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The public health risk of influenza in pigs – recent insights, key knowledge gaps

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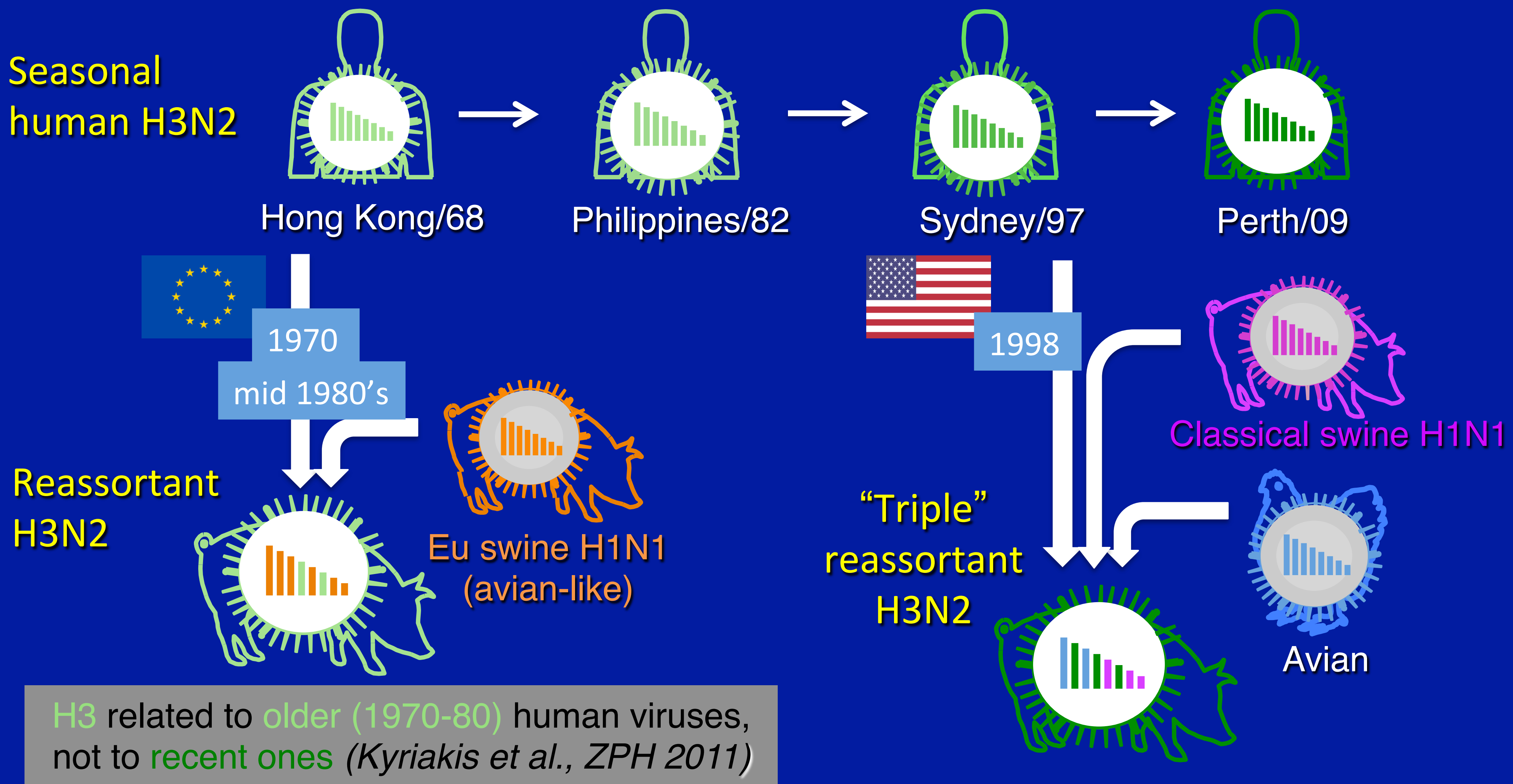
H1N1, H3N2 and H1N2 viruses established in swine populations worldwide

