LECTURE 1: Human-adapted influenza: B & A (H1N1/H3N2)

Focus: What seasonal flu teaches us about viral evolution and public health.

Introduction to Ecology & Evolution Concepts

- What we mean by ecology & evolution in a public health context.
- How host ecology, immunity, and virus evolution interact.
- Key tools: phylogenetics, phylodynamics, within-host vs population-level dynamics.

Seasonal Influenza Ecology

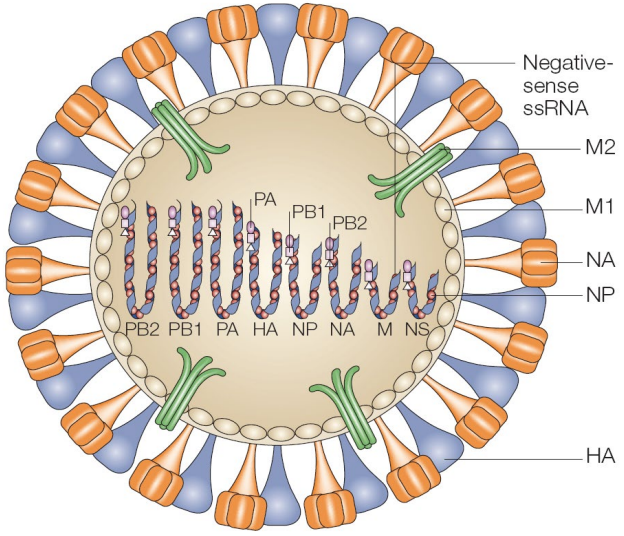
- Global circulation patterns of influenza A & B.
- Age-specific infection patterns.
- Differences between influenza A & B in host range and dynamics.
- Why influenza B matters: burden, Yamagata extinction(?), vaccination.

Evolution of Seasonal Influenza Viruses

- Antigenic drift & immune escape.
- Phylogenetic patterns: ladder-like trees, lineage replacement.
- Within-host diversity vs between-host selection.
- Why influenza A evolves faster than B — evidence & hypotheses. COVID, RSV, Measles?

Synthesis & Public Health Implications

- Vaccine strain selection.
- Importance of surveillance.
- What influenza B can teach us about viral evolution constraints.



What we mean by ecology & evolution in viruses

Ecology

- How viruses interact with hosts, environments, and populations.
- Host range & reservoirs (humans, birds, swine, others).
- Population structure (age, immunity, density) and seasonality.
- Transmission pathways: direct, indirect, migratory flyways.

What we mean by ecology & evolution in viruses

Evolution

- How viral genetic makeup changes over time under selection & drift.
- **Mutation (drift):** gradual accumulation of changes in HA & NA → immune escape.
- **Reassortment (shift):** exchange of gene segments when two viruses infect the same host → new combinations.
- Selection & bottlenecks shaping diversity at within-host and population levels.

Why it matters

- Seasonal influenza: Why do we need to update vaccines? (evolution)
- Why do pandemics emerge? (ecology + evolution)
- Why are some lineages (e.g., B/Yamagata) disappearing? (ecology + evolution)
- Why do zoonotic infections sometimes fizzle and sometimes explode? (ecology + evolution)

How ecology & evolution interact

Host population structure affects viral evolution:

- High immunity → **stronger selection** for escape.
- Bottlenecks during transmission shape diversity.
- Animal reservoirs act as sources of genetic diversity.

Examples:

- Wild bird ecology sustains LPAI genetic diversity.
- Poultry density & practices amplify HPAI outbreaks.

Key tools to study these processes

Phylogenetics:

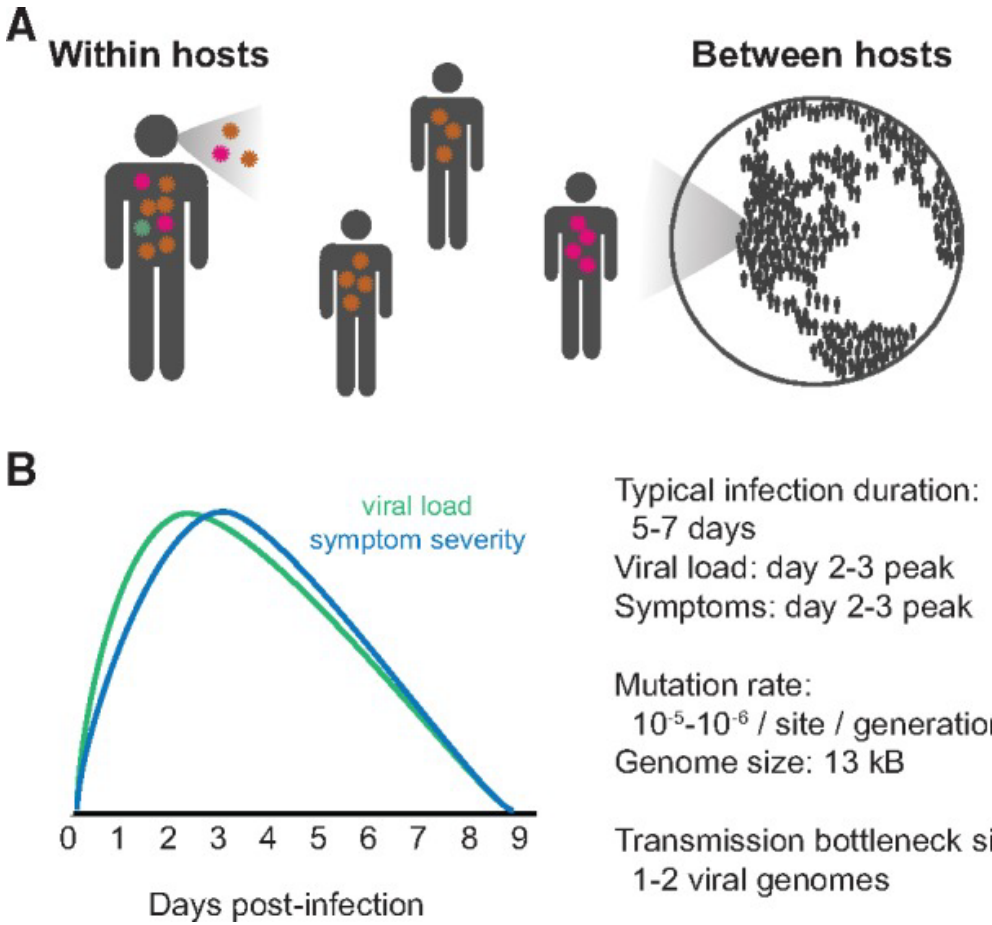
- Reconstruct trees of sequences to infer relatedness and evolutionary history.
- Detect lineages, reassortment events, host jumps.

Phylodynamics:

- Combine sequence data with epidemiological models to infer population dynamics (e.g., effective population size, R_0 over time).
- Visualize lineage turnover, clade replacement.

Within-host vs Between-host dynamics:

- Within-host: Diversity arising during infection, bottlenecks at transmission.
- Between-host: How mutations spread and persist in the population.

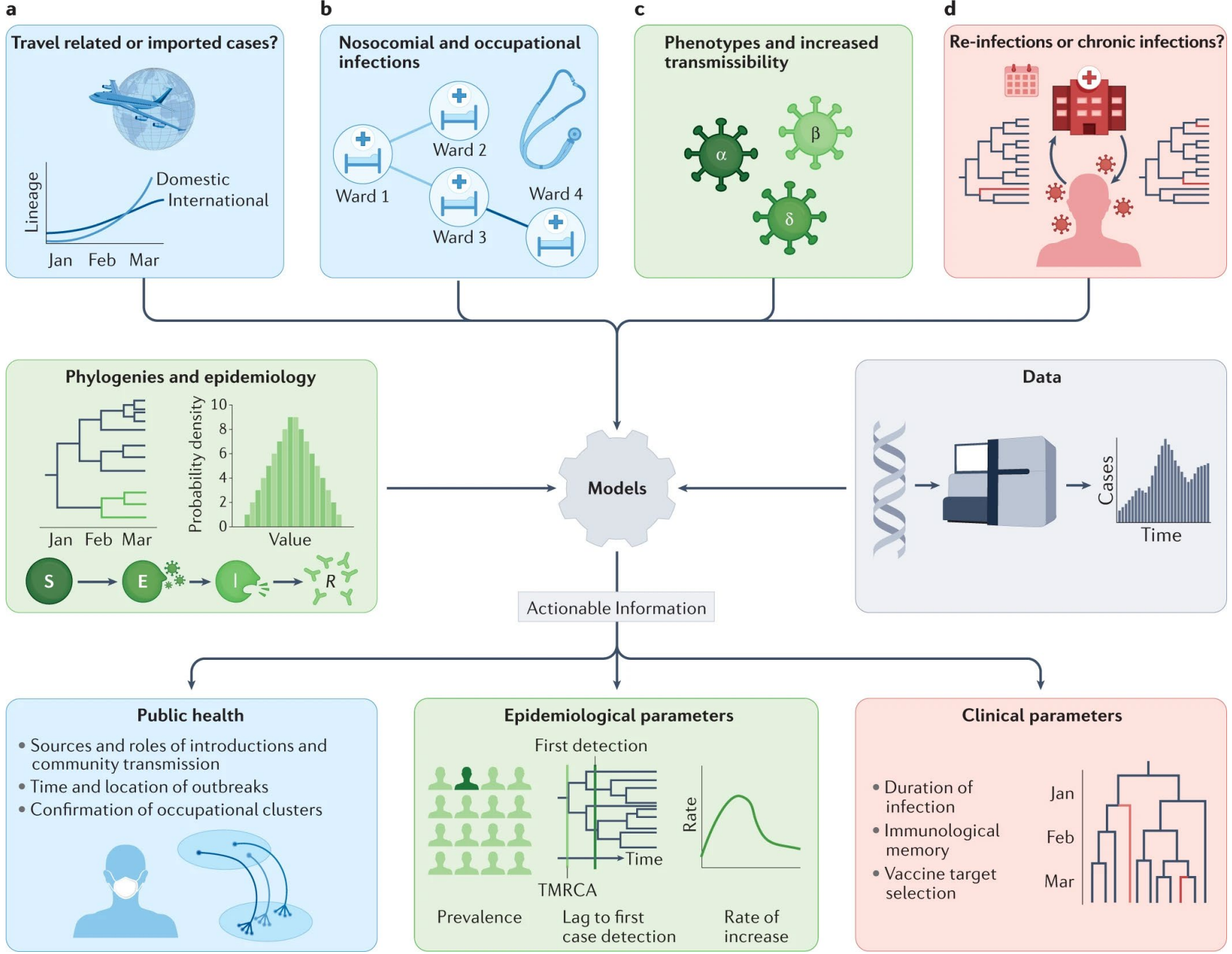


Xue KS, Bloom JD. Virus Evol. 2020 PMID: 32082616

hCoV-19 data sharing via GISAID

15,692,574

genome sequence submissions



Attwood et al. *Nature Reviews Genetics* **23**, 547-562 (2022).

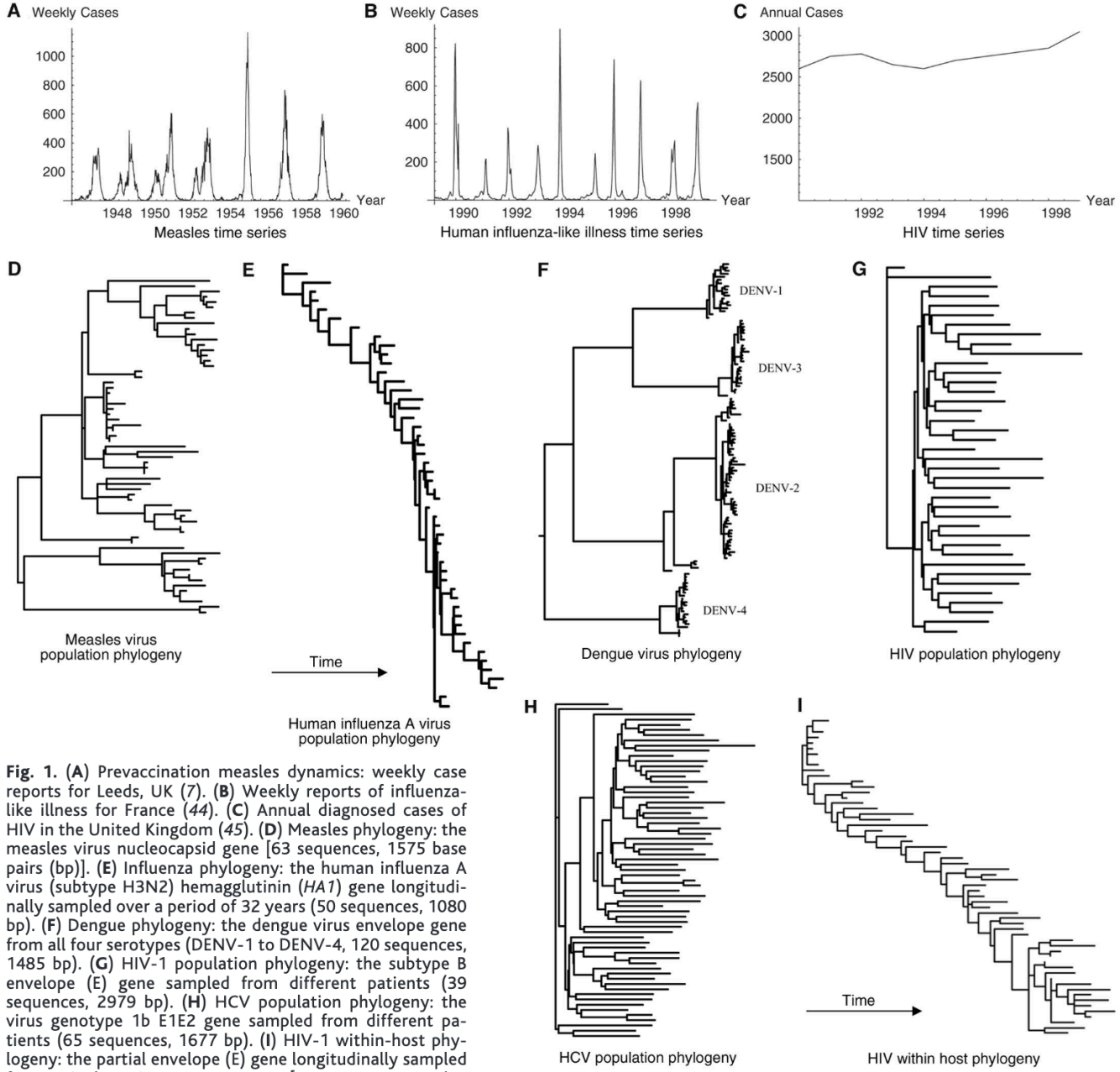
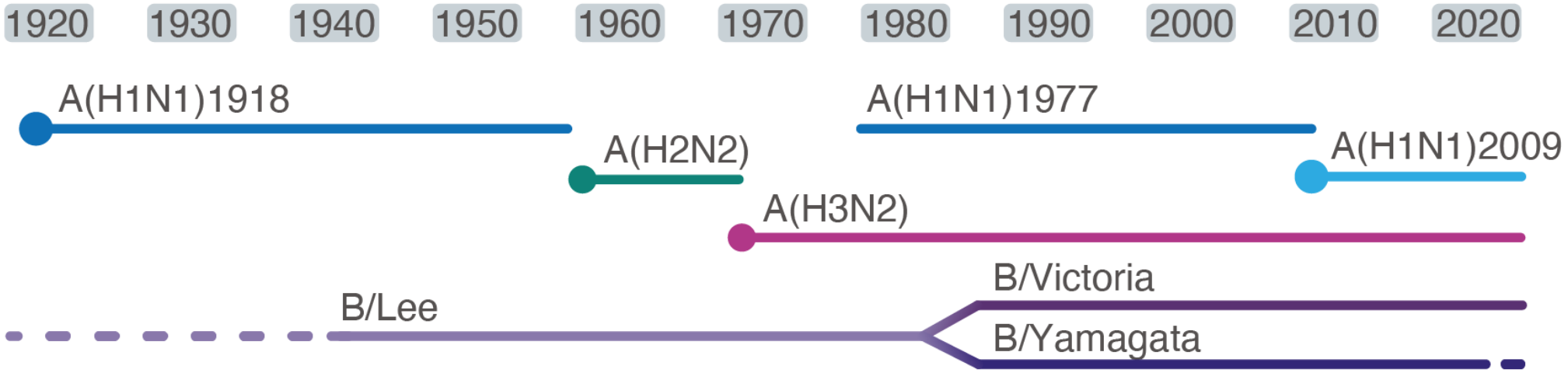


