



# Avian Influenza

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June 22, 2006

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# Seasonal, Avian, and Pandemic Influenza

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- Seasonal influenza viruses
    - A public health problem **every year**
    - Circulates throughout the human population
    - Spread easily from person to person
  - Avian influenza A (H5N1)
    - Devastating global outbreak in poultry
    - Severe but rare human infections
    - Does **not spread easily** from person to person
  - Pandemic influenza virus
    - A new influenza A subtype can infect humans
    - Causes serious illness
    - Spreads easily from human-to-human
- ❖ H5N1 is a likely candidate, but is not a pandemic virus yet



# Impact of Influenza



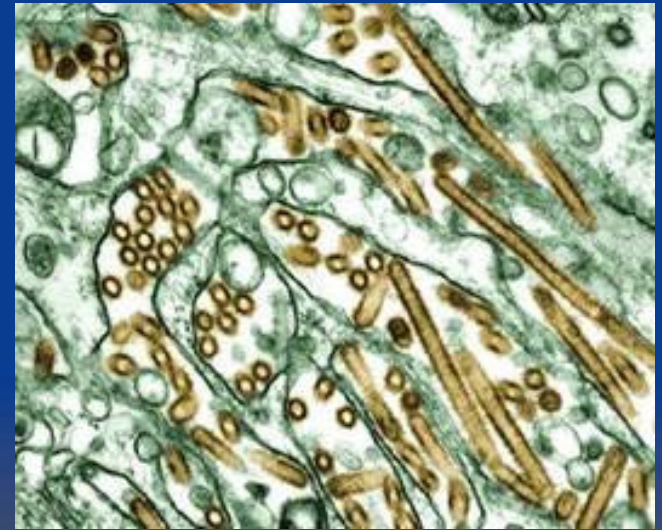
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- An annual public health problem
- Substantial health impact
  - 36,000 excess deaths per year
  - 200,000 hospitalizations per year
  - 10-35% of children each year
  - 5-20% of adults each year
- Substantial economic impact
  - Lost work / school days
  - Overwhelmed medical care systems

# Influenza Viruses

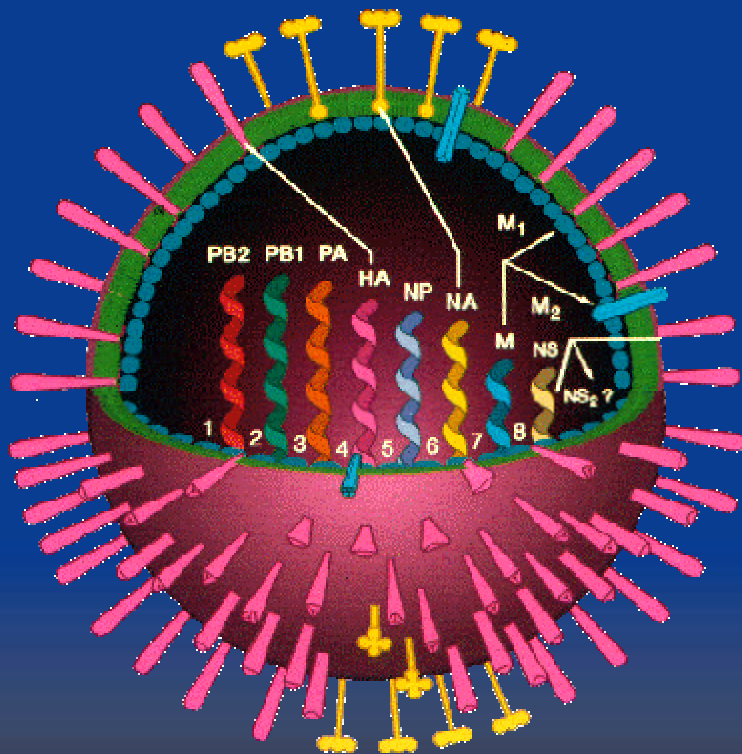


- Classified into types A, B, and C
- Only Types A and B cause significant disease
- Types B and C limited to humans
- Type A viruses
  - More virulent
  - Affect many species



