Investments in Innovation:

Seasonal Influenza Preparedness

Pandemic Influenza Preparedness

Bruce Gellin, MD, MPH
Director
National Vaccine Program Office
Department of Health and Human Services
Influenza Means War

“The appalling pandemic of 1918 in the last months of the exhausting conflict of World War I, with massive mobilization of armies and upheaval of civilian populations, has irrevocably linked those two catastrophes.”

“It demonstrated that virulent influenza may be more devastating to human life than war itself ... the onset of another war inevitably recalled the specter of 1918 and the possibility that ... [it] would again result in the epidemiologic conditions which would heighten the severity of influenza to a catastrophic level”

Dr. Thomas Francis Jr,
Chairman, US Influenza Commission (1941)
Influenza Vaccine’s WWII Origins

- Improving virus yields from embryonated eggs
- Improving titration accuracy
- Ultracentrifuge and electrophoresis purification
  - Concentrating and purifying the virus on a large scale
- Develop uniform standards for potency and purity
- Field studies to provide the first reliable proof of safety and efficacy.
  - Standardized record systems, observation procedures, and viral and serological tests
  - “It was possible to obtain participation of entire units so that vaccinated persons and controls could be properly designated rather than depending upon the less desirable and unpredictable use of volunteers”

Vaccine Supply and Innovation

Recent advances in all aspects of biotechnology and particularly gene manipulation offer powerful new approaches to many previously intractable problems. These technologies, combined with a better understanding of the immune process, have opened a new era in vaccine development.

Institute of Medicine 1985
HHS Pandemic Influenza Plan: Vaccine Goals

Vaccine Goal #1:
To establish and maintain a dynamic pre-pandemic influenza vaccine stockpile sufficient for 20 million persons (at 2 doses/person)

Vaccine Goal #2:
To provide pandemic vaccine to all U.S. citizens within 6 months of a pandemic declaration: 600 million doses pandemic vaccine
HISTORICAL PERSPECTIVE - 2005
Estimated Annual Domestic Production of Pandemic Influenza Vaccine: Capacity, and Need

A: Annual domestic capacity - 2005
B: National need

*Assumes 2 doses/person, 90 ug/dose
Influenza Vaccine: Surge Capacity

Vaccine Production After Pandemic Virus Emerges

Months After Pandemic Begins

- Month 1
- Month 2
- Month 3
- Month 4
- Month 5
- Month 6

Graph showing vaccine production over months.
Transforming Technology
Egg-based production → Cell-based production
Current and Projected US Pandemic Influenza Vaccine Capacity

<table>
<thead>
<tr>
<th>Year</th>
<th>Egg</th>
<th>Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H06</td>
<td>8.3</td>
<td>0</td>
</tr>
<tr>
<td>2H06</td>
<td>8.3</td>
<td>0</td>
</tr>
<tr>
<td>1H07</td>
<td>8.3</td>
<td>0</td>
</tr>
<tr>
<td>2H07</td>
<td>8.3</td>
<td>0</td>
</tr>
<tr>
<td>1H08</td>
<td>51.6</td>
<td>0</td>
</tr>
<tr>
<td>2H08</td>
<td>51.6</td>
<td>0</td>
</tr>
<tr>
<td>1H09</td>
<td>77.4</td>
<td>16</td>
</tr>
<tr>
<td>2H09</td>
<td>77.4</td>
<td>16</td>
</tr>
<tr>
<td>1H10</td>
<td>77.4</td>
<td>96</td>
</tr>
<tr>
<td>2H10</td>
<td>77.4</td>
<td>96</td>
</tr>
<tr>
<td>1H11</td>
<td>77.4</td>
<td>240</td>
</tr>
<tr>
<td>2H11</td>
<td>77.4</td>
<td>240</td>
</tr>
</tbody>
</table>
Transforming Technology:
Reverse Genetics

A flu virus contains eight gene segments. The goal is to combine the desired HA and NA genes from flu strain 1 with the six other genes from flu strain 2, which grows well in eggs and is harmless in humans.

1. After removing the dangerous part of the HA gene, scientists splice the HA and NA genes from flu strain 1 into circular pieces of DNA called plasmids.

2. Additional plasmids are created using the remaining six genes found in flu strain 2.

3. Scientists insert the HA and NA plasmids from flu strain 1 and the six plasmids carrying genes from flu strain 2 into animal cells growing in the laboratory.

4. The genes in the plasmids instruct the animal cells to make the desired new flu strain.

5. New flu strain

Biosecurity for the Birds

Link Studio for NIAID
GOAL: Decrease the timeline of vaccine production in response to a newly emerged pandemic influenza strain.

- The timeline for the availability of egg- and cell-based inactivated pandemic influenza vaccines in the U.S. is estimated at 20-23 weeks post-pandemic onset, which may be towards the end of a first pandemic wave.

- Recombinant-based influenza vaccines, which may not be dependent on pandemic influenza virus reference strain availability and the production and calibration of potency assay reagents needed for inactivated influenza vaccines, may be available 8 to 12 weeks post-pandemic onset.

