Emergence and Continuing Evolution of H5N1 Influenza

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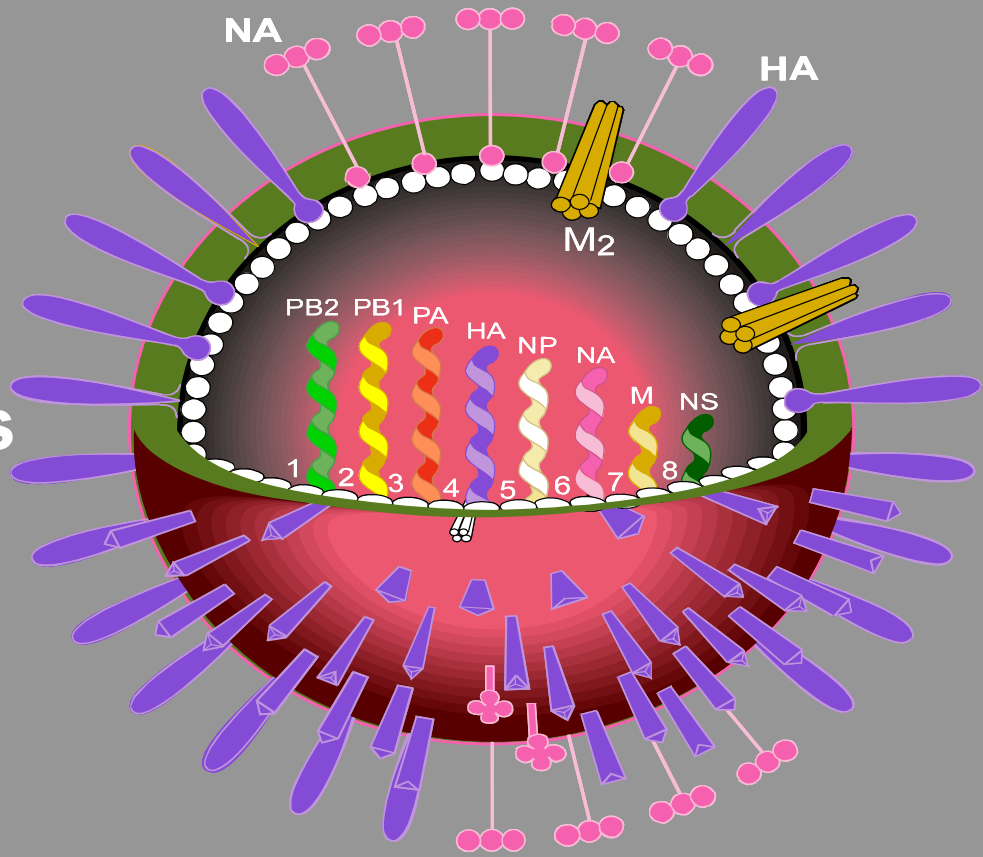
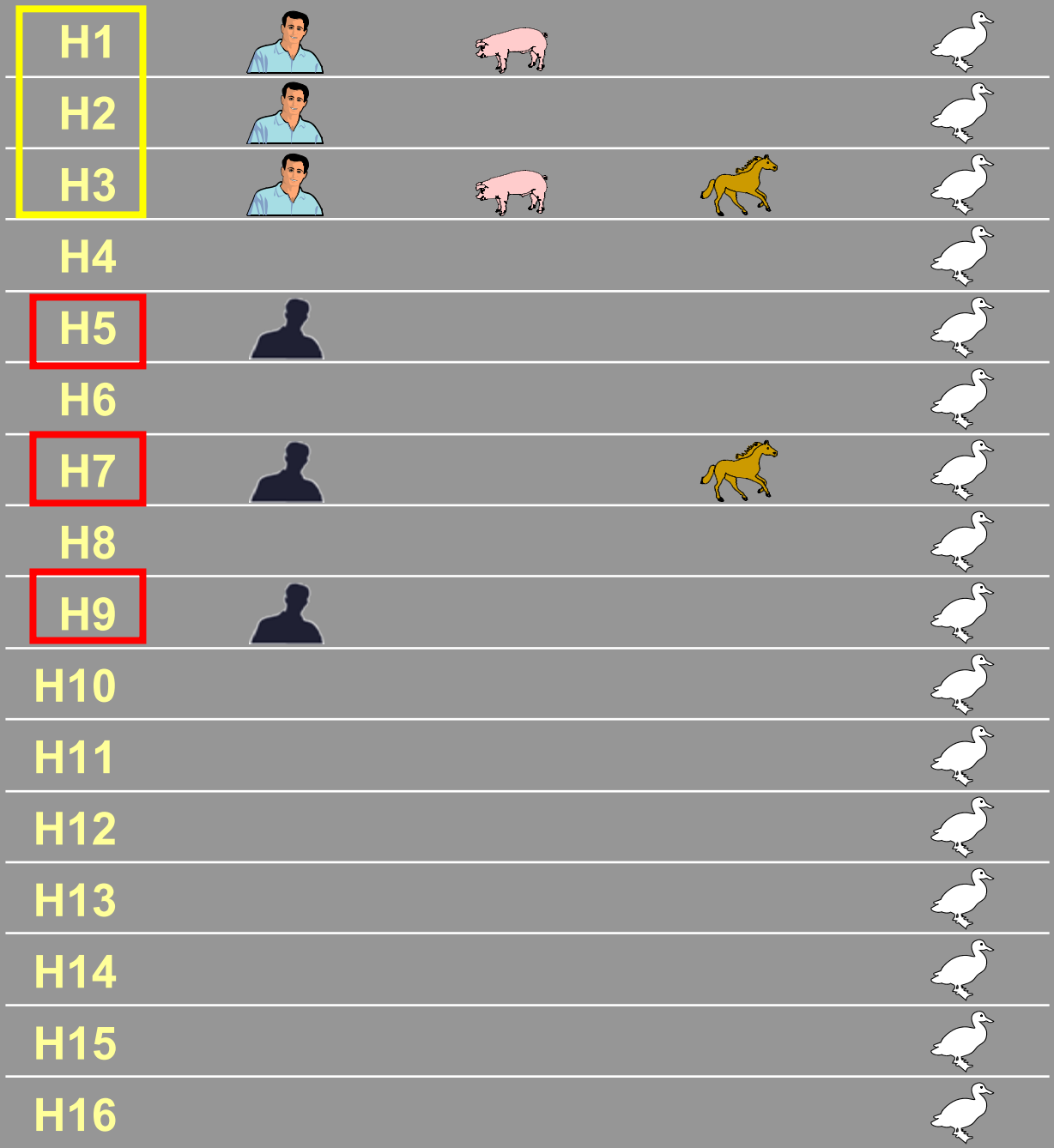
Evolution of Influenza A Viruses