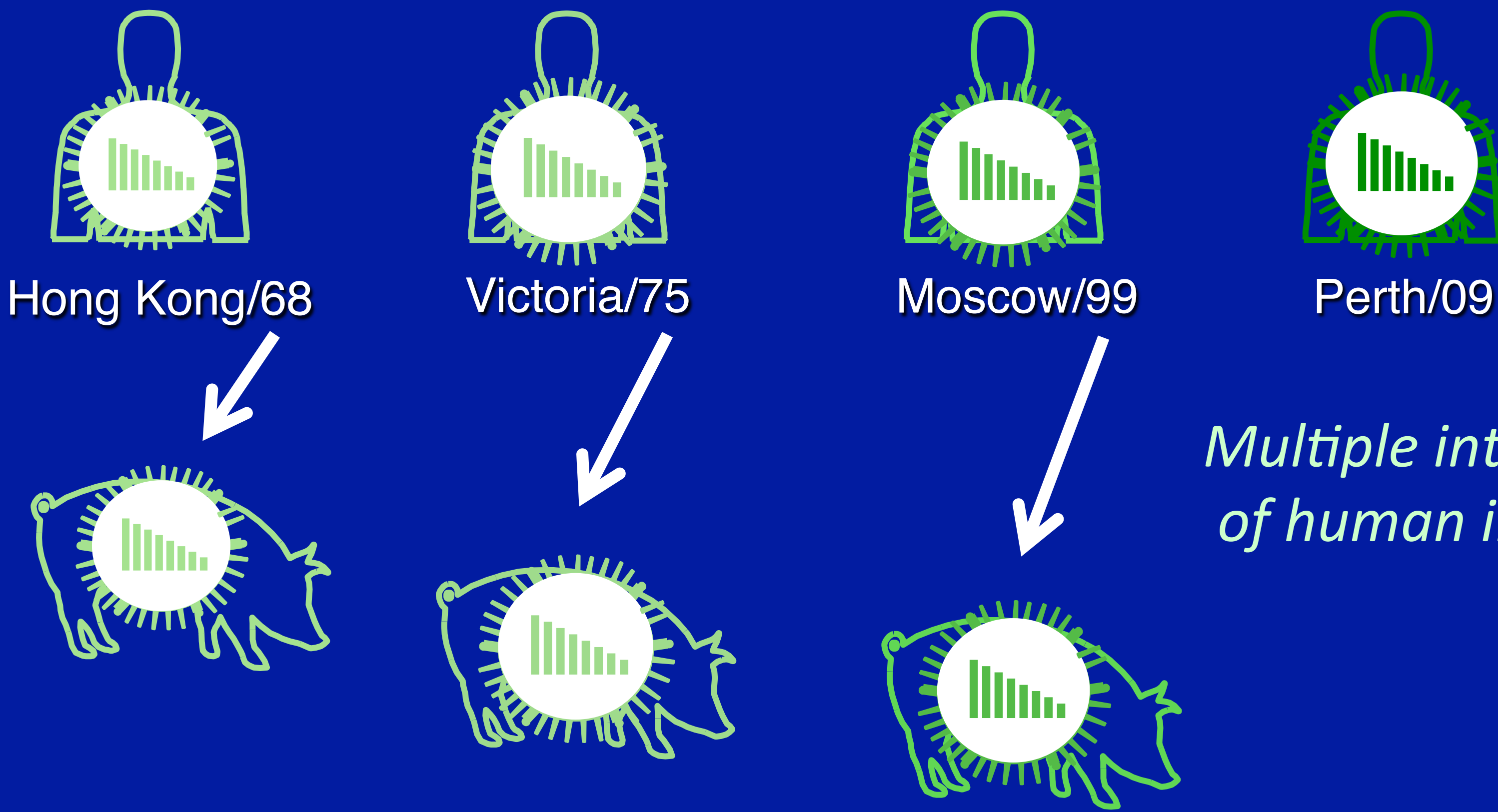
- SIVs are of human or avian origin, most viruses are reassortants with a mix of human/avian and swine-adapted genes
- Concurrent circulation of multiple subtypes and lineages, especially in swine-dense regions
- Distinct virus lineages in Northern America vs Europe (and Asia)

