



MRC Centre for
Global Infectious
Disease Analysis

Imperial College
London

Impact of Genomic Sequencing on Public Health: Experiences with Zika, SARS-CoV-2, chikungunya and yellow fever

Nuno R. Faria

Co-Lead Pathogen Genomic Epidemiology Unit

MRC Centre for Global Infectious Disease Analysis

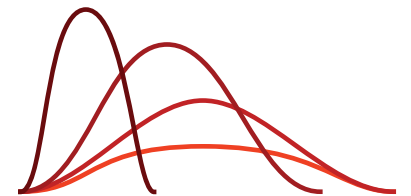
WHO Collaborating Centre for Infectious Disease modelling

WHO Technical Advisory Group – Global Arbovirus Initiative

School of Public Health, Imperial College London, UK (SPH-ICL)

Institute of Tropical Medicine, University of São Paulo, Brazil (IMT-USP)

Email: nfaria@ic.ac.uk – São Paulo, 11 July 2023



SPSAS

São Paulo School of
Advanced Science on
Epidemic Preparedness

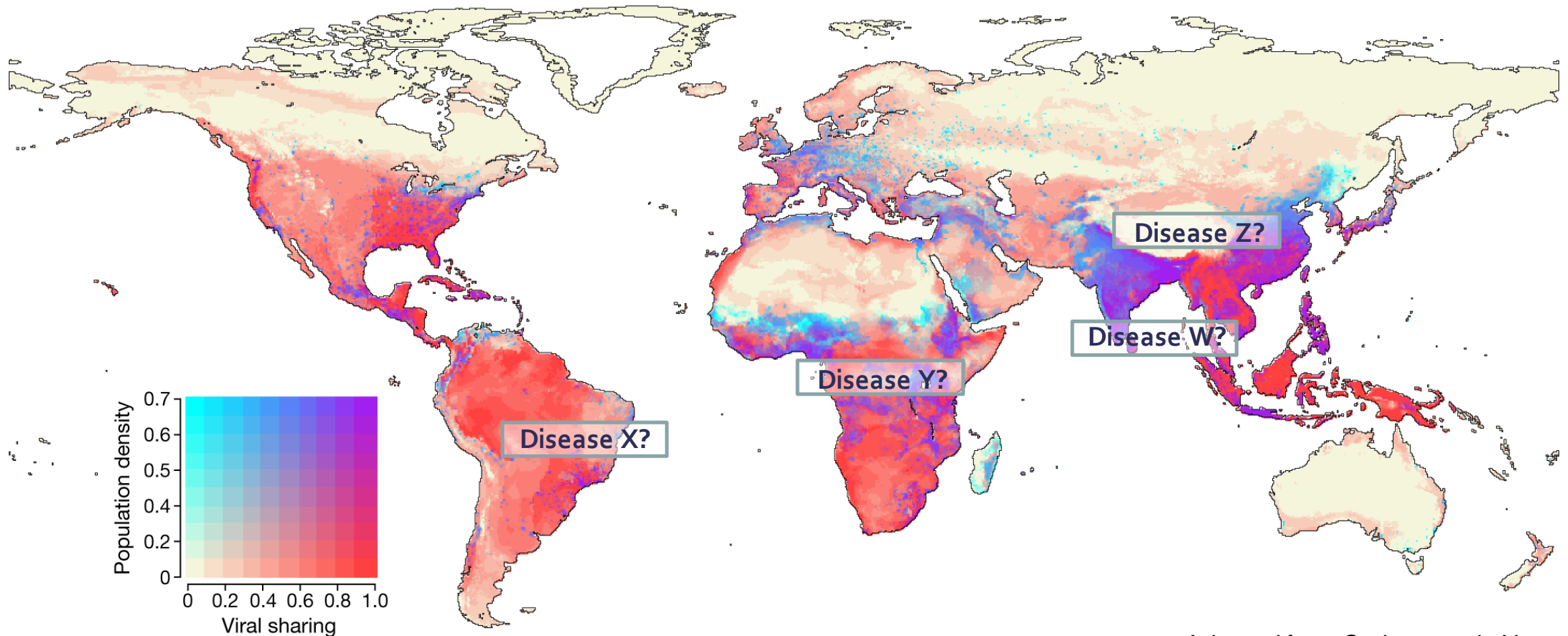
Outline of today's talk

1. Brief context
2. Zika virus emergence, evolution and spread
3. Real-time yellow fever virus surveillance in Brazil
4. Chikungunya virus epidemic waves in the Americas
5. Genomic epidemiology of SARS-CoV-2 in Brazil
6. Final considerations

Brief context

Climate change increases viral spillover risk

In 2020, human population centres in equatorial Africa, south China, India and southeast Asia will overlap with projected hotspots of cross-species viral transmission in wildlife.



Adapted from Carlson et al. *Nature* 2022

Anthropogenic environmental changes

Anthropogenic environmental changes disrupt ecosystems and climatic patterns, reduce biodiversity, increase the frequency of extreme weather events and create additional pressures on healthcare and food systems.

Changes in natural ecosystems and land use increase the risk of vector-borne diseases and affect human health.



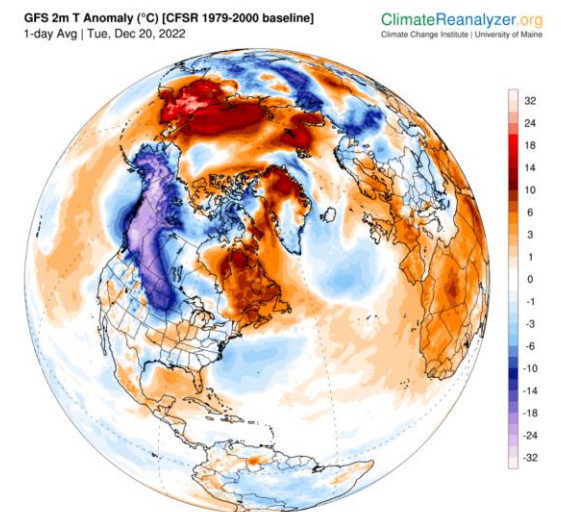
Unplanned urbanization



Deforestation



Environmental changes



Extreme weather events

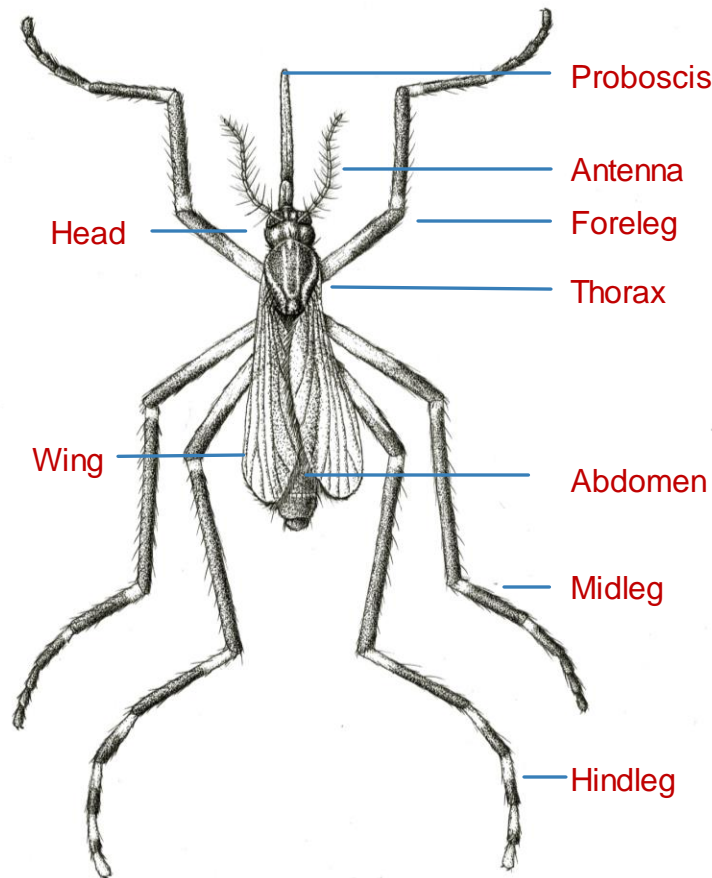
Anthropogenic environmental changes impact lifecycles and geographic distribution of Brazil's deadliest animals

Mosquito lifecycles are strongly influenced by rainfall, temperature, and relative humidity.

Aedes (Stg.) aegypti
Linnaeus, 1762

Naturally infected with the following viruses:
dengue 1–4, Zika, chikungunya, and yellow fever (outside Americas)

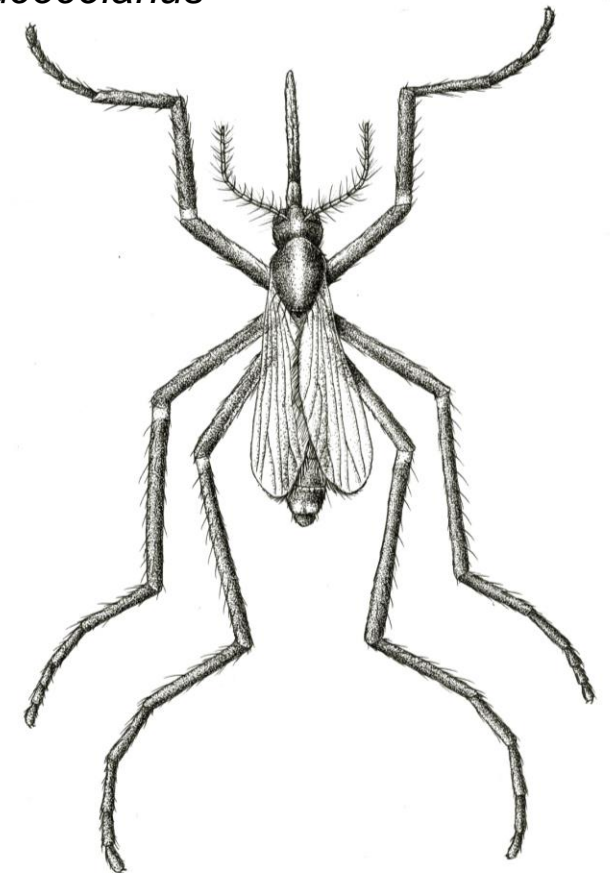
Family: *Culicidae*
Subfamily: *Culicinae*
Tribe: *Aedini*
Genus: *Aedes*
Subgenus: *Stegomyia*
Geographic distribution: urban mosquito, found in subtropical and tropical regions
Ecology: found in urban areas, including inside buildings and houses (mean dispersal 28 to 199m; lifespan two weeks)



Haemagogus (Con.) leucocelanus
Dyar & Shannon, 1924

Naturally infected with the following viruses:
yellow fever, Ilheus, Maguari, Una, Mayaro and Wyeomyia

Family: *Culicidae*
Subfamily: *Culicinae*
Tribe: *Aedini*
Genus: *Haemagogus*
Subgenus: *Conopostegus*
Geographic distribution: Argentina, Brazil and Paraguay
Ecology: found in forests but can take blood from hosts at ground level, with diurnal and acrodendrophilic habits (dispersal up to 11.5km?)

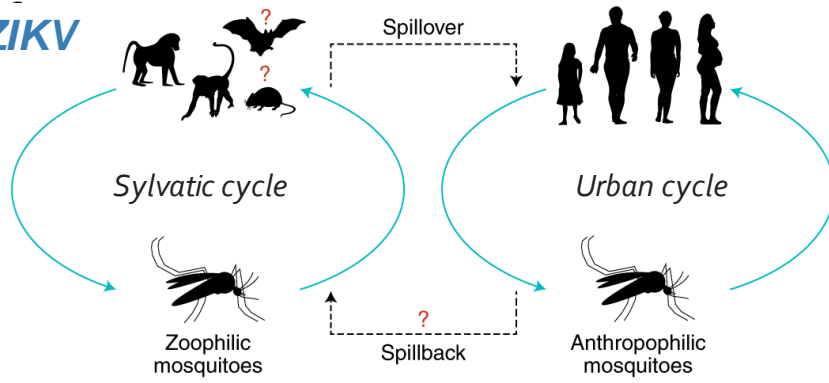


Segura & Castro, IEC-MS/SVS, Belém, 2007

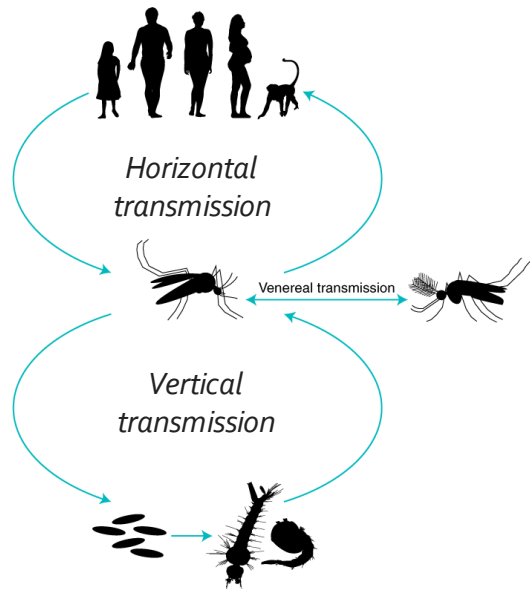
Zika virus

Zika virus in natural conditions

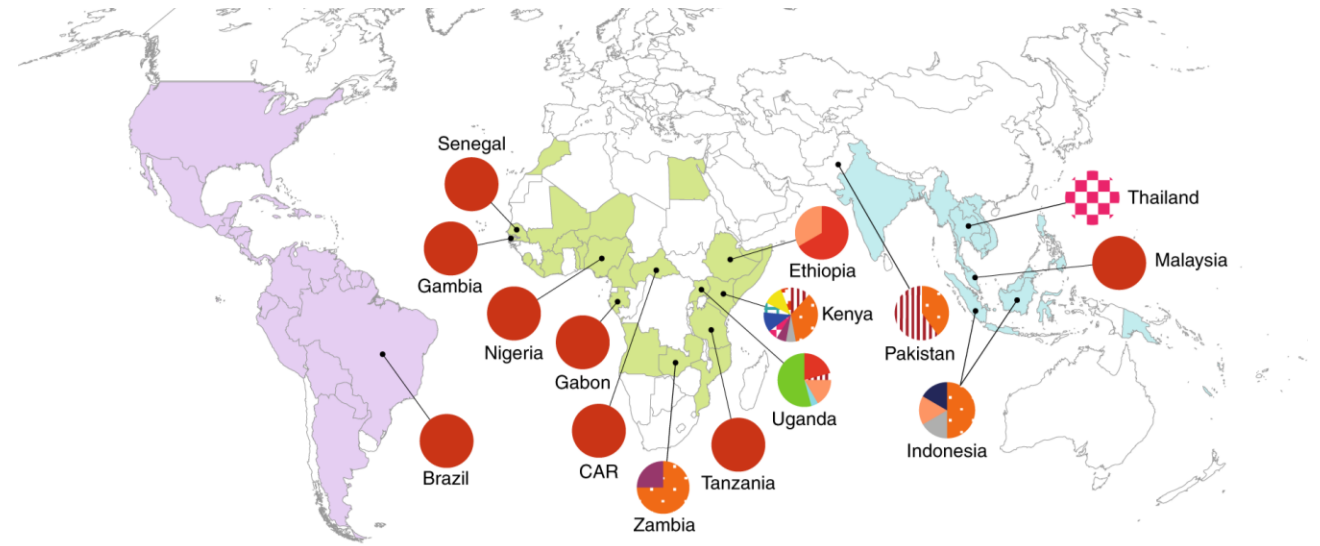
Horizontal transmission of ZIKV



Vector-borne transmission of ZIKV



ZIKV sylvatic transmission



Mammals



Birds



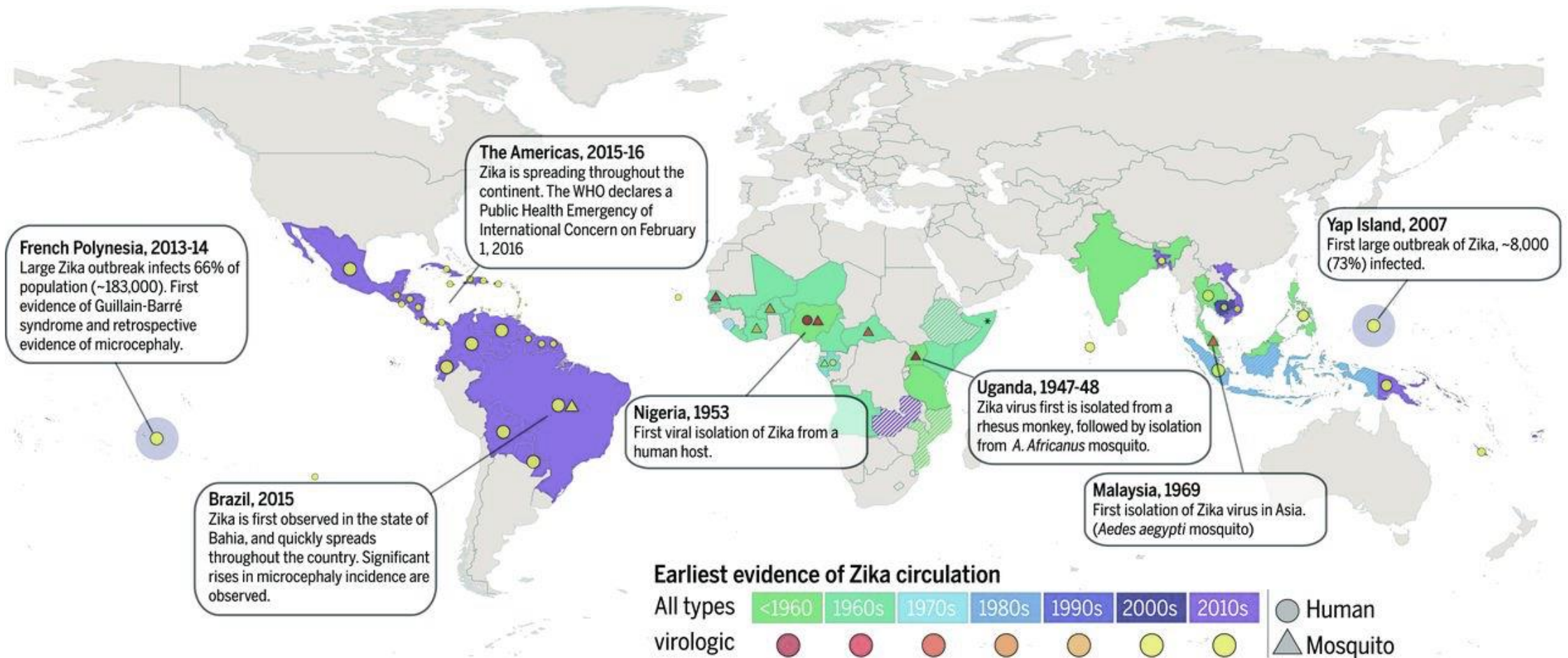
Reptiles



ZIKV lineages

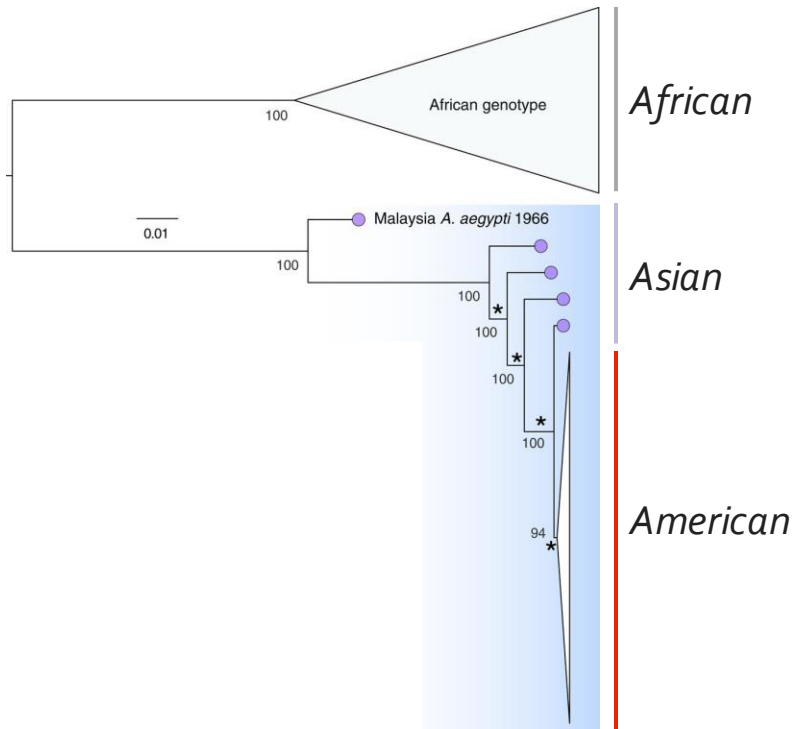


Zika virus pandemic: early stages

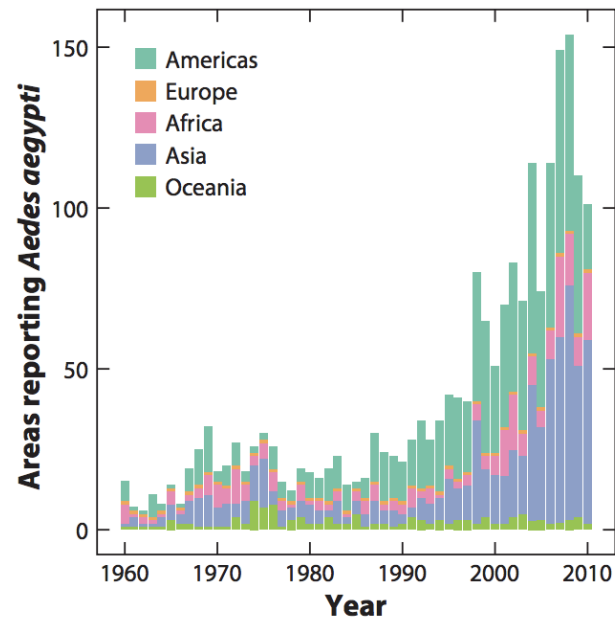


Expansion of *Aedes* spp. associated with arbovirus epidemics in the Americas

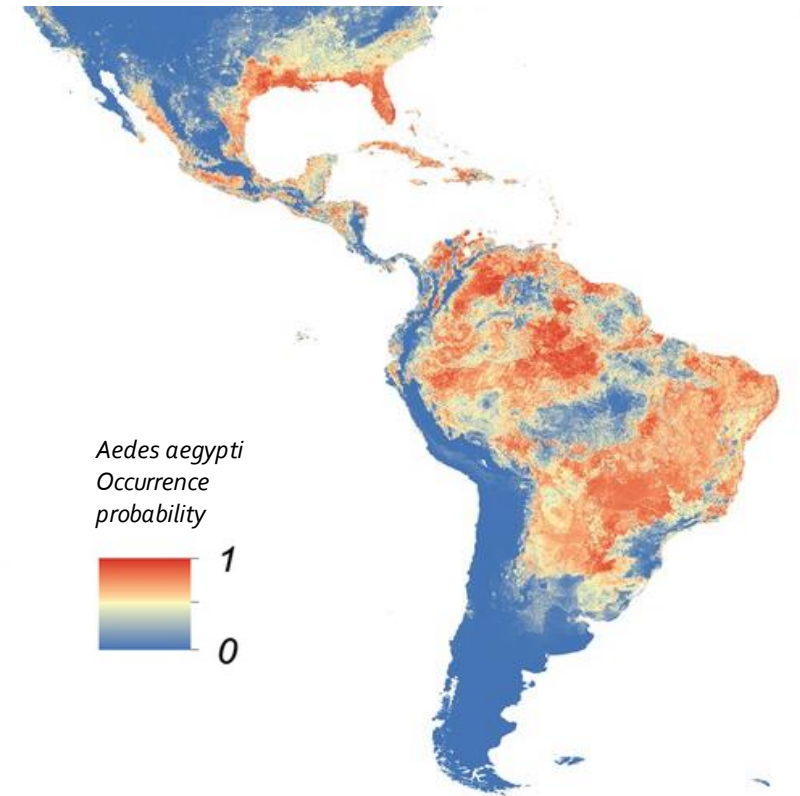
Zika virus lineages



Aedes aegypti expansion



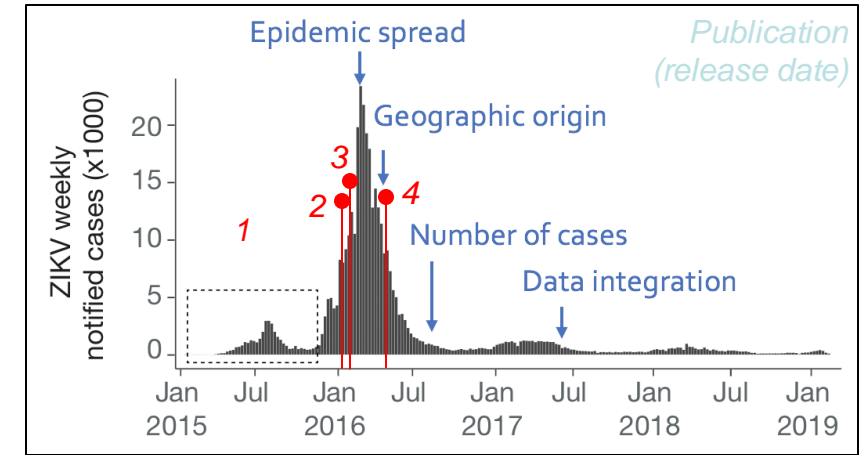
Aedes aegypti distribution



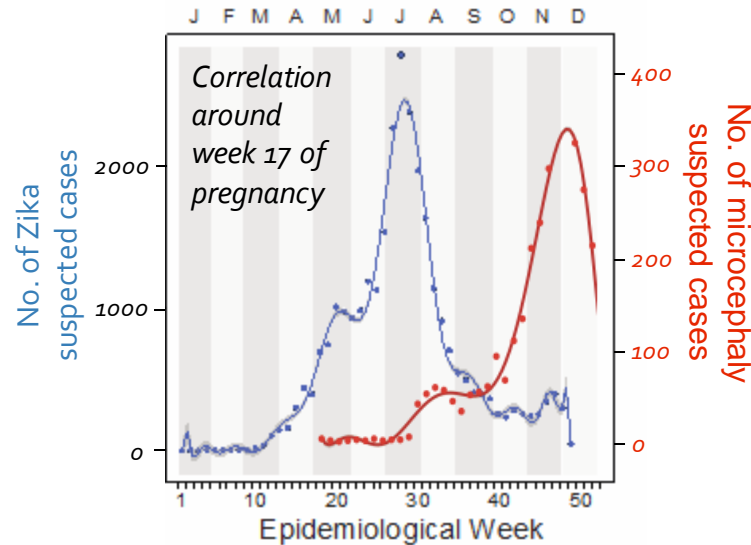
Faria et al. Science 2016; Brady and Hay, Annu Rev Entomol, 2019; Kraemer et al. eLife 2014

