

# Evolutionary insights into the biology of influenza viruses

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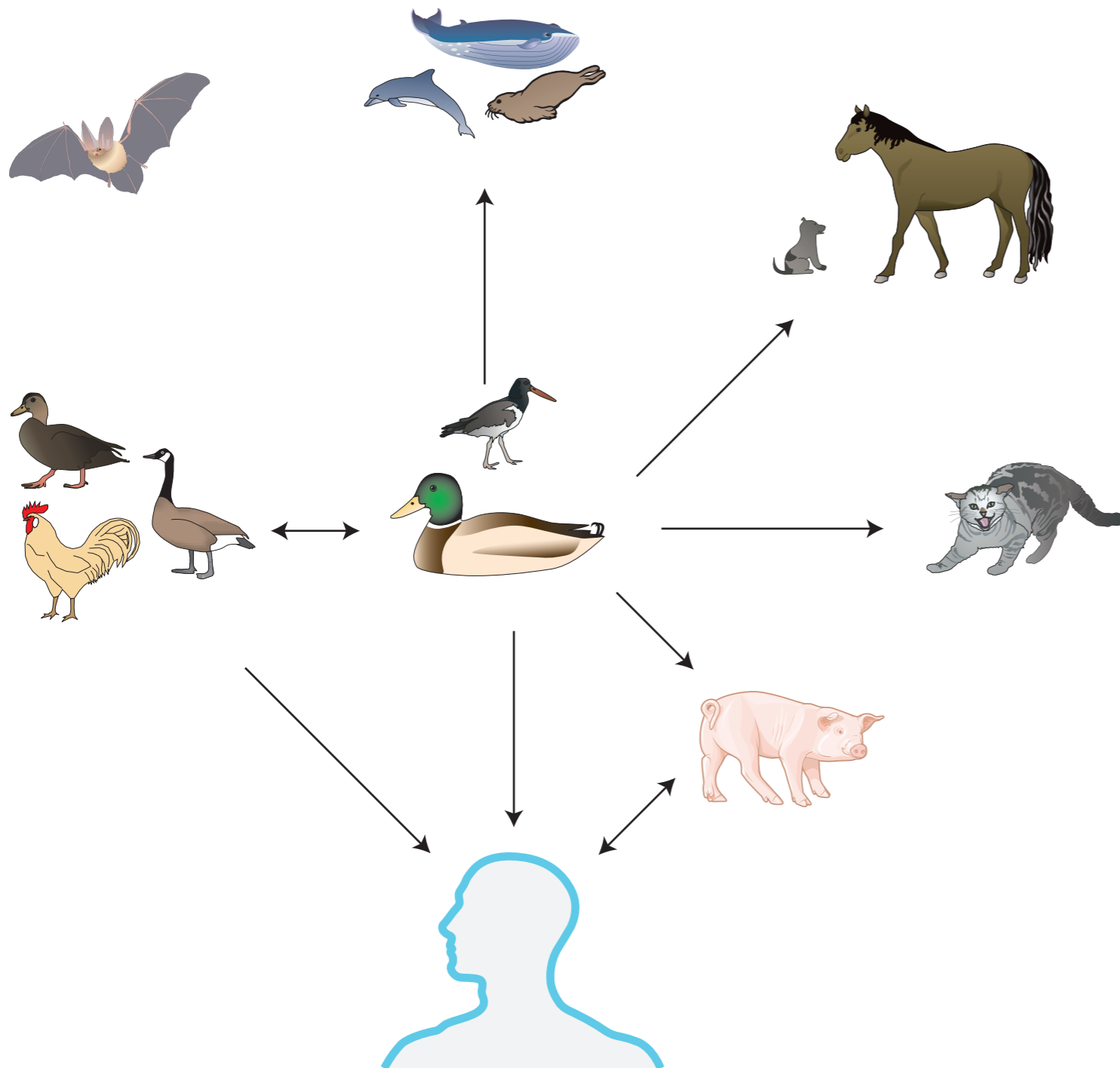


