Is fatality rate related to viral genotype?

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Chair ESWI (Europe)
Human influenza: three appearances

Seasonal influenza
(A: H3N2, H1N1; B)

Avian influenza
(A: H7N7, H5N1...)

Pandemic influenza
(A: H1N1, H2N2, H3N2, H1N1...?)
Last four pandemics

1918
“Spanish Flu”
>40 million deaths
A(H1N1)

1957
“Asian Flu”
1-4 million deaths
A(H2N2)

1968
“Hong Kong Flu”
1-4 million deaths
A(H3N2)

2009
“Mexican flu”
0.3-0.5 million deaths
A(H1N1)

Credit: US National Museum of Health and Medicine
Influenza virus - Structure -

Hemagglutinin (HA)
Neuraminidase (NA)
RNA
NP
Polymerase (PA, PB1, PB2)
MA

Types: A, B, C (NP, MA)
Subtypes:
H1-H16 (HA)
N1-N9 (NA)
(e.g. H5N1)

H5
H7
Highly pathogenic avian influenza (HPAI)
(Fowl plague)
Wild birds: LPAI
Poultry: LPAI + HPAI
The Global Circulation of Seasonal Influenza A (H3N2) Viruses

Science 2008, Russell et al.
Aquatic wild birds
Influenza A virus reservoir

De Jong et al., Nature 1997
Claas & Osterhaus, Nat.Med 1998
Fouchier et al., J Virol., 2005
Munster et al., EID., 2005
Olsen et al., Science., 2006
## INFLUENZA A VIRUS

### Recent zoonotic transmissions

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Country</th>
<th>Year</th>
<th># Cases</th>
<th># Deaths</th>
<th>CFR</th>
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<tbody>
<tr>
<td>H7N7</td>
<td>UK</td>
<td>1996</td>
<td>1</td>
<td>0</td>
<td></td>
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<tr>
<td>H5N1</td>
<td>Hong Kong</td>
<td>1997</td>
<td>18</td>
<td>6</td>
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<tr>
<td>H9N2</td>
<td>SE-Asia</td>
<td>1999</td>
<td>&gt;2</td>
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<tr>
<td>H5N1</td>
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<td>2003</td>
<td>2?</td>
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<td>2003</td>
<td>89</td>
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<td>H7N2</td>
<td>USA</td>
<td>2003</td>
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<td>H7N3</td>
<td>Canada</td>
<td>2004</td>
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<tr>
<td>H5N1</td>
<td>SE-Asia/M-East/Europe/W-Africa</td>
<td>2003-13*</td>
<td>&gt;630</td>
<td>&gt;350*</td>
<td>CFR ~ 60% (increasing)</td>
</tr>
<tr>
<td>H7N9</td>
<td>PR China</td>
<td>2013</td>
<td>123</td>
<td>24</td>
<td>(increasing rapidly)</td>
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</tbody>
</table>
Provinces in China with confirmed human cases for avian influenza A(H7N9) reported to WHO*

*All dates refer to onset of illness.

Data as of 24 April 2013, 14:45 GMT+1

Source: WHO/GIP
Epidemiological curve of confirmed cases for influenza A (H7N9) reported to WHO, by day, 2013
Epidemiological curve of confirmed cases for influenza A (H7N9) reported to WHO, by day, 2013

Today: 123 cases, 24 fatal
Attachment to upper or lower respiratory tract

<table>
<thead>
<tr>
<th>Seasonal H3N2</th>
<th>Pandemic H1N1</th>
<th>HPAIV H5N1</th>
</tr>
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<tbody>
<tr>
<td>[Image]</td>
<td>[Image]</td>
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van Riel et al., Science 2006
van Riel et al., Am J Pathol 2007
van Riel et al., Am J Pathol 2009
van Riel et al., Am J Pathol 2010
van Riel et al., PLoS Path. 2011
Transmission set up
- Ferrets -

Munster et al., Science 2009
Herfst et al., Science 2012
Experiment 3, virus passaging in ferrets (P1 to P10, passages 1 to 10).

A/H5N1
wildtype

NT
NT
NT
NT
NT
NW
NW
NW
NW
collect NW

P0 wt

P0 mut

A/H5N1
HAQ222L,G224S
PB2 E627K

P1
P2
P3
P4
P5
P6
P7
P8
P9
P10

P10 wt

P10 mut

S Herfst et al. Science 2012;336:1534-1541
Clinical disease in diving ducks only

(Keawcharoen et al. 2008 Emerg Infect Dis)

<table>
<thead>
<tr>
<th>Species</th>
<th>No. inoculated</th>
<th>Mild signs</th>
<th>Severe signs</th>
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<tr>
<td>Tufted duck</td>
<td>7</td>
<td>4</td>
<td>3</td>
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<td>Pochard</td>
<td>7</td>
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<tr>
<td>Mallard</td>
<td>8</td>
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<td>0</td>
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<tr>
<td>Teal</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wigeon</td>
<td>8</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Gadwall</td>
<td>8</td>
<td>0</td>
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IHC vs. H&E spreading?