Emergence of Zika virus in the Americas: early findings

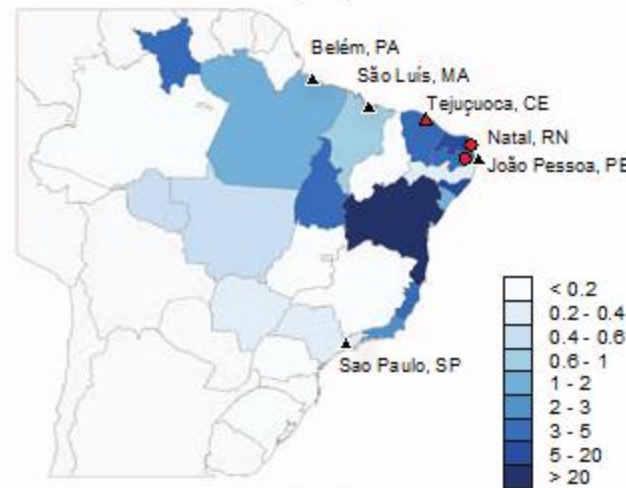
- Zika first confirmed cases in early May 2015 Brazil (1)
- First Zika genome sequence in January 2016 (2)
- WHO PHEIC by 1st Feb 2016 (3)
- Association ZIKV and microcephaly (13 April 2016) (4)



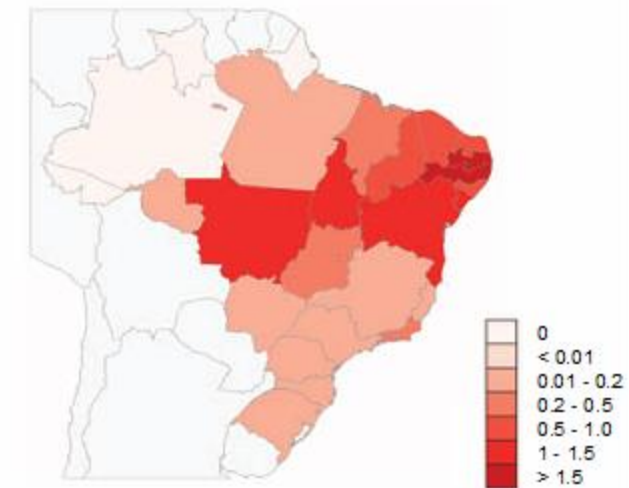
Zika and microcephaly cases 2015



Zika incidence (per 100,000 people) 2015

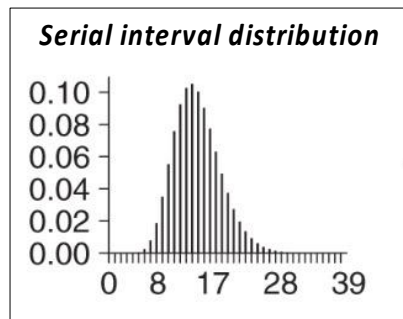
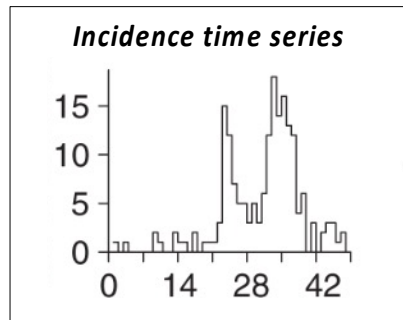


Microcephaly incidence (per 100,000 people) 2015



Faria et al. Science 2016 (IEC MS-SVS)

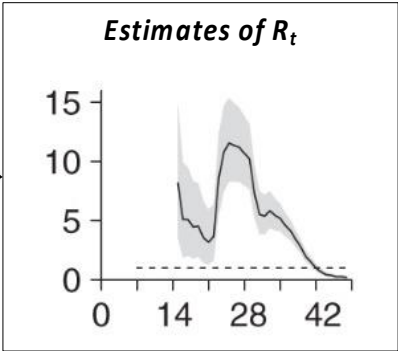
Factors determining scale and spread of an emerging infection in naïve populations



Analytical Bayesian method

Likelihood: $I_t \sim \text{Pois}\left(R_t \sum_{s=1}^t I_{t-s} w_s\right)$

Prior: $R_t \sim G(a, b)$



Human mobility
Large-scale connectivity of human populations

Transmissibility: R
average number of secondary cases infected by each case “at time t ”
($R < 1$ stops an epidemic)

Serial interval

Time from illness onset in the primary case to illness onset in the secondary case

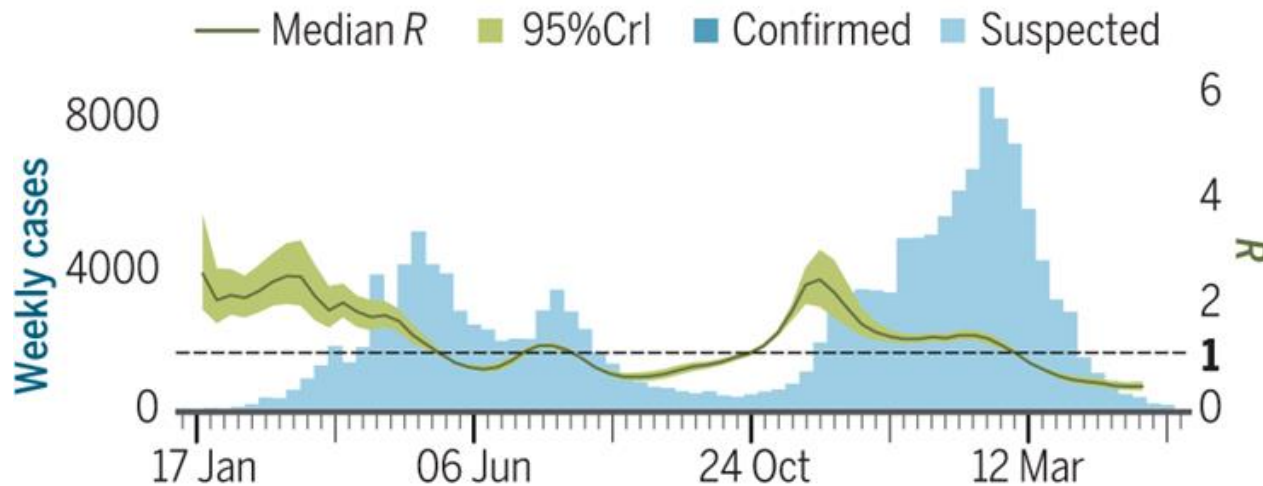
Predict the potential impact of the outbreak
Assess the feasibility of control measures
Track potential changes in transmissibility over time
Evaluate the effectiveness of control measures

Adapted from Anne Cori 2022

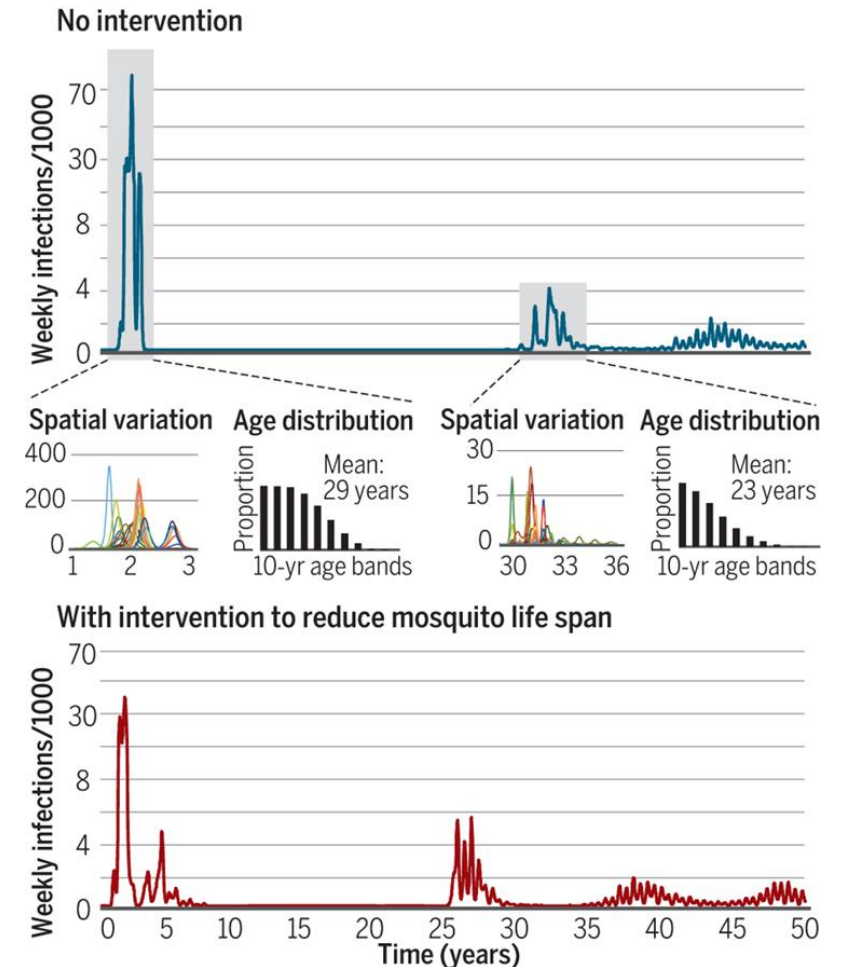
Countering the Zika epidemic in Latin America

Zika epidemic in Brazil was expected to be largely over in 3 years, with seasonal oscillations in incidence caused by transmissibility and variation in mosquito populations.

Zika surveillance data and estimated R , Brazil



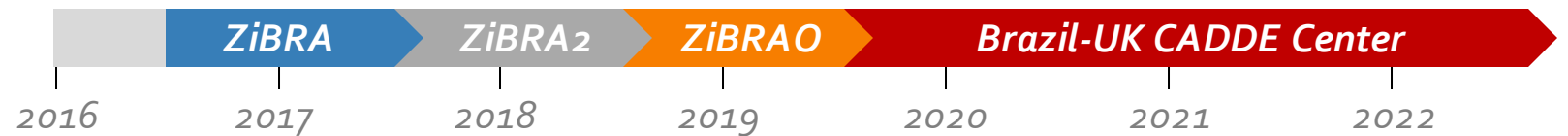
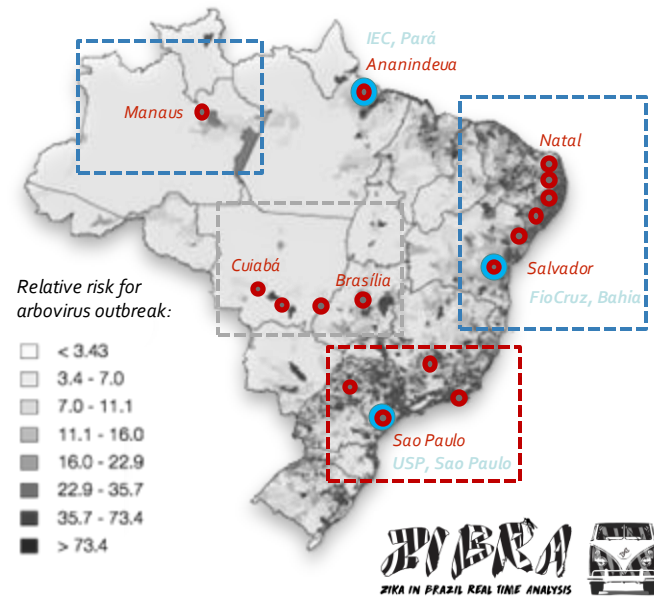
Zika epidemic simulations



Ferguson et al. Science 2016

Arbovirus genomic surveillance in Brazil

From mobile to fixed genomic sequencing and research laboratories

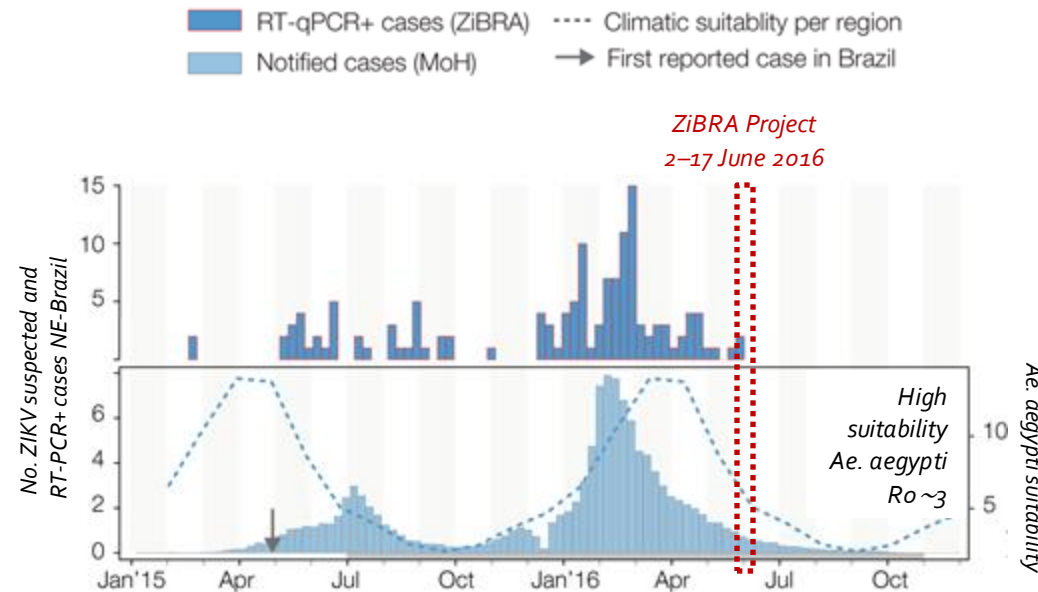


Time series of RT-qPCR+ cases correlated with suspected cases and *Aedes aegypti* suitability

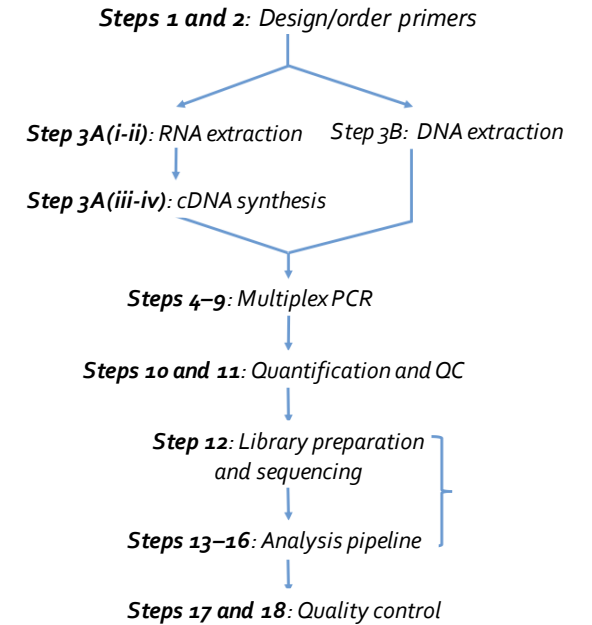
Monthly climatic suitability for *Aedes aegypti*



RT-PCR+ Zika cases (ZiBRA mobile lab) and weekly MoH notified cases



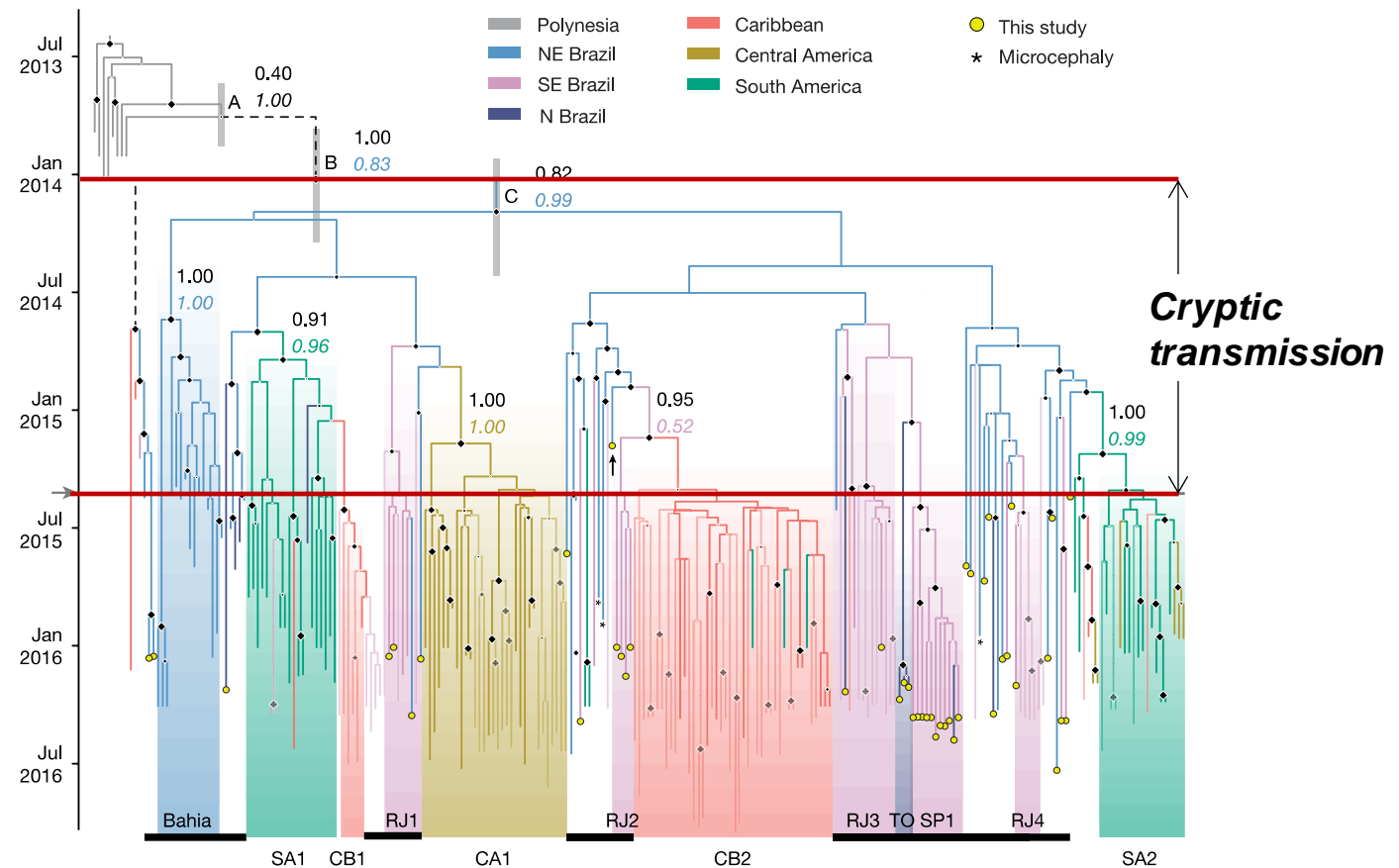
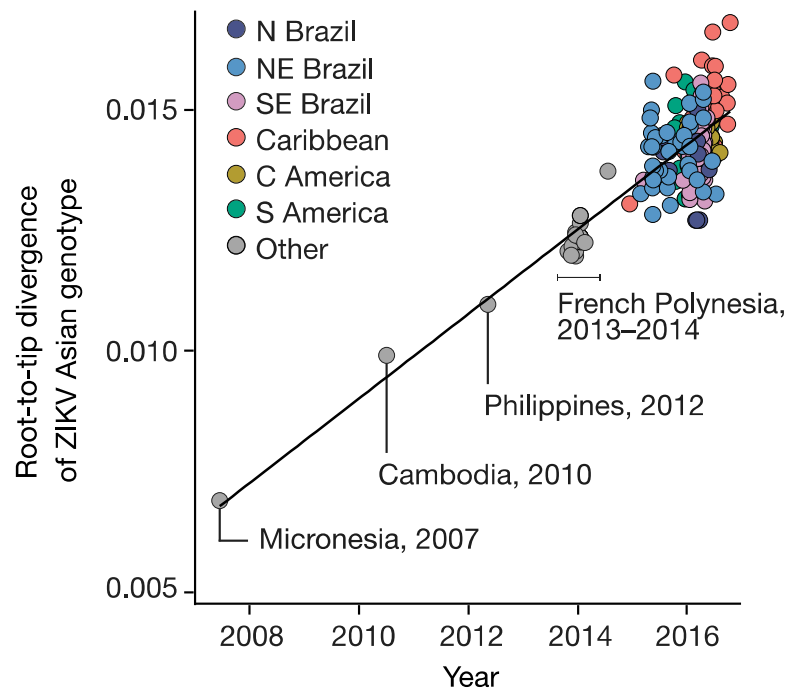
Amplicon-based sequencing and protocol optimisation in real-time



Faria et al. *Nature* 2017 (with MS/SVS and PAHO); Quick et al. *Nature Protocols* 2017; Kraemer et al. *eLife* 2014

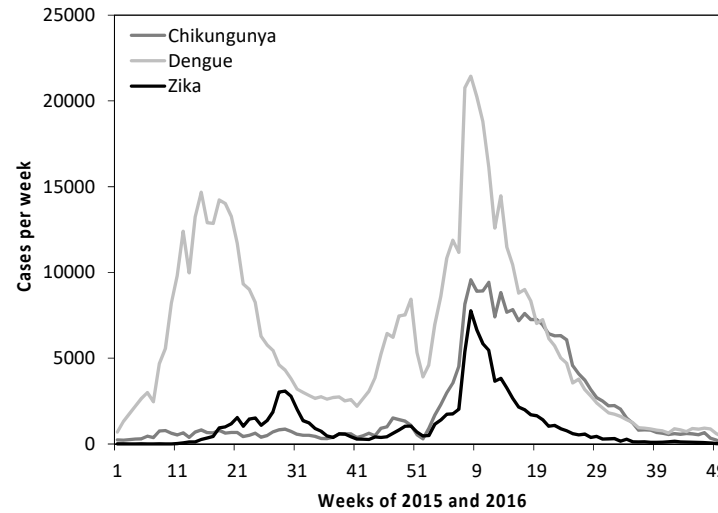
Establishment and cryptic transmission of Zika virus in Brazil and the Americas

Quantifying periods of transmission, investigating geographical spread and reintroductions between populations, and evaluation of possibly relevant mutations associated with phenotypic changes.



