Other Influenzas of Concern

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One Health, One Medicine, One World

Fact:
• 60%-75% of EID in human are zoonotic: Majority of wildlife origin!
• Effective surveillance and control requires integration of human and animal populations worldwide

Integration of these disciplines improves the lives of all species - human and animal
The veterinarian is the only health care professional likely to see both people and their animals
Global Examples of Emerging and Re-Emerging Infectious Diseases

Diseases at the Human-Animal Interphase

3 major events in last 10 years:
- SARS
- H5N1 (“avian flu”)
- Pandemic H1N1 (“swine flu”)
Global Trade

Source: Center for Global Food Issues

Courtesy of W. Karesh (WCS)

World Wide Air Traffic

Hufnagel et al., 2004. PNAS. 101: 15124
Economic Impact of Selected Infectious Diseases

**SARS:**
- China, Hong Kong, Singapore, Canada,...
- $50bn+

**Foot & Mouth Disease:**
- UK
- $30bn

**Avian Flu, EU:**
- $50bn

**Avian Flu, Asia:**
- US, Canada
- $50bn

**BSE:**
- UK
- $10-13bn

**Foot & Mouth Disease:**
- Taiwan, $5-8bn

**BSE, UK:**
- $10-13bn

**Avian Flu, Netherlands:**
- $2-3bn

**Nipah, Malaysia:**
- $350-400m

**Swine Flu, Netherlands:**
- $2.3bn

**Lyme disease:**
- US, $2.5bn

**Nipah:**
- Malaysia
- $350-400m

**BSE (mad cow disease):**
- Bovines
- Humans
- Highly promiscuous prion – also transmits to cats, exotic ungulates, non-human primates

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**TABLE 1. Examples of viruses that transferred between hosts to gain new host ranges so that they cause outbreaks in those new hosts**

<table>
<thead>
<tr>
<th>Virus</th>
<th>Original host</th>
<th>New host</th>
<th>Mode of transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles virus</td>
<td>Possibly cattle</td>
<td>Humans</td>
<td>Host switching and adaptation; Time not known; the establishment of a population sufficiently to allow transmission</td>
</tr>
<tr>
<td>Smallpox virus</td>
<td>Other primates or canines?</td>
<td>Humans</td>
<td>Host switching and adaptation; Time &gt;38,000 or ago</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>Water birds</td>
<td>Humans, pigs, horses</td>
<td>Host switching and adaptation, possible role of intermediate host; many variants. In humans, viruses emerged in the period 1910-1918 and in 1957 and 1968. Emergence involved in 1957 and 1968 emergencies. Earlier epidemic viruses not characterized. Changes in several genes required for access in new-host</td>
</tr>
<tr>
<td>CPV</td>
<td>Can or similar carnivores</td>
<td>Dog</td>
<td>Host switching and adaptation; several mutations at the capsid control binding site</td>
</tr>
<tr>
<td>HIV-1</td>
<td>Old World primates, chimpanzees</td>
<td>Humans</td>
<td>Host switching and adaptation; virus emerged human population approximately in 1955 and spread widely in 1956, multiple introductions likely to give the HIV-1 M, S, N, and O variants</td>
</tr>
<tr>
<td>SARS-CoV</td>
<td>Bats</td>
<td>Humans</td>
<td>Host switching, adaptation; some adaptation for binding to the ACE2 receptor in humans. 2003-2004</td>
</tr>
<tr>
<td>Dengue virus</td>
<td>Old World primates</td>
<td>Humans</td>
<td>Host switching, adaptation; some adaptation for binding to the ACE2 receptor in humans. 2003-2004</td>
</tr>
<tr>
<td>Marburg virus</td>
<td>African monkeys</td>
<td>Humans</td>
<td>Host switching, adaptation; some adaptation for binding to the ACE2 receptor in humans. 2003-2004</td>
</tr>
<tr>
<td>Hendra virus</td>
<td>Bats</td>
<td>Humans</td>
<td>Host switching, adaptation; some adaptation for binding to the ACE2 receptor in humans. 2003-2004</td>
</tr>
<tr>
<td>BSE (mad cow disease)</td>
<td>Bovines</td>
<td>Humans</td>
<td>Highly promiscuous prion – also transmits to cats, exotic ungulates, non-human primates</td>
</tr>
</tbody>
</table>
**Influenza viruses**

