

Pigs and pandemic influenza: thoughts from a swine flu virologist

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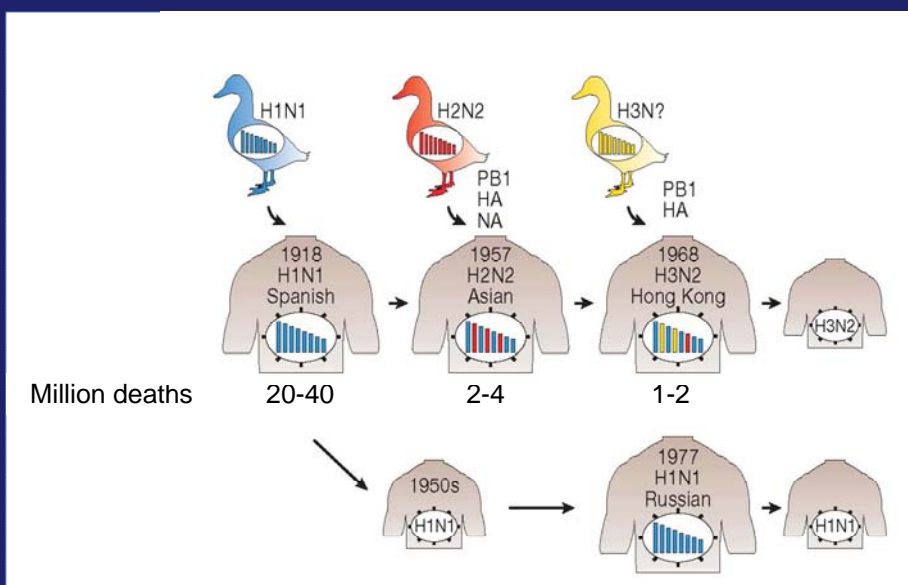
About swine influenza viruses (SIVs)

- Three influenza A virus subtypes - H1N1, H3N2, H1N2 - are enzootic in pigs worldwide
- Antigenic and genetic make-up differs
 - between swine and human influenza viruses
 - between swine viruses in different continents/regions
- Most SIVs are reassortants with swine and/or avian and/or human virus genes
- Major cause of acute respiratory disease, but most infections subclinical

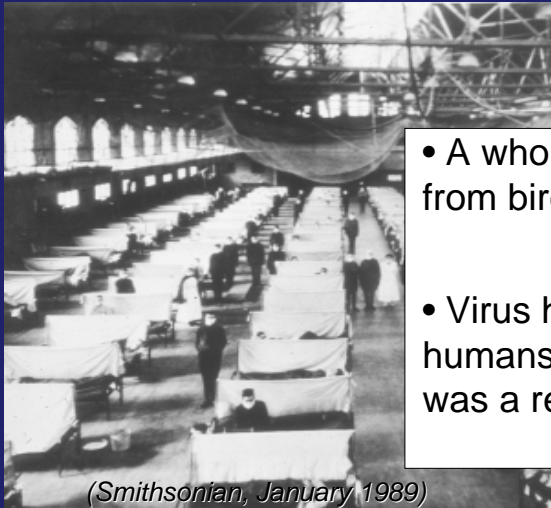
SI is a zoonosis

- Approx. 70 documented cases in humans 1958-present, almost any of the established SIV genotypes
- 6 fatal cases, 3 with underlying illness
- Most humans (>60%) had exposure to pigs, median age <25 years
- Human-to-human transmission very limited, no virus able to spread in human population

Human pandemics of the 20th century



1918 Spanish flu: simultaneous with first observations of swine influenza



- A wholly avian virus that jumped from birds to humans and pigs?

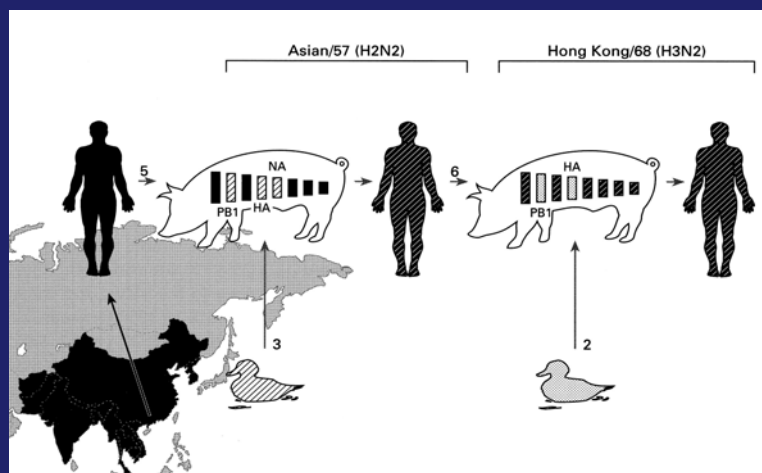
(Taubenberger et al., Nature 2005)

- Virus has been circulating in humans or pigs before 1918 and was a reassortant

(Smith et al., PNAS 2009)

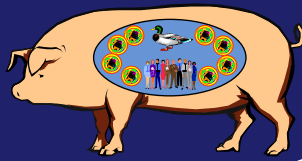
Did humans infect pigs or the other way around?

1957 Asian and 1968 Hong Kong flu viruses: reassortants with genes from circulating human virus and a novel avian virus



Did reassortment occur in the pig?

