INFLUENZA PART I:
OF MAMMALS, BIRDS AND MEN:
HUMAN INFLUENZA AND THE ROLE OF ANIMAL DISEASE

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MICHIGAN VETERINARY CONFERENCE
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OUTLINE

• Influenza Virology- Background
• Influenza As Human Illness
• Influenza Epidemics and Pandemics
• Influenza as Zoonosis
  • Avian Influenza
  • Swine Influenza
• Novel Strains and Controversies
INFLUENZA VIROLOGY

BACKGROUND
INFLUENZA

• Highly infectious viral illness
• Epidemics reported since at least 1510
• Four pandemics in 20th century
• Estimated 40 million deaths worldwide in pandemic of 1918-1919 (Spanish Flu”)
• Virus first isolated in 1933
### INFLUENZA VIRUS TYPES

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
</table>
| Type A | • moderate to severe illness  
          • animals and humans  
          • all age groups  
          • associated with pandemics  
          • milder epidemics |
| Type B | • humans only  
          • more commonly affects children  
          • no epidemics  
          • swine influenza; rarely reported in humans |
| Type C | • mild human illness |
Influenza A Virus

16 H – hemagglutinin
9 N – neuraminidase

Only 3 typically found in humans:
- H1
- H2
- H3

A/Fujian/411/2002 (H3N2)

Virus type
Geographic origin
Strain number
Year of isolation
Virus subtype
INFLUENZA A VIRUS

Figure 1 | Schematic diagram of an influenza A virus virion. Two surface glycoproteins, haemagglutinin (HA) and neuraminidase (NA), and the M2 ion-channel protein are embedded in the viral envelope, which is derived from the host plasma membrane. The ribonucleoprotein complex comprises a viral RNA segment associated with the nucleoprotein (NP) and three polymerase proteins (PA, PB1 and PB2). The matrix (M1) protein is associated with both ribonucleoprotein and the viral envelope. A small amount of non-structural protein 2 is also present, but its location within the virion is unknown.

Taisuke Horimoto and Yoshihiro Kawaoka; Influenza: Lessons From Past Pandemics, Warnings From Current Incidents. Nature 2005;5(3) www.nature.com/reviews/micro
INFLUENZA ANTIGENIC CHANGES

- Structure of hemagglutinin (H) and neuraminidase (N) periodically change

- Shift
  - Major change, new subtype, exchange of gene segment
  - Associated with pandemics (e.g. appearance of avian influenza [H5N1] in humans)

- Drift
  - Minor changes, same subtype, point mutations in gene,

  - Associated with epidemics (appearance of Fujian and Sydney strains of H3N2)
INFLUENZA: EPIDEMICS VS. PANDEMICs

• Seasonal influenza outbreaks or “epidemics” occur every year
  • Caused by virus subtypes already circulating in humans (e.g. H3N2)
• Influenza pandemics occur when new virus appears (e.g. H5N1, H1N1)
  • Humans lack immunity to this new subtype
  • Simultaneous epidemics occur worldwide
  • Significant number of human deaths and illness
## INFLUENZA TYPE A ANTIGENIC SHIFTS

<table>
<thead>
<tr>
<th>Year</th>
<th>Subtype</th>
<th>Severity of Pandemic</th>
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</thead>
<tbody>
<tr>
<td>1889</td>
<td>H3N2</td>
<td>Moderate</td>
</tr>
<tr>
<td>1918</td>
<td>H1N1</td>
<td>Severe</td>
</tr>
<tr>
<td>1957</td>
<td>H2N2</td>
<td>Severe</td>
</tr>
<tr>
<td>1968</td>
<td>H3N2</td>
<td>Moderate</td>
</tr>
<tr>
<td>1977</td>
<td>H1N1</td>
<td>Mild</td>
</tr>
<tr>
<td>2009</td>
<td>H1N1</td>
<td>Mild</td>
</tr>
</tbody>
</table>
INFLUENZA AS HUMAN ILLNESS
<table>
<thead>
<tr>
<th>Reservoir</th>
<th>Human, animals (type A only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission</td>
<td>Respiratory, probably airborne</td>
</tr>
<tr>
<td>Temporal pattern</td>
<td>Peak in December to March in temperate areas. May occur earlier or later</td>
</tr>
<tr>
<td>Communicability</td>
<td>Maximum 1 day before to 4-5 days after onset</td>
</tr>
</tbody>
</table>
Peak Month of Influenza Activity
Over the Previous 26 Seasons
1982-83 through 2007-08

