Presenter Reminders

- Please **turn on your video** during your assigned session. As a presenter / panelist, your video will be shown to the audience unless you turn it off.

- As a presenter, **you can mute / unmute yourself to speak**. Note that general attendees cannot do this – they can only speak if Francisco/Judy identifies an individual to take themselves off mute. If you would like to call on an attendee to speak, please state their first **and** last name.

- Please **say "next slide"** to advance the slides. Judy will be sharing her screen with everyone's presentations already loaded.

- If you do not see the correct slide on your screen, it may be due to internet connectivity issues. Please **say the name of the slide header** that you'd like to see on the screen. As a backup, please **open your slides separately in PowerPoint** to reference the materials in the event internet issues arise.

- We will be keeping time and **will issue reminders for 5 minutes to go and 2 minutes** to go in each session.

- During the discussion sessions, Karen and Bill will serve as moderator and Ana will be sifting through the Q&A and feeding questions to the main moderator.

Meeting Norms and Recording Disclaimer

- Throughout the workshop, please ask any questions in the "**Q&A**" function. If you see that your question is already asked, you can "like" the question in the "**Q&A**" function.

- This workshop will be **recorded**. Please be mindful of the diverse audience attending the meeting when participating in open discussions.

COVAX

Global and local approaches to detect and interpret SARS-CoV-2 variants

COVAX Enabling Sciences Workshop | Friday, April 16, 2021

CEPI

Gavi
The Vaccine Alliance

World Health Organization

Welcome & Meeting Objectives

Ivana Knezevic, co-lead of ES SWAT team, WHO

Context for today's workshop

Overall objectives:

Share information on how to efficiently connect local pathogen genomic sequencing, epidemiology, virology and immunology to rapidly generate actionable information on the immunological consequences of emerging SARS-CoV-2 variants

PART 1: Assessing emerging SARS-CoV-2 variants locally to inform the global response.

- What have we learned about immune escape from communities where variants have been detected?
- How can we enable more countries to rapidly generate interpretable data on immune escape that can inform local and global decisions, especially related to vaccine design and usage?

PART 2: Contribution of international collaborations and consortia to the global effort.

- Coordinating a global response and building consensus
- What opportunities are there for scientists to engage in international efforts?
- What resources are available to the international scientific community (reagents, standards, protocols, assays, data)?

Global & local approaches to detect and interpret SARS-COV-2 variants

Time (CET)	Presentation Title	Speaker
15:00-15:05	Welcome and meeting objectives	**Ivana Knezevic**, co-lead of ES SWAT team, WHO
***PART I:** Assessing emerging SARS-CoV-2 variants locally to inform the global response.*		
15:05-15:20	Variants of concern and interest in Africa scientific characterization in real time	**Tulio DeOliveira,** KRISP
15:20-15:30	Assessing immunological implications of VoCs in South Africa	**Penny Moore,** NICD
15:30-15:40	Immune escape and evidence for re-infection with P.1 in Brazil	**Ester Sabino**, U. Sao Paulo
15:40-15:50	Impact of B.1.1.7 on vaccine induced immune responses	**Ravi Gupta,** U. Cambridge
15:50-16:00	Understanding SARS-CoV-2 variants in 2021: Indian Perspective	**Anurag Agrawal**, CSIR/IGIB
16:00-16:25	**Panel Discussion**	Moderated by **Karen Makar**, BMGF
16:25-16:30	*BREAK*	
***PART II:** Contribution of international collaborations and consortia to the global effort.*		
16:30-16:40	WHO framework for response to new COVID vaccines	**Sylvie Briand,** WHO
16:40-16:50	Pulling it all together in the COG-UK	**Sharon Peacock,** COG-UK
16:50-17:00	CEPI's Agility program: a centralised approach to evaluate VoCs	**Simon Funnell**, PHE
17:00-17:10	Virus stock and sequencing QC- best practices & available resources	**Sujatha Rashid**, BEI
17:10-17:20	SARS-CoV-2 Interagency Group (SIG) Variant Assessment/Characterization	**Steve Oberste**, CDC
17:20-17:30	ACTIV/TRACE OpenData portal	**Christine Colvis,** NIH/NCATS
17:30-17:55	**Panel Discussion**	Moderated by**: Bill Dowling,** CEPI
17:55-18:00	Wrap up & Next Steps	**Ivana Knezevic**, co-lead of ES SWAT team, WHO

Variants of concern and interest in Africa scientific characterization in real time

Tulio De Oliveira, KRISP

Variants of concern and interest in Africa scientific characterization in real time.

Prof Tulio de Oliveira, Prof Koleka Mlisana, Prof Alex Sigal

for the Network for Genomic Surveillance South Africa (NGS-SA) and Africa CDC Pathogen Genomics Initiative (PGI)

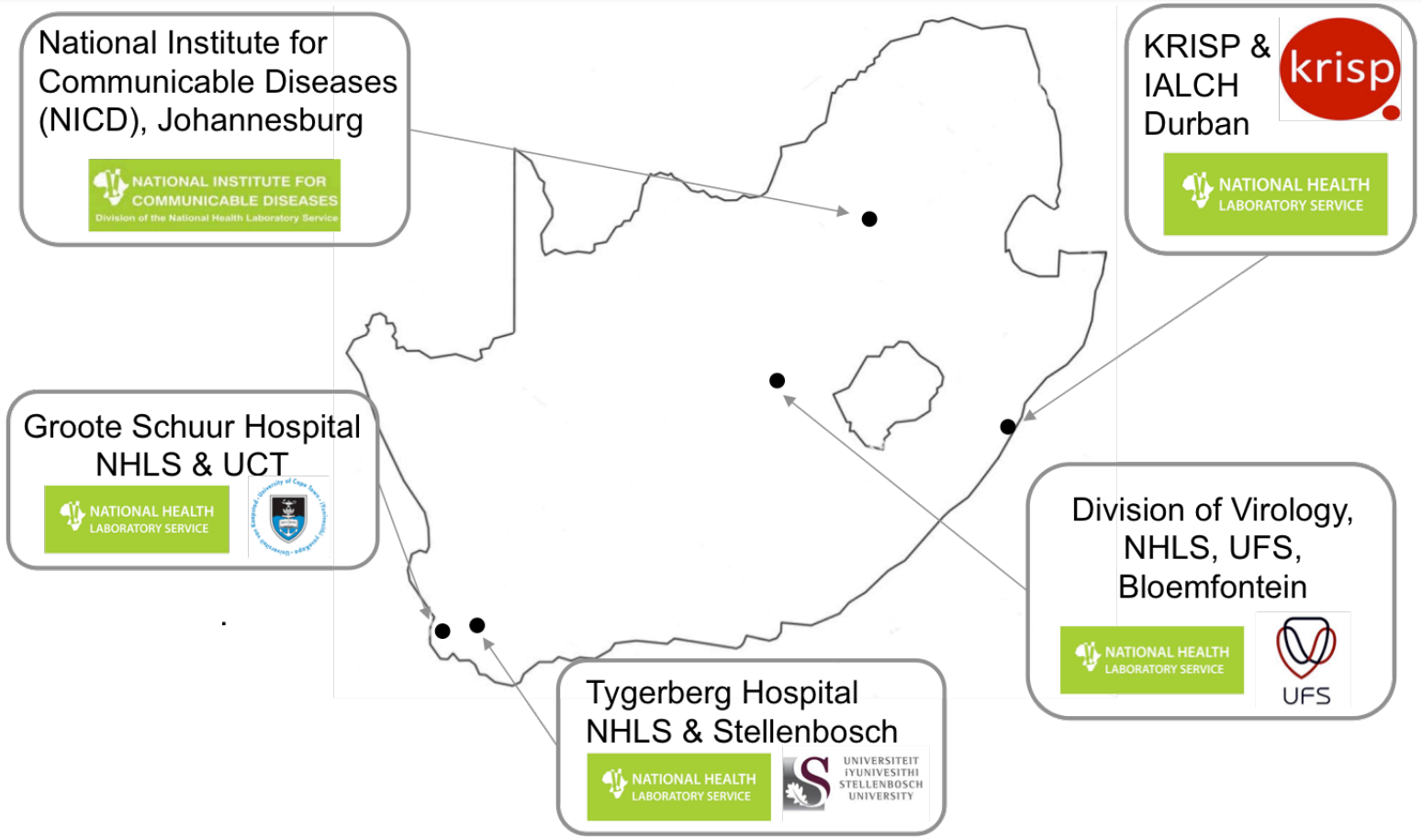
Media brief that highlight new scientific results on 501Y.V2

Update of NGS-SA and variants in SA.

Effect of 501Y.V2 (B.1.351) in neutralization of first wave virus and vaccines.

Expanding genomic surveillance and genotype-to-phenotype to Africa

Network for Genomic Surveillance in South Africa (NGS-SA)



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Department:
Science and Innovation
REPUBLIC OF SOUTH AFRICA

Supported by the DSI and the SA MRC

Msomi N, Mlisana K, et al. Lancet Microbe 2020

saMRC advancinglife

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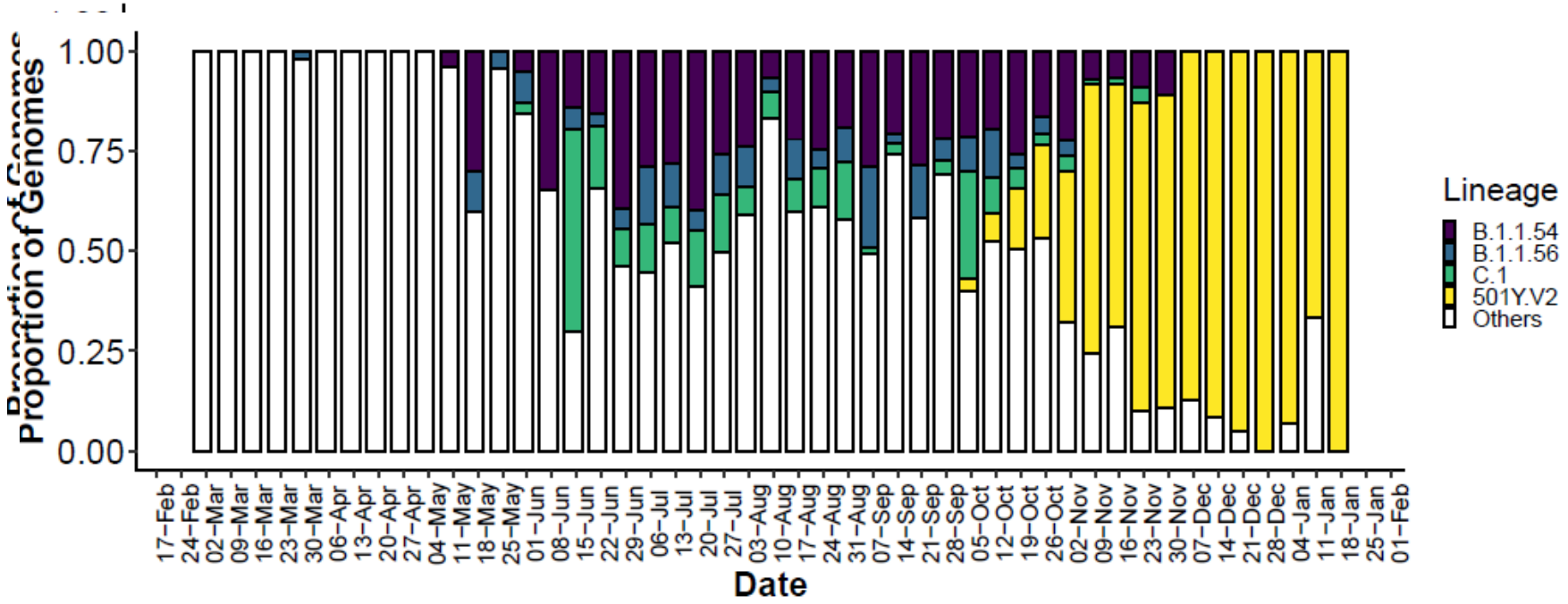
Distribution of SARS-CoV-2 lineages

South Africa



Data from **3324 sequences** from all 9 provinces, collected up to February

Tegally, Wilkinson et al. *Nature 2021*

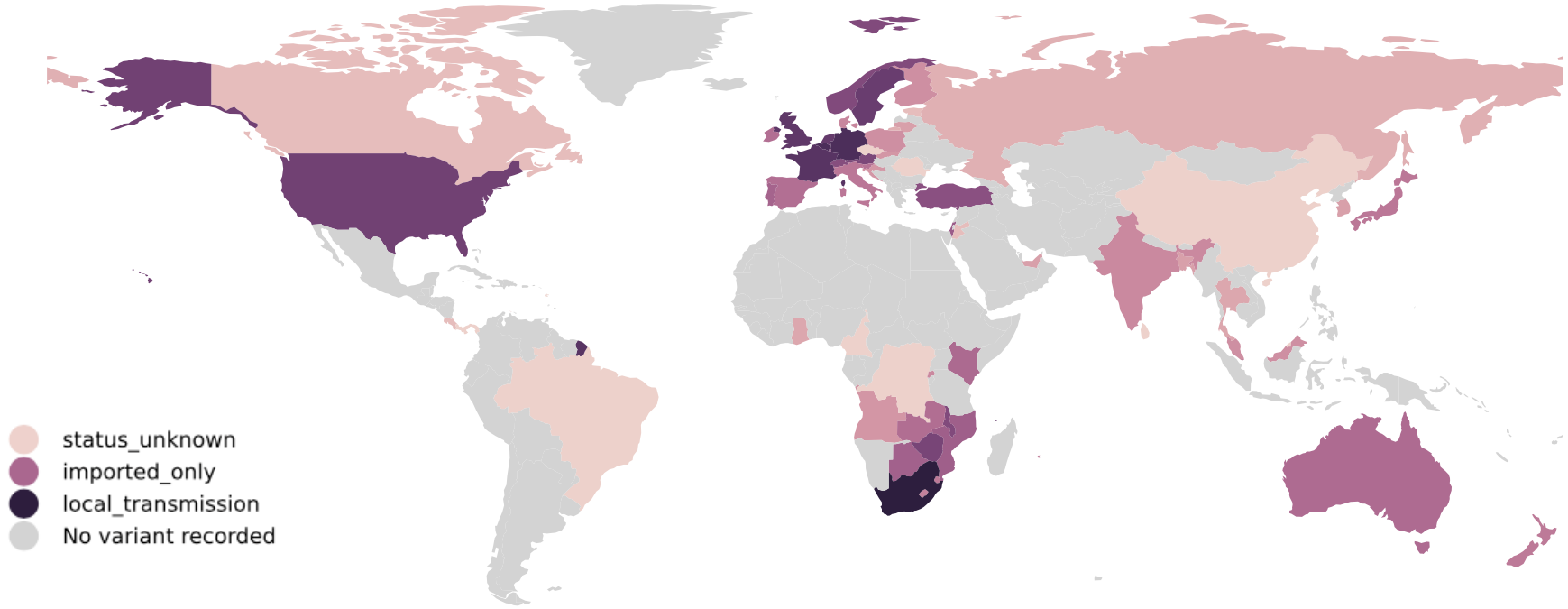
Dominance of 501Y.V2 (B.1.351)

South Africa sequence data

Month	Number of sequences	501Y.V2 sequences	Proportion
Oct 2020	392	44	**11%**
Nov 2020	505	302	**60%**
Dec 2020	415	362	**87%**
Jan 2021	255	239	**94%**
Feb 2021	245	236	**97%**
Mar 2021	345	332	**97%**

Identification of other variants with mutation in Spike:
B.1.1.7 x 5 (Western Cape, Jan, Feb, Mar) - Variant discovered in the U.K
A.23.1 x1 (Eastern Cape, Jan) - New variant of interest discovered in Uganda in 2021.

501Y.V2 global spread

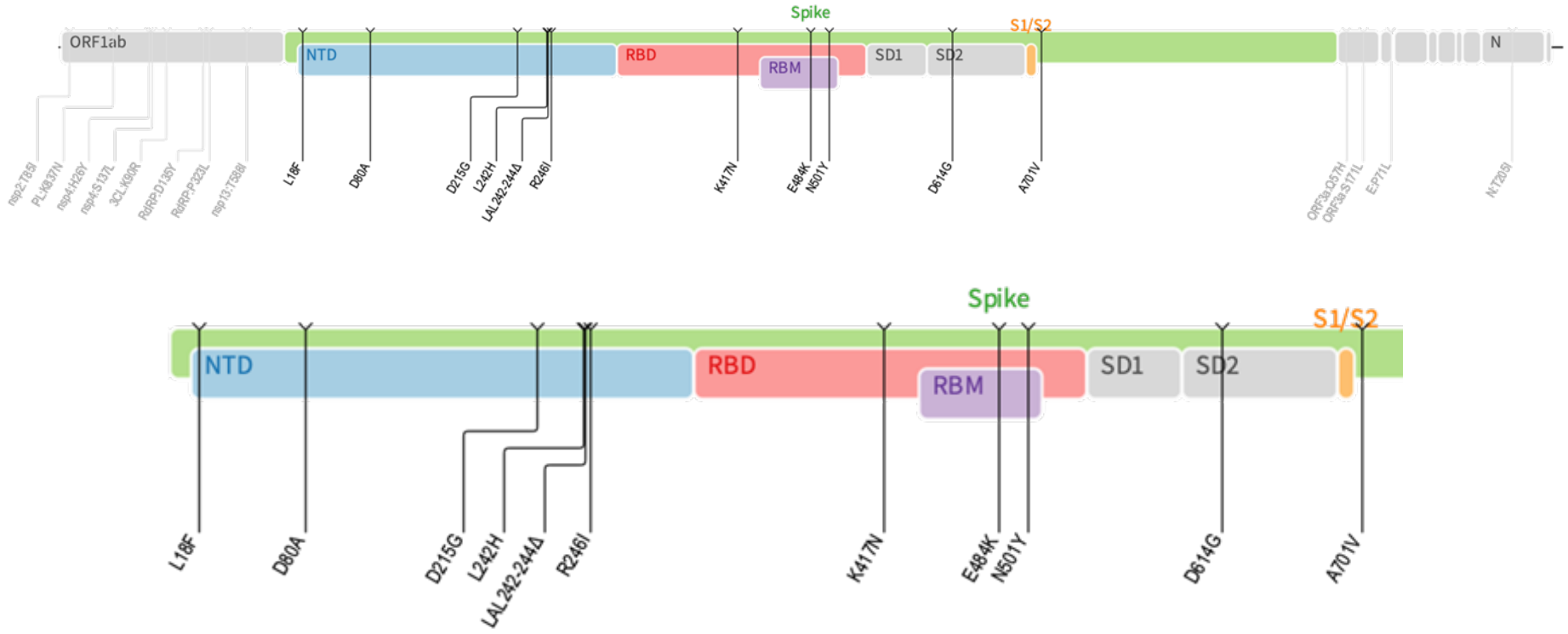


501Y.V2 (B.1.351, 20H) reported in 68 countries

! Do not make sense to call the SA variant !

Karim, de Oliveira, Loots, Science 2021

Genomic map of 501Y.V2

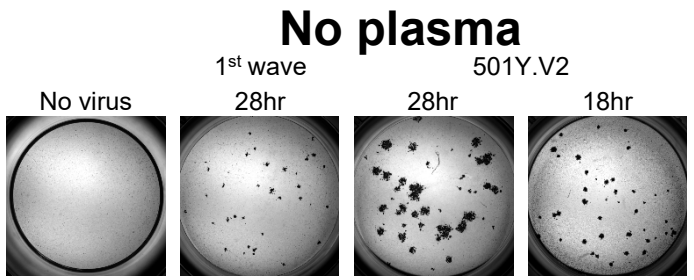


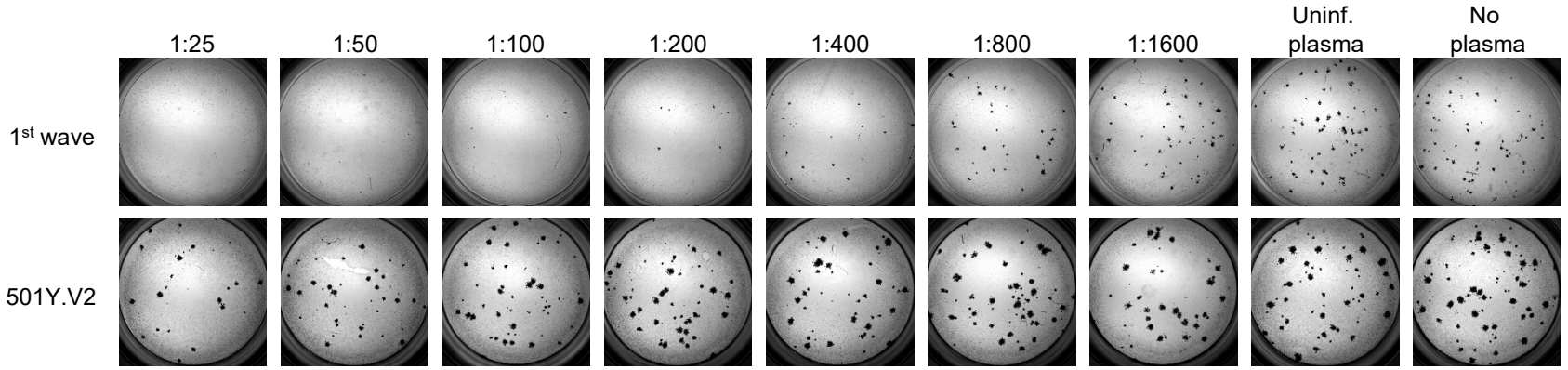
Three mutations in spike receptor-binding domain & cluster of mutations in N-terminal domain

Tegally, Wilkinson et al. *Nature 2021*

First wave plasma neutralization

Live virus neutralization focus forming assay





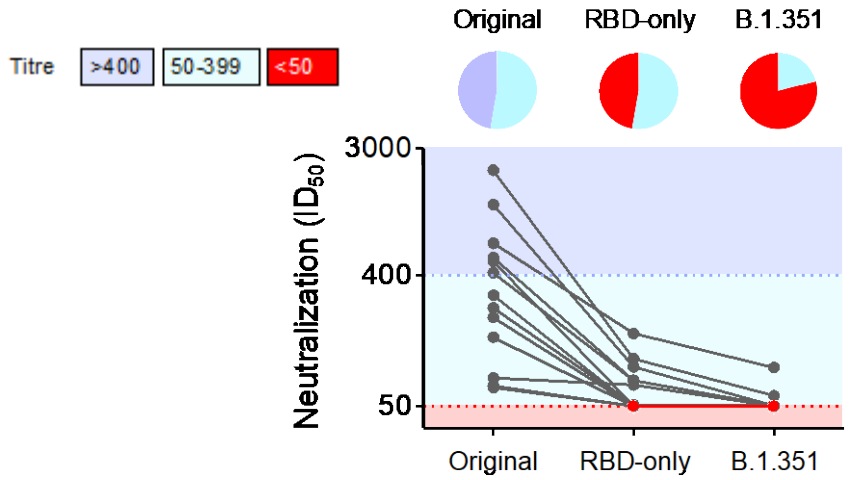
Cele et al. Nature 2021

501Y.V2 escape from vaccinee sera

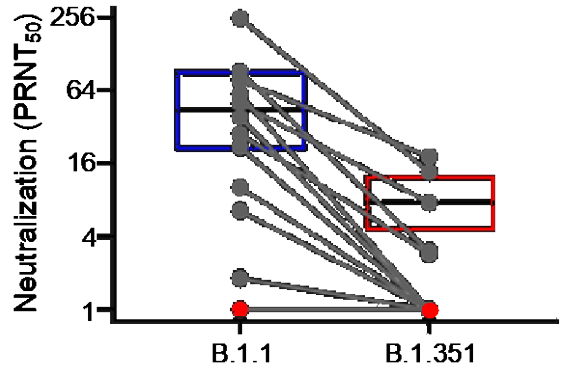
ChAdOx1 (Oxford/Astra Zeneca) phase 1b/2 trial

Question: Does plasma collected from people after receipt of the ChAdOx1 vaccine neutralize the 501Y.V2 virus?

Pseudovirus assay



Live virus assay



Answer: Neutralization strongly attenuated: 15/19 (79%) in pseudovirus assay and 11/19 (58%) in live virus assay had no detectable neutralization

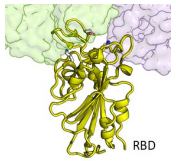
Shabir Madhi, *et al*. NEJM 2021

Is vaccine neutralisation impacted by 501Y.V2?

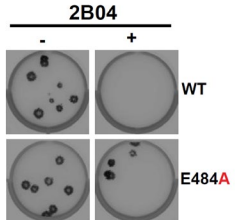
	Pseudovirion and live virus Lab assays against the 501Y.V2 (B.1.351) variant
* Single dose Johnson & Johnson	-
Pfizer	1 to 3 fold ↓
moderna	6.4 fold ↓
THE GAMALEYA NATIONAL CENTER OF EPIDEMIOLOGY AND MICROBIOLOGY	6.8 fold ↓
AstraZeneca	3 to 86 fold↓ / ko
NOVAVAX	-
Sinopharm	1.6 fold ↓
sinovac	-

Lab assays:

- Pseudovirion mutant assay



- Live virus plaque assay



Karim & de Oliveira. NEJM 2021

Is vaccine neutralisation impacted by 501Y.V2?

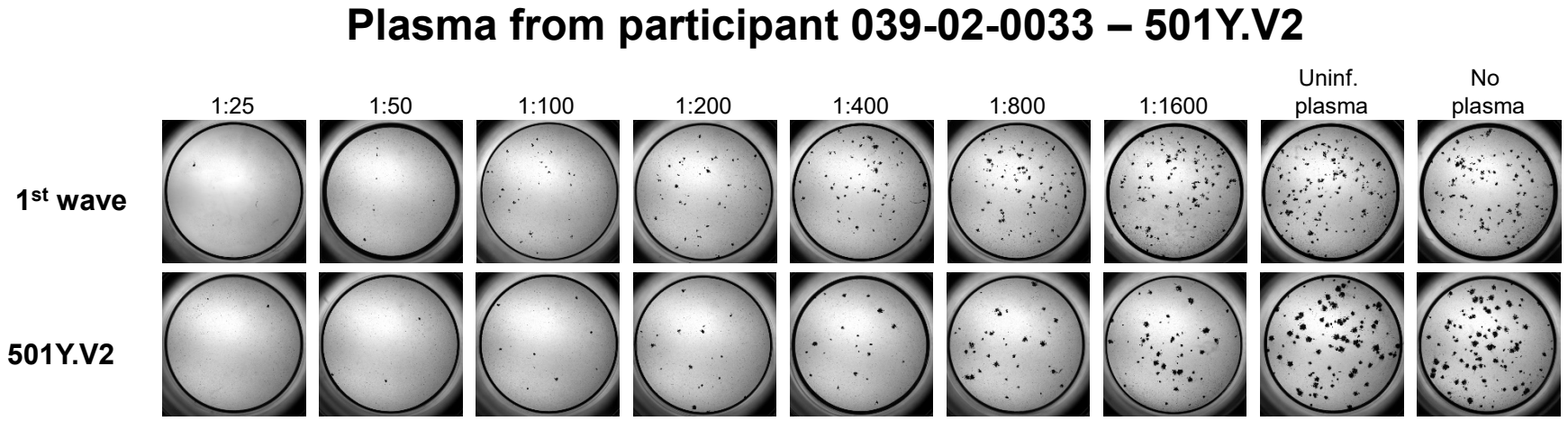
Question: Is vaccine efficacy affected by the 501Y.V2 variant?

	Pseudovirion and live virus Lab assays	Clinical efficacy (mild / mod)	Clinical efficacy (mod / severe)	Clinical efficacy (hosp / severe)
* Single dose Johnson & Johnson	-	-	57%	85%
Pfizer	1 to 3 fold ↓	-	-	-
moderna	6.4 fold ↓	-	-	-
The Gamaleya National Center of Epidemiology and Microbiology	6.8 fold ↓	-	-	-
AstraZeneca	3 to 86 fold↓ / ko	22%	-	-
Novavax	-	49%	-	-
Sinopharm	1.6 fold ↓	-	-	-
Sinovac	-	-	-	-

Answer: Efficacy of vaccines evaluated in SA seems to be reduced for mild/moderate disease (but may not be for severe disease)

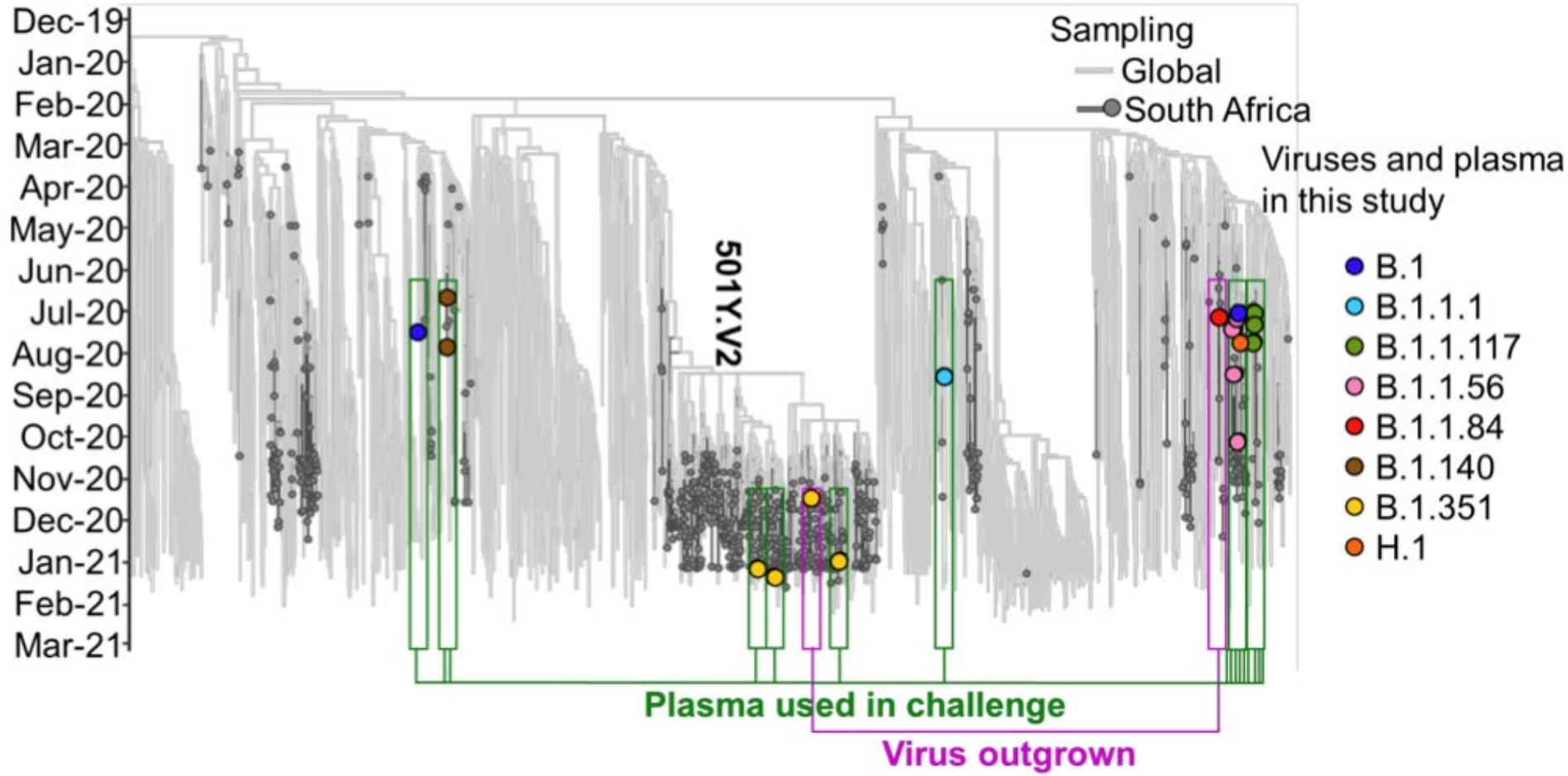
Karim & de Oliveira. NEJM 2021

Second wave plasma neutralization by 501Y.V2 – Live Virus



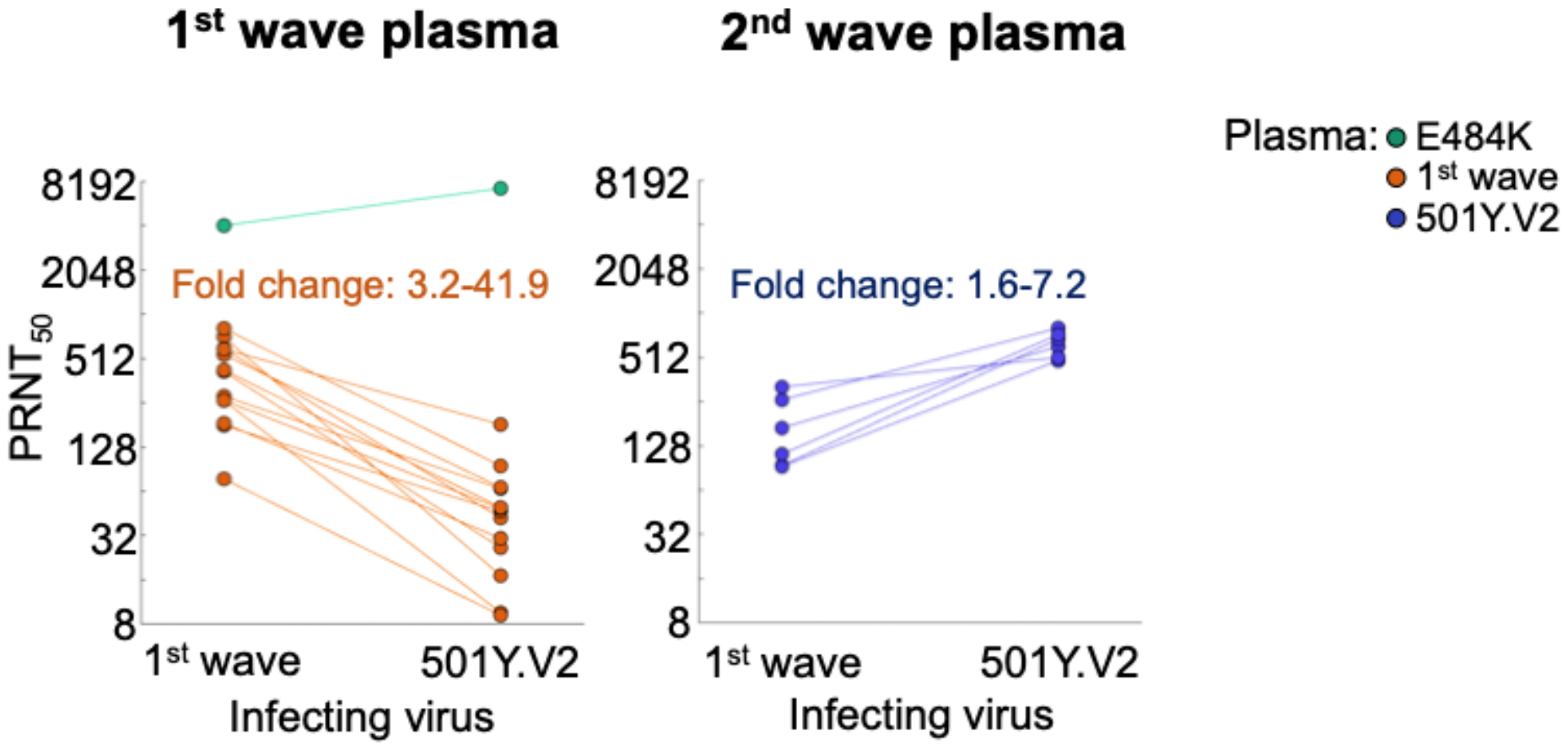
Cele et al. Nature 2021

South Africa had most of the diversity of virus in the world to experiments



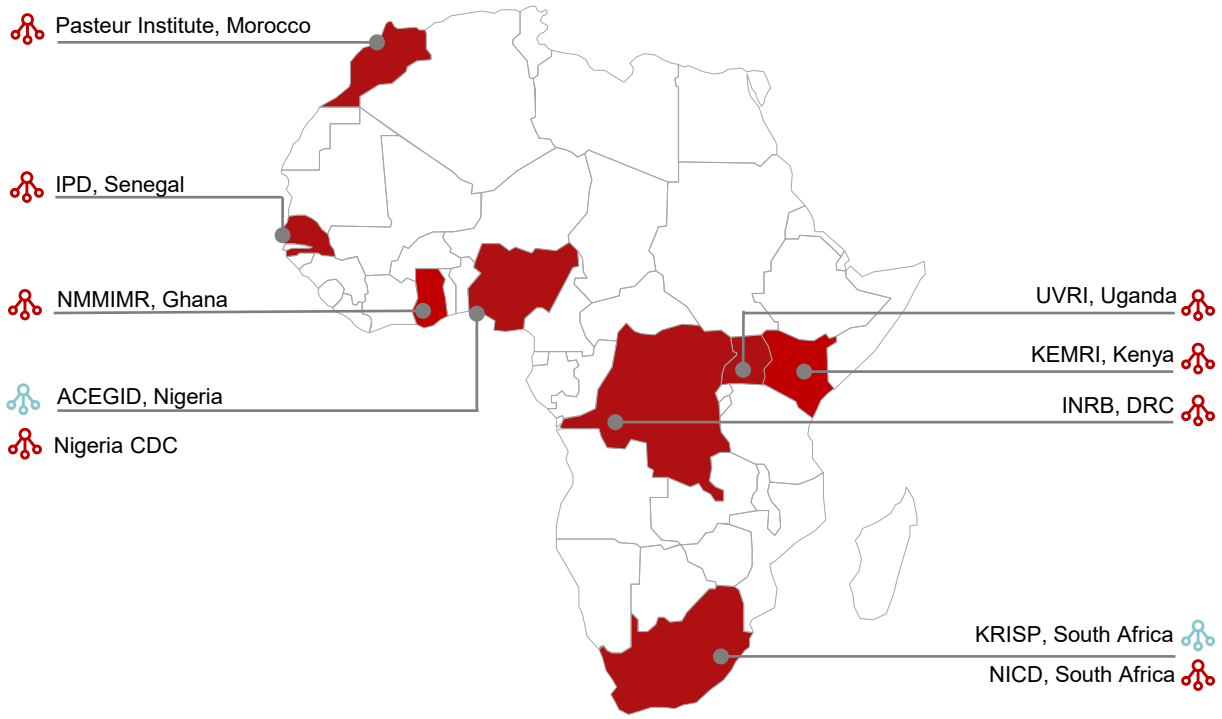
Cele et al. Nature 2021

Cross-neutralization of 501Y.V2 and intriguing finding with E484K only



Cele et al. Nature 2021

ACCELERATING SARS-COV-2 SEQUENCING IN AFRICA



1. **Mobilize resources and leverage on existing capacity**
2. **Start simple and establish routine surveillance**
3. **Support sample collection and shipment logistics**
4. **Support sequencing – reagents, equipment upgrades, and personnel**
5. **Support data analysis, sharing, and interpretation**

AFRICA CDC
Centres for Disease Control and Prevention
Safeguarding Africa's Health

World Health Organization

Tessema et al. Lancet Microbe 2021

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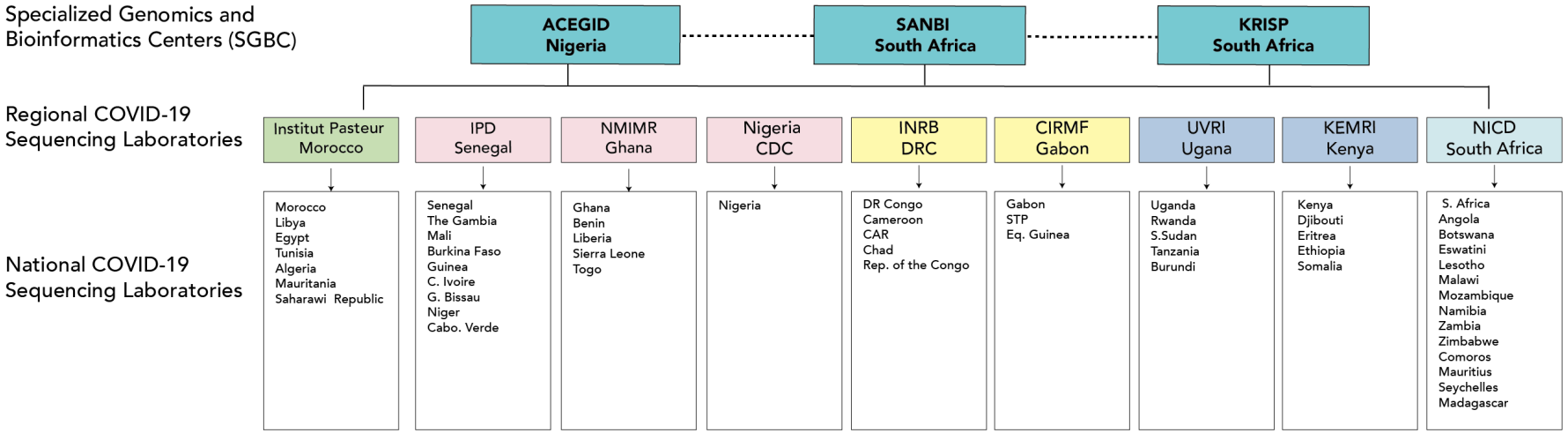
ACCELERATING SARS-COV-2 SEQUENCING IN AFRICA

Coordination

Operationalization of the network

Leverage on existing capacity



AFRICA CDC
Centres for Disease Control and Prevention
Safeguarding Africa's Health

World Health Organization

Access to sequencing facility

Tessema et al. Lancet Microbe 2021

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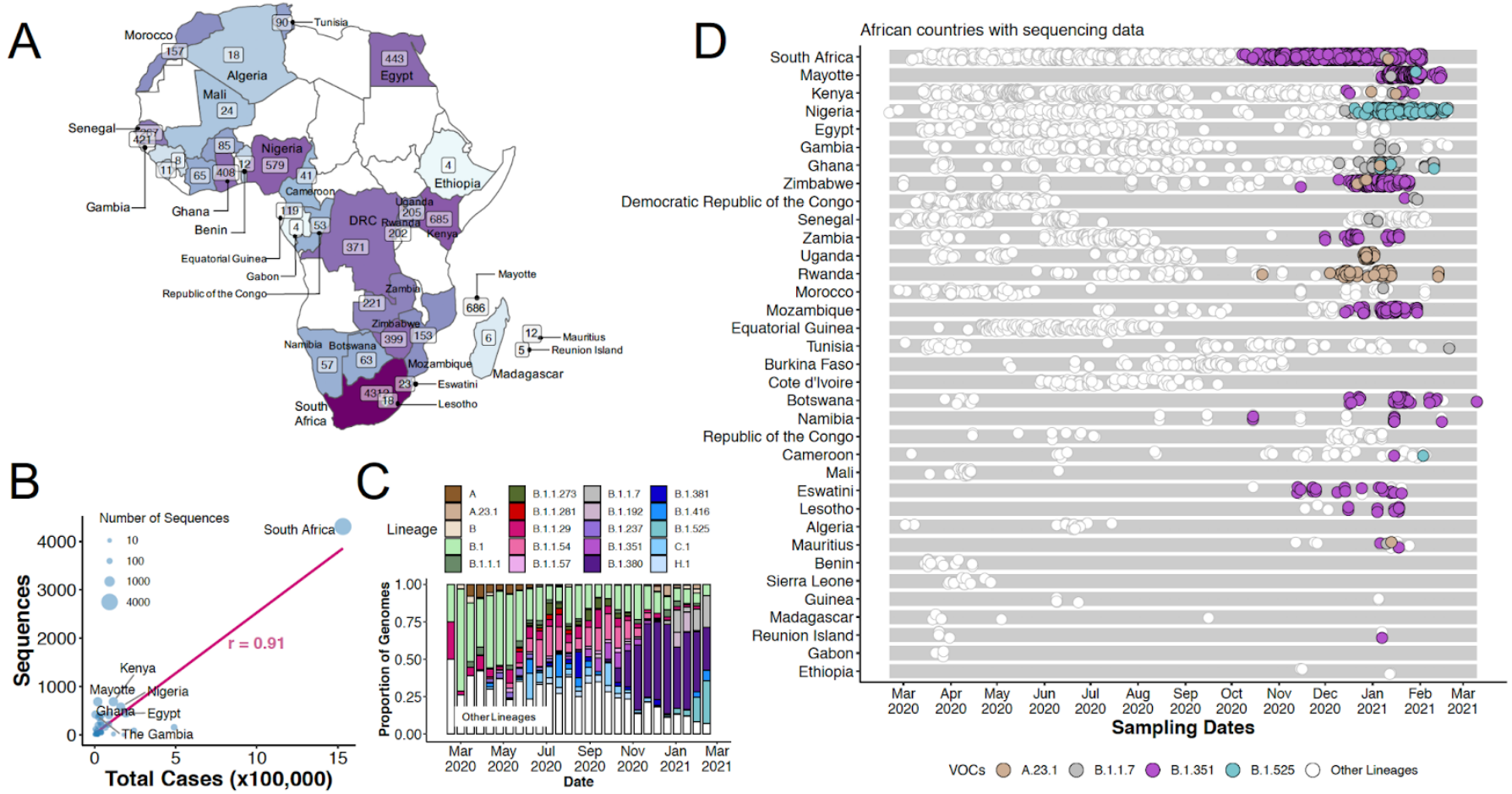
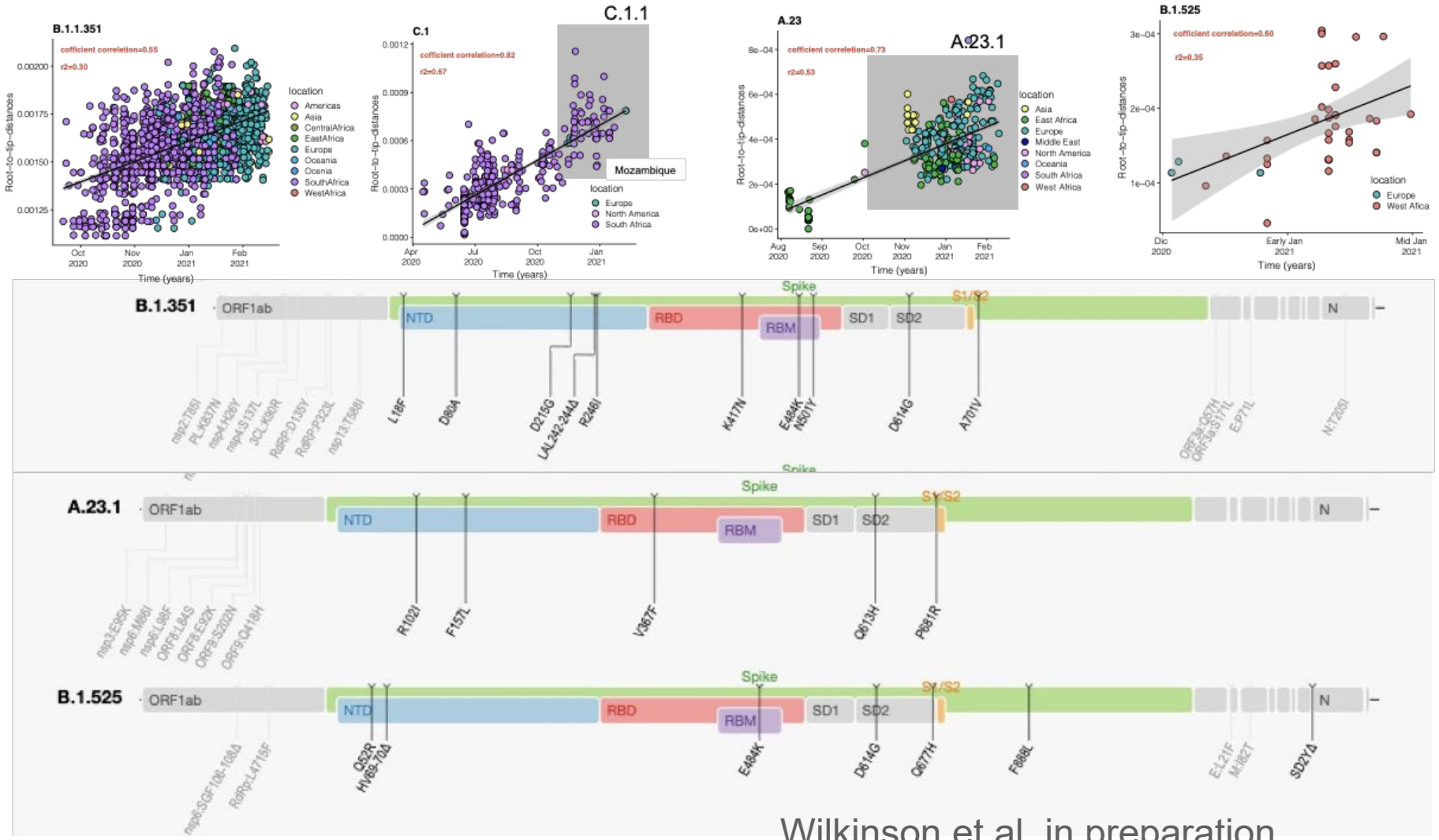
COLLABORATING ON SARS-COV-2 PAN-AFRICAN ANALYSIS



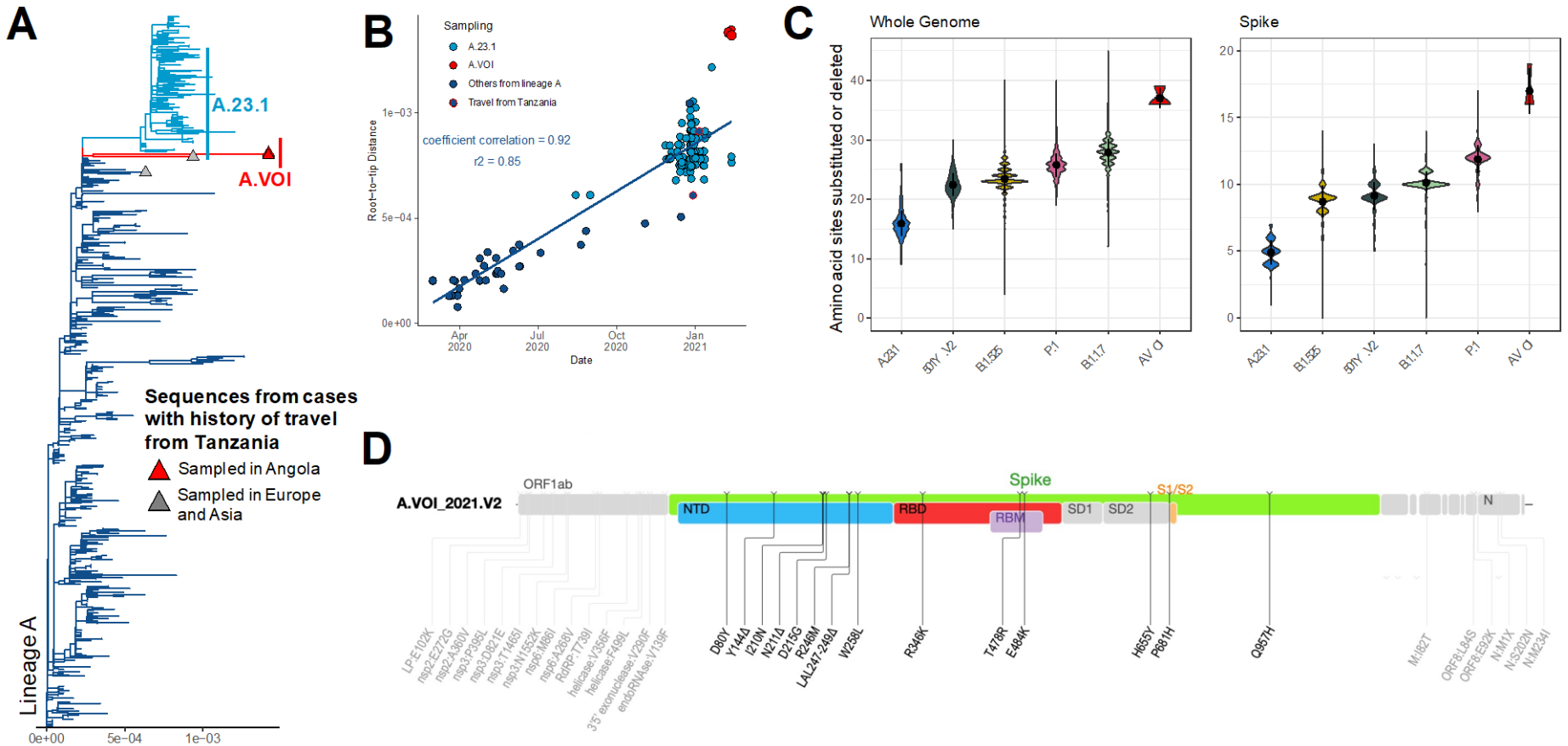
Wilkinson et al. in preparation

VARIANTS OF CONCERN OR INTEREST IN AFRICA



Wilkinson et al. in preparation

NEW VARIANT OF INTEREST IN AFRICA (A.VOI.V2)



de Oliveira, Lutucuta, Nkengasong et at. MedRxiv 2021

Conclusions

- Genomic surveillance is a critical component of the epidemic response.
- We detected a new variant with multiple spike mutations that affected some vaccine response.
- Plasma collected from people infected with 501Y.V2 has good neutralizing activity and also against ‘first wave’ viruses and potentially other variants of concern.
- People infected have immunity against the variant and other lineages.
- Expanding the methods developed in South Africa to other African countries