# Avian influenza ecology

Wild aquatic birds are the **natural reservoir** for influenza A viruses

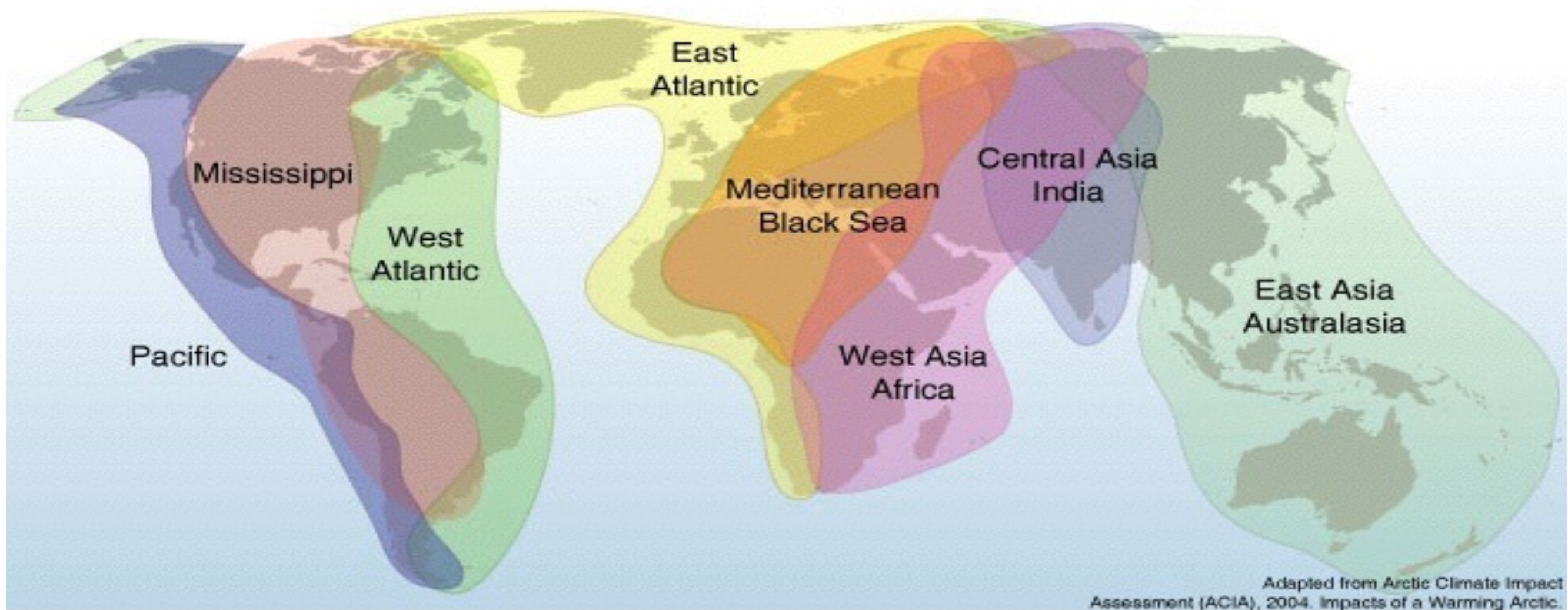
OR

The **natural gene pool** of influenza A viruses is found in wild aquatic birds



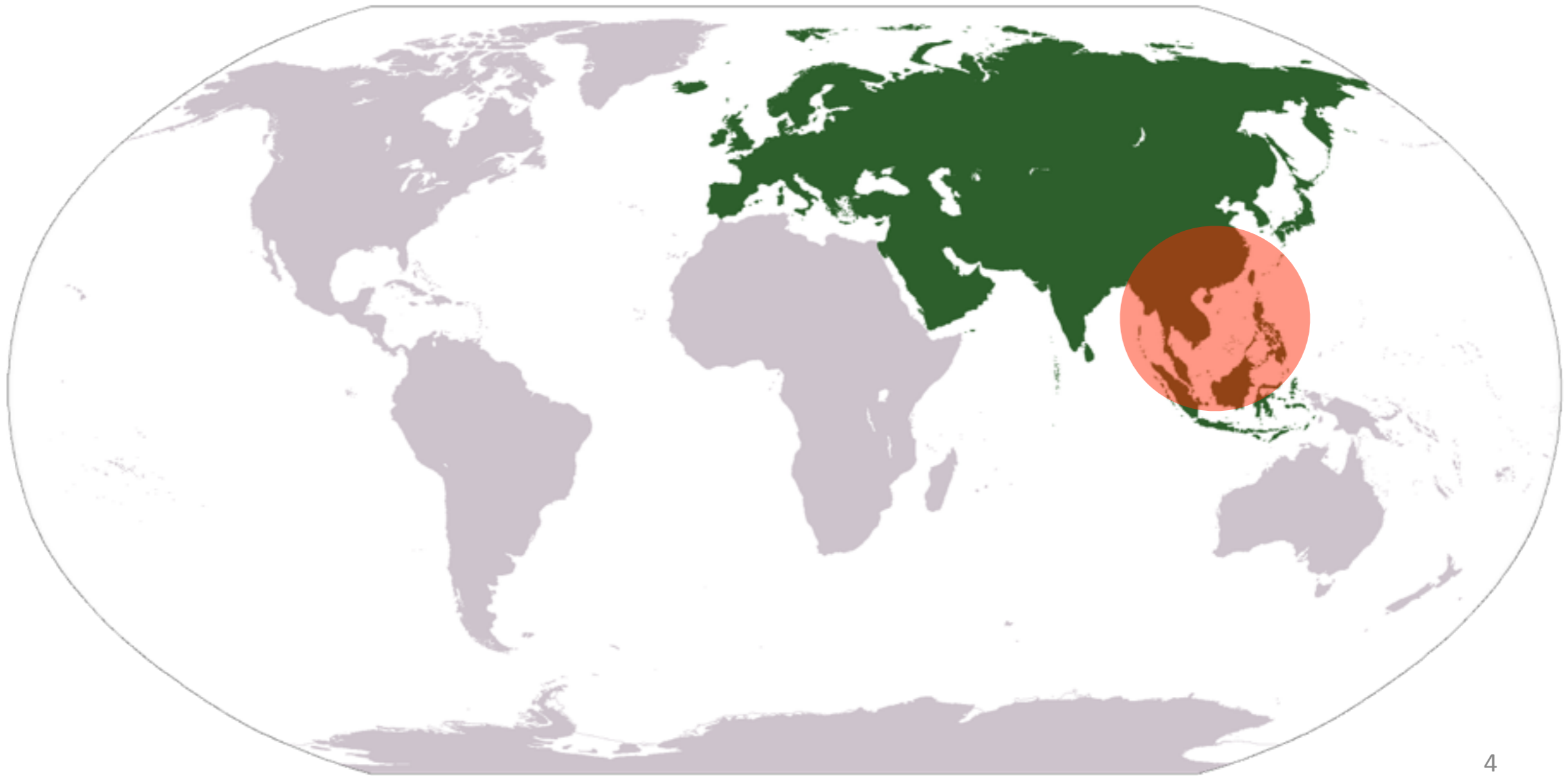
# Avian influenza ecology

- Geographical separation of host species has shaped influenza gene pool: Eurasian and American populations



# Eurasian gene pool

- Frequent interspecies transmission of virus between aquatic and terrestrial poultry (esp. Southern China and Southeast Asia)

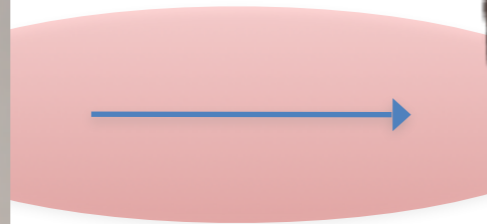




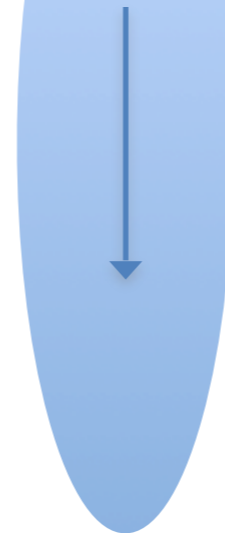
# Hypothesis of H5N1 emergence



I. Introduction  
of LPAI viruses



II. Regular reassortment of other  
subtypes with endemic H5N1 viruses



III. Transmission of reassortants within large highly  
connected populations of duck and other poultry species.

Selects for relatively fit viruses with broad host range which are  
subsequently exported to other geographical locations.

# Overview of Current H5N1 situation

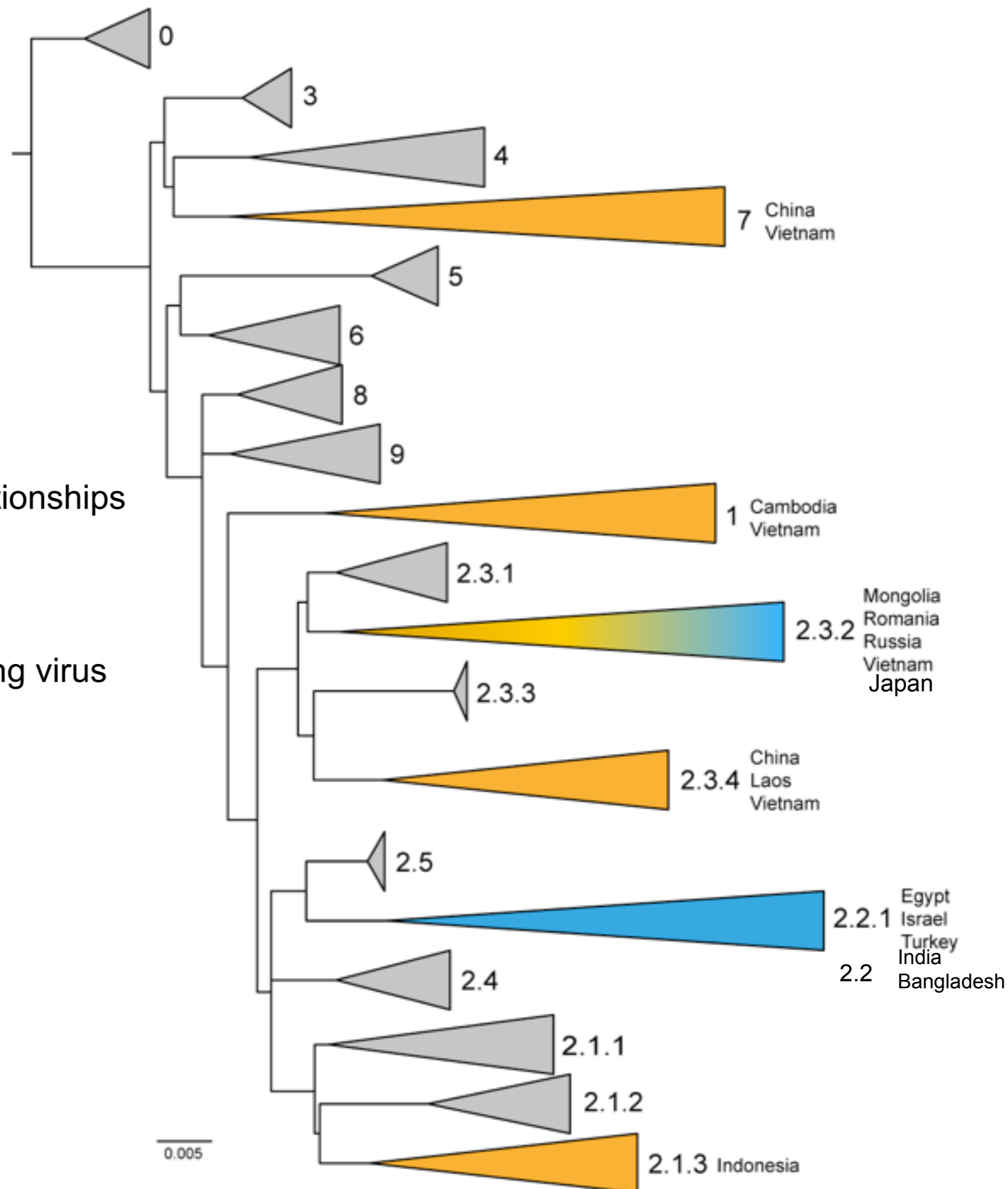
**Stylized phylogenetic tree of H5N1 virus hemagglutinin** illustrating evolutionary relationships of major virus lineages (clades).

