Frequently Asked Questions

• Will there be a pandemic?
• How virulent will it be?
• What’s the difference between pandemic and seasonal flu?
• How can I best prepare for a pandemic?
Useful Terms

• Pandemic influenza
  • Human disease
  • Novel influenza A viral strain
  • Satisfies WHO criteria for high transmission and high lethality (Level 6, general population)

• Avian influenza
  • Disease in animals (termed HPAI and LPAI) OR in humans

• Seasonal influenza
  • Less lethal human disease
  • Various strains of older (existing) virus
  • Migrate across the globe
Three criteria for a pandemic

An influenza pandemic is a global outbreak of disease that occurs when:

1. A novel influenza A viral strain appears or emerges in the human population, and
2. It causes serious illness in humans, and
3. It spreads easily from person to person worldwide
The Great Influenza

1918-1919

Credit: US National Museum of Health and Medicine
1918-19 Spanish Flu Pandemic (H1N1)

• At least 500,000 deaths in U.S.

• Est. 20-50 million deaths worldwide

• WWI: More troop deaths than in battle itself
U.S. Life Expectancy 1900-1960

![Graph showing U.S. Life Expectancy from 1900 to 1960. The graph displays a steady increase in life expectancy over time, with a significant dip during the years 1920 to 1925. The life expectancy in 2003 is 77.5 years.]
Can it happen again?

- Genomic code is quite similar
- Predilection for young adults
- High case-fatality rates (?)
- Human disease in 10 countries, 3 land masses (Asia, Middle East, Africa)
- Wild fowl and poultry affected in 52 countries, 4 land masses (incl. Europe)
Doubt

In the battle between you and the world,
Bet on the world.
What we DON’T know:

- When it will start
- Where it will start
- What specific virus it will be
- How virulent it is in humans
- How long it will last
- How transmissable it will be
- Whether it will reach our shores
Influenza Virus Types: A, B, C

• **Influenza A**
  - Human and avian strains
  - Epidemics and pandemics
  - Illness variable (age, co-morbid disease)

• **Influenza B**
  - Humans: the only reservoir
  - Less mortality than type A
  - Associated with epidemics, not pandemics

• **Influenza C**
  - Not associated with epidemics
  - Mild illness
Nomenclature

A / Sydney / 05 / 97 (H3N2)

Virus type  Strain number  Virus subtype

Place virus isolated  Year isolated
Influenza A Viruses

Single stranded RNA
Subtyped based on surface glycoproteins
  • 16 hemagglutinins (HA)
  • 9 neuraminidases (NA)
8 gene segments
Antigenic Drift: Seasonal flu

- Point mutations in viral RNA: copying error
- Continual process
- Causes yearly epidemics
- Requires annual re-vaccination that includes the 3 most likely strains for North America
Antigenic Shift: Pandemic flu

- Sporadic
- New subtype (H and/or H+N)
- NOVEL STRAIN---no natural or vaccine-based immunity
- May cause pandemic (not necessarily)
- Degree of virulence is key
H5N1 Hemagglutinin Vaccine Candidates

H5N1s are not all identical
20th Century Examples:

Degree of virulence is key

- **1918-19 Spanish Flu** (H1N1)
  - >500,000 deaths US
  - 20-50 million worldwide

- **1957-58 Asian Flu** (H2N2)
  - 70,000 deaths US

- **1968-69 Hong Kong Flu** (H3N2)
  - 50,000 deaths US
What we know: Pandemics

- Rare (1918-19, 1957, 1968)
- Transmission is highly efficient among humans, incubation is short
- EVERYONE is susceptible
- Virulence is variable
- Resistance to antiviral agents is variable
- Shedding precedes symptoms by ½ day
Methods of Spread
Methods of spread

1. Wild fowl to wild fowl (asymptomatic)
   - Flyways

2. Wild fowl to poultry (Lethal)
   - Flyways
   - Farms, villages

3. Poultry to humans (Sick or lethal)
   - Farms, villages, wet markets

4. Human to human
   - Non-sustained (Thailand, Indonesia)
   - Sustained (WHO Level 6 criteria for pandemic)
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Disposal of Dead Birds
For Duck Blood Pudding

Enjoyed especially at Tet New Year

Wet market, Hanoi
One Hen ($2.50) in Vietnam

- Produces 70 eggs per year
  - Half are eaten by family or sold ($3.06 US)
    - 60% of remaining half hatch
      - Six survive at one year, worth $15 ea.

