

Introduction to infectious disease phylodynamics

Oliver Pybus

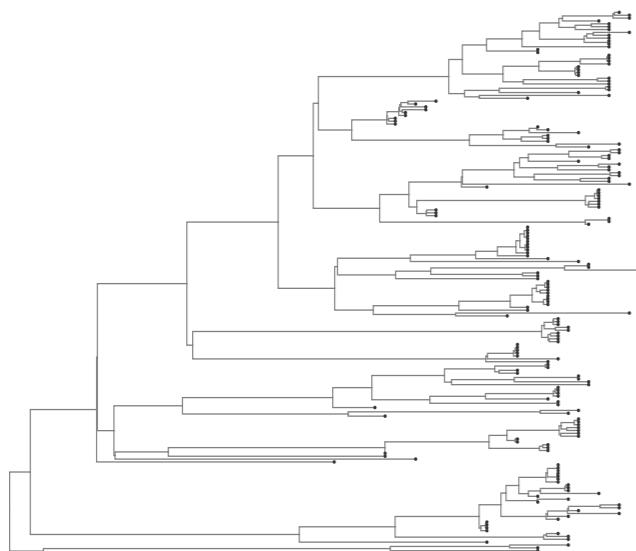
What is pathogen phylodynamics?

“ Rapidly evolving pathogens are unique in that their ecological and evolutionary dynamics occur on the same timescale and can therefore potentially interact. ”

What is phylodynamics?

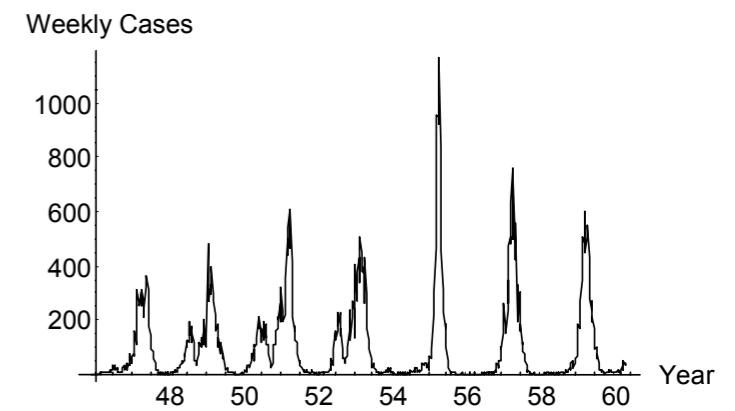
GENETIC DIVERSITY

(phylogenetics & population genetics)



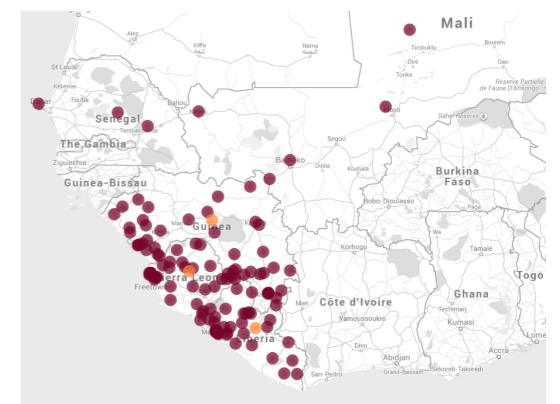
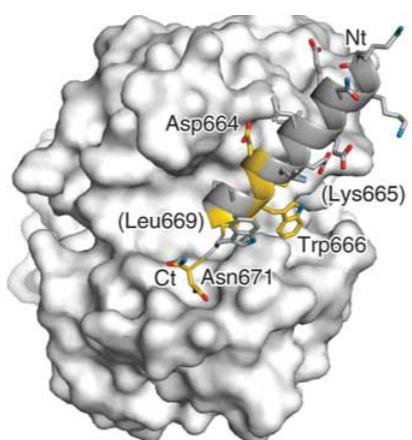
EPIDEMIC DYNAMICS

(mathematical & spatial epidemiology)

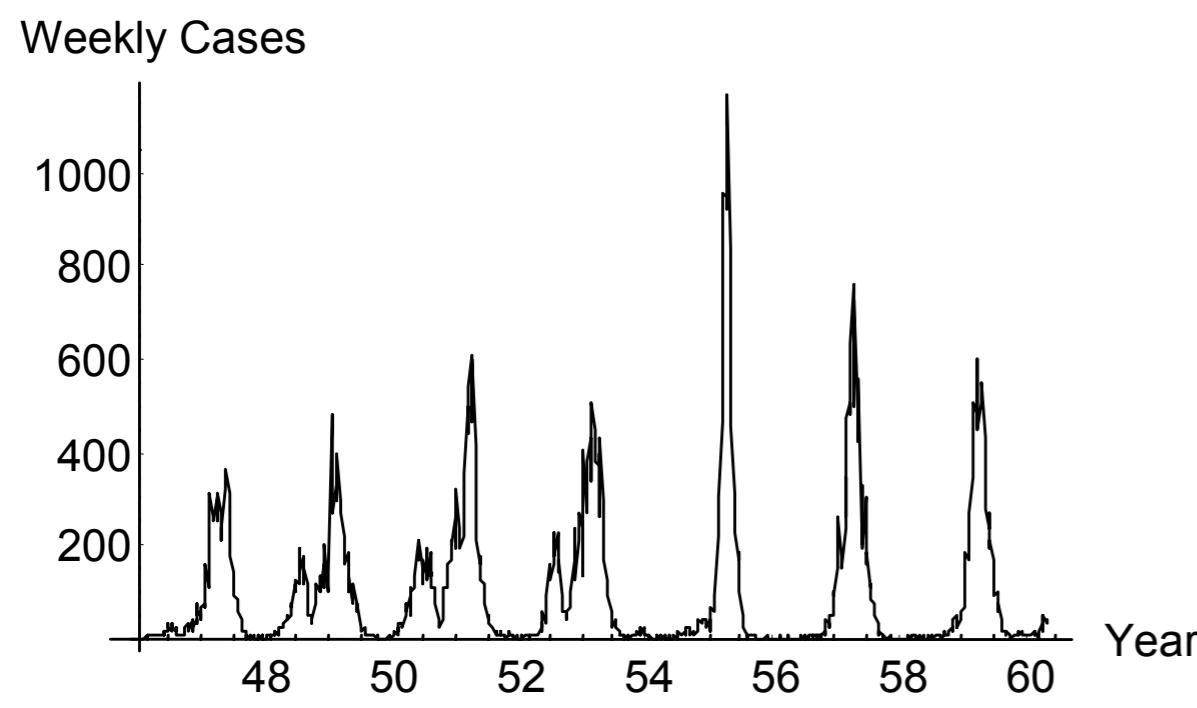


VIRUS PHENOTYPE

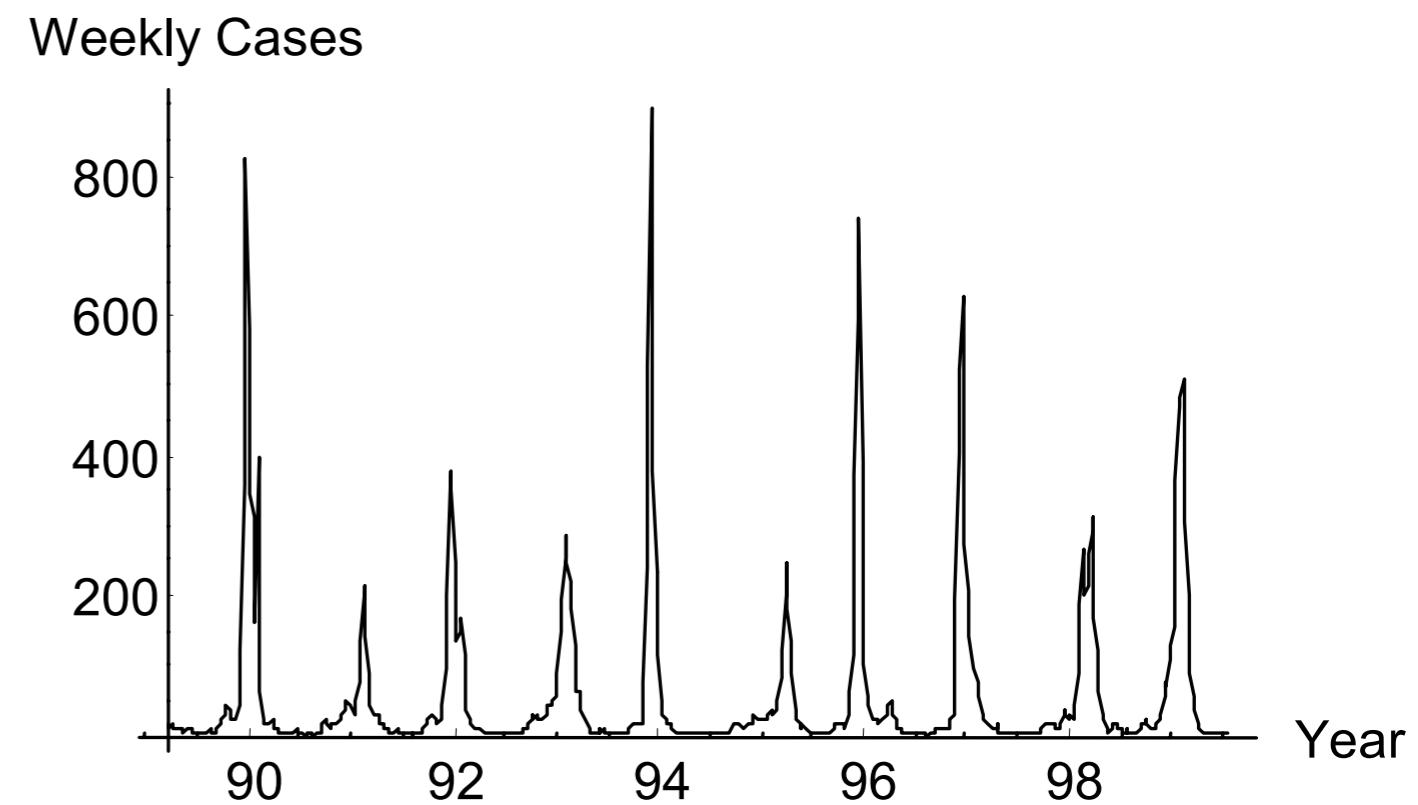
(molecular virology & immunology)



Measles vs Influenza Transmission Dynamics



Pre-vaccination dynamics
(1940-1960, Leeds UK)

