Pandemic Influenza Preparation Update
Defense Health Board – April 2008

LTC Wayne Hachey DO, MPH
Office of the Assistant Secretary of Defense (Health Affairs)
Force Health Protection and Readiness
Agenda

• Current status of H5N1
• Are we going down the right path?
  – Vaccines
  – Antivirals
  – Risk Communication
Areas with Confirmed Avian Flu Cases

Areas with confirmed human cases of H5N1 avian influenza since 1 January 2008 *

* All dates refer to onset of illness

Data Source: WHO
Map Production: Public Health Mapping and GIS
World Health Organization
© WHO 2008. All rights reserved

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO

- **Cases**
- **Deaths**

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>115</td>
<td>79</td>
</tr>
<tr>
<td>2007</td>
<td>86</td>
<td>50</td>
</tr>
<tr>
<td>2008</td>
<td>30</td>
<td>23</td>
</tr>
<tr>
<td>Total</td>
<td>431</td>
<td>240</td>
</tr>
</tbody>
</table>
Indonesia

• Sample sharing continues to be an issue
• Highest number of cases (case fatality 83%)
• High level of viral circulation in avian population
  – 20% of a 1.4B chicken population is scattered in 30M backyards
  – 31 of 33 provinces infected
    • Endemic in some areas
  – Highly decentralized administration, under-resourced national veterinary services, lack of engagement with commercial poultry producers, inability to implement a comprehensive communication strategy
  – Question if poultry vaccine continues to be effective
Indonesia

- International community is engaged

- 1350 local government officers have been trained and are working with village communities

- Surveillance and response teams are working in 193 out of 448 districts
  - By June 2000 teams in > 300 districts

- FAO providing technical and policy advise

- Major donors have invested $25M
Risk Associated With Close Contact*

- Risk of person to person transmission
- Clade 2.1
- Exposure of close contacts characterized
- 257 contacts investigated (130 HCW, 90 FM, 34 neighborhood contacts)
- 4% of HCW followed appropriate infection control measures to include PPE
- No evidence of H5N1 infection in any group

* S. Isfandari, MOH Indonesia presented at International Conference on Emerging Infectious Diseases 2008
H5N1 in Vietnam

Virus continues to be a moving target.

Multiple Sub lineages of H5N1 in Vietnam, 2005-07

*Tien Dung Nguyen, et al.*  *EID*  
Vol. 14, No. 4 • April 2008
• Goal: uniform designation of emerging lineages of highly pathogenic H5N1

• System developed by WHO, OIE, FAO H5N1 Evolution Working Group

• Good news: will maintain some of the previously designated clade numbers

• Bad news: Now 10 clades with subclades and sub-subclades

• http://h5n1.flugencode.org/
• Designation Criteria
  – Maintain previously designated clade numbers when possible (Clade 2 remains 2 and 1 remains 1)
  – New designation based on phylogenetic tree topology
    • H5N1 progenitors closest to gs/Guangdong/1/96 designated as Clade 0
    • Subsequent clades numbered starting from 3
    • Clades designated by presence of a distinct common node shared by at least 4 isolates
## Recent Human H5N1 Cases by Clade

<table>
<thead>
<tr>
<th>Country</th>
<th>Total Cases 2007</th>
<th>Total Cases 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Deaths</td>
</tr>
<tr>
<td>Cambodia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>China</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Egypt</td>
<td>25</td>
<td>9</td>
</tr>
<tr>
<td>Indonesia</td>
<td>43</td>
<td>37</td>
</tr>
<tr>
<td>Laos</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Myanmar</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nigeria</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pakistan</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>88</td>
<td>59</td>
</tr>
</tbody>
</table>
Human infections summary