H3N2 SIV in Europe and North America



H3N2 SIV in Asia (China)

Seasonal human H3N2

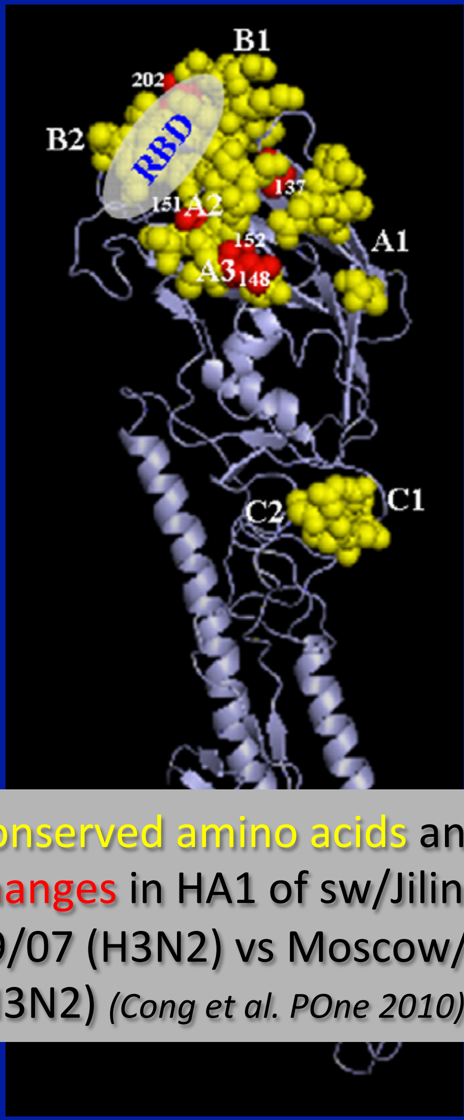


✓✓Wholly human viruses

Multiple introductions of human influenza

- ✓ Various double and triple H3N2 reassortants (Yu et al. J. Clin. Microbiol. 2008, Sun et al. J. Clin. Virol. 2009, Shu et.al. Virol. 1994)
- ✓ H3N2 reassortants with internal genes of avian viruses (H9N2 or H5N1) or avian N2 (Bi et al. EID 2010, Cong et al. Pone 2010)