Fig. 1. (**A**) Prevaccination measles dynamics: weekly case reports for Leeds, UK (*7*). (**B**) Weekly reports of influenza-like illness for France (*44*). (**C**) Annual diagnosed cases of HIV in the United Kingdom (*45*). (**D**) Measles phylogeny: the measles virus nucleocapsid gene [63 sequences, 1575 base pairs (bp)]. (**E**) Influenza phylogeny: the human influenza A virus (subtype H3N2) hemagglutinin (*HA1*) gene longitudinally sampled over a period of 32 years (50 sequences, 1080 bp). (**F**) Dengue phylogeny: the dengue virus envelope gene from all four serotypes (DENV-1 to DENV-4, 120 sequences, 1485 bp). (**G**) HIV-1 population phylogeny: the subtype B envelope (E) gene sampled from different patients (39 sequences, 2979 bp). (**H**) HCV population phylogeny: the virus genotype 1b E1E2 gene sampled from different patients (65 sequences, 1677 bp). (**I**) HIV-1 within-host phylogeny: the partial envelope (E) gene longitudinally sampled from a single patient over 5.8 years [58 sequences, 627 bp; patient 6 from (*26*)]. All sequences were collected from GenBank and trees were constructed with maximum likelihood in PAUP* (*46*). Horizontal branch lengths are proportional to substitutions per site. Further details are available from the authors on request.

Human-adapted influenza: B & A (H1N1/H3N2)

Human Seasonal Influenza viruses

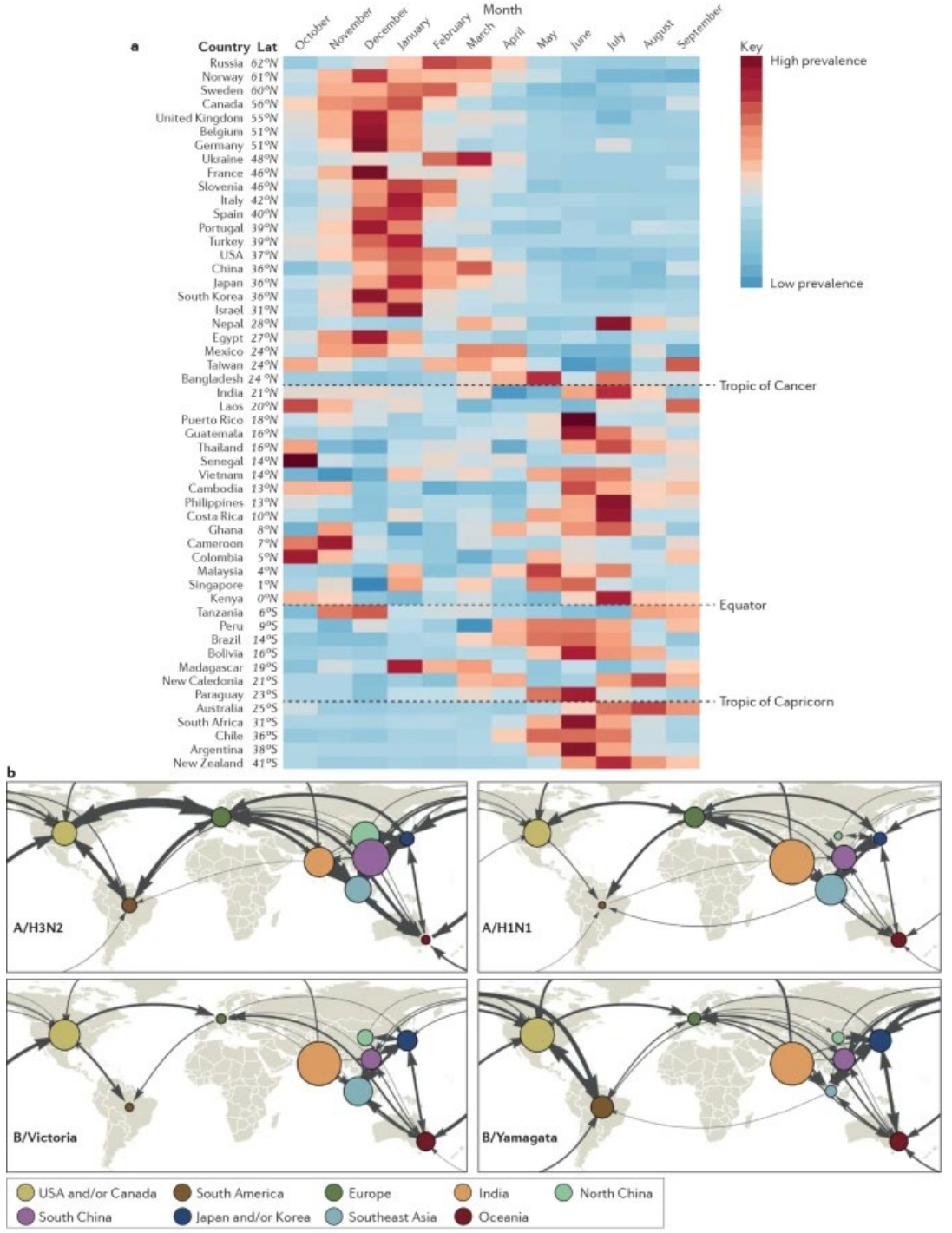


- Well studied !
- **Vaccines** that confer partial protection has been available for decades.
- Yet, 290,000 to 650,000 death annually, and estimated loss of over $11 billion to the US economy alone (before COVID-19).

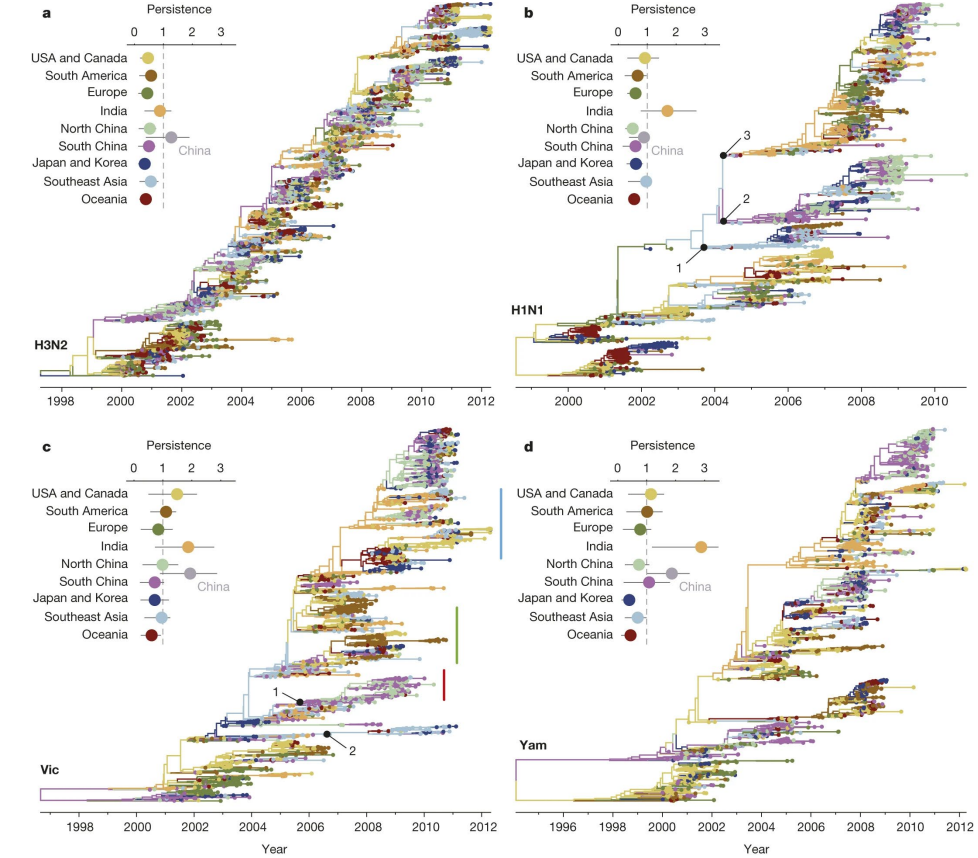
Dhanasekaran et al. *Nature Communications* 2022

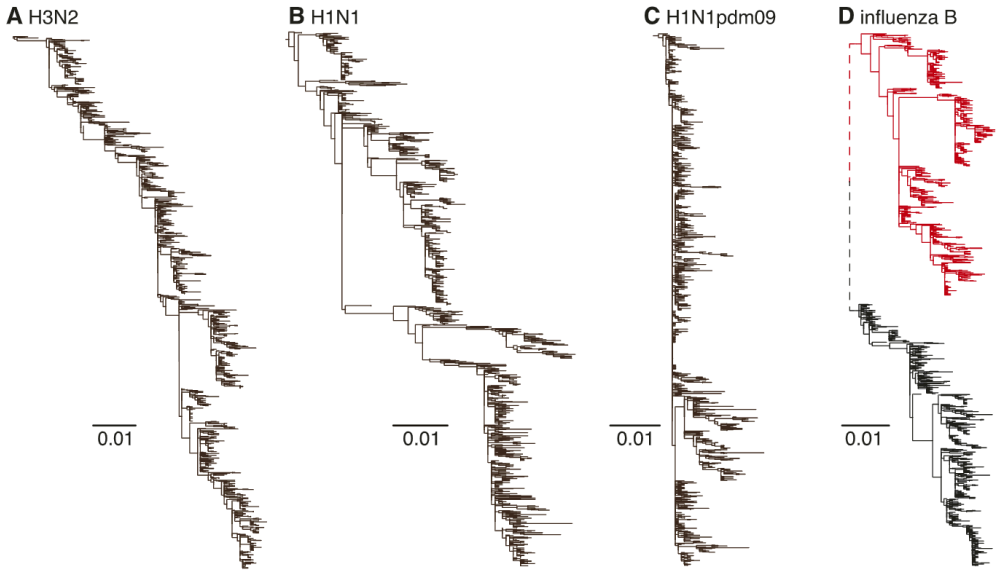
Background – Seasonal influenza virus circulation

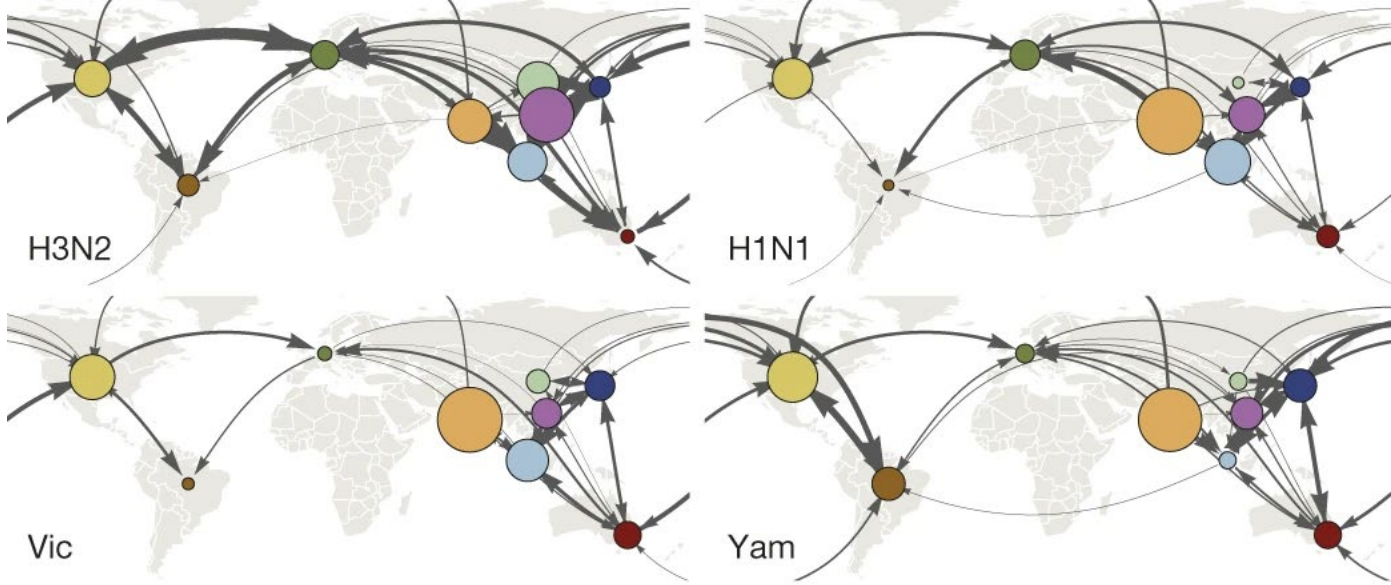
- *Seasonality* in temperate zones is maintained through continuous reintroduction from tropical regions and opposing hemispheres.
- Tropical and subtropical regions can sustain transmission lineages for a longer duration than temperate regions, providing more opportunities for antigenic drift.
- Population density and regional interconnectedness play an important role in maintaining viral metapopulations.
- Due to rapid migration, natural selection acts on a global scale.