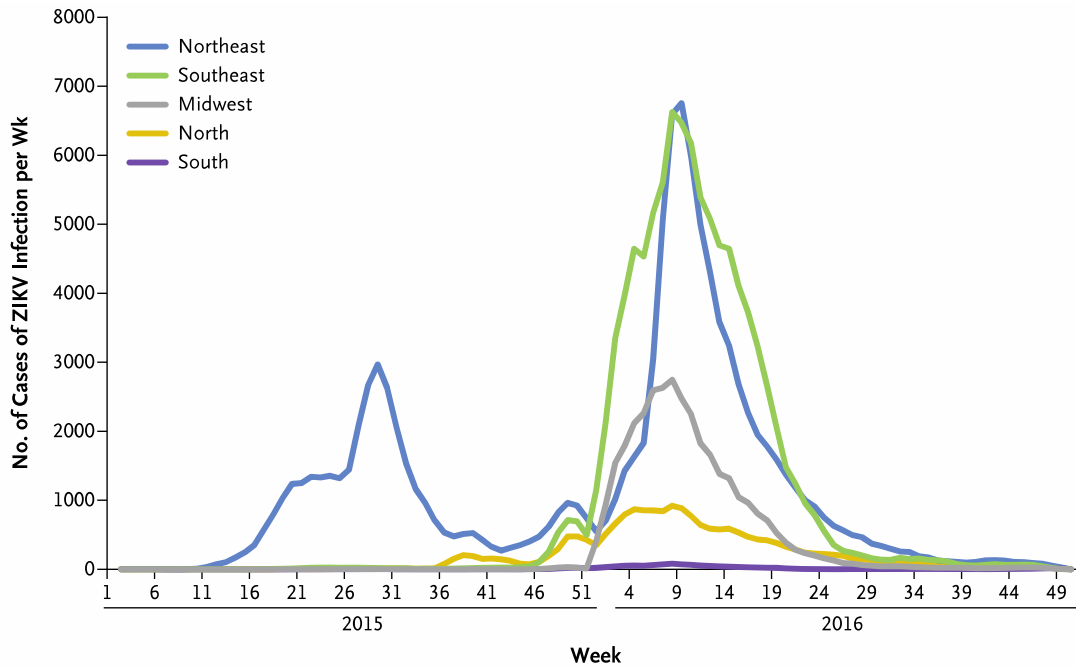
Faria et al. *Nature* 2017 (with MS/SVS, PAHO and WHO)

Zika Virus Infection and Associated Neurologic Disorders in Brazil

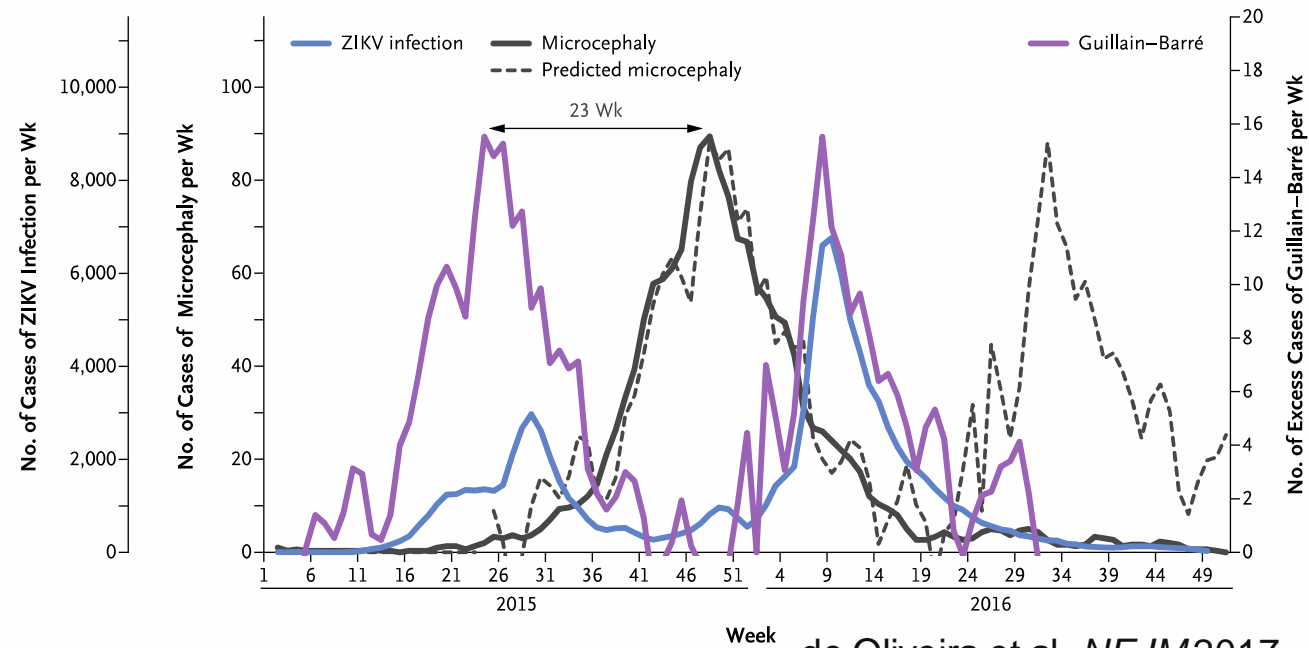


Co-existence in the North-East region of three arboviruses transmitted by *Aedes aegypti*

Suspected Cases of ZIKV Infection in the Five Major Regions of Brazil



Suspected Cases of ZIKV Infection, Guillain-Barré, and Microcephaly in Northeast Region

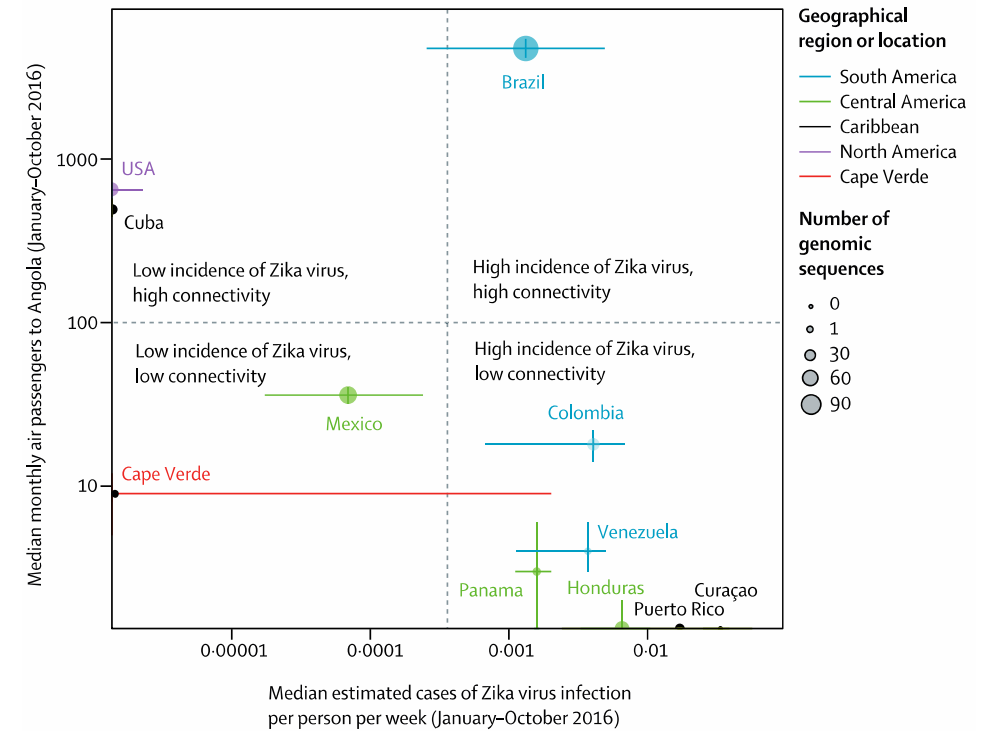
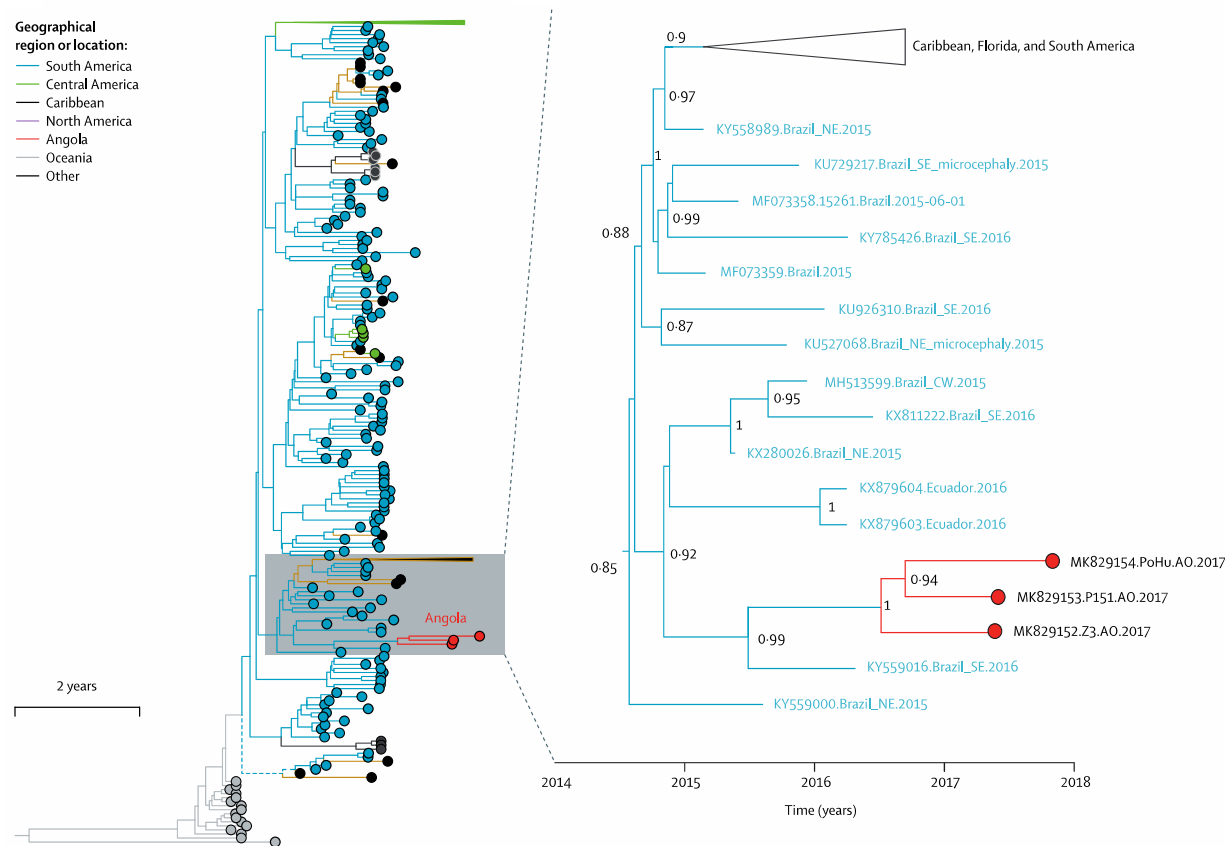


de Oliveira et al. *NEJM* 2017

Zika virus and microcephaly in continental Africa: what lineage and where from?

Introduction of Zika virus Asian lineage from Brazil, possibly causing 76 suspected microcephaly cases in Luanda

Factors affecting the likelihood of introduction of Zika virus Asian lineage to Angola



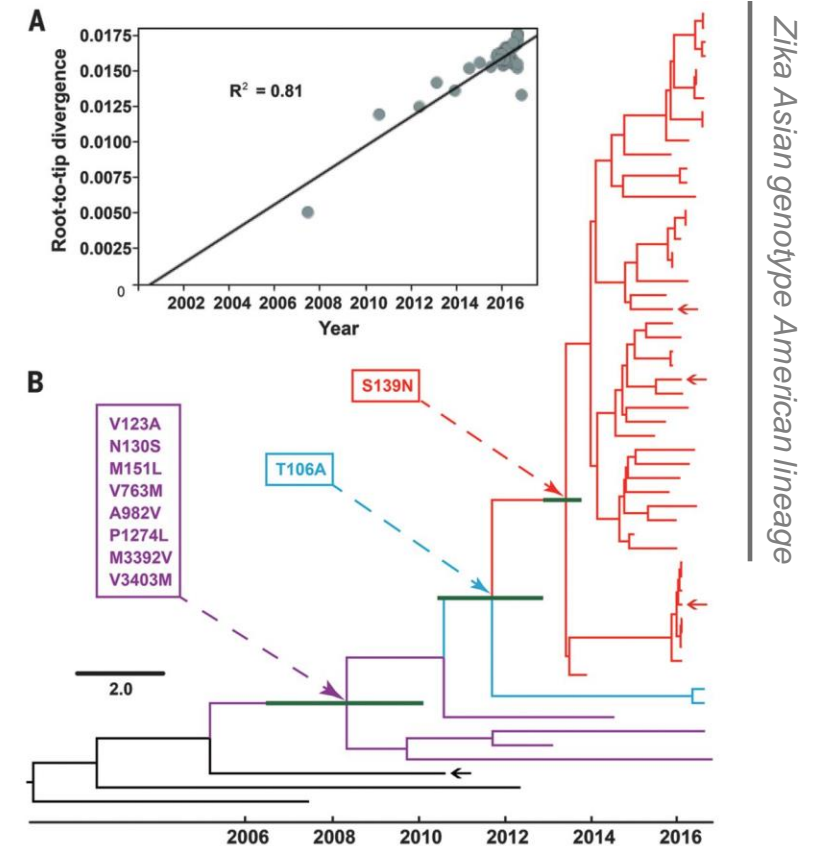
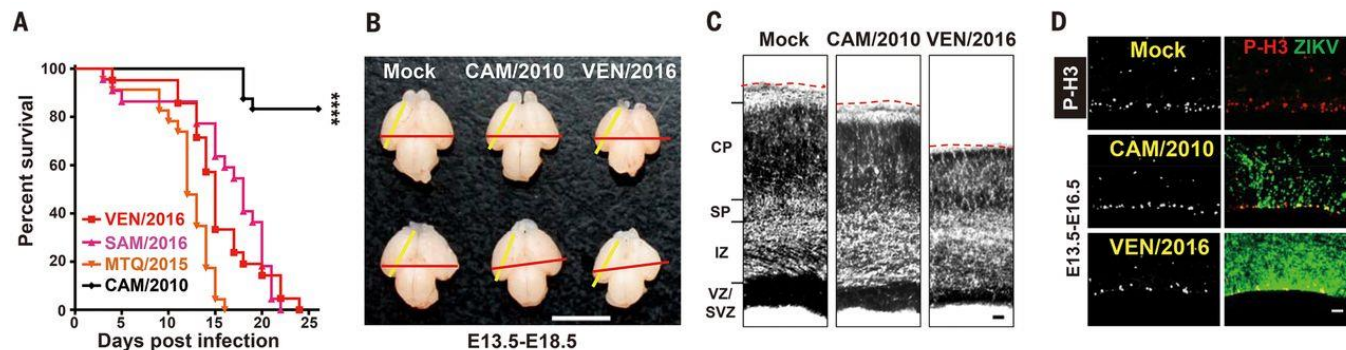
Hill, Vasconcelos et al. *Lancet Inf Dis* 2018 (Angolan MoH)

A single mutation in the prM protein of Zika virus contributes to fetal microcephaly

Supporting in vivo experiments with a mutant virus with the specific mutations of concern to confirm or reject the specific properties of the candidate variants.

- Single mutation (prM-S139N) contributes to foetal microcephaly
- prM-S139N mutation arose in 2013 in French Polynesia before the virus jumped to Brazil (*American lineage*).
- In vitro, prM-S139N makes ZIKV more infectious for mouse and human neural progenitor cells and promoted apoptosis.

Neurovirulence phenotypes of the contemporary ZIKV strains and their ancestral Asian strain:



Yuan et al. *Science* 2017

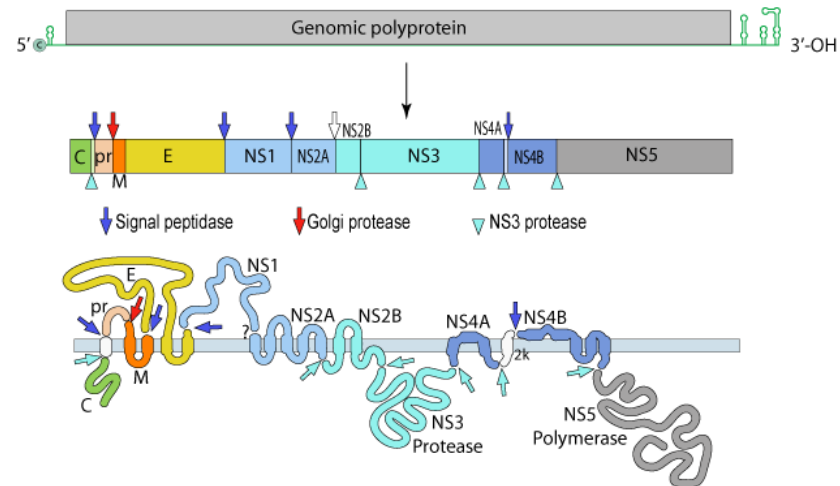
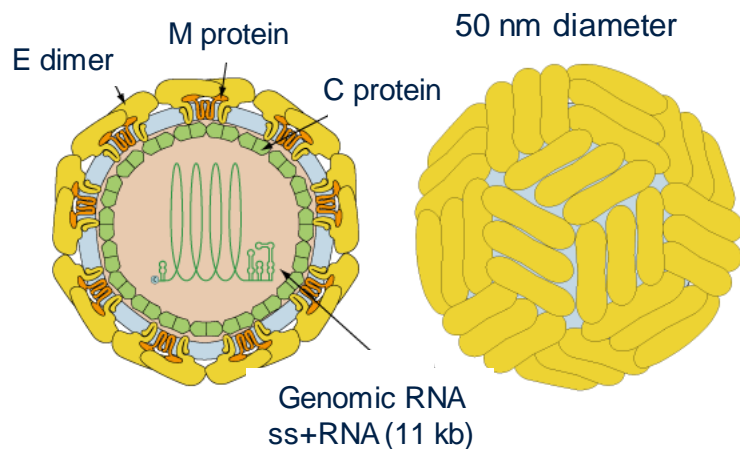
Yellow fever virus

Yellow fever virus: virion, genome and clinical symptoms

- RNA virus transmitted primarily by hematophagous arthropods.
- Member of the Flaviviridae family (flavus = yellow).
- Genus Flavivirus, as dengue, Zika and West Nile viruses.
- Primary amplifying hosts: non-human primates.
- Humans are accidental hosts and present range clinical forms
- Vaccine-preventable (very effective 17D, live-attenuated, long-life protection, available since 1938), yet >82,000 deaths annually worldwide.

The yellow fever iceberg:

1. Asymptomatic infection: 40 to 65%
2. Moderate form: 20 to 30%
3. Severe form: 10 to 20%
4. Fatal: 5 to 10%



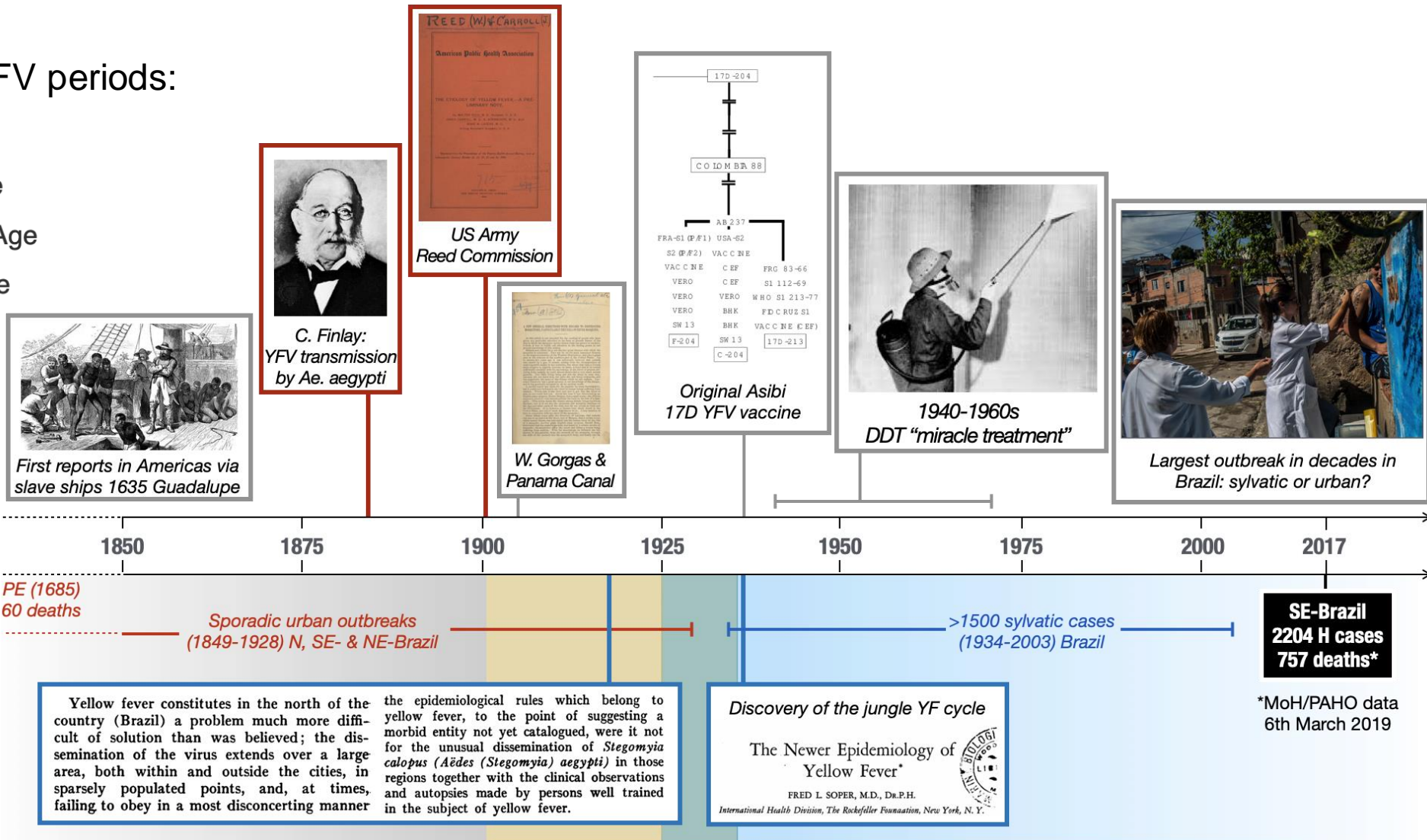
<https://viralzone.expasy.org>

Pariset & Mazet, 1819 (Wellcome Collections)
Vasconcelos P, Rev Soc Bras Med Trop, 2003; Gaythorpe et al eLife, 2021

Brief history of YFV in Brazil

Historical YFV periods:

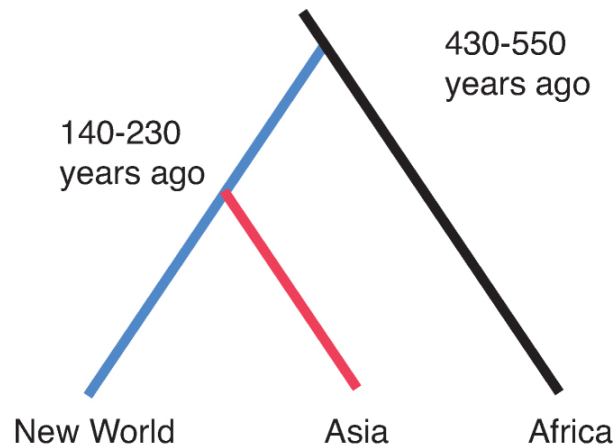
- Dark Age
- Golden Age
- Disillusion Age
- Vaccine Age



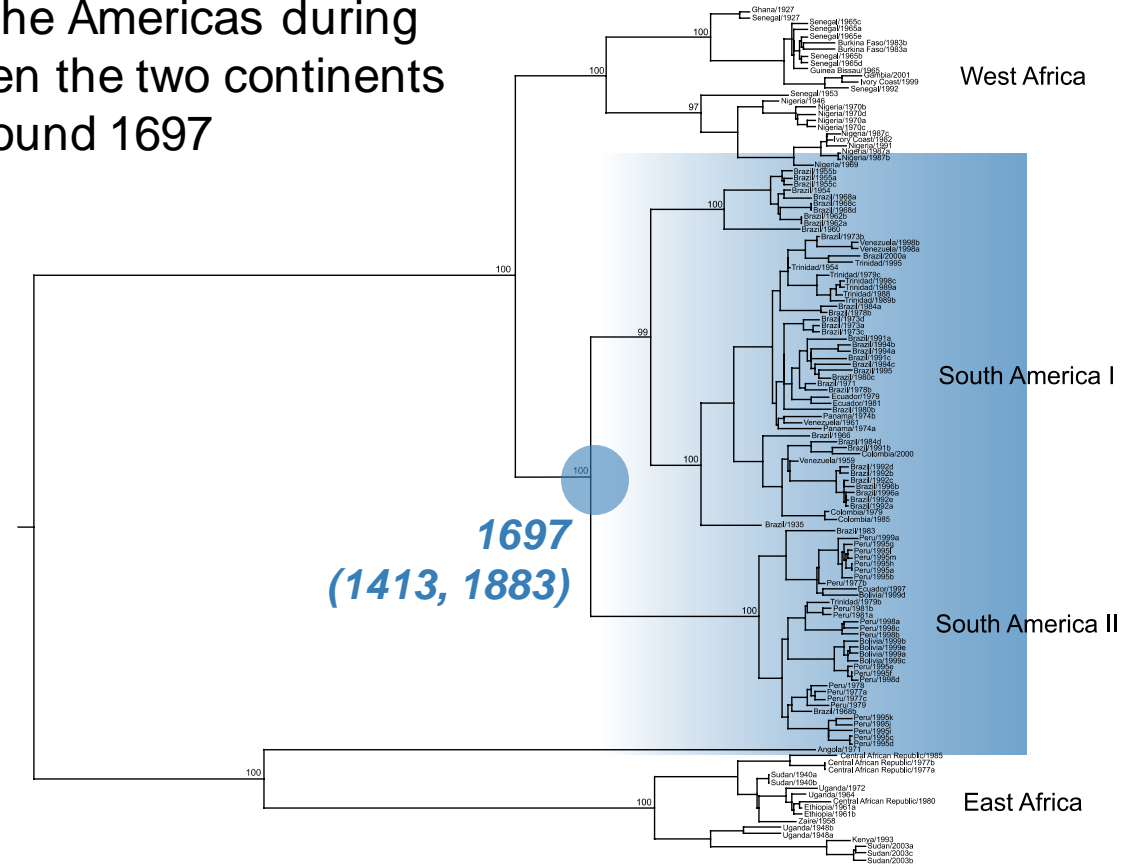
Spatial structure of YFV genetic diversity

Yellow fever virus (YFV) can be classified in four genotypes, two can be found in Africa, and two can be found in the Americas.