**Family** Orthomyxoviridae  
**Genus** Influenza A,B,C virus, Thogoto virus and Isavirus  
**Virion** enveloped  
**Genome** ssRNA negative polarity

<table>
<thead>
<tr>
<th>Genera</th>
<th>Genome</th>
<th>Host</th>
<th>Evolution</th>
<th>Pandemic potential</th>
<th>Subtypes</th>
</tr>
</thead>
</table>
| Influenza A | 13.6 kb  
8 segments  
10 or 11 proteins | Birds and mammals | Very fast  
>2-3 fold more than flu B | Yes  
Subtypes (strains) |
| Influenza B | 14.6 kb  
8 segments  
10 or 11 proteins | Human & seals | Fast | No  
No subtypes (strains) |
| Influenza C | 10 kb  
7 segments  
9 proteins | Human & pigs | Slow | No  
No subtypes (strains) |

**Influenza A virus**

HA: Receptor-binding Protein  
\[\alpha-2,6\text{-Gal (human-like)}\]  
\[\alpha-2,3\text{-Gal (avian-like)}\]  

M2  
PB1, PB2, PA  
NP  
M1, NEP

D. Perez, modified
Receptors for Influenza A viruses in Different Animal Species

Distribution of Influenza A Hemagglutinin Subtypes

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Host Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td></td>
</tr>
<tr>
<td>H2</td>
<td></td>
</tr>
<tr>
<td>H3</td>
<td></td>
</tr>
<tr>
<td>H4</td>
<td></td>
</tr>
<tr>
<td>H5</td>
<td></td>
</tr>
<tr>
<td>H6</td>
<td></td>
</tr>
<tr>
<td>H7</td>
<td></td>
</tr>
<tr>
<td>H8</td>
<td></td>
</tr>
<tr>
<td>H9</td>
<td></td>
</tr>
<tr>
<td>H10</td>
<td></td>
</tr>
<tr>
<td>H11</td>
<td></td>
</tr>
<tr>
<td>H12</td>
<td></td>
</tr>
<tr>
<td>H13</td>
<td></td>
</tr>
<tr>
<td>H14</td>
<td></td>
</tr>
<tr>
<td>H15</td>
<td></td>
</tr>
<tr>
<td>H16</td>
<td></td>
</tr>
</tbody>
</table>
The Pig, a “Mixing and Adaptation Vessel”:
Novel Influenza H2N3 Subtype in Pigs as a Result of Reassortment of avian/human/swine influenza genes (triple reassortant SIV)

Case Histories

- Respiratory disease in grower/finisher pigs in MO
- 2 farms with different owners (4 miles apart)
- Farms did not share:
  - Pigs
  - Feed
  - Personnel
  - Trucks
- Both used surface pond water for drinking and cleaning
- Isolates were not typable using “normal” HA/NA-specific diagnostic assays (UMN-VDL: Dr. M. Gramer)
### Sw/MO/07 Gene Composition

