Influenza: Virus and Disease, Epidemics and Pandemics

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- Studying the burden of disease due to vaccine-preventable infections in India, Sri Lanka, Bangladesh, and Nepal
- Developing diagnostic tests to better determine the etiology of pneumonia and meningitis infections
- Assessing the strategy of immunizing mothers to prevent disease in their infants
- Evaluating the best use of limited oxygen supplies in therapy of pneumonia
Outline

- What is influenza disease?
- What is the epidemiology of the virus?
- What is the biology of influenza virus?
- Current use of vaccines and antiviral drugs
- Planning for the pandemic
Influenza A Virus

- Only agent which causes **annual epidemics** of disease with attack rates of 10–40% over a six-week period
- Historically has caused **pandemics**, with millions of deaths worldwide
- In U.S., 10,000 to 40,000 excess deaths per year and about 200,000 hospitalizations are attributed to annual influenza epidemics
- Epidemics occur despite effective vaccine and antiviral drugs
- Influenza A virus is a highly mutable virus with frequent antigenic drift and occasional antigenic shift
Section A

Epidemiology
### Summary of Influenza Epidemiology

<table>
<thead>
<tr>
<th>Reservoir</th>
<th>Humans, animals (type A only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission</td>
<td>Respiratory route;</td>
</tr>
<tr>
<td></td>
<td>Airborne and direct contact</td>
</tr>
<tr>
<td>Temporal pattern</td>
<td>Peak: December–March in</td>
</tr>
<tr>
<td></td>
<td>northern temperate areas</td>
</tr>
<tr>
<td>Communicability</td>
<td>1–2 days before to 4–5 days</td>
</tr>
<tr>
<td></td>
<td>after onset of illness</td>
</tr>
</tbody>
</table>
Influenza in the U.S.

- Each year influenza causes:
  - 65 million illnesses
  - 30 million medical visits
  - 200,000 hospitalizations
  - 25,000 deaths
  - $3 to 5 billion in economic losses
Influenza Diagnosis

- Clinical and epidemiological characteristics (increase of febrile respiratory illness)
- Lab isolation of influenza virus from clinical specimen (e.g., nasopharynx, throat, sputum) by cell culture
- Direct antigen testing for type A virus
- Significant rise in influenza IgG by serologic assay (e.g., complement fixation, HAI)
Age-Specific Rates of Influenza Morbidity and Mortality

Pneumonia-Influenza Mortality

Hospitalizations

Medically Attended Illness

Rate per 100,000

Rate per 10,000

Rate per 100

Age (Years)

0 5 10 15 20 25 35 45 55 65 >65

Influenza Hospitalization by Age Group (U.S., 1990s)

Influenza Hospitalization by Age Group, United States, 1990’s

Adapted by CTLT from Centers for Disease Control and Prevention.

Source: Reprinted from Centers For Disease Control and Prevention
Influenza in the Community: Interpandemic Period in Houston

- Influenza in the community: interpandemic period (1974–1985), Houston, Texas
- Annual infection rate
  - 300 per 1,000
- 50% of infections seek medical care
  - 150 per 1,000
- 1% of care seekers are hospitalized
  - 1–2 per 1,000
- 8% of hospitalized patients die
  - 8–16 per 100,000

Seasonality Is Related to Latitude

Pie Graphs Showing Seasonal Incidence and Latitude

Airborne Transmission of Respiratory Pathogens
**Effect of Types of Contact and Living Conditions**

Effect of types of contact and living conditions on the likelihood of contagion from common bacterial and viral respiratory tract pathogens

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bacteria</th>
<th><em>Mycobacterium tuberculosis</em></th>
<th>Influenzavirus</th>
<th>Rhinovirus, RSV*</th>
<th>Other viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type or location of contact</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casual social contact</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>School, workplace</td>
<td>Moderate</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Bar, social club</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Travel tour</td>
<td>Moderate</td>
<td>Moderate</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Dormitory</td>
<td>Moderate</td>
<td>High</td>
<td>High</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Home</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Special conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of air circulation</td>
<td>Moderate</td>
<td>High</td>
<td>High</td>
<td>None</td>
<td>Low</td>
</tr>
</tbody>
</table>

