

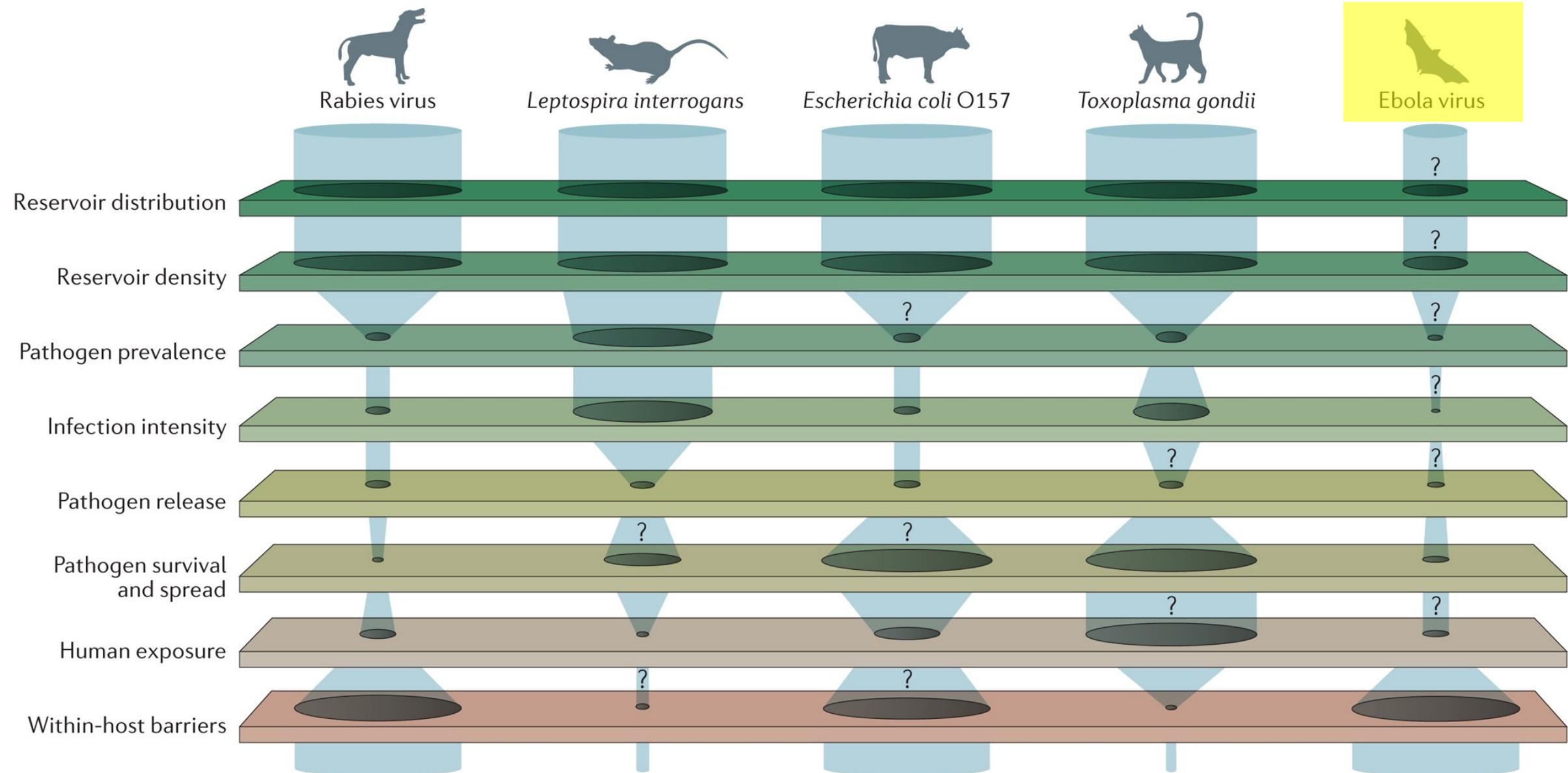
Introduction to Phylodynamics and Molecular Epidemiology

UChicago Center in Paris

Paris, France

January 2024

First:
Why do we hear so much about bats?

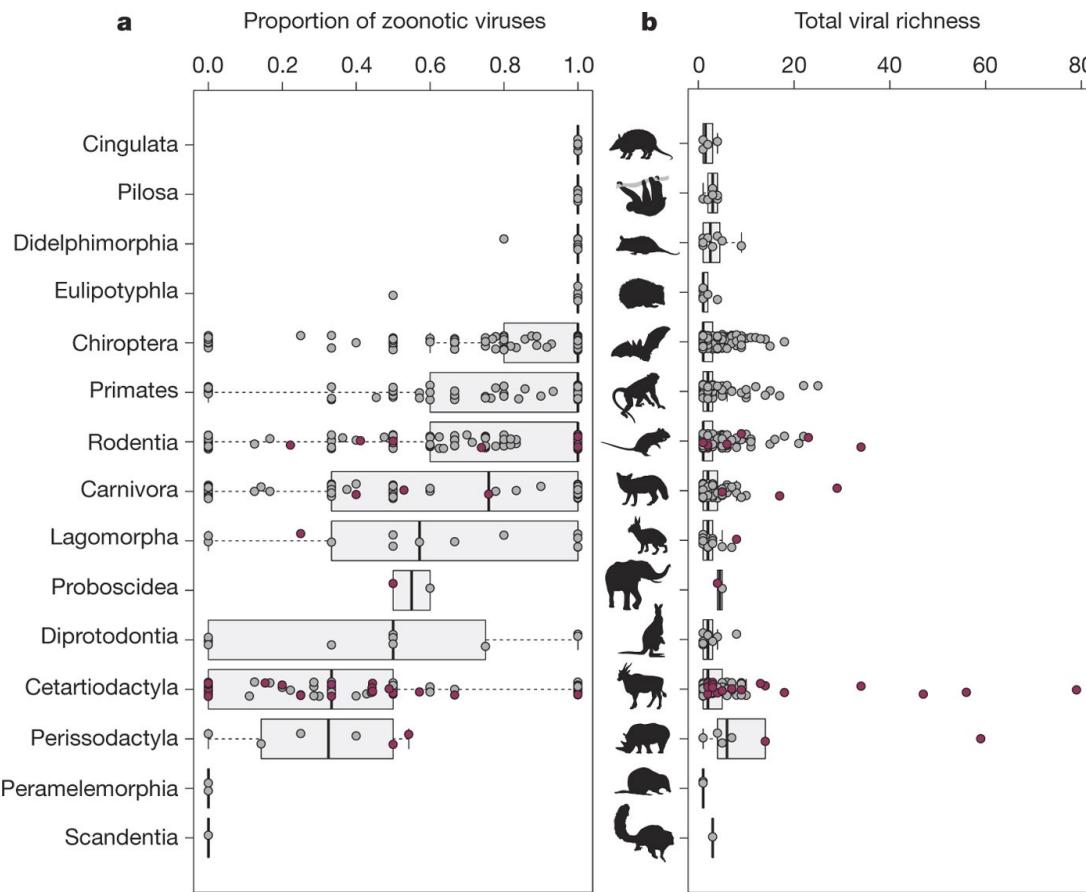


What's so special about bats?

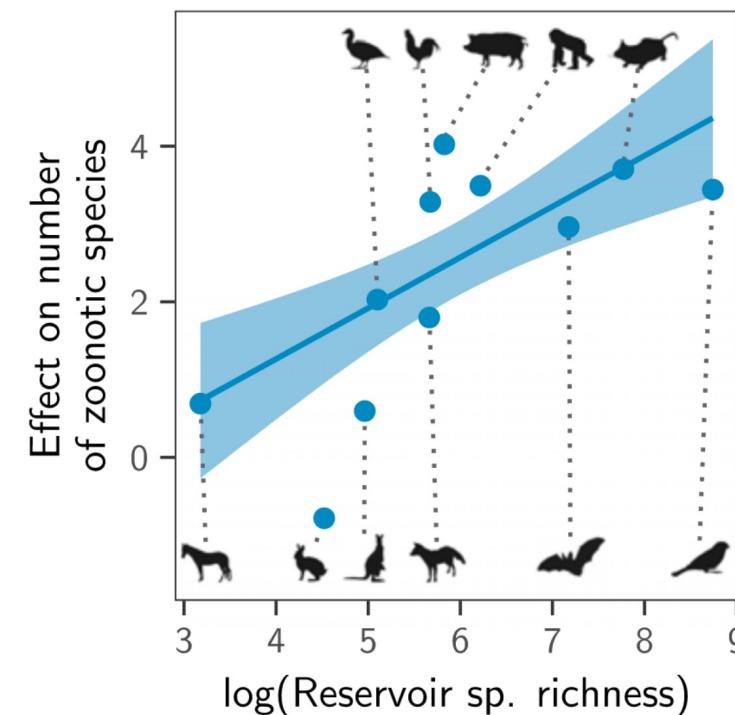
Plowright et al. 2017. *Nature Reviews Microbiology*.

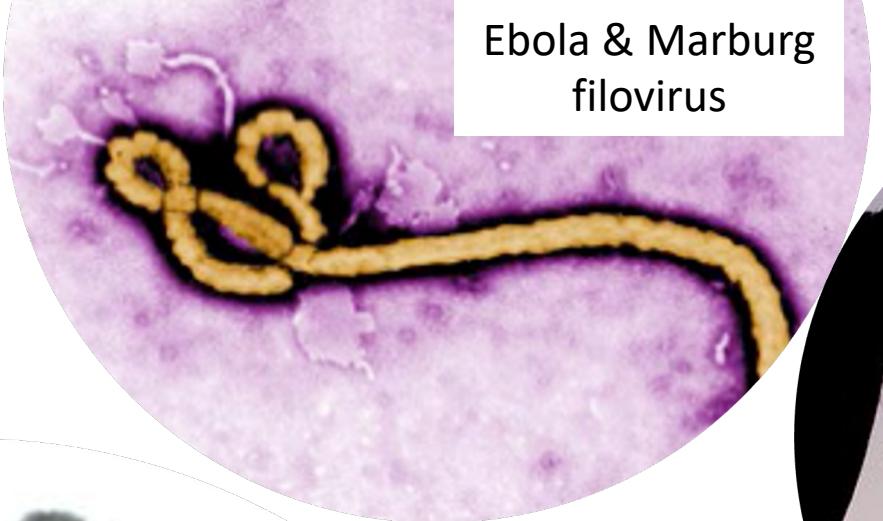
It is **debated** whether bats are reservoir hosts for **more zoonotic viruses** than other mammals.

Bats host a higher proportion of zoonotic viruses than other mammalian orders.



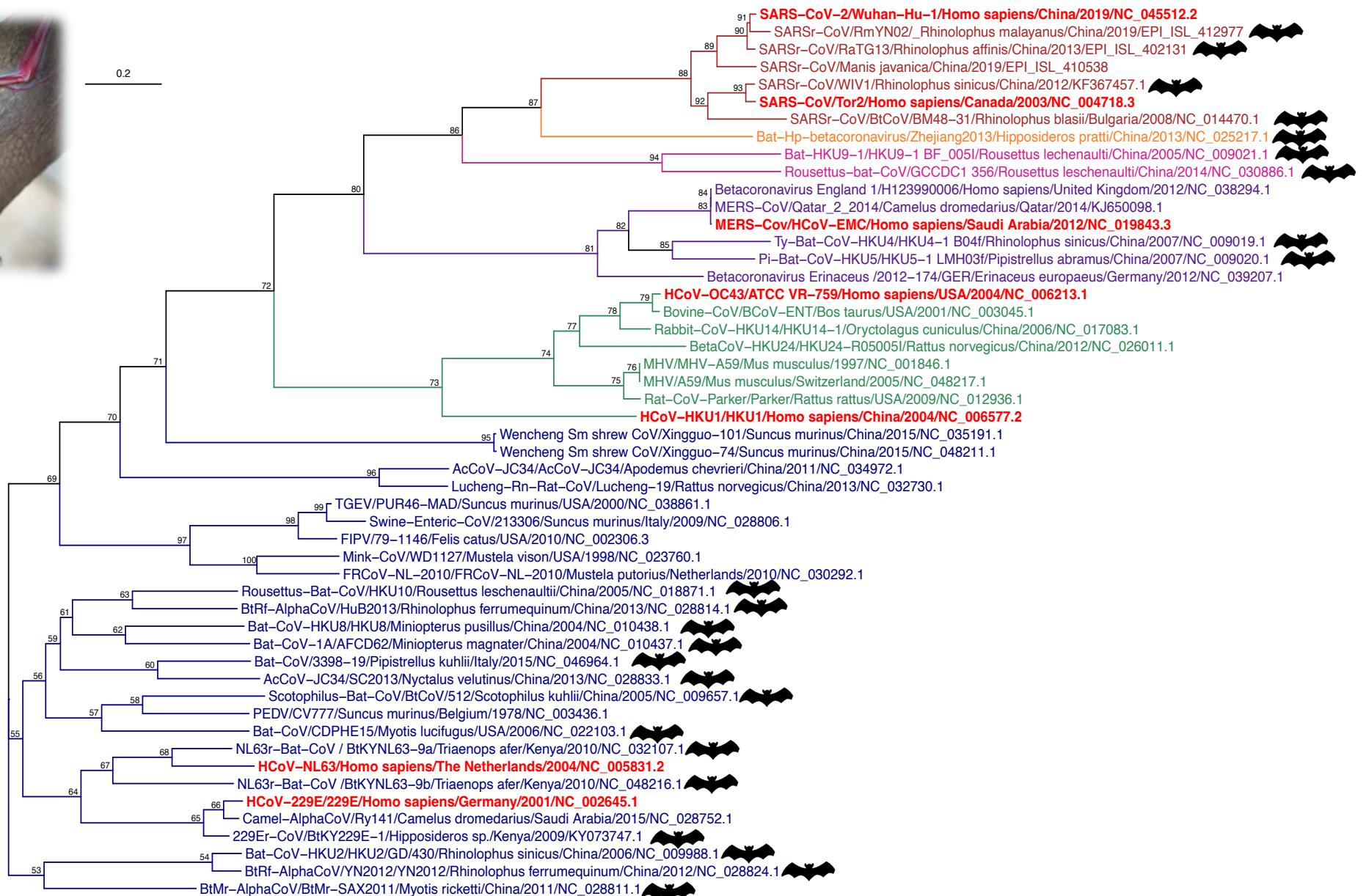
The number of zoonotic viruses hosted by bats scales with the total number of bat species in existence (>1400 spp.; 20% of mammalian diversity).



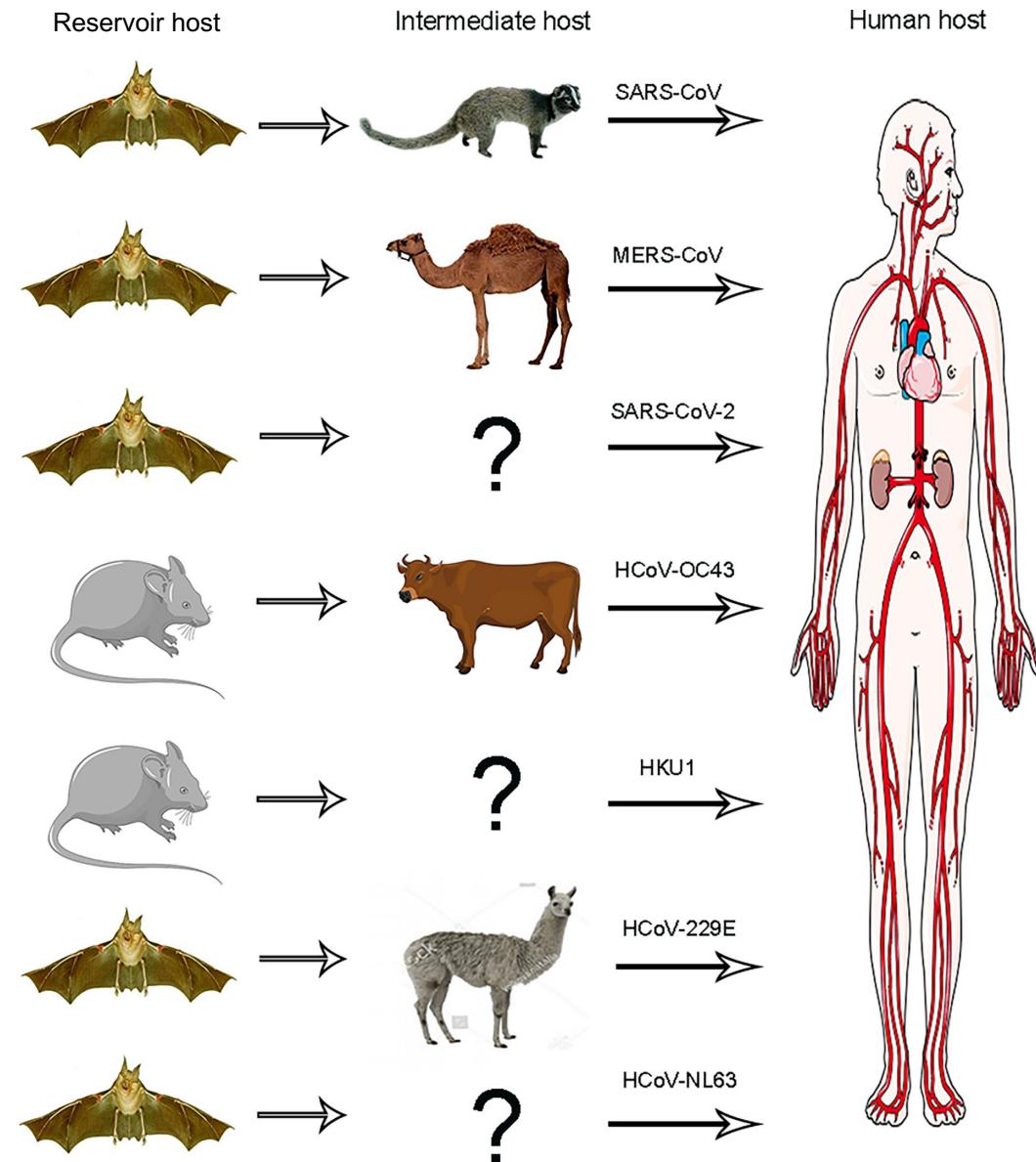


But it is known that bats do act as natural **reservoirs** and **maintenance hosts** for the majority of the world's **most virulent zoonotic viruses**.

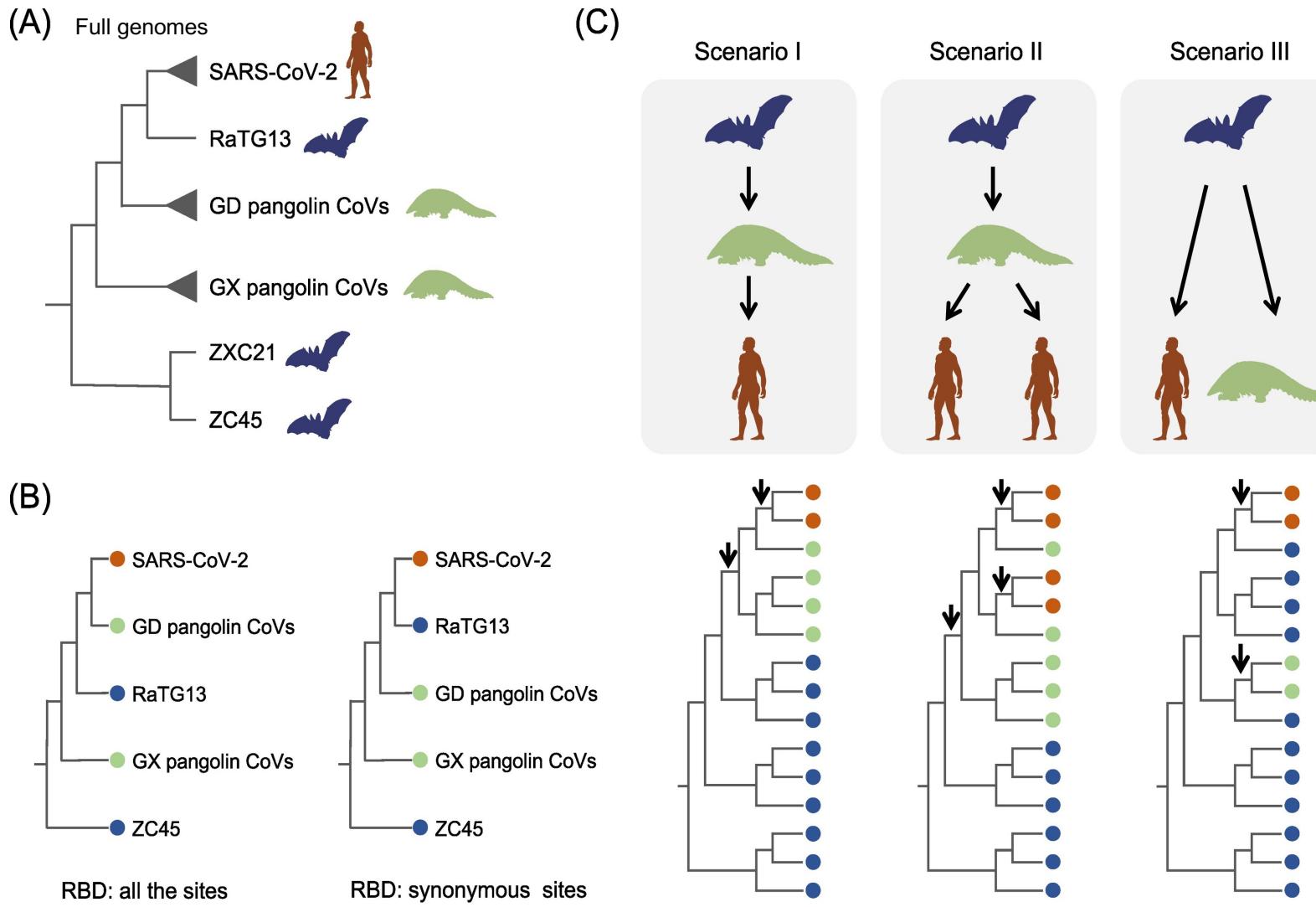
Bats are natural reservoir hosts for several subgenera of *Alpha*- and *Betacoronaviruses*. *Rhinolophus* spp. bats are reservoirs for the SARS-like *Sarbecoviruses*.



Many CoVs transmit (and adapt) via **intermediate hosts** prior to infecting humans.
An intermediate host for SARS-CoV-2 has **not yet been identified**.

