Control of influenza in a One Health perspective – do we have the tools and are they used properly?

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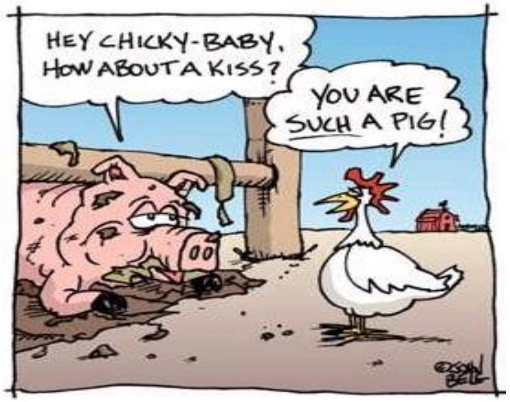
Professor
Influenza virus group
DTU

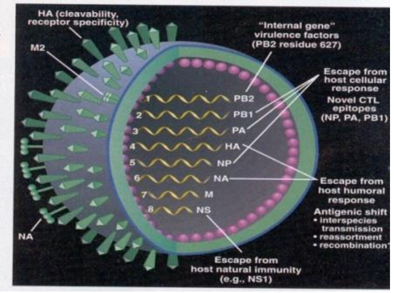
Outline

- Introduction to influenza
- Avian influenza
- Swine influenza and influenza in neglected species
- Vaccination of animals (and humans)
- Surveillance and legislation on influenza in Europe



Influenza A virus

- *Orthomyxoviridae* family
- Single stranded RNA segmented genome

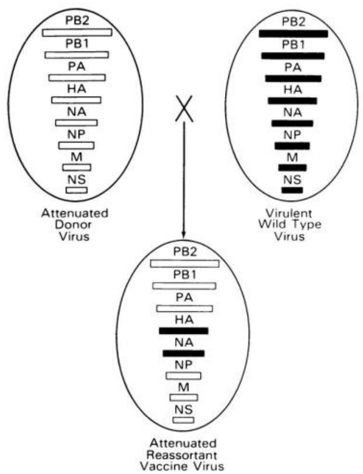


- Subtypes 16 HA, 9 NA major antigenic types in birds
  - H5N1
  - H7N1
  - H1N1
  - Etc.

- Non-avian hosts eg.:
  - Swine: H1N1, H1N2, H3N2
  - Human: H1N1, H1N2, H3N2
  - Horse: H3N8

Influenza A virus evolution

- Drift
  - Point mutations, RNA polymerase without proof-reading activity
- Shift/reassortment



- Species jump followed by adaptation

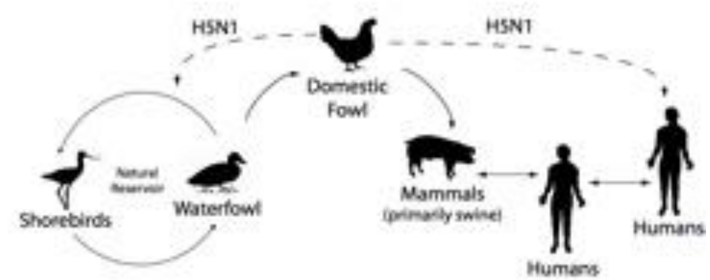
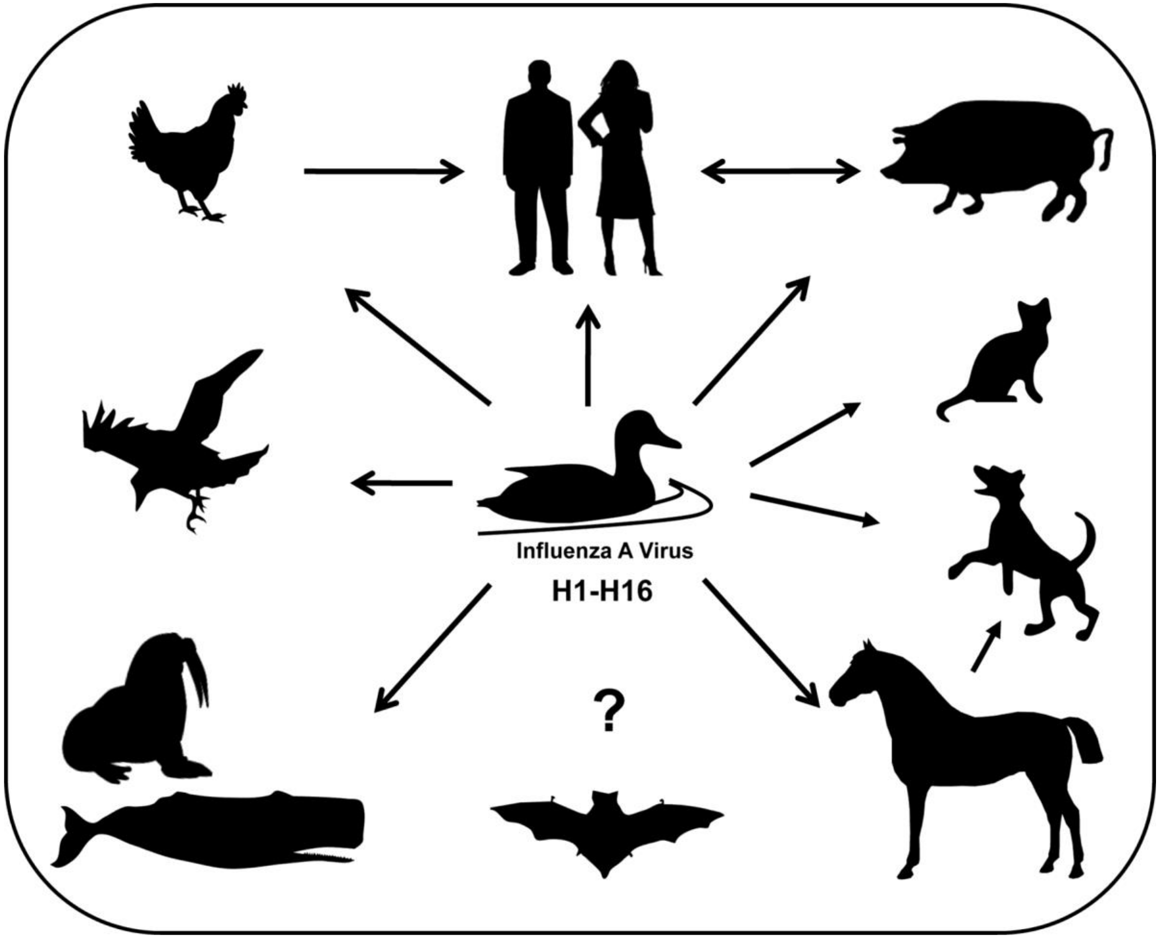


Figure 1. Possible transmission pathways for avian influenza.

U.S. Department of the Interior
U.S. Geological Survey

Printed on recycled paper

Influenza A virus host range



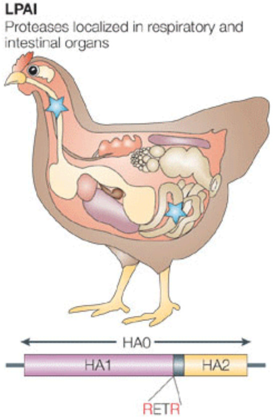
Mänz B et al. J. Virol. 2013;87:7200-7209

Low and highly pathogenic avian influenza A viruses

Bird flu

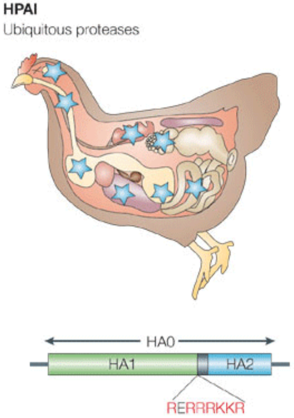
H1,H2,H3……H16

Low pathogenic influenza (LPAI) often result in no or little clinical disease in poultry