Antigenic drift in SIV HA

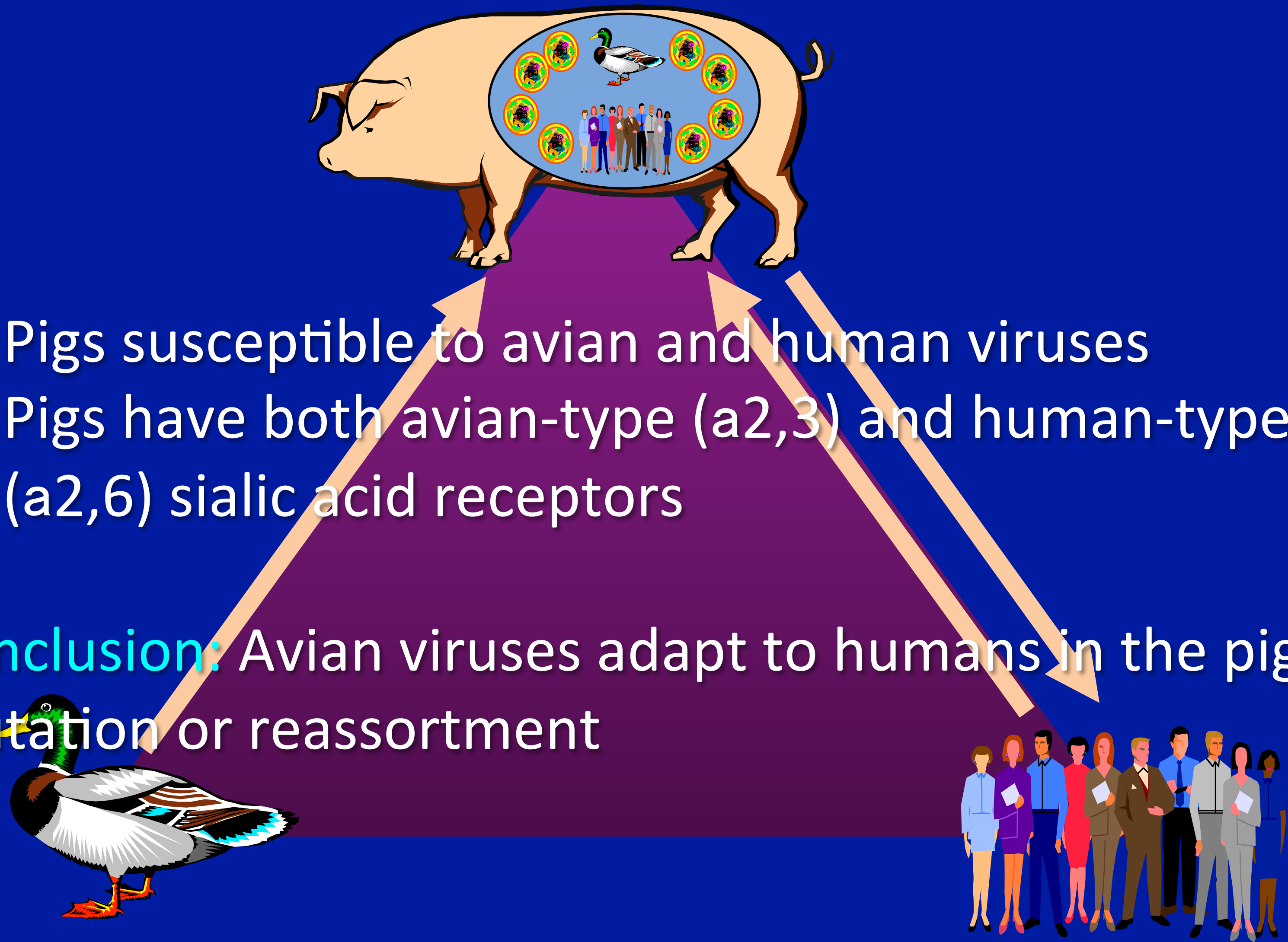


Conserved amino acids and changes in HA1 of sw/Jilin/19/07 (H3N2) vs Moscow/10/99 (H3N2) *(Cong et al. POne 2010)*

- European swine H3N2: genetic drift at similar rate as human H3N2, but slower drift because changes outside antigenic domains (de Jong et al. Vaccine 2007)
- Substantial genetic/antigenic diversity between H1 lineages:

  N. America: classical H1 vs more recent H1 clusters (β, γ, δ1, δ2, 2009p)
  Eu: avian-like H1N1 vs human-like H1N2 and 2009 pH1N1
- Need for exhaustive antigenic analyses, study of immunodominant epitopes