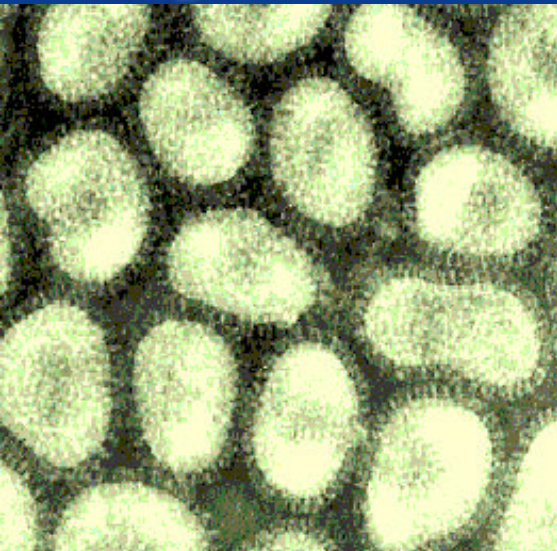
C Goldsmith, CDC

# Influenza virus



- **SS negative-sense RNA virus**
- **8 gene segments encoding at least 10 proteins**
  - **Surface glycoproteins:**
    - Hemagglutinin (HA)
    - Neuraminidase (NA)

# Key Influenza A Viral Features



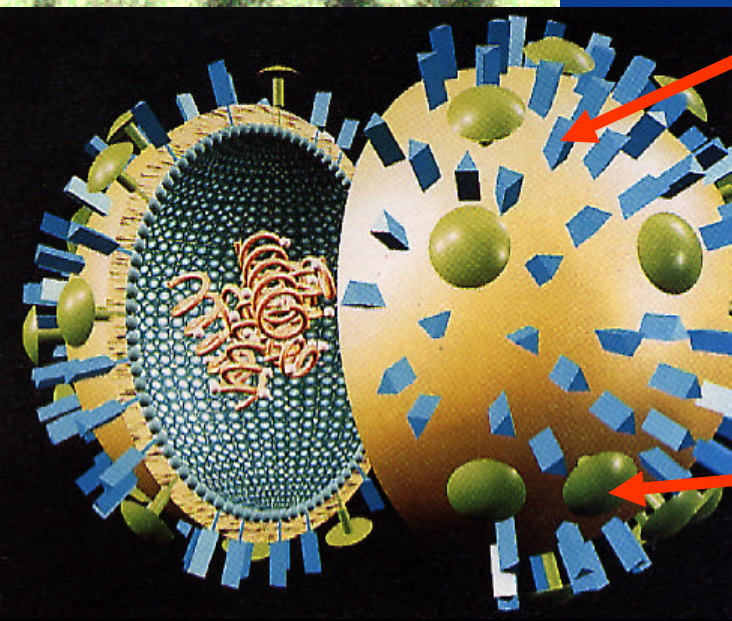
## Two Surface proteins (major antigens)

- **Hemagglutinin (HA)**

- Site of attachment to host cells
- Antibody to HA is protective

- **Neuraminidase (NA)**

- Helps release virions from cells
- Antibody to NA can help modify disease severity

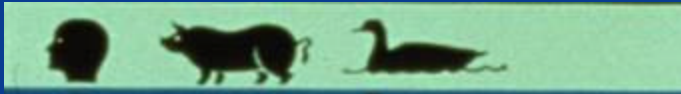


**HA**

**NA**

# Influenza A HA and NA Subtypes

H1



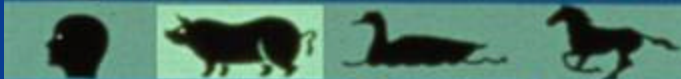
N1

H2



N2

H3



N3

H4



N4

H5



N5

H6



N6

H7



N7

H8



N8

H9



N9

H10



H11



H12



H13



H14



H15, H16



# Avian Influenza A Viruses

- Wild waterfowl are natural reservoir
  - Infect respiratory and gastrointestinal tracts of birds
  - Usually do not cause disease
  - Genetic re-assortment is frequent
- Viruses are present in respiratory secretions, feces
  - Can survive at low temperatures and low humidity for days to weeks, and in water







# Avian Influenza Viruses



- Usually do not jump species
  - Each “subtype” infects a specific set of animals
  - Wild bird strains do not usually infect domestic poultry
- Usually do not infect people
- Classified by subtype, and **pathogenicity**
  - High and low pathogenic avian influenza (HPAI, LPAI)
    - Molecular sequencing
    - Pathogenicity criteria (in chickens)
  - High path only found in H5 and H7 subtypes
  - High path usually mild in wild birds but severe in poultry

