



MRC Centre for
Global Infectious
Disease Analysis

Imperial College
London



Surveillance and enhanced diagnostics for emerging infectious diseases

Session Report from the Future

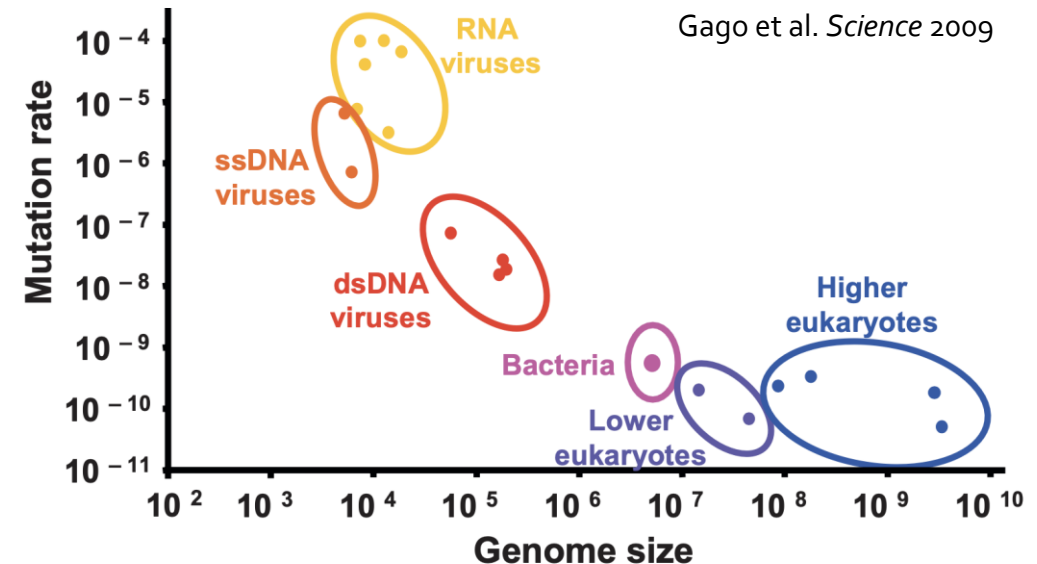
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Visiting Professor at Institute Tropical Medicine, University of São Paulo
WHO Global Arbovirus Initiative Technical Advisory Group

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Public Health Emergencies of International Concern have all been caused by viruses

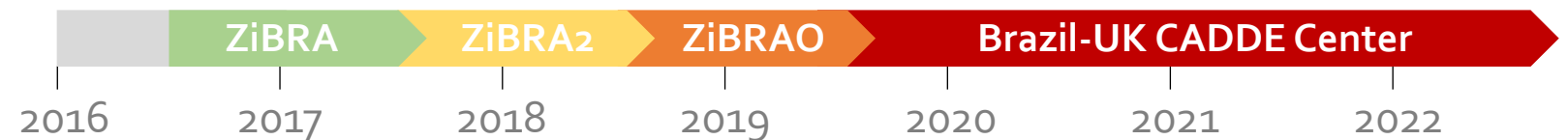
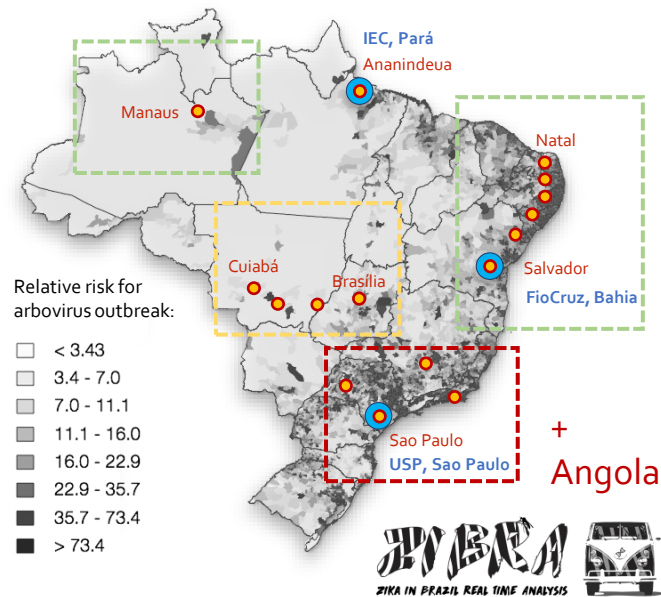
1. H1N1pdm (2009) **RNA** | Zoonotic
2. Polio (2014) **RNA** | Zoonotic?
3. Ebola virus (2014) **RNA** | Zoonotic
4. Zika virus (2016) **RNA** | Zoonotic
5. Kivu Ebola (2018–2020) **RNA** | Zoonotic
6. SARS-CoV-2 (2020) **RNA** | Zoonotic
7. Monkeypox (2022) **DNA** | Zoonotic



Rapid mutation rates, short generation times, and large population sizes facilitate the rapid accumulation of genetic diversity over observable timescales (days, weeks, months) and host species plasticity of RNA viruses.

RNA virus genomic surveillance in Brazil

From mobile to fixed genomic sequencing and research laboratories

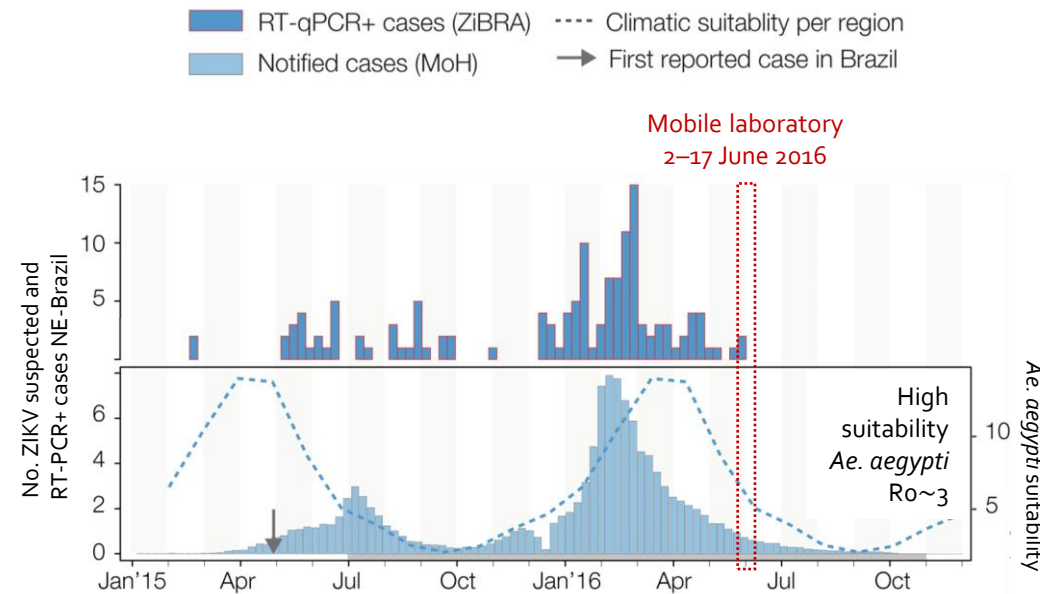


Time series of RT-qPCR+ cases correlated with weekly suspected cases and *Aedes aegypti* suitability

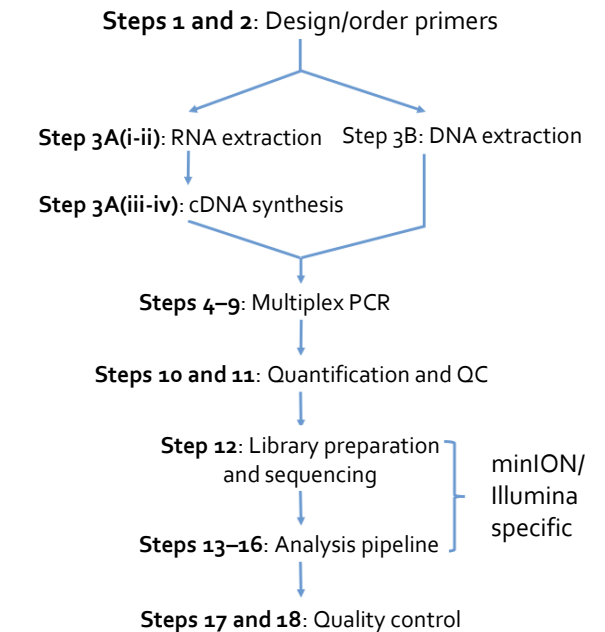
Monthly climatic suitability for *Aedes aegypti*