Coloured triangles indicate actively circulating virus lineages in

**Asia (orange)**

**North Africa and the Middle East (blue),**

**Asia and Europe (orange/blue gradient).**



# Type A

Avian origin

H10N8  
H7N9



H5N1



swine origin



Human influenza viruses

H3N2

1968

H2N2

1957

H1N1

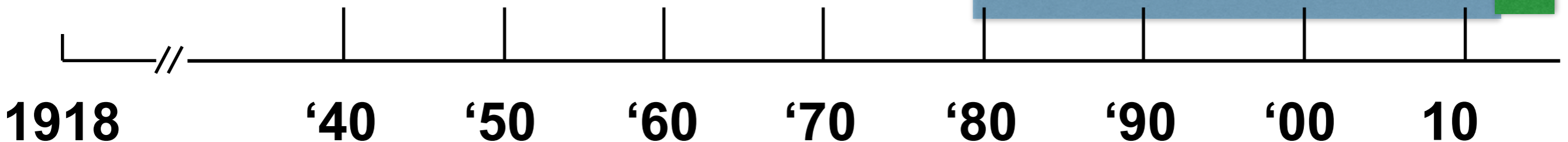


1977

H1N1/2009

Quadrivalent

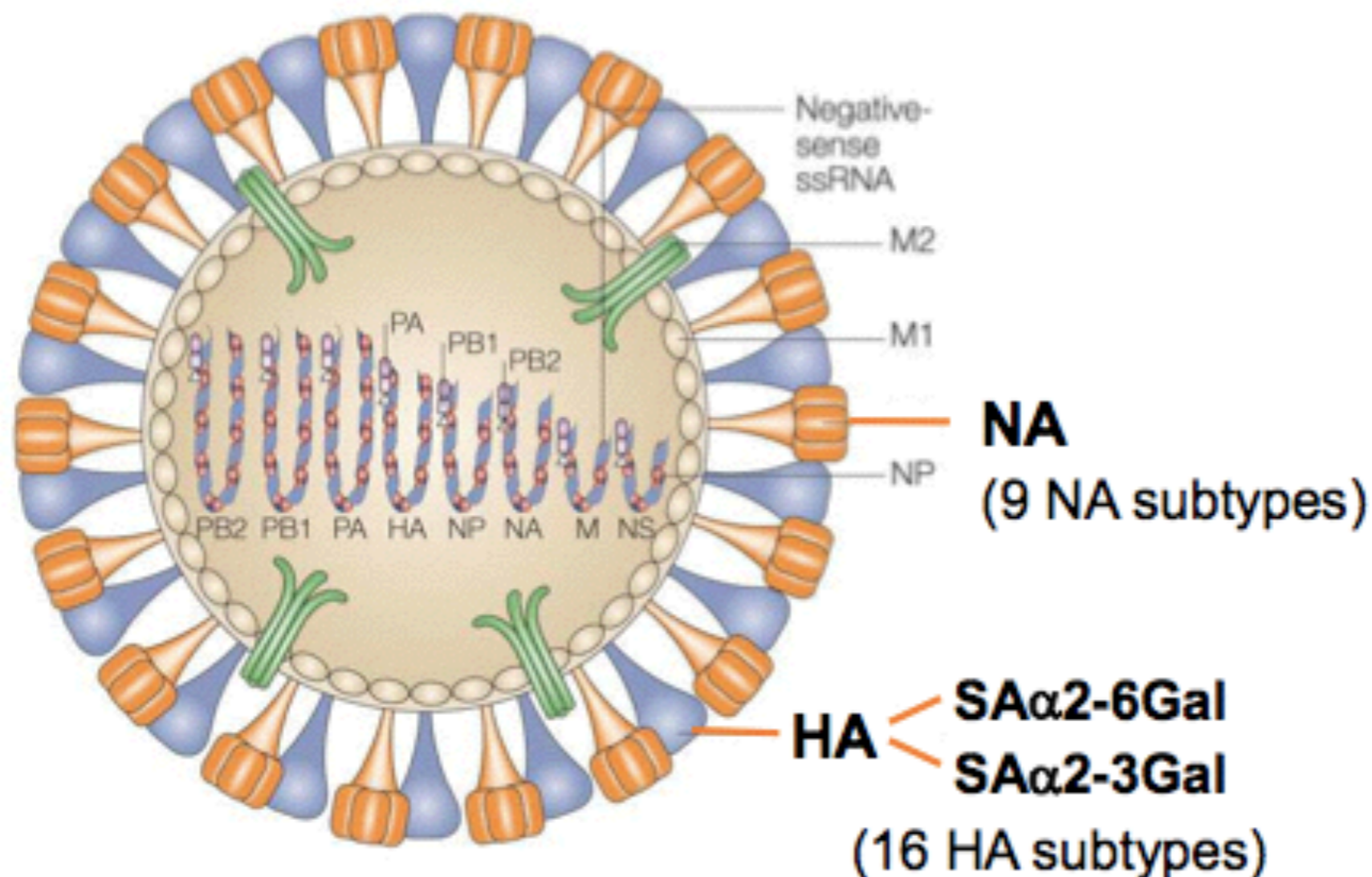
# Type B



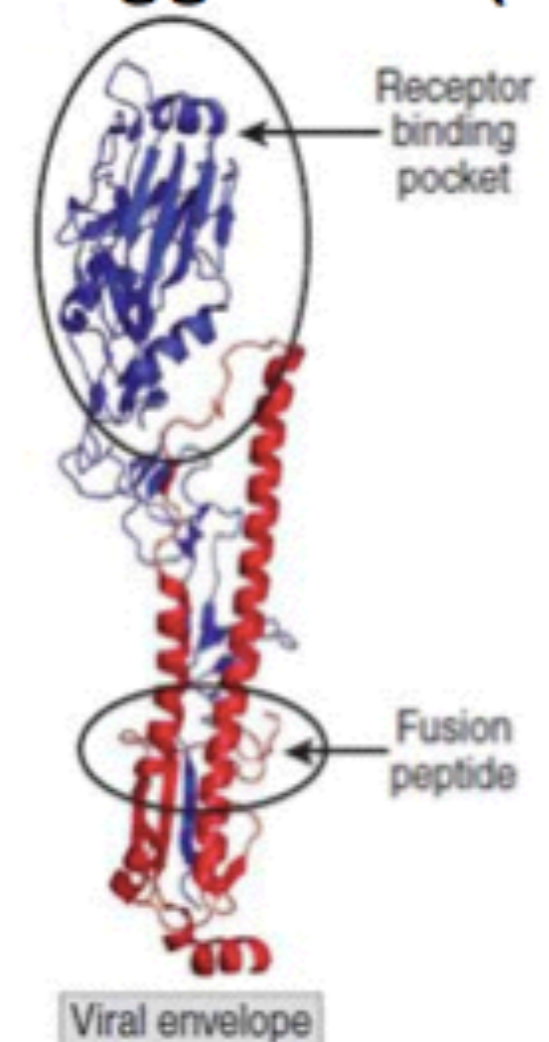
# Influenza A virus

☼ Family: lacks proof-reading abilities and is very error-prone; thus “drift” mutants can be selected for:

1. Host switch (jump from birds to pigs to humans)
2. Antiviral drug resistance
3. Antigenic drift (escape from immune detection and elimination)



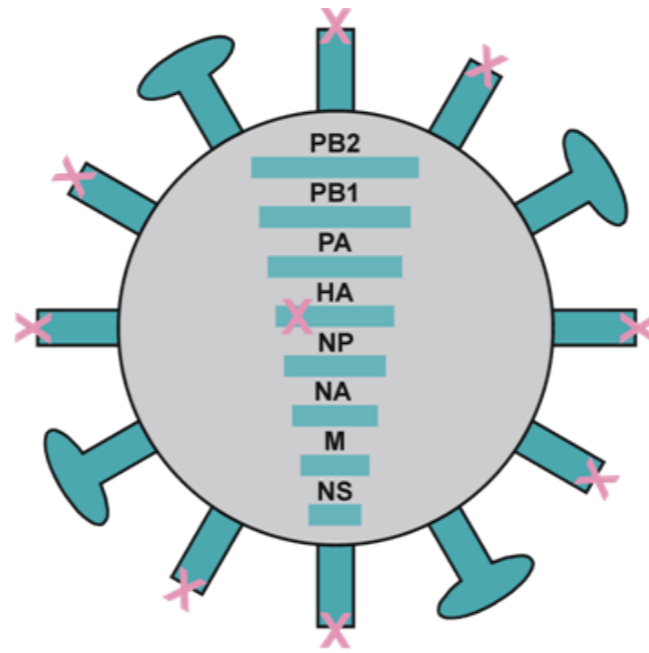
## Hemagglutinin (HA)



# Influenza A evolutionary strategies

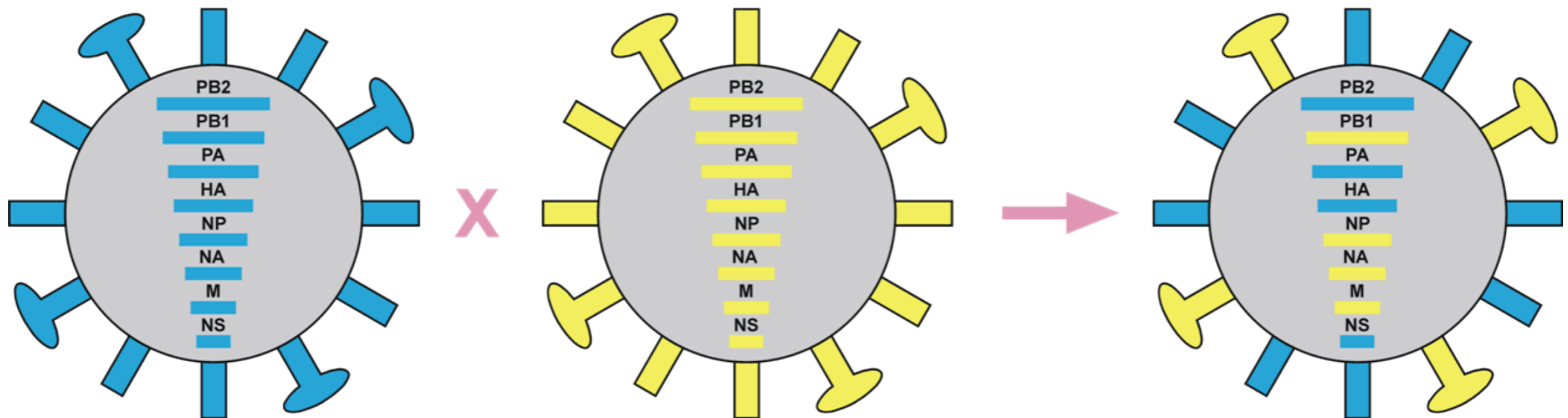
Antigenic drift: mutation

Mutation:



