INFLUENZA VACCINES DEVELOPMENT
IN COLLABORATION WITH
WHO, BARDA, AND PATH

Geneva, Nov 18th 2016
Introduction

- Institute of Vaccines and Medical Biologicals (IVAC) was established in 1978. It is a state-owned unit which self-finance a part of its operations, under the control of the Ministry of Health.
- IVAC is one of four vaccine manufacturers in Vietnam. It consists of 2 establishments:
  - Nha Trang headquarter with an area of 13,946m²
  - Suội Đâu breeding farm with an area of 116 hectares, 20 kms from the Southern of Nha Trang
Functions, Responsibilities

Functions: Research, manufacture, business, consultancy and service, cooperation in vaccines and medical biologicals; personnel training

Responsibilities:
1. Research; applying scientific and technological advances.
2. Production of vaccines and medical biologicals for EPI
3. Post-graduate and graduate, specialized in epidemiology, medical microbiology, immunology and biotechnology.
4. International co-operation, technological transfer
• Total: 221 staffs
• In current 5 years, IVAC has sent staffs to developed countries for upgrading technical/professional skills and Quality Assurance knowledge (over 100 times).
• IVAC has 13 products, in which 4 kinds of vaccine are being used for EPI
• 2 products are developed under the national vaccine program
Influenza vaccines Development

- 2005: Research on egg-derived inactivated influenza vaccine
- 2007: WHO funded to build up an influenza vaccine facility
- 2010: Established reliable egg supply
- 2011: Funding and technical support from PATH
- 8/2011: Production of influenza A/H1N1/09 vaccine
- 2012: Conducted phase 1 CT for A/H1N1/09 vaccine, and production of A/H5N1 vaccine
- 2013: Developed A/H7N9 and seasonal vaccine production
- 2014: Conducted phase 1 CT for A/H5N1 and production of seasonal influenza vaccine.
- 2015: Conducted phase 1 CT for seasonal influenza vaccine
- 2016: Finished phase 2 CT for A/H5N1, Preparation for P3 of A/H5N1 and P2/3 for seasonal vaccine in 2017
IVAC started research work on avian influenza vaccines in the early 1990s in response to the threat of a highly pathogenic avian influenza pandemic.
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>2005</td>
<td>Started by itself a preliminary research on egg-derived inactivated influenza vaccine</td>
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<td>2008</td>
<td>Funding and technology transfer from the WHO under a project to enhance influenza vaccine production in developing countries</td>
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<td>Funding and technical support from PATH, sponsored by BARDA/HHS</td>
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<td>2014</td>
<td>2014-2015: WHO-technology transfer project</td>
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<td>2015</td>
<td>2014-2016: Technical support from PATH, sponsored by BARDA/HHS</td>
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The WHO Grant: 2008-2010
Building an influenza vaccine facility

Project goal:
500,000 doses of monovalent influenza vaccine produced under appropriate biosafety and cGMP standards, potential scaling up to >3 million doses per year (in case of pandemic)

Project specific objectives:
• To build and equip a small-scale manufacturing facility to produce egg-derived, inactivated, whole-virion, aluminum adjuvanted influenza vaccine for pandemic using
• Complemented by a waste treatment system and a chicken farm to secure supplies of qualified eggs
The WHO seed grants, supplemented by international partner support, enabled IVAC to build in four years an influenza vaccine manufacturing plant under GMP and relevant biosafety standards.
The WHO Grant: 2008-2010
Building an influenza vaccine facility

• Each area is installed with separate heating, ventilation and air-conditioning (HVAC) systems
• Digital direct controller system (DDC) to stabilize room temperature, pressure and humidity
• SL2-production areas are kept at positive pressures to negative pressures sink surrounded by airlocks
• Independent technical units have been set up to serve as a hot and cold rooms in a dedicated space contaminated area, a non-contaminated area, and egg-handling and entrance
• Separate zones for in-process testing and the preparation of media and cleaning of equipment; inoculation and harvesting; and purification
Influenza vaccine development and production (2011-2016)

With support from BARDA/HHS, IVAC and PATH established a collaboration in 2011 to improve IVAC’s influenza vaccine manufacturing capacity. At the same time, WHO continue funding for upgrading facilities and developing seasonal influenza vaccine.