* RSV denotes respiratory syncytial virus
Three levels of nomenclature

1. Type—influenza "A, B, or C"
2. Subtype—specific HA, NA: influenza A "H3N2" (defines major surface antigens)
3. Strain—specific site and year of isolation: "A/Victoria/75 (H3N2)" (defines specific minor antigens)
Influenza Gene Segments and Proteins

From Webster RG. Virology. A Molecular Whodunit. Science 2001;293: 1773. Reprinted with permission from AAAS. All rights reserved.
# The Genes of Influenza A Virus and Their Protein Products

<table>
<thead>
<tr>
<th>RNA segment number</th>
<th>Gene production description</th>
<th>Name of protein</th>
<th>Proposed functions of protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PB1</td>
<td>Polymerase</td>
<td>RNA transcriptase</td>
</tr>
<tr>
<td>2</td>
<td>PB2</td>
<td>Polymerase</td>
<td>RNA transcriptase, virulence</td>
</tr>
<tr>
<td>3</td>
<td>PA</td>
<td>Polymerase</td>
<td>RNA transcriptase</td>
</tr>
<tr>
<td>4</td>
<td>HA</td>
<td>Hemagglutinin</td>
<td>Attachment to cell membranes; major antigenic determinant</td>
</tr>
<tr>
<td>5</td>
<td>NA</td>
<td>Neuraminidase</td>
<td>Release from membranes; major antigenic determinant</td>
</tr>
<tr>
<td>6</td>
<td>NP</td>
<td>Nucleoprotein</td>
<td>Encapsidates RNA</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>Matrix</td>
<td>Surrounds viral core; involved in assembly and budding</td>
</tr>
<tr>
<td>8</td>
<td>– NS1</td>
<td>– Nonstructural</td>
<td>– RNA binding, interferon antagonist</td>
</tr>
<tr>
<td></td>
<td>– NS2</td>
<td>– Nonstructural</td>
<td>– Unknown</td>
</tr>
</tbody>
</table>
The 15 HA and 9 NA subtypes are widely distributed in nature, though they clearly favor GI tract of aquatic birds.

It is thought that feral and domestic fowl are the natural host, with stable adaptation, little disease.
Viral Mutability: I

- RNA genome viruses have high rate of spontaneous mutation: 10^-3 to 10^-6/incorporated nucleotide (DNA viruses 10^-8 to 10^-11)
- About 1 base substitution in HA gene per viral generation, which generates an “exploration” of all variations of amino acid sequence (sim to HIV)
- High rate of replication with low fidelity will generate many new amino acid substitutions in surface glycoproteins, leading to new "drift" variants
Antigenic Variation in Influenza Virus: I

I. **Antigenic drift**: frequent minor antigenic change
   a) Point mutation (in HA: 1% change per year 1968–1979)
   b) Short insertion/deletions in surface protein genes
   c) Changes in non-surface proteins may influence replication, transmission, or tissue tropism
Changes in the influenza vaccine composition recommended by the WHO, 1973–2001. The viruses listed are the prototypes recommended for inclusion in the bivalent or trivalent (1977 onwards) vaccine. Adapted from World Health Organization.
Viral Mutability: II

- Viruses with segmented genomes generate new variants by reassortment to produce hybrids
- Co-infection of mammalian cell with 2 different 8-segmented genomes can generate 254 different variants (= viral sex)
- Variant which can replicate well in humans, and has novel surface determinants which evade existing antibodies, could be a new "shift" pandemic variant
II. **Antigenic shift:** major change; pandemic
   a) Direct infection by animal virus
   b) New genes from animal viruses: avian strains to humans, pig as intermediate “mixing vessel”
   c) Recycling of viral strains: ? release from lab
Antigenic Shift: 1968 pandemic

Gene Segment

Antigen

PB2
PB1
NS
PA
HA
NA
M
NS

PB2
PB1
NS
PA
HA
NA
M
NS

PB2
PB1
NS
PA
HA
NA
M
NS

PB2
PB1
NS
PA
HA
NA
M
NS

Epidemic Human Virus A(H2N2)

Avian Virus A(H3N?)

New Epidemic Virus A(H3N2)

Co-infection in Mixing vessel host
Chronologic History

1889-1900 (H2N2) [swine]

1900-1918 (H3N8) [swine]

1918-1958 H1N1 [swine]

1959-1967 H2N2 [swine]

1968-1989 H3N2 [avian]

1989- H1N1 [swine]
All human influenza pandemics since 1930 have originated in China.