Antigenic shift: reassortment

Reassortment:



256 combinations

# Continental distribution of major SIV (H1 subtype) viruses

## NORTH AMERICA

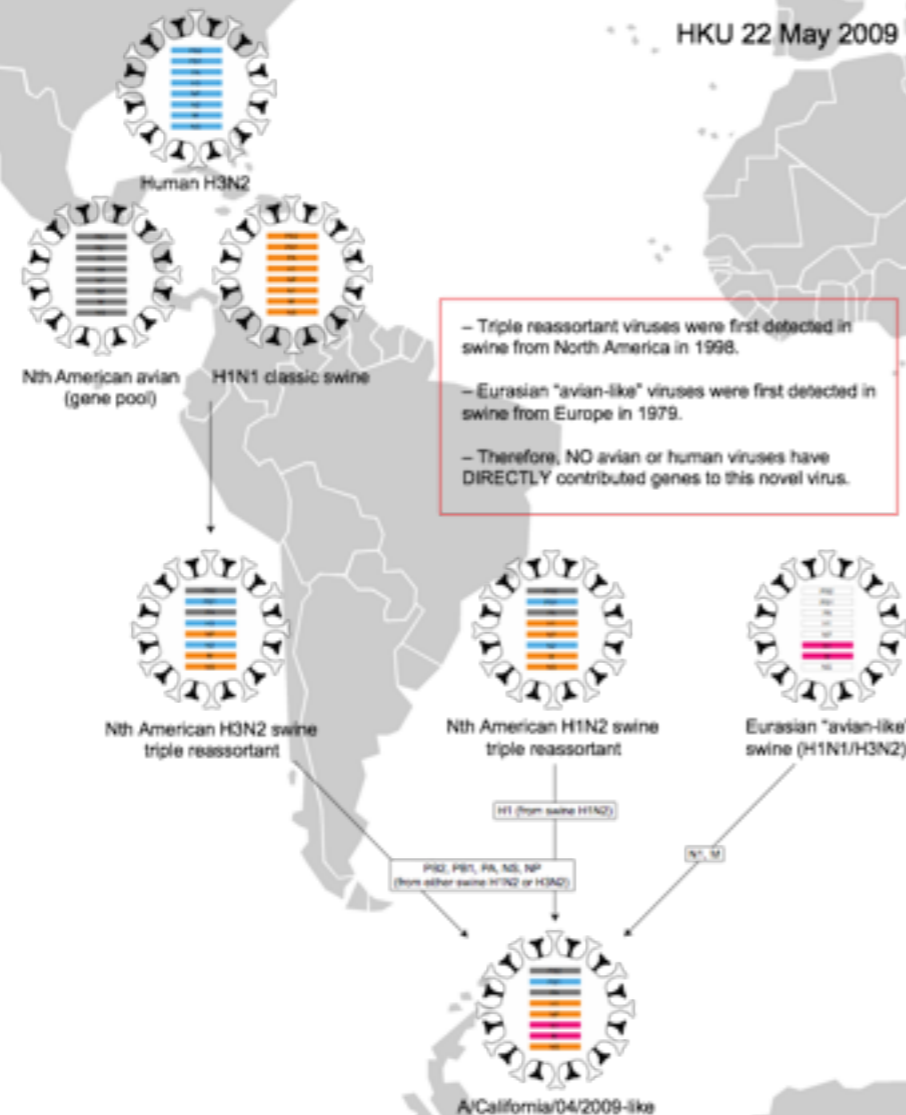
1. Classic swine
2. Triple reassortant
3. Human seasonal H1N1

