Experiences with Live Attenuated Influenza Vaccine Trials in Thailand and Future Plan

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For MOPH, CDC, MU, Geneva meeting Dec 3, 2012
Background

- Thailand one of 11 developing countries chosen to join WHO's influenza vaccine development scheme
  - Received ~$4 million in funding
  - State-run drug maker Government Pharmaceutical Organization (GPO)
- GPO produced pandemic LAIV
  - Vaccine made in pilot plant in Saraburi Province for inactivated vaccine
  - Licensed for pandemic use by Thai FDA in July 2011
- Currently developing trivalent LAIV
Clinical Trial Development Plan

- LAIV H1N1 vaccine
- Avian H5N2 vaccine
- Seasonal trivalent LAIV
- Seasonal inactivated influenza vaccine

Project Manager/Director: Suwit W
Protocol PI: Punnee P
Phase I/II Safety and Immunogenicity of Pandemic Live Attenuated Influenza Vaccine (PLAIV) Candidate Strain A/17/CA/2009/38 (H1N1) in Healthy Thais

Objectives

- To evaluate safety and reactogenicity of PLAIV manufactured by GPO, Thailand
- To evaluate humoral immune response of the above vaccine after intranasal application by using HAI test, micro neutralization assays
- To determine the vaccine induced local IgA response by ELISA
**Study Design**

- It is a double blind randomized study using the 6.6-7.5 log10 EID50 dose.
- 324 participants (243 vaccines and 81 placebos) will be enrolled.

**Vaccine: Placebo = 3:1 (108 each group)**

<table>
<thead>
<tr>
<th>Group</th>
<th>&gt;12 – 18 years</th>
<th>&gt;18 – 49 years</th>
<th>&gt;49 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>81</td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td>Placebo</td>
<td>27</td>
<td>27</td>
<td>27</td>
</tr>
</tbody>
</table>
Vaccine:

Pandemic Live Attenuated Influenza Vaccine (PLAIV) Candidate Strain A/17/CA/2009/38 (H1N1) (0.5 ml intra-nasaly) by nasal spray
Activities

- Immunization D1, D21
- Safety follow up for 7 days after each immunization
- Nasal wash D1, 21, 42, 60 (ONLY 40 IN ADULT GROUP)
- Blood drawn D1, 21, 42, 60
Local reactions post-immunizations

Events declined with subsequent immunization
Systemic reactions post-immunizations (Cont.)

- Headache
- Chills
- Malaise
- Myalgia
- Arthralgia
- Fatigue
- Post Nasal Drippings
- Poor Appetite
- Diarrhea
- Rash
- Urticaria
- Shortness of Breath
- Tiredness on exertion

% cases with systemic reactions

- Vaccine 1st Immunization
- Vaccine 2nd Immunization
- Placebo 1st Immunization
- Placebo 2nd Immunization
Intention-to-treat Population four fold increased

<table>
<thead>
<tr>
<th>Age group</th>
<th>Day 21</th>
<th>Day 42</th>
<th>Day 60</th>
<th>Day 21</th>
<th>Day 42</th>
<th>Day 60</th>
<th>Day 21</th>
<th>Day 42</th>
<th>Day 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>All age group</td>
<td>22.13</td>
<td>30.33</td>
<td>16</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>2.33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Age group: &gt;12-18</td>
<td>7.38</td>
<td>3.61</td>
<td>6.02</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>2.33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Age group: &gt;18-49</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age group: &gt;49</td>
<td>0</td>
<td>4.82</td>
<td>3.57</td>
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</tbody>
</table>

Vaccine
Placebo
Conclusion For H1N1 LAIV

- Vaccine appeared to be safe
- The most common reported systemic reaction was headache which of mild in intensity
  The local reactogenicity declined after second immunization
- 30% developed >4 fold rise of immune responses measured by HAI
  However, if account for all 3 assays in adults: 39 % had more than 4 folds rise
- The vaccine was licensed for pandemic use in 2011
Phase I safety and immunogenicity of live attenuated influenza H5 candidate vaccine strain A/17/turkey/Turkey/05/133 (H5N2) in healthy Thai volunteers

Punnee Pitisuttithum,
Supat Chamnanchanunt, Pilaipan Puthavathana, Nathamon Ngaosuwankul, Suda Louisirirotchanakul, Veerawan -, Vipa-, Sit Thirapakpoomanunt, and Suwit Wibulpolprasert
Primary Objective

• To evaluate safety and reactogenicity of live attenuated influenza H5 vaccine candidate strain A/17/turkey/Turkey/05/133 (H5N2) manufactured by GPO, in Thailand to previously healthy Thais

Secondary Objective

• To evaluate humeral immune response by using hemagglutination inhibition (HAI) test and micro neutralization assay, vaccine induced local IgA response by ELISA and assess shedding and stability of the viral strain by using PCR method
Study Design