Acknowledgements

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Sofonias Tessema

Netcare:
Richard Friedland
Craig Murphy
Caroline Maslo
Liza Sitharam

DSI
Glaudina Loots

SA MRC
Glenda Gray

Assessing immunological implications of VoCs in South Africa

Penny Moore, PhD
NICD

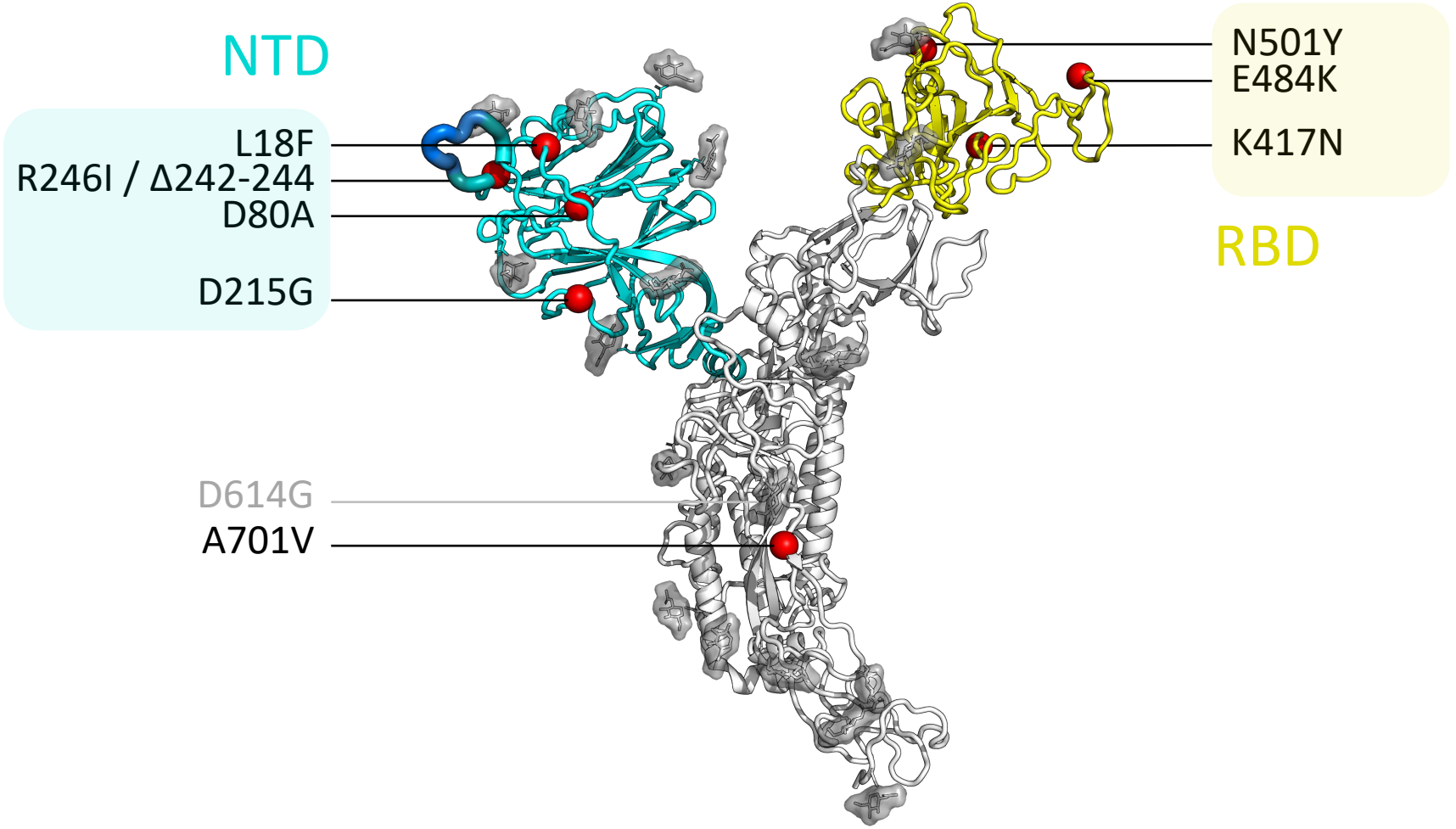
Assessing immunological implications of VoCs in South Africa

Penny Moore, PhD

University of the Witwatersrand,
National Institute for Communicable Diseases of the National Health Laboratory Service
and
CAPRISA, South Africa

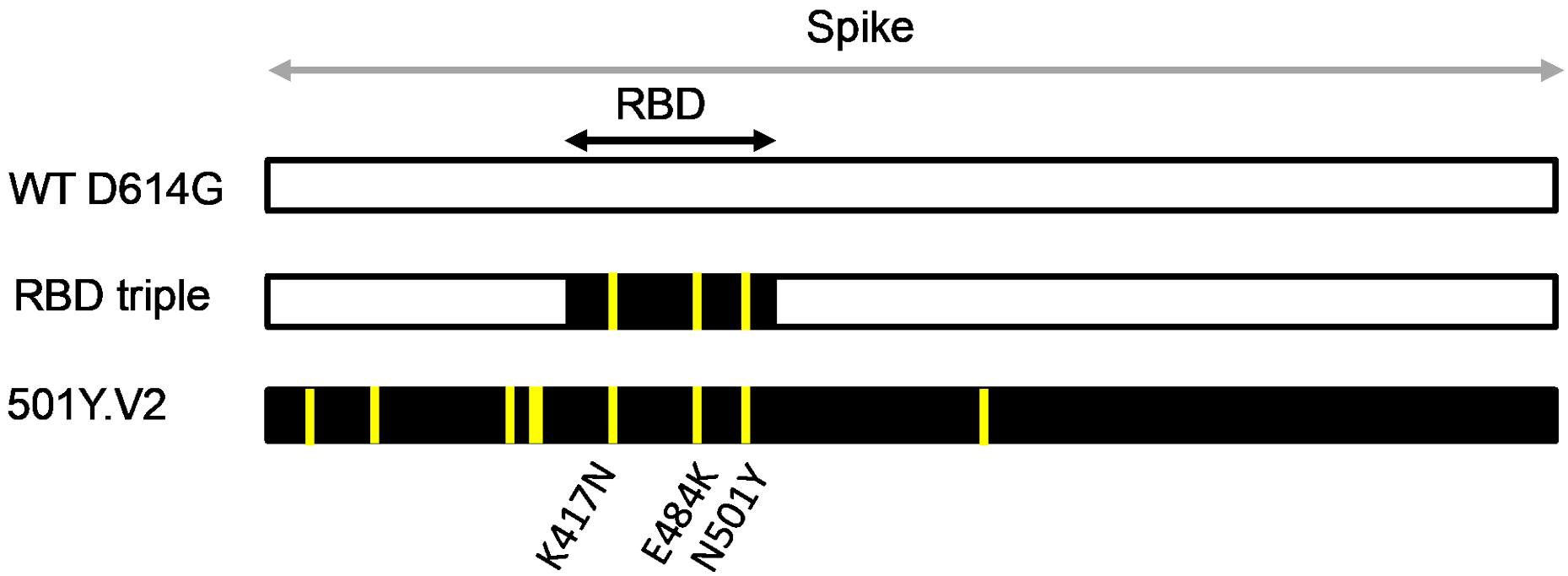
16 April 2021

Studies of plasma immunity to 501Y.V2 (B.1.351)



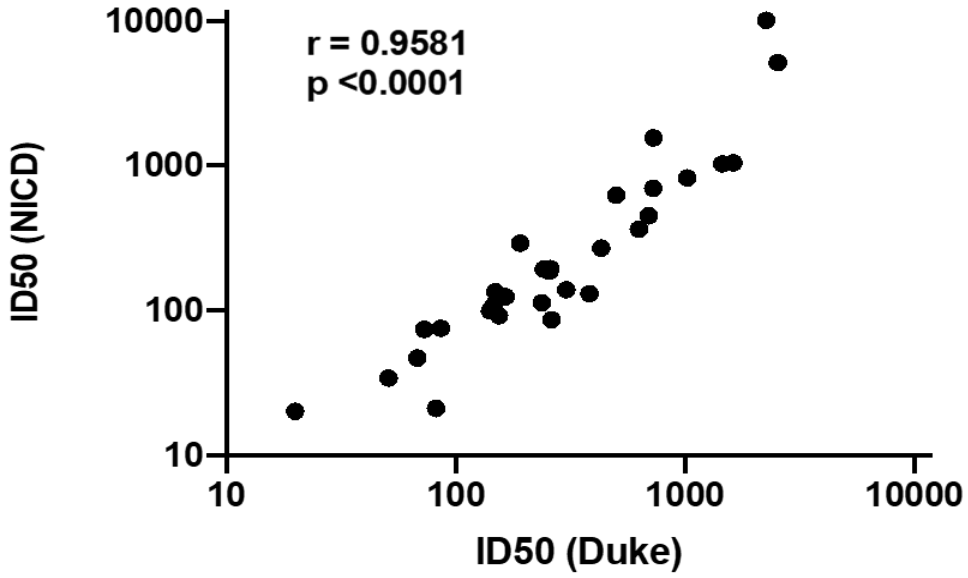
Kurt Wibmer, NICD

Re-purposing an HIV assay for measuring neutralizing antibodies



PSV assay using 293T cells over-expressing ACE-2 as a target cell line (Mike Farzan)

Comparative studies of PSV data



NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

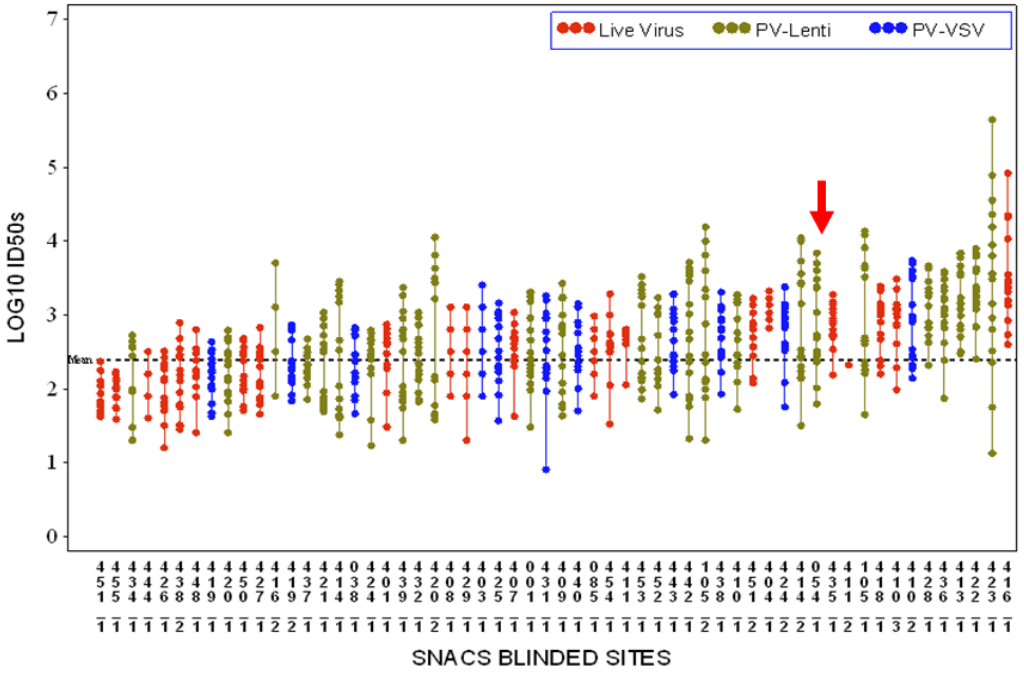
Duke Human Vaccine Institute
Duke University School of Medicine

VQA Virology Quality Assurance Program An NIH, NIAID, DAIDS Program

EQAPOL External Quality Assurance Program Oversight Laboratory An NIH, NIAID, DAIDS Program

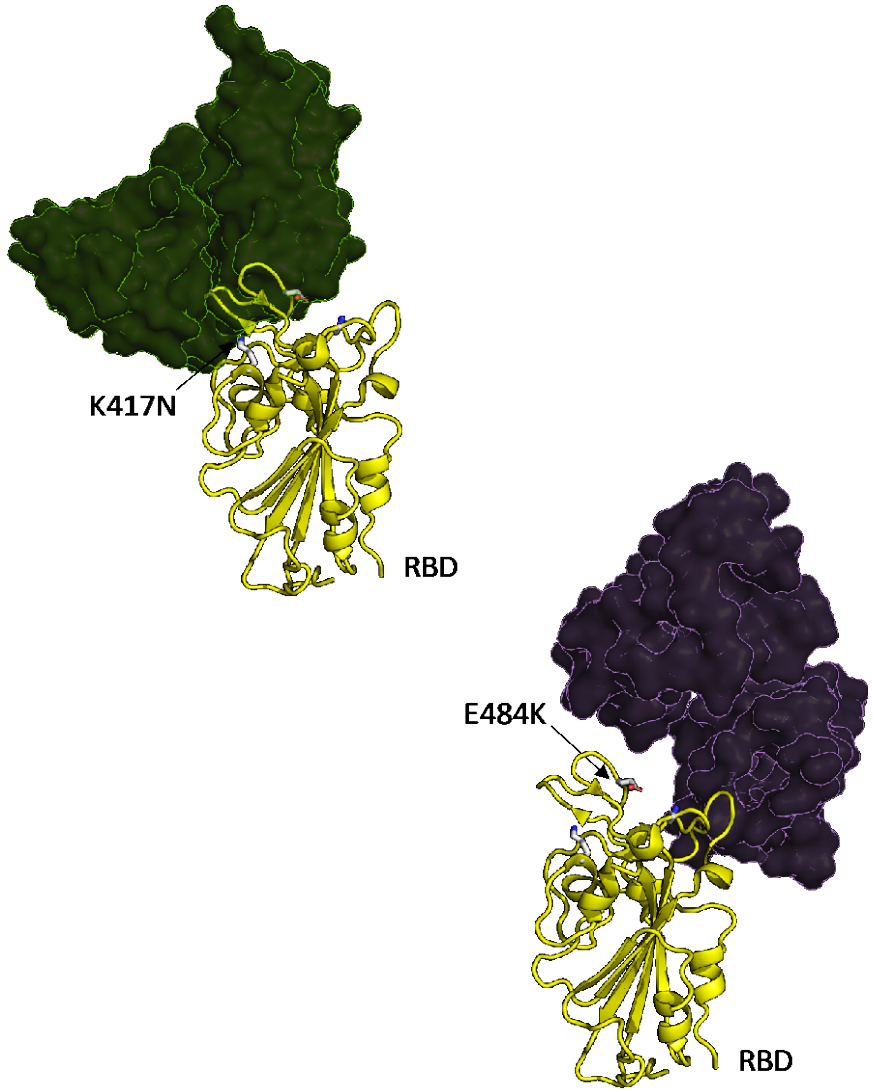
SARS-CoV-2 Neutralizing Assay Concordance Survey (SNACS) Concordance Survey 1 (CS1) Summary Report 11/24/2020

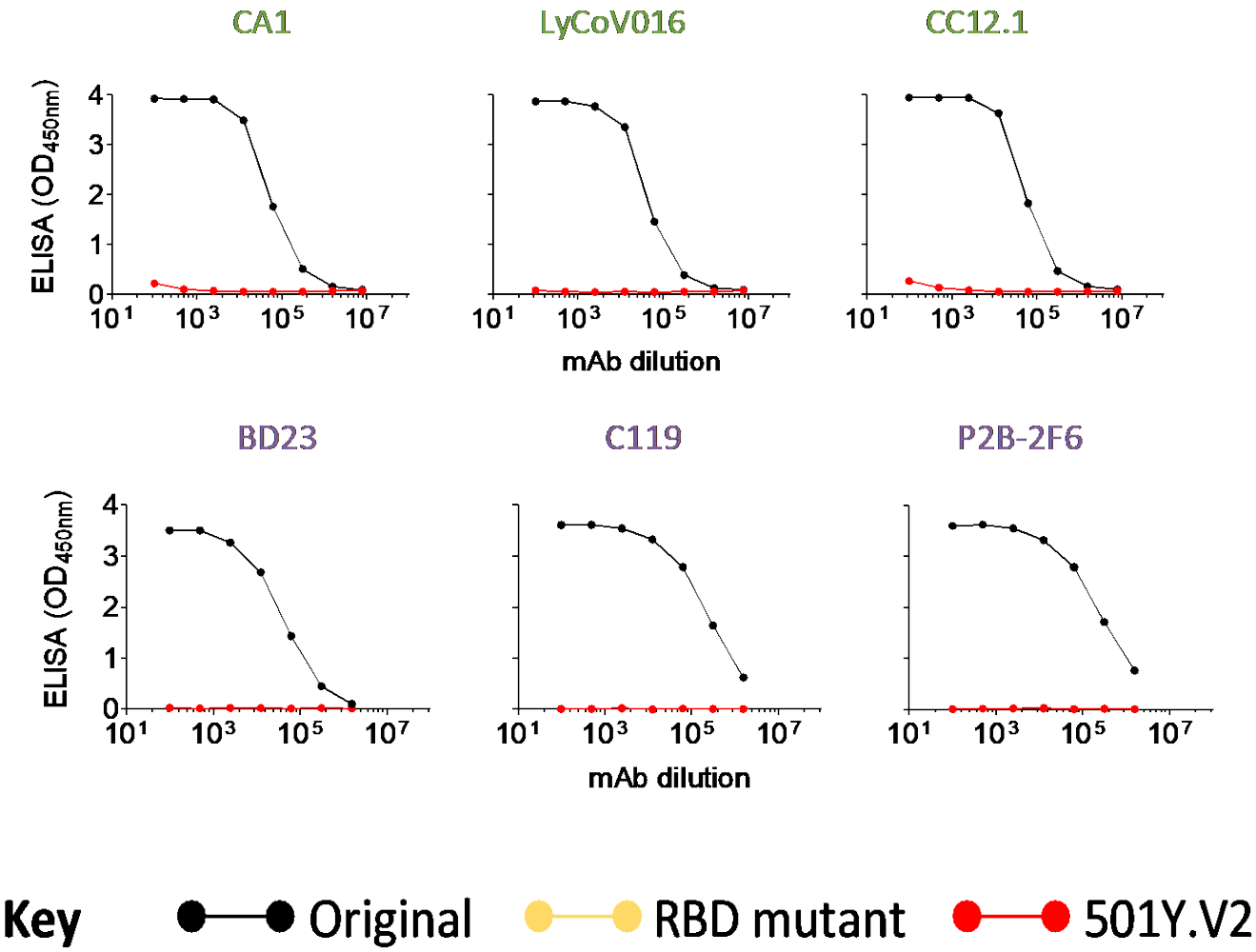
SNACS Graph for ID50 Titer Values: All Positive Samples Pseudovirus vs Live Virus Comparison



Use of well-described mAbs as internal controls

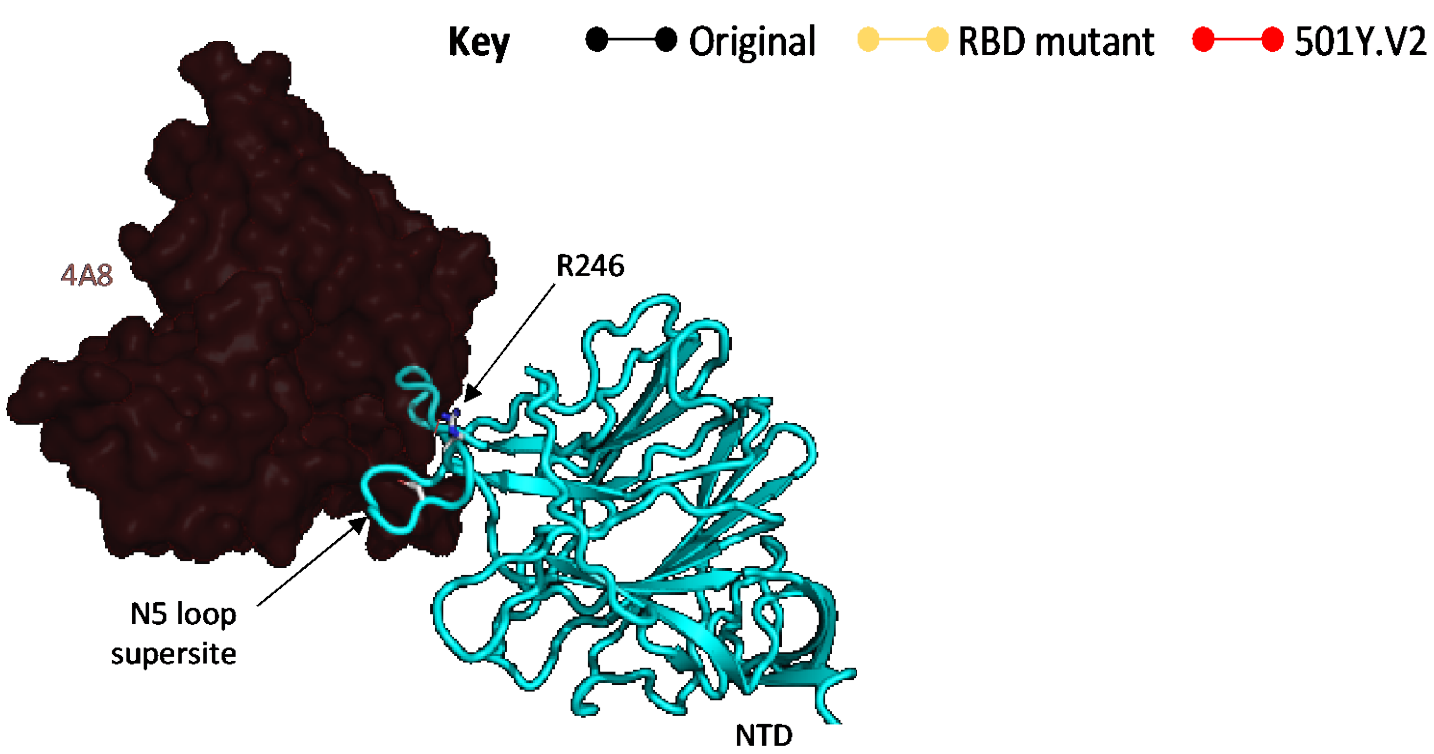
501Y.V2 resistant to “class I” and “class II” mAbs

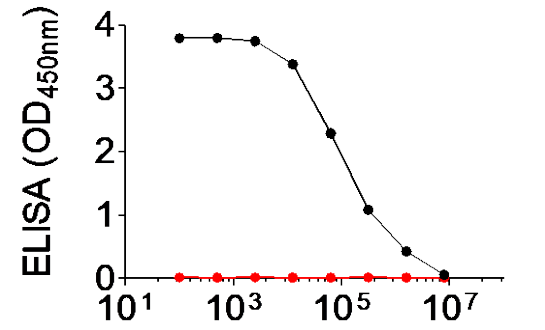


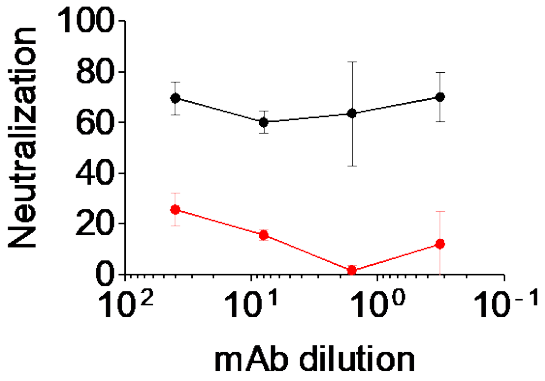


Wibmer et al, Nature Medicine, 2021

501Y.V2 resistant to NTD-directed mAbs



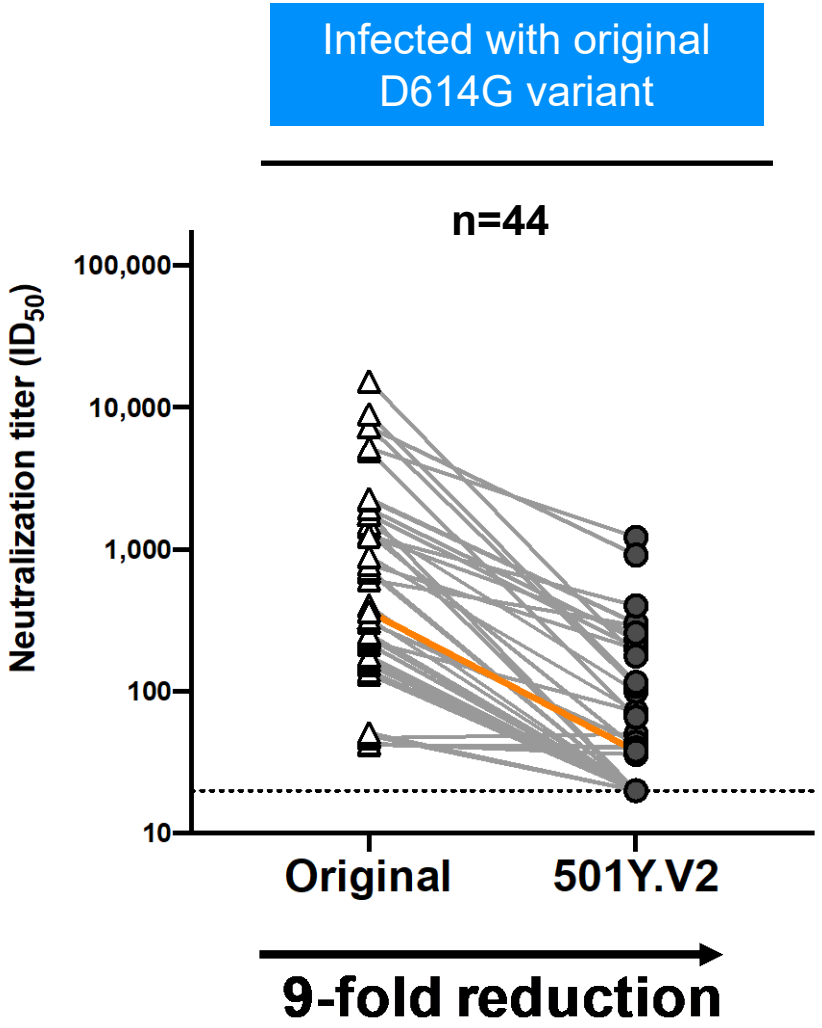


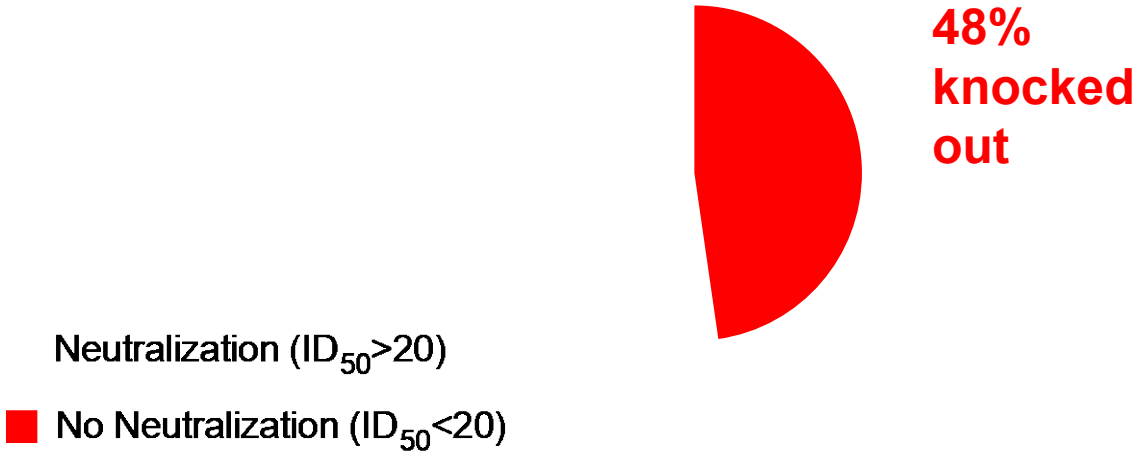


The 501Y.V2 lineage exhibits complete escape from three classes of therapeutically relevant monoclonal antibodies.

Wibmer et al, Nature Medicine, 2021

SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma

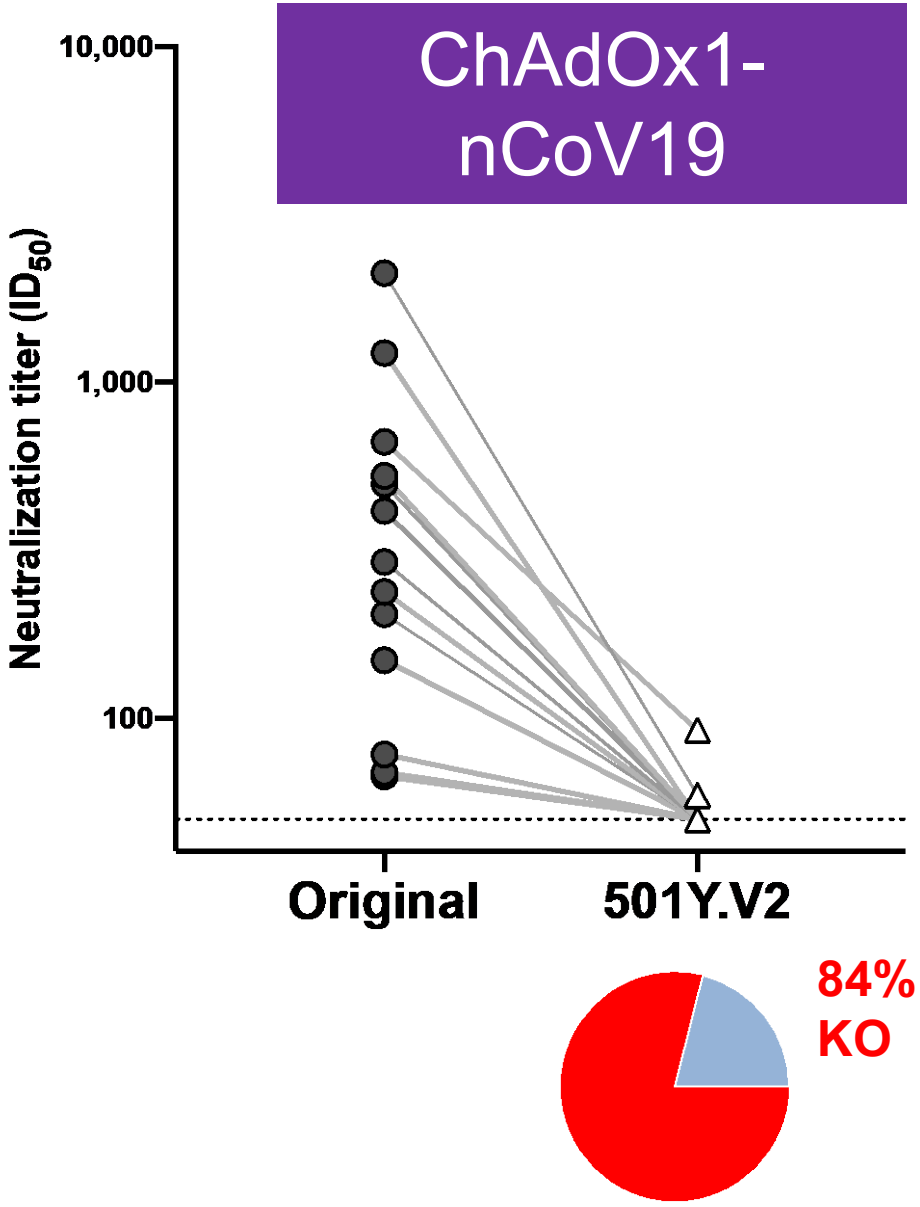


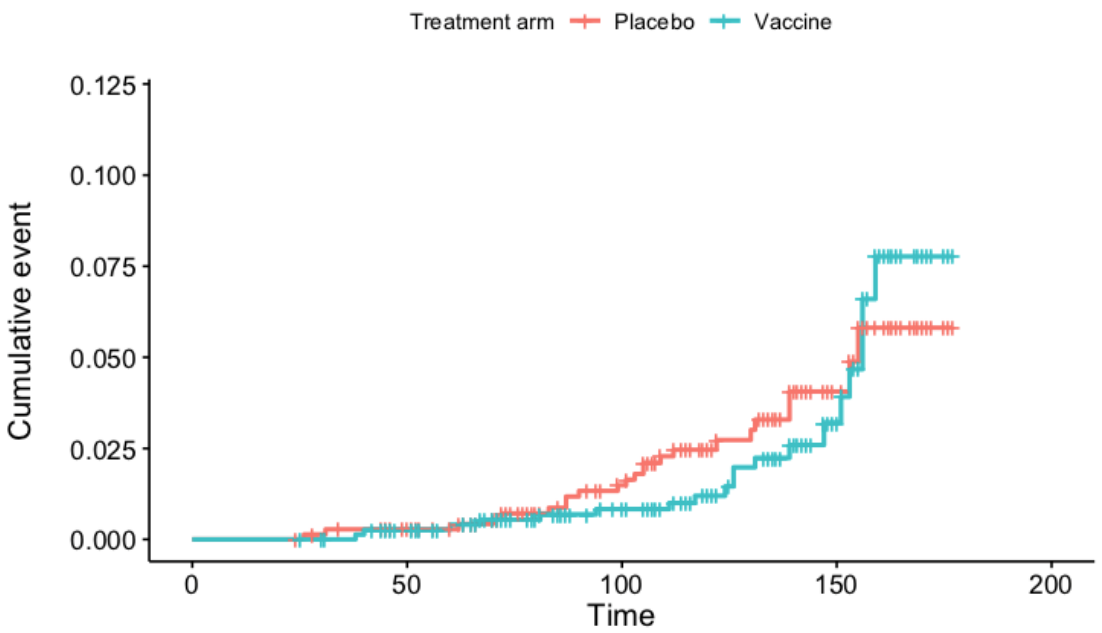


Implications of immune escape for vaccine efficacy?

Wibmer et al, Nature Medicine, 2021

How well do vaccinee sera neutralize 501Y.V2?





Two-dose regimen of ChAdOx1-nCoV19 show no protection against mild/moderate COVID-19 due to 501Y.V2

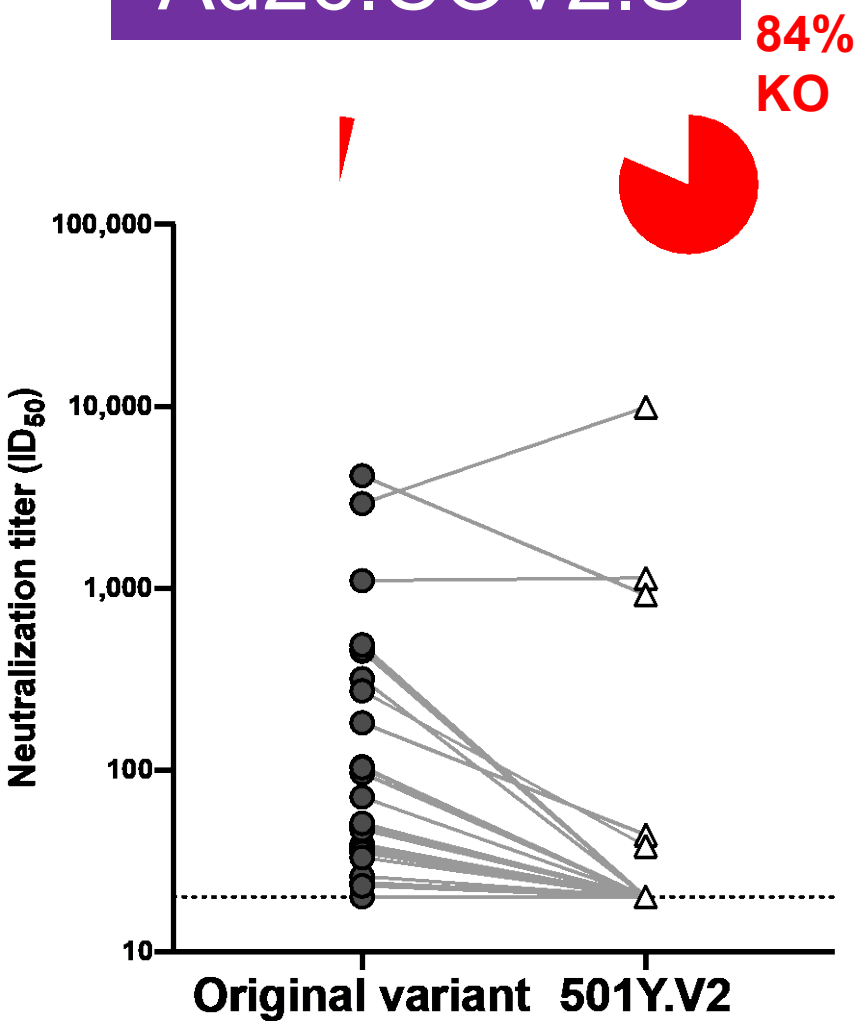
-

Protection against severe disease?

Madhi et al, NEJM, 2021

501Y.V2 also escapes Ad26.COV2.S nAbs, despite *high level protection*

Ad26.COV2.S



BUT…

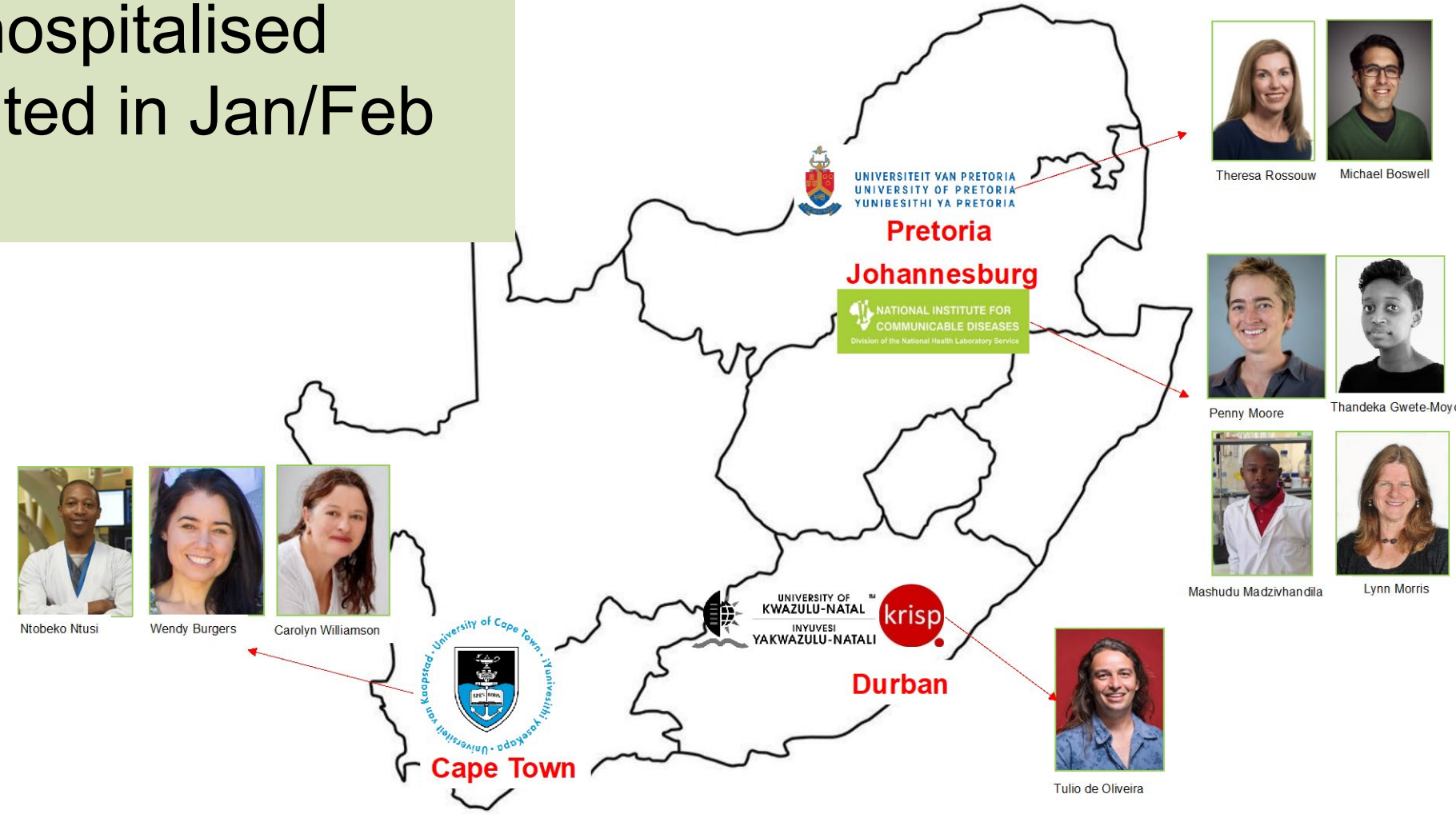
Phase 3 ENSEMBLE trial showed 64% protection vs moderate/severe disease and 82% protection against severe/critical disease

Moore, Bekker, Schuitmaker, Gray unpublished data

How robust is the immune response to 501Y.V2?

Cohort of 89 hospitalised patients recruited in Jan/Feb 2021

Groote Schuur Hospital

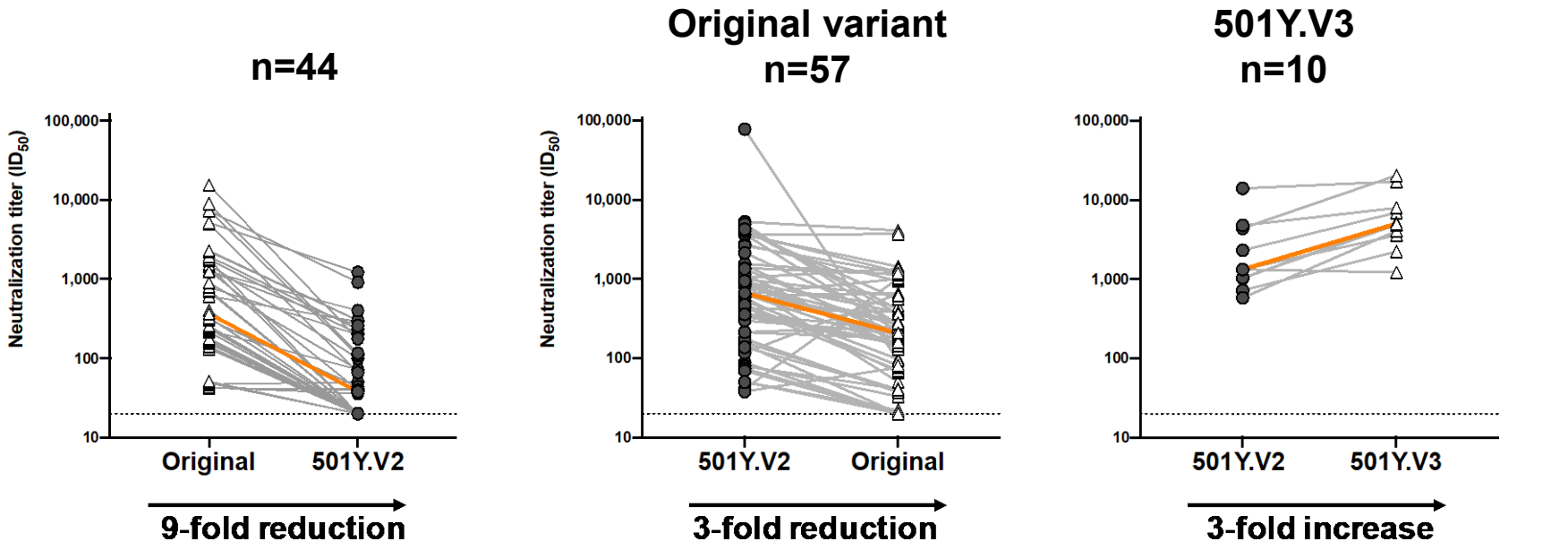


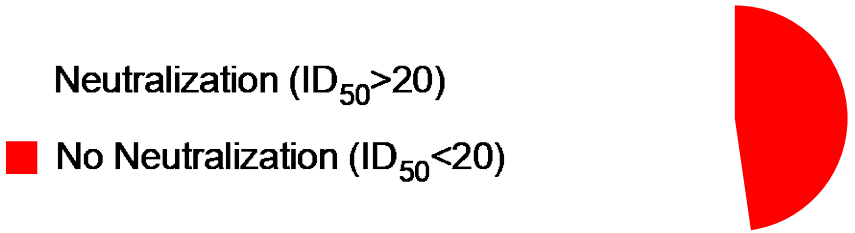
Moyo-Gwete, Madzivhandila et al, NEJM, in revision

Are neutralizing antibodies to 501Y.V2 cross-reactive?