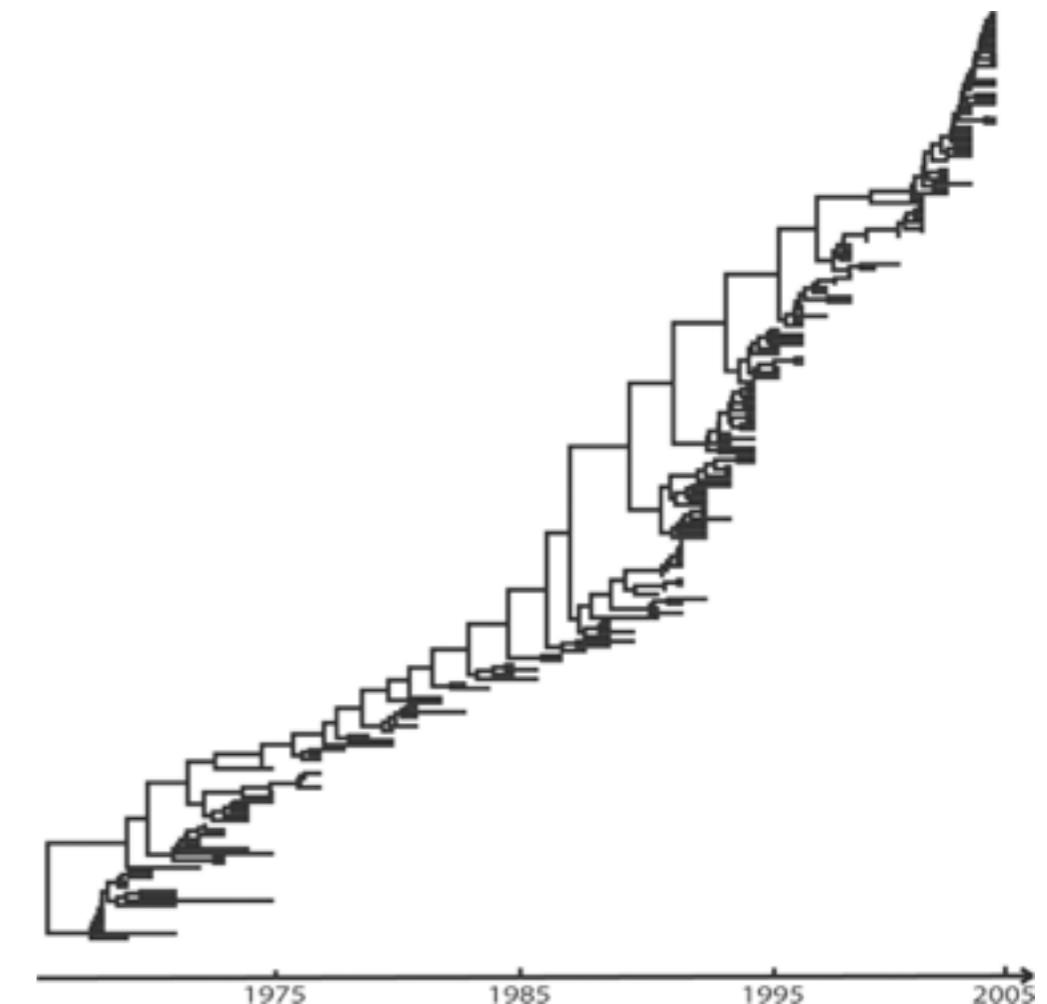


Influenza-like illness
(1989-1999, France)

Measles vs Influenza Genetic Dynamics



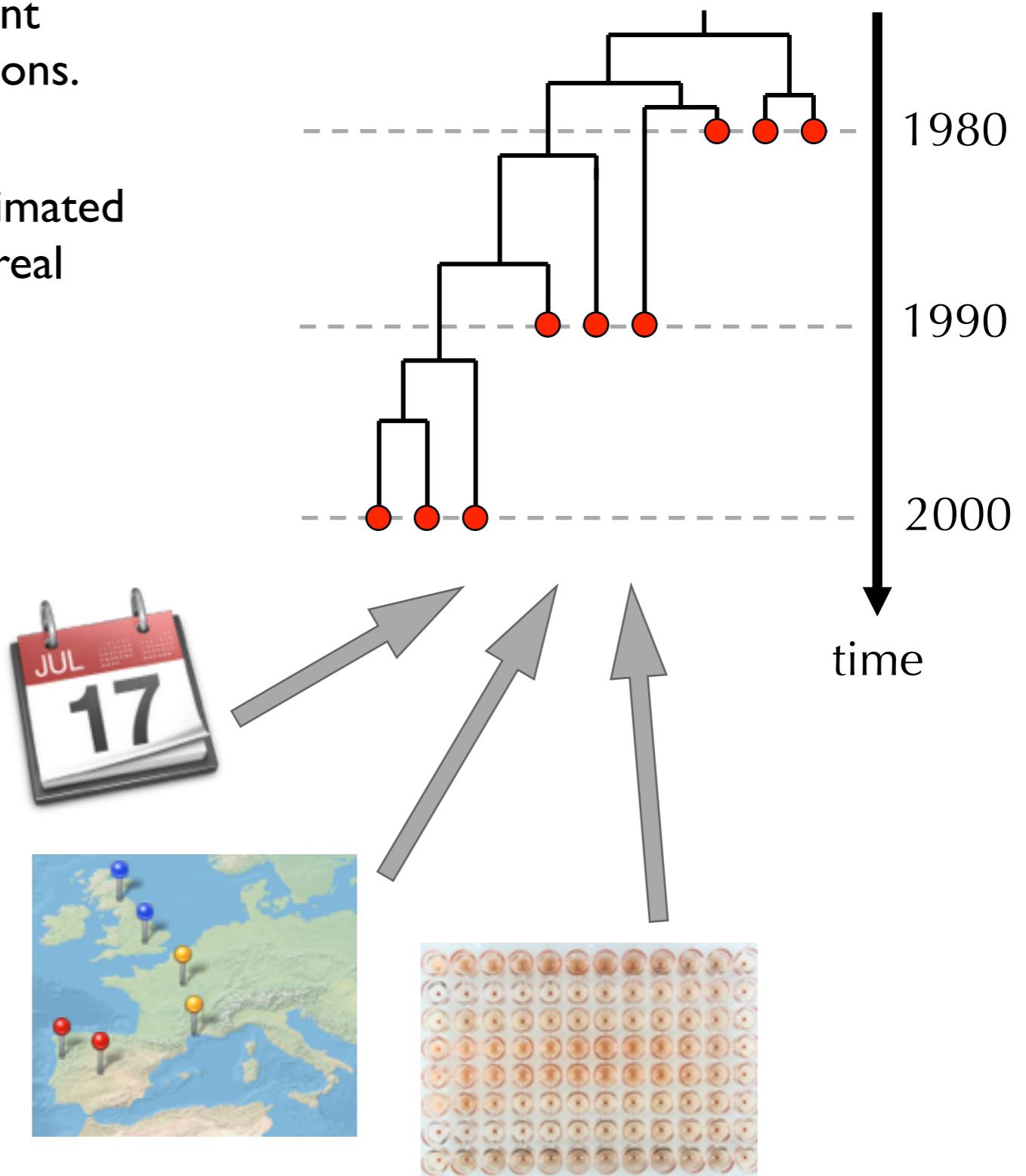
Global measles virus genetic diversity



Global human influenza A H3N2 genetic diversity

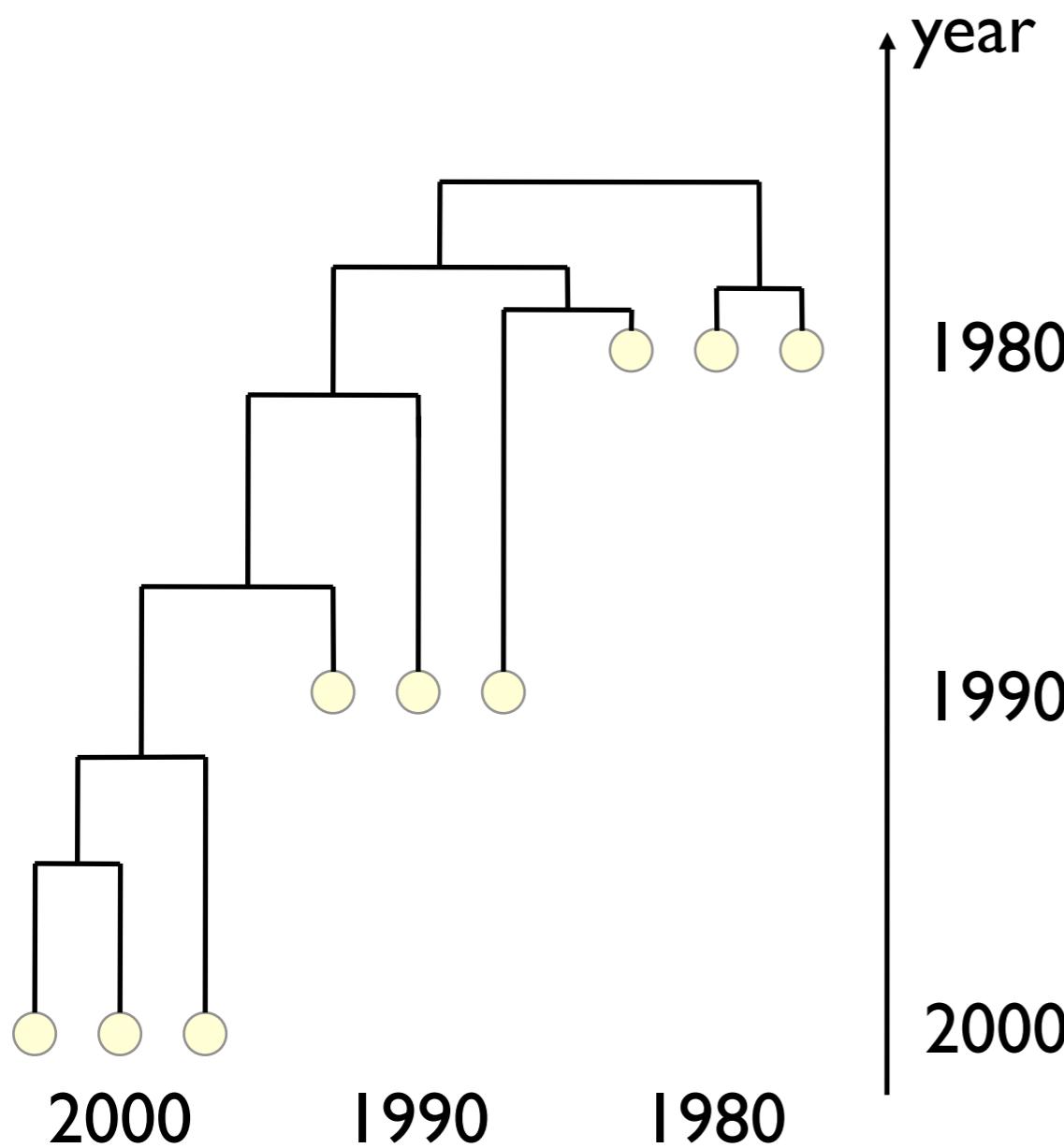
Phylogenetic Data

- Gene sequences are sampled at different points in time and from different locations.
- Hence transmission history can be estimated on a real time-scale (e.g. years) and in real space (e.g. countries, cities).

