Influenza and Dengue: Pandemics and Epidemics
but Don’t Panic

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September 17th, 2009

Foro Educativo para maestros
de ciencia en la UPRH

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(Courtesy of Linda Stannard,
University of Cape Town, S.A.)
OUTLINE (Influenza)

- Virus Classification and Nomenclature
- Human Flu Pandemics
- Avian and Swine Flu in Humans
- Clinical Presentation
- Epidemiological data
- Treatment and Profilaxis
- Quiz
Schematic Representation of the Influenza Virus Particle

- Family Orthomixoviridae
- RNA virus, genome consists of 8 segments
- Enveloped virus, with haemagglutinin (HA) and neuraminidase (NA) spikes
3 Types of the influenza virus: A, B and C

Reflect differences in the M protein on the envelope that contains the virus

Type A undergoes antigenic shift and drift. Infect Multiple Species. All human pandemics have been due to Influenza A

Type B undergoes antigenic drift only. Infect only Humans

Type C is relatively stable. Infect Humans and Swine
Subtypes according envelope’s glycoproteins

15 HA (H)
9 NA (NA)

• Human disease historically linked to
  • H1, H2 and H3 and N1 - N2
  • “Swine Flu” viruses comprises H1-H3 and N1-N2
  • “Avian flu” viruses are Influenza A viruses (H1-H15; N1-N9): H5 and H7 typically cause severe outbreaks in birds
Influenza Virus Nomenclature

A/Puerto Rico/8/34 (H1N1)

- Virus type
- Geographic origin
- Strain number
- Year of isolation
- Virus subtype

Type of M Protein

Hemagglutinin

Neuraminidase
Antigenic Drift and Shift

Amazing ability to change:

- **Antigenic Drift (A and B)**
  - Comparatively minor antigenic change
  - We need a new vaccine each year
  - Causes epidemics: a higher than normal level in the population, usually much higher than endemic, and usually short-term

- **Antigenic Shift (A only)**
  - Major antigenic change
  - Leads to pandemics—novel strain, little immunity, epidemic spreading between continents
Summary

- Flu have 8 different genomic segments
- There are 3 types of Flu, A, B, C.
- There are many subtypes, H15 and N9
- Only Type A undergoes antigenic shift
- Occurs in humans, pigs, horses, birds, and certain marine mammals.
- Human disease historically linked to H1 - H3 and N1 - N2
- “Avian flu” viruses are Influenza A viruses (H1-H15; N1-N9): H5 and H7 typically cause severe outbreaks in birds
- “Swine Flu” viruses are Influenza A viruses and like humans are linked to H1-H3 and N1-N2
- Pandemic occurs after an antigenic SHIFT
Human Flu Pandemics/Epidemics

1918-19 Spanish Flu (H1N1)
- 20-50 million deaths worldwide
- >500,000 U.S. deaths

1957-58 Asian Flu (H2N2)
- 2 millions
- 70,000 U.S. deaths
HA, NA, PB1 = Avian

1968-69 Hong Kong Flu (H3N2)
- 1 million
- 34,000 U.S. deaths
HA, PB1 = Avian

H3N2 (68 years)
H2N2 (59 years)
H1N1 (59 years)
“Spanish” Flu Waves
W and U shaped Curves
Theories Behind Antigenic Shift

1. **Reassortment** of the H and N genes between human and avian influenza viruses through a third host. There is good evidence that this occurred in the 1957 H2N2 and the 1968 H3N2 pandemics.

2. **Recycling** of pre-existing strains – this probably occurred in 1977 when H1N1 re-surfaced.