In one year, $2.50 investment becomes $93.06, plus provides family with a major protein source

Ergo, 8 million backyard farmers in Vietnam alone
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Transmission and Virulence
Human and Animal Disease
Jan 11, 2005

Clade 1
Clade 2
Human Cases
Note: USAID will only support AI programs in less-developed countries.
### Human Cases of Avian Influenza (9-12-06 WHO)

<table>
<thead>
<tr>
<th>Country</th>
<th>Cases</th>
<th>Deaths</th>
<th>CFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vietnam</td>
<td>93</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Indonesia</td>
<td>63</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Thailand</td>
<td>24</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>21</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Egypt</td>
<td>14</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>12</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Azerbaijan</td>
<td>8</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Cambodia</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Iraq</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Djibouti</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>244</strong></td>
<td><strong>143</strong></td>
<td><strong>59%</strong></td>
</tr>
</tbody>
</table>
Two methods of transmission

- Virus **mutates** and jumps species
- Virus **reassorts** (recombines) with another virus to make a hybrid virus
  - Requires **two** viruses simultaneously:
    1. Avian influenza virus (highly virulent)
    2. Human influenza virus (seasonal, highly transmissible)
- Requires a **mixing vessel**: pig or human
Mutation

AVIAN virus

HUMAN virus

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
Reassortment

AVIAN virus

HUMAN virus

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
Influenza is always present:
Seasonal occurrence worldwide
(Reichelderfer PS, et al. Current Topics in Medical Virology, 1988)
H5N1 Hemagglutinin

Vaccine Candidates

Clade 1

Clade 1'

Clade 2

H5N1s are not all identical
Implications

• For populations
  • Different attack rates, different virulences

• For public health
  • We must continue laboratory surveillance if/until a pandemic strain develops

  • A “good match” is an absolute necessity, lest the vaccine have low effectiveness in prevention.

• Thus, we must know the correct strain to make the appropriate vaccine
Transmission of Virus

• **Total course**  5.5 days
  • Latency           1.5 days
  • Infectious to others, but no symptoms yet 0.5 days
  • Infectious (with or w/o symptoms) 3.5 days

• R0 approx 1.6

• Intergeneration period:
  Approx 2.6 days, or 12 periods per month

• Respiratory droplets >> aerosol >> fomites:
  • Active 8-24 hrs; 15 min on tissues

• Infection rate 50-60%; about half asymptomatic yet infectious to others
Pandemic Transmission: First month

• Allow Reproductive Number (R0) to vary in the model
  • If R0 = 1.6........282 infected (=1.6^{12}).... 5 - 70 deaths
  • If R0 = 1.8........1157 infected............23 - 289 deaths
  • If R0 = 2.0........4096 infected.............81 - 1024 deaths

• Roughly half of infected persons have symptoms

• Roughly 2 - 50% of persons with symptomatic pandemic flu die

• Worst-case scenario: 2% of 3 billion people die worldwide, or 60 million people worldwide
100 exposed

50-60 infected (and shed)*

25 have symptoms

? 1 death

*Some models estimate 15-35% attack rate, based on 1968 epidemic
Estimated Impact of a Future Influenza Pandemic in the U.S.*

- Deaths: 89,000 - 207,000
- Hospitalizations: 314,000 - 734,000
- Outpatient visits: 18 - 42 million
- Additional illnesses: 20 - 47 million
- Economic impact: $71.3 - 166.5 billion

How ready are we?

Estimated Hospital Demand at Peak of Pandemic

Estimated needs per 1000 population during the peak week of a community pandemic outbreak

<table>
<thead>
<tr>
<th></th>
<th>Mild Pandemic</th>
<th>Severe Pandemic</th>
<th>Available capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Beds</td>
<td>0.58</td>
<td>6.59</td>
<td>2.69 + .54 surge</td>
</tr>
<tr>
<td>ICU Beds</td>
<td>0.14</td>
<td>1.70</td>
<td>0.27 + ? surge</td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td>0.07</td>
<td>0.84</td>
<td>0.33 + .013 surge</td>
</tr>
</tbody>
</table>
VACCINE
The Bird Flu Vaccine

- Egg-based
- In NIH testing
- Needs FDA approval
- Six-month production cycle needed (assuming no interference w/seasonal)
- Dose? 90ug x 2 = 180 ug total (vs. 15 ug)
- Cell culture technology?
- Additional factories?
U.S. Pandemic Influenza Vaccine: Relative Supply, Capacity, and Need

Assumes:

All capacity dedicated to pandemic vaccine

No annual influenza is manufactured
Current Influenza Vaccine Production Timeline: 6-9 months

Influenza Vaccine Production Timeline

Jan  | May  | Jun - Jul  | Aug  | Sep  | Oct - Nov

**Virus Selection**
- FDA advisory panel selects 3 strains
- CDC provides new strains of the seed virus to the FDA
- FDA distributes the 3 seed viruses to manufacturers