Infected with original variant

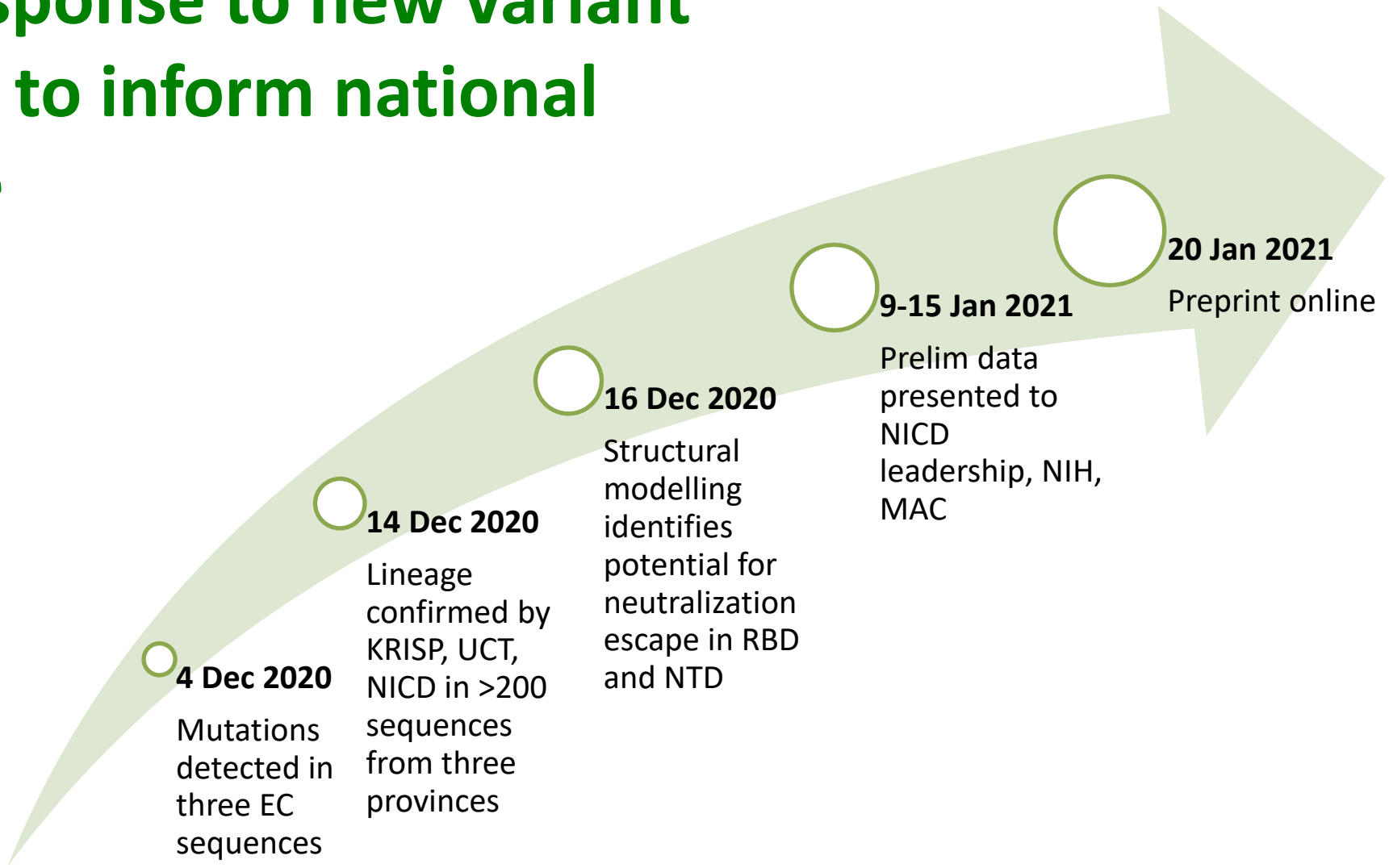
infected with 501Y.V2





Moyo-Gwete, Madzivhandila et al, NEJM, 2021

Rapid response to new variant essential to inform national response



<50 days days to preprint after identification of the VOC

Wibmer *et al*. Nature Medicine, 2021

Conclusions

- The 501Y.V2 variant shows substantial or complete escape from:
  - Three classes of therapeutically relevant monoclonal antibodies
  - Neutralizing antibodies in COVID-19 convalescent plasma
  - Vaccinee sera, including ChAdOx1-nCoV19
- Sera from 501Y.V2 infections show cross-reactivity, neutralizing the original variant and 501Y.V3 (P.1)
- Positive implications for vaccine design as developers move to incorporate other spikes into existing platforms

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Shabir Madhi and
ChAdOx team

501Y.V2 consortium of South African scientists, chaired by Drs W Hanekom and Dr T De Oliveira

Clinical teams and participants

Immune escape and evidence of re-infection by P.1

Ester Sabino, MD, PhD

U Sao Paulo

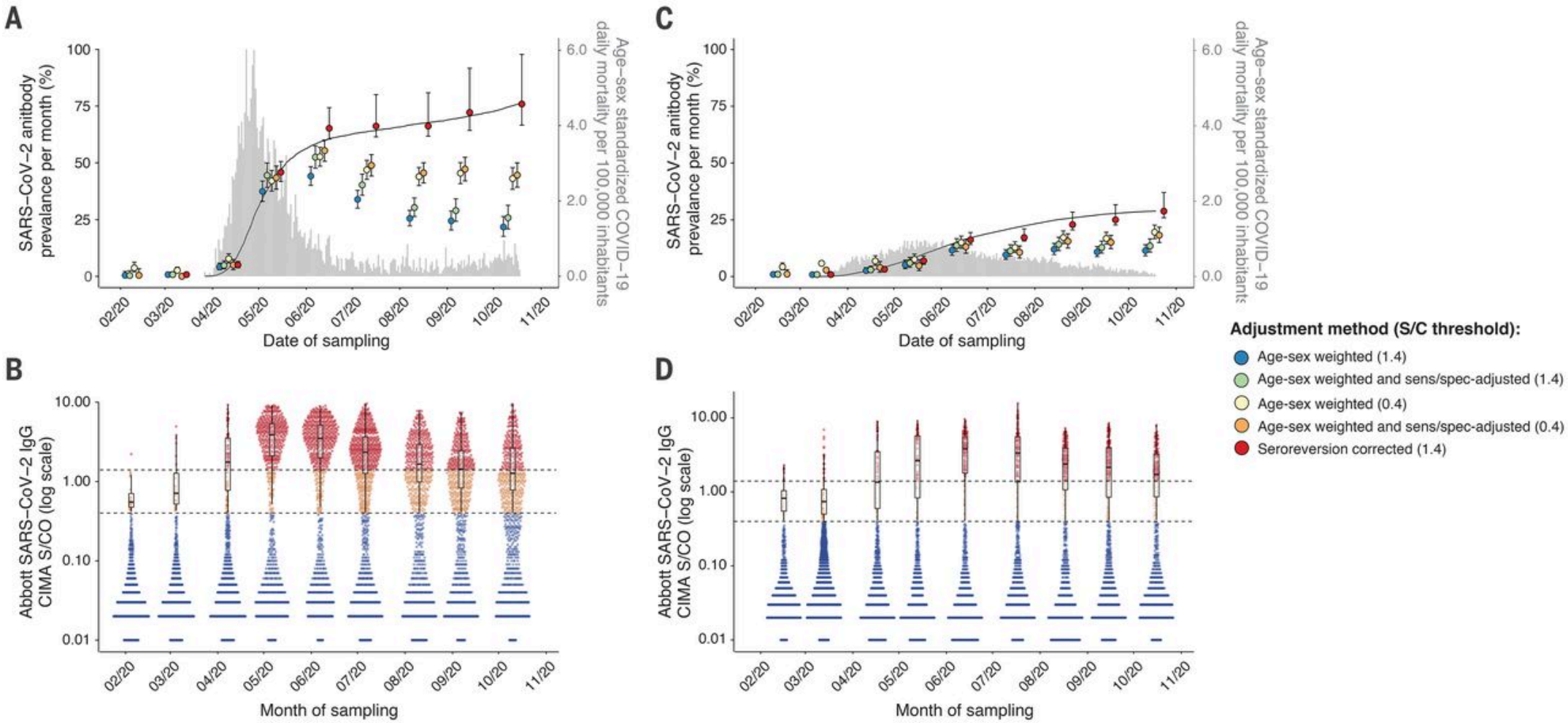
Immune escape and evidence of reinfection by P1

Ester C Sabino, MD, PhD

Instituto de Medicina Tropical

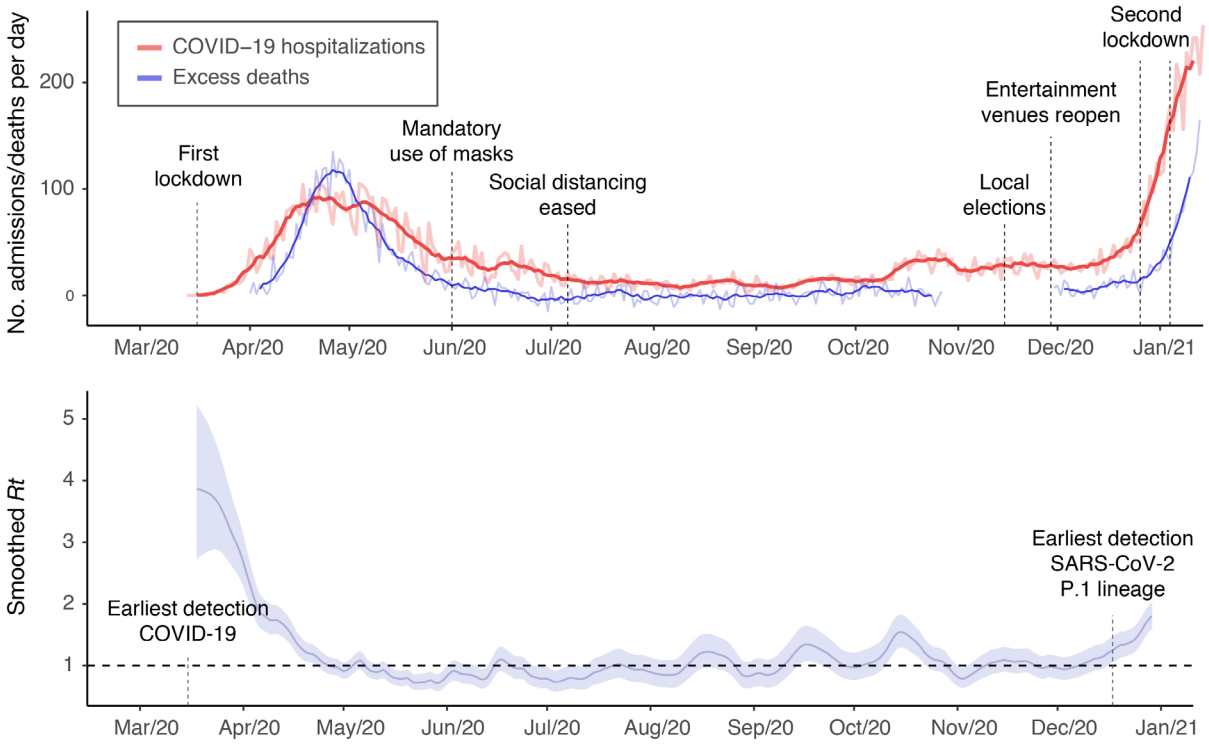
Faculdade de Medicina da Universidade de Sao Paulo

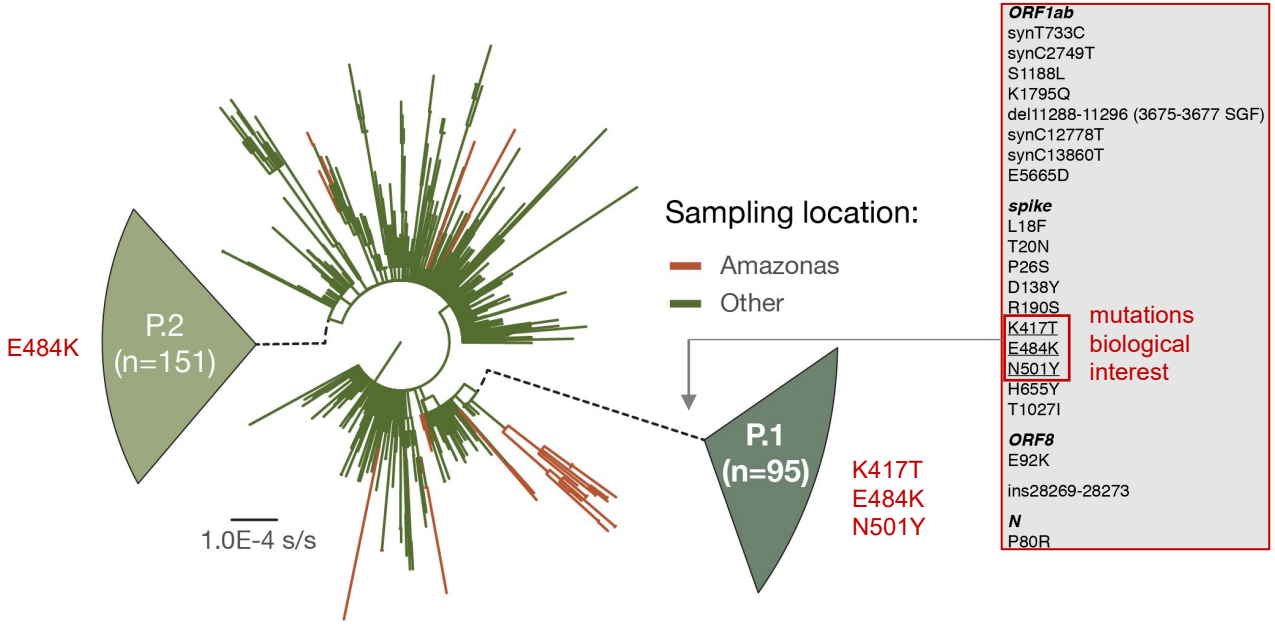
Monthly antibody prevalence and signal-to-cutoff (S/C) reading in Manaus and São Paulo.



Lewis F. Buss et al. Science 2021;371:288-292

Resurgence of SARS-CoV-2 in Manaus, despite seroprevalence

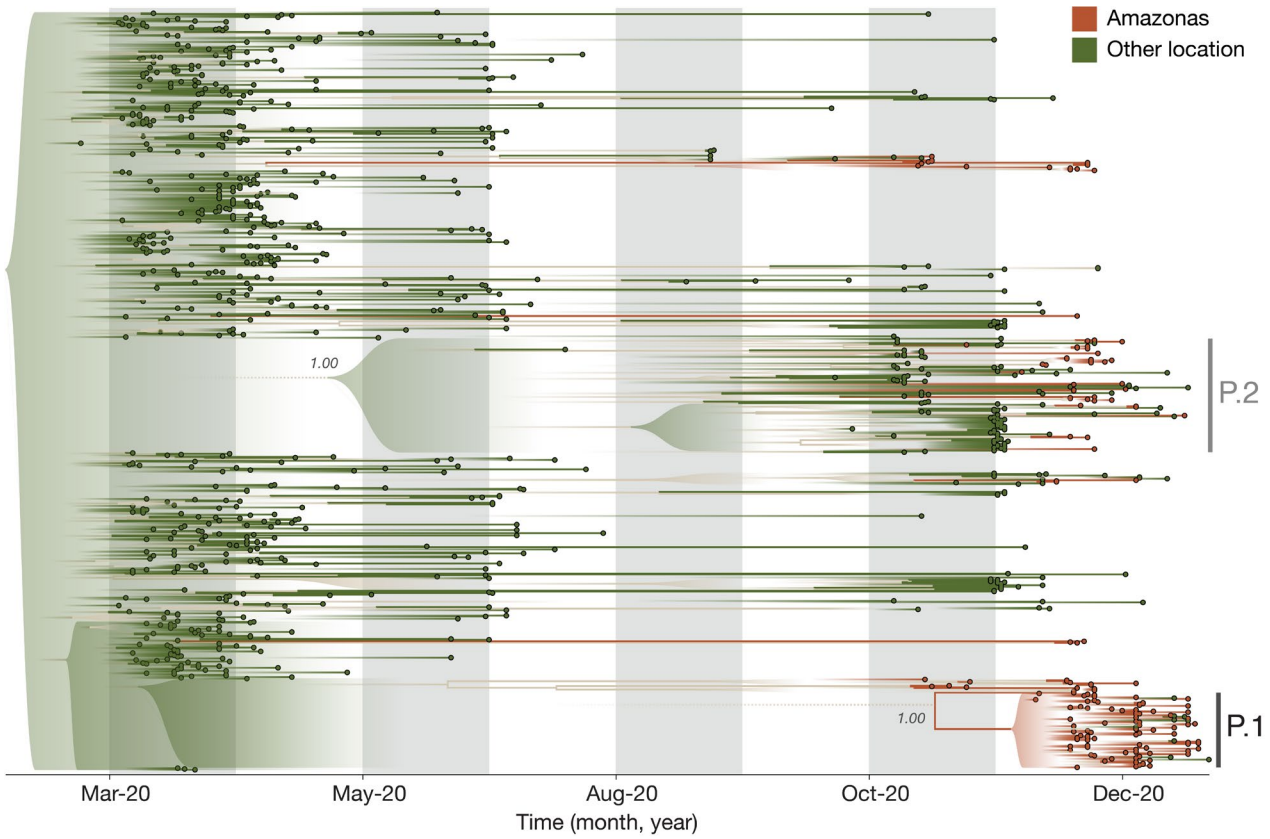




Identification of P.1 in Manaus

Dating the emergence of P.1 lineage

P.1 emerged around 6 Nov 2020 (95% BCI, 9 Oct – 30 Nov 2020)

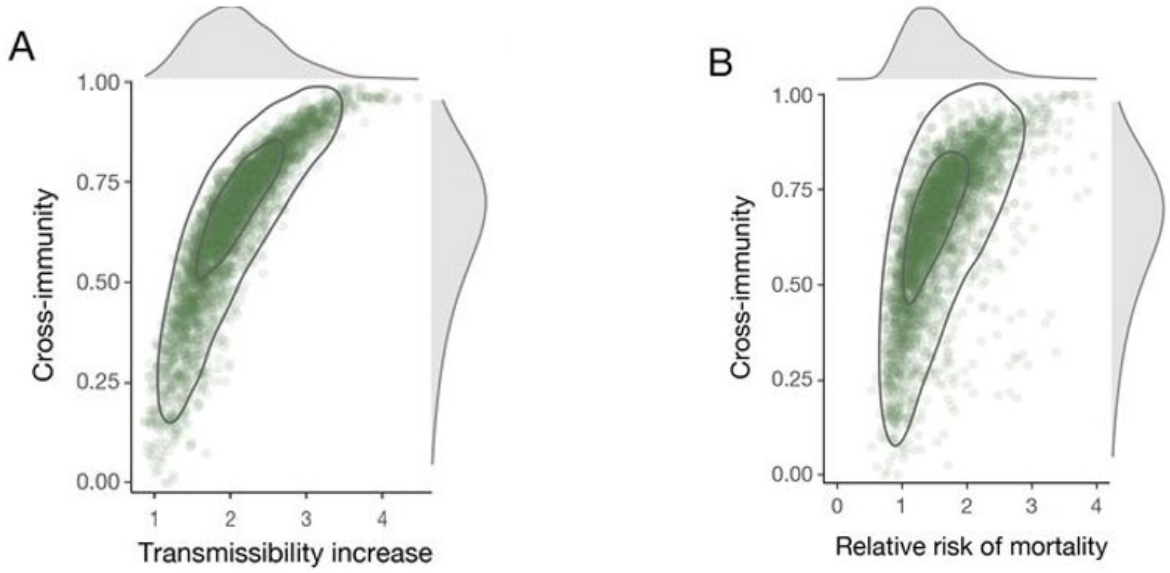


Faria et al. https://science.sciencemag.org/content/early/2021/04/13/science.abh2644
Naveca et al https://www.researchsquare.com/article/rs-275494/v1

Altered epidemiological characteristics of P.1 lineage in Manaus

Two-category mathematical model to investigate transmissibility, immune evasion and disease severity of P.1 lineage in Manaus:

- P.1 is 1.7–2.4 more transmissible compared to non-P1 lineages in Manaus
- Previous (non-P.1) infection provides 54–79% of the protection against infection with P.1 that provides against non-P.1



Faria et al https://science.sciencemag.org/content/early/2021/04/13/science.abh2644

How to detect rates of reinfection

- Data from the notification was not made available in a way that the same individual can be identified
- Very few people were tested by PCR in Manaus. Most people were confirmed by antibody testing.

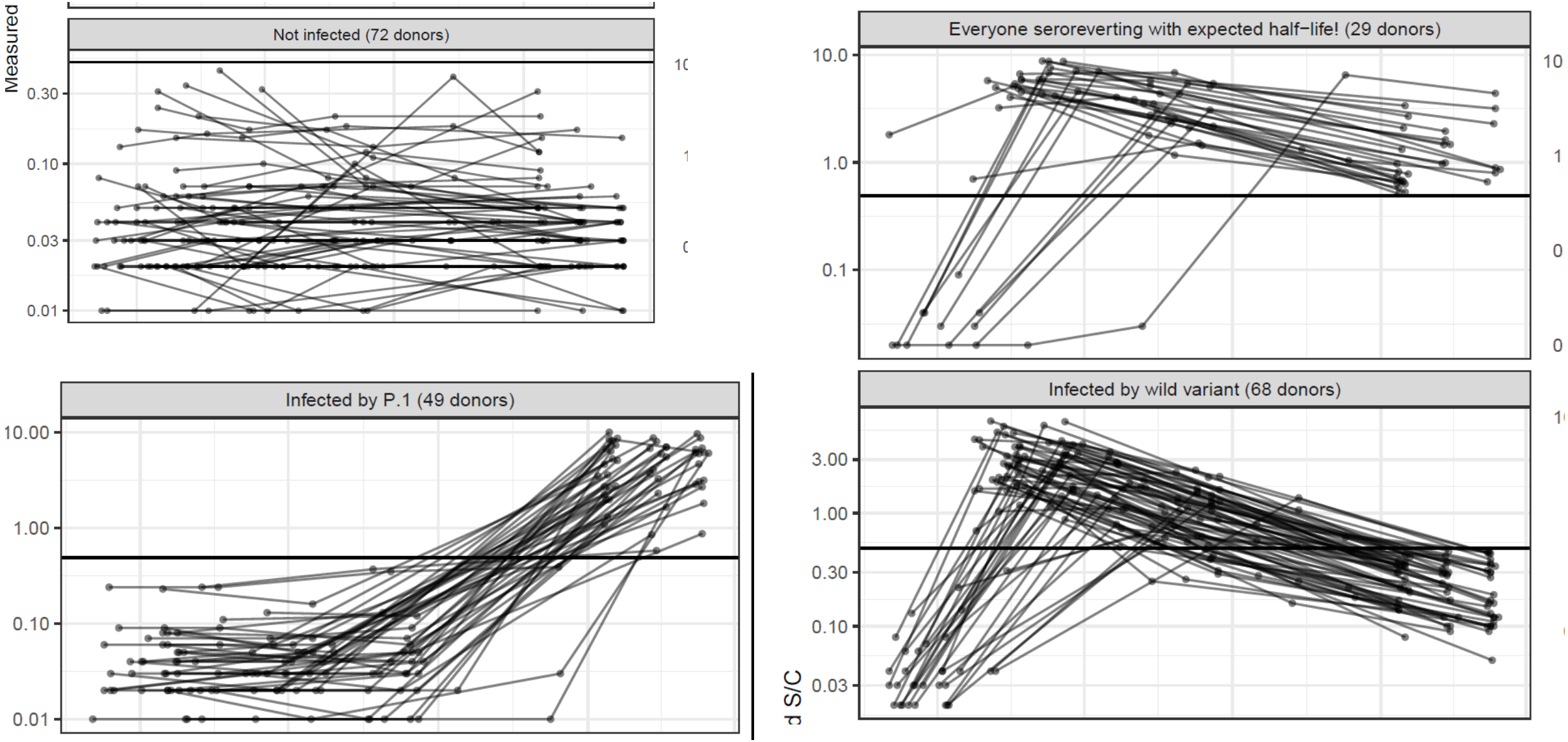
- Using repeat donor & a test that decline over time we hypothesized that reinfection would induce “boosting” of circulating IgG antibody giving a V-shaped time series of antibody titer.

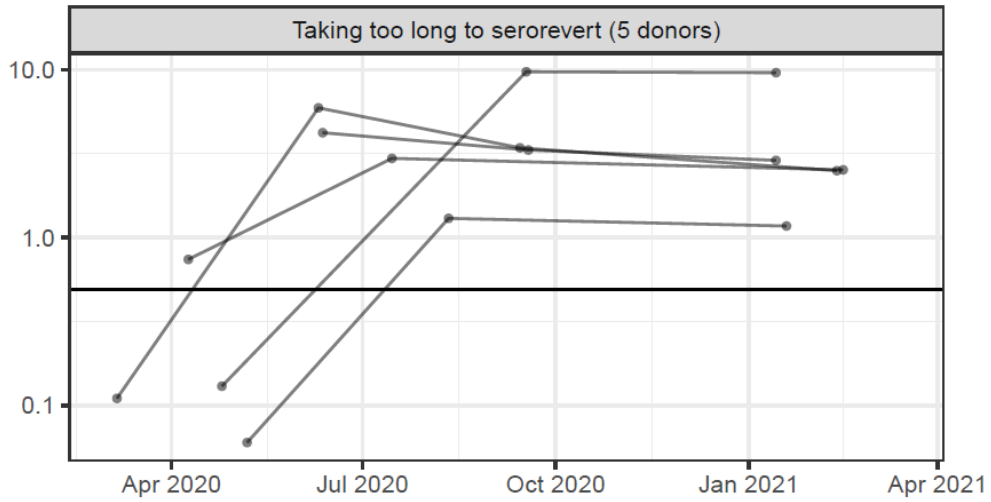
Criteria for Informative Repeat Donors

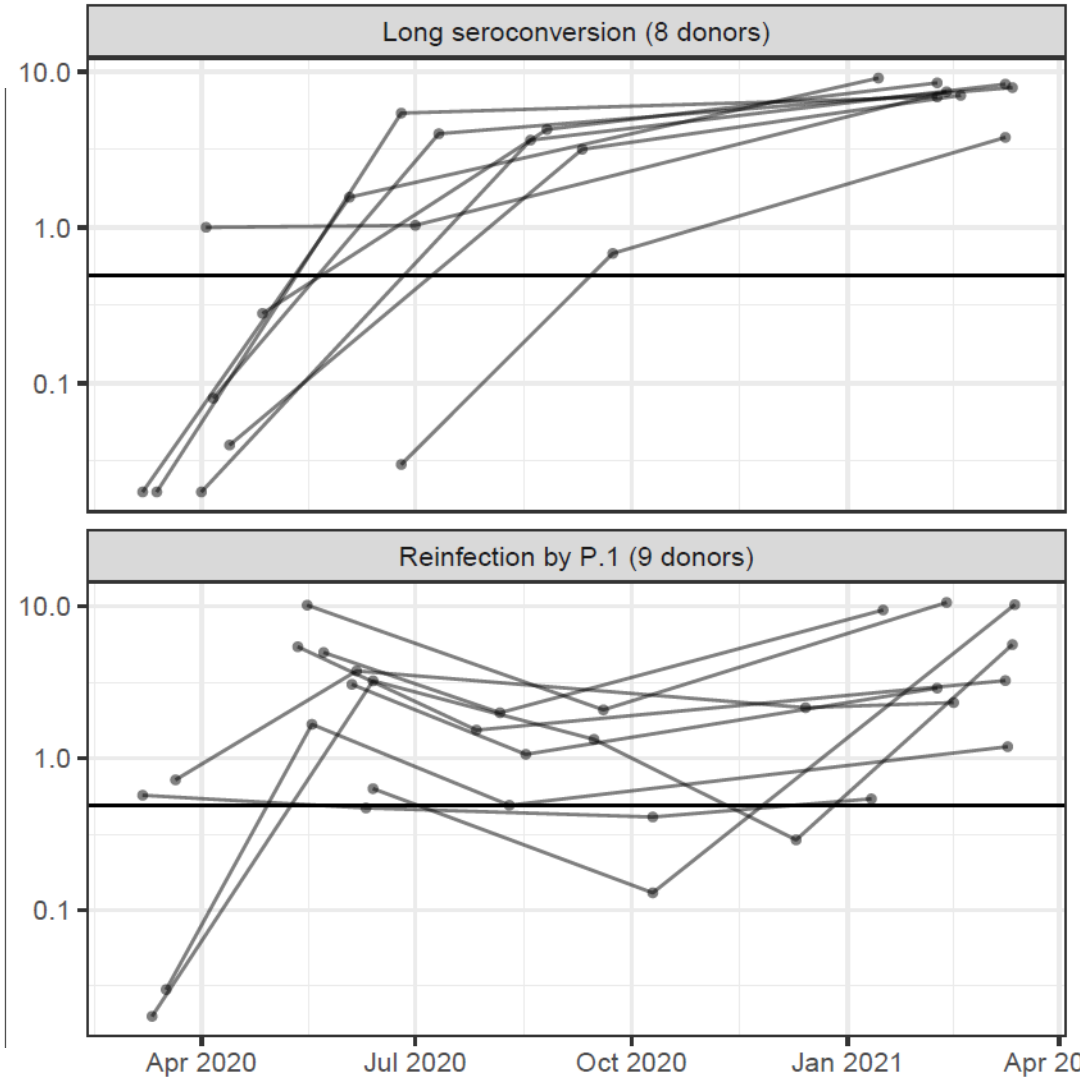
2747	Repeat donors with more than one donation from April 1st to March 31st
271	Repeat donors with 3 donations: at least one during April 1st –June 30, 2020 and one during Jan 1st –March 31st 2021
240	Not vaccinated

Classification : 240 repeat blood donors

GROUPS	N	RULES
1. Persistently seronegative – no evidence of infection	72	No results >0.49 S/C
2 Primary infection by P.1	49	All results <=0.49 in periods 1 and 2. At least one result > 0.49 in period 3
3.1 Primary infection by wild type variant but not P1	68	At least one result > 0.49 in period 1 or 2. All results <=0.49 in period 3
3.2 Primary infection by wild type and reinfection by P1 unlikely	29	One result > 0.49 in period 1 or 2. Antibody level in period 3 is compatible with antibody decline
4.1 Primary infection by wild type and suggestive of reinfection by P.1	9	One result > 0.49 in both periods 1 and 3, and an intermediate result with value below these two readings (V-shaped S/C time series)
4. 2 Primary infection by wild type and probable reinfection by P.1	13	One result > 0.49 in periods 1 or 2. Antibody level in period 3 is incompatible with the expected rate of antibody decline


Measured
Not infected (72 donors)
0.30
0.10
0.03
0.01
Everyone seroreverting with expected half−life! (29 donors)
10.0
1.0
0.1
Infected by P.1 (49 donors)
10.00
1.00
0.10
0.01
Infected by wild variant (68 donors)
3.00
1.00
0.30
0.10
0.03
d S/C


Taking too long to seroreverted (5 donors)
10.0
1.0
0.1
Apr 2020
Jul 2020
Oct 2020
Jan 2021
Apr 2021


Long seroconversion (8 donors)
Reinfection by P.1 (9 donors)
10.0
1.0
0.1
Apr 2020
Jul 2020
Oct 2020
Jan 2021
Apr 20

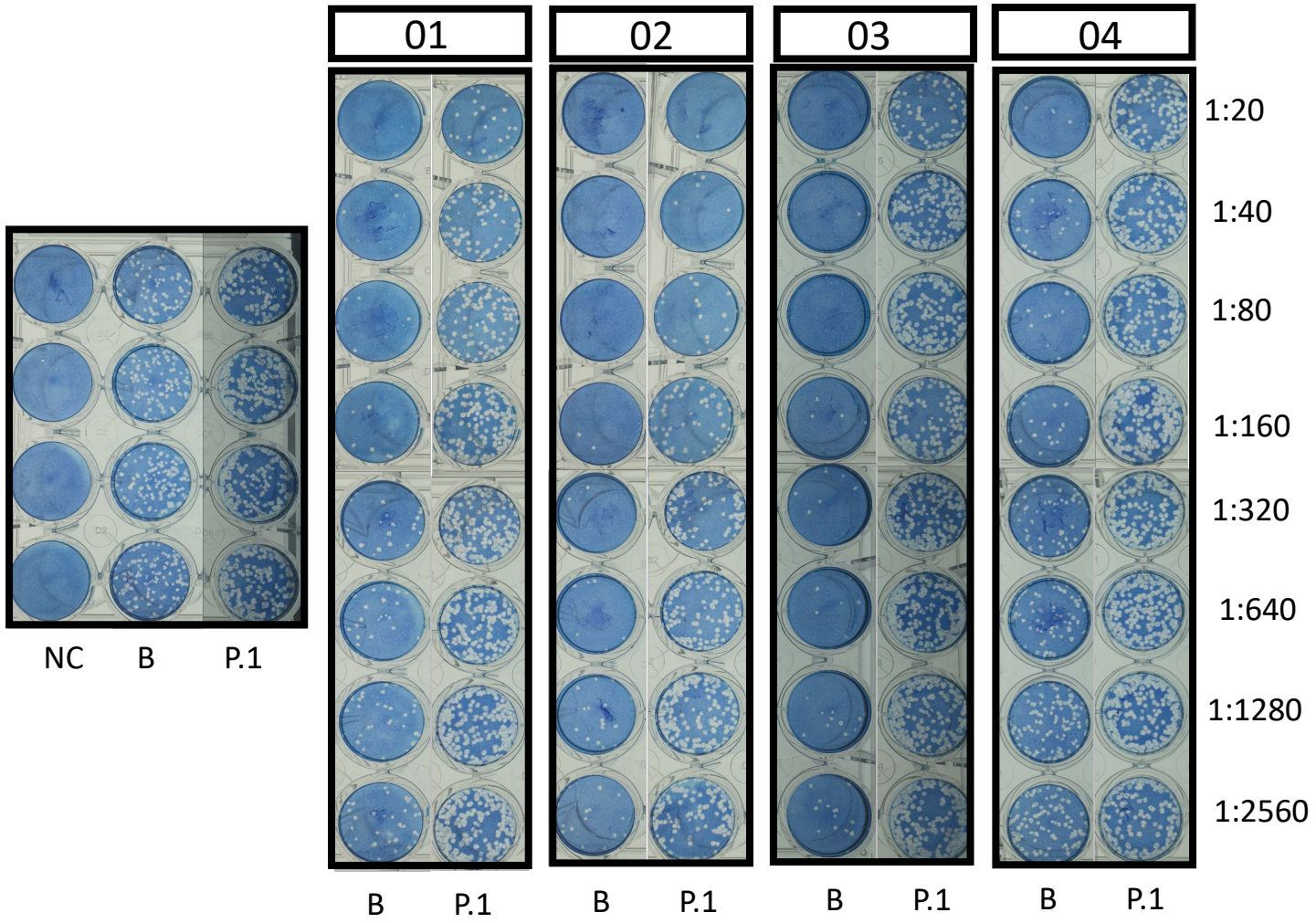
Conclusion

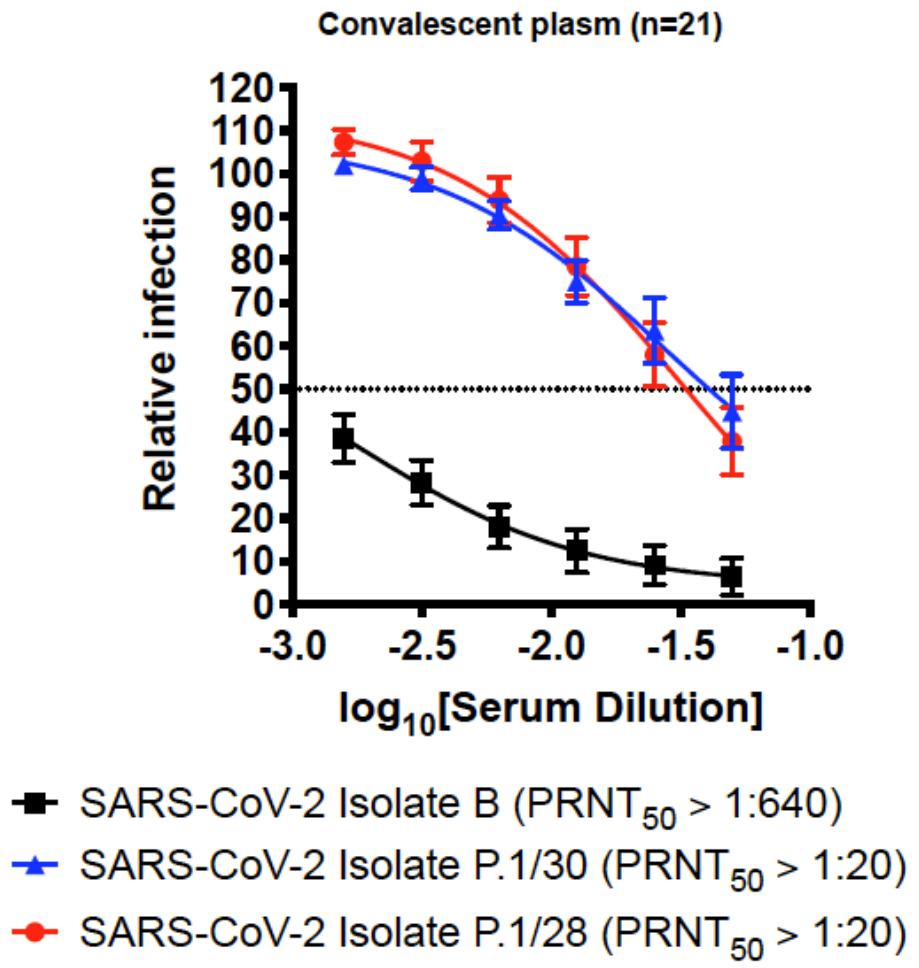
- Out of all infections in period 3, reinfections = 31% or 15.5% if a more restrictive definition is assumed for reinfection (V curve)

- Individuals that had a primary infection in period 1 or 2 had 24.3% or 10.0% (V curve) chance of being re-infected by P1

- Non-reactive individuals had a chance of 40.5% of becoming infected by P.1.

Does neutralizing antibodies elicited by previous SARS-CoV-2 infection can neutralize P.1 isolates?
Dr Modena (UNICAMP)

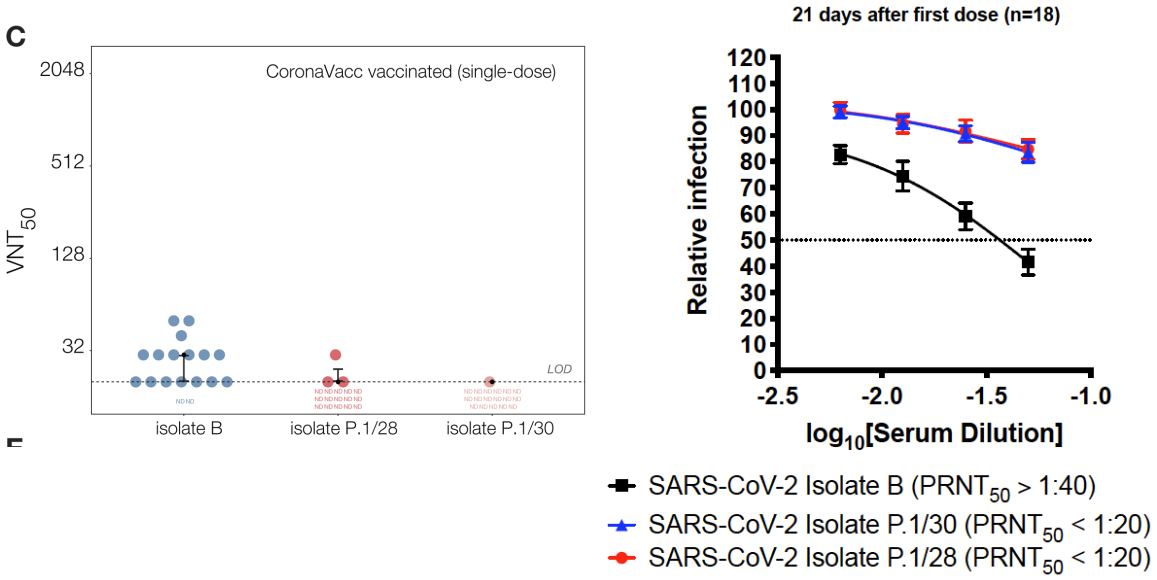




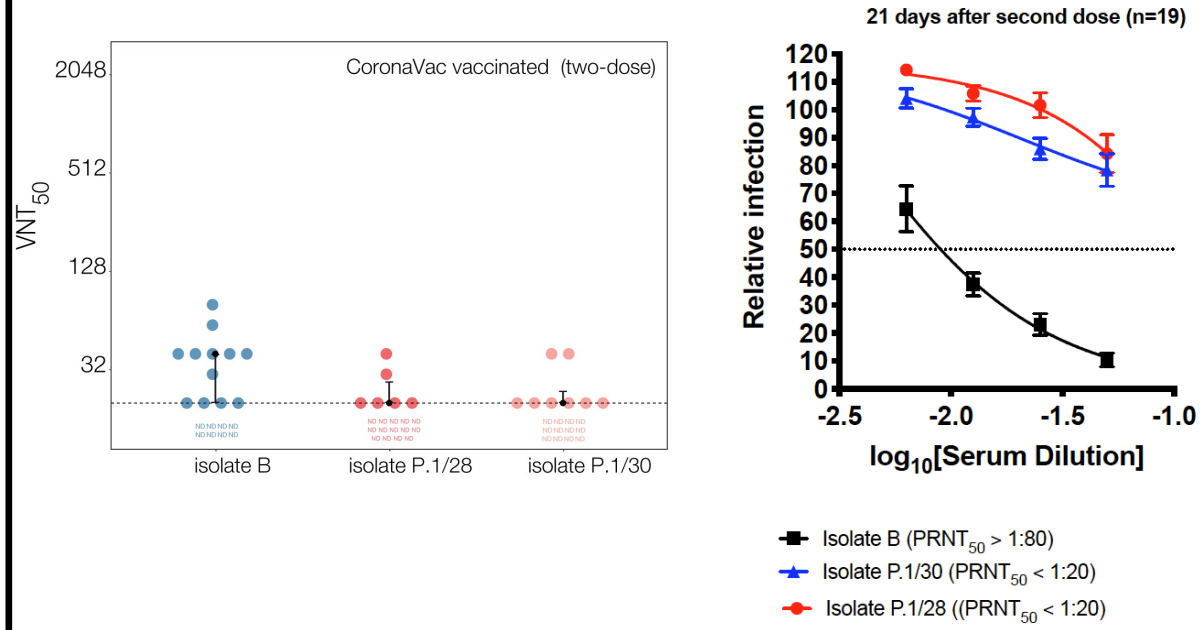
Our data suggest that P.1 lineage is able to escape from
neutralizing antibody responses generated by prior SARS-CoV-2 infection

Does neutralizing antibodies elicited by CoronaVac vaccined can neutralize P.1 isolates?

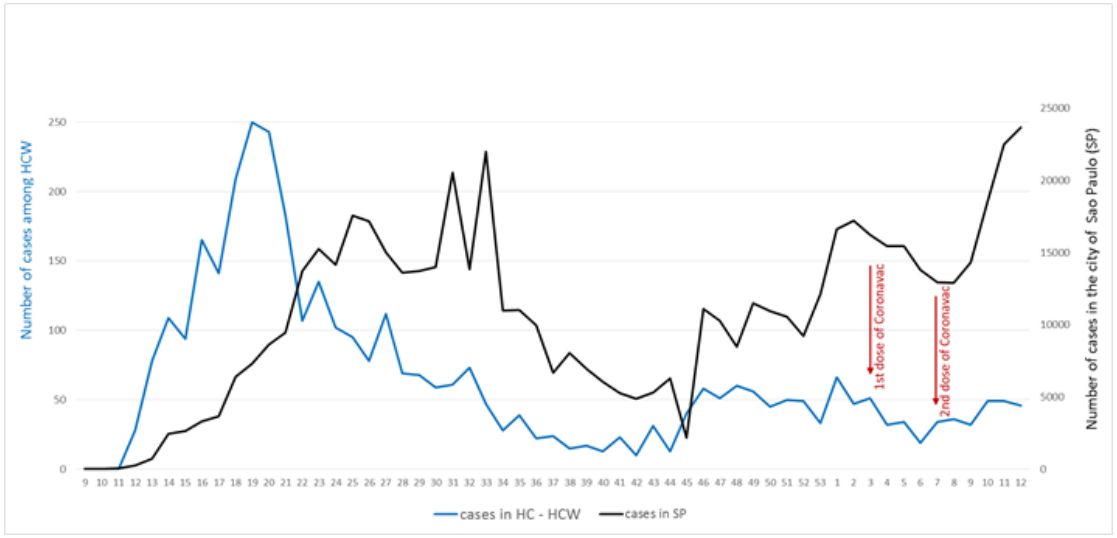
CoronaVacc vaccinated (single dose) plasma, n=18, VNT and PRNT assays

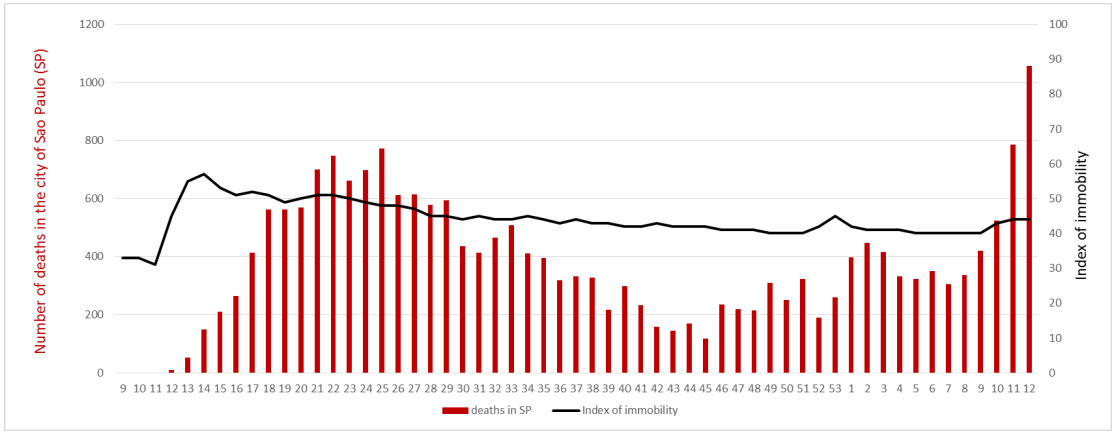


CoronaVacc vaccinated (two doses) plasma, n=20, VNT assays



These results show that the titers of neutralizing antibodies induced by an inactivated SARS-CoV-2 vaccine (i.e., CoronaVac) is **low after first and second dose against the two variants**





Hospital das Clínicas, USP
Tertiary care, teaching hospital with 2,200 beds
Dr Anna Levin (USP)

- Approximately 30,000 HCW

- 1st dose: 22,402 HCW (epi week 3: 18-21 January, 2021)
- 2nd dose: 21,652 HCW (epi week 7: 14-16 February, 2021)

Table 1: Number of cases of COVID-19 in healthcare workers (HCW) of Hospital das Clinicas (HC), and predicted cases in HCW based on the reported cases in the city of São Paulo, after vaccination with CoronaVac

Epi week 2021	Number of cases, city of São Paulo	Number of cases among HC HCWs		Prediction interval (95%)	
		Observed	Predicted	Inferior limit	Superior limit
3 (1st dose)	16,232	51	79.5	59.0	108.0
4	15,432	32	73.0	55.0	94.1
5	15,460	34	73.2	53.0	97.0
6	13,788	19	61.2	45.0	80.0
7 (2nd dose)	12,954	34	56.0	42.0	72.0
8	12,906	36	55.7	40.0	74.0
9	14,332	30	64.9	47.0	85.0
10	18,536	49	101.6	71.0	147.0
11	22,511	49	155.2	102.0	267.1
12	23,889	46	175.6	110.0	317.1

Centre for Arbovirus
cadde
Discovery, Diagnostics, Genomics & Epidemiology

USP
Universidade de São Paulo

PER ARDUA AD ALTA

UNIVERSITY OF OXFORD

SCIENTIA

FAPESP
FUNDAÇÃO DE AMPARO À PESQUISA DO ESTADO DE SÃO PAULO

MRC | Medical Research Council

todos pela saúde

REDS-IV-P
Optimizing Transfusion Across the Lifespan
NHLBI/NIH

Immunity from vaccines against SARS-CoV-2 B.1.1.7

Ravi Gupta,
U. Cambridge

Immunity from vaccines against SARS-CoV-2 B.1.1.7

Ravi Gupta
Professor of Clinical Microbiology
Cambridge Institute for Therapeutic Immunology
and Infectious Diseases
April 2021 COVAX Meeting

COG UK
COVID-19 GENOMICS UK CONSORTIUM

CITIID

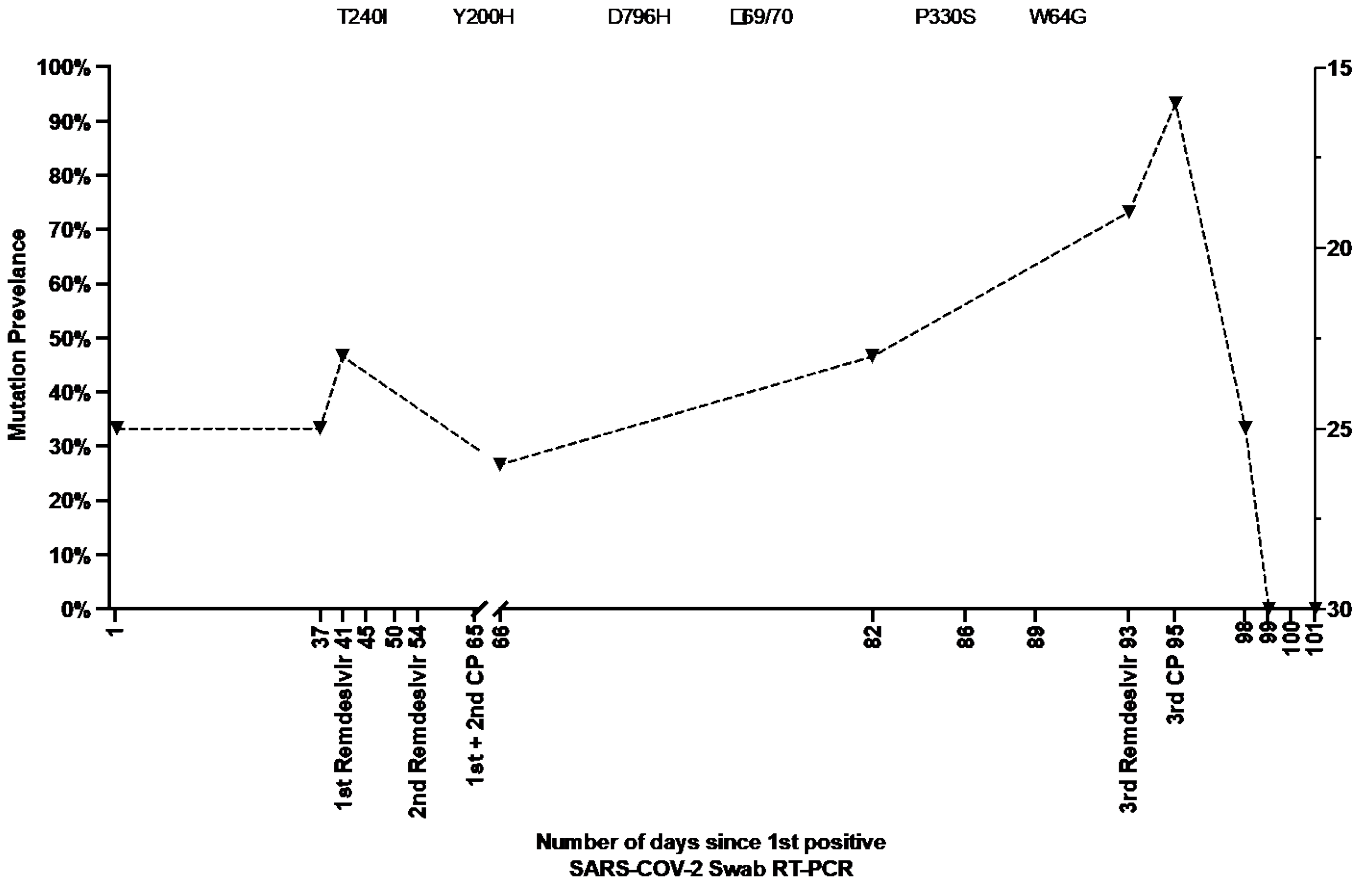
UNIVERSITY OF CAMBRIDGE

Introduction: SARS-Cov-2 mutation

- Mutation rate globally estimated at 2 per month
- Short incubation period, asymptomatic transmission
- Rapid cell infection turnover ‘hit and run’
- All these contribute to relatively low selection pressure

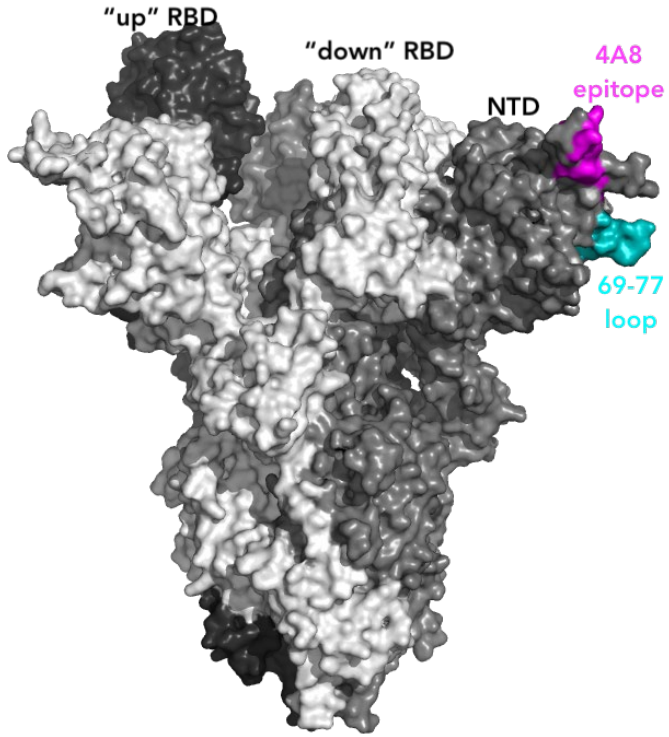
Chronic COVID-19 and Variants

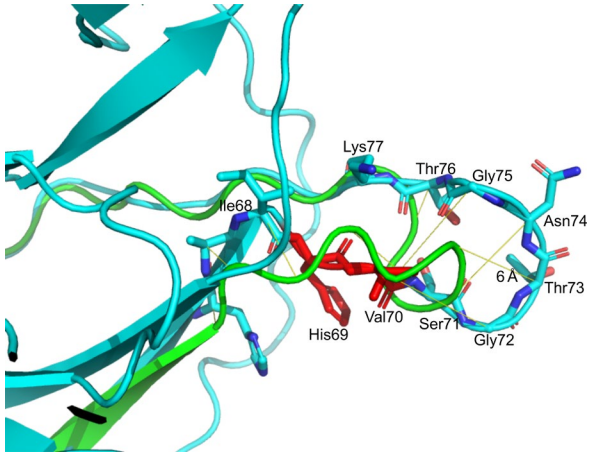
- Chronic infection/shedding recognized as an entity by mid 2020.
- Key features include Spike RBD mutations, NTD deletions
- **Are these individuals the source of Variants of Concern?**