# H5N1 Epizootic 2003-06

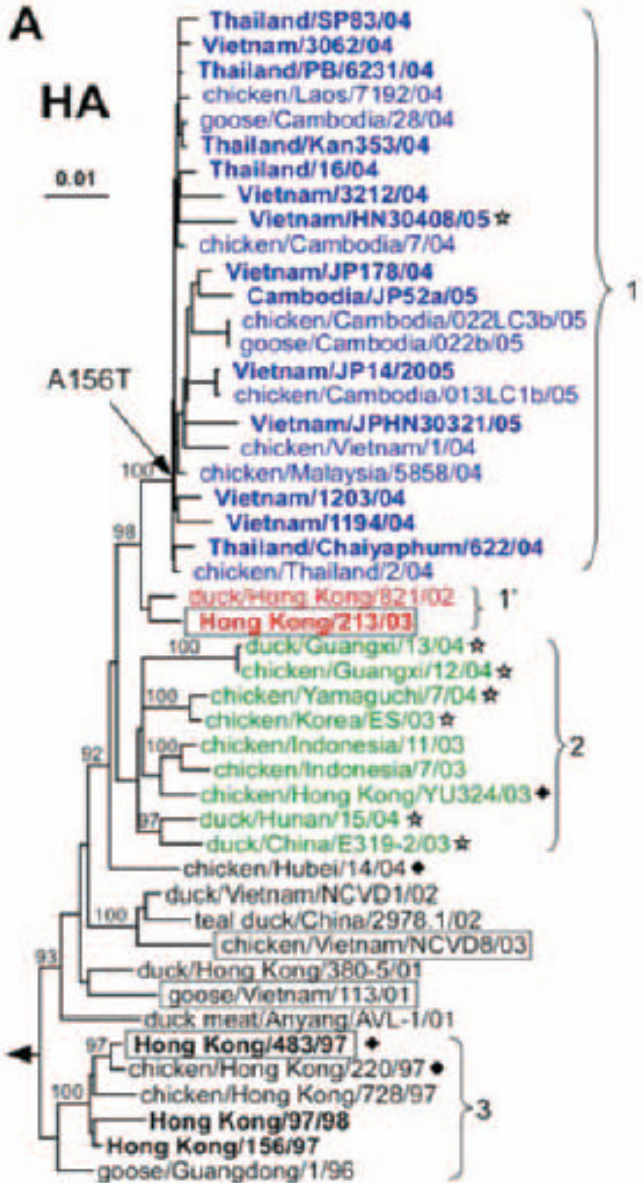
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- **Unprecedented HPAI (H5N1) outbreak among poultry**
  - Commercial farms, backyard flocks affected
  - Millions of poultry died or killed
- **Reported outbreaks**
  - **2003:** Hong Kong, Republic S. Korea
  - **2004:** Thailand, Laos, Cambodia, Indonesia, Malaysia, China, Japan
  - **2005:** Kazakhstan, Romania, Russia, Turkey, Ukraine, Croatia, Mongolia
  - **2006:** Iraq, Nigeria, Azerbaijan, Bulgaria, Greece, Italy, Slovenia, Iran, Austria, Germany, Egypt, India, France, Bosnia/Herzegovina, Albania, Niger, Cameroons, Czech Republic, Denmark, Hungary, Poland, Serbia/Montenegro, Slovakia, Sweden, Switzerland, Jordan, Israel, Georgia, Afghanistan, Pakistan, Myanmar, Djibouti...

# H5N1 Epizootic 2003-2006

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- Since December 2004, a third wave of H5N1 poultry outbreaks has been ongoing
- Virus continues to change
  - Now causes disease in wild birds
  - Asymptomatic in domestic ducks
  - Increasingly pathogenic in experimental infections
  - Infections in felines, pigs
  - 2 virus clades





# Human Infections with LPAI



- Mild or uncomplicated illness with LPAI  
*(usually without poultry outbreaks)*
- H7N7 (conjunctivitis)
  - 1996: U.K. (1 case, no death)
- H9N2 (influenza-like illness)
  - 1998: China (6 cases, no deaths)
  - 1999: Hong Kong (2 cases, no deaths)
  - 2003: Hong Kong (1 case, no death)
- H7N2 (influenza-like illness)
  - 2002, 2003: U.S. (2 cases, no deaths)



# Human infections with HPAI



Mild to severe human illness with HPAI  
*(usually associated with poultry outbreaks)*