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



Amplicon-based sequencing and protocol optimisation in real-time

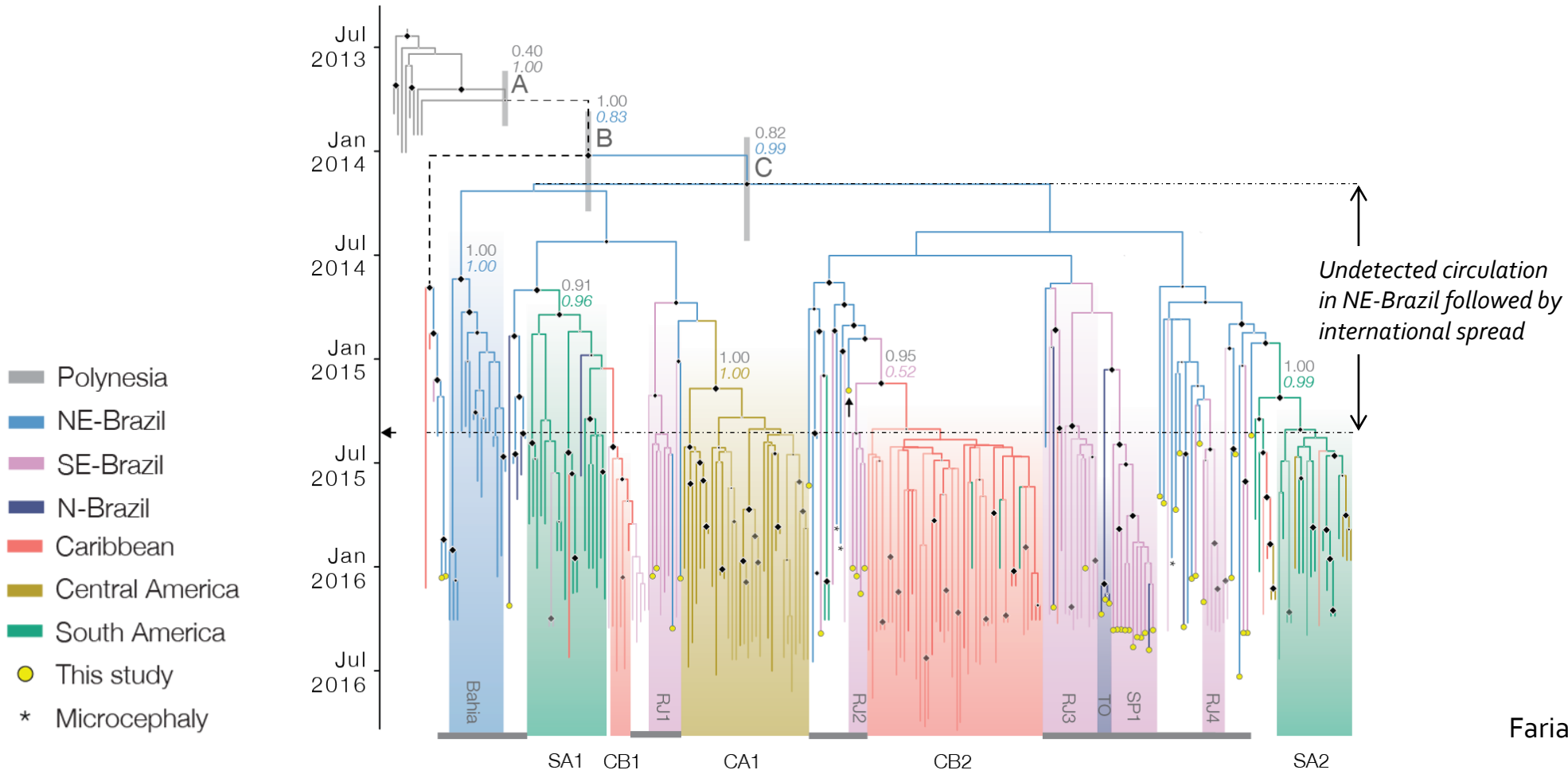


Video adapted from *Ae. aegypti* suitability maps
originally reported in Kraemer et al. *eLife* 2014

Faria NR, Quick J, Morales I, Theze J, Jesus JG,
Giovanetti M, et al. *Nature* 2017

Quick J, Grubaugh N, Pullan S,
Claro I. et al. *Nature Protocols* 2017

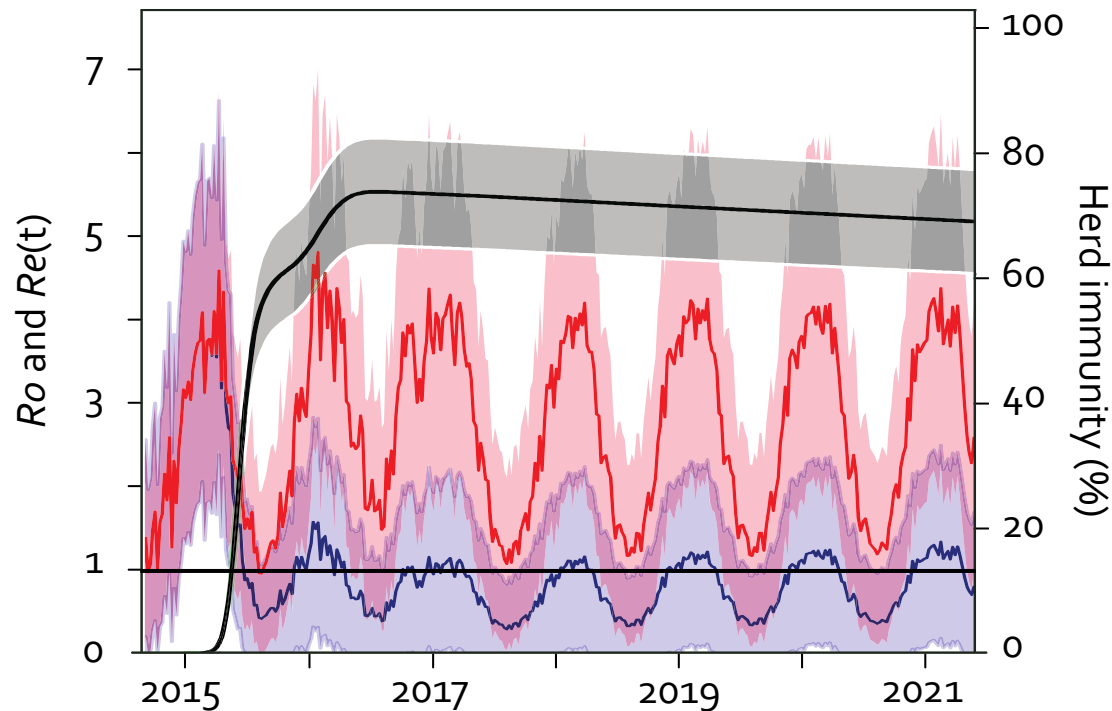
Establishment and cryptic transmission of Zika virus in Brazil and the Americas



Faria NR et al. *Nature* 2017

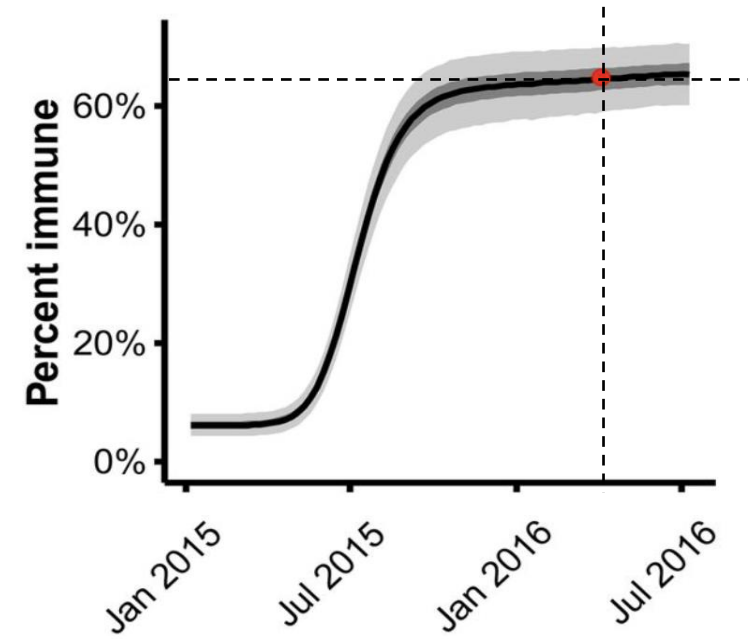
$R_0 \sim 3$, with herd immunity threshold $\sim 67\%$,
with 60% exposed by the end of 2015 in Bahia

Epidemiological modelling of Zika virus
in Feira de Santana (Bahia)



Lourenco, Lima, Faria et al. *eLife* Sep 2017

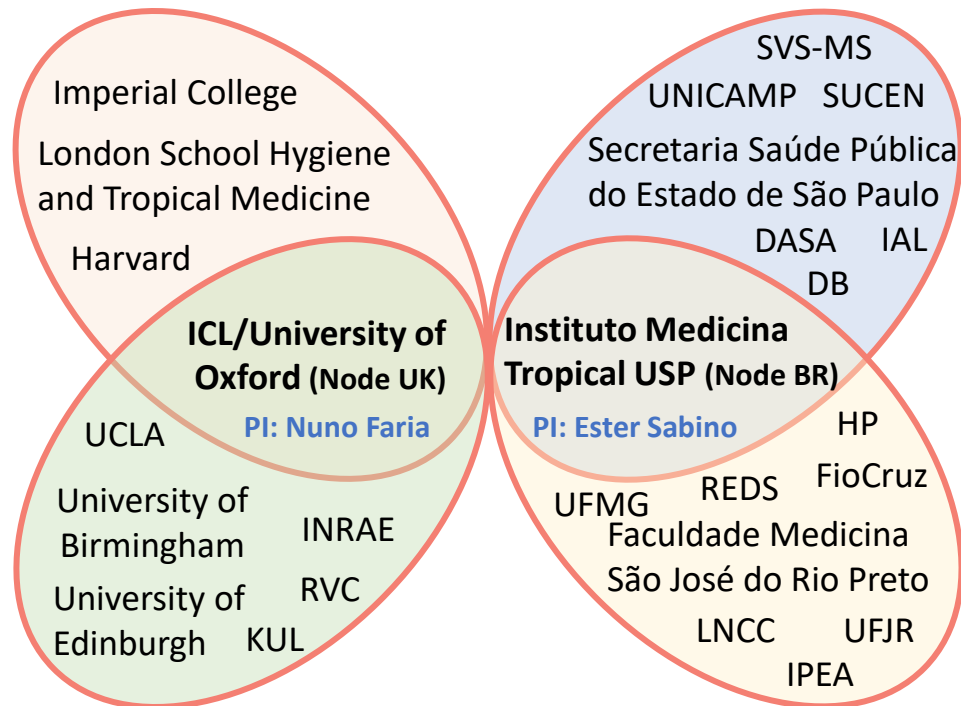
Zika seroprevalence in Salvador (n=663) using
ELISA: 63.3% by 2016 (95% CI: 59.4 to 66.8%)



