Lecture 7: Influenza
The Plague of Athens (may have been the flu)

• The Plague of Athens - early years of the Peloponnesian War
  – First outbreak summer of 430-429BC - lasted two years
  – Second outbreak winter of 426 - lasted no less than a year

• Athens was under siege by Sparta
  – Crowding took place
  – Perfect conditions for a virus to run rampant

• The “Golden Age” of Greece ended

• Account of Thucydides is the only record
  – Medical historians and epidemiologists love reconstructing what it might have been: anthrax, ebola, flu, plague, tularemia, typhoid, leptospirosis
  – Most ideas include the zoonotic route, since it was a documented epizootic as well as human epidemic
What is the ‘flu?’

- Influenza (the flu) is a contagious respiratory illness caused by influenza viruses. It can cause mild to severe illness, and at times can lead to death.

- Seasonal influenza epidemics are annually responsible for between 3 million and 5 million cases of severe illness and between 250,000 and 500,000 deaths worldwide*

- Older people, young children, and people with certain health conditions, are at high risk for serious flu complications.

Source: CDC [http://www.cdc.gov/flu/about/disease/index.htm](http://www.cdc.gov/flu/about/disease/index.htm)

What is the ‘flu? 

Every year in the United States:

• on average 5% to 20% of the population gets the flu

• > 200,000 people are hospitalized from flu complications

• About 36,000 people die from flu

Source: CDC http://www.cdc.gov/flu/about/disease/index.htm
What is the ‘flu?

- **Symptoms** of flu include:
  - fever (usually high)
  - headache
  - extreme tiredness
  - dry cough
  - sore throat
  - runny or stuffy nose
  - muscle aches
  - Stomach symptoms, such as nausea, vomiting, and diarrhea - more common in children than adults

Source: CDC
What is the ‘flu?  

**Complications** of flu can include:

- bacterial pneumonia
- ear infections
- sinus infections
- dehydration
- worsening of chronic medical conditions, such as congestive heart failure, asthma, or diabetes.

Source: CDC
Flu Spread

Flu viruses spread mainly from person to person through coughing or sneezing of people with influenza.

Sometimes people may become infected by touching something with flu viruses on it and then touching their mouth or nose.

Most healthy adults may be able to infect others beginning 1 day before symptoms develop and up to 5 days after becoming sick.
Influenza – the ABCs of flu viruses

• Influenzavirus A, B and C are genera of the Orthomyxoviridae

• Influenza A, B and C viruses are distinguished on the basis of their internal nucleoprotein and matrix proteins which are specific for each viral type

• Influenza A viruses (only one species) are naturally able to infect a range of animal species, including humans, swine, birds, seals and horses.

Source: CDC
Influenza – the ABCs of flu viruses

- Influenza B viruses infect only humans

- Influenza C virus infects humans and swine.

- A and B cause seasonal epidemics in the US almost every year

- C is mild and doesn’t really catch on

Source: CDC
The U.S. Flu report (as of April 5th)

Although influenza A (H1N1) viruses predominated through mid-January, as the season progressed, an increasing proportion of subtyped influenza A viruses were influenza A (H3N2) viruses.

Influenza A (H3N2) viruses are now the predominant virus for the 2007-08 season, however, in recent weeks, an increasing proportion of the viruses studied have been influenza B viruses.

Source: CDC
• Strains of all subtypes of influenza A virus have been isolated from wild birds, although disease is uncommon.

• Some isolates of influenza A virus cause severe disease both in domestic poultry and, rarely, in humans.

• Occasionally viruses are transmitted from wild aquatic birds to domestic poultry
  – may cause an outbreak or give rise to human influenza pandemics.

• Influenza A viruses are further categorized into subtypes that are determined by the antigenicity of the surface glycoproteins, the hemagglutinin (H) and neuraminidase (N).