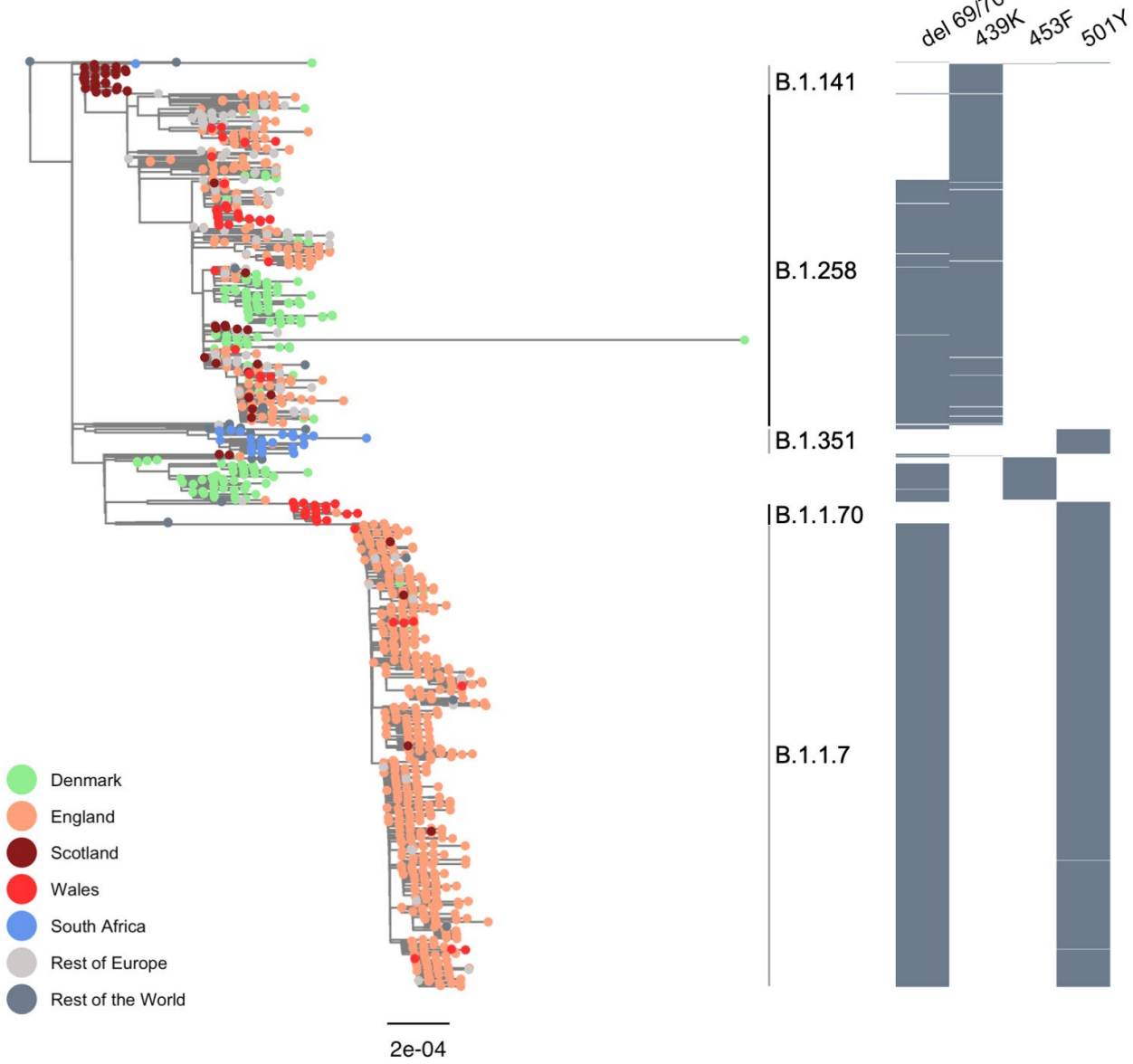


Kemp et al, Nature 2021

Spike Deletion H69V70



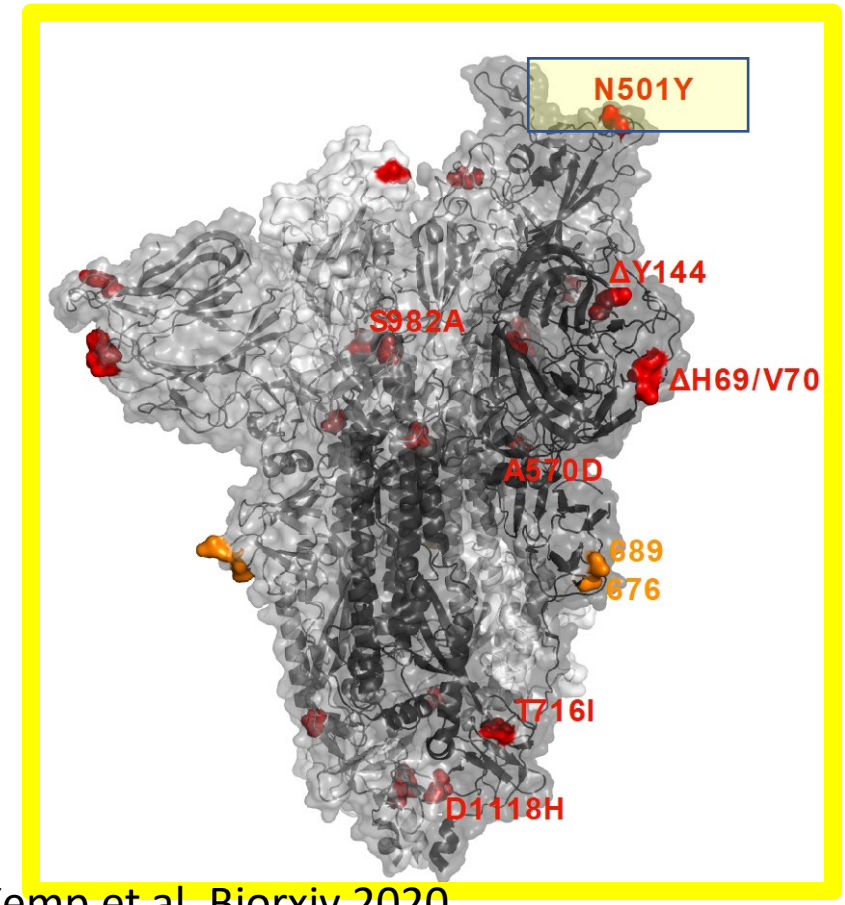




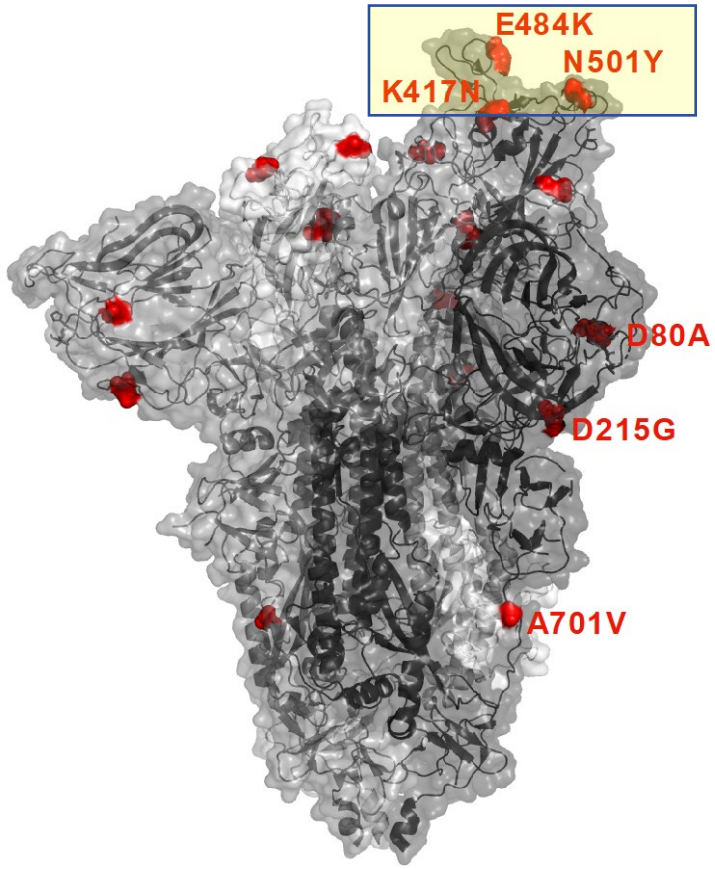
Kemp et al, Biorxiv 2020

Three main variants of concern (VOC)

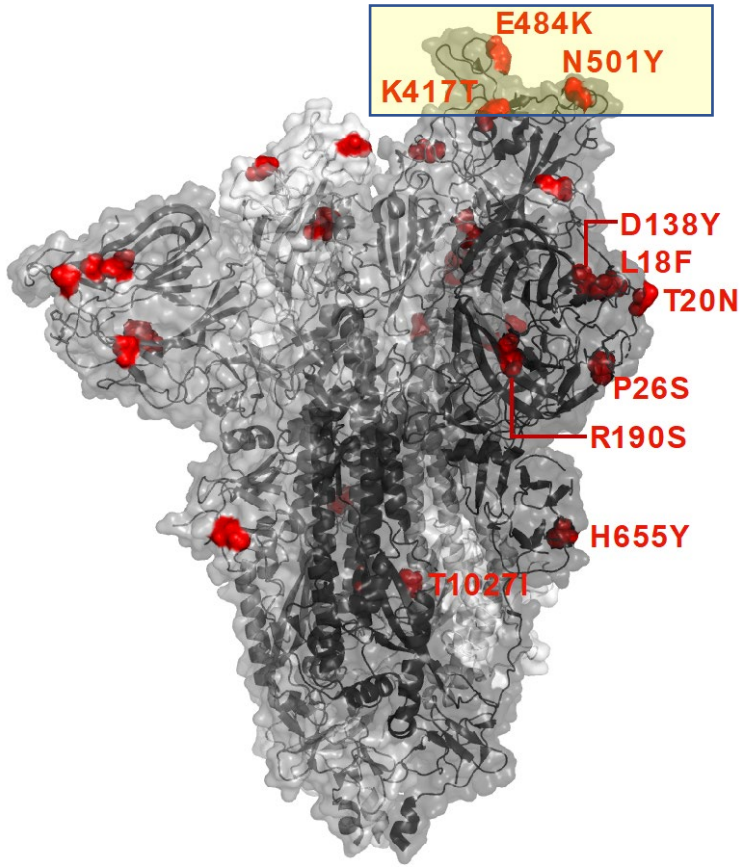
B.1.1.7
501Y.V1. - UK



B.1.351
501Y.V2 – South Africa

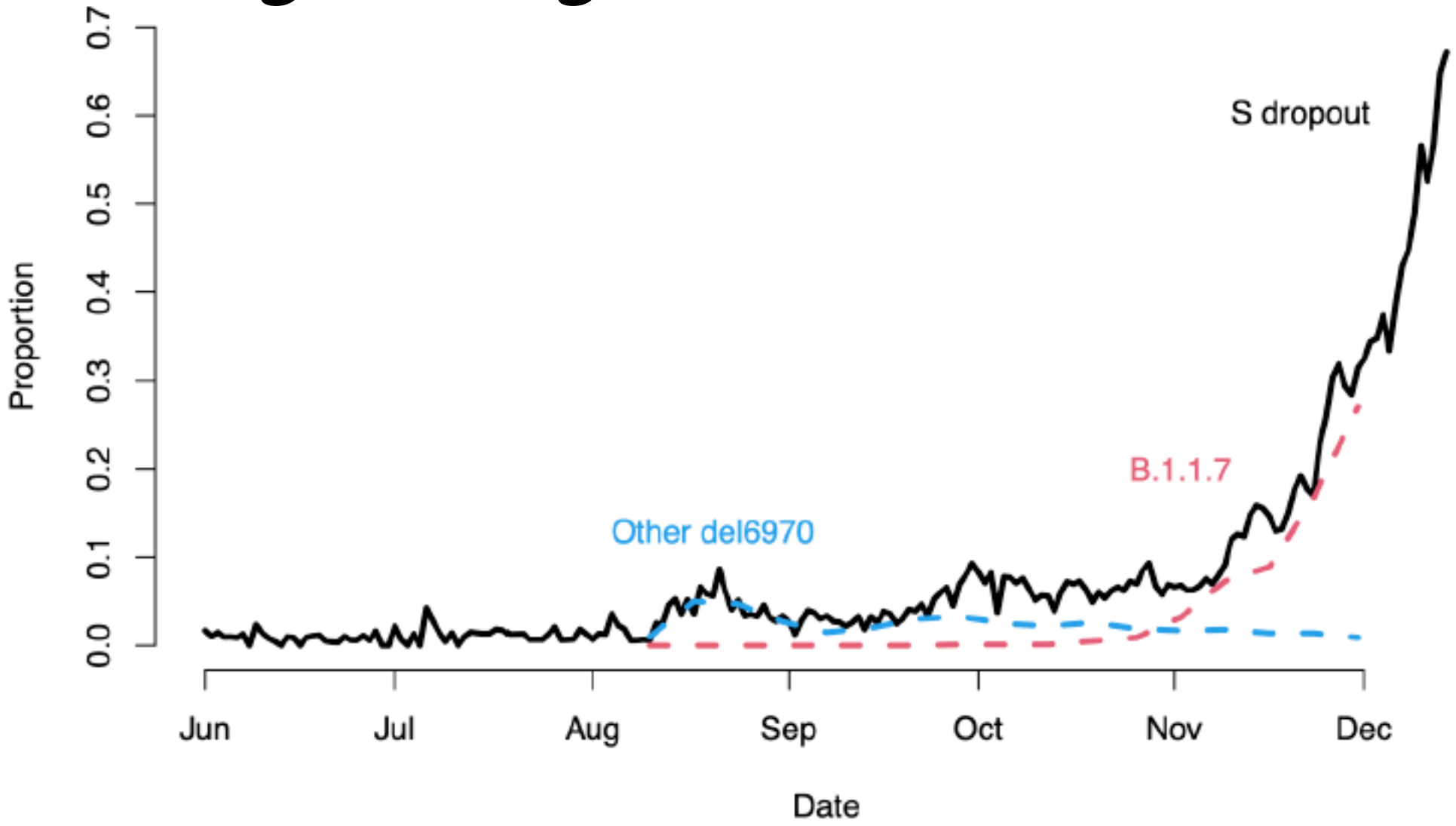


P.1
501Y.V3 - Brazil



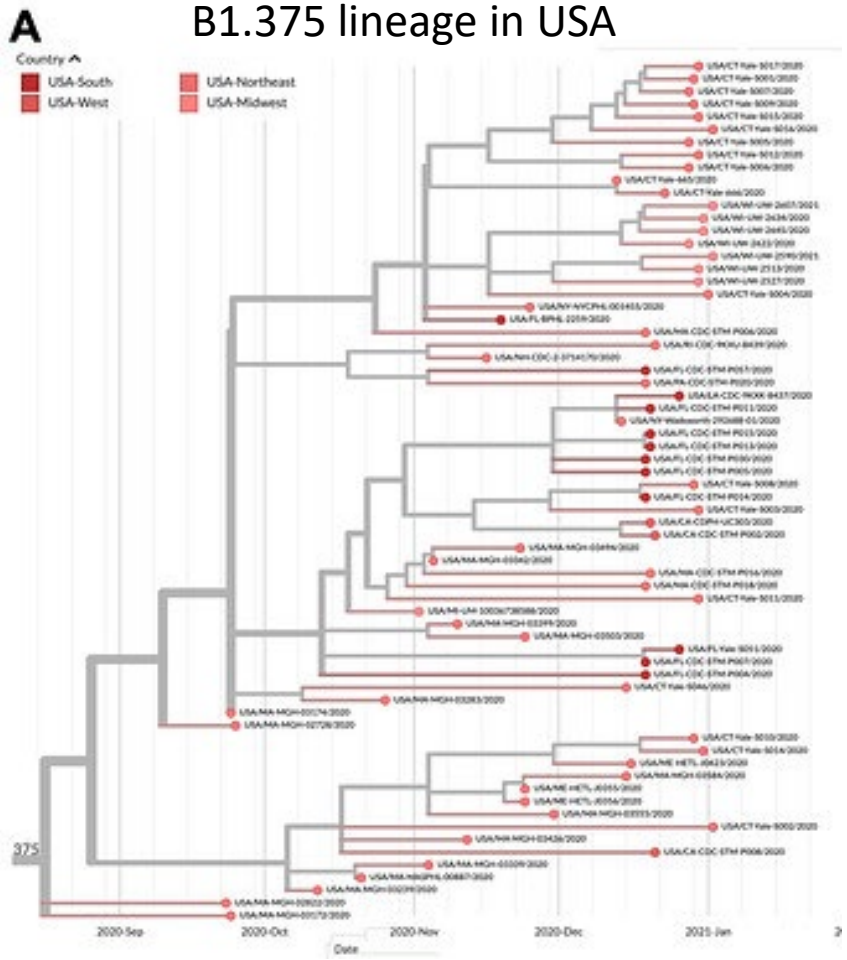
Kemp et al, Biorxiv 2020

S gene Target Failure and B.1.1.7

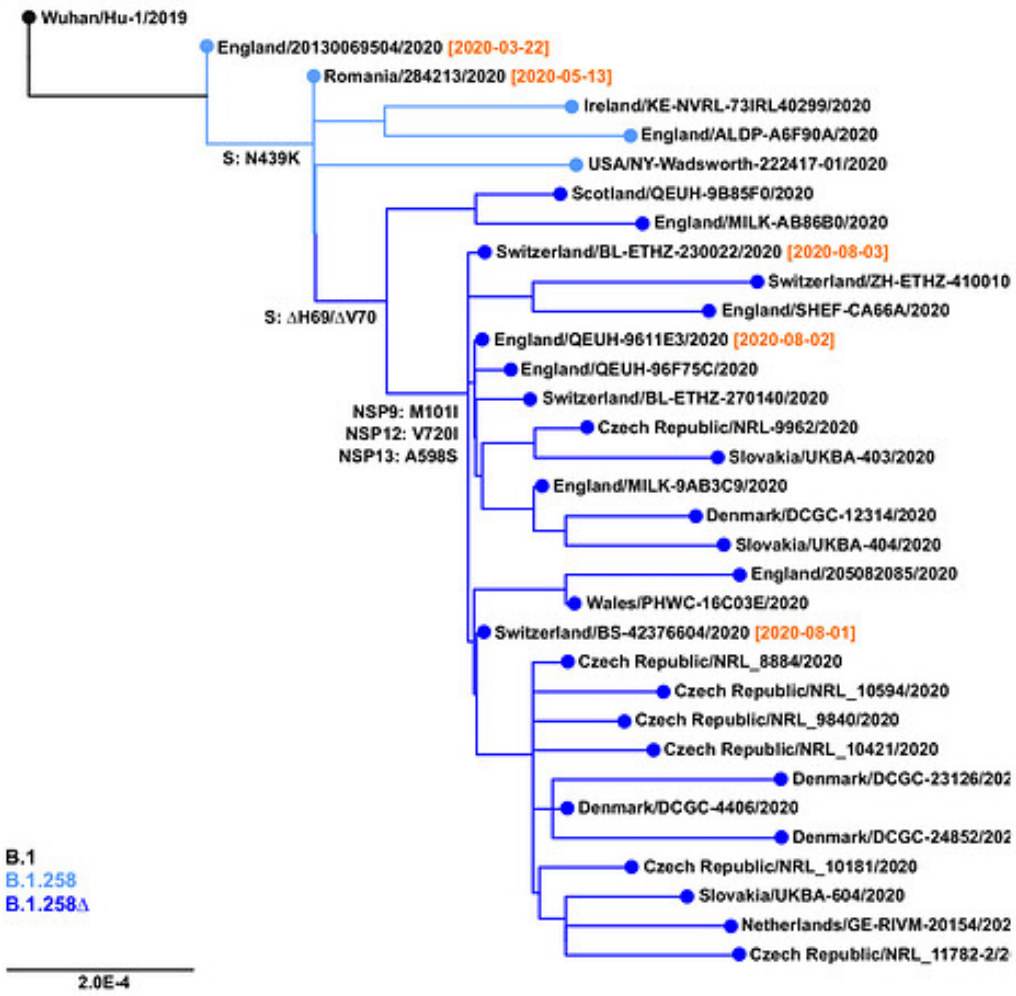


Caution against assuming SGTF = B.1.1.7

B1.375 lineage in USA

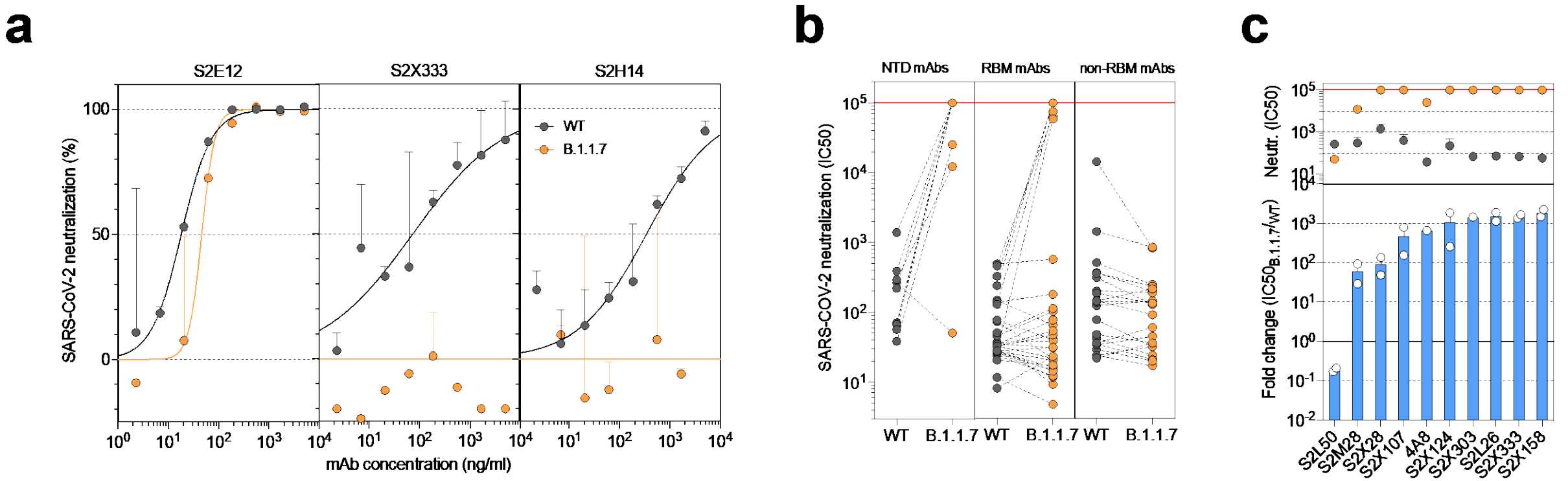


Larsen et al, Virologica 2021



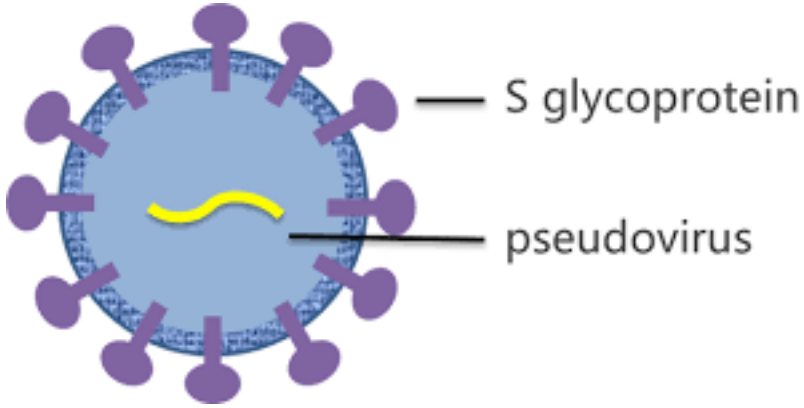
Brejova et al, Virological 2021

Monoclonal antibodies and B.1.1.7

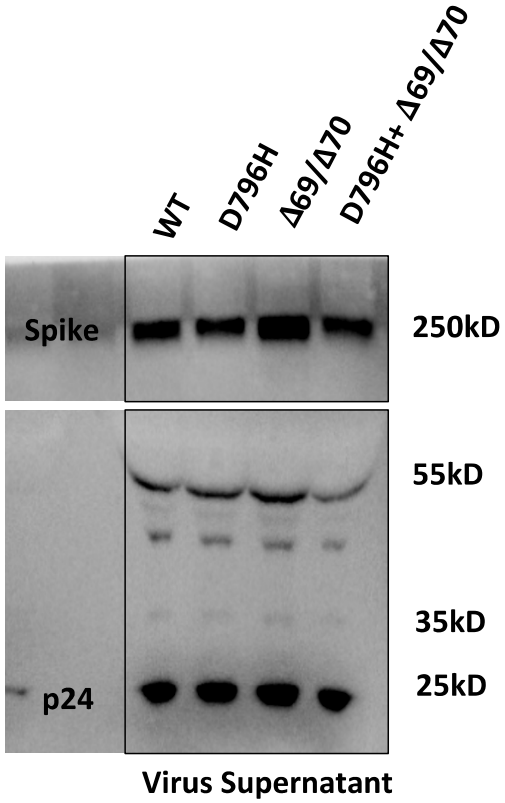


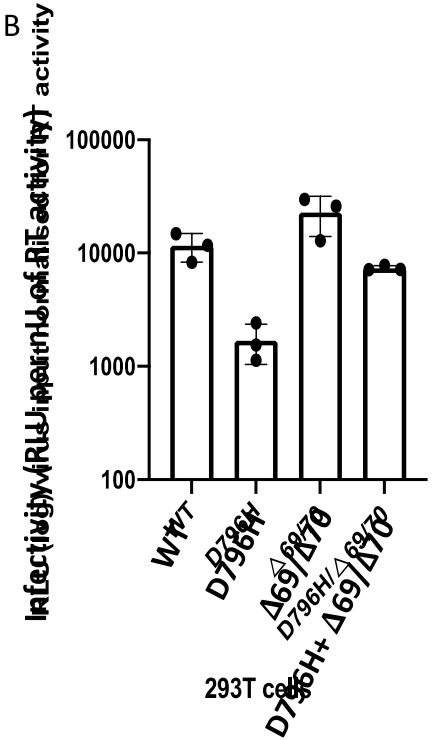
Collier et al, Nature 2021

Spike Mutations and Infectivity of pseudoviruses bearing Spike



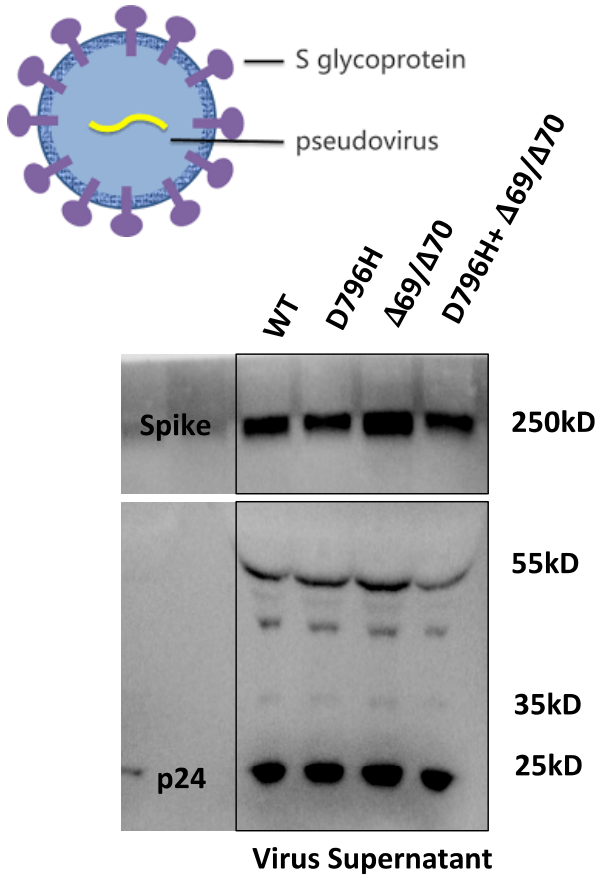
Virus input normalized for RT activity

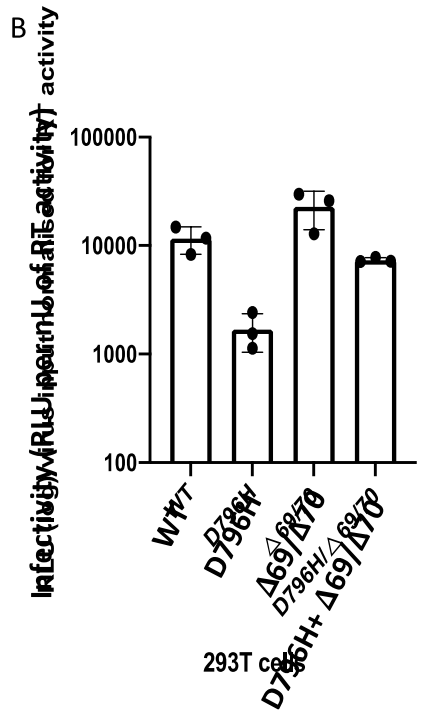




UNIVERSITY OF CAMBRIDGE

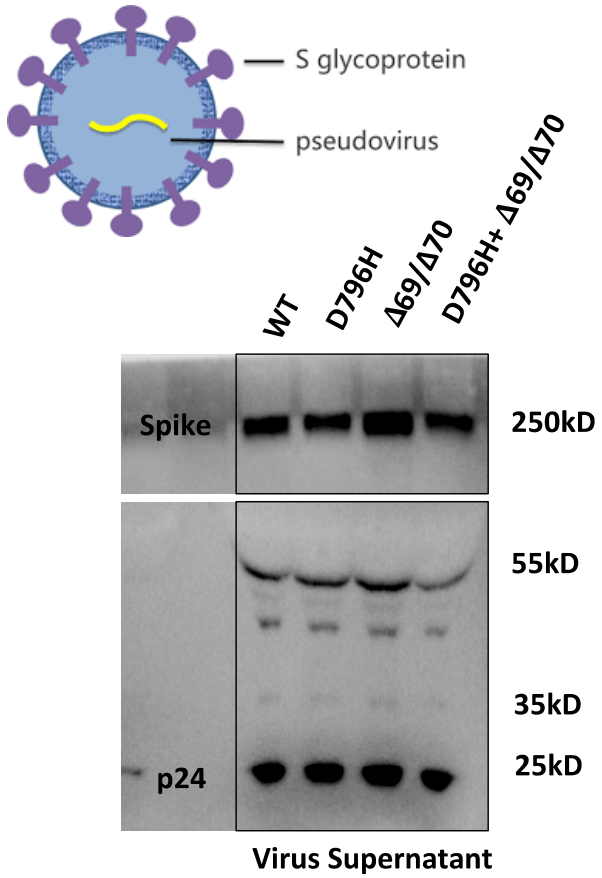
In vitro efficacy of Pfizer vaccine sera v B.1.1.7

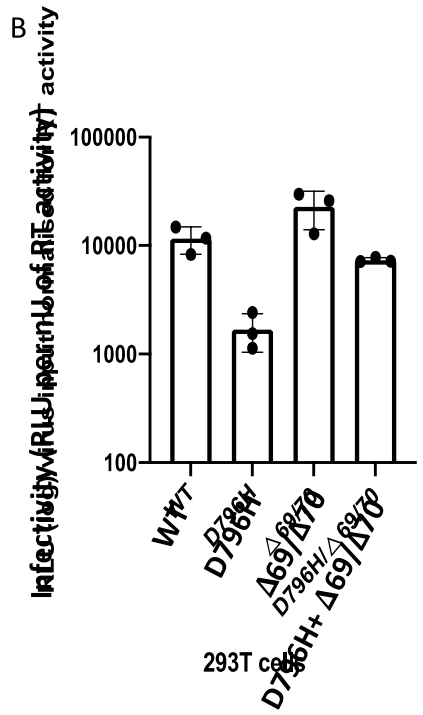


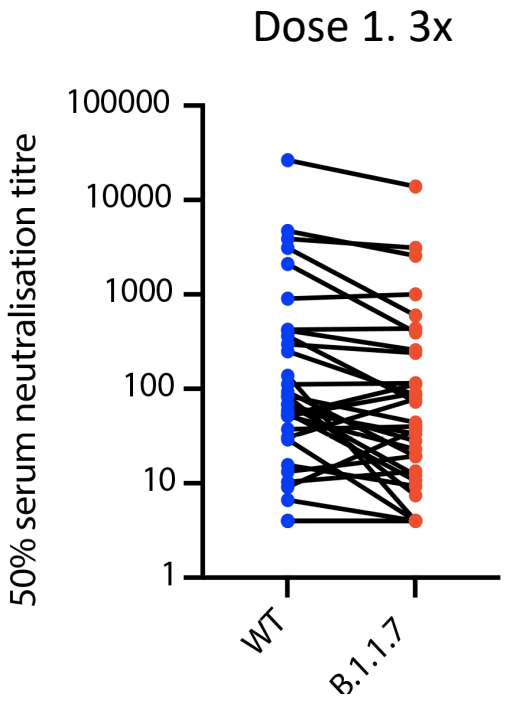


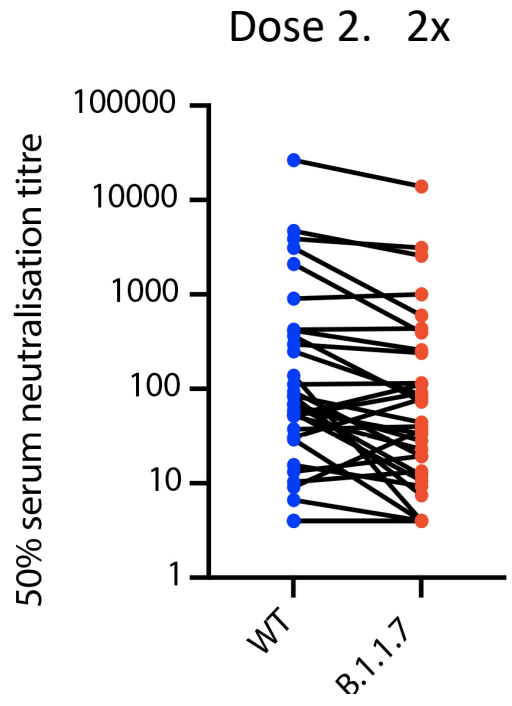
Collier et al, Nature 2021; Muik et al, Science 2021, Wang et al, Nature 2021; Shen et al, CHM 2021 and others

In vitro efficacy of Pfizer vaccine sera v B.1.1.7



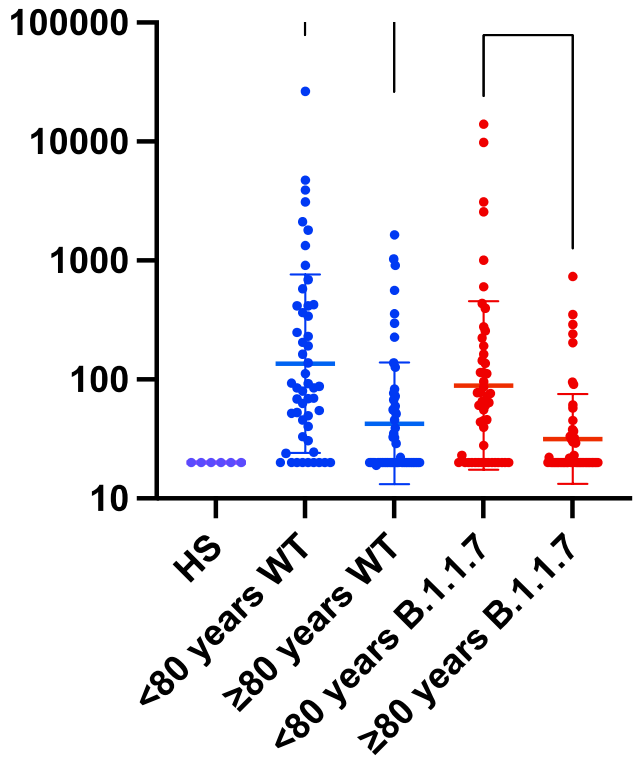


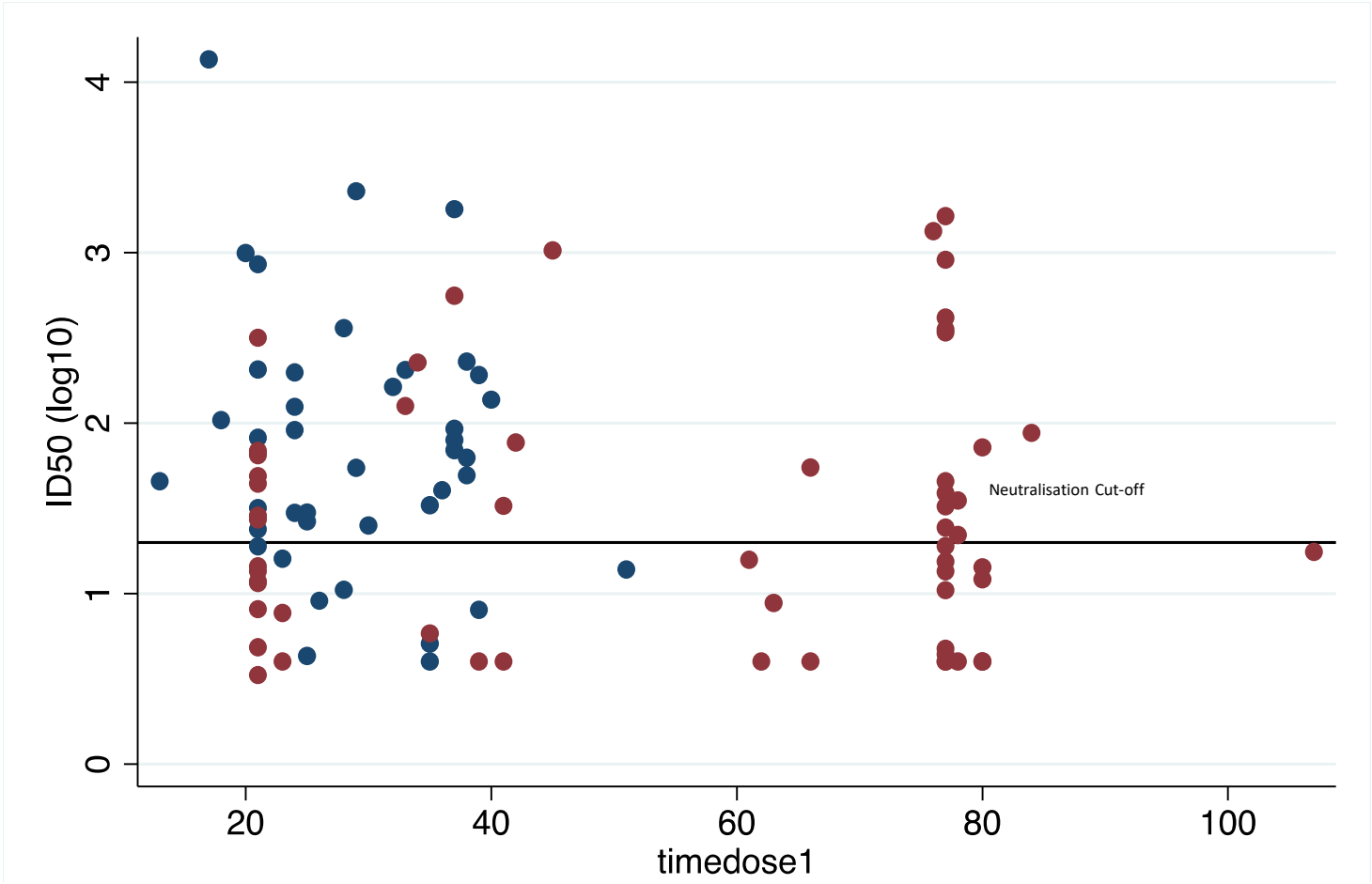




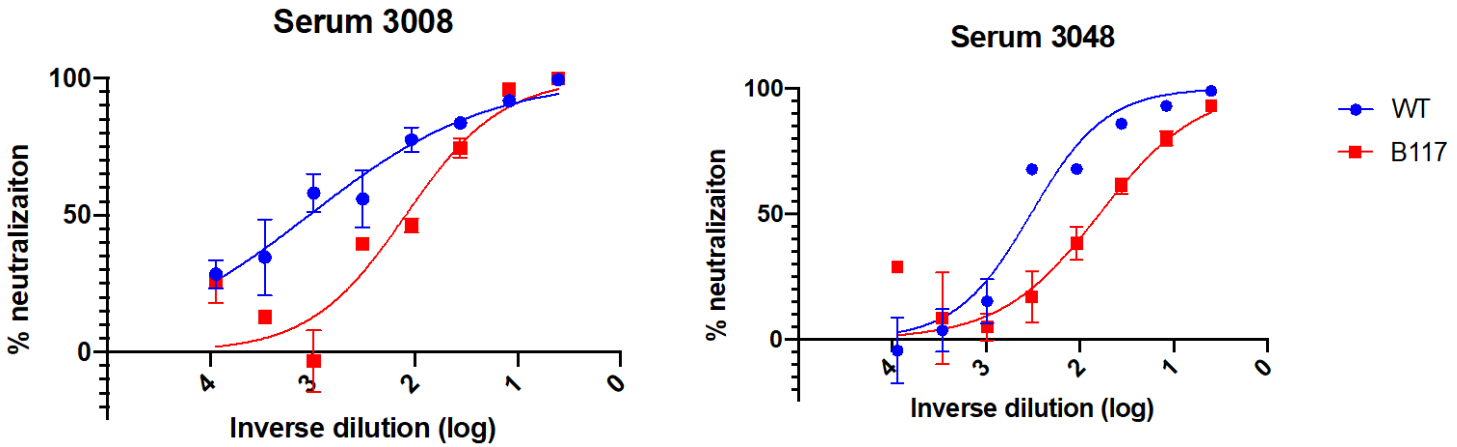
Collier et al, Nature 2021; Muik et al, Science 2021, Wang et al, Nature 2021; Shen et al, CHM 2021 and others

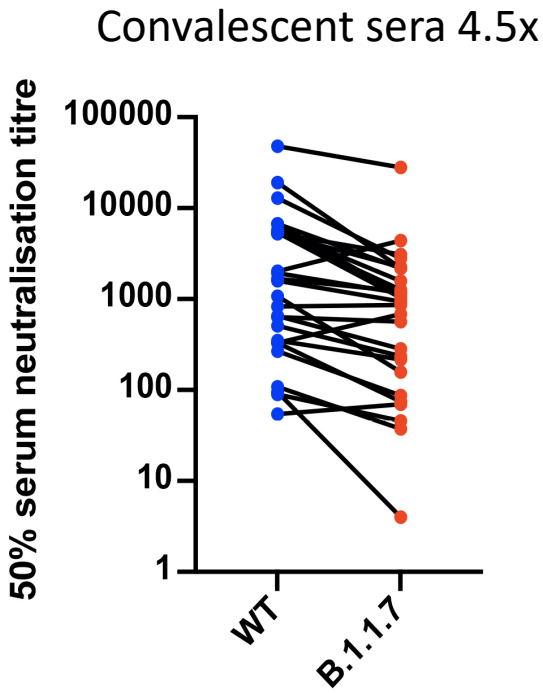
Age related heterogeneity in responses – first dose





Convalescent sera and B.1.1.7





Live virus versus pseudotyped virus NA

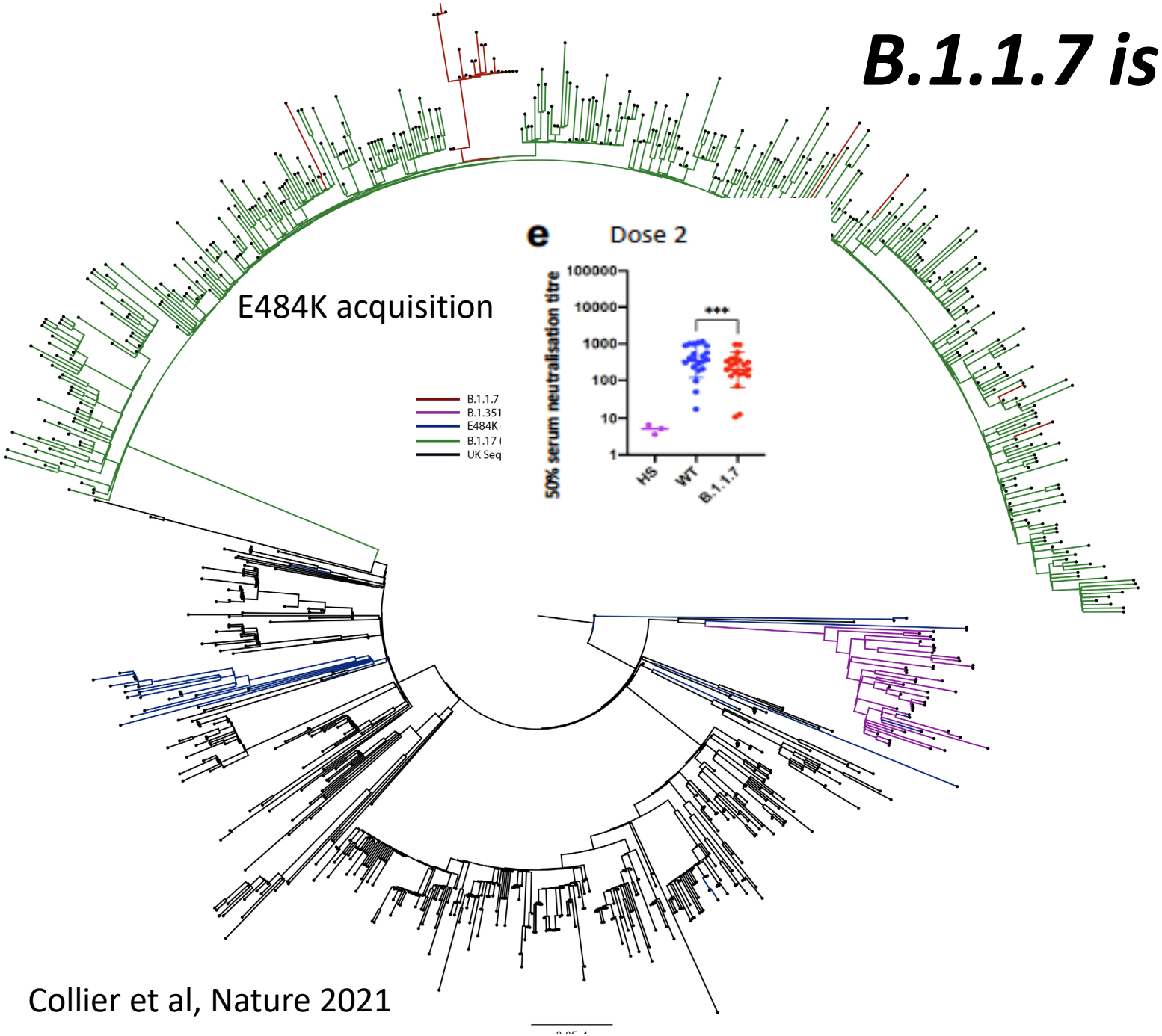
- Use of PV allowed rapid assessment of susceptibility
- Data for PV in serum NA for B.1.1.7 was confirmed with live virus
- Need for standardization as more labs do these assays
- NIBSC has standards; G2P consortium advocating this

What about real world vaccine efficacy against B.1.1.7?

Real world vaccine efficacy against B.1.1.7

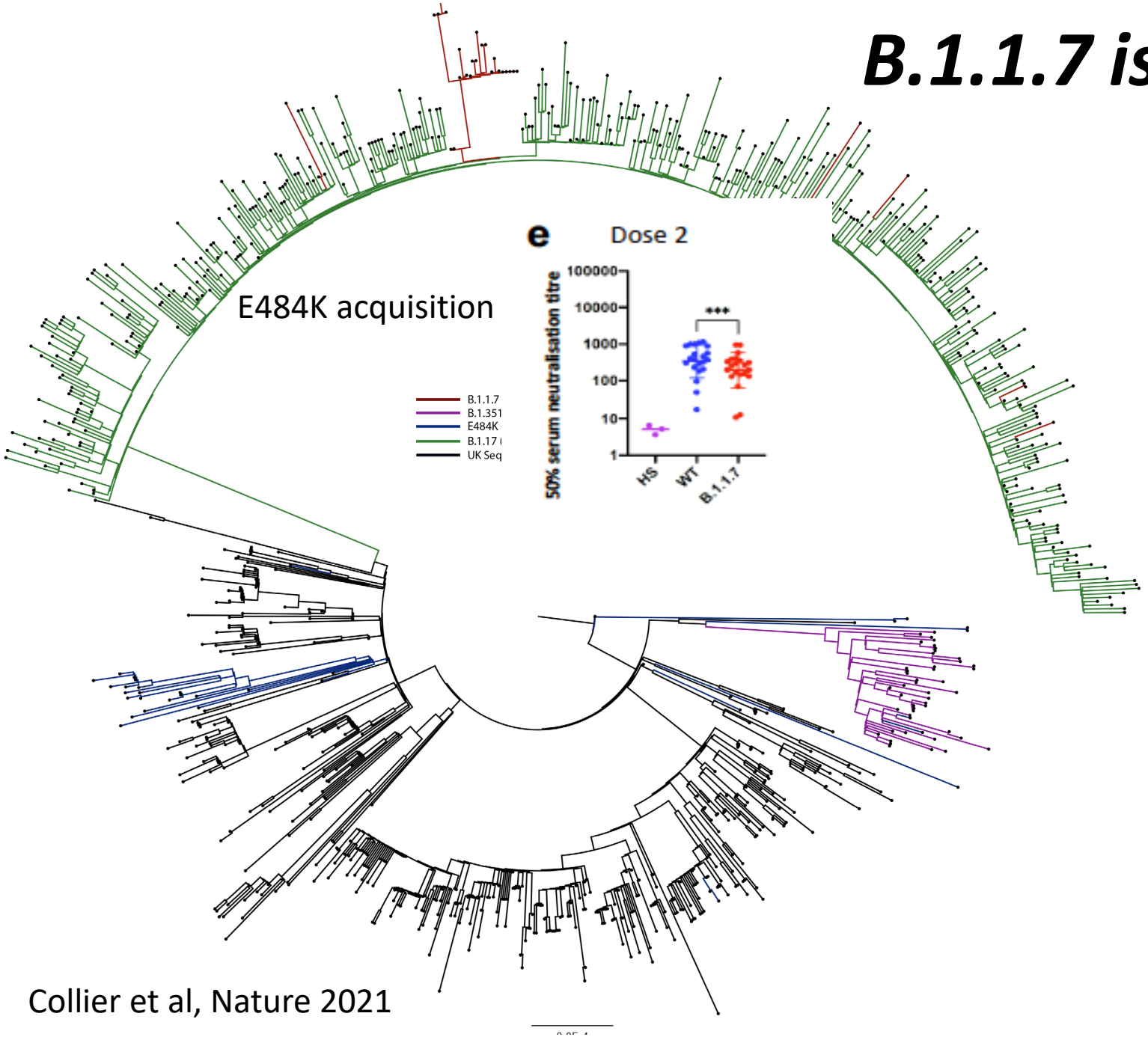
	Platform	Storage	Efficacy Pre VOC	Efficacy B.1.1.7
BNT162b2 Pfizer	mRNA	-70C freezer	95% moderate 90% severe	>90%
mRNA-1273 Moderna	mRNA	-20C for 6months	95%	NA
Novavax	Protein subunit	2-8C Fridge	89% moderate 100% severe	86%
Azd1222 ChadOx1 AZ	Chimpanzee adenovirus	2-8C Fridge	62-90%* 100% severe	75%*
AD26.COV2.S J&J	Human adenovirus	2-8C Fridge 3 months	66% moderate 85% severe	NA

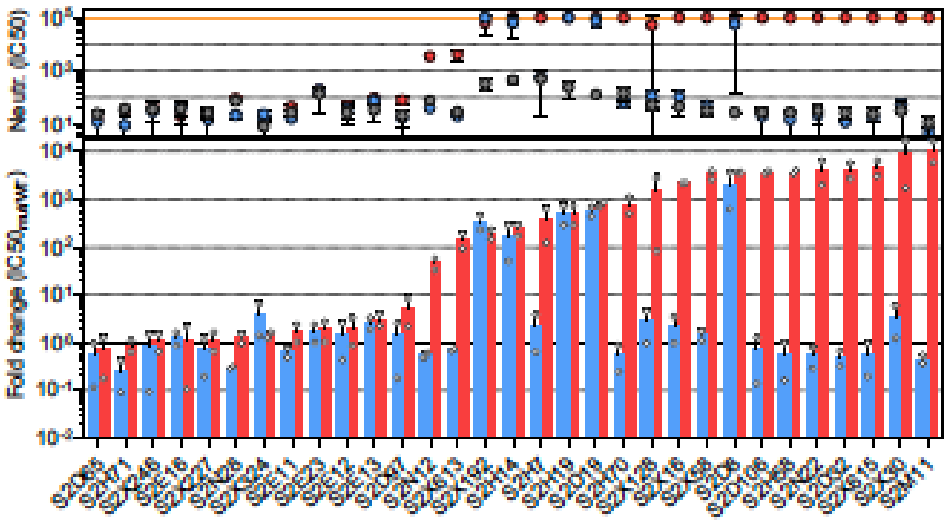
B.1.1.7 is still evolving….