- Clade 1 – only a few recent samples isolated but antigenic variants detected – appears to be replaced by clade 2.3.4 in SE Asia
- Clade 2.1 – remains restricted to Indonesia – largest number of cases
- Clade 2.2 – increasing geographical range with increasing incidence in human cases
- Clade 2.3.4 – has expanded in SE Asia and is now the predominate strain in SE Asia
<table>
<thead>
<tr>
<th>Virus</th>
<th>Clade</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/Vietnam/1203/2004</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>A/Vietnam/1194/2004</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>A/Indonesia/5/2005</td>
<td>2.1</td>
<td>Req Indo Gov Perm</td>
</tr>
<tr>
<td>A/Bar-headed goose/Qinghai/1A/2005</td>
<td>2.2</td>
<td>Yes</td>
</tr>
<tr>
<td>A/Whooper swan/Mongolia/244/2005</td>
<td>2.2</td>
<td>Yes</td>
</tr>
<tr>
<td>A/turkey/Turkey/1/2005</td>
<td>2.2</td>
<td>Yes</td>
</tr>
<tr>
<td>A/Anhui/1/2005</td>
<td>2.3.4</td>
<td>Yes</td>
</tr>
<tr>
<td>A/Japanese white-eye/Hong Kong/1038/2006</td>
<td>2.3.4</td>
<td>Yes</td>
</tr>
<tr>
<td>Virus</td>
<td>Clade</td>
<td>Availability</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>--------</td>
<td>---------------</td>
</tr>
<tr>
<td>A/chicken/India/NIV33487/2006</td>
<td>2.2</td>
<td>Pending</td>
</tr>
<tr>
<td>A/duck/Laos/3295/2006</td>
<td>2.3.4</td>
<td>May 2008</td>
</tr>
<tr>
<td>A/Cambodia/R0405050/2007</td>
<td>1</td>
<td>May 2008</td>
</tr>
<tr>
<td>A/duck/Hunan/795/2002-like</td>
<td>2.1</td>
<td>Candidate</td>
</tr>
<tr>
<td>A/egret/Egypt/1162/2007-like or A/Egypt/2321/2007-like</td>
<td>2.2</td>
<td>Candidate</td>
</tr>
<tr>
<td>A/Common Magpie/Hong Kong/5052/2007</td>
<td>2.3.2</td>
<td>Candidate</td>
</tr>
</tbody>
</table>
Proposed Vaccine Strategy

• Multitude of vaccine candidates
  – DOD does not have the resources nor does the industrial base have the ability to support protecting the force against each threat
  – Even with matched strains immunogenicity is not reassuring

• Current strategy: delay pre-pandemic vaccine acquisition until an effective vaccine with adequate cross protection is available
Vaccine Stability

- Good news and bad news
- Stability an issue for A/Vietnam 04 & 05
- Filled and finished appears to be stable
- Most of DOD supply is filled and finished

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Potency loss to date</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/Vietnam 2004 - bulk</td>
<td>18%</td>
</tr>
<tr>
<td>A/Vietnam 2005 - bulk</td>
<td>45%</td>
</tr>
<tr>
<td>A/Indonesia 2006 - bulk</td>
<td>0%</td>
</tr>
<tr>
<td>A/Vietnam 2004 – filled</td>
<td>0%</td>
</tr>
<tr>
<td>A/Vietnam 2005 – filled</td>
<td>0%</td>
</tr>
</tbody>
</table>
Vaccines on the Horizon

- Cross protection issues
- Universal vaccine
- Adjuvantated vaccine
- Live attenuated vaccine
• Following two doses @ 3.8, 7.5, 15 & 30ug with/without adjuvant

• Adjuvanted formulations more immunogenic

• Cross reactivity with adjuvanted vaccine @ 3.8ug
  – Clade 2.1 77%

Leroux-Roels et al., 2007; Lancet 370: 580-589
• After 2 90ug doses of Clade I vaccine
  – 40% had > 4 fold increase by microneut

• Converters tested for reactivity to clade 2 H5N1 viruses
  – 83% for clade 2.1
  – 67% for clade 2.2
  – 28% for clade 2.3.4
Following immunization of 2 doses of adjuvanted and non-adjuvanted vaccine

Those who were seropositive were tested for cross reactive titers

- 98% Alternate Clade 1
- 64% Clade 2.1
- 80% Clade 2.2

- No consistent result associated with adjuvant and level of cross protection

Hoschler et al., 2008; Influenza and Other Respiratory Viruses 1:177-182
Universal Vaccine

- **ACAM-FLU-A**
  - With and without adjuvant
  - Best response (90% conversion rates) ACAM-FLU-A with QS-21 adjuvant
  - Animal studies demonstrated 70% survival following a Clade 1 H5N1 challenge
  - Phase 1 trial now completed
M2 Protein Based Vaccine

- Previous research noted deletions on M2 cytoplasmic tail results in growth defect of H1N1 virus in vitro
- Used M2 tail mutant as a live attenuated vaccine against H5N1
- Mice received lethal challenge with homologous VN1203 clade 1 virus and heterologous Indonesia/7/05 clade 2 virus – vaccine provided protection against each
Live Attenuated Vaccine
Current Activities

