AI/PI Update
Defense Health Board

LTC Wayne Hachey
Force Health Protection & Readiness

May 2007
Agenda

- AI
  - Human and Avian disease
  - Current Epidemiology
  - Recent research activities

- PI
  - Vaccine
  - Antivirals
  - Community Mitigation
  - Surveillance
  - Communication
Human Cases

- 291 Cases, 172 deaths (27 April 07)
- 2006 Indonesia remained the hot spot with 55 cases/45 deaths out of a total global 115 cases and 79 deaths
- Mortality rate
  - 2007 50%
  - 2006 68.9%
  - 2005 43.3%
  - 2004 69.5%
Confirmed human cases of avian influenza A/(H5N1) by date of onset and country from January 2006 up to date
(Data as of 01 March 2007)
Avian Cases

- 63 Countries (12 April OIE)
- Re-emergence of disease
  - Vietnam
  - Russia
  - Myanmar
  - Egypt
  - Kuwait
- Bird migration still plays a less prominent role in comparison with domestic poultry
KEEP Bird Flu Out OF THE UNITED STATES

It’s illegal to smuggle birds – wild and domestic – and their products into the United States.

If you do, it will cost you:

- Up to $250,000 fine and 5 years in prison for any individual
- Up to $500,000 fine and 5 years in prison for any business or organization

CALL 1-800-BE ALERT to report bird smuggling or undeclared bird products brought into the United States.

www.avianflu.gov

USDA is an equal opportunity provider and employer. • May 2007
H5N1 Risk via Wild Bird Migration via Asia/Alaska Routes

- Diverse avian hosts from Asia and the Americas overlap in Alaska
- 7 yrs of AI surveillance representing 8,254 samples
  - Yield 5 isolates (H3, H4, H6) with no evidence of Eurasian origin for any virus
- Risk and probably the frequency of intercontinental virus transfer in this region is low
- But close genetic association between H6 in ducks from Alaska and a poultry outbreak in California
  - Reflects real-time connections of migratory ducks between Alaska and California with the vector connection extending into the Russian Far East
Avian influenza restricted zone sign at a road junction close to an infected turkey farm in the United Kingdom (Keith Evans)
Outbreaks of Avian Influenza (subtype H5N1) in poultry. From the end of 2003 to 30 April 2007.
H5N1 Avian Disease Distribution
Clades

Evolution of the H5N1 haemagglutinin gene

Fig. 1
Clades

- 2 discrete lineages resulting in human disease both descended from A/Goose/Guangdong/96
- Clade 1 (2004-5) Vietnam, Thailand, Cambodia (2 cases in Thailand 06)
- Clade 2 circulated in birds in China and Indonesia in 03-04 and spread to Europe, Middle East & Africa in 05-06
  - Six subclades, 3 with distinct geographic distributions & human infections
    - 2.1 Indonesia
    - 2.2 Europe, Middle East, Africa (EMA)
    - 2.3 China
- 2 emerging clades
  - Worrisome lack of avian vaccine cross protection
Antigenic/Genetic Diversity
European-Middle Eastern-African (EMA) Clades (EID Vol 13, May 07, Salzberg et al.)

- Complete genome recently sequenced
- Responsible for several human infection in Egypt & Iraq
- Introduced at least 3 times into the European-African region
- Split into 3 distinct, independently evolving sub lineages
  - One isolate may represent 2 of these sub lineages that have recently reassorted
EMA Clades

- Represent viruses isolated in Europe, the Middle East, and Africa (Côte d'Ivoire, Nigeria, Niger, Sudan, Egypt, Afghanistan, Iran, Slovenia, Croatia, and Italy).
- Shared lineage suggests a single genetic source for introduction—Russia or Qinghai Province origin.
- The broad dispersal throughout these countries during a relatively short period, coupled with weak biosecurity standards, implicates human-related movement of live poultry and poultry commodities as the source of introduction.
- The virus' presence in wild birds leaves open the alternative possibility that migratory birds may have been the primary source, with secondary spread possibly caused by human-related activities.
European-Middle Eastern-African Clades
Clades
Vaccine and Antivirals

• Vaccine
  – Non adjuvanted Clade 1 vaccines do not inhibit any Clade 2
  – Non adjuvanted Clade 2.1 vaccine does not inhibit Clade 1 & does not inhibit 2.2 and 2.3 well

• Antivirals
  – Resistance to M2 Channel Blockers
    • Clade 1 resistant
    • Clade 2.1 mixed (80% resistant)
    • Clade 2.2 & 2.3 sensitive
  – Resistance to NA inhibitors
    • Clade 1, 2.1, 2.3 sensitive
    • Clade 2.2 some cases of moderate resistance
What Else Is New?
H5N1