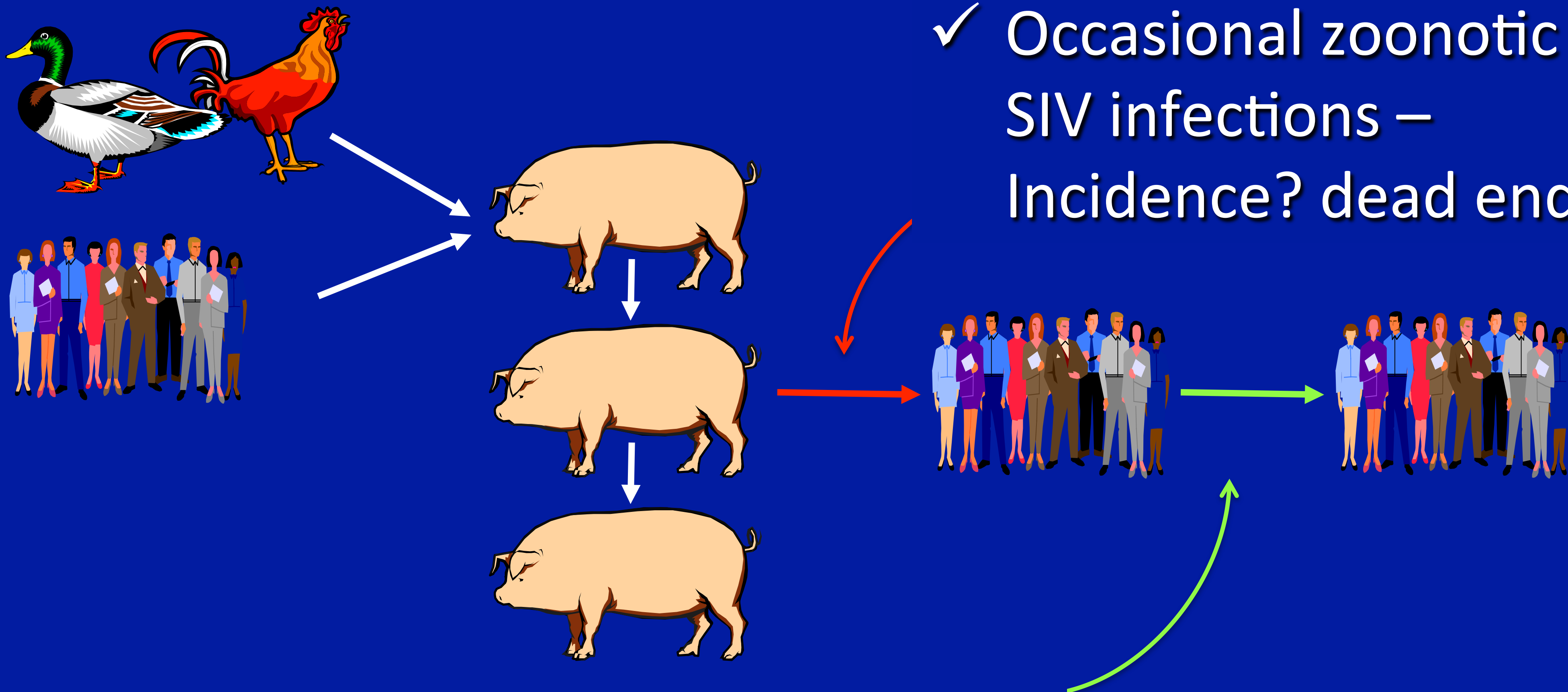
Central dogma: pigs as unique intermediate hosts for pandemic influenza viruses



- ✓ Pigs susceptible to avian and human viruses
- ✓ Pigs have both avian-type (a2,3) and human-type (a2,6) sialic acid receptors

Conclusion: Avian viruses adapt to humans in the pig by mutation or reassortment

Facts



✓ Occasional zoonotic SIV infections – Incidence? dead end!