Petrova, V., Russell, C. *Nat Rev Microbiol* **16,** 47–60 (2018).



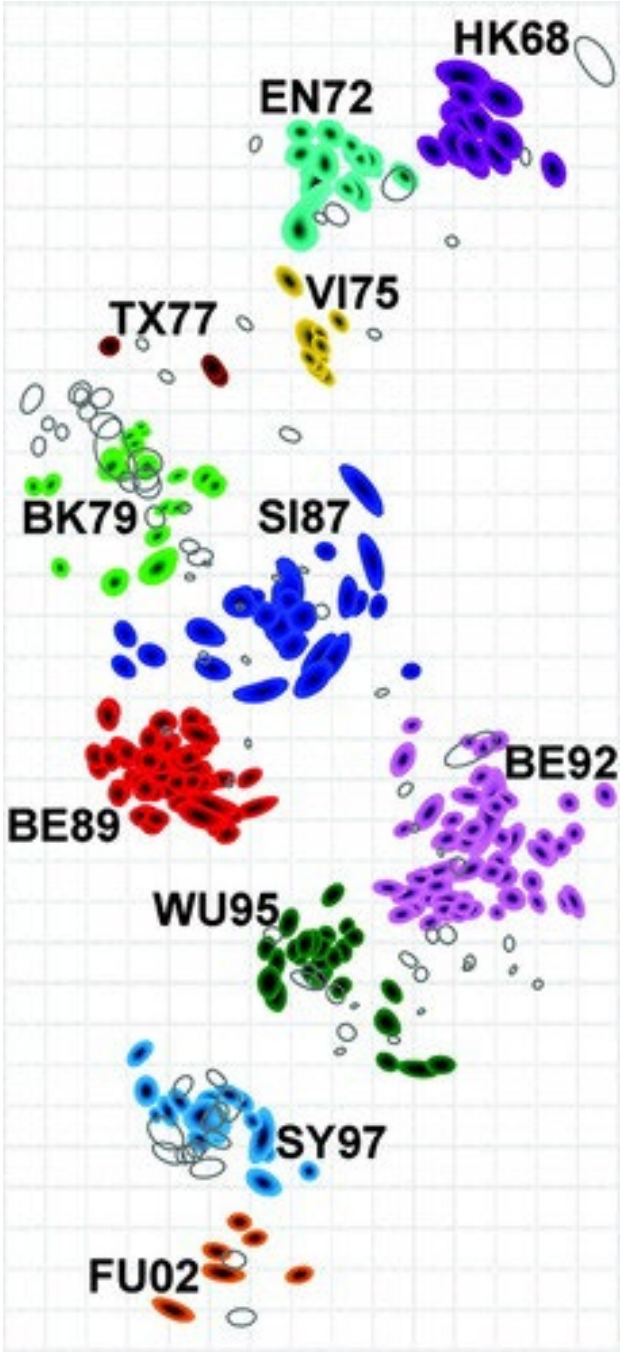




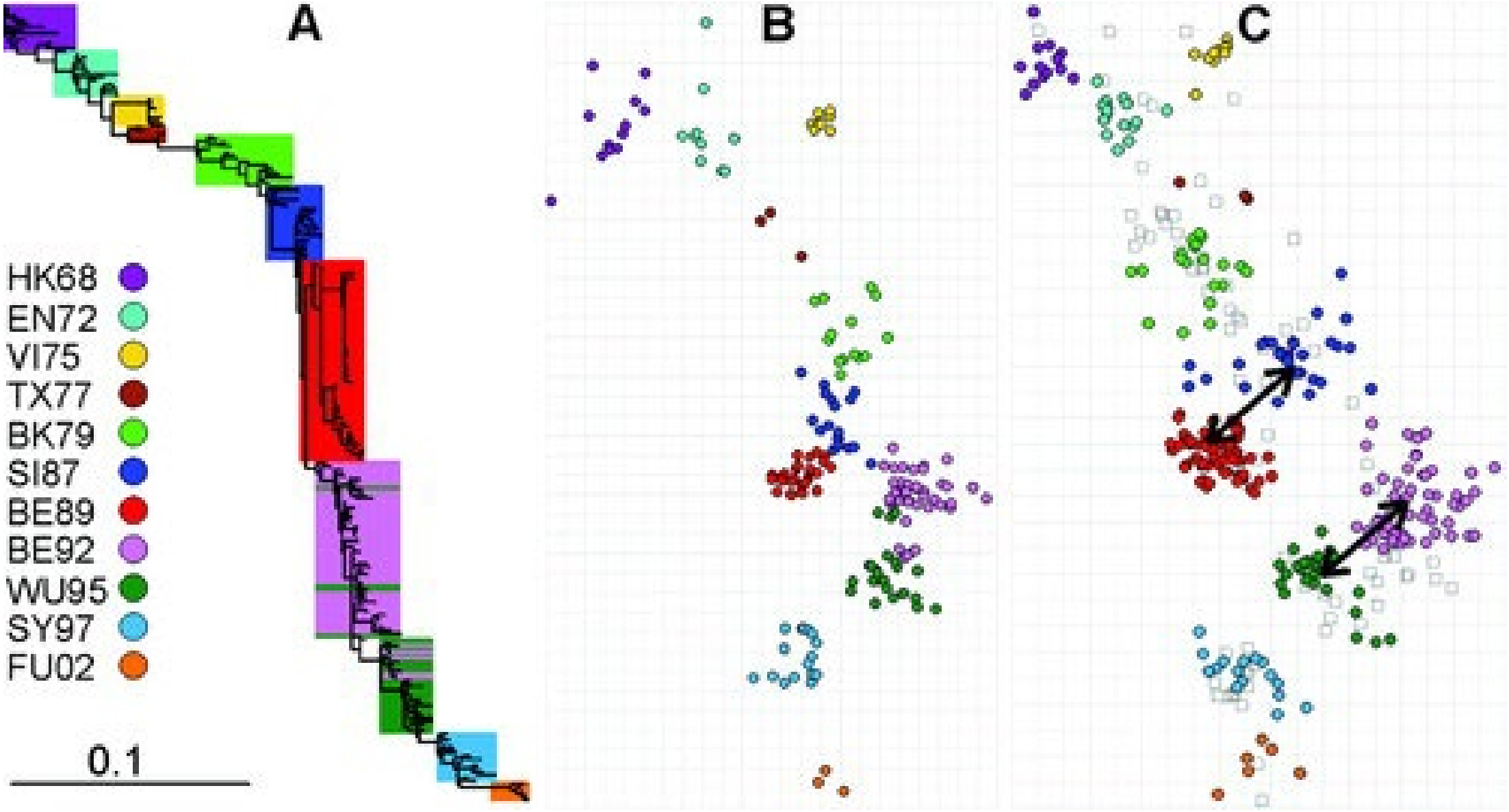
Bedford et al. 2015 *Nature*

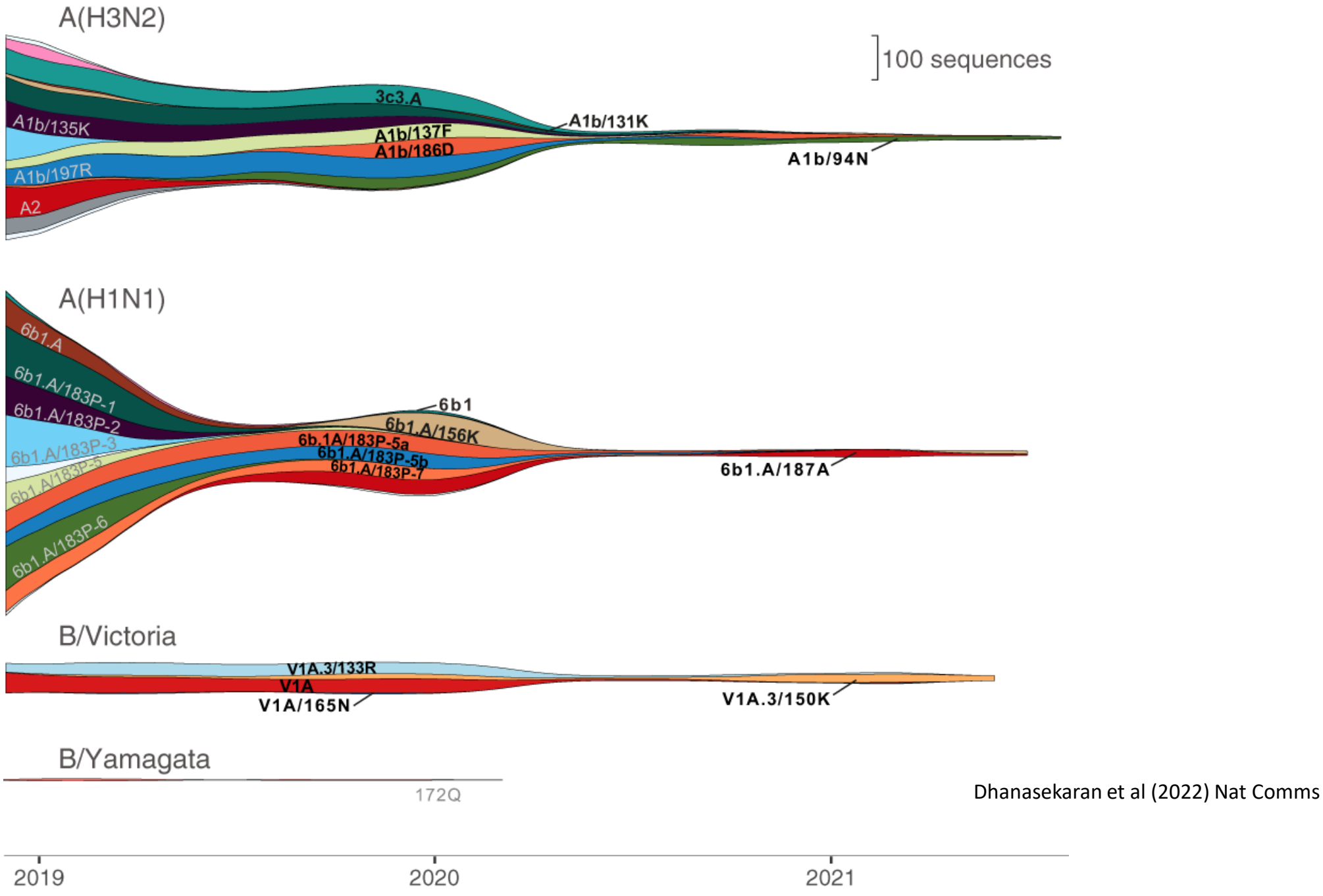
- Evade pre-existing immunity and gain competitive advantage via surface protein mutations which yield new antigenic **variants**