3. **Gradual adaptation** of avian influenza viruses to human transmission. There is some evidence that this occurred in the 1918 H1N1 pandemic.
Origins of novel H1N1

Taia T. Wang and Peter Palese,* Cell 137, June 12, 2009 ©2009 Elsevier Inc.
Swine Flu in Humans

1976 (H1N1)

1988 (H1N1) 32-year-old pregnant woman

December 2005 through February 2009
12 cases of human infection

March 2009 -
Avian Influenza in Humans (Antecedents)

**H5N1**
- 1997, Hong Kong (18 infected, 6 Deaths)
  - 1.5 million birds, was culled in 3 days

**H9N2**
- Hong Kong 1999

**H7N2**
- 2003, the Netherlands

**H7N7**
- 2004, Canada and USA
Avian Influenza H5N1 in Humans (Waves)

H5N1 Wave I April 2003-March 2004
• 35 cases, 24 deaths (Viet Nam and Thailand)

H5N1 Wave II July 2004-Nov 2004
• 9 cases, 8 deaths (Viet Nam and Thailand)

H5N1 Wave III Dec 2004-Up to now
• 440 cases, 262 deaths (Viet Nam, Thailand, Indonesia, Egypt)
# H5N1 vs. H1N1

**Table 1. Comparison of Avian and Swine Influenza Viruses**

<table>
<thead>
<tr>
<th></th>
<th>2009 Swine H1N1</th>
<th>1997 Avian H5N1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission between humans</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Causes human disease</td>
<td>Yes (mild)</td>
<td>Yes (severe)</td>
</tr>
<tr>
<td>Degree of immunity in population</td>
<td>Likely</td>
<td>No</td>
</tr>
<tr>
<td>Known molecular markers of pathogenicity</td>
<td>No</td>
<td>PB1-F2; polybasic cleavage site in hemagglutinin</td>
</tr>
</tbody>
</table>

Taia T. Wang and Peter Palese,* Cell 137, June 12, 2009 ©2009 Elsevier Inc.
Summary

• In the last century three Flu pandemics occurred
• The one of probably Avian origin caused 20-50 millions deaths (Spanish Flu, 1918)
• For a pandemic to occur a Shift it is necessary
• Three theories to explain a Shift: Recycling, Reassorment and Direct Transmission from fowls.
• Specie restriction is due to specific cellular receptors
• Swine flu occasionally infect humans (H1N1) and only ONE epidemic (Current) have been recorded so far.
• By September 2009 no markers of virulence have been detected in novel H1N1 strain
Epidemiology of Human Transmission
Avian flu threat: Influenza A is spread by migratory birds along major global flyways
Status as of: 30 August 2009

Chinese Taipei has reported four deaths associated with pandemic (H1N1) 2009.

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Influenza Positive Tests Reported to CDC by U.S. WHO/NREVSS Collaborating Laboratories, National Summary, 2008-09
## 20th century flu pandemics

<table>
<thead>
<tr>
<th>Pandemic</th>
<th>Year</th>
<th>Influenza A virus subtype</th>
<th>People infected (approx)</th>
<th>Deaths (est.)</th>
<th>Case fatality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918 flu pandemic</td>
<td>1918–19</td>
<td>H1N1[^9][^10]</td>
<td>0.5 to 1 billion (near 50%)</td>
<td>20 to 100 million[^11][^12][^13]</td>
<td>&gt;2.5%[^14]</td>
</tr>
<tr>
<td><strong>Seasonal flu</strong></td>
<td>Every year</td>
<td>mainly A/H3N2, A/H1N1, and B</td>
<td>5–15% (340 million – 1 billion)[^15]</td>
<td>250,000–500,000 per year[^7]</td>
<td>&lt;0.1%-0.05%</td>
</tr>
</tbody>
</table>