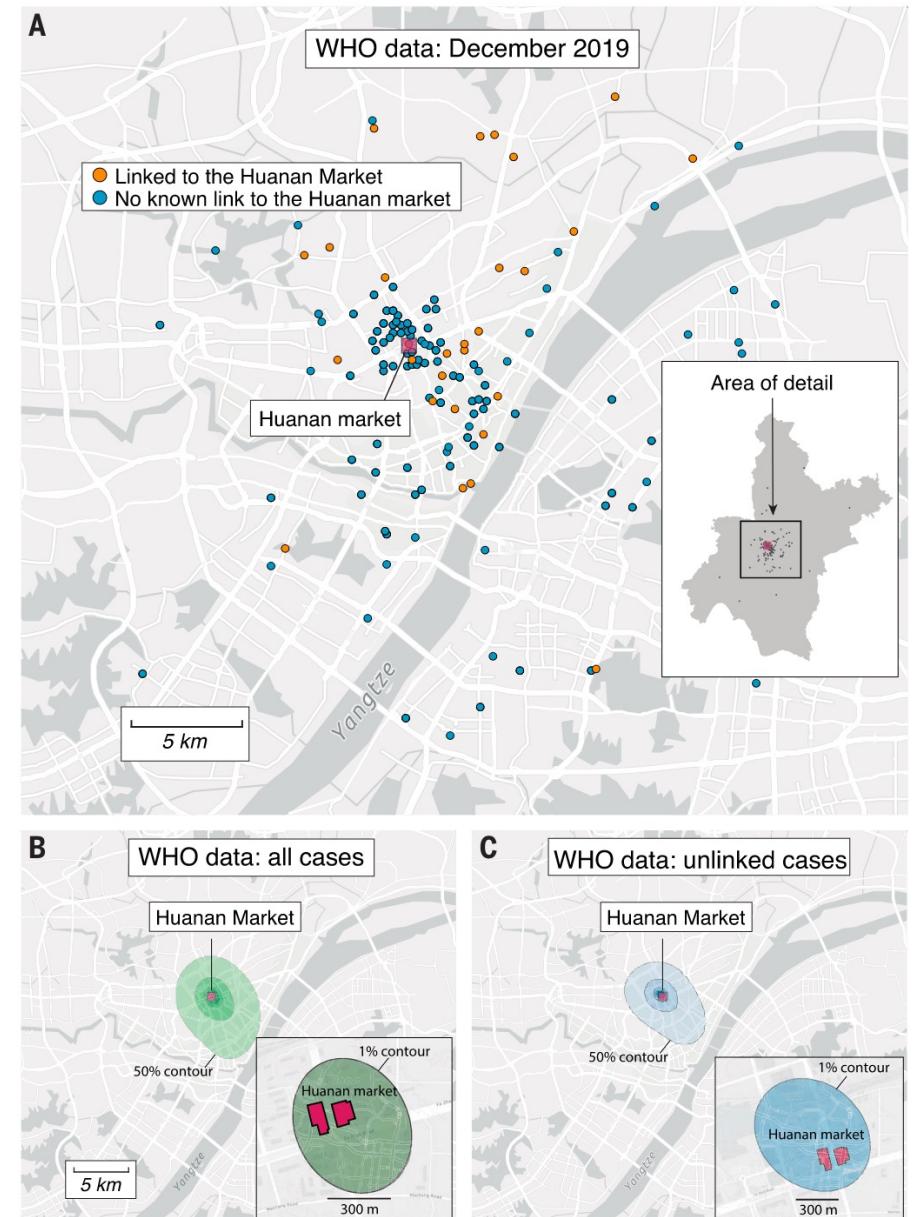
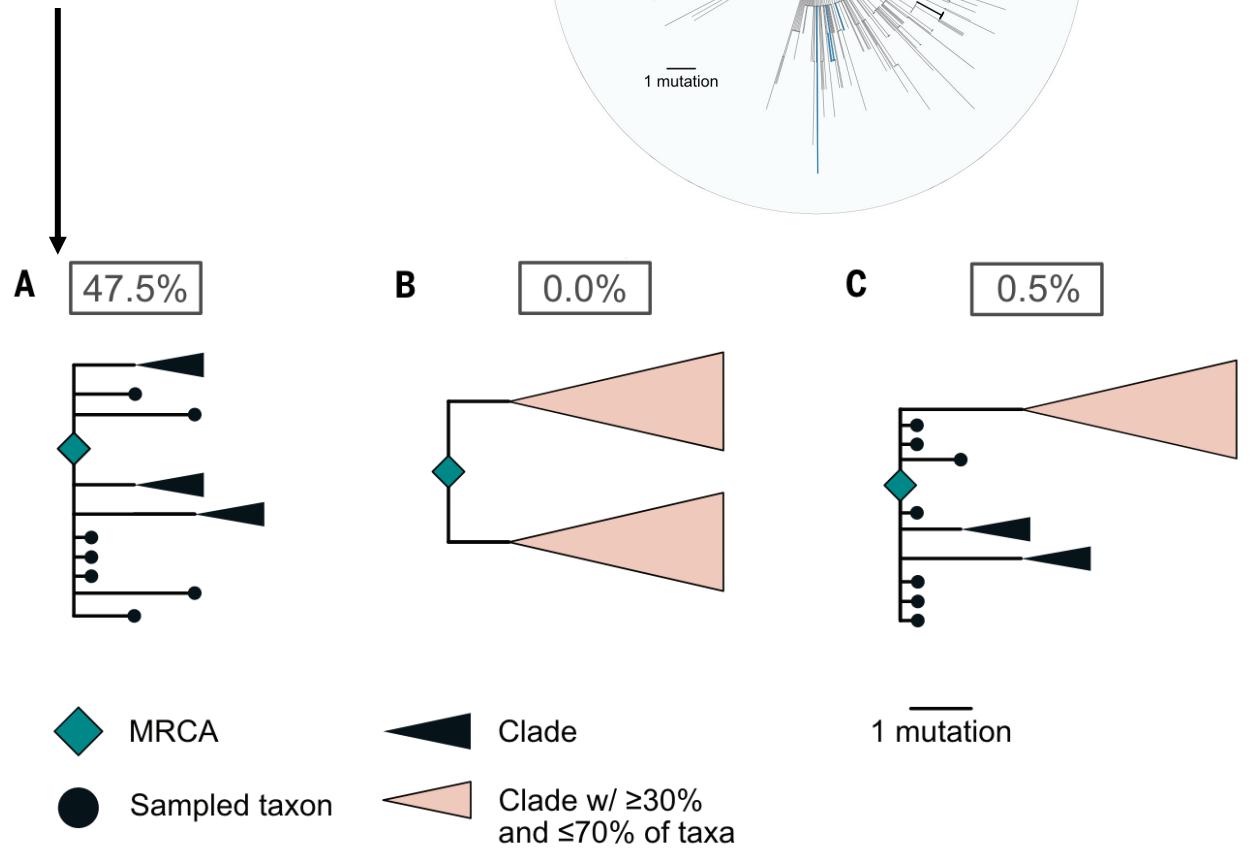


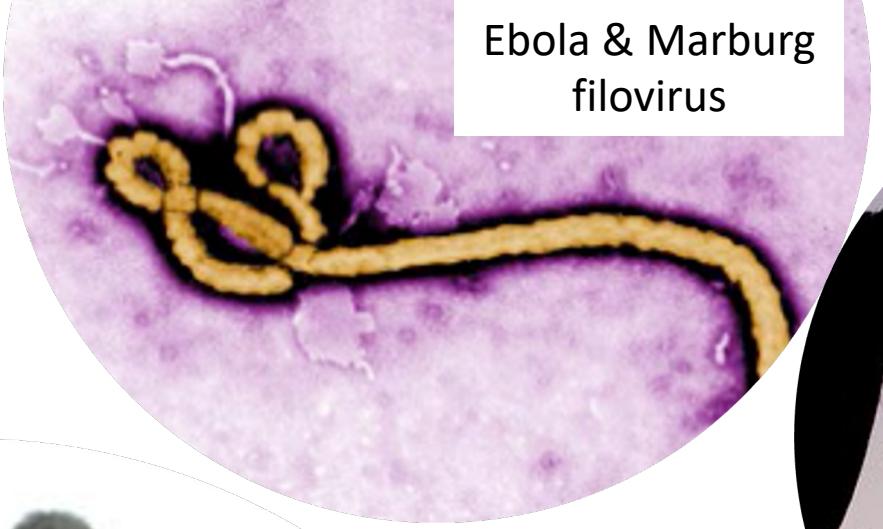
Bats likely sourced infections to both humans and pangolins in disparate spillover events (Scenario III)



Phylogenetic analysis suggests multiple spillover origins of SARS-CoV-2 to humans. Both lineages appear to have emerged from the Huanan Seafood Market.

Polytomy: a node on a phylogeny where more than 2 lineages descend from an ancestral lineage



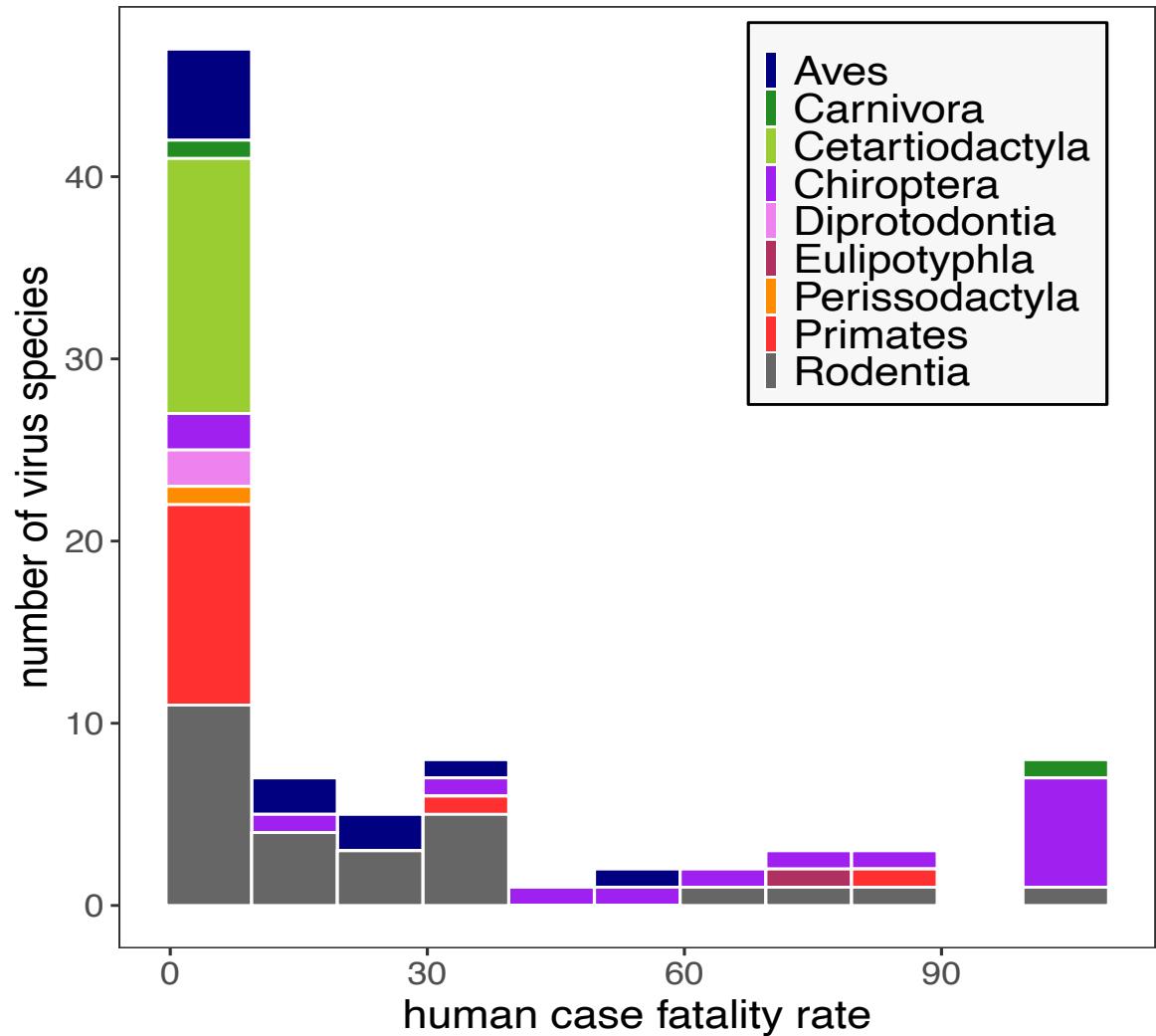


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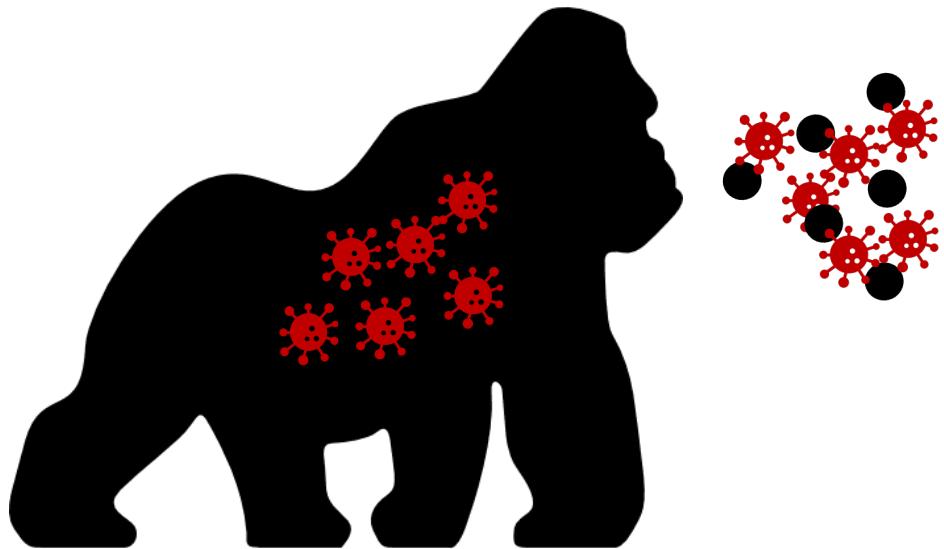
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Why do pathogens make us sick?

A virus will evolve to
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between-host infections (R_0).

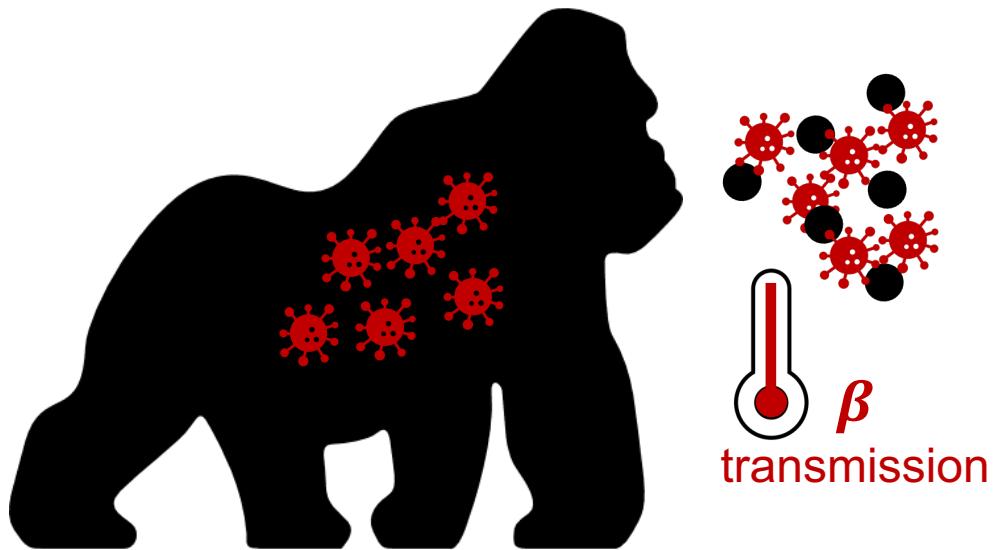
*Why do pathogens
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Alizon et al. 2008. *J Evolutionary Biology*
Anderson and May 1982. *Parasitology*.

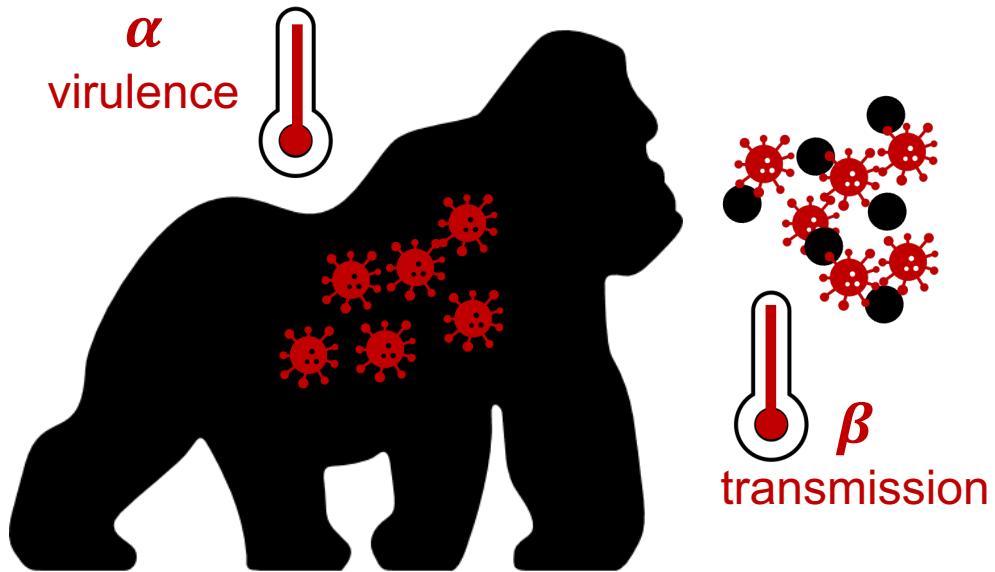
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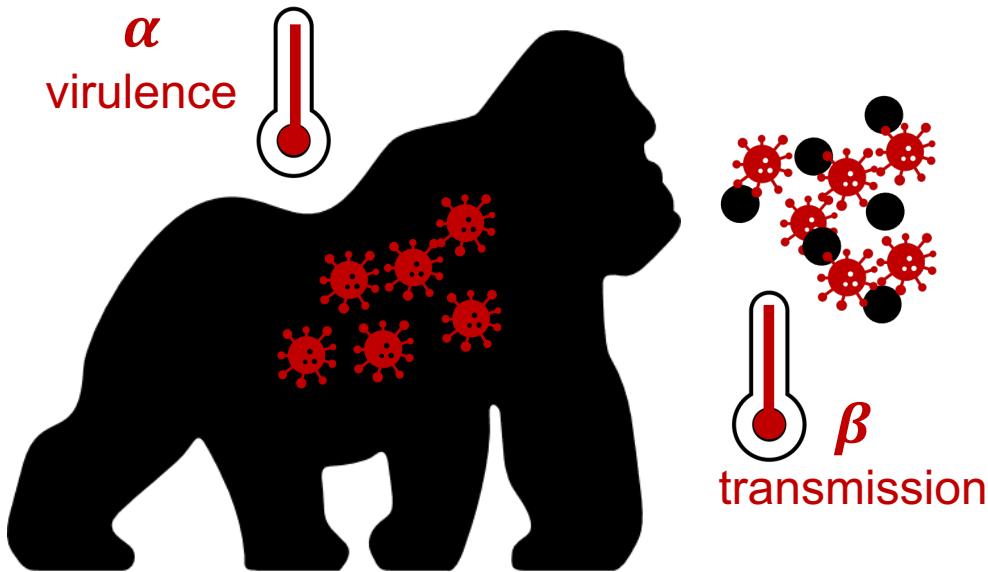
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Mechanisms that promote
transmission may also enhance
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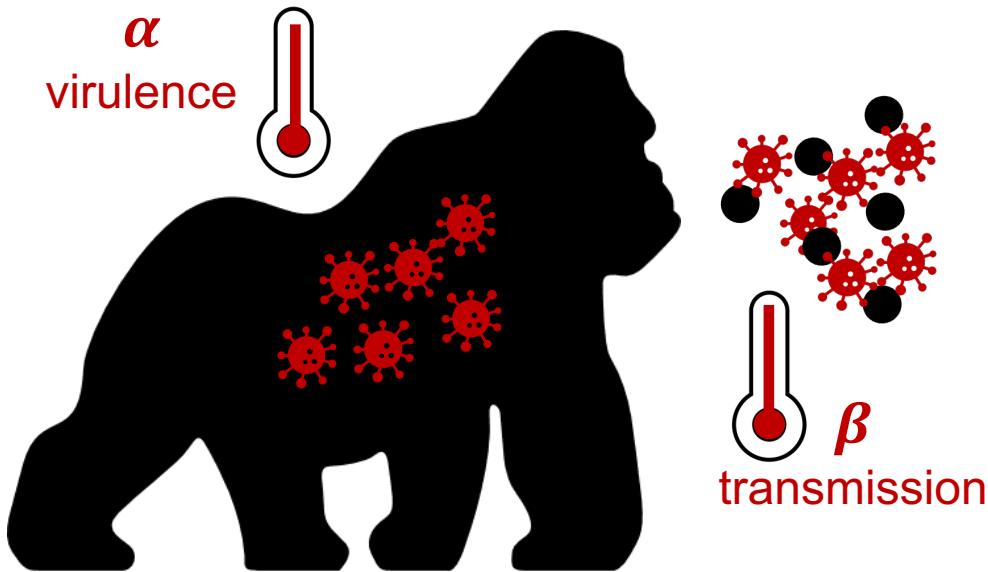


Mechanisms that promote **transmission** may also enhance **virulence** to the host.

Why do pathogens make us sick?

Virulence, then, is a by-product of a pathogen's need to transmit for reproduction!

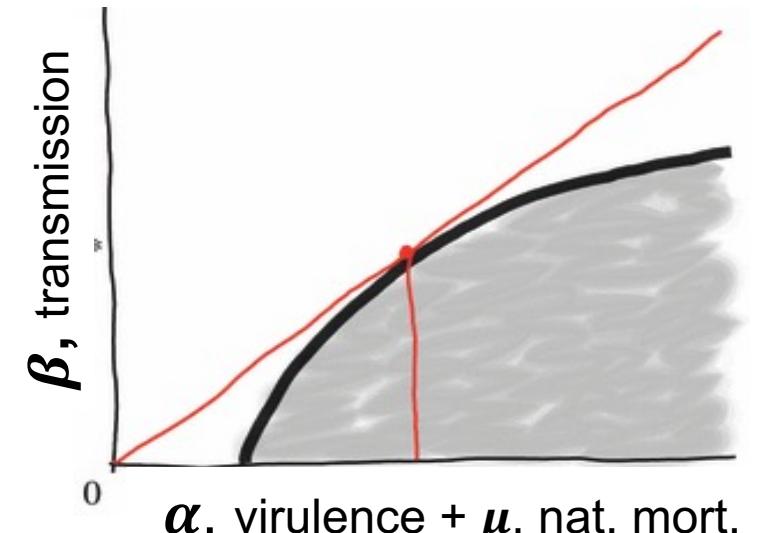
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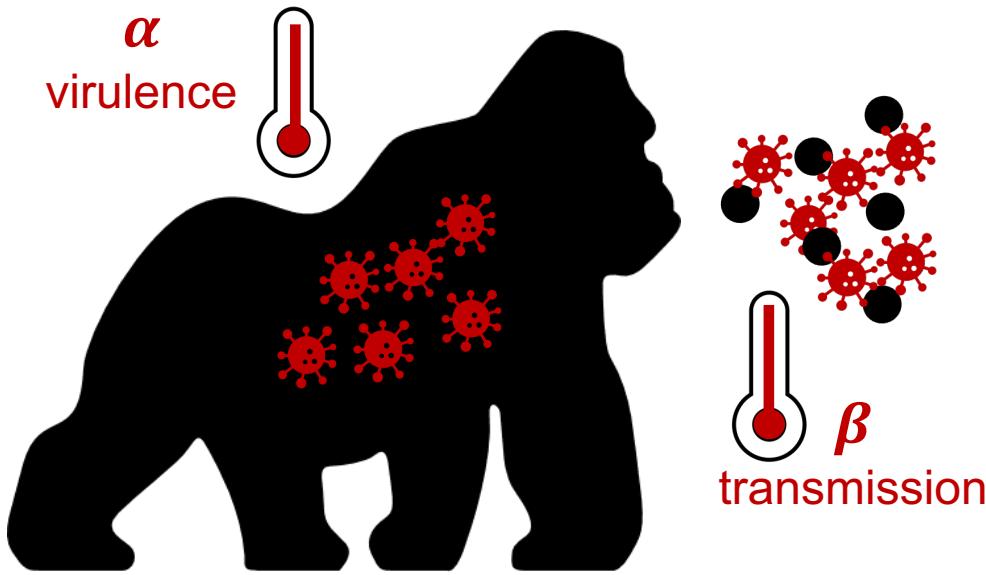
As a result, we predict the evolution of "**optimal virulence**."



$$R_0 = \frac{\beta(\text{virus density})}{\gamma + \mu + \alpha(\text{virus density})}$$