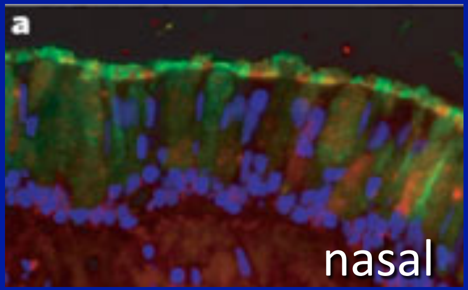
✓ 2009 pH1N1 is first pandemic virus (that is almost certainly) of swine origin

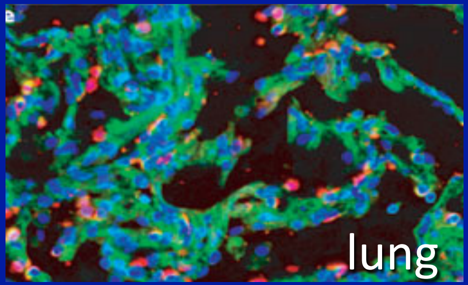
✓ H5N1 has infected humans directly, not through pigs

Research Issue #1 – Factors that make influenza viruses adapted for replication in pigs, transmission between pigs and from pigs to humans

- Can we identify genetic markers of adaptation (e.g. mutations, sets of genes)?
- Can non-H1 or -H3 viruses (e.g. H5, H9) become adapted to swine or human populations?
- Are pigs preferred "mixing vessels" as compared to humans or birds?
- Is the barrier between pigs and humans weaker than that between birds and humans?

Research Issue #1 cont– Significance of α2,3 (avian-type) and α2,6 (human-type) sialic acid receptors in porcine respiratory tract? (Ito et al 1998)

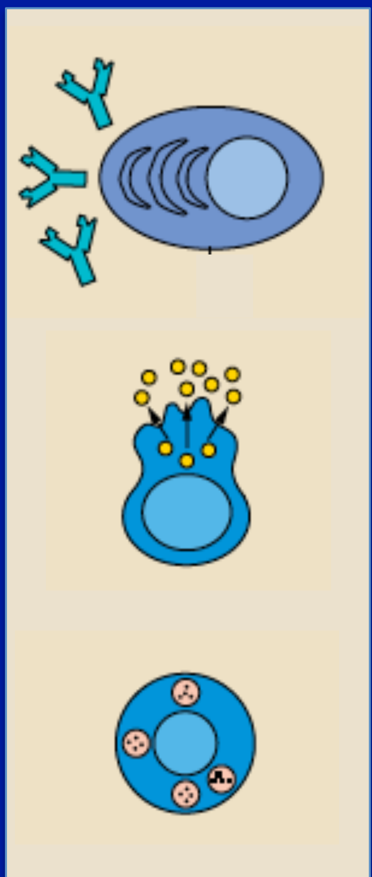




α2,6 = human receptor = green α2,3 = avian receptor = red

- Humans and some land-based poultry species also express both types of sialic acids (Shinya et al. 2006; Wan and Perez 2006; Kuchipudi et al. 2009) Expression pattern similar to pigs (Nelli et al. 2010, Van Poucke et al. 2010)
- Virus binding to a given sialic acid may not lead to productive infection of cells: co-receptors? other barriers of infection?

Research Issue #2 – Cross-protective immunity between viruses from swine and humans (and birds)?: Significance of heterovariant/heterosubtypic immunity, mechanisms, viral targets



- Differences between mice and swine/men!
  - ✓Novel generation vaccines (DNA, rec M2e, adenovector) not protective in pigs
  - ✓Cross-protection between H1N1 and H3N2 limited to mice
- Post-infection immunity in swine is broad , not entirely dependent on HA-Abs

Experimental cross-protection studies pigs

Cross-protection between antigenically distinct H1N1 swine influenza viruses from Europe and North America

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Prior infection of pigs with swine influenza viruses is a barrier to infection with avian influenza viruses

