Emerging infectious diseases: spotlight on influenza A

George W. Rutherford, M.D.
Rebecca Grossman-Kahn
University of California, San Francisco
Institute for Global Health
San Francisco, CA

Prepared as part of an education project of the Global Health Education Consortium and collaborating partners
Learning objectives

• Understand common factors for disease emergence & identify specific examples of each
• Appreciate how ecological and human technological and behavioral changes have influenced the emergence of infectious diseases
• Understand antigenic drift and shift
• Understand the different types of Influenza and the basic biology of the virus
• Outline recent history of avian influenza and discuss why it is an urgent public health concern
Emerging infectious diseases

Infectious diseases whose incidence in human populations has increased in the past 20 years or threatens to increase in the near future

- Not previously seen in humans (e.g. SARS)
- Virtually disappeared but made comeback (e.g. diphtheria)
- Genetics changed to make disease greater threat (e.g. multidrug-resistant bacterial infections)

(Institute of Medicine, 1992).
Examples of emerging and re-emerging infectious diseases

**Viruses and prions**
- Dengue Fever
- Ebola Virus
- HIV
- Hepatitis C
- Influenza A (H5N1, H7N7)
- Monkeypox
- Rift Valley Fever
- SARS coronavirus
- Sin nombre hantavirus
- vCJD/BSE

**Bacteria**
- Lyme Disease
- Diphtheria
- Legionnaire’s Disease
- Cholera
Why are they emerging?

Group A streptococci

Vibrio cholerae

Ebola virus

Mycobacterium tuberculosis
“The spectrum of infectious disease is changing rapidly in conjunction with dramatic changes in our society and environment. Worldwide, there is explosive population growth with expanding poverty and urban migration; international travel is increasing; and technology is rapidly changing—all of which affect our risk of exposure to the infectious agents with which we share our environment. Despite historical predictions to the contrary, we remain vulnerable to a wide array of new and resurgent infectious diseases.”

Dr. David Satcher, then director of CDC, in the preface to a report *Addressing Emerging Infectious Diseases Threats: A Prevention Strategy for the United States*
Factors contributing to emerging infectious diseases

- Global travel
- Globalization of food supply and central processing of food
- Population growth, urbanization & crowding
- Increased crowding with domestic animals
- Population movements due to civil wars, famines, and other man-made or natural disasters
Factors contributing to emerging infectious diseases (cont.)

- Irrigation, deforestation, reforestation projects that alter habitats of diseases carrying insects and animals
- Human behaviors such as IV drug use and risky sexual behavior
- Increased use of antimicrobial agents and pesticides, thus lending to resistance
- Increases human contact with tropical rain forests and other wilderness habitats
Challenges in preventing disease emergence and re-emergence

• Rationalizing use of antibiotics
• Population-level increased susceptibility to less pathogenic organisms because of immunosuppression
• Increased efficiency of human-to-human transmission afforded by modern medical practices (e.g. transfusion & transplantation)
• Risk of novel pathogens crossing into humans through environmental degradation & medical procedures (e.g. harvesting organs from animals for xenotransplantation)
How to prevent disease emergence has become an important topic nationally. CDC published its updated plan, *Preventing Emerging Infectious Diseases: A Strategy for the 21st Century*, in 1998. The plan outlined four goals: surveillance and response, applied research, infrastructure and training, and prevention and control. These goals are to focus on nine specific problems:

**Antimicrobial resistance** in bacteria, parasites, viruses, fungi and arthropod vectors is caused by antibiotic overuse and misuse, leading to fewer treatment choices and infections that are more difficult, if not impossible, to treat.

**Foodborne and waterborne diseases** are facilitated by new methods of food procurement (globalization of the food supply), multistate food distribution systems and emergence of waterborne pathogens resistant to routine disinfection.

**Vectorborne and zoonotic diseases** will increase as habitats of animals and arthropod vectors change and increase the risk of exposure for humans. For instance, if sea levels rise as a result of climate change, vast new stretches of the Central Valley will become wetlands again with a resultant increase in vector density.