Netto et al. *mBio* Nov 2017

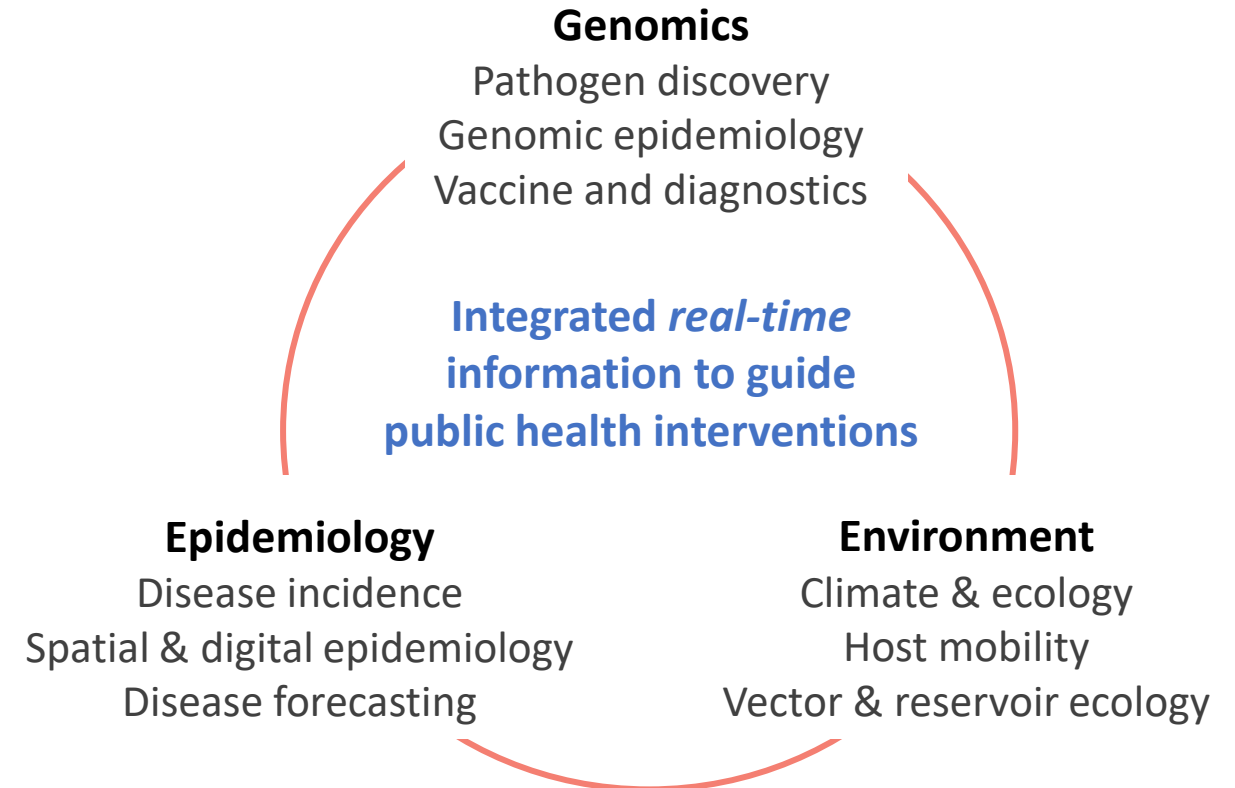
Brazil-UK CADDE: open collaborative network sharing data & protocols in real-time

Main Structure



www.caddecentre.org
data & protocols online 2nd Dec 2019

Main Aims

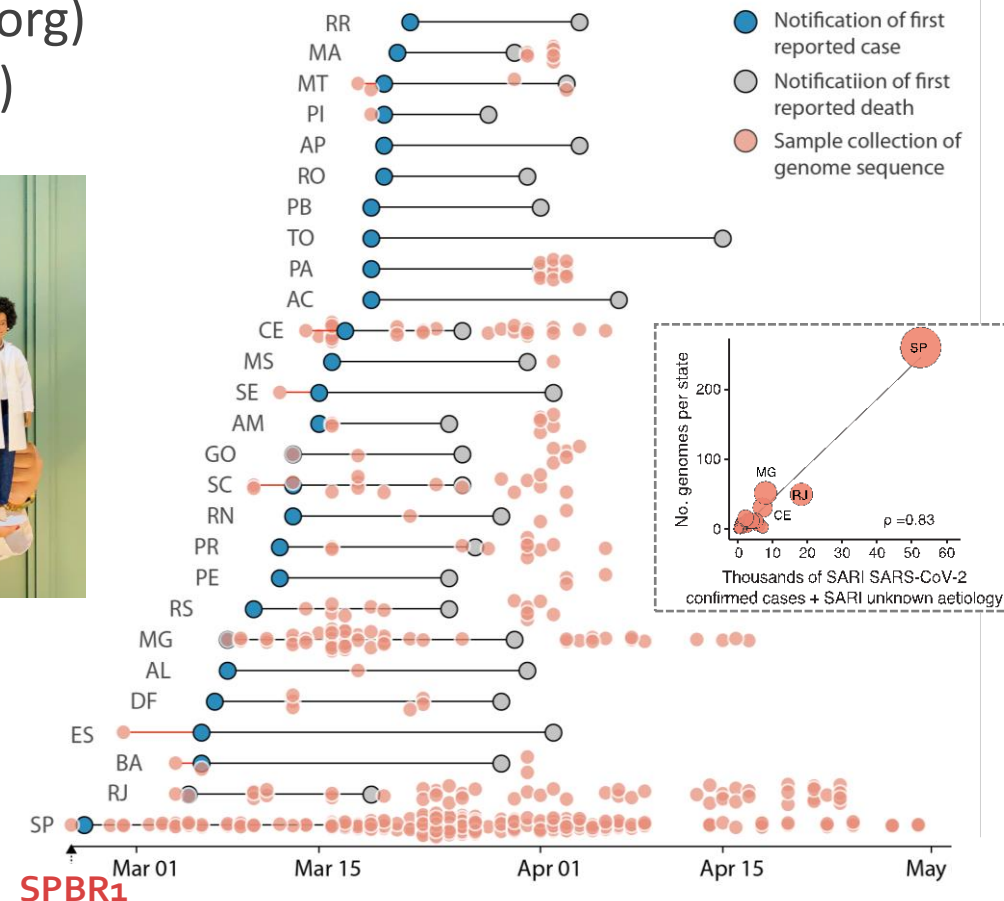


First SARS-CoV-2 sequence and representative genomic datasets

- SPBR1 genome and report in record 48 hours (virological.org) in collaboration with Instituto Adolfo Lutz (February 2020)

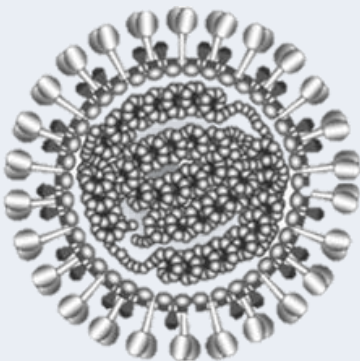
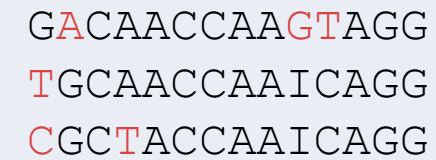
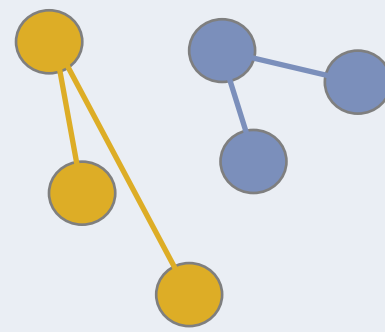
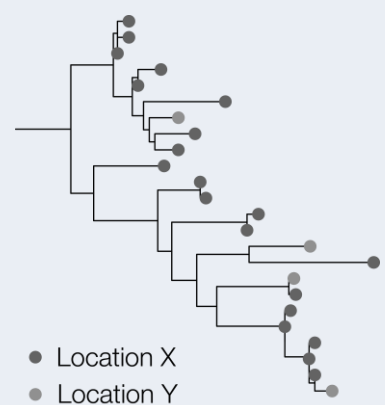


- June 2020: 427 genomes, 85 municipalities, 21 states
- Direct evidence of *earlier* circulation in 8 states
- Harmonized protocols in coordinated network with LNCC, UFMG, UNICAMP and Rede CoronaOmica.