<table>
<thead>
<tr>
<th>Gene</th>
<th>Identity (%)</th>
<th>Virus designation</th>
<th>Subtype</th>
<th>Genbank accession #</th>
</tr>
</thead>
<tbody>
<tr>
<td>HA</td>
<td>97.8</td>
<td>A/Mallard/Alberta/79/2003</td>
<td>H2N3</td>
<td>CY003992</td>
</tr>
<tr>
<td></td>
<td>97.1</td>
<td>A/Mallard/Alberta/149/2002</td>
<td>H2N4</td>
<td>CY003984</td>
</tr>
<tr>
<td>NA</td>
<td>98.3</td>
<td>A/blue-winged teal/Barbados/21/04</td>
<td>H4N3</td>
<td>DQ236167</td>
</tr>
<tr>
<td></td>
<td>98.2</td>
<td>A/GSC_chicken_B/British Columbia/04</td>
<td>H7N3</td>
<td>AY648289</td>
</tr>
<tr>
<td>PB1</td>
<td>97.8</td>
<td>A/Swine/Minnesota/00395/2004*</td>
<td>H3N1</td>
<td>DQ145544</td>
</tr>
<tr>
<td></td>
<td>97.7</td>
<td>A/Wisconsin/10/98*</td>
<td>H1N1</td>
<td>AF342823</td>
</tr>
<tr>
<td>PB2</td>
<td>97.8</td>
<td>A/Swine/Illinois/100084/01#</td>
<td>H1N2</td>
<td>AF455738</td>
</tr>
<tr>
<td>PA</td>
<td>99.2</td>
<td>A/Mallard/Alberta/154/2003</td>
<td>H6N5</td>
<td>CY004279</td>
</tr>
<tr>
<td></td>
<td>97.2</td>
<td>A/Mallard/Maryland/881/2002</td>
<td>H6N2</td>
<td>CY011117</td>
</tr>
<tr>
<td>NP</td>
<td>98.3</td>
<td>A/Swine/Michigan/PU243/04#</td>
<td>H3N1</td>
<td>DQ150426</td>
</tr>
<tr>
<td></td>
<td>97.9</td>
<td>A/Swine/Indiana/PUS42/04#</td>
<td>H3N1</td>
<td>DQ150434</td>
</tr>
<tr>
<td>M</td>
<td>98.7</td>
<td>A/Swine/Indiana/PUS42/04#</td>
<td>H3N1</td>
<td>DQ150436</td>
</tr>
<tr>
<td></td>
<td>98.4</td>
<td>A/Swine/Ontario/33853/2005#</td>
<td>H3N2</td>
<td>DQ469993</td>
</tr>
<tr>
<td>NS</td>
<td>97.2</td>
<td>A/Swine/Indiana/14810-S/01#</td>
<td>H1N2</td>
<td>AY060136</td>
</tr>
<tr>
<td></td>
<td>97.2</td>
<td>A/SW/Indiana/14810-T/01#</td>
<td>H1N2</td>
<td>AY060135</td>
</tr>
</tbody>
</table>

*TRIG: PB1 human lineage; *TRIG: PB2 & PA avian lineage; *TRIG: NP, M, & NS swine lineage

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### H2N3 Swine Influenza Virus

- Isolated in early 2006 from two separate swine herds in Missouri with respiratory disease
- HA, NA, PB2 and PA genes were of avian origin
- PB1 gene was of human origin
- M, NP, and NS genes were of swine origin
- H2N3 replicated well in mice, swine and ferrets
- H2 HA: Glutamine (Q) to Leucine (L) at codon 226 (Q226L)
- The potential to infect humans is unknown; since many hallmarks of a pandemic virus are present, close monitoring is warranted (NHP pathogenesis study)
Subtype H9N2 avian influenza viruses

A/guinea fowl/Hong Kong/WF10/99 (H9N2) 
RGWF10

Nature

Aquatic birds

Before 1988

Land-based poultry

After 1988-1994

Laboratory

Early isolates do not or replicate poorly (1997 and before)

Recent field isolates replicate well (1998 and later)

Bind preferentially to human-like α-2,6-Gal sialic acid receptors

1999 and later 1998 and later

Is the Quail Overlooked as Intermediate Host?

Hypothesis: Quail can act as an intermediate host for the genesis of influenza viruses that are able to cross the species barrier

Courtesy of D. Perez
Equine Influenza

Equine influenza is the leading cause of acute infectious respiratory disease in horses in the USA. ~37%.

Circulates in much of the world.
Spread internationally.

Conventionally considered not a hazard to humans or other species!

Not a notifiable disease in USA.
The horse is a "luxury" animal.

Most work on equine influenza is related to disease prevention—surveillance, vaccinology, diagnostics.