} infections created
} infections lost

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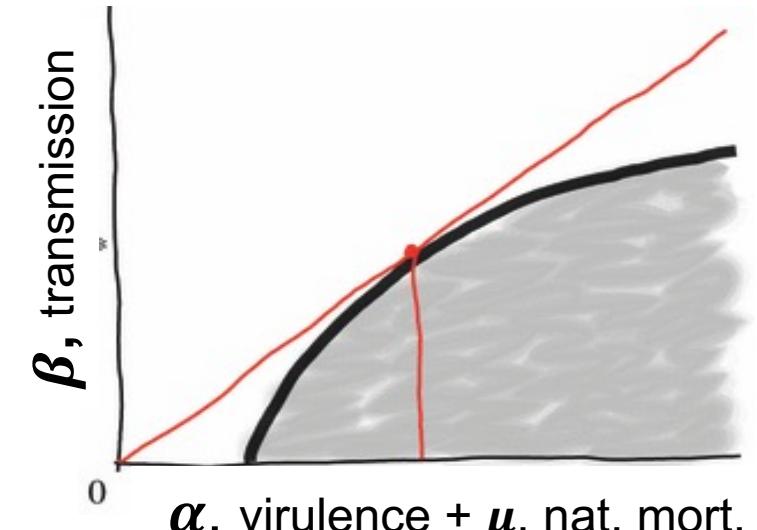
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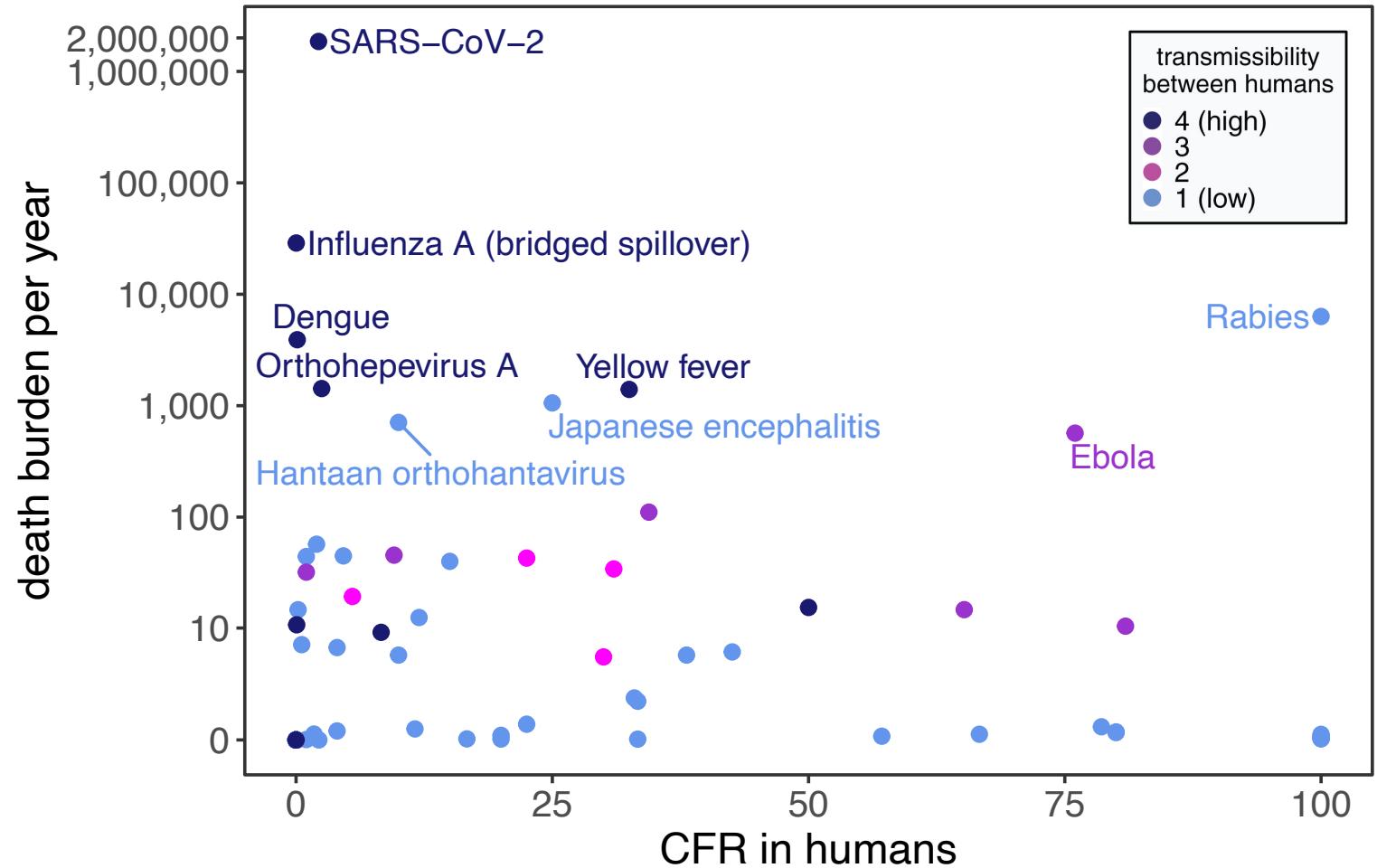
Note that originally Anderson and May (1982) represented this link to virus density as acting on the disease recovery rate, though it is now more commonly expressed as a function of virulence!

$$R_0 = \frac{\beta(\text{virus density})}{\gamma + \mu + \alpha(\text{virus density})}$$

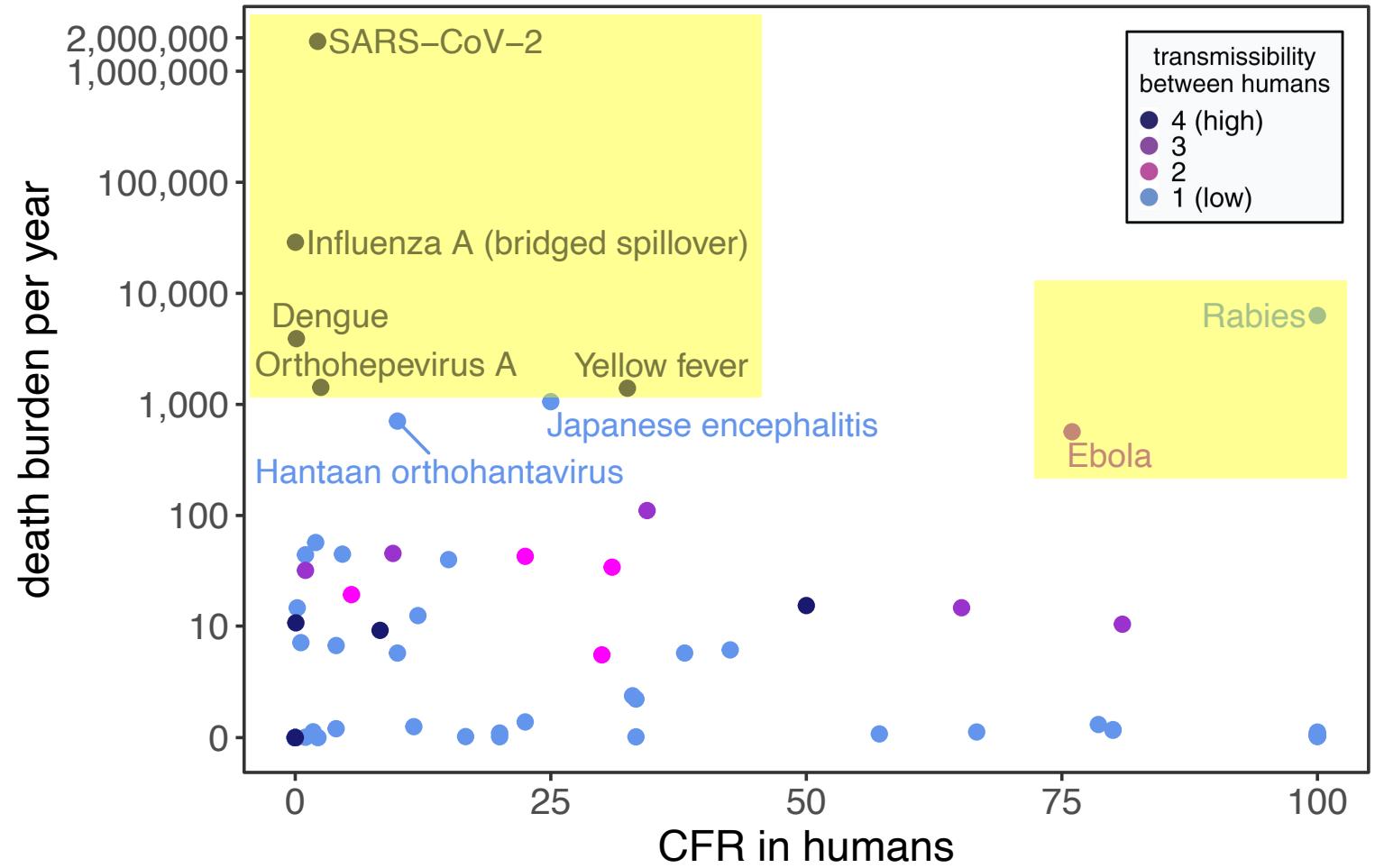
Legend:
} infections created
} infections lost



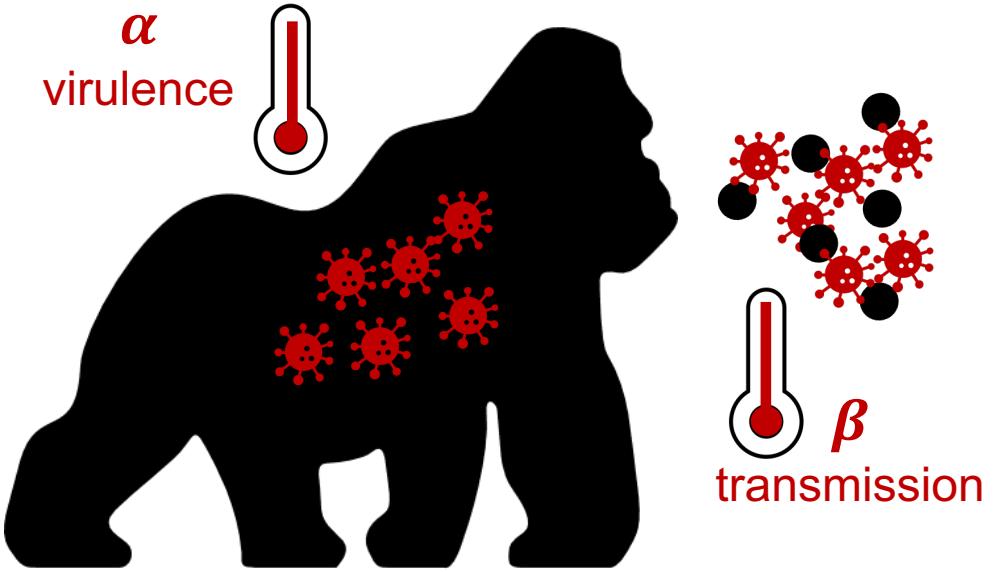
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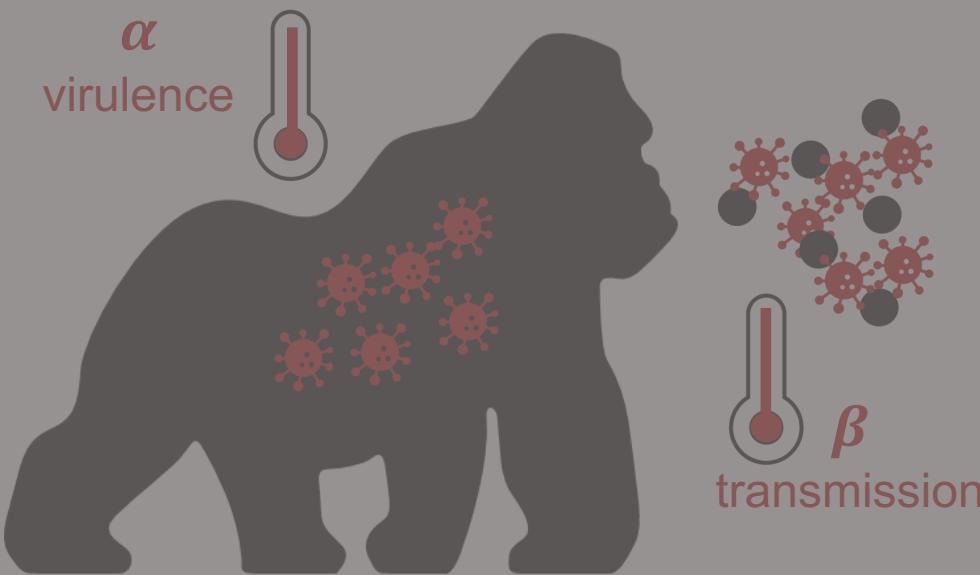


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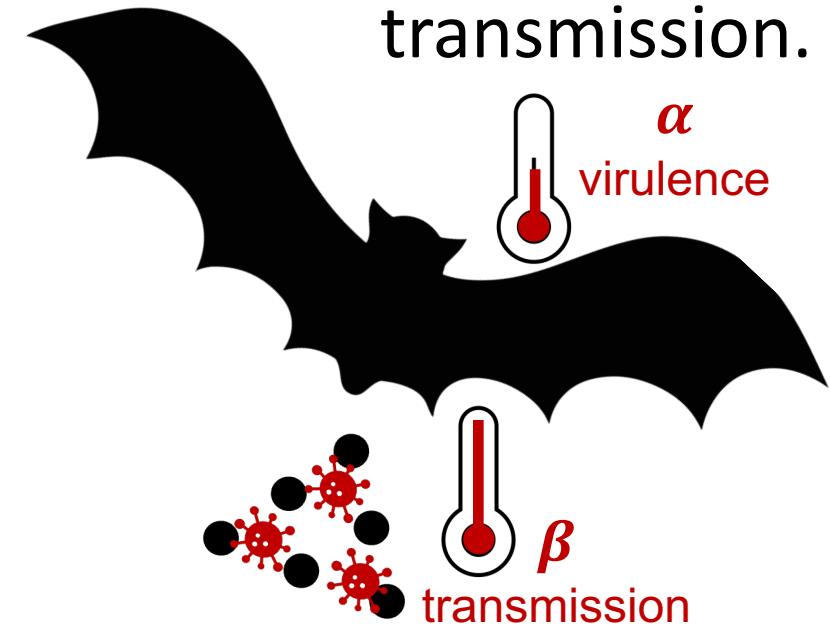
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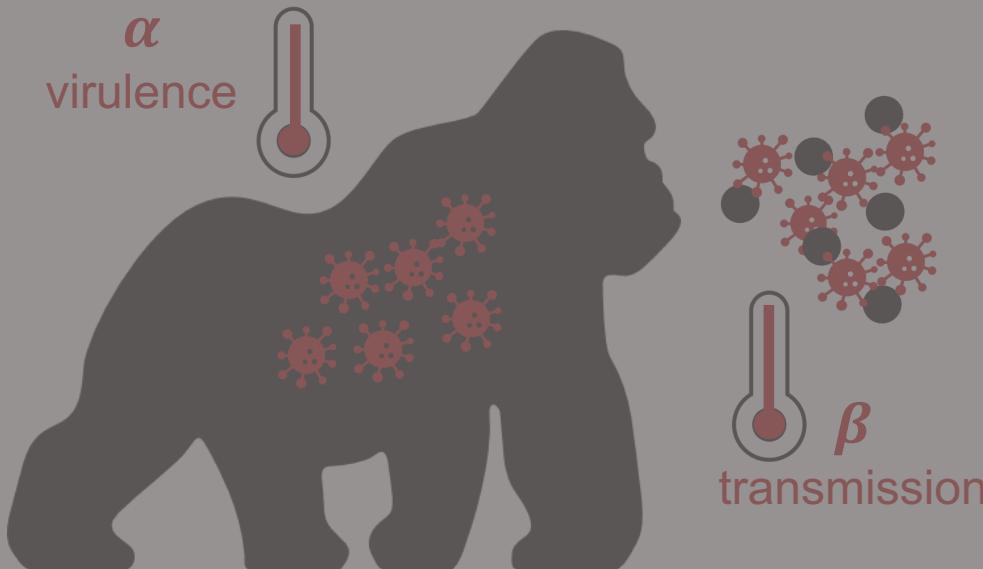


Mechanisms that promote **transmission** may also enhance **virulence** to the host.

Bats accrue **less virulence** for a given level of transmission.

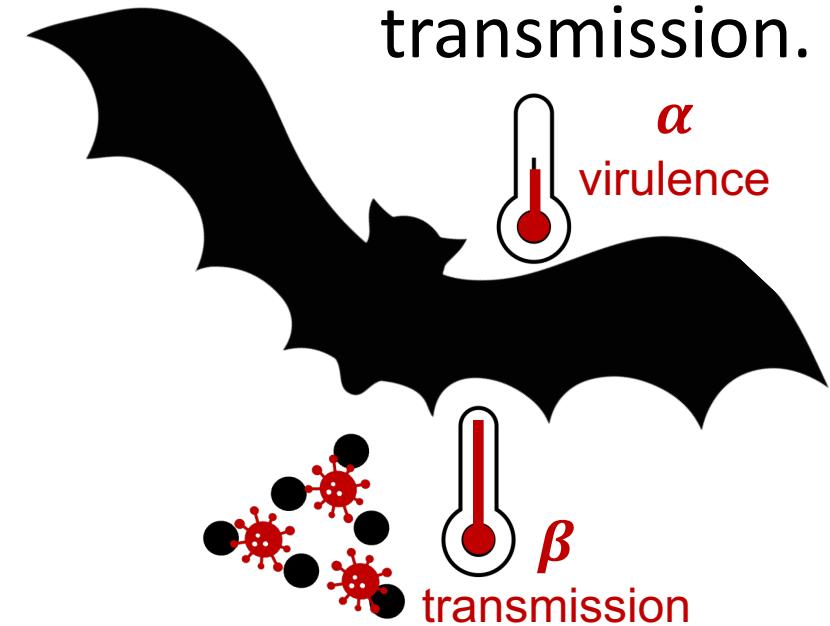


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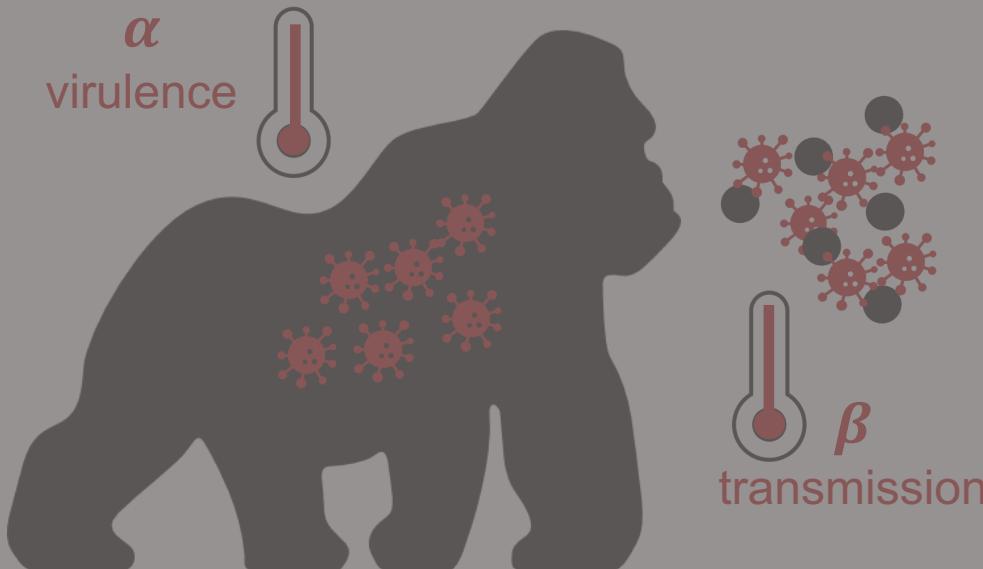
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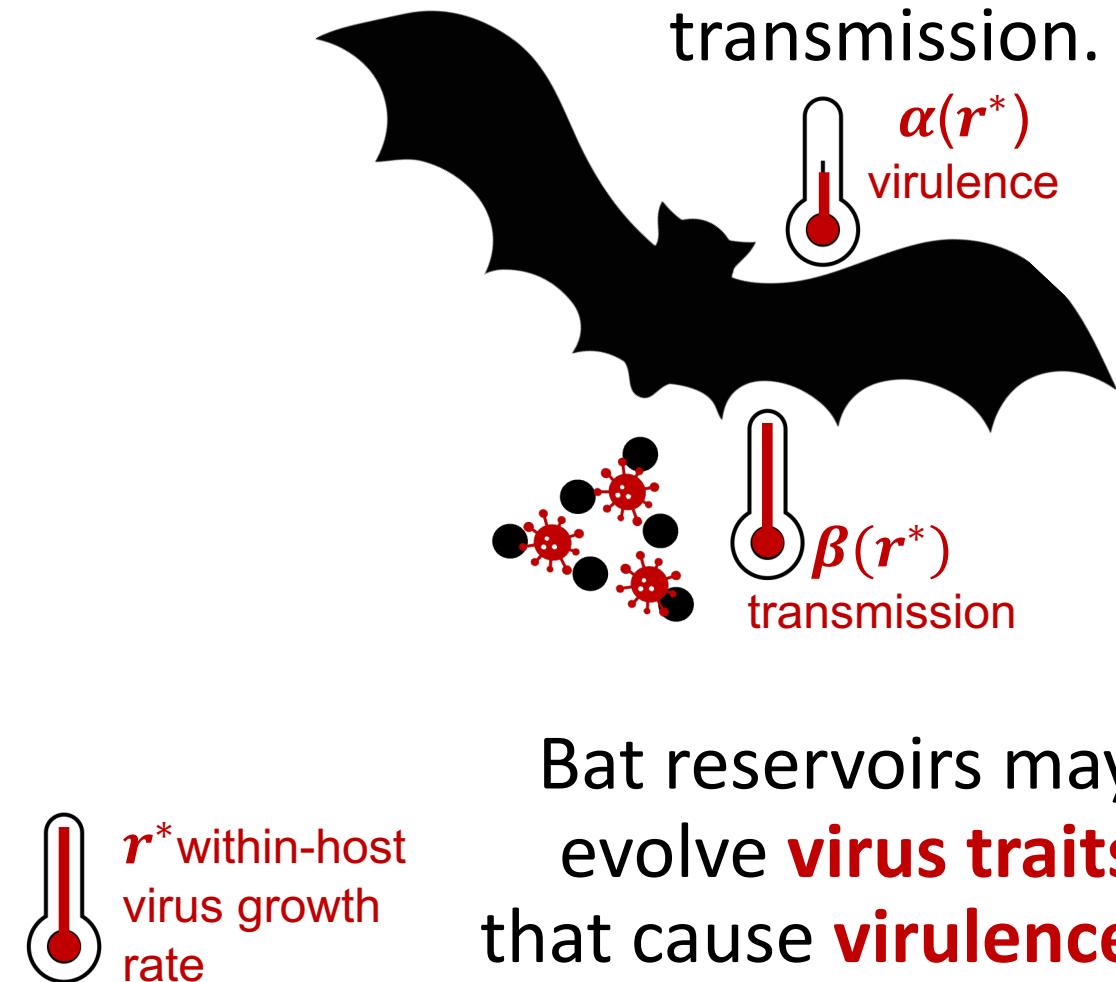
Bat reservoirs may evolve **virus traits** that cause **virulence in non-bats**.

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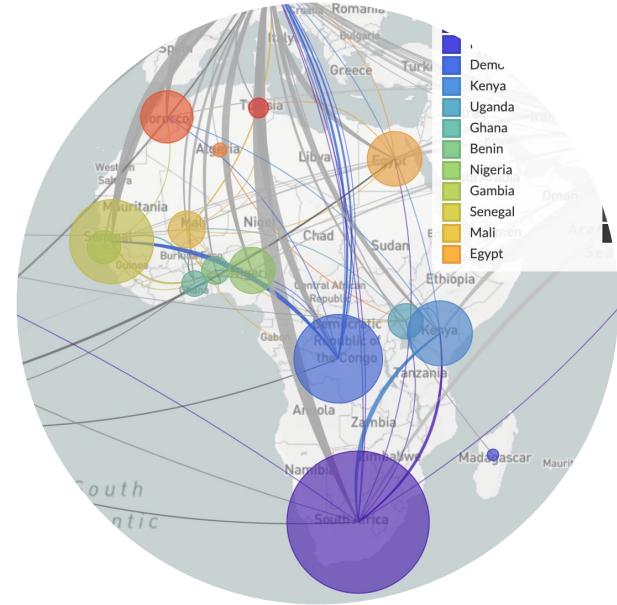


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Now:
What does sequencing have to do with it?