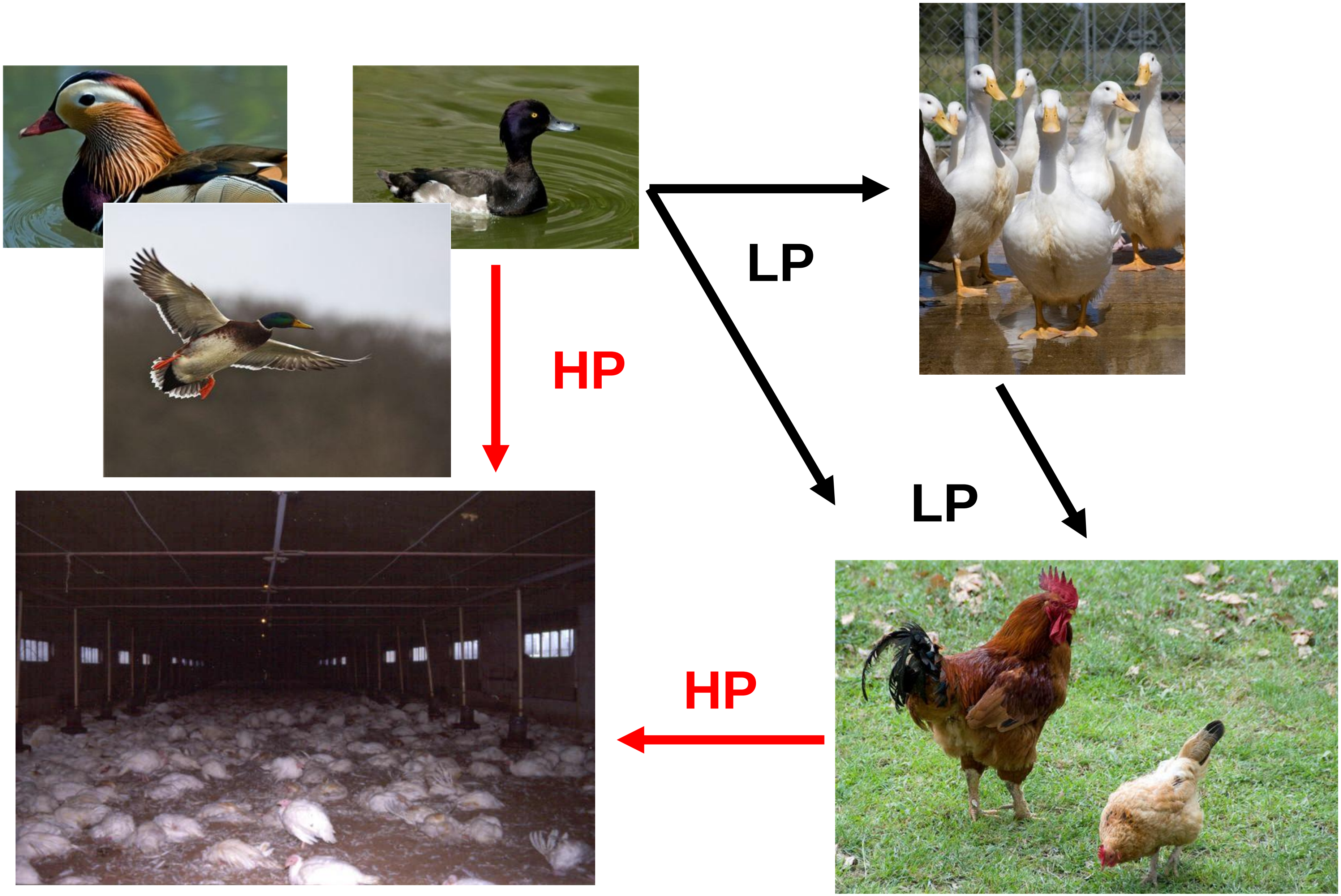


H5,H7

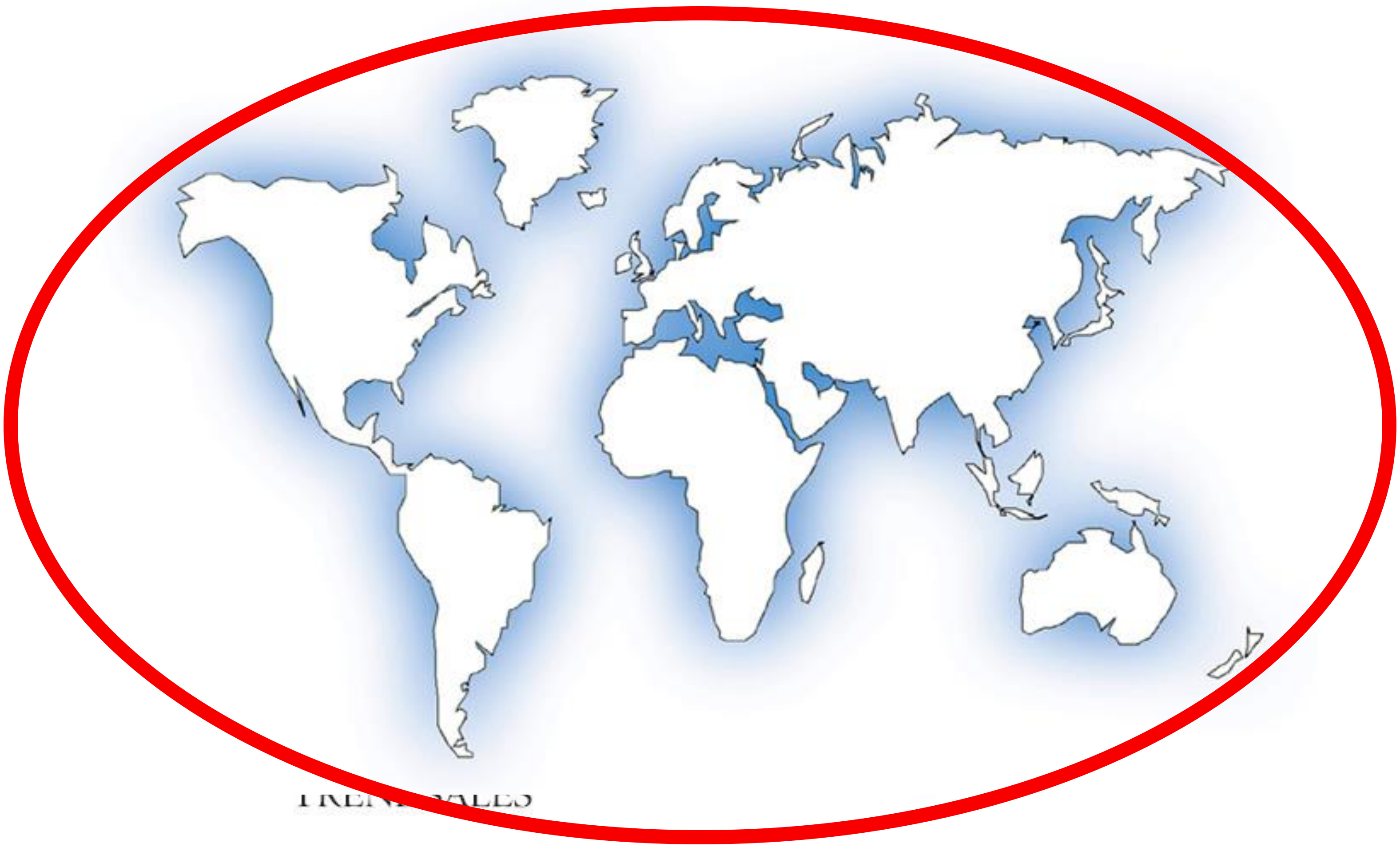
Highly pathogenic influenza (HPAI) result in up to 100 % mortality in 48 hours in some poultry species



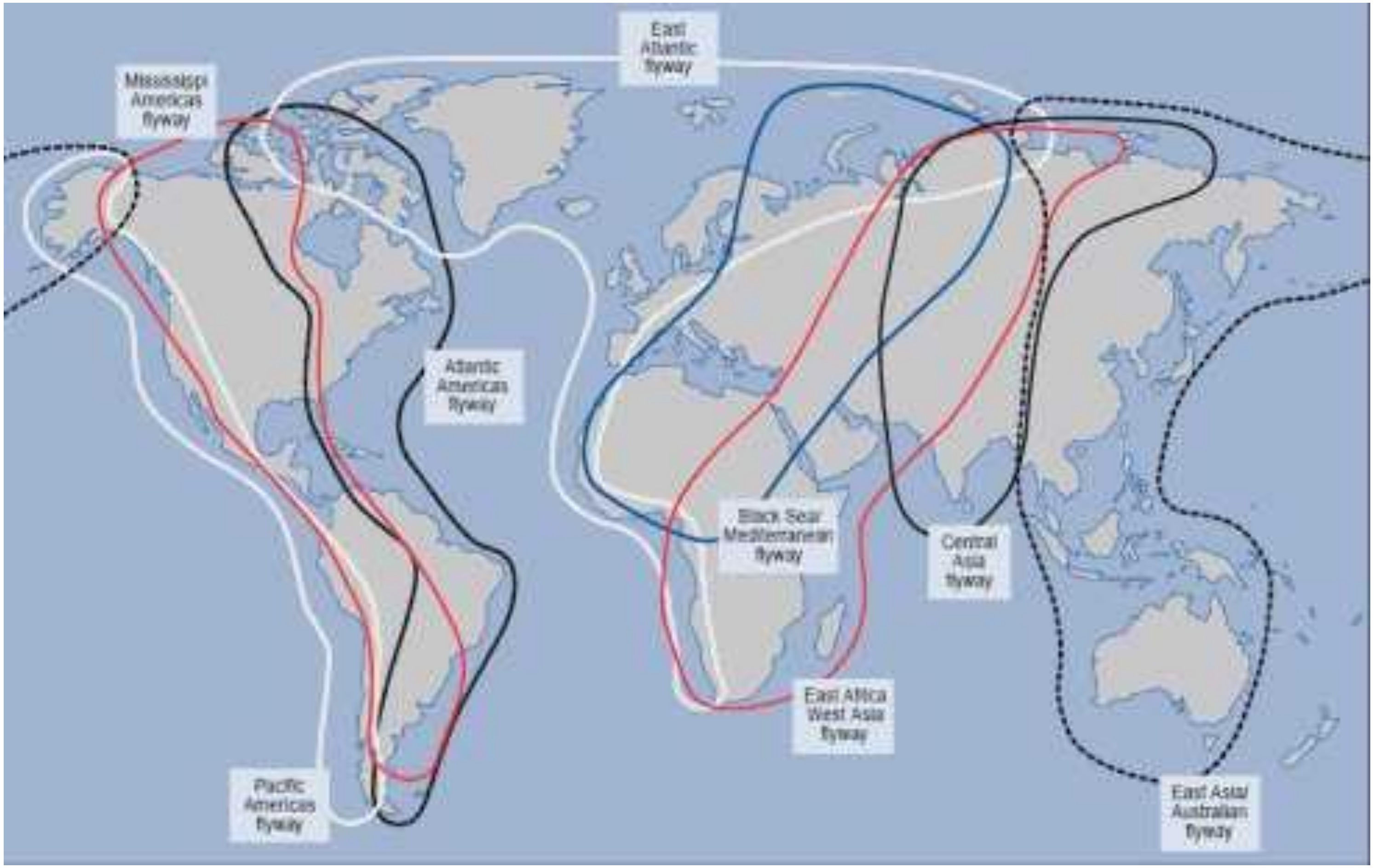
H5 & H7 AIVs transmissions



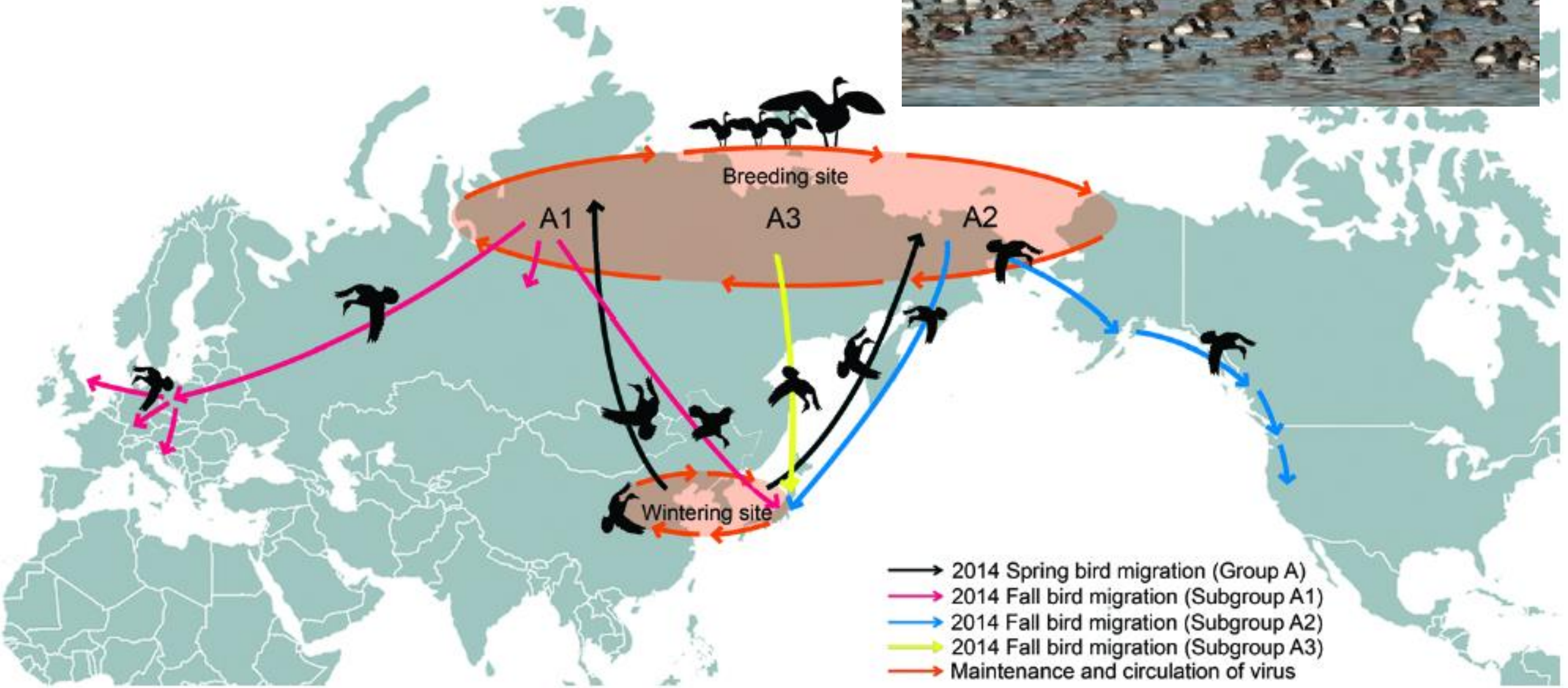
Where is avian influenza detected?



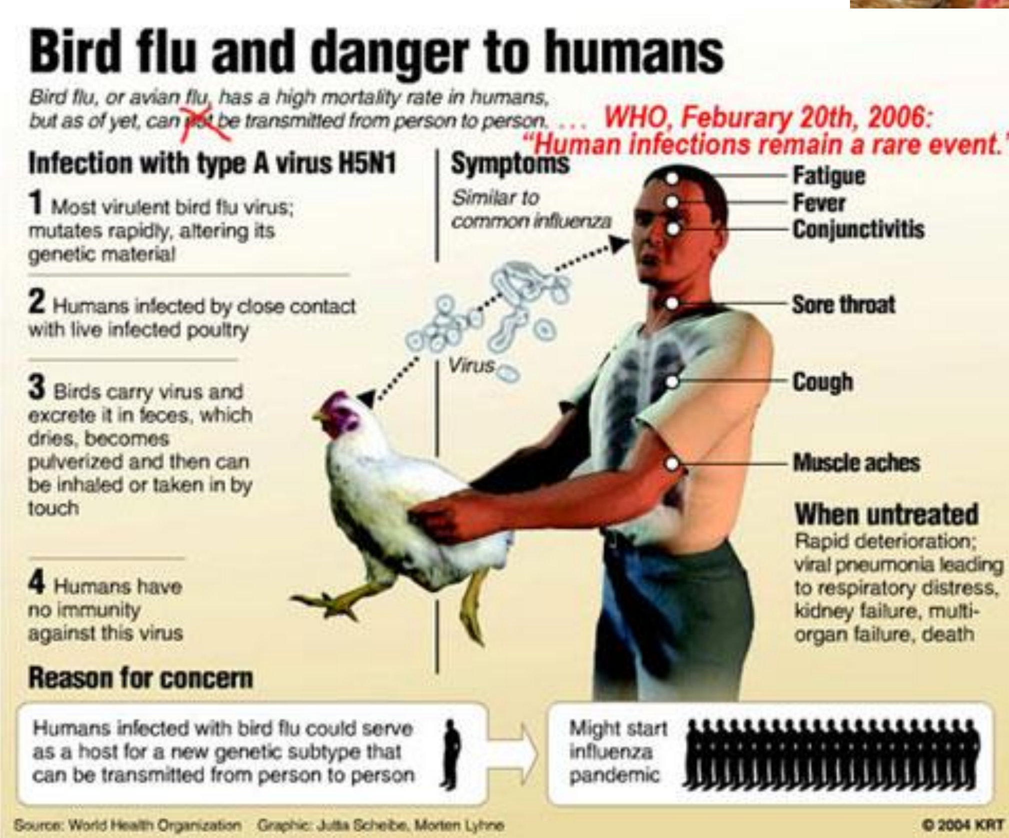
Wild birds can act as vectors for AI virus