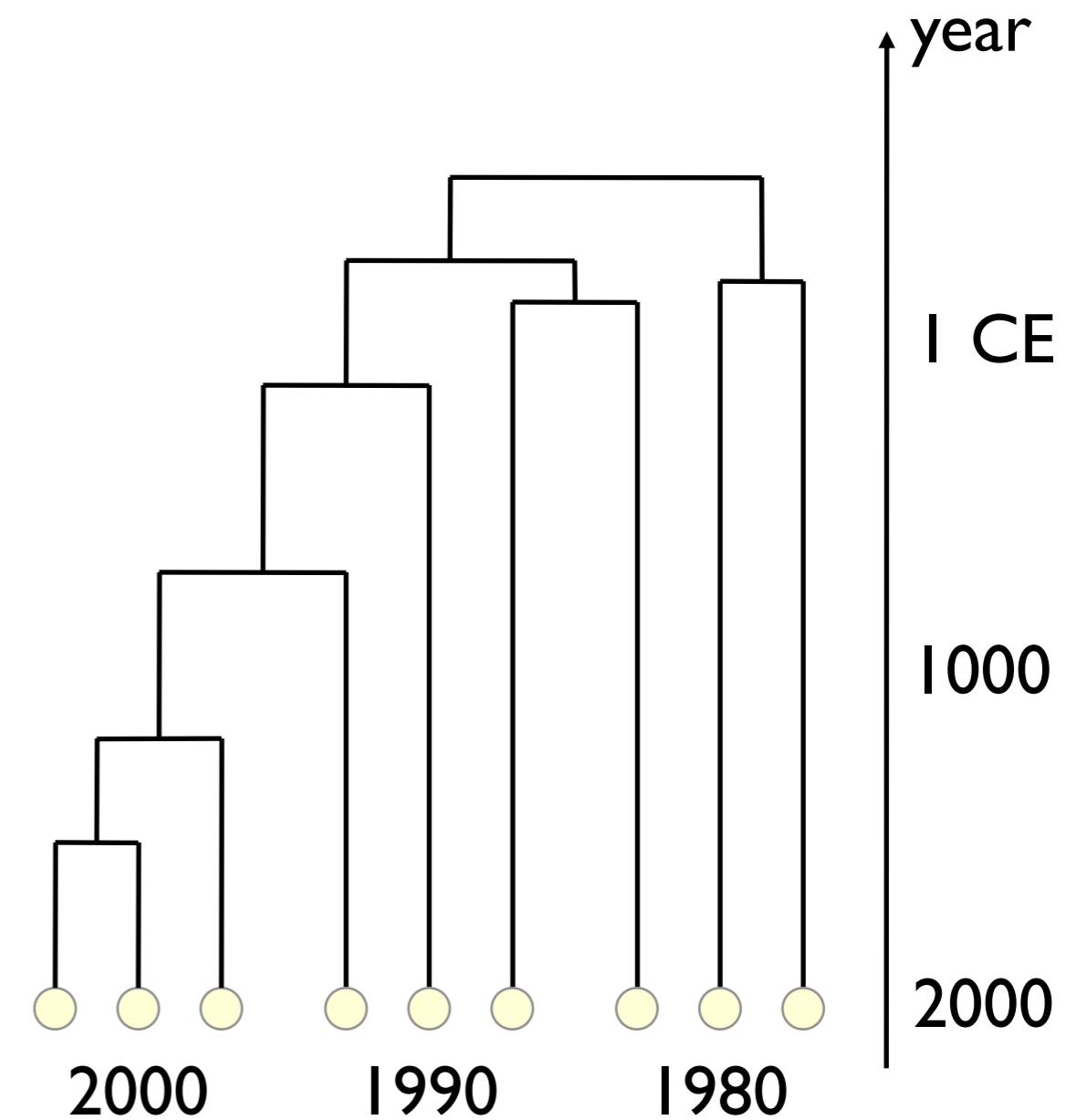


Same sampling times, different rates of evolution

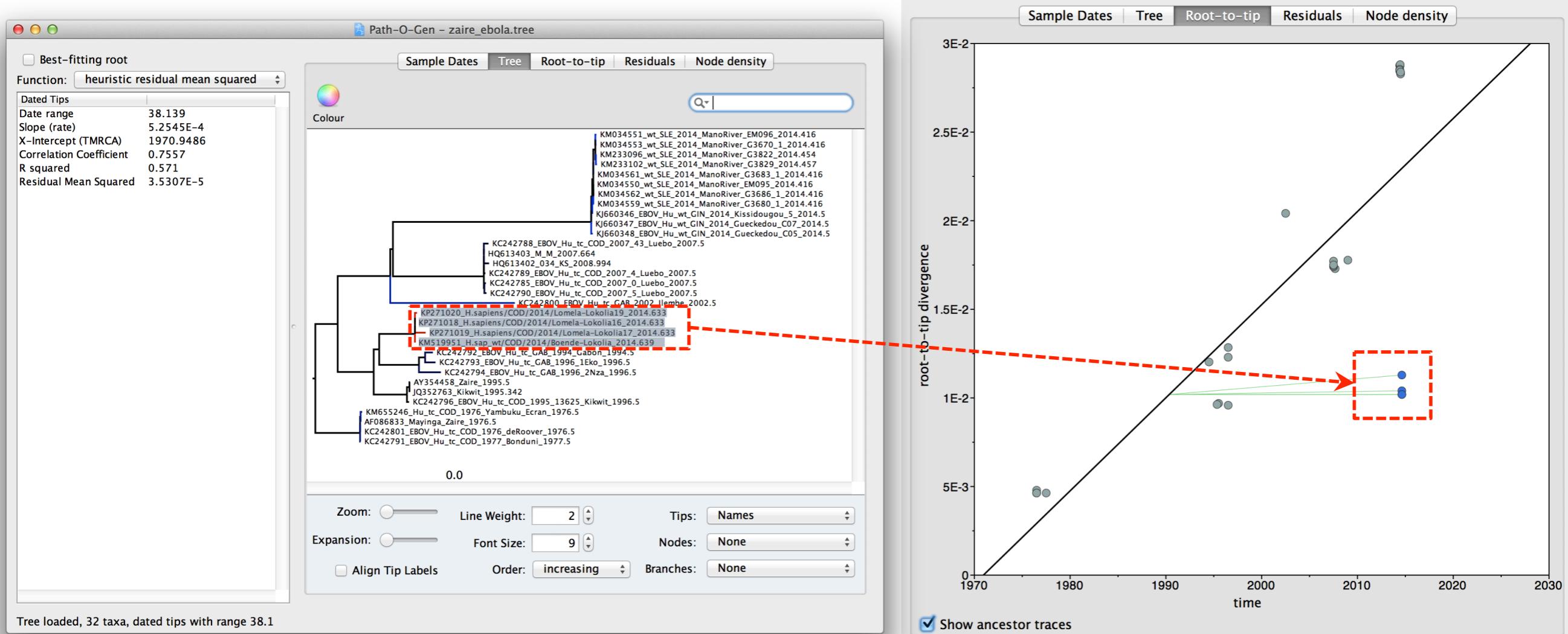
Measurably-evolving population
("heterochronous" or
"serially-sampled")



Not measurably-evolving
("isochronous" or
"contemporaneous sampling")



Phylogenetic Data

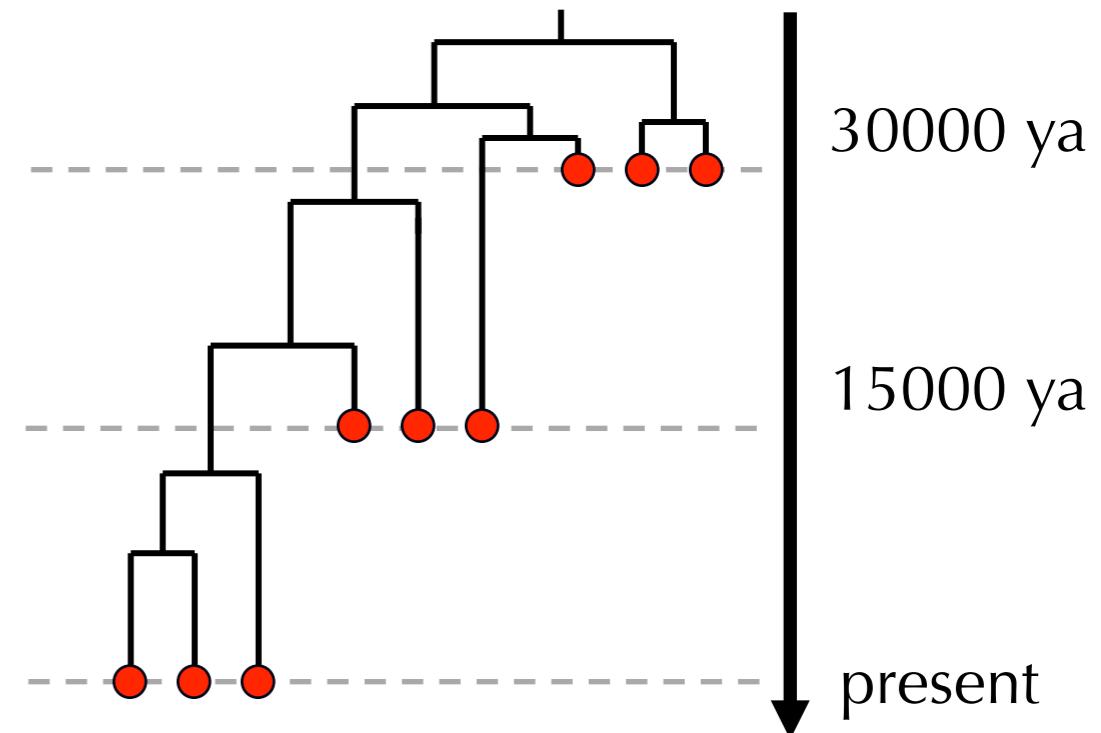


Use TempEst to determine if your sequences are **heterochronous**.
Do they exhibit a correlation between genetic divergence and time?