Dhanasekaran et al. 2015 *eLife*

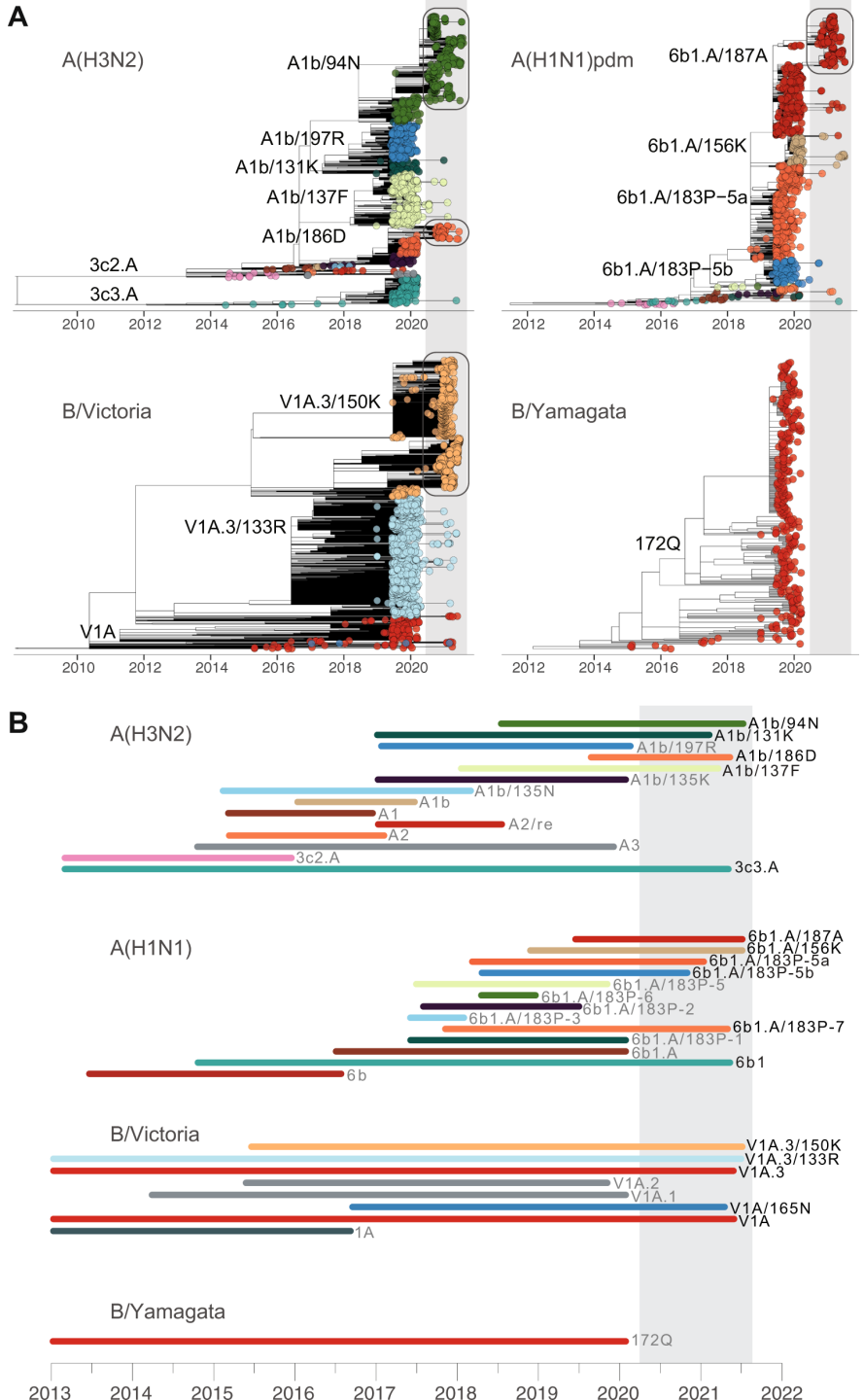


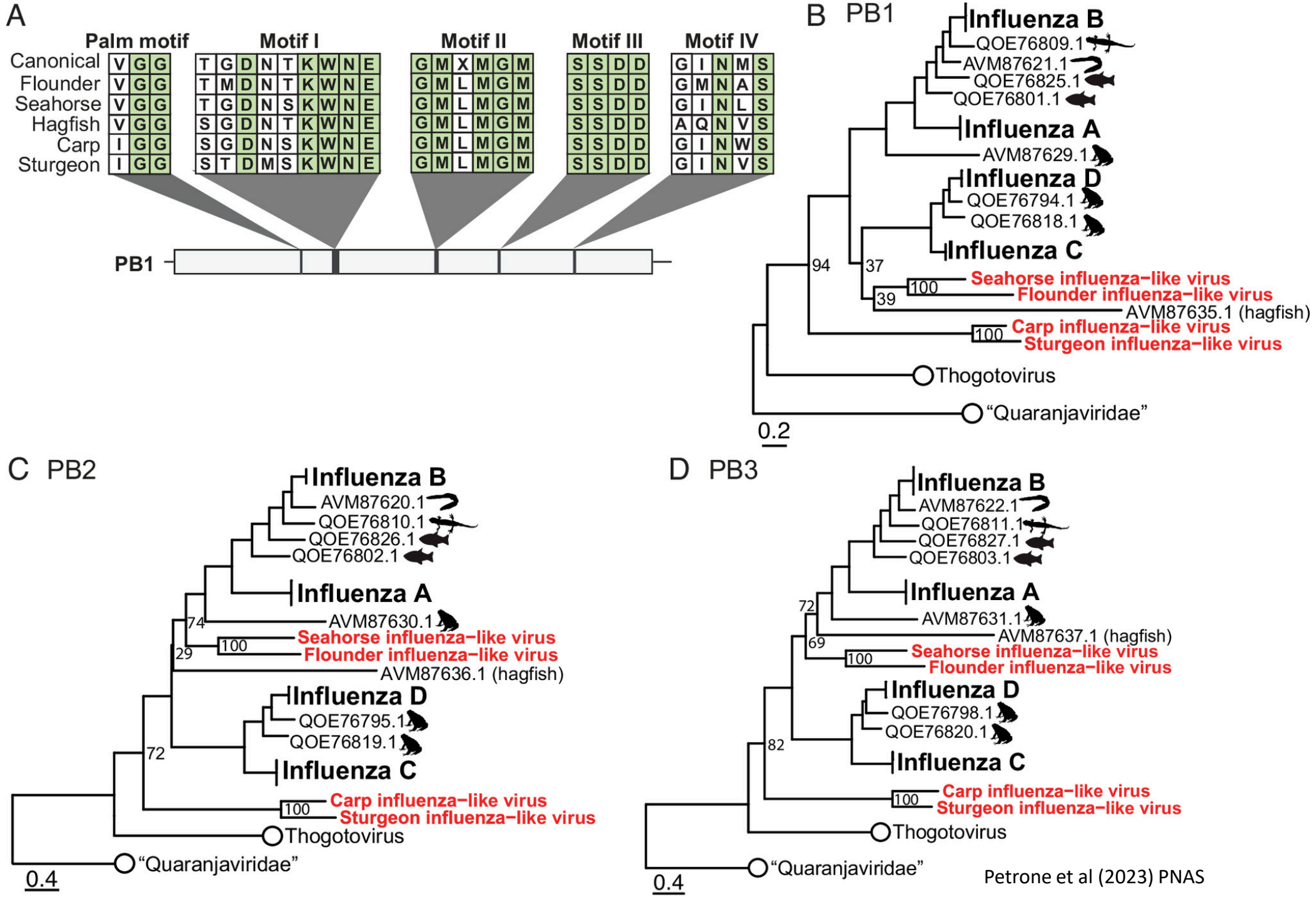
Smith et al. 2004 Science


A
B
C
HK68
EN72
VI75
TX77
BK79
SI87
BE89
BE92
WU95
SY97
FU02
0.1



Dhanasekaran et al (2022) Nat Comms

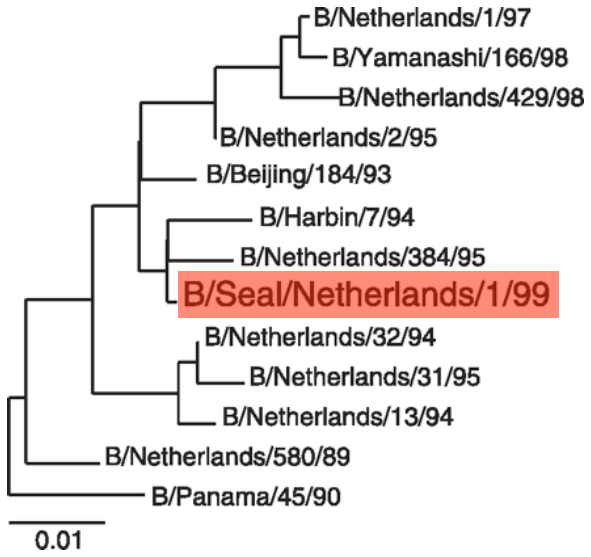

A
A(H3N2)
A1b/94N
A1b/197R
A1b/131K
A1b/137F
A1b/186D
3c2.A
3c3.A
2010
2012
2014
2016
2018
2020
A(H1N1)pdm
6b1.A/187A
6b1.A/156K
6b1.A/183P−5a
6b1.A/183P−5b
2012
2014
2016
2018
2020
B/Victoria
V1A.3/150K
V1A.3/133R
V1A
2010
2012
2014
2016
2018
2020
B/Yamagata
172Q
2012
2014
2016
2018
2020
B
A(H3N2)
A1b/94N
A1b/131K
A1b/197R
A1b/186D
A1b/137F
A1b/135K
A1b/135N
A1b
A1
A2/re
A2
A3
3c2.A
3c3.A
A(H1N1)
6b1.A/187A
6b1.A/156K
6b1.A/183P-5a
6b1.A/183P-5b
6b1.A/183P-5
6b1.A/183P-6
6b1.A/183P-2
6b1.A/183P-3
6b1.A/183P-7
6b1.A/183P-1
6b1.A
6b1
6b
B/Victoria
V1A.3/150K
V1A.3/133R
V1A.3
V1A.2
V1A.1
V1A/165N
V1A
1A
B/Yamagata
172Q
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022



Petrone et al (2023) PNAS

Influenza B virus in seals

Osterhaus et al. Science 2000





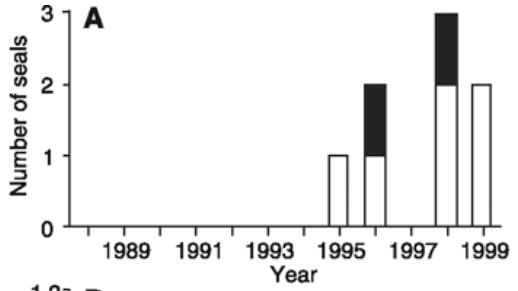


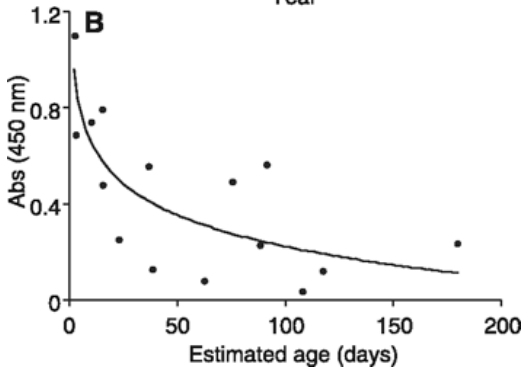
- most closely related to viruses that circulated 4 years before in humans

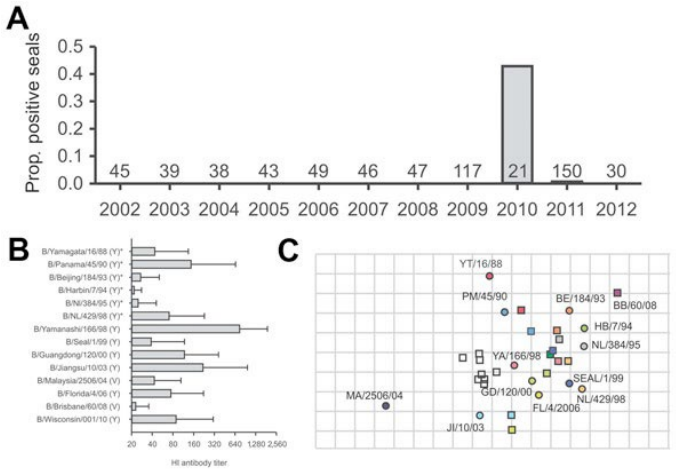
- 2% were seropositive since 1995

- prolonged shedding may explain little genetic drift

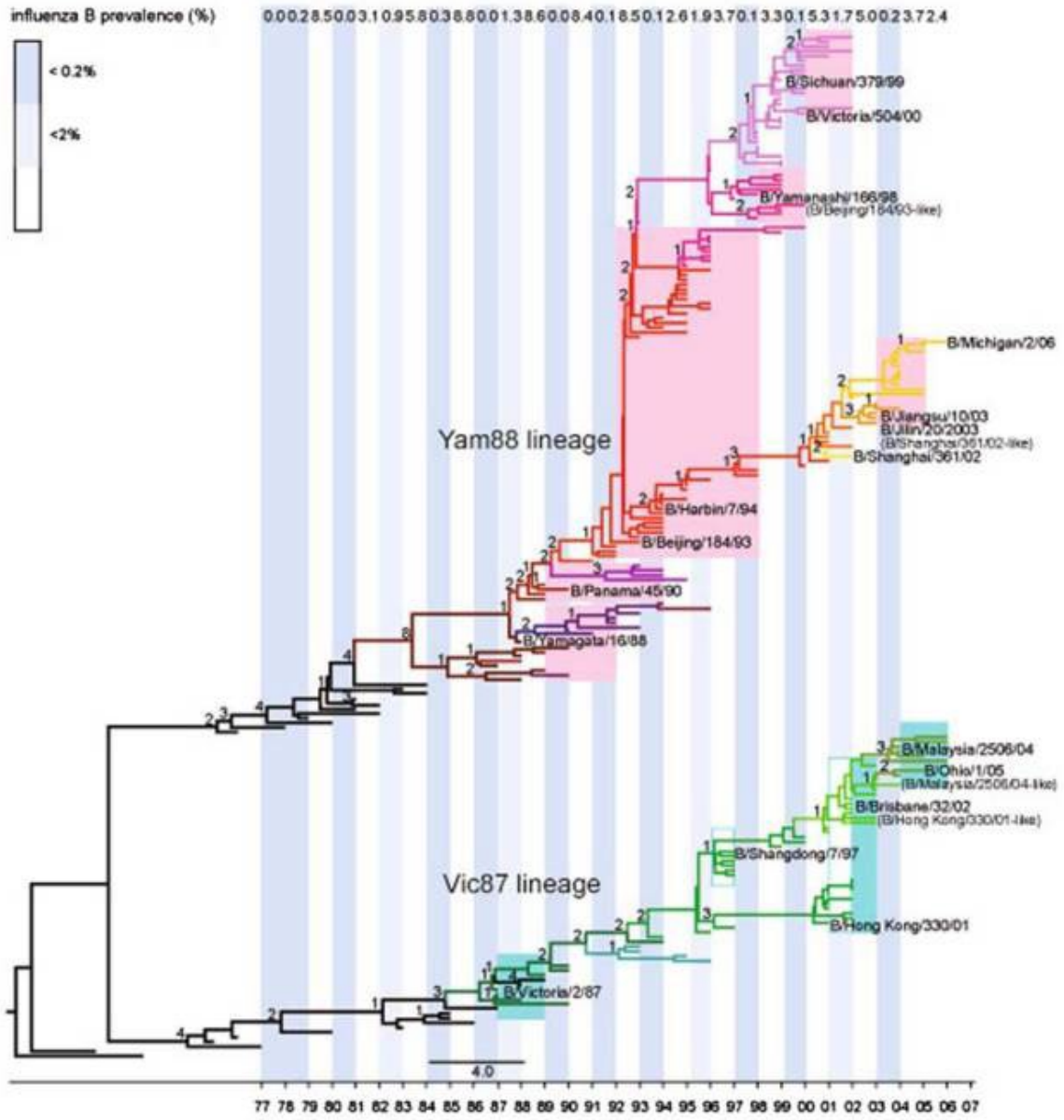
- suggesting they can act as reservoirs (short-term) for re-emergence in humans