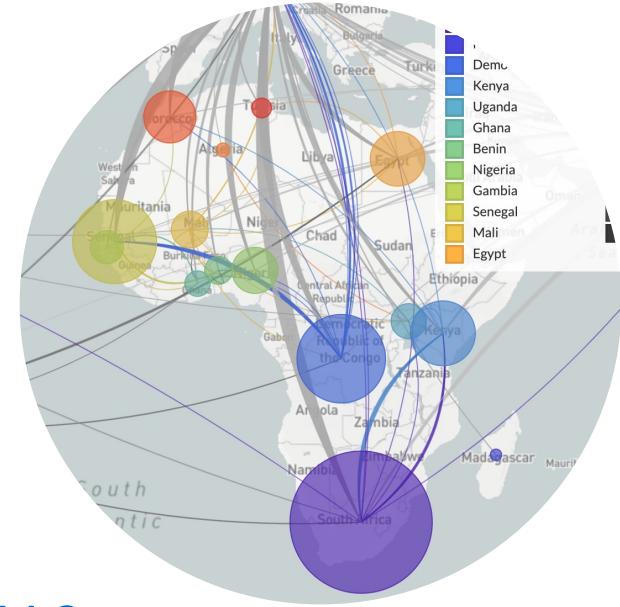
Phyldynamics

- The field represents the union:
 - Phylogenetics
 - Epidemiological dynamics



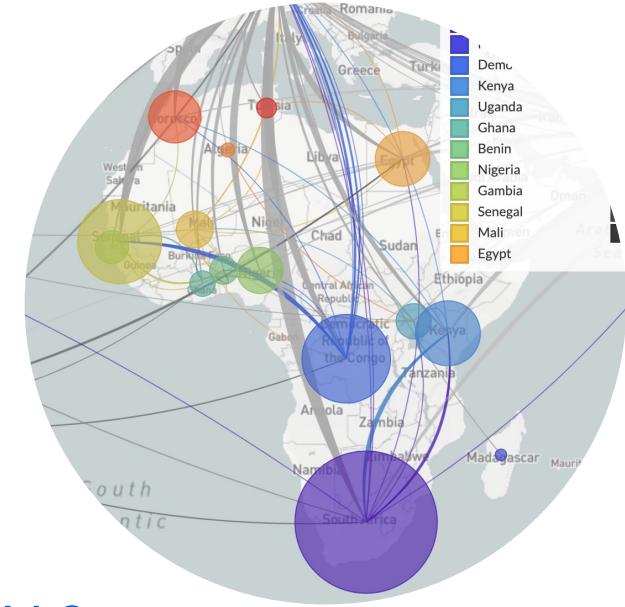
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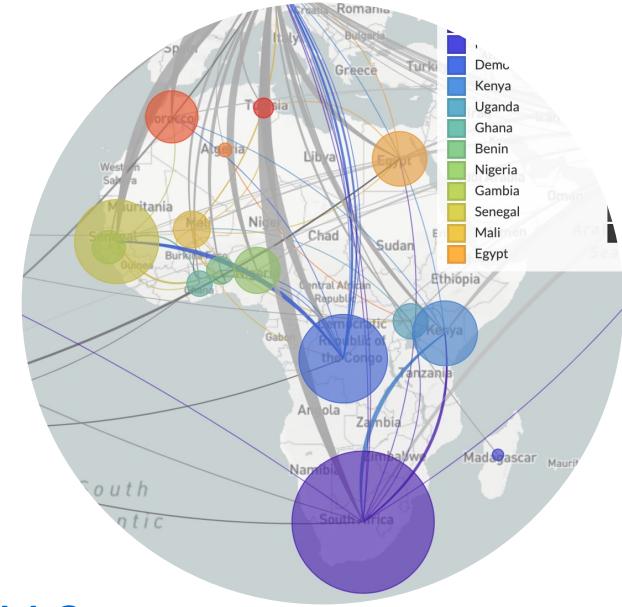
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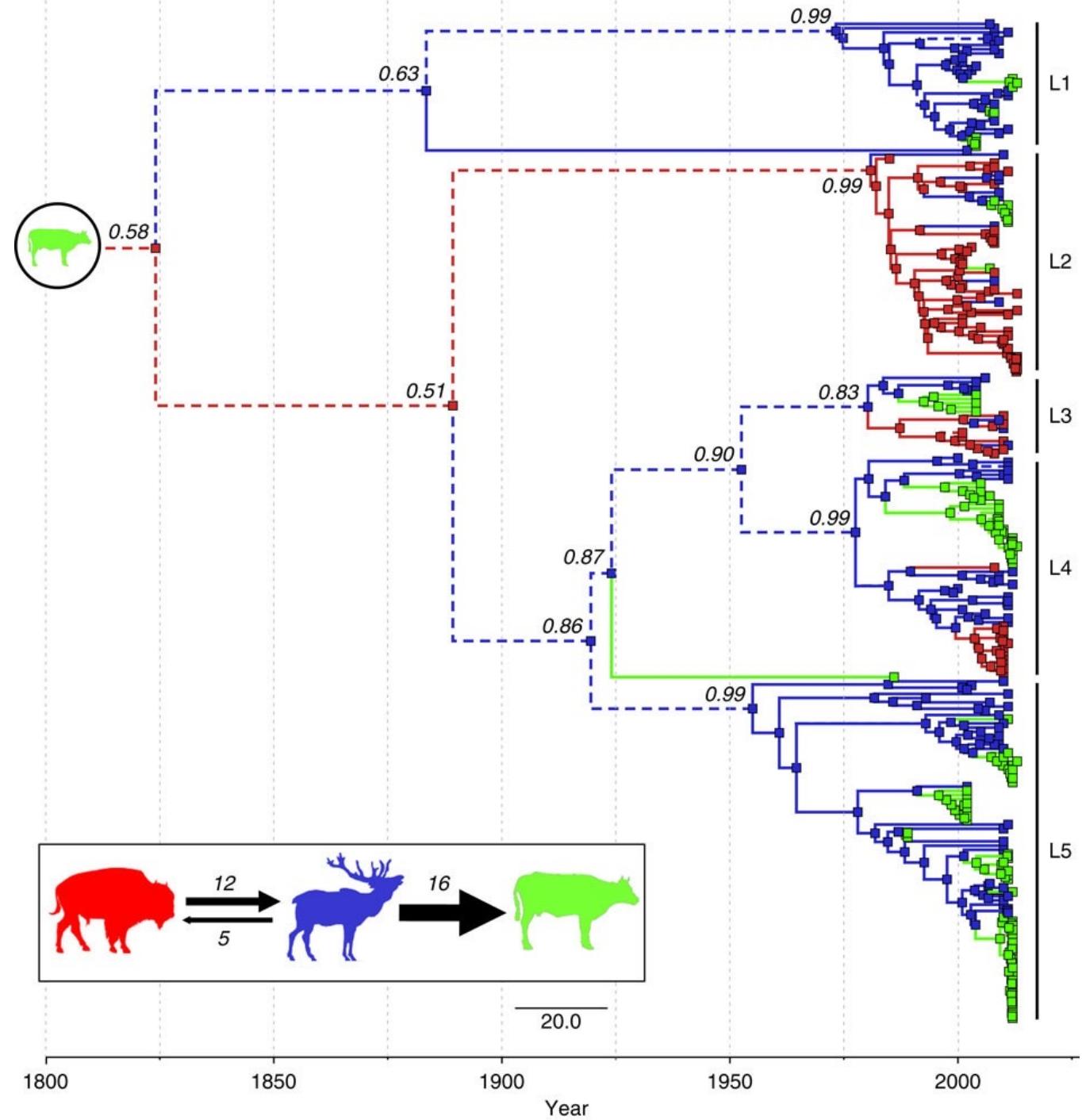


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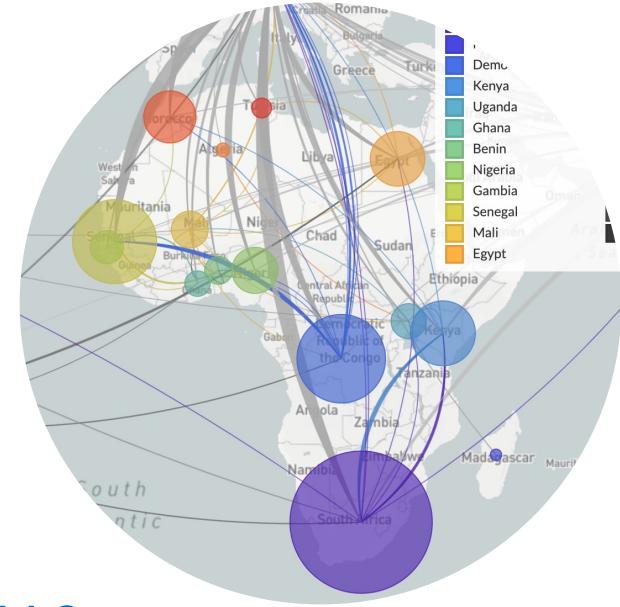


Host relationship:
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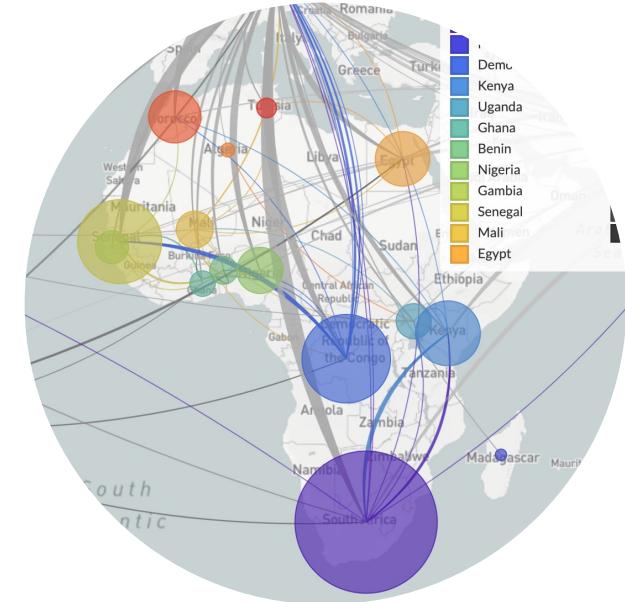
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- What are the two kinds of models we discussed in class?
 - Which of the above is closest to a phylodynamic tree?



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- What are the two kinds of models we discussed in class?
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- phylogenetic tree \approx statistical model
- phylodynamic tree \approx mechanistic model

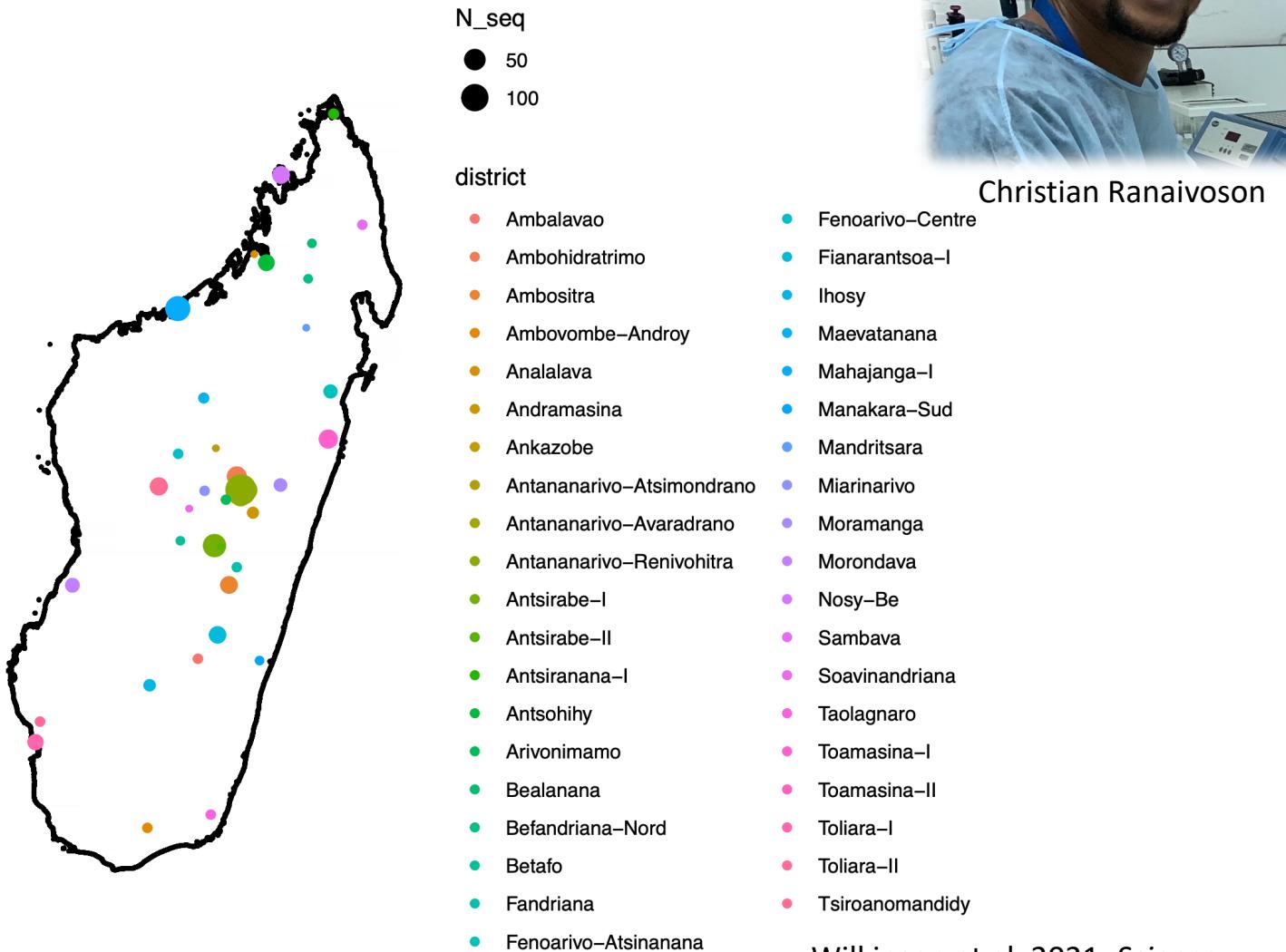
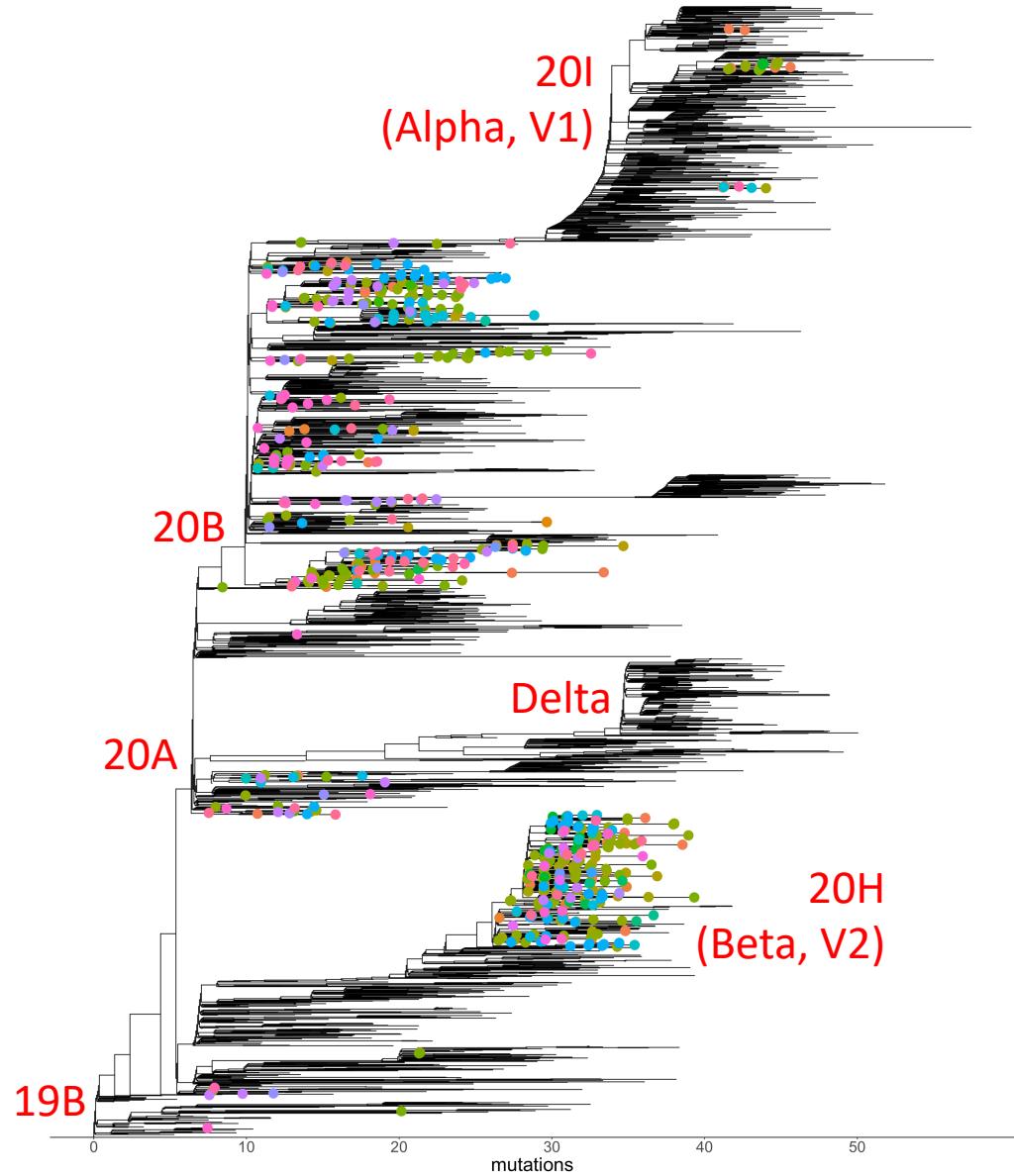


iSeq arrived in
Madagascar in
late Feb 2020...

GCE funding to
identify the
etiology of
human fevers...



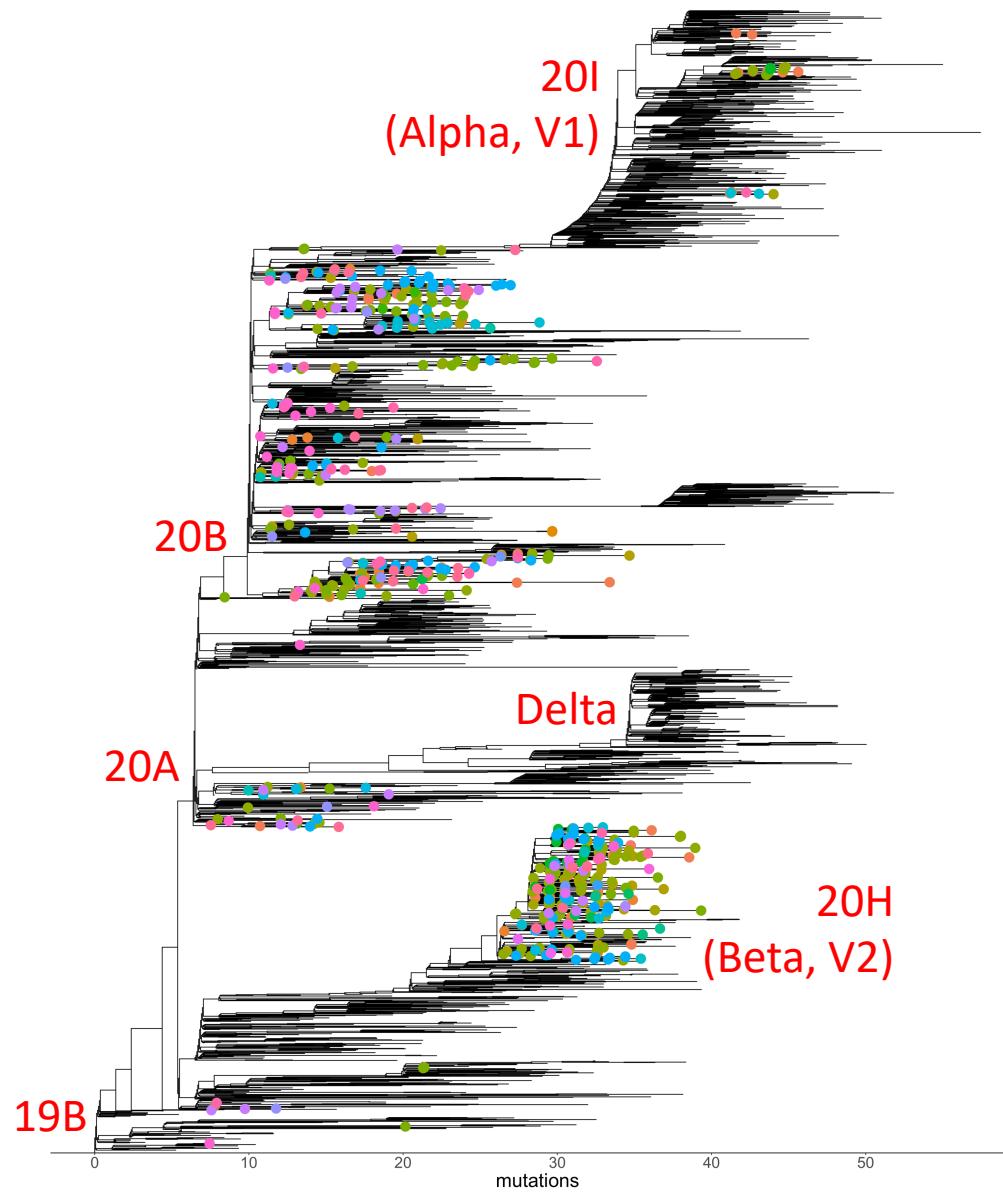
We used this technology to contribute >1000 SARS-CoV-2 genomes to GISAID...