HHS Request for Proposal: August 2007
Transforming Technology: Adjuvants
U.S. Pandemic Influenza Vaccine Capacity Forecast

U.S. PANDEMIC VACCINE GOAL TIMELINES
(300 M Vaccine Courses)

<table>
<thead>
<tr>
<th>Months</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag Alone (90 ug)</td>
<td>115.4</td>
<td>52.9</td>
<td>23.7</td>
<td>10.4</td>
<td>5.7</td>
</tr>
<tr>
<td>Adjuvants</td>
<td>12.8</td>
<td>5.9</td>
<td>2.6</td>
<td>1.2</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Evolution of the H5N1 Hemagglutinin Gene

Candidate Vaccine Reference Viruses

Clade 2.1
- ck/Shannxi/62/04
- dk/Guangxi/13/04
- ck/Yunnan/374/04
- Indonesia/7/05
- Indonesia/5/05
- Indonesia/CDC742/06
- Indonesia/CDC940/06
- Indonesia/CDC1047/06
- Indonesia/CDC837/06
- Indonesia/CDC686/06
- Indonesia/CDC1032/07
- Indonesia/CDC1046/07
- Barhdgs/Qinghai/1A/05
- ck/Liaoning/23/05
- Barhdgs/Qinghai/12/05
- ck/Krasnodar/01/06
- Azerbaijan/001161/06
- swan/Iran/754/06
- Turkey/15/06
- Iraq/207/NAMRU-3/06
- ck/Nigeria/641/06
- whswan/Mongolia/244/05
- tky/Turkey/1/05
- Egypt/14774/NAMRU-3/06
- dk/Egypt/22533/06
- egret/Egypt/1162/NAMRU-3/06
- Egypt/0636/NAMRU-3/07

Clade 2.2
- dk/Hunan/15/04
- scalybreastedMunia/HongKong/45/07
- Anhui/1/05
- dk/Laos/3295/06
- ck/Malaysia/935/06
- common magpie/Hong Kong/645/06
- Guanxi/105/05
- House Crow/Hong Kong/7/19/07
- JapaneseWhiteEye/Hong Kong/727/07
- WhiteBackedMunia/Hong Kong/026/07

Clade 2.3
- Thailand/676/05
- Vietnam/JPHN30321/05
- Vietnam/1203/04
- Vietnam/HN30408/05
- Thailand/16/04
- Hong Kong/213/03
- mdk/Jiangxi/1653/05
- ck/Hunan/41/04

Clade 1
- Vietnam/JPHN30321/05
- Vietnam/1203/04
- Vietnam/HN30408/05
- Thailand/16/04
- Hong Kong/213/03
- mdk/Jiangxi/1653/05
- ck/Hunan/41/04
- ck/Shannxi/62/04
- ck/Guangxi/13/04
- ck/Yunnan/374/04
- Indonesia/7/05
- Indonesia/5/05
- Indonesia/CDC742/06
- Indonesia/CDC940/06
- Indonesia/CDC1047/06
- Indonesia/CDC837/06
- Indonesia/CDC686/06
- Indonesia/CDC1046/07
- Barhdgs/Qinghai/1A/05
- ck/Liaoning/23/05
- Barhdgs/Qinghai/12/05
- ck/Krasnodar/01/06
- Azerbaijan/001161/06
- swan/Iran/754/06
- Turkey/15/06
- Iraq/207/NAMRU-3/06
- ck/Nigeria/641/06
- whswan/Mongolia/244/05
- tky/Turkey/1/05
- Egypt/14774/NAMRU-3/06
- dk/Egypt/22533/06
- egret/Egypt/1162/NAMRU-3/06
- Egypt/0636/NAMRU-3/07

New subgroup

New subgroup
### HHS Prepandemic Vaccine Stockpile

<table>
<thead>
<tr>
<th>H5N1 Vaccine Strain</th>
<th>Clade</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/VTN/1203/04</td>
<td>1</td>
<td>0.45</td>
<td>7.05</td>
<td>0.91</td>
<td></td>
<td>8.41</td>
</tr>
<tr>
<td>A/Indo/05/05</td>
<td>2.1</td>
<td></td>
<td>6.44</td>
<td>2.25</td>
<td></td>
<td>8.69</td>
</tr>
<tr>
<td>A/BHG/QL/1A/05*</td>
<td>2.2</td>
<td></td>
<td></td>
<td>6.42</td>
<td>6.42</td>
<td></td>
</tr>
<tr>
<td>A/Anhui/1/05</td>
<td>2.3</td>
<td></td>
<td></td>
<td>2.51</td>
<td>2.51</td>
<td></td>
</tr>
<tr>
<td>Totals (90 ug/dose)</td>
<td></td>
<td>0.45 M</td>
<td>7.05 M</td>
<td>7.35 M</td>
<td>11.18 M</td>
<td>26.03 M</td>
</tr>
<tr>
<td>Totals w/adjuvants 7.5 ug/dose</td>
<td></td>
<td>5.4 M</td>
<td>84.6 M</td>
<td>88.2 M</td>
<td>134.2 M</td>
<td>312 M</td>
</tr>
</tbody>
</table>

^ doses represented as 90 ug HA/dose antigen alone
HHS Pandemic Vaccine Mix and Match Study

• Strategic Goal: Expand the supply of influenza vaccines available during a pandemic by optimization of antigen content using adjuvants.

• Specific Aim: Determine whether stockpiled H5N1 antigens manufactured by one company can be used safely and effectively with adjuvants from other manufacturers during an influenza pandemic under Emergency Use Authorization.
Seasonal Influenza Preparedness

- Enhanced immunogenicity
- Broader Protection
- New delivery platforms
- Different vaccines for different populations
- Shortening vaccine production times
- Improving distribution and vaccine tracking

Pandemic Influenza Preparedness

Decreasing impact of seasonal and pandemic influenza