- Point mutations
- Reassortment
- Insertions and deletions
- Recombination

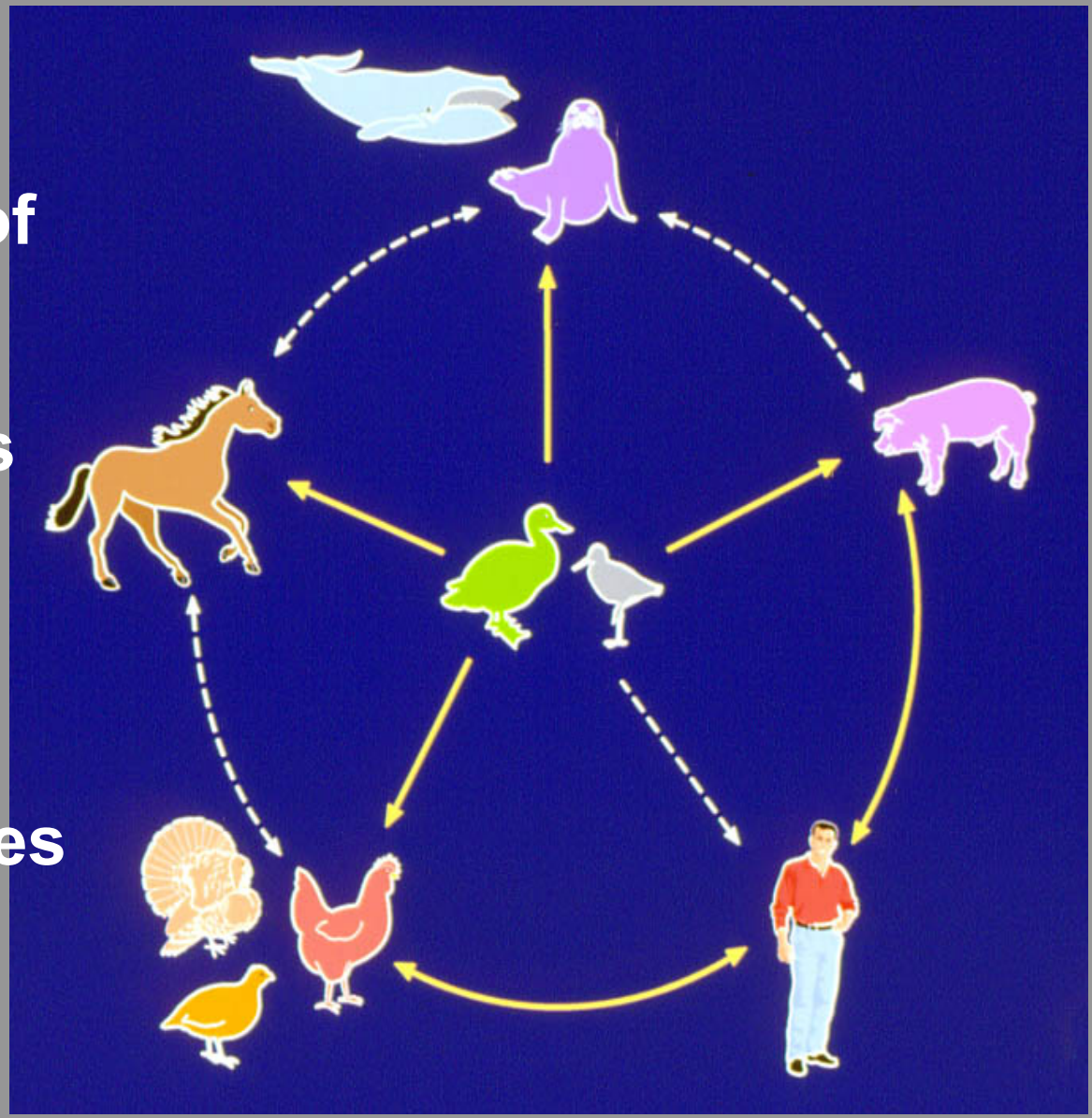


Influenza A Virus Host Range

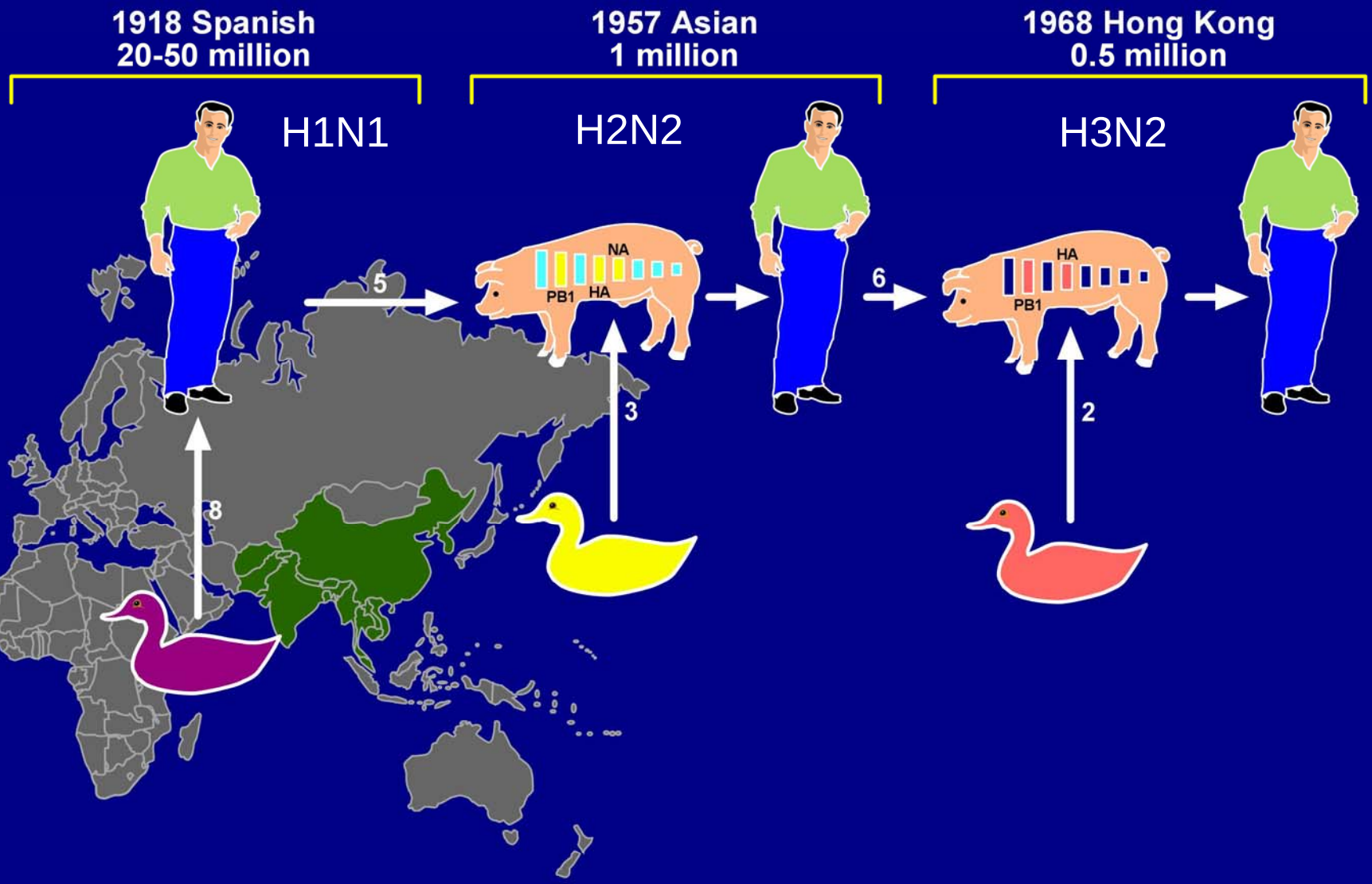


The Ecology of Influenza Viruses