Phyldynamic Data

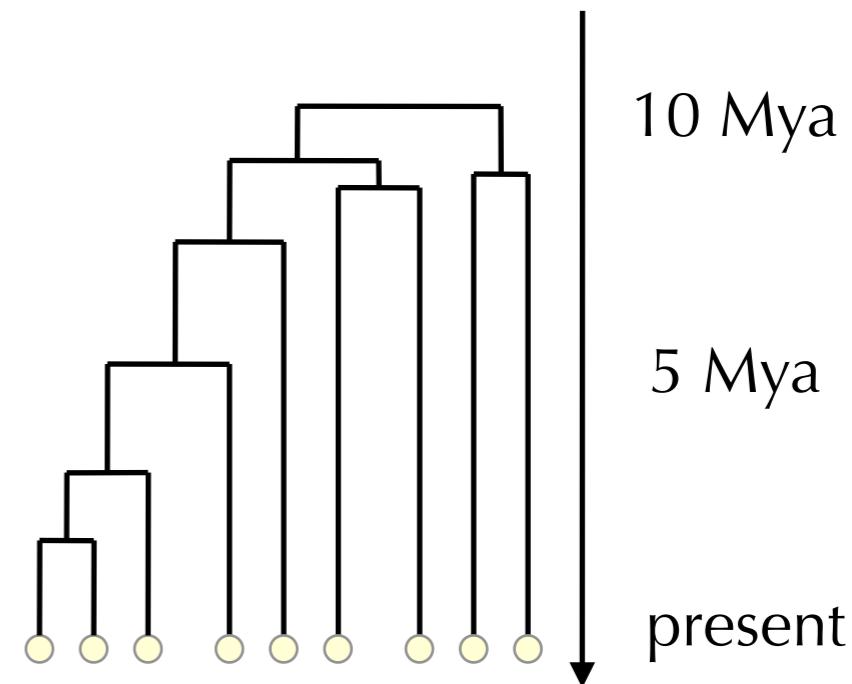
- Are rapidly-evolving pathogens the only source of heterochronous data?

No. Ancient DNA can be recovered from biological material that is >100,000 years old.



- Can phylodynamics be applied to isochronous data?

Yes, although statistical power is weaker for many questions. And external information about rates or dates is needed.



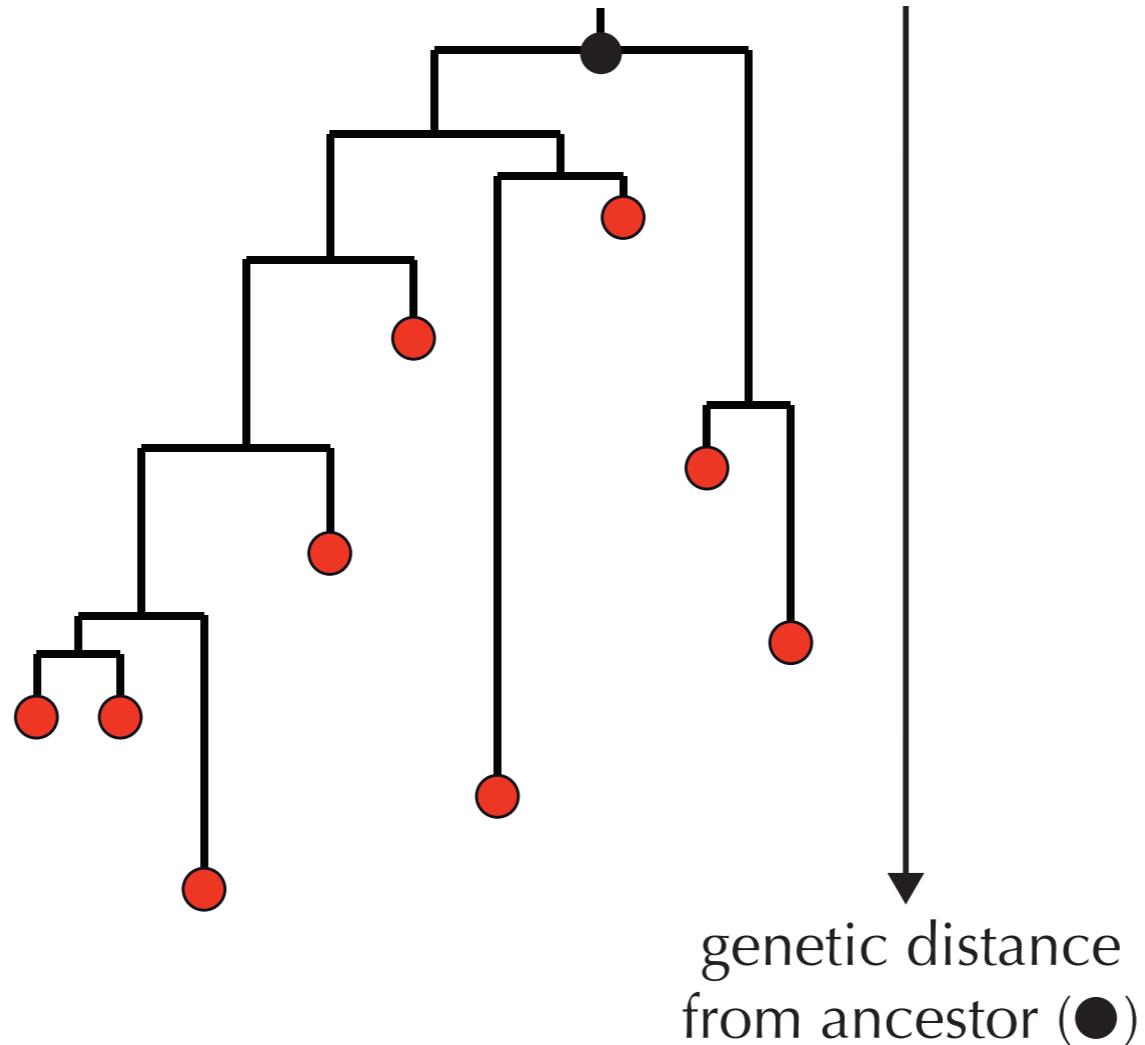
Phylodynamic Questions

- How genetically diverse is a pathogen population?
- How do pathogen genomes change through time?
- How does pathogen genetic diversity vary through space?
- How does recombination and natural selection shape genetic diversity?
- When did an epidemic start?
- Where did it come from?
- How fast is it transmitting?
- In what direction is it spreading?
- Are hosts X,Y & Z epidemiologically linked?
- Is epidemic composed of one or multiple chains of transmission?
- Are lineages associated with particular transmission routes?

Commonly-used methods for the evolutionary analysis of rapidly-evolving pathogens

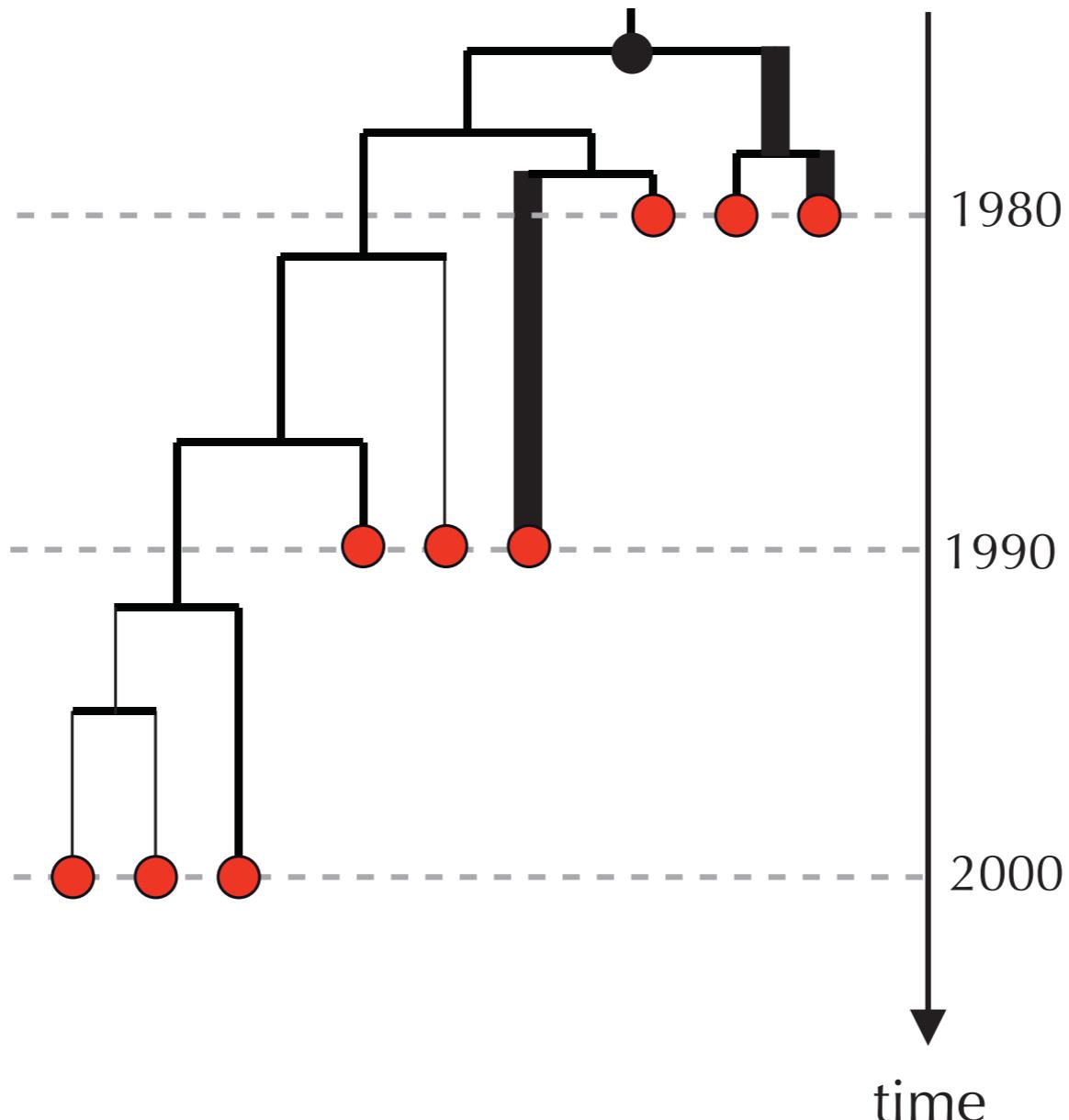
- Phylogenetics
- Molecular clocks
- Coalescent / Birth-Death models
- Phylogeography
- Selection analysis
- Recombination analysis