Bodewas et al (2013) EID



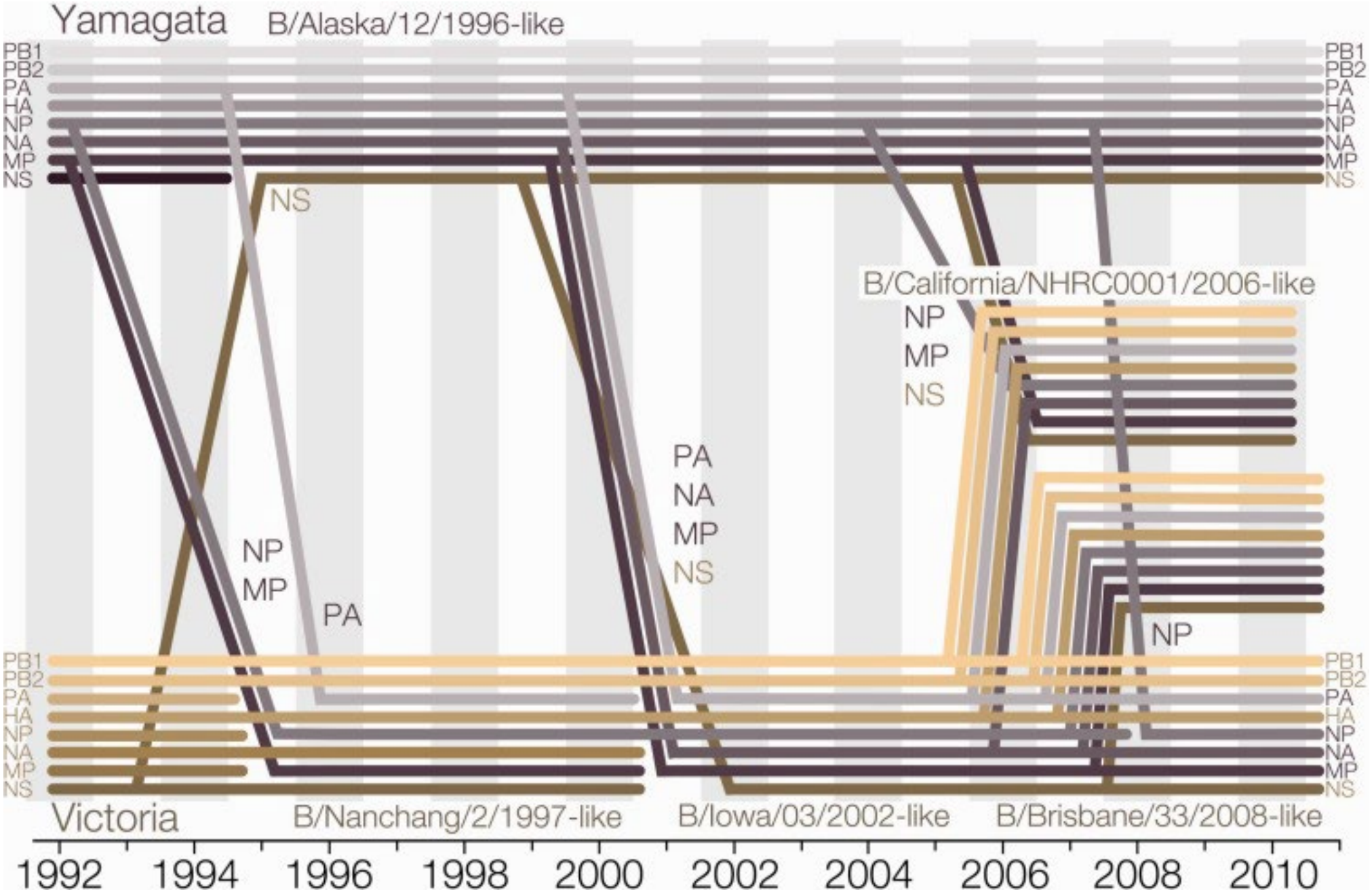
Evolution of flu B Circulation of two lineages (2001–2020)