• Get their names from these – e.g. H1N1
Where the H’s are, normally

<table>
<thead>
<tr>
<th>Humans</th>
<th>Domestic swine</th>
<th>Water mammals</th>
<th>Migratory water birds</th>
<th>Domestic birds</th>
<th>Farm animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Where the N’s are, normally

<table>
<thead>
<tr>
<th>Distribution of Neuraminidases in Nature</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
</tr>
<tr>
<td>N2</td>
</tr>
<tr>
<td>N3</td>
</tr>
<tr>
<td>N4</td>
</tr>
<tr>
<td>N5</td>
</tr>
<tr>
<td>N6</td>
</tr>
<tr>
<td>N7</td>
</tr>
<tr>
<td>N8</td>
</tr>
<tr>
<td>N9</td>
</tr>
</tbody>
</table>
Gimme an A!

- Historically, influenza A human infections have been caused by three subtypes of hemagglutinin (H1, H2 and H3) and two neuraminidase subtypes (N1 and N2).

- More recently human infections by previously avian-only subtypes H5, H7 and H9 have been reported.

- A total of 16 distinct hemagglutinin and 9 neuraminidase influenza A subtypes have been identified - all prevalent in birds.
  - Swine and horses, like humans, are limited to a much narrower range of subtypes.
A bit of virology

- **Antigenic drift:**
  - The hemagglutinin (H) and neuraminidase (N) proteins mutate (point mutations in the amino acids) without affecting viral replication
  - Small changes allow evasion of the immune response – the antibody response can be escaped and infection can occur
  - Monitoring the antigens in strains around the world enables vaccine production
  - Drift is thus ‘okay’ for the pharmaceutical industry!
A bit of virology

• Antigenic shift:
  – A sudden change in the antigens, presenting a novel flu to a naïve population
  – The cause of pandemic strains
  – Several ways they can arise
  – Not good for vaccines – unanticipated

Workers inspecting hens (and pigs), Vietnam
A bit of virology – Antigenic shift

• Co-infection of a single host, such as swine (implicated in 1957 and 1968 pandemics)
  – Simple segmented RNA allows for big “swaps” and reassortment

• Straight jump
  – Animal host flu has a mutation that enables human infection (1918 pandemic from avian strain)
Generation of a Pandemic Influenza Strain

Avian virus → Avian reassortant virus → Human virus → Reassortment in humans → Avian-human pandemic reassortant virus

Reassortment in swine

Source: CDC | Influenza Division, Centers for Disease Control and Prevention. Modified from Emergence of H5N1 influenza virus and control options. (Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 12, No. 1, January 2006)
Avian Influenza – old and always new

• The ancestor of human and classic swine viruses is a virus that contained genes from avian sources.

• Avian influenza was first identified in Italy in 1878, and was initially known as the fowl plague.

• Avian influenza can be traced to five host-specific virus groups: ancient equine, recent equine, gull, swine, and human.

• Avian influenza viruses in their natural reservoirs have reached their 'optimum' – they haven’t evolved new amino acids for an estimated 60 years, unlike the human and swine versions
Avian Influenza

• An infection in birds caused by avian strains of influenza A

• Representatives of each of the known subtypes of influenza A have been isolated from aquatic birds worldwide, in both wild and domesticated species.

• The natural reservoir of the virus is wild water birds in which the infection is generally avirulent, such “low pathogenic avian influenza virus” (LPAIV) strains causing little, or no, evident symptoms.

• LPAIV strains may be readily transmitted to poultry species (chickens, turkeys) which are more susceptible to infection – mild clinical symptoms may result, for example ruffled feathers and a drop in egg production.
Avian Influenza

- The mode of transmission from aquatic to domesticated birds may be through direct physical contact of the animals, or through contact with surfaces, water or feed that have been contaminated with the virus.

- The majority of LPAIV strains replicate in the lungs and the cells lining the intestinal tract of aquatic birds with high titers of virus excreted with feces into the water leading to the continuation of an oral-fecal cycle of transmission.

- Virus may also be excreted in the animal’s saliva and nasal secretions.

- Lakes and overwintering locations for waterfowl may serve as viral “mixing bowls”
  - Birds that migrate longitudinally seem to be key in transmission
  - Birds that migrate latitudinally (Eurasia to America) appear not to be

- Avian influenza has been responsible for outbreaks in seals, whales, pigs and poultry
Influenza in History

- Historical patterns indicate that an average of three to four influenza pandemics occur each century.