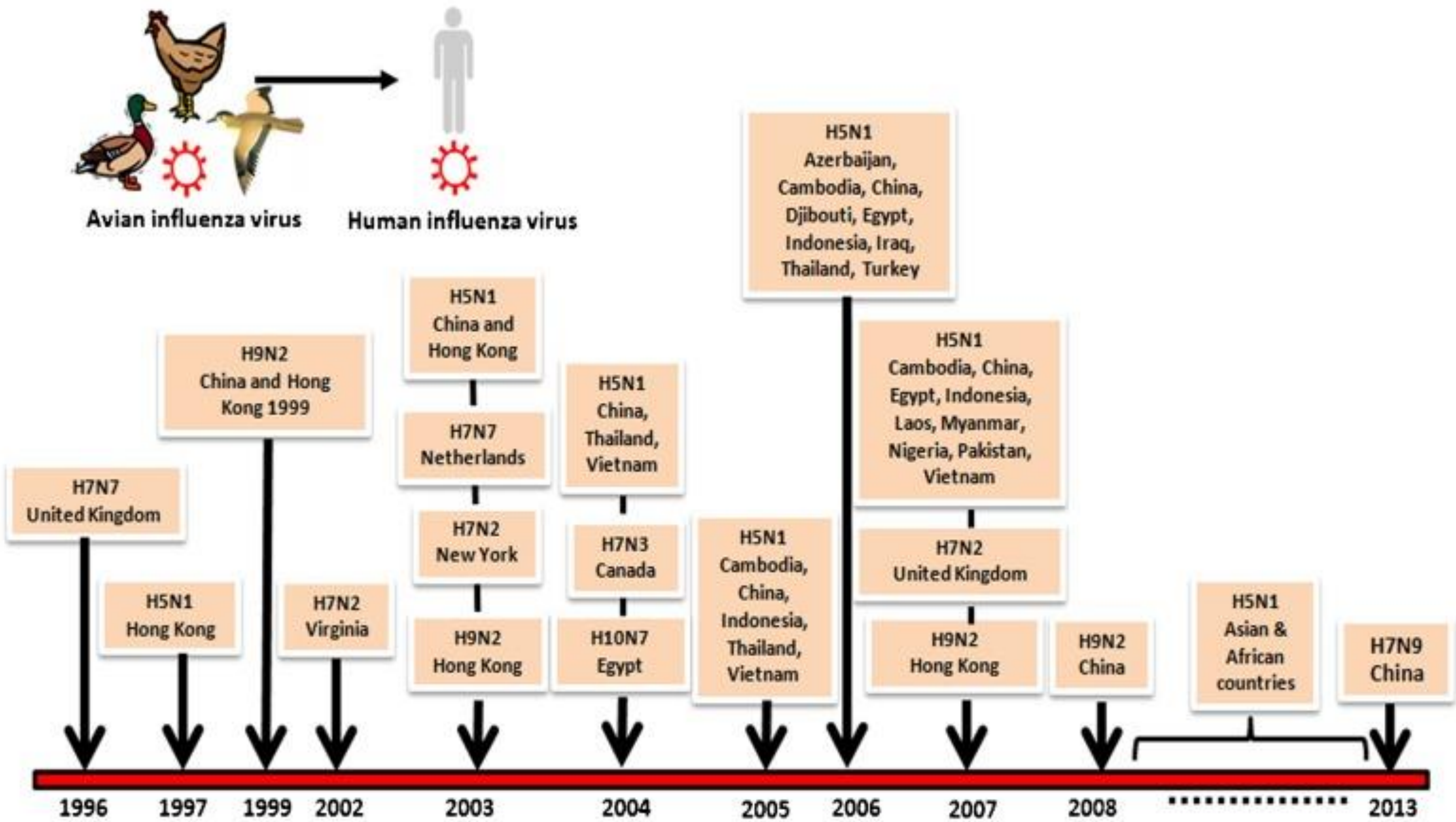
Intercontinental spread of HPAI H5N8 viruses
Lee et al. (2015) Journal of Virology



HPAI as a zoonosis



Avian Influenza Human Cases



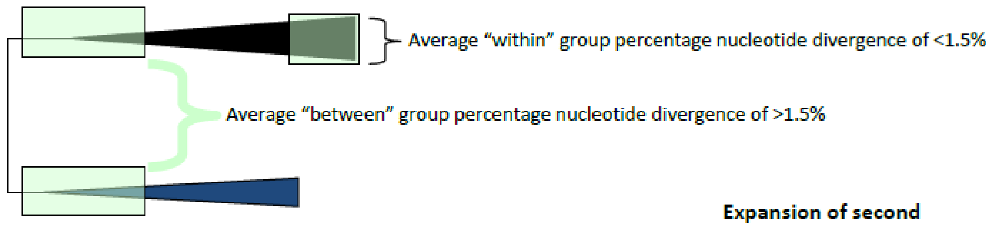
- H5N8
  - No reported cases, but some H5N6 positive human cases in Korea

http://gamapserver.who.int/mapLibrary/Files/Maps/2003_AvianInfluenza_GlobalMap_01Feb13.png

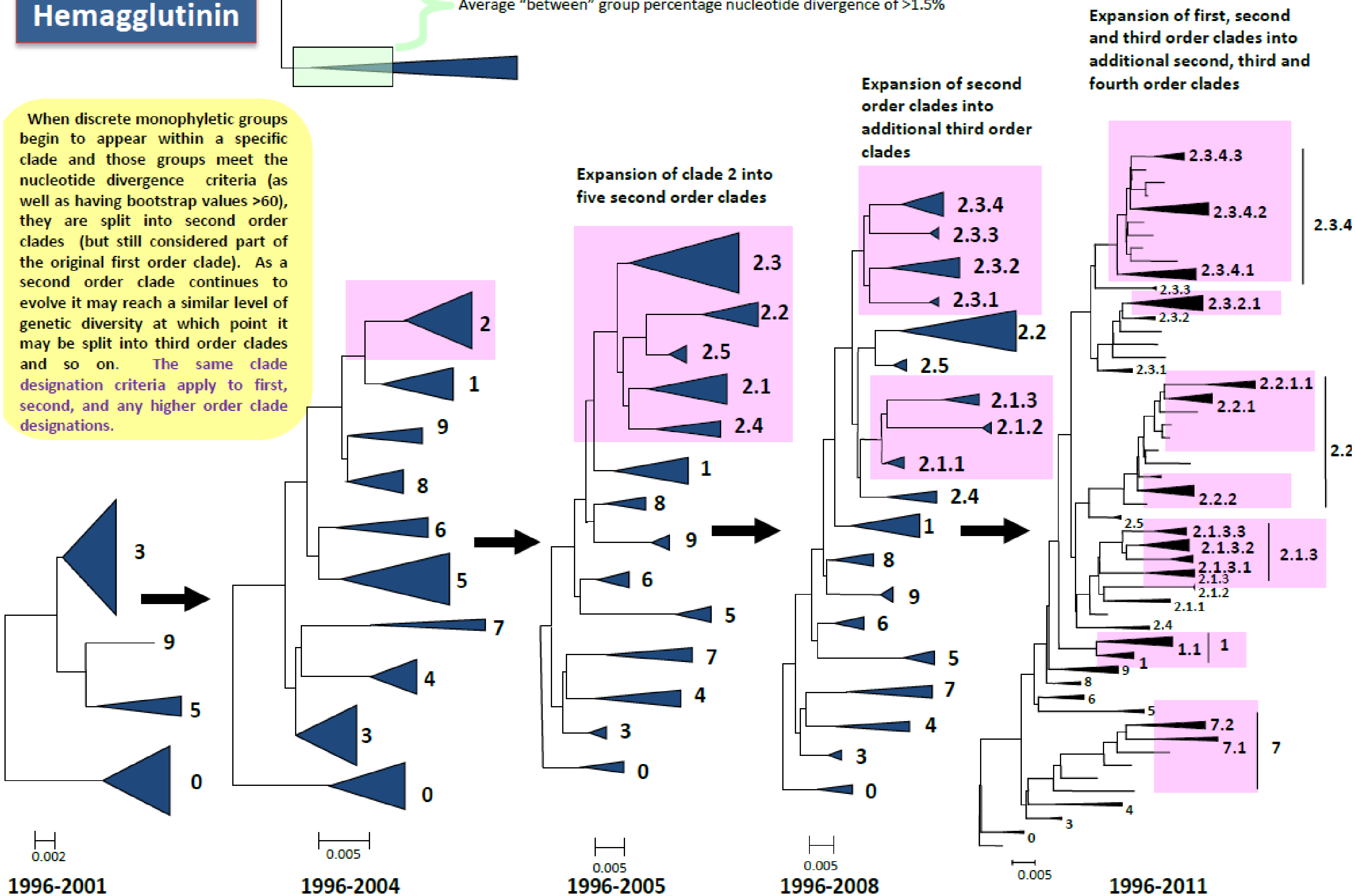
H5 evolution - drift

DTU

Evolution of the Asian H5 Hemagglutinin



When discrete monophyletic groups begin to appear within a specific clade and those groups meet the nucleotide divergence criteria (as well as having bootstrap values >60), they are split into second order clades (but still considered part of the original first order clade). As a second order clade continues to evolve it may reach a similar level of genetic diversity at which point it may be split into third order clades and so on. The same clade designation criteria apply to first, second, and any higher order clade designations.



The bloody past of the H5 gd-like viruses

- 1996 H5N1 China geese
- 1997 H5N1 Hong Kong Poultry, wild birds and humans
- 2004 H5N1 Asia Poultry and wild birds
- 2005 H5N1 Quinhai Lake 60.000 dead waterbirds
- 2006 H5N1 Europe 55 different countries incl. DK
- 2006-12 H5N1 Only Asia

- 2014 H5N8 S. Korea 19 mill. birds killed

- 2014 H5 clade 2.3.4.4 reassorted with N2, N3, N6 and N8 in China

- 2014-18 H5N8 Europe and N. America……..clade 2.3.4.4
  H5N2 N. America…………………………..clade 2.3.4.4
  H5N6 Europe………………………………..clade 2.3.4.4

Vaccines against avian influenza virus

- Classical 1st. and 2nd. generation vaccines

Vaccine Platform	Advantages	Disadvantages
Inactivated vaccines	• Safe	• Limited immunogenicity • Short-lasting immunity • Often multiple doses required • Poor induction cellular immunity
Subunit vaccines	• Safe • Selection of antigen possible	• Limited immunogenicity • Short-lasting immunity • Poor induction cellular immunity
Live attenuated vaccines	• Present conformational epitopes • Single dose sufficient • Induction cellular immunity	• Safety risk in immunocompromized • Reversion to wildtype possible • Interference by maternal antibodies

Vaccines **2018**, *6*, 46; doi:10.3390/vaccines6030046

Vaccines against avian influenza virus

- 3rd generation vaccines

Virus-like particles	• Safe • Present conformational epitopes	• Complicated production process
DNA vaccines	• Present conformational epitopes • Selection of antigen possible • Induction cellular immunity • Effective in heterologous prime-boost	• Often poorly protective when used exclusively
Vector-based vaccines	• Safe • Present conformational epitopes • Selection of antigen possible • Induction humoral and cellular immunity • Effective in heterologous prime-boost	• Often multiple doses required • Interference by vector-specific immunity

Vaccines **2018**, *6*, 46; doi:10.3390/vaccines6030046

Recombinant viral-vectored vaccines - examples

- **Fowlpox-AIV vaccines**
  - Used for H5 LPAI in Mexico
  - Limited transmission to unvaccinated animals
  - Low antibody response as measured by HI test
  - Good cellular response
  - Can be used in 1-day old animals (bypass MDA)
  - DIVA possible (ELISA)

- **NDV-AIV**
  - China and Mexico against H5 HPAI
  - Primer-boost neccessary
  - Cannot be used in very young animals
  - Transmission to unvaccinated animals

- **Alfavirus-AIV (RNA vaccine)**
  - Only one replication cycle – no transmission
  - Commercial avilable for swine influenza in USA
  - Stock-piled in the US after the 2014/15 outbreak

Vaccines – long range perspectives/sweet dreams

- One vaccine for all subtypes
  - Conserved part of the HA
  - NA targeted vaccines
  - Vaccines targeting other proteins
  - RNA polyvaccines
- Primer-boost vaccine strategy
- VAERD!!!
- It will take years before its available!
- The flu may be too smart!