## EUROPE

1. Classic swine
2. European “avian-like”
3. European H1N2

## ASIA

1. Classic swine
2. Triple reassortant
3. European “avian-like”



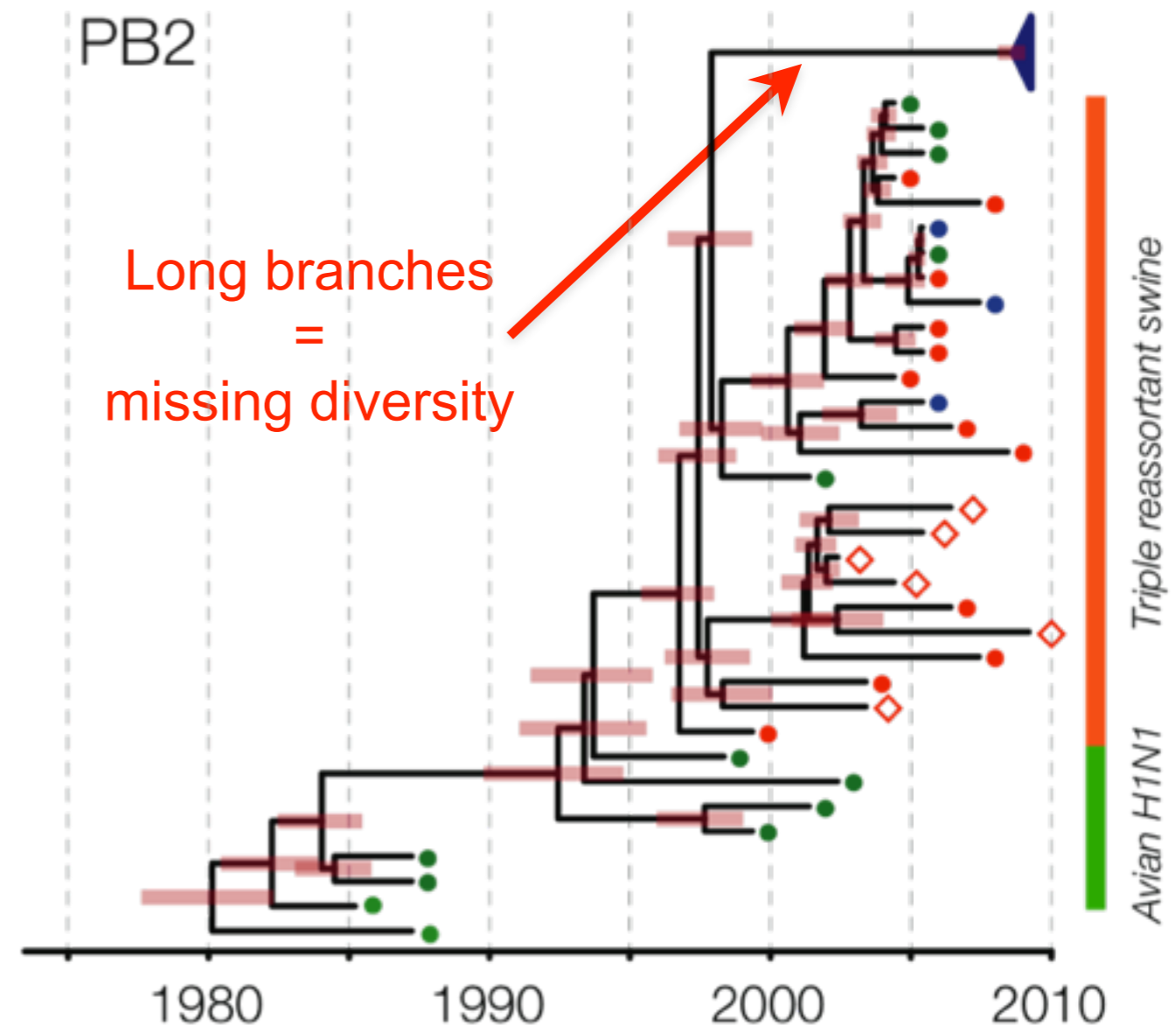
# Gaps in surveillance

## Species distribution of genomes

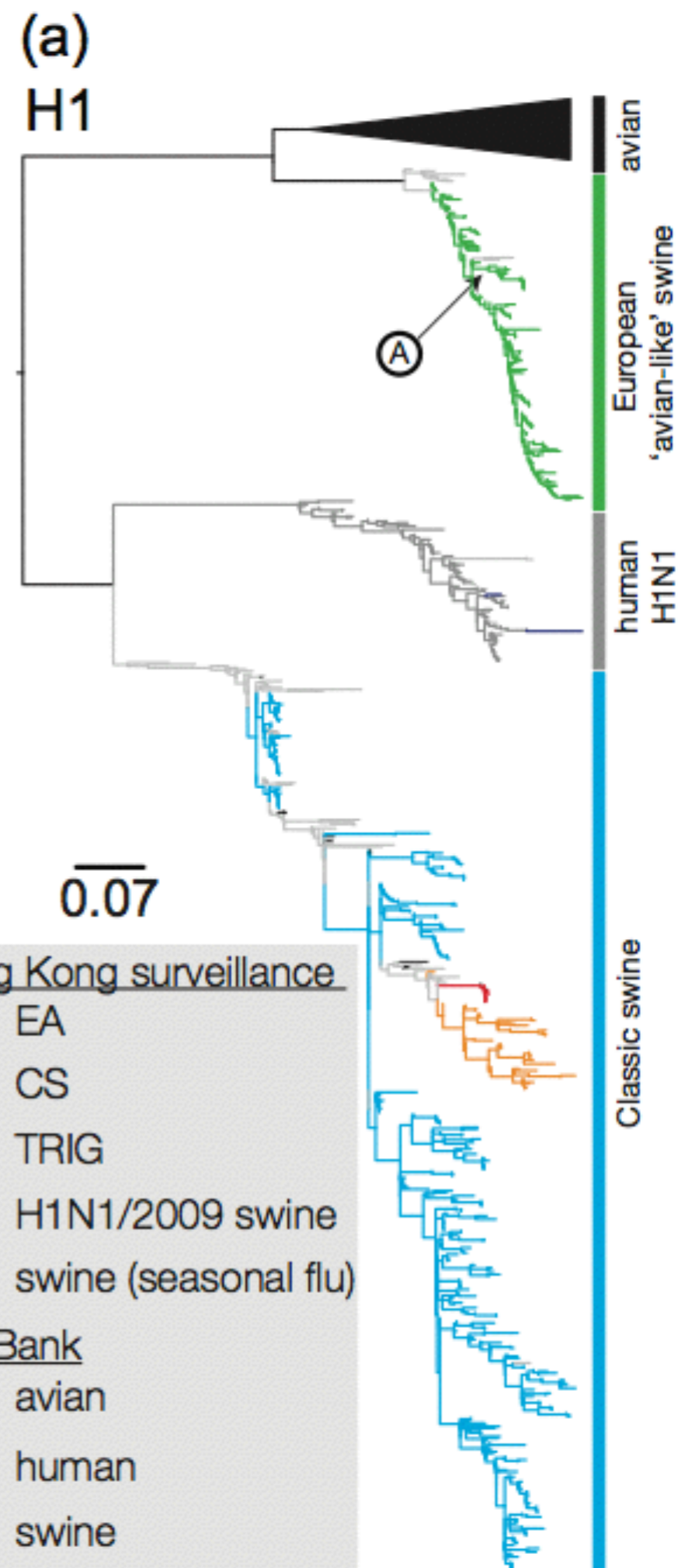
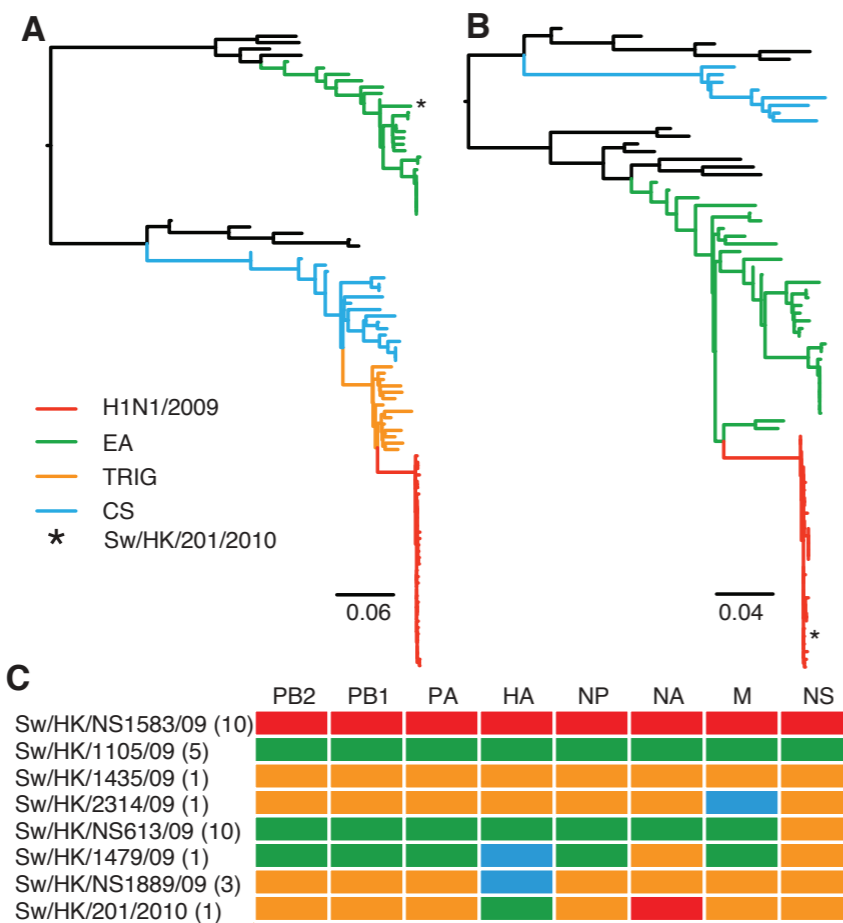
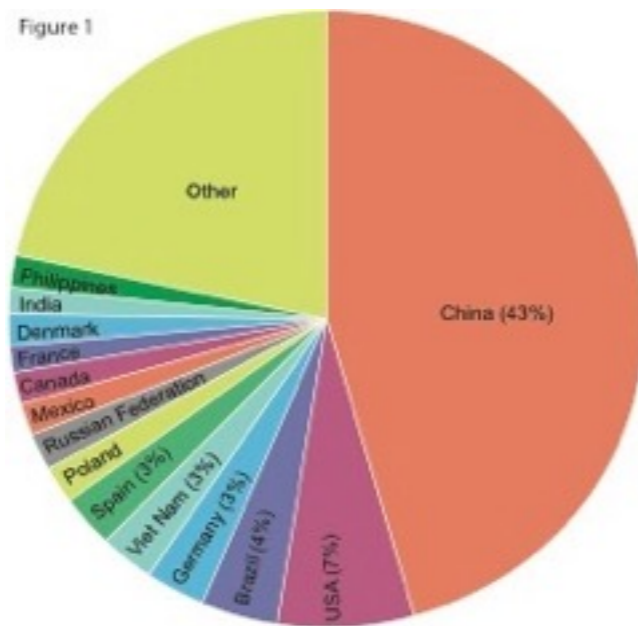
- Avian 1,944
- Human 5,143
- Swine 294
- Cats & dogs 35

## Geographic distribution of genomes

- USA 4,053
- China 665
- Japan 140
- Asia (ex HK & Japan) 600
- Africa 26
- South America 36