Collier et al, Nature 2021

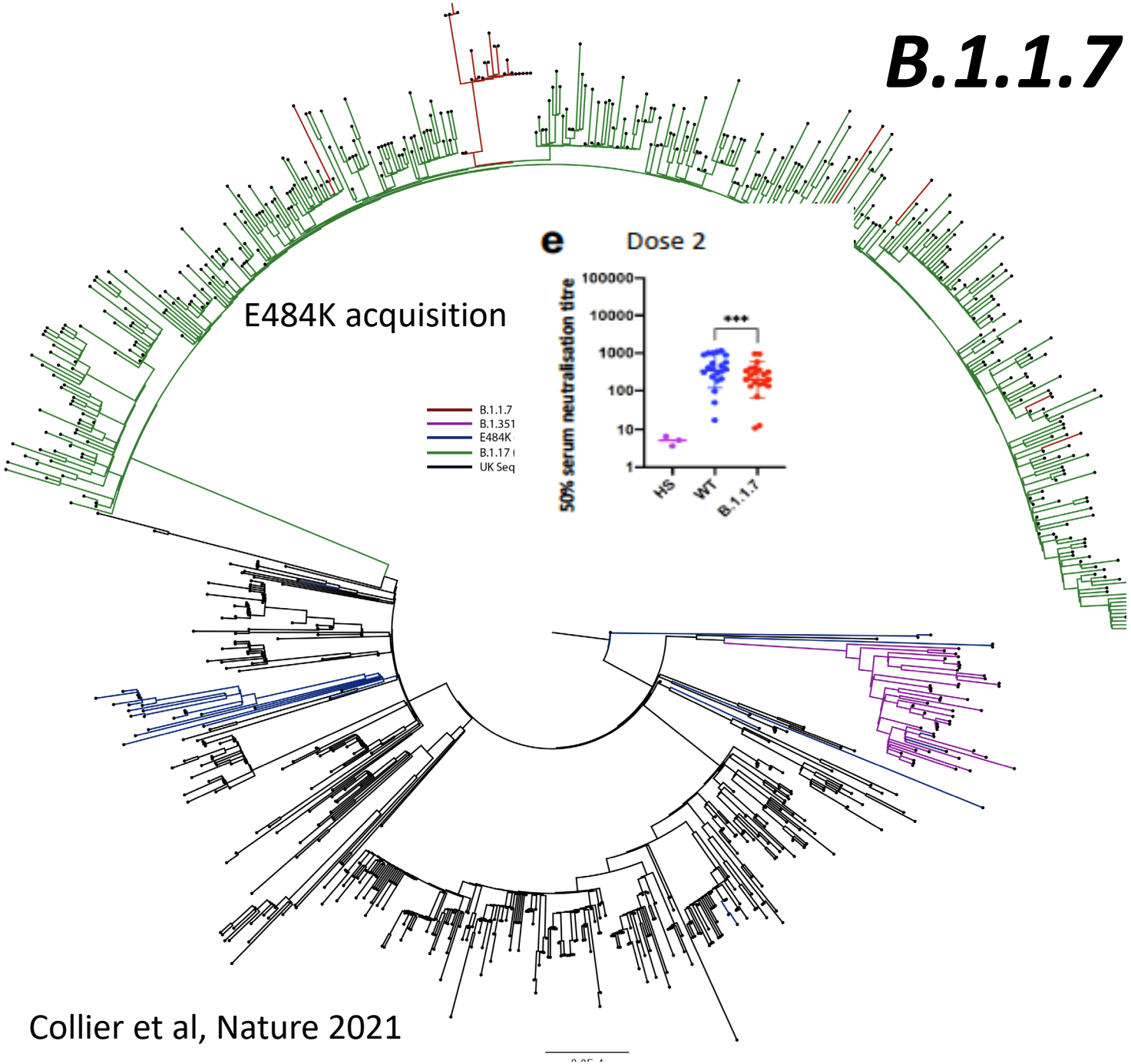
B.1.1.7 is still evolving….

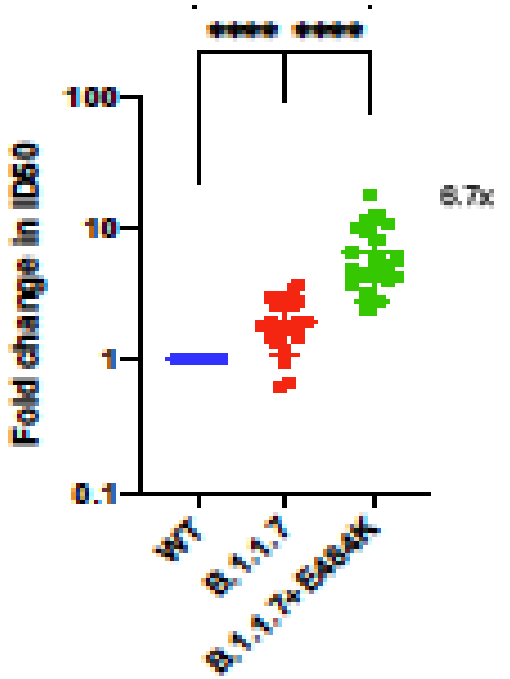


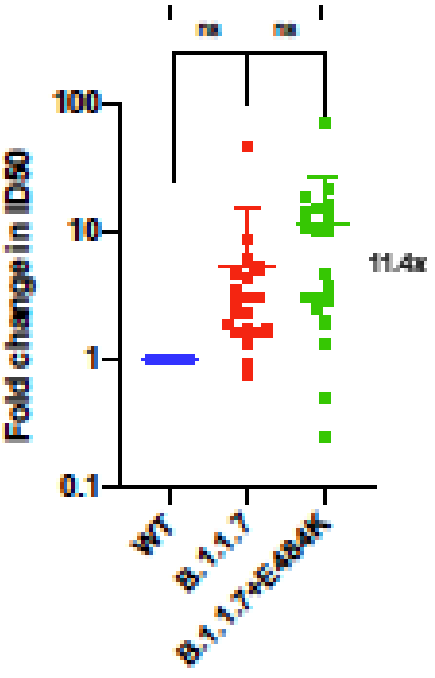


Collier et al, Nature 2021

B.1.1.7 is still evolving….







Collier et al, Nature 2021

Discussion

- B.1.1.7 shows modestly reduced susceptibility after first and second doses. Potency greater after second dose.
- Caution against extending dosing schedule in the elderly especially.
- Real world efficacy of all vaccines against B.1.1.7 high
- However, escape mutations such as E484K are appearing on B.1.1.7

UNIVERSITY OF CAMBRIDGE

Acknowledgements

Cambridge University

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UCL

Steven Kemp

Dami Collier

Chloe Rees-Speers

MJ van Gils

Richard Goldstein

Laura McCoy

CUH NHS Trust

Salma Gayed

Rainer Doffinger

Katherine Sharrocks

Jordan Skittrall

Effrossyni Krana-Glottsis

Anna Smielewska

Anita Chandra

NIHR CRF

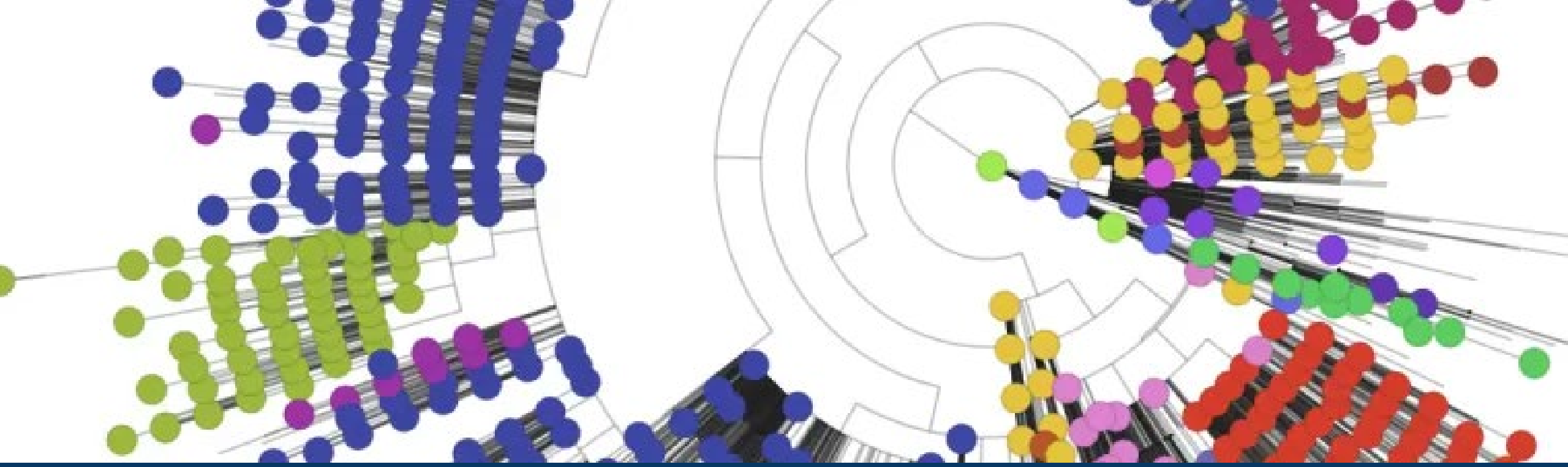
NHSBT

David Roberts

Ines Ushiro Lumb

Understanding SARS-CoV-2 variants in 2021: Indian Perspective

Anurag Agrawal
CSIR/IGIB



Understanding SARS-CoV-2 variants in 2021: Indian Perspective

~~Double Mutant~~

There are other double mutants in genomic datasets

~~Indian Variant~~

There is no single genetic lineage which can explain the genetic diversity of SARS-CoV-2 in India.

B.1.617 Lineage

B.1.617 lineage of SARS-CoV-2 virus

Sub lineage of B.1

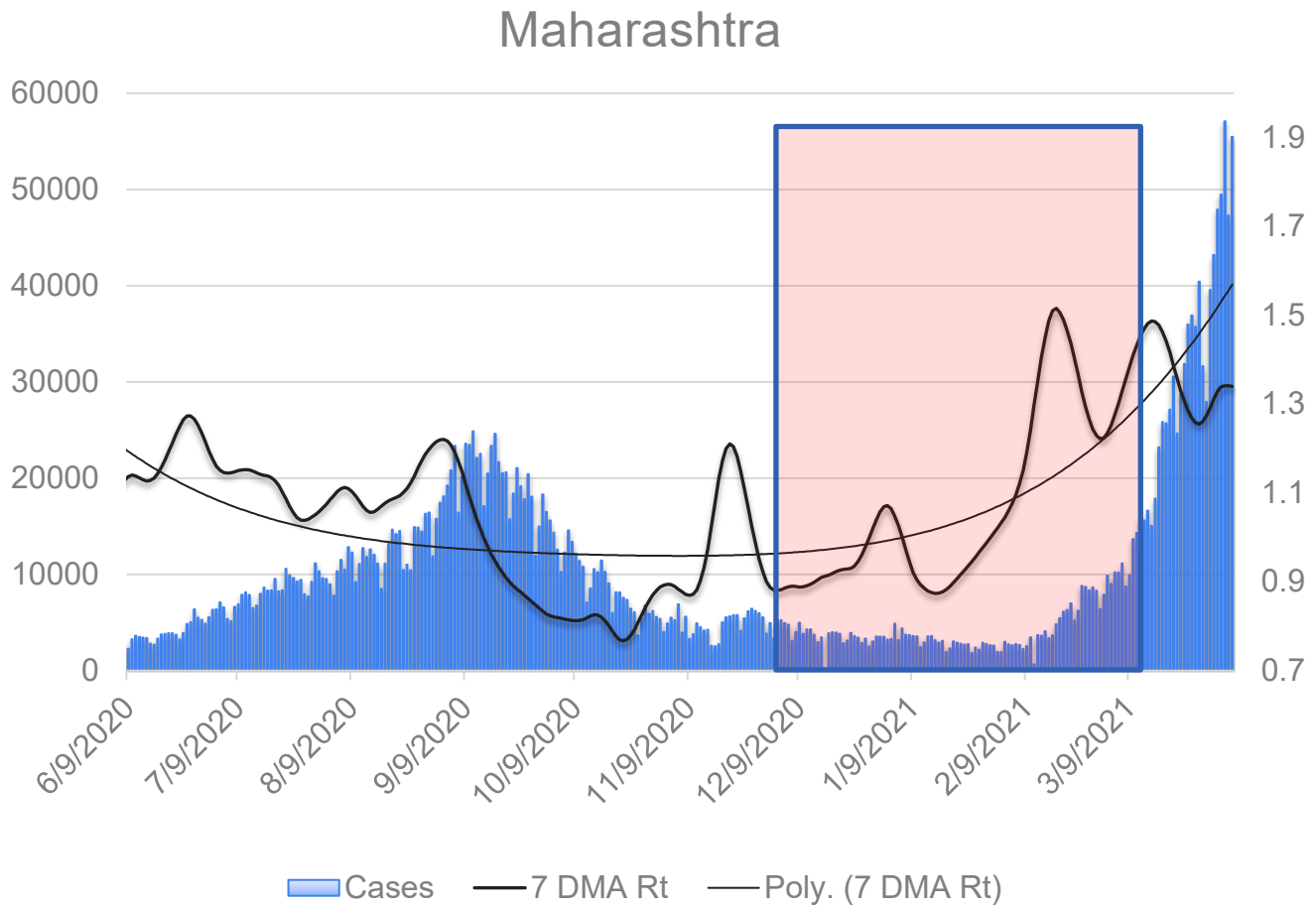
Earliest sequence: 2020-12-07
Recent sequence: 2021-03-17

Found in - **India**, UK, Australia, New Zealand, Singapore, USA, Germany, Canada

15 lineage defining variations

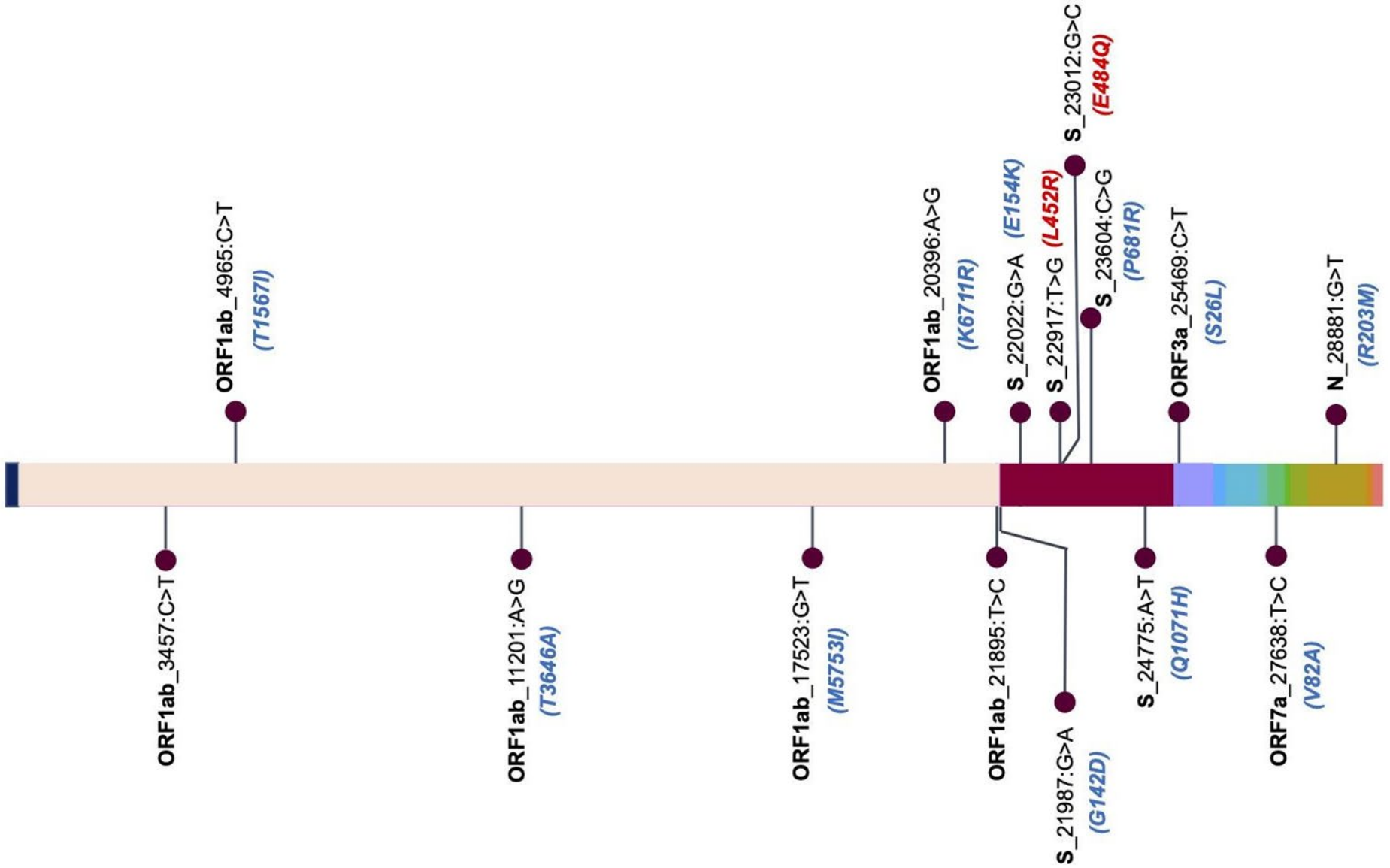
Indian Picture (B.1.617)

- B.1.617 first seen in Maharashtra and Gujarat, but now with multiple states
- B.1.617 fraction going up from rare in December 2020, to 15-20% in Feb 2021, to 60-80% in March 2021, with adequate sampling for each period

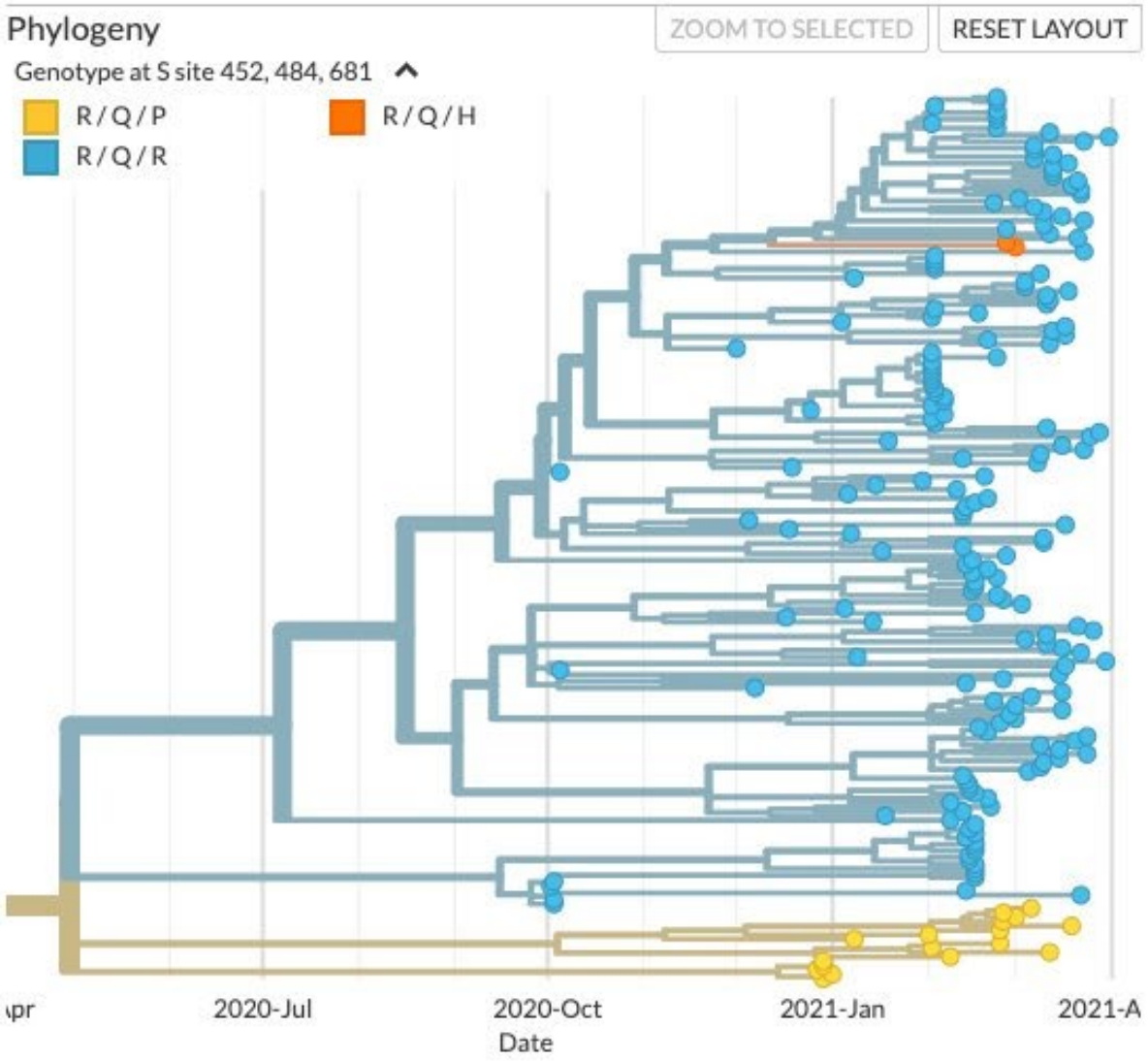


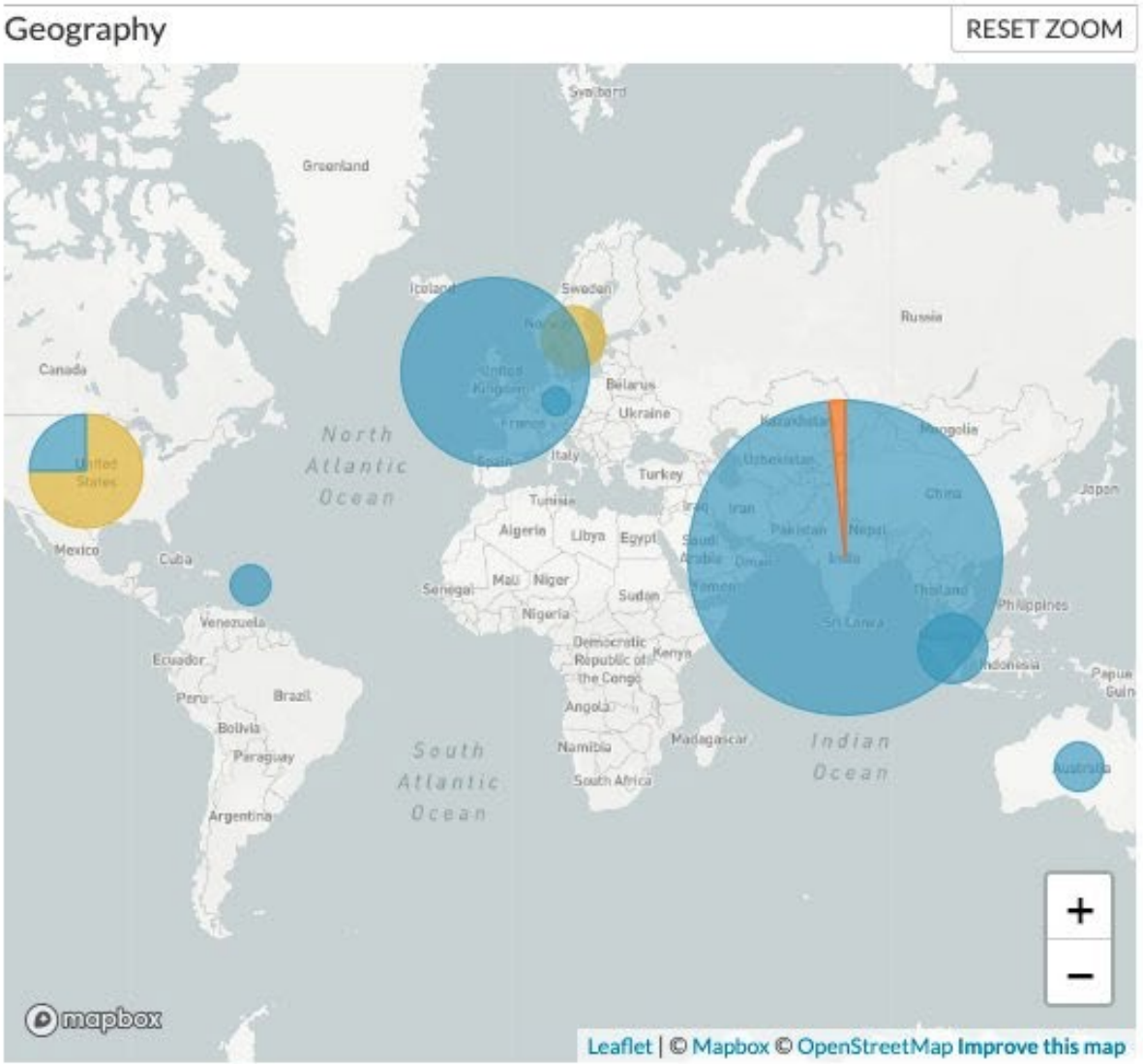
Genetic variants defining the B.1.617 lineage

Gene	Amino Acid	Nucleotide Change
orf1ab	-	3457C>T
orf1ab	T1567I	4965C>T
orf1ab	T3646A	11201A>G
orf1ab	M5753I	17523G>T
orf1ab	K6711R	20396A>G
orf1ab	-	21895T>C
S	**G142D**	**21987G>A**
S	**E154K**	**22022G>A**
S	**L452R**	**22917T>G**
S	**E484Q**	**23012G>C**
S	**P681R**	**23604C>G**
S	**Q1071H**	**24775A>T**
orf3a	S26L	25469C>T
orf7a	V82A	27638T>C
N Gene	R203M	28881G>T

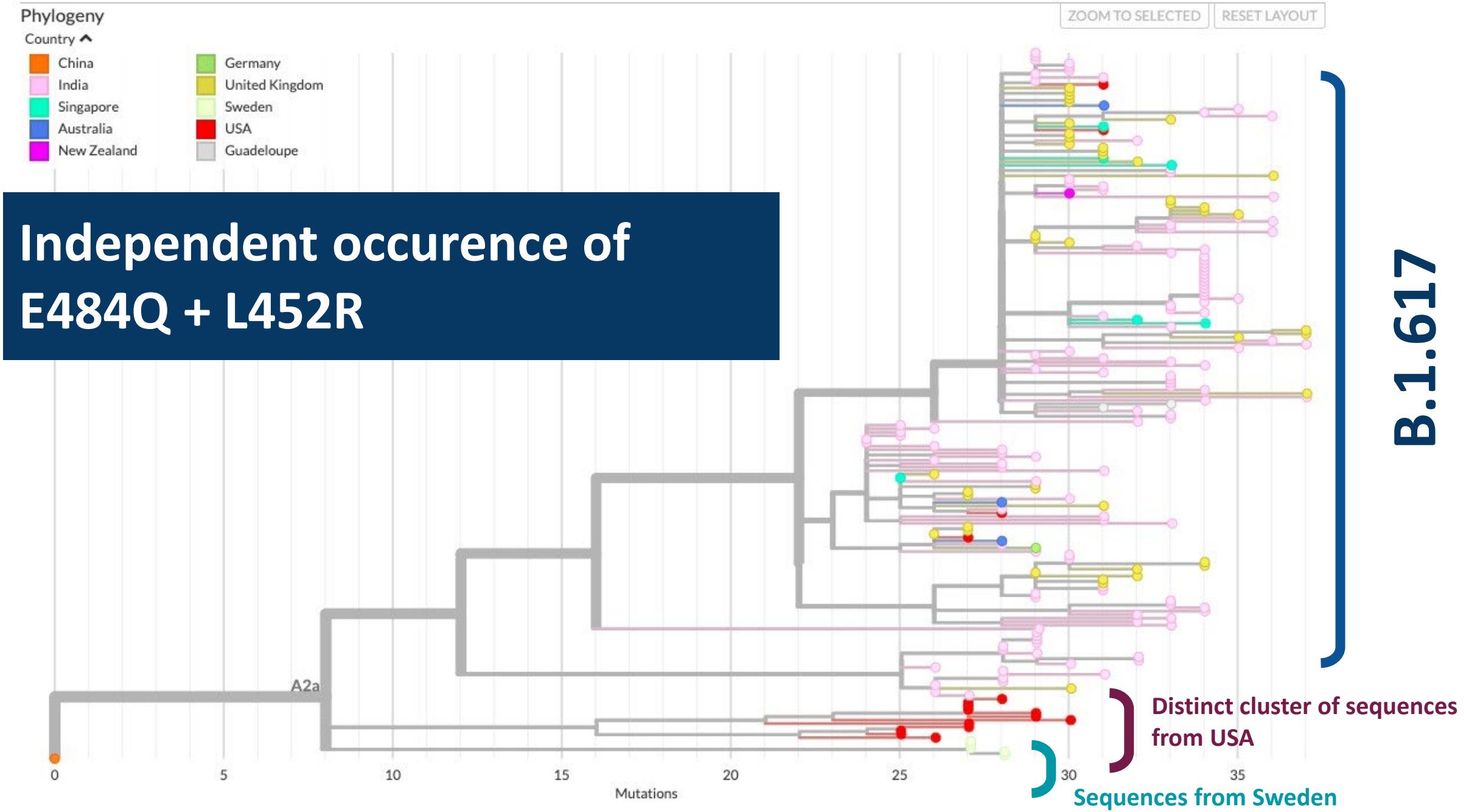


Genomes from India are characterized by E484Q, L452R and P681R on Spike

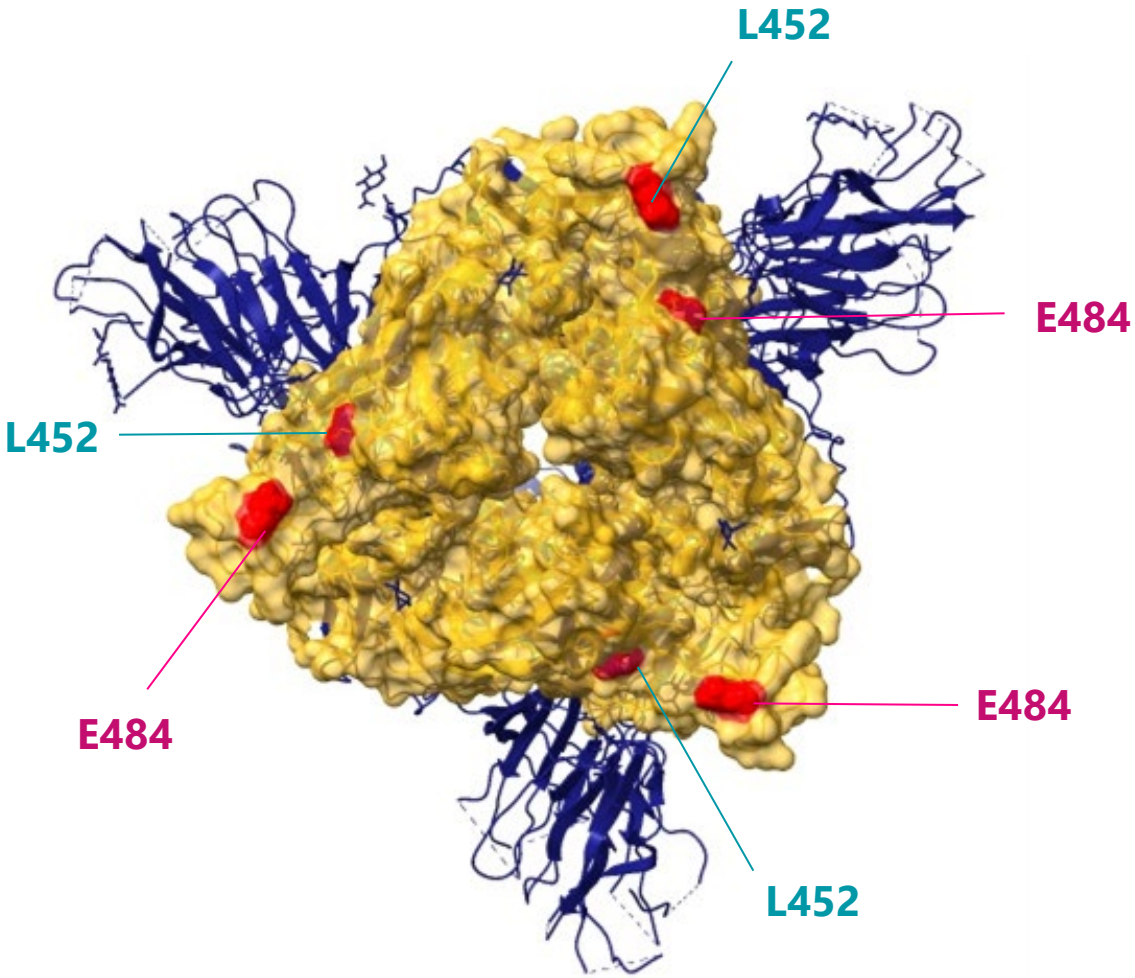


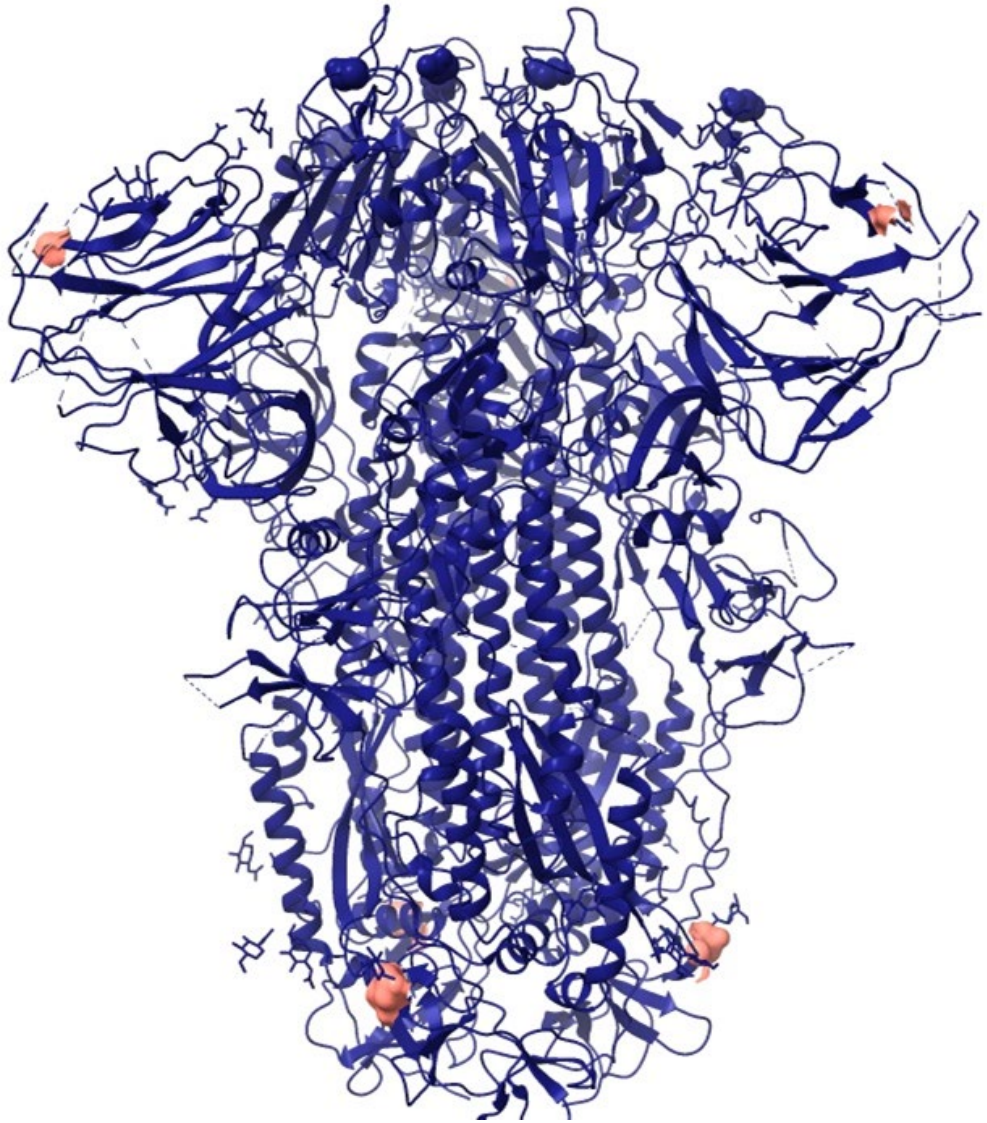


Independent occurence of E484Q + L452R



Structural context of the Spike protein variants





E484Q

E484 located on the edge of **CC12.1**, **P2B-2F6** and **ACE2** interface

E484Q, a **destabilizing mutant in P2B-2F6 interface** but permissive with ACE2

Shang and Axelsen, 2020

E484 - Potential antibody / immune escape site against COV2-2832, COV2-2479 and COV2-2050

Reduced neutralization by patient polyclonal sera

Greaney et al, 2021

L452R

Resistant to X593 and P2B-2F6 monoclonal antibodies

Li et al, 2020

Resistance to BD-368-2. Leu452 critically involved in BD-368-2 RBD binding interface

Du et al, 2020

L452R conferred resistance to SARS2-01 and SARS2-32 antibodies along with observed resistance to patient polyclonal sera

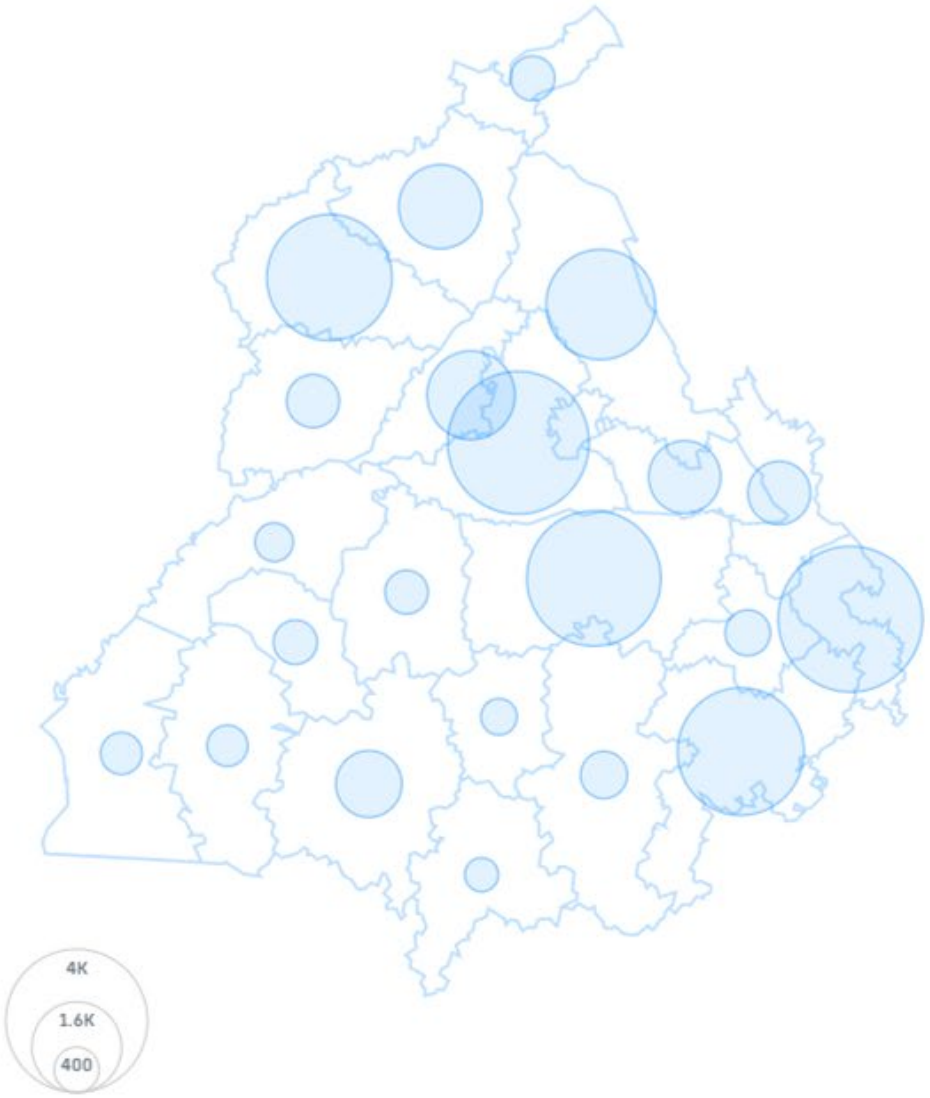
Liu Z et al, 2021

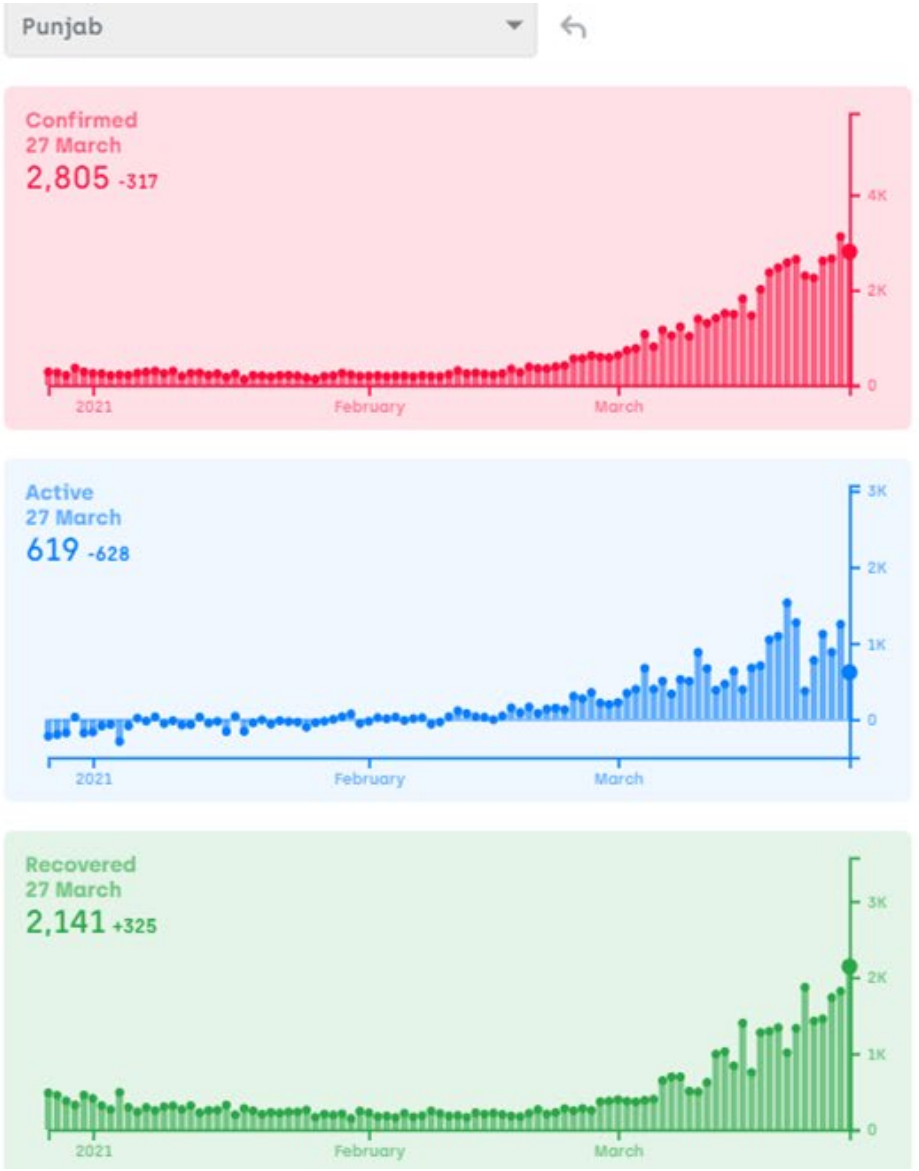
Spike RBD:L452R, **infectivity strengthening mutation** in RDB hotspot residue.

Significant changes in binding free energy between wild type and mutated strains

Chen J et al, 2020

B.1.1.7 outbreak in North India, starting with Punjab

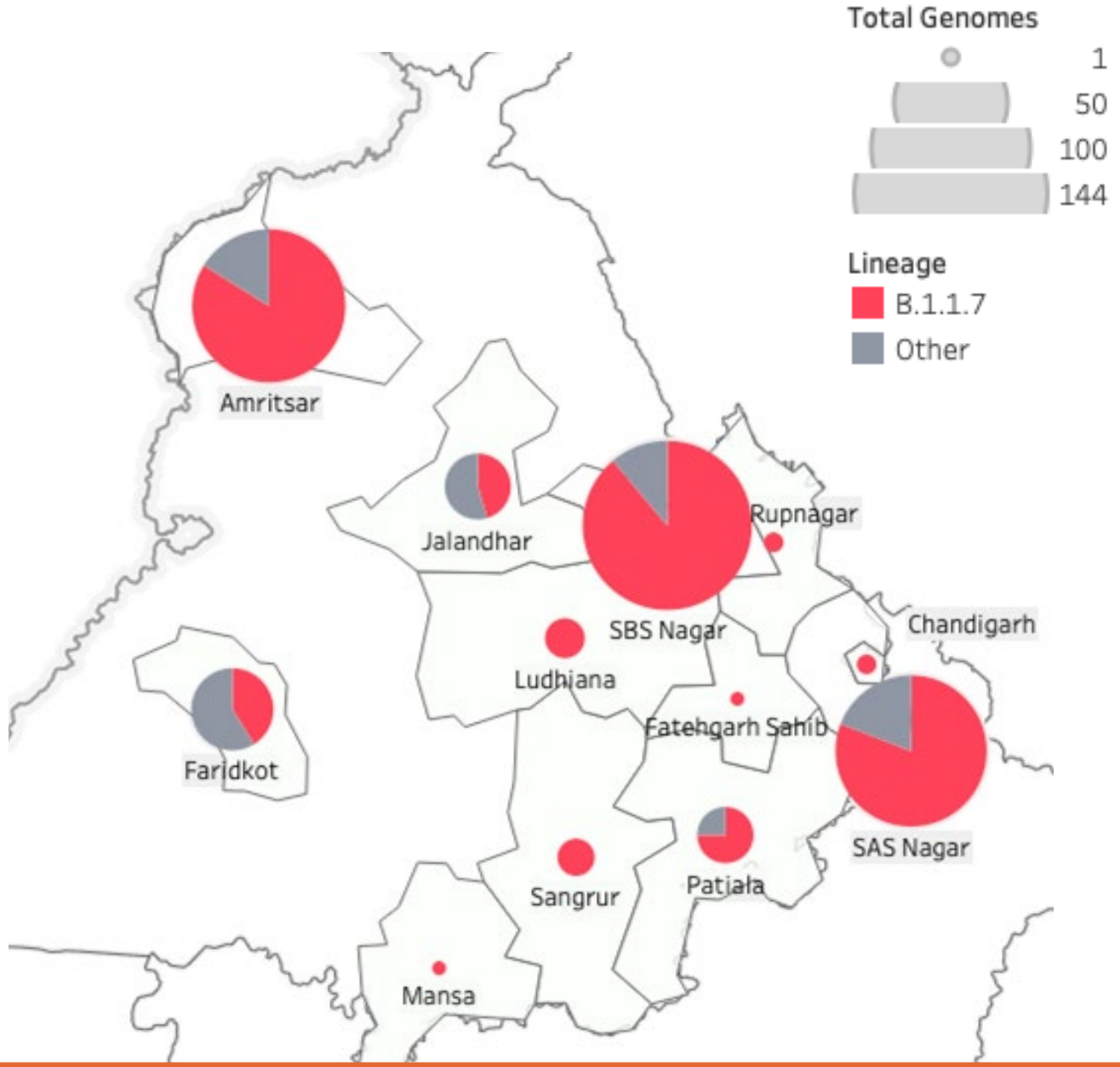




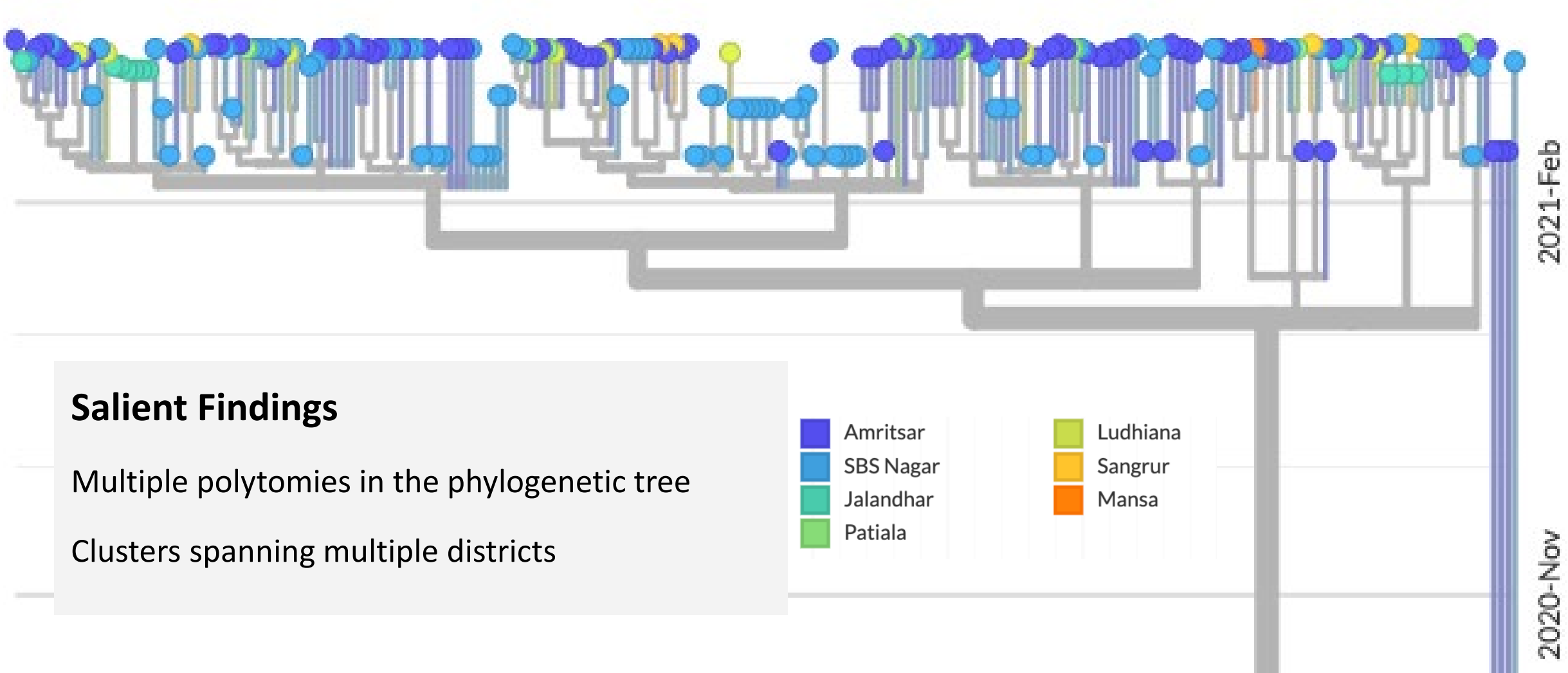
Source: covidindia.org : retrieved 27th March 2021

B.1.1.7 in Punjab

- **Majority of samples tested positive for B.1.1.7 in Feb-March**
- (501Y.V1, VOC 202012/01, or B.1.1.7) **first detected in UK** (earliest sample on **2020-09-20**)
- Associated with **increased transmissibility and now reported from over 70 countries**



Phylogenetic Map of SARS-CoV-2 Genomes from Punjab



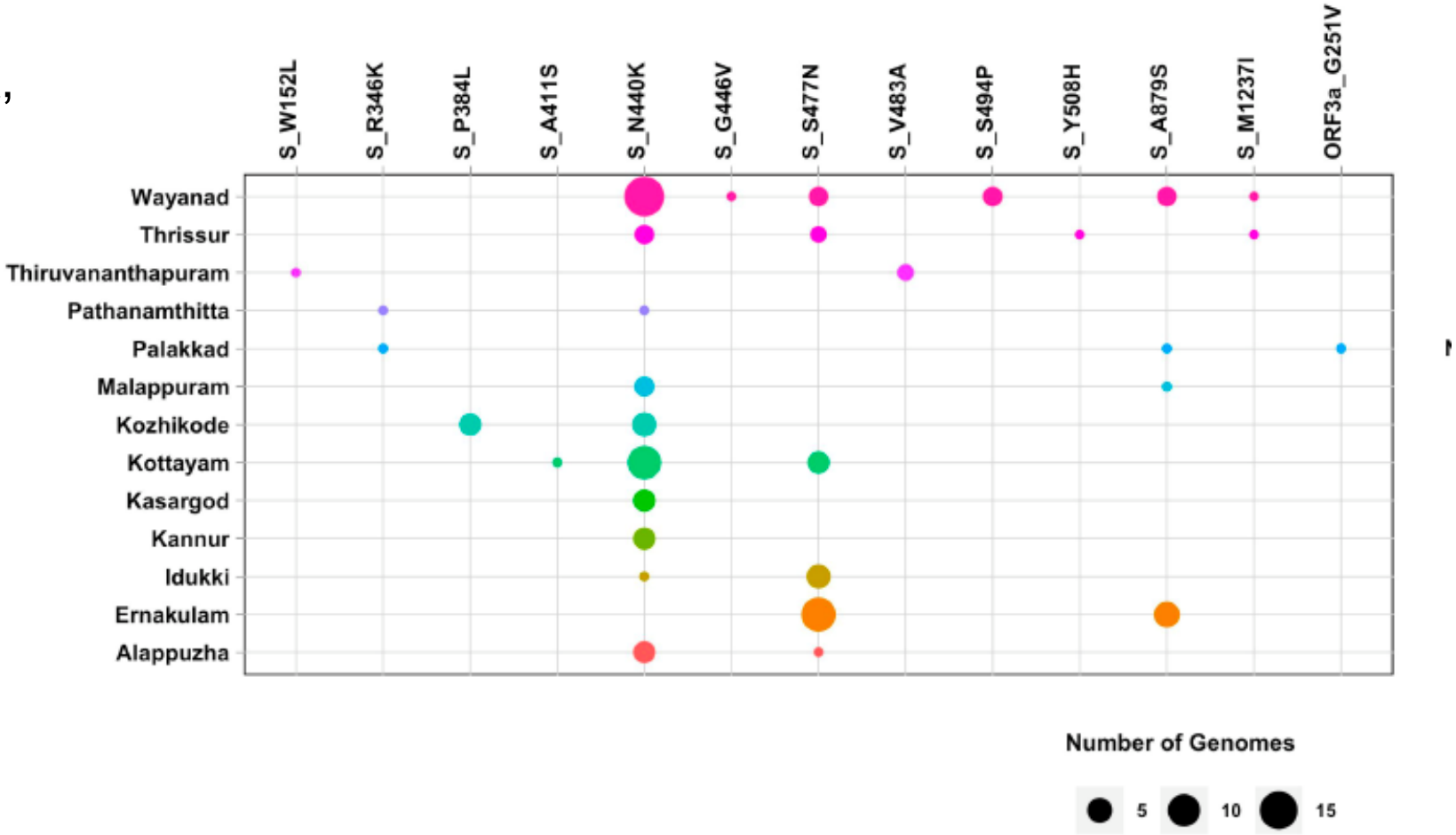
Salient Findings

Multiple polytomies in the phylogenetic tree

Clusters spanning multiple districts

Not always the variant: N440K in Kerala

- During Jan 2021 outbreak, new cases were rising, as was fraction of N440K, an escape variant
- However, based on fixed temporal and districtwise sampling, there was lack of concordance between outbreaks and N440K



Ongoing activities and things to do

- Culture and neutralization assays for B.1.617, as well as recent addition sublineages with additional mutations V382L / W152L
  - Other new lineages B.1.618 (E484K, without N501Y)
- Pseudovirus assays

- Step up global coordination and post vaccine surveillance
- Increase integration of clinical stratification, sentinel collections, sequencing, viral research and public health response

Panel Discussion

Moderated By:

Karen Makar, PhD

BMGF

Discussion Panel Members and Example Questions

Panel Members

- **Tulio de Oliveira,** KRISP (KwaZulu-Natal Research and Innovation Sequencing Platform), South Africa
- **Penny Moore,** NICD (National Institute for Communicable Diseases), South Africa
- **Ester Sabino,** University of São Paulo, Brazil
- **Ravindra Gupta,** University of Cambridge, UK
- **Anurag Agrawal,** CSIR-IGIB (Council of Scientific and Industrial Research - Institute of Genomics and Integrative Biology), India
- **Karen Makar**, Bill & Melinda Gates Foundation, USA

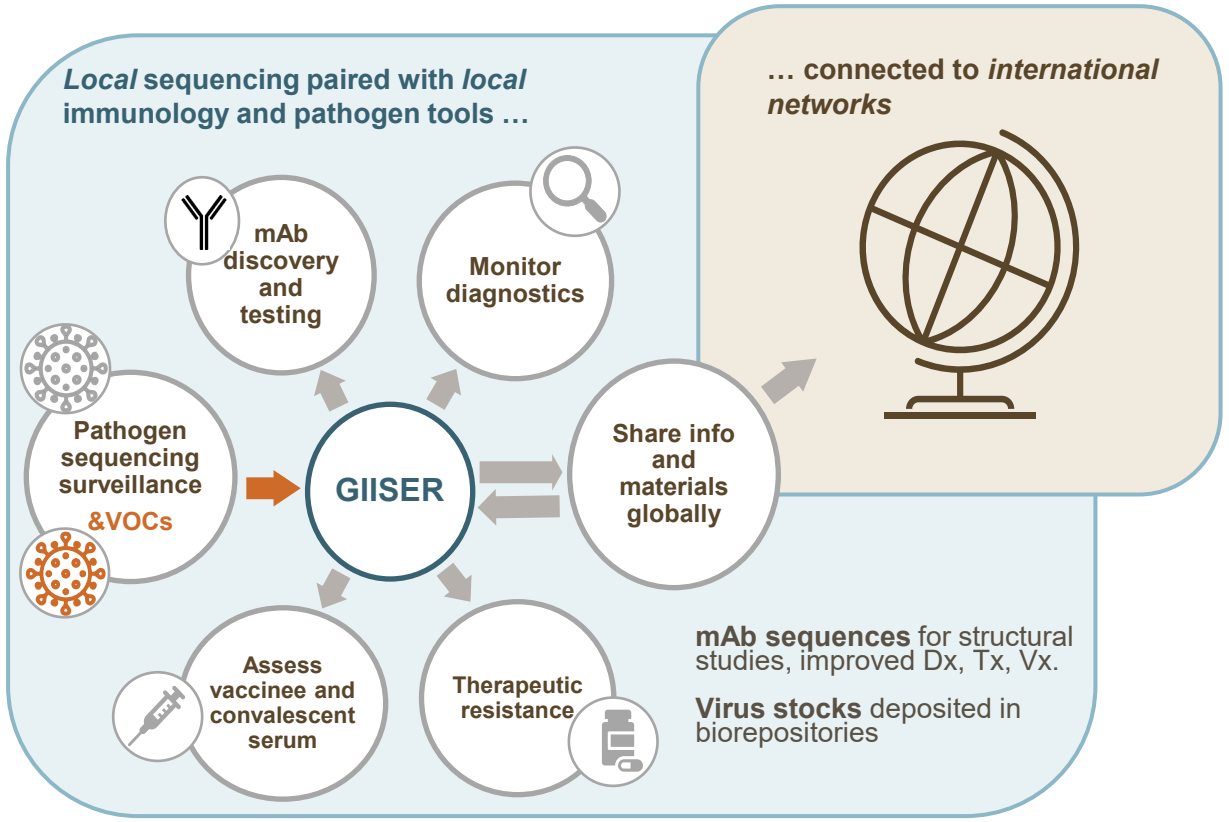
Potential Discussion Questions

1. What can other countries learn from the South African example about how to rapidly and efficiently connect surveillance sequencing and epidemiology with immunological assessment to inform vaccine design and useage?
2. How can we best harmonize neutralization and binding assays and incorporate international standards to improve our ability to interpret immune escape data generated in different labs and geographies?
3. What is needed to enable more countries to rapidly generate interpretable data on immune escape that can inform local and global decisions?
4. What other in-country efforts & data are needed to understand the implication of emerging variants for vaccines specifically?
5. Much of the focus on immune escape has centered on neutralizing antibody responses. For informing vaccine-related decisions, is this the appropriate focus?