(I) Phylogenetics



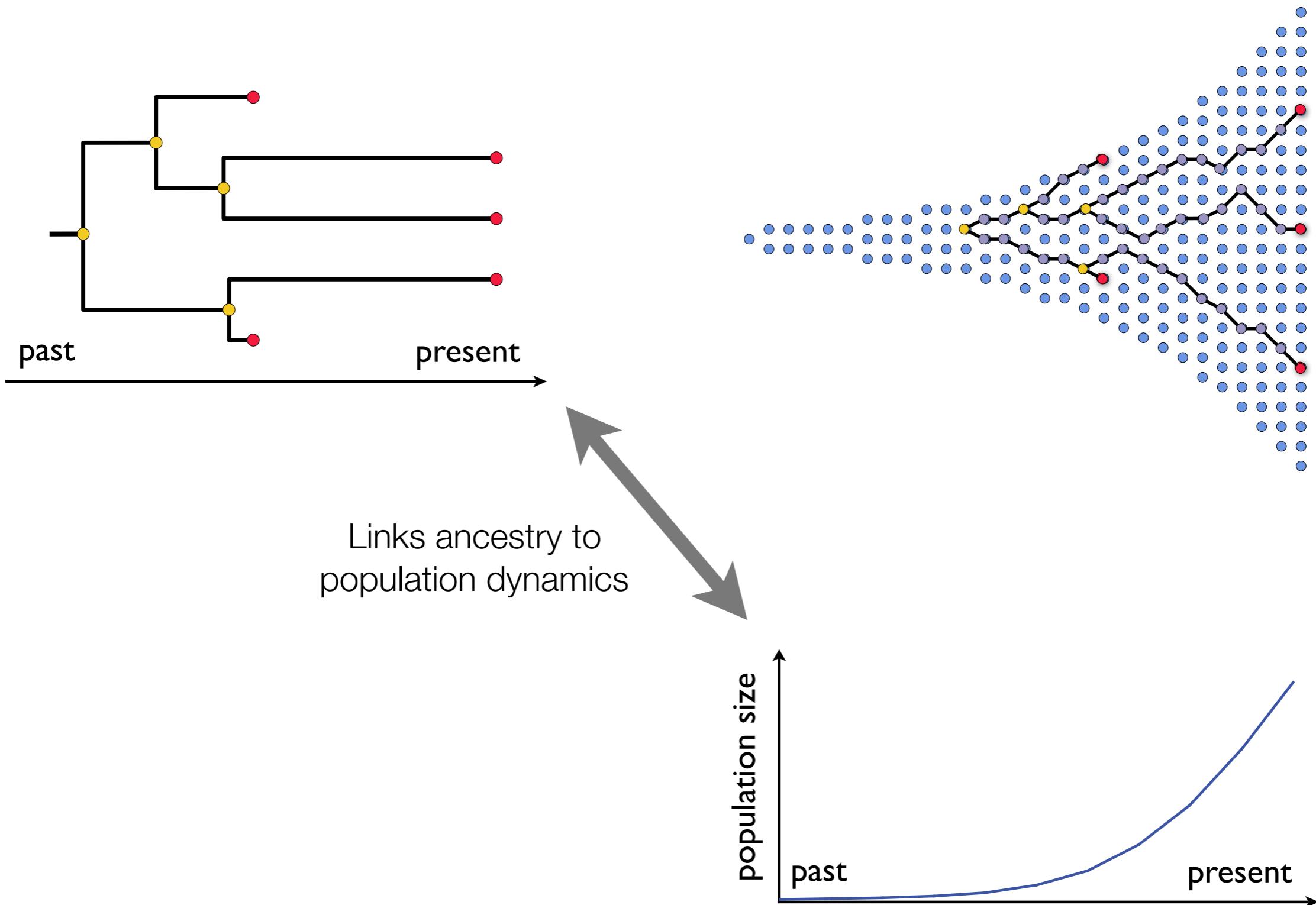
Shows shared ancestry and enables classification