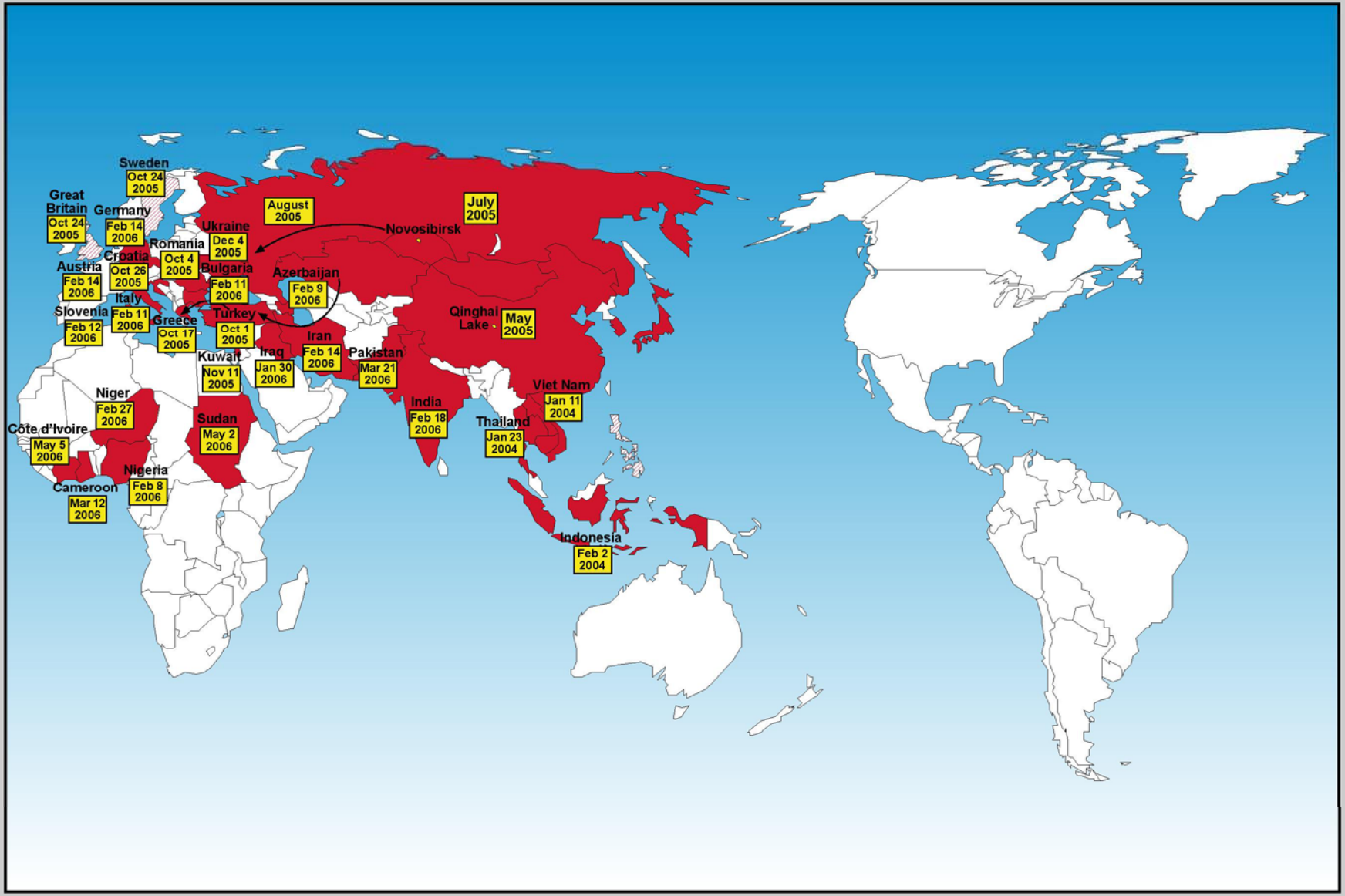
- That there are a limited number of host specific lineages of influenza viruses
- There is geographical separation into Eurasian and American lineages