Rational for vaccination

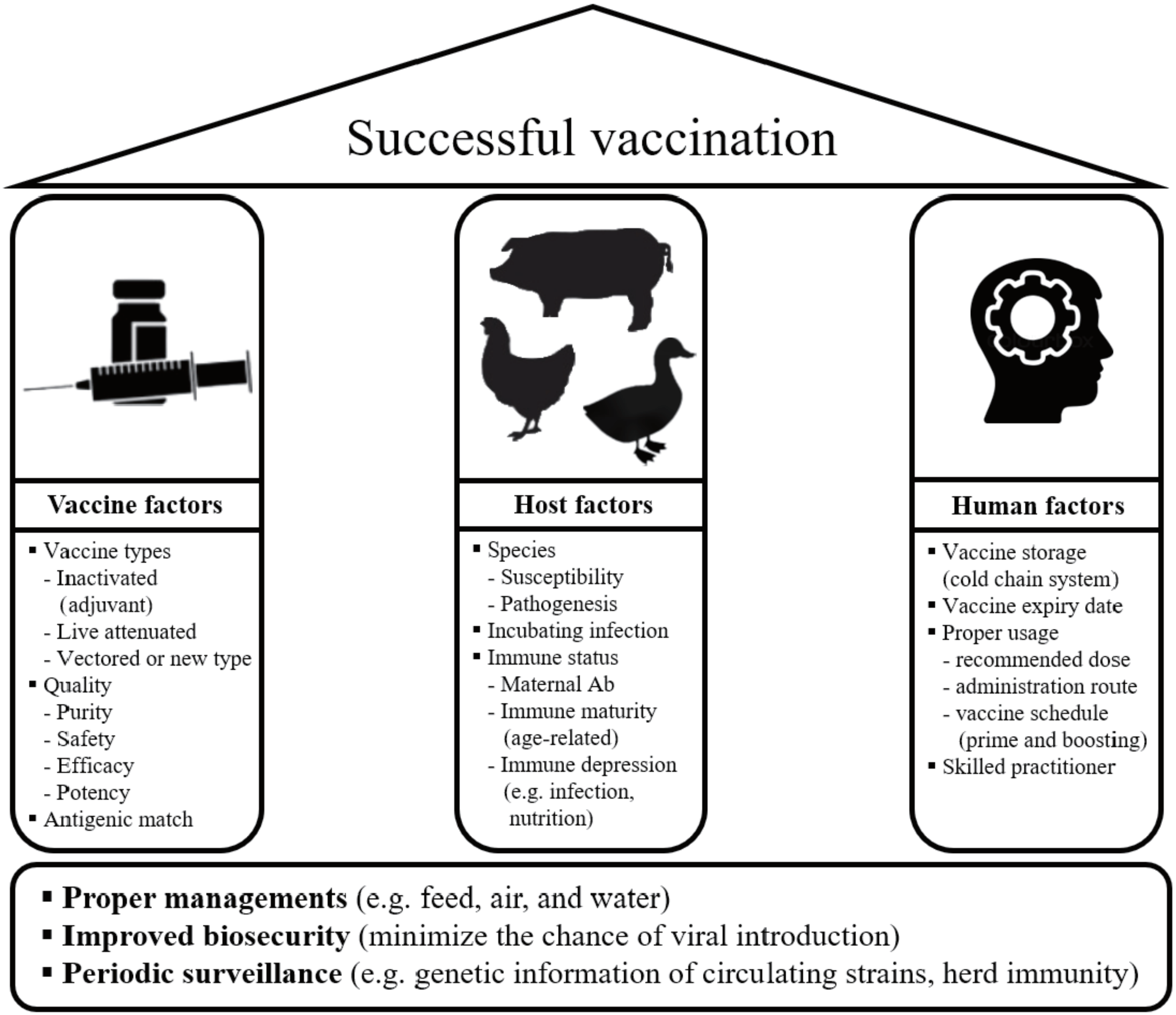
In all cases – also consider zoonotic risk!

H5/H7 virus pathogenicity	Index case flock	Evidence of spread to industrial sector	Population density in area	Policy
HPAI/LPAI	Backyard	No	High/Low	Stamping-out
HPAI/LPAI	Backyard	Yes	Low	Stamping-out
			High	Vaccination
HPAI/LPAI	Industrial	No	[illegible]	Stamping-out
HPAI/LPAI	Industrial	Yes	Low	[illegible]
			High	Vaccination

99% of avian influenza vaccines are used in four countries: China (90 %), Egypt, Vietnam and Indonesia

Ilaria Capua[1] & Stefano Marangon[2]

71st General Session – World organisation for animal health – International Committee – Paris, 18-23 May 2003 – OIE

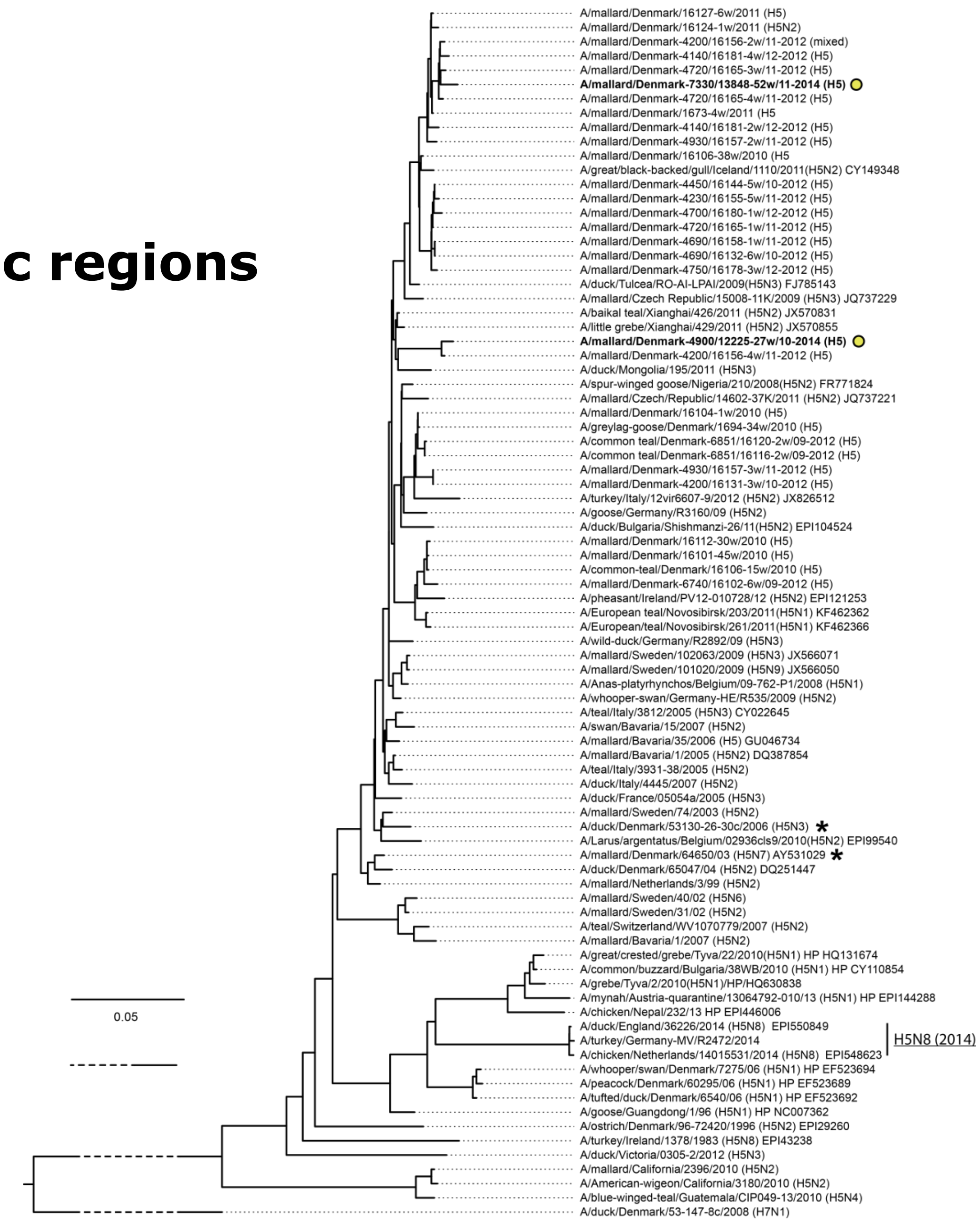

Successful vaccination
Vaccine factors
▪ Vaccine types
- Inactivated (adjuvant)
- Live attenuated
- Vectored or new type
▪ Quality
- Purity
- Safety
- Efficacy
- Potency
▪ Antigenic match
Host factors
▪ Species
- Susceptibility
- Pathogenesis
▪ Incubating infection
▪ Immune status
- Maternal Ab
- Immune maturity (age-related)
- Immune depression (e.g. infection, nutrition)
Human factors
▪ Vaccine storage (cold chain system)
▪ Vaccine expiry date
▪ Proper usage
- recommended dose
- administration route
- vaccine schedule (prime and boosting)
▪ Skilled practitioner
▪ Proper managements (e.g. feed, air, and water)
▪ Improved biosecurity (minimize the chance of viral introduction)
▪ Periodic surveillance (e.g. genetic information of circulating strains, herd immunity)

Vaccination against LPAI

- **Vaccination against enzootic LPAI – examples**
  - Mexico vaccinate chicken against LPAI H5N2
  - Has been used temporally for Turkeys in the US and Canada
  - Vaccination against LPAI H9 in Asia and Middle East
  - H7 vaccines were used in Italy 2000-20002 to eradicate the H7N1 LPAI virus
- **Can LPAI vaccination ”hide” introductions of HPAI?**

Vaccination against LPAI in non-enzootic regions

Which virus?



Vaccination against enzootic HPAI H5

- Vaccination against H5N1 has been performed in several countries in Asia and Middle East for a number of years

- Human cases of H5N1 are declining, but still a high number of H5N1 and H5 reassortments (H5N8, H5N2, H5N6) detected globally

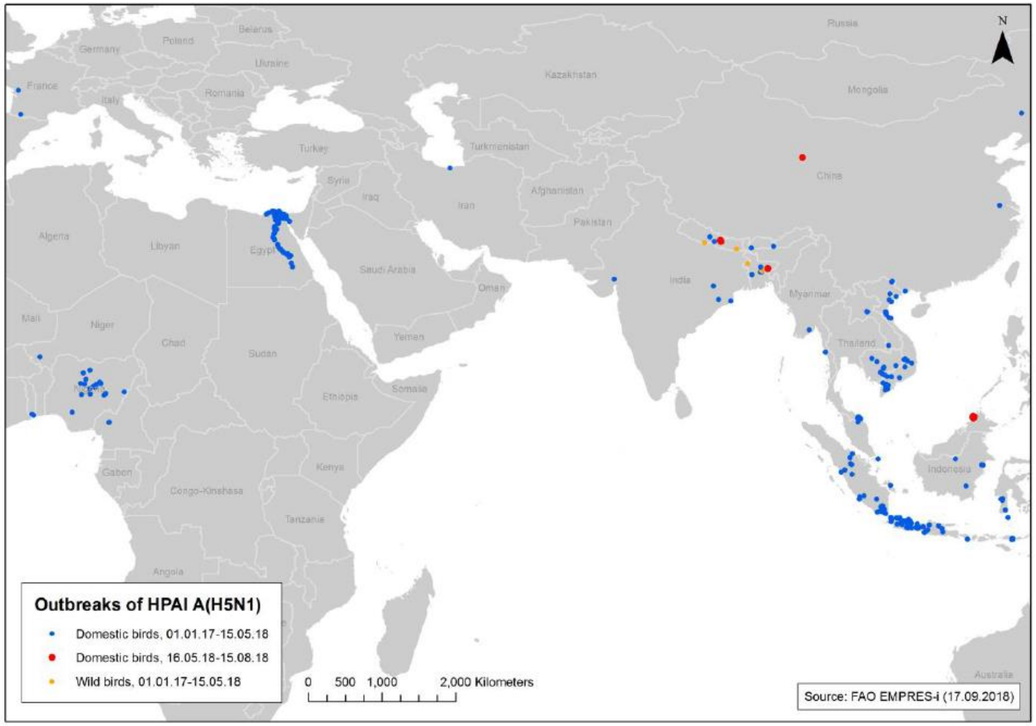
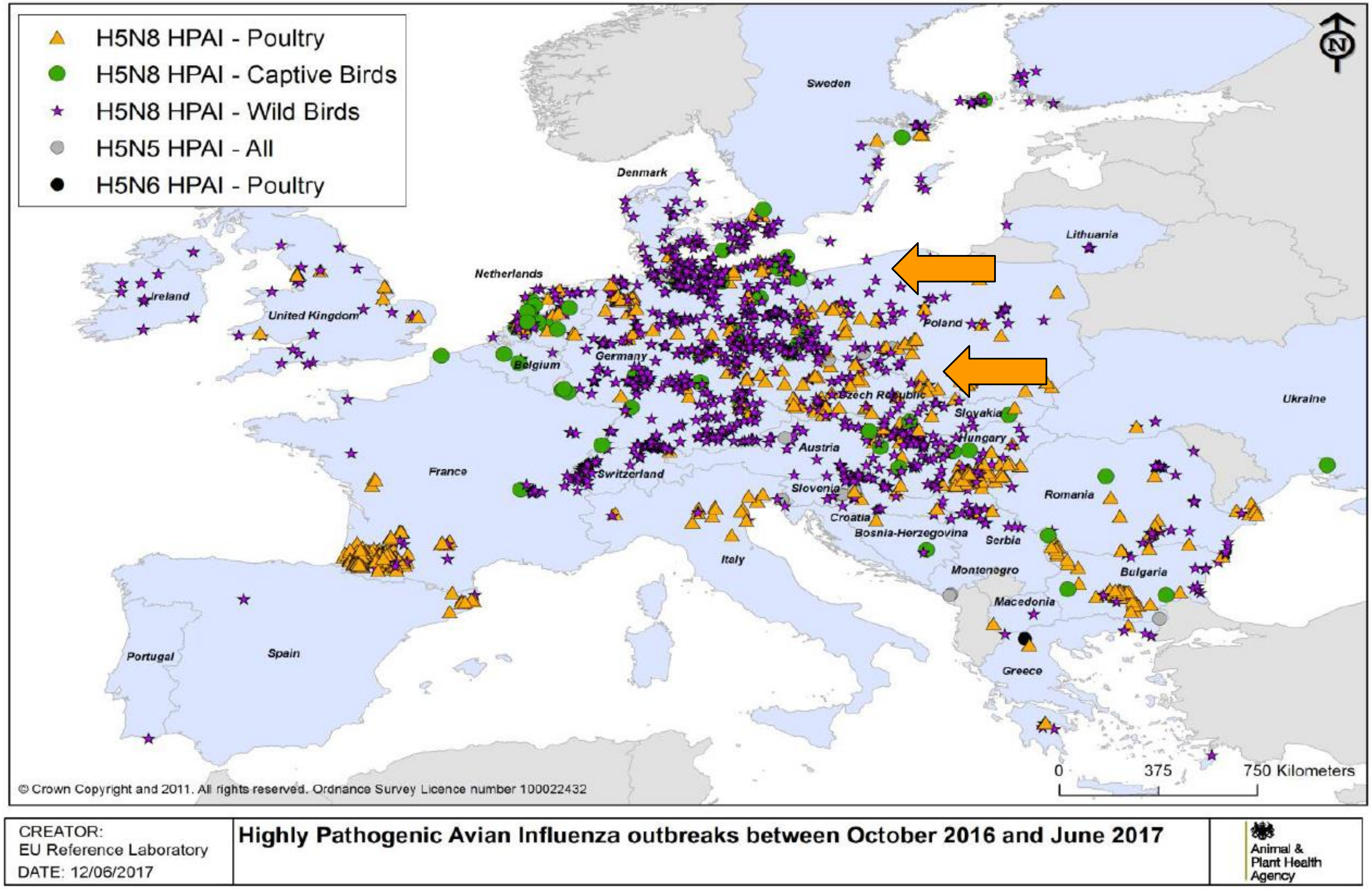