- Higher viral load and wider tissue tropism than seasonal flu
- HPAI cleavage site is not limited to the normal trypsin specific like protease but are ubiquitous proteases
- Suppressive effect for Interferon alpha & gamma and TNF leading to an aberrant immune response – cytokine storm
Viral Replication

- H5N1 has 1-3 log greater viral load than seasonal influenza
  - Increased in fatal vs. non-fatal cases

<table>
<thead>
<tr>
<th>Viral Replication</th>
<th>H5N1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood</strong></td>
<td></td>
</tr>
<tr>
<td>Virus Isolation</td>
<td>17%</td>
</tr>
<tr>
<td>Detectable RNA</td>
<td>56%</td>
</tr>
<tr>
<td><strong>Rectum</strong></td>
<td></td>
</tr>
<tr>
<td>Virus Isolation</td>
<td>14%</td>
</tr>
<tr>
<td>Detectable RNA</td>
<td>71%</td>
</tr>
</tbody>
</table>

H5N1 HA Cleavability

• HA precursor cleaved into HA1 and HA2
  – Prerequisite for infectivity
• LPAI: single Arg residue
  – Recognized by trypsinlike proteases
• HPAI: multiple basic amino acids
  – Recognized by ubiquitous proteases

Aberrant Immune Response

- Cytokines increased in fatal vs. non-fatal H5N1 cases
- Cytokines increased in H5N1 infections vs. H3/H1
- INF$_{\alpha,\gamma}$ and TNF$_{\alpha}$ increased

Seo SH et al. Nat Med. 2002;8:950-4
• Humoral immunity elicited by huN1 may provide partial protection against H5N1 (mice and human models)
• Another indication for universal influenza immunization?
• PLoS Medicine Feb 07/Vol 4/Issue 2/e59
Mice

- Mice immunized against the NA of a human H1N1 strain
- Naïve mice injected with sera from vaccinated mice
- Both challenged with H5N1 (Vietnam/1204/04)
- 50% survival in both treatment groups
- 100% mortality in control groups
Men

- Human serum samples
- 31/38 demonstrated reactivity with H1N1 A/ New Caledonia/20/99
  - NA inhibition titers ranged from 20->320
- 8/38 had low inhibitory titers (20-80) against the NA of A/Vietnam/1203/03
- Small sample size but some individuals may have functionally significant levels of avN1-reactive antibodies
**Is Gray Hair a Possible Protective Factor?**

- 229 confirmed cases of H5N1 over 30 months
  - Age skewed toward children and young adults
  - Mean age 19.8 yrs
  - 10-19 yrs 29% vs. >40 yrs 5.9%
  - Age Specific case rates/million
    - 0-9 yrs & 10-19yrs = 0.15
    - 20-29 yrs = 0.13
    - 30-39 yrs = 0.08
    - >40 yrs = 0.02
H5N1: a Disease of the Young?
Could Ferrets Lie About Tamiflu?
Ferrets as Animal Models for Influenza

- Naturally susceptible host
- Receptor in upper airway similar to humans (predominant SA $\alpha$ 2,6 Gal)
- Clinical symptoms closely resemble humans
**Early Post-exposure Administration of Tamiflu - Survival Endpoint**

<table>
<thead>
<tr>
<th>Virus Dose</th>
<th>Experimental Group</th>
<th>No. dead/Total no.</th>
<th>Day of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 EID$_{50}$</td>
<td>Treatment</td>
<td>0/3</td>
<td>No</td>
</tr>
<tr>
<td>100 EID$_{50}$</td>
<td>Control</td>
<td>2/3</td>
<td>10, 10</td>
</tr>
<tr>
<td>100 EID$_{50}$</td>
<td>Treatment</td>
<td>0/3</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>3/3</td>
<td>7, 7, 9</td>
</tr>
</tbody>
</table>

Infect with 10 or 100 EID$_{50}$ A/VN/1203/04

![Ferrets]

Day 0: Inoculation
Day 1 - 5: Treatment with Oseltamivir (5 mg/kg/d)

5 mg/kg/d (equiv. to half approved human dose of 75 mg bid)

Oseltamivir 2x daily for 5 days

Day 21: End of study
Upper Respiratory Track Viral Titers
Tamiflu Tx - Vietnam 1203 Challenge

