AI/PI UPDATE

September 2007
Defense Health Board

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Office of the Assistant Secretary of Defense (Health Affairs)
Force Health Protection & Readiness
H5N1 Avian Influenza

• Virus continues to mutate
  – Persistence in wild and domestic bird population since at least 1987 is both worrisome and reassuring
  – Now four distinct strains causing human disease (2 clades, 3 subclades)
    – Indonesian subclade 2.1 with highest mortality (80%), largest number of cases, smallest geographic distribution
    – Strain affecting Europe, Africa, Middle East with lowest mortality (30%), next to highest number of cases, largest geographic location – coincides with majority of deployed forces
H5N1 Avian Influenza

- Geographic spread consistent with domestic and wild bird distribution
- No significant change in human-to-human transmission – sporadic cases continue
- Birds remain the primary host
  - Cats, dogs and other mammals have developed disease without effective transmission
  - No evidence of transmission to humans other than via avian or human routes
### H5N1 Avian Influenza Clades Causing Human Infections Since 2003

<table>
<thead>
<tr>
<th>H5N1 clade</th>
<th>Cases</th>
<th>Deaths</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clade 1</td>
<td>125</td>
<td>66</td>
<td>Cambodia, China, Thailand, Vietnam</td>
</tr>
<tr>
<td>Clade 2.1</td>
<td>106</td>
<td>85</td>
<td>Indonesia</td>
</tr>
<tr>
<td>Clade 2.2</td>
<td>63</td>
<td>27</td>
<td>Azerbaijan, Djibouti, Egypt, Iraq, Nigeria, Turkey</td>
</tr>
<tr>
<td>Clade 2.3</td>
<td>27</td>
<td>18</td>
<td>China, Laos, Vietnam</td>
</tr>
<tr>
<td>Total</td>
<td>321</td>
<td>196</td>
<td></td>
</tr>
</tbody>
</table>
Sample Sharing Issues

- Indonesia demanding guaranteed access to benefits stemming from samples
  - Threatens existing Global Influenza Surveillance Network
- Ongoing negotiations
- Currently engaged in limited sample sharing
- Recent events questioning GOI transparency
  - Recent denial of previously confirmed limited human-to-human transmission
What’s New Potpourri

- WHO recently changed its criteria for diagnosis of cases by in-country labs
  - Improved real time reporting of positive cases
- 7 Seroprevalence Studies
  - Studies in Vietnam, Thailand, Cambodia, Russia all with negative findings
  - Only one with + results: 4/2000 poultry workers in Korea all without clinical disease
- Two required mutations identified for transition from avian to human binding site affinity
  - Despite change, not able to sustain transmission
Neuraminidase Resistance

• Two new mutations (in vitro) identified
  – Oseltamivir no longer alone
  • Potential Oseltamivir, Zanamivir and Peramivir resistance Clade 2.1
    – Specific mutation is rare
    – Zanamivir resistant hemagglutinin mutants easier to generate
DoD Activities- Recently Published Guidance and Policy

- Antiviral guidance
  - Guidance for use is based on variable supply and disease severity
    - Uses National Pandemic Severity Categories
    - Reinforces need for early and consistent implementation of non-pharmacologic mitigation measures
    - Introduces a post-exposure prophylaxis strategy
Vaccine
Current Pre-Pandemic Vaccine Targets

- **HHS**: Establish and maintain stockpiles of pre-pandemic vaccines adequate to immunize 20 million persons against influenza strains that present a pandemic threat.

- **DoD**: Establish stockpiles of H5N1 vaccine and other influenza subtypes determined to represent a pandemic threat adequate to immunize 1.35 million persons.
Current Status of National Pre-Pandemic Vaccine Stockpiling

- Includes 14.85 million doses of H5N1 vaccines
  - DoD portion 1.2 million doses
  - Vaccines produced in 2004-07
  - Products from 3 manufacturers
  - Products use different reference strains reflecting the evolution of H5N1 viruses in birds and humans
  - One product licensed
  - Most of HHS stockpile stored by manufacturers in bulk
  - Most of DoD stockpile in vials – pursuing shelf life extension

- Additional vaccine contracts being completed for 2007-08
  - Will include vaccine to new H5N1 virus strains
Current Strategies for Use of Civilian Stockpile of Pre-Pandemic Vaccine