- no spreading?
- spreading?
## Avian influenza H5N1, Eastern hemisphere - H5N1 human - 2003-2011 -

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<tr>
<th>Country</th>
<th>2003</th>
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<td>5</td>
<td>7</td>
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<td>Total</td>
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<td>46</td>
<td>32</td>
<td>98</td>
<td>43</td>
<td>115</td>
<td>78</td>
<td>90</td>
<td>59</td>
<td>321</td>
</tr>
</tbody>
</table>

**Case fatality rate ~ 60% ??**

Source: [www.who.int](http://www.who.int)
Pathology
"naturally" and experimentally HPAI-H5N1 infected cats

Severe necrosis and inflammation in:
- Lung
- Brain
- Heart
- Kidney
- Liver
- Small intestine
- Adrenal gland

Kuiken et al., Science (2004); Keawcharoien et al., EID (2004); Rimmelzwaan et al., Am. J. Pathol. (2006); Kuiken et al., Nature 2006.
HPAI H7N7 virus
- Virulence determinants; human cells -

De Wit et al., J. Virol. 2010

HA; Receptor binding

NA; particle release (receptor cleavage)

PB2, PA; Transcription/replication
Avian influenza A virus
Adaptation:
Based on data
Spanish flu (H1N1), H7N7 and H5N1 viruses
E. De Wit et al., J.Virol 2010
Influenza A virus: major determinants of pathogenicity for mammals

Spanish flu (H1) virus:
- PB2 E627K (Taubenberger et al., 2005)
- HA (Kobassa et al., 2004)
- NA (Tumpey et al., 2005) replication in absence trypsine
- NS1 (Geiss et al., 2002) IFN pathway (not in mice lacking Mx1 gene)

H7 viruses (LPAI/HPAI)
- PB2 E627K (Munster et al., 2007; Shinya et al., 2007)
- HA (Munster et al., 2007) attachment pattern

H5 viruses (HPAI)
- PB2 E627K (Hatta et al., 1997)
- PB2 D701N (Li et al., 2005) duck virus in mice
- HA (van Riel et al., 2006; Shinya et al, 2006) attachment pattern
- NS1 (Seo et al., 2002)
2009 influenza A (H1N1) virus: relevant mutations

Virulence associated substitution in HA: D222G
(Herfst et al., J.Virol. 2010)

Oseltamivir resistance substitution in NA: H275Y
(de Vries et al., J.Clin Microbiol. 2010)

Zanamivir resistance substitution in NA: I223R
(de Vries et al NEJM 2010)
ANIMAL MODEL THE FERRET

Clinical, Pathology & Virological Parameters

Seasonal H1N1  pH1N1 2009  HPAI H5N1

Temperature  Virus Load  Lung Weight

Munster et al., Science 2009
Del Giudice et al., Science TM 2009
Chutinimitkul et al., J.Virol 2010
Herfst et al., Vet.Pathol. 2010
Bosch et al., J.Virol. 2010
Kreijtz et al., J.Gen.Virol. 2010
v.d.Brand et al., JID 2010
v.d.Brand et al., J.Virol 2010
Bodewes et al., Am J Pathol. 2011
Pandemic H1N1 (2009)-induced lung lesions as measured by CT and histopathology

“used for testing antiviral and vaccine candidates”
Prolonged influenza virus infection (shedding) and development of resistance

Erhard van der Vries et al. PLoS Path. 2013
Prolonged shedding and rapid emergence of resistance

Immunocompetent

E. van der Vries et al. PLoS Path. 2013
CONCLUSIONS

• Pathogenicity differs among influenza virus types and subtypes

• Determinants of pathogenicity differ among host species:
  - avian: HA cleavage site (H5 and H5)
    (differences individual species)
  - mammalian: HA, PA, PB1, PB2, NS
    (differences individual species)

• Innate immunity plays a crucial role

• Anamnestic adaptive immunity plays a crucial role
CONCLUSIONS

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    (differences individual species)
  - mammalian: HA, PA, PB1, PB2, NS
    (differences individual species)

• Innate immunity plays a crucial role

• Anamnestic adaptive immunity plays a crucial role

• Environmental factors (e.g. bacterial co-infections) important (?)