GIISER: GLOBAL IMMUNOLOGY & IMMUNE SEQUENCING FOR EPIDEMIC RESPONSE

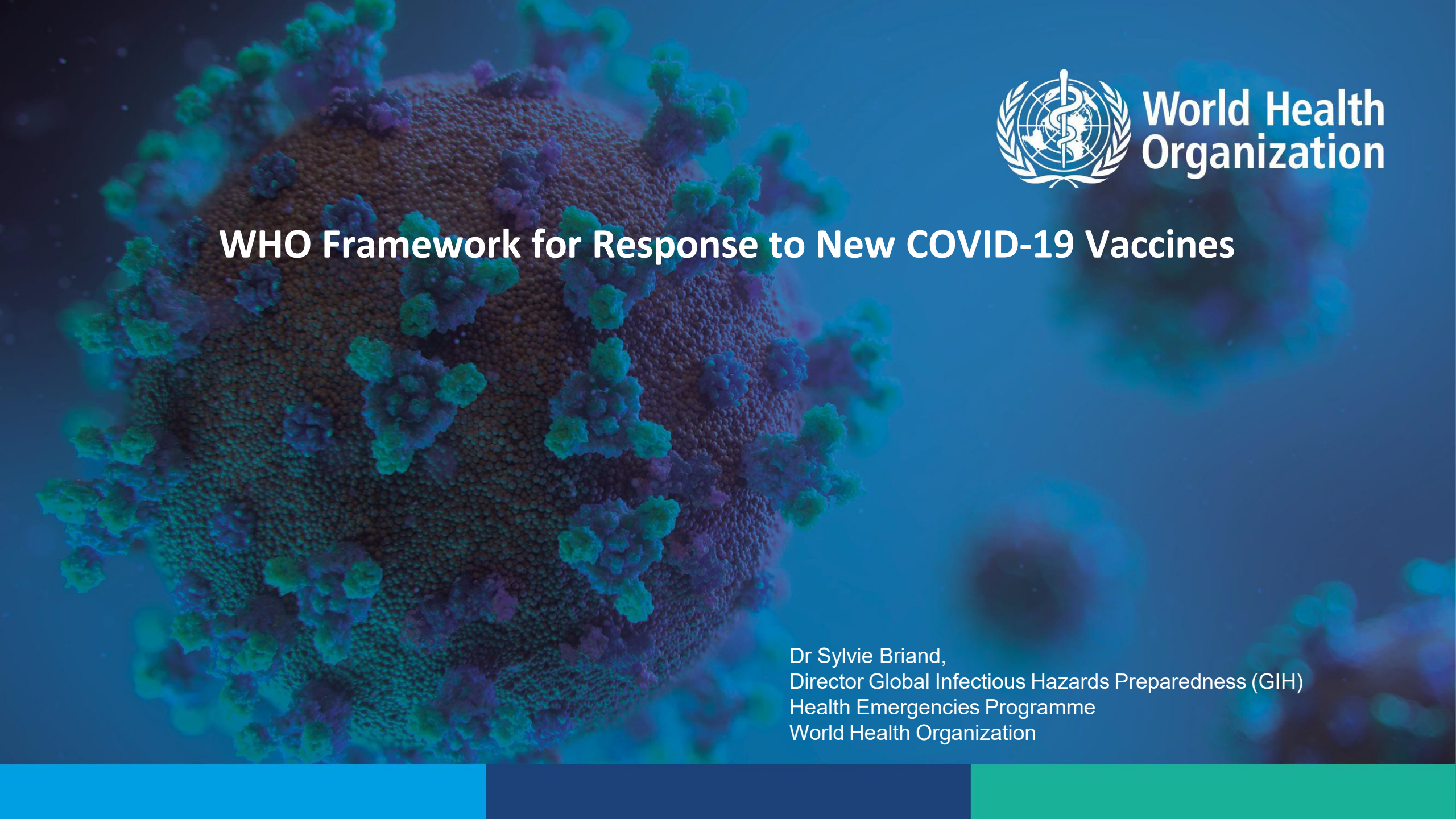
The Bill & Melinda Gates Foundation aims to strengthen capacity for viral immune monitoring in low- and middle-income countries and build on the global networks

- Pathogen outbreaks and/or Variants of Concern emerge locally but have potential to give rise to regional epidemics or spread globally.
- Pathogen sequencing should be **directly linked to R&D** to inform Vx, mAb and Tx and Dx efforts.
- Strengthening local capacity to evaluate emerging pathogens using cutting edge immunological & pathogen tools can expedite translation to **product development**
- To achieve this, immunology and immunosequencing should be **co-located and closely aligned** with pathogen genomic surveillance in order to evaluate antigenicity.
- Regional capacity should include assessment of immune escape from convalescent/vaccine serum, plus discovery of monoclonal **antibodies** for use as tools and interventions.



WHO framework for response to new COVID vaccines

Sylvie Briand,
WHO



WHO Framework for Response to New COVID-19 Vaccines

Dr Sylvie Briand,
Director Global Infectious Hazards Preparedness (GIH)
Health Emergencies Programme
World Health Organization

World Health Organization

LEGEND
Epidemic
Pandemic

MAJOR EPIDEMIC THREATS SINCE 2000

COVID-19
Ebola (DRC)
Yellow fever (Central Africa, Brazil)
Zika
H7N9
Ebola (West Africa)
H1N1
H5N1
MERS
SARS
Cholera (Haiti)
Cholera (Yemen)
Plague (Madagascar)

2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020

INTERNATIONAL COLLABORATION EFFORTS TO FIGHT EPIDEMIC THREATS

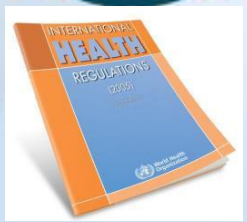
GAVI

Gavi, the Vaccine Alliance, is an international organisation that was created in 2000 to improve access to new and underused vaccines for children living in the world's poorest countries.

GOARN

The **Global Outbreak Alert and Response Network (GOARN)** is a technical collaboration of existing institutions and networks who pool human and technical resources for the rapid identification, confirmation and response to outbreaks of international importance.

IHR (2005)



The **International Health Regulations (2005)** or IHR (2005) are an international law which helps countries work together to save lives and livelihoods caused by the international spread of diseases and other health risks. The IHR (2005) aim to prevent, protect against, control and respond to the international spread of disease while avoiding unnecessary interference with international traffic and trade.

PIP Framework

The **Pandemic Influenza Preparedness (PIP) Framework** brings together Member States, industry, other stakeholders and WHO to implement a global approach to pandemic influenza preparedness and response. Its key goals include:
- to improve and strengthen the sharing of influenza viruses with human pandemic potential; and
- to increase the access of developing countries to vaccines and other pandemic related supplies.

R&D Blueprint

R&D Blueprint is a global strategy and preparedness plan that allows the rapid activation of research and development activities during epidemics. Its aim is to fast-track the availability of effective tests, vaccines and medicines that can be used to save lives and avert large scale crises.

PIP Review

IHR Review

Access to COVID-19 Tools (ACT) Accelerator is a global collaboration to accelerate the development, production and equitable access to new COVID-19 diagnostics, therapeutics and vaccines.

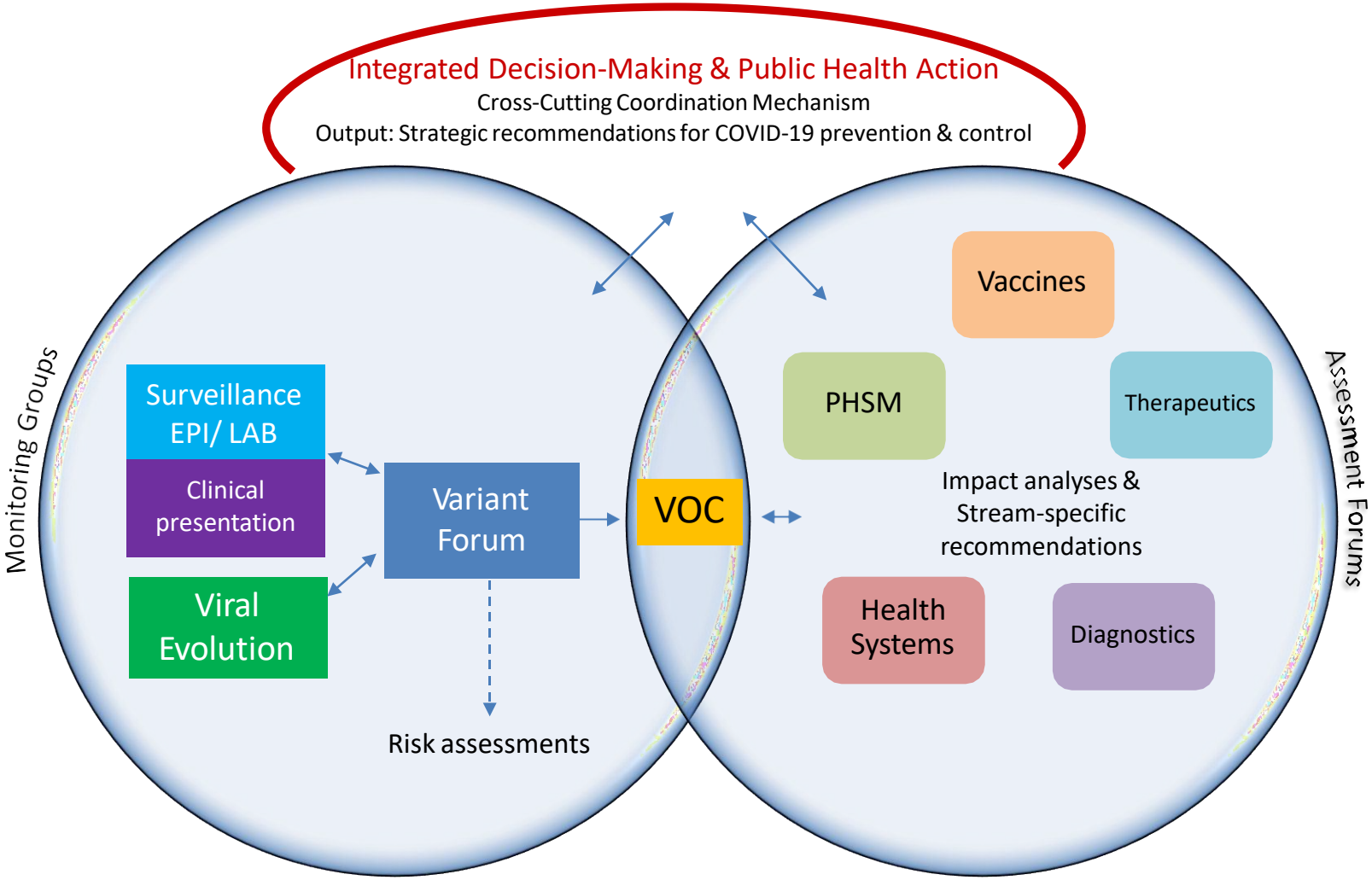
ACT Accelerator

Timeline

Major infectious threats in the 21st Century & collaboration mechanisms to fight against them

Last update: 04 May 2020

WHO's role: Monitor SARS-CoV-2 variants and and coordinate global health action

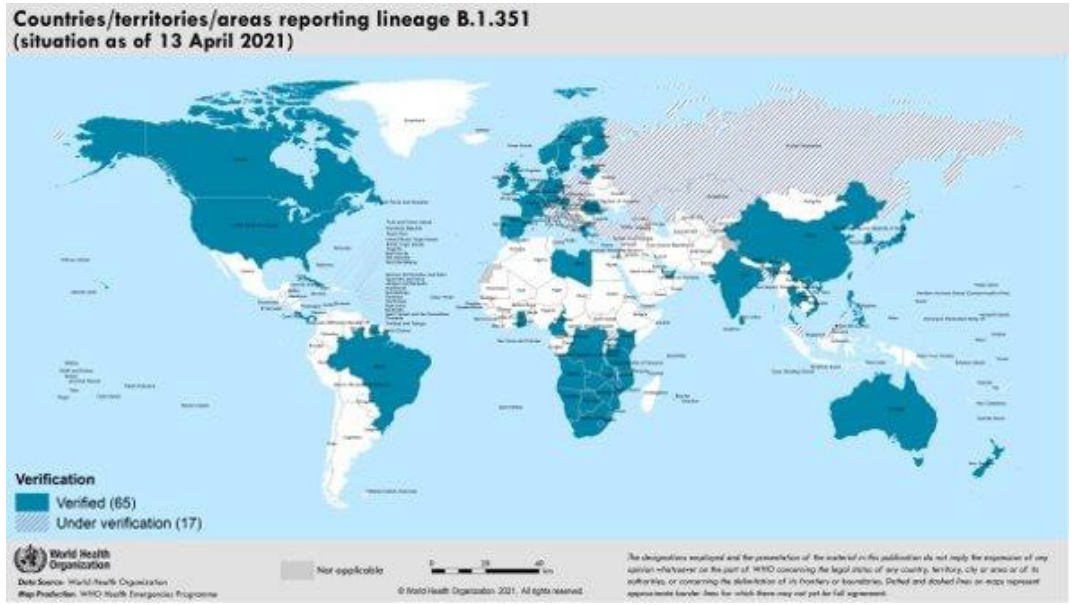


The emergence of variants is a game changer

Table 2: Overview of emerging information on key variants of concern, as of 23 March 2021*

Nextstrain clade	20I/501Y.V1	20H/501Y.V2†	20J/501Y.V3
PANGO lineage	B.1.1.7	B.1.351	B.1.1.28.1, alias P.1†
GISAID clade	GR	GH	GR
Alternate names	VOC 202012/01†	VOC 202012/02	-
First detected by	United Kingdom	South Africa	Brazil / Japan
First appearance	20 September 2020	Early August 2020	December 2020
Key spike mutations	H69/V70 deletion; Y144 deletion; N501Y; A570D; and P681H	L242/A243/L244 deletion; K417N E484K, N501Y	K417T, E484K; N501Y
Key mutation in common	S106/G107/F108 deletion in Non-Structural Protein 6 (NSP6)		
Countries reporting cases (newly reported in last week)**	125 (7)	75 (11)	41(3)

†*While work is ongoing to establish standardized nomenclature for key variants, these are the names by which WHO will refer to them in this publication.*
**Generalized findings as compared to non-VOC viruses. Based on emerging evidence from multiple countries, including nonpeer-reviewed preprint articles and reports from public health authorities and researchers – all subject to ongoing investigation and continuous revision.*
***Includes official and unofficial reports of VOCs detections in countries among either travellers (imported cases only) or community samples (local transmission).*



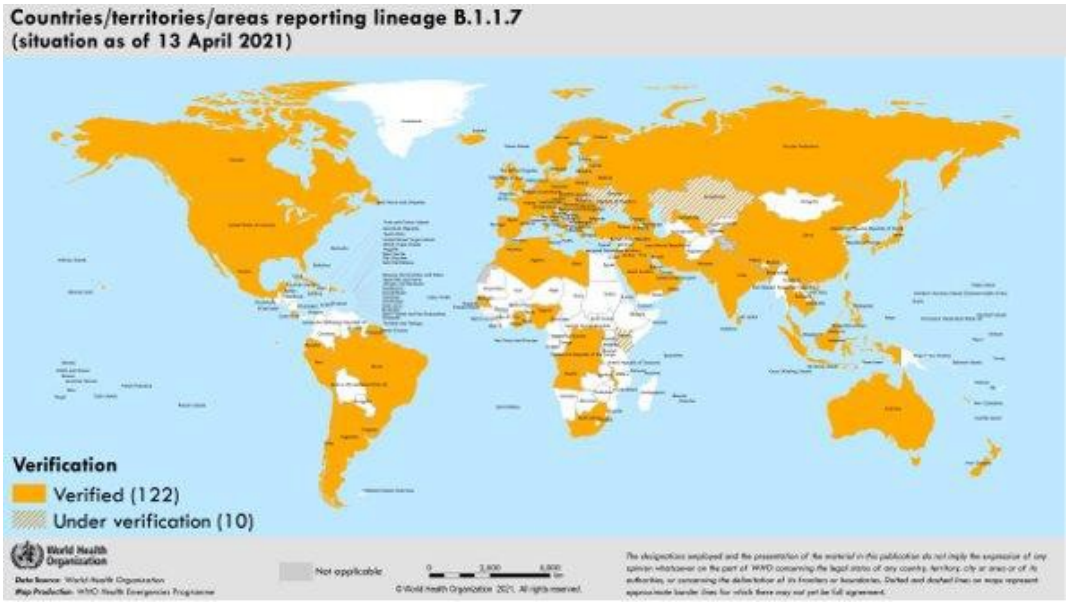
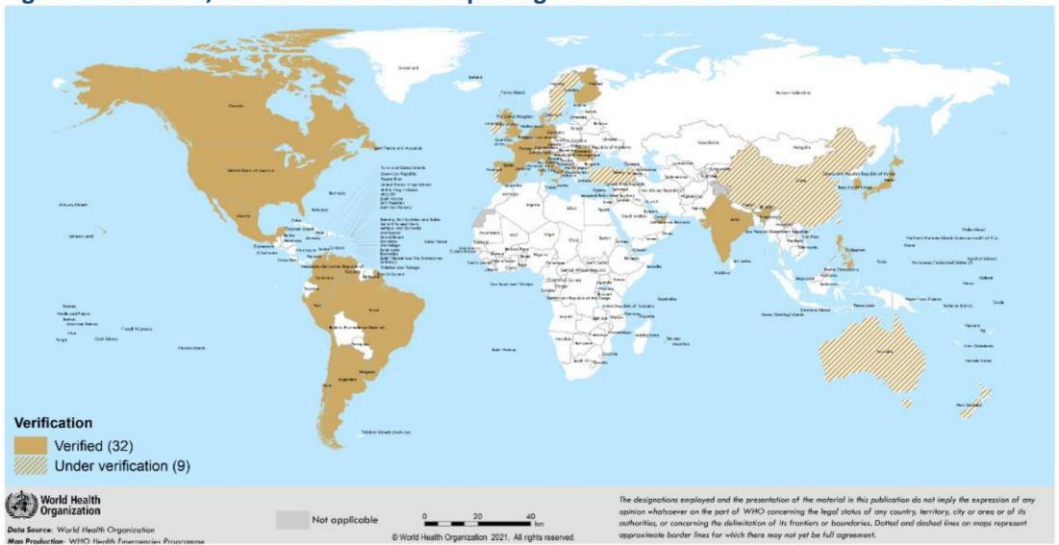
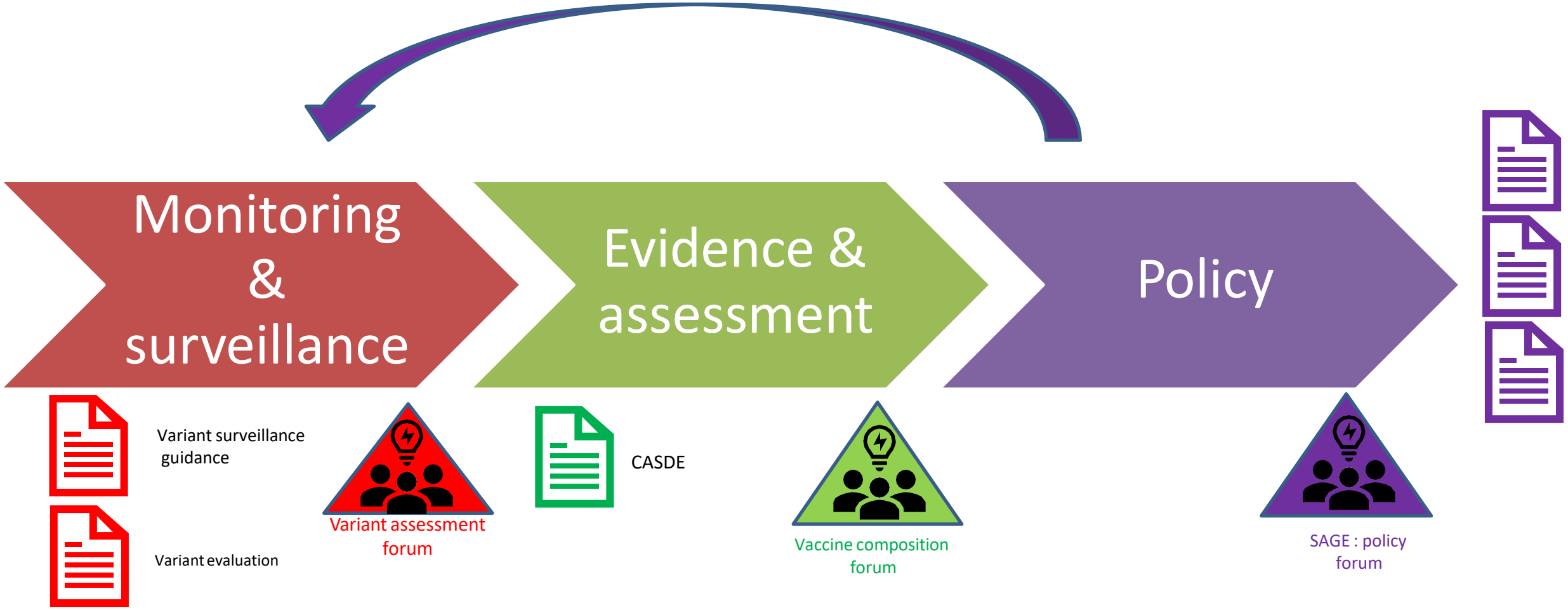


Figure 7. Countries, territories and areas reporting SARS-CoV-2 P.1 variant as of 23 March 2021



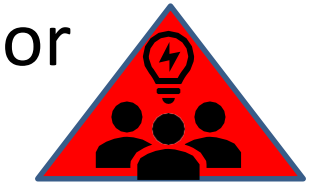
Life of a variant – considerations for decision-making (e.g. vaccine)



World Health Organization

Key questions on surveillance and monitoring of variants

Monitoring & surveillance



- What are the variant of concern? How can we detect and monitor them ?
- What is the impact of each SARS-CoV-2 variant on transmissibility and disease severity?
- What is the impact on risk groups?

- Challenges : uneven capacity for sequencing, need for standardized approaches for monitoring, need to bridge with other data sources (clinical, phylogenetic, disease surveillance, …)

Key questions on evidence and assessment (e.g. vaccine)

Evidence & assessment

- What is the impact of each variant on vaccine efficacy and effectiveness?
- Are changes to vaccine composition needed?
- What is the impact on research for new or modified vaccines?

COVID-19 Vaccine Composition forum

Evidence & assessment

- Vaccine composition forum purpose : Advise if vaccine composition changes are needed, to and if so, what would be the antigen(s) and what evidence is needed to ensure the best decision?
- Resources:
  - CASDE : Evidence framework,
  - Global data repository

Challenges :

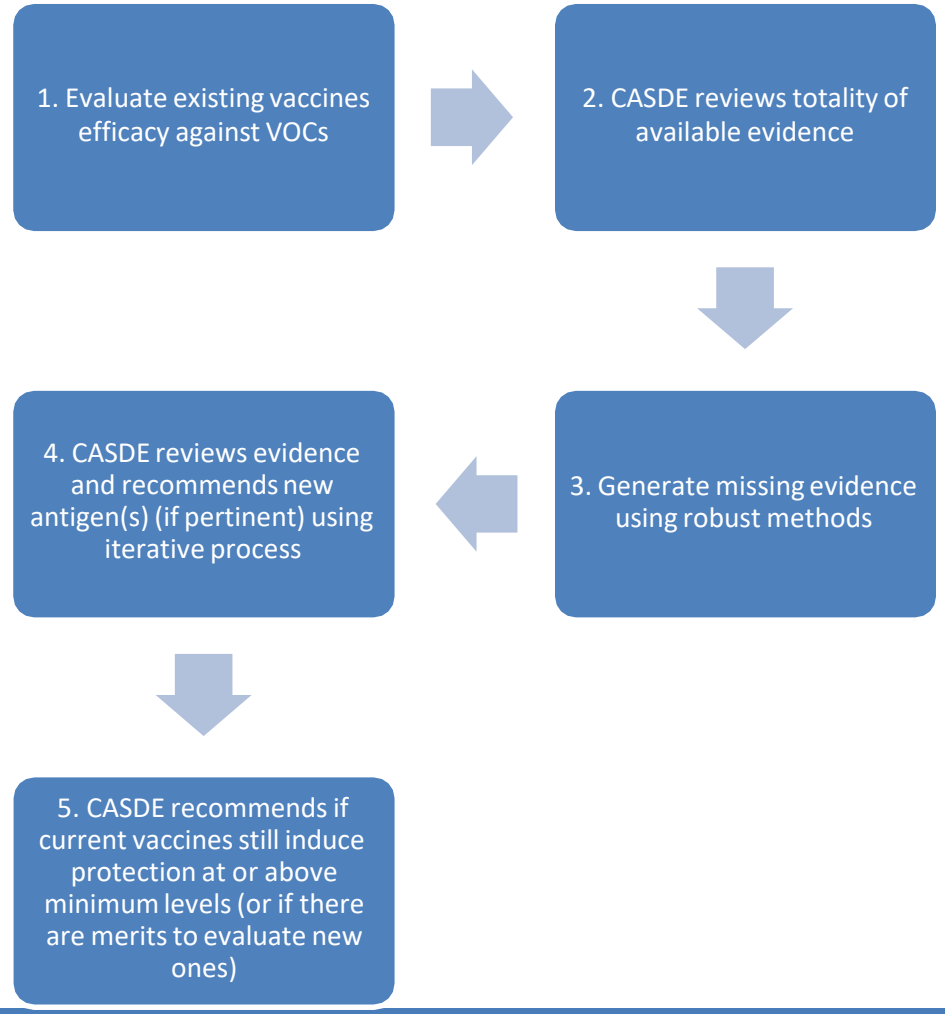
- different vaccines platforms and different immune responses, (duration of immunity?)
- lack of standardized assays
- need to define correlates of protection

World Health Organization

COVID-19 Antigen Selection, Development and Evaluation (CASDE) - DRAFT

Evidence & assessment

- Evidence framework for COVID-19 antigen selection, development, and evaluation
  - Do we need a new antigen?
  - What should the new antigen be?
  - How to evaluate modified vaccines or new vaccines?
- Provide recommendations on:
  - Evaluation of existing, modified, and new vaccines
  - Need for a new antigen for the COVID-19 vaccines
  - Interpretation of totality of evidence on the effect of VOCs on vaccines



World Health Organization

Key questions on policy

Policy

- Do vaccination policies need to be adapted because of the variant ?
- Should COVID-19 prevention and control recommendations be modified?
  - e.g. lifting Public health and social measures when the population is vaccinated?
  - Adapting the screening protocols in hospitals when a variant is circulating?

STAG–IH

STAG-IH & SAGE

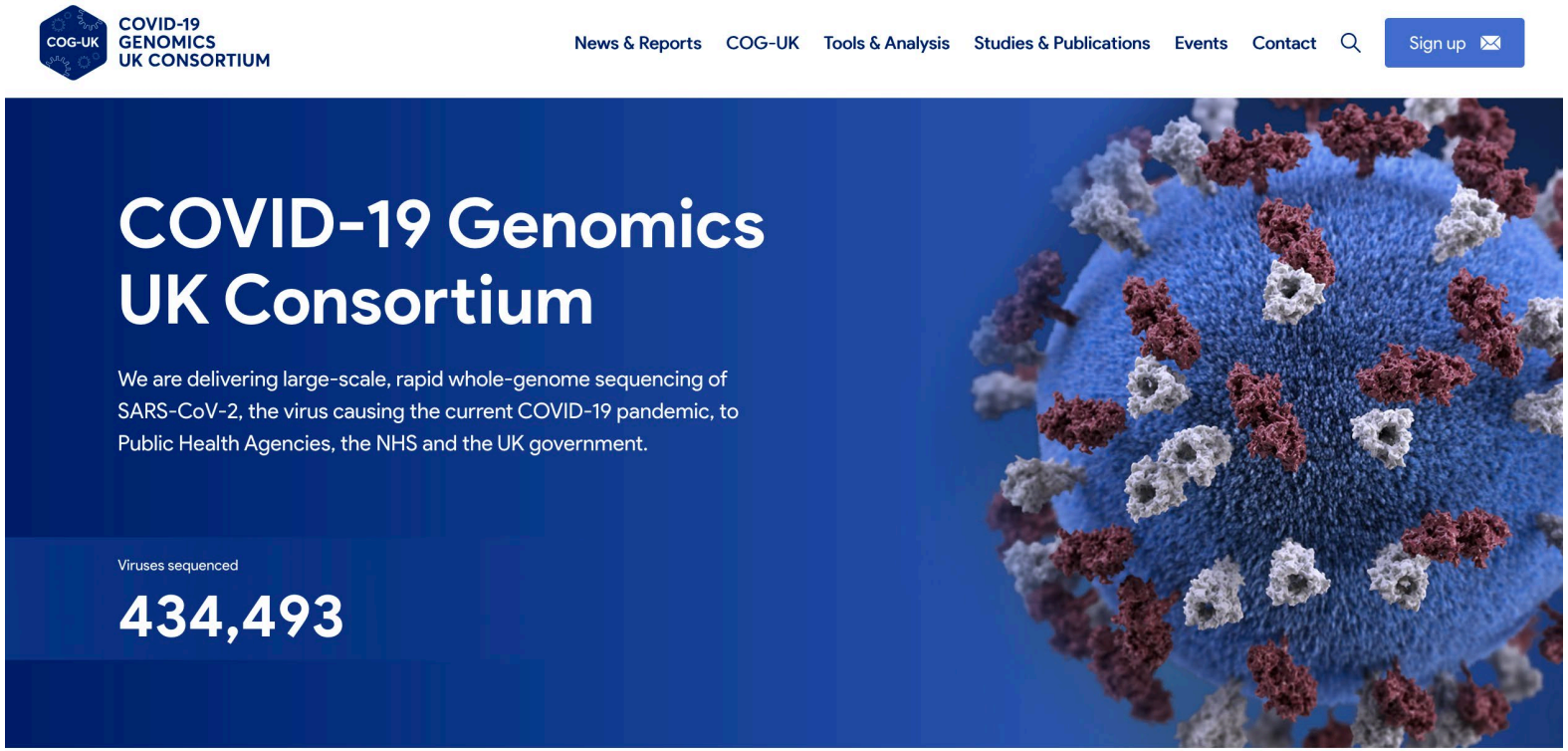
- Strategic and Technical Advisory Group for Infectious Hazards (STAG-IH)
  - Advises on overarching COVID-19 prevention and control

- Strategic Advisory Group of Experts on Immunization
  - Advises on vaccination strategies and policies, including strategies to limit spread of escape variants
  - COVID Vx Working Group
    - Weekly deliberations to gather and review evidence


World Health
Organization
Thank You

Pulling it all together in the COG-UK

Sharon Peacock,
COG-UK



Global & local approaches to detect and interpret SARS-COV-2 variants

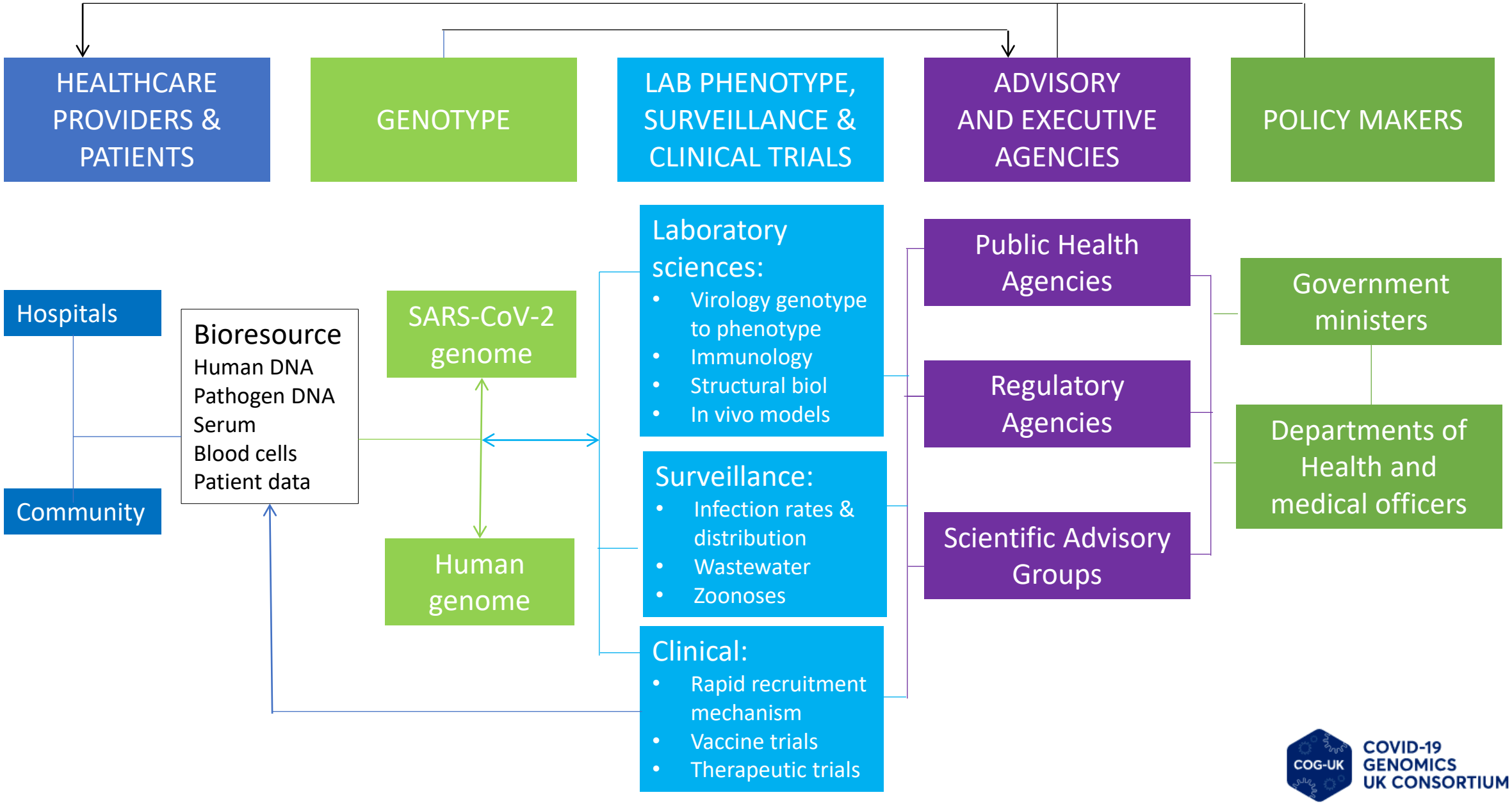
Pulling it all together in COG-UK

Sharon Peacock, 16th April 2021
University of Cambridge

COG-UK COVID-19 GENOMICS UK CONSORTIUM

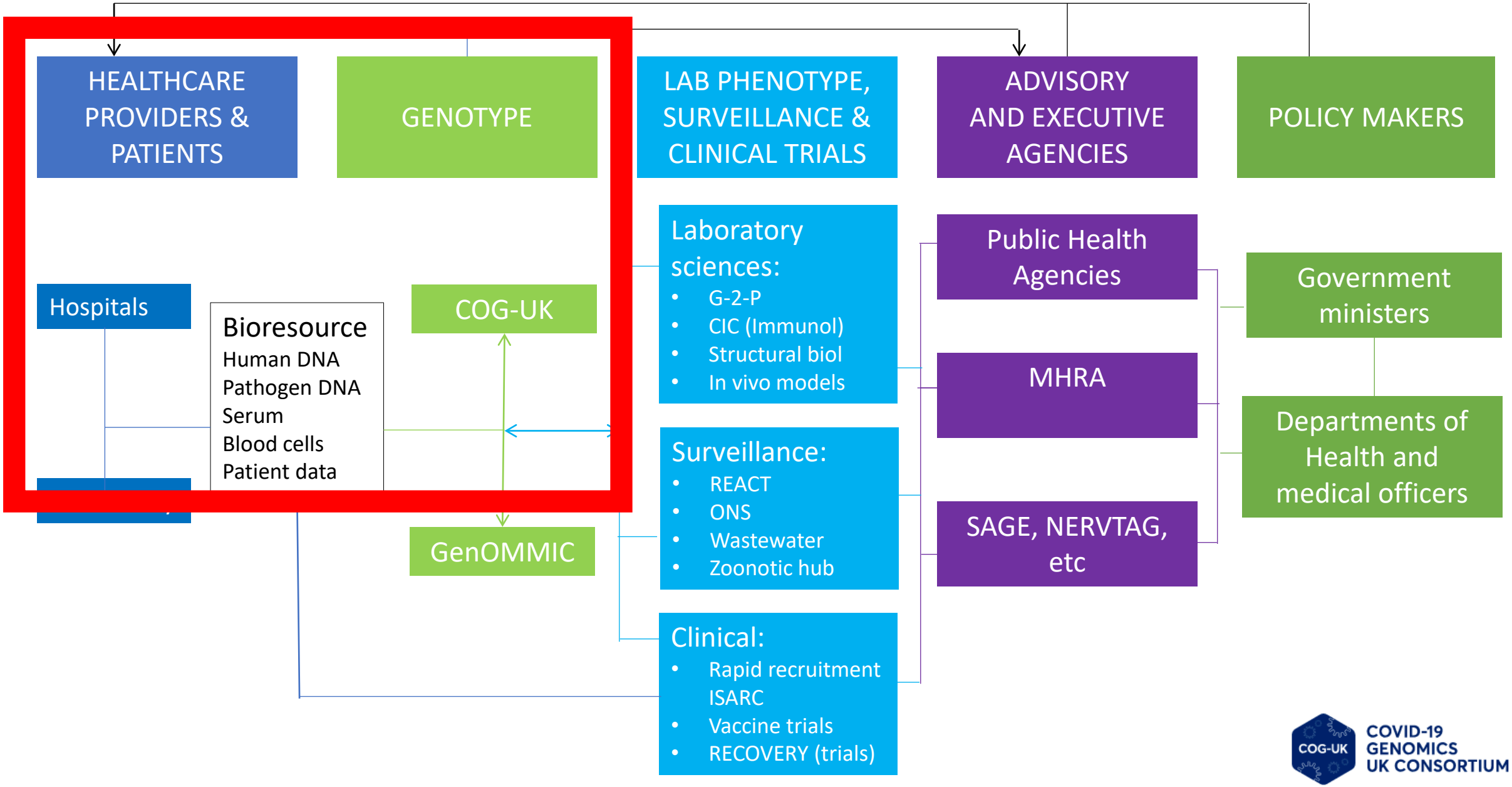
“How the UK has connected sequencing, epidemiology, virology and immunology to rapidly generate actionable information on the immunological consequences of SARS-CoV-2 variants”

Hypothetical national blueprint



COG-UK COVID-19 GENOMICS UK CONSORTIUM

UK National Situation



COG-UK COVID-19 GENOMICS UK CONSORTIUM

COVID-19 GENOMICS UK (COG-UK) consortium

16 regional sequencing sites

Central sequencing hub

wellcome sanger institute

Four public health agencies

Public Health England

GIG CYMRU NHS WALES | Iechyd Cyhoeddus Cymru Public Health Wales

HSC Public Health Agency | Public Health Scotland

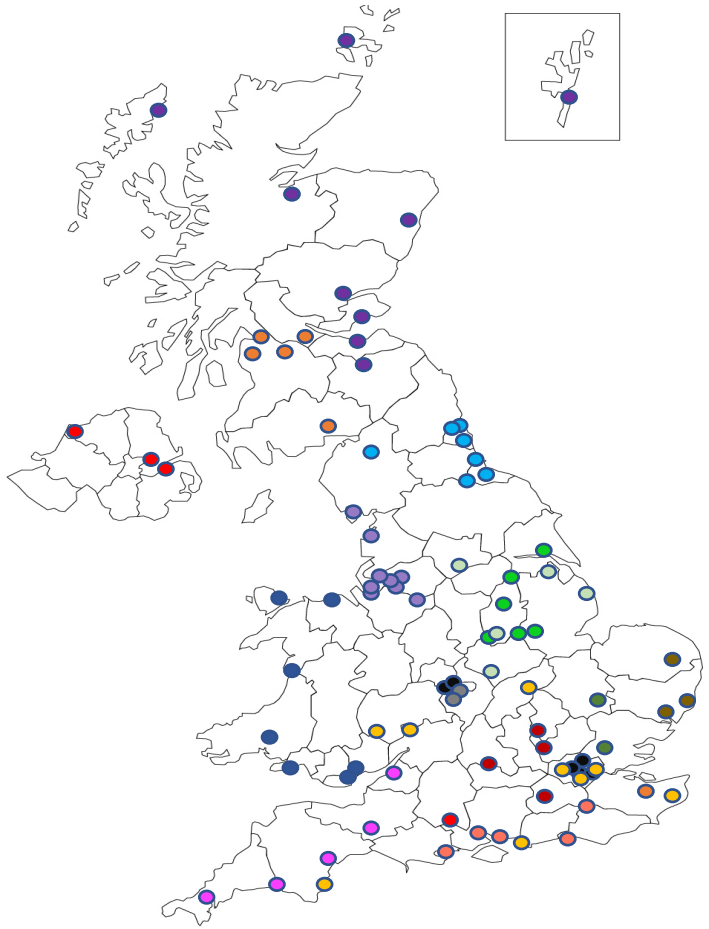
Project administration

UNIVERSITY OF CAMBRIDGE

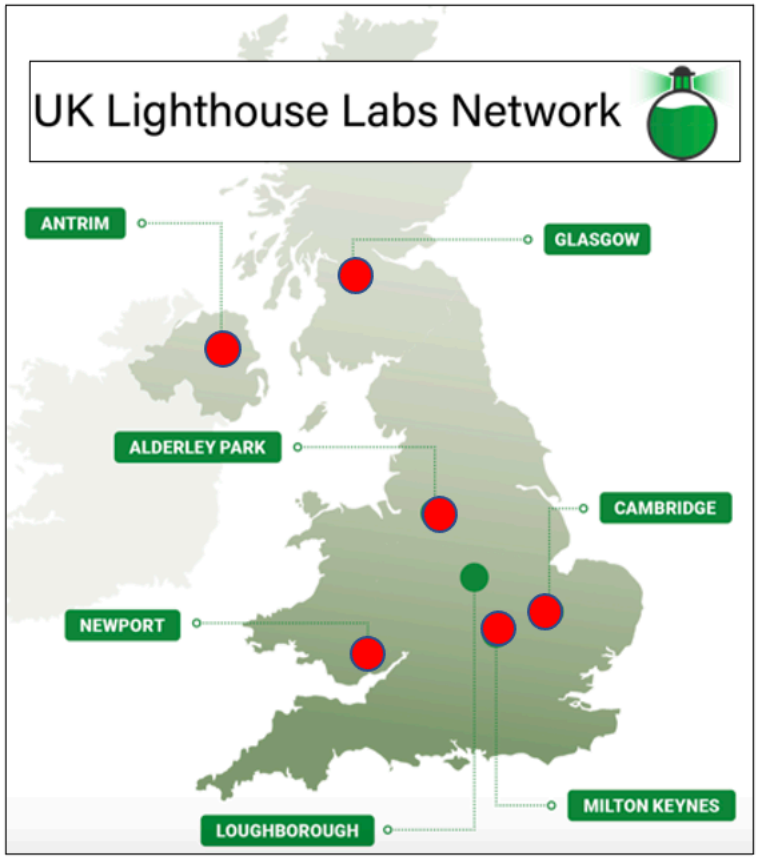
COG-UK COVID-19 GENOMICS UK CONSORTIUM

COG-UK sampling network, supported by sampling strategy

Hospital labs



Community testing



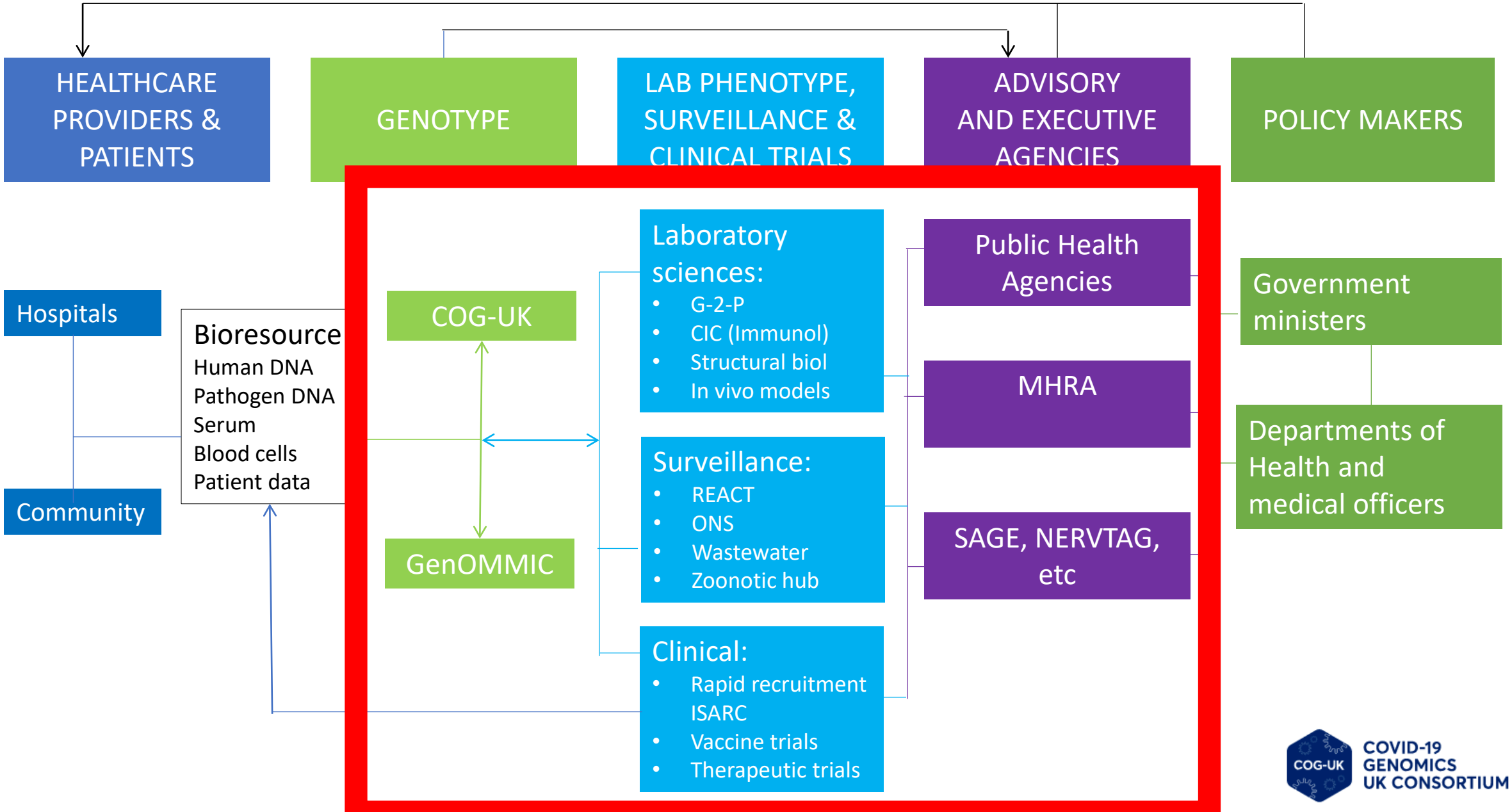
COG-UK COVID-19 GENOMICS UK CONSORTIUM

How and why did COG-UK work?