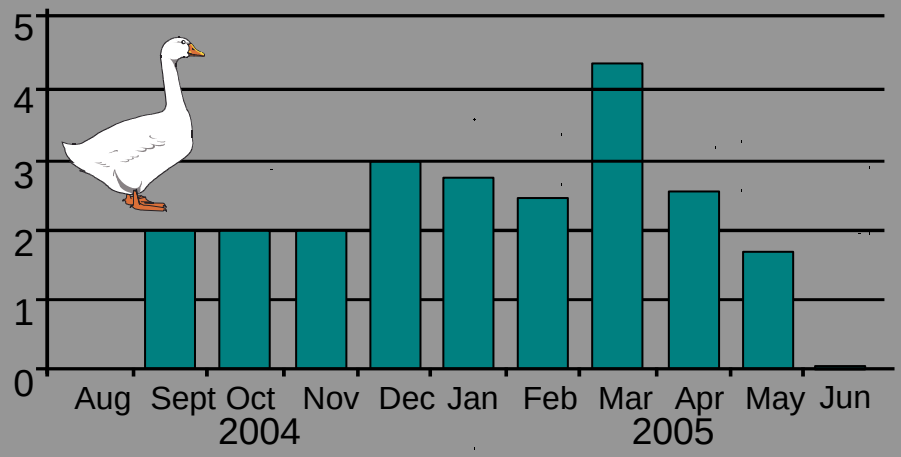
Pandemics of the 20th Century

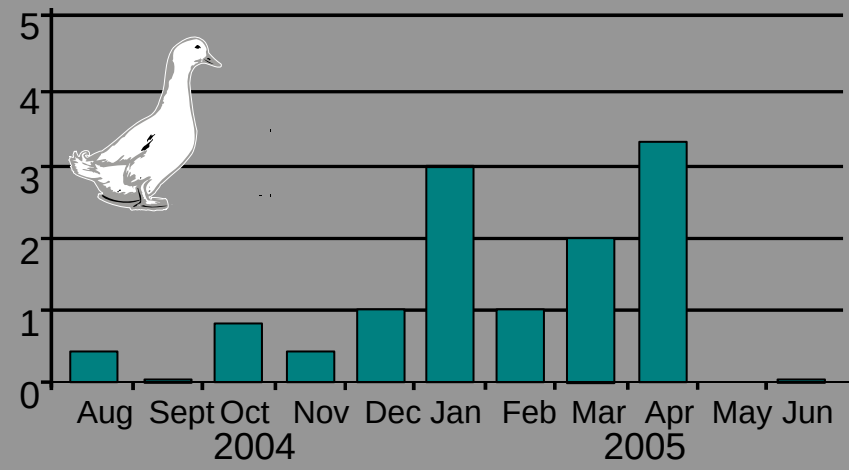


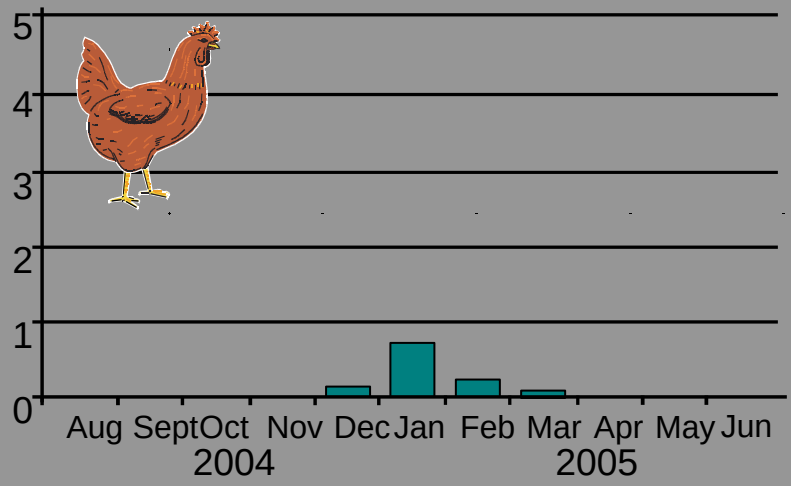
Spread of H5N1: 2005 - 2006



Isolation of H5N1 Viruses From Live Poultry Markets in S. China







% Positive

Based on numbers (%) from August 2004 to June 2005

How Did the H5N1 Virus Spread Westwards So Quickly

- Migratory birds/globalized poultry industry
- Cold winter, Baltic Sea froze
- Europe – 700 wild bird outbreaks
  - –4 commercial bird outbreaks
- Africa
  - –Introduction to Nigeria
  - –Not in wild birds
  - –Will it burn out?

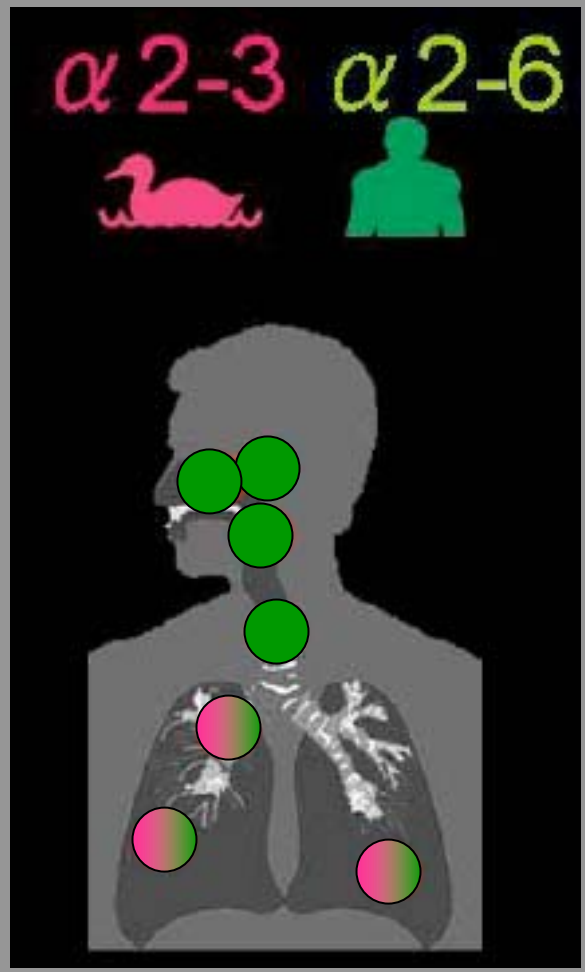
"The Trojan Horses"

How Pathogenic Is This Virus?