- In 1957, Asian/57 (H2N2) acquired 3 genes by reassortment from Eurasian avian viruses and kept 5 gene segments from circulating human strains.

- In 1968, Hong Kong/68 (H3N2) acquired 2 genes by reassortment from Eurasian avian viruses and kept 6 gene segments from circulating human strains.
Section B

Policy: Vaccines and Drugs
Problems in Control of Influenza: I

- Despite relatively effective vaccine and antiviral therapy, influenza epidemics occur annually.
- Surface antigens, intrinsic virulence, transmissibility all vary independently and unpredictably.
- Ceaseless random antigenic variation mandates new vaccine production and delivery every year.
- Pandemic will occur, sooner or later.
Policy options: individual protection of high-risk subjects vs. reduction of transmission in population

Interruption of transmission requires major effort

- Close all schools, colleges, daycare, work places (effect of bad weather)
- Vaccinate >80% of population (1976 swine flu program: 45 million doses)

Use of vaccine in low-risk healthy individuals
Antiviral Therapy

- M2 inhibitors (amantadine, rimantidine)
  - Only flu A, rapid resistance develops
  - For >1 year old
- NA inhibitors (oseltamvir, zanamvir)
  - Both flu A, and B (H5N1 not clear)
  - Effective in treatment and prophylaxis (82% reduction in family contacts)
  - For >1 year (Tamiflu, since Dec 22, 2005)
Risk Factors for Severe Influenza

- Chronic pulmonary or cardiac disease
- Immunosuppression, HIV
- Sickle cell anemia, hemoglobinopathy
- Aspirin therapy: rheumatoid arthritis, Kawasaki disease
- Diabetes, renal and metabolic disease
- Pregnancy (if >14 weeks during flu season)
- Age greater than 65 years, [now 50 years]
Influenza Vaccine Recommendations

- Influenza vaccine recommendations for healthy persons without high risk
  - Health care providers, including home health care
  - Employees of long-term care facilities
  - Household members of high-risk persons
  - Persons aged 50 to 64 years
Influenza Virus and Pregnancy

- Excess mortality in pregnant women noted in 1918 Spanish flu pandemic
- Recent U.S. data shows 4.7 relative risk for hospitalization of third trimester women vs. post-partum control women
- Hospitalization rate = 250 per 100,000 pregnant women (equal to rate in cardiac or pulmonary high-risk women)
- Hence, inactivated influenza vaccine recommended for second, third trimester (1,000 doses will prevent 1–2 hospitalizations)
Neuzil et al. showed a 4.5 fold increase in hospitalization during the third trimester.

Excess hospitalization rate per 10,000 healthy women of child-bearing age range during influenza season compared to the season when influenza virus is not circulating (adapted by Neuzil et al.)
Effectiveness of Influenza Vaccine: Healthy Adults 18–64

Effectiveness of influenza vaccine in healthy adults ages 18 to 64 years


Difference ~ 11 days/100 vaccinees
Adapted by CTLT from Wilds, Steinhoff et al. JAMA 1999;281:908

New Vaccination Paradigm

- High rates of flu illness in infants and young children
- Children are important disseminators of influenza in community
- Immunization of healthy young children is a new policy
- Nasal vaccine may be the tool needed for implementation
The U.S. CDC since 2005 recommends annual flu vaccination of all infants and children older than 6 months