Elena A. Govorkova, St Jude Children’s Research Hospital
Presented at: Seasonal & Pandemic Influenza 2007
### Late Post-exposure Administration of Tamiflu - Survival Endpoint

**Infect with 100 EID\(_{50}\) A/VN/1203/04**

**Day 0**

- **Day 1**
- **Day 2**
- **Day 3**
- **Day 4**
- **Day 5**
- **Day 6**
- **Day 21**

<table>
<thead>
<tr>
<th>Virus Dose</th>
<th>Experimental Group</th>
<th>No. dead/ Total no.</th>
<th>Day of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 EID(_{50})</td>
<td>10 mg/kg/d</td>
<td>3/3</td>
<td>7, 7, 8</td>
</tr>
<tr>
<td></td>
<td>25 mg/kg/d</td>
<td>0/3</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>3/3</td>
<td>6, 7, 8</td>
</tr>
</tbody>
</table>

- 24 hours Delay

- **10 mg/kg/d (equiv. to approved human dose of 75 mg bid)** or **25 mg/kg/d (equiv. to 2.5x human dose of 75 mg bid)**

Oseltamivir 2x daily for 5 days

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Elena A. Govorkova, St Jude Children’s Research Hospital
Presented at: Seasonal & Pandemic Influenza 2007
Re-infection with a Lethal H5N1 Dose

Infect with 100 EID$_{50}$ A/VN/1203/04

Day 0  Day 1  Day 2  Day 3  Day 4  Day 5  Day 6

24 hours Delay

25 mg/kg/d Oseltamivir 2x daily for 5 days

Re-infection with 100 EID$_{50}$ A/VN/1203/04

All animals survived lethal challenge

Day 21

HI titers 1:20-1:40

Elena A. Govorkova, St Jude Children’s Research Hospital
Presented at: Seasonal & Pandemic Influenza 2007
Antivirals
The Way Ahead?

- **Parenteral Zanomivir:**
  - IV Q12 hrs, t1/2 1.8 hrs
  - Protective when administered 4 hours prior to infection
- **Peramivir**
  - Phase II trials
  - IV and IM
  - Good but not complete protection in ferret and mouse models with Vietnam 1203 challenge
  - Easier to make and easier to achieve higher blood levels
WHO Clinical Recommendations March 07

- Tamiflu
  - Treatment warranted even with late presentation
  - Higher dose & combination therapy with amantadine considered on a case by case basis
  - NO corticosteroids unless septic shock with suspected adrenal insufficiency
  - NO antibiotic prophylaxis
  - Lung protective mechanical ventilation strategies
DoD Antivirals

- Antiviral Guidelines & Release Policy
  - Oseltamivir
    - 3 Million treatment courses ÷ 3 Depots
    - MTF 470,000 treatment courses
  - Zanamivir
    - 242,000 treatment courses
  - Use guidelines based on variable pandemic severity and supply
DoD Antiviral Guidance

- Establishes local use and release for MTF stockpiles
- Primary Stockpile release remains at ASD(HA) level
- Treatment is primary use with limited, targeted prophylaxis
  - Depending on effectiveness of nonpharmacologic measures expanded prophylaxis is an option
    - Post exposure
    - Outbreak/operational
- Uses CDC’s Pandemic Severity Index for disease severity metrics and reinforces Community Mitigation Guidelines for case rate reduction and greater antiviral flexibility
Vaccine
Ferrets and Vaccine

- Unadjuvanted vaccine HI data suggest poor cross protection between clades and subclades
- Ferrets given Clade 1 vaccine have cross protection against Clade 2 challenges
  - Survival endpoint
  - Indo 5/05 challenge
Ferrets and Adjuvanted Vaccine

- Clade 1 vaccine – Clade 1 challenge
  - Poor immunogenicity without adjuvant
  - HI titer > 40 with 3.8ug dose of adjuvanted vaccine
  - 90% protective @ 2.9ug
- Heterologous challenge (Indo 5/05)
  - Clade 1 vaccine 3.8ug
    - Neutralization inhibition with Clade 2 challenge 77% vs. 83% with homologous challenge
    - All controls died
    - 1/6 died @ 1.7ug dose all other 100% survival (3.8, 7.5, 15)
    - CD4 T cell response following Clade 1 vaccine and Clade 2 challenge: 4 fold increased response
Clade 3 Vaccine Primer for Clade 1 Challenge (Human)

- "Revaccination Study" n=37 who received 2 doses of a Clade 3 H5 Vaccine in 1998-9 were given a single 90ug dose of Vietnam 1203 Clade 1 vaccine
- Antibody responses in primed subjects compared to H5 vaccine naïve subjects
  - Exceeded those who were unprimed
  - Exceeded those in original 1989-9 study
  - Exceeded those who received two 90ug doses without prime
  - Responses may be due to generation of long-lived memory CD4 cell and/or memory B cells
  - ? Similar effect with Clade 1 primer and Clade 2 boost???

