Emergence and Spread of a New SARS-CoV-2 Variant (501Y.V2) in South Africa

Dr Richard Lessells on behalf of the Network for Genomic Surveillance South Africa (NGS-SA) and 501Y.V2 National Research Consortium

Genomics a potent tool in the response to the COVID-19 epidemic

- Used to discover the virus associated with COVID-19 (i.e. SARS-CoV-2)
- To develop diagnostics (i.e. qPCR)
- To develop vaccines (i.e. mRNA and vector vaccines)
- To track transmission (i.e. introductions, outbreaks, spread)
- To identify re-infection
- To understand host-virus interactions

~530 000 genomes produced and shared globally -
3420 genomes from South Africa

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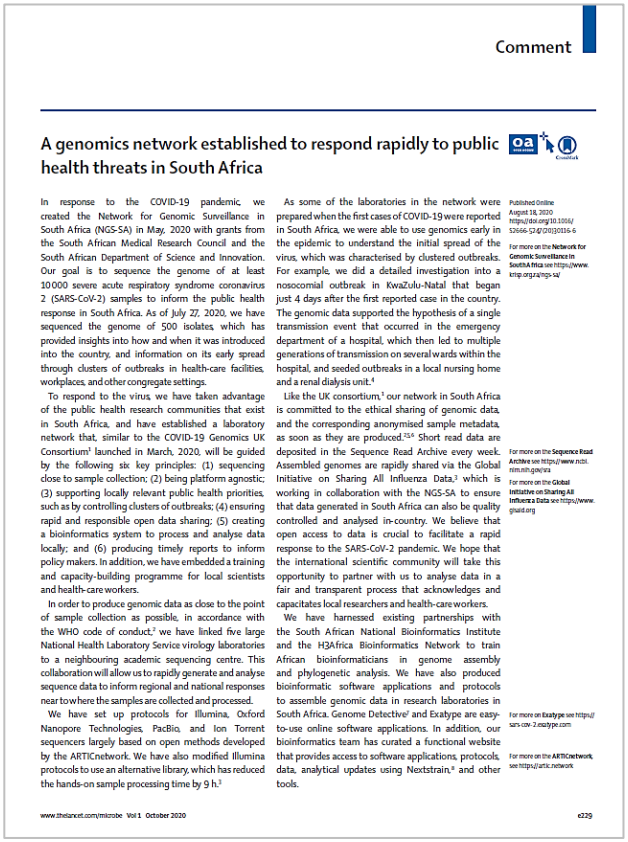
Network for Genomic Surveillance in South Africa (NGS-SA)



Comment

A genomics network established to respond rapidly to public health threats in South Africa

In response to the COVID-19 pandemic, we created the Network for Genomic Surveillance in South Africa (NGS-SA) in May, 2020 with grants from the South African Medical Research Council and the South African Department of Science and Innovation. Our goal is to sequence the genome of at least 10 000 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) samples to inform the public health response in South Africa. As of July 27, 2020, we have sequenced the genome of 500 isolates, which has provided insights into how and when it was introduced into the country, and information on its early spread through clusters of outbreaks in health-care facilities, workplaces, and other congregate settings.

To respond to the virus, we have taken advantage of the public health research communities that exist in South Africa, and have established a laboratory network that, similar to the COVID-19 Genomics UK Consortium[1] launched in March, 2020, will be guided by the following six key principles: (1) sequencing close to sample collection; (2) being platform agnostic; (3) supporting locally relevant public health priorities, such as by controlling clusters of outbreaks; (4) ensuring rapid and responsible open data sharing; (5) creating a bioinformatics system to process and analyse data locally; and (6) producing timely reports to inform policy makers. In addition, we have embedded a training and capacity-building programme for local scientists and health-care workers.

In order to produce genomic data as close to the point of sample collection as possible, in accordance with the WHO code of conduct,[2] we have linked five large National Health Laboratory Service virology laboratories to a neighbouring academic sequencing centre. This collaboration will allow us to rapidly generate and analyse sequence data to inform regional and national responses near to where the samples are collected and processed.