- Vaccination of laboratory personnel who work with H5N1 and pandemic response personnel is ongoing (using licensed vaccine under a CDC IND)

- Vaccination of defined target groups when a pandemic is imminent
  - 2 doses per vaccine recipient
  - Level of protection depends on similarity between vaccine and pandemic viruses
DoD Activities — Pre-Pandemic Vaccine Policy

- Pre-Pandemic Vaccine Use
  - Offer FDA approved vaccine to lab personnel and response teams with direct contact with High Path H5N1
  - Establishes tracking, effectiveness and adverse event monitoring
  - With imminent onset of pandemic designates JS with NORTHCOM as COCOM synchronizer to determine priorities based on risk, ability to receive two doses and critical role
National and DoD Strategy May Change

• If production can be substantially increased
  – Added/expanded facilities – long term
  – Non-egg based production – intermediate
  – Adjuvanted vaccine – short term

• If there is a better vaccine
  – Universal vaccine
  – Improved cross protection
H5N1 Vaccine Studies

- Split virion and whole cell vaccines
- Adjuvants (alum, MF59, AS)
- Intradermal vs. IM vaccination
- Mix and Match Adjuvant Study
- Data on cross immunogenicity between clades and subclades
Results of Phase 1/2 study of Baxter vero-derived whole cell A/Vietnam/1203/2004 (H5N1) vaccine, 7.5 ug unadjuvanted, in persons aged 18-44, who received doses on day 0 and 21*

<table>
<thead>
<tr>
<th>Day</th>
<th>Number (%) with microneutralization titer $\geq$1:20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A/Vietnam/1203/2004</td>
</tr>
<tr>
<td>0</td>
<td>0/42 (0%)</td>
</tr>
<tr>
<td>21</td>
<td>17/42 (40.5%)</td>
</tr>
<tr>
<td>42</td>
<td>32/42 (76.2%)</td>
</tr>
</tbody>
</table>

Notes:
1) Microneutralization test not standardized; titer $\geq$1:20 may not correlate with protection
2) Other manufacturers also have evaluated cross-immunogenicity (e.g., GSK AS adjuvanted vaccine)

*WHO meeting on H5N1 vaccines, February 2007
Immune Priming and Cross-Immunogenicity After a Booster Dose

Stephenson I, J Infect Dis, 2005

• Subjects received 2 doses (21 day interval) of plain or MF59 adjuvanted Dk/Sing/97 (H5N3)
• 16 months later, 26 subjects received a third dose of the same vaccine
<table>
<thead>
<tr>
<th>Test antigen, # doses</th>
<th>% with ≥4-fold rise HAI titer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MF59</td>
</tr>
<tr>
<td>Dk/Sing/97 (H5N3)</td>
<td></td>
</tr>
<tr>
<td>2 doses</td>
<td>64%</td>
</tr>
<tr>
<td>3 doses</td>
<td>100%</td>
</tr>
<tr>
<td>HK/213/03 (H5N1)</td>
<td></td>
</tr>
<tr>
<td>2 doses</td>
<td>14%</td>
</tr>
<tr>
<td>3 doses</td>
<td>100%</td>
</tr>
<tr>
<td>VN/1203/04 (H5N1)</td>
<td></td>
</tr>
<tr>
<td>2 doses</td>
<td>9%</td>
</tr>
<tr>
<td>3 doses</td>
<td>27%</td>
</tr>
<tr>
<td>Thai/16/04 (H5N1)</td>
<td></td>
</tr>
<tr>
<td>2 doses</td>
<td>14%</td>
</tr>
<tr>
<td>3 doses</td>
<td>71%</td>
</tr>
</tbody>
</table>

Stephenson I, J Infect Dis, 2005
Booster Immune Response Following Priming with an Antigenic Variant

(Goji, IDSA 2006, Abstract LB-4)

- 37 persons vaccinated in 1998 with 2 doses of 90 ug unadjuvanted A/HK/156/1997 (H5N1)
- Vaccinated 8 years later with 1 dose, 90 ug unadjuvanted A/VN/1203/2004 (H5N1)
- Antibody responses compared with H5 naïve subjects who received a single 90 ug dose of the latter vaccine