Ali Gogi, N. IDSA 2006
Pre-Pandemic Vaccine

- **VRBPAC**
  - Recommended FDA approval of Clade 1 Vietnam 1203/04 vaccine
  - FDA approved in April 07

- **DoD**
  - 1.6M doses
  - Draft Pre-pandemic vaccine policy
    - Includes storage and distribution requirement, AE tracking mechanisms, immunogenicity monitoring
• Offer to lab personnel who have direct contact with High Path H5N1
• MILVAX/Service to track administration
• MILVAX/VHC to monitor for AE
• GEIS to coordinate immunogenicity studies
• With impending pandemic JS/NORTHCOM to designate prioritization based on risk, critical role and ability to receive two doses.
2006-7 Pre-pandemic Vaccine Production

• HHS awarded total of $199M for Clade 2 vaccine (Indo 5/05)
  – $117.9M Sanofi Pasteur 3.7M doses (90ug)
  – $40.95M Novartis 800K doses (90ug)
  – $40.6M GSK 800K doses (90ug)
  – Actual number of doses yet to be determined pending reagent development & production yield

• Distribution allocation recommendations being developed by interagency work group for pandemic and pre-pandemic vaccine prioritization

• DOD to pursue acquisition of pre-pandemic vaccine to vaccinate 1.3M personnel as required in the National Pandemic Implementation Plan
Response Goals

Graph shows cases compared to days since first case.

- No intervention
- Slow Pandemic
- Slow and reduce spread
TLC Interventions

• Voluntary Isolation & Quarantine
• Infection Control Measures
• Social Distancing
  – School closure
  – Reduce adult social contact
• All included in DoD CPG (community mitigation strategies)
  – Uses Pandemic categories as triggers
  – TLC to be employed EARLY by installations
Mathematical Models Predict a Reduction in Attack Rate When Multiple Community Mitigation Interventions are Used*

*Based on multiple mathematical models that included various assumptions of compliance (30%, 60%, 90%) and the percentage of ill individuals and household contacts identified and treated with antiviral medications (60%, 80%).

Attack Rate is the proportion of an exposed population at risk who either become infected or develop clinical illness during the epidemic period.

A combination of interventions, even with poor compliance, may reduce the attack rate.

Sensitivity analyses point to school closure, workplace and generic social distancing as significant components.

Removing one source of transmission may make other sources relatively more important.

When schools are closed, the primary source of transmission shifts to the home.

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**Graph Details:**

- **Imperial College (Imp)**
- **University of Washington (UW)**
- **Virginia Bioinformatics Institute (VBI)**

<table>
<thead>
<tr>
<th>R₀</th>
<th>Imp</th>
<th>UW</th>
<th>VBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.9</td>
<td>3.40</td>
<td>4.30</td>
<td>4.20</td>
</tr>
<tr>
<td>2.1</td>
<td>2.80</td>
<td>4.00</td>
<td>4.40</td>
</tr>
</tbody>
</table>
Pandemic Influenza Illness Rates With and Without TLC Interventions
Source: MIDAS (Imperial College- Ferguson et al.)

*All identified cases isolated, full school closure, 50% adult social contact reduction
30% compliance HH Quarantine, 60% case identification,
NPI=Nonpharmaceutical intervention
Rx= antiviral treatment, Px= antiviral prophylaxis for household (HH) contacts
Effect of Public Health Measures on 1918 Pandemic (Bootsma & Ferguson PNAS 6 April 2007)

• Unlike Europe in 1918 U.S. employed Public Health measures
• City specific per-capita mortality was correlated with how early interventions were introduced
• Modeling reproduced the observed epidemic patterns
  – Time limited interventions reduced mortality by 10-30%
  – Cities with the most effective interventions reduced rates by up to 30-50%
Public Health Interventions and Epidemic Intensity During the 1918 Pandemic (Hatchett, Mecher & Lipstich, PNAS Apr 06)

- Used data on the timing of 19 classes of NPI in 17 cities during the 1918 pandemic
- Cities that implemented multiple interventions at an early phase had peak death rates ~ 50% lower than those that did not
- Also had a trend toward lower cumulative excess mortality ~ 20%
- Few cities maintained NPI > 6 weeks
Pandemic Severity Index

