Influenza Vaccine
and
Adjuvant Stockpiles

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Influenza Division Stockpiling Mission Is Defined By Several Key Documents:

• The National strategy for Pandemic Influenza (November 2005) designated the HHS as the lead agency for public health and preparedness.

• Under the HHS Pandemic Influenza Plan (November 2005) the Department’s key goals for vaccine preparedness are:
  » Stockpile enough pre-pandemic influenza vaccines to cover 20 million people in the critical workforce;

  » Develop sufficient domestic manufacturing capacity to produce pandemic vaccine for the entire US population of 300 persons within six months of pandemic onset.
Pre-Pandemic H5N1 Vaccine Stockpile Acquisition Strategy

• Utilize manufacturers of US-licensed seasonal inactivated influenza vaccines

• Support commercial scale manufacturing of pre-pandemic vaccines using manufacturing process, facilities, systems and trained personnel for US-licensed seasonal inactivated influenza vaccines

• Support manufacturing during off-season for US-licensed seasonal inactivated influenza vaccines

• Maintain vaccine as bulk product at manufacturers or storage facilities for fill finish when clinical data and circumstances support final container formulations
Key Considerations When Selecting A Strain For The US Pre-Pandemic Stockpile

• What strains are currently circulating and causing disease?
  » Human H5N1 infections: frequency and location
  » HA genetic variation

• What candidate strains are available for vaccine production?

• What is known about the “manufacturability” of the candidate strain?

• What are the manufacturing availability/ capabilities?
Current Pre-Pandemic Vaccine Stockpile Contracts

- Between 2004 and 2008 nine contracts were awarded to three contractors (GSK-Novartis-Sanofi Pasteur) for the acquisition of pre-pandemic avian influenza H5N1 vaccine

- The USG acquired 152 million doses @ 15μg/ dose (25.3 M doses @ 90μg/ dose)

- Indefinite Delivery/ Indefinite Quantity (ID/IQ) type of contracts were awarded and the manufacturers were requested (if task order issued) to:
  > Manufacture bulk lots of vaccine
  > Store bulk vaccine and perform stability testing
  > Formulate-fill-finish product
  > Modified for the 2009 H1N1 response
Current Pre-Pandemic Vaccine Stockpile

<table>
<thead>
<tr>
<th>H5N1 Bulk Vaccine (Clade)</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>Totals M doses @ 90 µg/dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/VTN/1203/04 (1)</td>
<td>2.27</td>
<td>1.77</td>
<td>0.85</td>
<td></td>
<td></td>
<td>4.89</td>
</tr>
<tr>
<td>A/Indo/05/05 (2.1.3)</td>
<td></td>
<td>5.95</td>
<td>2.22</td>
<td>0.04</td>
<td></td>
<td>8.21</td>
</tr>
<tr>
<td>A/BHG/QL/1A/05 (2.2)</td>
<td></td>
<td></td>
<td>4.23</td>
<td></td>
<td></td>
<td>4.23</td>
</tr>
<tr>
<td>A/Anhui/1/05 (2.3.4)</td>
<td></td>
<td></td>
<td></td>
<td>1.75</td>
<td></td>
<td>1.75</td>
</tr>
<tr>
<td><strong>Bulk Vaccine Doses @ 90 µg/dose</strong></td>
<td>2.27</td>
<td>7.72</td>
<td>8.20</td>
<td>0.89</td>
<td></td>
<td>19.08*</td>
</tr>
</tbody>
</table>

* Number of doses adjusted to reflect usage and current potency level of bulk vaccine
<table>
<thead>
<tr>
<th>Adjuvant (MF59 and ASO3)</th>
<th>Total Doses (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk</td>
<td>120.2</td>
</tr>
<tr>
<td>Final Container (FC)</td>
<td>5.2</td>
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</tbody>
</table>
## US Pre-Pandemic Vaccine/Adjuvant Stockpile

<table>
<thead>
<tr>
<th>90μg/dose</th>
<th>7.5μg/dose</th>
<th>3.75μg/dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A/VTN/1203/04 (1)</strong></td>
<td>4.89</td>
<td>58.6</td>
</tr>
<tr>
<td><strong>A/Indo/05/05 (2.1.3)</strong></td>
<td>8.21</td>
<td>98.5</td>
</tr>
<tr>
<td><strong>A/BHG/QL/1A/05 (2.2)</strong></td>
<td>4.23</td>
<td>50.7</td>
</tr>
<tr>
<td><strong>A/Anhui/1/05 (2.3.4)</strong></td>
<td>1.75</td>
<td>21.0</td>
</tr>
</tbody>
</table>