- It is a double blind randomized study using the dose $7.5-8.5 \log EID_{50}$ per 0.5 ml
- 24 participants age 18 -45 years (16 vaccines and 8 placebos) were enrolled
- Vaccine: *ca-ts* attenuated candidate strain A/17/turkey/Turkey/05/133 (H5N2) was prepared at Institute of Experimental Medicine (IEM) in St. Petersberg, Russia and was manufactured by GPO in Thailand.
Vaccine:

vaccine is A/17/turkey/Turkey/05/133 (H5N2). The vaccine strain was produced by the method of classical genetic reassortment in chicken embryos (0.25 ml administered into each nostril) by nasal spray

• Immunization D1,D21
• Safety follow up for 9 days after each immunization,D42,60

• Nasal wash D1,D21,42,60
• Blood drawn D1, 7, 21,42,60
64 were screened for eligibility

24 were enrolled

1st D1, 8 placebo
2nd D21, 8 placebo

D1, 16 vaccinee
D21, 15 vaccine
Safety & Laboratory Evaluations

- Using diary card by nurse staff and each follow up visits and blood chemistry and CBC for safety evaluation
- Nasal swabs for monitoring virus excretion on D2, D3, D5, D7, D9 after each immunization
- Nasal washing for local immune responses-sIgA.
- Specific antibodies vaccine strain (HAI test, ELISA, micro-neutralization assay)

**Immunological end point**

Vaccine is able to induce 2-4 folds rise of either HAI mNT, sIgA in 40% of vaccines.
Adverse events by systemic organ class

- Blood and lymphatic system disorders
- Eye disorders
- Gastrointestinal disorders
- Injury, poisoning and procedural complications
- Musculoskeletal and connective tissue disorders
- Investigations
- Nervous system disorders
- Reproductive system and breast disorders
- Respiratory, thoracic and mediastinal disorders
- Skin and subcutaneous tissue disorders

Vaccine (N=35)
Placebo (N=16)
Local reactions post-immunizations

<table>
<thead>
<tr>
<th>Local Reaction</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Stiffness of Neck</td>
<td>6</td>
</tr>
<tr>
<td>Runny/Nose</td>
<td>4</td>
</tr>
<tr>
<td>Scratchy Throat</td>
<td>3</td>
</tr>
<tr>
<td>Shortness of Breath (SOB)</td>
<td>3</td>
</tr>
<tr>
<td>Sore Throat</td>
<td>2</td>
</tr>
<tr>
<td>Bad Taste in Mouth</td>
<td>22</td>
</tr>
<tr>
<td>Nasal Blockage</td>
<td>11</td>
</tr>
<tr>
<td>Burning Sensation of Nose</td>
<td>2</td>
</tr>
<tr>
<td>Redness of Nose</td>
<td>3</td>
</tr>
</tbody>
</table>

- 1st immunization Vaccine (N=16)
- 1st immunization Placebo (N=8)
- 2nd immunization Vaccine (N=15)
- 2nd immunization Placebo (N=8)
Systemic reactions post-immunizations

Diarrhea occurred as food born outbreak from Salmonella C fish ball
Seasonal LAIV Clinical R&D Collaborators

- Thailand Ministry of Public Health
- Mahidol University
- Nakhon Phanom Province
- GPO
- Influenza Program, Thai MOPH – U.S. CDC Collaboration
- Influenza Division, U.S. CDC
Timeline

Late 2013 - Early 2014

Mid 2014
Phase I Trial

Early 2015
Phase II Trial
Phase III Protocol Submission

Mid 2015
Phase III Trial
Active Surveillance

End 2015 - Early 2016
Community Engagement Program
Selection of Vaccine Trial Site

- Joint team assessed four provinces (Sep/Oct 2012)
  - Sa Kaeo
  - Nakhon Phanom
  - Rayong
  - Khampengphet
- Considerations included
  - Interest and engagement of local site
  - Experience in doing research, clinical trials
  - No conflicting commitments
  - Ease of transport of specimens to Bangkok
Nakhon Phanom

Thailand

Loas

NE
Community engagement

• To prepare and evaluate the readiness and willingness

• Community engagement activities/community health forums are essential to establishing networks to access target populations for vaccine trials and also means to detect rumors at the earliest stage and attack the rumor in real time
Objectives

• To explore the knowledge of influenza, influenza vaccination, and vaccination in general among Nakhon Phanom community members (community leaders, parents, teachers, and healthcare workers)
• To develop educational material and implement a community engagement program that promotes child influenza vaccination and addresses
• To identifies misconceptions, concerns, and barriers related to child influenza vaccination.
Community Engagement Activities