### Recommended Childhood and Adolescent Immunization Schedule

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Birth</th>
<th>1 month</th>
<th>2 months</th>
<th>4 months</th>
<th>6 months</th>
<th>12 months</th>
<th>15 months</th>
<th>18 months</th>
<th>24 months</th>
<th>4–6 years</th>
<th>11–12 years</th>
<th>13–18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B&lt;sup&gt;1&lt;/sup&gt;</td>
<td>HepB #1</td>
<td>HepB #2</td>
<td></td>
<td></td>
<td></td>
<td>HepB #3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria, Tetanus, Pertussis&lt;sup&gt;2&lt;/sup&gt;</td>
<td>DTaP</td>
<td>DTaP</td>
<td>DTaP</td>
<td></td>
<td></td>
<td>DTaP</td>
<td></td>
<td></td>
<td></td>
<td>DTaP</td>
<td>Td</td>
<td>Td</td>
</tr>
<tr>
<td>Haemophilus influenzae type b&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Hib</td>
<td>Hib</td>
<td>Hib</td>
<td></td>
<td></td>
<td>Hib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Inactivated Poliovirus</td>
<td>IPV</td>
<td>IPV</td>
<td>IPV</td>
<td></td>
<td></td>
<td>IPV</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Measles, Mumps, Rubella&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MMR #1</td>
<td>MMR #2</td>
<td>MMR #2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Varicella</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal&lt;sup&gt;6&lt;/sup&gt;</td>
<td>PCV</td>
<td>PCV</td>
<td>PCV</td>
<td></td>
<td></td>
<td>PCV</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Influenza&lt;sup&gt;7&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Influenza (Yearly)</td>
<td>Influenza (Yearly)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A&lt;sup&gt;8&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Vaccines below red line are for selected populations
Effect of Live Attenuated Trivalent Flu Vaccine in Children

Adapted by CTLT from Belshe, NEJM 1998;378:1405

**Flu Vaccine in Day Care Children**

- **Design**
  - 24- to 60-month-old children in day care
  - Randomized to flu (IM) or hepatitis A vaccine
- **Outcome**
  - Illness in contacts at home
- **Results**
  - In 5- to 17-year-old contacts

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missed school days</td>
<td>72%</td>
</tr>
<tr>
<td>MD visits</td>
<td>91%</td>
</tr>
<tr>
<td>A/B Rx</td>
<td>88%</td>
</tr>
<tr>
<td>Adult missed work</td>
<td>100%</td>
</tr>
</tbody>
</table>

Influenza of Children Protects Nearby Adults

Influenza Vaccination of Children Protects Nearby Adults

Percent of Children Immunized

Percent Reduction in Adult Disease

TX

MI

CA
Section C

Vaccine Production and Surveillance
Graphic summary of annual vaccine production system

Production depends on fertilized hens' eggs. Flocks of layers must be ready and laying to have 100,000 egg batches for production from April through August.

The layers come from eggs…

Influenza Surveillance Definitions

1. Influenza-like illness (ILI)
   - Fever ( >100°F) or feverishness, plus cough or sore throat

2. Culture-confirmed influenza (CCI)
   - Laboratory isolate of influenza virus

3. Influenza activity in states: none, or
   a) Sporadic: sporadic CCI or ILI, no outbreaks
   b) Regional: outbreaks of CCI/ILI in counties, <50% state population
   c) Widespread: outbreaks of CCI/ILI in counties, >50% state population
Pneumonia and Influenza Mortality in 122 U.S. Cities

Pneumonia and Influenza Mortality for 122 U.S. Cities
(Week Ending March 5, 2005)

Percent of All Death Due to Pneumonia and Influenza

Weeks

2001 2002 2003 2004

Epidemic Threshold Seasonal Baseline
Percentage of Visits for Influenza-like Illness Reported by Sentinel Providers, National Summary 2004-2005 and Previous Two Seasons
Reported Influenza Activity, Week 9 2005

Weekly Influenza Activity Estimates Reported by State and Territorial Epidemiologists (Week ending 3/5/05 - Week 9)

- No report
- Local activity
- Regional
- Widespread
Section D

Pandemic
1918–1919 Influenza Pandemic

- Called “Spanish flu”
- Caused at least 20 million deaths worldwide in one year
- Associated with end of WW I
  - Caused 43,000 U.S. military deaths, compared to 54,000 battle deaths
- In the U.S. 550,000 (about 1 in 200) died in winter 1918–1919
  - About 2% of all Native Americans died
- Case fatality was up to 50% in even young patients
- Mostly ignored by historians
In the U.S. 550,000 (about 1 in 200) died in winter 1918–1919
  - About 2% of all Native Americans died
- Case fatality was up to 50% in young adults, death within 24–48 hours with “heliotrope cyanosis”
- Unusual mortality in 20 to 40 age group and pregnant women
- Major crisis in September–October 1918: shortage of coffins, hospital staff were ill or dying, public admin flailing and failing
In U.K., two epidemics, November and March
First-Wave Diffusion of Influenza, Spring 1918
Death Rates in the United States, by Month

