Influenza: Continuing evolution and threat

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Influenza: Structure and Variation

- “Born to breed”
- Designed to evolve
  - No proof reading mechanism
  - Segmented genome
- Pandemics antigenic shift - reassortant
- Epidemics antigenic drift - mutations
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Influenza Pandemics of the Past century

Deaths
- >40 million Spanish
- 1.5 million Asian
- "mild" Russian
- over 18,000 2009 H1N1
- 1 million Hong Kong
Influenza-lessons learned

- Beware of predictions-The lesson(s) from pandemic H1N1 2009
- Preparing for H5N1-H1N1 emergence
- Continuing circulation of a subtype does not preclude it’s reemergence: Seasonal H1N1 was circulating
- Antigenic and structural similarities are not predictors of severity
- A pandemic can emerge anywhere in the world
- Vaccines were not available during the first waves of infections
# Influenza - Current Threats

<table>
<thead>
<tr>
<th>Virus</th>
<th>Details</th>
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<tbody>
<tr>
<td>H5N1</td>
<td>640 human infections/380 deaths</td>
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<tr>
<td>H7N9</td>
<td>138 human infections/45 deaths</td>
</tr>
<tr>
<td>vH3N2</td>
<td>18 infections-children-fairs</td>
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<td><strong>H2N2</strong></td>
<td><strong>Precedence in humans: High</strong></td>
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<tr>
<td>H9N2</td>
<td>Human infections China, Hong Kong and Bangladesh</td>
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<tr>
<td>H6N1</td>
<td>Taiwan 1 human case</td>
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<tr>
<td>H7N3</td>
<td>Mexico-Chickens-Conjunctivitis in humans</td>
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</table>
Low pathogenic/High pathogenic influenza viruses

- All 16 HA subtypes in migratory birds are low pathogenic
  - Cause no disease signs
  - Replicate predominantly in the intestinal tract
- Only H5 and H7 become highly pathogenic after transfer to gallinaceous poultry.
  - Acquire a series of basic amino acids at the cleavage site of the hemagglutinin
  - Cause systemic infection
  - Lethal
Ongoing H5 and H7 events: Worldwide

**H5N1 “Bird flu” 1996-present**
- Eurasia
- Millions of poultry, 642 human case 381 deaths

**H7N3 June 2012 -present**
- Mexico
- Spread to poultry in 7 states, conjunctivitis (human)

**H7N2 October 2013 -present**
- Australia
- Chickens, 2 farms

**H7N7 September 2013 -present**
- Italy
- Chickens, conjunctivitis (human)

**H7N9 Second “Bird flu” 2013-present**
- China
- 137 human cases 45 deaths
H9N2 – The enabler

- Avian H9N2 emerged in Asia in early 1990s
- Mild to inapparent disease in poultry
- Endemic in the poultry industry in most of Eurasia
- Occasional transmission to humans and swine
- Acquired human receptor specificity
- Has high reassortment potential

Provided the backbone (6 gene segments) of HP H5N1 and LP H7N9
Emergence of the second “Bird Flu”

- H7N9 first detected in humans-February 2013
  - Severe respiratory disease
- Rapid sharing of information with Global Initiative on Sharing Avian Influenza Data (GISAID)
- H7N9 is low pathogenic in domestic poultry
  - No sentinel disease in poultry
- H5N1 is highly pathogenic in domestic poultry
H7N9-a triple reassortant
H5N1-A triple reassortant

Goose/Guangdong/1/96  
H5N1 - like

Teal/Hong Kong/W312/97  
H6N1 - like

Quail/Hong Kong/G1/97  
H9N2 - like

Human Cases  
Infections 641  
Deaths 380
H5N1: The continuing global threat

### China/Vietnam
- Clade: 2.3.2.1/2.3.4.2

### Indonesia
- Clade: 2.1.3.2/2.3.2.1

### Egypt
- Clade: 2.3.2.1
- Clade: 2.2.2/2.3.2.1

### Bangladesh
- Clade: 2.2.2/2.3.2.1

- **Continued evolution** - multiple clades and subclades

### Human Cases 2013
- Infections: 31
- Deaths: 20

- **Wild birds: Clade 2.3.2.1**
  - Whooper swan, Grebes, Tufted duck, passerines
  - China, Japan, Mongolia, Israel, Vietnam, South Korea,
Vaccination as a driver of evolution

• In humans
  – Continuing selection of dominant variants in human seasonal influenza viruses H1N1, H3N2, B

Antigenic domains on the HA
Vaccination as a driver of evolution-H5N1

- H5N1 influenza: Those countries that opted for control by using vaccination now have endemic H5N1 in poultry farms:
  - China, Vietnam, Indonesia, Egypt, Bangladesh?
- Evolution of 32 clades and subclades of H5N1
  - Dominance of clade 2.3.2.1
Vaccination as a driver of evolution-
H5N2 and H7N3 Mexico

- H5N2 “Effect of vaccine use in the evolution of
Mexican lineage H5N2 avian influenza virus” Lee CW,
“..findings indicate that multilineage antigenic
drift...aided by large antigenic difference from the
vaccine strain”

- H7N3 Highly pathogenic in poultry
- Failure to control by vaccination
Will H7N9 re-emerge in China?

• Shanghai live poultry markets (102) reopened June 20th

• Time for poultry flocks to “swell” in preparation for Chinese New Year January 31, 2014 - Year of the Horse
China confirms new human H7N9 infection
Oct 15, 2013

HANGZHOU, Oct. 15 (Xinhua) -- One new human H7N9 avian influenza case has been confirmed in east China's Zhejiang Province, local authorities said Tuesday.

China reports new human H7N9 bird flu case
Oct 23, 2013

HANGZHOU, Oct. 23 (Xinhua) -- A new human H7N9 bird flu case was reported on Wednesday in east China's Zhejiang Province, the second in China this autumn, according to the provincial health authority.

Boy, 3, positive for H7N9 bird flu in Guangdong
By Cai Wenjun | November 5, 2013, Tuesday | ONLINE EDITION

A 3-year-old boy was confirmed to be infected with H7N9 bird flu, Guangdong Province Health and Family Planning Commission said in a statement today.

China reports 4th H7N9 case since Sept
Updated: 2013-11-09 20:30
(Xinhua)

HANGZHOU - A 64-year-old farmer in East China's Zhejiang province has been confirmed to have contracted H7N9 bird flu, bringing the total number of avian influenza cases in China to four this autumn, local health authorities said on Saturday.
Comparative replication in human ex-vivo lung culture

- H1N1-grows like a weed
- H5N1-struggles to replicate
- H7N9-grows like a bomb

Comment by Malik Peiris
Conflicting Results

- Ministry of Agriculture tested 68,060 poultry samples, markets, farms, slaughterhouses. 46 positive - 0.07%

- Hong Kong University Collaborators tested 1,341 poultry, 1006 water and fecal samples. 60 positive - 2.6%

- 6% of poultry workers in China have H7N9 antibodies
  - None in the general population
  - “The tip of the iceberg”
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Chunlong Ma, Lawrence H. Pinto, and Robert A. Lamb
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Marc Lipsitch and Derek Smith
Jonathan S. Nguyen-Van-Tam and Joseph Bresee
Thomas J. Braciale, Robert G. Webster
Summary

- Vaccination against influenza contributes to antigenic drift in influenza.

- Vaccination is the best strategy for controlling influenza in humans.

- Vaccination of poultry reduces disease signs but does not lead to eradication.
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