<table>
<thead>
<tr>
<th>Group</th>
<th>4-fold rise</th>
<th>HAI titer ≥1:40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primed</td>
<td>68%</td>
<td>70%</td>
</tr>
<tr>
<td>Unprimed</td>
<td>23%</td>
<td>24%</td>
</tr>
</tbody>
</table>
Adjuvanted Clade 1 Vaccine Safety and Efficacy Data


• Design
  – Observer blind randomized trial
  – 2 doses inactivated split
    A/Vietnam/1194/2004 vaccine
  – Doses administered 21 days apart
  – N= 400 (eight groups of 50 aged 18-60)
  – 4 antigen doses (3.8, 7.5, 15, 30 ug)
  – Vaccine with and without adjuvant
# Demographics

<table>
<thead>
<tr>
<th></th>
<th>Total 3.8ug n=50</th>
<th>3.8 adj n=51</th>
<th>7.5ug n=50</th>
<th>7.5 adj n=50</th>
<th>15ug n=50</th>
<th>15 adj n=50</th>
<th>30ug n=50</th>
<th>30 adj n=49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>34.3</td>
<td>33.7</td>
<td>35.3</td>
<td>33.0</td>
<td>34.4</td>
<td>35.1</td>
<td>33.9</td>
<td>35.3</td>
</tr>
<tr>
<td>Gender %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>54</td>
<td>54</td>
<td>71</td>
<td>50</td>
<td>44</td>
<td>50</td>
<td>60</td>
<td>54</td>
</tr>
<tr>
<td>Ethnicity %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>96</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>African</td>
<td>&lt;1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>&lt;1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Extracted from Leroux-Roels et al. Lancet Aug 18, 2007
Immune Response to Adjuvanted (AS) H5N1 Vaccine, A/VN/1194/2004

Derived from Hehme, GSK, presentation at WHO, Geneva, 2/15-16/07
HI Antibody Response to Homologous Vaccine Strain Non-Adjuvanted Vaccine

<table>
<thead>
<tr>
<th></th>
<th>3.8 ug</th>
<th>7.5 ug</th>
<th>15 ug</th>
<th>30 ug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prime +21 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seroprotection titer &gt;1:40</td>
<td>0%</td>
<td>8%</td>
<td>20%</td>
<td>29%</td>
</tr>
<tr>
<td>Boost + 21 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seroprotection titer &gt;1:40</td>
<td>4%</td>
<td>16%</td>
<td>35%</td>
<td>43%</td>
</tr>
</tbody>
</table>

Extracted from Leroux-Roels et al. Lancet Aug 18, 2007
# HI Antibody Response to Homologous Vaccine Strain Adjuvanted Vaccine

<table>
<thead>
<tr>
<th>Prime +21d</th>
<th>3.8 ug + ad</th>
<th>7.5 ug + ad</th>
<th>15 ug + ad</th>
<th>30 ug + ad</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seroprotection titer &gt;1:40</td>
<td>26%</td>
<td>50%</td>
<td>49%</td>
<td>58%</td>
</tr>
</tbody>
</table>

| Boost + 21d | 84% | 90% | 96% | 85% |
| Seroprotection titer >1:40 | 84% | 90% | 96% | 85% |

Extracted from Leroux-Roels et al. Lancet Aug 18, 2007
Results

• All eight vaccine formulation had a good safety profile with no serious adverse events reported
• Adjuvanted vaccine induced more injection-site and general symptoms
  – Most mild to moderate and all transient
• Adjuvanted formulations significantly more immunogenic at all doses

In Praise of Ferrets

- Excellent model for human H5N1 infection
- Susceptible to infection with human and avian flu viruses
- High path strains replicated in upper and lower respiratory tracks
- More severe disease with H5 vs. H3
- Infection with human isolates results in
  - Severe systemic disease
  - Mortality
- H5N1 from 2004 isolates results in more severe disease than that seen in 1997
Ferret Data Adjuvanted Vaccine

- Immunization with low dose adjuvanted split H5N1 vaccine protects ferrets against homologous and heterologous challenges
  - Ferrets immunized with an A/Vietnam/1194/2004 adjuvanted vaccine
  - Challenge with Clade 1 A/Vietnam/1194/2004 and Clade 2.1 A/Indonesia/5/2005
Homologous Challenge Protection
Day 5 Post-challenge