- Recent history of genomics
- In-country expertise
- Scientific leadership
- Early funding
- Existing NHS structures

- Bold, proactive decisions
- Pace over perfection
- Relentless organization on the hoof
- Willingness to give everything away
- Recognition of the wider science ecosystem and team science across disciplines

Assessing immune escape in the UK



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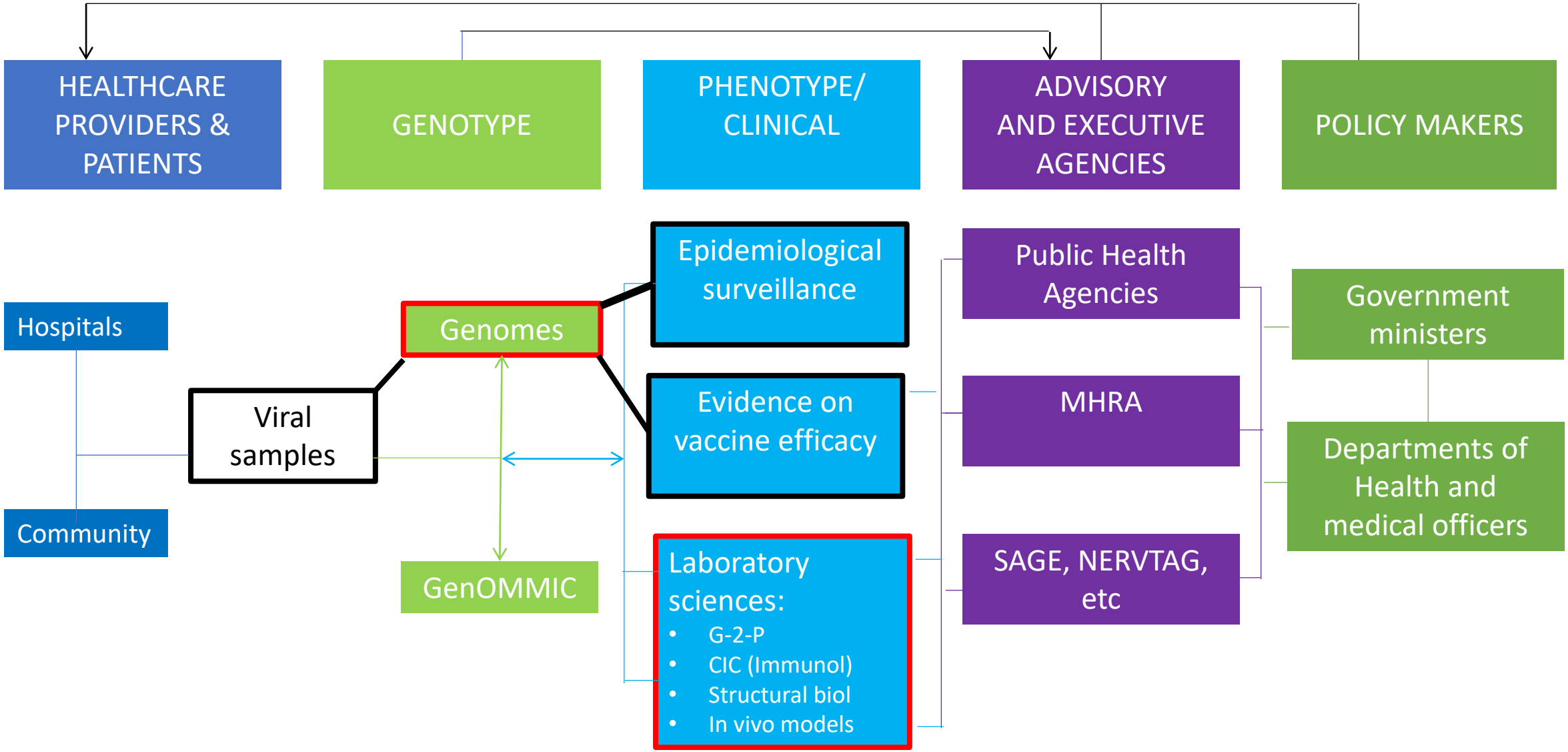
Priorities for assessing immune escape in LMIC



COG-UK COVID-19 GENOMICS UK CONSORTIUM

CEPI’s Agility program: a centralised approach to evaluate VOCs

Simon Funnell
PHE

Public Health England

Protecting and improving the nation's health

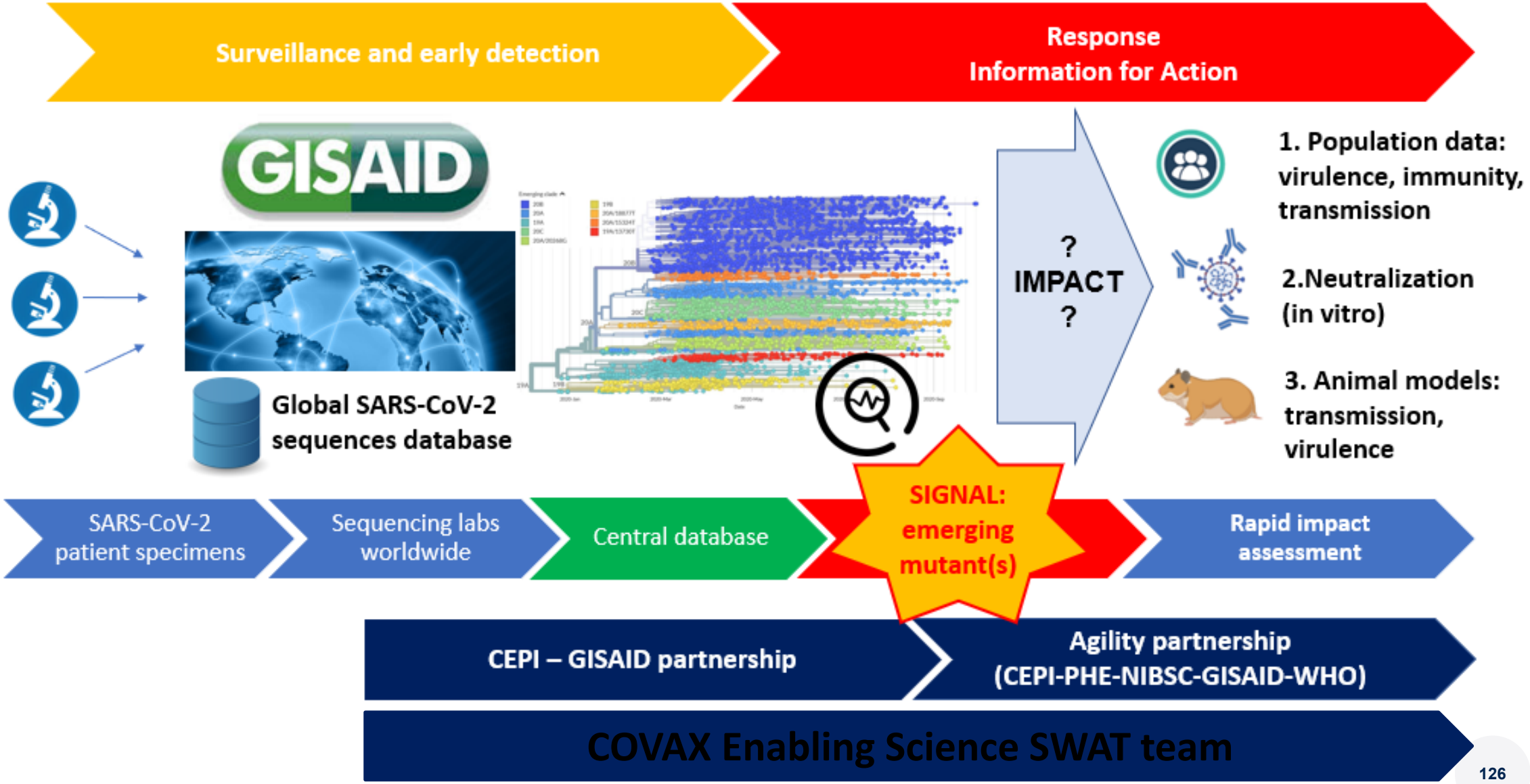
CEPI's Agility program: a centralised approach to evaluate VOCs

16 APRIL 2021

Dr Simon Funnell, Scientific Leader PHE
Drs S Charlton, Y Hall, K Bewley, B Hallis and PHE team including Dr Naomi Coombes
Drs Y LeDuff, N Berry and NIBSC team
Drs Celine Gurry, Amy Shurtleff and CEPI staff
GISAID, WHO and clinical and global collaborators

Public Health England

Agility project: Genomic surveillance and response for COVID-19 R&D



Public Health England

Aims of Agility project

- **Rapid identification of new variants** of SARS-CoV-2 that may impact COVID-19 vaccines and countermeasures
- **Comparative neutralisation testing** of identified variants of concern using a panel of sera and WHO International antibody standard
- **Timely reports and information sharing on the biological activity** (antigenic characteristics and pathogenesis in animals) of emerging variants
- **Predictability** and **comparability** achieved through standard procedures and parallel testing in 2 independent laboratories

CEPI

Public Health England

Cross-cutting project & integration of CEPI Enabling Sciences programmes

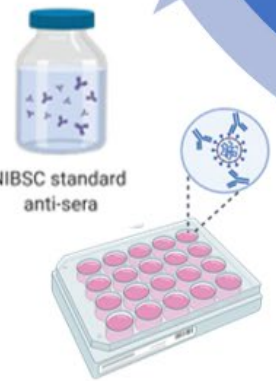
CEPI Animal Models

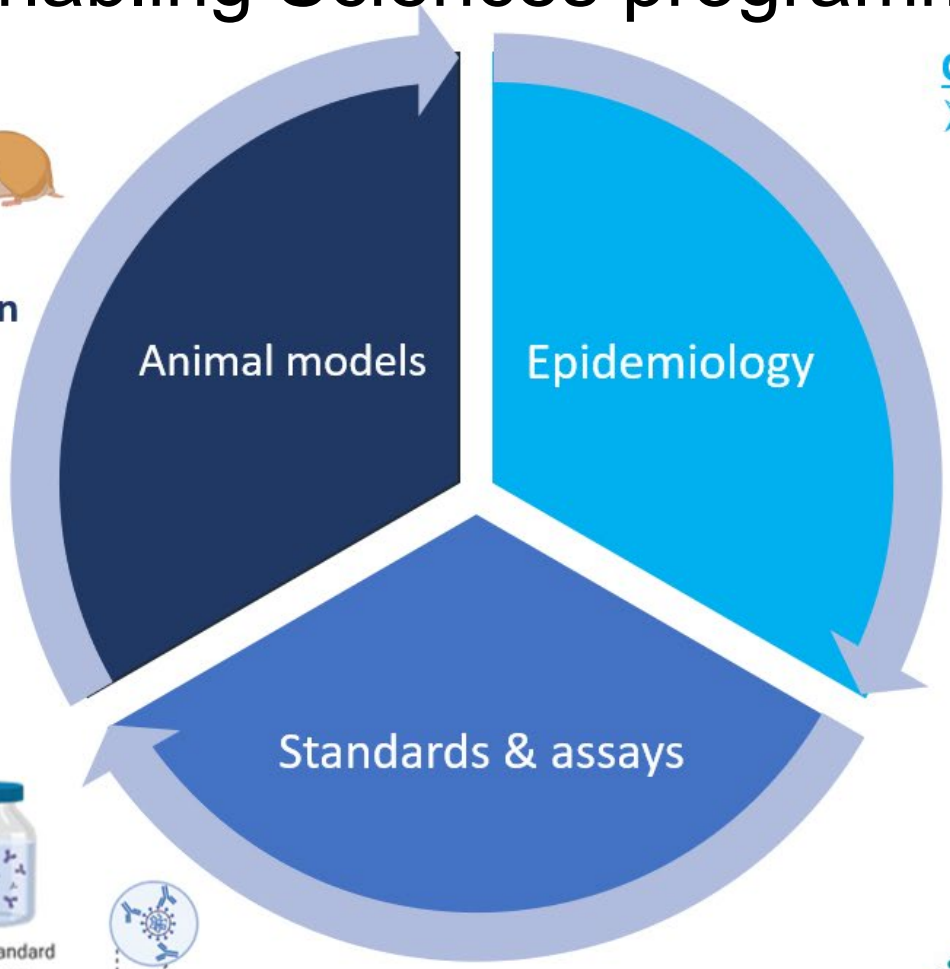
- **Virulence investigation in hamster model**

UK Health Security Agency
NVAP and others

Public Health England

- **Preparation and characterization of virus stock**

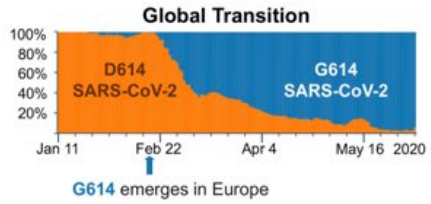


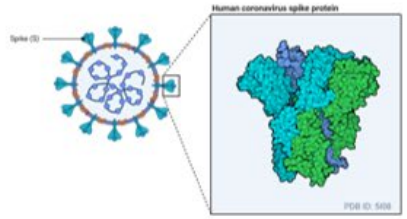


CEPI Epidemiology

- **Genomic surveillance (population-level)**

GISAID





CEPI Standards and Assays Program

- **Neutralisation testing of new virus**
- **Use of antibody standard**

NIBSC
Confidence in Biological Medicines

Public Health England

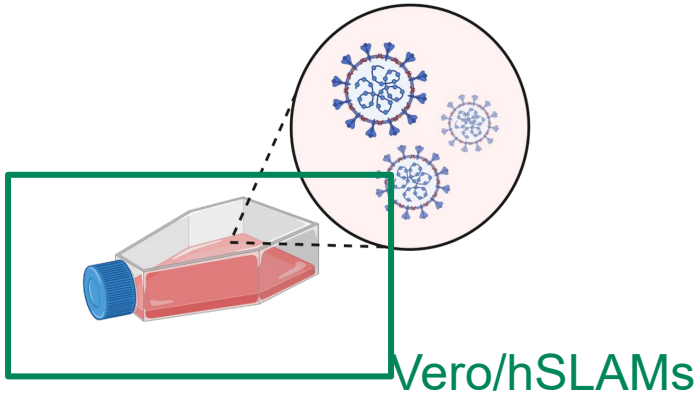
ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

UK Health Security Agency
NVAP and others

Public Health England

Summary of steps in Agility project

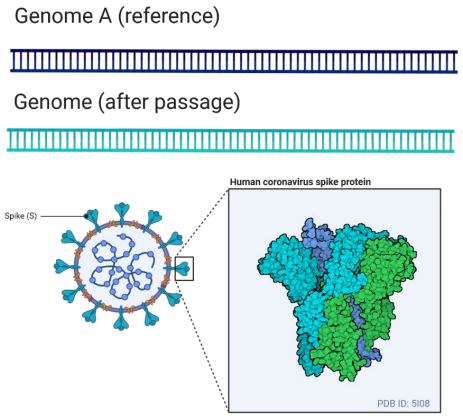
A Propagation and viral stock for availability for R&D



Outputs

Viral stock propagated according to best practice for fidelity and availability of stock for lab work and R&D partners

B Sequencing (post-expansion)

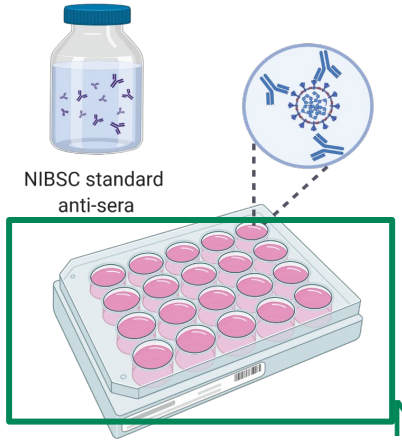


Outputs

Characterisation of viral stock

Information on viral stability and growth

C In vitro testing: neutralization (NIBSC antibody std)



Outputs

Comparative neutralisation sensitivity (**results from parallel testing in 2 independent facilities)**

If possible, cross-neutralisation by vaccinated sera

D In vivo testing: transmission / pathogenesis (hamster model)

Outputs

Information on changes in virulence in animal models

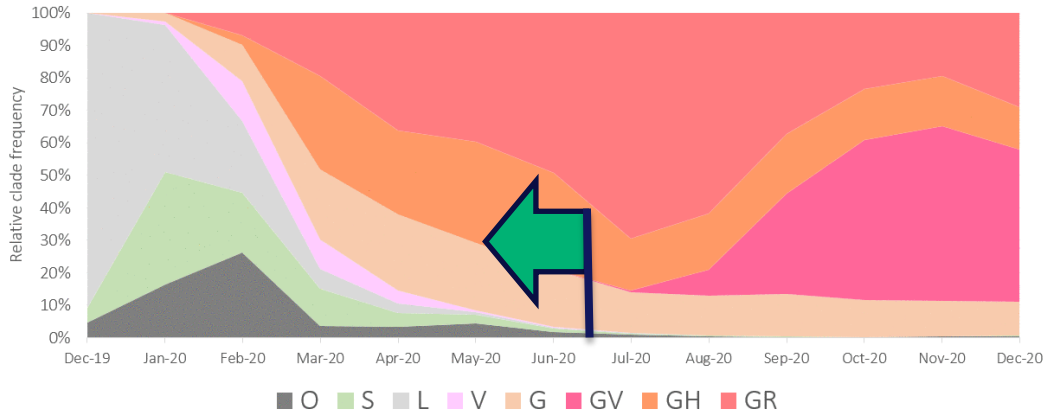
Cross-protection studies (whether infection with earlier variant protective)

Public Health England

The NIBSC Agility convalescent panel

All sera were taken before July 2020

Clade evolution in the first year



GISAID clades and PANGO lineages

by BII/GIS, A*STAR Singapore

GISAID

Public Health England

Wild virus neutralisation data (ND50)

	Vic01	Kent	V/K	SA	V/SA	JxB	V/SA
NIBSC ID	B	B.1.1.7	Fold lower	B.1.351*	Fold lower	P.1*	Fold lower
NIBSC 7	21,789	2,202	9.9	298	73.1	1043	20.1
NIBSC 24	5,386	1,349	4.0	123	43.8	665	8.1
NIBSC 32	7,003	672	10.4	43	163	276	25.4
NIBSC 33	8,288	718	11.5	88	94.2	858	9.5
NIBSC 31	3,952	739	5.3	78	50.7	259	5.3
NIBSC 61	4,258	344	12.4	78	50.6	308	13.8
NIBSC 82	4,374	587	7.5	143	30.6	355	12.3
NIBSC 78	7,333	1,593	4.6	131	56.0	588	12.5
20/136	7,545	1,039	7.3	211	35.7	417	18.1
	Average reduction		8.2		66.4		13.9

* Data using WHO IS as reference for curve fitting

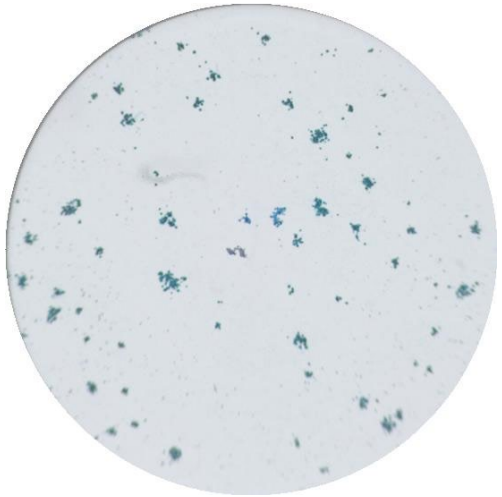
1. All sera neutralised all viruses 2. The performance of the NIBSC International standard against B.1.351 was better than the panel but similar for B.1.1.7 and P.1

Public Health England

Foci Morphology

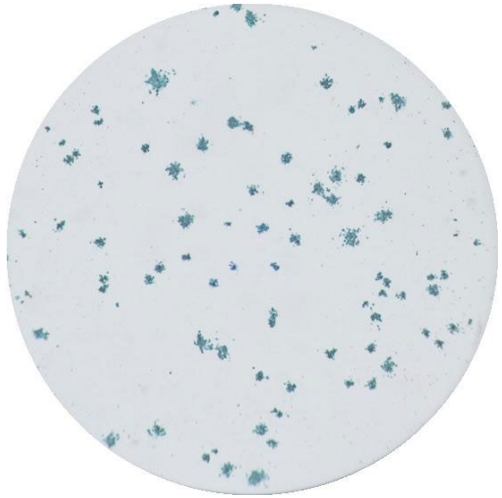
B Foci (Victoria)
24 h post-infection

“Cluster 5” (Danish)Foci
24 h post-infection

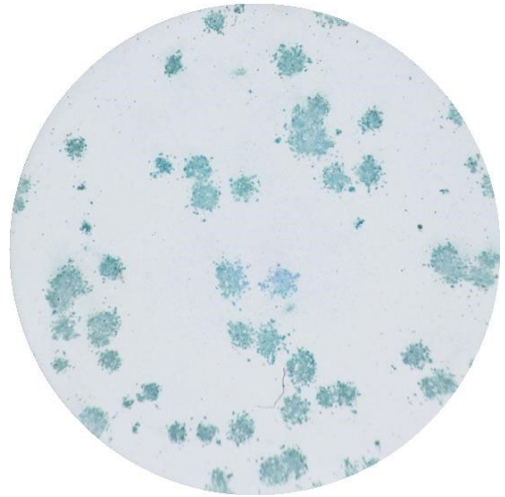


B.1.1.7 (Kent) Foci
24 h post-infection

P.1 (JxB) Foci
24 h post-infection



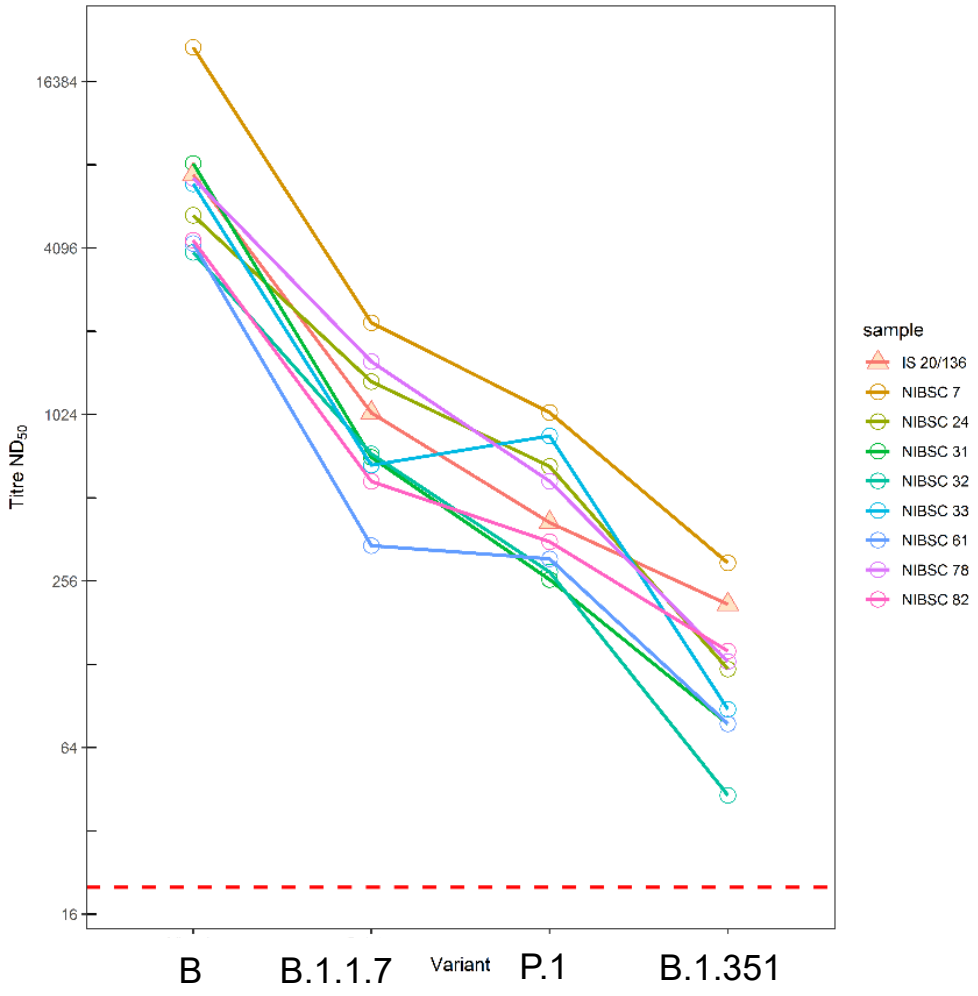
B.1.351 (RSA) Foci
24 h post-infection

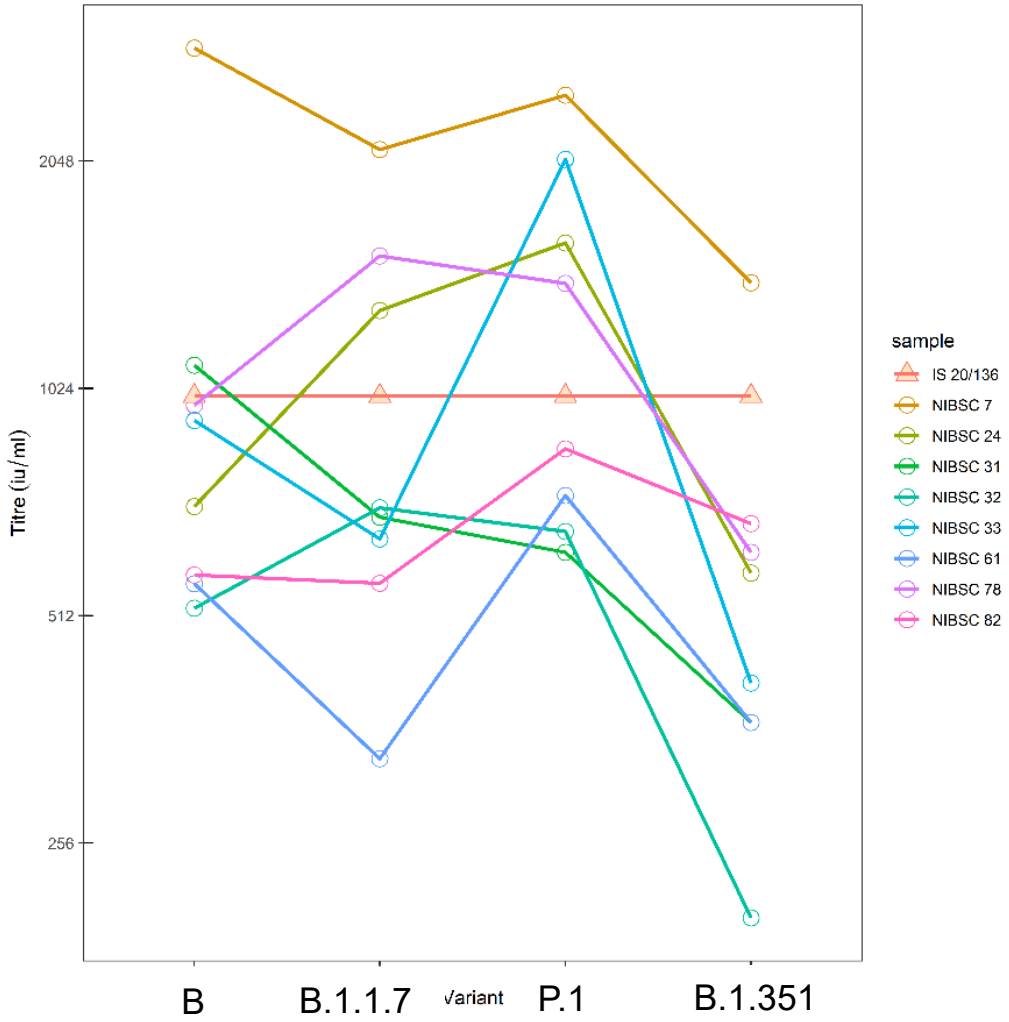


Post-infection fixation time (P.1, B.1.351) optimised further to standardise foci appearance for automated counting

Public Health England

IS 20/136 ND50 pattern is different

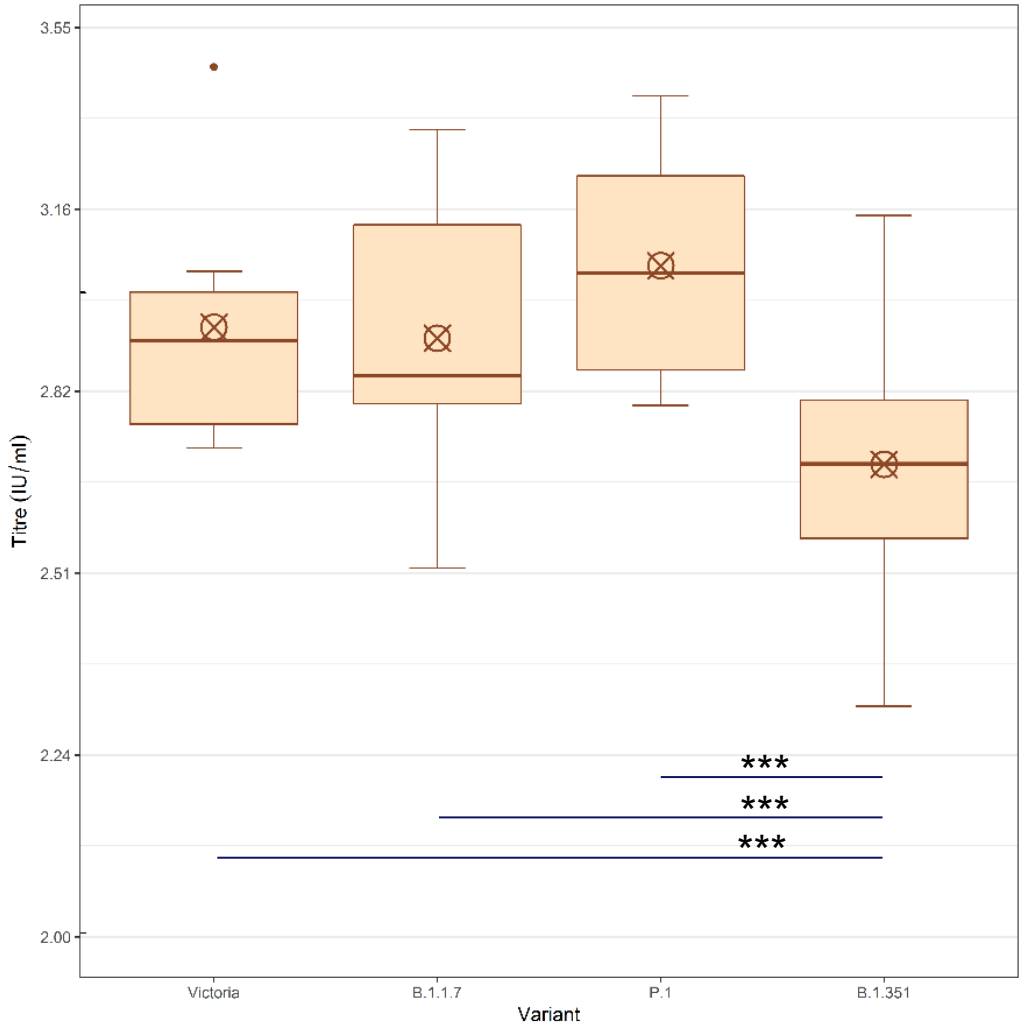




Lines drawn for illustration purposes only

Public Health England

Graphical summary in IU/ml



B B.1.1.7 P.1 B.1.351

Parametric testing including repeat measures adjustment

contrast	estimate	fold	std.error	statistic	adj.p.value
B.1.1.7 - Victoria	-0.018	1.043	0.069	-0.263	0.994
P.1 - Victoria	0.116	1.308	0.069	1.690	0.329
B.1.351 - Victoria	-0.242	1.748	0.069	-3.519	0.002
P.1 - B.1.1.7	0.135	1.363	0.069	1.953	0.206
B.1.351 - B.1.1.7	-0.224	1.676	0.069	-3.256	0.006
B.1.351 - P.1	-0.359	2.285	0.069	-5.209	0.000

These tests only show B.1.351 to be less susceptible using the contemporary convalescent panel

Public Health England

Ongoing and prospective studies

- Horizon scanning – ongoing with global input from multiple sources

- Sourcing of VOCs – challenging to remain “Agile”
  - Reliance on international collaborations (NVAP and others)
  - Hindered by MTA and regulatory shipping restrictions

Public Health England

Building partnerships and collaborations

CEPI

World Health Organization

NIBSC
Confidence in Biological Medicines

GISAID

Public Health England

UK Health Security Agency

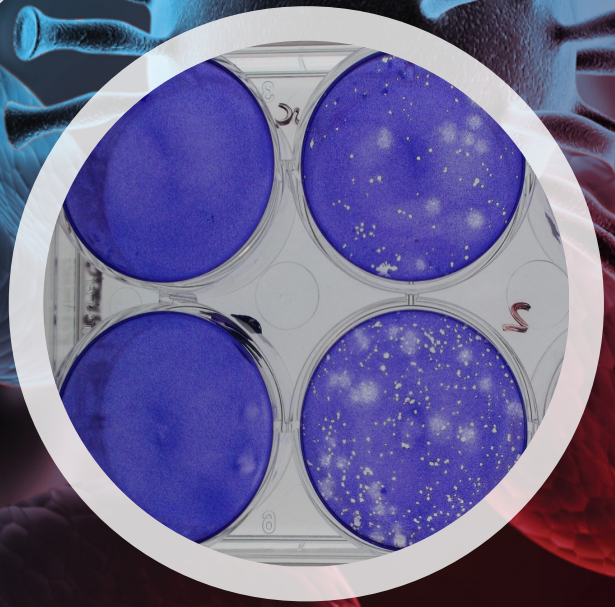
NVAP & others

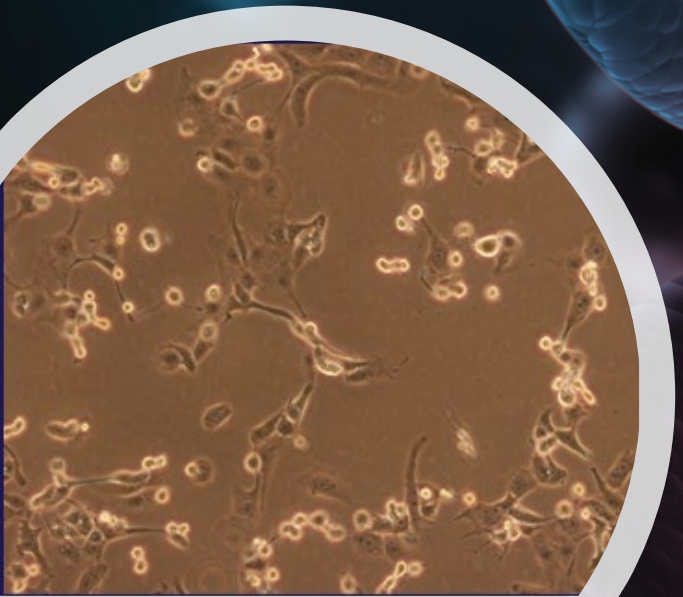
ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

Production of SARS-CoV-2 Stocks

Sujatha Rashid, PhD

BEI





PRODUCTION OF SARS-CoV-2 STOCKS

HHSN272201600013C

Sujatha Rashid, Ph.D.
Program Manager
BEI Resources

ATCC | Credible leads to In™

Outline

- Brief Introduction to BEI Resources
- Propagation of SARS-CoV-2
- NGS pipeline
- Recommendations
- Acknowledgements

b|e|i RESOURCES

SUPPORTING INFECTIOUS DISEASE RESEARCH

History

The National Institute of Allergy and Infectious Diseases (NIAID) awarded the BEI Resources contract to ATCC in 2003.

Mission of BEI Resources

Provide NIAID with a central bioresource program for the acquisition, authentication, production, preservation, storage, and distribution of a broad range of unique and quality assured research materials for the infectious disease research community that will aid in the development and evaluation of vaccines, therapeutics, and diagnostics.

SARS-CoV-2 Response

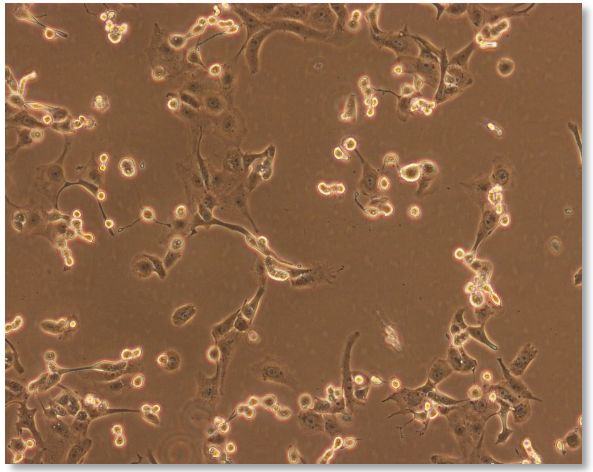
- Receipt, production, authentication and distribution of global SARS-CoV-2 isolates
- Optimization of methods for SARS-CoV-2 propagation, assays and sequencing
- Catalog of ~170 SARS-CoV-2 products to support the research community including derivative reagents, proteins, antibodies, cell lines, plasmids/vectors, human clinical samples and peptide arrays

Propagation of SARS-CoV-2 (Vero cell lines)

- Vero cell lines: Vero 76, Vero E6, Vero/hSLAM
- Virus acquire adaptive mutations, specifically point mutations or deletions in spike cleavage site
- Adaptive mutant populations quickly accumulate with increasing virus passages
- Reproducibility/reported discrepancy compounded as all Vero lines are heterogenous population of cells (e.g., affects accuracy in titers)
- Critical role of furin cleavage site in pathogenesis
- Vero E6/TMPRSS2 for reducing selection of spike mutants

Johnson et al. Nature, Vol 59, 11 March 2021

Loss of furin cleavage site attenuates SARS-CoV-2 pathogenesis

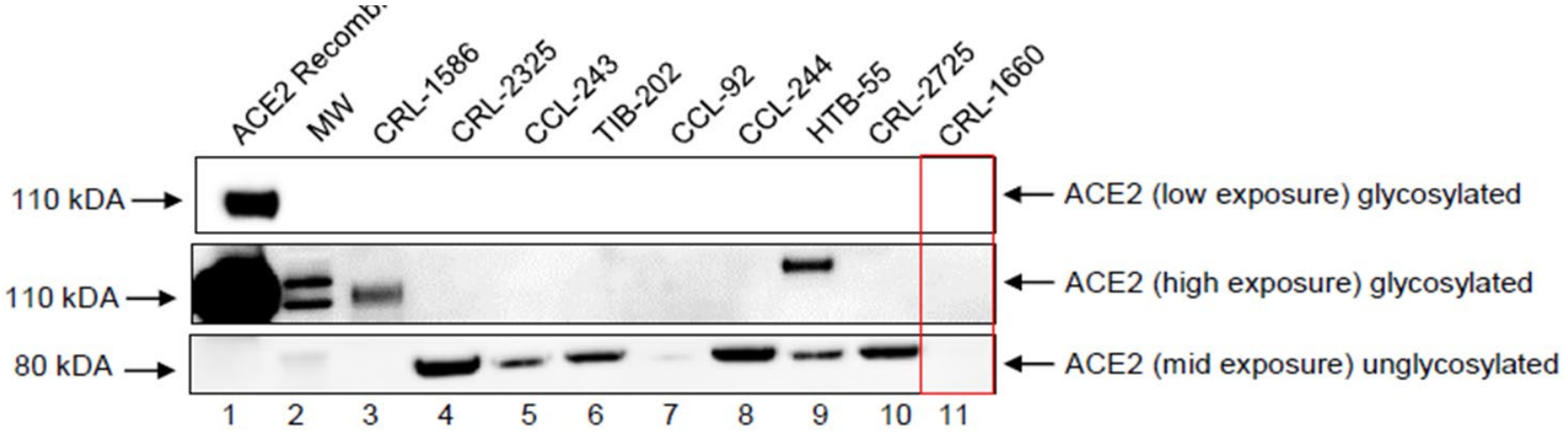


NR-52281 - SARS-CoV-2, Isolate USA-WA1/2020 grown in Vero E6

b|e|i RESOURCES
SUPPORTING INFECTIOUS DISEASE RESEARCH

Propagation of SARS-CoV-2 (Calu-3)

- Calu-3 (ATCC® HTB-55™), derived from human lung adenocarcinoma
- Expresses high endogenous ACE2 (see figure below)
- Virus genome appears to be more stable as evidenced by very low frequency of point mutations
- Slow grower, requires frequent media changes for healthy monolayer
- Heterogenous population requires good batch of cell bank



Variant Analysis for Virus stock 1.351 (EPI_ISL_678615)

Position in Wuhan-Hu-1	Position in Reference	Wuhan-Hu-1	Reference	Sample	Sample Frequency	Region	AA change
1963	1961	T	T	A	6%	Nsp2	--
10809	10807	C	C	T	54%	Nsp5	P252L
11020	11018	C	C	T	25%	Nsp6	--
11750	11739	C	C	T	10%	Nsp6	L260F
13339	13328	T	T	G	26%	Nsp10	N105K
14679	14668	T	T	C	18%	Nsp12	--
17339	17328	C	C	T	7%	Nsp13	A368V
21651	21640	A	A	C	12%	Spike	N30T
22114	22103	T	T	C	11%	Spike	--
23593	23573	G	G	T	90%	Spike	Q677H
23606	23586	C	C	T	90%	Spike	R682W
25806	25786	A	A	G	5%	ORF3a	--
25810	25790	C	C	T	14%	ORF3a	L140F
26822	V	C	C	T	7%	M	--
26984	26874	C	C	T	6%	M	--
27393	27373	C	C	T	63%	btw ORF6/7	--
27627	27607	T	T	A	28%	ORF7a	--
28237	28217	G	G	T	90%	ORF8	R115L
28368	28348	G	G	A	9%	N	R32H
29821	29801	T	T	G	12%	3'UTR	--

Vero/hSLAM

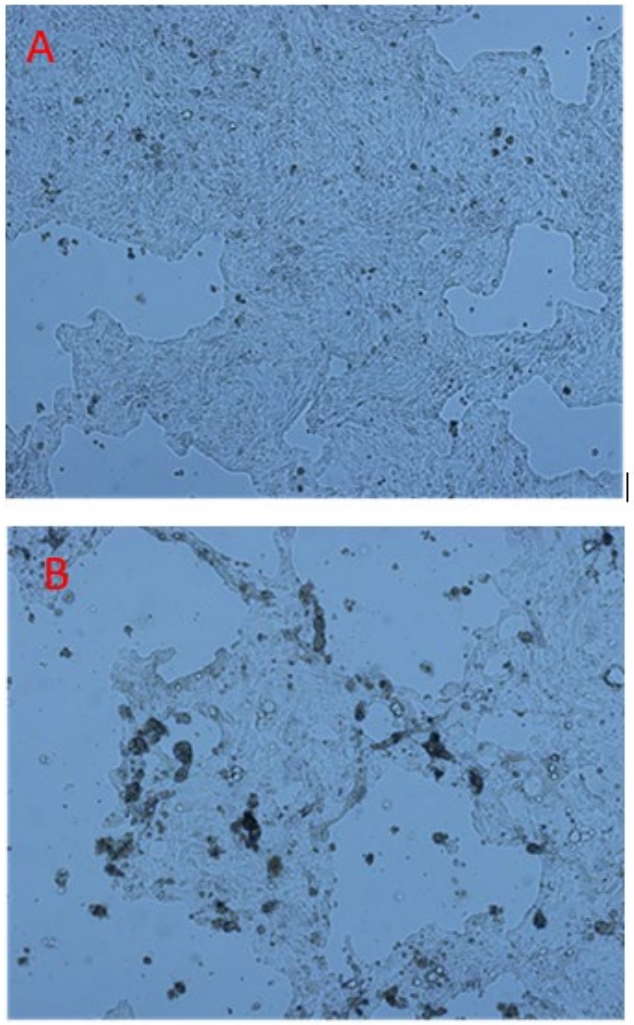
- **p3 received (isolated in H1299-hACE2-E3, followed by 2 passages in Vero E6)**
- **BEI p4:Vero/hSLAM vs Calu-3 (Blue:** SNPs in both stocks)

Position in Wuhan-Hu-1	Position in Reference	Wuhan-Hu-1	Reference	Sample	Sample Frequency	Region	AA change
1963	1961	T	T	C	9%	Nsp2	--
1963	1961	T	T	G	6%	Nsp2	--
3721	3719	T	T	C	9%	Nsp3	--
8821	8819	A	A	G	9%	Nsp4	--
10082	10080	T	T	C	5%	Nsp5	S10L
10451	10449	A	A	G	9%	Nsp5	N133D
11020	11018	C	C	T	95%	Nsp6	--
13339	13328	T	T	G	94%	Nsp10	N105K
14679	14668	T	T	C	22%	Nsp12	--
15909	15898	T	T	C	6%	Nsp12	--
22114	22103	T	T	C	12%	Spike	--
25806	25786	A	A	G	6%	ORF3a	--
28237	28217	G	G	T	6%	ORF8	R115L
28368	28348	G	G	A	90%	N	R32H
29821	29801	T	T	G	92%	3'UTR	--