*Confirmed Lab cases as by Sept 03, 2009*
<table>
<thead>
<tr>
<th>Pos.</th>
<th>Estado</th>
<th>Población</th>
<th>Casos confirmados</th>
<th>Muertes confirmadas</th>
<th>Tasa de mortalidad (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Puerto Rico</td>
<td>3,964,511</td>
<td>362</td>
<td>34</td>
<td>9.12</td>
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<tr>
<td>2</td>
<td>Nueva York</td>
<td>19,490,297</td>
<td>2080</td>
<td>43</td>
<td>2.06</td>
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<tr>
<td>3</td>
<td>Misuri</td>
<td>5,911,605</td>
<td>58</td>
<td>1</td>
<td>1.72</td>
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<tr>
<td>4</td>
<td>California</td>
<td>36,756,666</td>
<td>1294</td>
<td>19</td>
<td>1.46</td>
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<tr>
<td>5</td>
<td>Arizona</td>
<td>6,500,180</td>
<td>729</td>
<td>10</td>
<td>1.37</td>
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<tr>
<td>6</td>
<td>Utah</td>
<td>2,736,424</td>
<td>874</td>
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<td>1.14</td>
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<td>7</td>
<td>Carolina del Norte</td>
<td>9,222,414</td>
<td>179</td>
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<td>8</td>
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<td>138</td>
<td>3</td>
<td>1.03</td>
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<tr>
<td>10</td>
<td>Nueva Jersey</td>
<td>8,682,661</td>
<td>609</td>
<td>6</td>
<td>0.98</td>
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<tr>
<td>11</td>
<td>Rhode Island</td>
<td>1,050,788</td>
<td>137</td>
<td>1</td>
<td>0.72</td>
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<tr>
<td>12</td>
<td>Oklahoma</td>
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<td>144</td>
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<td>0.69</td>
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<td>13</td>
<td>Connecticut</td>
<td>3,501,252</td>
<td>877</td>
<td>5</td>
<td>0.57</td>
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<tr>
<td>14</td>
<td>Washington</td>
<td>6,549,224</td>
<td>588</td>
<td>3</td>
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<td>15</td>
<td>Texas</td>
<td>24,326,974</td>
<td>2982</td>
<td>15</td>
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<tr>
<td>16</td>
<td>Illinois</td>
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<td>2858</td>
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<td>17</td>
<td>Nevada</td>
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<td>240</td>
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<td>0.41</td>
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<td>18</td>
<td>Virginia</td>
<td>7,769,089</td>
<td>249</td>
<td>1</td>
<td>0.4</td>
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<td>19</td>
<td>Maryland</td>
<td>5,633,597</td>
<td>370</td>
<td>1</td>
<td>0.27</td>
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<tr>
<td>20</td>
<td>Pensilvania</td>
<td>12,448,279</td>
<td>1539</td>
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<td>0.25</td>
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<tr>
<td>21</td>
<td>Florida</td>
<td>18,328,340</td>
<td>941</td>
<td>18</td>
<td>0.21</td>
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<tr>
<td>22</td>
<td>Hawái</td>
<td>1,288,198</td>
<td>503</td>
<td>1</td>
<td>0.19</td>
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<tr>
<td>23</td>
<td>Minnesota</td>
<td>5,220,393</td>
<td>565</td>
<td>1</td>
<td>0.17</td>
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<td>24</td>
<td>Massachusett</td>
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<td>1287</td>
<td>2</td>
<td>0.15</td>
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<tr>
<td>25</td>
<td>Wisconsin</td>
<td>5,627,967</td>
<td>4390</td>
<td>4</td>
<td>0.09</td>
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<tr>
<td></td>
<td>Estados Unidos</td>
<td>306,798,000</td>
<td>27,321</td>
<td>155</td>
<td>0.56</td>
</tr>
</tbody>
</table>
How many peoples die from Influenza?

• Centers for Disease Control and Prevention (CDC) of the US does not know exactly how many people die from flu each year

Determining this is a tricky business!!

• States are not required to report to the CDC individual influenza cases, or deaths of people older than the age of 18,
• Influenza is rarely listed as a cause of death on death certificates, even when people die from influenza-related complications,
• Many flu-related deaths occur one or two weeks after the initial infection, when influenza can no longer be detected from respiratory samples.,
• Most people who die from influenza-related complications are not given diagnostic tests to detect influenza.
Second Wave Projection (US/CDC) by President's Council of Advisors on Science and Technology

- A more aggressive mutation of the virus could infect 30 percent to 50 percent of the population, lead to as many as 1.8 million hospitalizations and cause between 30,000 to 90,000 deaths compared to the annual number of 36,000.