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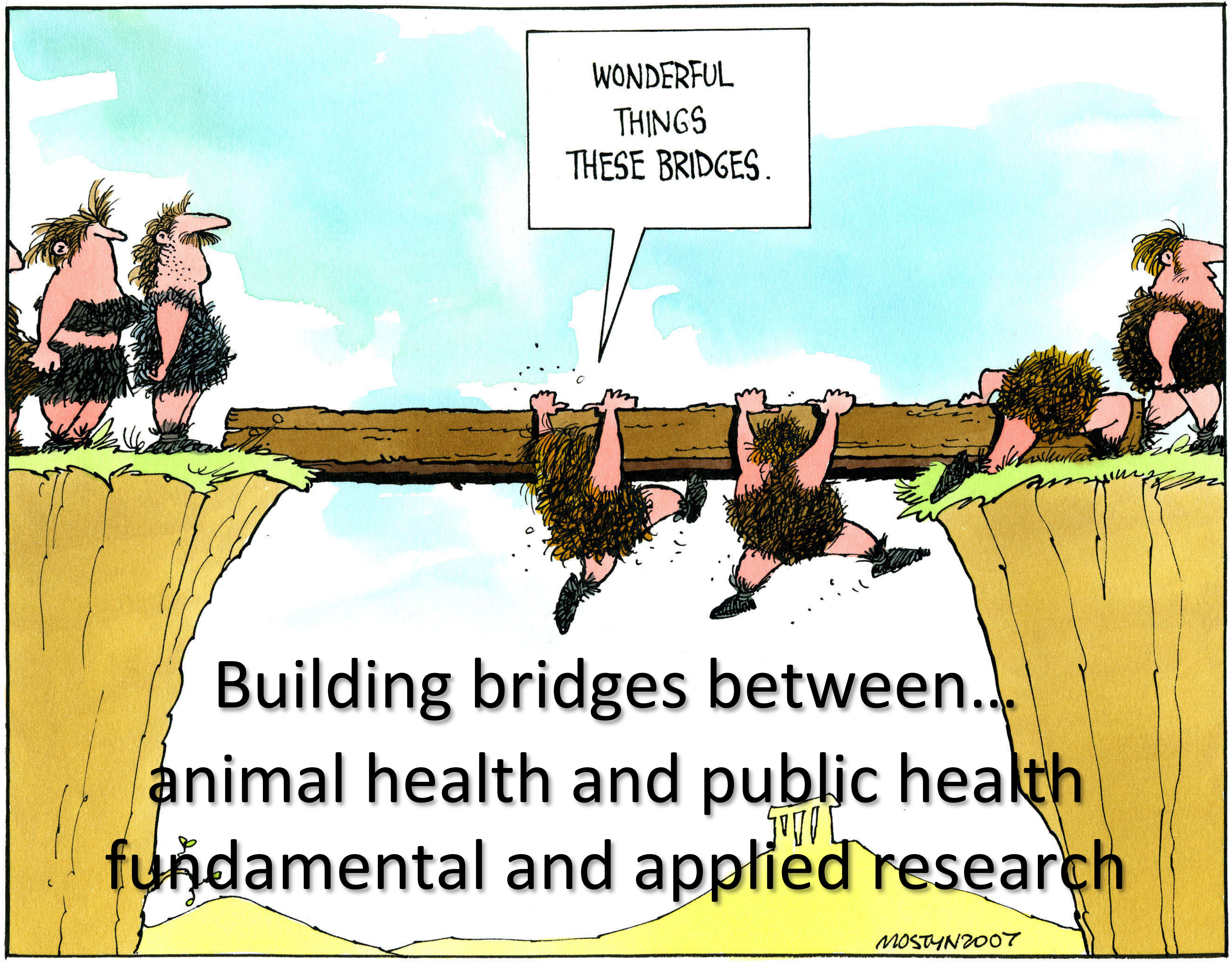
Determinants of pathogenicity may also differ between mice and other species

- Reconstructed 1918 virus was lethal in mice, ferrets and macaques, but not in pigs
  Weingartl et al. JVi 2009
- Pathogenicity of SIVs with different PB2 genes and mutation of codon 627 in mice does not correlate with pathogenicity of SIVs in the pig
  Ma et al. Virology 2000