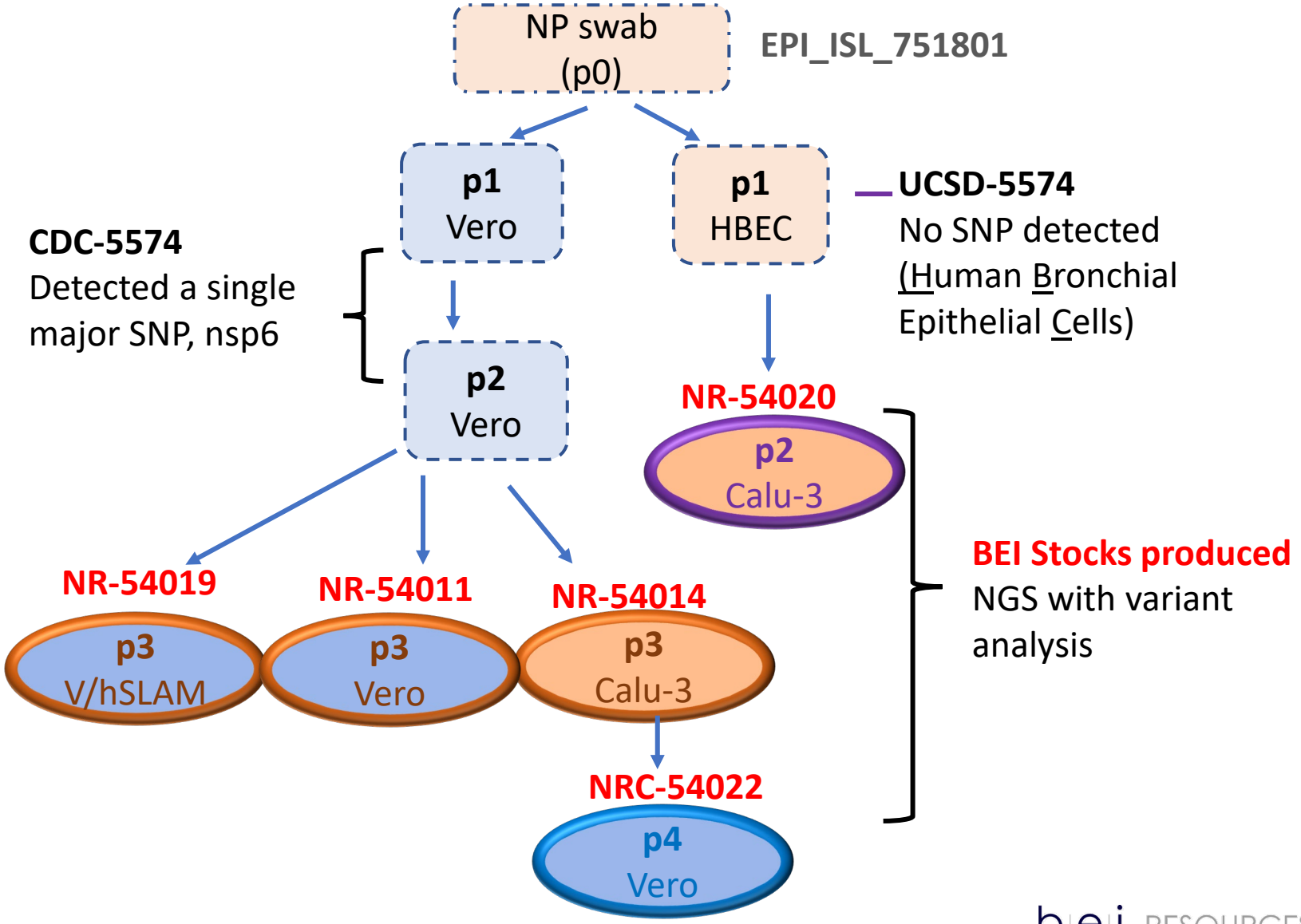
Calu-3

beiresources
SUPPORTING INFECTIOUS DISEASE RESEARCH

B.1.1.7 variant, Sample: hCoV-19/USA/CA-SEARCH-5574/2020



NR-54014 (A) mock (B) virus infected; Calu-3, 3dpi, 4X bright



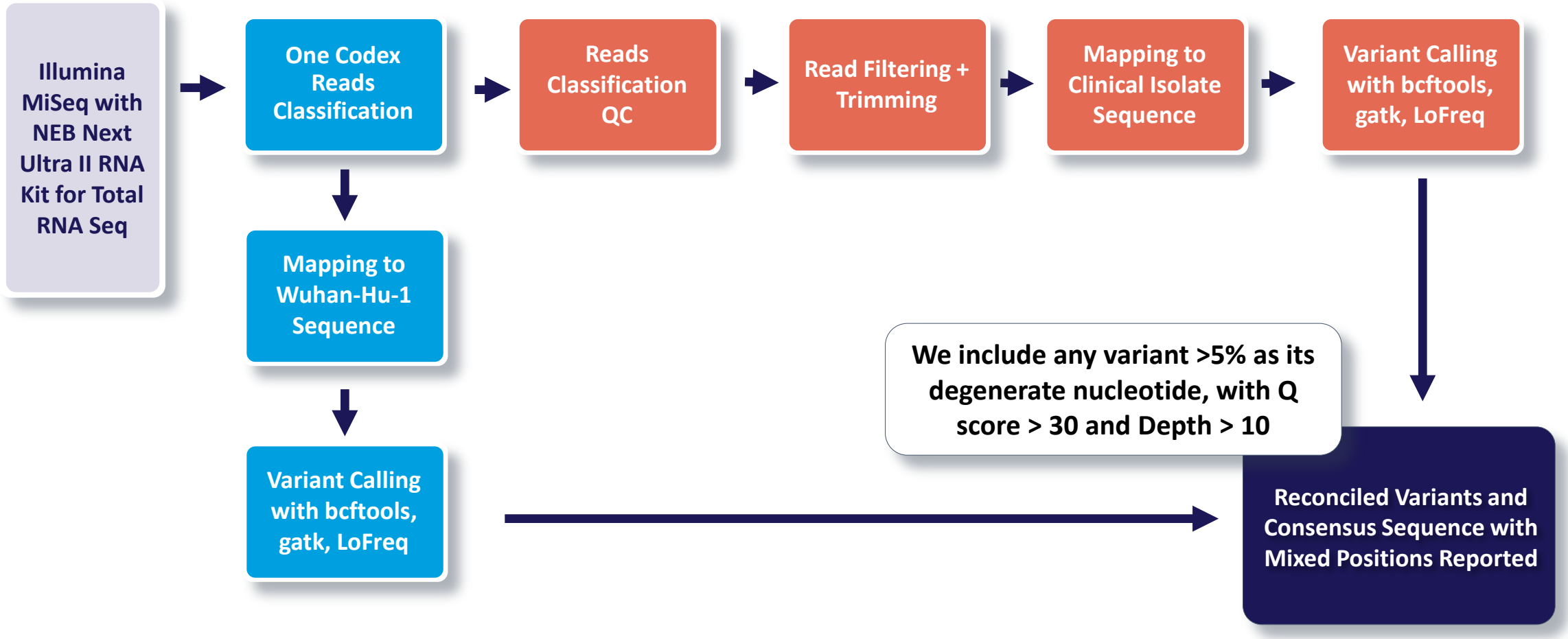
Variant Analysis for Virus stocks (B.1.1.7)

b|e|i RESOURCES
SUPPORTING INFECTIOUS DISEASE RESEARCH

BEI Cat.#	Position in Wuhan-Hu-1	Position in Reference	Wuhan-Hu-1	Reference	Sample	Sample Frequency	Gene (Region)	AA Mutation
NR-54011 p3 (Vero) 2.8 × 10 E4 $TCID_{50}$/mL	11750	11687	C	C	T	100%	ORF1ab (nsp6)	L260F
	14679	14616	T	T	C	6%	ORF1ab (nsp12)	--
NR-54019 p3 (V to V/hSLAM) 2.8 x 10 E6 $TCID_{50}$/mL	3625	3571	A	A	G	5%	ORF1ab (nsp3)	--
	8123	8069	C	C	T	8%	ORF1ab (nsp3)	L1802F
	11750	11687	C	C	T	99%	ORF1ab (nsp6)	L260F
	14679	14616	T	T	C	6%	ORF1ab (nsp12)	--
	21784	21715	T	T	A	5%	S	N74K
NR-54014 p3 (V to C) 8.9 x 10 E5 $TCID_{50}$/mL	3625	3571	A	A	G	5%	ORF1ab (nsp3)	--
	11750	11687	C	C	T	95%	ORF1ab (nsp6)	L260F
	28144	28072	T	T	C	6%	ORF8	L84S
NRC-54022 p4 (V to C to V) 5.0 x 10 E4 $TCID_{50}$/mL	3625	3571	A	A	G	5%	ORF1ab (nsp3)	--
	8123	8069	C	C	T	13%	ORF1ab (nsp3)	L1802F
	11050	10996	C	C	T	7%	ORF1ab (nsp6)	--
	11750	11687	C	C	T	96%	ORF1ab (nsp6)	L260F
	17895	17832	T	T	C	5%	ORF1ab (nsp13)	--
	25201	25129	A	A	G	5%	S	--
	26345	26273	T	T	G	12%	E	L34R
NR-54020 p2 (HBEC to C) 2.8 x 10 E4 $TCID_{50}$/mL	1963	1909	T	T	G	5%	ORF1ab (nsp2)	--
	4456	4402	C	C	T	19%	ORF1ab (nsp3)	--
	8821	8767	A	A	G	5%	ORF1ab (nsp4)	--
	14679	14616	T	T	C	6%	ORF1ab (nsp12)	--
	15909	15846	T	T	C	6%	ORF1ab (nsp12)	--
	22114	22042	T	T	C	9%	ORF8	L84S

Reference-Based RNA Virus Pipeline

Sequencing SARS-CoV-2 Isolates



b|e|i RESOURCES
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Recommendations

- Use low MOI (0.00001), reduce number of passages
- QC check virus stock: NGS with variant analysis with Wuhan and the specific virus (p0) as references
- Develop sequencing pipeline to help detect minor variants and deletions (Lofreq, bcf tools, Freebayes)
- Virus titer and other cell-based assays standardization
- Virus isolation of variants, consider using Vero/TMPRSS2
- Other cell lines: Vero/TMPRSS2/ACE2, Vero/furin, Calu-3 2B4 (heACE2)
- Check our website www. Beiresources.org (variants, cell lines, Knowledge Base for tips)
- Any questions/inquiries **Contact@Beiresources.org**

Acknowledgments

- NIAID (Kimberly Stemple, Mark Williams, Clint Florence)
- BEI Resources Virology staff
- ATCC Sequencing Core Facility
- Virus Depositors

SARS-CoV-2 Interagency Group (SIG) Variant Assessment/ Characterization

Steve Oberste

CDC

SARS-CoV-2 Interagency Group

APRIL 16, 2021

MANAGING LEADERSHIP: CDC, BARDA, NIAID

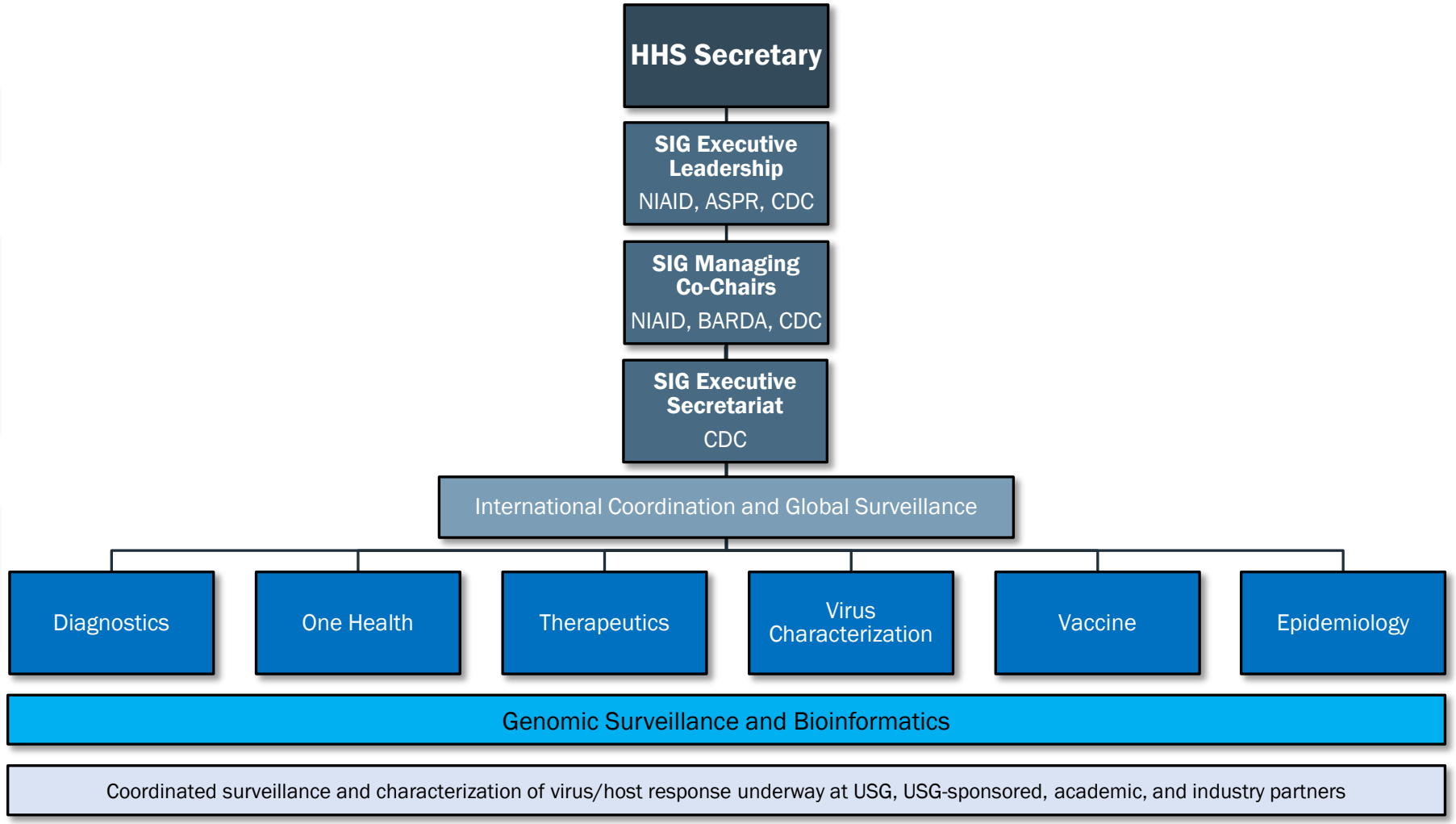
SARS-CoV-2 Interagency Group (SIG) Structure

Coordinating the Response to SARS-CoV-2 Variants

- Decision Making
- Recommendations

- Coordination of tools/assays
  - Harmonization
  - Development
  - Validation
- Quality assurance and control
- Regulatory Impacts

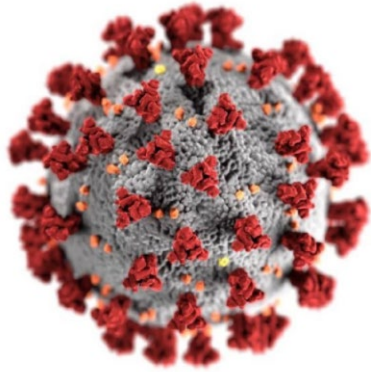
- Risk assessment
- Variant prioritization
- Gap identification
- Cross-sector coordination



ASPR: Assistant Secretary for Preparedness and Response
BARDA: Biomedical Advanced Research and Development Authority

CDC: Centers for Disease Control and Prevention
NIAID: National Institute of Allergy and Infectious Diseases

SARS-CoV-2 Interagency Working Group (SIG) Mission & Goals



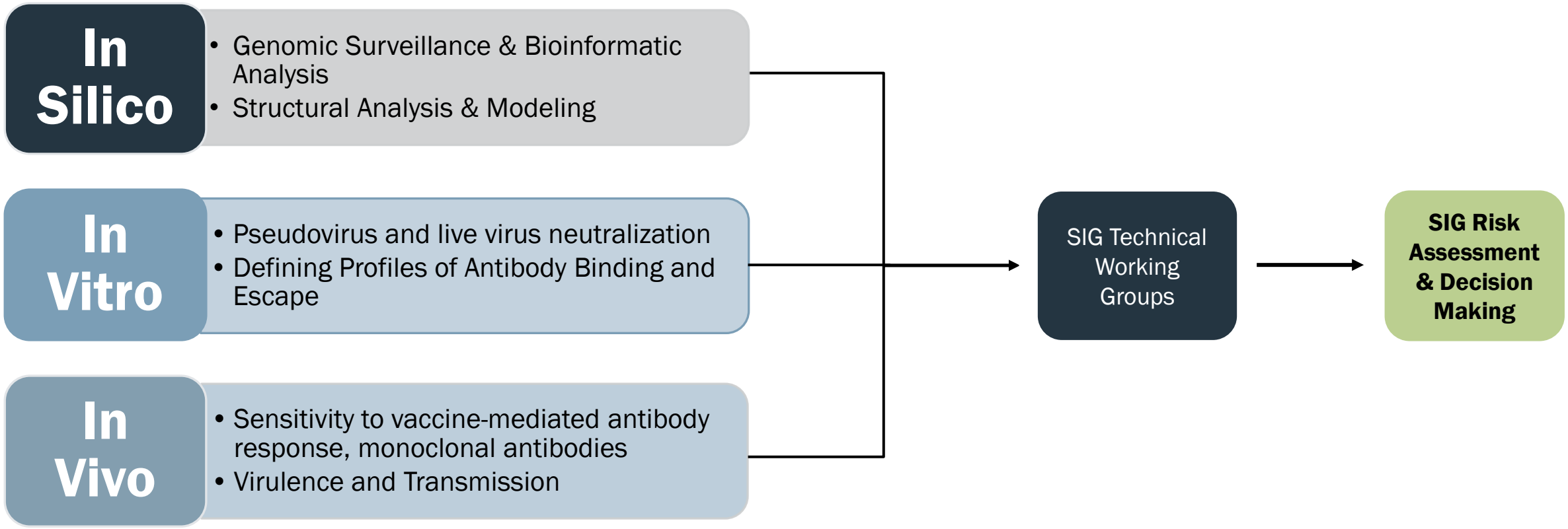
MISSION

Make provisional decisions and recommendations to mitigate COVID-19 morbidity and mortality based on risk assessment of the potential impact from emerging SARS-CoV-2 variants on the effectiveness of vaccines, therapeutics, diagnostics, and public health control efforts.

GOALS

- Identify & mitigate the impact of SARS-CoV-2 variants on vaccines, therapeutics, diagnostics, and public health control efforts.
- Improve interagency coordination
- Provide the scientific evidence needed for defensible decision-making, implementation of timely and effective public health measures, & effective operational and risk assessment communications

SARS-CoV-2 Interagency Group (SIG) Data Streams



SIG Virus Analysis Workflow

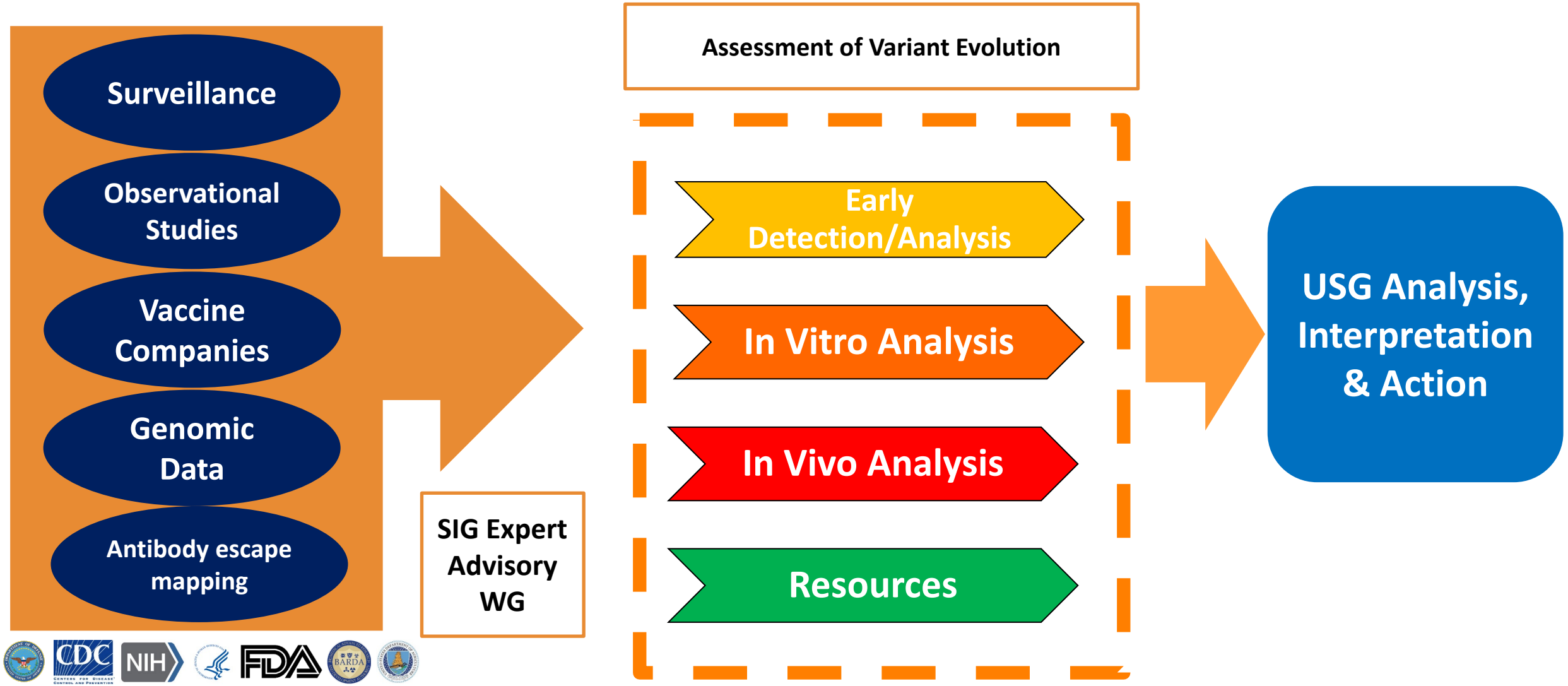
Technical Plan

- Genome analysis and variant classification
- Initial virus characterization
- Synthetic constructs
- Impacts on diagnostics (molecular, antigen)
- Antigenic characterization
- Correlation of genotype with phenotype in vivo

Operational Plan

- Key partners for in vitro and in vivo testing
- Share specimens, virus isolates, serum panels, clones, other reagents via BEI Resources or direct transfer
- Critical data for vaccines, therapeutics & diagnostics

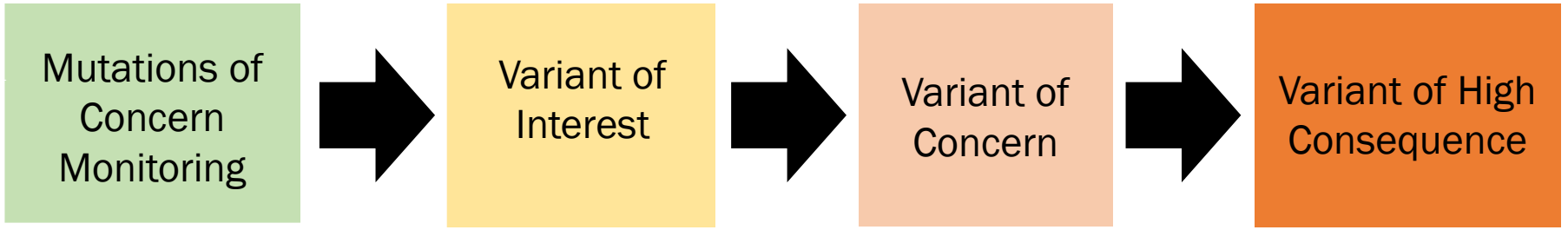
SIG: Variant Analysis Work Streams for COVID Vaccines



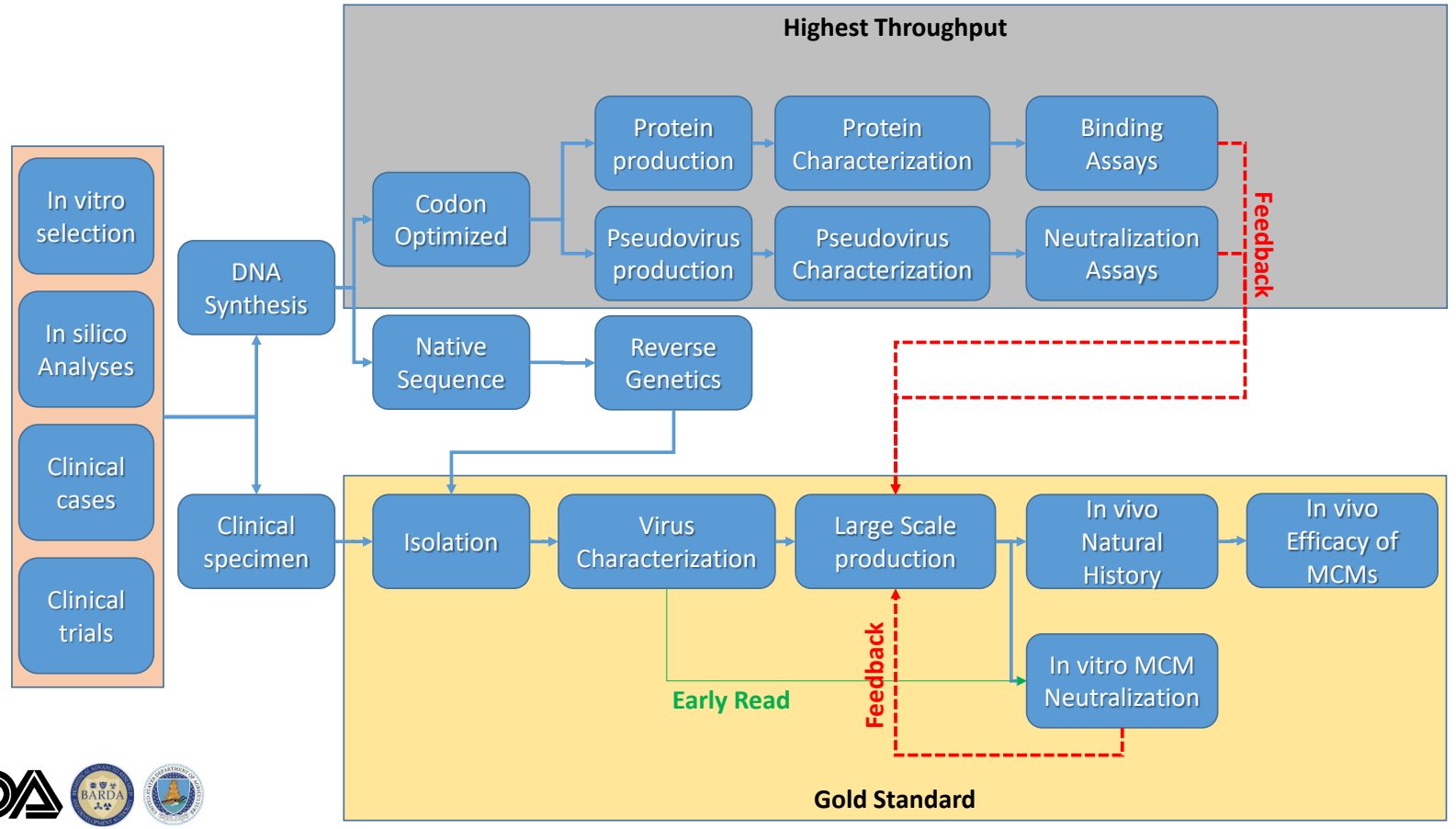
Variant Testing Pipeline

Data-generating components for the SIG

- Provides a rational, structured, and living risk-assessment pipeline for SARS-CoV-2 variant viruses
- Identify variant characteristics that raise concern
- Define key assays and experiments to evaluate the impact of variants
- Generate data to enable risk assessment
- Produce resources needed to perform key experiments



Virus Characterization Workflow Summary



USG Partners

- Genome sequencing
  - DHHS/CDC (in-house and via contracts)
  - DoD/Walter Reed Army Institute of Research
- Variant tracking, in silico phenotypic analyses
  - DHHS/CDC
  - DoD/Naval Medical Research Center
  - DoD/Walter Reed Army Institute of Research
  - DHHS/NIH/NIAID Vaccine Research Center
  - DHHS/NIH/NIAID academic partners
- In vitro virus characterization: Virus isolation, propagation, sharing; variant virus isolation, live virus and pseudovirus neutralization, reverse genetics, spike expression, Ab binding
  - DHHS/CDC
  - DoD/Naval Medical Research Center
  - DoD/Walter Reed Army Institute of Research
  - DHHS/NIH/NIAID Vaccine Research Center
  - DHHS/NIH/NIAID (academic partners
- In vivo studies: Vaccine & MCM efficacy, transmission
  - DHHS/BARDA
  - DHHS/CDC
  - DoD/USAMRIID
  - DoD/Naval Medical Research Center
  - DHHS/NIH/NIAID Vaccine Research Center
  - DHHS/NIH/NIAID academic partners

Variant Classes

Variant of Interest A variant with specific genetic markers that have been associated with changes to receptor binding, reduced neutralization by antibodies generated against previous infection or vaccination, reduced efficacy of treatments, potential diagnostic impact, or predicted increase in transmissibility or disease severity.

Possible attributes of a variant of interest:

- Specific genetic markers that are predicted to affect transmission, diagnostics, therapeutics, or immune escape
- Evidence that demonstrates it is the cause of an increased proportion of cases or unique outbreak clusters
- Limited prevalence or expansion in the US or in other countries

Variant of Concern A variant for which there is evidence of an increase in transmissibility, more severe disease (increased hospitalizations or deaths), significant reduction in neutralization by antibodies generated during previous infection or vaccination, reduced effectiveness of treatments or vaccines, or diagnostic detection failures.

Possible attributes of a variant of concern:

In addition to the possible attributes of a variant of interest:

- Evidence of impact on diagnostics, treatments, and vaccines
  - Widespread interference with diagnostic test targets
  - Evidence of substantially increased resistance to one or more class of therapies
  - Evidence of significant decreased neutralization by antibodies generated during previous infection or vaccination
  - Evidence of reduced vaccine-induced protection from severe disease
- Evidence of increased transmissibility
- Evidence of increased disease severity

Ongoing international global COVID-19 variant surveillance efforts

- Support sequencing capacity in >50 countries
- Establish/expand sampling strategies, technology, trainings and bioinformatics with global partners
- Work with partners to track spread of variants globally
- Define standardized approaches and provide technical assistance to investigate variants
- Review data-driven changes to mitigation
- Coordinate with international partners to share samples that are made available to the broader research community, including the private sector for the development of MCMs and to further SARS-CoV-2 research.
- Coordinate with international partners to align activities to ensure global consensus

ACTIV/TRACE OpenData portal

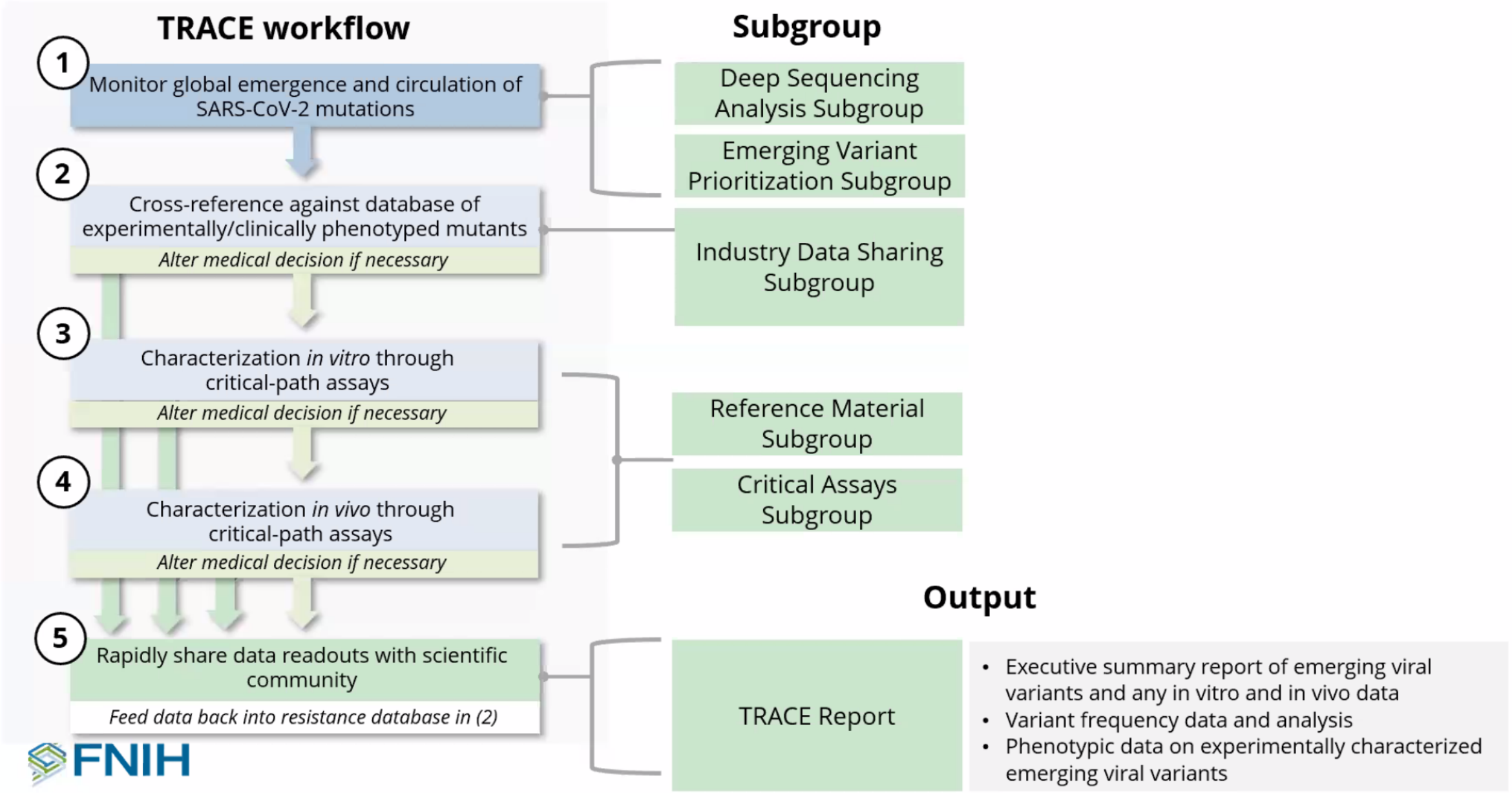
Christine Colvis, PhD
NIH/NCATS

ACTIV/TRACE: OpenData Portal

Christine Colvis, PhD

NCATS/NIH

ACTIV TRACE Working Group



FNIH

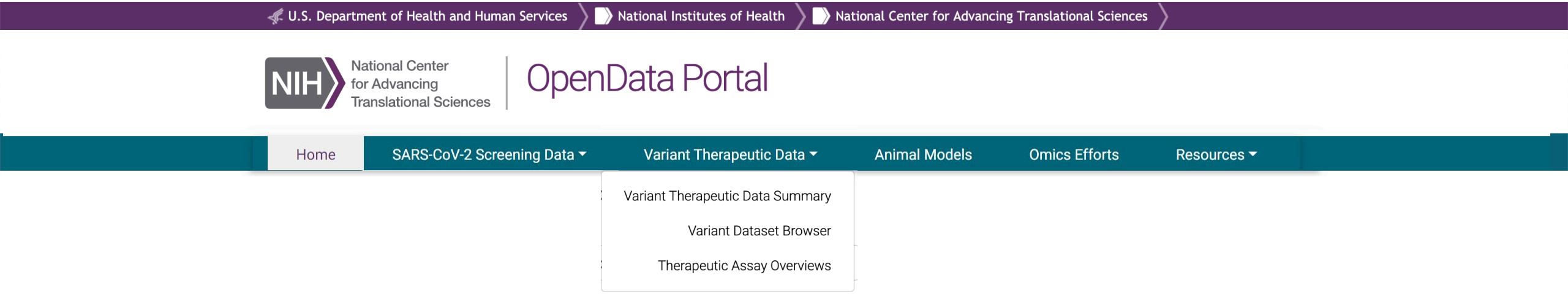
NCBI is monitoring publicly available data for variant frequency changes

Data is current as of 04-02-2021

	ASSESSMENTS						FREQUENCY AND TRENDS														
							Global-USA Total		USA Total		Global-USA Month					USA Month					
Lineage	Defining Mutations	CDC Class	Variations in Therapeutic Epitopes or Binding Sites	Variations in Other Epitopes	Therapeutics with Available Data*	ACTIV Assay Status	Sequence Record Count	Percent	Sequence Record Count	Percent	Percent Records Released Last Calendar Month	Percent New Records Released this Calendar Month to Date	New Records Expected this Calendar Month	Doubling Time (Months)	Growth Rate (Records/ Month)	Percent Records Released Last Calendar Month	Percent New Records Released this Calendar Month to Date	New Records Expected this Calendar Month	Doubling Time (Months)	Growth Rate (Records/ Month)
A.23.1	surface glycoprotein: F157L; P681R; V367F; Q613H			F157L P681R Q613H V367F			48	0.019%	3	0.007%	0.00%	0.00%	0	NA	NA	0.00%	0.00%	0	NA	NA
B.1.1.7	ORF8 protein: Q27*; Y73C nsp3: T183I nucleocapsid phosphoprotein: S235F surface glycoprotein: N501Y; D1118H; S982A; A570D; P681H; T716I	VOC	N501Y	A570D D1118H P681H S235F S982A T716I Y144-	link to data	In vitro assays anticipated	27990	11.018%	772	1.894%	0.00%	0.00%	0	2.31	12,118.00	50.80%	0.00%	108	1.49	517.00
B.1.351	3C-like proteinase: K90R ORF8 protein: F120F envelope protein: P71L leader protein: nsp3: K837N nucleocapsid phosphoprotein: T205I surface glycoprotein: K417N; A701V	VOC	E484K K417N N501Y	A701V D80A K90R	link to data	In vitro assays anticipated	935	0.368%	19	0.047%	0.00%	0.00%	0	2.62	357.35	1.70%	0.00%	1	NA	NA
B.1.427	helicase: P53L; D260Y membrane glycoprotein: F53F nsp4: S395T nucleocapsid phosphoprotein: ; T205I surface glycoprotein: L452R; W152C; S13I	VOC	L452R	W152C	link to data	In vitro assays anticipated	1	0.000%	933	2.289%	0.00%	0.00%	0	NA	NA	6.10%	0.00%	22	5.00	186.42
B.1.429	helicase: D260Y membrane glycoprotein: F53F nsp9: I65V nucleocapsid phosphoprotein: T205I; surface glycoprotein: S13I; L452R; W152C	VOC	L452R	W152C	link to data	In vitro assays anticipated	2	0.001%	1484	3.641%	0.00%	0.00%	0	NA	NA	16.20%	0.00%	53	4.23	350.65
B.1.525	membrane glycoprotein: I82T surface glycoprotein: Q677H; Q52R; E484K; F888L	VOI	E484K	Q52R Q677H			16	0.006%	51	0.125%	0.00%	0.00%	0	NA	NA	3.20%	0.00%	8	NA	NA
B.1.526	surface glycoprotein: A701V; S477N; D253G; T95I; E484K; L5F	VOI	E484K S477N	A701V D253G L5F T95I			0	0.000%	73	0.179%	0.00%	0.00%	NA	NA	NA	9.70%	0.00%	42	NA	NA

https://ftp.ncbi.nlm.nih.gov/pub/ACTIV-TRACE/

OpenData Portal / **Variant Therapeutic Pages**



MVP Launch Features and Functions:

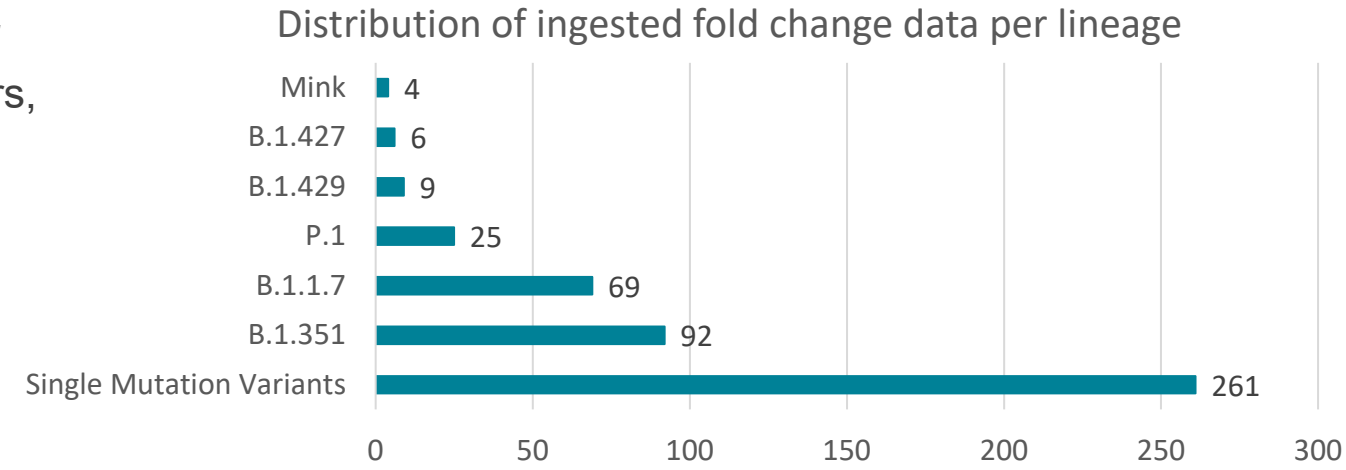
1) Datasets collated into the **Variant Therapeutic Data Summary** table to summarize which variant-therapeutic pairs have data available

2) **Variant Dataset Browser**, featuring searchable list of variant/therapeutic datasets from pharma/govt partners, with rich metadata and links to source reports

3) **Therapeutic Assay Overviews** to describe common SARS-CoV-2 variant assays and provide context to guide interpretation of activity data

Continued to ingest industry/govt published & provided reports

- >25 publications ingested onto portal
- >625 variant & therapeutics data pair



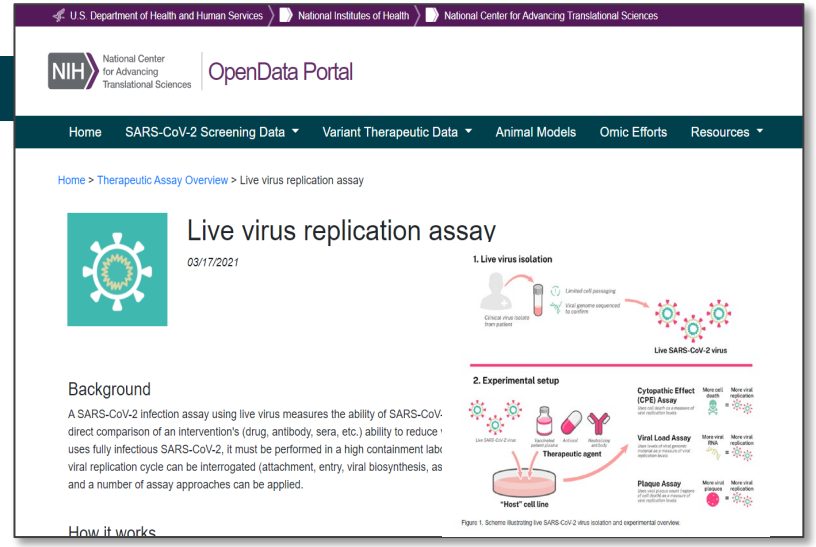
OpenData Portal / **Variant Therapeutic Pages**

Home | SARS-CoV-2 Screening Data | Variant Therapeutic Data | Animal Models | Omic Efforts | Resources

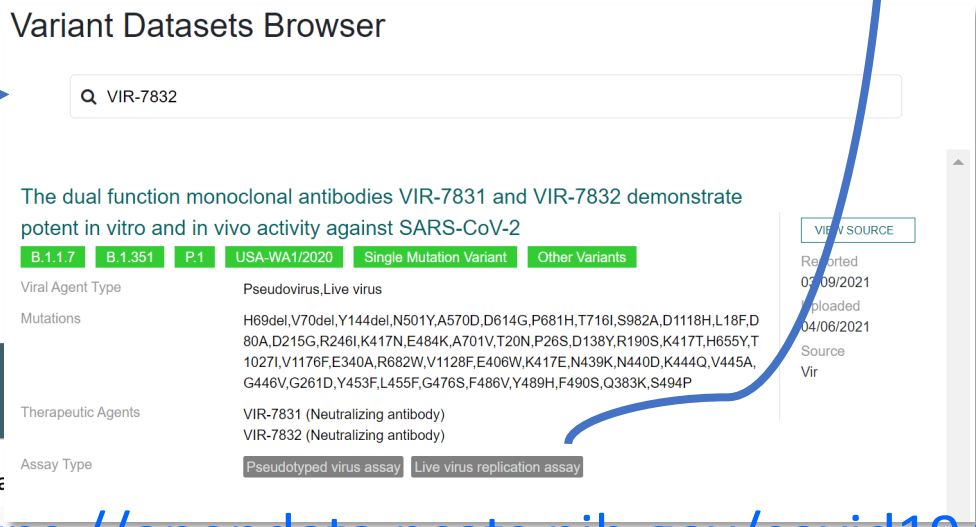
Home > Variant Therapeutic Data Summary

Variant Therapeutic Data Summary

Variant Lineage	Preclinical data available: Vaccines	Antivirals	Neutralizing Antibodies		Convalescent plasma
B.1.1.7					
	BNT162b2	Plitidepsin	AZD1061	Casirivimab	COVID-19 Convalescent plasma
	ChAdOx1 nCoV-19	Ralimetinib	AZD8895	Etesevimab	
	NVX-CoV2373	Remdesivir	AZD8895+AZD1061	Imdevimab	
	mRNA-1273		BRII-196	REGEN-COV	
			BRII-196+BRII-198	REGN10985	
			BRII-198	S2E12	
			Bamlanivimab	S309	
			Bamlanivimab+Etesevimab	S309+S2E12	
			Brii-196	VIR-7831	
			Brii-196+Brii-198	VIR-7832	
			Brii-198		
B.1.351					
	BNT162b2		AZD1061	C135+C136	COVID-19 Conva plasma
	ChAdOx1 nCoV-19		AZD8895	C136	
	mRNA-1273		AZD8895+AZD1061	Casirivimab	



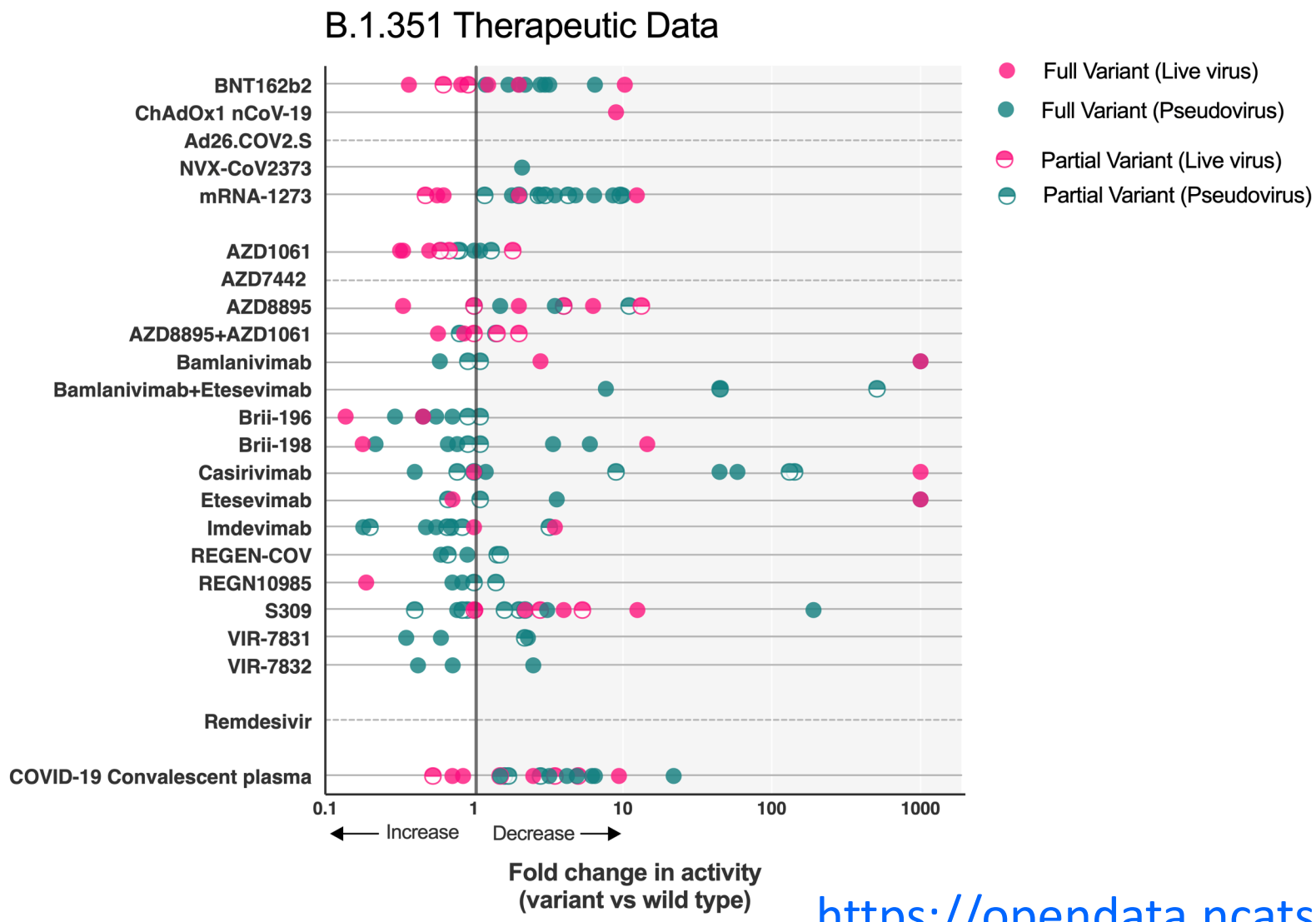
Assay names link to assay overview pages to provide context/limitations of each



Therapeutic names link to underlying datasets

https://opendata.ncats.nih.gov/covid19/

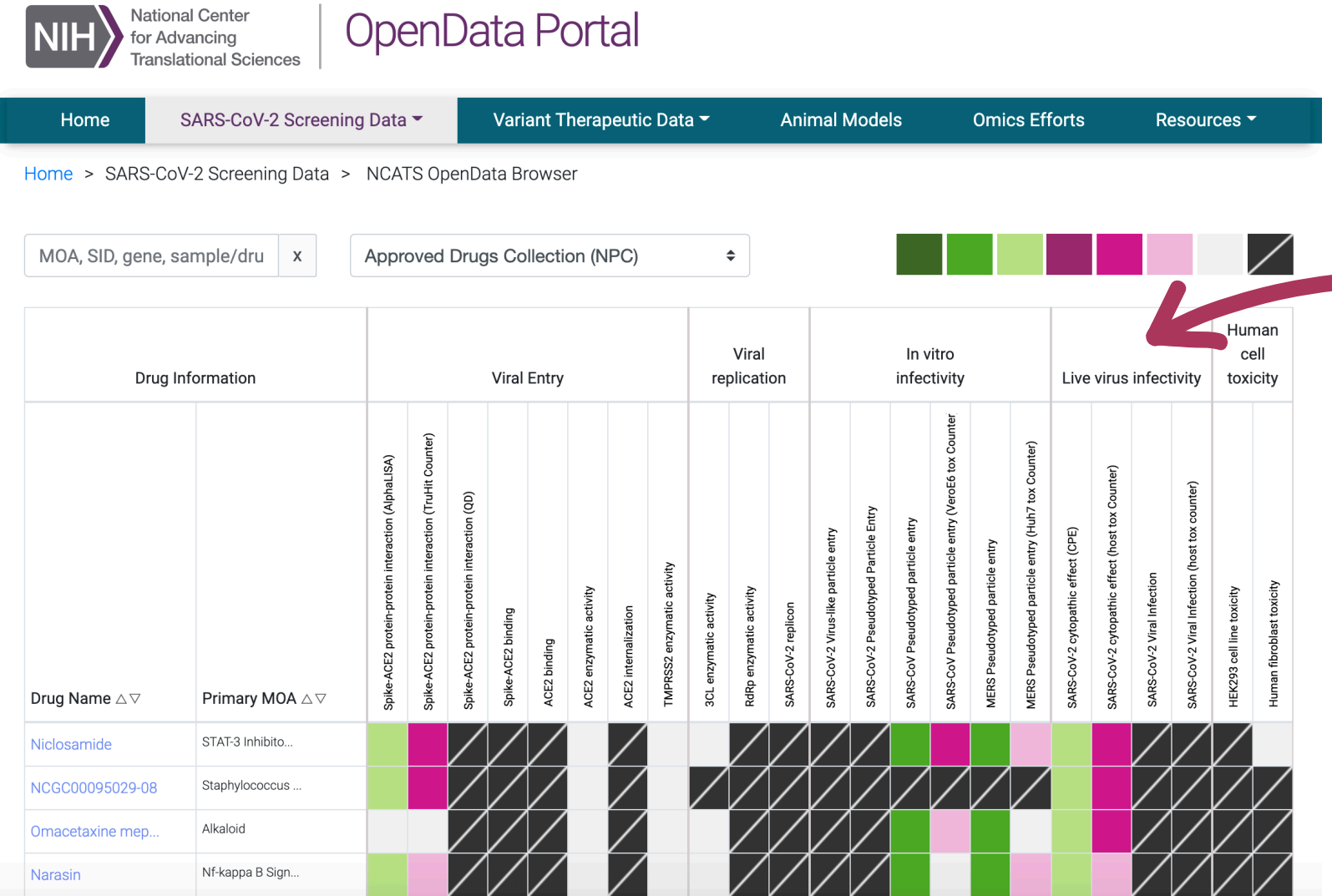
OpenData Portal / **Visualizing Variant Therapeutics Data**



https://opendata.ncats.nih.gov/covid19/

OpenData Portal hosts a diverse panel of SARS-CoV-2-related data & information

https://opendata.ncats.nih.gov/covid19/



1. **NCATS SARS-CoV-2 screening datasets against 10K approved drugs/annotated molecules**
   - Data can be viewed, sorted and searched in browser
   - Assay information and experimental protocols are shared openly on the site to allow others to run/adapt them
2. Detailed information on SARS-CoV-2 animal models (FNIH)
3. Curated list of SARS-CoV-2 omics efforts
4. **Variant Therapeutic Data (ACTIV TRACE)**

Panel Discussion

Moderated By:

William Dowling

CEPI

Discussion Panel Members and Example Questions

Panel Members

- **Divya Shah,** Wellcome Trust, UK
- **Sylvie Briand,** WHO (World Health Organization)
- **Sharon Peacock,** COG-UK (COVID-19 Genomics UK)
- **Simon Funnell,** PHE (Public Health England), UK
- **Sujatha Rashid,** BEI Resources, USA
- **Steve Oberste,** CDC (Centers for Disease Control and Prevention), USA
- **Christine Colvis,** NIH/NCATS (National Institutes of Health / National Center for Advancing Translational Sciences), USA
- **Bill Dowling,** CEPI (Coalition for Epidemic Preparedness Innovations)

Potential Discussion Questions

1. What opportunities are there for scientists to contribute data on the impact of SARS-CoV-2 variants to international efforts?
2. What resources can be made available to the international scientific community in order to identify and characterize new variants (reagents, standards, protocols, assays, data)?
3. How can we best harmonize neutralization and binding assays and incorporate international standards to improve our ability to interpret immune escape data generated in different labs and geographies?
4. How will programs decide how much immune escape is ‘enough’ to warrant a change in vaccine antigen?

Wrap Up & Next Steps

Ivana Knezevic, co-lead of ES SWAT team, WHO

Closing remarks

- Thank you all for your participation and engagement today
- Workshop report distributed shortly to summarize today's conversation
- The COVAX Enabling Sciences SWAT Team plans to continue sharing learnings across developers as we pursue our common goal – a global supply of safe and effective vaccines

Enabling Sciences SWAT Team