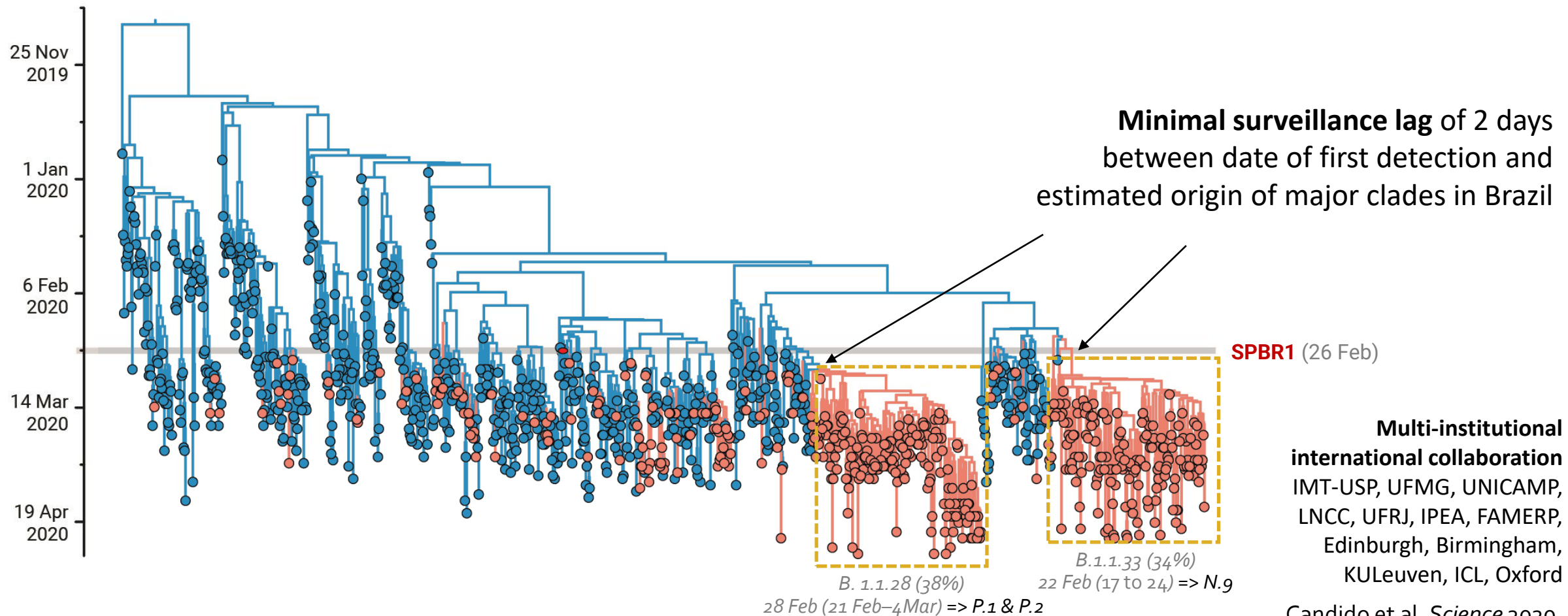
de Jesus et al. *JSPITM* 2020; Candido et al. *Science* 2020

Real-time virus genome sequencing to maximize public health impact

	Untargeted sequencing	Targeted sequencing		Population sequencing
				
Goal	Pathogen identification, understand origins of novel outbreak	Design of diagnostics, therapeutics, phenotypic changes (e.g., Alpha, Omicron)	Investigate transmission clusters & complement epi approaches (e.g., <i>outbreaks in hospitals, travelers</i>)	Large-scale patterns, drivers and assess detection (e.g., <i>R, pop size, dispersal patterns</i>)
Requires	Metagenomic sequencing of human and non-human samples	Sequencing of S-gene dropouts, extensive experimental work	Non-random, dense cluster & community sequencing	Random population sequencing

Adapted from WHO SARS-CoV-2 Sequencing Guidelines 2021

Genomic epidemiology of SARS-CoV-2 in Brazil reveals hundreds of introductions

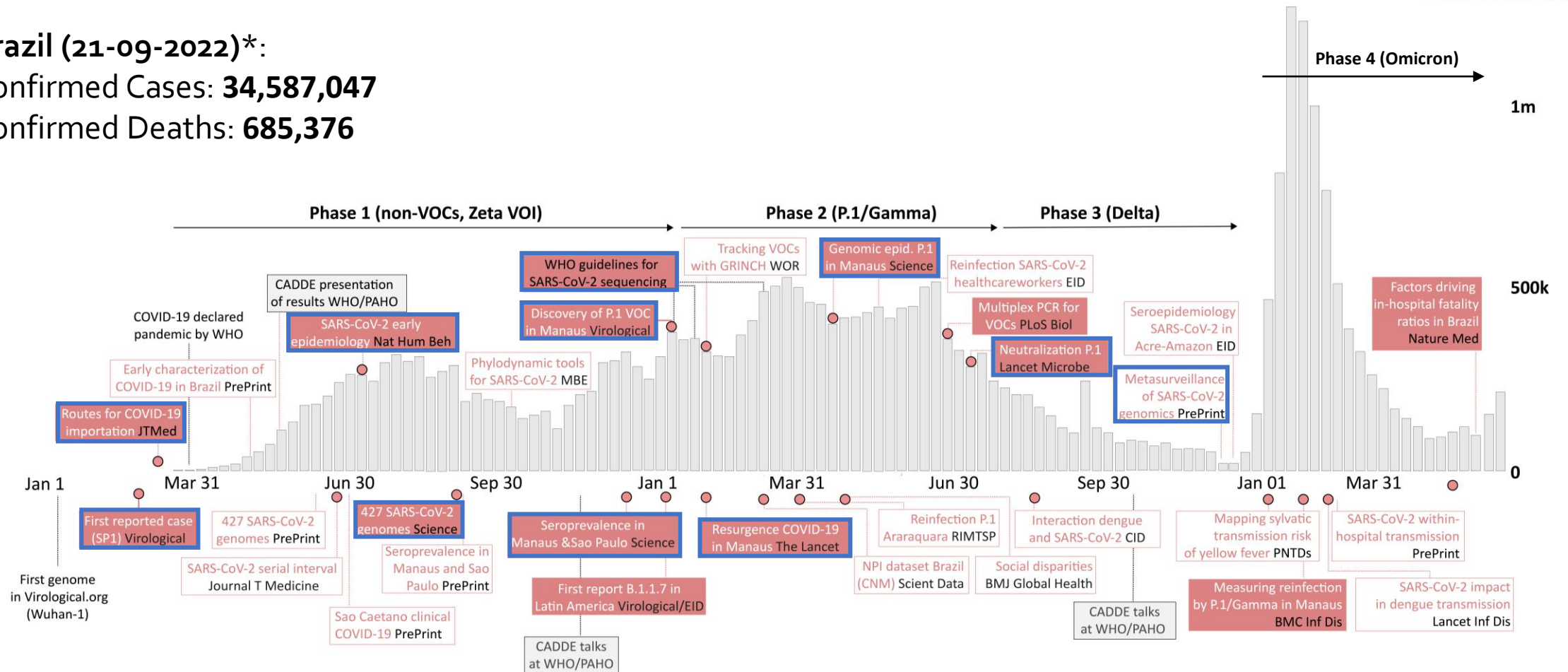


CADDE's timeline of SARS-CoV-2 studies during the ongoing pandemic in Brazil

Brazil (21-09-2022)*:

Confirmed Cases: **34,587,047**

Confirmed Deaths: **685,376**

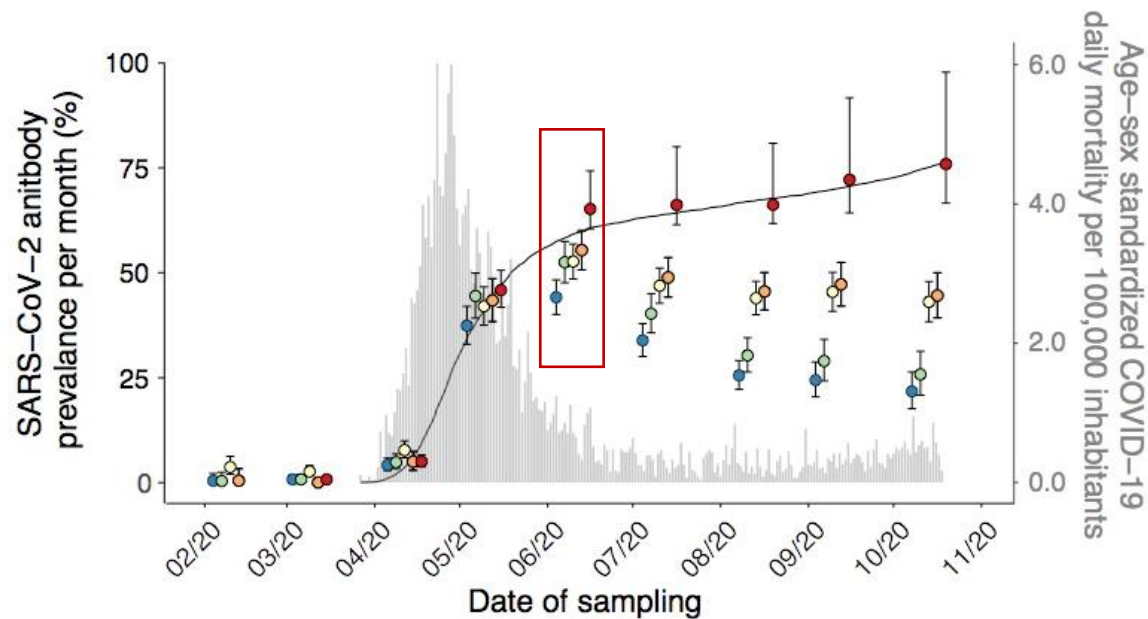


Full >53 COVID-19 publications: www.caddecentre.org/publications; *Epi. data: <https://covid19.who.int/region/amro/country/br>