- Similar timing of arrival of *Aedes aegypti* and YFV in the Americas during period of Atlantic Slave Trade and first contact between the two continents
- South American genotypes arrival has been dated around 1697
- *Ae. aegypti* arrival to Americas dated before 1618

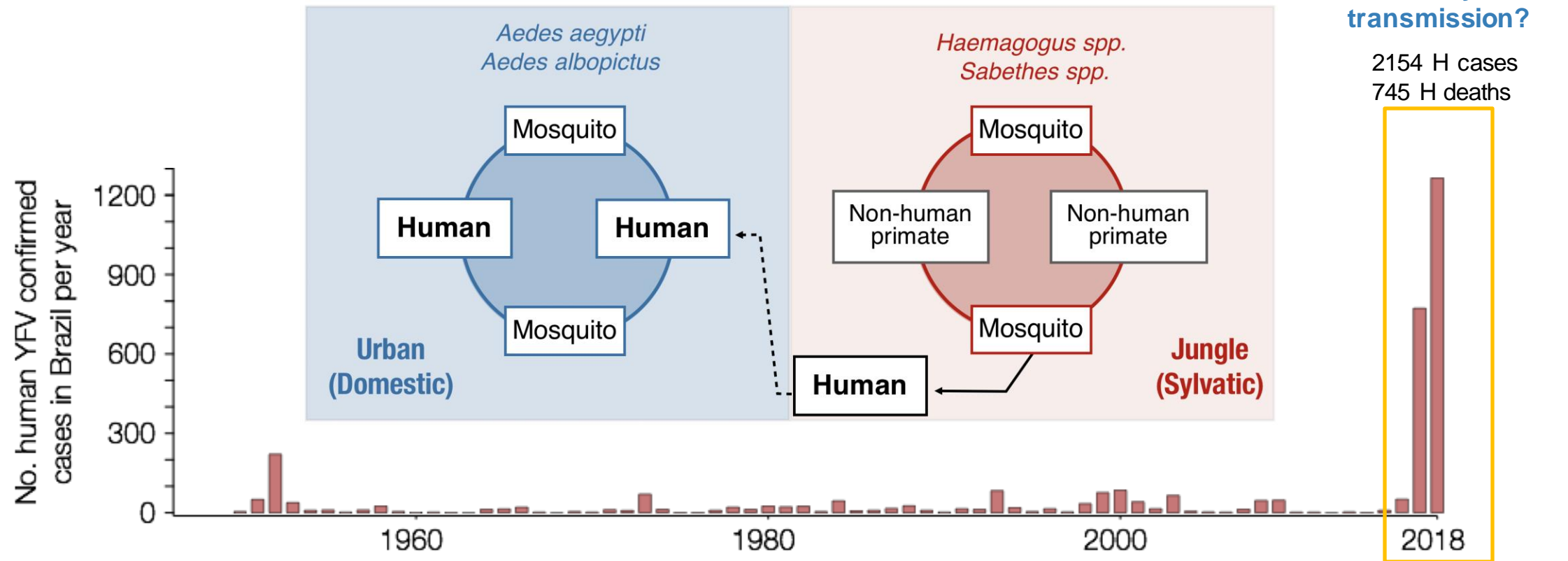


Powel et al. *Bioscience* 2018



Bryant et al. *PLoS Pathogens*, 2007

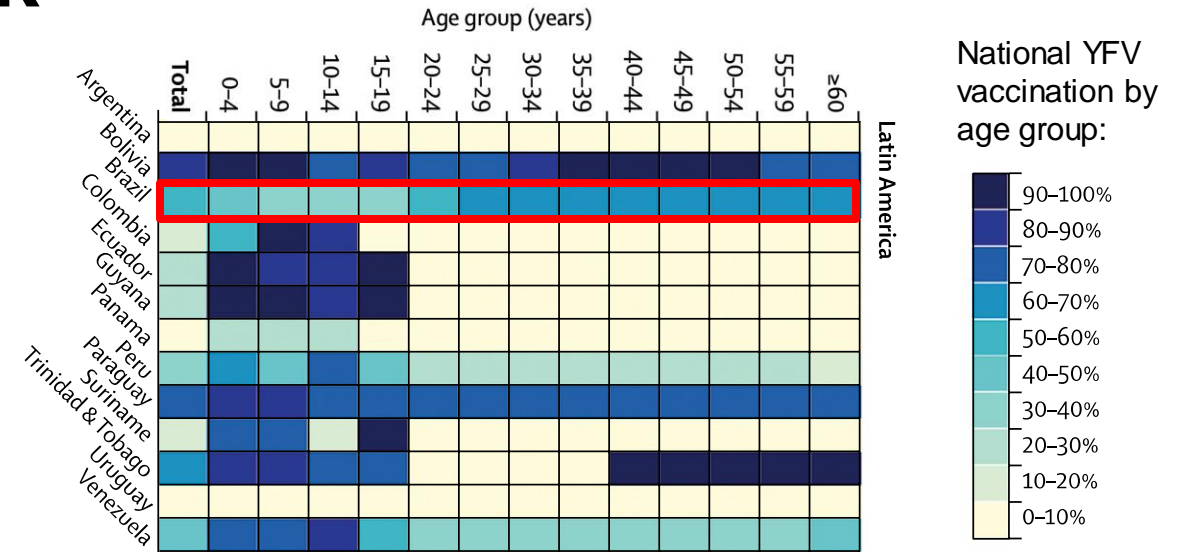
Time-series of yellow fever human cases in Brazil from 1950–2019



Adapted from MS-SVS 2019

Factors hypothesised to explain recent explosive YFV outbreak

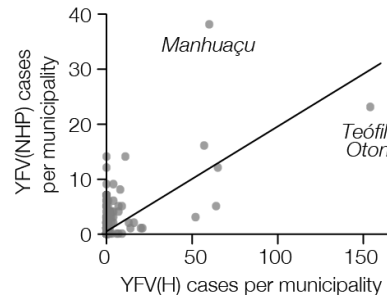
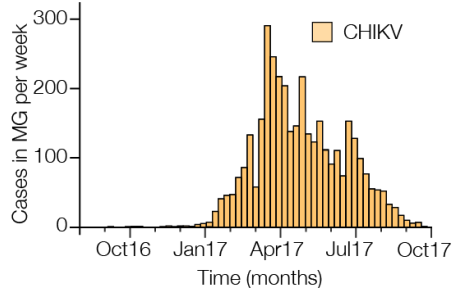
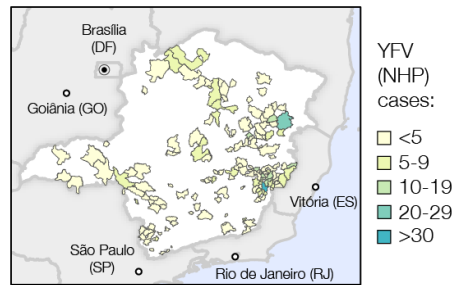
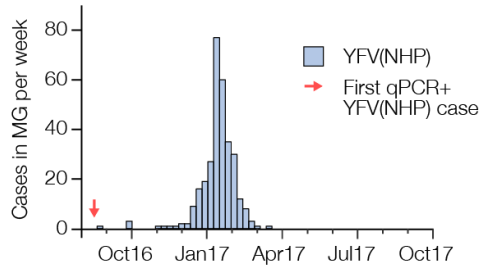
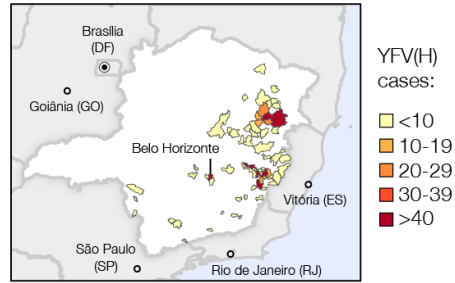
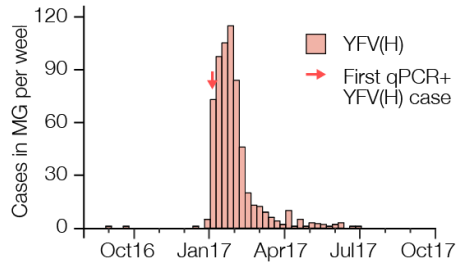
- Low vaccination coverage in areas that were previously not at risk, particularly the larger states in SE-Brazil (São Paulo, Rio de Janeiro and Minas Gerais states).
- Waning of YFV immunity in reservoir hosts (non-human primates?) in the Amazon region, where the virus is endemic.
- Anthropogenic environmental changes favoured mosquito populations (including urbanization, land use and climate change).
- Increased mobility due to illegal trade of reservoir populations (non-human primates?) and vector expansion via air and fluvial travel.
- High altitude migration of windborne mosquitoes carrying YFV for hundreds of kilometres (observed for *Anopheles spp.*)



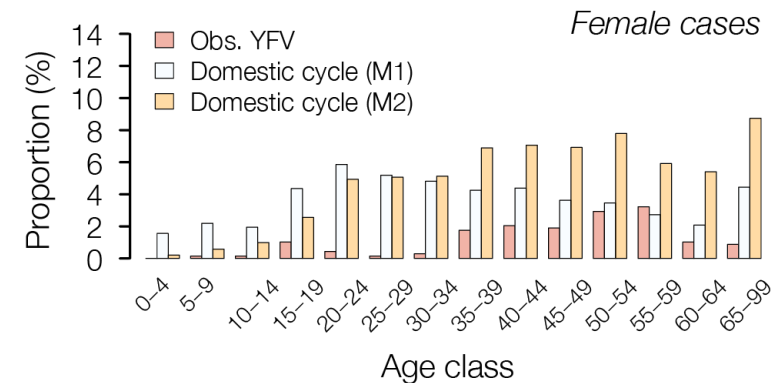
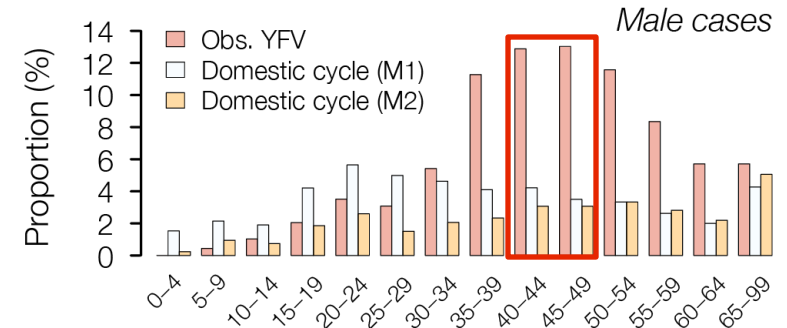
Shearer et al. *Lancet Infect Dis* 2017

Using epidemiological data to shed light on the mode of YFV transmission

Strong cross correlation between human and NP cases: human cases lagged by 4 days



Comparison between **chikungunya** (urban/domestic transmission) and **yellow fever** in Minas Gerais (SE Brazil)



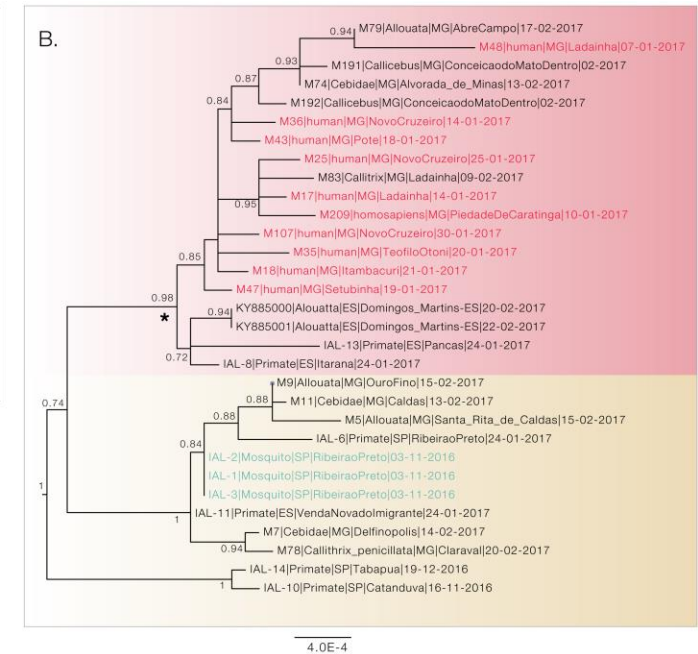
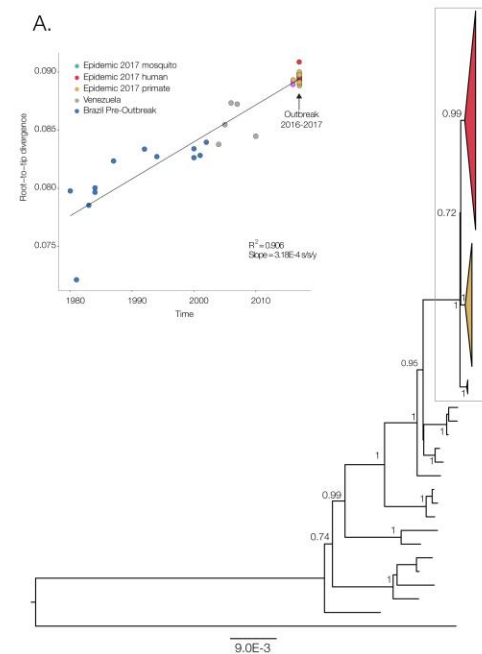
Faria et al. *Science*2018 (with PAHO)

Sharing pathogen sequence data, analyses and interpretation in real-time at outbreak epicenter (I)

- Largest outbreak for decades in Brazil (>2204 human cases, 757 deaths)
- Pathogen GSD helped to answer key epi question: **sylvatic transmission** or urban transmission?
- Preliminary data, interpretation and protocols shared **6 days upon arrival** at the epicentre of outbreak
- Maximum impact on public health, no negative impact on peer review publication

Yellow fever virus ▾ Latest Top

| Topic | Replies | Views | Activity |
|--|---------|-------|----------|
| Real-time Genomic Surveillance of the Yellow Fever Virus Outbreak in Brazil, 2017 | 0 | 9.0k | May '17 |
| Yellow fever outbreak in Nigeria 2018 | 2 | 5.1k | Jul '19 |
| Yellow fever virus in Angola | 6 | 4.7k | Jun '16 |
| Yellow Fever Virus genomic sequence from a Dutch traveller returning from Suriname | 1 | 4.6k | May '17 |
| New insights into the origin of the YFV 2017 Brazilian outbreak | 2 | 4.5k | Apr '17 |
| Genomic characterisation of sylvatic yellow fever virus epizootic in Trinidad | 0 | 2.9k | Mar '21 |

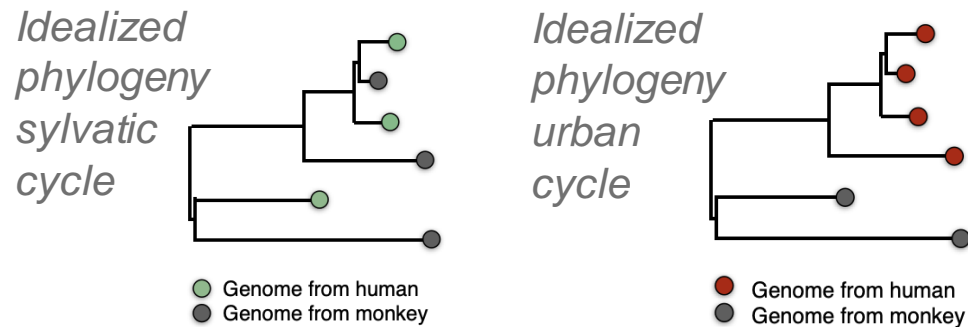


<https://virological.org/t/real-time-genomic-surveillance-of-the-yellow-fever-virus-outbreak-in-brazil-2017/182> (5 May 2017)

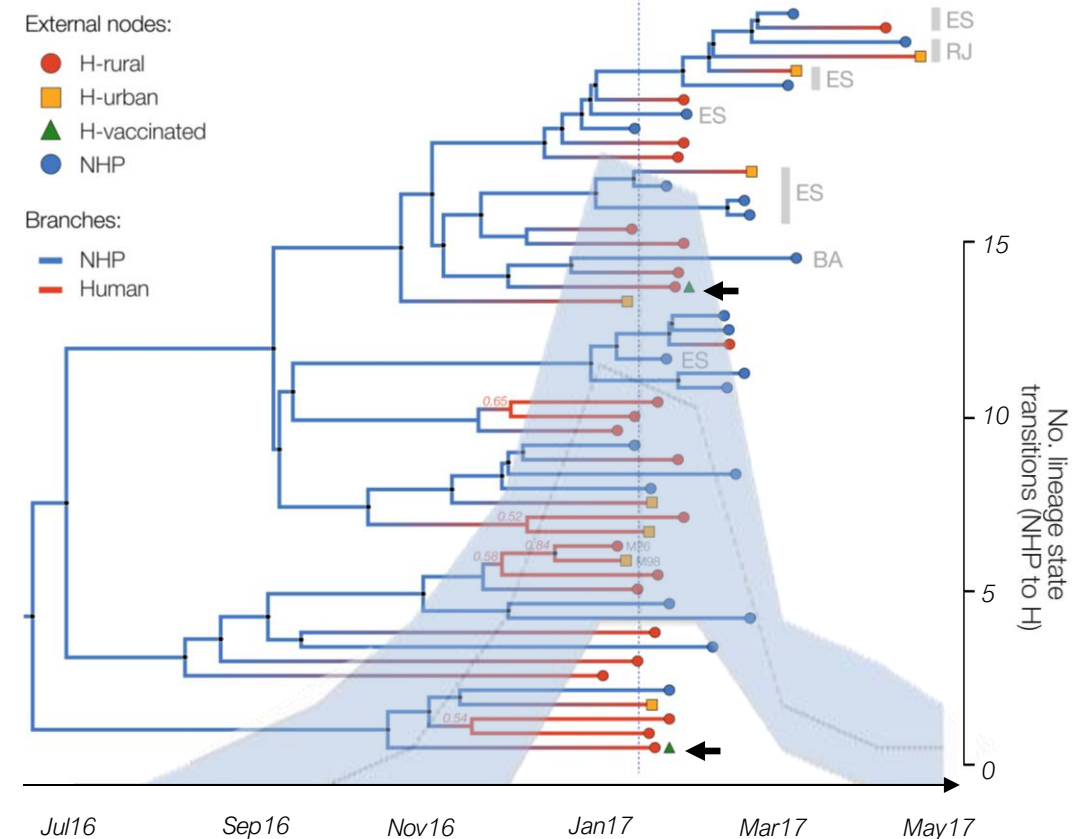
Frequent spillover of yellow fever detected within days at the outbreak's epicentre

Tracking zoonotic reintroduction in both directions over the species barrier and identifying (or ruling out) vaccine reversions.

- Real-time genomic sequencing in FUNED–MG: within 5 days, GSD data showed a pattern consistent with wildtype YFV SA1 lineage infection, indicating frequent spillover while ruling-out urban transmission.

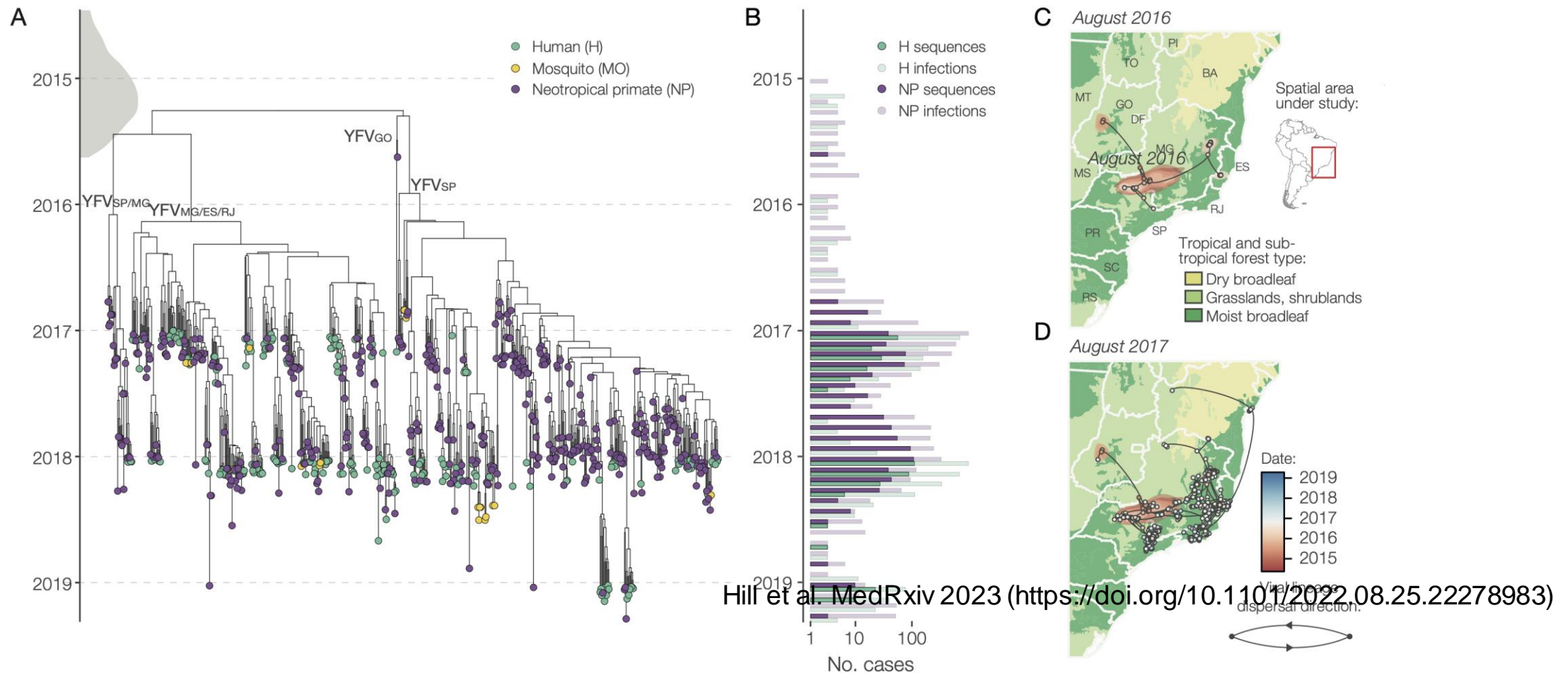


- At least **two patients** living in rural areas in Minas Gerais died 2d after receiving the YFV vaccine. Real-time GSD analysis ruled out YFV vaccine reversion.



Faria et al. *Science* 2018 (with PAHO)

Tripling the amount of YFV genomes from Brazil to elucidate drivers of spread



Hill et al. MedRxiv 2023 (<https://doi.org/10.1101/2022.08.25.22278983>)

Hill, Claro () Faria, Sabino, MedRxiv 2023 (<https://doi.org/10.1101/2022.08.25.22278983>)

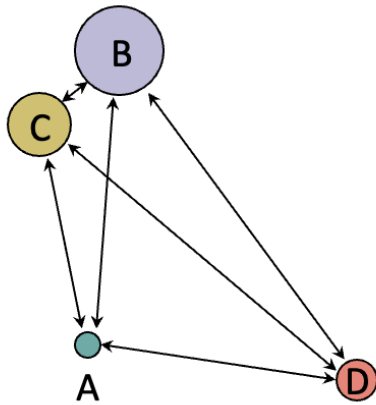
YFV enzootic and spillover transmission are driven by spatial proximity

Identifying drivers of virus zoonotic spread.