- Diversified into two lineages prior to 1980s

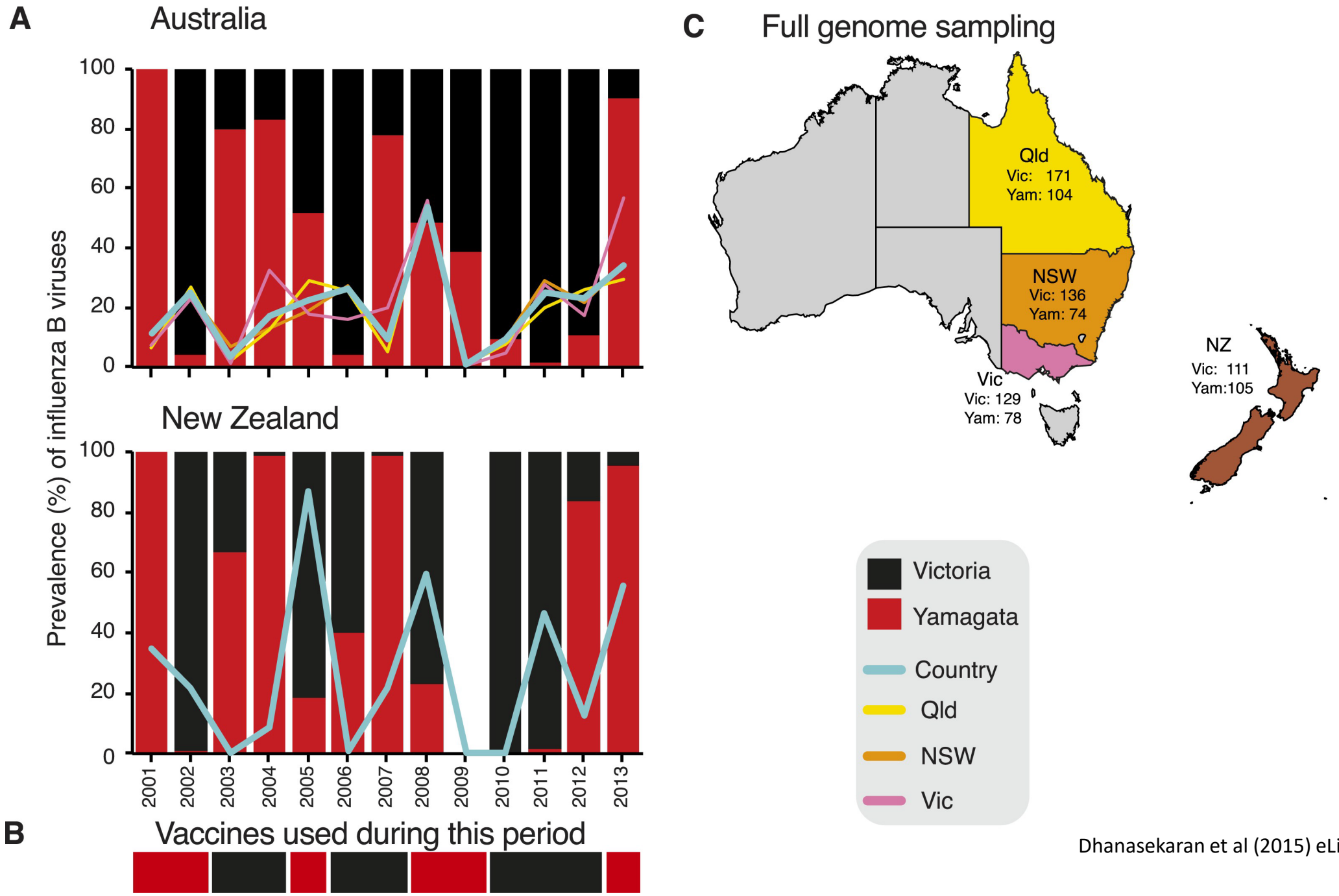
- Consistent in all 8 genes

- suggesting a major genomic event during their evolution

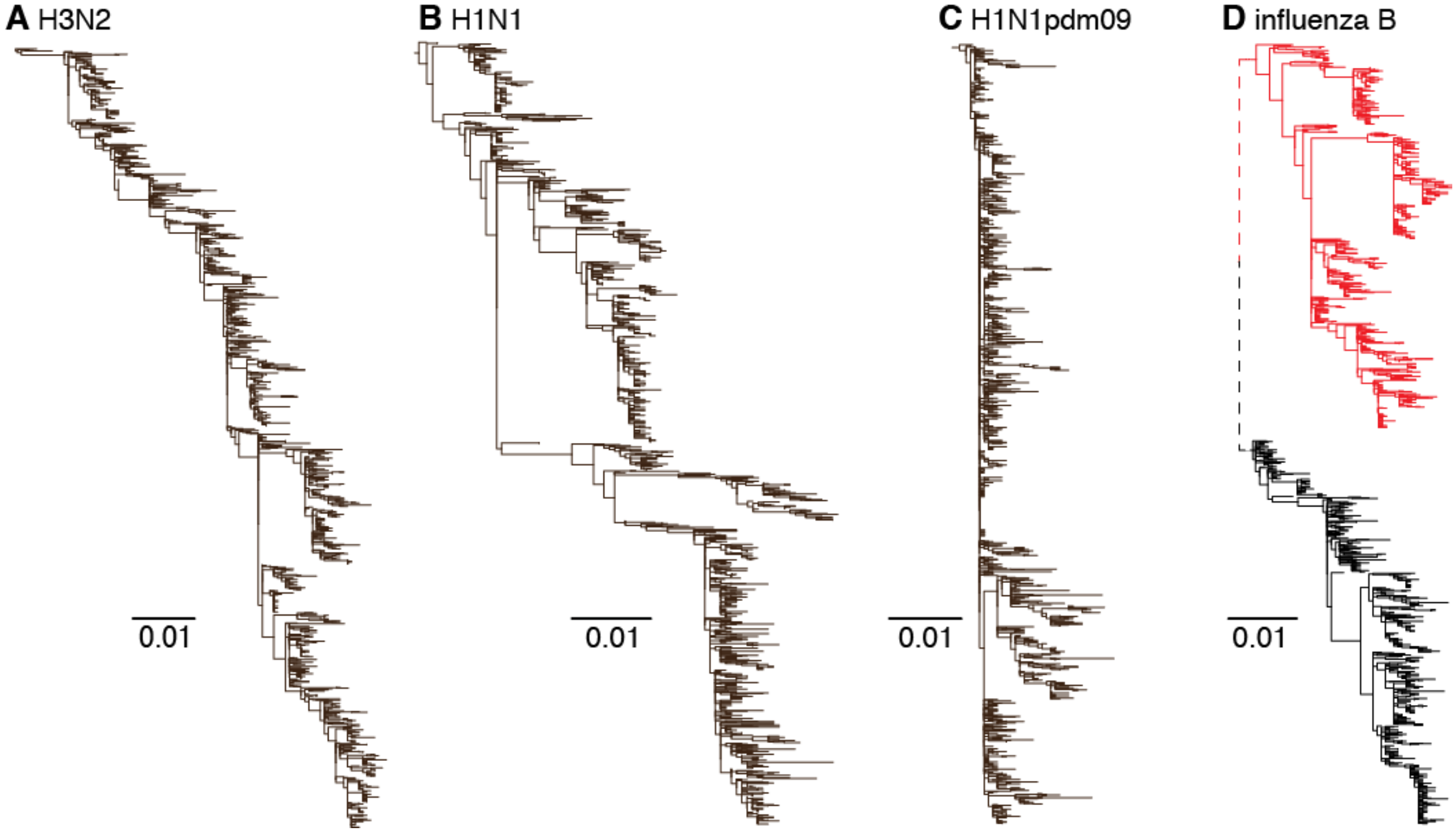
Chen, Holmes (2008) J Mol Evol



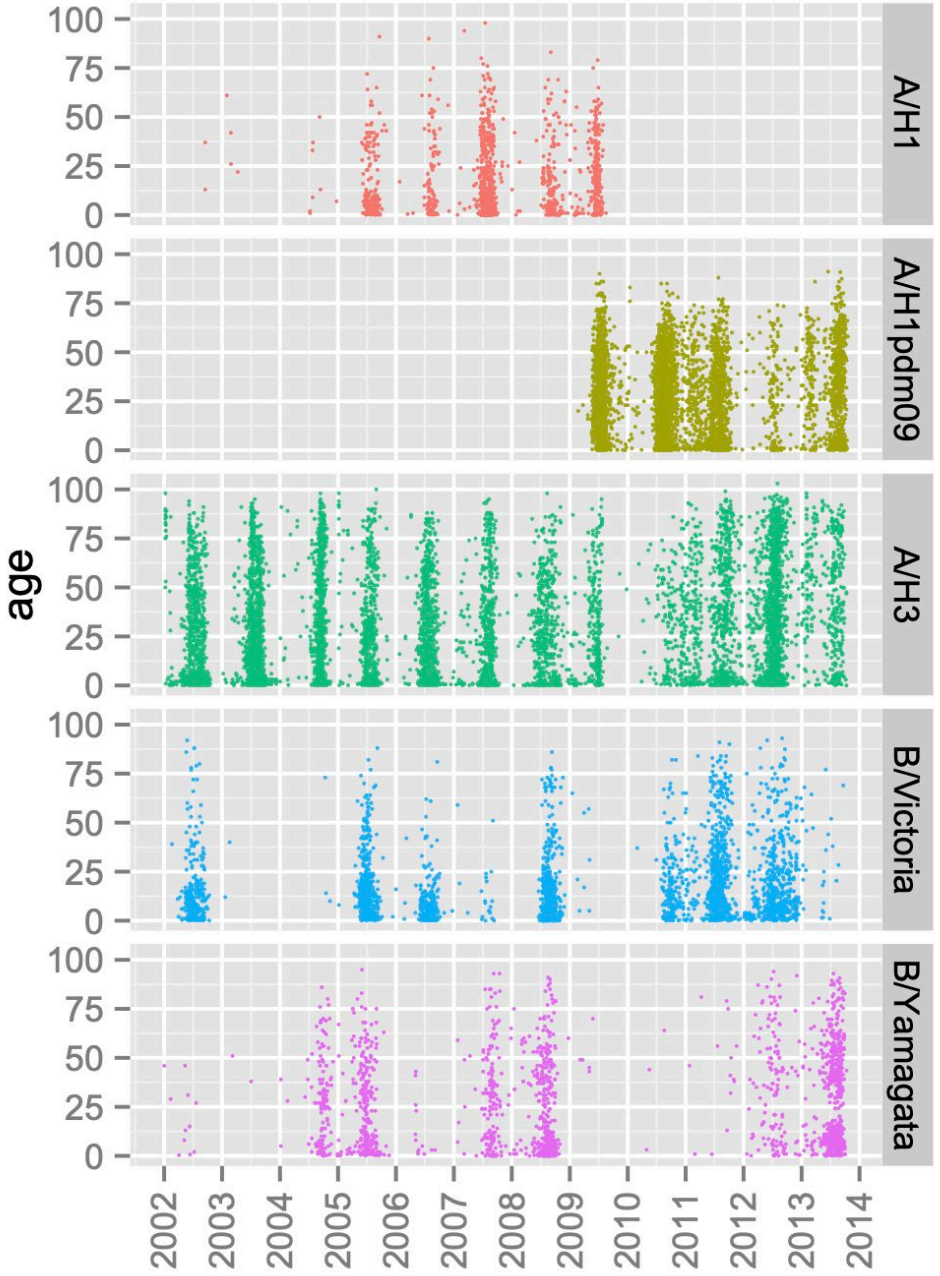
Dudas et al (2015) Mol Biol Evol



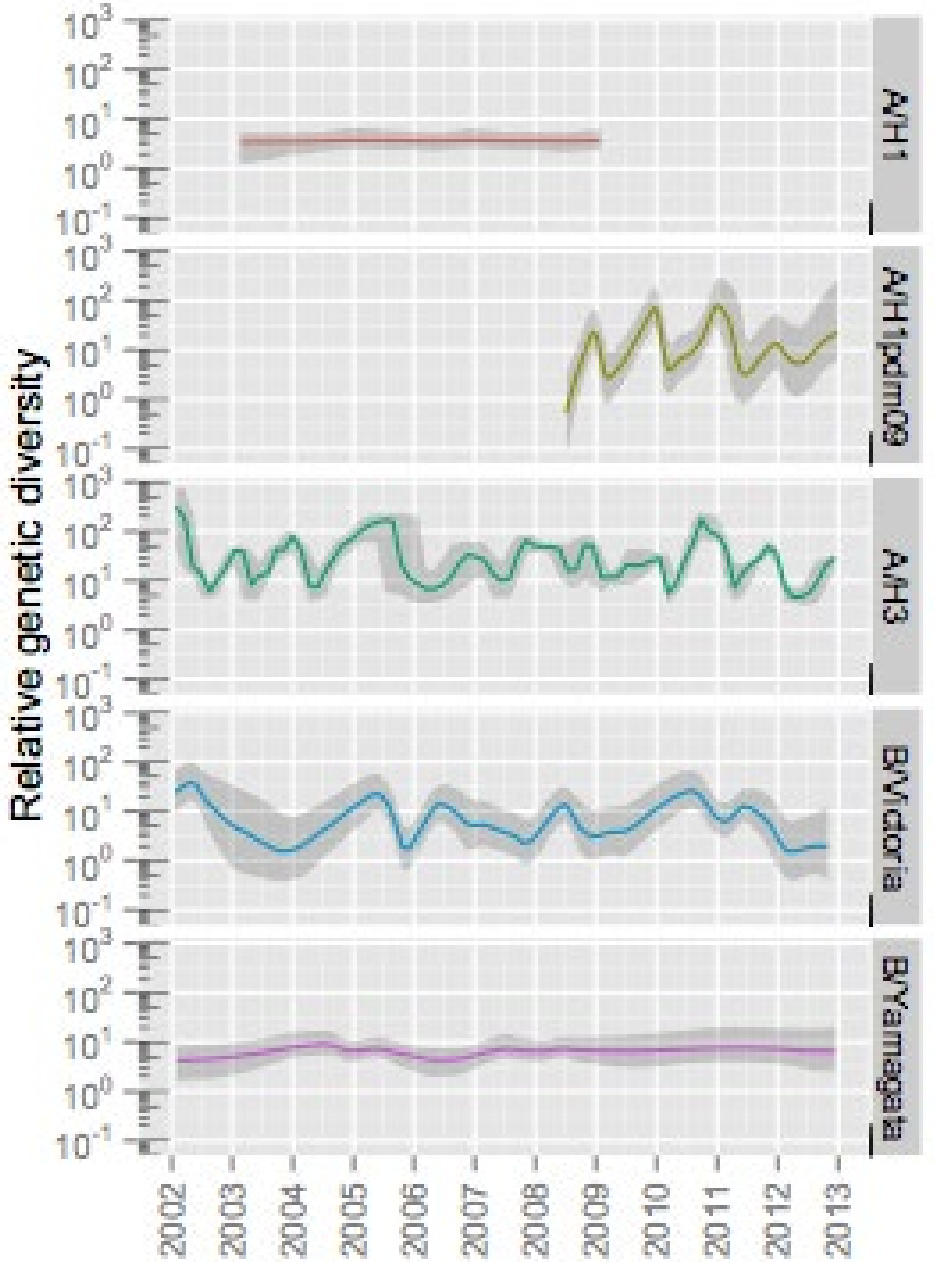
Dhanasekaran et al (2015) eLife

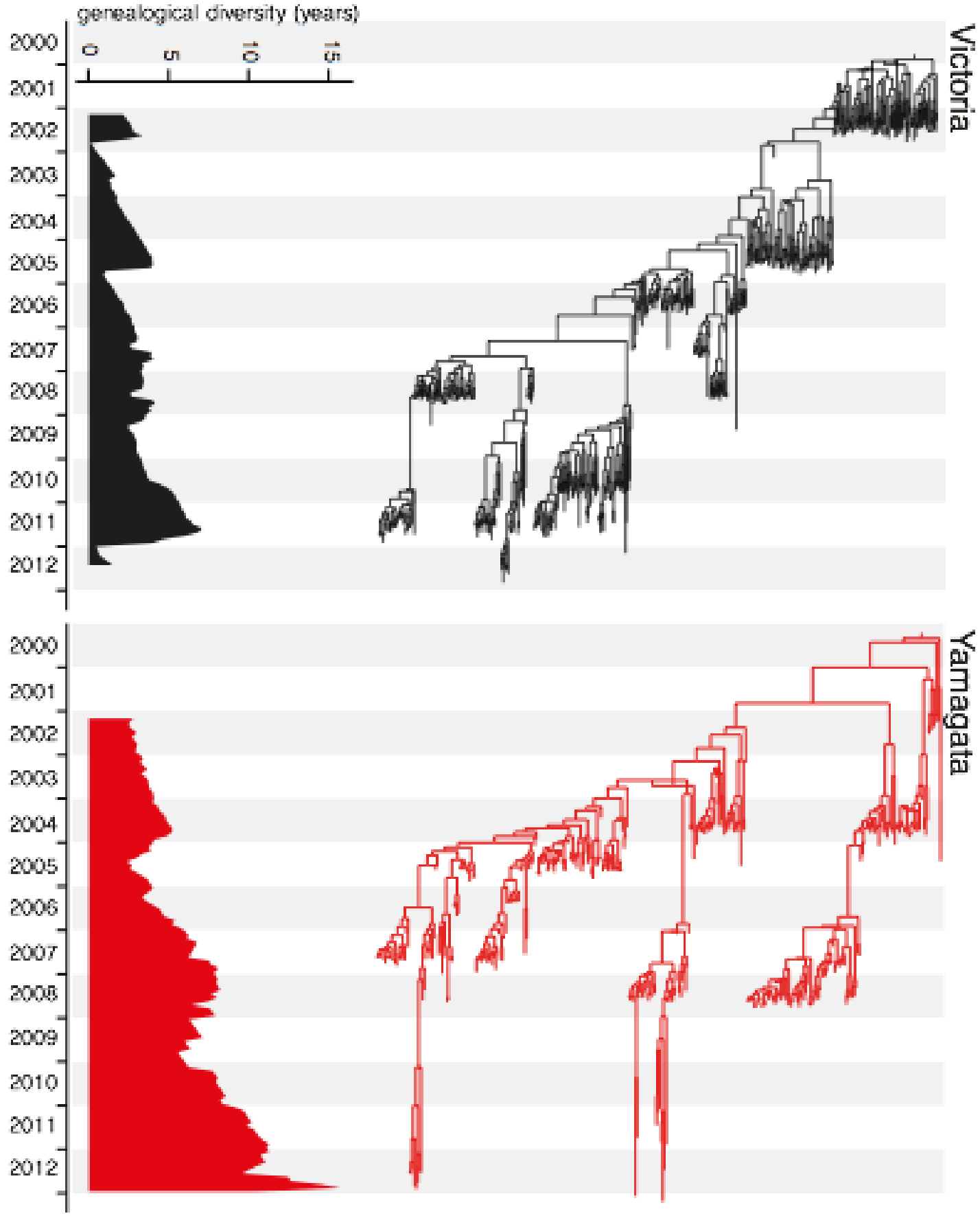

A H3N2
0.01
B H1N1
0.01
C H1N1pdm09
0.01
D influenza B
0.01

Cases

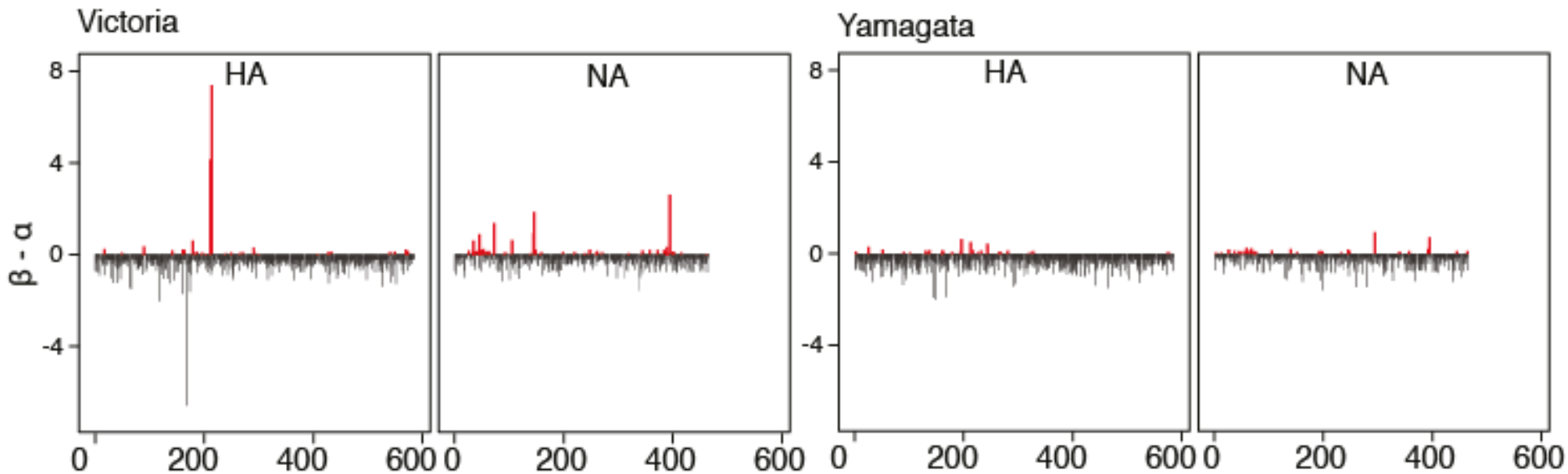


Relative genetic diversity

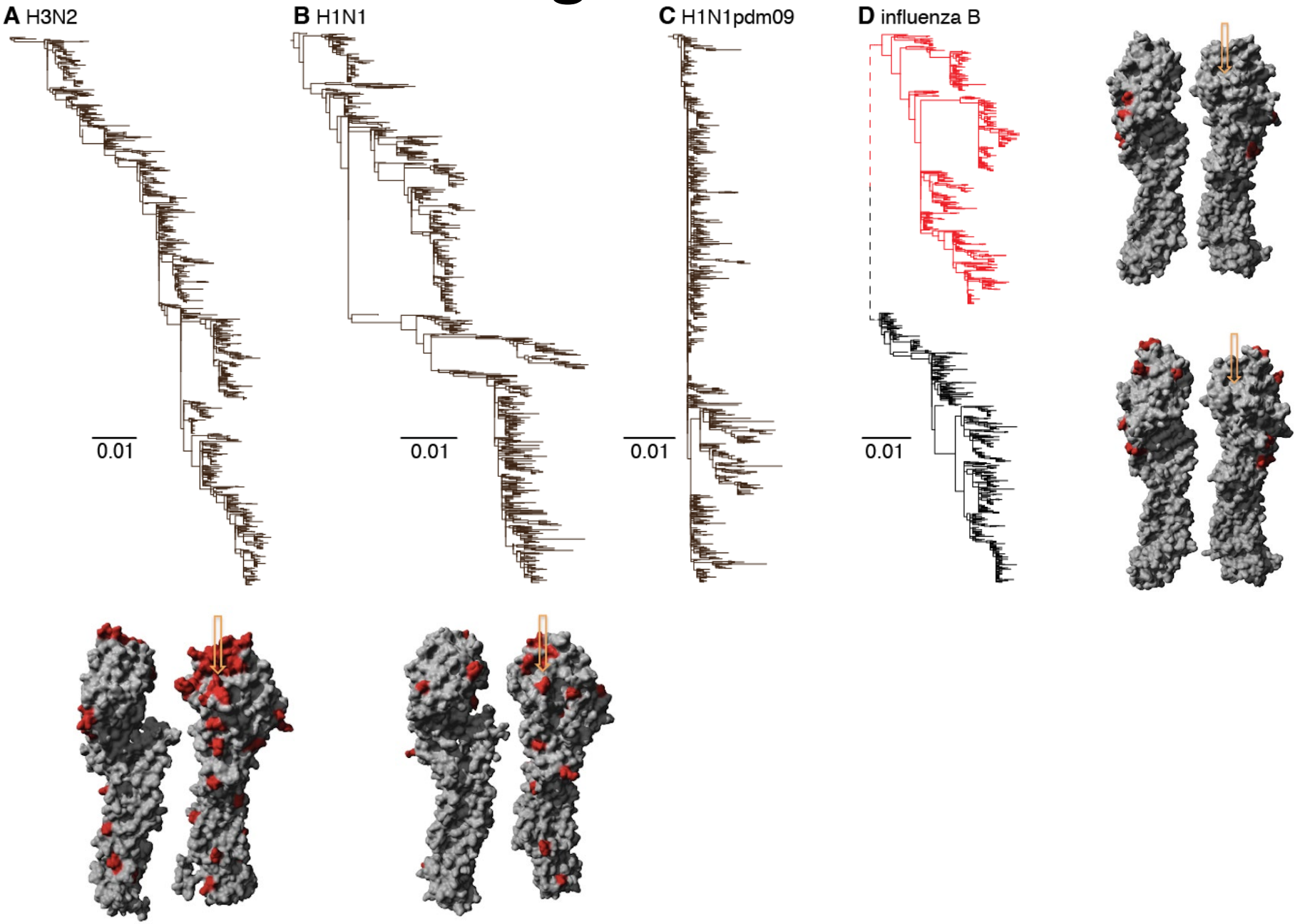



genealogical diversity (years)
0
5
10
15
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
Victoria
Yamagata