Total Bulk Vaccine Doses @ 90μg/dose: 19.08

Total Bulk Vaccine Doses @ 7.5μg/dose: 228.8

Total Bulk Vaccine Doses @ 3.75μg/dose: 457.6
Pre-pandemic Vaccine Stockpile
H5N1 Stability Profile

![Graph showing stability profile over time for different strains of H5N1 virus](chart.png)
Importance Of Maintaining The US Pre-Pandemic Vaccine Stockpile

• Large USG investment (~$1B)

• H5N1 Pre-Pandemic vaccine of several clades/ sub-clades is ready to be FFF in case of pandemic

• Long-term storage influenza vaccine

• Keep monitoring the H5N1 vaccine potency

• Clinical evaluation is needed to confirm stability and provide data for potential EUA
H1N1 2009 Pandemic

• To respond to the H1N1 2009 pandemic the USG modified the three existing vaccine stockpile contracts and awarded two additional contracts

  » 230 million bulk doses of H1N1 were supplied by the manufacturers

  » 186 million doses of H1N1 vaccine were filled by the manufacturers
    – 149 million doses provided to CDC for distribution to public
    – 16 million doses donated internationally
    – 2.7 million doses supplied to the US military

• 120 Million doses of bulk adjuvants (ASO3 and MF59) were also purchased as a contingency
H1N1 2009 Pandemic – Lesson Learned

• Need to deliver vaccine sooner
  » Study of high productivity strains to improve candidate viruses
  » Rapid sterility testing methods to shorten lot release
  » Improved potency assays that don’t require the current wait for reagents

• Need vaccines produced by methods that don’t require virus replication
  » Recombinant vaccine awards

• Need to expand formulation, fill and finish (FFF) capabilities – all manufacturers in 2009 added FFF to respond to the needs for H1N1 vaccine
Adjuvant-H5N1 Vaccine Antigen
“Mix-N-Match Study”

• **Goal:**
  In response to a pandemic, expand the coverage of the influenza vaccine stockpile using the antigen sparing properties of adjuvants. Collaboration between Industry partners and other Federal agencies (NIAID; VTEU’s) enhancing response to pandemic.

• **Objective:**
  To determine whether adjuvants under advanced development by BARDA and H5N1 vaccines stockpiled by the USG can be used safely and effectively during an influenza pandemic under EUA.

• **Products:**
  Vaccine: H5N1 A/Indonesia/05/05
  Adjuvants: ASO3 and MF59
Mix N Match Status

• Physicochemical analysis of adjuvant/antigen mixture  
  » no issues

• Animal immunogenicity studies  
  » no issues

• Rabbit toxicology studies  
  » no issues

• Phase 1 clinical dose-ranging studies for safety and immunogenicity  
  » in progress
US Pre-Pandemic Vaccine Stockpile Program - Accomplishments

• National stockpile comprised of bulk product forms of H5N1 vaccine antigen and oil-in-water adjuvants
• Multiple vaccine manufacturers
• Multiple sub-clades of H5N1 viruses represented
• Vaccine licensed in U.S. by one manufacturer as antigen-alone formulation (90 μg HA/dose) in 2007
• Two oil-in-water adjuvants with H5N1 and H1N1 vaccine Mix-n-Match studies performed with HHS support
Pre-Pandemic Vaccine Stockpile
Future Directions

• Informative Documents
  » The Public Health Emergency Medical Countermeasures Enterprise Review (August 2010)
  » President’s Council of Advisors on Science and Technology (PCAST) Report to the President on reengineering the influenza vaccine production enterprise to meet the challenges of pandemic influenza (August 2010)

• Future Directions
  » Investment in technology and methods to produce and release vaccines more rapidly
  » Improve productivity and expand the number of available candidate viruses for pre-pandemic vaccine production
    - Improve the understanding of the productivity of available candidate viruses
  » Continued stability monitoring of existing stockpiles
    - Support with clinical testing program