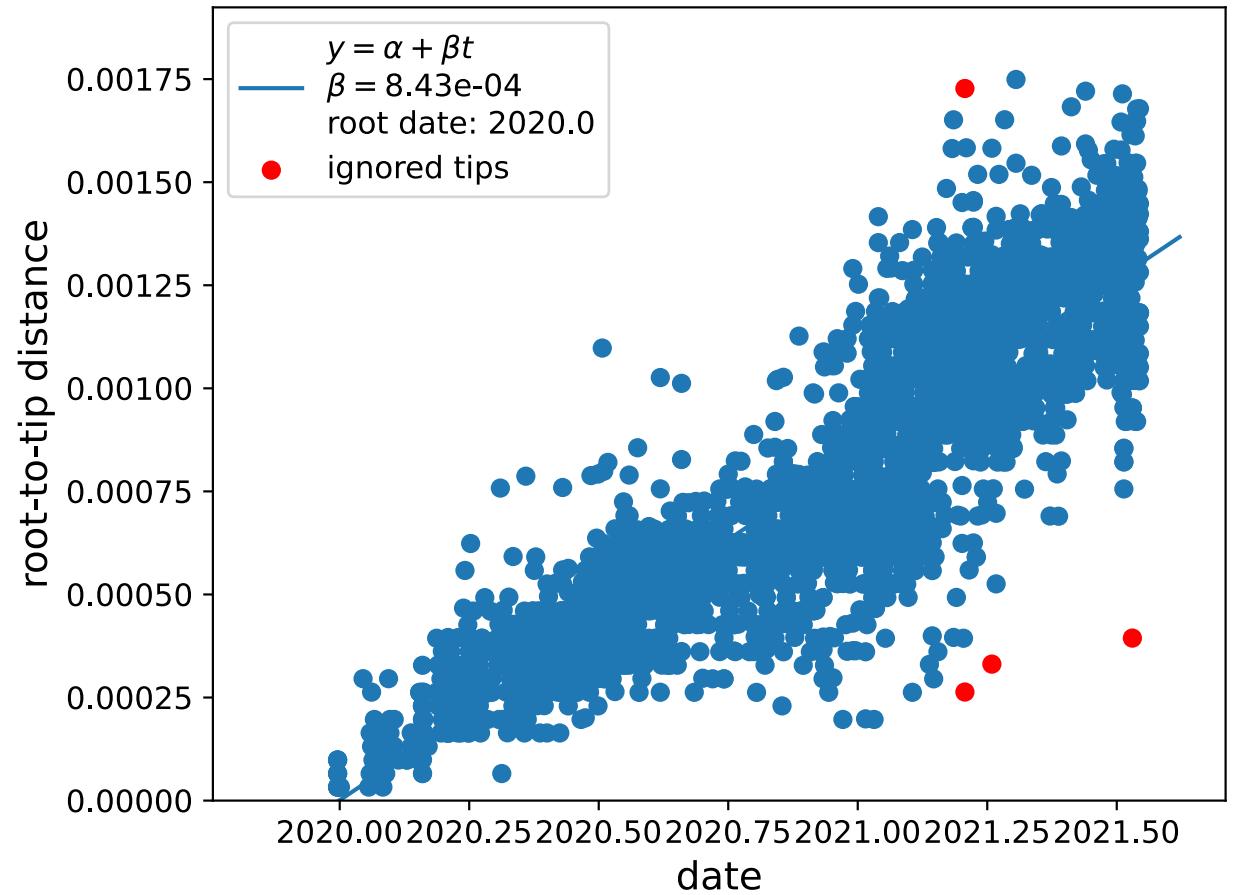
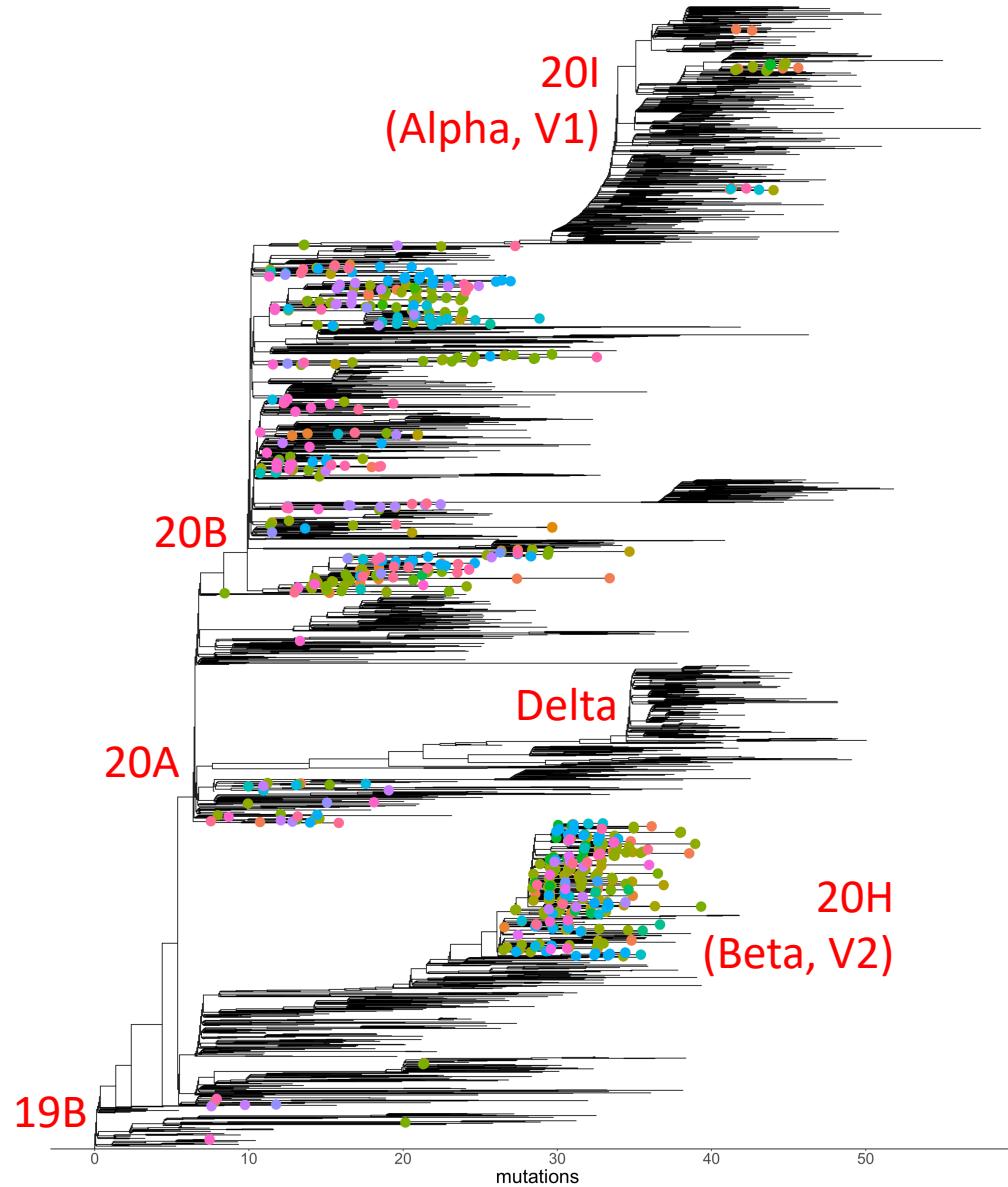
Christian Ranaivoson

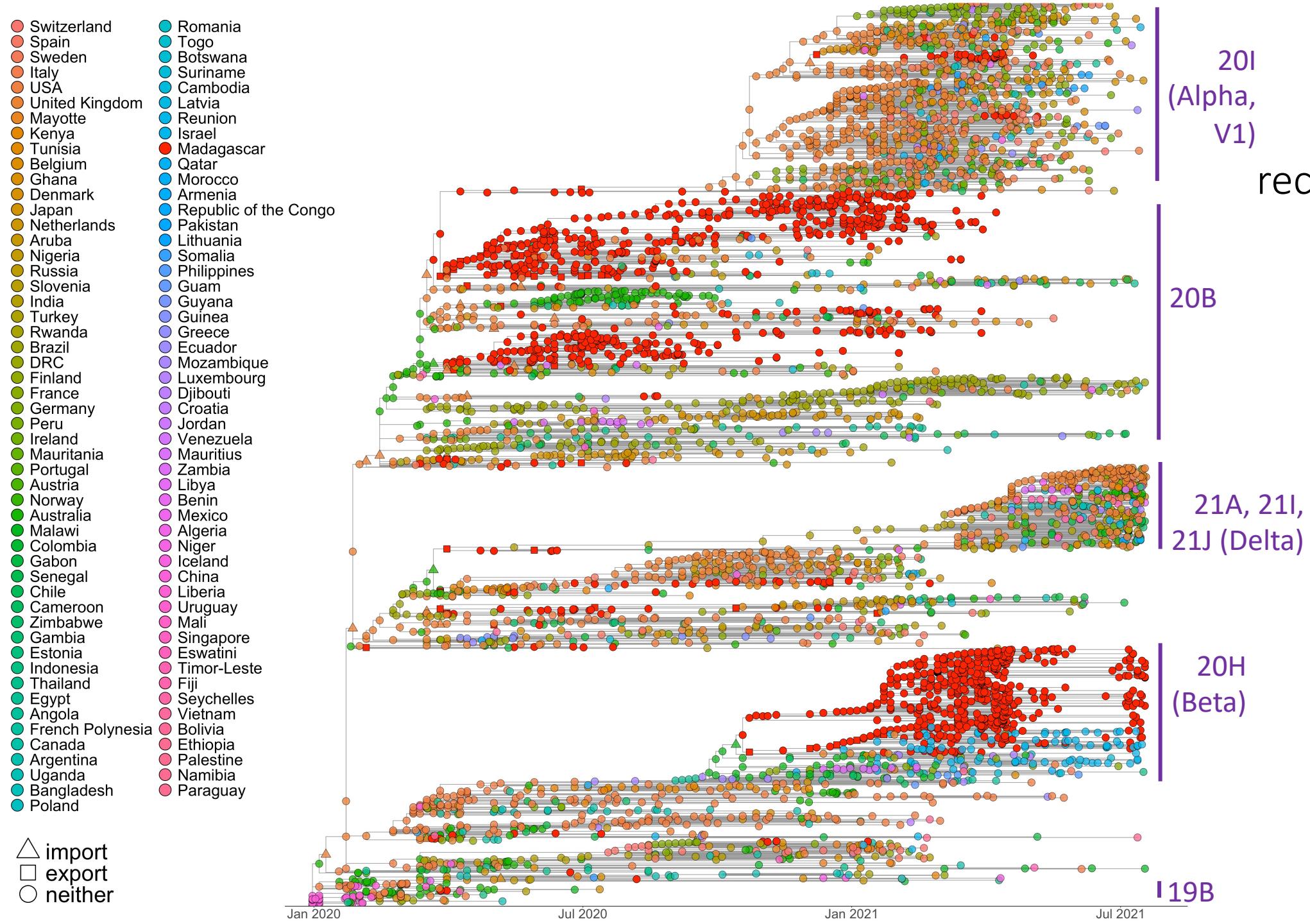
Wilkinson et al. 2021. *Science*
Randremana et al. 2021. *Influenza & Other Resp Viruses*

We start with a Maximum Likelihood phylogeny...



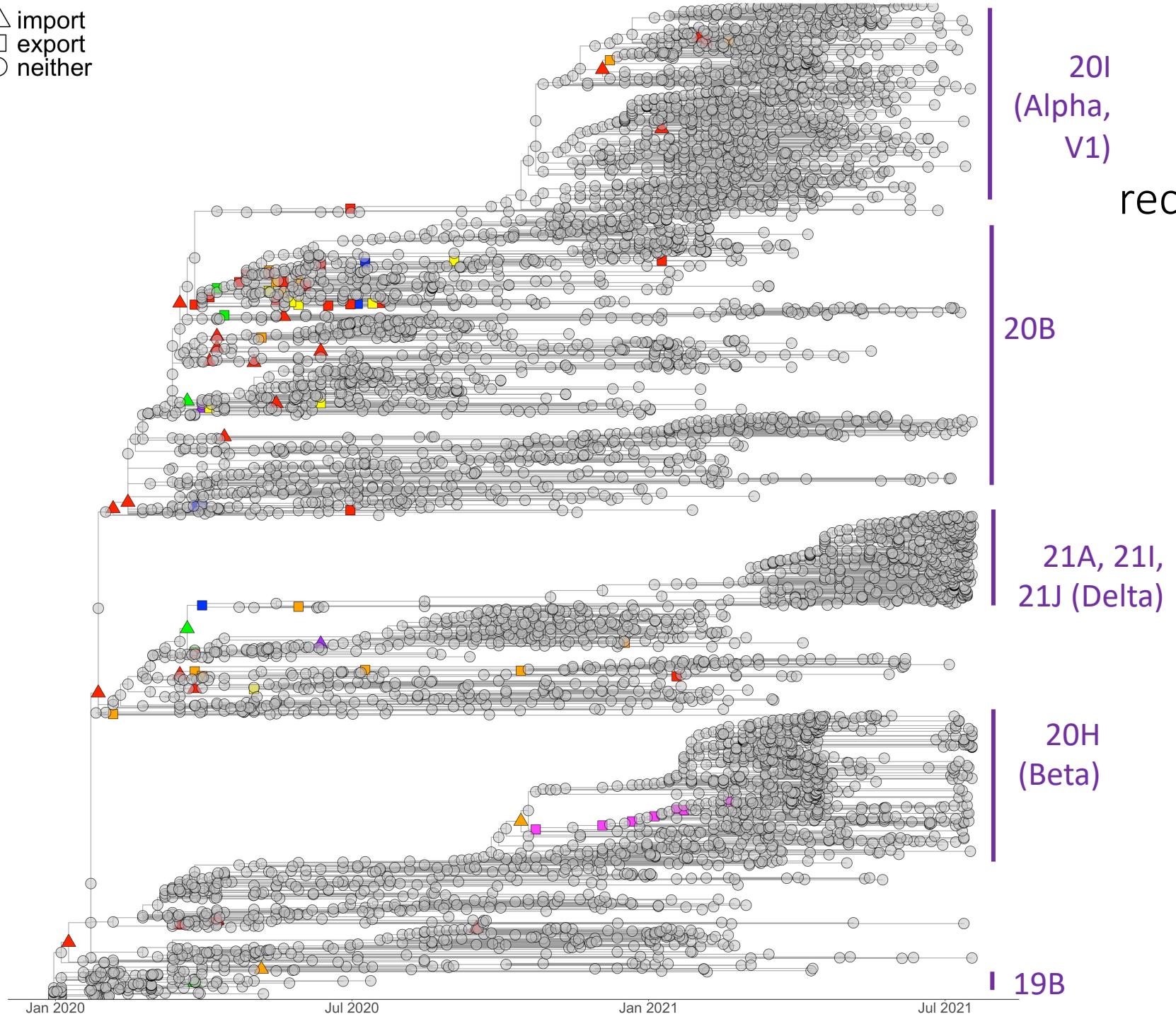
We apply a molecular clock to the ML phylogeny to convert to timetree...





Then we apply a migration model down the tree to reconstruct ancestral sequences and states...

- Europe
 - Africa
 - South-America
 - Australia
 - Asia
 - SWIO
 - North-America
 - neither
- import
 - export
 - neither

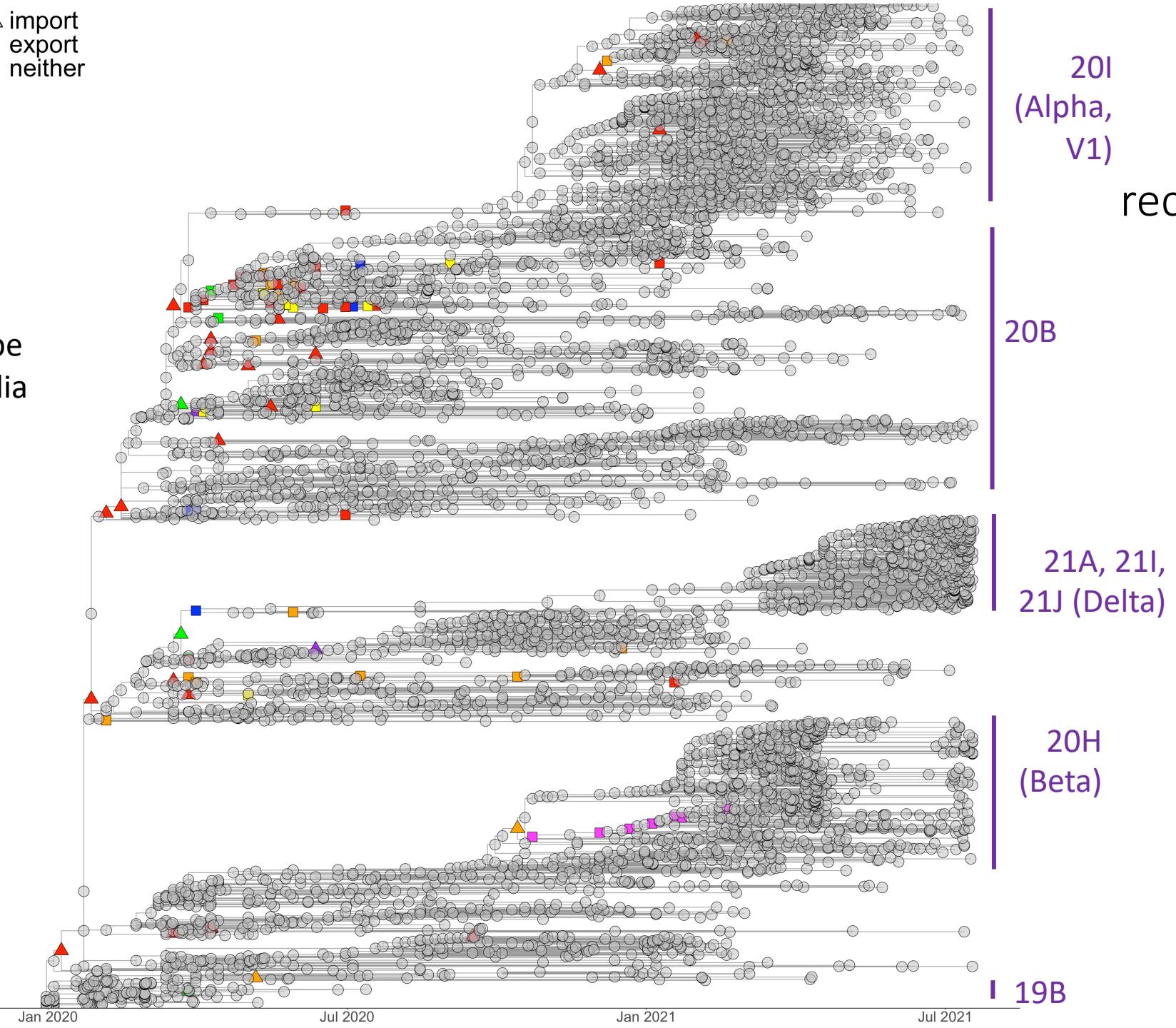


Then we apply a migration model down the tree to reconstruct ancestral sequences and states...



32 Importations:

- 23 from Europe
- 4 from Australia
- 2 from North America
- 2 from Africa
- 1 from Asia



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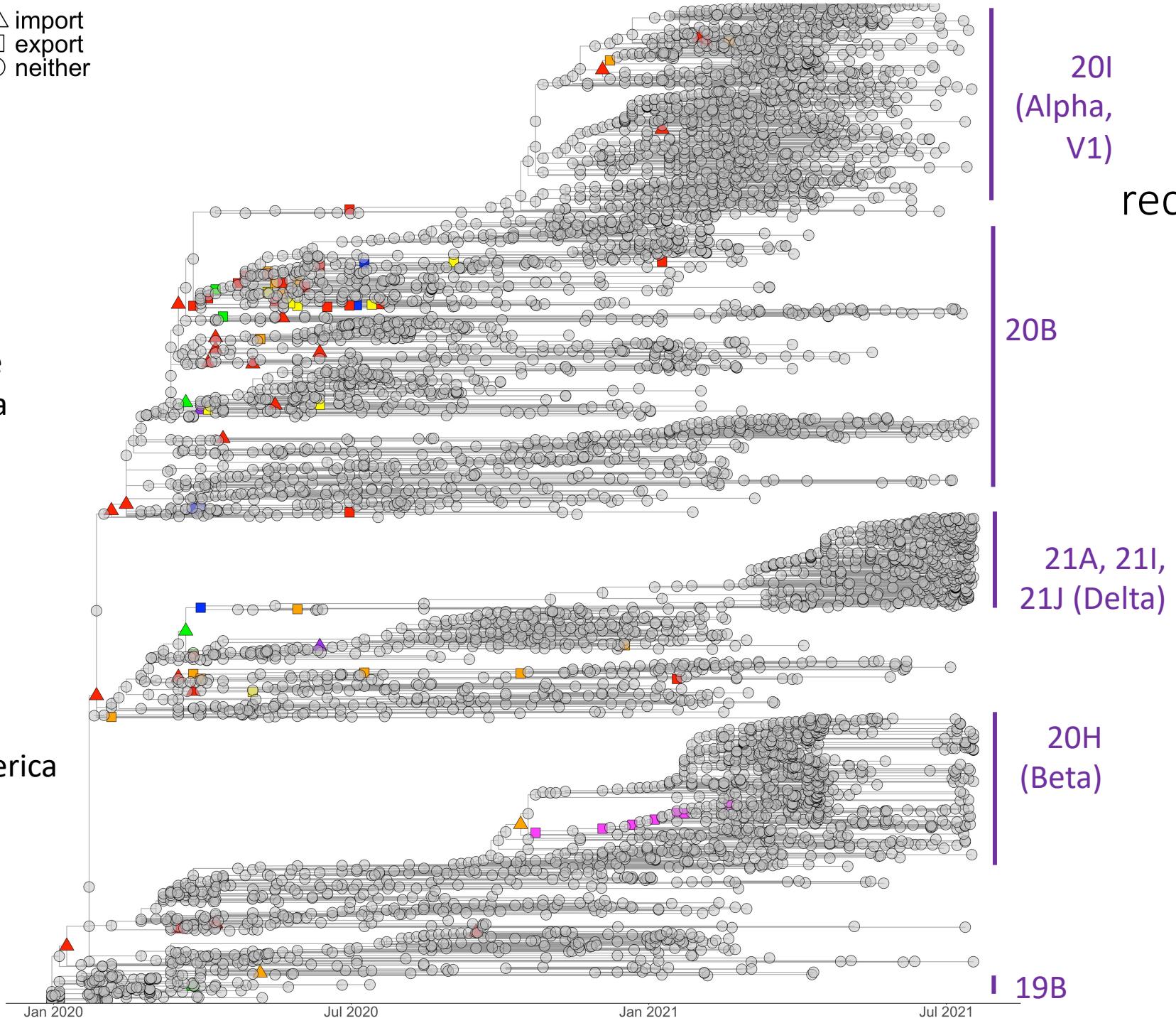


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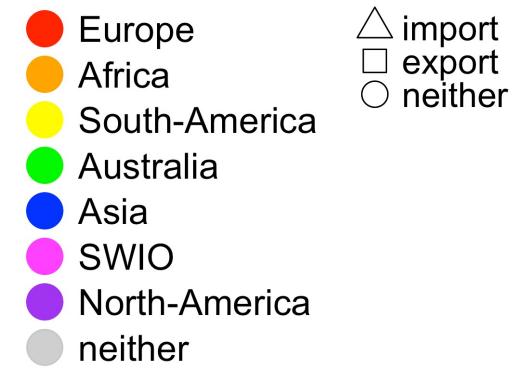
- 23 from Europe
- 4 from Australia
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58 Exports:

- 18 to Europe
- 17 to Africa
- 8 to South America
- 7 to SWIO
- 4 to Australia
- 4 to Asia



Then we apply a migration model down the tree to reconstruct ancestral sequences and states...