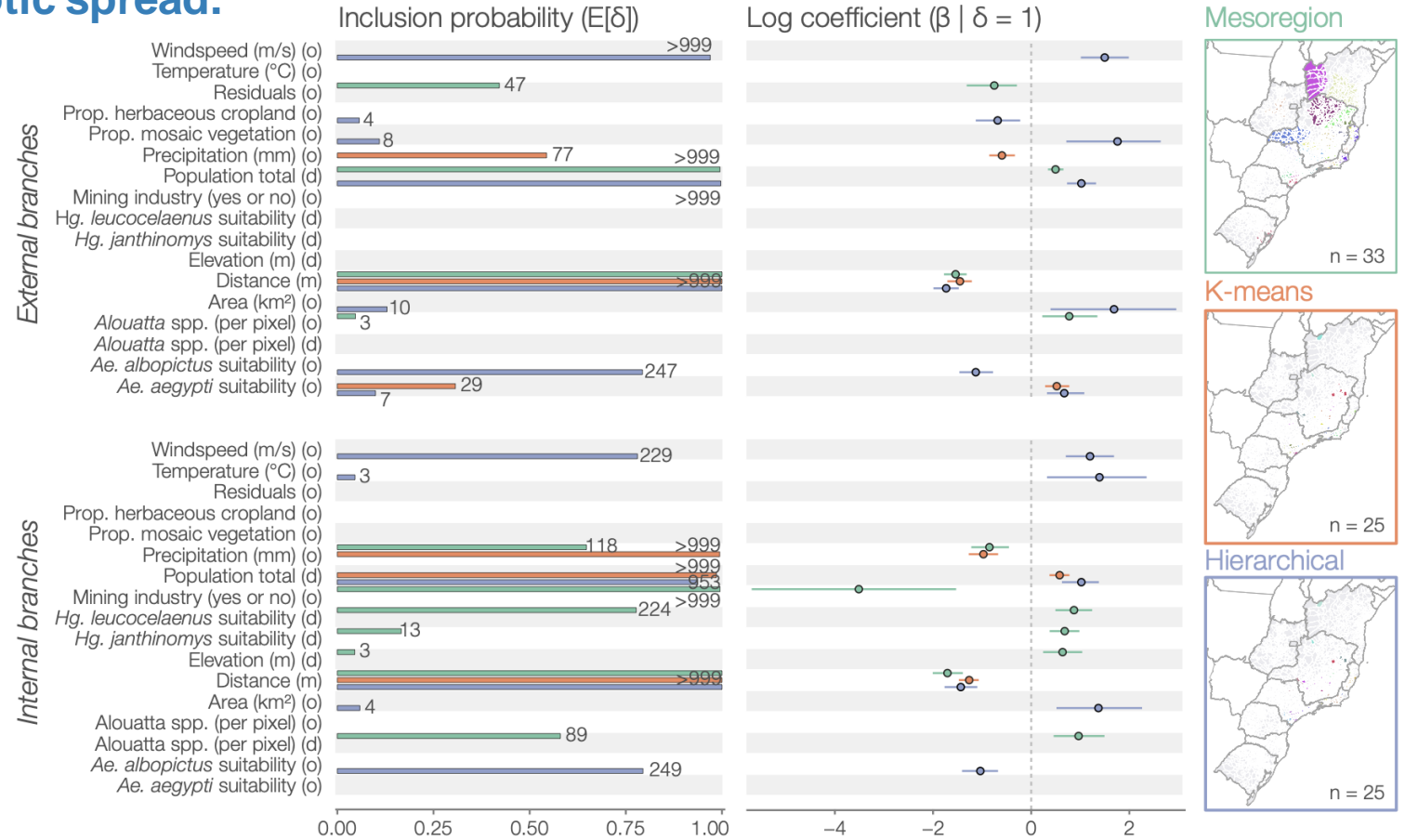
$$\log \lambda_{AB} = \delta_1 \beta_1 P_{1AB} + \delta_2 \beta_2 P_{2AB} + \delta_3 \beta_3 P_{3AB}$$

Phylogenetic generalised linear model

support weight



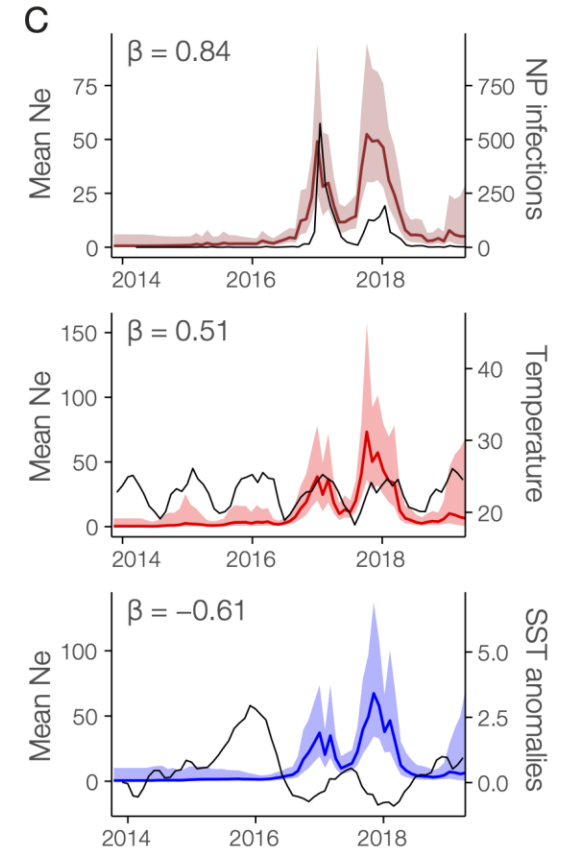
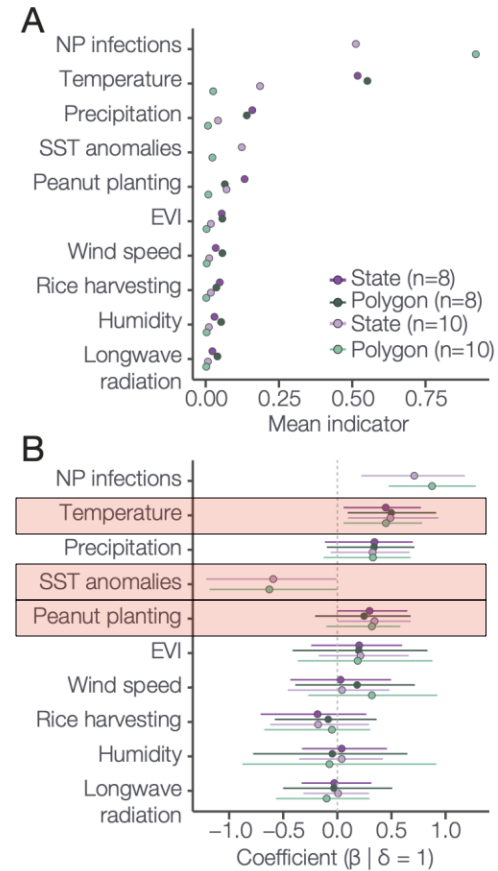
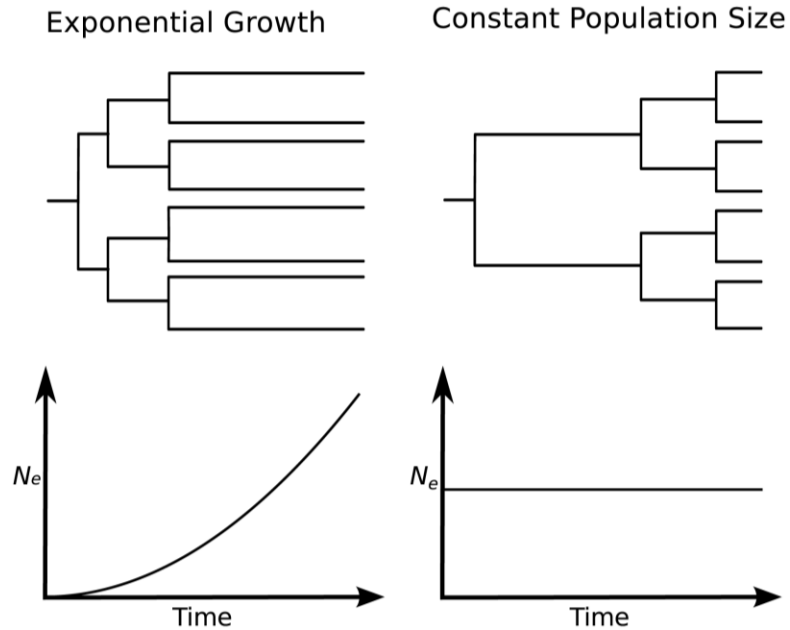
Faria et al. *Phil Trans Roy Soc B* 2013;
Lemey et al. *PLoS Pathogens* 2014



Hill, Claro () Faria, Sabino, MedRxiv 2023 (<https://doi.org/10.1101/2022.08.25.22278983>)

Temporal dynamics of yellow fever are largely driven by land usage and climate

Coalescent phylodynamic models – underlying principle is that we can recover population sizes from phylogenetic tree shapes

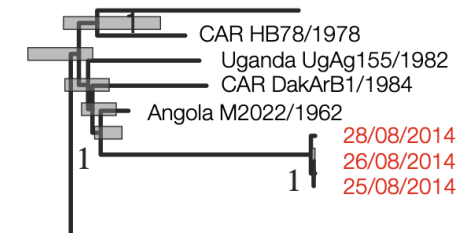
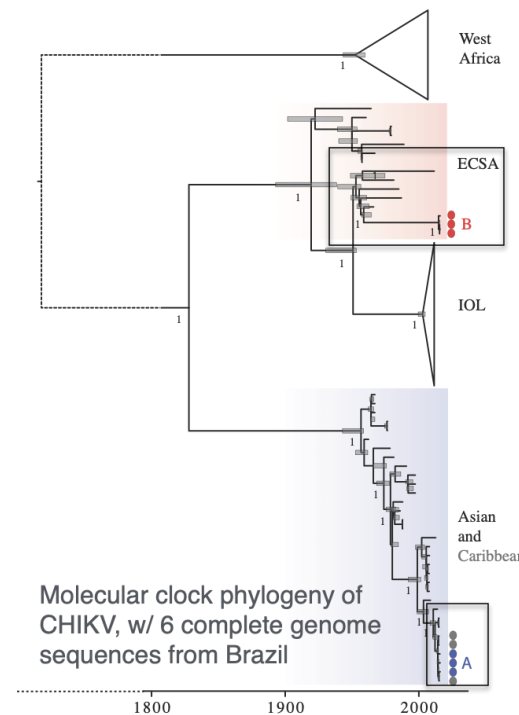


Chikungunya virus

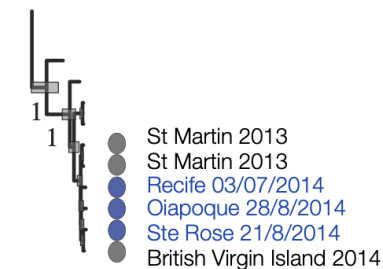
Chikungunya virus: co-circulation of multiple genotypes in the Americas

Establish the contribution of local transmission compared to imported cases can help make policy decisions, including vector control and vaccination.

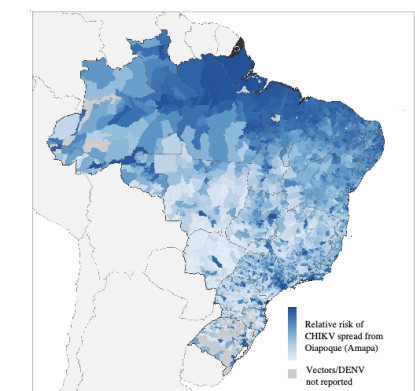
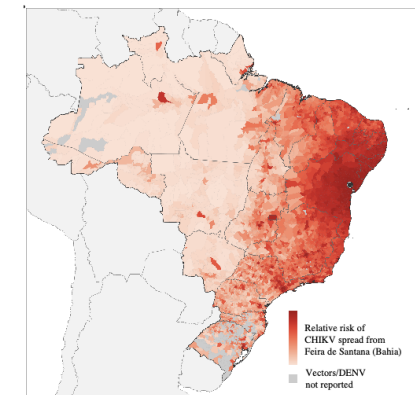
- Chikungunya virus (CHIKV) is an *Aedes* mosquito-borne alphavirus (12kb) that has caused large epidemics linked to acute, chronic, and severe clinical outcomes.
- Asian genotype (Caribbean origin) local transmission detected in Oiapoque, N-Brazil, in July 2014.
- East-Central-South-African (ECSA) genotype (Angola origin) local transmission detected in Feira de Santana, NE-Brazil, in Aug 2014.
- Identification of introductions and monitoring of viral diversity, together with human mobility data can provide accurate short term (but not long term) forecasts of virus transmission.



Index case for ECSA genotype
Returning traveller from Angola



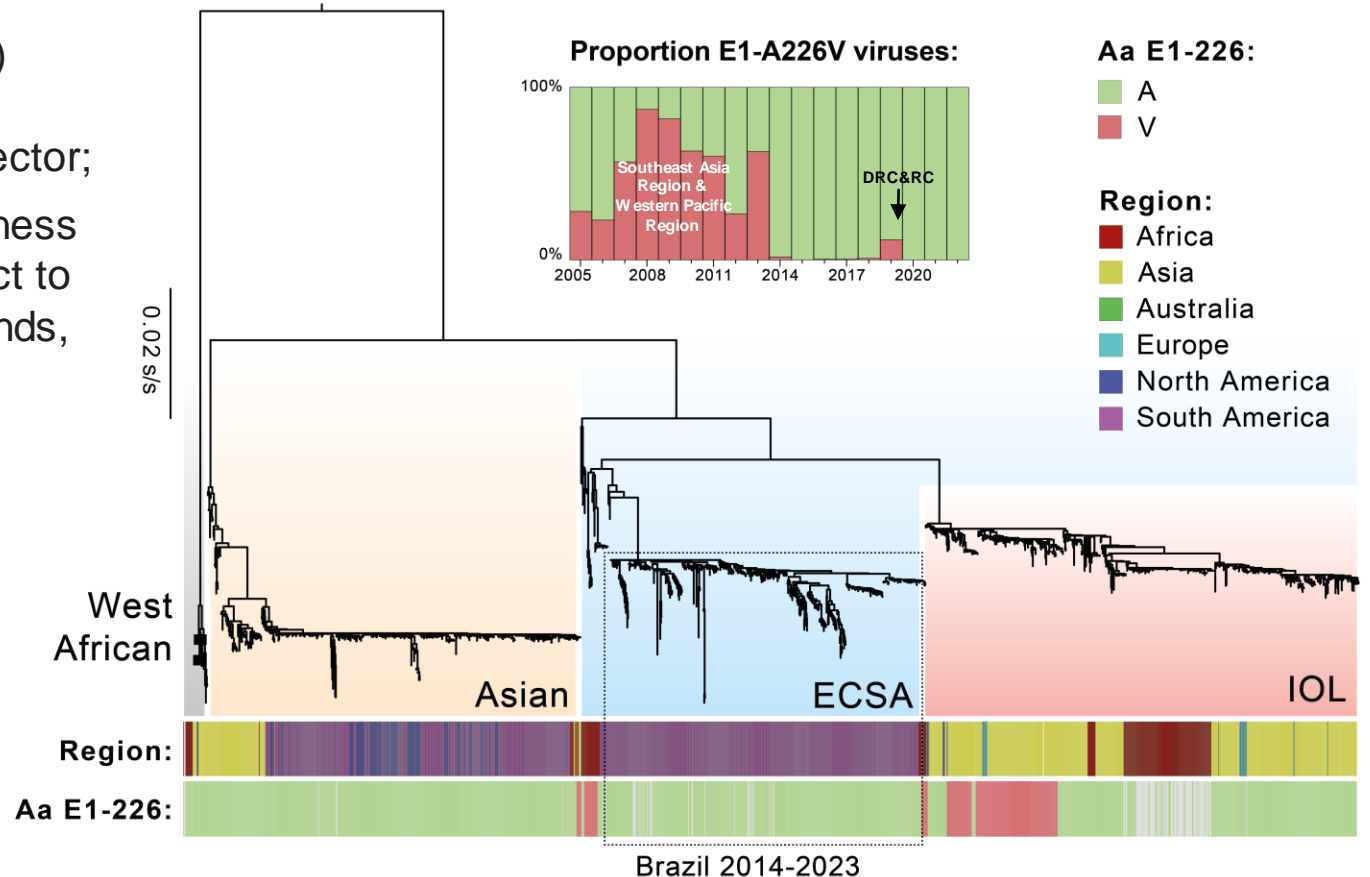
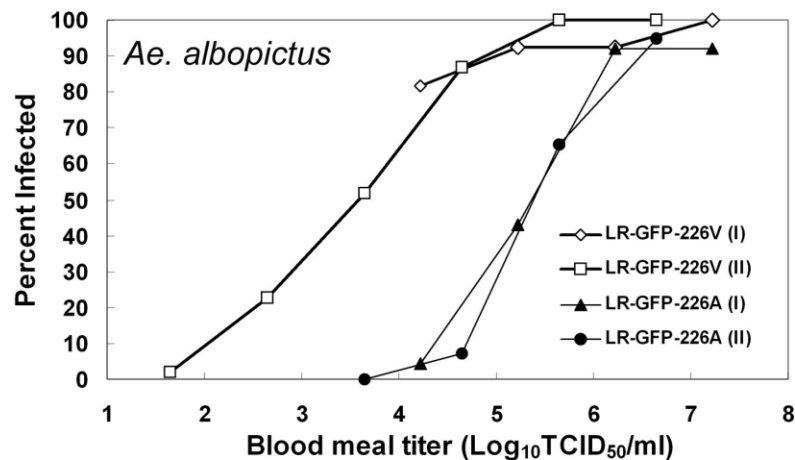
Index case for Asian genotype
Returning traveller from French Guiana



Chikungunya virus: recent genotype replacement in the Americas

Single mutations in the ECSA and IOL lineages may change viral behaviour, transmissibility, pathogenicity and fitness in alternative *Aedes albopictus*.

- CHIKV ECSA outbreak in La Reunion (2005-2006) (38% attack rate): 1st documented report of an alphavirus outbreak with *Ae. albopictus* as main vector;
- **E1-A226V** mutation in CHIKV ECSA: increased fitness of CHIKV in *Ae. albopictus* mosquitoes with respect to midgut infectivity, dissemination to the salivary glands, and transmission to a vertebrate species.



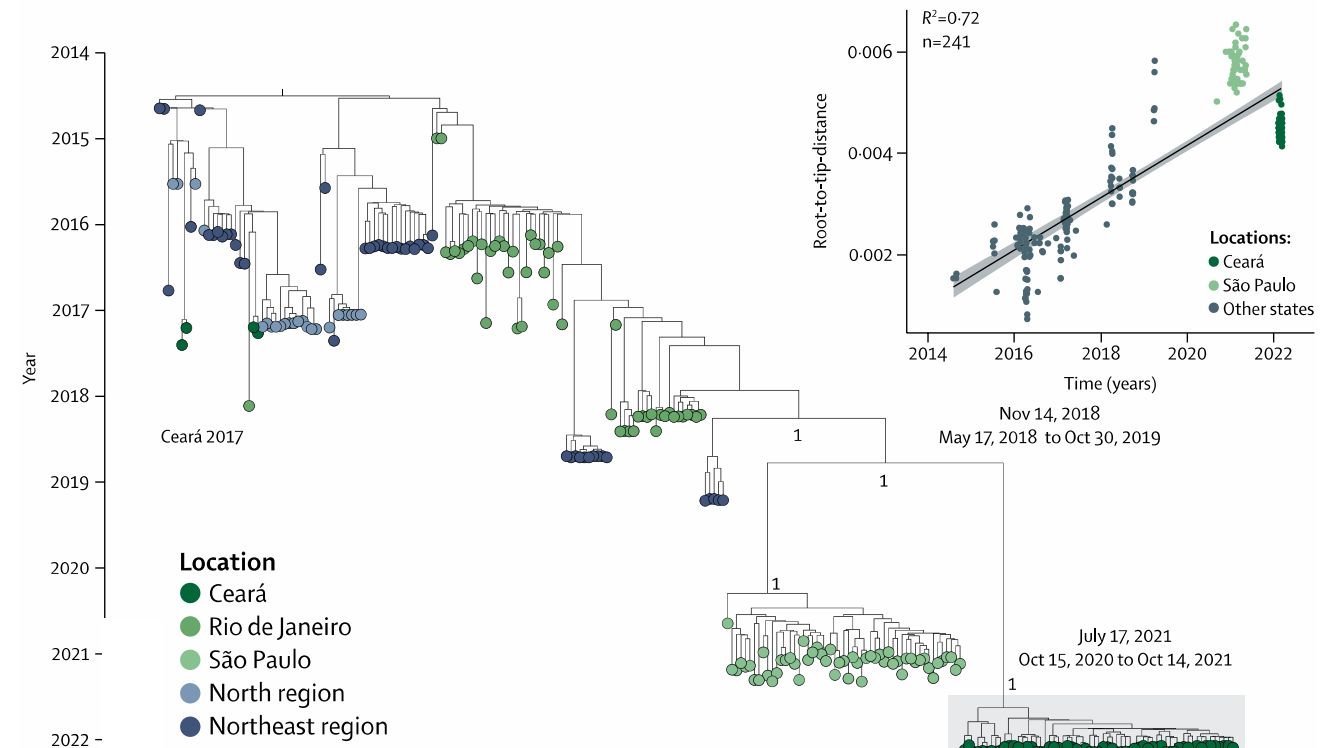
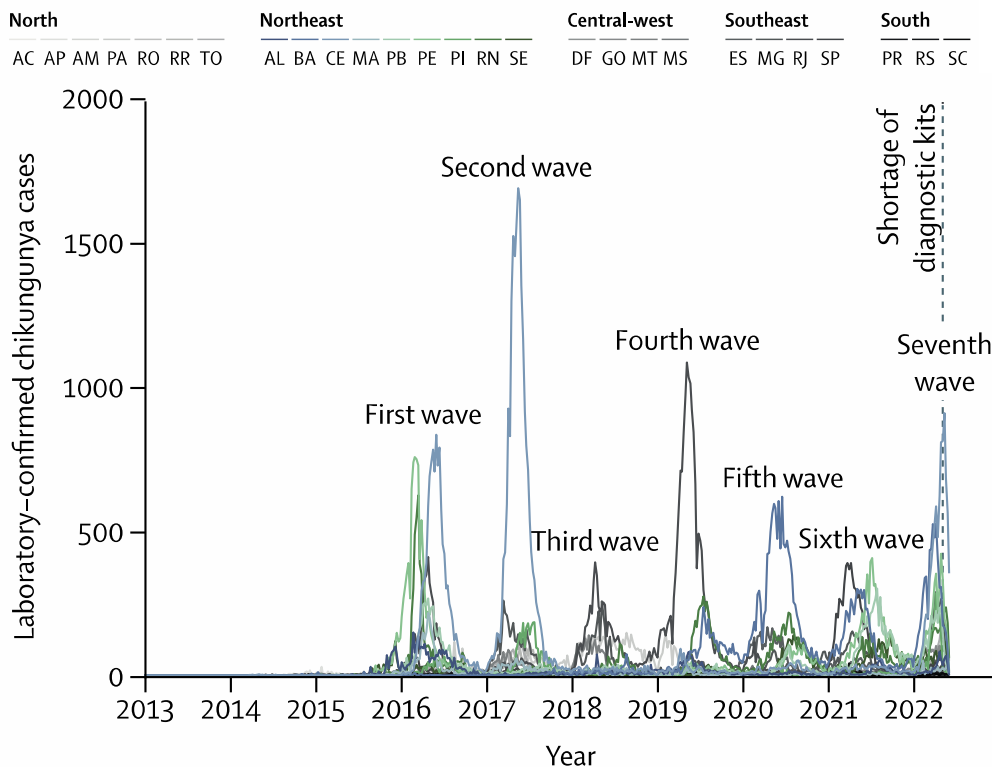
Tsetsarkin et al. *PLoS Pathogens*, 2007; Faria NR, 2023 (n=1661, updated 16 June 2023)

Seven epidemic waves of chikungunya virus in Brazil

Over 59.5% of Brazilian municipalities reported CHIKV laboratory-confirmed cases between 2013 and 2022. Between 2015 onwards, all sequences cases belonged to the CHIKV ECSA genotype.

No mutations previously associated with enhanced transmission potential for *Ae. albopictus* mosquitoes (e.g., E1-A226V) in the CHIKV strains circulating in Brazil.

Spatial heterogeneity of CHIKV spread and population immunity might explain the recurrence pattern of CHIKV in Brazil.



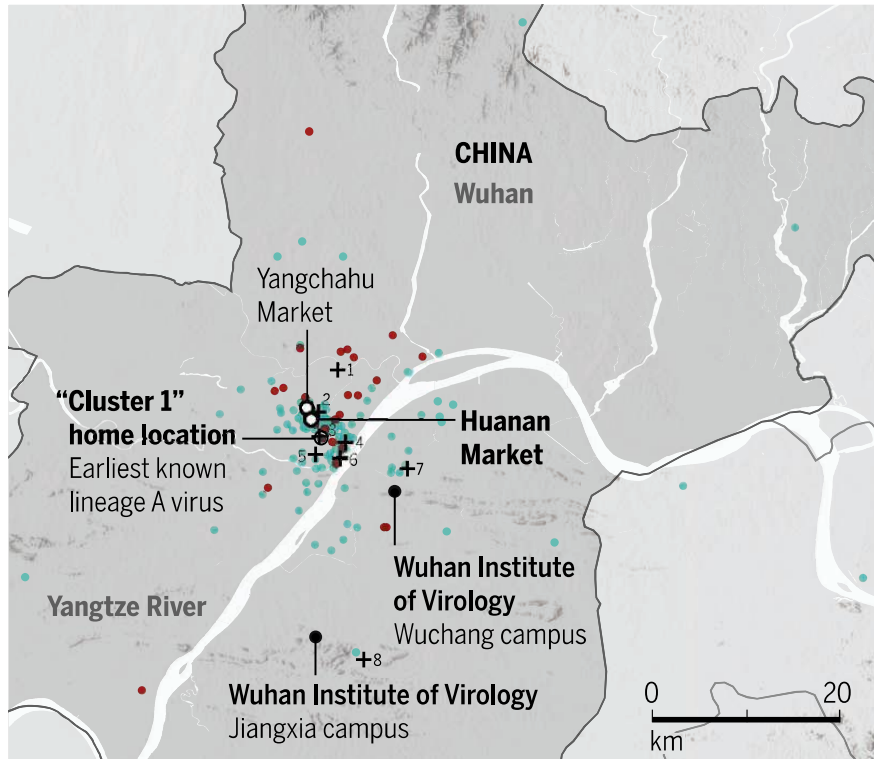
William de Souza, Shirlene de Lima et al. *Lancet Microbe* 2023

SARS-CoV-2

Early cases of SARS-CoV-2 in Wuhan, December 2019

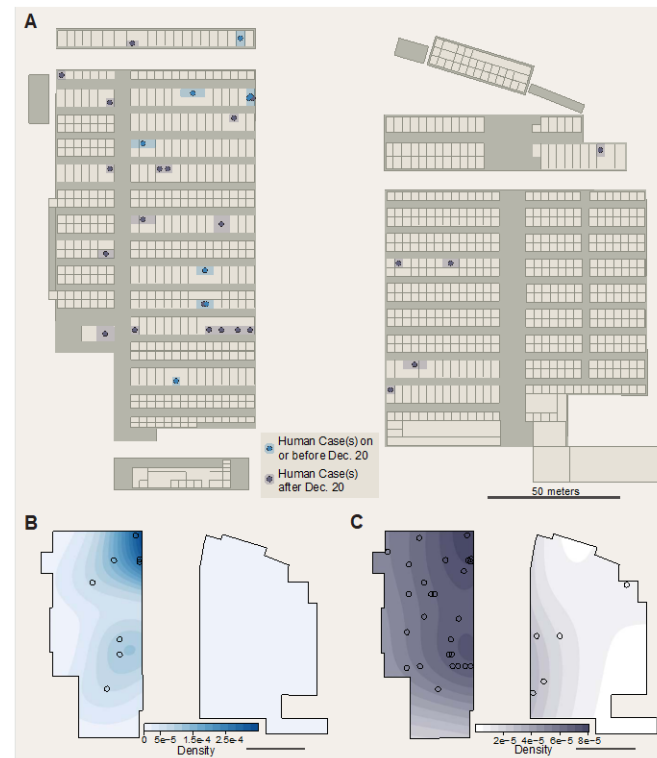
COVID-19 cases in Wuhan in December 2019

- Home address of cases with epidemiological link to Huanan Market
- No link to Huanan Market ○ Market + Hospital



1–7. Hospitals in the vicinity of the Huanan seafood market, Wuhan, China.

Location and timing of human cases in Huanan market



Outline colours correspond to the timing of the first known case in each business.