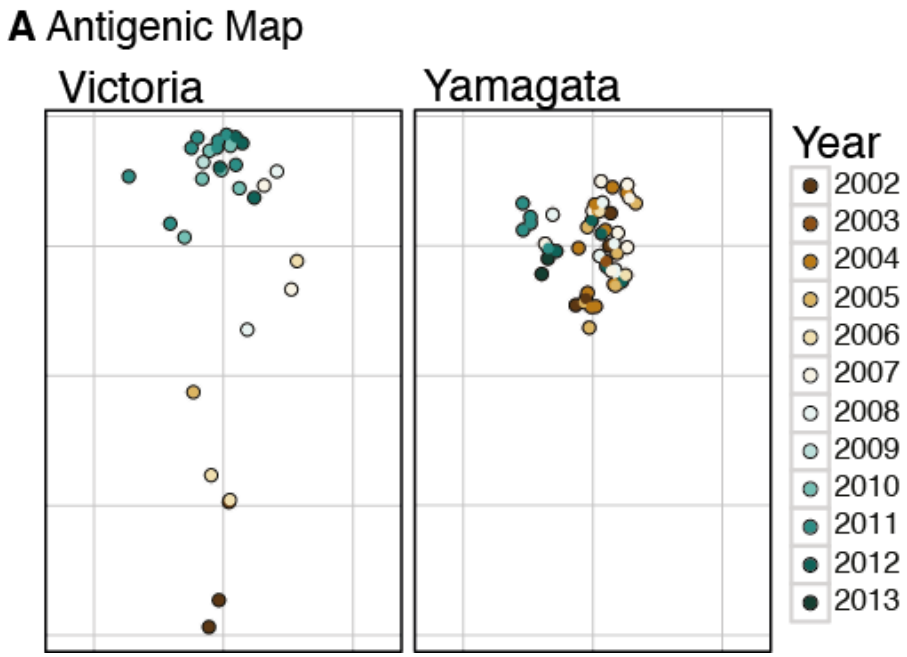
Selection

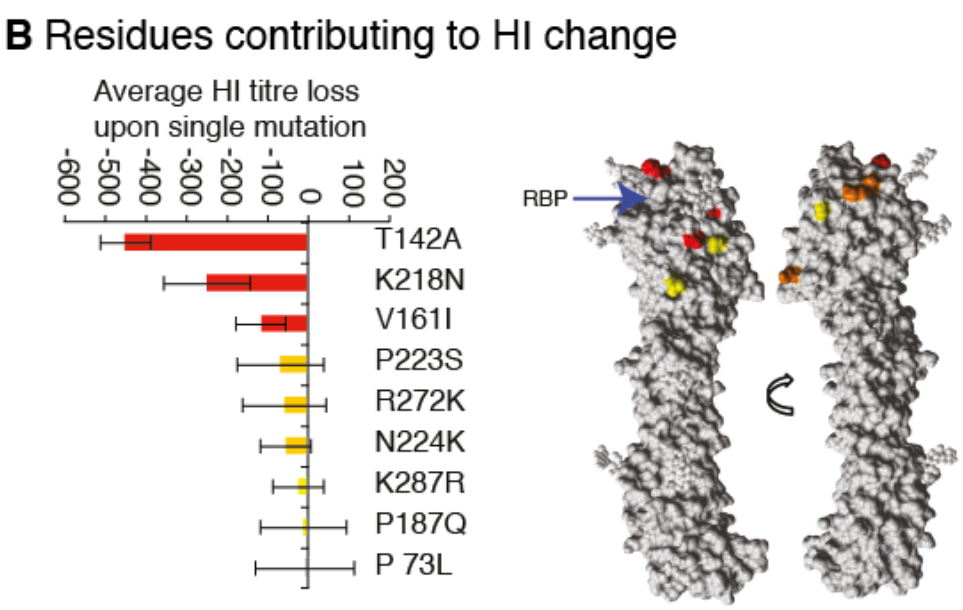


Antigenic drift

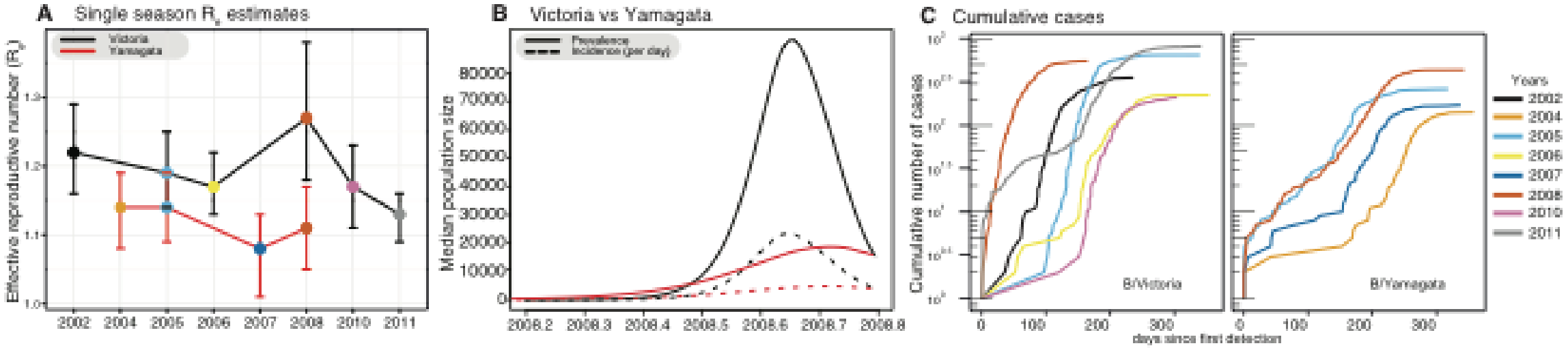


Hemagglutinin inhibition

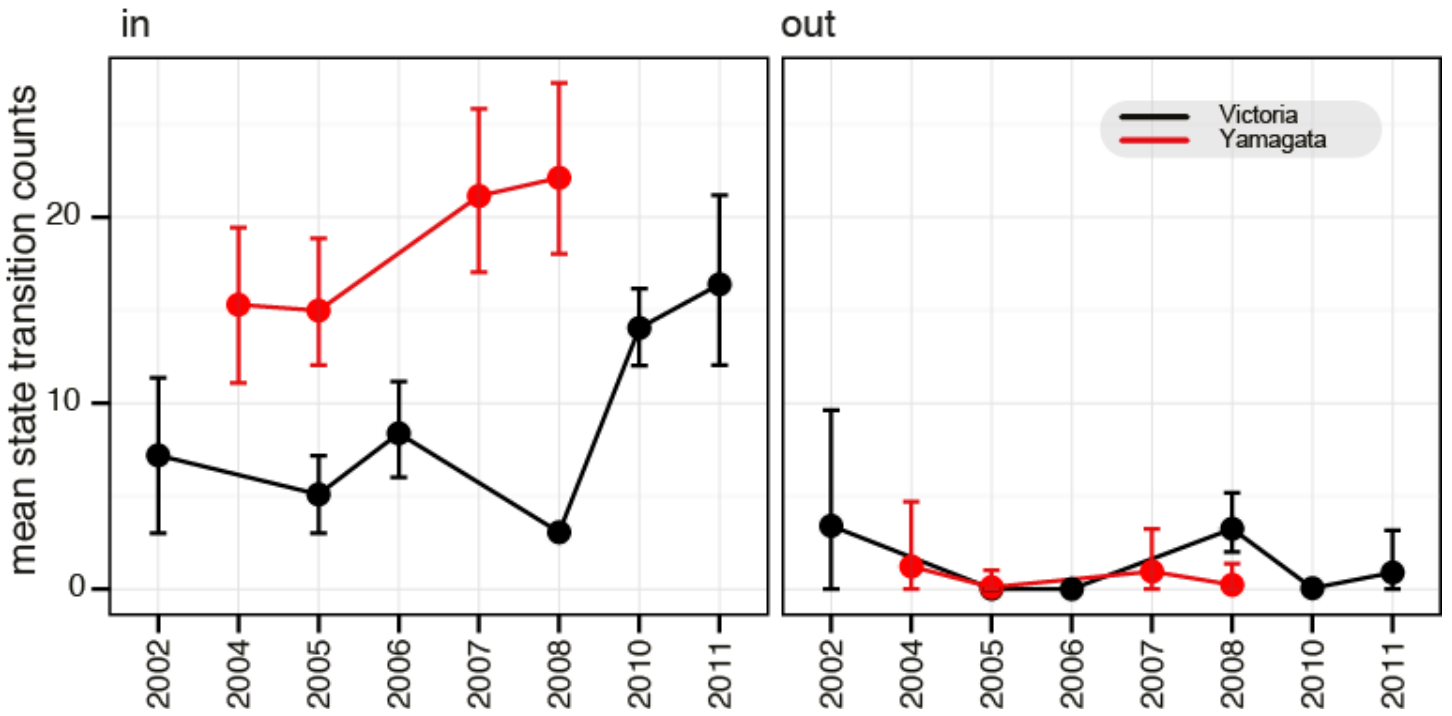




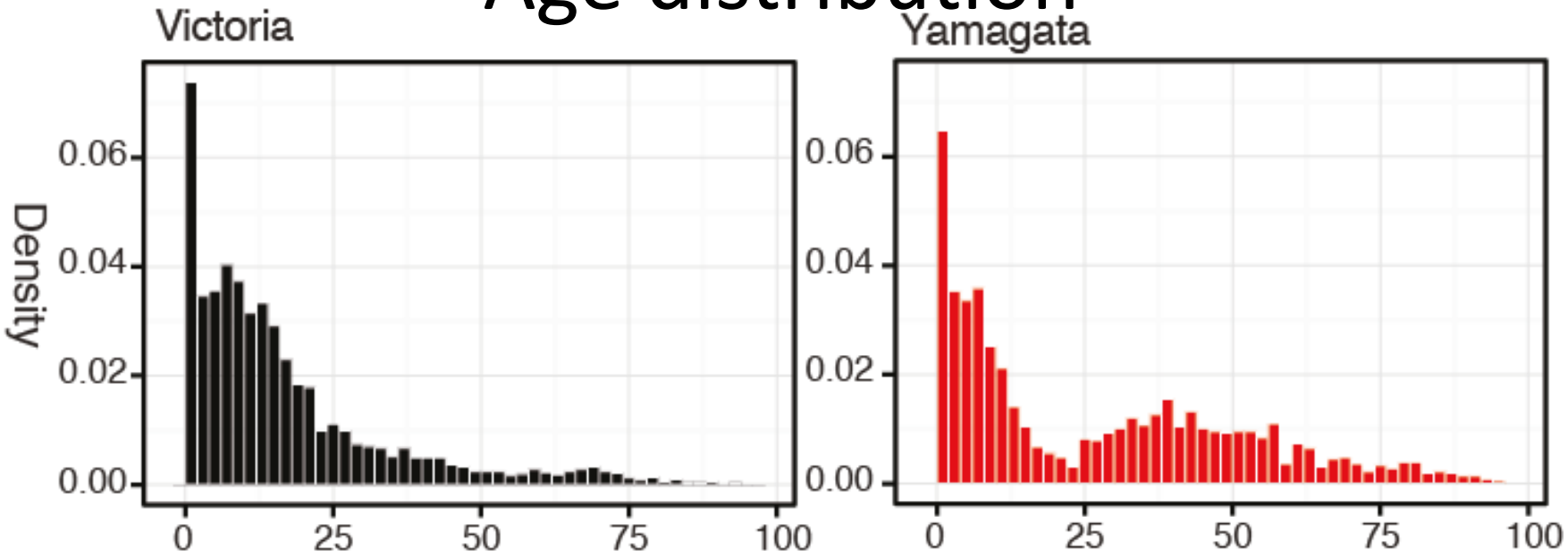
Epidemic differences

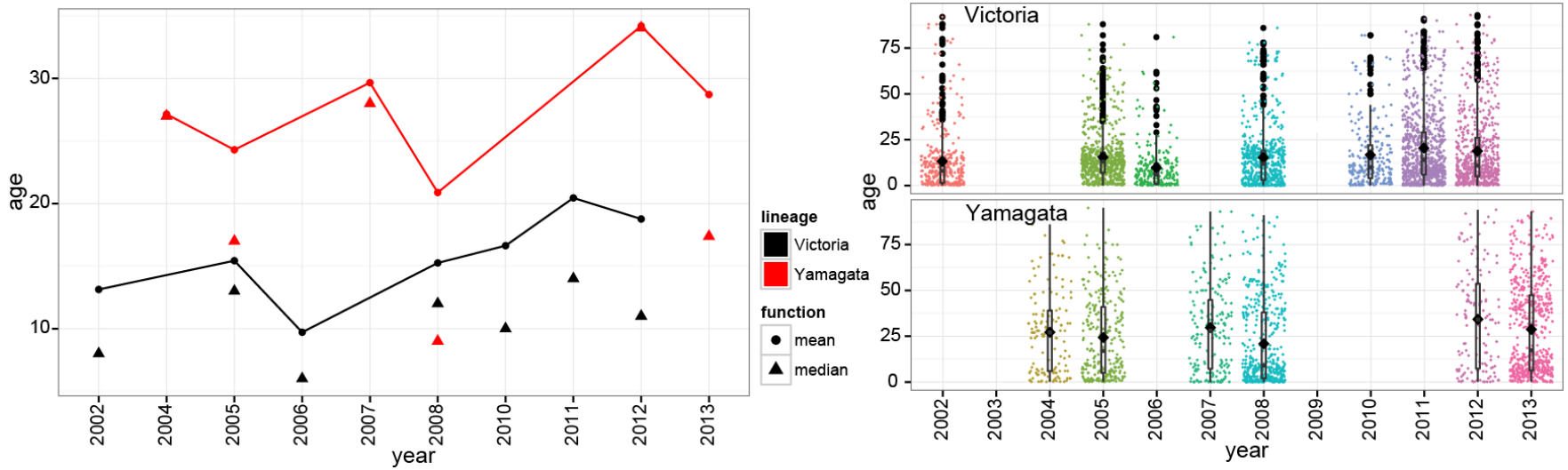


Migration


in
out
mean state transition counts
0
10
20
2002
2004
2005
2006
2007