Number of Seasons

Month
November December January February March
1 4 5 12 4

SOURCE: CENTERS FOR DISEASE CONTROL AND PREVENTION
INFLUENZA CLINICAL FEATURES

• Incubation period 1-5 days
• Transmission from 1 day before clinical symptoms until 5 days after
• Respiratory transmission
• Abrupt onset of fever, myalgia, sore throat, nonproductive cough, headache
• Severity of illness depends on prior experience with antigenically related variants
• Case fatality ~0.5-1 per 1,000 cases
ANNUAL IMPACT OF INFLUENZA IN US

• 5% to 20% of general population acquires flu in a given season

• >200,000 persons are hospitalized from flu complications each year, mainly persons >65 years old

• 20,000 to 40,000 die each year from flu, mainly persons >65 years old
INFLUENZA COMPLICATIONS- HUMAN

- Bacterial pneumonia
- Severe dehydration
- Exacerbation of chronic conditions like congestive heart failure, asthma, diabetes
- Severe complications more common in those >65 years of age, chronically ill, immunocompromised, pediatric deaths less common
INFLUENZA COMPLICATIONS 2009 H1N1

• Pregnant women*
  • 1-2% of US population, however:
    • 7-10% of hospitalized patients with 2009 H1N1
    • 6-9% of ICU patients with 2009 H1N1
    • 6-10% of deaths with 2009 H1N1

• Obesity
  • Among pts. with severe or fatal cases of 2009 H1N1, rates of severe obesity 5-15x > general pop
  • As independent risk factor unknown

• 25-50% had no underlying medical conditions*

• Indigenous populations- AI/AN 4x greater mortality**

*WHO Writing Committee, Clinical Aspects of Pandemic 2009 Influenza A (H1N1), NEJM 362;18, May 2010
**MMWR, December 9, 2009 Deaths Related to 2009 Pandemic Influenza A(H1N1) Among American Indian/Alaska Natives - 12 States, 2009
INFLUENZA AS PANDEMICS
20TH CENTURY CONTROL OF INFECTIONOUS DISEASE

FIGURE 1. Crude death rate* for infectious diseases — United States, 1900-1996†

- 40 States Have Health Departments
- Influenza Pandemic
- First Continuous Municipal Use of Chlorine in Water in United States§
- Last Human-to-Human Transmission of Plague
- First Use of Penicillin
- Salk Vaccine Introduced
- Passage of Vaccination Assistance Act

*Per 100,000 population per year.
20TH CENTURY INFLUENZA PANDEMCIS

- **All 20th century pandemics exhibited HAs from avian viruses**

- **1918 – 1919, “Spanish Flu” (H1N1)**
  - Influenza A (H1N1) viruses still circulates today
  - U.S. mortality: approx. 500,000+
  - Avian genome adapted to humans- ? process ??

- **1957-58, “Asian Flu” (H2N2)**
  - Identified in China in February 1957 with spread to U.S. by June of same year
  - U.S. mortality: 69,800
  - three genes from circulating H1N1 human influenza virus were replaced by avian-like genes: HA, NA, PB1 subunit **

- **1968-69, “Hong Kong Flu” (H3N2)**
  - Influenza A H3N2 viruses still circulates today
  - First detected in Hong Kong in early 1968 and spread to US later that year
  - U.S. mortality: 33,800
  - HA and PB1 genes were replaced by avian-like genes**

*Taisuke Horimoto and Yoshihiro Kawaoka; Influenza: Lessons From Past Pandemics, Warnings From Current Incidents. Nature 2005;5(3) www.nature.com/reviews/micro