Research Issue #3 – Determinants of pathogenicity

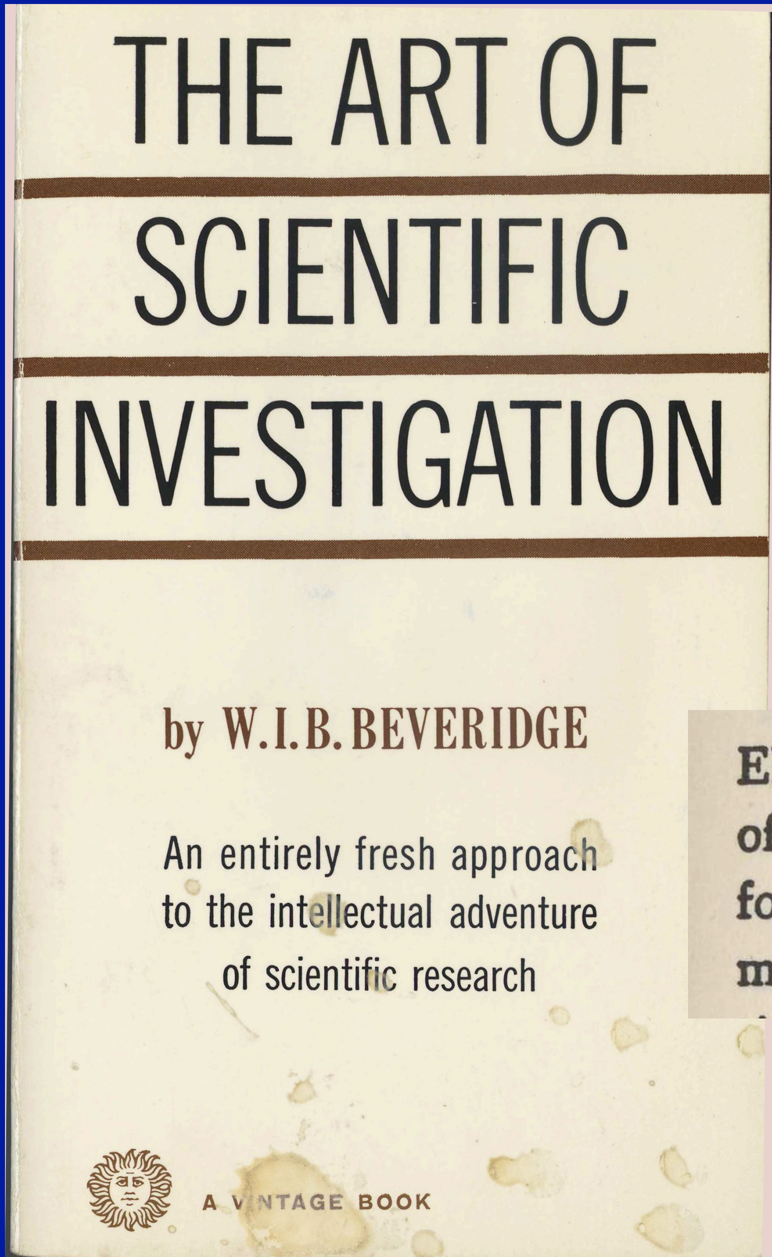
- Can H1 or H3 influenza viruses become highly pathogenic for swine or humans?
- Can H1 or H3 viruses induce a cytokine "storm"?
- NS1 is an IFN antagonist in continuous cell lines, but does it interfere with the IFN system in pigs and people???



Building bridges between…

animal health and public health

fundamental and applied research



Elaborate apparatus plays an important part in the science of to-day, but I sometimes wonder if we are not inclined to forget that the most important instrument in research must always be the mind of man. It is true that much

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Co-ordination actions

European Surveillance Network for Influenza in Pigs: ESNIP

2001-04, 2006-08, 2010-13

Collaborative project

Pathogenesis and transmission of influenza virus in pigs

2010-14

FLUPIG

- ✓ Research priorities for SI
- ✓ Harmonization of global surveillance for influenza in swine