- Med Immune in conjunction with JHU and NIH
- Creating a library of vaccines representing each subtype of pandemic potential (H2, H4-16)
- Phase 1 Proof-of-Principle Trials
  - Safety, infectivity, 1-dose vs. 2-dose regimen, immunogenicity, shedding in healthy adults
- Bank sera from vaccinated volunteers
  - Test newly emerging viruses for degree of drift
  - Predict ability of library vaccine to cross-protect against actual pandemic strain
All vaccines contain the FluMist® A/Ann Arbor/6/60 attenuated genetic “backbone”

- H5N1 A/VietNam/1203/2004*
- H5N1 A/HongKong/213/2003*
- H9N2 A/chicken/Hong Kong/G9/97
- H7N3 A/chicken/British Columbia/CN-6/2004
Pre-pandemic LAIV

• All vaccines were well tolerated by healthy adults

• Vaccines are more restricted in replication and less immunogenic than seasonal LAIV
  – Replication: H7 (81%) > H9 (31%) > H5 (10 – 47%)
    • Majority of subjects shed virus only on Day 1
  – Immunogenicity (HAI): H9 (92%) > H7 (62%) > H5 (0-11%)

• Avian HA and NA genes further attenuate the vaccine for humans and studies are warranted to investigate the role of
  – Receptor specificity, Virus entry, & Interaction between avian HA and NA and internal protein genes of AA ca
  – Mouse and ferret data demonstrated low replication but good matched and unmatched cross protection with viral challenge
GSK adjuvanted vaccine (Prepandrix™)

- Received Positive Opinion from Europe’s Committee for Medicinal Products for Human Use
- Using a Clade 1 (Vietnam) antigen
  - Acceptable safety and reactogenicity profile
  - 4 fold increase in serum neutralizing antibodies
    - 77.1% Indonesian Clade 2.1
    - 75% Anhui Clade 2.3.4
    - 85% Turkey Clade 2.2
  - Animal models demonstrate 100% survival following 2 doses of 3.8 ug and heterologous challenge
Remember mice lie and ferrets exaggerate

- Good news if you’re
- Wait and see for
Antivirals
DOD Antiviral Strategy

- Establish local supplies equal to 30% of population at risk @ both fixed and deployed settings

- Strategy focuses on early treatment and post-exposure prophylaxis for close contacts
  - Outbreak prophylaxis limited to high risk individuals (HCW & 1st responders) & select few without access to medical support
  - For the overall strategy to work early and consistent implementation of NPI is mandatory
  - Rapid diagnostics will enable more effective use of antivirals
Rapid Diagnostics

• Nothing commercially available yet

• Rapid antigen test strip *
  • Testing underway at NHRC & NAMRU3
    – No false positives (100 clinical samples)
    – Of 29 H5N1 samples tested 26 +

• Multiplex antibody panel for detection of influenza A & B**
  • Couples an antibody sandwich assay with electrochemiluminescent detection
  • 100 samples tested (20 fluA, 20fluB, 20 Adeno)
  • 88% sensitivity, 96% specificity
  • Evaluation for specific H1, H3 and H5 antibodies ongoing

*Myers et al; ** McDonough et al. Presented at International Conference on Emerging Infectious Diseases 2008
The Journal of Infectious Diseases 2008;197:

Oseltamivir Prophylactic Regimens Prevent H5N1 Influenza Morbidity and Mortality in a Ferret Model

David A. Boltz, Jerold E. Rehg, Jennifer McClaren, Robert G. Webster, Elena A. Govorkova

Department of Infectious Diseases (Division of Virology) and Department of Pathology, St. Jude Children’s Research Hospital, Memphis, Tennessee
Study Methods

- Ferrets given oseltamivir for 10 days
  - 5 or 10mg/kg QD
  - 2.5 or 5mg/kg BID
  - Treatment – started 4 hours after infection
  - Prophylaxis started 1 day before infection
- Challenge – lethal dose of A/Vietnam/1203/04

5mg/kg in ferrets=75mg dose in humans
Results

- 5mg/kg QD prevented death but not severe illness
- 10mg/kg QD reduced symptoms but pathology still observed in internal organs
- 2.5 or 5mg/kg BID had 100% survival, no symptoms, no systemic viral spread and no organ pathology. 5mg BID had no viral replication in upper airway after 3 days

5mg/kg in ferrets=75mg dose in humans
• Oseltamivir did not prevent infection but did prevent the release of virus from infected cells

