause hospitalizations, and protocol-defined wheezing illness (PDWI) among children receiving Trivalent LAIV and placebo
LAIV Phase II Study

• Secondary Objectives
  1. To determine vaccine immunogenicity
  2. To determine post-vaccination nasal shedding/vaccine-take
  3. To describe the clinical characteristics of influenza illness
  4. To describe the viral etiologies of acute respiratory and febrile illness
LAIV Phase II Study

• **Design:** Single center, phase II, double-blind, parallel group, placebo-controlled, block randomized, clinical vaccine trial

• **Participants:** 300 healthy children aged 24 months through 59 months at the time of enrolment from Kamalapur area
  – Randomized in a 1:1 ratio
  – Group 1: 150 children received LAIV
  – Group 2: 150 children received placebo
## Study Milestones

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<thead>
<tr>
<th>Event</th>
<th>Date</th>
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<tbody>
<tr>
<td><strong>ICDDR,B Ethical Review Committee (ERC) Approval</strong></td>
<td>27 May 2012</td>
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<tr>
<td><strong>Western Institutional Review Board (WIRB) Approval</strong></td>
<td>13 Jan 2012</td>
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<td><strong>Bangladesh Drug Authority Approval</strong></td>
<td>12 Jun 2012</td>
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<td><strong>Site Initiation</strong></td>
<td>19-20 Jun 2012</td>
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<td><strong>First Subject In</strong></td>
<td>21 Jun 2012</td>
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<td><strong>Last Subject In</strong></td>
<td>14 Jul 2012</td>
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<tr>
<td><strong>Anticipated Last Subject Out</strong></td>
<td>14 Jan 2013</td>
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Outcomes

- No vaccine-related SAEs
- No adverse safety signal
- Vaccine safe and tolerated in children 24 – 59 months
- Cleared to proceed to Phase III Efficacy Study
Next Steps

• LAIV Phase III Efficacy Trial
  – Double-blind, placebo-controlled, randomised, single-country, multi-site
    • Kamalapur (Urban)
    • Matlab (Rural)
  – Sponsor: PATH
  – Collaborating: US CDC Influenza Division
• Completion of TIV Influenza Pneumonia trial
• Completion other respiratory pathogen trials
• PCV impact study
Where will we be over next 1 – 5 years?

• 1) Influenza-associated pneumonia via probe study in kids 6 – 24 months
  – Both clinical and radiographic
  – Effects on non-flu and other pathogen pneumonia
  – Proof of principal use of TIV as a childhood pneumonia vaccine
• 2) Potential effect of combined maternal and infant/child flu vaccination on childhood pneumonia
• 3) Efficacy of Russian LAIV against lab-confirmed influenza in kids 2 – 5 y
  – Effect on childhood pneumonia
• 4) Comparison data on fraction of prevented pneumonia (total and pathogen-specific) by vaccine
Thank You