Avian Influenza: The Next Human Pandemic?

Brian L. Hoffman, PhD
17 November 2005

Figures updated to 07 December 2005
Program

- Influenza – Disease and Virus
- Epidemic and Pandemic Influenza
- Notable Human Pandemics
- Avian Influenza in Birds
- Avian Influenza in Humans
- The Future
Some Language

- **Endemic** – sporadic incidence of disease - yearlong incidence at roughly same rate
- **Epidemic** – widespread incidence of disease, generally within a country or continental area.
  - Influenza season in US, Europe and Asia – October – May
- **Pandemic** – widespread incidence of disease caused by new or novel pathogen; crossing national and continental boundaries – worldwide; often with excessive mortality
Influenza – The Disease

- Humans – respiratory infection
  - Digestive tract and blood infection other animals
- Transmission – droplets from infected person
- Incubation period – 1-5 days postinfection
- Communicability – 1 to 2 days before symptom onset; 4-5 days after
Influenza – Disease Symptoms

- Rapid onset
- Chills
- Fever
- Nonproductive cough
- Body aches
- Runny nose
- Headache
- Lasts about 7 days
Influenza Impact - US

- 36,000 deaths per year
- 200,000 hospitalizations

- Target populations
  - Infants
  - Pregnant women
  - Immunocompromised
  - 65 yrs +
  - Nursing home residents
Influenza

- Infectious agent – RNA virus
  - Segmented genome – 8 segments
- Three serotypes – Influenza A, B, C
  - Influenza A – epidemic and pandemic flu
  - Influenza B – epidemic flu; primarily in children
  - Influenza C – no disease state associated
- Portal of entry – respiratory tract, conjunctiva via direct contact
Influenza II

- Target systems – respiratory, digestive, blood, conjunctiva (rare)
- Portal of exit – respiratory droplets, blood, feces
Virus Replication Cycle

- Attachment – virus sticks to cell
- Penetration – virus enters cell
- Uncoating – genome unpackaged
- Biosynthesis – genome read, proteins made
- Replication – genome copied
- Maturation – genome and proteins processed
- Assembly – genome and proteins put together
- Exit – release from cell
Virus Life Cycle

Influenza A Virus Replication
Important Parts – Virulence Factors

- Hemagglutinin (H) – virus attachment
  - 16 subtypes (H1 – H16) – H1, H2, H3 typical in humans

- Neuraminidase (N) – virus release and passage through mucous membranes
  - 9 Subtypes (N1 – N9) – N1 and N2 typical in humans

- H and N genes are located on different RNA segments

Virulence Factors

Hemagglutinin and Neuraminidase on outside of virus particle

Association with target cells and target cell membranes

Yasuo Suzuki (Department of Biochemistry, University of Shizuoka School of Pharmaceutical Sciences)
Epidemic Flu

- Caused by antigenic drift
  - Mutations occur in RNA as virus is passed from host to host
  - HA and NA proteins changed slightly in sequence
  - Same subtype H1N1 → H1N1
  - Some antibodies to previous HA and NA proteins no longer recognize mutated version
    - Breaks down host immunity to influenza virus allowing reinfection of individual
    - Some antibodies exist that still recognize influenza virus – dulling intensity of disease symptoms in otherwise healthy individuals
Antigenic Drift

Human Influenza H3N2
Pandemic Flu

- Host individual (birds, humans and/or swine in human disease) infected with two different strains of influenza A simultaneously
- Viral RNA recombined into unique virus
- Different subtypes
  - H1N1 + H2N3 $\rightarrow$ H2N1
Antigenic Shift

H1N1
# Influenza Strains from Previous Pandemics

<table>
<thead>
<tr>
<th>Pandemic Year</th>
<th>Strain</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1889</td>
<td>H2N2</td>
<td></td>
</tr>
<tr>
<td>1900</td>
<td>H3N8</td>
<td></td>
</tr>
<tr>
<td>1918 – “Spanish Flu”</td>
<td>H1N1</td>
<td>500,000+ US 20+ million world</td>
</tr>
<tr>
<td>1957 – “Asian Flu”</td>
<td>H2N2</td>
<td>70,000+ US 1-4 million world</td>
</tr>
<tr>
<td>1968 – “Hong Kong Flu”</td>
<td>H3N2</td>
<td>34,000+ US ~2 million world</td>
</tr>
</tbody>
</table>
Origin of Current Human Influenza A Viruses

Worldwide Spread in 6 Months
Spread of H2N2 Influenza in 1957
“Asian Flu” CDC

Feb-Mar 1957
Apr-May 1957
Jun-Jul-Aug 1957
The Problem with Pandemics

- New viral subtype often causes different symptoms than the previous dominant subtype
- With little to no immunity against the virus, the majority of humans become infected
- Worldwide spread occurs quickly
- Pandemics occur in waves
- 2 million – 7.4 million deaths expected
1918 Pandemic - USA
FIG. 1. Photomicrographs of hematoxylin-and-eosin-stained lung sections of mice inoculated with New Caledonia, WSN, and 1918 recombinant influenza viruses at 72 h postinoculation. (A) Normal morphology observed in mock-infected murine lung. (B) Moderately severe purulent bronchitis with epithelial necrosis and moderate lymphocytic peribronchitis after infection with New Caledonia recombinant virus. (C) Moderate necrotizing bronchitis with moderate histiocytic alveolitis and edema after infection with WSN virus. (D) Moderate necrotizing bronchitis with severe histiocytic alveolitis after infection with 1918 HA/NA:WSN recombinant virus.