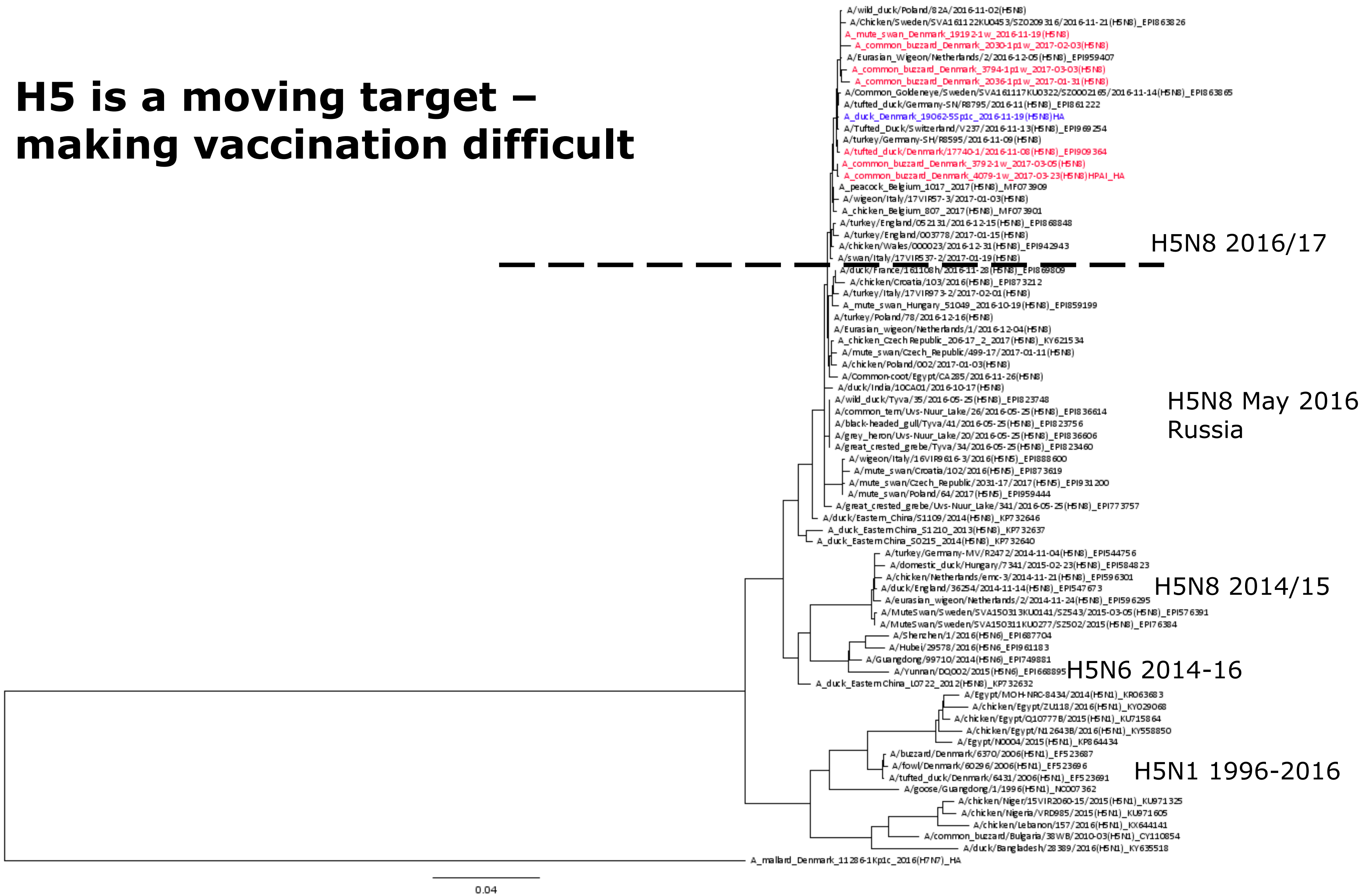
Figure 3: Distribution of confirmed HPAI A(H5N1) outbreaks in birds by place of origin, 1 January 2017-15 August 2018 (FAO, online-a)

Also in Europe!



Will HPAI H5 become enzootic in wild birds in Europe?

H5 is a moving target – making vaccination difficult



Antigenic drift and vaccine efficacy (VE)

Vaccine 35 (2017) 4859–4869

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

ELSEVIER

Review

Vaccine efficacy against Indonesian Highly Pathogenic Avian Influenza H5N1: systematic review and meta-analysis

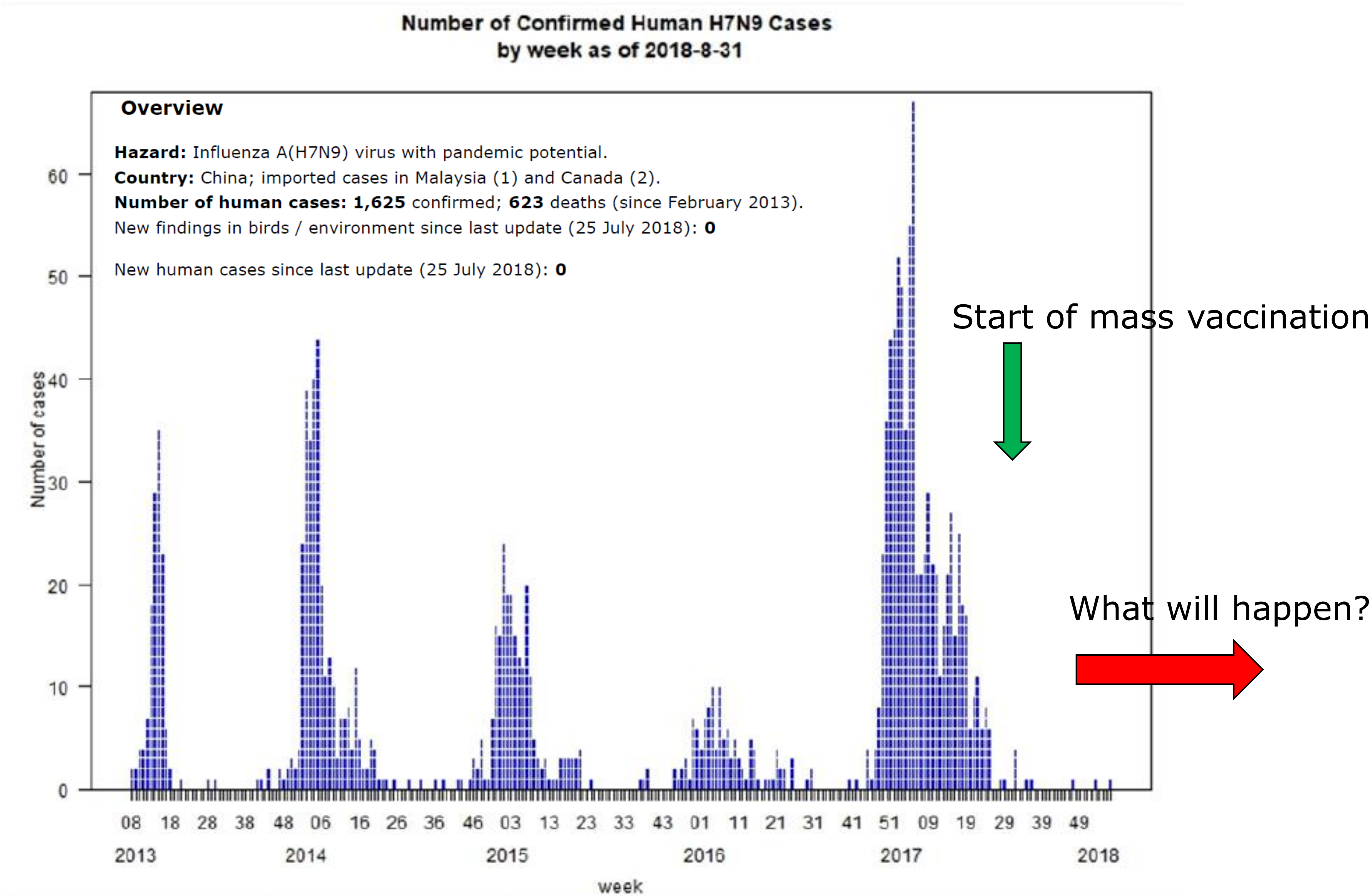
CrossMark

Juan P. Villanueva-Cabezas [a,b,*], Mauricio J.C. Coppo [c], Peter A. Durr [b], Jodie McVernon [a,d,e]

[a] *Modelling and Simulation Unit, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Carlton, Victoria, Australia*
[b] *Australian Animal Health Laboratory, CSIRO, Geelong, Victoria, Australia*
[c] *Asia-Pacific Centre for Animal Health, Faculty of Veterinary and Agricultural Sciences, The University of Melbourne, Parkville, Victoria, Australia*
[d] *Victorian Infectious Disease Reference Laboratory, The Royal Melbourne Hospital and The University of Melbourne, at the Peter Doherty Institute for Infection and Immunity, Victoria, Australia*
[e] *Murdoch Children's Research Institute, Royal Children's Hospital, Parkville, Victoria, Australia*

We conclude that the VE of commercial vaccines in Indonesia changes as Indonesian HPAI/H5N1 evolve into new clades, which should warrant continuous matching between vaccine-seeds and emerging HPAI/H5N1. Furthermore, given the characteristics of the new Indonesian dominant HPAI/H5N1 clade, further studies to confirm VE across species are warranted.

Vaccination of poultry to prevent human cases: H7N9



Vaccination in Europe to prevent HPAI?