We have set up protocols for Illumina, Oxford Nanopore Technologies, PacBio, and Ion Torrent sequencers largely based on open methods developed by the ARTICnetwork. We have also modified Illumina protocols to use an alternative library, which has reduced the hands-on sample processing time by 9 h.[3]

As some of the laboratories in the network were prepared when the first cases of COVID-19 were reported in South Africa, we were able to use genomics early in the epidemic to understand the initial spread of the virus, which was characterised by clustered outbreaks. For example, we did a detailed investigation into a nosocomial outbreak in KwaZulu-Natal that began just 4 days after the first reported case in the country. The genomic data supported the hypothesis of a single transmission event that occurred in the emergency department of a hospital, which then led to multiple generations of transmission on several wards within the hospital, and seeded outbreaks in a local nursing home and a renal dialysis unit.[4]

Like the UK consortium,[1] our network in South Africa is committed to the ethical sharing of genomic data, and the corresponding anonymised sample metadata, as soon as they are produced.[2,5,6] Short read data are deposited in the Sequence Read Archive every week. Assembled genomes are rapidly shared via the Global Initiative on Sharing All Influenza Data,[3] which is working in collaboration with the NGS-SA to ensure that data generated in South Africa can also be quality controlled and analysed in-country. We believe that open access to data is crucial to facilitate a rapid response to the SARS-CoV-2 pandemic. We hope that the international scientific community will take this opportunity to partner with us to analyse data in a fair and transparent process that acknowledges and capacitates local researchers and health-care workers.

We have harnessed existing partnerships with the South African National Bioinformatics Institute and the H3Africa Bioinformatics Network to train African bioinformaticians in genome assembly and phylogenetic analysis. We have also produced bioinformatic software applications and protocols to assemble genomic data in research laboratories in South Africa. Genome Detective[7] and Exatype are easy-to-use online software applications. In addition, our bioinformatics team has curated a functional website that provides access to software applications, protocols, data, analytical updates using Nextstrain,[8] and other tools.

Published Online August 18, 2020 https://doi.org/10.1016/S2666-5247(20)30116-6

For more on the **Network for Genomic Surveillance in South Africa** see https://www.krisp.org.za/ngs-sa/

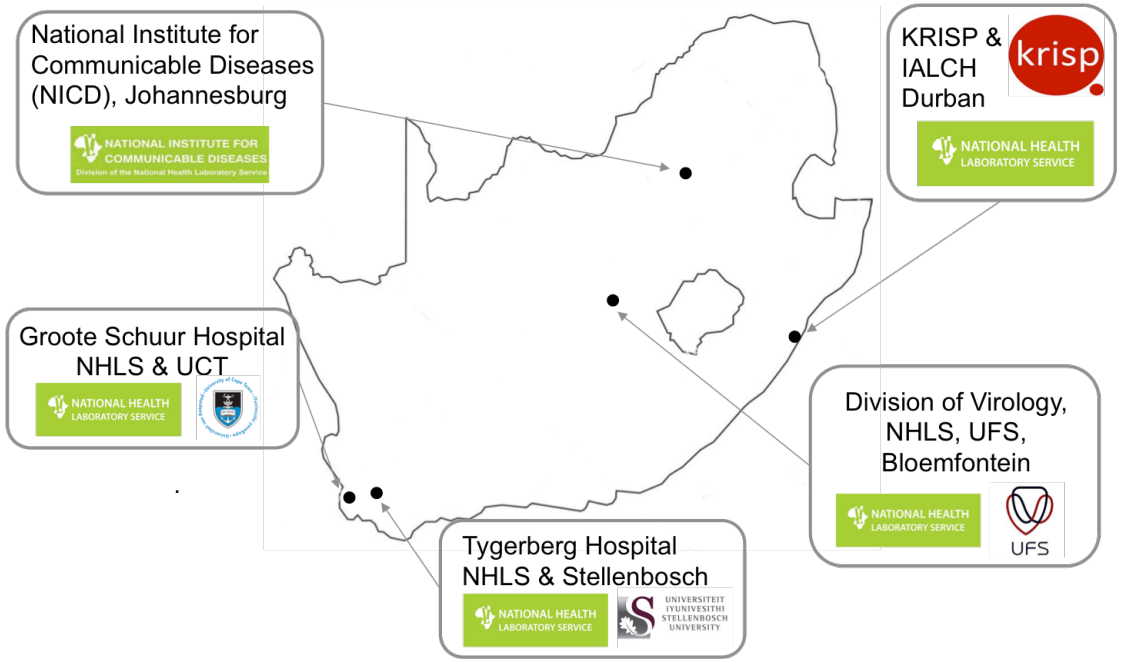
For more on the **Sequence Read Archive** see https://www.ncbi.nlm.nih.gov/sra