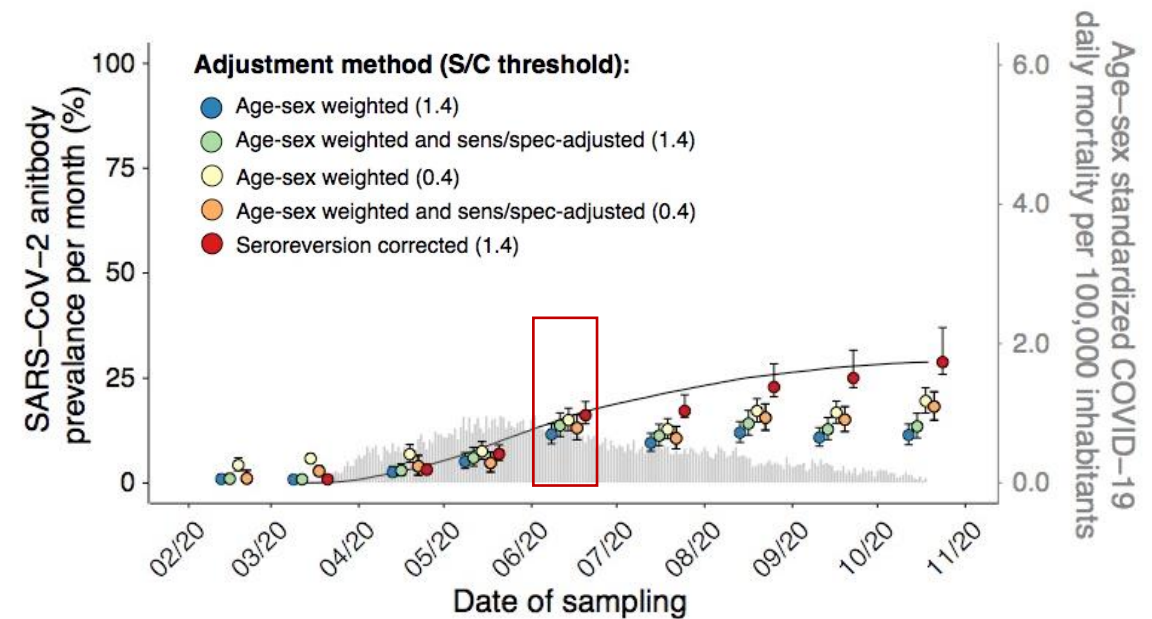
SARS-CoV-2 serosurveillance reveals high attack rate in Manaus by Oct 2020



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

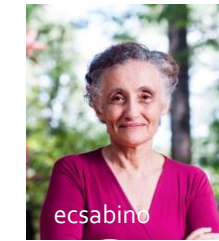


São Paulo (Population: 12.325.232) in Oct 2020:
Adjusted cumulative incidence **28.8% (95% CI 26–37)%**

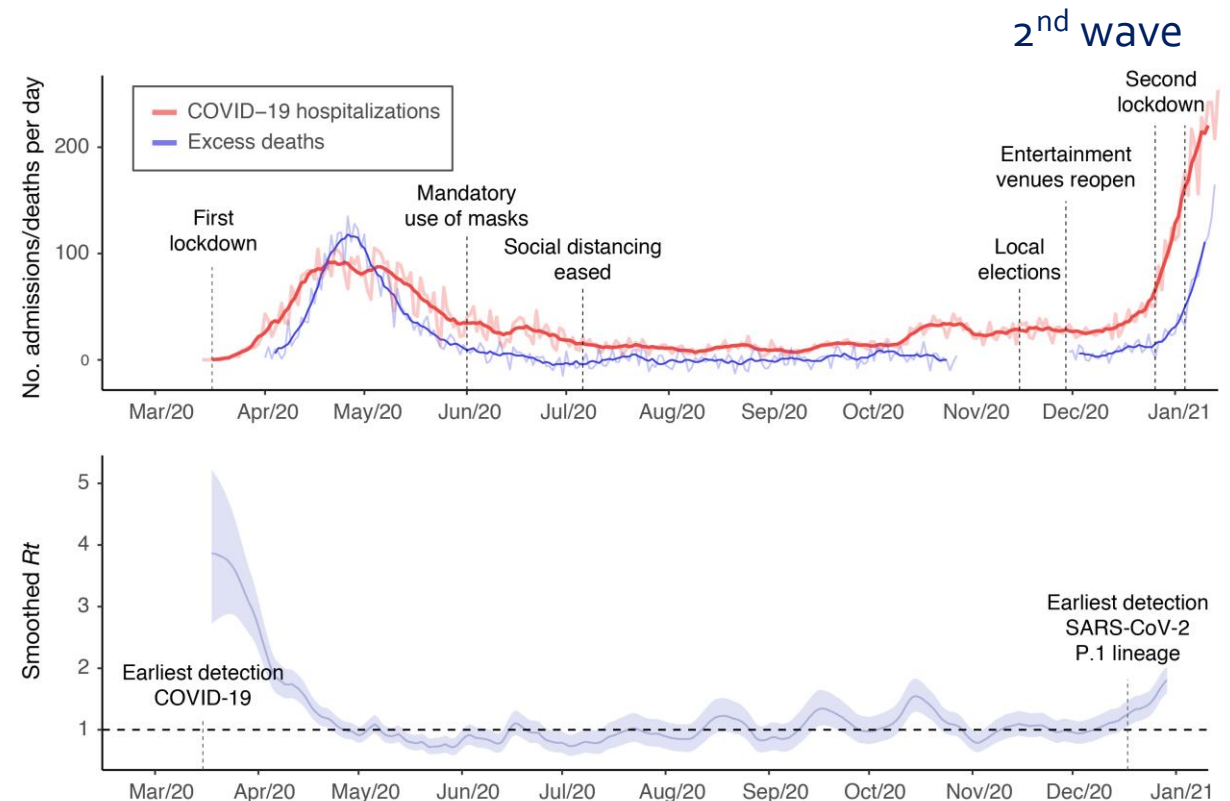


Buss L et al. *Science* 2021. Collaboration with the REDS-IV-P Programme (Mike Bush and Brian Custer)