4. **Diseases transmitted through blood transfusions and blood products** have been problematic since the introduction of blood transfusion in World War I. Several parenterally transmissible pathogens have been recognized since the 1980s, including HIV, hepatitis C and *Trypanosoma cruzi*, the causative agent of Chaga’s disease. As the population ages and blood transfusions increase, there is a distinct possibility that new pathogens may emerge; this happened very recently with West Nile virus.
Chronic diseases caused by infectious agents, as exemplified by *Helicobacter pylori* as a cause of peptic ulcer disease and speculation around *Chlamydia pneumoniae* as a cause of coronary heart disease, have been recently recognized. Older examples include the recognition of syphilis as the cause of the psychiatric disorder generalized paresis of the insane in the 19th century and the recognition of Lyme disease as the cause of a peculiar cluster of juvenile rheumatoid arthritis in the 1970s. As research matures, new microbial prevention and treatment targets may emerge for diseases previously through to be mediated by environmental factors.

Vaccine development and use are needed to keep certain infectious diseases under control, to bring new immunizations into public health program (e.g., human papillomavirus vaccine) and to create new immunizations for huge public health problems (e.g., HIV and malaria). Note that the re-emergence of diphtheria was the direct consequence of the collapse of childhood immunization programs at the end of the Soviet Union.

Diseases of persons with impaired immunity due to medical treatment, age or infection (e.g., HIV) are of particular concern both in the U.S. and worldwide as the number of immunosuppressed persons has exploded worldwide (primarily as the result of HIV).

Diseases of pregnant women and neonates of concern include asymptomatic diseases in pregnant women that can increase fetus’s risk of premature birth (e.g., Group B Streptococcus) or can be transmitted from mother to child during pregnancy, delivery or breastfeeding. Worldwide, mother-to-child transmission of HIV and congenital syphilis are two daunting public health problems.

Diseases of travelers, immigrants and refugees will only increase. Persons who travel into new areas are at risk of acquiring locally endemic disease (for example, retirees who move to southern Arizona and are exposed to coccidioidomycosis) and can also disseminate diseases to relatively susceptible populations. Transmission of tuberculosis from the persons born in endemic regions to non-immune Californians is a major public health problem.
Influenza virus

- Orthomyxoviridae family
- Single stranded RNA
- 3 types: A, B, C
- Subtype of A determined by hemagglutinin and neuraminidase surface antigens
Influenza virus

- Type A – Moderate to severe illness
  Affects humans of all age groups and other animals
- Type B – Milder illness
  Affects only humans, mostly children
- Type C – Rarely reported in humans
  No epidemics

CDC: [http://www.cdc.gov/flu](http://www.cdc.gov/flu)
Influenza virus

Influenza type  Year of isolation  Hemagglutinin subtype

A/Sydney/5/97 (H3N2)

Geographic source  Isolate number  Neuraminidase subtype

Note that the RNA is broken up into 8 separate strands.
Genome organization
(what the different RNA strands code for)

<table>
<thead>
<tr>
<th>SEGMENT</th>
<th>PROTEINS</th>
<th>ACTIVITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PB2</td>
<td>POLYMERASE</td>
</tr>
<tr>
<td>2</td>
<td>PB1</td>
<td>POLYMERASE</td>
</tr>
<tr>
<td>3</td>
<td>PA</td>
<td>POLYMERASE</td>
</tr>
<tr>
<td>4</td>
<td>HA</td>
<td>ATTACHMENT</td>
</tr>
<tr>
<td>5</td>
<td>NP</td>
<td>NUCLEOCAPSID</td>
</tr>
<tr>
<td>6</td>
<td>NA</td>
<td>NEUROAMINIDASE</td>
</tr>
<tr>
<td>7</td>
<td>M1, M2</td>
<td>MATRIX</td>
</tr>
<tr>
<td>8</td>
<td>NS1, NS2</td>
<td>PROCESSING, INTERFERON</td>
</tr>
</tbody>
</table>

Polymerases are enzymes involved in the reproduction of the virus’s RNA.

**Hemagglutinin** and **neuraminidase** are surface proteins that the immune system recognizes.

Nucleocapsid and matrix code for proteins involved in the internal structure of the virus.
Influenza A in nature

• Influenza A is a virus of waterfowl (Class Anseriformes) that accidentally infects other birds and mammals

• Most commonly infects chickens and other poultry (Class Galliformes), pigs, horses and humans; other avian classes can be infected

• The density of these different species (especially humans, ducks, pigs and chickens) and the proximity at which they live with each other has a lot to do with how easily they can be transmitted
Hemagglutinin and neuraminidase subtypes of influenza A