**Production Begins**

**FDA Testing, Licensure**

**Filling/ Packaging**
- Vaccine is filled into vials and syringes; packaged for distribution

**Product Release/ Shipping**

**Vaccination Begins**
- Immunity develops approximately 2 weeks after vaccination
Why get an annual flu shot?

• Little or no cross-immunity occurs among strains

• Production easier to increase
  • Key political reason

• Annual flu might be R/O if vaccination given

• Good example of healthy practice
  • Key health reason
Antiviral drugs

Amantadine
Rimantadine
Oseltamivir
Zanamivir
Antiviral drugs

• Limits to use
  • Effectiveness for disease?
  • Effectiveness in ring containment?
  • Effectiveness in disease environment?

• Limits of availability

• Private stockpiling
# Antiviral priority groups

<table>
<thead>
<tr>
<th>Tier</th>
<th>Priority groups</th>
<th>Popn. (10^6)</th>
<th>Cum pop</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>A. Essential HCW; vaccine &amp; antiviral mfrs.</strong></td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td><strong>B. Highest risk persons (age &amp; underlying dis.)</strong></td>
<td>26</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td><strong>C. Household contacts of &lt;6 mo &amp; severely immunocompromised; pregnant women</strong></td>
<td>11</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td><strong>D. Key govt. leaders &amp; pandemic responders</strong></td>
<td>&lt;1</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td><strong>A. Other high risk persons</strong></td>
<td>59</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td><strong>B. Critical infrastructure &amp; other pandemic resp.</strong></td>
<td>9</td>
<td>115</td>
</tr>
<tr>
<td>3</td>
<td><strong>Key govt. health decision-makers; mortuary</strong></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td><strong>Healthy 2-64 yr old not in other groups</strong></td>
<td>186</td>
<td>300</td>
</tr>
</tbody>
</table>
“Before everything else, getting ready is the key to success.”
What is CDC doing?
How does CDC respond?

- **Predict**
  - Mathematical models project size of outbreaks, prevention, and treatment needs

- **Prepare**
  - State/local health depts
  - Strategic national stockpile
  - Internal staff training
  - Laboratory readiness (CDC and states)

- **Respond**
  - DEOC: Incident Command Structure
  - Epidemiology and laboratory field teams
Recent CDC history:
Public health emergencies and preparations
CDC Director’s Emergency Operations Center (DEOC)
U.S. Strategic National Stockpile
Other CDC Responses

- Deliver foreign health aid
  - US bilateral agreements
  - Help develop foreign stockpiles
- Provide advice, consultation, secondments to WHO and individual countries
  - Conduct local site visits for guidance
- Prepare and distribute PCR reagents, test kits
- Prepare and distribute protocols and policies
Available U.S. stock and capacity

- Current influenza vaccine production capacity
  - 1 U.S.-based manufacturer
  - Capacity depends on amount of vaccine needed per dose; H5N1 capacity is sufficient for ~2 million people/mo

- Current oseltamivir (Tamiflu) availability
  - 10 million treatment courses in the SNS
  - U.S. based production capacity ~1.5 million courses/mo
HHS Pandemic Vaccine Goals

- With industry, accelerate development of new methods
- Dose-sparing techniques
- Adjuvants, immunostimulants, delivery technologies
- With industry, develop broad-spectrum influenza vaccine
HHS Pandemic Antiviral Goals

- Stockpile Goal: 81M treatment courses
  - 25% of US population (75 million treatment courses)
  - Containment: 6 million treatment courses

- Funding mechanism
  - Full funding for 50 million treatment courses
  - Subsidy to states: 25% of 31 million treatment courses

- Advanced development of new antiviral agents
Other federal aid

• $350M to state/local for preparedness

• $334M pledge from U.S. via grants and technical assistance to at-risk countries
  • National preparedness plans, surveillance and response systems
  • Evaluate the use and distribution of animal vaccine
  • Produce and test vaccines for humans
  • Train local rapid-response teams and medical personnel
  • Support communications and public awareness campaigns
  • Conduct international research activities
CDC Advice

- [www.cdc.gov/flu/pandemic](http://www.cdc.gov/flu/pandemic)
  - Checklists
  - Information
Useful references

- Knobler SL et al. *The Threat of Pandemic Influenza: Are We Ready?* (Workshop summary). Institute of Medicine, Nat. Academies Press, Washington, DC, 2005

- Davis M. *The Monster at Our Door*. The New Press, NY, 2005

Thank you for preparing!