A/Vietnam/1203/04 (H5N1)

- Kills chickens in less than one day
- Kills ducks in 1-2 days
- High risk of death in humans
  - Diarrhea
  - Respiratory symptoms
- High Risk of death in ferrets
  - Respiratory symptoms
  - Diarrhea
  - Hind Leg paralysis

Receptor Distribution in Humans



Shinya et al Nature 2006

Does H5N1/04 Replicate and Transmit in Pigs?

	Infected	Contact
Vietnam/1203/04	+++	0
Ck/Vietnam/C-58/04	+++	0
DK/TH/D4AT/04	+++	0
GS/TH/G7CS/04	+++	0

Choi et al 2005

Expanding Host Range for Influenza

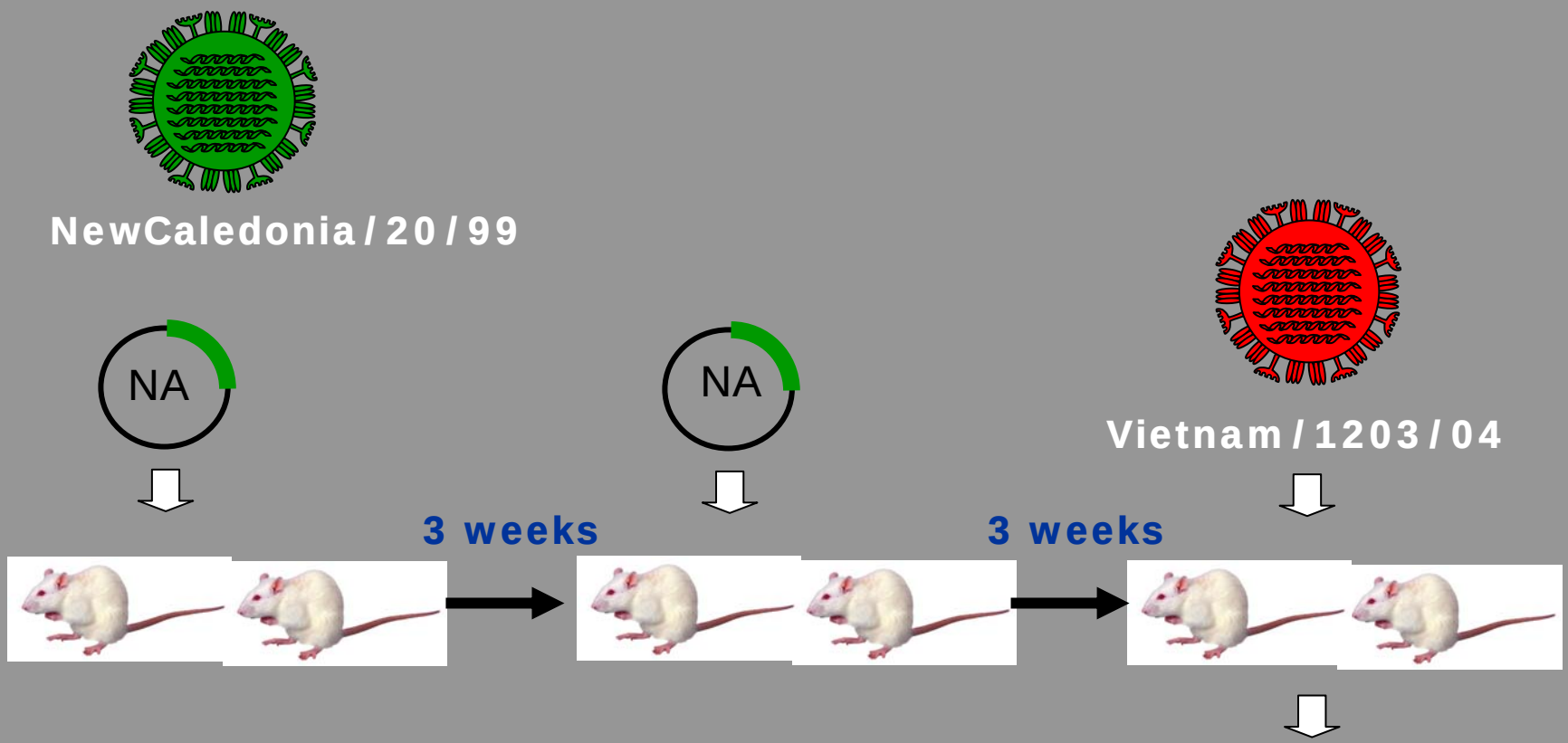
H5N1 in Thailand