Smith, *et al. Nature* 2009



# Evolution of human influenza

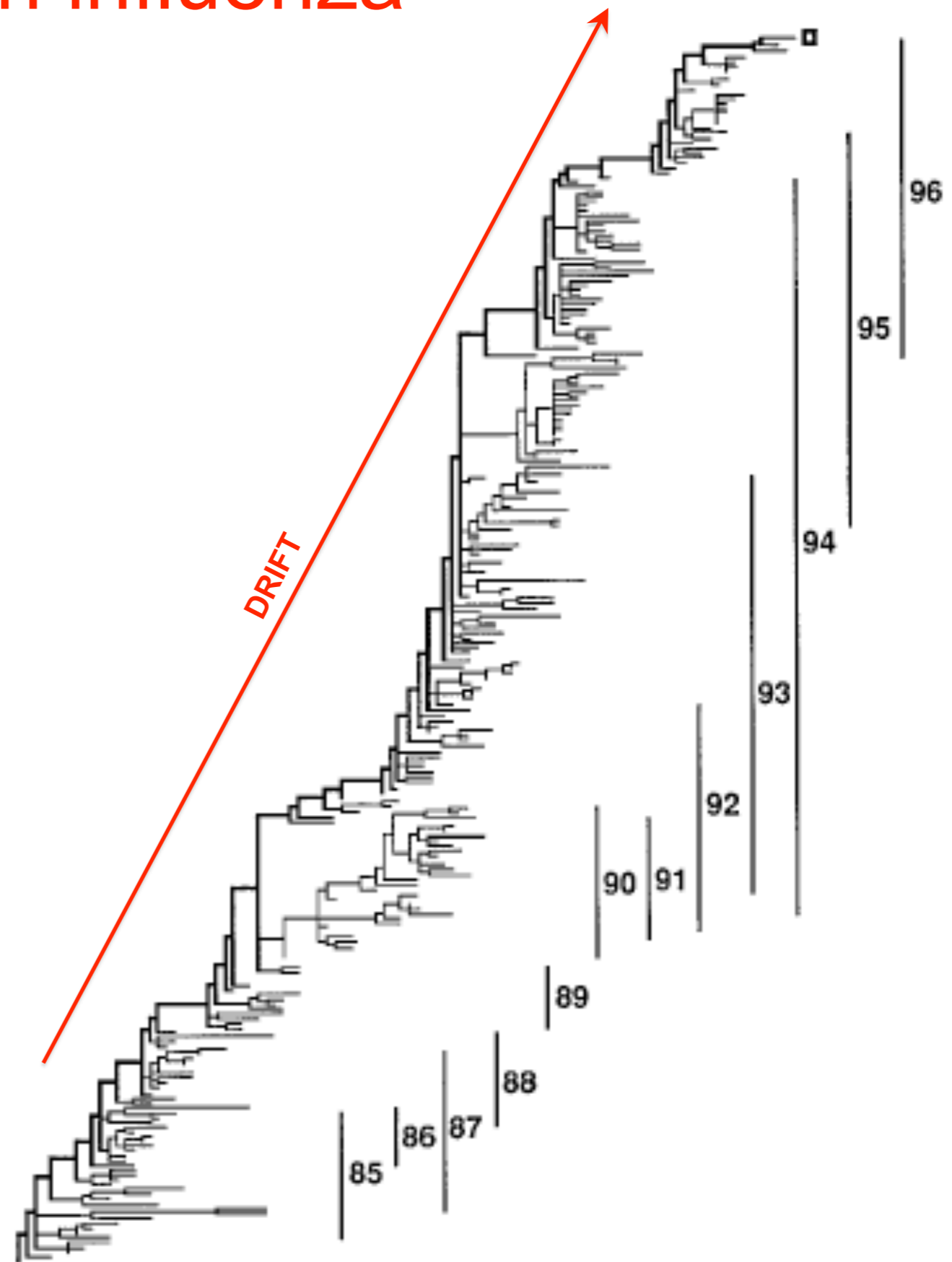
## “Pre-genomic” era

- Sequencing labor intensive & expensive
- Concentrated on HA gene
  - Relevant to vaccine strain selection
- In the late 1990's a series of studies investigated the evolution of the H3-HA
- Key findings included
  - Dramatic visualization of antigenic drift
  - Viral lineages with the greatest number of mutations in positively selected amino acids (AAs) were the progenitors of future seasonal strains
  - AAs under positive selection were associated with antigenic or receptor binding sites

Fitch *et al.* 1997. *PNAS* **94**:7712–7718

Bush *et al.* 1999. *Science* **286**:1921–1925

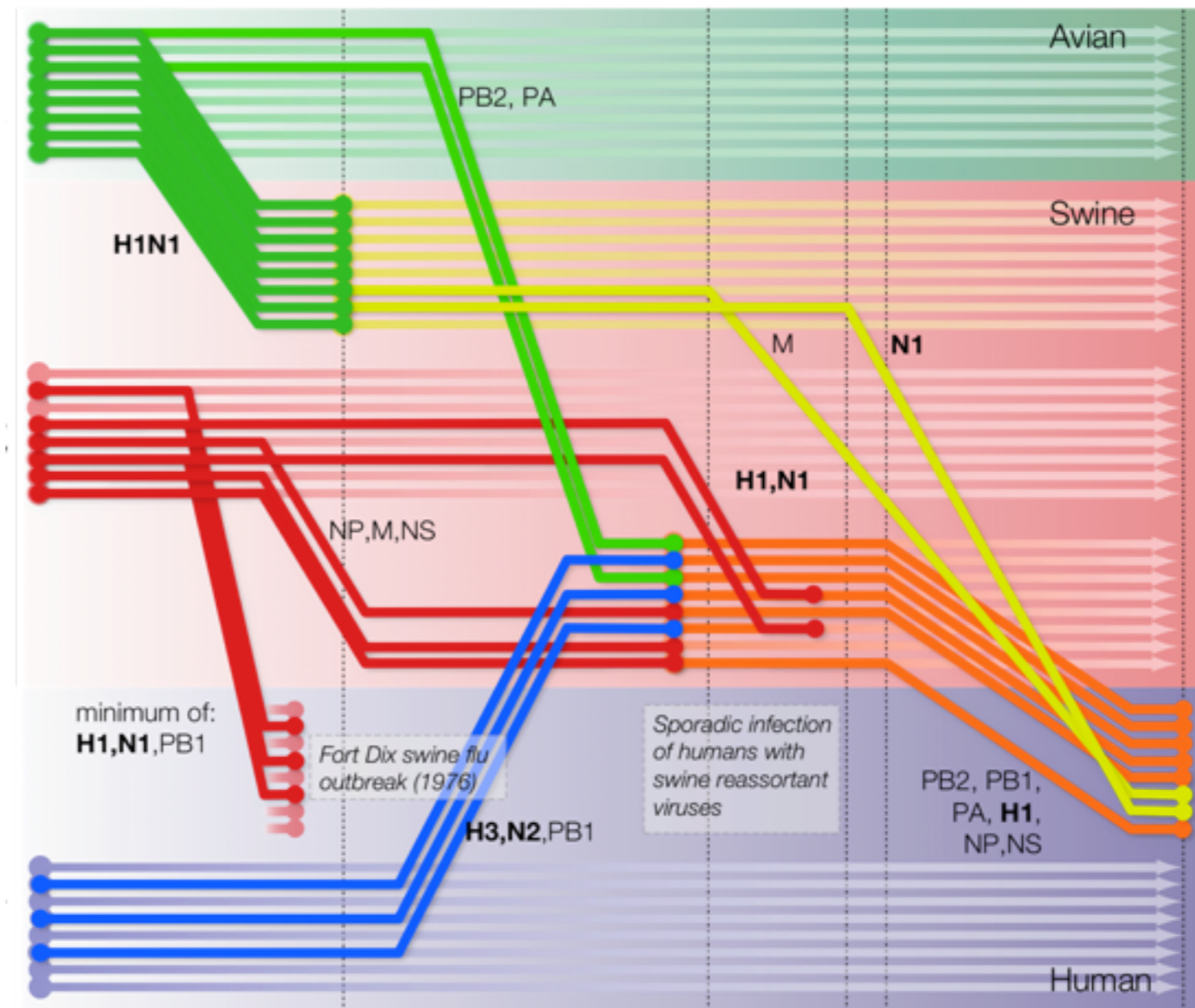
Bush *et al.* 1999. *Mol Biol Evol* **16**:1457–1465