**Taubenberger and Morens. Influenza: The Once and Future Pandemic. Public Health Reports / 2010 Supplement 3 / Volume 125
Origins of Pandemic Influenzas

The Origins of Pandemic Influenza — Lessons from the 1918 Virus
The Inevitability of Pandemic Influenza

- Historical evidence: Periodicity of previous pandemics
- H5N1 has been circulating for several years with no pandemic
THE INEVITABILITY OF PANDEMIC INFLUENZA (2)

- Appearance of many different A subtypes in birds and later humans (H9N2, H7N2, and H5N1)
- More rapid genetic re-assortment of influenza between animals and humans
- Human population density rising
- Intense, sustained animal contact common in many countries
- International travel/migration increasing
SLIPPING IN THROUGH THE BACK DOOR

THE A(H1N1)PDM09 PANDEMIC
Fig. 1 Host and lineage origins for the gene segments of the 2009 A(H1N1) virus: PB2, polymerase basic 2; PB1, polymerase basic 1; PA, polymerase acidic; HA, hemagglutinin; NP, nucleoprotein; NA, neuraminidase; M, matrix gene; NS, nonstructural gene


Published by AAAS
The Persistent Legacy of the 1918 Influenza Virus
David M. Morens, M.D., Jeffery K. Taubenberger, M.D., Ph.D., and Anthony S. Fauci, M.D.
AVIAN INFLUENZA-
THE ONGOING THREAT
Species Affected by Influenza Virus

Genetic Reservoirs

H1, H2, H3

H1, H3, H4, H7, H13

H3, H7

H1, H3, H4, H7, H13

H14-15

H1-2, 4-7, H9-13, 15-16

Commercial, LBMs

Others

Other Aquatic Birds?
WILD BIRDS AS INFLUENZA A RESERVOIR

• Avian influenza A viruses have been isolated from more than 100 different species of wild birds.

• The majority of the wild birds from which these viruses have been recovered represent gulls, terns and shorebirds or waterfowl such as ducks, geese and swans.
LOW PATHOGENIC AND HIGHLY PATHOGENIC AVIAN INFLUENZA

• Low pathogenic avian influenza A (LPAI) viruses
  • Infection of poultry with LPAI viruses may cause no disease or mild illness and may only cause mild signs (such as ruffled feathers and a drop in egg production) and may not be detected
  • *Past pandemics arose from LPAI viruses*

HIGHLY PATHOGENIC AVIAN INFLUENZA

• Highly pathogenic avian influenza A (HPAI) viruses

• Infection of poultry with HPAI viruses can cause severe disease with high mortality.

• Both HPAI and LPAI viruses can spread rapidly through flocks of poultry.

• HPAI virus infection can cause disease that affects multiple internal organs with mortality up to 90-100%, often within 48 hours
AVIAN INFLUENZA A (H5N1)

- HPAI
- Discovered in Hong Kong, 1997
- Now multiple epizootics worldwide
- Still has not entered the Western Hemisphere
- Still has not met “WHO” criteria for pandemic
  - Severe clinical course
  - Rapid deterioration
  - High fatality
  - Low transmissibility human-to-human
H5N1 UPDATE

• 633 laboratory–confirmed cases; 377 deaths (9/13)
  • Official reports from 15 countries
  • Case fatality - 60%
• “Overall public health risk assessment for avian influenza A(H5N1) viruses:
  • Whenever influenza viruses are circulating in poultry, sporadic infections or small clusters of human cases are possible, especially in people exposed to infected household poultry or contaminated environments.
  • However, currently, this influenza A(H5N1) virus does not appear to transmit easily among people and therefore the risk of community-level spread of this virus remains low.
  • Therefore, the overall public health risk associated with this virus remains unchanged. “
Areas with confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2013*

CumulativeNumberH5N1cases.pdf. Downloaded 08/29/2013. Cumulative lab-confirmed cases reported to WHO. Total cases include deaths.