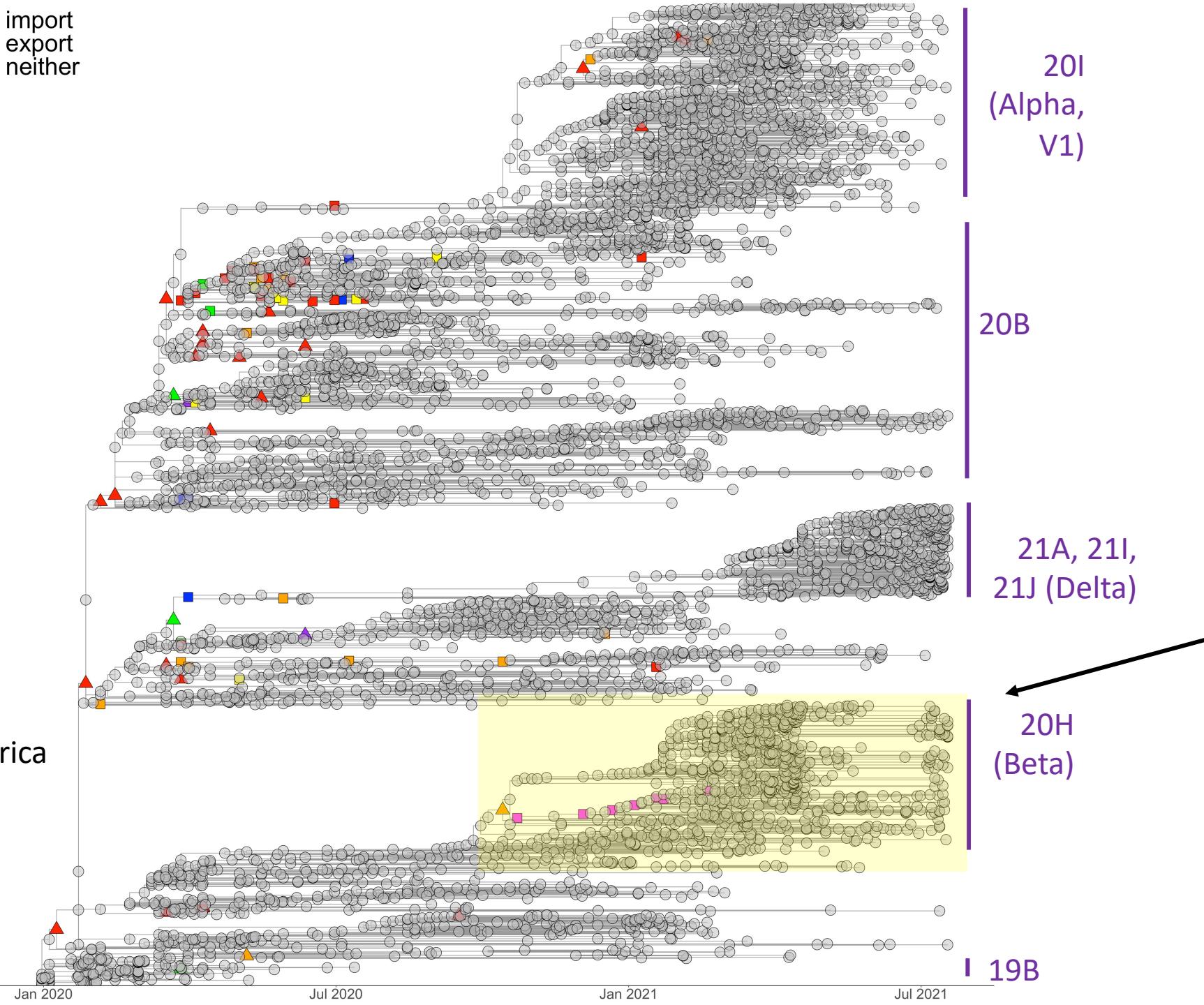


32 Importations:

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58 Exportations:

- 18 to Europe
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- 7 to SWIO
- 4 to Australia
- 4 to Asia



Imported from East Africa. Exported to SWIO.

20I
(Alpha,
V1)

20B

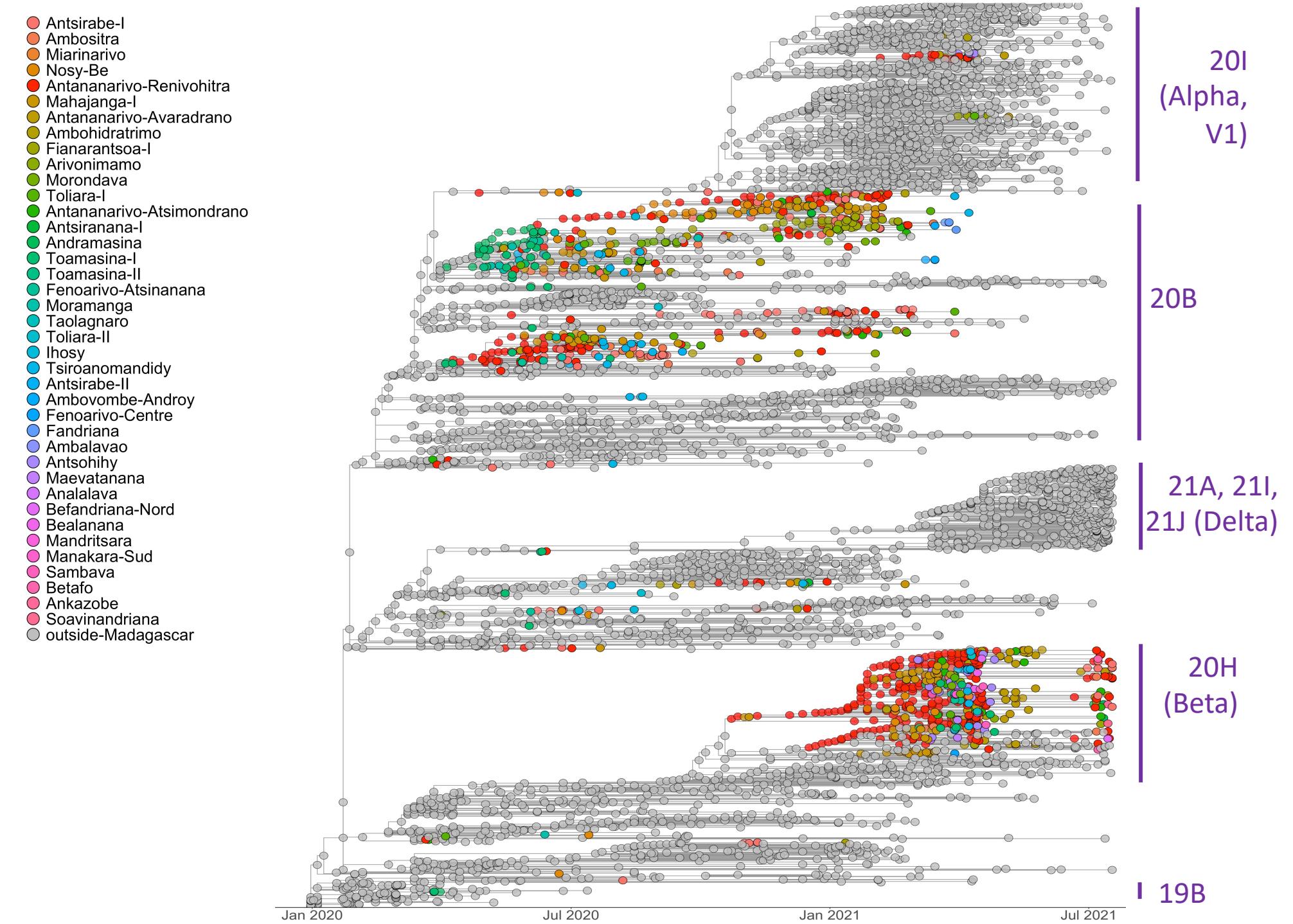
21A, 21I,
21J (Delta)

20H
(Beta)

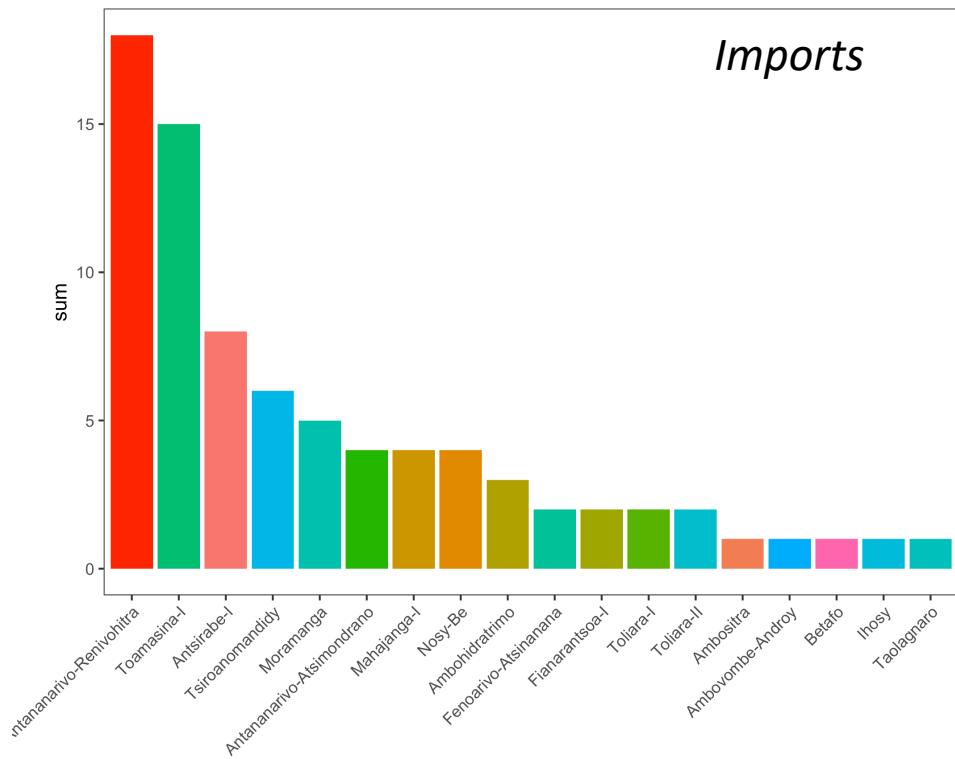
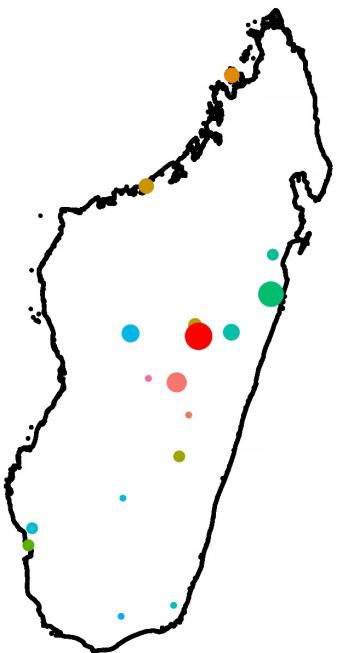
| 19B



Imported
from East
Africa.
Exported to
Réunion.

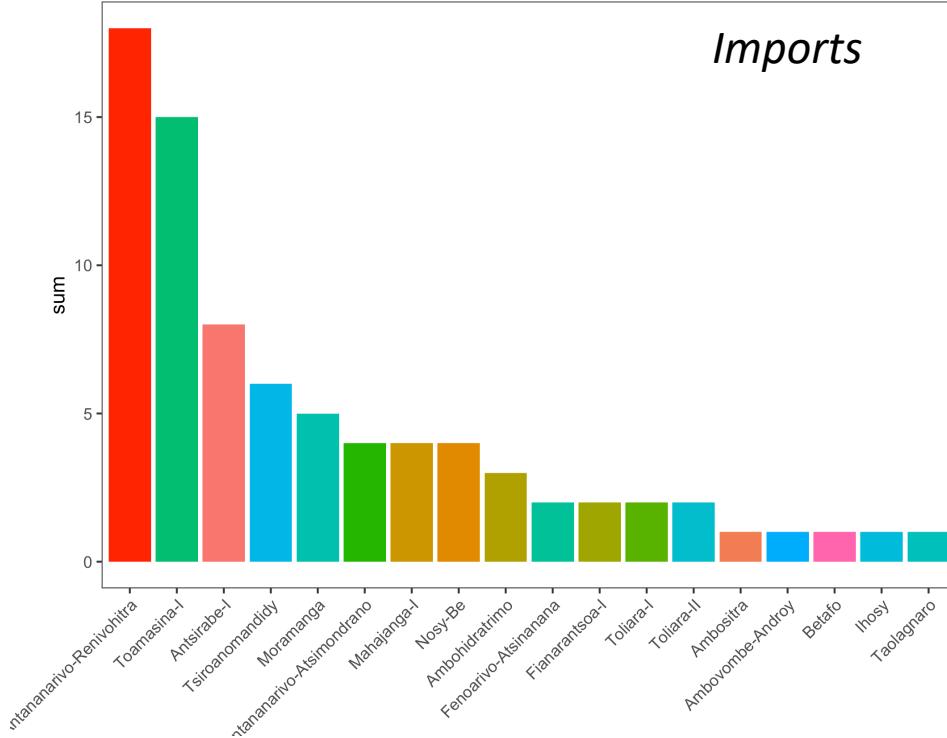
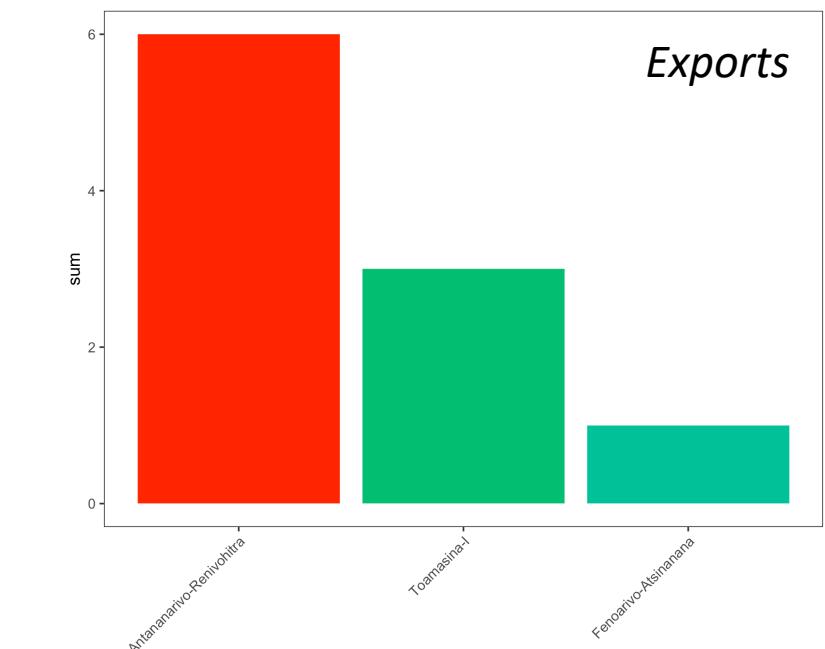
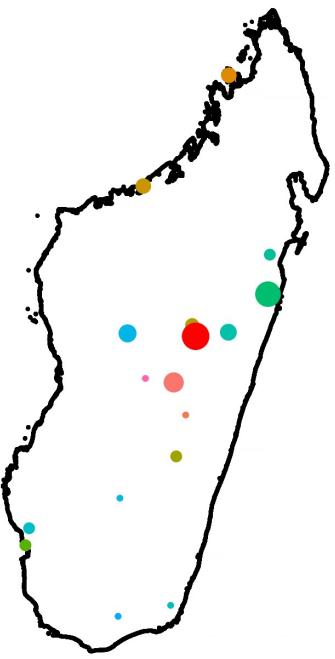
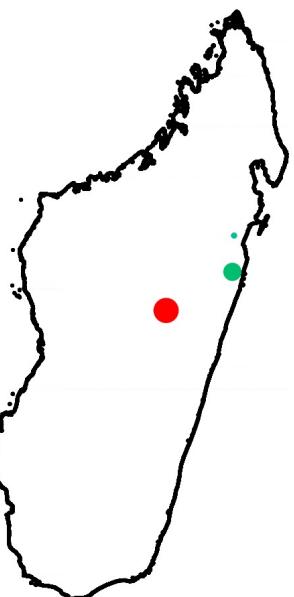


We can use the same approach with regional localities too...



International imports and exports
are primarily concentrated in the
capital and the major sea port of
Toamasina...

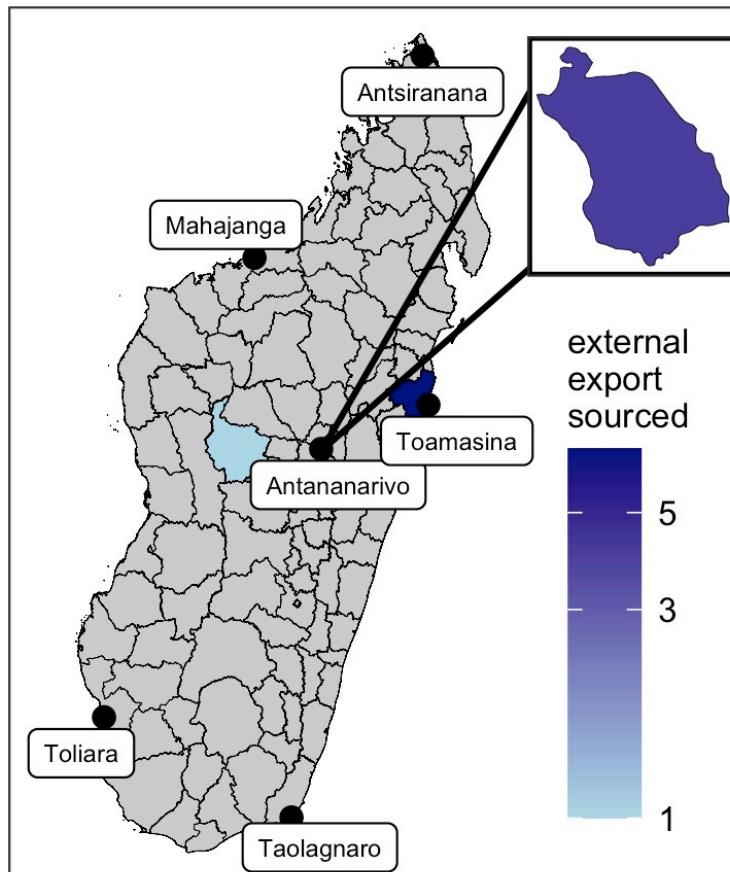
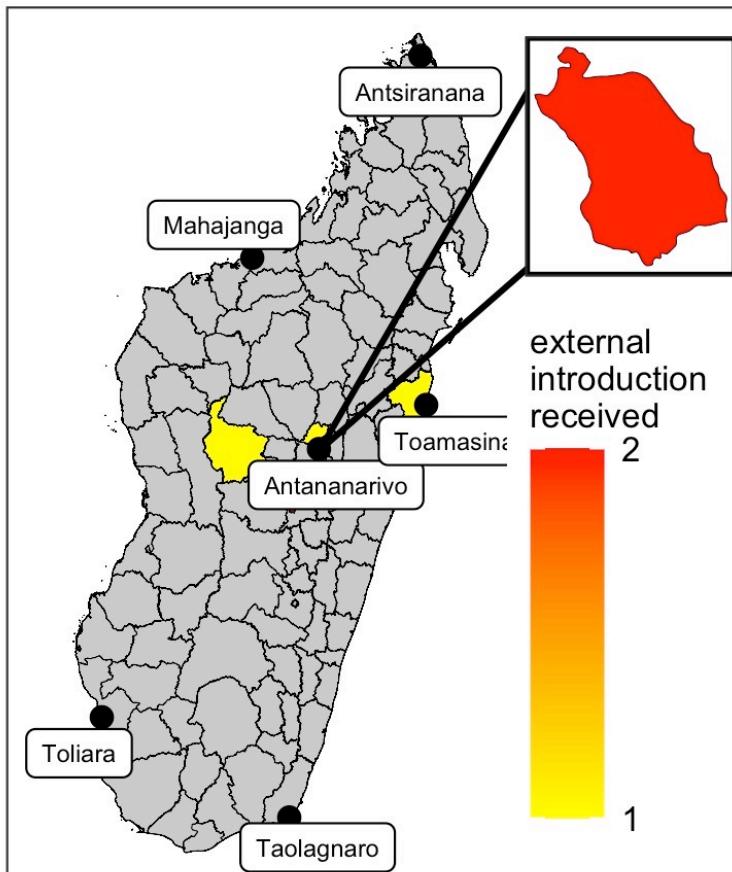
sum		
● 5		
● 10		
● 15		
district		
●	Antsirabe–I	Toliara–II
●	Ambositra	Ihosy
●	Miarinarivo	Tsiroanomandidy
●	Nosy–Be	Antsirabe–II
●	Antananarivo–Renivohitra	Ambovombe–Androy
●	Mahajanga–I	Fenoarivo–Centre
●	Antananarivo–Avaradrano	Fandriana
●	Ambohidratrimo	Ambalavao
●	Fianarantsoa–I	Antsohihy
●	Arvonimamo	Maevatanana
●	Morondava	Analalava
●	Toliara–I	Befandriana–Nord
●	Antananarivo–Atsimondrano	Bealanana
●	Antsiranana–I	Mandritsara
●	Andramasina	Manakara–Sud
●	Toamasina–I	Sambava
●	Toamasina–II	Betampona
●	Fenoarivo–Atsinanana	Ankazobe
●	Moramanga	Soavinandriana
●	Taolagnaro	outside–Madagascar



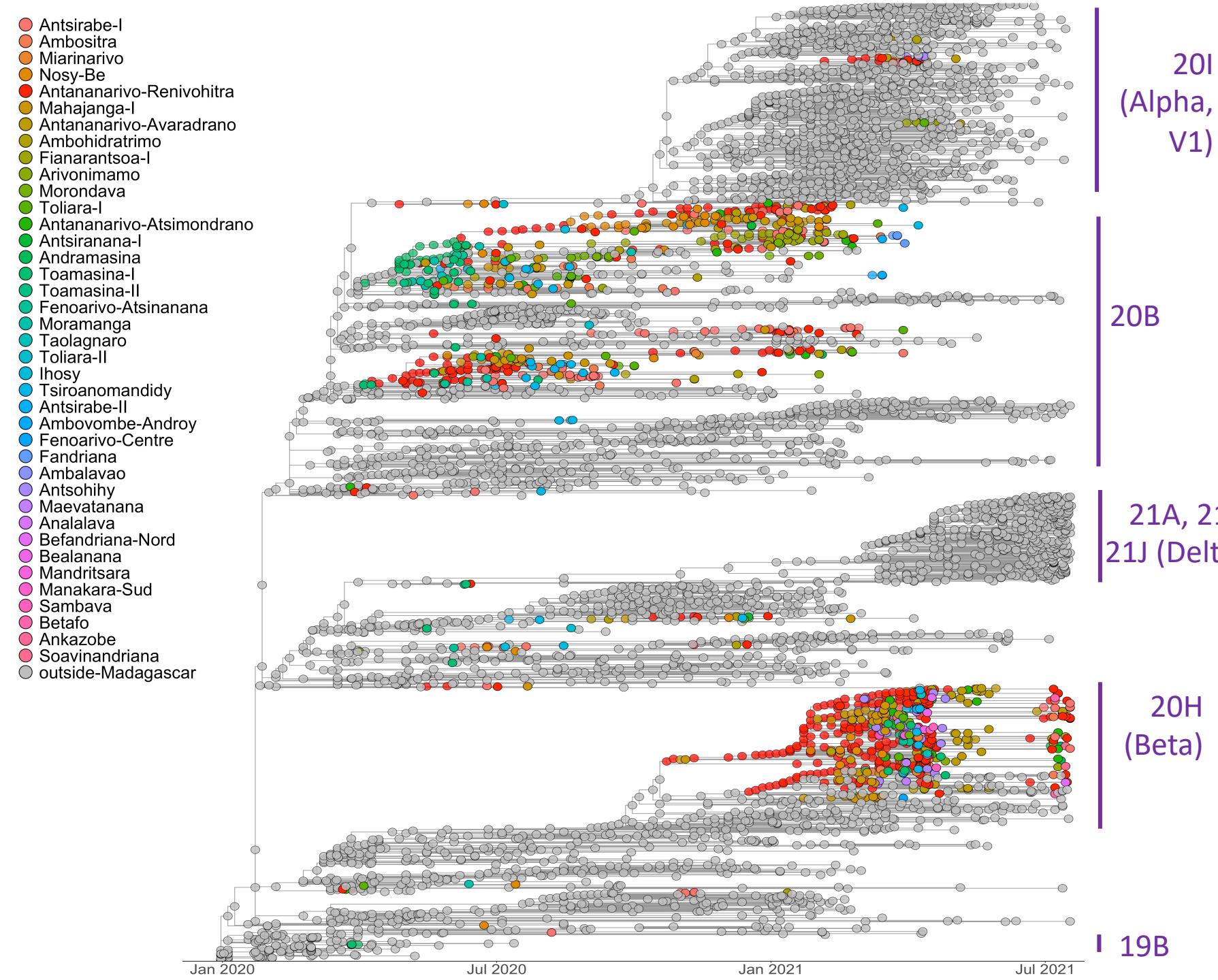
International imports and exports are primarily concentrated in the capital and the major sea port of Toamasina...

