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Zoonotic potential of non-avian influenza A viruses

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(1) Several documented cases of influenza virus transmission from pigs to humans

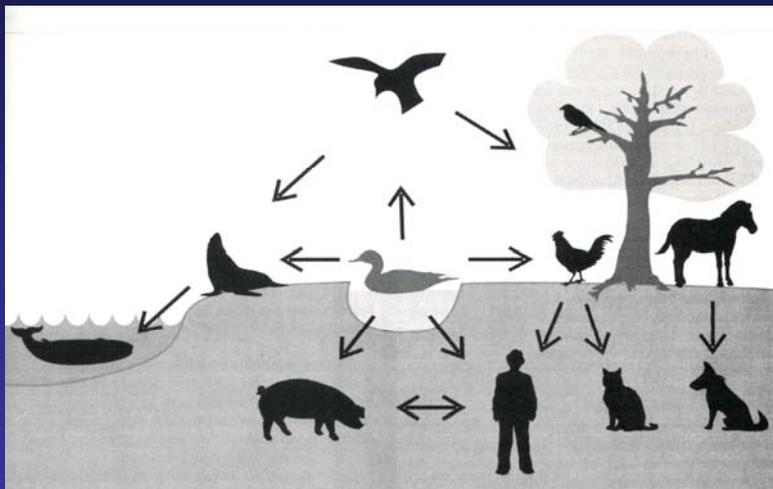


Illustration from Fields VIROLOGY, 5th edition

About swine influenza viruses (SIVs)

- Influenza A viruses of H1N1, H3N2 and H1N2 subtypes are enzootic in pigs worldwide *but antigenic and genetic differences with human viruses*
- SIVs in Europe differ in their antigenic and genetic makeup from those in North America
- Most SIVs are reassortants with swine and/or human and/or avian genes; antigenic drift is slower with swine than with human influenza viruses

SIVs in the US: Only classical H1N1 until 1998, various reassortants thereafter

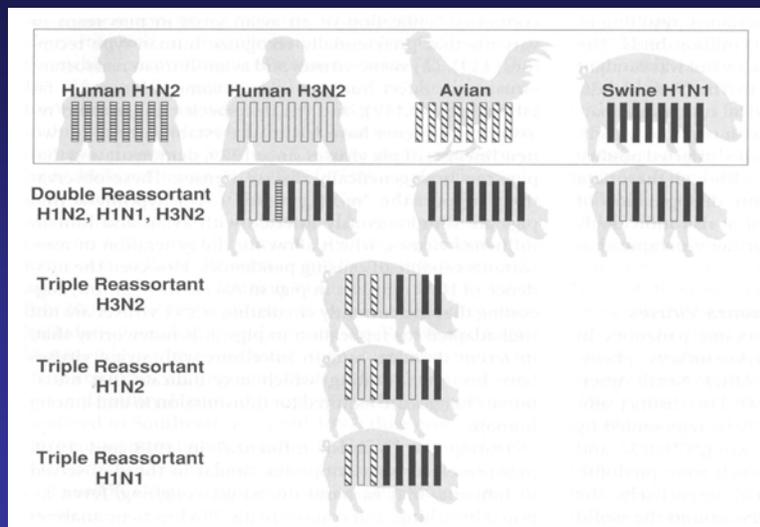


Illustration from Fields VIROLOGY, 5th edition

SIVs in Europe: Avian-like H1N1 replaced classical H1N1; H3N2 and H1N2 reassortants



Avian-like
H1N1 (1979)

Reassortant
H3N2 (1984)

Reassortant
H1N2 (since 1994)



40 documented cases of SIV in humans since 1958; excludes Fort Dix incident, New Jersey, 1976 serological studies

Cases of Swine Influenza in Humans: A Review of the Literature

Kendall P. Myers,^{1,2} Christopher W. Olsen,³ and Gregory C. Gray¹

¹Center for Emerging Infectious Diseases, Department of Epidemiology, and ²Department of Occupational and Environmental Health, College of Public Health, University of Iowa, Iowa City, and ³Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin-Madison

Clinical Infectious Diseases 2007; 44: 1084-8

Robinson et al., EID 2007; 13: 1865-70

Komadina et al., Virus Genes 2007; 35: 161-5

Fourty cases of SIV in humans

- 20 cases in North America, 17 in Europe/Russia, 3 in Asia
- most humans (> 60%) had exposure to pigs, median age < 25 years
- all SIV subtypes, classical H1N1 most frequent
- all patients showed influenza-like illness and/or pneumonia; 6 died, 3 with underlying illness
- little evidence for human-to-human transmission