- In the nineteenth century, three major pandemics took place, mostly around Europe: in 1830-33, 1847, and the Russian Flu in 1889-90

- In the twentieth century, pandemics have occurred three times: in 1918-19, 1957-58, and in 1968-69

- Ten pandemics have taken place in the past 300 years; the last pandemic was the Hong Kong Flu in 1968.
# Influenza A Dynasties

<table>
<thead>
<tr>
<th>Era</th>
<th>Origin</th>
<th>Virus Subtype</th>
<th>Mode of Antigenic Shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source: The Monster at Our Door Mike Davis, 2005*</td>
<td>Source: The Monster at Our Door Mike Davis, 2005*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1890s</td>
<td>Guangdong</td>
<td>H2N2</td>
<td>Not known</td>
</tr>
<tr>
<td>1900s</td>
<td>Not known</td>
<td>H3N8</td>
<td>Not known</td>
</tr>
<tr>
<td>1918-1957</td>
<td>Kansas, France, or China</td>
<td>H1N1</td>
<td>Species jump or recombination</td>
</tr>
<tr>
<td>1957-1968</td>
<td>Yunnan</td>
<td>H2N2</td>
<td>Reassortment (pig?)</td>
</tr>
<tr>
<td>1968-Present</td>
<td>Guangdong</td>
<td>H3N2</td>
<td>Reassortment (pig?)</td>
</tr>
<tr>
<td>1977-Present</td>
<td>China or Russia</td>
<td>H1N1</td>
<td>Reintroduction from cryptic reservoir</td>
</tr>
<tr>
<td>1997</td>
<td>Guangdong</td>
<td>H5N1</td>
<td>Species jump</td>
</tr>
</tbody>
</table>

*someone should really review this book*
Coughs and Sneezes Spread Diseases

As Dangerous as Poison Gas Shells

SPREAD OF SPANISH INFLUENZA MENCES OUR WAR PRODUCTION

U.S. Public Health Service Begins Nation-wide Health Campaign.

A warning posted in a 1918 issue of the New York Times
(dmla.clan.lib.nv.us)
INFLUENZA
FREQUENTLY COMPlicated WITH
PNEUMONIA
IS PREVALENT AT THIS TIME THROUGHOUT AMERICA.
THIS THEATRE IS CO-OPERATING WITH THE DEPARTMENT OF HEALTH.
YOU MUST DO THE SAME
IF YOU HAVE A COLD AND ARE COUGHING AND
SNEEZING. DO NOT ENTER THIS THEATRE
GO HOME AND GO TO BED UNTIL YOU ARE WELL

Coughing, Sneezing or Spitting Will Not Be Permitted In The Theatre. In case you must cough or sneeze, do so in your own handkerchief, and if the Coughing or Sneezing Persists Leave The Theatre At Once.

This Theatre has agreed to co-operate with the Department Of Health in disseminating the truth about Influenza, and thus serve a great educational purpose.

HELP US TO KEEP CHICAGO THE
HEALTHIEST CITY IN THE WORLD

JOHN DILL ROBERTSON
COMMISSIONER OF HEALTH
“Spanish Flu” – Influenza A(H1N1) 1918-1919

Approximately 20-40 million people died worldwide, and over 500,000 in US.

Source: National Museum of Health and Medicine

Copyright 2006, The Johns Hopkins University and Rashid Chotani.
U.S. life expectancy 1900-1960

Copyright 2006, The Johns Hopkins University and Rashid Chotani.
“Asian Flu” A(H2N2) 1957-58

• More than a million people died worldwide
• About 70,000 in the US
• Genetic re-assortment in pigs is believed to have been the cause of the 1957 and 1968 pandemics.
Spread of “Asian Influenza” (H2N2), 1957

- February – March 1957
- April – May 1957
- June – August 1957

Copyright 2006, The Johns Hopkins University and Rashid Chotani.
Hong Kong Flu A(H3N2), 1968-9