2013

<table>
<thead>
<tr>
<th>Jan</th>
<th>Feb</th>
<th>March</th>
<th>April</th>
<th>May</th>
<th>June</th>
<th>July</th>
<th>Aug</th>
<th>Sep</th>
<th>Oct</th>
<th>Nov</th>
<th>Dec</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-Depth Interviews</td>
<td>Create Health Promotion message</td>
<td>Distribute Health Promotion Materials</td>
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<tr>
<td>Focus Groups</td>
<td>Analysis</td>
<td>Implement Childhood LAIV message</td>
<td>Collect Contact Information for LAIV Trial</td>
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A Phase III randomized, double blind, placebo-controlled assessing efficacy of GPO’s seasonal Live Attenuated Influenza Vaccine in a Thai Population
Primary Objectives

- To evaluate the efficacy of the GPO trivalent seasonal LAIV against symptomatic, laboratory-confirmed influenza among children aged 2-18 years

Secondary Objectives

1. To assess the safety profile of the seasonal LAIV that is produced by GPO
2. To assess the immune responses stimulated by the vaccine at Day21, Day 42 and Day60
## Sample Size

<table>
<thead>
<tr>
<th>Symptomatic Influenza Attack Rate</th>
<th>Lower Limit of Detectable VE</th>
<th>Sample size w/out Accounting for Loss to follow-Up</th>
<th>Sample Size Accounting for Loss to Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>15%</td>
<td>50%</td>
<td>676</td>
<td>795</td>
</tr>
<tr>
<td>15%</td>
<td>60%</td>
<td>428</td>
<td>504</td>
</tr>
<tr>
<td>15%</td>
<td>50%</td>
<td>676</td>
<td>966</td>
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<tr>
<td>15%</td>
<td>60%</td>
<td>428</td>
<td>611</td>
</tr>
<tr>
<td>10%</td>
<td>50%</td>
<td>988</td>
<td>1162</td>
</tr>
<tr>
<td>10%</td>
<td>60%</td>
<td>630</td>
<td>741</td>
</tr>
<tr>
<td>10%</td>
<td>50%</td>
<td>988</td>
<td>1411</td>
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<tr>
<td>10%</td>
<td>60%</td>
<td>630</td>
<td>900</td>
</tr>
<tr>
<td>5%</td>
<td>50%</td>
<td>1926</td>
<td>2266</td>
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<tr>
<td>5%</td>
<td>60%</td>
<td>1240</td>
<td>1459</td>
</tr>
<tr>
<td>5%</td>
<td>50%</td>
<td>1926</td>
<td>2751</td>
</tr>
<tr>
<td>5%</td>
<td>60%</td>
<td>1240</td>
<td>1771</td>
</tr>
</tbody>
</table>

Loss to FU rate is 10% as sample size = 2546
Potential Vaccine

• Government Pharmaceutical Organization (GPO) Russian-backbone trivalent seasonal live-attenuated influenza vaccine (LAIV) against

• Giving by nasal sprayer – one dose for age >9-18 years and two doses for children age 2-9 years
Safety and Immune Response Assessment

- Diary card for 7 days will be used for parent to record for assessment of safety
- All AEs and SAEs will be collected
- ~500 subjects will be evaluated for immunogenicity at days 0, 21, 42 and 60
- Nasal wash specimens will be collected at days 0 and 21 post-vaccination
- For children 2-9 years two doses will be given so the blood drawn will be at D42 as well.
Surveillance for Influenza and Case Definitions

- Weekly contact will be made with the families to remind parents to notify study personnel if the subject has ILI symptoms, fever, runny nose or nasal congestion, sore throat, cough, headache, muscle aches, chills, vomiting, suspected or confirmed otitis media, decreased activity, irritability, wheezing, shortness of breath, and pulmonary congestion.
Surveillance for Influenza

• Participants who attend school, school absenteeism records will be checked on all week days during the school term
• Home visits will be conducted if patients cannot be contacted after more than 2 attempts
• Those with ILI, Nasal and throat swabs for PCR testing and culture will be done within
• within four days after the onset of any ILI symptoms
Case Definitions

• A case of influenza will be defined as any illness detected by active surveillance that is associated with a positive PCR/culture for wild-type influenza virus

• Positive viral cultures obtained within 28 days after the first or second dose of vaccine will be phenotyped

• All data will be collected and analyzed after one and two influenza season
Summary

• Thailand has made progress in producing LAIV
• Aim to do community engagement program next year
• Results generated will facilitate expansion of the national vaccine campaign
• Anticipate to do phase III trial early 2015?
## Acknowledgement

**Clinical:** Vaccine Trial Centre and Department of Clinical Tropical Medicine, Mahidol University

**Laboratory:** Department of Microbiology, Faculty of Medicine, Siriraj Hospital, Mahidol University

**Statistical:** Center of excellence for biomedical and public health informatics (BIOPHICS) Faculty of Tropical Medicine, Mahidol University

**Consultants:** Suwit Wibulpolprasert, MD, Ministry of Public Health, Pratap Singhasivanon, MBSS, DTM&H, PhD, Faculty of Tropical Medicine, Mahidol University

**Manufacturer:** The Government Pharmaceutical Organization (GPO)

**Sponsor:** World Health Organization (WHO)

**US-CDC**

Thanks to all participants