Location and timing of human cases in Huanan market



(a) King rat snake, (b) Chinese bamboo rat, (c) Amur hedgehog, (d) Raccoon dog.

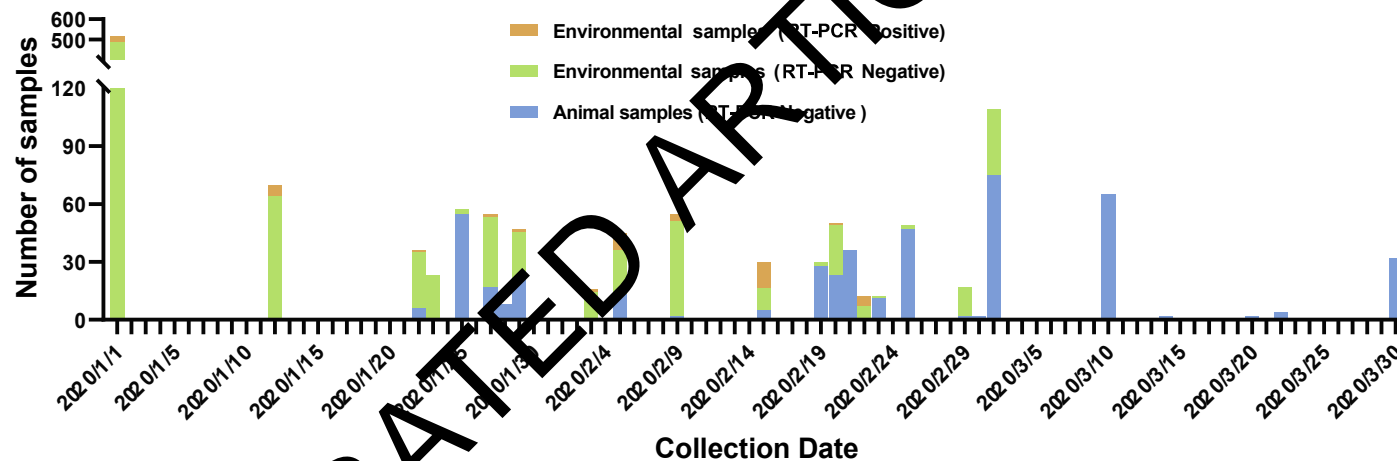
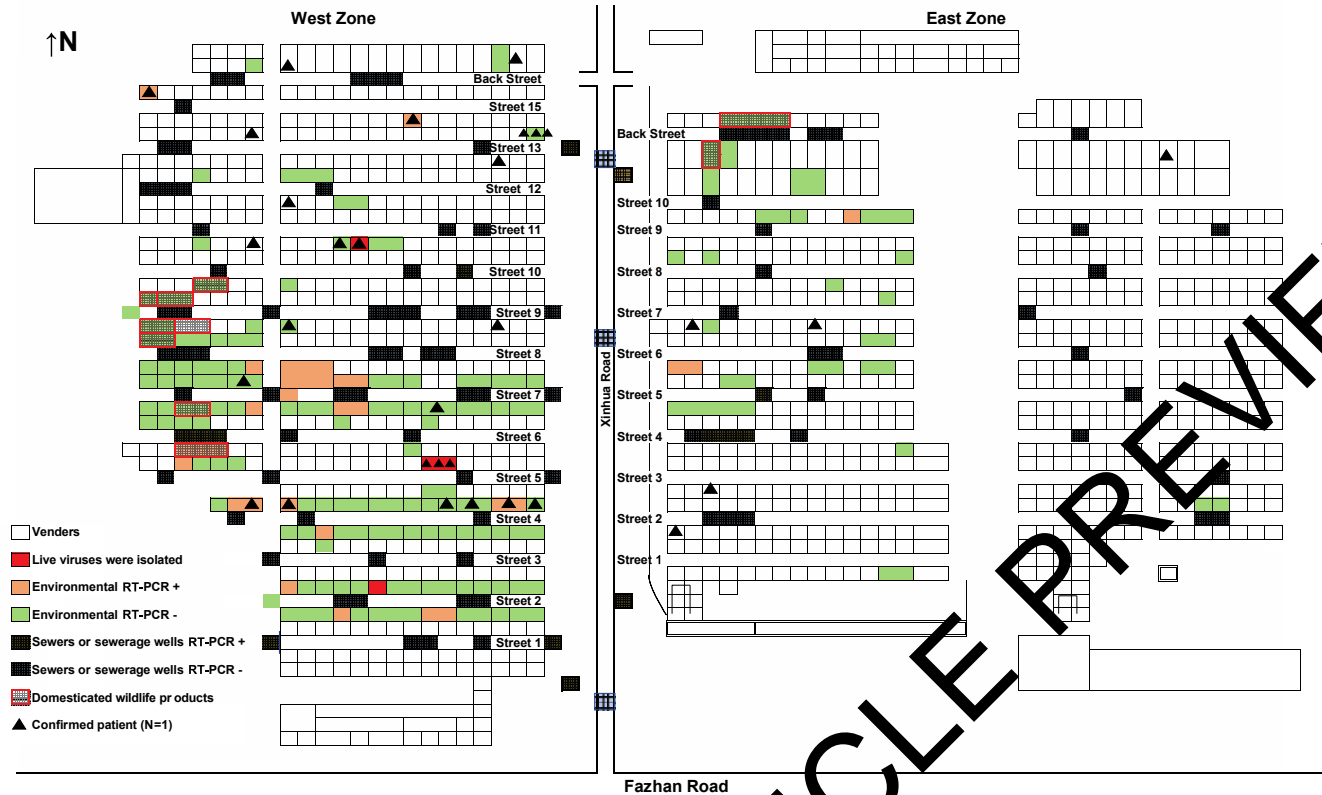
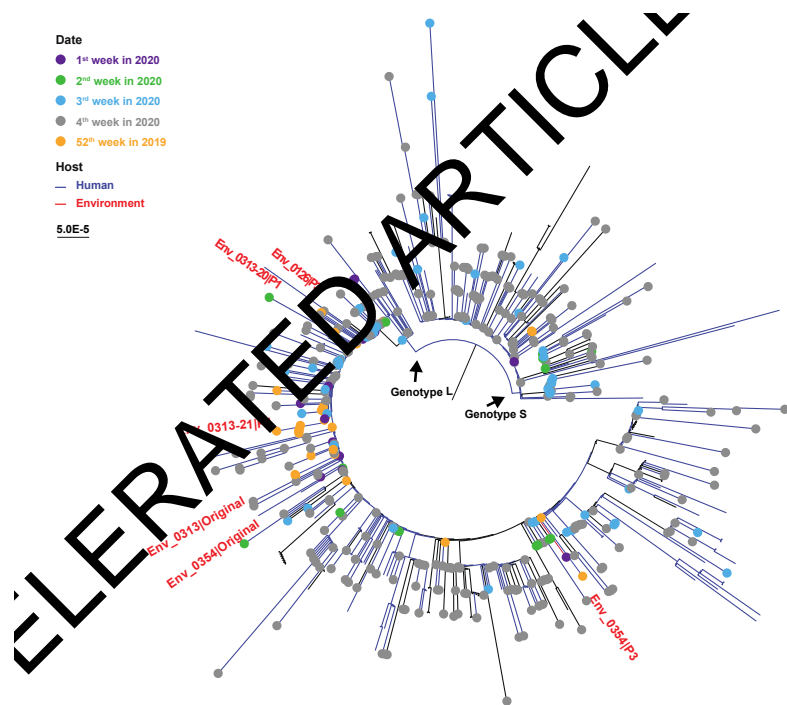
Worobey, *Science* 2021; Worobey et al. *Science* 2022; Xiao et al. *Scientific Reports* 2021

Earliest confirmed cases of SARS-CoV-2 in Huanan seafood market in 01 Jan 2020

Date
 1st week in 2020
 2nd week in 2020
 3rd week in 2020
 4th week in 2020
 52nd week in 2019

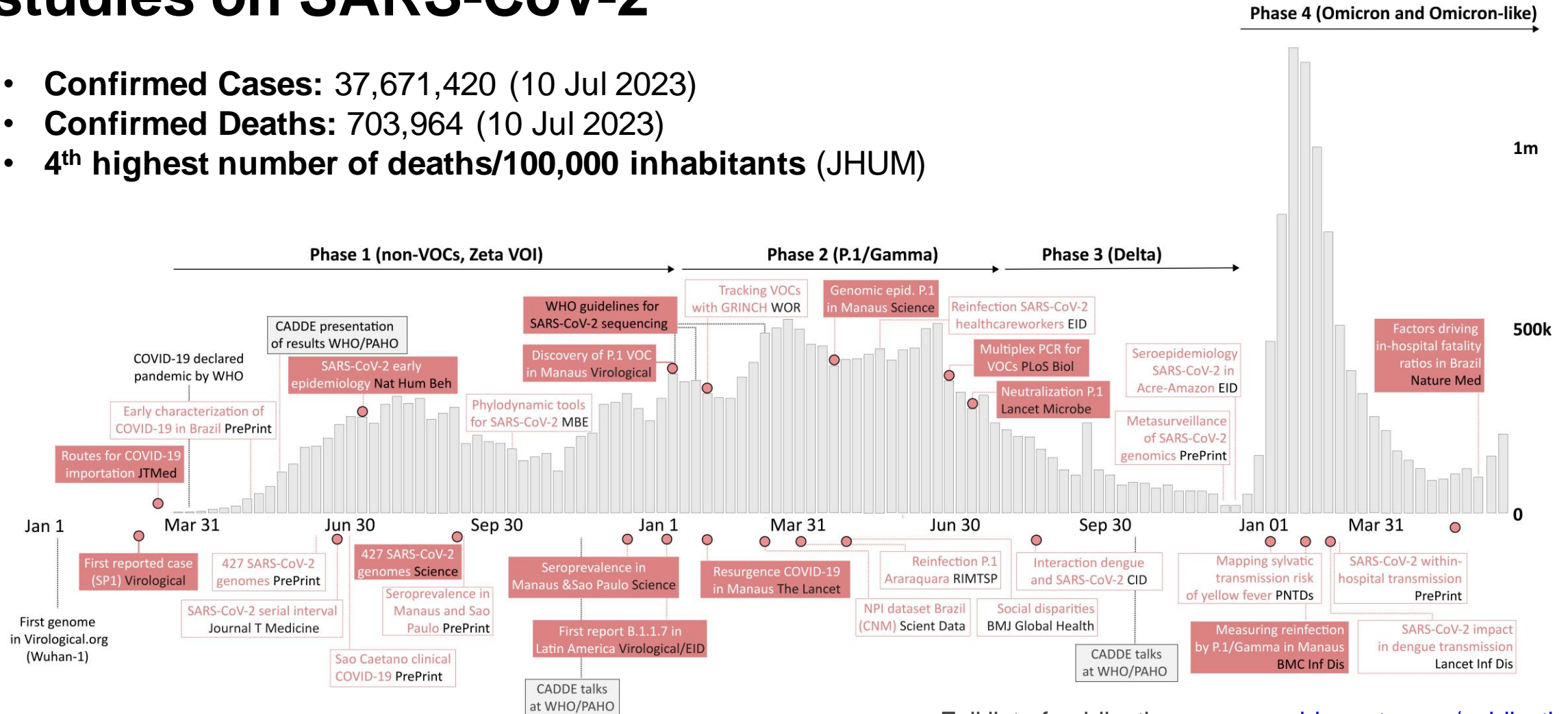
Host
 Human
 Environment

5.0E-5



Timeline of Brazil-UK CADDE studies on SARS-CoV-2

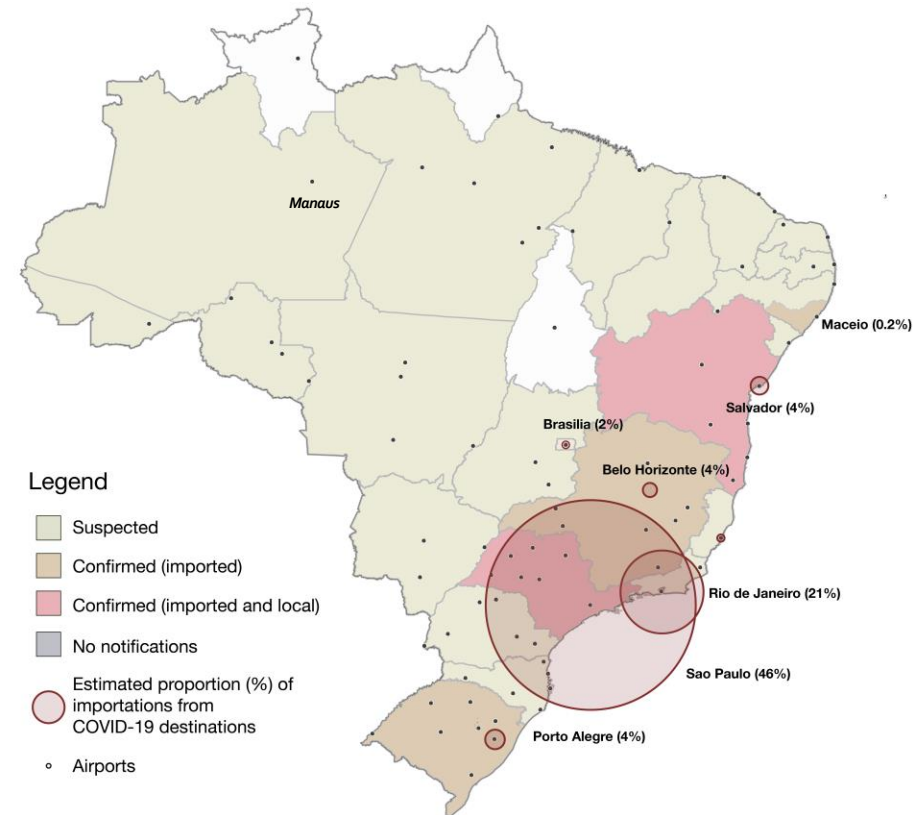
- **Confirmed Cases:** 37,671,420 (10 Jul 2023)
- **Confirmed Deaths:** 703,964 (10 Jul 2023)
- **4th highest number of deaths/100,000 inhabitants (JHUM)**



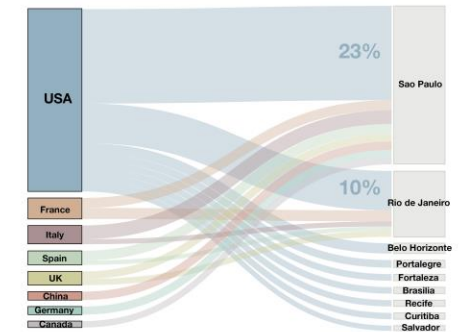
Full list of publications: www.caddecentre.org/publications;
 data & protocols online 2nd Dec 2019 *Epid. Data from WHO Dashboard, 12-06-2022)

Mobility data to predict and improve detection of SARS-CoV-2 in Brazil

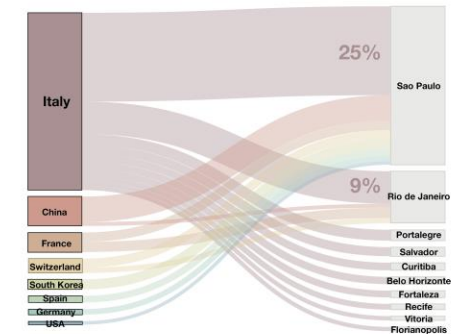
- Early identification of predicted source of introductions is critical for pandemic preparedness.
- Frequency of introductions: volume of passengers and incidence at source.
- Strong post-hoc correlation between predicted and confirmed cases ($r=0.9$, $p\text{-value}<0.001$).



Proportion % passengers from affected countries



Estimated % of COVID importations

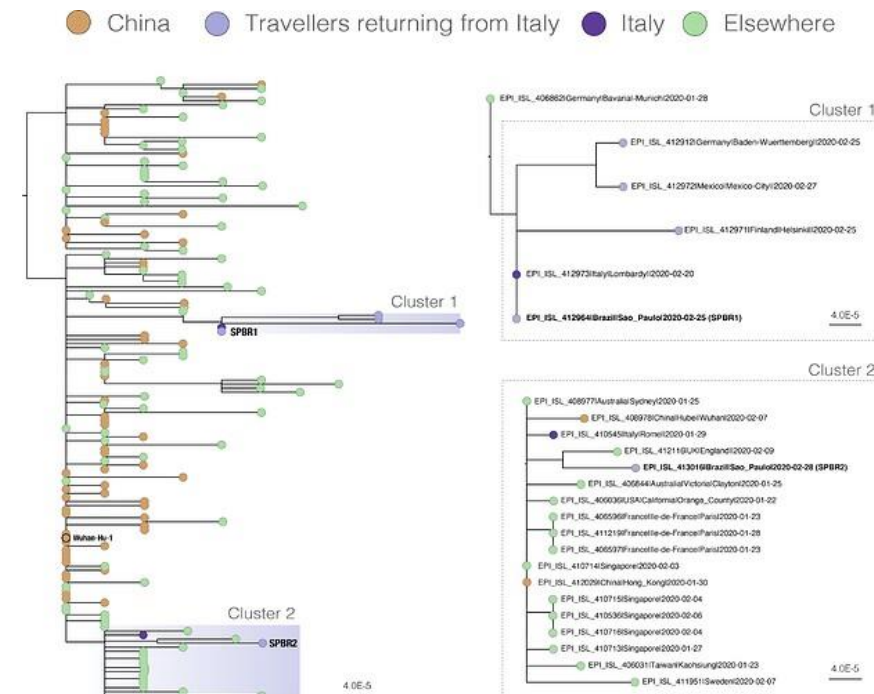


First SARS-CoV-2 genome from Latin America, analyses and interpretation shared within 48h

- First confirmed cases in Latin America (and Brazil): **48 hours from RT-PCR to genome and interpretation**
- Required a multidisciplinary team with laboratory diagnostic capacity, previous expertise in pathogen genome sequencing and in sequencing data analysis.

SARS-CoV-2 coronavirus ▾ | Genome Reports ▾ | Latest | Top

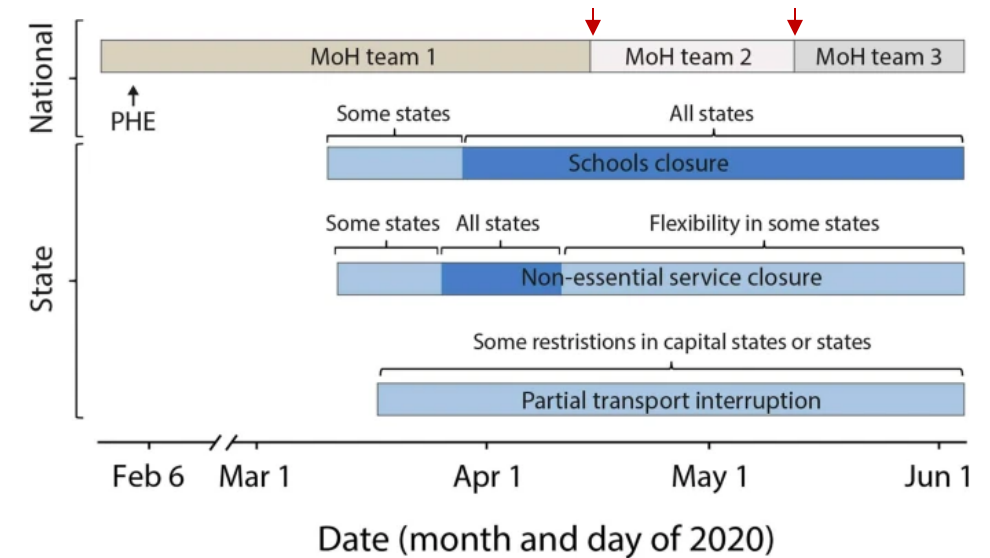
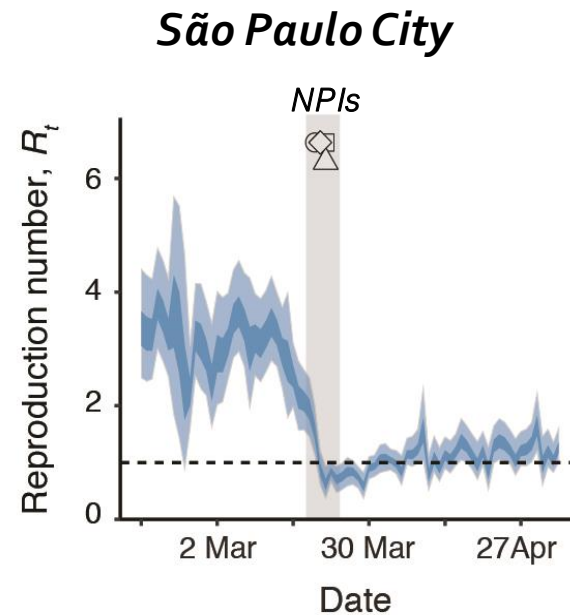
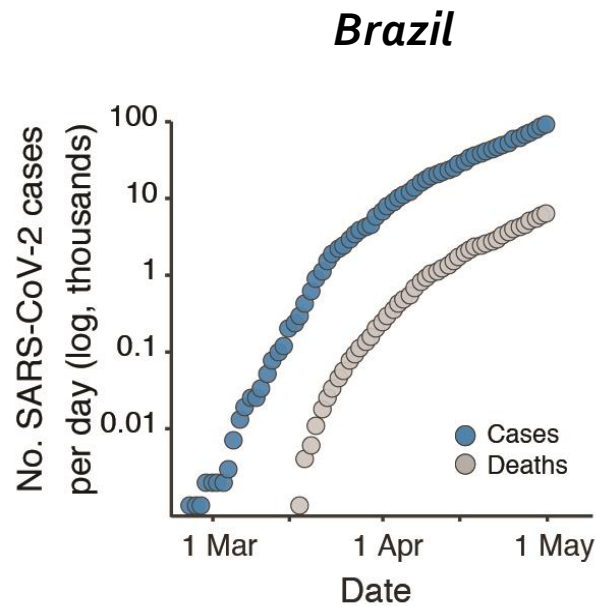
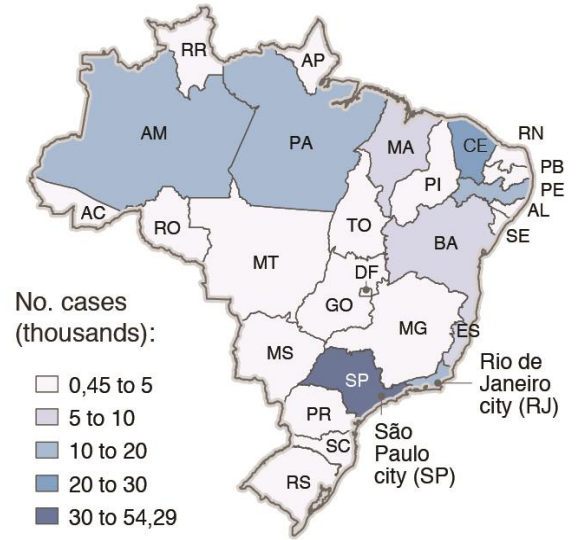
| Topic | Replies | Views | Activity |
|--|---------|-------|----------|
| First cases of coronavirus disease (COVID-19) in Brazil, South America (2 genomes, 3rd March 2020) | 1 | 89.8k | Feb '20 |



<https://virological.org/t/first-cases-of-coronavirus-disease-covid-19-in-brazil-south-america-2-genomes-3rd-march-2020/409> (28 Feb 2020)

Rapid spread of SARS-CoV-2 in Brazil

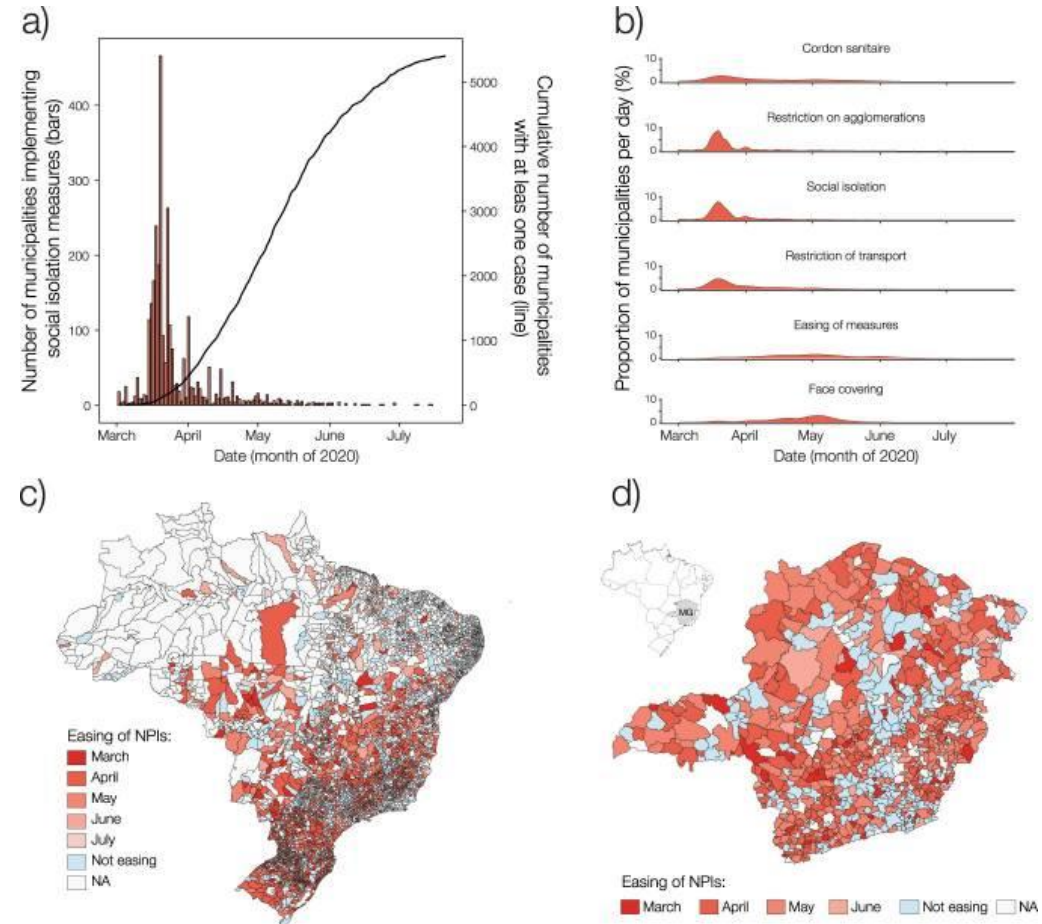
- Rapid increase in number of cases and deaths, but decline in epidemic spread (R) after implementation of NPIs in late March
- NPIs halted by lack of public health centralized strategies