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



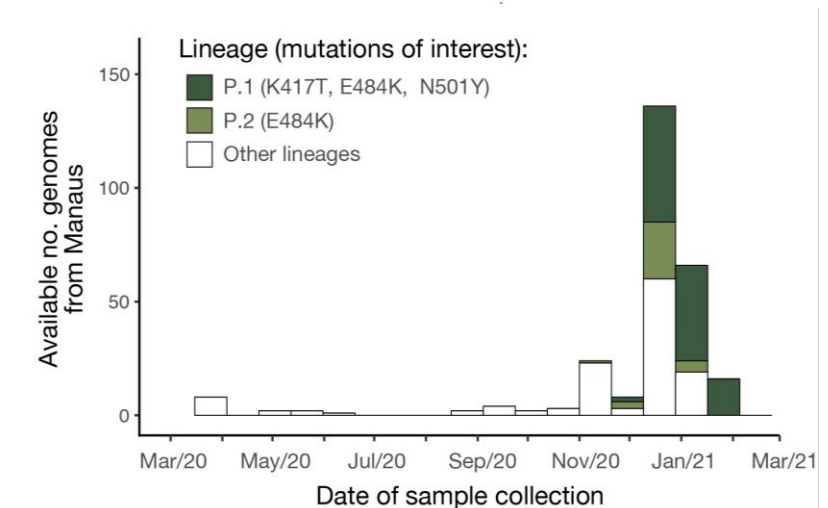
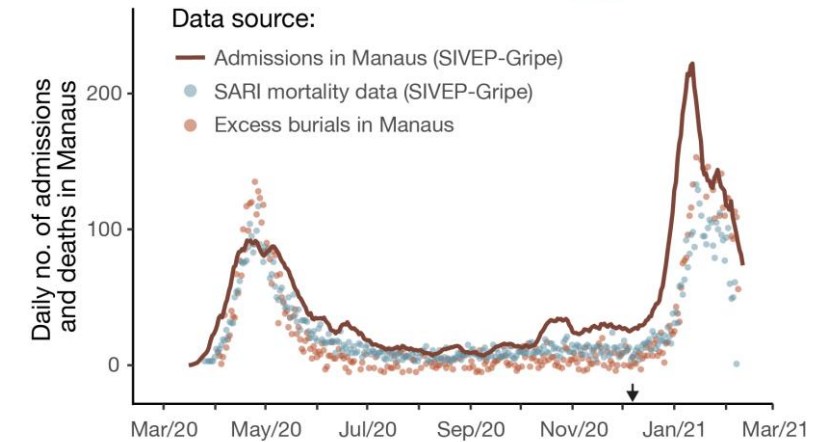
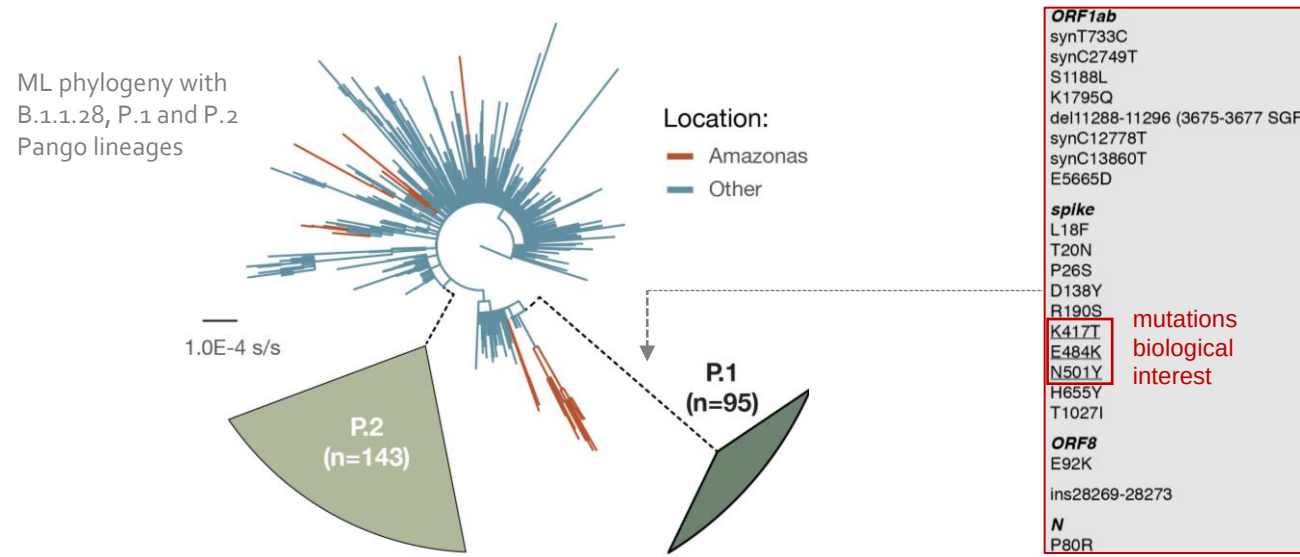
- **H1:** Virus lineages circulating in the 2nd wave could be better at *evading immunity* generated in response to previous infection
- **H2:** Virus lineages circulating in the 2nd wave may have higher inherent *transmissibility* compared to preexisting lineages circulating in Manaus
- Pioneering in sharing serological and epidemiological data in real-time



Sabino (...) Faria *The Lancet* 2021. Prospective monthly data available at <https://github.com/CADDE-CENTRE>

Identification of a novel P.1/Gamma lineage in Manaus (12 Jan 2021)

- Outbreak investigation *guided* by serosurveillance
- Identification of a local cluster with 17 unique aa mutations
- Simultaneous increase in Gamma cases with increase in SARS-CoV-2 deaths and hospitalizations

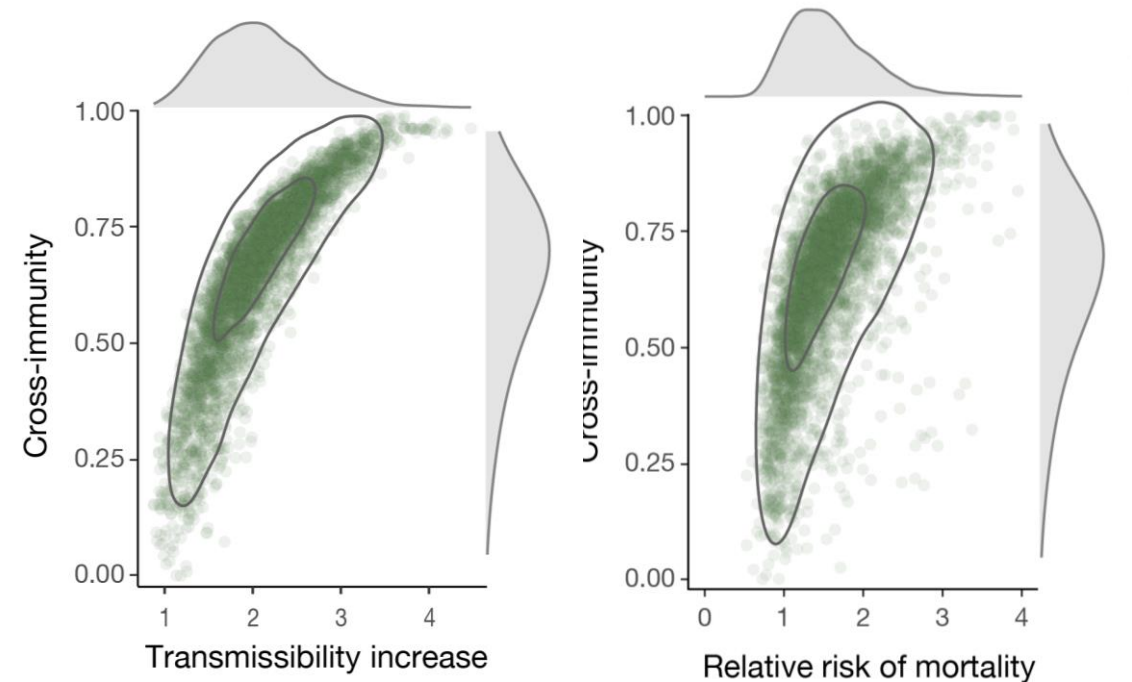


Faria NR et al. *Science* 2021 [shared 11 Jan 2021 with FioCruz, WHO, PAHO]; 12 Jan on Virological.org and GISAID.

Altered epidemiological characteristics of the Gamma VOC in Manaus

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

- Gamma is **1.7–2.4** (50% BCI) **more transmissible** compared to non-Gamma lineages in Manaus.
- Gamma can **evade 21-46%** (50% BCI) of **protective immunity** elicited by previous infection with non-Gamma lineages.
- **1.2–1.9** (50% BCI) **times more likely to result in mortality**: strained healthcare systems?
- Validated by subsequent studies on reinfection, disease severity and transmissibility

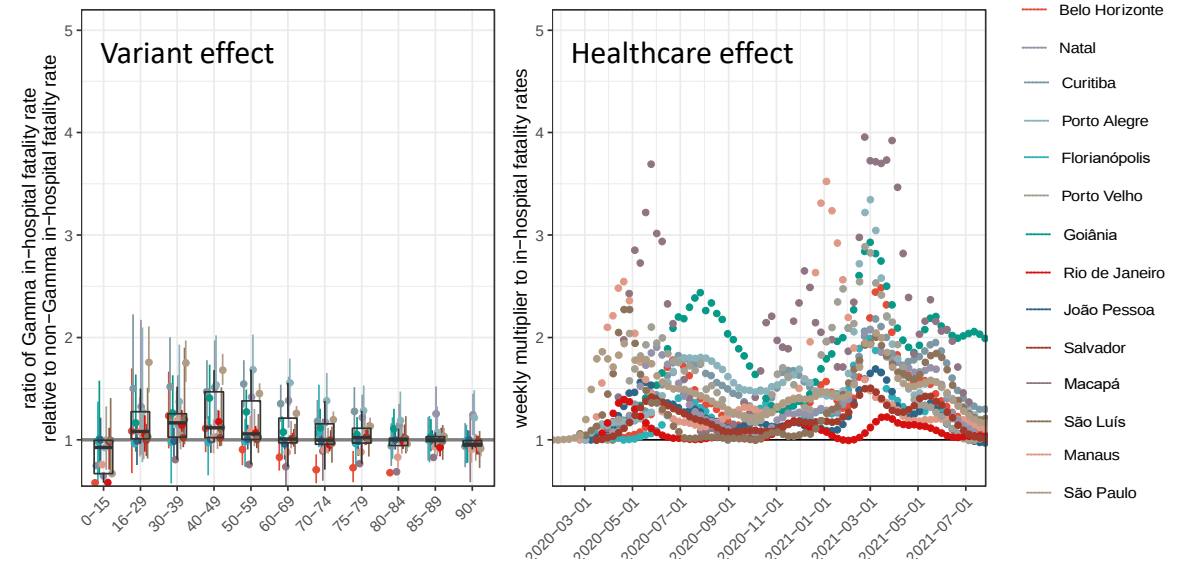
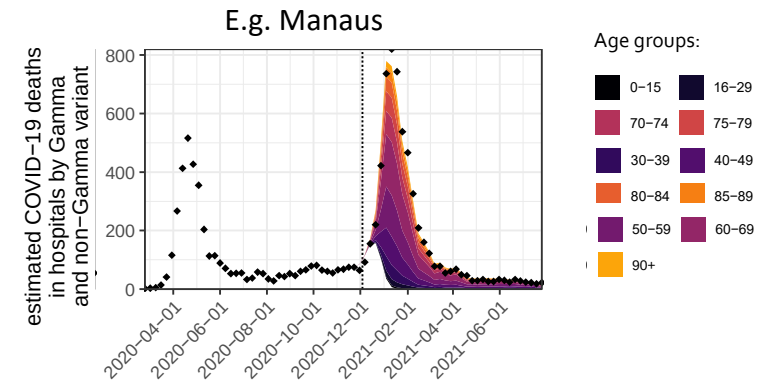


Faria NR et al. *Science* 2021 [shared 11 Jan 2021 with FioCruz, WHO, PAHO]; 12 Jan on Virological.org and GISAID.