2008
2010
2011
Victoria
Yamagata

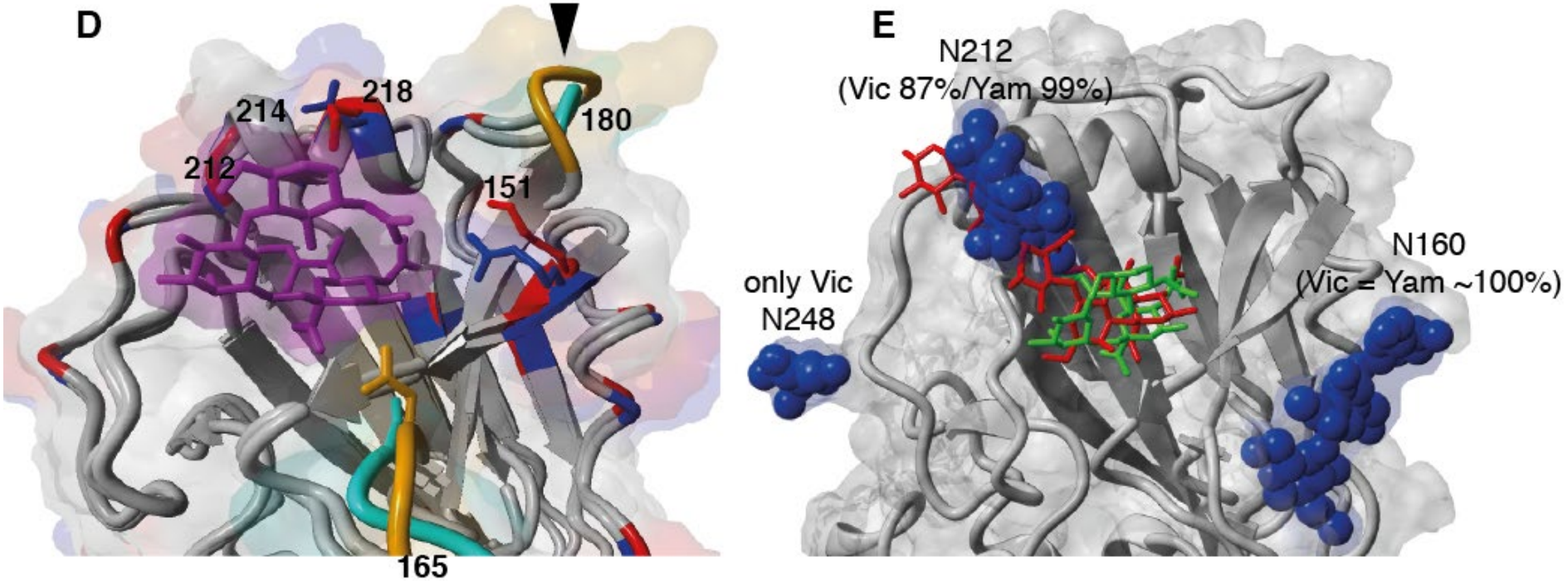
Age distribution

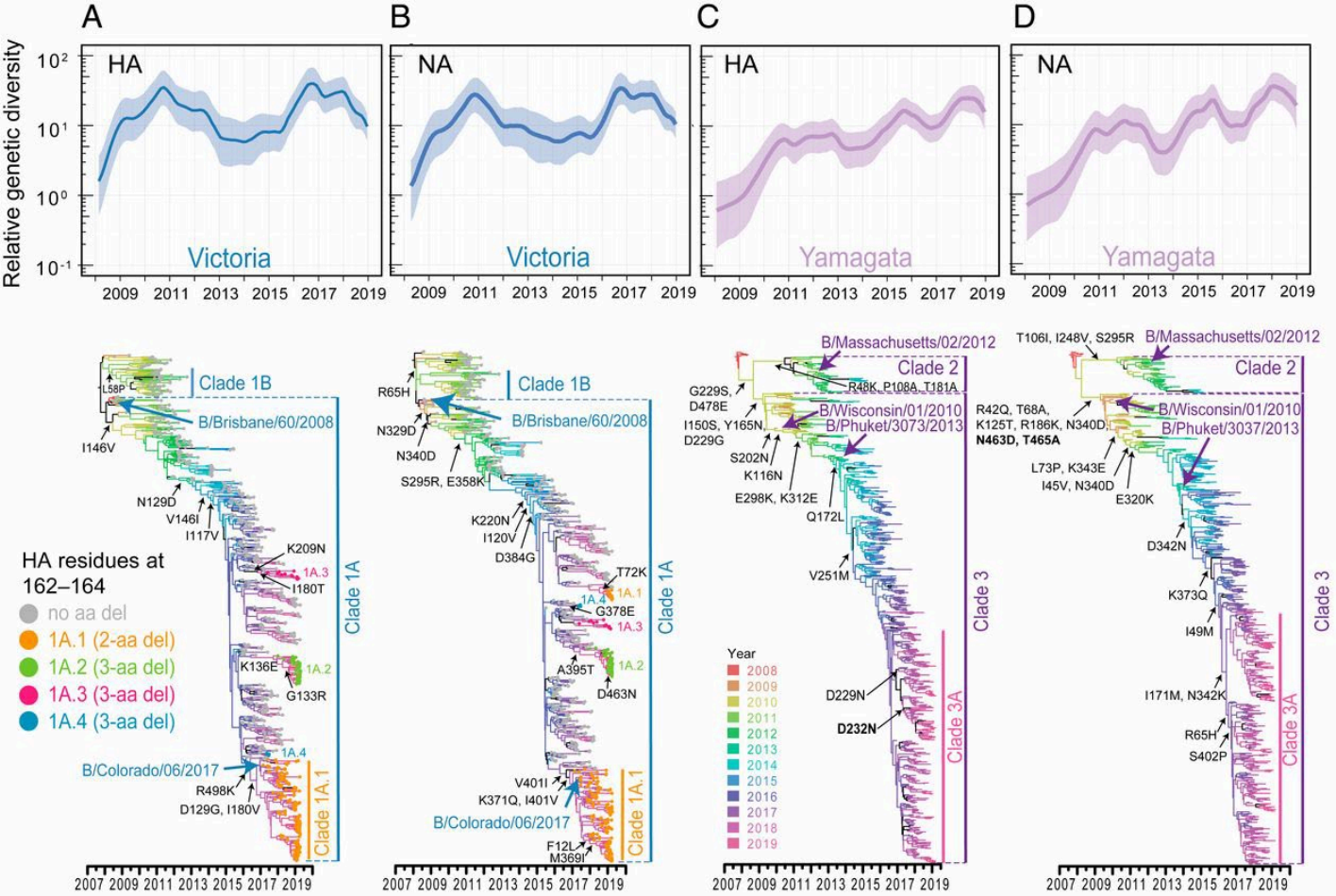


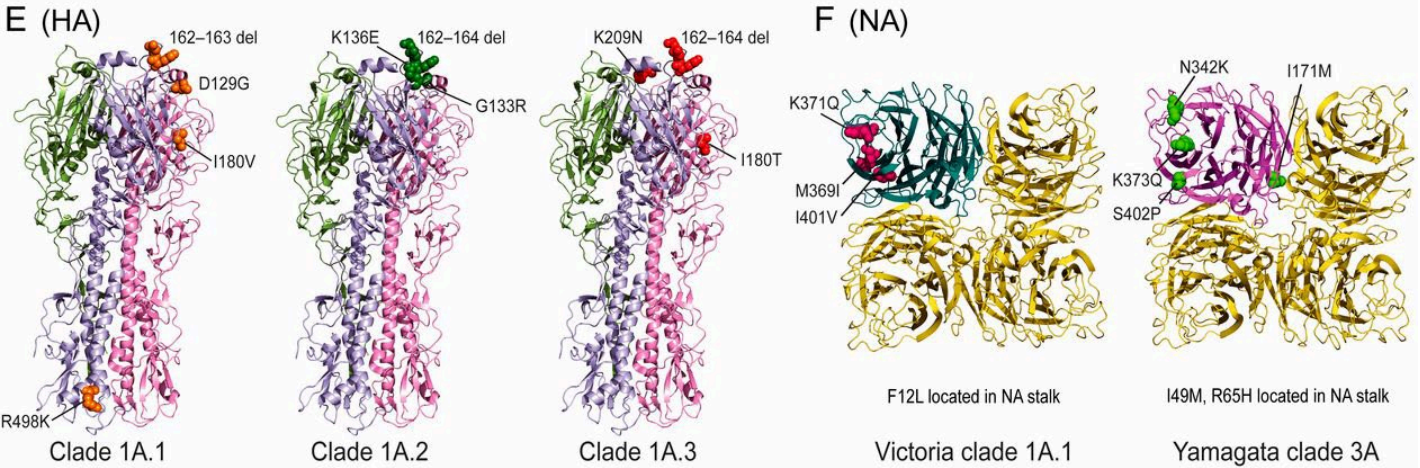


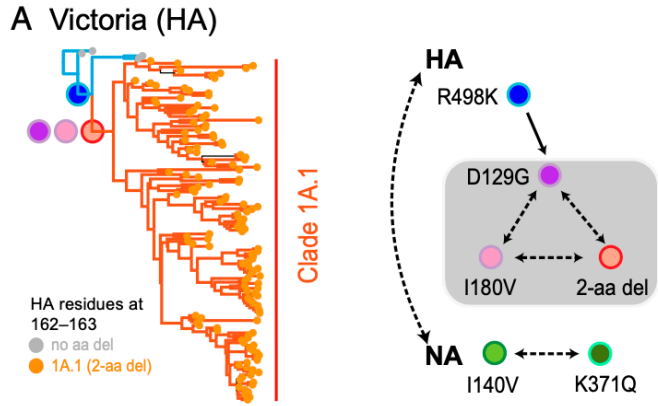
Structural differences of the HA

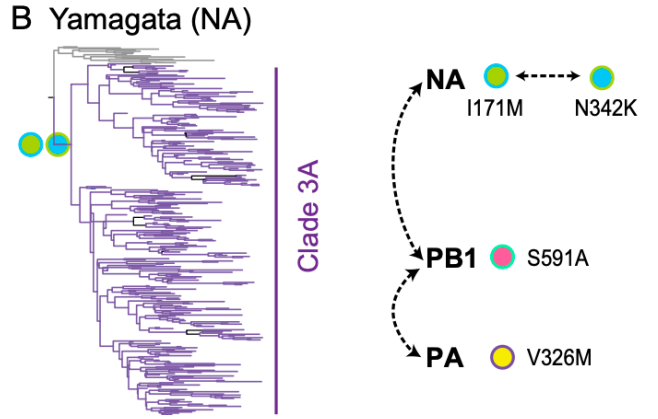
α-2,3 or α-2,6 - linked sialic acid receptors

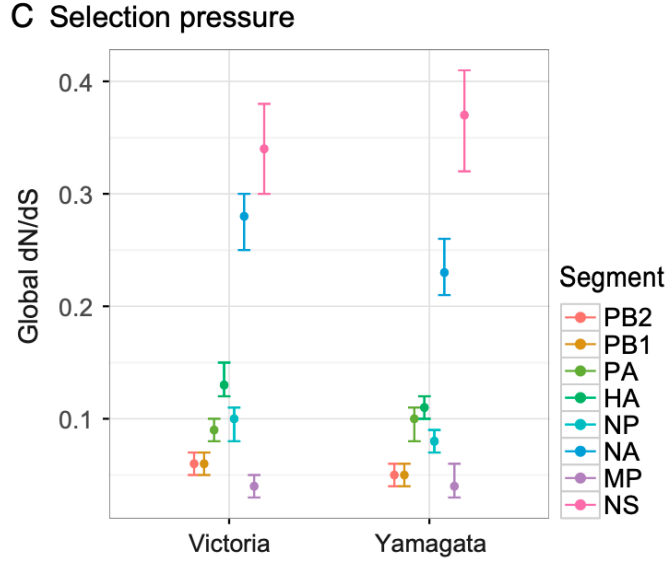












Virk et al (2020) PNAS