Souza et al. *Nature Hum Behaviour* 2020; Candido et al. *Science* 2020

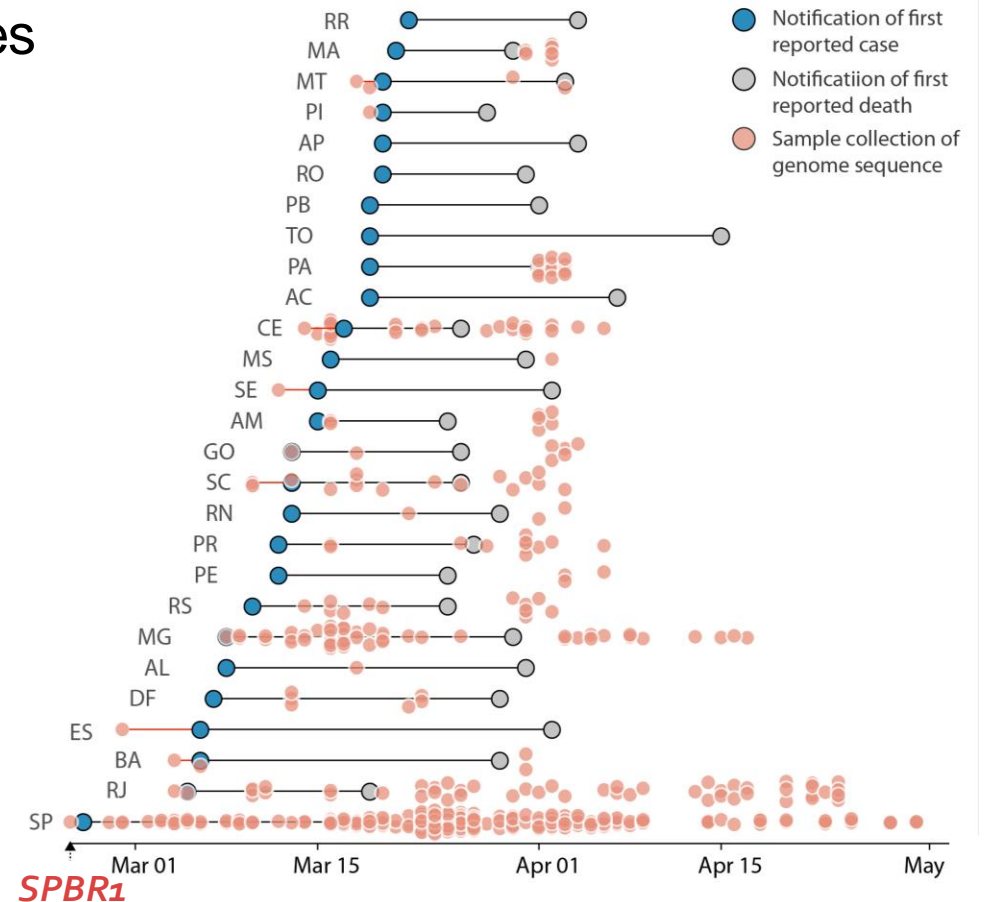
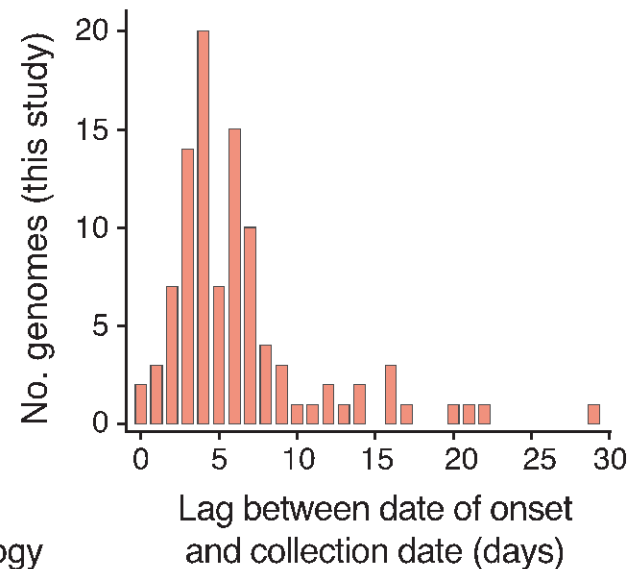
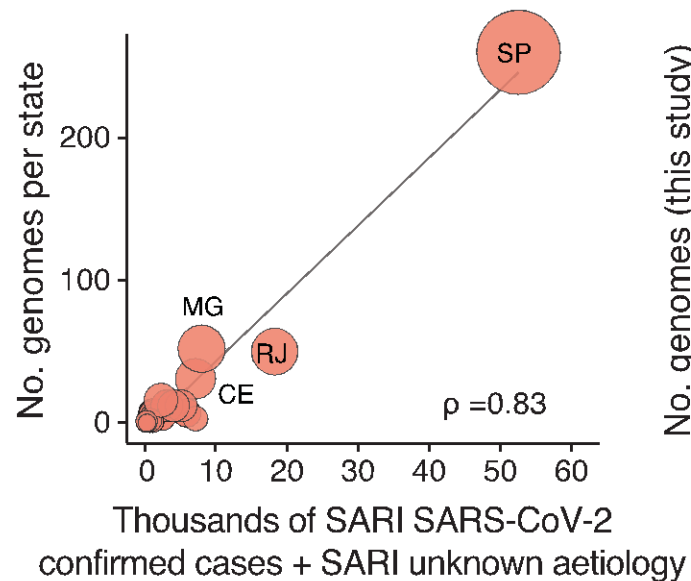
Asynchrony and complexity of COVID-19 non-pharmaceutical interventions in Brazil

- Novel dataset with survey responses from 4,027 mayors, covering 72.3% of all municipalities in the country (2020).
- Asynchrony in implementation of non-pharmaceutical interventions (NPIs) of control measures in Brazil.
- Impact of control measures poorly understood and complicated by delays in reporting => need for complementary pandemic assessments from genomic & serological data.



First SARS-CoV-2 representative genomic dataset

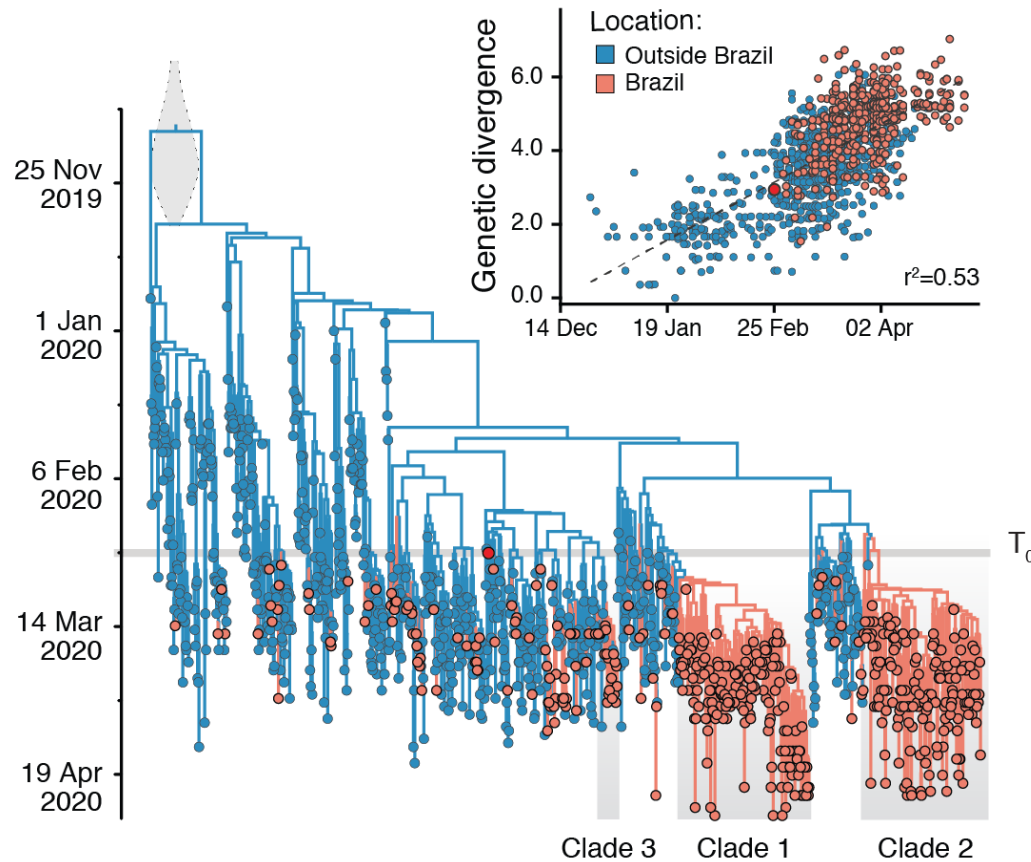
- June 2020: 427 genomes, 85 municipalities, 21 states
- Direct evidence of earlier circulation in 8 states
- Harmonized protocols in coordinated network with LNCC, UFMG, UNICAMP and Rede CoronaOmica.



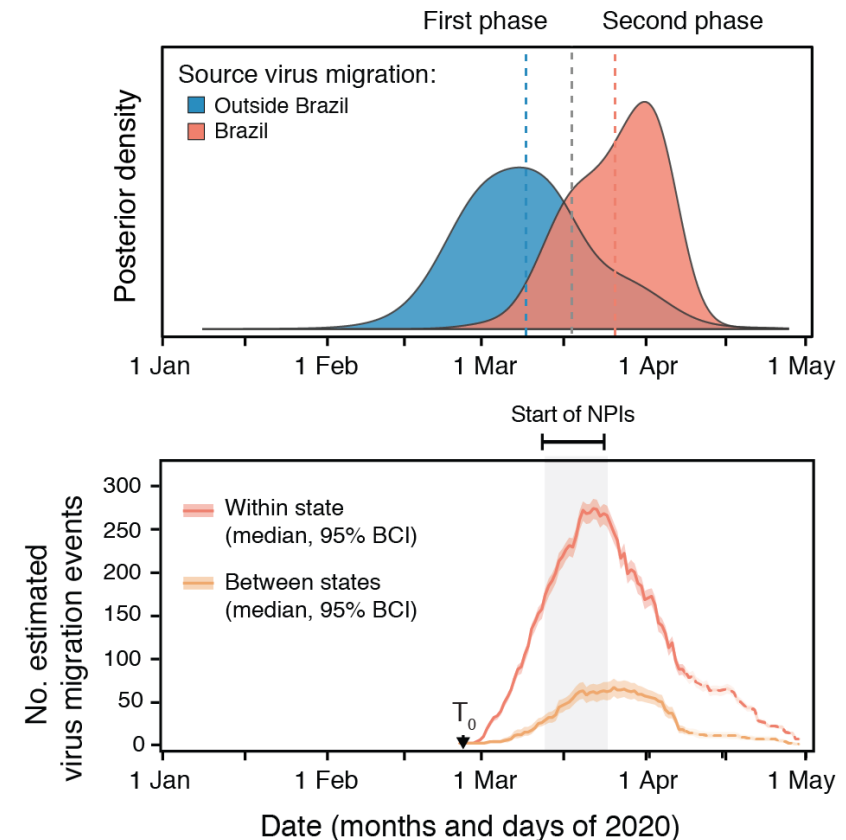
D Candido, Ingra Claro, Jaqueline Goes et al. *Science* 2020

Thousands of introductions and three main lineages of SARS-CoV-2 in Brazil

Minimal surveillance lag of 2 days between date of first detection and arrival of major clades in Brazil.



Significant decline of within- & between-virus lineage migrations after start of NPIs

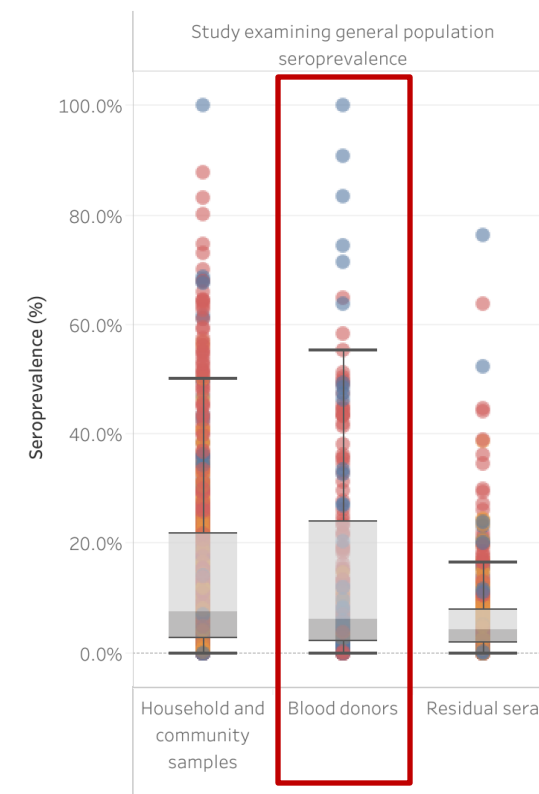
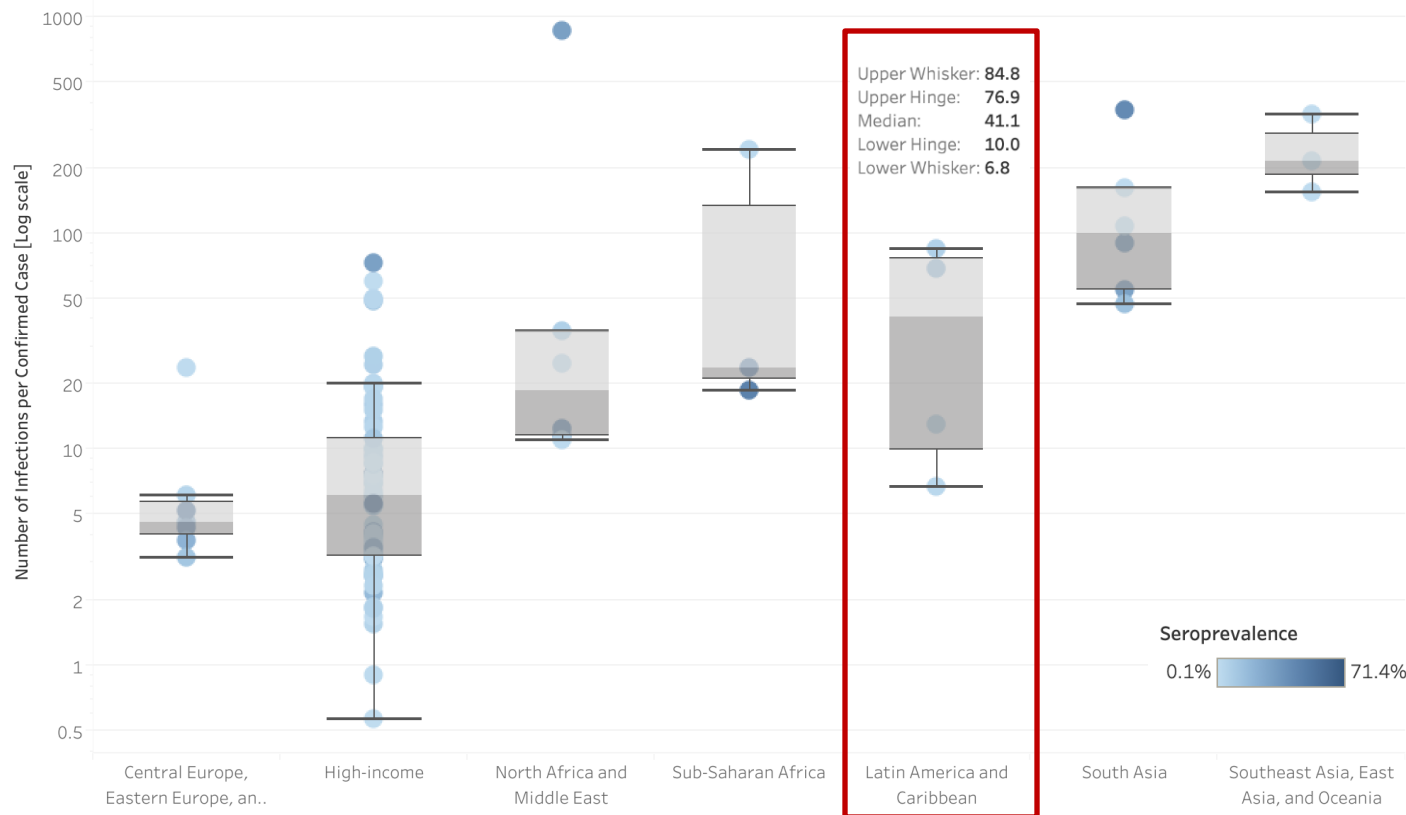


D Candido, Ingra Claro, Jaqueline Goes et al. *Science* 2020

History of exposure to SARS-CoV-2: high rates of underreporting in Latin America

On average: there were 41 SARS-CoV-2 infections per reported confirmed case in Latin America

Blood donors: cost-effective & representative population to study exposure to viral pathogens

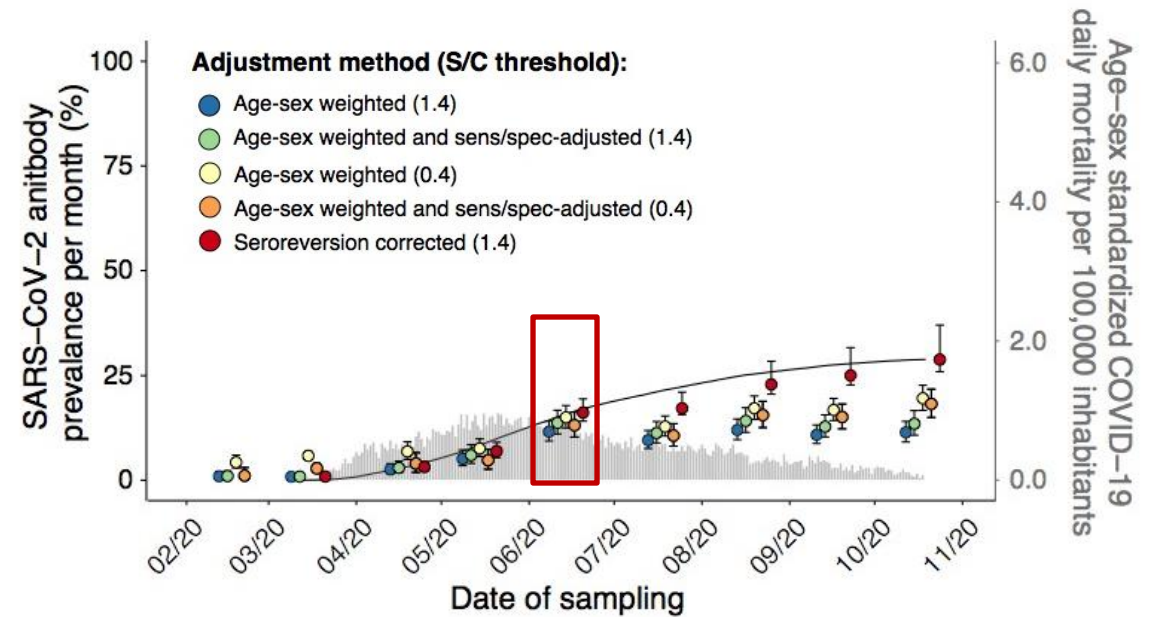
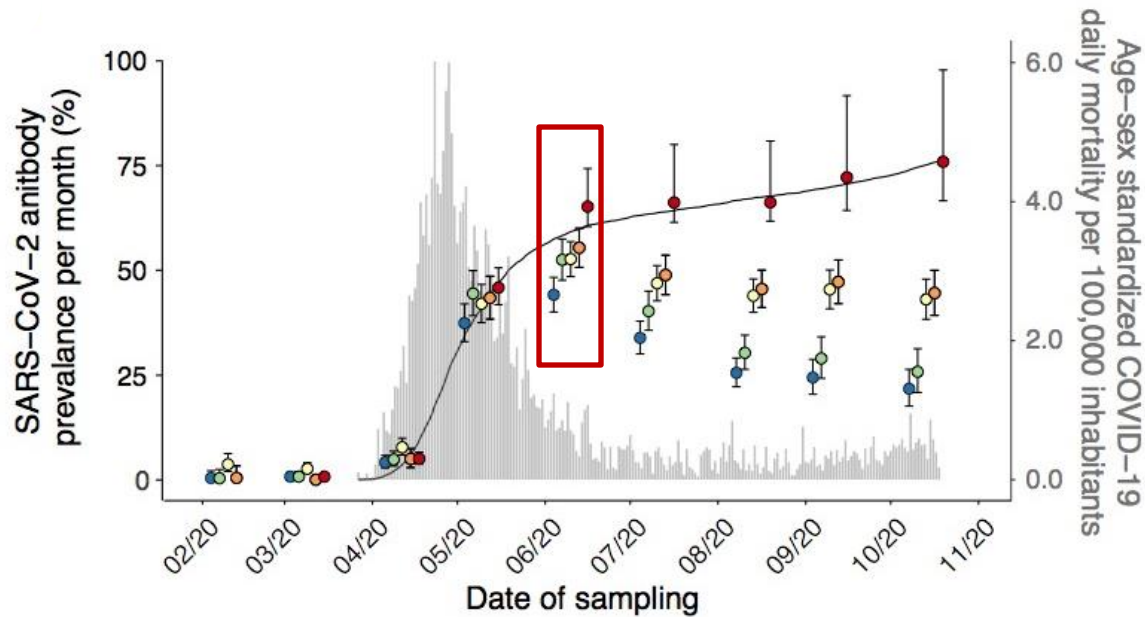


Arora et al. *LID* 2021 (<https://serotracker.com>)

SARS-CoV-2 serosurveillance reveals high attack rate in Manaus by Oct 2020

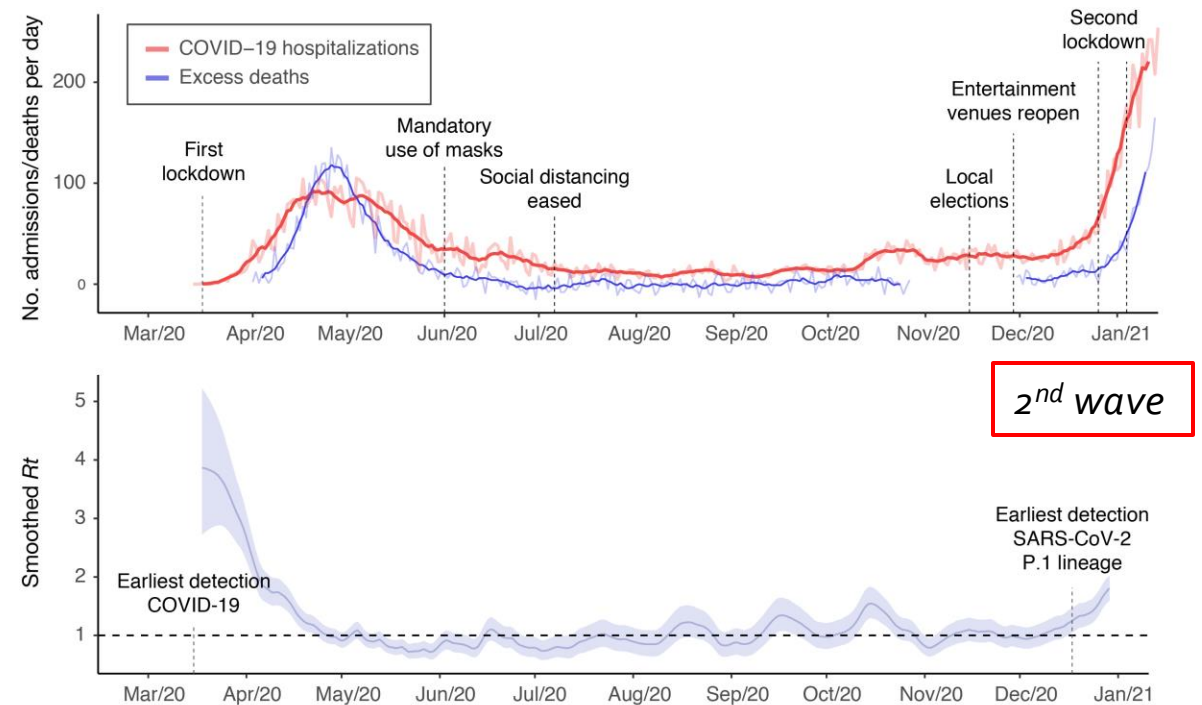
Manaus (Population: 2.219.580) in Oct 2020:
Adjusted cumulative incidence **76% (95% CI 66 – 98)%**

São Paulo (Population: 12.325.232) in Oct 2020:
Adjusted cumulative incidence **28.8% (95% CI 26–37)%**



Resurgence of SARS-CoV-2 in Brazilian Amazon, despite high seroprevalence

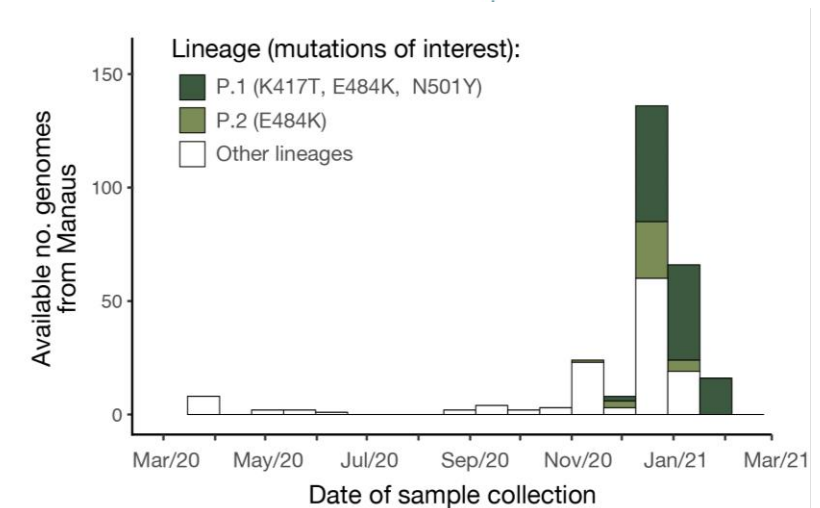
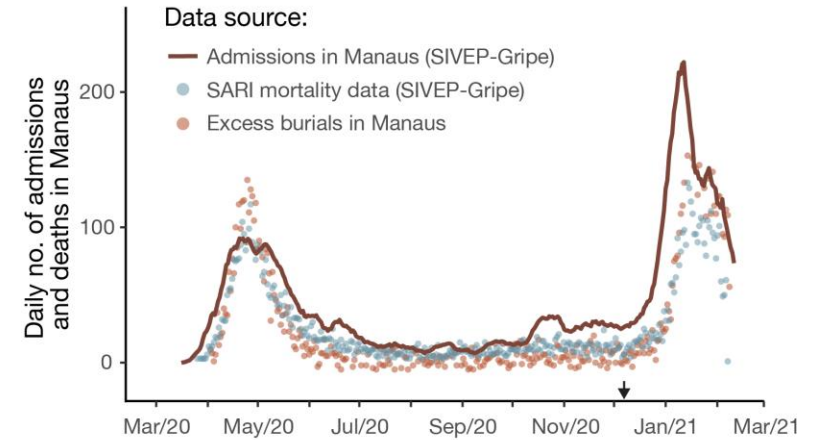
- **Hypothesis 1:** Virus lineages circulating in the 2nd wave could be better at evading immunity generated in response to previous infection.
- **Hypothesis 2:** Virus lineages circulating in the 2nd wave may have > inherent transmissibility compared to preexisting lineages circulating in Manaus.
- Only **6 sequences available from Manaus until 12 January 2021.**
- Genomic & serological data shared in real-time.