Moderate vs. Mild
Novel H1N1 trends
Age Distribution

Patients ≥ 65 y/o
Seasonal
Novel H1N1

Hospitalized 60% 5%
Deaths 90% 8%

Median age of Hospt: 20 y/old
Median age of death: 34 y/old
Visit for Influenza Like Illness (ILI)

*There was no week 53 during the 2006-07 and 2007-08 seasons, therefore the week 53 data point for those seasons is an average of weeks 52 and 1.*
Pneumonia and Influenza Mortality
for 122 U.S. Cities
Week Ending 08/22/2009

% of All Deaths Due to P&I

Epidemic Threshold

Seasonal Baseline

Weeks 2005 2006 2007 2008 2009

Weeks 31 40 50 10 20 30 10 20 30
Number of Influenza-Associated Pediatric Deaths by Week of Death:
2005-06 season to present

- **2005-06**
  - Number of Deaths Reported = 46

- **2006-07**
  - Number of Deaths Reported = 78

- **2007-08**
  - Number of Deaths Reported = 88

- **2008-09**
  - Number of Deaths Reported = 110

Legend:
- Blue: Deaths Reported Current Week
- Yellow: 2009 Influenza A (H1N1) Deaths Reported Current Week
- Green: Deaths Reported Previous Weeks
- Pink: 2009 Influenza A (H1N1) Deaths Reported Previous Weeks
Summary

• Novel H1N1 displaced circulating seasonal Flu strains
• The CFR of novel H1N1 seems to be similar to the seasonal Flu
• Target population of novel H1N1 is similar to the H1N1 1918
• So far, in USA novel H1N1 do not produce a substantial increase in the number of Flu-associated dead
Influenza Virus

Clinical Presentation and Treatment
Novel H1N1

- Clinical presentation similar to Seasonal Influenza
- Fever > 38.5 to 40 °C
- Sore Throat
- Body aches
- Headache
- Chills and fatigue
- Runny or stuffy nose
- Cough, dyspnea, productive cough respiratory rate >40
- Diarrhea and vomiting
- mild cases of infection and the vast majority of patients recover quickly and fully.
- 65 % of severe cases had medical risk factors
Avian Influenza

- Fever > 38.5 to 40 °C
- Lymphopenia and thrombocytopenia
- 7/10 diarrhea
- Cough, dyspnea, productive cough in 5/10, respiratory rate >40 in 9/10
- No rash, myalgias, rhinorrhea, or conjunctivitis
- **All had abnormal chest radiographs**
- 8/9 had exposure to poultry
- Presentation with diarrhea followed by encephalitis without respiratory symptoms has been reported
- Mortality 55%-80%
Why Peoples died from Influenza?

- Bacterian Pneumonia
  - Pneumocococcus
  - Staphylococcus
“Cytokine Storm”

Influenza Treatment

- **Interfere with influenza A virus M2 protein**
  - Amantadine/Rimantadine
    - Membrane ion channel protein and inhibit viral replication
    - Not active against H5N1/Novel H1N1

- **Neuraminidase inhibitors**
  - Zanamivir/Oseltamivir
    - Results in viral aggregation at the host cell surface and reduces the number of viruses released from the infected cell
    - Can be used against H5N1/H1N1
Avian or Novel H1N1 Influenza Therapy

• TAMIFLU (OSELTAMIVIR) (ROCHE) 75 mg -120 capsules ($1,099.99)

• RELENZA (ZANAMIVIR) 5mg (GlaxoSK) -1 x 5 rotadisk + 1 inhaler ($199.99)
Human Influenza Prevention
Human Influenza Prevention

**VACCINE**
(Contain 2 type A viruses (H1N1-H3N2 and 1 type B virus)
Time: 4-6 month egg based manufacturing process

- **Inactivated Influenza Vaccine**
  Sanofi/Adventis and Chiron
  Recently, FLUARIX, GlaxoSK

- **Live Attenuated Influenza Vaccine**
  FluMist®, produced by MedImmune
  Administered by nasal spray

**H1N1 Vaccine**
- **Monovalente** (A/California/07/2009 H1N1)
Influenza Vaccine Timeline

Manufacturers may not have time to produce large quantities of vaccine specific to a pandemic strain before a new strain emerges.