<table>
<thead>
<tr>
<th></th>
<th>Dead</th>
<th>Alive</th>
<th>% Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjuvanted Vaccine</td>
<td>4</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Adjuvant alone</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vaccine-AS (0.6 ug)</td>
<td>2</td>
<td>4</td>
<td>67</td>
</tr>
<tr>
<td>Vaccine-AS (1.7 ug)</td>
<td>1</td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>Vaccine-AS (5 ug)</td>
<td>0</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>Vaccine-AS (15 ug)</td>
<td>0</td>
<td>6</td>
<td>100</td>
</tr>
</tbody>
</table>
Heterologous Challenge Protection Day 5 Post-challenge

<table>
<thead>
<tr>
<th></th>
<th>Dead</th>
<th>Alive</th>
<th>% Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjuvanted Vaccine</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adjuvant alone</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vaccine-AS (1.7 ug)</td>
<td>1</td>
<td>5</td>
<td>83</td>
</tr>
<tr>
<td>Vaccine-AS (3.8 ug)</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Vaccine-AS (7.5 ug)</td>
<td>0</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>Vaccine-AS (15 ug)</td>
<td>0</td>
<td>6</td>
<td>100</td>
</tr>
</tbody>
</table>
Summary of H5N1 Pre-Pandemic Vaccine Studies

• Adjuvants increase immunogenicity and cross-immunogenicity of H5N1 vaccines

• A single dose of GSK AS adjuvanted H5N1 vaccine could protect ~1/2 vaccine recipients

• Priming with 1 or 2 vaccine doses leads to a booster response to a subsequent dose of the same or a different H5N1 vaccine

• Pending studies
  – “Mix-and-match” GSK AS adjuvant with other companies’ influenza antigen
  – Further trials of cross-immunogenicity and of priming
If you are sick, **STAY HOME!**

**PANDEMIC INFLUENZA EXERCISE IN PROGRESS**

**ARE YOU READY?**

**Beat the flu...**

**PRACTICE SOCIAL DISTANCING!**
Exercise Purpose

To ensure P&R’s preparedness to continue mission essential operations, with a diminished force, and to safeguard its staff during a pandemic influenza health crisis.

The exercise was designed to:

• Assess overall preparedness to handle a pandemic influenza
• Identify vulnerabilities in plans, policies and procedures
• Identify strengths that could be expanded/exported
• Capture lessons learned to help frame policies for use in the field and to share best practices/lessons learned with other Federal agencies
• Identify Way Forward for improvement
Exercise Goals

Assess:

✓ Ability to work at home
  - IT connectivity/server capacity

✓ Capability of Communication Systems
  - 1-800 Call-In Number
  - Telephone Trees

✓ Ability to socially distance at work

✓ Ability to execute a sample of mission essential functions with a diminished workforce
  - Flow of order of succession
  - Delegation of authorities

✓ Ability to muster using web based tool

All goals accomplished!
Exercise Accomplishments

• At endstate, the overall readiness rating at P&R was 96%.
  – Total number of participants: 1506
  – Total number of on-site employees: 1201 (81%)
  – Total number of teleworkers: 251 (17%)
  – Total number of incapacitations: 54 (3%)

• Telework Practice Helps
  – First day of exercise: 32 Force Net IT Help Desk Calls
  – Second day: 14 Force Net IT Help Desk Calls

Input from satellite organizations reflects similar statistics.
Leadership Decisions

• Continue with readiness preparations to resolve identified vulnerabilities
  
  - PI Way Forward should be incorporated in P&R COOP plan
  - Future exercises should:
    ▪ More fully stress IT capabilities when working from home
    ▪ Include more contractors
    ▪ Assess impact of PI on Pentagon parking and food service
    ▪ Test OSD and interagency integration

• Consideration of appointment of a full time P&R Emergency Preparedness Program Manager to oversee preparation and exercise for COOP, Pandemic and other crises
Next update

- Expanded PI exercise results
- Policy adjustment after increase in antiviral stockpile
- Pre-pandemic vaccine
  - Acquisition plans
  - More data
- Vaccine modeling results
She’s coming to your next meeting...

PRACTICE SOCIAL DISTANCING!
Any Questions?

Tell us your thoughts and suggestions:
http://fhp.osd.mil/feedback.jsp

Visit the new FHP&R home page
http://fhp.osd.mil