For more on the **Global Initiative on Sharing All Influenza Data** see https://www.gisaid.org

For more on **Exatype** see https://sars-cov-2.exatype.com

For more on the **ARTICnetwork** see https://artic.network

www.thelancet.com/microbe Vol 1 October 2020 e229



Supported by the Department of Science and Innovation & SA Medical Research Council

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

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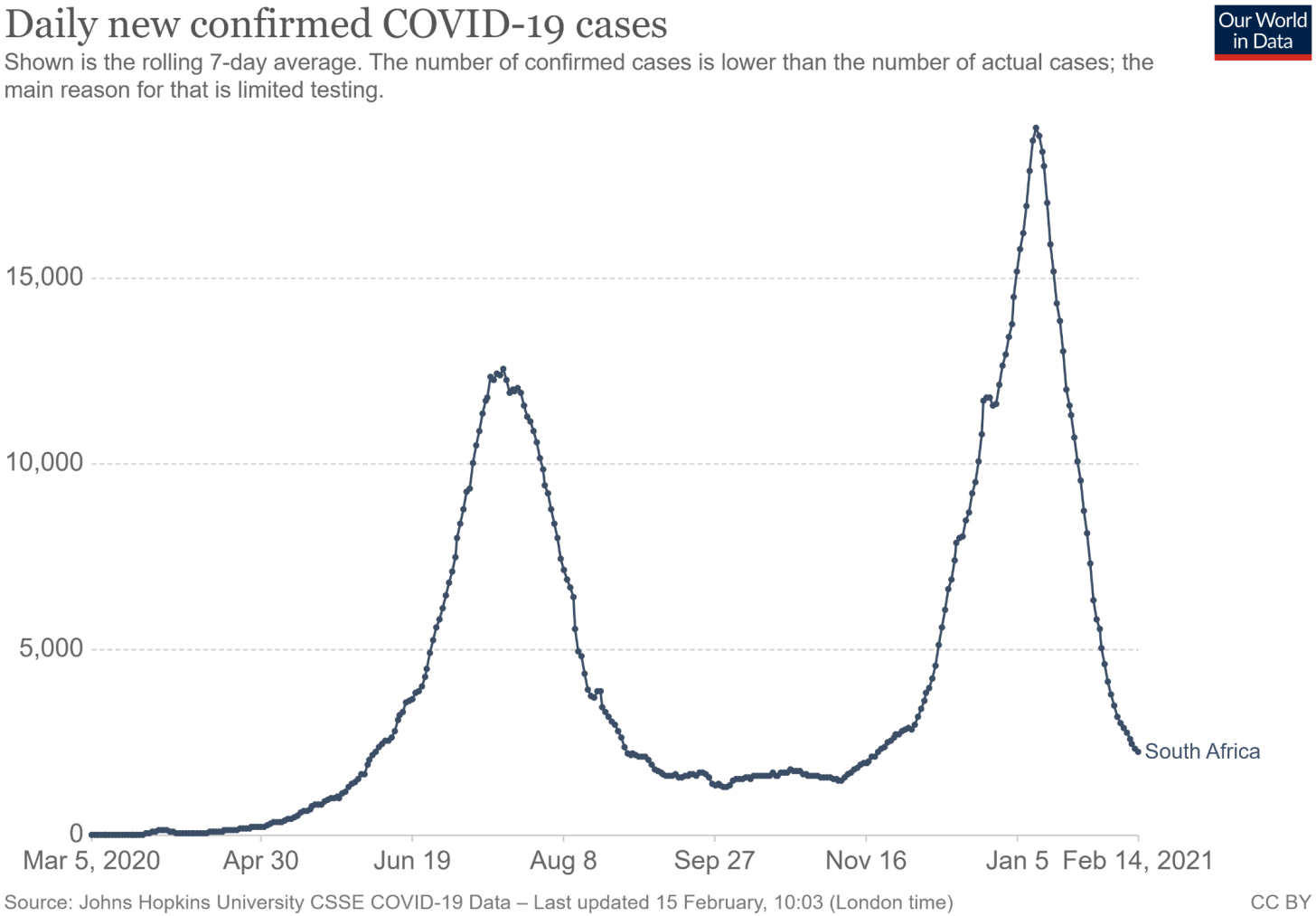
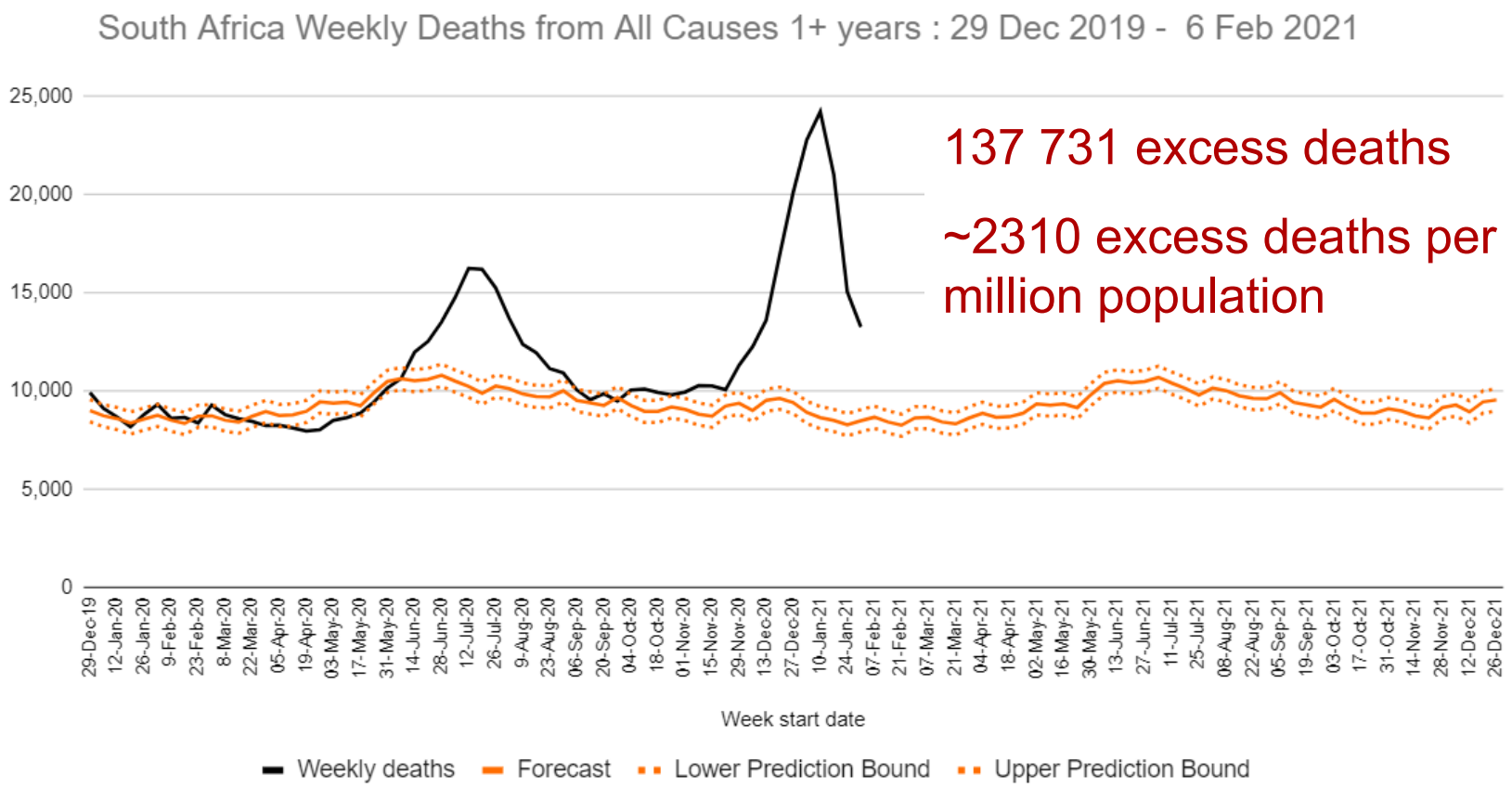
SARS-CoV-2 epidemic in South Africa