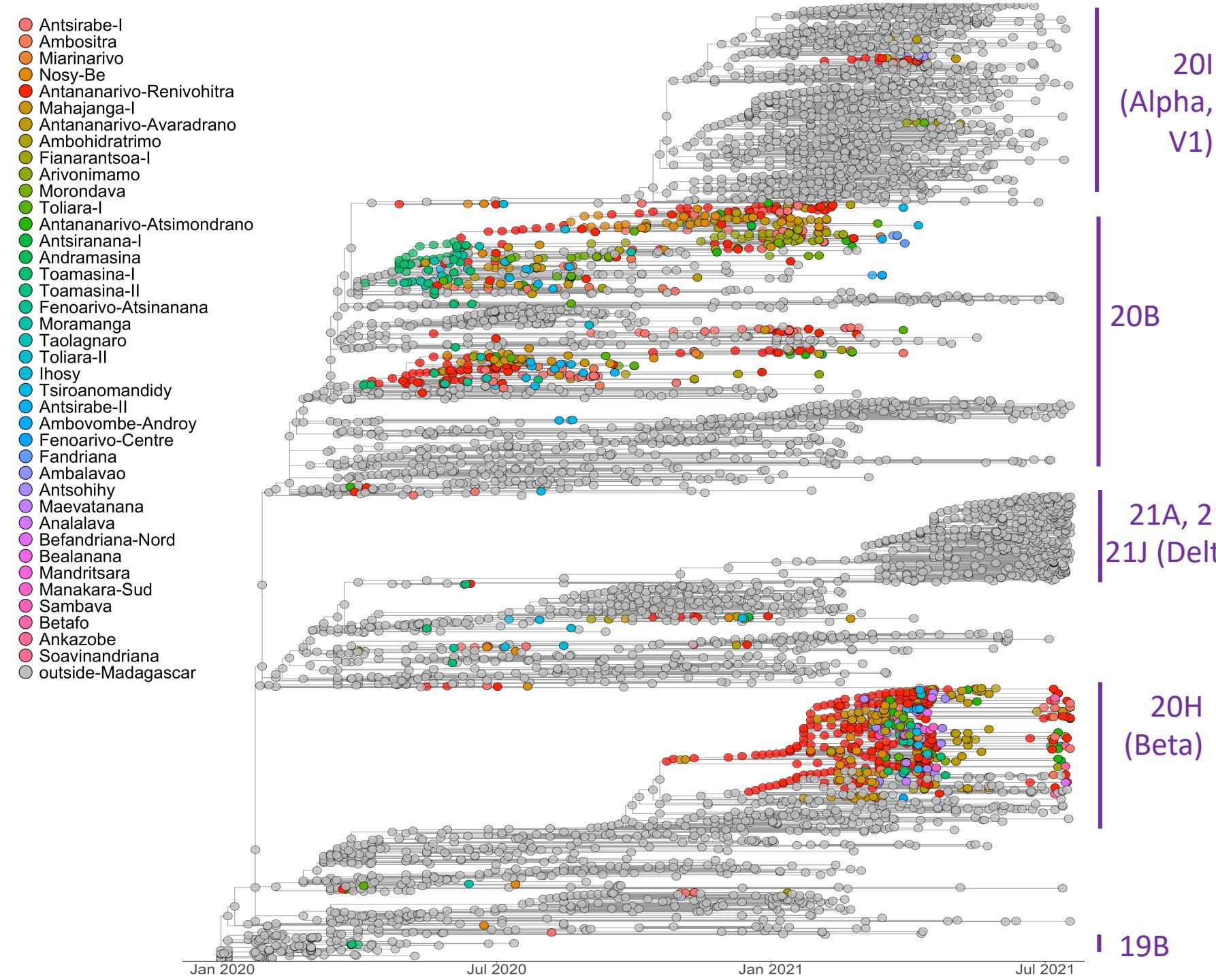
sum	district
● 5	Antsirabe-II
● 10	Ambositra
● 15	Miarinarivo
● 20	Nosy-Be
● 25	Antananarivo-Renivohitra
● 30	Mahajanga-II
● 35	Antananarivo-Avaradrano
● 40	Ambohidratrimo
● 45	Fianarantsoa-II
● 50	Arvonimamo
● 55	Morondava
● 60	Toliara-II
● 65	Antananarivo-Atsimondrano
● 70	Antsiranana-II
● 75	Andramasina
● 80	Toamasina-II
● 85	Fenoarivo-Atsinanana
● 90	Moramanga
● 95	Taolagnaro
● 100	outside-Madagascar

International imports and exports are primarily concentrated in the capital and the major sea port of Toamasina...



In-country
transmission
largely radiates out
from the capital...



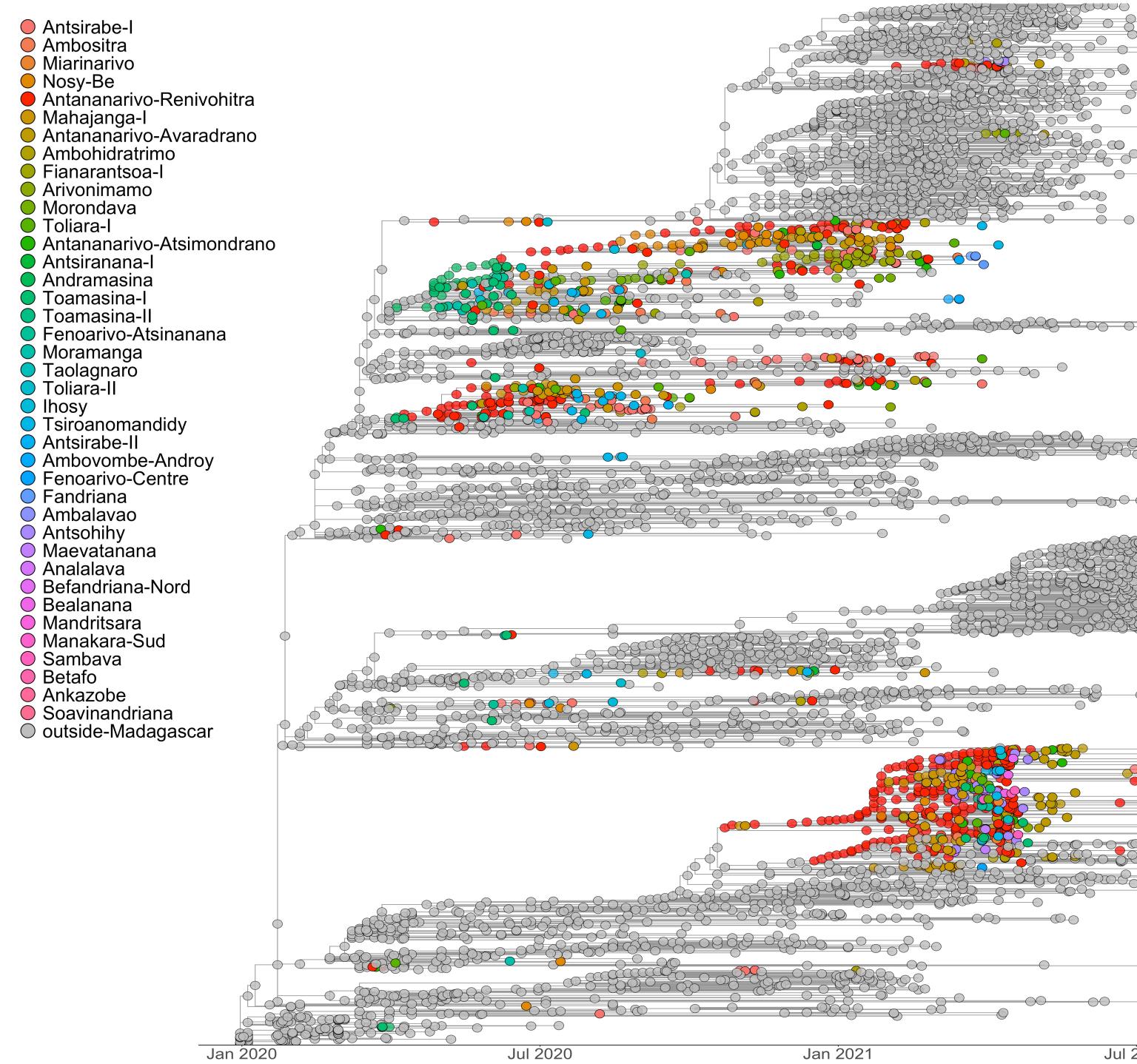


In-country transmission largely radiates out from the capital...

352 internal transmissions:

sourcing

- 225 from Antananarivo-Renivohitra
- 31 from Mahajanga-I
- 19 from Antsirabe-I
- 18 from Toamasina-I
- 17 from Fianarantsoa-I



In-country transmission largely radiates out from the capital...

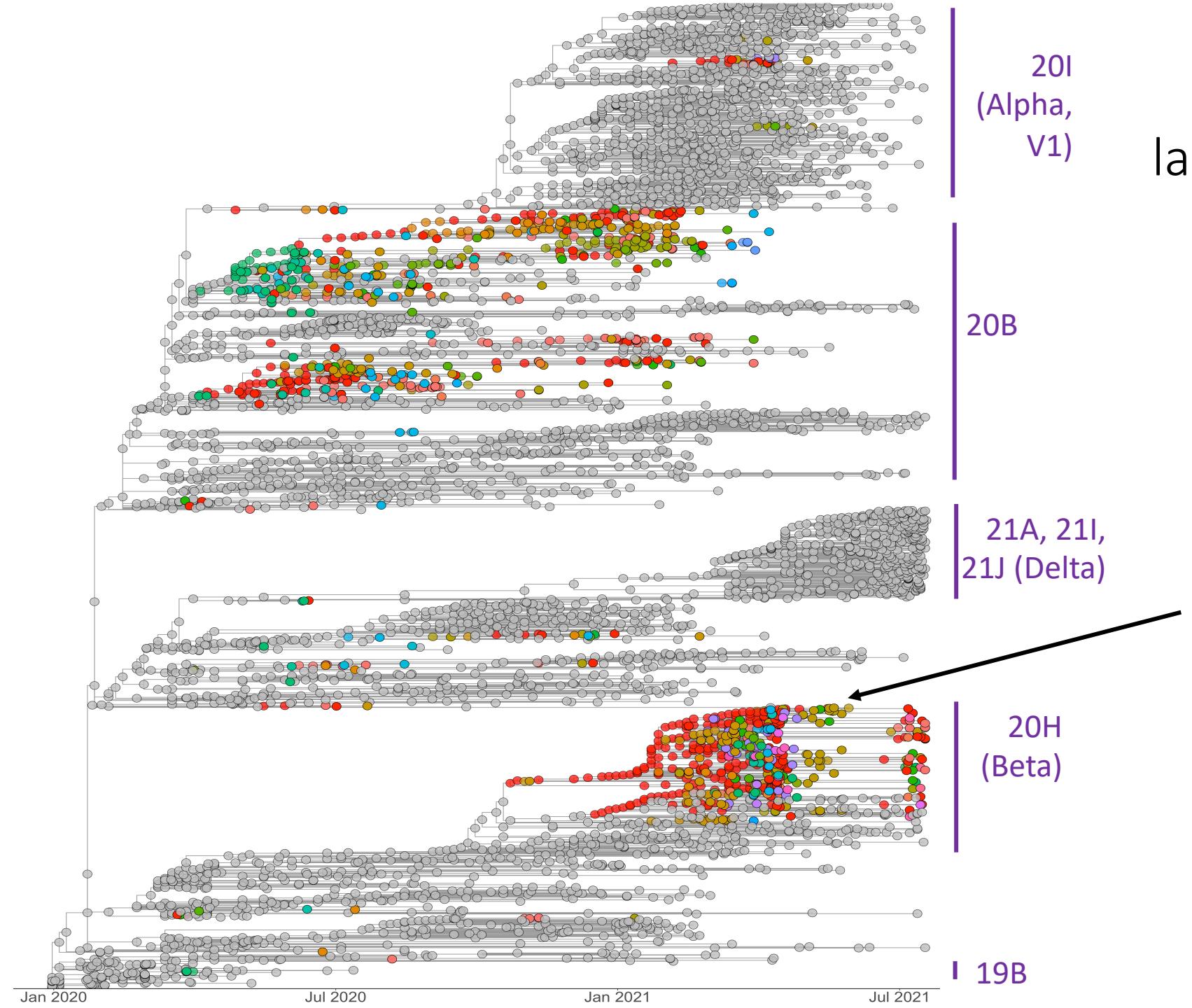
352 internal transmissions:

- sourcing*
- 225 from Antananarivo-Renivohitra
- 31 from Mahajanga-I
- 19 from Antsirabe-I
- 18 from Toamasina-I
- 17 from Fianarantsoa-I

sinking:

- 44 to Antananarivo-Avaradrano
- 31 to Ambohidratrimo
- 29 to Antananarivo-Atsimondrano
- 29 to Antsirabe-I
- 24 to Mahajanga-I

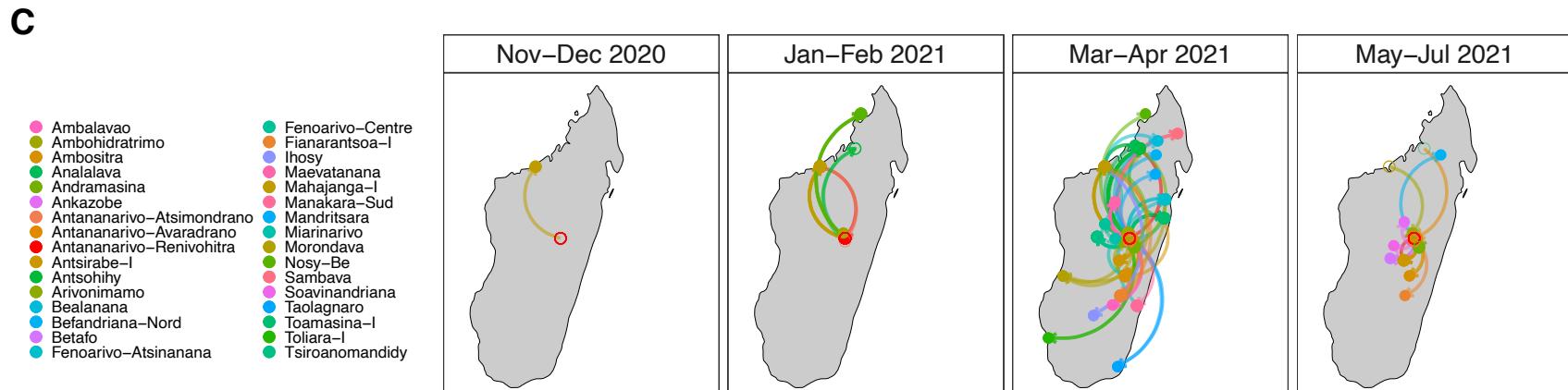
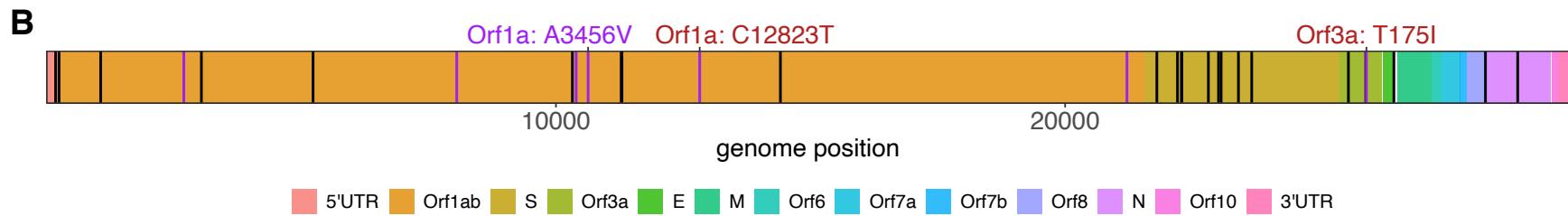
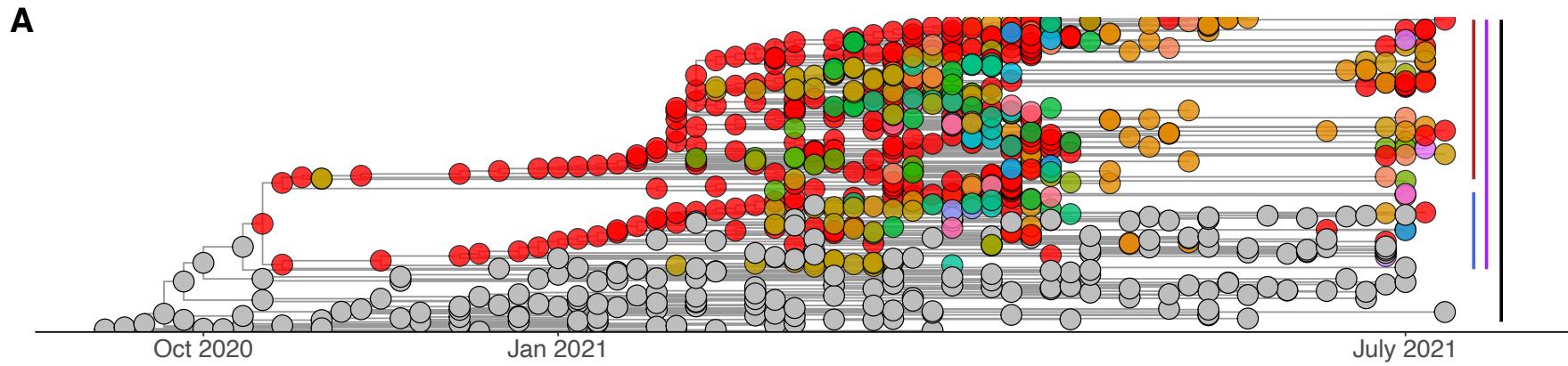
- Antsirabe-I
- Ambositra
- Miarinarivo
- Nosy-Be
- Antananarivo-Renivohitra
- Mahajanga-I
- Antananarivo-Avaradrano
- Ambohidratrimo
- Fianarantsoa-I
- Arivonimamo
- Morondava
- Toliara-I
- Antananarivo-Atsimondrano
- Antsiranana-I
- Andramasina
- Toamasina-I
- Toamasina-II
- Fenoarivo-Atsinanana
- Moramanga
- Taolagnaro
- Toliara-II
- Ihosy
- Tsiroanomandidy
- Antsirabe-II
- Ambovombe-Androy
- Fenoarivo-Centre
- Fandriana
- Ambalavao
- Antsohihy
- Maevatanana
- Analalava
- Befandriana-Nord
- Bealanana
- Mandritsara
- Manakara-Sud
- Sambava
- Betafo
- Ankazobe
- Soavinandriana
- outside-Madagascar



In-country transmission largely radiates out from the capital...

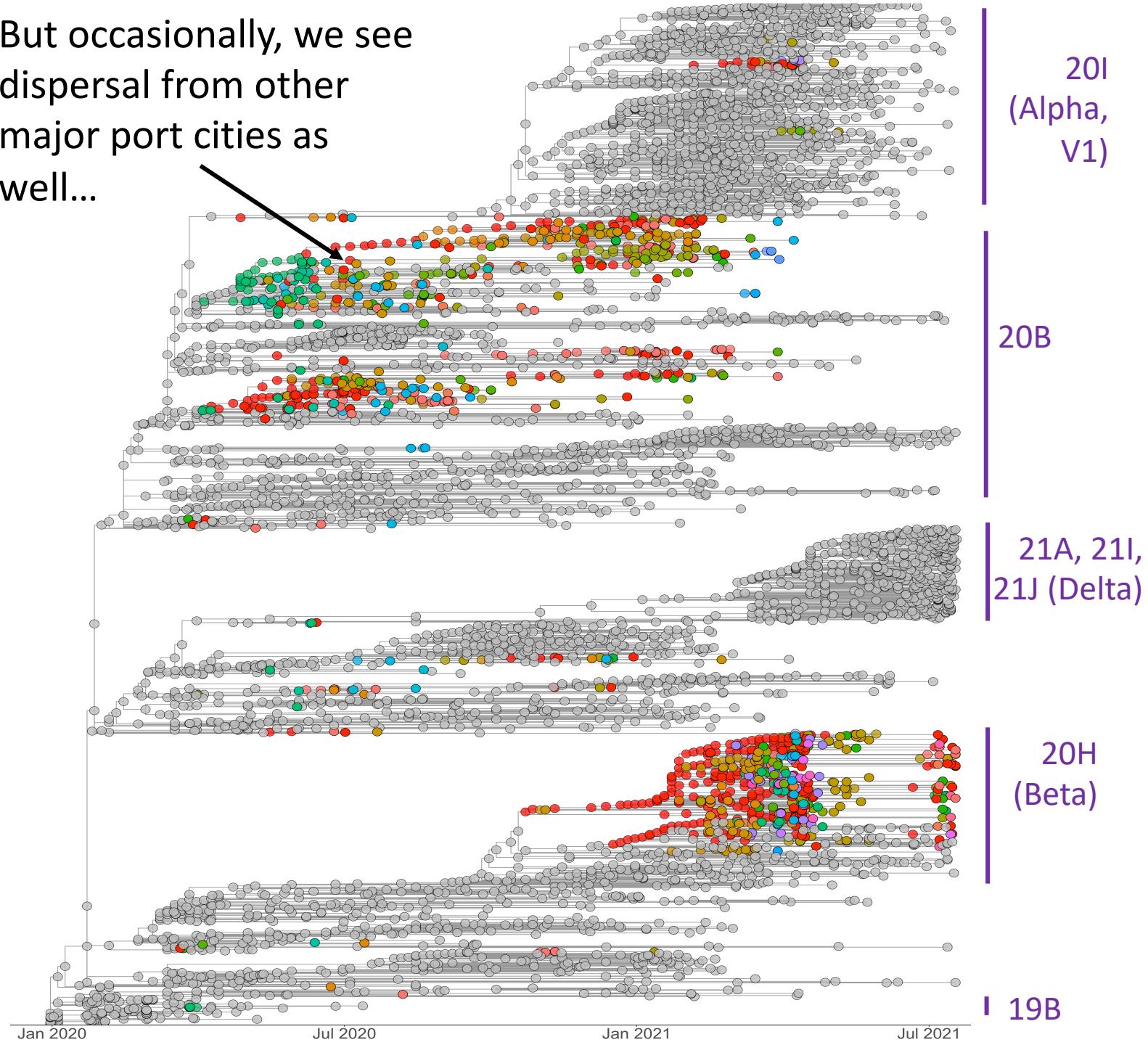
Beta clade disperses from Tana to neighboring districts.