<table>
<thead>
<tr>
<th>Hemagglutinin</th>
<th>Neuraminidase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Human</td>
</tr>
<tr>
<td>H1</td>
<td>x</td>
</tr>
<tr>
<td>H2</td>
<td>x</td>
</tr>
<tr>
<td>H3</td>
<td>x</td>
</tr>
<tr>
<td>H4</td>
<td></td>
</tr>
<tr>
<td>H5</td>
<td>x</td>
</tr>
<tr>
<td>H6</td>
<td></td>
</tr>
<tr>
<td>H7</td>
<td>x</td>
</tr>
<tr>
<td>H8</td>
<td>x</td>
</tr>
<tr>
<td>H9</td>
<td>x</td>
</tr>
<tr>
<td>H10</td>
<td></td>
</tr>
<tr>
<td>H11</td>
<td></td>
</tr>
<tr>
<td>H12</td>
<td></td>
</tr>
<tr>
<td>H13</td>
<td></td>
</tr>
<tr>
<td>H14</td>
<td></td>
</tr>
<tr>
<td>H15</td>
<td></td>
</tr>
</tbody>
</table>

There is a lot of variation in these surface proteins with $15 \times 9$ different possible combinations.
## New non-pandemic influenza strains in humans

<table>
<thead>
<tr>
<th>Year</th>
<th>Flu</th>
<th>Virus</th>
<th>Geography</th>
</tr>
</thead>
<tbody>
<tr>
<td>1977</td>
<td>“Russian”</td>
<td>Type A (H1N1)</td>
<td>Northern China</td>
</tr>
<tr>
<td>1997</td>
<td></td>
<td>Type A (H5N1)</td>
<td>Hong Kong</td>
</tr>
<tr>
<td>1999</td>
<td></td>
<td>Type A (H9N2)</td>
<td>Hong Kong</td>
</tr>
<tr>
<td>2002</td>
<td></td>
<td>Type A (H7N2)</td>
<td>Virginia</td>
</tr>
<tr>
<td>2003</td>
<td></td>
<td>Type A (H7N7)</td>
<td>Netherlands</td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td>Type A (H7N3)</td>
<td>Canada</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type A (H10N7)</td>
<td>Egypt</td>
</tr>
</tbody>
</table>

Inhibition of Influenza virus replication by antivirals

Palese, Nat. Med. 2005
Influenza antigenic changes

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

- Drift: Minor change, same subtype, e.g. H3N2
  - Point mutations that occur during viral replication
  - Allows a person to get several infections in lifetime with same type or subtype of influenza

- Shift: Major change, new subtype (new HA or HA & NA)
  - Exchange of gene segment (reassortment)
  - May result in pandemic

A pandemic is an epidemic over a wide geographic area and affecting a large proportion of the population
Mechanisms of influenza virus antigenic ‘shift’

15 HAs
9 NAs

Direct

Non-human virus

Human virus

Reassortant virus
Occurrence of influenza pandemics and epidemics

- Incidence of clinically manifest influenza
- Mean level of population antibody vs A HxNx
- Mean level of population antibody vs A HyNy

Introduction of hypothetical A HxNx virus

Significant minor variation in A HxNx may occur at any of these points. Epidemics may or may not be associated with such variations.

Introduction of hypothetical A HyNy (major new subtype), variant A HxNx disappears.

Greatest infectious disease mortality in the 20th century was caused by the 1918-1919 influenza A strain.

What was so special about the 1918 virus?

- Researchers have recovered virus from pathological specimens from 1918 and from excavations of influenza victims buried in permafrost in 1918
- H1N1 virus but the three polymerase genes are very, very different from current strains
- More efficient polymerases mean that new viruses are made more rapidly and in higher numbers
- So, don’t forget reassortment completely but know that there are other things that can go wrong
Sequencing Flu 1918 strain

• Frozen material cloned and sequenced
• Sequence analysis: differences to avian strains
  PB1 (7 aa), PB2 (5 aa), PA (7 aa)
• 1918 strain derived entirely from an avian strain
  (1957 and 1968 were part avian & part human)
  Taunbenberg et al., Nature, 2005
1918 hemagglutinin causes severe lung damage

Kobasa et al. Nature 2004; 431:703
## Influenza pandemics in the 20th century

<table>
<thead>
<tr>
<th>Years</th>
<th>Flu</th>
<th>Virus</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918-1919</td>
<td>“Spanish”</td>
<td>Type A (H1N1)</td>
<td>20 million worldwide</td>
</tr>
<tr>
<td>1957-1958</td>
<td>“Asian”</td>
<td>Type A (H2N2)</td>
<td>2 million worldwide</td>
</tr>
<tr>
<td>1968-1969</td>
<td>“Hong Kong”</td>
<td>Type A (H3N2)</td>
<td>1 million worldwide</td>
</tr>
</tbody>
</table>