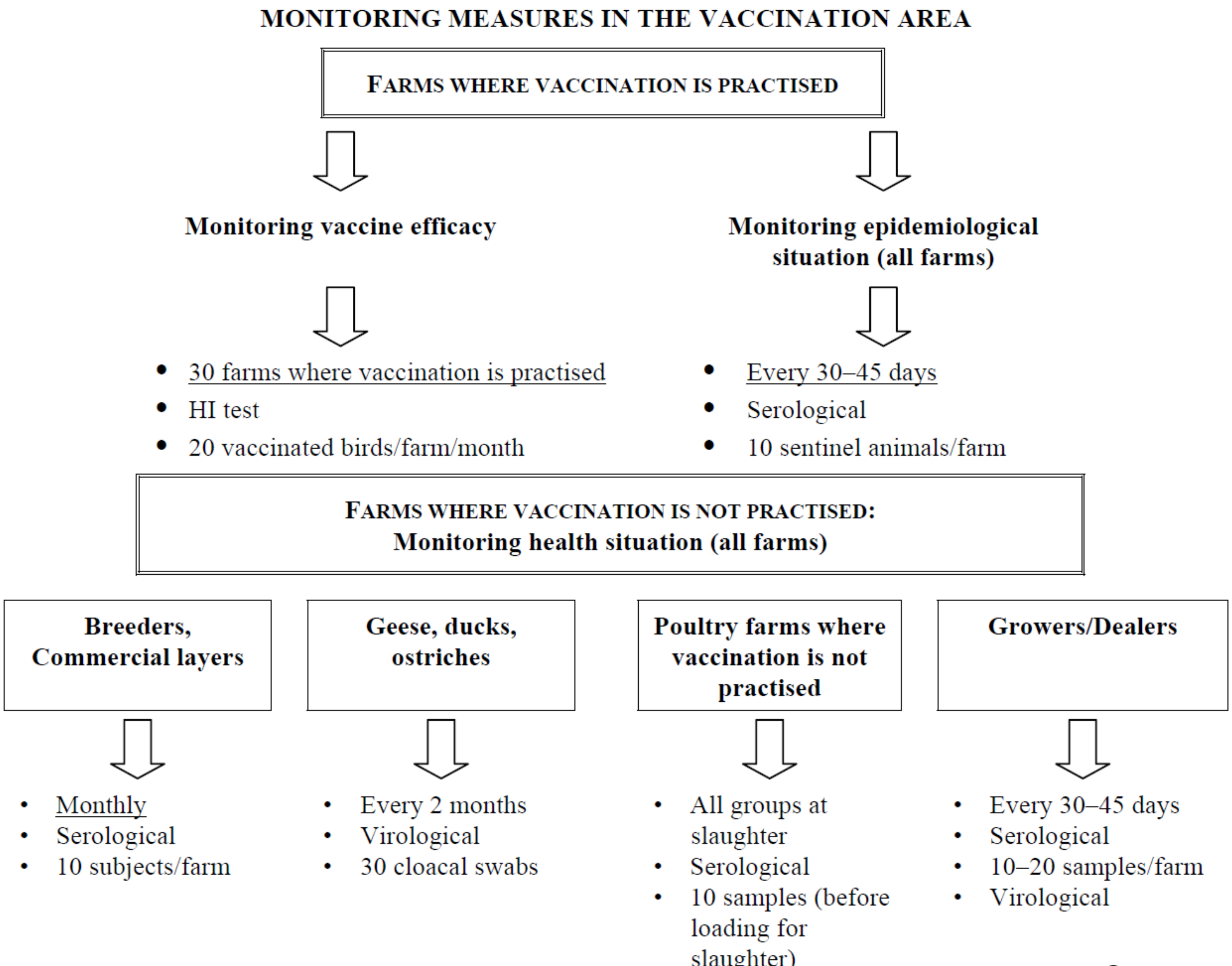
- Impossible to predict which strain that will be next – difficult to prepare vaccine stocks up front

- Classical vaccines takes 22-26 weeks to produce – chasing the tail of the dog!

- If H5XN becomes enzootic in wild birds in Europe it would be easier to select a homologeous vaccine strain – but still need for regular updates

- Cost-benefit positive or negative?
  - Cost of vaccines
  - Cost of monitoring
  - Trade consequences

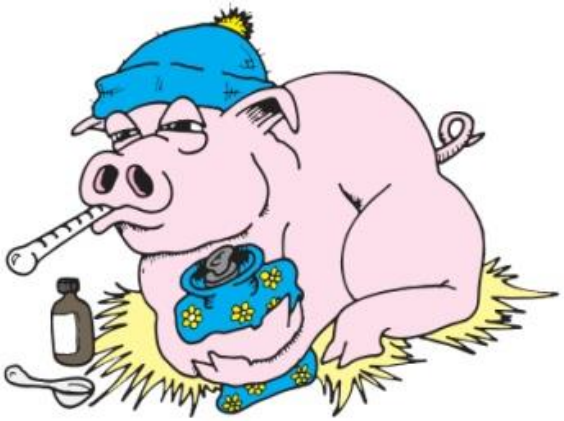
Monitoring in vaccinated areas (example from Italy 2002)



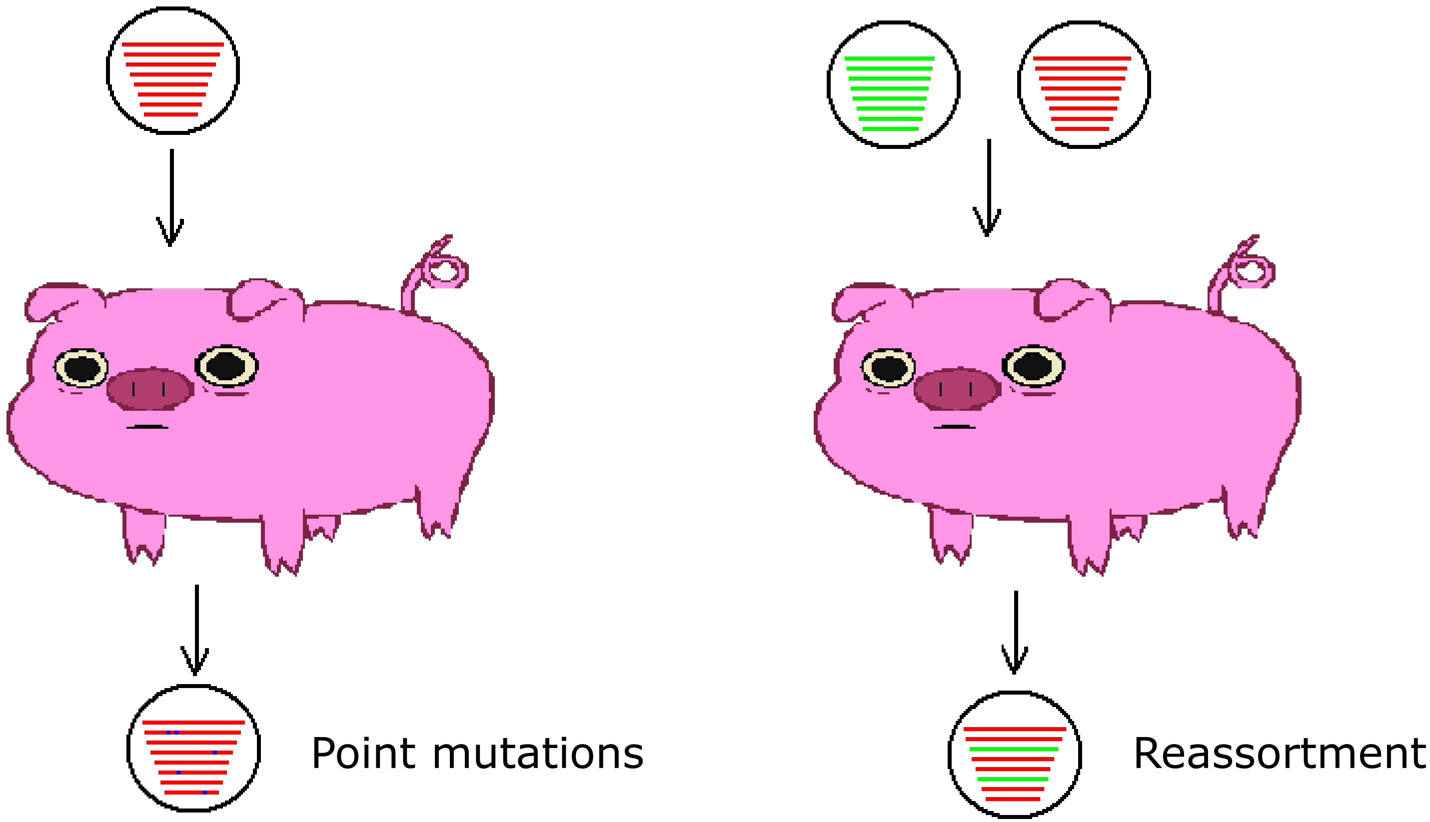
Capua et al., 2002

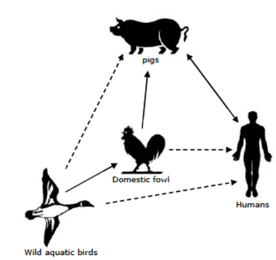
Influenza A in swine

- Important veterinary disease
- Highly prevalent in most countries
- Zoonotic potential
- Available vaccines contains 10-15 years old isolates