- **Too Little, Too Late**
  - Detection of outbreak
    - Development of prototype strain by WHO
    - Standardising manufacture
- **Vaccine Production Begins**
- **Vaccine Production**
- **New Variant Virus Emerges**
  - Pandemic strain emerges
  - Arrives on all continents

(Source: WHO)
"We're expecting somewhere between 45 million and 52 million doses of vaccine to be available by mid-October. This will be followed by weekly availability of vaccine up to about 195 million doses by the end of the year... these numbers are driven by a number of variables in the manufacturing process. There are five manufacturers working, so and everybody's doing the best they can to get as much vaccine available as soon as possible."

Dr. Jay Butler, head of the CDC's vaccine task force, September 2009
The Advisory Committee on Immunization Practices (ACIP) recommendations on the use of influenza A (H1N1) 2009 monovalent vaccine.

Posted: 04 Sep 2009 04:30 AM PDT
Initial Target Groups

1- Pregnant women,
2- Persons who live with or provide care for infants aged <6 months (e.g., parents, siblings, and daycare providers),
3- Health-care and emergency medical services personnel,
4- Children and young adults aged 6 months--24 years,
5- Persons aged 25-64 years who have medical conditions that put them at higher risk for influenza-related complications*.

* Asthma, cardiovascular (not HTA), renal, hepatic, cognitive, neurologic/neuromuscular, hematologic, or metabolic disorders (including diabetes mellitus) and immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus).
Subset of initial target groups

1- Pregnant women,
2- Persons who live with or provide care for infants aged <6 months (e.g., parents, siblings, and daycare providers),
3- Health-care and emergency medical services personnel who have direct contact with patients or infectious material,
4- Children and young adults aged 6 months--24 years,
5- Persons aged 25-64 years who have medical conditions that put them at higher risk for influenza-related complications.
Would Seasonal Vaccine to protect against novel H1N1?

Prevalence of Antibodies to novel H1N1

Groups of age

18-40
18-64
>60

%
What’s Needed For a Pandemic Strain?

• Novel virus (little to no immunity in human population) Both H5N1 and H1N1

• Capable of causing disease in humans Both H5N1-H1N1

• Highly pathogenic / virulent Only H5N1

• Capable of sustained person to person transmission Only H1N1
Worst Scenario

Origin of a new reassortant: novel H1N1 and H5N1

<table>
<thead>
<tr>
<th>Table 1. Comparison of Avian and Swine Influenza Viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009 Swine H1N1</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Transmission between humans</td>
</tr>
<tr>
<td>Causes human disease</td>
</tr>
<tr>
<td>Degree of immunity in population</td>
</tr>
<tr>
<td>Known molecular markers of pathogenicity</td>
</tr>
</tbody>
</table>
A Pandemic
H5N1/novel H1N1

• Novel virus (little to no immunity in human population)

• Capable of causing disease in humans

• Highly pathogenic / virulent

• Capable of sustained person to person transmission
Summary

• Clinical presentation of novel H1N1 is similar to seasonal influenza
• Most of fatal cases associated to H1N1 had medical risk factors
• Avian Flu is a more aggressive infection with CRF between 50-80%
• Pneumonia after flu infection are the main cause of dead
• Neuroaminidase inhibitors are the only treatment available for both viruses
• Seasonal Vaccine do not protect against novel H1N1…but if you can get it don’t doubt it!
• A monovalent H1N1 vaccine would be available in limited amounts by the fall 2009.
• Novel H1N1 pandemic should be considered as a training to fight a potential worst Flu pandemic due to a H5N1 like virus