- **Phase 1 (2011-2013):** Project to enhance WHO-GMP compliant production of influenza vaccines at IVAC
- **Phase 2 (2014-2016):** Chemistry, manufacturing, and control (CMC) and clinical trial technical support for influenza vaccine manufacturers project
Major achievements (2011-2013)

• **Goal:** to build regionally based, independent, and sustainable influenza vaccine production capacity in Vietnam
Major achievements (2011-2013)

Specific objectives:

- Operationalize influenza vaccine manufacturing facility
- Document influenza vaccine manufacturing facility as operating under WHO-GMP standards
- Establish reliable egg supply for influenza vaccine manufacturing
- Set up the influenza A/H1N1 phase 1 clinical trial protocol and conduct clinical evaluation of the influenza A/H5N1 vaccine in a phase 1 study
- Develop a monovalent influenza A/H7N9 vaccine in response to the influenza A/H7N9 outbreak
- Improve influenza A/H5N1 vaccine manufacturing process
- Produce and non-clinically test influenza A/H5N1 vaccine candidate
Major achievements (2011-2013)

- Improved reverse osmosis and water for injection systems

- Manufacturing equipment qualified to meet operational standards and staff trained to operate the equipment
Major achievements (2011-2013)

- Quality assurance activities completed to fully document and control the manufacturing and lot release process
- Quality control laboratory upgraded to meet international standards for influenza vaccine testing
- Staff qualified at all levels
A reliable egg supply was established for influenza vaccine manufacturing, making IVAC the sole qualified clean egg producer in Viet Nam.
Major achievements (2011-2013)

- Improve quality management system to meet WHO-GMP standards
- High-quality influenza vaccine candidates developed (A/H1N1, A/H5N1, A/H7N9 and seasonal)
  - Equipment, training, and systems qualified using a series of manufacturing runs of increasing size and complexity leading to full-scale lots in full GMP compliance
  - Significant improvement in production was observed
  - The influenza vaccine manufacturing facility received ISO 9001:2008 certification, and GMP certification by the MOH, and is strengthening compliance with WHO-GMP
Major achievements (2011-2013)

- Influenza A/H1N1 vaccine development
  - The process was finalized, established and demonstrated the consistency
  - Three last batches of H1N1 bulk: 21, 22, 23 was chosen for clinical trial with 6368, 5280, and 6192 doses
  - Finish phase 1 clinical trial for A/H1N1/09 influenza vaccine with cooperation and support of PATH and PIHCMC, approved by MOH in 2013
Major achievements (2011-2013)

- **Influenza A/H7N9 vaccine development**
  - Developing A/H7N9 vaccine for pandemic preparedness purposes
  - Working seed virus (WSV) banks are established and characterized
  - Production 05 lots A/H7N9 bulk within 5 months of receiving the seed virus, with no failures
Major achievements (2011-2013)

- Influenza A/H5N1 vaccine development
  - With technical and financial support from PATH, IVAC developed successfully influenza A/H5N1 vaccine base on core process established
  - Produced successfully 11 consecutive lots of influenza A/H5N1 bulk vaccine. These lots showed an improved consistency in the production upon testing.
  - Vaccine was filled and released in required formulations for non-clinical testing and clinical trial use.
Influenza vaccine development and production (2014-2016)

- Technology transfer project for seasonal influenza vaccine (IVAC/WHO)
- Chemistry, manufacturing, and control and clinical trial technical support project (Funding by WHO, technical support by PATH)

<table>
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<tr>
<th>WHO’s role</th>
<th>PATH’s role</th>
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<tr>
<td>Project operational budget</td>
<td>Technical support for designing, conducting, and monitoring H5N1 vaccine</td>
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<td>Funding for implement clinical trial</td>
<td>Consultant provision for improvement of QMS, optimizing manufacture process, and developing analytical methods for influenza A/H5N1 vaccine and seasonal influenza vaccine</td>
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<td>influenza A/H5N1 vaccine</td>
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<td>Additional equipment for developing seasonal</td>
<td>Technical support for conducting, and monitoring H5N1 vaccine phase 2 &amp; 3, and seasonal influenza vaccine phase 1 clinical trials</td>
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Major achievements (2014-2016)

Objectives:

- Conduct influenza A/H5N1 vaccine clinical studies (Phase 1 and 2/3)
- Establish seasonal influenza vaccine production process

Progress of project:

Influenza A/H5N1 vaccine

- Phase 1 clinical trial conducted with good results
- Preparation for phase 2/3 clinical trial in March 2016

Seasonal influenza vaccine

- Phase 1 clinical trial conducted with good preliminary results
- Phase 3 clinical trial is estimated finish in 2017
Major achievements (2014-2016)
Next steps through 2016

With the commitment to continue funding from WHO and continue support technique from PATH, sponsored by BARDA/HHS, IVAC will conduct:

1. Phase 2/3 clinical trial for influenza A/H5N1 vaccine
2. Phases 1 and 2/3 clinical trials for split seasonal vaccine
3. Register products
4. Continued QMS improvement
THANK YOU!