Pandemic Influenza

October 9, 2006

1918 influenza epidemic: realization of a worst-case scenario

First case: Albert Mitchell, Camp Funston, KS, March 11, 1918
Up to 20% of all humans infected
20-50 million deaths worldwide, 650,000 in the US
2.5% average case mortality rate; up to 16% in some cities
1918 death rate unusually high in males and people ages 20-40

Damage due to overzealous immune response?
Kash et al., 2006 Nature epub ahead of print doi:10.1038/nature05181

Influenza A

Pleomorphic enveloped virus, 80-120 nm
Orthomyxoviridae family, isolated from ferrets in 1933
Endemic in water birds (ducks, gulls, shorebirds)
Invasion mediated by HA protein (hemagglutinin)
binding to sialic acid
Birds mostly α2,3 linkage to galactose, humans mostly α2,6 linkage
Neuraminidase cleaves sialic acid links; required for viral shedding (target of Tamiflu)
Virus also encodes an RNA-dependent RNA polymerase
Genome has 8 RNA segments

<table>
<thead>
<tr>
<th>RNA segment</th>
<th>Nucleotides</th>
<th>Protein</th>
<th>Amino acids</th>
<th>Molecules per virion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2241</td>
<td>polymerase PB2</td>
<td>759</td>
<td>20-40</td>
</tr>
<tr>
<td>2</td>
<td>2341</td>
<td>polymerase PB1</td>
<td>757</td>
<td>30-60</td>
</tr>
<tr>
<td>3</td>
<td>733</td>
<td>polymerase PA</td>
<td>716</td>
<td>30-60</td>
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<tr>
<td>4</td>
<td>2278</td>
<td>hemagglutinin HA</td>
<td>666</td>
<td>900</td>
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<tr>
<td>5</td>
<td>1565</td>
<td>nucleoprotein NP</td>
<td>698</td>
<td>900</td>
</tr>
<tr>
<td>6</td>
<td>1415</td>
<td>neuraminidase NA</td>
<td>414</td>
<td>100</td>
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<td>7</td>
<td>1077</td>
<td>matrix protein M1</td>
<td>257</td>
<td>3000</td>
</tr>
<tr>
<td>8</td>
<td>892</td>
<td>matrix protein M2</td>
<td>97</td>
<td>30-100</td>
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</table>

Each viral RNA segment is packaged by the nucleoprotein NP with a polymerase heterotrimer (PA, PB1, PB2) ready to go

Segments reassort when distinct viruses infect the same cell

Major antigenic determinants are HA (hemagglutinin) and NA (neuraminidase)

16 HA types and 9 NA types found in waterfowl

Antigenic SHIFT is due to a new HA or NA type

Antigenic DRIFT is due to point mutations in HA and NA

PANDEMICS arise when human populations are immunologically naïve for a new type
Currently H3N2 and H1N1 cause most of the yearly infectious cycle

Note that influenza and pneumonia USUALLY cause ~8% of all reported deaths during the winter months

Influenza vaccine production

Currently grown in embryonated chicken eggs
Live virus inactivated by formaldehyde treatment
~ 3 eggs per dose; availability would be severely compromised with avian influenza epidemic
Lag time from seed strain choice to large-scale availability is 28 weeks
Cell-based vaccine culture methods are under development
Public confidence in vaccines is generally low
Swine flu - 1976
Compare public response to MMR vaccine
Drug treatments for influenza

Amantidine and Rimantidine
- Approved by FDA in 1976
- Active only against influenza A
- Inhibitors of M2; virus cannot escape envelope
- Widespread resistance; no longer recommended

Oseltamivir (Tamiflu) and Zanamivir (Relenza)
- Approved by FDA in 1999
- Active against both influenza A and influenza B
- Inhibitors of neuraminidase; prevent viral shedding from cell surface
- Oseltamivir delivered orally as an ethyl ester pro-drug
- Found by screening sialic acid derivatives

Wednesday papers:


1918 flu recovered from US Army pathology samples and one person buried in the Alaska permafrost

Recombinant expression strategy: Hoffmann et al., 2000, PNAS 97:6108

Only 10 aa changes in polymerase subunits consistently distinguish human from avian

<table>
<thead>
<tr>
<th>Gene</th>
<th>Residue no.</th>
<th>Avian</th>
<th>IFB</th>
<th>Human H1N1</th>
<th>Human H2N2</th>
<th>Human H3N2</th>
<th>Classical swine</th>
<th>Equine</th>
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<tr>
<td>PB2</td>
<td>194</td>
<td>A</td>
<td>S</td>
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<td>S</td>
<td>S</td>
<td>S</td>
<td>T</td>
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</tr>
</tbody>
</table>

PB2: 5 changes, found rarely in avian lineages but occasionally in high pathogenicity avian strains (HPAI) H5N1, H7N7, or H9N2 that infected humans

PB2: Lys627 crucial for high pathogenicity

PB1: replaced by reassortment in both 1957 and 1968; replicative advantage?

PB1: Asn375 to Ser found in swine and equine as well as human isolates

Tradeoffs between function and antigenicity?
Questions

Can this work help us to predict the next pandemic?
What else do we need to know?
Pandemics require virulence plus transmissibility;
    how can we study transmissibility?
What are the dangers of this project?
Should this project have been approved by the NSABB? Should the sequences have been published?
How should we be preparing for the next influenza pandemic?

H5N1: The next big thing?

Highly pathogenic avian influenza (HPAI):
    communicated directly from birds to humans but not (so far) communicated among humans
H5N1 - 1997    H9N2 - 1999    H7N2 - 2002
H7N7 - 2003    H7N3 - 2004    H10N7 - 2005
H5N1 returns most years
    Cumulative laboratory-confirmed cases through
        October 2006: 242
    Cumulative deaths: 148

www.who.int
H5N1 spread - October 2006