- The 1968 pandemic arose when the H3 hemagglutinin gene and one other internal gene from an avian donor reassorted with the N2 neuraminidase and five other genes from the H2N2 human strain that had been in circulation.
- Killed more than a million people worldwide and 34,000 in the USA

1968: Chairman Mao ordered the Red Guard to wear facemasks to prevent flu spread

Source: National Museum of Health and Medicine
Timeline of Emergence of Influenza Viruses in Humans

1918: H1 - Spanish Influenza
1957: H2 - Hong Kong Influenza
1968: H3 - Influenza
1977: H1
1997: H5
2003/4: H5
1198/9: Avian Influenza

Source: CDC

Copyright 2006, The Johns Hopkins University and Rashid Chotani.
Real Bird Flu, in birds

• In 1983 an H5N2 influenza virus infected chickens and turkeys in Pennsylvania and became highly pathogenic for poultry. Virologic and serologic studies provided no evidence of transmission to humans.

• The virus was eventually eradicated by quarantine and extermination of more than 17 million birds at a direct cost of more than US$60 million and an indirect cost to the industry of more than US$250 million.

• A highly pathogenic H5N2 influenza virus emerged in domestic chickens in Mexico in October 1993.

• The depopulation of live bird markets and farms in the New Territories of Hong Kong (December 29, 1997) stopped the spread of H5N1 influenza viruses.
Real Bird Flu – direct delivery

Migratory water birds → Domestic birds

Source: WHO/WPRO
Real Bird Flu, in humans

- H5N1 On May 21, 1997, a 3-year-old boy from Hong Kong died in an intensive care unit in Hong Kong on the fifth day of his hospitalization, with a final diagnosis of Reye syndrome, acute influenza pneumonia, and respiratory distress syndrome
  - 18 cases in the Hong Kong area, 6 deaths
- H9N2 – Hong Kong, 1999
- H7N7 – The Netherlands, 2003
- H5N1 – Hong Kong, 2003
- H5N1 – Vietnam, 2003-2005
- Avian infection in Hong Kong
  - 18 human cases and six deaths (33%)
  - Culled poultry

- Ongoing avian H5N1 infections

- Avian infection in nine countries
  - 34 human cases and 23 deaths (68%)
  - Culled >100 m chickens

- Avian infection in four countries
  - Seven human cases and six deaths (86%)
  - Person-to-person?
2006: H5N1 Avian Flu, confirmed human cases
Cat flu?

March 7th 2006, Rome – the European Union responds to a dead cat found with H5N1 in Germany

Public pet owners in avian flu areas advised to ask their vets for advice

Is that a control measure?
Bird flu?

- “Bird Flu” is the big scare
- Avian Flu is the ancestral strain
- Can we vaccinate everyone?
- Should we manage the zoonotic end first?
- Do we have the capacity to?

This is Iowa, not Asia
Bird flu vaccine?

Normally, a flu vaccine is harvested in fertilized chicken eggs, which are then killed and split. When scientists tried to make an H5N1 vaccine, they found that the virus killed the eggs.

Leading flu researcher Robert Webster and a team of scientists used genetic engineering to solve this problem. They altered various genes in order to 'tame' the virus and accelerate its growth. This method worked, and early tests of the vaccine have shown potential.
Counting Issues on the vaccine website

- 70% of global vaccine production located in Europe (5 companies)
  - 50% of that production is exported outside of Europe

Source: EVM Press Release 30 April 2004

Source: WHO Global Influenza Program
H5 is “poorly immunogenic”
Bad for making vaccines

Antiviral treatment?
Shortens the flu
Already generating antiviral resistance
As a preventative, works about 40-70% of the time
Fantastic investment, stock-wise

Tamiflu, a neuraminidase inhibitor
Preventions?

- Wash your hands
- Wear a facemask/respirator (national shortages)
- Wear a nanomask (6 manufacturers in the US)
- Clean surfaces frequently
- Cook your chicken and eggs properly
  - Refrigeration and freezing don’t work
    - Virus transmission from runny eggs has been proven now