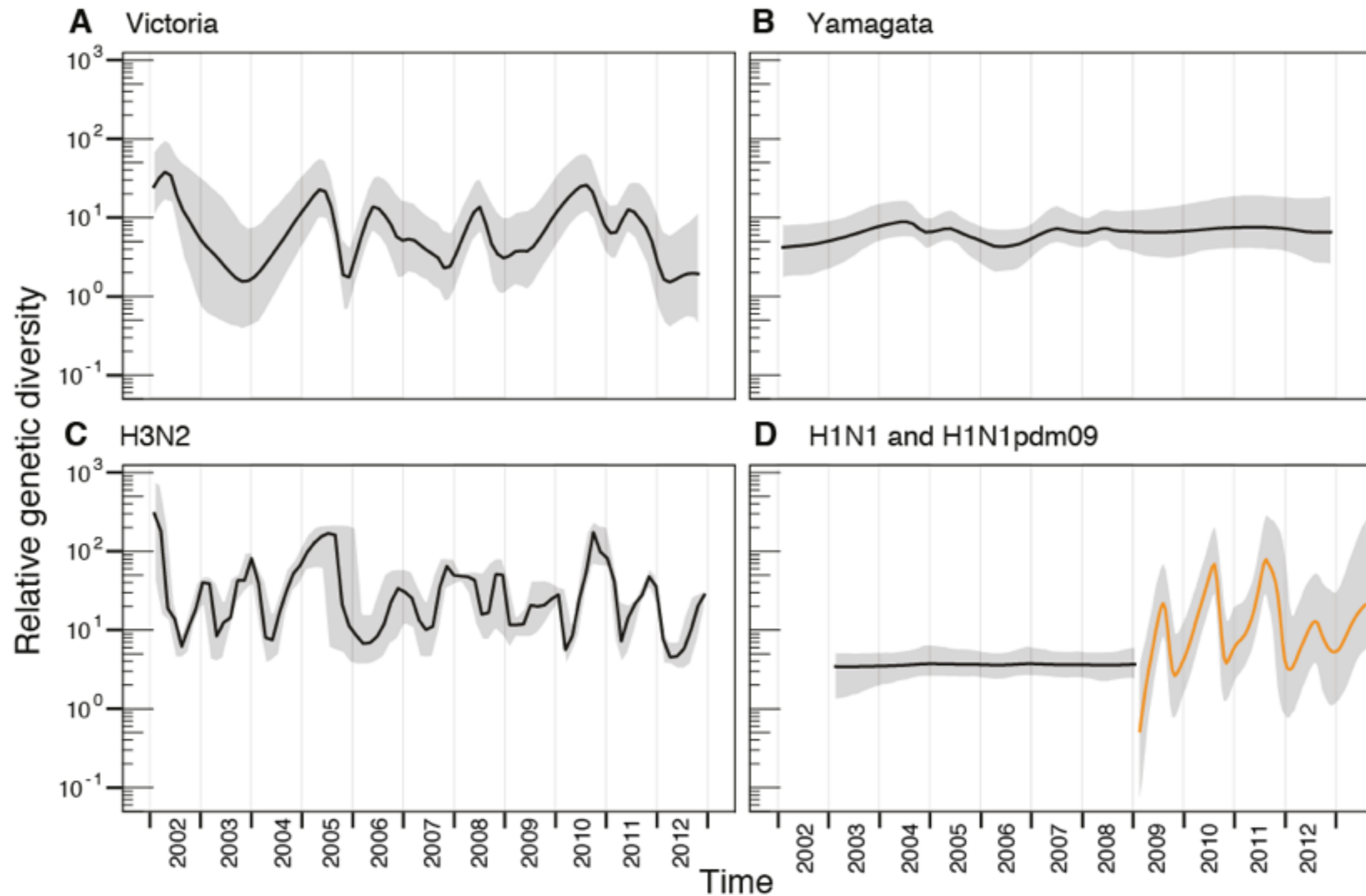
# “Genomic” era

- Inexpensive (relatively) high-throughput sequencing
- Provides information on drug resistance, host adaptation signatures & reassortment
- Corresponding developments in analytical methodologies

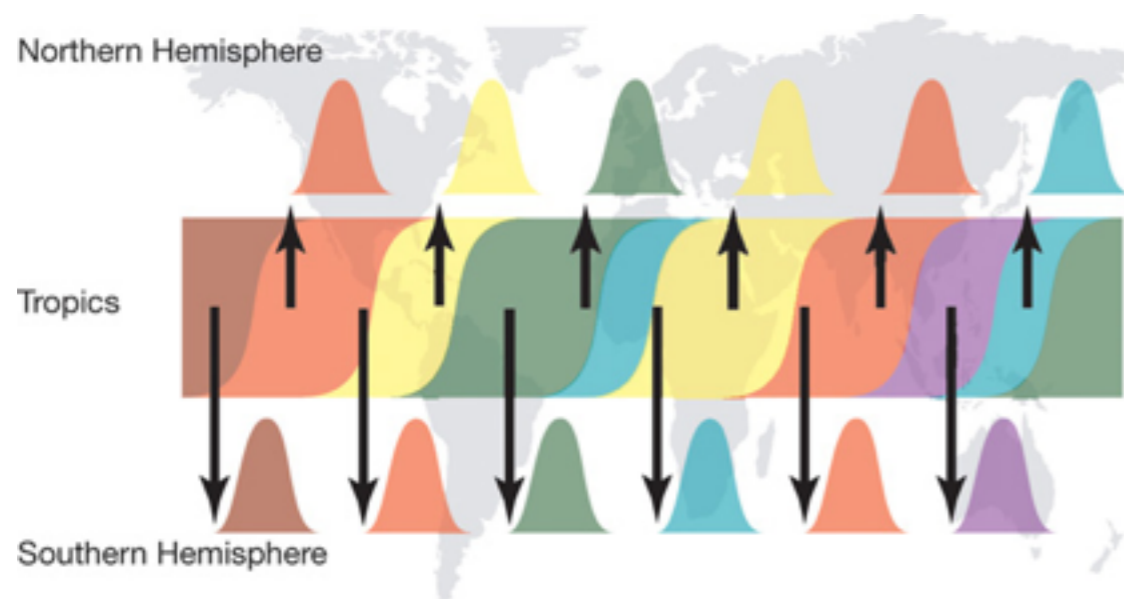
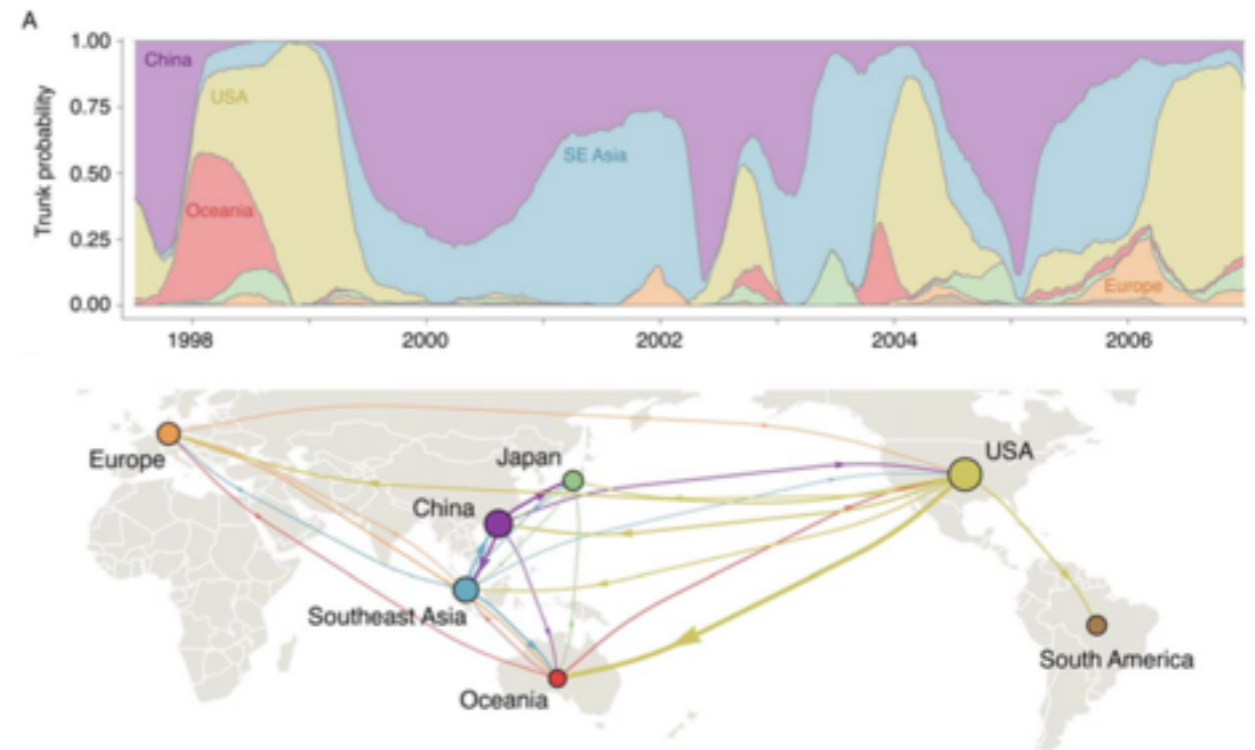
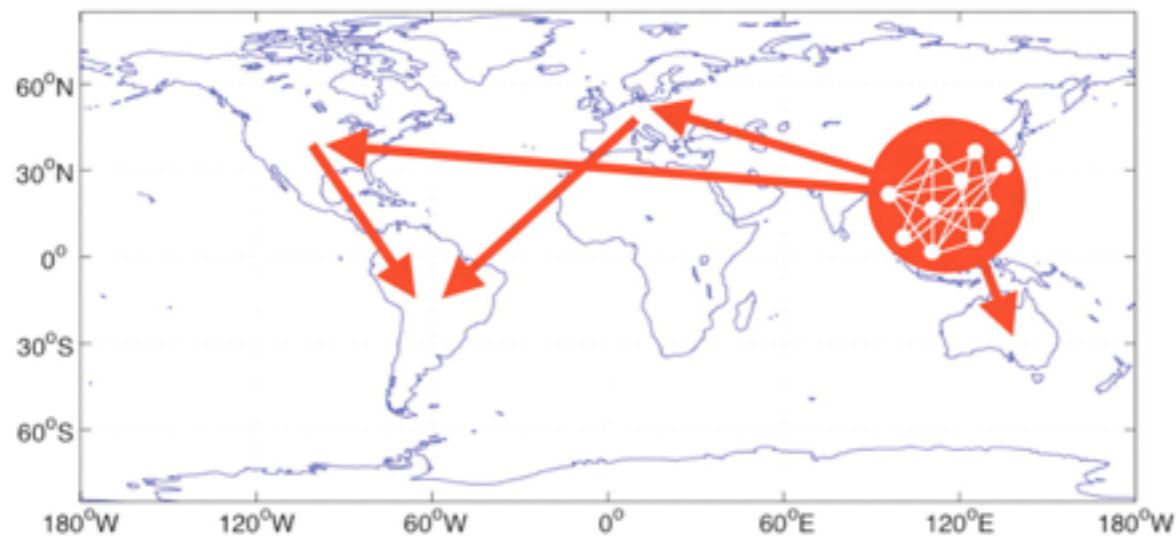
## Reassortment diagram