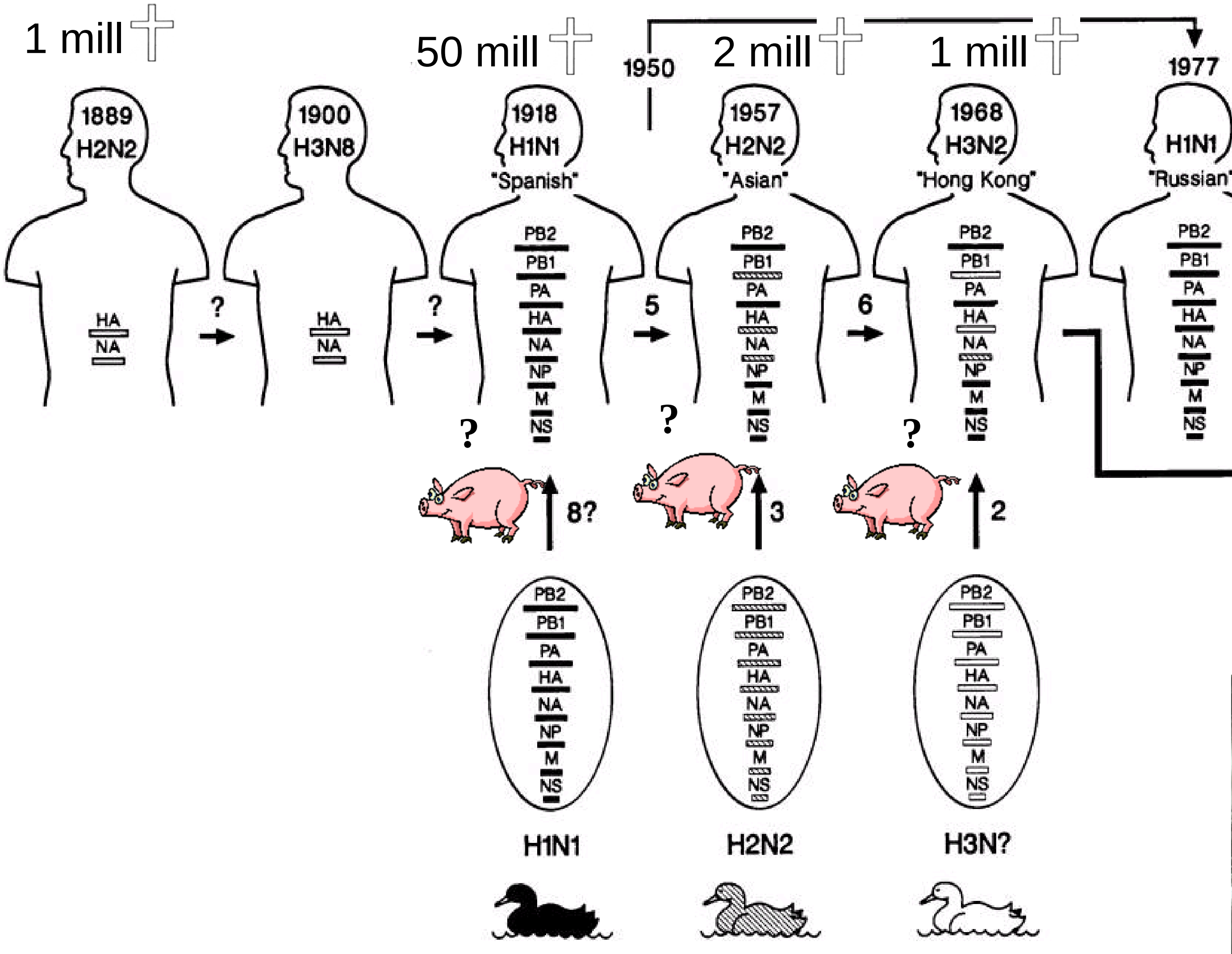


Evolution of influenza A virus

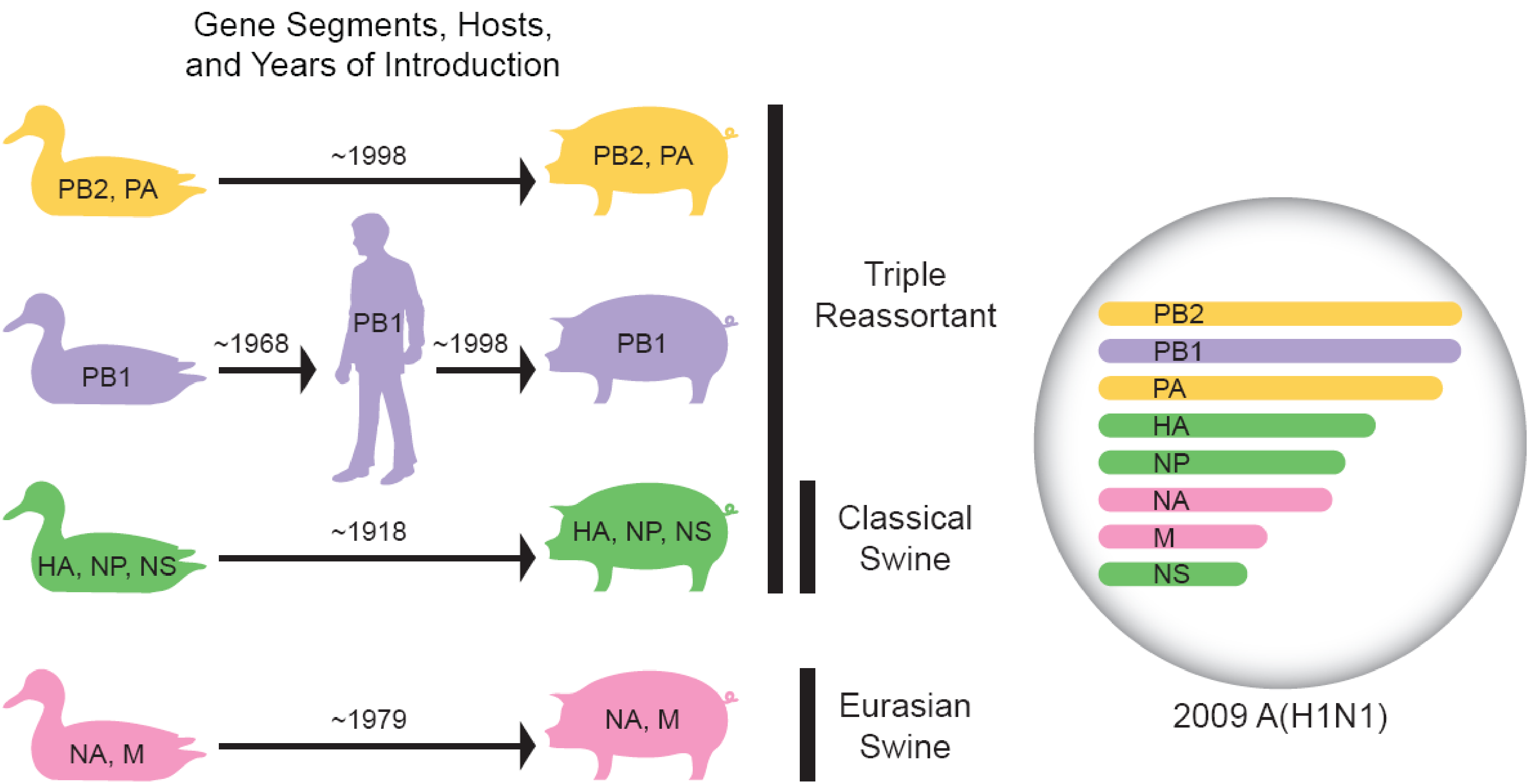




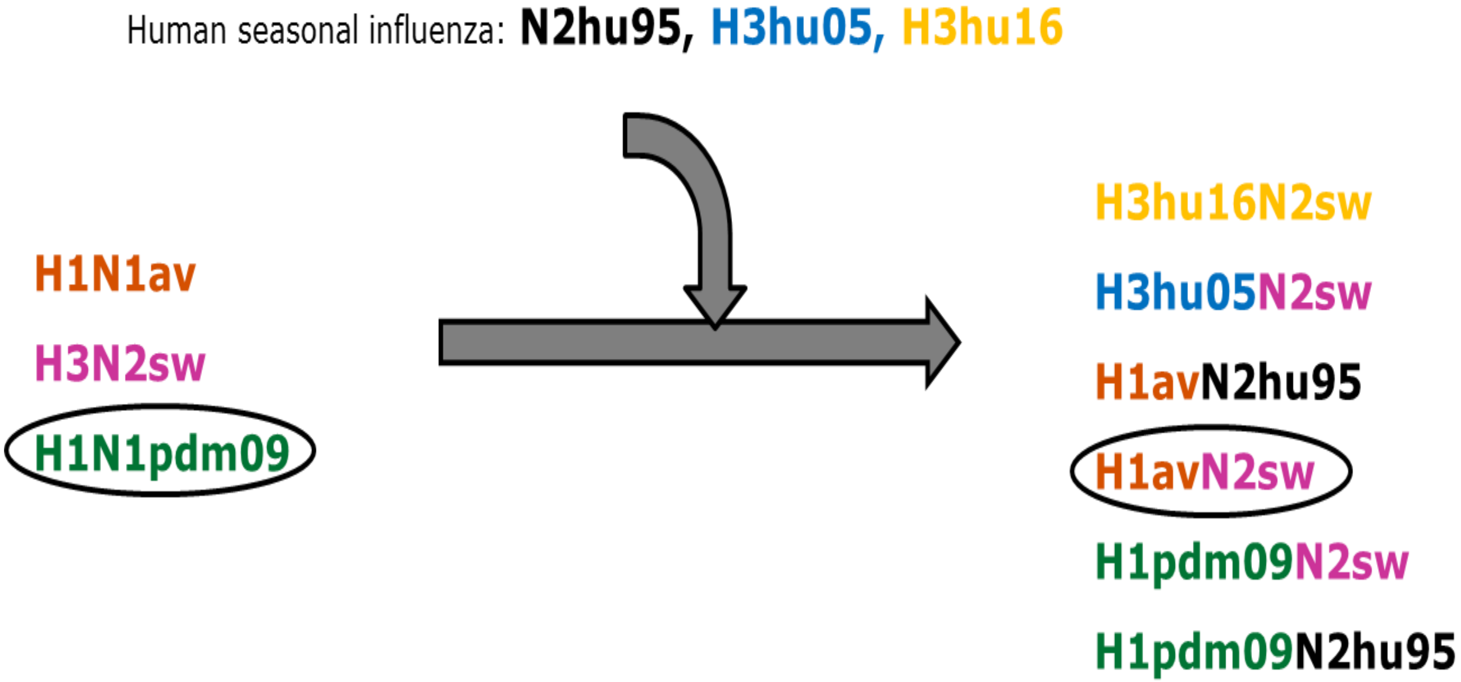
Previous human pandemics +/- swine?



Pandemic 2009H1N1 - origin



Reassortments



In Germany – 35 different variants of influenza in swine

In China more than 100 different variants

Several reports on zoonotic transmission

Accepted: 14 February 2017

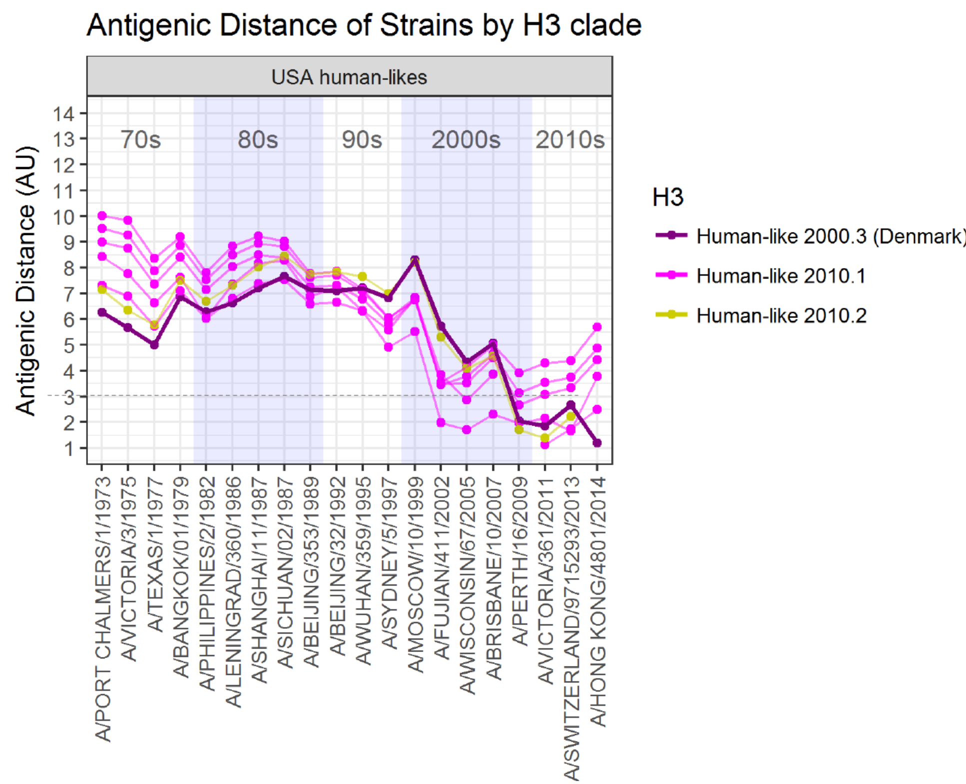
DOI: 10.1111/irv.12451

WILEY

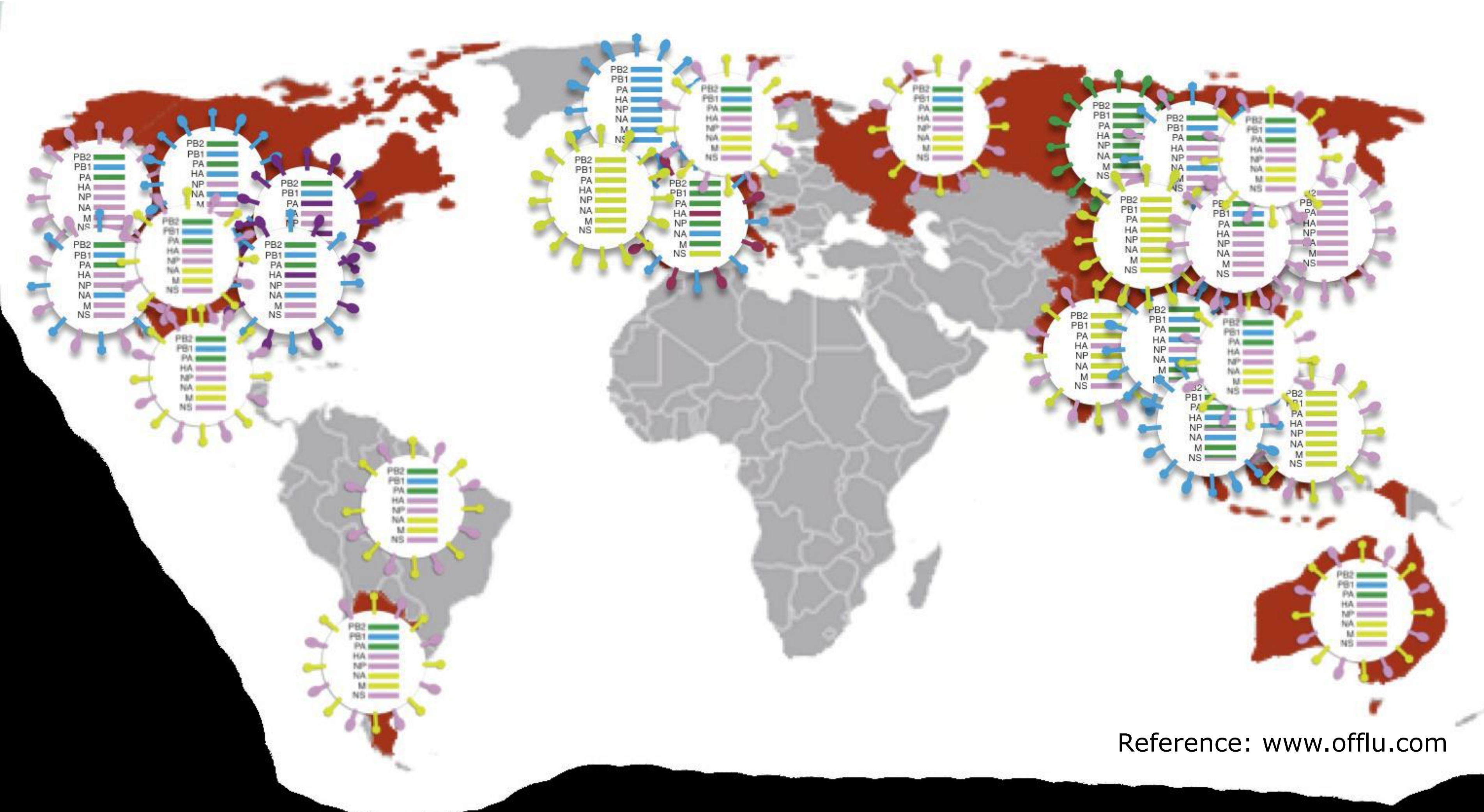
SHORT ARTICLE

Triple-reassortant influenza A virus with H3 of human seasonal origin, NA of swine origin, and internal A(H1N1) pandemic 2009 genes is established in Danish pigs

Jesper Schak Krog[1] | Charlotte Kristiane Hjulsager[1] | Michael Albin Larsen[2] | Lars Erik Larsen[1]