Deep dive on a Madagascar-specific Beta variant

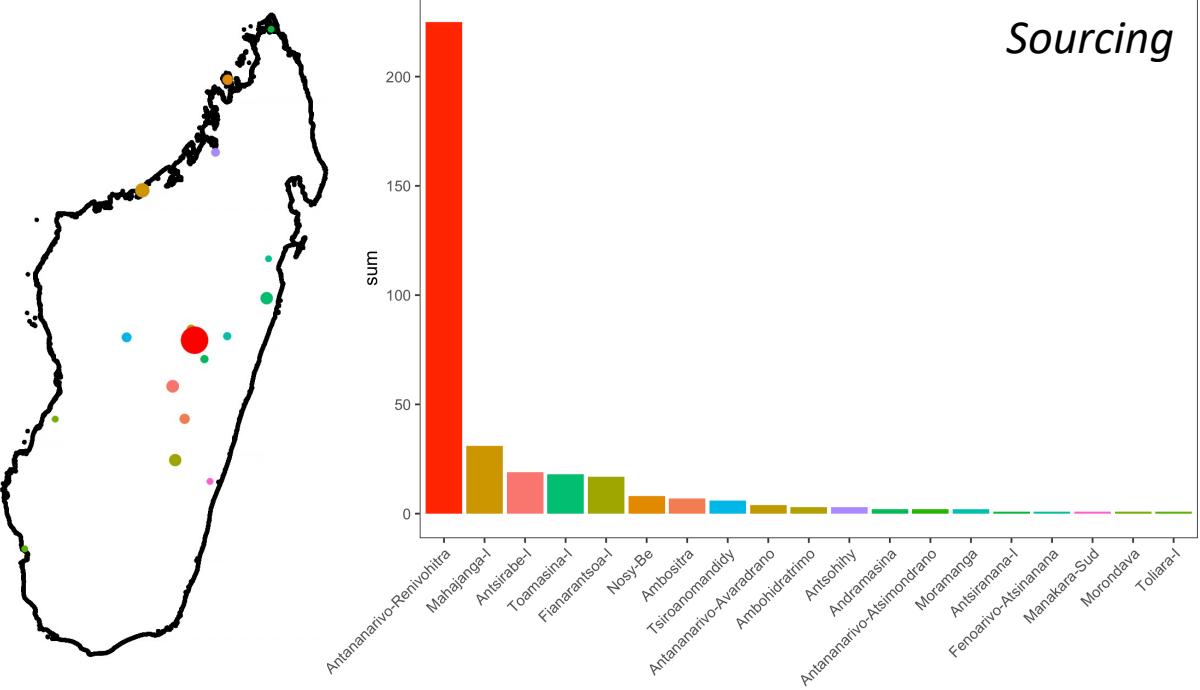


- Antsirabe-I
- Ambositra
- Miarinarivo
- Nosy-Be
- Antananarivo-Renivohitra
- Mahajanga-I
- Antananarivo-Avaradrano
- Ambohidratrimo
- Fianarantsoa-I
- Arivonimamo
- Morondava
- Toliara-I
- Antananarivo-Atsimondrano
- Antsiranana-I
- Andramasina
- Toamasina-I
- Toamasina-II
- Fenoarivo-Atsinanana
- Moramanga
- Taolagnaro
- Toliara-II
- Ihosy
- Tsiroanomandidy
- Antsirabe-II
- Ambovombe-Androy
- Fenoarivo-Centre
- Fandriana
- Ambalavao
- Antsohihy
- Maevatanana
- Analalava
- Befandriana-Nord
- Bealanana
- Mandritsara
- Manakara-Sud
- Sambava
- Betafo
- Ankazobe
- Soavinandriana
- outside-Madagascar

But occasionally, we see dispersal from other major port cities as well...



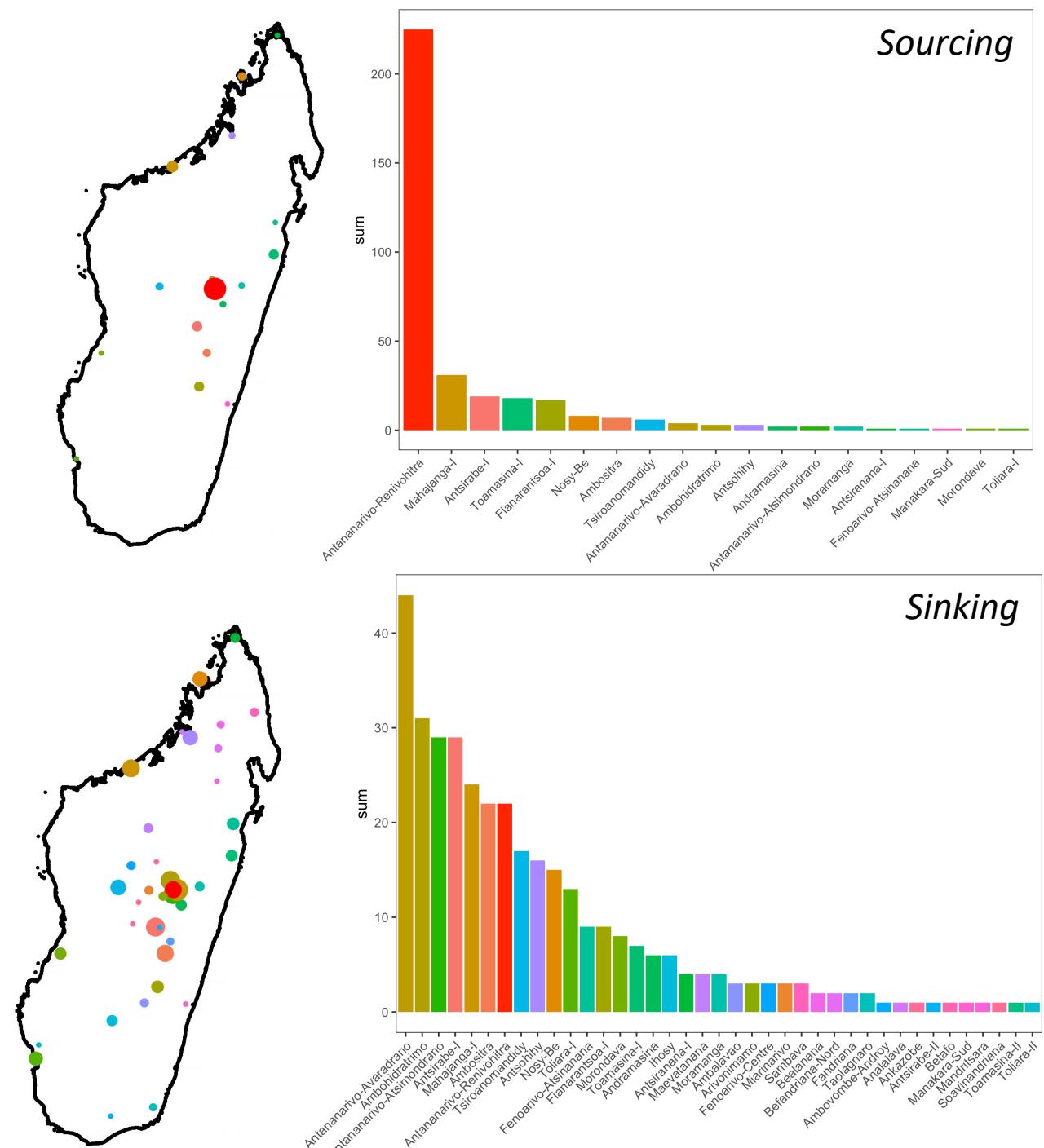
In-country transmission largely radiates out from the capital...



In-country transmission largely radiates from the capital to adjacent regions or other major cities...

district

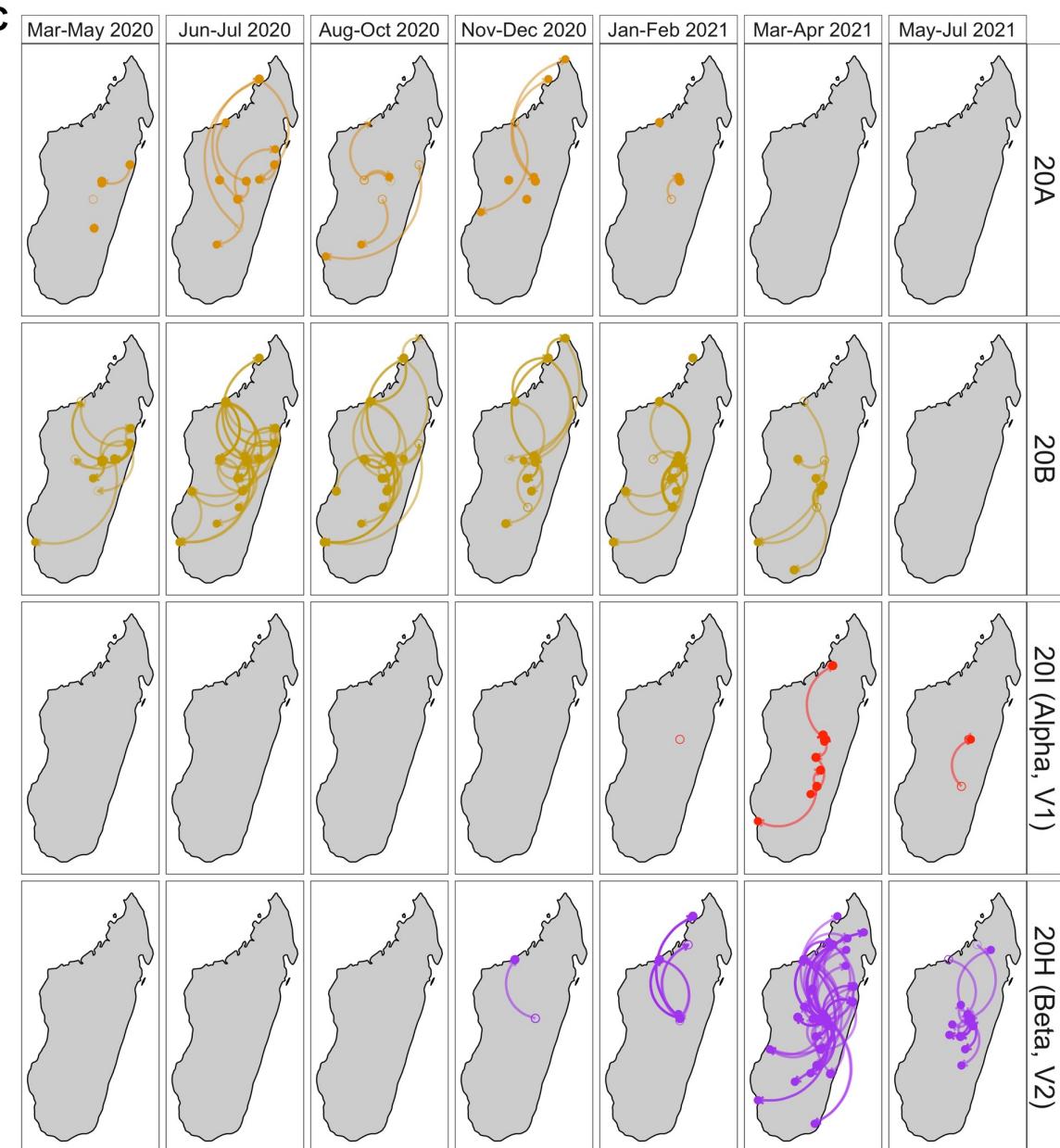
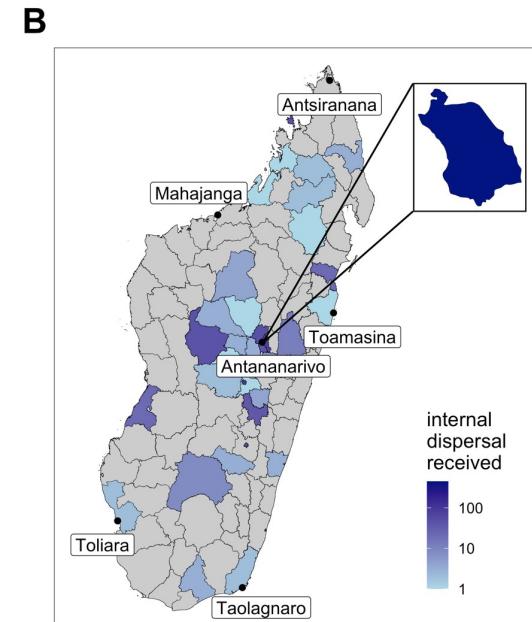
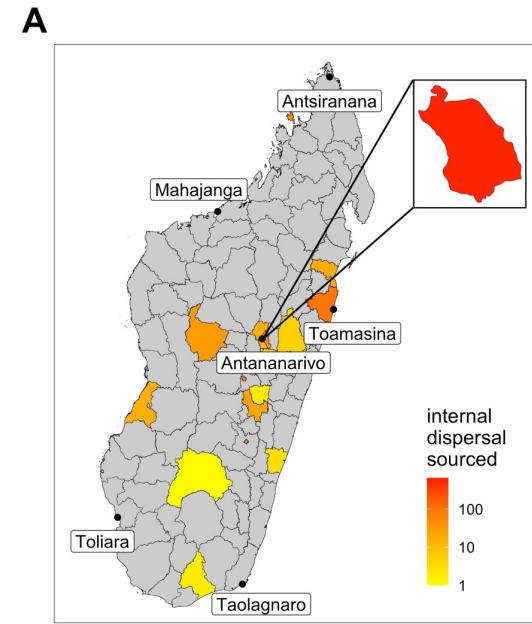
- Antsirabe-I
- Antsirabe-II
- Ambositra
- Miarinarivo
- Nosy-Be
- Antananarivo-Renivohitra
- Mahajanga-I
- Antananarivo-Avaradrano
- Ambohidratrimo
- Fianarantsoa-I
- Arivonimamo
- Morondava
- Toliara-I
- Antananarivo-Atsimondrano
- Antsiranana-I
- Andramasina
- Toamasina-I
- Toamasina-II
- Fenoarivo-Atsinanana
- Moramanga
- Taolagnaro
- Toliara-II
- Ihosy
- Tsiroanomandidy
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- Soavinandriana
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In-country transmission largely radiates from the capital to adjacent regions or other major cities...



In-country transmission largely radiates from the capital to adjacent regions or other major cities...



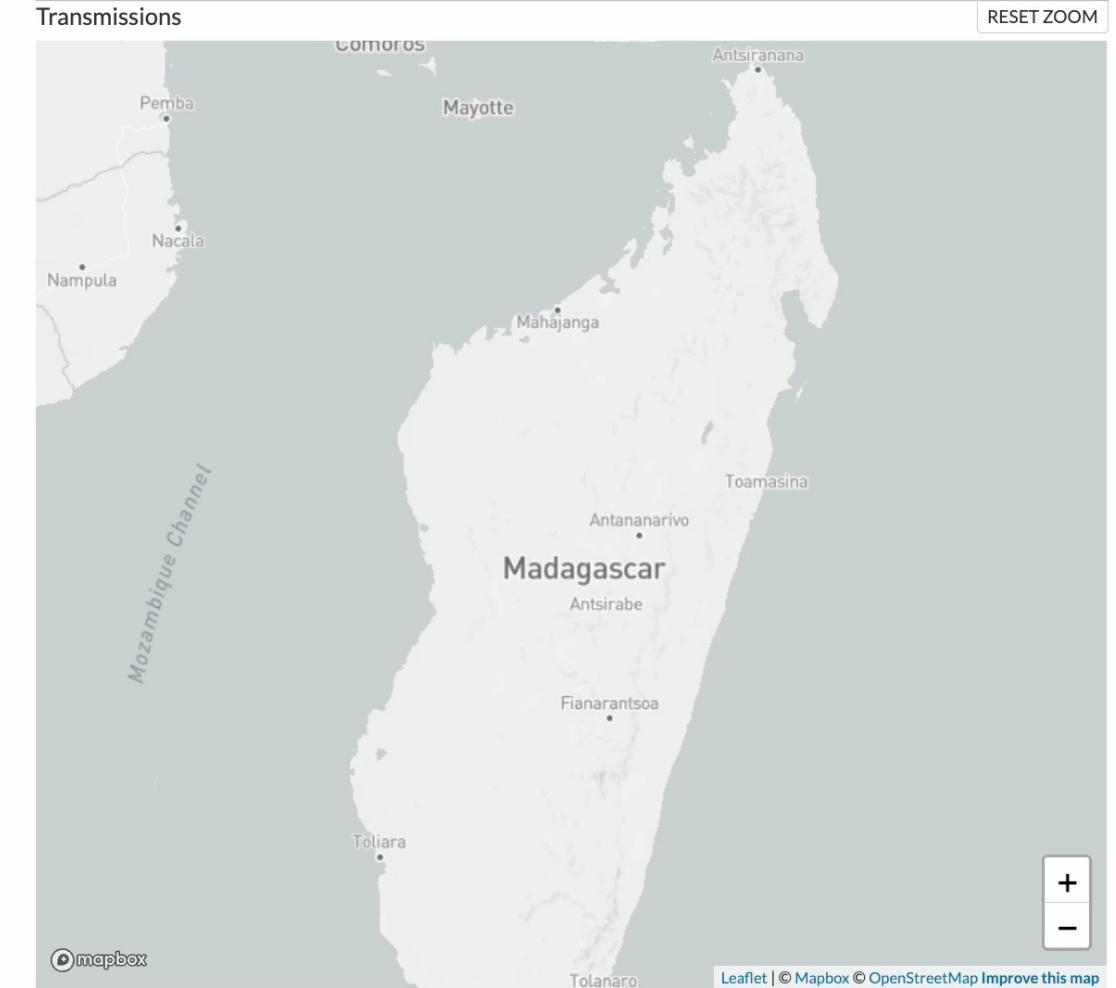
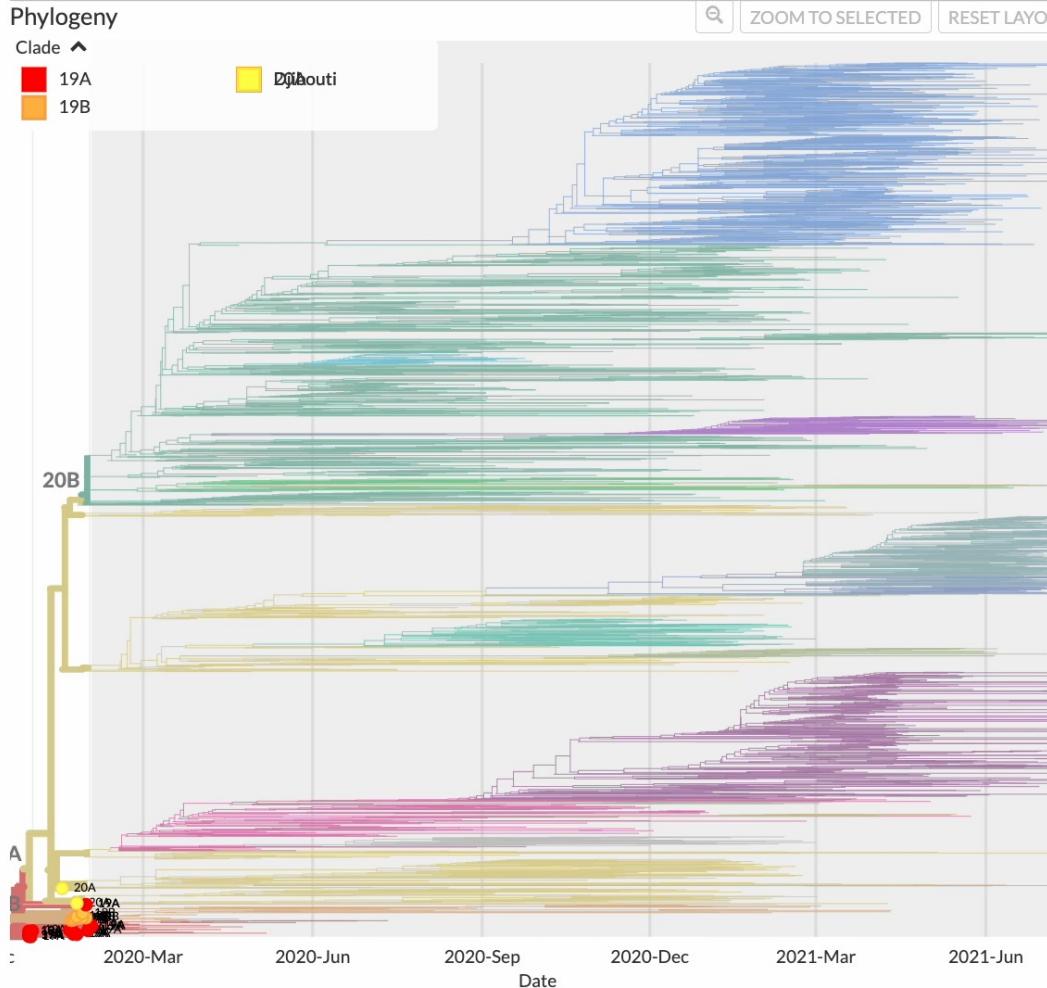
This tree captures spatial and temporal information that we can visualize in real time.

SARS-CoV-2 Sequences in Madagascar

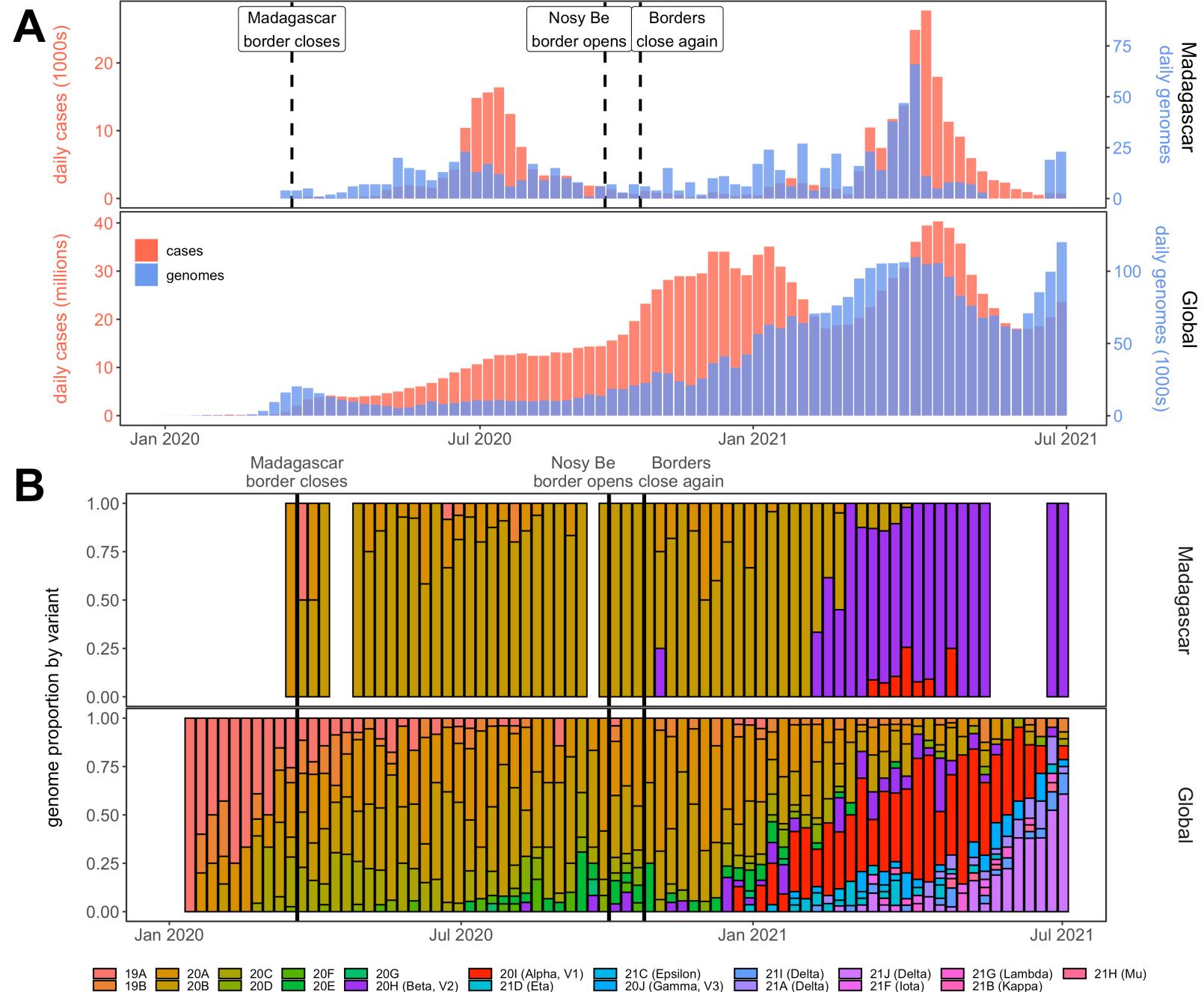


Built with [brooklabteam/ncov-Madagascar/](#). Maintained by [Cara Brook](#).

Showing 32 of 2662 genomes sampled between Dec 2019 and Feb 2020. Filtered to [Dec 2019 to Feb 2020](#)



In general,
Madagascar's COVID
epidemic largely
mirrors that of the rest
of the globe, but with a
substantial delay...



Genomic epidemiology offers a powerful means of quantifying transmission when case data are sparse – and can also highlight risks posed by new mutations that could alter the dynamics of the epidemic.