*All dates refer to onset of illness
Data as of 01 February 2013
Source: WHO/MPH
IMPLICATIONS FOR HUMAN HEALTH - H5N1

- Asian Strain H5N1 in humans more aggressive than seasonal flu strains
  - Severe clinical course
  - Rapid deterioration
  - High fatality
  - Low transmissibility human-to-human
- Incubation may be longer than seasonal influenza
  - Seasonal influenza: 2-3 days
  - H5N1: possibly up to 10 days
- More studies needed
H7 VIRUSES

• Most in wild birds and poultry are LPAI
• Prior to 2013- if human infection, mild URI
• LPAI (H7N2, H7N3, H7N7) virus infections have caused mild to moderate illness.
• HPAI (H7N3, H7N7) virus infections have caused mild to severe and fatal illness.
• Netherlands HPAI H7N7 outbreak of human cases, 2003

INFLUENZA A (H7N9)

- First reported April 1, 2013 in China by World Health Organization
- >130 human infections reported
- Many in contact with poultry
- “Most concerning is the pandemic potential of this virus.”
- LPAI-intravenous pathogenicity index test data indicates that infections in chickens are sub-clinical
  - Huge issue for surveillance!!

http://www.cdc.gov/flu/avianflu/h7n9-virus.htm
INFLUENZA H7N9

- The median age of the cases approximately 60 years
- Most cases have experienced severe respiratory illness
  - 6.3% impacted population/workers w/ antibodies (subclinical disease)
  - No evidence of antibodies in the general population
- 24 reported deaths (as of 9/13) - 40% CF
- Attaches more strongly to lower respiratory tract airway cells (compared to H3N2, H1N1, H5N1)
  - Potential increased virulence- abundant attachments to bronchiolar and alveolar epithelial cells
  - More concentrated attachments in upper airways-potential risk for efficient transmission

http://www.cdc.gov/flu/avianflu/h7n9/risk-assessment.htm


INFLUENZA H7N9 AND SWINE

• Potential to infect pigs
• Potential for additional mammalian adaptations
• Fall 2013- Chinese surveillance has not found H7N9 in more than 4,000 animal or environmental samples

INFLUENZA A (H9N2)

- Identified in China and Hong Kong
- Enzootic in poultry in Africa, Asian and Middle East
- Human infections in 1998
- 6.2% of poultry workers in India seropositive
- Non-fatal, mild URI
- No evidence of H-H transmission
- Infrequent isolation in swine and humans reported

WHO. Antigenic and genetic characteristics of zoonotic influenza viruses and development of candidate vaccine viruses for pandemic preparedness February 2013
OTHER INFLUENZAS AT THE HUMAN-ANIMAL INTERFACE

MAMMALIAN INFLUENZAS
**CANINE INFLUENZA A(H3N8) AND A(H3N2)**

- **CIV A(H3N8)**
  - Originally an equine virus (over 40 years)
  - 2004 cases in FL dogs
  - Spreads efficiently between dogs
  - 2005-“newly-emerging pathogen in the dog population”
  - No human disease

- **CIV A(H3N2)**
  - Avian origin
  - Canine influenza virus- first reported 2007
  - Can be transmitted to cats, with C-C transmission
  - Cats as a new host?
  - No human disease

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http://www.cdc.gov/flu/canine/
INFLUENZA A(H3N8)

• Influenza A/harbor seal/Massachusetts/1/2011
• Avian origin - circulating since 2002 in US
• 2011 new England seal die-off
• Mutations causing mammalian adaptation
  • PB2 D701N (seen also in H5N1)
• “...potential for persistence and cross-species transmission.”

HUMAN VARIANT INFLUENZAS – SWINE ORIGIN

• Swine influenza-respiratory disease of pigs

• Variant influenza virus - virus that normally circulates in swine is detected in human-

  • e.g., “H3N2v”, “HiN21v”, “H1N2v”
SWINE AS “MIXING VESSEL”

• Birds are reservoir for all A influenzas
• Swine susceptible to infection from both human and avian influenza
• Role in emerging novel influenza viruses
• Human cases associated with swine viruses reported in US since 1970’s
• Until A(H1N1)pdm09, no sustained H-H transmission reported
VARIANT INFLUENZAS, US
DATA AS OF SEPTEMBER 18, 2013