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 622 thousands deaths in Brazil could have been avoided.**



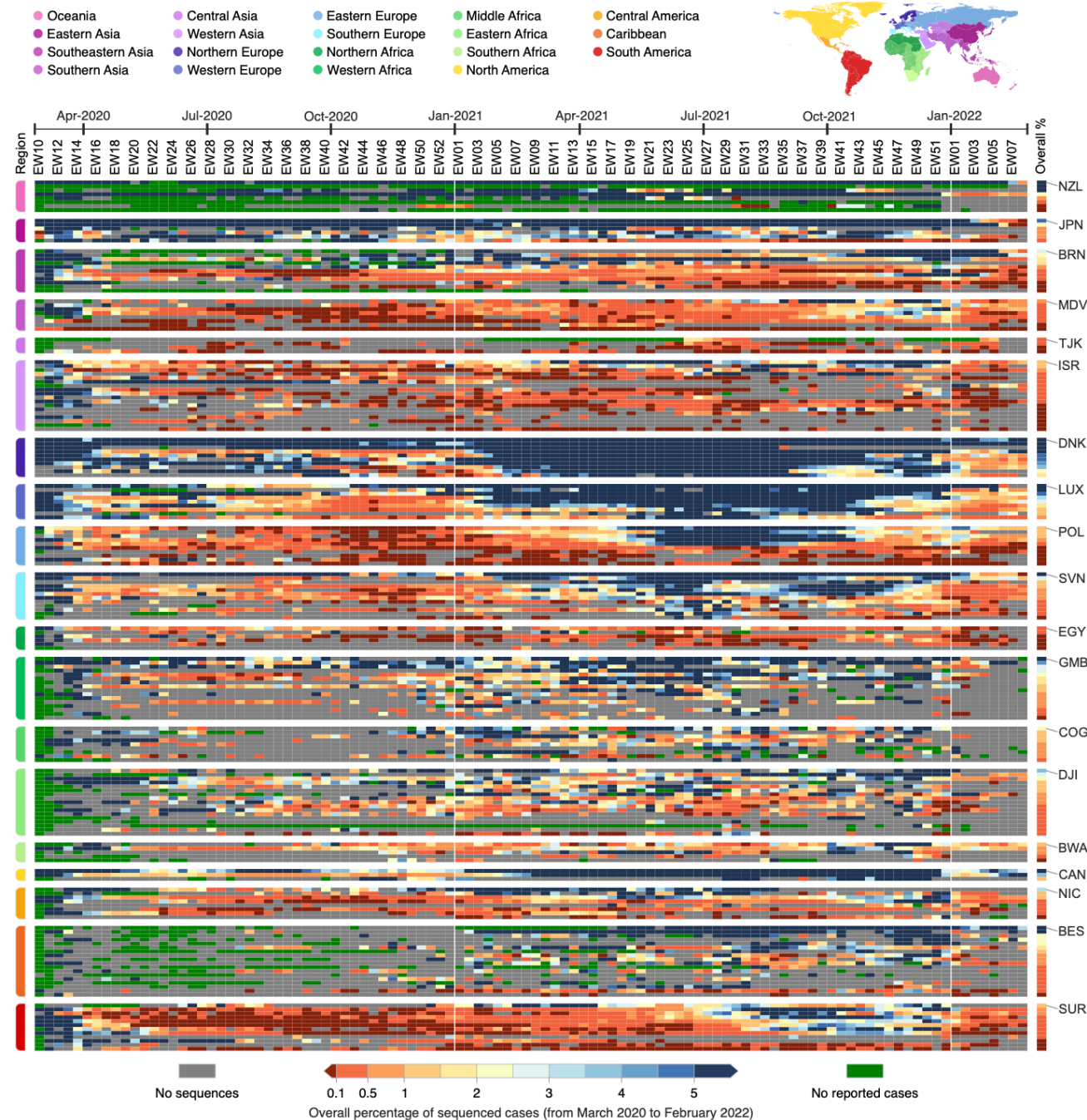
Brizzi A, Whittaker C et al . *Nature Medicine* 2022

Metasurveillance of global genomic surveillance efforts

- Identification of surveillance “coldspots” and delays in data reporting
- Implemented by GISAID:
gisaid.org/submission-tracker-global/
- Brazil sequenced **0.51%** of reported SARS-CoV-2 cases with **53 days** turnaround time
- How much sequencing is enough to detect early emergence of outbreaks caused by known and divergent or unknown viruses?

Brito (...) Faria, *Nature Communications*, 2022 in press.

CADDE Collaboration with WHO & GISAID

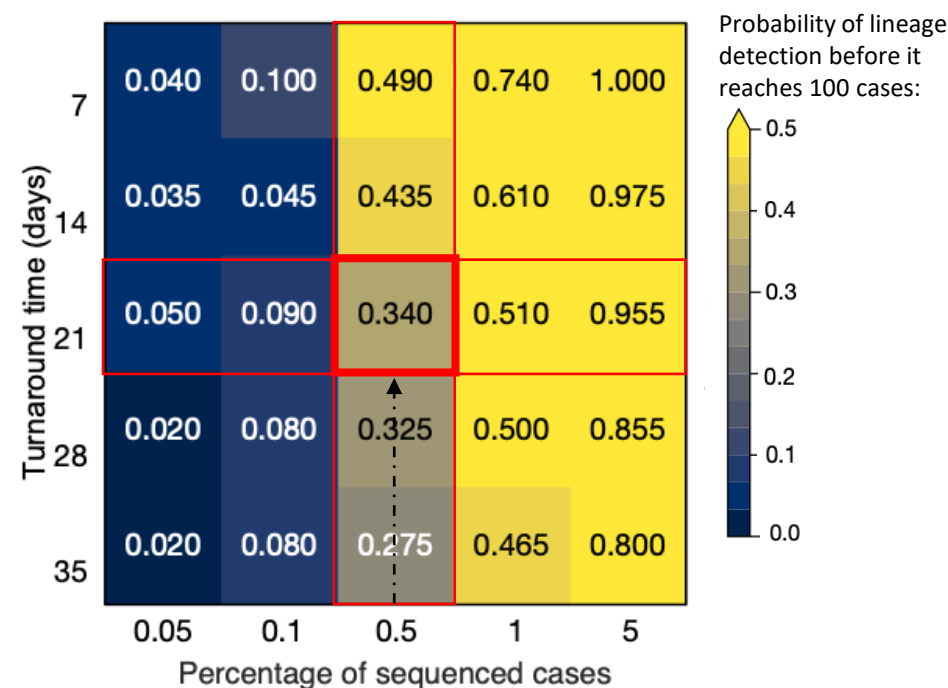
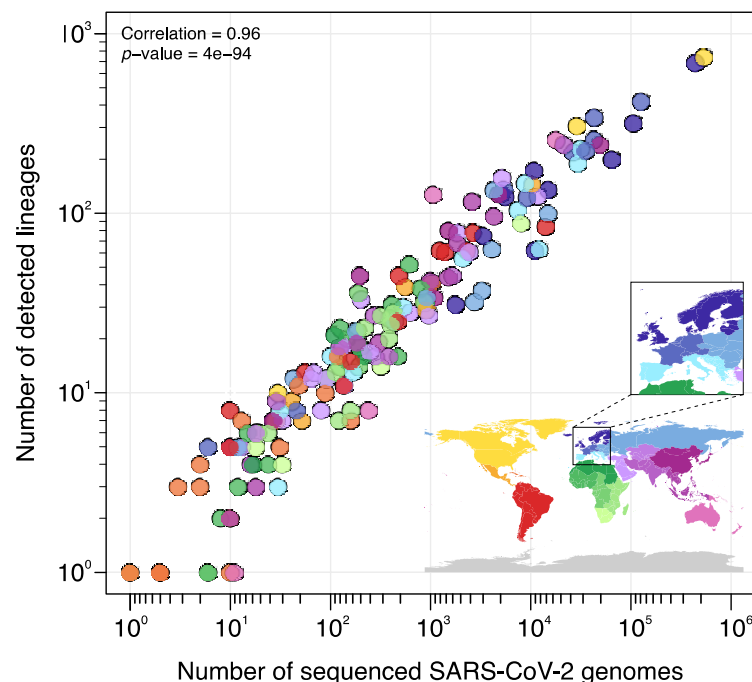


How much sequencing is enough to detect early emergence of viral outbreaks?



Limited genome sequencing intensity affects identification and response to VOCs/VOIs.

TAT = 21 days & 0.5% sequenced cases => 34% probability that a lineage is detected before it reaches 100 cases.

