Phylogenetic analysis of NP in different hosts

How do you interpret this graph?

Note the lack of correlation of dates with branch lengths for the avian sequences = large reservoir of sequences at stasis (near top of fitness peak)

Dated phylogenies of influenza A virus genes.

Note 1918 PA sequence clusters with a clade of avian sequences
In the initial years of the pandemics up to 30% of the human population becomes infected.

Transfer of segments from avian influenza strains leads to new pandemic human strains. This is “shift”.

H1N1: All avian segments Spanish flu
H2N2: PB1, HA, and NA from avian strain Asian flu
H3N2: PB1 and HA from avian strain Hong Kong flu

H3N8 in 1889? H1N8 in 1900?

H3N2

H1N1

H2N2

H3N2

All avian segments Spanish flu
PB1, HA, and NA from avian strain Asian flu
PB1 and HA from avian strain Hong Kong flu

Russian flu (1977)
Unusual cluster of respiratory illness in La Gloria, Mexico

Late in flu season in 2009
Severe illness in young adults
Typed to influenza A, but could not subtype
Samples sent to CDC and to Manitoba and typed as “swine flu”
Matched two cases in San Diego

“attack rate” = 28% overall (616/2155)
57% in children
22% in adults >65 years old

Spread world-wide by fall of 2009

Vaccine came too late to help
swine-origin H1N1 influenza virus (S-OIV)
H1N1pdm

Note scale in millions!
Unusual for the lack of infection and morbidity in persons >65 yrs old

So, more people were infected than in a normal flu year (~70,000,000 in US),
But fewer deaths than in a normal flu year (~15,000)

There is antigenic similarity between the 2009 H1N1 and much older strains

Older people have more pre-existing immunity to 2009 H1N1

The neutralizing epitopes on 2009 H1N1 are similar to a virus that previously circulated in the human population
H5N1 aka “Bird flu” aka HPAI

- Dramatic and unpredictable spread among wild and domestic birds
- Exceptionally high mortality in humans
- Limited human-to-human spread so far.

H5N1
1997, Hong Kong - 6 /18 fatal cases
100 million domestic birds killed
Areas with confirmed human cases of H5N1 avian influenza since 2003
(as of January 2014)

Notice high fatality rate. Very little human-human spread

Why is H5N1 fatal in humans?

Higher viral loads

Viral load in throat swab (log10 cDNA copy per ml)
median; range

<table>
<thead>
<tr>
<th></th>
<th>H5N1</th>
<th>H3/H1</th>
<th>H5N1 fatal</th>
<th>H5N1 not fatal</th>
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</thead>
<tbody>
<tr>
<td>median</td>
<td>7.0; 4.3-8.2</td>
<td>4.8; 4.2-5.8</td>
<td>7.5; 4.7-8.2</td>
<td>5.9; 4.3-7.0</td>
</tr>
</tbody>
</table>

Increased levels of chemokines and cytokines produced by bronchial epithelial cells and aveolar macrophages

<table>
<thead>
<tr>
<th>Median level (log10/ml)</th>
<th>H5N1</th>
<th>H3/H1</th>
<th>control</th>
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</thead>
<tbody>
<tr>
<td>IP-10</td>
<td>5.1</td>
<td>3.8</td>
<td>2.7</td>
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<tr>
<td>MIG</td>
<td>4.3</td>
<td>3.2</td>
<td>2.6</td>
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<td>MCP-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-8</td>
<td>2.0</td>
<td>0.8</td>
<td>0.7</td>
</tr>
</tbody>
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H7N9: A recent transfer from birds that had never been seen before

Several waves of infection in China with a previously unseen serotype in 2013/14

High morbidity and mortality

Mostly older men with direct contact with poultry, but at least 4 confirmed clusters of human-human transmission

Not generally pathogenic in poultry, so more difficult to pick up

“Fifth wave” particularly troubling because of greater geographical and age/gender spread

A complex reassortment with segments from wild birds, domestic waterfowl, and from chickens. Probably evolved in birds within the last 2 years.

There is a parallel virus in chickens that differs in N (H7N7), but has all the other segments similar to the H7N9 that infects humans.

What adaptations are necessary for human-human transmission of H5N1?

PB2 from avian species (627E) can be rescued by chicken versions of the gene, ANP32A, a cofactor for the polymerase

Important: there does not seem to be a simple answer to how avian flu strains adapt to humans

SAα2,3Gal (used by avian HA) is limited to the lower airways in humans, while the upper airway has SAα2,6Gal (used by human HA).

Nature 529, 101-104 (2016)

Lancet (2008) 371; p1464-75
The 1918 Influenza was unusual in its high death rate among 15-45 year olds

Mortality usually highest in the very young and very old

Why is there a W-shaped curve?
Hypothesis of original antigenic sin and a possible H3 outbreak in 1880-1900

Reid et al Microbes and Immunity 3, 81-87, 2001

Vaccines

- Inactivated (standard) and live attenuated (newer) vaccines
- Given in ~Oct.–Nov. each year
- Includes four envelope variants chosen in February of the previous year. 2017/18 season is
  + option of second B type (2013)
- Not as good as they used to think = ~60% efficacy for standard; but much less for >65 year olds.
- Get your flu vaccine
- New attempts to make “universal” vaccines
Universal flu vaccines

Most neutralizing antibodies target variable regions involved in receptor binding

Some antibodies conserved regions involved in fusion

Can be induced by "prime-boost" vaccinations

Alternative idea: vaccinate with internal proteins

2013 was an H1N1 year, but H3N2 increased late in the season

R W Doms Science 2010;329:1021-1022
In the 2014/15 season a new variant of H3N2 had taken over in the US.

2016/17 was again an H3N2 year.
Things you should know about influenza pandemics

• Antigenic shifts = reassortments with viruses from a different host into humans
• Origin of the pandemics
• What is the bird flu, and what are the concerns?
• Vaccine issues
• Paper for next time. Don’t get lost in the weeds with this one. The two things I want to look for are
  – What results show that H7N9 has scary potential for a pandemic?
  – What do the experiments show that sequence information alone could not necessarily predict?
  – What other data would you want to know?