Kash et. al. (2004). J. Virology 78: 9499-9511
Phases in Progression toward a Pandemic - WHO

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interpandemic phase</td>
<td>Low risk of human cases</td>
<td>1</td>
</tr>
<tr>
<td>New virus in animals, no human cases</td>
<td>Higher risk of human cases</td>
<td>2</td>
</tr>
<tr>
<td>Pandemic alert</td>
<td>No or limited human-human transmission</td>
<td>3</td>
</tr>
<tr>
<td>New virus causes human cases</td>
<td>Evidence of increased human-human transmission</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Evidence of significant human-human transmission</td>
<td>5</td>
</tr>
<tr>
<td>Pandemic</td>
<td>Efficient and sustained human-human transmission</td>
<td>6</td>
</tr>
</tbody>
</table>
Avian influenza H5N1

Photo: C. Goldsmith, CDC
Avian Influenza – Disease in Birds

- Natural reservoirs – wild waterfowl, gulls, shorebirds
  - Usually asymptomatic, especially ducks
  - Migratory – carry virus long distances
- Fowl plague – Domestic poultry
  - Disease state ranges from asymptomatic to "chicken Ebola" (massive hemorrhage and near 100% mortality within 48 hrs of infection)
Avian Influenza – Virus Strains

- Since 1959:
  - 14 outbreaks of type H7 avian influenza A
  - 11 outbreaks of type H5 avian influenza A
- H5 and H7 strains may cause high mortality in domestic birds
- Virus may be shed for more than 10 days in feces and respiratory droplets
- Outbreaks often centered around water sources
2003-2004 Avian Influenza Outbreak in Vietnam

Source: http://www.who.int/mediacentre/events/2005/05_Vietnam_Bui_Ba_Bong_L.pdf
Avian H5N1 Infections

Outbreaks of Avian influenza (type H5)
(as of 10 November 2005)

- Cambodia: 15
- Croatia: 60
- Hong Kong (SARPRC): 2
- Indonesia: 4
- Japan: 216
- Kazakhstan: 10
- Korea (Rep. of): 1
- Laos: 19
- Malaysia: 1
- Mongolia: 10
- Romania: 2
- Russia: 4
- Thailand: 51
- Turkey: 1
- Vietnam: 1,838
Southeast Asia Outbreaks – 2003-2004

- Republic of Korea (12 December 2003 – first outbreak of this disease ever reported)
- Viet Nam (8 January 2004 – first outbreak of this disease ever reported)
- Japan (12 January 2004 – first outbreak of this disease since 1925)
- Thailand (23 January 2004 – first outbreak of this disease ever reported)
- Cambodia (24 January 2004)
- China (27 January 2004)
- Laos (27 January 2004 – H5 confirmed, testing for H5N1 under way)
- Indonesia (2 February 2004 – first outbreak of this disease ever reported)
- Malaysia (17 August 2004) – first outbreak of this disease ever reported
Avian Influenza outbreak spreads towards Europe 2005

- Russia (23 July 2005)
- Kazakhstan (02 August 2005)
- Mongolia (12 August 2005)
- Turkey (13 October 2005)
- Romania (15 October 2005)
- Croatia (26 October 2005)
- Kuwait (11 November 2005 – one flamingo)
- Ukraine (03 December 2005)
H5N1 Avian Outbreaks Asia 2003-2004 and 2005
H5N1 Avian Outbreaks Europe
July-December 2005
Control of Avian Influenza

- Isolation of domestic poultry from wild or feral waterfowl, gulls and shorebirds
- Rapid culling of sick or exposed birds
- Proper disposal of carcasses
- Protection of workers – boot covers, gloves, disposable suits, masks, eye protection
- Disinfection of farms
- Restriction of movement of live poultry
- Vaccination of domestic flocks
## Avian Influenza – Infections in Humans Before 2003

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Strain</th>
<th>Cases</th>
<th>Deaths</th>
<th>Symptoms</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1959</td>
<td>USA</td>
<td>H7N7</td>
<td>1</td>
<td>0</td>
<td>Respiratory</td>
<td>Travel</td>
</tr>
<tr>
<td>1995</td>
<td>UK</td>
<td>H7N7</td>
<td>1</td>
<td>0</td>
<td>Conjunctivitis</td>
<td>Pet ducks</td>
</tr>
<tr>
<td>1997</td>
<td>Hong Kong SAR</td>
<td>H5N1</td>
<td>18</td>
<td>6</td>
<td>Respiratory</td>
<td>Poultry</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Conjunctivitis</td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>China</td>
<td>H9N2</td>
<td>5</td>
<td>0</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>1999</td>
<td>Hong Kong SAR</td>
<td>H9N2</td>
<td>2</td>
<td>1</td>
<td>Respiratory</td>
<td>Poultry</td>
</tr>
</tbody>
</table>
## Avian Influenza – Human Infections 2003