- **H7N7 (mild illness, conjunctivitis)**
  - 2003 Netherlands (89 cases, 1 death)
    - Most cases were poultry workers
- **H7N3 (mild illness, conjunctivitis)**
  - 2004 Canada (2 cases, 0 deaths)
- **H5N1 (severe respiratory disease)**
  - 1997 Hong Kong (18 cases, 6 deaths)
    - Risk factor: visiting live poultry market
  - 2003 Hong Kong (2 cases, 1 death)
  - 2003-05 Vietnam, Thailand, Cambodia, Indonesia, China
  - 2006 Turkey, Iraq, Azerbaijan, Egypt, Djibouti

# Avian Influenza in Humans



Year	Subtype	Location	Cases	Deaths
1996	H7N7	United Kingdom	1	0
1997	H5N1	Hong Kong	18	6
1998	H9N2	China	6	0
1999	H9N2	Hong Kong	2	0
2002	H7N2	United States	1	0
2003	H7N2	United States	1	0
2003	H9N2	Hong Kong	1	0
2003	H5N1	Hong Kong	2	1
2003	H7N7	The Netherlands	89	1
2004	H7N3	Canada	2	0
2003- 06	H5N1	Worldwide		

Yellow = HPAI

As of May 21, 2006

# H5N1 in Humans, 2003-06\*

Turkey  
Cases: 12  
Deaths: 4

Azerbaijan  
Cases: 8  
Deaths: 5

China  
Cases: 19  
Deaths: 12

Iraq  
Cases: 2  
Deaths: 2

Vietnam  
Cases: 93  
Deaths: 42

Egypt  
Cases: 14  
Deaths: 6

Thailand  
Cases: 22  
Deaths: 14

Cambodia  
Cases: 6  
Deaths: 6

Djibouti  
Cases: 1  
Deaths: 0

Indonesia  
Cases: 51  
Deaths: 39

\*December 2003 – June 20, 2006

**Total: 228 Cases, 130 Deaths Case Fatality Proportion: 57%**



# H5N1 in Humans – 2003-2006

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- As of June 20, 2006: **228 cases, 130 deaths**
  - Ten countries
  - Millions have been exposed to poultry
- Sporadic, with occasional clusters
- Most had touched or handled sick poultry
- Few cases of probable, limited human-to-human transmission
- All lived in countries with poultry outbreaks

# Influenza A Transmission

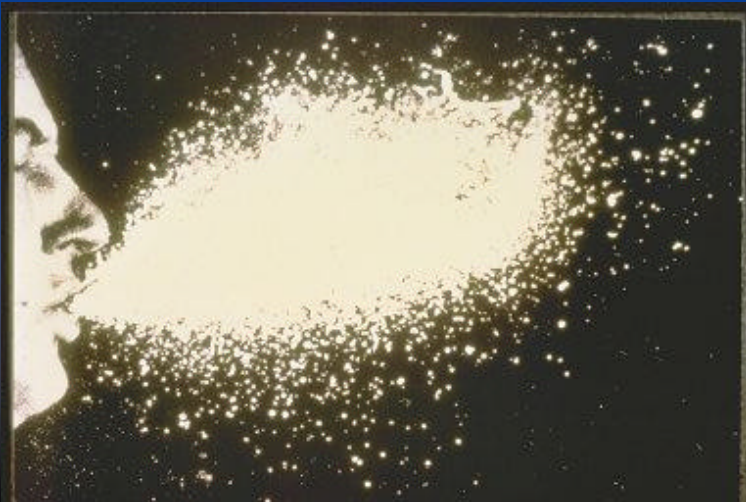


## Regular (Seasonal) Influenza (H3N2, H1N1)

- Respiratory Droplet
  - Cough
  - Sneeze
- Contact Transmission
  - Contaminated Hands

## Avian Influenza (H5N1)

- Direct or Close Contact
  - Contaminated Hands



# H5N1 Virus Replication in Humans

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- Does not appear to replicate as well in the nasopharynx as other strains
- Replication site may be lower in the respiratory tract
  - Preferential attachment of H5N1 to Type II pneumocytes, alveolar macrophages and terminal bronchiole epithelia
    - Van Riel et al, Scienceexpress, 23 March, 2006
    - Shinya et al, Nature, 440: 23 March, 2006

# H5N1 Clinical Features



- Median age: 19.5 years (range 1-81)\*
- Previously healthy children, young adults
- Incubation period: 2-10 days
  - 1 case up to 17 days
- Preferred specimens for H5N1
  - Throat swab
  - Lower respiratory tract (eg, tracheal aspirate)
    - Best to collect nasopharyngeal swabs also
    - Serial samples may also be of value