Equine Influenza subtypes: H7N7 & H3N8

1800s
1900s
1950s
1960s
1970s
1980s
1990s
2000s

Equine-1
H7N7 virus
Primitive origin for internal genes

Equine-2
H3N8 virus
Presumed avian origin

Hypothesized reassortment

Isolated in horses 1956

Last confirmed isolate

Isolated in horses 1963

Equine/avian
H3N8 virus
avian origin
All genes

Eurasian lineage
American lineage

Courtesy of T. Chambers
Outbreaks at the international level
Economic Impact to the Industry

OUTBREAKS OF EQUINE INFLUENZA RESULTING FROM INTERNATIONAL MOVEMENT OF EQUIDS

<table>
<thead>
<tr>
<th>Virus Strain</th>
<th>Importing Country</th>
<th>Year</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>USA</td>
<td>1963</td>
<td>S. America</td>
</tr>
<tr>
<td>2</td>
<td>Western Europe</td>
<td>1965</td>
<td>N. America</td>
</tr>
<tr>
<td>1</td>
<td>England, Ireland</td>
<td>1977</td>
<td>Europe</td>
</tr>
<tr>
<td>1</td>
<td>Singapore, Malaya</td>
<td>1977</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>2</td>
<td>England, Ireland</td>
<td>1979</td>
<td>Europe</td>
</tr>
<tr>
<td>2</td>
<td>South Africa</td>
<td>1986</td>
<td>United States</td>
</tr>
<tr>
<td>2</td>
<td>India</td>
<td>1987</td>
<td>France</td>
</tr>
<tr>
<td>2</td>
<td>Jamaica</td>
<td>1989</td>
<td>United States</td>
</tr>
<tr>
<td>2</td>
<td>Hong Kong</td>
<td>1992</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>2</td>
<td>U.A.E. (Dubai)</td>
<td>1995/6</td>
<td>?</td>
</tr>
</tbody>
</table>
| 2            | Puerto Rico       | 1997 | United States?
| 2            | Philippines       | 1997 | ? |

Recent outbreaks in South Africa and Australia

Cross-species Transmission of Equine H3N8 Influenza virus to Dogs: Canine Influenza Virus

Canine influenza virus surfaces

Researchers identify transmission of equine influenza virus to dogs
Cross-species Transmission of Equine H3N8 Influenza virus to Swine and Humans

Swine?
Two strains of equine H3N8 influenza isolated from swine in China, 2004-06. Respiratory disease signs including coughing, depression.
Tu et al., Arch Virol 154:887, 2009

Humans?
Univ. Iowa sero-survey of 94 persons with horse contact: 3.2% to 10.6% (depending on method) were seropositive for equine H3. Needs confirmation by anti-N8 testing.
Leedom et al., personal communication

Cross-species Transmission of Equine H7N7 Influenza virus to Mice


• Positively associated with H1A.
• Neither equine H3N8, duck H3N8, human H3N2, human H1N1, nor swine H1N1 were lethal on first passage.
• Virus in lung, liver, occasionally brain.
Equine Influenza: A Problem?

- Outbreaks of H3N8 at the international level (recently in Australia and South Africa)
- Current vaccines do not provide complete protection (as with other animal species)
- Drift and shift of H3 HA protein: Eurasian vs. American lineage
- H7N7 disappeared >20 years ago: A high path virus in poultry with a natural mammalian host (low path in horses)
- Cross-species transmissions into different host species: dogs (H3N8), swine (H3N8), humans (?)

The 1872 Panzootic: The “Great Epizooty” or “Zooty”

- Almost every horse and mule in the United States was affected
- The fatality rate was 1-2% from acute illness; about 1% got “dropsy” a few weeks later, and up to 28% of these horses died
- Trade, commerce, transportation, and agriculture was virtually shut down
- Horses were treated in horse hospitals, horse hotels (above) and stables
- People caught influenza from their horses, with only rare fatalities
Equine Influenza: A Problem?

- Outbreaks of H3N8 at the international level (recently in Australia and South Africa)
- Current vaccines do not provide complete protection (as with other animal species)
- Drift and shift of H3 HA protein: Eurasian vs. American lineage
- H7N7 disappeared >20 years ago: A high path virus in poultry with a natural mammalian host (low path in horses)
- Cross-species transmissions into different host species: dogs (H3N8), swine (H3N8), humans (?)
- Is H7N7 a “snake in the grass”??