(2) The Molecular Clock

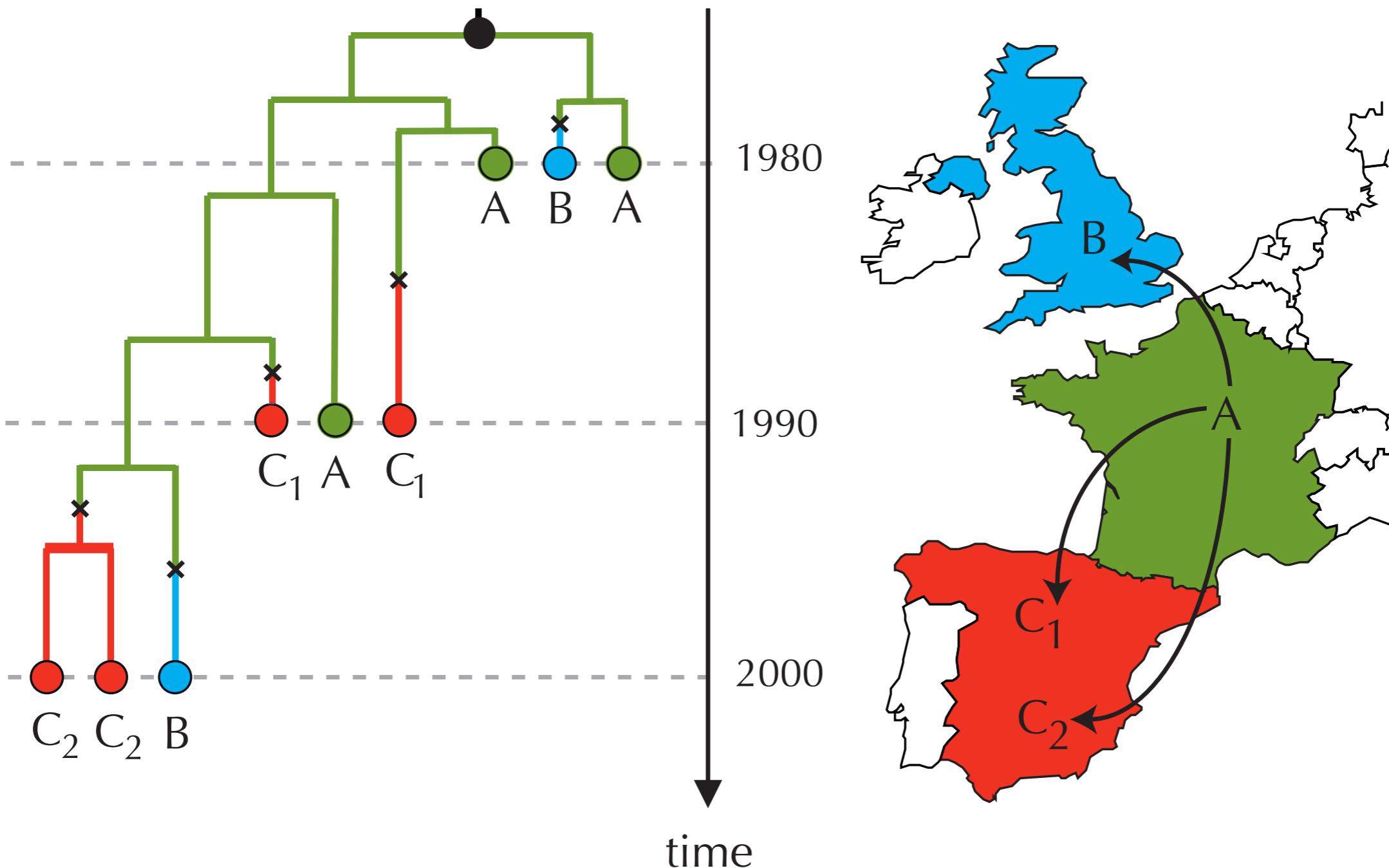


Places ancestry on a temporal frame of reference

(2) Coalescent / Birth Death Models

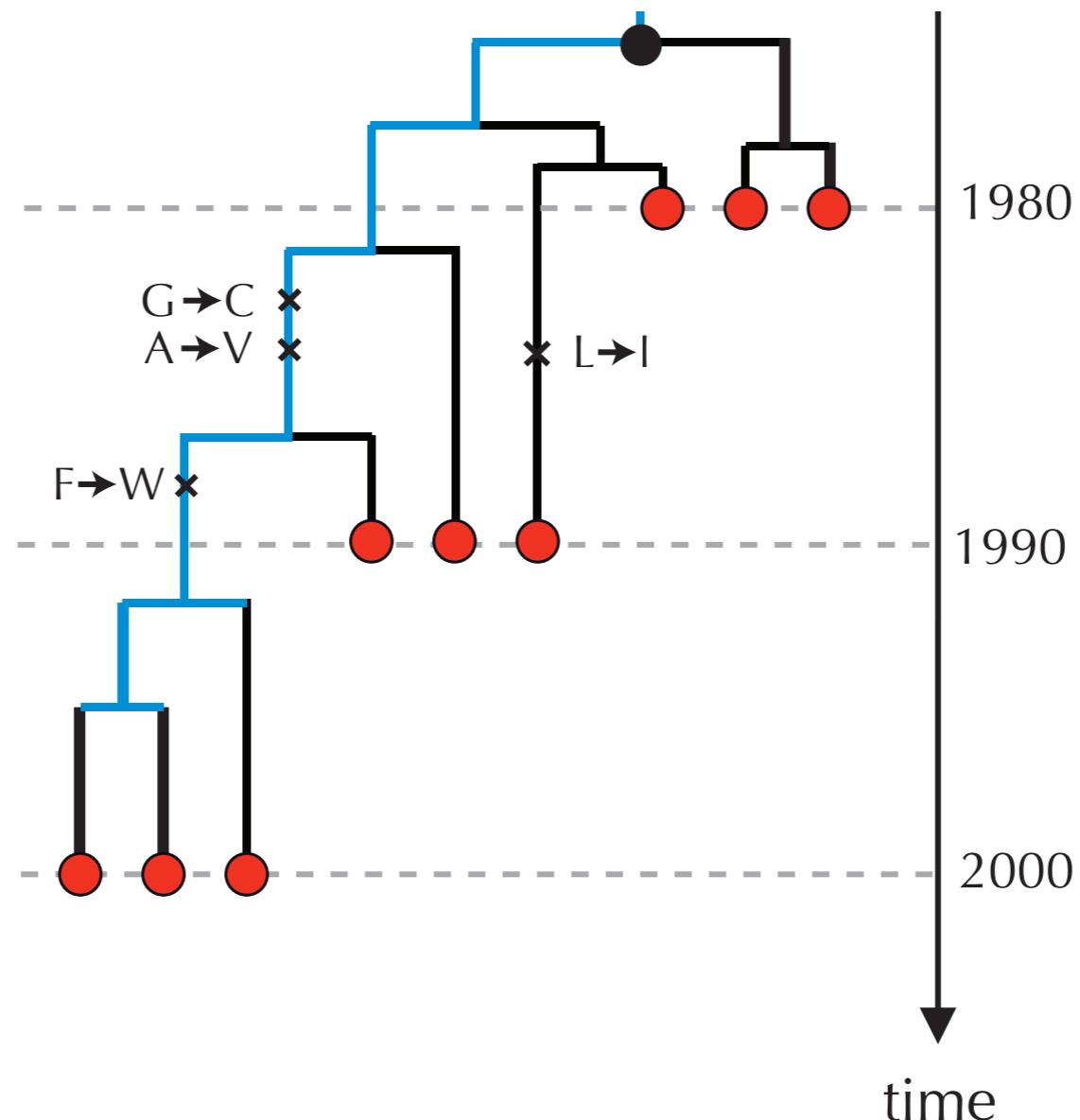


(3) Phylogeography

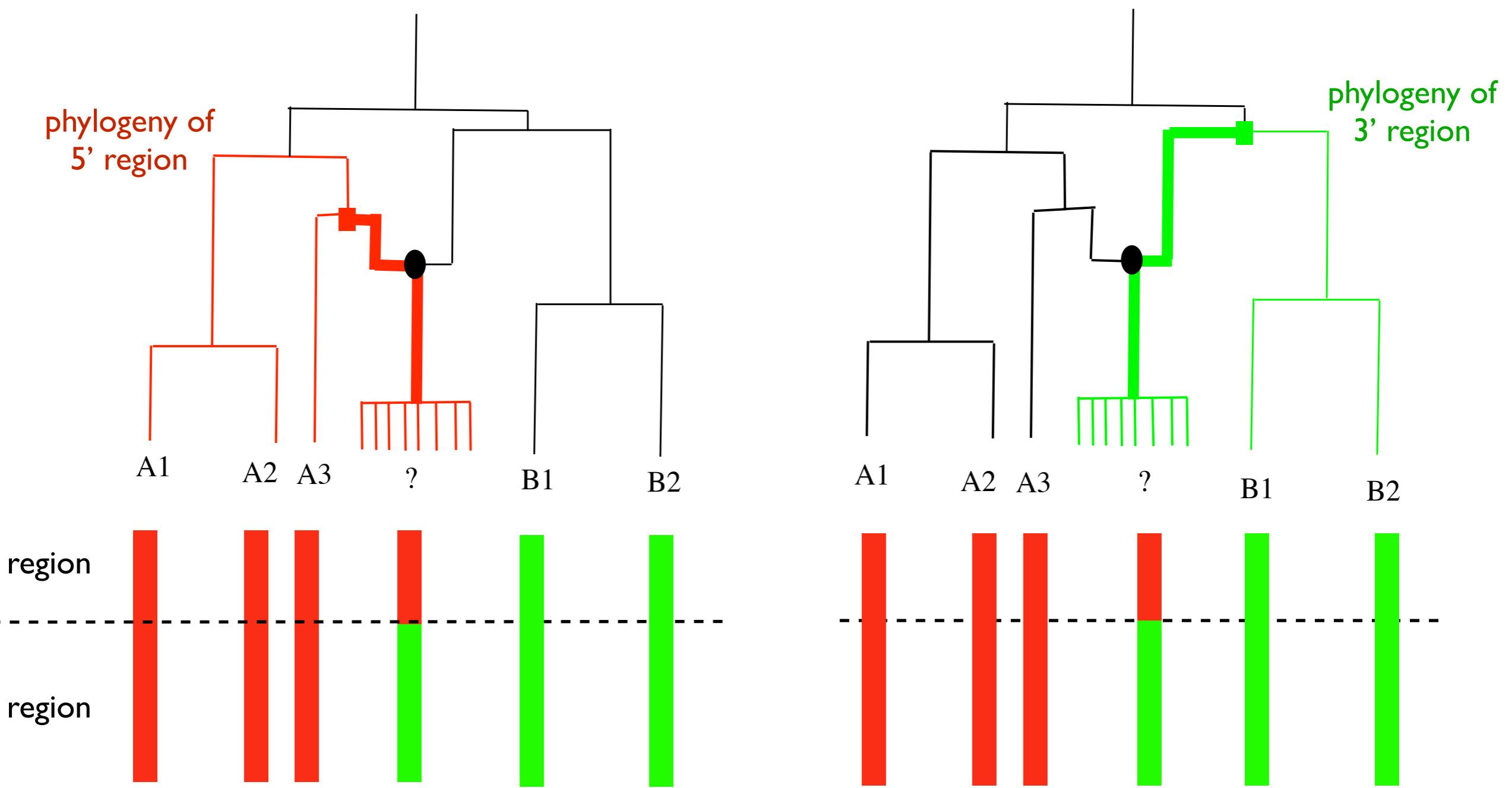


Places ancestry on a spatial frame of reference

(4) Selection Analysis

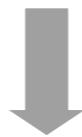


(5) Recombination Analysis



SAMPLES FROM INFECTED INDIVIDUALS

*Clinical Virology
Genomics*



PATHOGEN GENOME SEQUENCES

*Alignment Methods
Sequence Evolution Models*



GENETIC DISTANCES

Recombination Analysis

Phylogenetic Methods



PHYLOGENY

(time scale = genetic distance)

*TempEst
Molecular Clocks*



PHYLOGENY

(time scale = years)