**Annually 36,000 deaths and 200,000 hospitalizations from influenza in US**
Avian influenza

- Influenza viruses are viruses of waterfowl (Anseriformes) that can spread to domestic poultry (Galliformes)
- Probably fecal-oral transmission in wild, respiratory transmission in closed spaces (such as hen houses)
- Highly pathogenic (to birds) are H5 and H7
- Circulation of low pathogenic avian flu in domestic poultry leads to mutations and highly pathogenic forms over time (drift); highly pathogenic strains lead to die offs
- Co-infection of avian strains in swine or humans infected with human influenza can result in genetic reassortment and highly pathogenic strains (shift)
Interspecies transmission requires opportunity...
For birds of many species and from many sources come together
And for Many people to come in contact with poultry
Avian influenza has typically been thought to be relatively non-pathogenic in wild birds. But H5N1 has caused mortality in a growing number of species. Dead birds don’t fly far.
Mildly pathogenic avian influenza
Highly pathogenic avian influenza
History of avian influenza

- 1959 - 2005: 21 outbreaks of highly pathogenic avian influenza (HPAI) reported worldwide; five outbreaks with significant spread
- 1983: Pennsylvania (H5N2). 17 million birds culled
- 1997: Hong Kong (H5N1). 1.5 million birds culled, 18 human cases, 6 deaths
- 2003: Netherlands (H7N7). 30 million birds culled, 89 human cases, one death
What’s going on now

• We’re worried about two things
  – Continued spread of H5N1 influenza around the world by migratory birds, which can cause human cases of avian influenza when people come into close contact with infected birds
  – Reassortment of H5N1 so that it can be easily transmitted from human to human

• Substantial evidence of spread
  – 2003-now: Asia (H5N1). Avian outbreaks ongoing in domestic poultry and wild birds in Asia, Africa, Europe; human cases in Vietnam, Thailand, Cambodia Indonesia, China, Turkey, Iraq, Azerbaijan
  – Minimal or no evidence of reassortment (yet)
H5N1 influenza isolates from birds, cumulative and 2006

H5N1 influenza cases in humans, cumulative and 2006
How will H5N1 influenza virus get to North America?
First case of avian influenza in California?
Continuing activity in Southeast Asia

• No isolates from 1997-2003
• Since December 2003 outbreaks among poultry and wild birds reported in Cambodia, China, Indonesia, Japan, Kazakhstan, Laos, Malaysia, Mongolia, Philippines, Russia, South Korea, Taiwan, Thailand, Vietnam
  – 150 M deaths in birds
  – 154 human cases and 87 deaths in Cambodia, Indonesia, Thailand and Vietnam
• Spread to Africa and Europe in migratory birds
• 2 potential clusters of human-to-human transmission in families in Vietnam and Thailand
And spread across Asia...
New cases of human H5N1 influenza, 2006 through May 8
Affected areas with confirmed human cases of H5N1 avian influenza since January 2006

Status as of 27 April 2006

Turkey
Cases: 12
Deaths: 4

Azerbaijan
Cases: 8
Deaths: 5

China
Cases: 10
Deaths: 7

Egypt
Cases: 12
Deaths: 4

Iraq
Cases: 2
Deaths: 2

Cambodia
Cases: 2
Deaths: 2

Indonesia
Cases: 15
Deaths: 13

Areas with confirmed human cases

Country, area or territory
Cases: cumulative number
Deaths: cumulative number

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: WHO / Map Production: Public Health Mapping and GIS Communicable Diseases (CDS) World Health Organization

© WHO 2006. All rights reserved
H5N1 clinical presentation
Chotpitayasunondh et al, Emerg Inf Dis Feb 2005;11(2)

- Twelve confirmed H5N1 cases in Thailand 2003
- Eight died for a 67% case fatality rate
- Initial symptoms include fever, cough and shortness of breath
- Myalgias and diarrhea in 50%
- Progression to organ failure (respiratory, cardiac and renal) within one week
- Lymphopenia (58%) and thrombocytopenia (33%)
- Development of ARDS associated with death
Influenza A (H5N1) pneumonia