• Antibody production observed following inoculation

• Oseltamivir did not interfere with serum antibody production at any dose

• So if people act like ferrets we need to know who we treated
Modeling targeted layered containment of an influenza pandemic in the United States

M. Elizabeth Halloran†‡, Neil M. Ferguson§, Stephen Eubank¶, Ira M. Longini, Jr.†¶, Derek A. T. Cummings§,
Bryan Lewis¶, Shifu Xu†, Christophe Fraser§, Anil Vullikanti¶, Timothy C. Germann‖, Diane Wagener**,
Richard Beckman¶, Kai Kadaul‖, Chris Barrett¶, Catherine A. Macken‖, Donald S. Burke‡‡, and Philip Cooley**

Virginia Bioinformatics Institute, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061; †‡Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15261; **Research Triangle Institute, Research Triangle Park, NC 27709; §Department of Infectious Disease Epidemiology, Imperial College, London W21PG, England; ¶Los Alamos National Laboratories, Los Alamos, NM 87545; *Department of Biostatistics, School of Public Health and Community Medicine, University of Washington, Seattle, WA 98195; and †Program in Biostatistics and Biomathematics, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA 98109

Edited by Barry R. Bloom, Harvard School of Public Health, Boston, MA, and approved January 15, 2008 (received for review July 23, 2007)

www.pnas.org/cgi/doi/10.1073/pnas.0706849105
• 3 separate models of targeted layered containment
• Assumes 67% of infections are symptomatic
  – 60 & 80% ascertainment of Sx cases
• All ascertained cases treated
• All household contacts receive antivirals
<table>
<thead>
<tr>
<th>Intervention</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sx Cases Ascertained</td>
<td>0</td>
<td>60</td>
<td>60</td>
<td>80</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>Tx Threshold</td>
<td>0</td>
<td>1.0</td>
<td>0.1</td>
<td>0.01</td>
<td>0.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Tx Index Case &amp; Close Contacts</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Isolation</td>
<td>0</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Quarantine</td>
<td>0</td>
<td>30</td>
<td>60</td>
<td>60</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Close Schools</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Threshold</td>
<td>0</td>
<td>1.0</td>
<td>0.1</td>
<td>0.01</td>
<td>0.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Compliance</td>
<td>0</td>
<td>30</td>
<td>60</td>
<td>60</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Social Distancing 50% compliance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work Place Threshold</td>
<td>0</td>
<td>1.0</td>
<td>0.1</td>
<td>0.01</td>
<td>0.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Community Threshold</td>
<td>0</td>
<td>1.0</td>
<td>0.1</td>
<td>0.01</td>
<td>0.1</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Sensitivity Analysis for Workplace and Community Social Distancing

[Graph showing attack rates for different scenarios]
Comparison of No Intervention with Intervention Scenarios 2 & 3 with NPI alone, Plus Treatment and Plus TAP

- Imperial College Model
- University of Washington
- Virginia Bioinformatics Institute Model

Attack Rate (%)

<table>
<thead>
<tr>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions</td>
<td>NPIs</td>
<td>Plus Case Treatment</td>
</tr>
<tr>
<td>No Interventions</td>
<td>42.4</td>
<td>11.6</td>
</tr>
<tr>
<td>NPIs</td>
<td>46.8</td>
<td>12.5</td>
</tr>
<tr>
<td>Plus Case Treatment</td>
<td>44.7</td>
<td>11.0</td>
</tr>
<tr>
<td>Plus TAP</td>
<td>3.8</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>7.5</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>2.8</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>3.9</td>
<td>3.1</td>
</tr>
</tbody>
</table>
Primary purpose is as a risk communication tool & provides examples of supplies

Pandemic Influenza risk mitigation guidelines
- Social distancing
- Infection Control - Hand washing
- Mask use
- Where to get information

Includes
- Instructions
- Masks (2) N95 & (4) Surgical
- Waterless hand-washing supplies
Mask Types

Is there a difference for community mitigation?

- N95 vs. Surgical masks
- Recruited 28 people with suspected flu- yielded 9 Flu A or B
- 2\textsuperscript{nd} day of illness
- Participants coughed into Petri dishes 10 cm away wearing no mask, N95 or Surgical mask
- Both mask groups had no viral growth whereas Petri dish well inoculated following no mask group attempt at inoculation
Questions?

She’s coming to your next meeting...

PRACTICE SOCIAL DISTANCING!