- 1911-1917
- 1918

1918–1919 Influenza Pandemic
1918–1919 Influenza Pandemic

Influenza Diffusion Pathways:
First Autumn Wave, Pandemic of 1918-19

Note: Numbers indicate weeks beginning Sept 14, 1918.
Baltimore, 1918--1919

- Influenza mortality rate per 1,000 population (population 599,653 in 1918)

Influenza Mortality Rate, Baltimore, 1918-1919

Population 599,653 in 1918.
Mortality for four months = 23.6/1000 or 2.4%
Age-Specific Mortality, U.K., 1918 (MOH 1920)

20-30 age group peak in winter 1918, but not in 1917

Death Rate per 1,000 Population

Age (Years)


Adapted by CTLT from Blackwell Science Ltd, Oxford, UK
Excess P&I Mortality in U.S.A., 1910 to 1921

Excess P&I Mortality in United States, 1910 to 1921
(35 Large U.S. Cities)


In Philadelphia the number of dead quickly overwhelmed the city’s ability to handle bodies. It was forced to bury people, without coffins, in mass graves and soon began using steam shovels to dig the graves.
Public health authorities desperately recommended many procedures now regarded as useless: spraying disinfectant, wearing gauze masks, banning spitting and shaking hands. Churches were closed, and bars were open.
### Biological Criteria for a Pandemic Influenza Virus

1. New surface antigen
2. Human virulence
3. Human transmissibility
4. Other factors

<table>
<thead>
<tr>
<th></th>
<th>1918 H1N1</th>
<th>1997–04 H5N1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. New surface antigen</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2. Human virulence</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3. Human transmissibility</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>4. Other factors</td>
<td>(WW I?)</td>
<td>?</td>
</tr>
</tbody>
</table>
Influenza Virus

CDC
Little warning: 1–6 months from emergence to U.S. epidemic
Outbreaks simultaneously in many airport cities
CDC estimate of impact over 2–3 months
- 200 million infected
- 40 to 100 million ill
- 18 to 45 million clinic visits
- 300,000 to 800,000 hospital admissions
- 88,000 to 300,000 deaths
Antivirals will be in short supply
Six months to produce vaccine
Projected Influenza Pandemic Deaths

Projections of Numbers of Deaths During the Next Influenza Pandemic
(Based on Statistics from the 1918-1919 Pandemic)


The Next Influenza Pandemic: Current Plans

- Worldwide surveillance, with rapid identification of new viruses (in place)
- Plan for rapid vaccine production
- Stockpile antivirals, especially for military, emergency, and medical staff
Global Lab Surveillance for Influenza Is Limited

600 Million to 1,200 Million Cases Worldwide

157,759 Total Samples Collected

134,210 Influenza-Negative (85% of Total)

23,549 Influenza-Positive (15% of Total)

17,750 Type A

18 Subtype H1N1

5,799 Type B

5,801 Subtype H3N2

Pandemic Policy Problems

- Not enough vaccine
- Not enough antivirals (oseltamvir)
- Classical epidemic control
  - Physical restriction of people
    - Isolation of the sick
    - Quarantine of the exposed
    - Ban all public gatherings: work, school, shopping malls, theaters, churches, and yes, bars and clubs
WHO Pandemic Alert, August 2006

Current WHO phase of pandemic alert

November 2005

CURRENT PHASE OF ALERT IN THE WHO GLOBAL INFLUENZA PREPAREDNESS PLAN

Inter-pandemic phase
- New virus in animals, no human cases
- Pandemic alert
- New virus causes human cases

Low risk of human cases

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No or very limited human-to-human transmission</td>
</tr>
<tr>
<td>2</td>
<td>Evidence of increased human-to-human transmission</td>
</tr>
<tr>
<td>3</td>
<td>Evidence of significant human-to-human transmission</td>
</tr>
<tr>
<td>4</td>
<td>Efficient and sustained human-to-human transmission</td>
</tr>
</tbody>
</table>