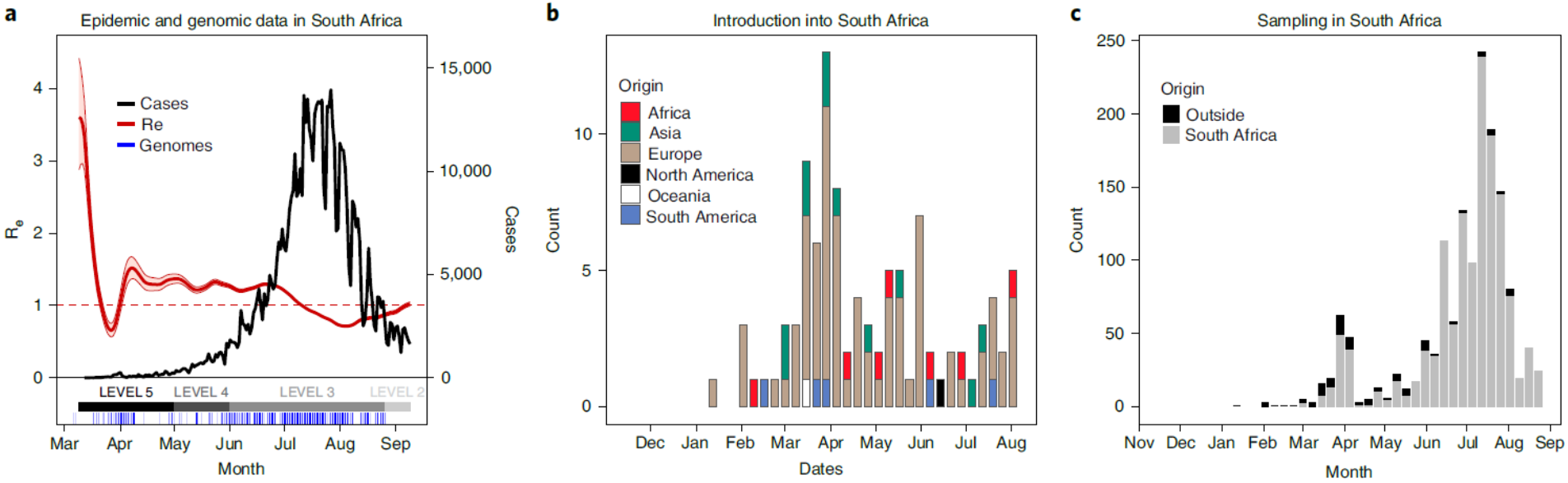


SARS-CoV-2 epidemic in South Africa



Genomic epidemiology

Introductions and early epidemic phase



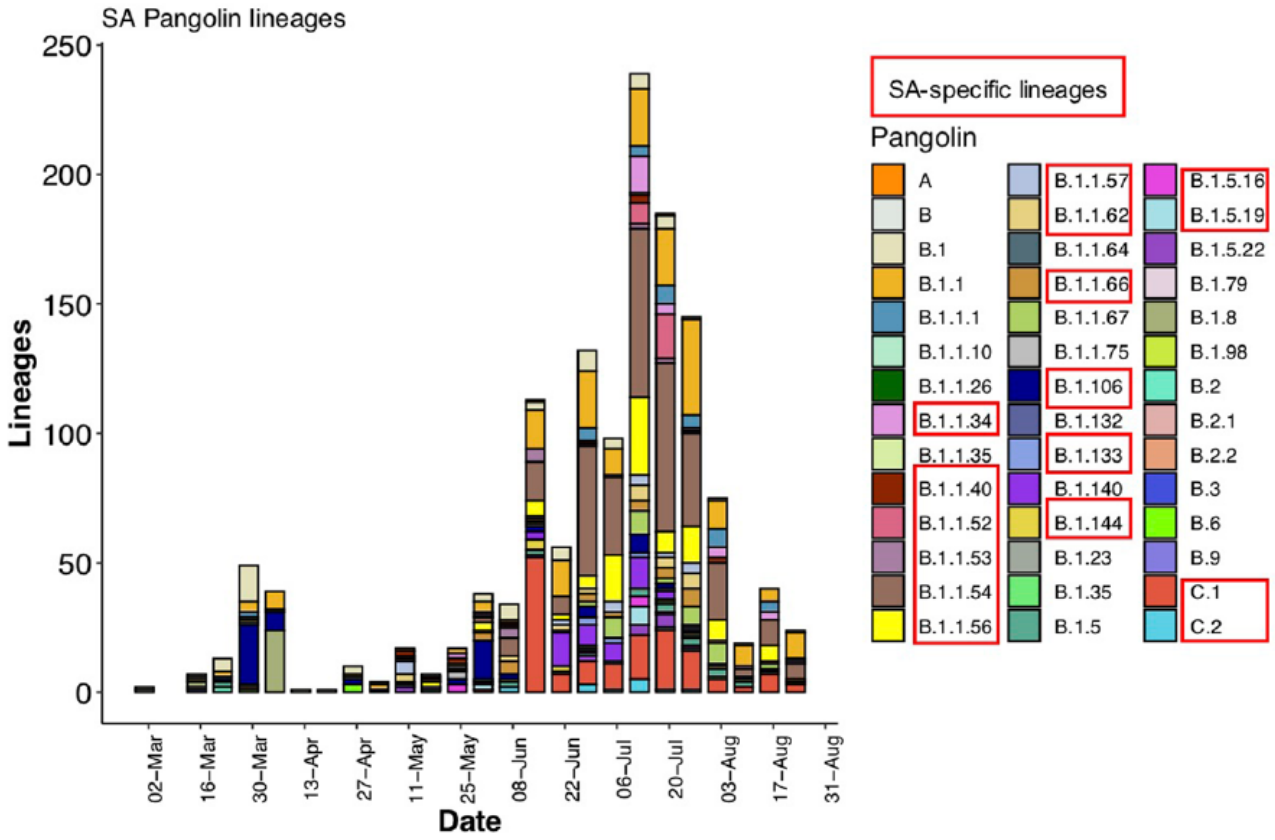
Multiple introductions of SARS-CoV-2 (mainly from Europe)