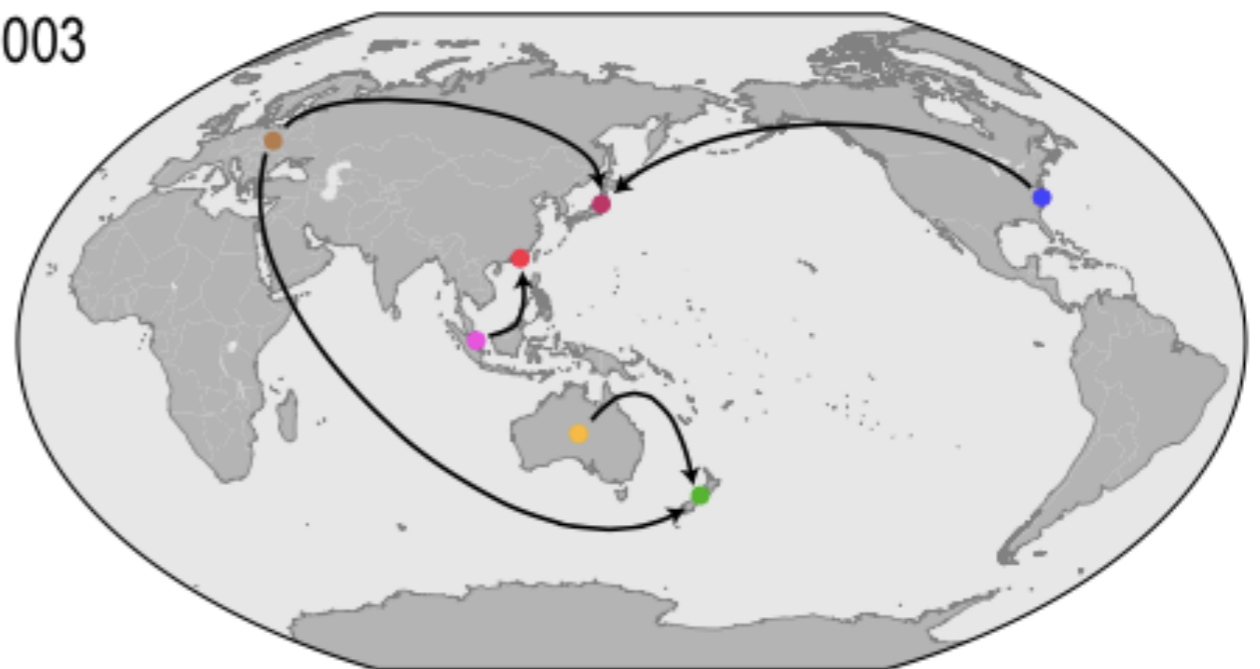
# Changes in genetic diversity



# Phylogeography



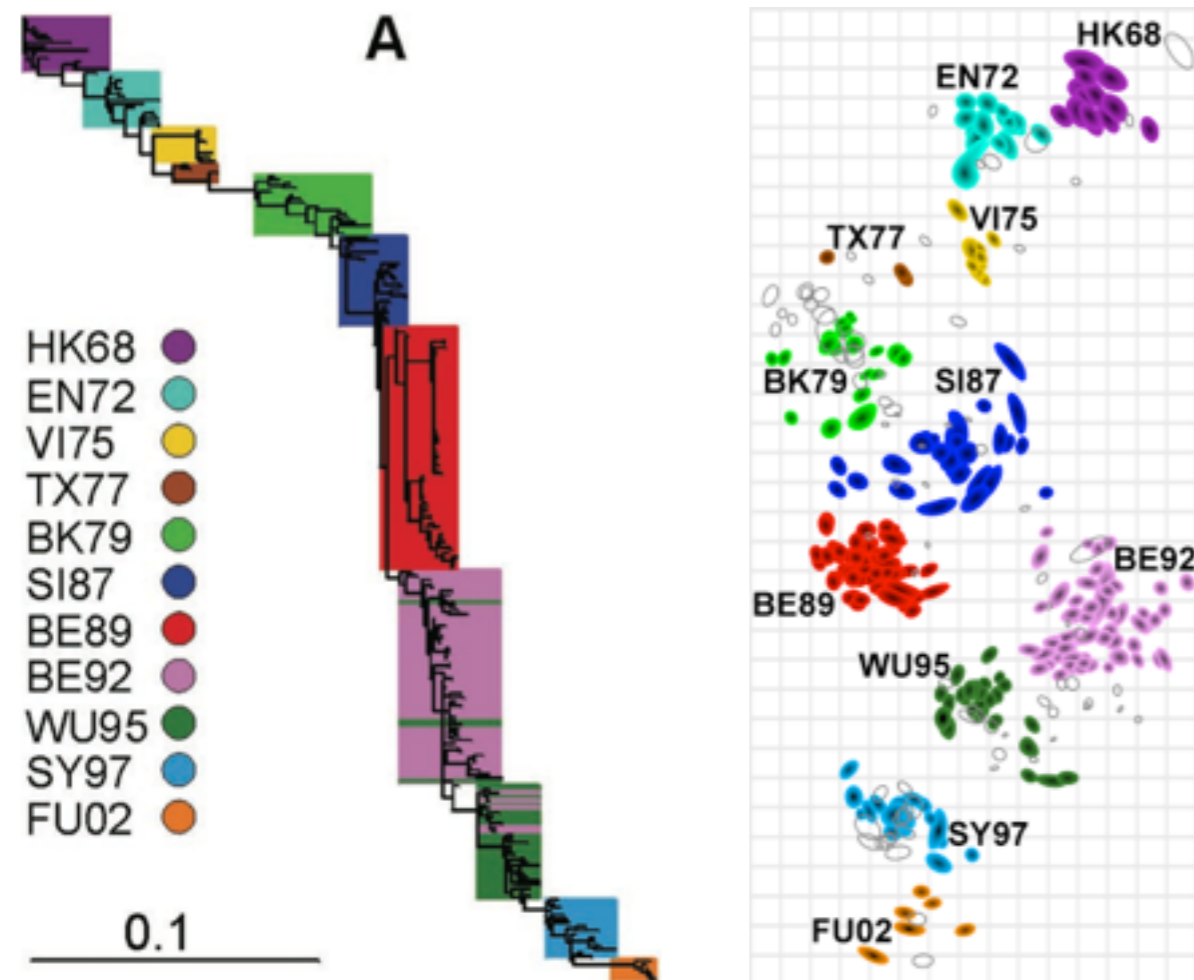
2003



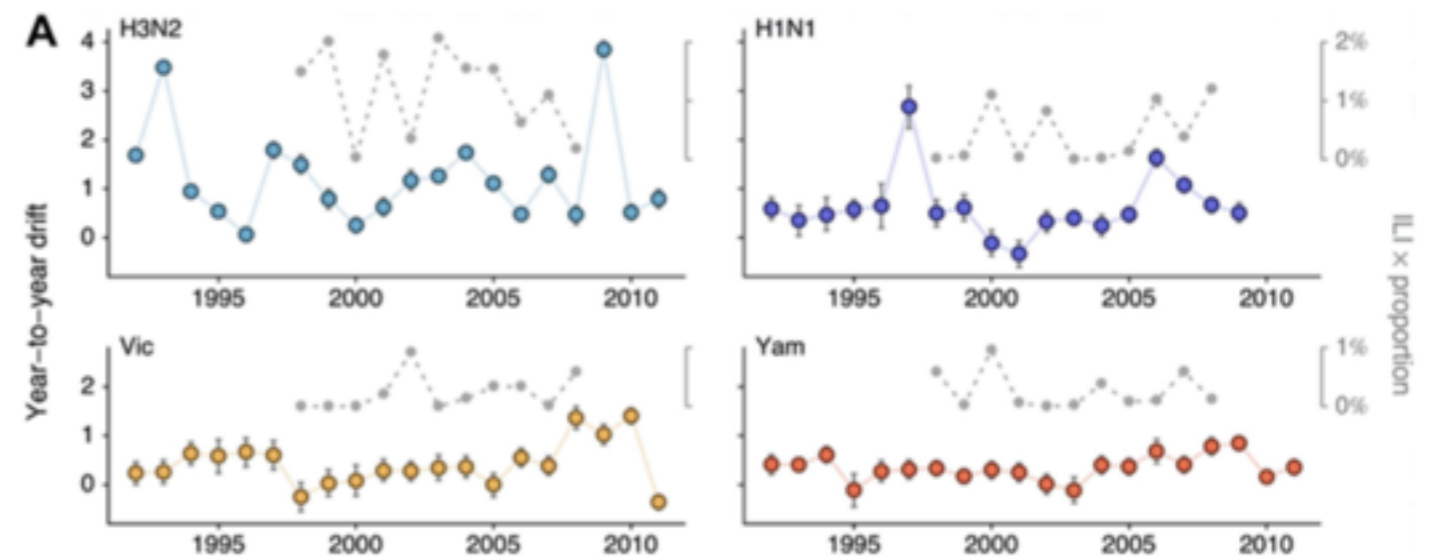
2004



# Integration of genetic and antigenic data



Smith DJ et al *Science* 2004



Bedford et al *eLife* 2014