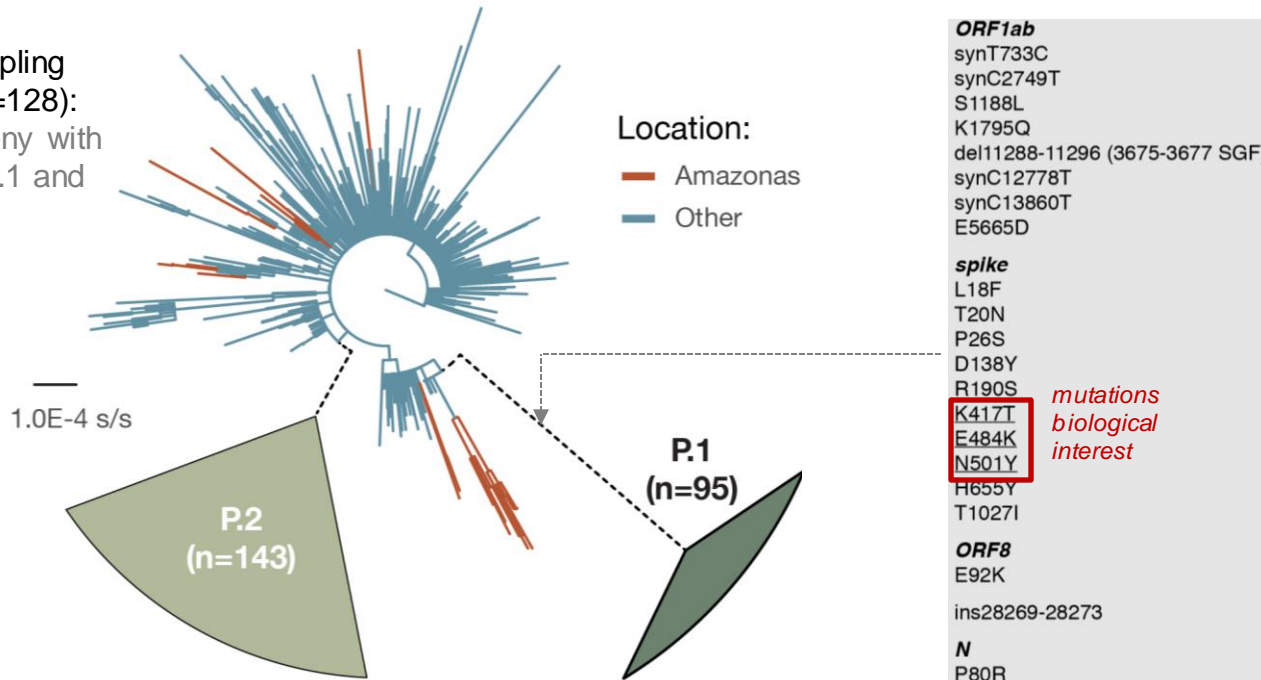
Sabino (...) Faria. *The Lancet* 2021. Prospective monthly data made available.

Targeted sequencing of SARS-CoV-2 to investigate Manaus' second epidemic wave

- **Outbreak investigation** in Manaus guided by serosurveillance
- Amplicon-based sequencing ARTIC protocol of available samples
- Identification of a **local cluster with 17 unique aa mutations**.
- **Identification of a novel P.1/Gamma lineage**: simultaneous increase in lineage frequency, deaths and hospitalizations.



Dense sampling strategy (n=128): ML phylogeny with B.1.1.28, P.1 and P.2 Pango lineages.

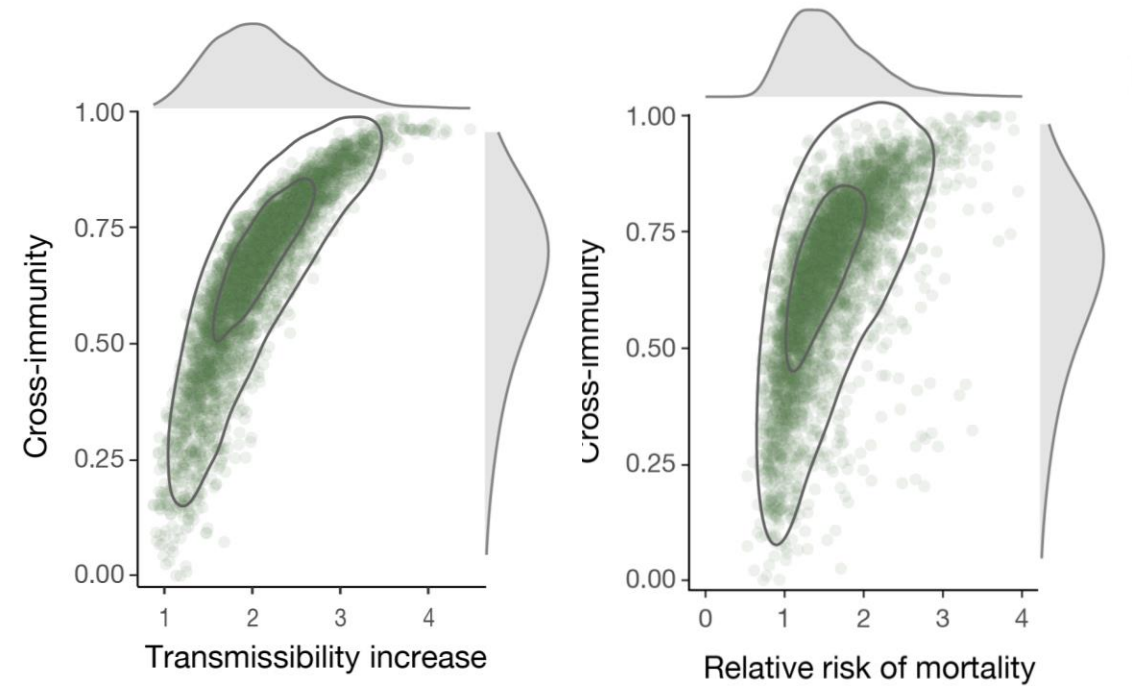


<https://virological.org/t/genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-manaus-preliminary-findings/586>

Altered epidemiological characteristics of the P.1/Gamma VOC in Manaus

Two-category mathematical model to investigate transmissibility, immune evasion and disease severity of Gamma VOC in Manaus:

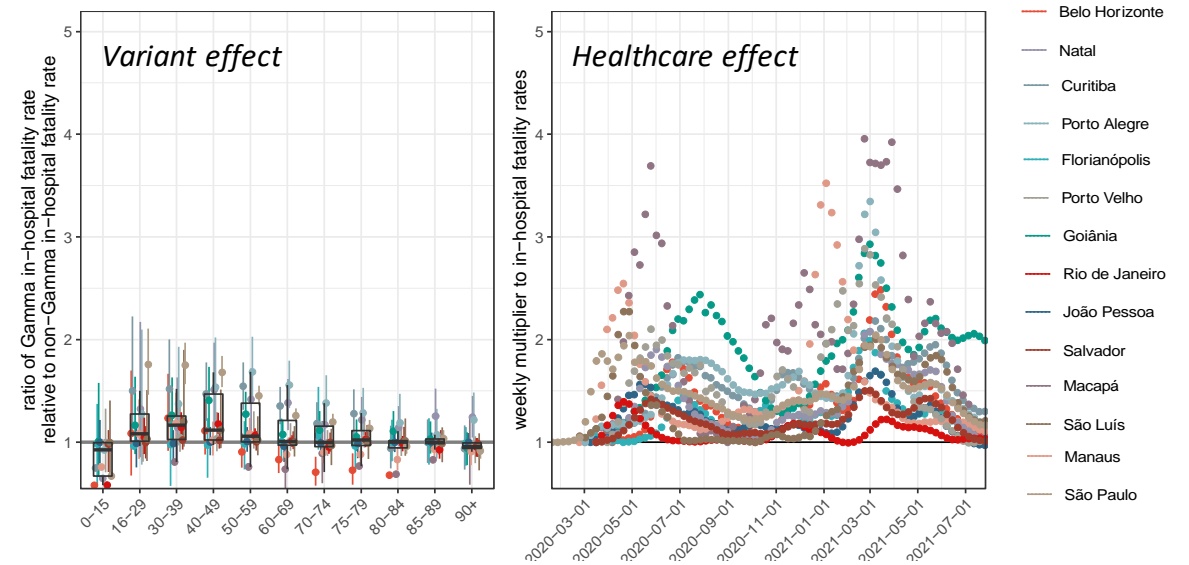
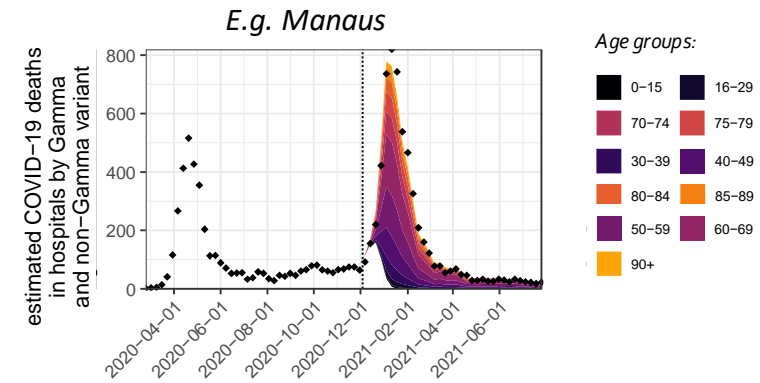
- **Increased transmissibility:** Gamma is 1.7–2.4 (50% BCI) more transmissible compared to non-Gamma lineages in Manaus.
- **Immune evasion:** Gamma can evade 21-46% (50% BCI) of protective immunity elicited by previous infection with non-Gamma lineages.
- **Disease burden:** Gamma 1.2–1.9 (50% BCI) times more likely to result in mortality: strained healthcare systems?



Healthcare inequities drove fluctuations of fatality ratios across Brazil

Semi-mechanistic age-structured model to investigate effect of Gamma vs. healthcare accessibility in in-hospital fatality ratios.

- Pre-vaccination data SIVEP-Gripe (hospitalization) from 14 cities.
- In-hospital fatality rates associated with increased demand on healthcare resources *following* infection waves.
- **Without lack of healthcare resources, nearly 50% of the >700 thousands deaths in Brazil could have been avoided.**

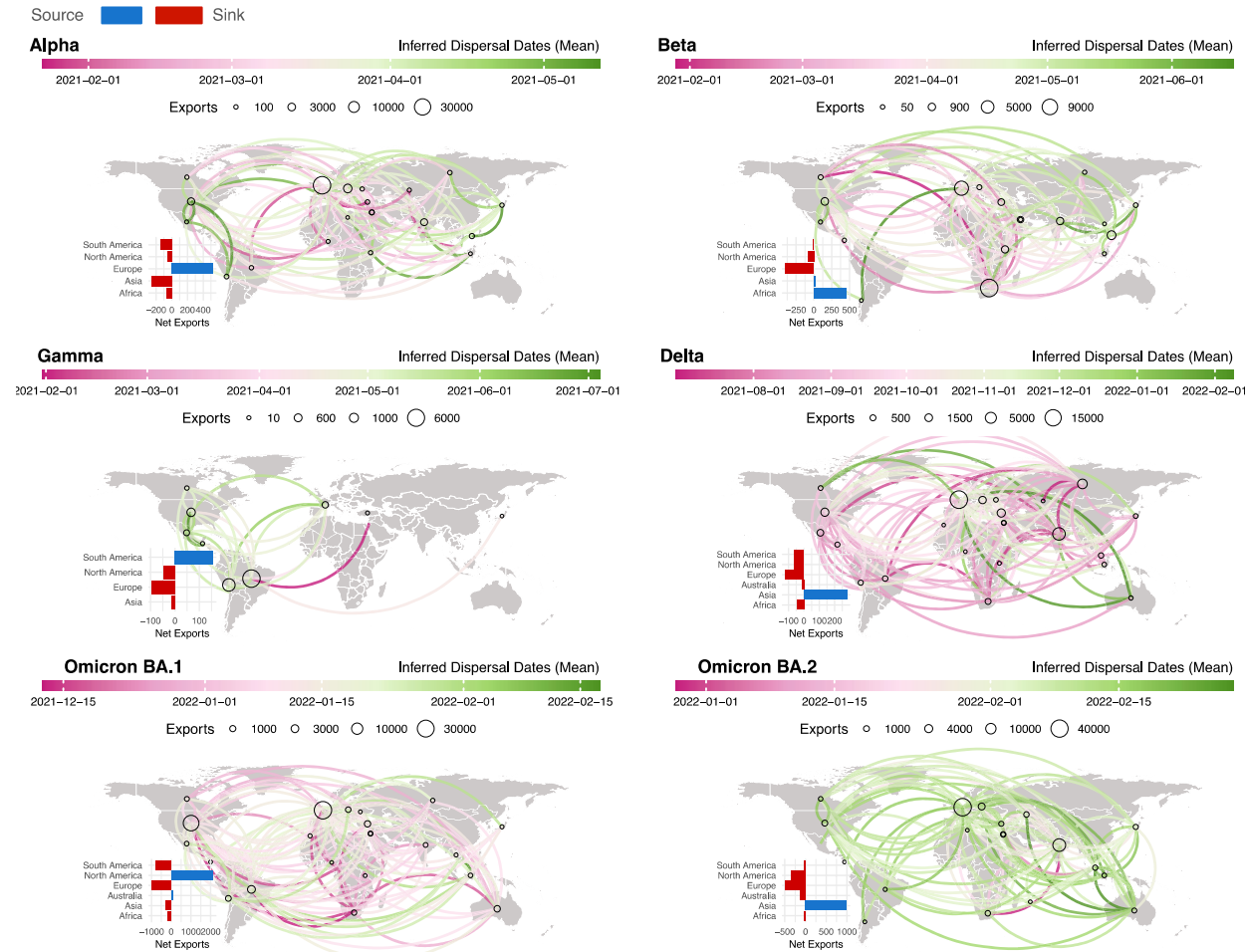
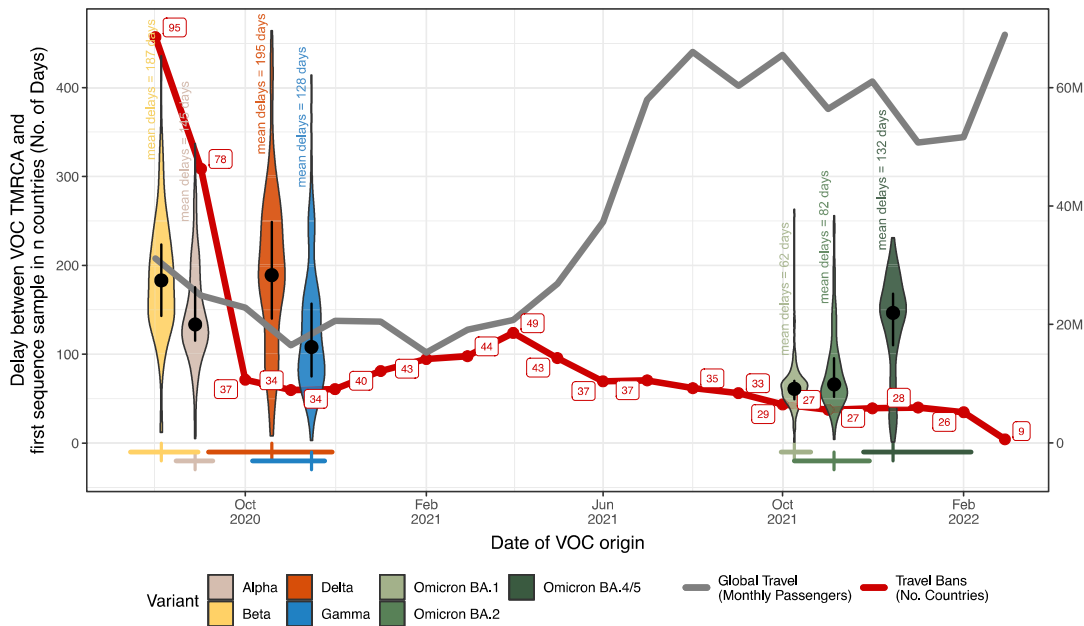


Brizzi A, Whittaker C et al . *Nature Medicine* 2022

Final considerations

Global and regional hubs in VOC dispersal

Key role of global and regional **mobility** and VOC **transmissibility** means that many VOCs circulate outside of their birthplace before their detection and characterization through genomic surveillance (e.g. Gamma surveillance lag was around 128 d).

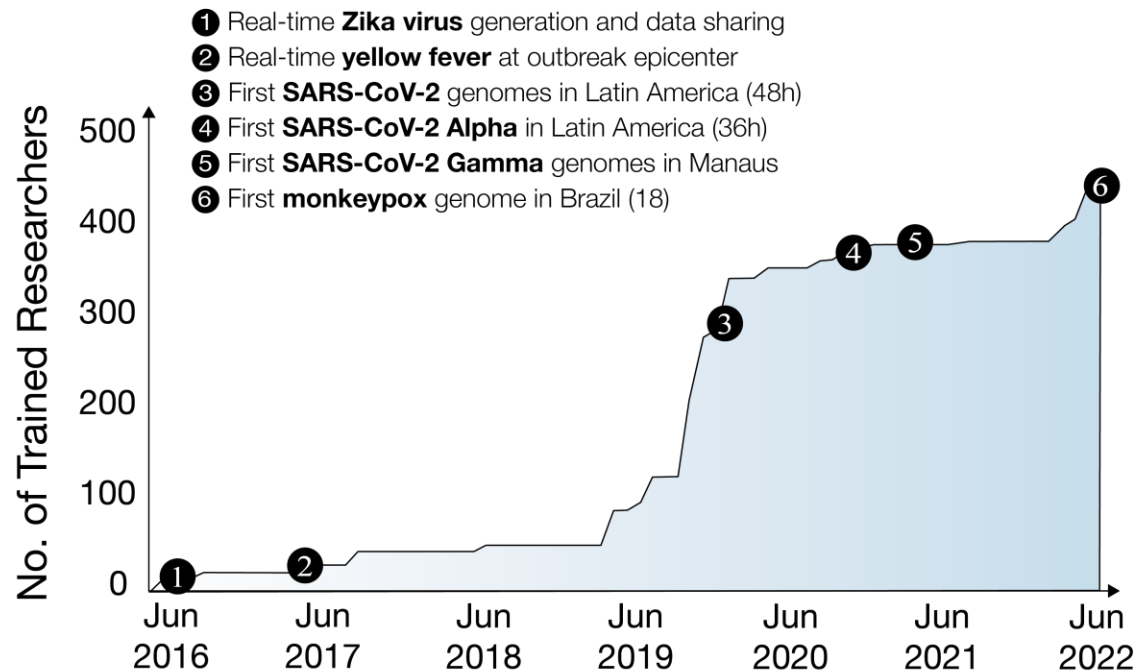


How to improve surveillance against new VOCs?

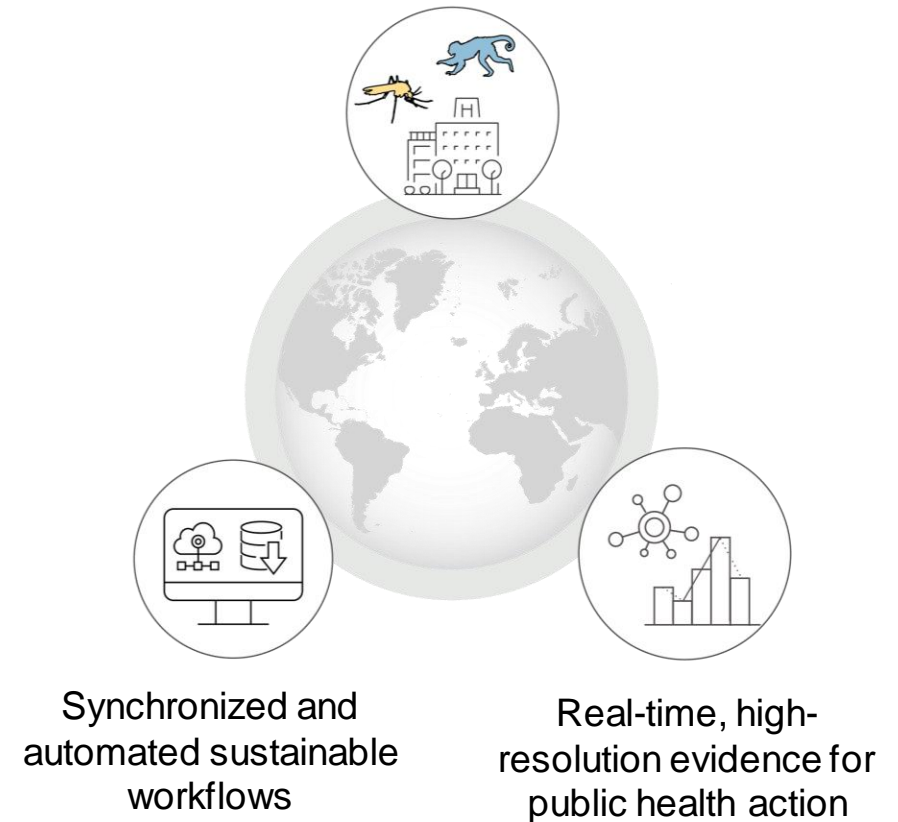
Tegally et al. *Cell* 2023

Towards a standardized, real-time viral metagenomic surveillance framework to improve pandemic detection

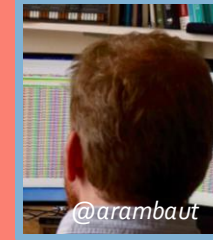
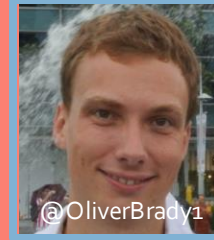
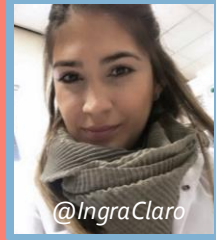
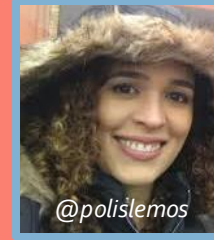
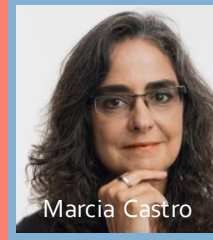
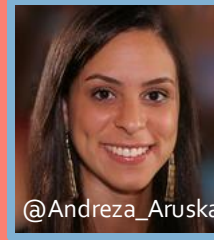
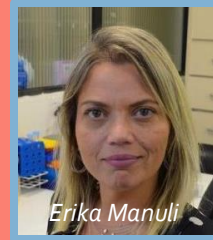
Training and capacity strengthening initiatives for researchers and public health practitioners



Systematic multi-host real-time metagenomic sequencing, with Open Data for science and health



Acknowledgments



Funding:



John Fell Fund



Institutions:



Get in touch via Email: nfaria@ic.ac.uk Follow our work on Twitter: [@CaddeProject](https://twitter.com/CaddeProject) Check out our website: caddecentre.org