- Michigan – 2 cases 2013
  - As of Sept 2013
  - County fair contacts (8/2012, 8/2013)

Table. Case Count: Detected U.S. Infections with Variant Influenza Viruses by State since December 2005

<table>
<thead>
<tr>
<th>Reporting State</th>
<th>H3N2v</th>
<th>H1N1v</th>
<th>H1N2v</th>
<th>Total Detected Influenza Variant Virus infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawaii</td>
<td>1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Illinois</td>
<td>5</td>
<td>1</td>
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<tr>
<td>Indiana</td>
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<td>3</td>
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<td>Kansas</td>
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<tr>
<td>Maine</td>
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<tr>
<td>Maryland</td>
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<td>Minnesota</td>
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<td>Ohio</td>
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<td>Pennsylvania</td>
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<tr>
<td>Wisconsin</td>
<td>21</td>
<td>2</td>
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<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>347</strong></td>
<td><strong>14</strong></td>
<td><strong>5</strong></td>
<td><strong>366</strong></td>
</tr>
</tbody>
</table>

* Includes H3N2v viruses with the M gene from the influenza A (H1N1)pdm09 virus without the M gene from the influenza A (H1N1)pdm09 virus.

For more detailed information about previously detected human cases of variant influenza infection, see [Reports of Human Infections with Variant Viruses](#).
A(H3N2)V

- Circulating in US swine population
- April 2012 MMWR-6 cases did not have exposure to swine: H-H transmission?
- Limited-modest seasonal vaccine cross-protection to A(H3N2)v for adults (20-30%); none for young children
- “A vaccine virus specific for A (H3N2)v has been developed and could be used to produce an H3N2v vaccine, if needed”
- First H3N2v-associated death reported in Ohio 2012
  - Older male with multiple underlying conditions- direct exposure to pigs in fair setting

MMWR Weekly / Vol. 61 / No. 14, April 13, 2012; WHO Update May 7, 2012; http://www.cdc.gov/flu/spotlights/h3n2v-more-cases.htm; August 2012
TRIPLE-REASSORTANT SWINE INFLUENZA A(H1)

• Genes from avian, swine and human influenza
• Enzootic since mid-1990’s
• 2005-2009 11 human cases
  • Median age 10 y
  • 9 with exposure to pigs (5 with direct contact, 4 to environment here pigs present)
  • 4 patients hospitalized; two ventilated
  • All recovered

WHAT’S IN A NAME?

“Swine”, “Novel”
“Novel”, “Pandemic”
“A(H1N1)pdm09”

USDA: Please Call It H1N1, Not Swine Flu

Tuesday, April 28, 2009

American agriculture officials want to change the name for the virus that’s broken out in Mexico and the U.S. from "swine flu" to something else.

The problem, they say, is that the name "swine flu" suggests a problem with pork products. Agriculture Secretary Tom Vilsack points out that the virus is not food-borne and has nothing to do with consuming pork products. He said he wants Americans and citizens of other countries to know that no American pigs have tested positive for swine flu and that it is "perfectly" safe to eat pork from the U.S.

Speaking Tuesday at a daily news briefing on the government’s response to the outbreak, Secretary of Homeland Security Janet Napolitano repeatedly referred to the strain of influenza as H1N1, the technical name for the virus, rather than swine flu, as health officials have previously called it.

Vilsack, speaking at the same news briefing, said he’s concerned that misunderstandings could have a negative impact on farmers who provide pork products to consumers around the world. He said the American hog industry is sound and that consumers everywhere should know that U.S. pork products are safe.

Vilsack said if U.S. trade partners begin to shun American pork it could do further harm to a country already struggling with a recession.

He said the USDA is working with farm families to make sure they continue to raise healthy pork that they can sell here and around the world.

The Associated Press contributed to this story
Current pandemic phase: 4 -

“Post-pandemic – Influenza disease activity has returned to levels normally seen for seasonal influenza. It is expected that the pandemic virus will behave as a seasonal influenza A virus. It is important to maintain surveillance and update pandemic preparedness/response plans accordingly”

(MDCH MiFLuFocus September 13, 2013)