The pig as an intermediate host

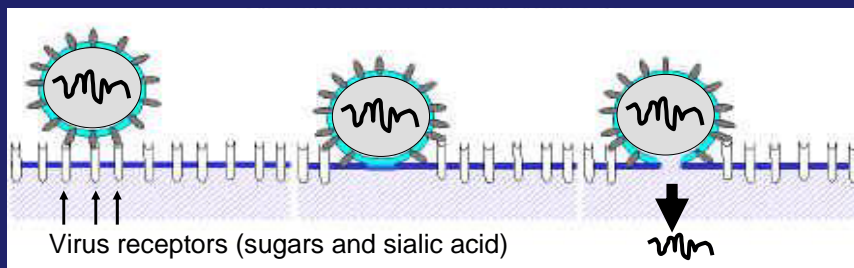


Pigs are susceptible to avian influenza in contrast to humans

Influenza viruses can transmit from pigs to humans

Avian viruses undergo adaptation to mammalian hosts in the pig by **mutation** or **genetic reassortment** (pig as a mixing vessel)

Avian influenza viruses prefer different type of receptors ($\alpha 2,3$) than human or swine viruses ($\alpha 2,6$)



$\alpha 2,3$ avian-type



$\alpha 2,6$ human-type



$\alpha 2,3 + \alpha 2,6$

Pigs are the single animal species with both types of receptor

(Ito et al. 1998, Suzuki et al. 1998)

Summary

- **Most SIVs are reassortants** with avian virus genes, but they transmit rarely to humans and fail to spread between humans
- **Human pandemic viruses** of 1957 and 1968 were reassortants, but no direct evidence that they emerged in the pig



H5N1: a pandemic scare

- Direct infections of humans via infected poultry
- Total number of infected humans remains low, no human-to-human transmission
- Humans have both avian-type and human-type receptors!



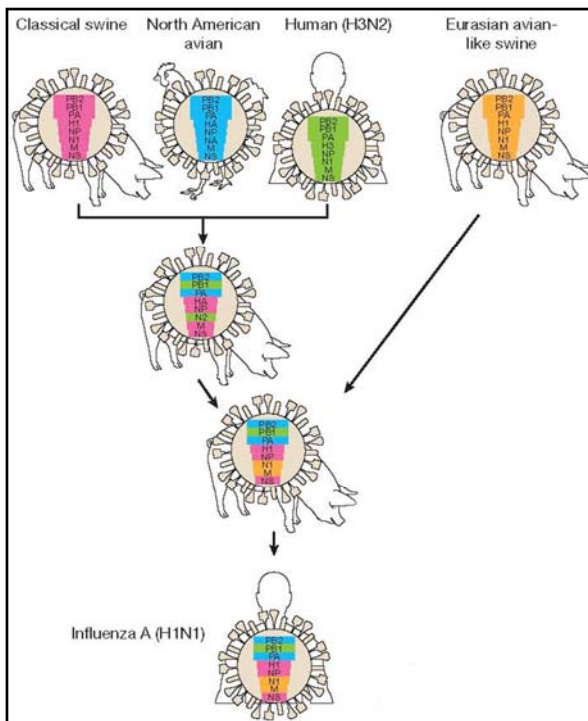
Highly pathogenic H5N1 in pigs

- Low incidence in pigs in Asia
- Low susceptibility in experimental studies:
 - generally subclinical
 - infection limited to respiratory tract,
 - much lower titers than SIV
 - no transmission between pigs

(Shortridge et al. 1998, Isoda et al. 2004, Choi et al. 2005, Lipatov et al. 2008)
- Pigs have both types of receptors, but the avian receptor is mainly confined to the deeper airways

Lessons from H5N1

- Pigs are NOT uniquely susceptible to avian influenza viruses, they are NOT essential intermediate hosts
- Pigs are NOT the single animal species with both avian- and human-type receptors
- Avian influenza viruses must undergo **genetic changes (mutation or reassortment)** to establish full replication potential in pigs
- It is unknown whether genetic adaptation occurs more readily in pigs



Novel 2009 H1N1:
a swine-origin virus that was never reported in swine

6 genes from North American 3R SIV including “classical H1”

NA, M genes from Eurasian SIV

Neumann and Kawaoka, Nature 2009

Novel 2009 H1N1 and swine

- Reassortment most likely occurred in pigs, but virus is not endemic in pigs - swine cases in Canada, Argentina, Australia, (Northern) Ireland, link with human cases
- Pigs did not play a role in virus spread in human population
- Cross-protection between enzootic SIVs (eg European H1N1) and novel H1N1
- Why does virus spread so readily between humans, in contrast to established SIVs?

Summary

- Genetic reassortment is extremely common in the pig. They serve as reservoirs for human and avian flu gene collections.
- There is only one documented case of a pandemic caused by a *presumed* swine-origin influenza virus: a virus that replicates very efficiently in pigs is not necessarily successful in humans

Research needs

- Viral genetic changes that favour
 - replication efficiency of influenza viruses in pigs and transmissibility between pigs
 - transmission to and between humans
- How likely is adaptation in humans themselves or in other animal species ?
- Extent of cross-protection between influenza virus variants (eg seasonal human H1N1- novel H1N1) and subtype (eg H1-H3)