# H5N1 Illness in Humans



- Fever and cough or dyspnea
- More frequent diarrhea
- Lower respiratory tract symptoms develop early
  - Clinically suggestive of pneumonia
  - Abnormal X-Rays (multi-focal consolidations) which rapidly worsen
  - Primary viral pneumonia
  - Mechanical ventilation required
- Lymphopenia, Thrombocytopenia
- Multi-organ failure
  - Renal and cardiac dysfunction

# H5N1 Influenza Severe Pneumonia - Vietnam 2004

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DAY 5

DAY 7

DAY 10



# H5N1 Treatment



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- Supportive care
- Broad-spectrum antibiotics
- Antivirals
  - Oseltamivir (neuraminidase inhibitor)
- Other possible therapies
  - Corticosteroids, other immunomodulators



# Human Clusters



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- 3 or more persons with
  - Severe respiratory illness
  - Onset of symptoms within 7-10 days of each other
  - Epi link to suspected/confirmed H5
- Causes
  - Common source exposure
  - Different exposures at different times
  - Human-to-human transmission
- Investigation
  - Exposures: occupation, behaviors, environment
  - Virologic





# Intervention Paradigm



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- Control outbreaks in poultry
- Work closely with animal health authorities
- Surveillance for severe respiratory illness
  - Look for human cases where bird cases found
  - Look for risk factors when severe pneumonia diagnosed
- Isolate cases
- Actively investigate cases, especially clusters
- Protect occupationally exposed
  - Health care workers
  - Poultry workers/cullers

# Who should be tested?

- Hospitalized and/or fatal **AND**
- Has documented fever  $\geq 38^{\circ}\text{C}$  **AND**
- Has pneumonia (CXR), ARDS, or other severe respiratory illness, with no alternate diagnosis **AND**
- Meets criteria **A OR B OR C** below, within 10 days of symptom onset

**A: History of travel to a country with H5N1 cases in birds or humans**  
**AND has at least one of the following**

1. Direct contact (touching) with sick or dead poultry
2. Direct contact with surfaces contaminated with poultry feces
3. Consumed raw or incompletely cooked poultry or poultry products
4. Direct contact with sick or dead wild birds suspected or confirmed to have H5N1
5. Close contact (within 1 meter) of a person hospitalized or dead due to a severe unexplained respiratory illness

**B: Close contact of an ill patient who was confirmed or suspected to have H5N1**

**C: Worked with live H5N1 influenza virus in a laboratory**



# Consider Testing (Case by Case Basis)



- 
- Someone with mild or atypical disease who meets criteria A, B or C

*OR*

- Someone with severe or fatal respiratory disease whose epidemiological information is uncertain, unavailable or otherwise suspicious, for example:
  - Returned traveler from H5N1-affected country with unknown exposure(s)
  - Person who has contact with sick or well-appearing poultry



# **Samples to Collect** **(after notifying local or state health department)**

- **Oropharyngeal, bronchoalveolar lavage or transtracheal aspirate preferred**
  - Nasal/nasopharyngeal swabs acceptable, but may contain less virus
  - Dacron tip swabs with aluminum or plastic shaft
  - Place at 4°C immediately after collection
- **Within 3 days of illness onset preferred**
  - Serial samples over several days
  - Multiple samples on multiple days
- **Use appropriate PPE (N95 if collecting BAL)**
- **Do not depend on rapid tests**
  - Have low sensitivity
  - Negative result does NOT exclude diagnosis of H5N1
  - Positive result does NOT distinguish between seasonal flu and H5N1
- **Updated Interim Guidance for Laboratory Testing of Persons with Suspected Infection with Avian Influenza A (H5N1) Virus in the United States**
  - Health Alert Network June 07, 2006
  - [www.cdc.gov/flu/avian/](http://www.cdc.gov/flu/avian/)

# Influenza Pandemic Viruses

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## Requirements:

- A new influenza A subtype can infect humans  
AND
- Causes serious illness  
AND
- Spreads easily from human-to-human

The first two prerequisites have been met,  
but not the last

- Each new human infection is an opportunity for the virus to change



# Summary

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- H5N1 will not be eradicated soon
- Virus continues to change
- H5N1 influenza: 2 of 3 requirements for pandemic met
- Opportunities for the third, as long as human and bird infections continue



# Summary

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- Get vaccinated
- Practice good hygiene
  - Stay informed



# Thank You

*“The findings and conclusions in this presentation have not been formally disseminated by CDC and should not be construed to represent any agency determination or policy.”*