• RNA virus - segmented genome
  - negative sense
• Error prone replication
• No proof reading mechanisms
• Exist as a quasi-species

Consequence:
• Highly variable
  - antigenic drift - continuous
  - antigenic shift ~ 3 per century
Pneumonia and Influenza Mortality
For 122 U.S. Cities

Week Ending 02/15/03

% of All Deaths Due to P&I

“Epidemic” Threshold

Seasonal Baseline

Weeks

1998 1999 2000 2001 2002

12 10 8 6 4
Influenza 2002-2003

On average, influenza kills 20,000 persons in the US

- Mild early in the season

- Outbreaks in Jan. and Feb. 2003
  - Closing schools in Memphis area
  - H1N1, H3N2, B virus circulating

- Recent deaths in children in Virginia - influenza B

- Increase in encephalopathy cases in children associated with H1N1, H1N2, B
  - cf. Japan: H3N2
Influenza Vaccine Strains for 03-04
WHO Recommendations Feb 2003

B/Hong Kong/330/2001 - like
A/New Caledonia/20/99 (H1N1) - like

A/Moscow/10/99 (H3N2) - like!!!
## Pandemics in the 20th Century

<table>
<thead>
<tr>
<th>Time</th>
<th>Name/Subtype</th>
<th>Source</th>
<th>Comment (excess deaths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918 → 1956</td>
<td>Spanish - H1N1</td>
<td>Avian or Pig/whole virus</td>
<td>Catastrophic &gt; 20 million deaths</td>
</tr>
<tr>
<td>1957 → 1967</td>
<td>Asian - H2N2</td>
<td>Human-avian reassortment</td>
<td>~ 70,000 (US)</td>
</tr>
<tr>
<td>1968 → Present</td>
<td>Hong Kong - H3N2</td>
<td>Human-avian reassortment</td>
<td>~ 34,000 (US)</td>
</tr>
<tr>
<td>1977 → Present</td>
<td>Russian - H1N1</td>
<td>Reintroduction from “Frozen Source”</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Spanish Influenza in U.S.

• 28% of total U.S. population estimated to have been infected

• Deaths among young adults.
  - In 15 – 34 year old group 20x higher than in previous years

• Killed 675,000 Americans.

• Depressed the life expectancy by more than 10 years.
1918 Spanish Influenza

Which host was infected first?
The Ecology of influenza viruses

Dogma 1-2

• Wild aquatic birds are the natural reservoirs of all influenza A viruses in other species

• In wild aquatic birds, influenza viruses replicate predominately in the intestinal tract and are shed by fecal oral transmission often through water
The Ecology of influenza viruses

Dogma 3-4

- That there are a limited number of host specific lineages of influenza viruses
- There is geographical separation into Eurasian and American lineages
The Ecology of influenza viruses

Dogma 5-6

- Influenza viruses in their natural reservoirs are in evolutionary stasis
- Rapid evolution occurs after transfer to new hosts
The Pol-I / Pol-II 8 Plasmid System for Reverse Genetics of Influenza viruses

Plasmids expressing (-)vRNA, (+)mRNA / Proteins

Human cells + Canine kidney cells (MDCK)

Hoffmann et al., 2000
Pathogenesis
A polygenic trait

PB2
PB1
PA
HA
NP
NA
M
NS

627
PQRERRRRKGRGLF
HB2

92
PQRERRRRKGRGLF
NS1
Symptoms of H5N1 in Humans

- High fever
- Pneumonia
- GI Symptoms (vomiting, diarrhea)
- Liver dysfunction
- Kidney dysfunction
- Death

Yuen et al. Lancet 1998
Virulence of A/HK/97 H5N1 in Mice

Infected
A/HK/486/97

PB2 residue 627
HA-cleavability

Infected
A/HK/483/97

Hatta et al
Science 2001
H5N1 Influenza Outbreaks in Hong Kong

1997 - Poultry and humans
   - Two distinguishable variants

2001 - Poultry only
   - Five new genotypes

2002 (Feb) - Poultry only
   - Four new genotypes, one from 2001

2002 (Nov)
   - Emergence of three genotypes

• All H5N1
H5N1 Influenza in Humans in Hong Kong
Feb 2003

- 2 confirmed cases
- Family of five traveled from HK to Fujian late January
- Daughter: 8 years old died in Fujian on Jan 28 of respiratory infection
- Son: 9 years developed respiratory symptoms Feb 9th, admitted in hospital Feb 12, recovered
- Father: respiratory symptoms Feb 7th, returned to Hong Kong Feb 10, died Feb 16
- Mother and other child - no disease
- No spread to contacts detected
Properties of H5N1 Viruses from Humans - 2003

- Avian-like H5N1 virus in all 8 genes
- Antigenically distinguishable from H5N1/97
- Most closely related to H5N1 from wild ducks and egrets in Penfold Park
- Sequence of HA has polybasic amino acids at cleavage site ($\notin$ highly pathogenic)
Respiratory Disease in Guangzhou Mainland China

- Started mid-November 2002
- Rapid spread in hospitals
- 300-500 cases of respiratory disease
  - 7 or 8 deaths
- Any relationship to H5N1 in Hong Kong?!
The Future

- Will the new H5N1 spread?
- Antigenic drift will continue
- A pandemic will occur
- We are unprepared!
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