Adaptation Analysis



POPULATION DYNAMICS

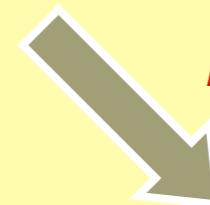
*Coalescent Theory
Birth/Death Models*



NATURAL SELECTION ANALYSES

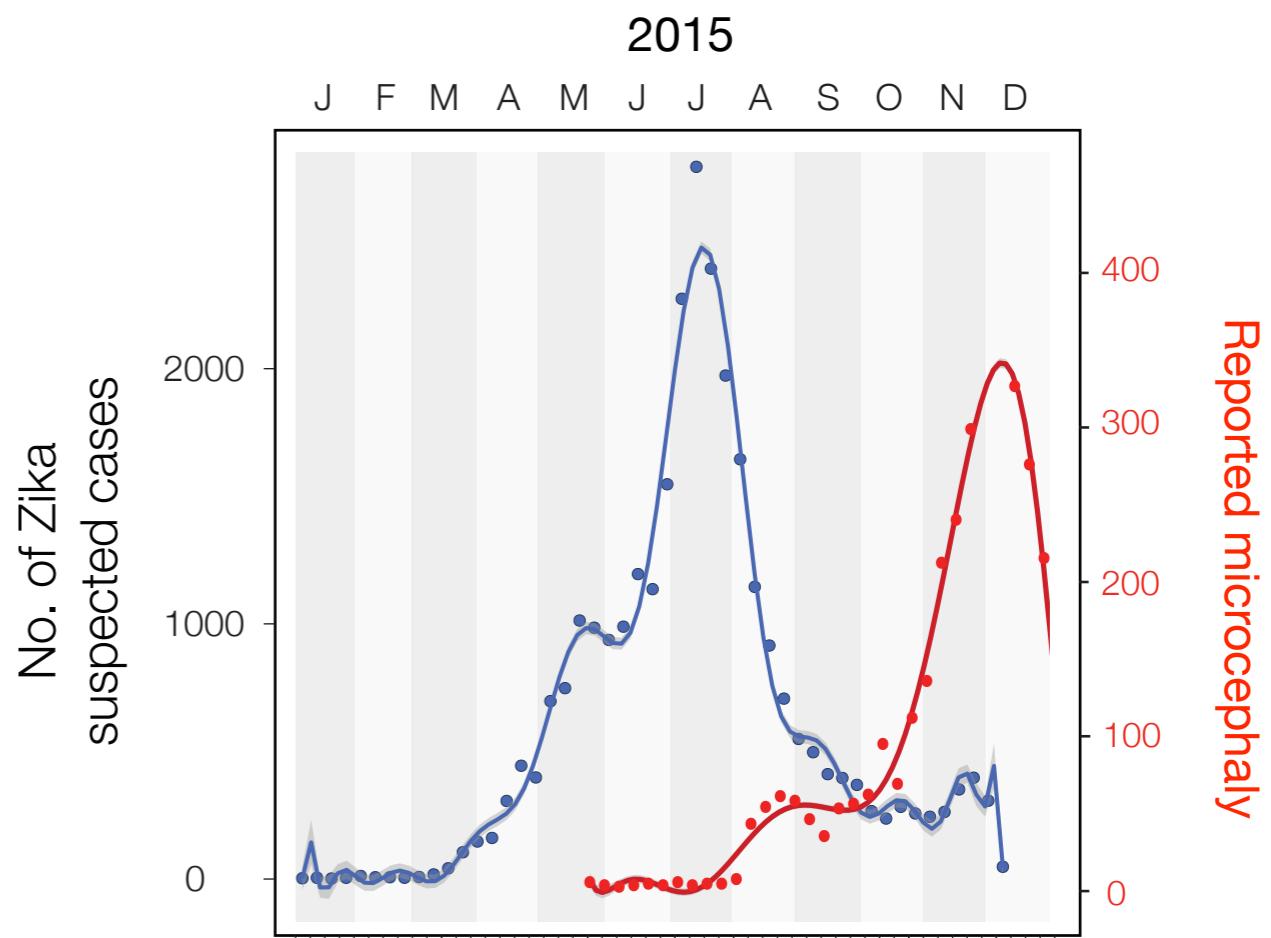
SPATIAL DYNAMICS

*Discrete/Continuous Trait Analysis
Structured coalescent models*

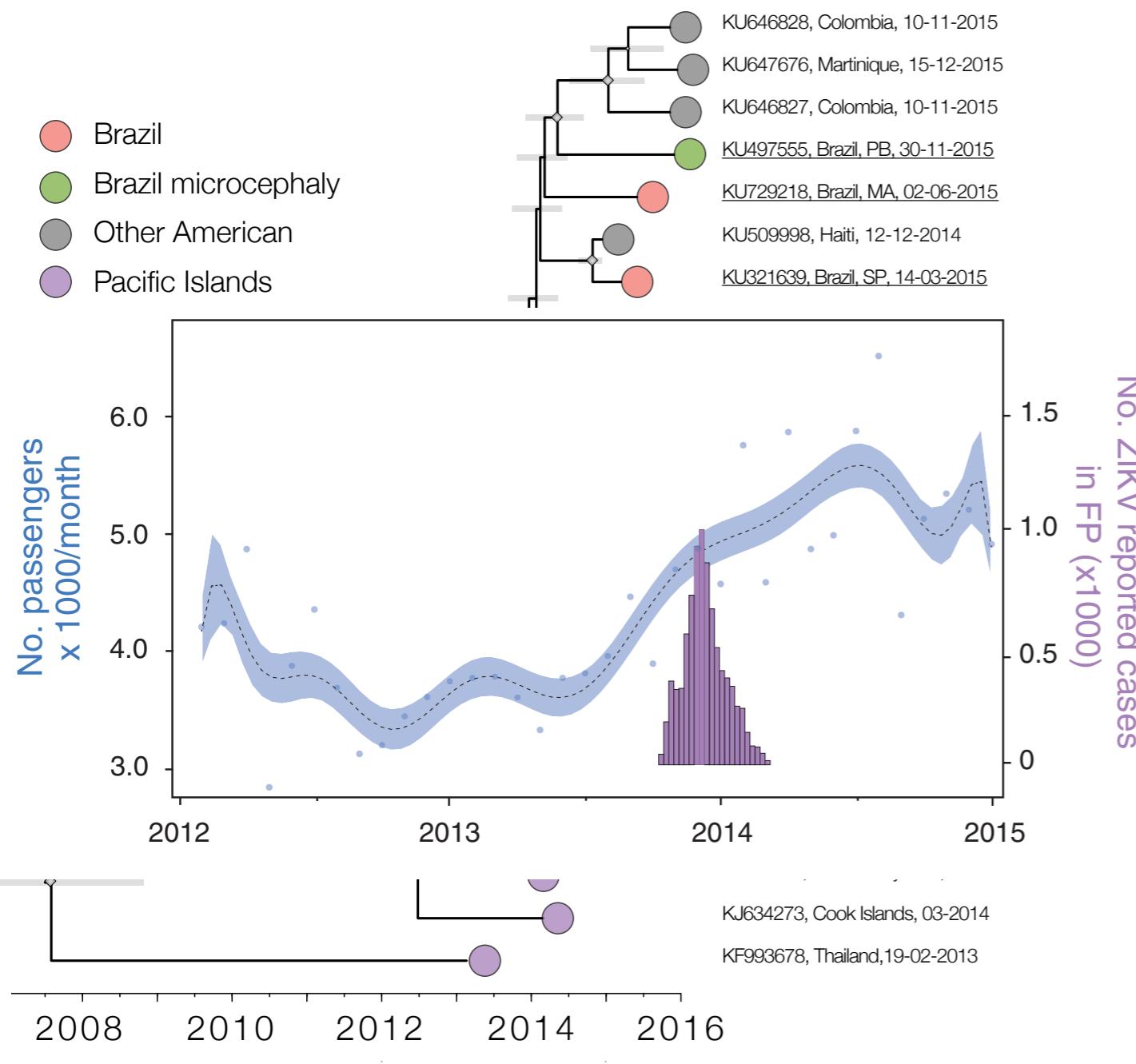


Zika virus in the Americas

- Flavivirus with 11kb ssRNA genome
- Transmitted by Aedes mosquitoes, some sexual transmission
- Typically causes mild fever, only 16 cases known before 2007
- April 2015: first detection of Zika transmission in the Americas, in Brazil
- Summer 2015: Zika epidemic in Brazil
- Winter 2015: rise in reported microcephaly in newborns in Brazil
- Feb 2016: WHO declares Zika is a PHEIC



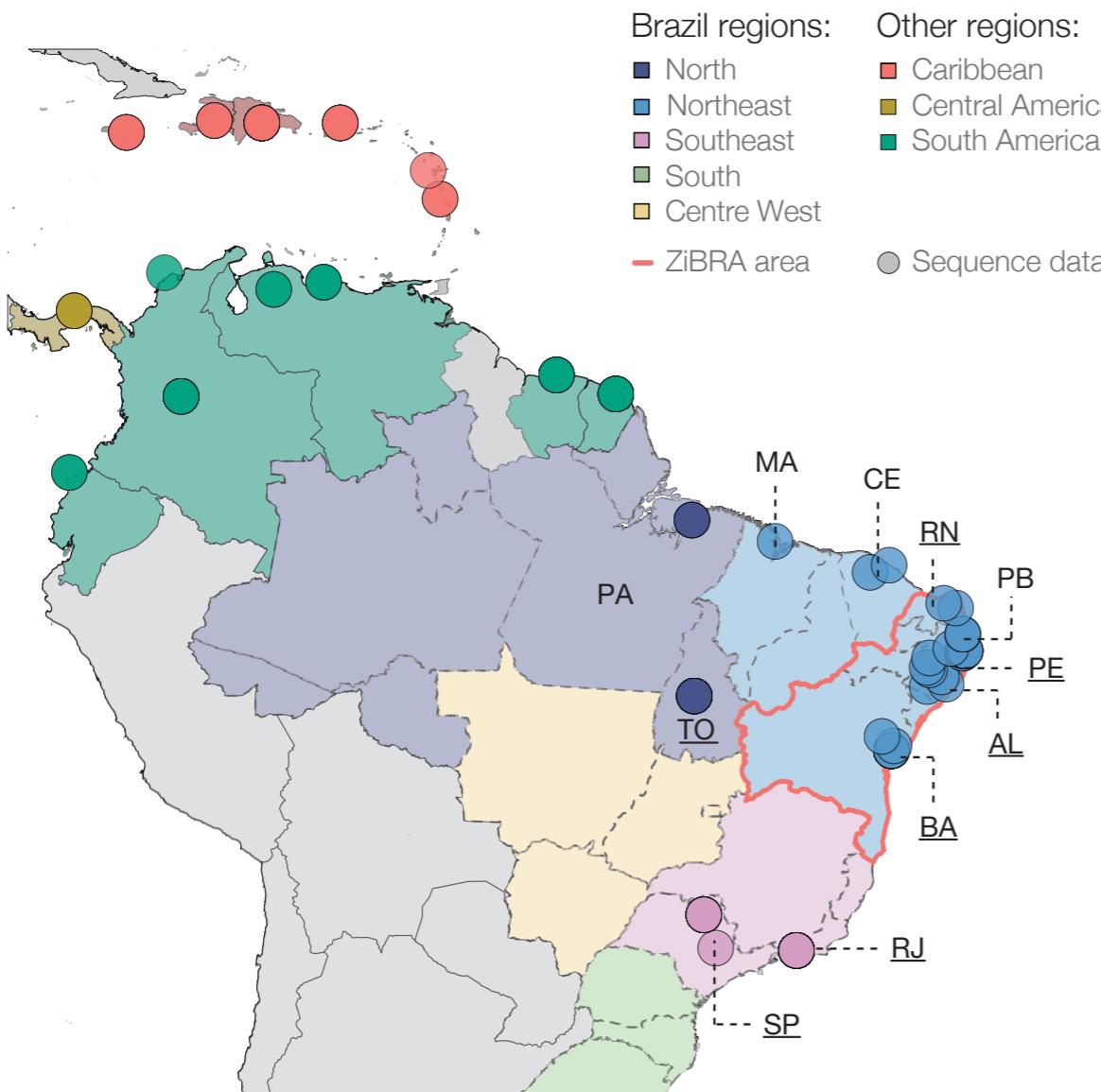
Preliminary genetic results



- Epidemic caused by lineage of Asian Zika genotype
- Zika arrived in the Americas in late 2013, >12 months before it was discovered there
- No viral mutations seemed to be associated with microcephaly
- Introduction coincided with large outbreak in French Polynesia & increase in air passengers from endemic regions



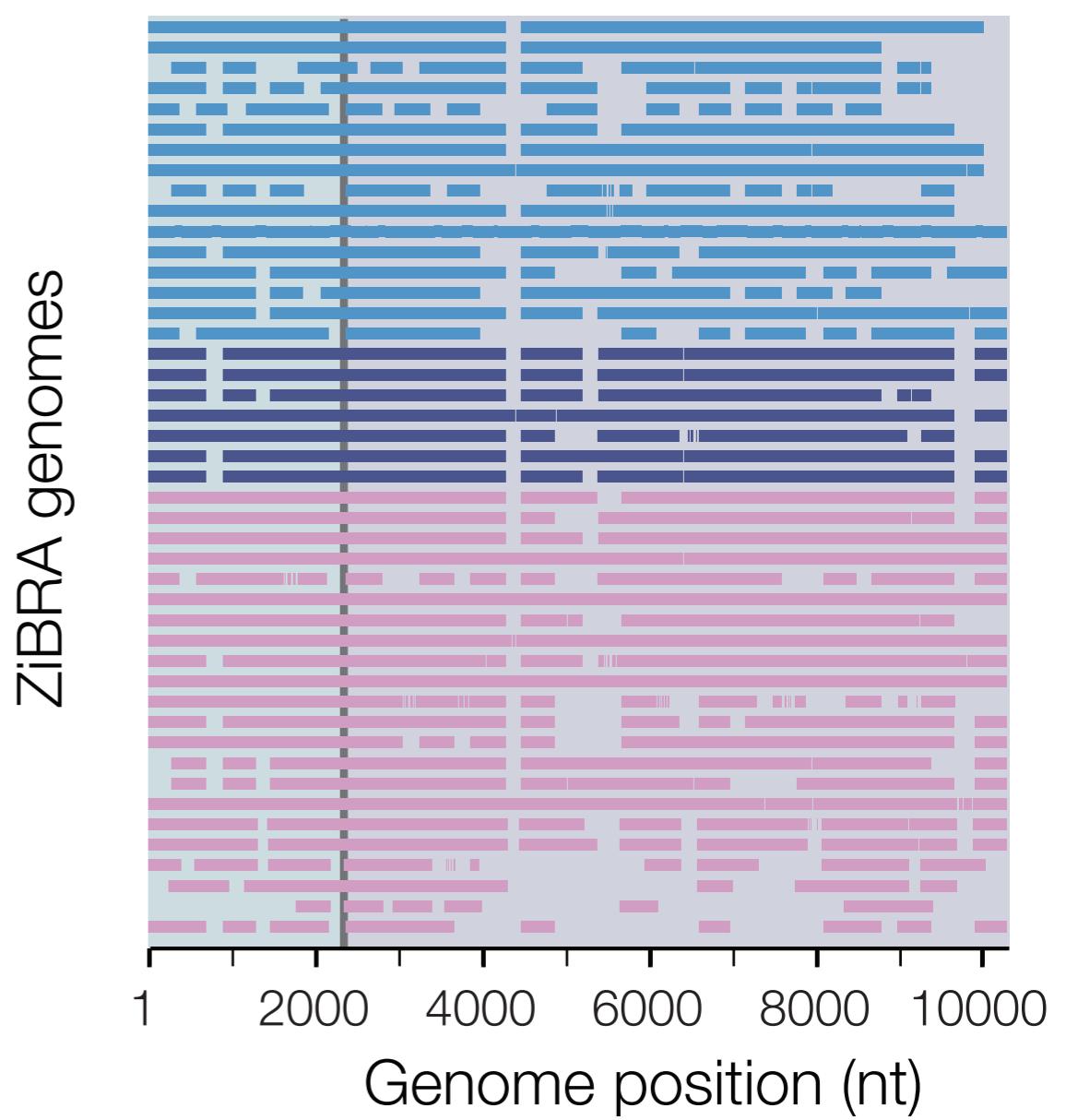
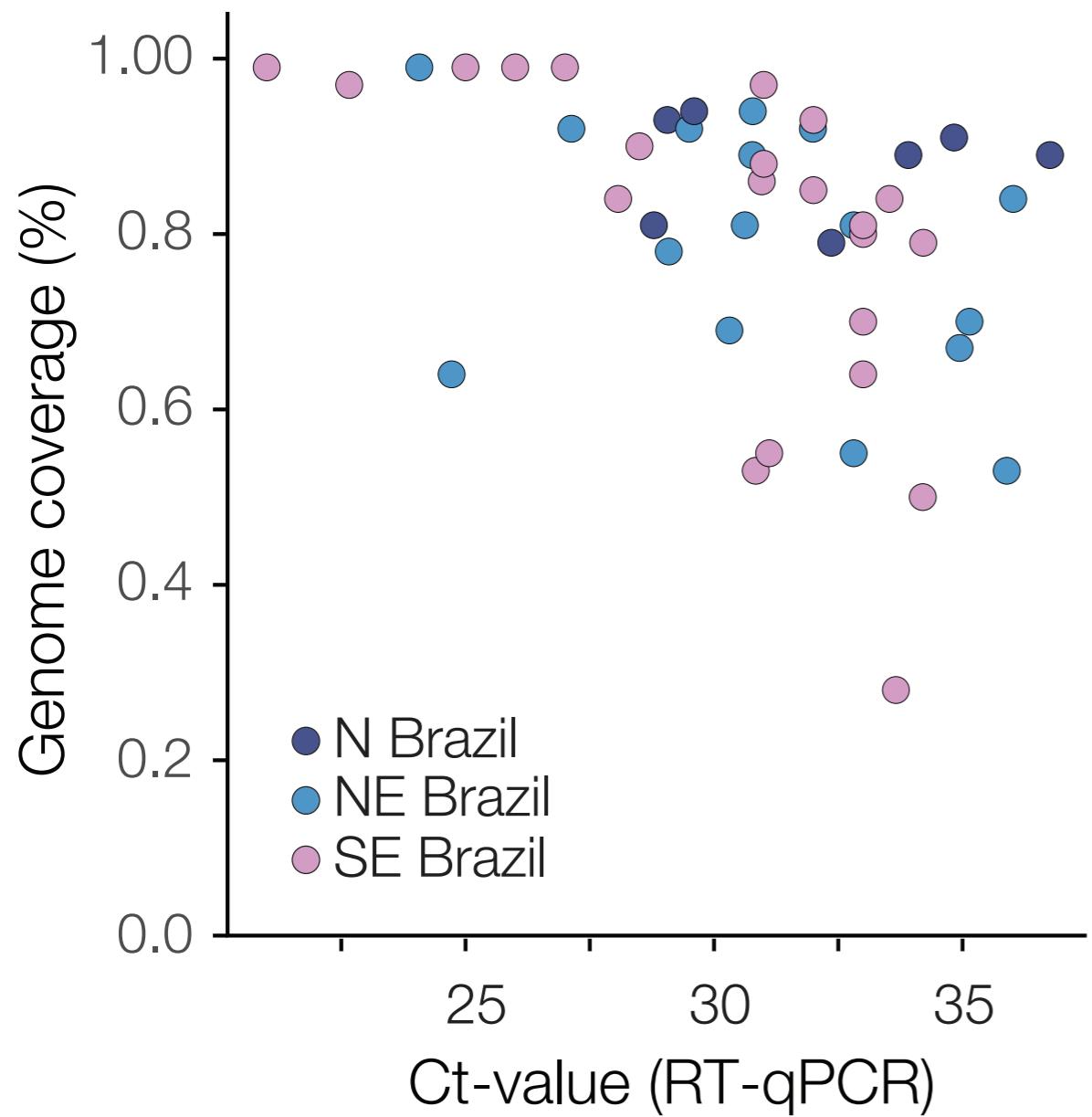
ZIKA IN BRAZIL REAL TIME ANALYSIS