Higher risk of human cases

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>No or very limited human-to-human transmission</td>
</tr>
<tr>
<td>3</td>
<td>Evidence of increased human-to-human transmission</td>
</tr>
<tr>
<td>4</td>
<td>Evidence of significant human-to-human transmission</td>
</tr>
<tr>
<td>5</td>
<td>Efficient and sustained human-to-human transmission</td>
</tr>
<tr>
<td>6</td>
<td>Pandemic</td>
</tr>
</tbody>
</table>

printable version
### Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO

**21 March 2006**

<table>
<thead>
<tr>
<th>Country</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cases</td>
<td>deaths</td>
<td>cases</td>
<td>deaths</td>
<td>cases</td>
</tr>
<tr>
<td>Azerbaijan</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>3</td>
<td>3</td>
<td>29</td>
<td>20</td>
<td>61</td>
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<tr>
<td><strong>Total</strong></td>
<td>3</td>
<td>3</td>
<td>46</td>
<td>32</td>
<td>95</td>
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</table>

*Total number of cases includes number of deaths.*

*WHO reports only laboratory-confirmed cases.*
Vaccine for H5N1 Influenza

- Vaccine difficult to grow in routine egg system, since pathogenic to chickens and chick embryos
- Preliminary Phase I trials at Johns Hopkins and elsewhere have shown safety and immunogenicity, though doses for immunization are much higher than for previous vaccines
Nine Countries Produce Flu Vaccine in 2005

- Australia
- Canada
- France
- Germany
- Italy
- Japan
- Netherlands
- United Kingdom
- United States
Worldwide Distribution of Influenza Vaccine Doses

Number of Influenza Vaccine Doses Distributed in Various Regions (1994-2003)

Adapted by CTLT from WHO Global Influenza Programme.
“Silver lining” factor
  - Improved surveillance
  - Planning for vaccine strategies, vaccine supply
  - Attention of media, governments, markets
  - May break the vicious cycle of neglect, followed by no effort or investment
Concluding Remarks: Infectiousness

William Moss, MD, MPH
Johns Hopkins University
Infectiousness

- Probability of a susceptible person coming in contact with an infected person
  - Probability of being susceptible
  - Prevalence of infection in population
- Probability that infectious agent is transmitted during the contact
  - Characteristics of contact
Basic Transmission Equation

\[ R_0 = \beta cD \]

- \( R_0 \): basic reproductive number
- \( \beta \): rate of transmission per contact
- \( c \): rate of new contacts
- \( D \): average infectious period
Number of cases among people at risk

Total number of people at risk

Assumptions:

1. All persons in denominator were exposed
2. All persons in denominator were susceptible
3. All cases were detected (e.g., no subclinical cases)
Infectiousness in the Household

Infectiousness of communicable diseases in the household (measles, chickenpox, and mumps)

“Infectiousness, the ability of a disease to spread in a community, is a measurable characteristic and should be susceptible of being expressed precisely.”
“It is insufficient to recognize that measles is more infectious than mumps. How much more infectious? Does infectiousness vary from time to time, and from place to place? What other attributes are quantitatively associated with its degree of infectiousness?”
Study of household chains of transmission of measles, mumps, and chicken pox

- Gloucestershire, England
- 1947 to 1951
- Active household case surveillance after identification of index case
- Identified susceptible siblings through parental report
Measurement of Exposure

- Household secondary attack rate

\[
\frac{\text{number of cases in household*}}{\text{number of susceptible children in household}}
\]

- “Susceptible exposure attack rate”

\[
\frac{\text{number of transmissions in household*}}{\text{number of exposures to susceptibles in household}}
\]

Need to distinguish generations of cases

* not including the index case
Household Secondary Attack Rate

Household Secondary Attack Rate = 2/4 = 50%
Susceptible Exposure Attack Rate = \frac{2}{9} = 22\%
<table>
<thead>
<tr>
<th></th>
<th>Measles</th>
<th>Varicella</th>
<th>Mumps</th>
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<tbody>
<tr>
<td><strong>Infectiousness (%)</strong></td>
<td>76</td>
<td>61</td>
<td>31</td>
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<tr>
<td><strong>Mean age of infection (years)</strong></td>
<td>5.6</td>
<td>6.7</td>
<td>11.5</td>
</tr>
<tr>
<td><strong>Age by which 90% of cases have disease</strong></td>
<td>8.3</td>
<td>10.7</td>
<td>29</td>
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</table>
First quantitative estimate of infectiousness
- Measles most infectious
- As infectiousness increases, the average age of infection decreases
- Little seasonal variation in infectiousness