<table>
<thead>
<tr>
<th>Country</th>
<th>First Case confirmed</th>
<th>Cases</th>
<th>Deaths</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong Kong SAR</td>
<td>H5N1</td>
<td>2</td>
<td>1</td>
<td>Respiratory</td>
</tr>
<tr>
<td>Netherlands</td>
<td>H7N7</td>
<td>89</td>
<td>1</td>
<td>Conjunctivitis Respiratory (death)</td>
</tr>
<tr>
<td>Hong Kong SAR</td>
<td>H9N2</td>
<td>1</td>
<td>0</td>
<td>Respiratory</td>
</tr>
</tbody>
</table>
## Avian Influenza – Human non-H5N1 cases in 2004-2005

<table>
<thead>
<tr>
<th>Country</th>
<th>Cases</th>
<th>Deaths</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada H7N?</td>
<td>2</td>
<td>0</td>
<td>Conjunctivitis</td>
</tr>
</tbody>
</table>
## Human H5N1 infections reported since January 2004

<table>
<thead>
<tr>
<th>Country</th>
<th>First case confirmed</th>
<th>Cases</th>
<th>Deaths</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viet Nam</td>
<td>January 2004</td>
<td>93</td>
<td>42</td>
<td>Respiratory</td>
</tr>
<tr>
<td>Thailand</td>
<td>January 2004</td>
<td>21</td>
<td>13</td>
<td>Respiratory</td>
</tr>
<tr>
<td>Cambodia</td>
<td>February 2005</td>
<td>4</td>
<td>4</td>
<td>Respiratory</td>
</tr>
<tr>
<td>Indonesia</td>
<td>July 2005</td>
<td>13</td>
<td>8</td>
<td>Respiratory</td>
</tr>
<tr>
<td>Peoples Republic of China</td>
<td>November 2005</td>
<td>4</td>
<td>2</td>
<td>Respiratory</td>
</tr>
</tbody>
</table>
Human H5N1 Infections since 2004
Why so much influenza in Asia?

- Most poultry kept in backyard farms – hard to isolate from wild/feral birds
- Many types of animals that can be infected with influenza kept in close proximity
- Lack of sterile technique in working with bird waste, diseased carcasses, butchered birds
- Live animals transported across countryside
Why so much influenza in Asia?

- Poor health status of individuals
- Cramped living quarters
- Inadequate sanitation
- Lack of education about influenza
- Lack of appropriate health care
- Consumption of undercooked meats, eggs, and blood products
Avian Influenza is not pandemic influenza

- Currently, human disease caused by avian influenza A H5N1 does not satisfy the criterion for a pandemic
  - Not widespread (human cases confined to Southeast Asia)
  - Not easily transmitted from human to human
Why the Concern?

- H5N1 viruses passed directly from birds to humans (first instance in 1997)
- H5N1 viruses in circulation have 5 of 10 virulence genes detected in 1918 Spanish Flu virus
- Difficult to contain – migratory birds
- Difficult to detect – most wild birds asymptomatic
- Human cases coincide with outbreaks in poultry
- H5N1 now endemic in most countries in which it has appeared
- Recombination with human influenza A virus can create a virulent strain passing easily between humans
Where are we?

- Phase 3: New virus causes human cases, no evidence of human-human contact
- While a pandemic is not eminent, it looks to be in the future
- More avian influenza outbreaks occurring than at any other time in recorded medical history
- Mortality increased in human H5N1 infections compared to other avian influenza strains
How can we avert a pandemic or dull its effects?

- Control animal reservoir
- Vaccinations - monovalent
  - Viet Nam may test a vaccine against H5N1 in 2006 (pending approval of Ministry of Health)
  - Vaccinations exist for poultry
  - First line of defense – reduce number of susceptibles
- Antivirals
  - Neuraminidase inhibitors such as Tamiflu and Relenza promise to be effective
  - As prophylaxis must be taken long term, until the wave of infection is over
  - As treatment, it will have to be taken within a couple of days of symptom onset
How can we avert a pandemic or dull its effects?

- Quarantine or cohort infected patients
- Defer/restrict travel to infected areas
- Health care workers take precautions against respiratory droplets
- Wash hands and public surfaces often
- Close schools, daycares if outbreak occurs
- Mask infected individuals
The Ultimate Conclusion

Pandemic Flu

Not If

But When

Natural History of the Virus
“The pandemic clock is ticking, we just don’t know what time it is”

E. Marcuse