Experimental transmission in domestic cats

Kuiken et al, Science 2004

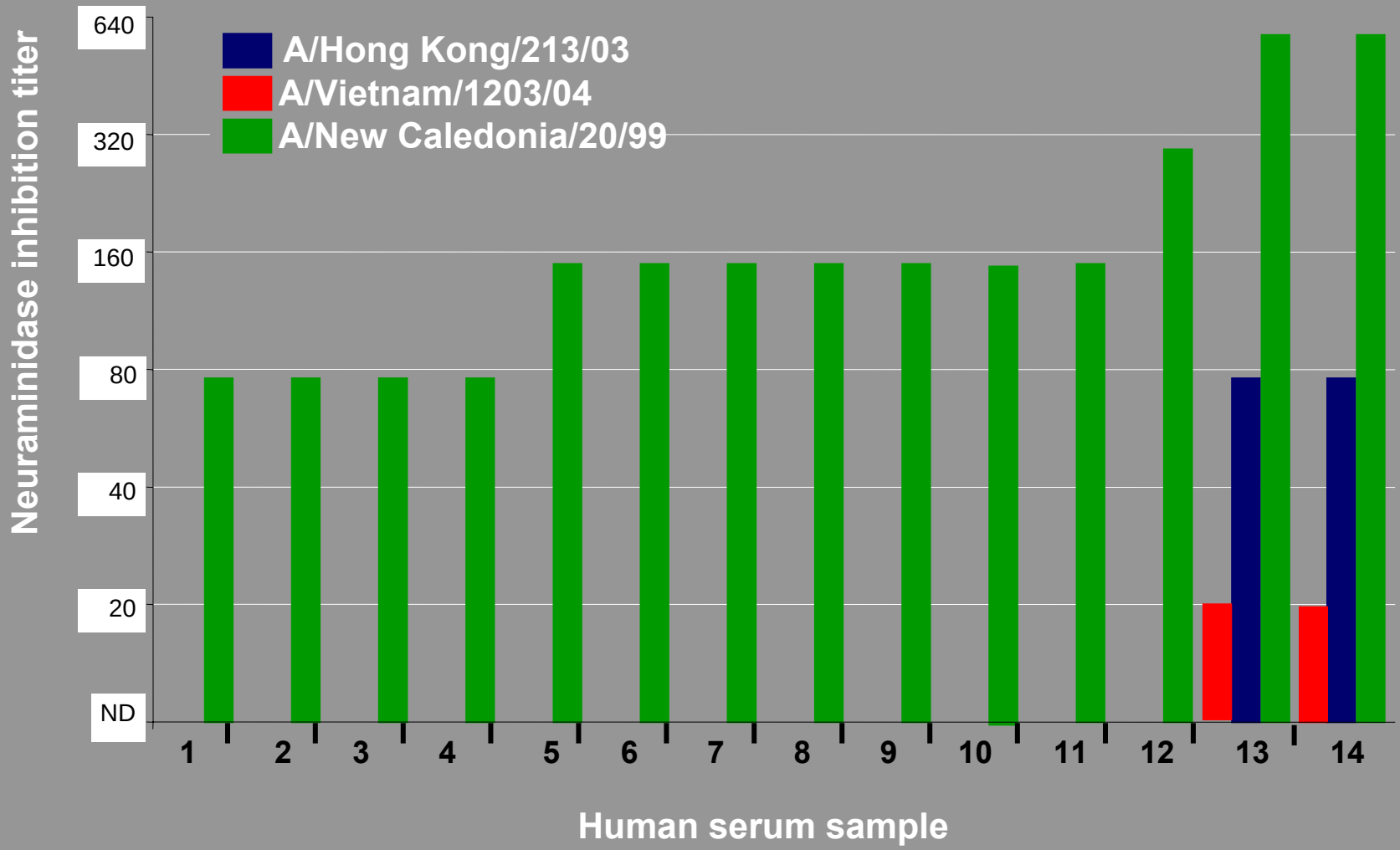
Vaccines

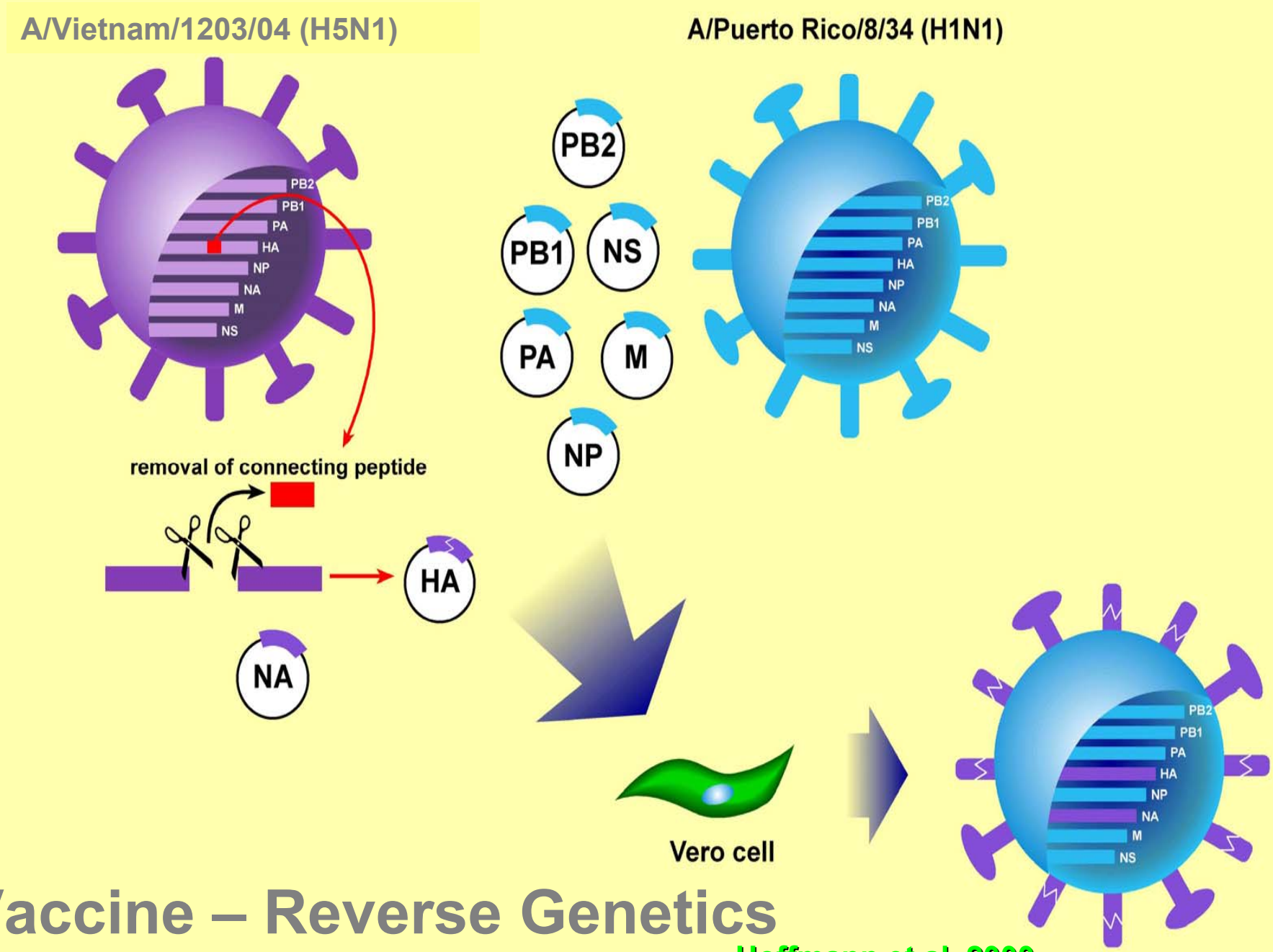
Potential Value of Seasonal Influenza Vaccine for H5N1



Sandbulte, Webby

Anti-N1 Antibody in Human Sera





Vaccine – Reverse Genetics

Hoffmann et al. 2000

Studies on r.g. H5N1 Vaccines in Ferrets

- r.g. Hong Kong/213/04 (H5N1)
- Complete protection from homologous challenge
- Cross protection from challenge with A/Vietnam/1203/04
  - Virus shedding reduced
  - Weight loss
  - No virus in brain
  - No disease signs