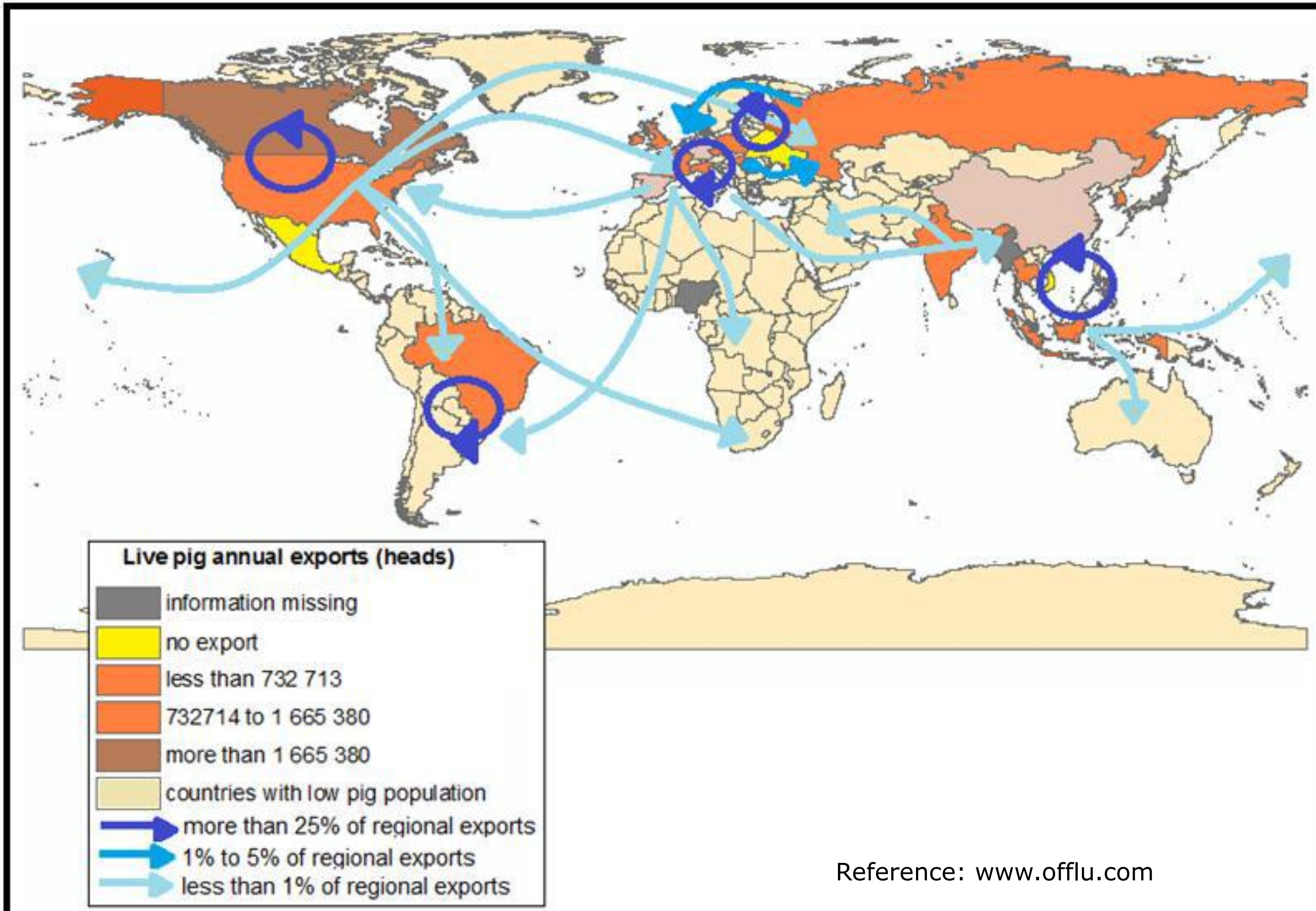


Swine influenza subtypes globally



Reference: www.offlu.com

Live Hog Exports

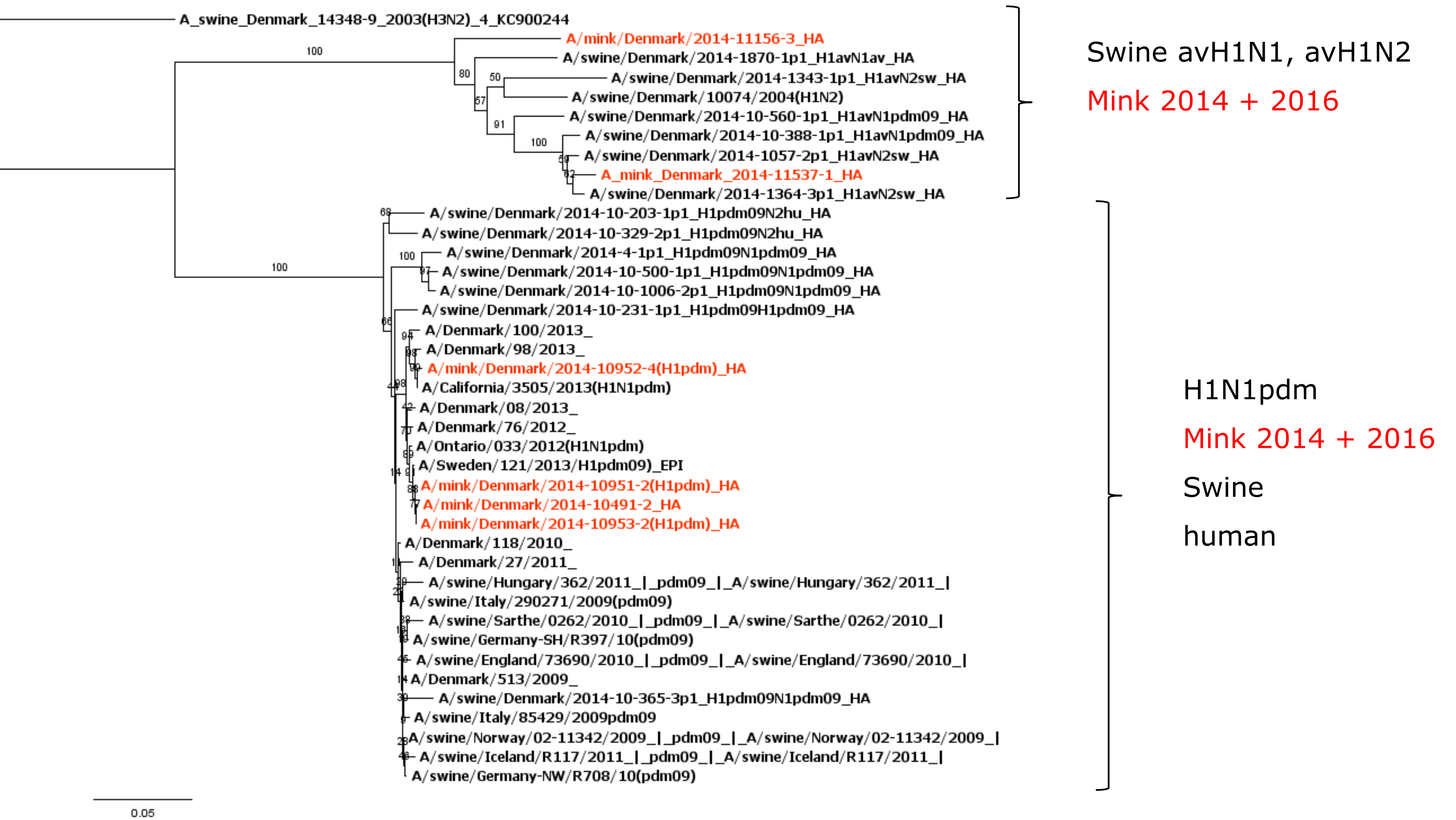


Reference: www.offlu.com

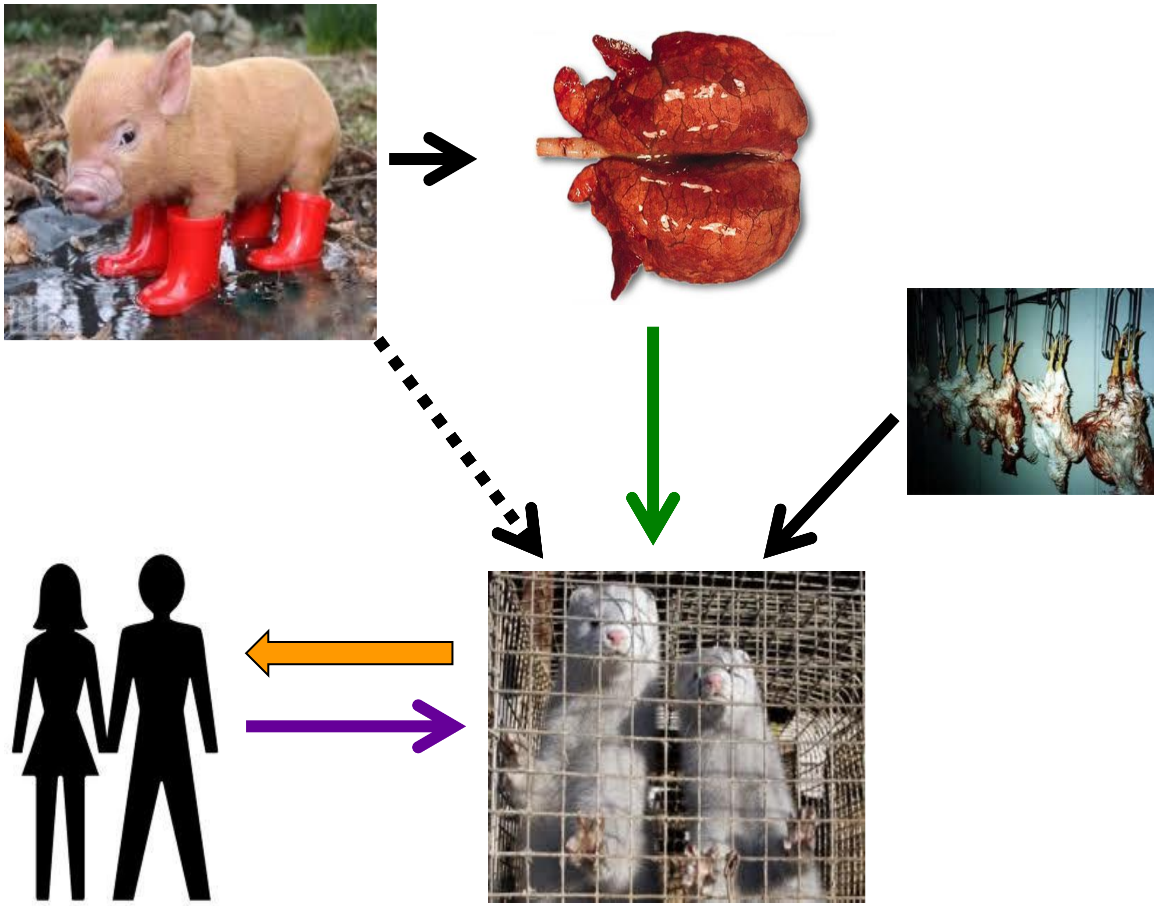
Influenza in mink

	2009	2010	2011	2012	2013	2014	2015	2016	2017
No of submissions	54	9	7	5	18	42	6	25	15
Positive submissions	25	6	1	0	8	30	1	16	7
Subtype	H3N2	H1pdm09 (n=4)	H1pdm09 (n=1)	-	H1pdm09 (n=6)	H1pdm09 (n=22) H1N1sw (n=1) H1N2sw (n=2)		H1pdm09 (n=12) H1N2sw (n=1)	Not H1pdm09
Positive, season	29/9-30/10	3/8-14/9	12/10	-	10/9-6/11	30/9-26/11	9/10	11/5-22/11	8/9-13/10

Influenza in mink from humans – also during summer!



Transmissions – human influenza genes found in mink



Surveillance and legislation in EU

- **Avian influenza**
  - Passive surveillance in poultry etc – **mandatory**
  - Active surveillance in poultry and wild birds – **mandatory**
  - Active surveillance in wild birds
    - **Not mandatory**
    - National programs if any
    - No EU coordination nor mandatory reporting system
  - Consequence of detection in poultry etc.
    - Eradication even for LPAI without zoonotic potential
      - Is this necessary/ ethical sound/cost effective?

- **Swine influenza and influenza in mink etc.**
  - **No** requirement nor support for surveillance
  - **No** EU involvement
  - **No** follow-up on detection of strains with zoonotic potential
  - **No** formalized system for exchange of data

Room for improvement for handling of influenza virus in Europe – personal view!

- Wild bird surveillance – joint EU surveillance with focus on hot spots
- More research on wild bird migrations routes
- Compartmentalization of sectors should be implemented
- EU should support and coordinate surveillance in other species including swine
- Detection of influenza virus in animals with human influenza genes should be notifiable
- Mandatory sharing of sequence data of influenza virus from all species should be mandatory
- EMA should allow fast update of vaccine strains in swine influenza vaccines– presently it takes 5 years to change the viral strains

Thank you for the attention