Initial spread through cluster outbreaks during lockdown, followed by more widespread community transmission

Tegally H, *et al.* Nature Med 2021

Genomic epidemiology

Introductions and early epidemic phase



Multiple circulating SARS-CoV-2 lineages during first wave

Tegally H, *et al.* Nature Med 2021

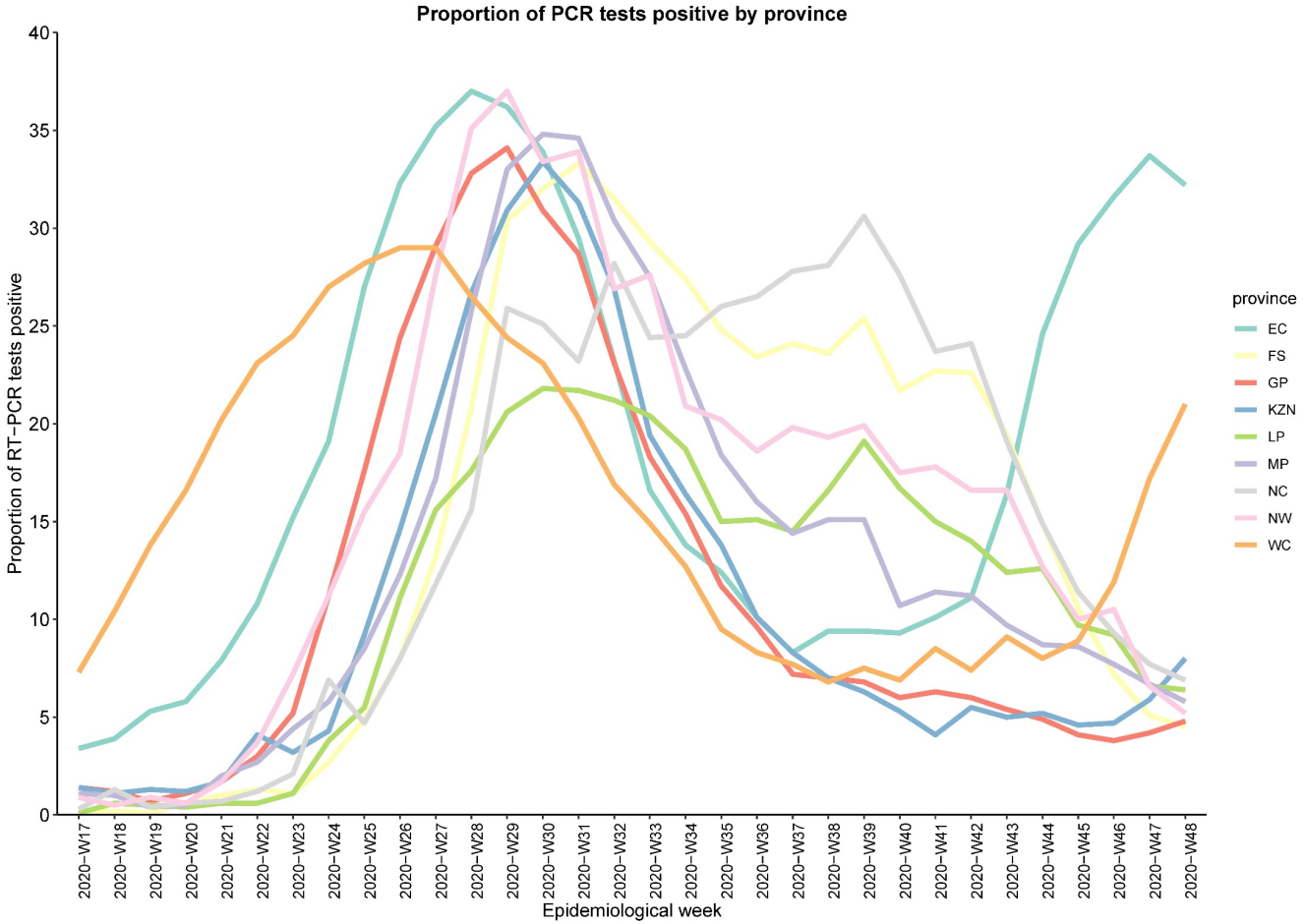
November 2020 – Eastern Cape

Greenacres Hospital was among the Netcare hospitals in South Africa where doctors spotted an unexplained spike in cases in October. Samantha Reinders for The New York Times

New York Times 9 Jan