Efficacy of H5N3 Vaccine in Khaki Campbell Ducks

Outcome

Treatment	*Disease/Death /Total*	*Virus Shedding*	*Transmission to Non-vaccinated Contacts*
Vaccine-1x	0/0/10	0/10	0/10
Vaccine -- boost	0/0/10	0/10	0/10
Control	10/8/10	10/10	

Thaweesak Songserm-SJCRH

Vaccine: Chicken/Vietnam/C58/04 (H5); dk/Germany/1215/73 (N3); PR/8/34 internal genes
Dose: 0.25µgm HA antigen
Schedule: Vaccinate day 0, boost day 14, challenge 28 days
Challenge: DK/Thailand/D4AT/04 (H5N1)
Ducks: 4 weeks old at day 0

Control Strategies: H5N1 Poultry

Vietnam: The ongoing experiment.

Vaccination → Eradication of Virus?
→ Eradication of Symptoms
↓
Residual Virus?

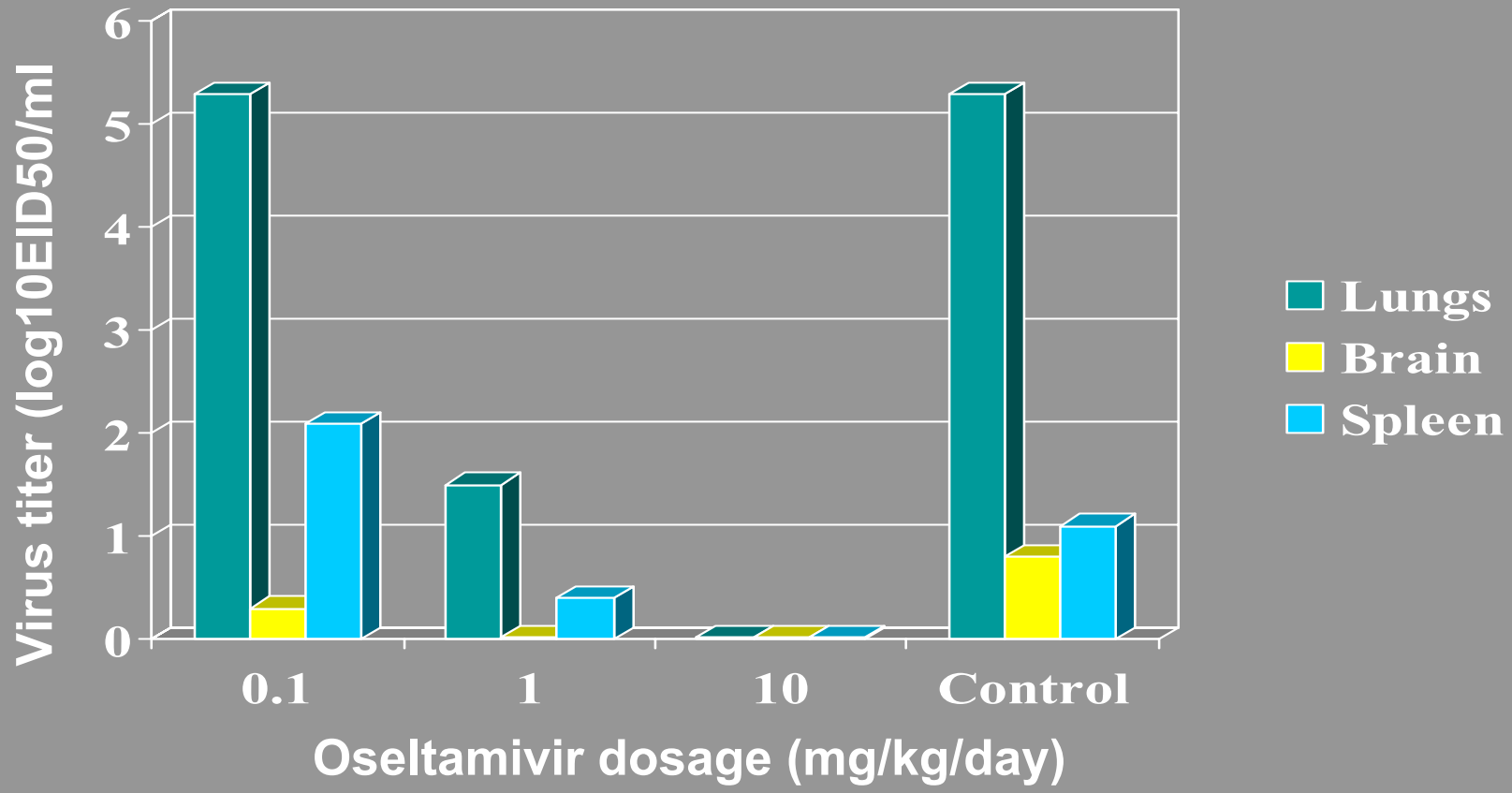
- October 2005 → 170 million doses of H5N1 poultry vaccines used.
- November 2005 → Present -- No human or poultry cases of H5N1

Antivirals

Sensitivity of Human H5N1 Influenza Viruses to Amantadine

Year	Virus	Sensitivity	Amino acid change on M2 protein
1997	A/HK/156/97	Yes	Ser31
2003	A/HK/213/03	No	Ser31→Asn
2004	A/Vietnam/1203/04	No	Ser31→Asn
	A/Vietnam/1194/04	No	Ser31→Asn

Reduction of A/Vietnam/1203/04 (H5N1) Virus Replication after Prophylactic Treatment of Mice with Oseltamivir



The Current Situation

Humans →

New human cases in:

Indonesia:

- ► **Family cluster of H5N1**
- ►**Seasonal influenza**
- ►**Antigenically and genetically different viruses in Indonesia, China, Europe (3 clades)**