Hien. NEJM 2004;350:1179
Human H5N1 is most common in children

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Onset</th>
<th>Exposure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>M</td>
<td>3 Jan</td>
<td>Dead poultry at neighbors</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>6 Jan</td>
<td>Dead poultry at neighbors</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>7 Jan</td>
<td>Sick poultry at neighbors</td>
<td>Died</td>
</tr>
<tr>
<td>58</td>
<td>F</td>
<td>19 Jan</td>
<td>Sick poultry in backyard</td>
<td>Died</td>
</tr>
<tr>
<td>27</td>
<td>F</td>
<td>20 Jan</td>
<td>Purchased, cooked chicken from affected area</td>
<td>Recovered</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>21 Jan</td>
<td>Sick/dead fighting cocks, poultry in backyard</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>24 Jan</td>
<td>Dead poultry in backyard</td>
<td>Died</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>25 Jan</td>
<td>Sick poultry in backyard</td>
<td>Recovered</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>26 Jan</td>
<td>Sick poultry in backyard</td>
<td>Died</td>
</tr>
<tr>
<td>47</td>
<td>F</td>
<td>3 Feb</td>
<td>Sick/dead fighting cocks in backyard</td>
<td>Recovered</td>
</tr>
<tr>
<td>29</td>
<td>M</td>
<td>13 Feb</td>
<td>Sick/dead fighting cocks, chicken in backyard</td>
<td>Recovered</td>
</tr>
<tr>
<td>39</td>
<td>F</td>
<td>1 Mar</td>
<td>Dead fighting cock at neighbors</td>
<td>Died</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>31 Aug</td>
<td>Sick/dead fighting cock in backyard</td>
<td>Died</td>
</tr>
</tbody>
</table>

Chotpitayasunondh. MMWR 2004;53:100
H5N1 – Concerning Developments

• H5N1 in pigs – pigs in China tested in 2003 showed evidence of H5N1 infection (risk of reassortment)
• Increased virulence in mammals – a Chinese researcher showed increased virulence of recent H5N1 strains in a mouse model
• H5N1 has become endemic in wild birds – thus culling infected domestic poultry is unlikely to prevent recurrent outbreaks
• But H5N1 has been circulating in China since 1996
### WHO stages of pandemic alert

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interpandemic phase</td>
<td>Low risk of human cases</td>
<td>1</td>
</tr>
<tr>
<td>New virus in animals, no cases in humans</td>
<td>Higher risk of human cases</td>
<td>2</td>
</tr>
<tr>
<td>Pandemic alert</td>
<td>No or very limited human-to-human transmission</td>
<td>3</td>
</tr>
<tr>
<td>New virus causes human cases</td>
<td>Evidence of human-to-human transmission</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Evidence of significant human-to-human transmission</td>
<td>5</td>
</tr>
<tr>
<td>Pandemic</td>
<td>Efficient and sustained human-to-human transmission</td>
<td>6</td>
</tr>
</tbody>
</table>
Disease prevention and control

- Basic respiratory hygiene measures
- Specific Vaccine for avian H5N1 virus
- Anti-viral medications
- Community measures for outbreak containment
- Basic Message: Stay home when sick
Seasonal influenza

- Seasonal (intra-pandemic) influenza is a significant cause of morbidity and mortality in its own right
- Can be prevented either by vaccine or antiviral prophylaxis (if known exposure)
- Because of antigenic drift influenza vaccine needs to be reformulated annually
- Current vaccine is trivalent -- A (H1N1), A (H3N2), B
- Given preferentially to persons at highest risk of severe morbidity and mortality (or those in close contact with them (e.g., health care workers)
Persons who should receive influenza vaccine - 2006

- Children aged 6–59 months
- Women who will be pregnant during the influenza season
- Persons aged >50 years
- Children and adolescents (aged 6 months–18 years) who are receiving long-term aspirin therapy and might be at risk for experiencing Reye syndrome after influenza infection
- Adults and children who have chronic disorders of the pulmonary or cardiovascular systems
- Adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases
- Adults and children who have any condition that can compromise respiratory function or the handling of respiratory secretions, or that can increase the risk for aspiration
- Residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions
- Persons who live with or care for persons at high risk for influenza-related complications, including healthy household contacts and caregivers of children aged 0–59 months
- Health-care workers
Papers

Web links
2. CDC Emerging Infectious Diseases: http://www.cdc.gov/ncidod/diseases/eid/index.htm
Credits

George W. Rutherford, M.D.
Rebecca Grossman-Kahn
University of California, San Francisco
Institute for Global Health
San Francisco, CA 2006
Acknowledgements

The Global Health Education Consortium gratefully acknowledges the support provided for developing these teaching modules from:

Margaret Kendrick Blodgett Foundation
The Josiah Macy, Jr. Foundation
Arnold P. Gold Foundation

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 3.0 United States License.