Serologic studies demonstrate higher seroprevalence rates and HI antibody titers to any US SIV in swine workers than in controls

(Woods et al. 1981, Olsen et al. 2002, Ayora-Talavera et al. 2005, Ramirez et al. 2006, Myers et al. 2006, Gray et al. 2007)

Chinese women who raised pigs in their homes were no more likely to have been exposed to influenza viruses than controls

(Zhou et al. 1996)

“Titers of 20 are at the lower limit of specificity and are of doubtful reliability. Seropositivity to human-like H3N2 swine viruses may reflect the triggering of antibody memory generated in response to recent human H3N2 strains”

Gray et al., EID 2006; 12: 1871-8

> 650 rural farmers examined for HI antibodies against swine H1N1 and H1N2, and human H1N1 and H3N2; 24-month follow-up, combined with virus detection attempts

- Swine-exposed participants as well as their nonswine-exposed spouses had elevated HI antibody titres to SIVs compared to controls
- Among participants who seroconverted to ≥ 1 SIV, < 25 % reported an influenza-like illness (ILI) during the 2 years; 74 gargle or nasal swab specimens were submitted by 66 participants with ILI: 22 were positive for human influenza virus, **only 1 for H1N1 swine influenza virus (3R)**

Limitations of serologic studies for SIV in humans

- (1) Serologic cross-reactivity between some influenza viruses of humans and pigs
e.g. Elevated titers against US swine H3N2 were associated with having elevated titers against human H3N2 strains (Myers et al. 2006)
- (2) Recent exposure to human influenza viruses or vaccination may boost antibody titers to older human viruses and/or broaden serologic cross-reactivity
e.g. Being ≥ 50 years of age, and vaccination with SIV human vaccine in 1976-77 or any human influenza vaccine was associated with SIV seropositivity (Olsen et al. 2002)
- (3) Few data on serologic profile in patients from which SIV was isolated
e.g. "It is possible that the elevated titers compared by proportional odds modeling do not correlate with infection" (Myers et al. 2006)

Conclusions

- The total number of reported zoonotic SIV infections remains small compared to the number of people worldwide involved in swine farming, and there is sparse evidence for human-to-human transmission
- Serologic studies suggest that many zoonotic SIV infections go undetected, but the interpretation of serologic data is often difficult
- The true incidence of zoonotic SIV infections remains unknown

(2) Infectivity and pathogenicity of SIVs for humans

No experimental studies with SIVs in human volunteers or human cell culture (contrasts with avian viruses)



Comparative studies with *A/Sw/Ontario/97* (wholly human H3N2, not reisolated subsequent to initial appearance) and *A/Sw/Minnesota/99* (triple reassortant H3N2, spread throughout US) by C. Olsen and coworkers, UW Madison show a clear barrier to infection of pigs with wholly human influenza viruses

Early triple reassortant H3N2 virus (*Sw/Minnesota/99*) compared to wholly human H3N2 virus (*Sw/Ontario/97*):

- More extensive lung pathology, greater infectivity and accelerated nasal shedding *in vivo* in pigs (Landolt et al. 2003)
 - Phenotypes could be reversed by exchanging HA plus NA (Landolt et al. 2006)
- Higher infectivity *in vitro* in swine respiratory epithelial cells (Busch et al. 2008)
 - Amino acid 138 is a major determinant of infectivity

Conclusions

- The (determinants of) infectivity of SIVs for humans or human cell cultures has never been examined.
- It remains unknown whether the species barrier between pigs and humans is less stringent than that between birds and humans.

Most urgent questions

- Infectivity of SIVs for human respiratory tract epithelial cells; determinants of infectivity (*in vitro* studies)
- Effect of immunity to human influenza viruses on infection with homosubtypic and heterosubtypic SIVs (animal models: ferrets, pigs)
- Effect of immunity to human influenza viruses on serologic response to SIVs (animal models)

The European Surveillance Network for Influenza in Pigs (ESNIP 2)

- Coordination Action, Jan 2006-Dec 2008
- EC contribution 300 000 euros
- Coordinator Kristien Van Reeth, UGent, Belgium
- 9 partners from Europe including 2 SIV vaccine manufacturers
1 partner from US, 1 from Hong Kong

<http://www.esnip.ugent.be>