Current Human Situation

 # infected → 231

 # deaths → 133

Poultry →

H5N1 causing asymptomatic infection in ducks but killing swans/geese

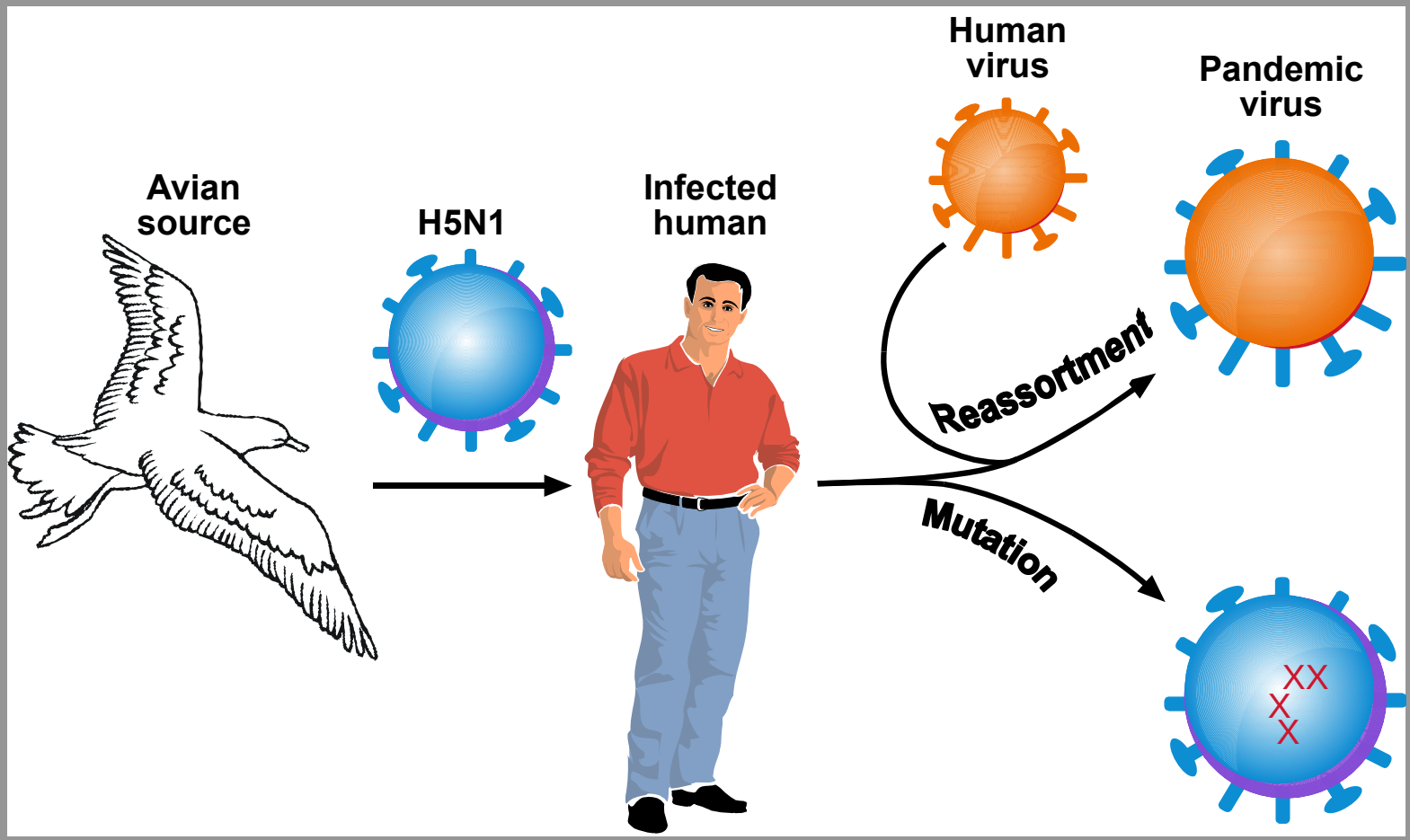
Wild birds →

Highly pathogenic H5N1 is endemic across Eurasia

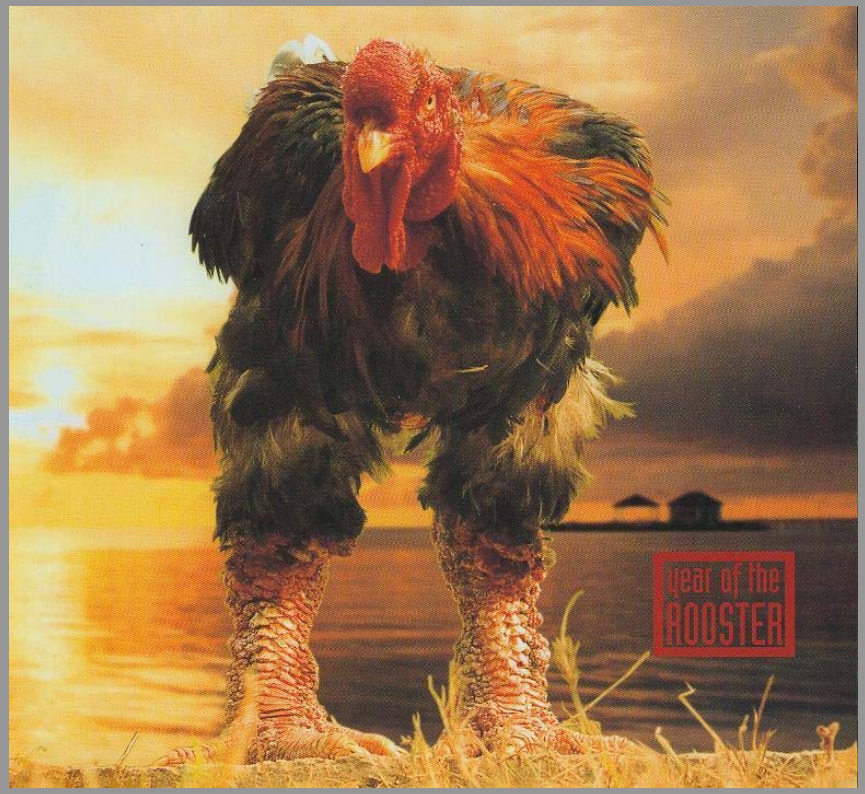
H5N1: Pandemic Outlook

- It is extremely difficult for humans to be infected
- People cannot contact H5N1 from cooked poultry
- The healthcare industry would be running beyond surge capacity
- If there is a cytokine storm pregnant women and 15-40 year olds would be hardest hit
- Urgent need to increase influenza vaccine manufacturing capacity

Will H5N1 Acquire Transmissibility?



HAPPY NEW YEAR OF THE DOG



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