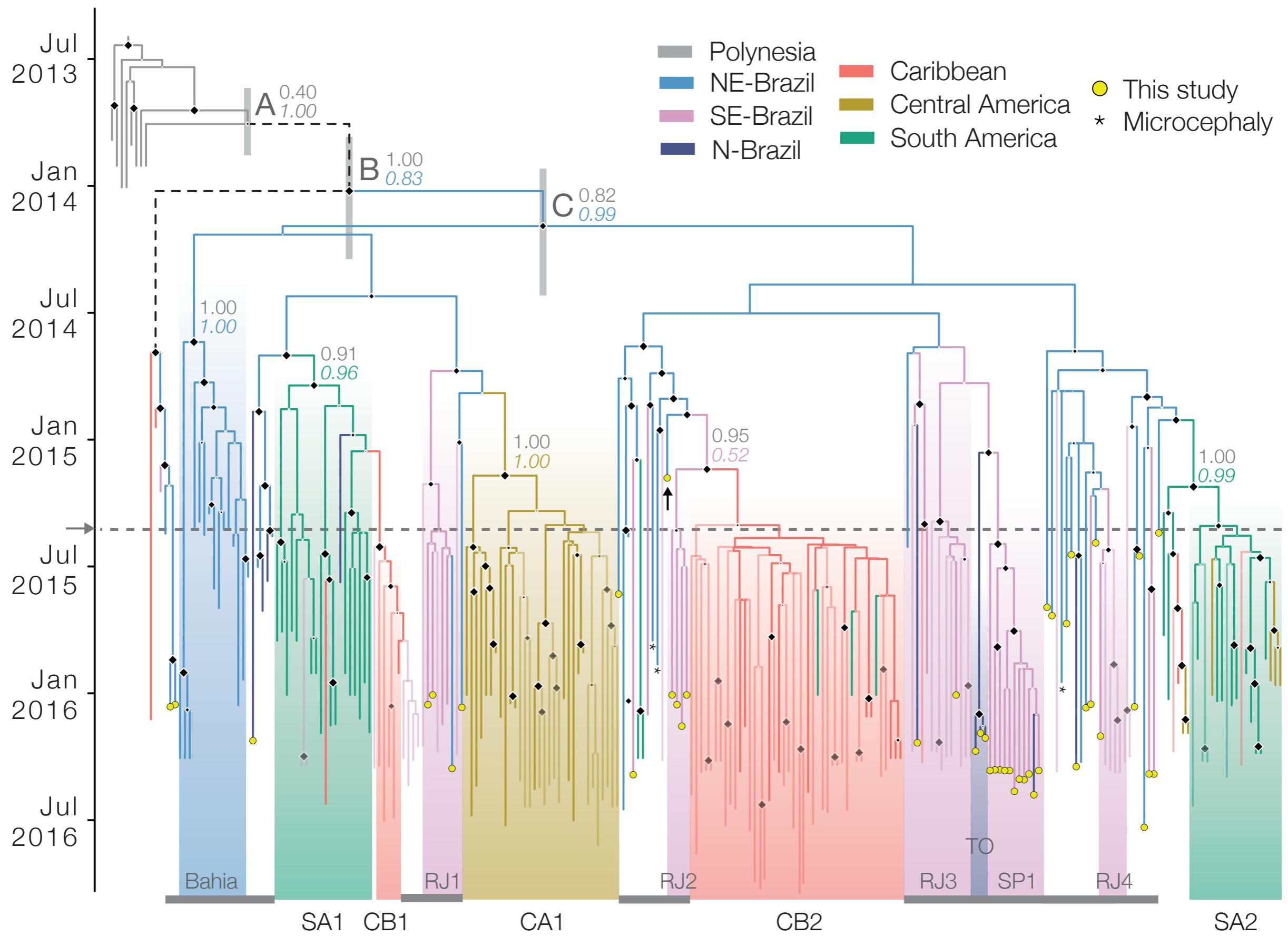
15 days on the road
5 public health laboratories
1330 human samples tested
838 mosquitoes captured



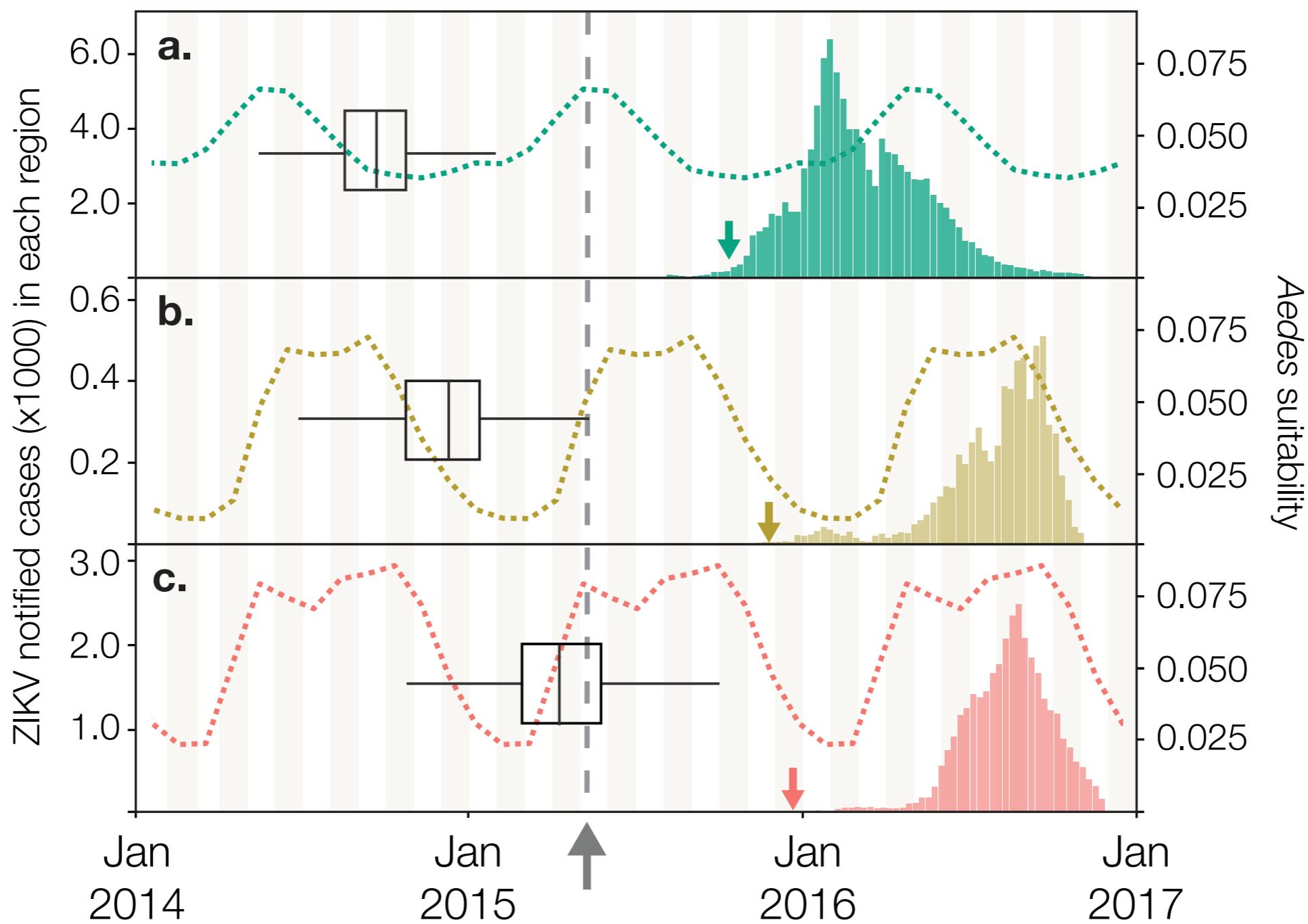
RT-PCR diagnoses
communicated to local and
national health agencies
within 48h



Establishment of ZIKV in Brazil and the Americas



Exportation & cryptic circulation outside of Brazil



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