- Community mitigation trigger points based on severity index
- Based on hurricane categories
- Range 1-5
- Category 1 similar to seasonal influenza
- Category 5 mild version is 1918 type
- Interventions vary with pandemic severity
Pandemic Severity Index

Case Fatality Ratio

- >2.0%: Category 5
- 1.0 - <2.0%: Category 4
- 0.5 - <1.0%: Category 3
- 0.1% - <0.5%: Category 2
- <0.1%: Category 1

Projected Number of Deaths

- >1,800,000: Category 5
- 900,000 - <1,800,000: Category 4
- 450,000 - <900,000: Category 3
- 90,000 - <450,000: Category 2
- <90,000: Category 1

* Assumes 30% Illness Rate
## Strategies by Severity Index

<table>
<thead>
<tr>
<th>Interventions* by Setting</th>
<th>Pandemic Severity Index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Home</strong></td>
<td></td>
</tr>
<tr>
<td>Voluntary isolation of ill at home (adults and children), combine with use of antiviral treatment as available and indicated</td>
<td>Recommend††</td>
</tr>
<tr>
<td>Voluntary quarantine of household members in homes with ill persons †† (adults and children), consider combining with antiviral prophylaxis if effective, feasible, and quantities sufficient</td>
<td>Generally not recommended</td>
</tr>
<tr>
<td><strong>School</strong></td>
<td></td>
</tr>
<tr>
<td>Child social distancing</td>
<td></td>
</tr>
<tr>
<td>- dismissal of students from schools and school based activities, and closure of child care programs</td>
<td>Generally not recommended</td>
</tr>
<tr>
<td>- reduce out-of school social contacts and community mixing</td>
<td>Generally not recommended</td>
</tr>
<tr>
<td><strong>Workplace / Community</strong></td>
<td></td>
</tr>
<tr>
<td>Adult social distancing</td>
<td></td>
</tr>
<tr>
<td>- decrease number of social contacts (e.g., encourage teleconferences, alternatives to face-to-face meetings)</td>
<td>Generally not recommended</td>
</tr>
<tr>
<td>- increase distance between persons (e.g., reduce density in public transit, workplace)</td>
<td>Generally not recommended</td>
</tr>
<tr>
<td>- modify, postpone, or cancel selected public gatherings to promote social distance (e.g., stadium events, theater performances)</td>
<td>Generally not recommended</td>
</tr>
<tr>
<td>- modify workplace schedules and practices (e.g., telework, staggered shifts)</td>
<td>Generally not recommended</td>
</tr>
</tbody>
</table>
## Triggers

<table>
<thead>
<tr>
<th>Pandemic Severity Index</th>
<th>WHO Phase 6, U.S. Government Stage 3*</th>
<th>WHO Phase 6, U.S. Government Stage 4 and First human case in United States</th>
<th>WHO Phase 6, U.S. Government Stage 5 and First laboratory-confirmed cluster in State or region¶</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td>Alert</td>
<td>Standby</td>
<td>Activate</td>
</tr>
<tr>
<td><strong>2 and 3</strong></td>
<td>Alert</td>
<td>Standby</td>
<td>Activate</td>
</tr>
<tr>
<td><strong>4 and 5</strong></td>
<td>Standby**</td>
<td>Standby/Activate ††</td>
<td>Activate</td>
</tr>
</tbody>
</table>
Traders at Onipanu poultry market in Lagos, February 2007 (AFP)
## Surveillance

<table>
<thead>
<tr>
<th>Capability</th>
<th>FY 05</th>
<th>FY 06</th>
<th>FY 07</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total # Countries in Network</td>
<td>30</td>
<td>56</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>S America, Africa, Mid East, SE Asia</td>
</tr>
<tr>
<td>Sampling Capacity # specimens/year</td>
<td>~9000</td>
<td>~16000</td>
<td>~18000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increased surge capacity and analytical capability</td>
</tr>
<tr>
<td># BSL 3 labs</td>
<td>3</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>USAMRIID, LRMC, AFRIMS, NHRC</td>
</tr>
<tr>
<td>Data Integration</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td></td>
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<td></td>
<td>Coord Center 24/7</td>
</tr>
</tbody>
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Communication

• Health Affairs pandemic flu watchboard now evolved into DoD Pandemic flu site
• Easier URL www.dod.mil/pandemicflu
• Content expanded to include non-medical guidance
  – MARFORPAC, NORTHCOM, PACOM, DoD Education Activity, Civilian Personnel Management Service
Questions