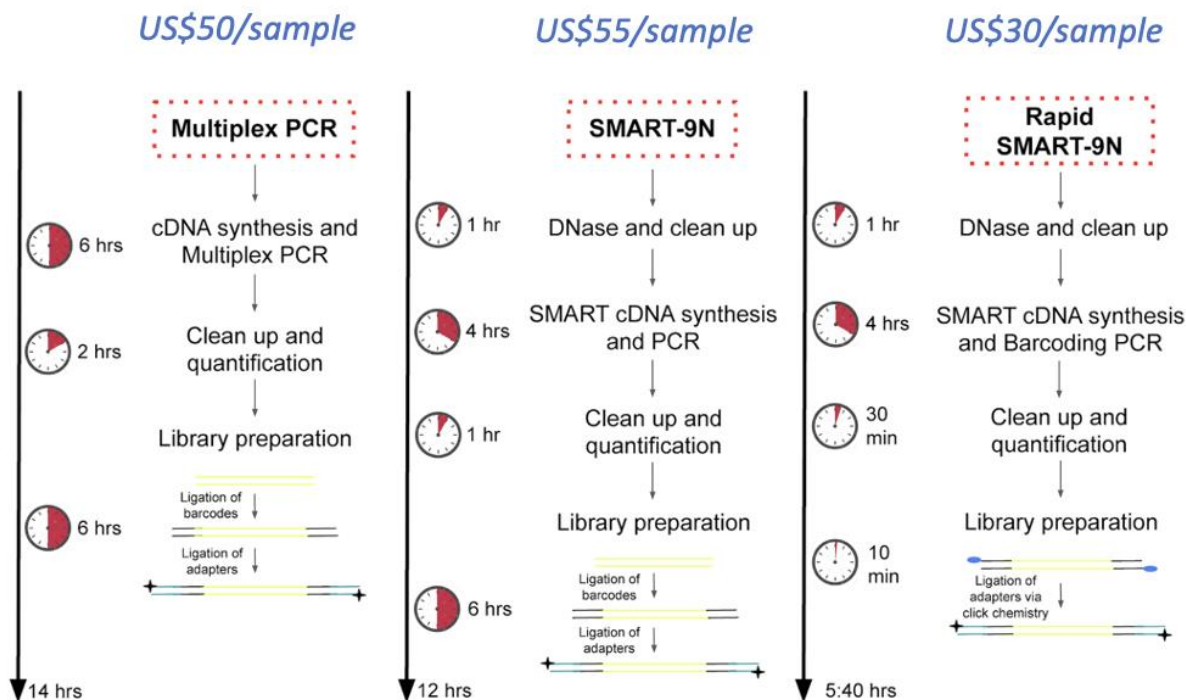


Brito (...) Faria, *Nature Communications*, 2022 in press.

Viral metagenomics – detection and whole genome sequencing of monkeypox in 18h



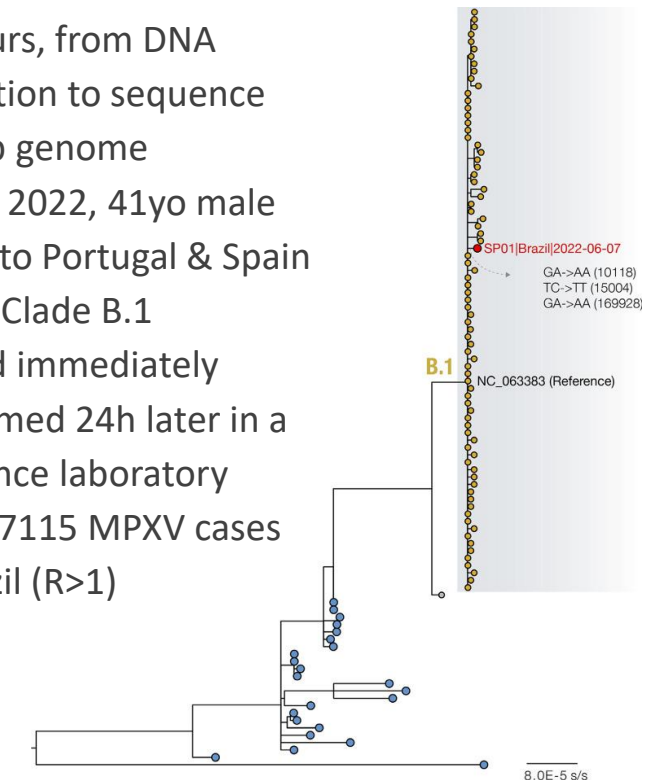
Low-cost, scalable and sensitive viral metagenomics



Claro IM. *et al.*, *Wellcome Open Res* 2021, 6:241

First case of monkeypox virus in Brazil, 2022

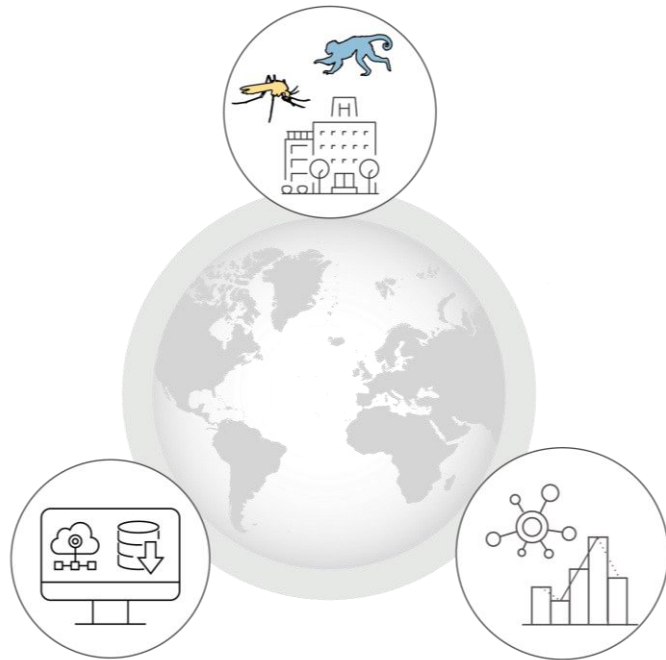
- 18 hours, from DNA extraction to sequence
- 197-kb genome
- 7 June 2022, 41yo male
- Travel to Portugal & Spain
- MPXV Clade B.1
- Shared immediately
- Confirmed 24h later in a reference laboratory
- Today 7115 MPXV cases in Brazil ($R>1$)



Claro IM. *et al.*, *RIMT 2022*; *Carvalho et al. EID 2022*

Next step – standardized, real-time viral metagenomics to improve pandemic preparedness

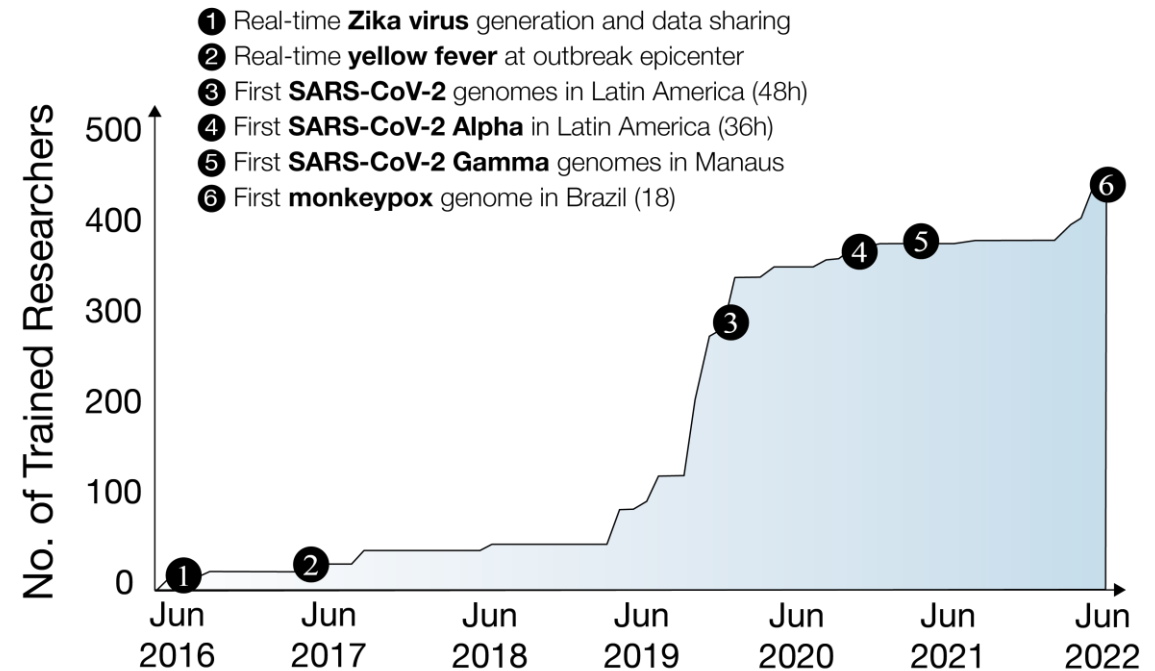
Systematic multi-host real-time
metagenomic sequencing, with
Open Data for science and health



Synchronized and
automated sustainable
workflows

Real-time, high-
resolution evidence for
public health action

Training and capacity strengthening
initiatives for researchers and public
health practitioners



Conclusions

- Integration of epidemiological, clinical, genomic, serological, digital data is crucial to characterise transmission, severity, and immunity of viral pathogens and viral lineages.
- Longitudinal synchronized serosurveillance studies can help target outbreak investigations before they occur in human populations.
- One Health surveillance in humans, non-human host, environment and vectors may be able to improve surveillance of pathogen spillover.



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