As Coronavirus Mutates, the World Stumbles Again to Respond

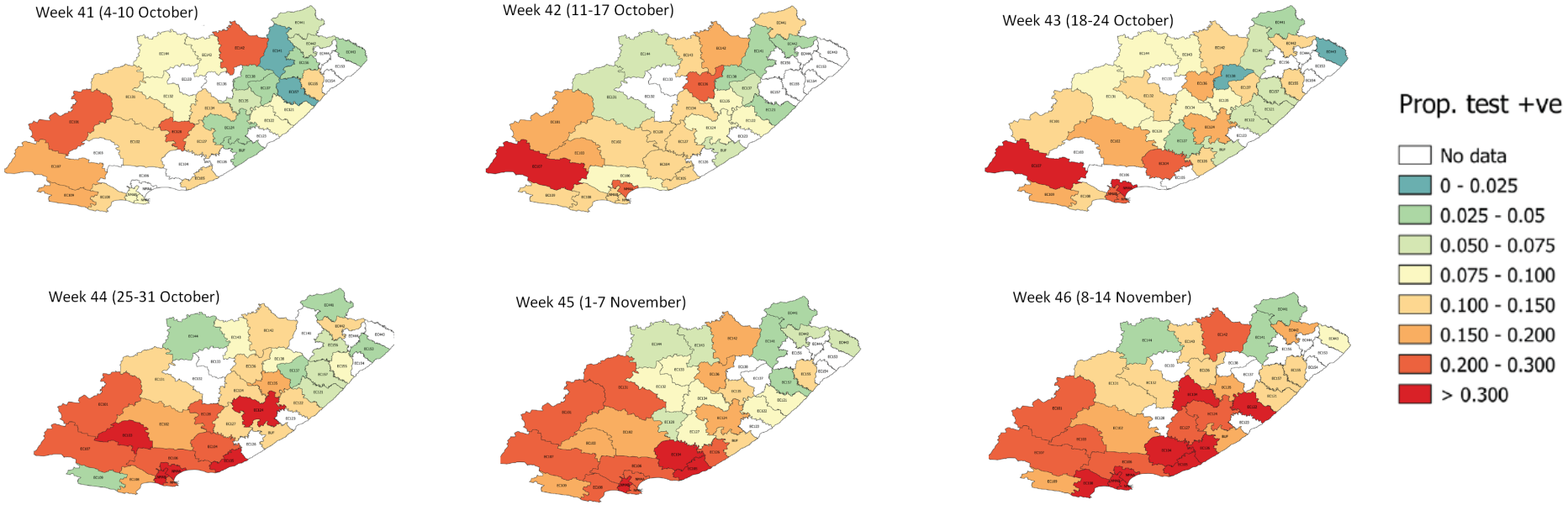
- Clinical teams in Nelson Mandela Bay concerned about rapid resurgence of cases and admissions from October onwards
- Also concerned that clinical spectrum of disease was different
- Contacted us – “Is this a different strain?”

Early resurgence in Eastern Cape



Data from NICD Weekly Testing Reports
https://www.nicd.ac.za/diseases-a-z-index/covid-19/surveillance-reports/weekly-testing-summary/

Early resurgence in Eastern Cape



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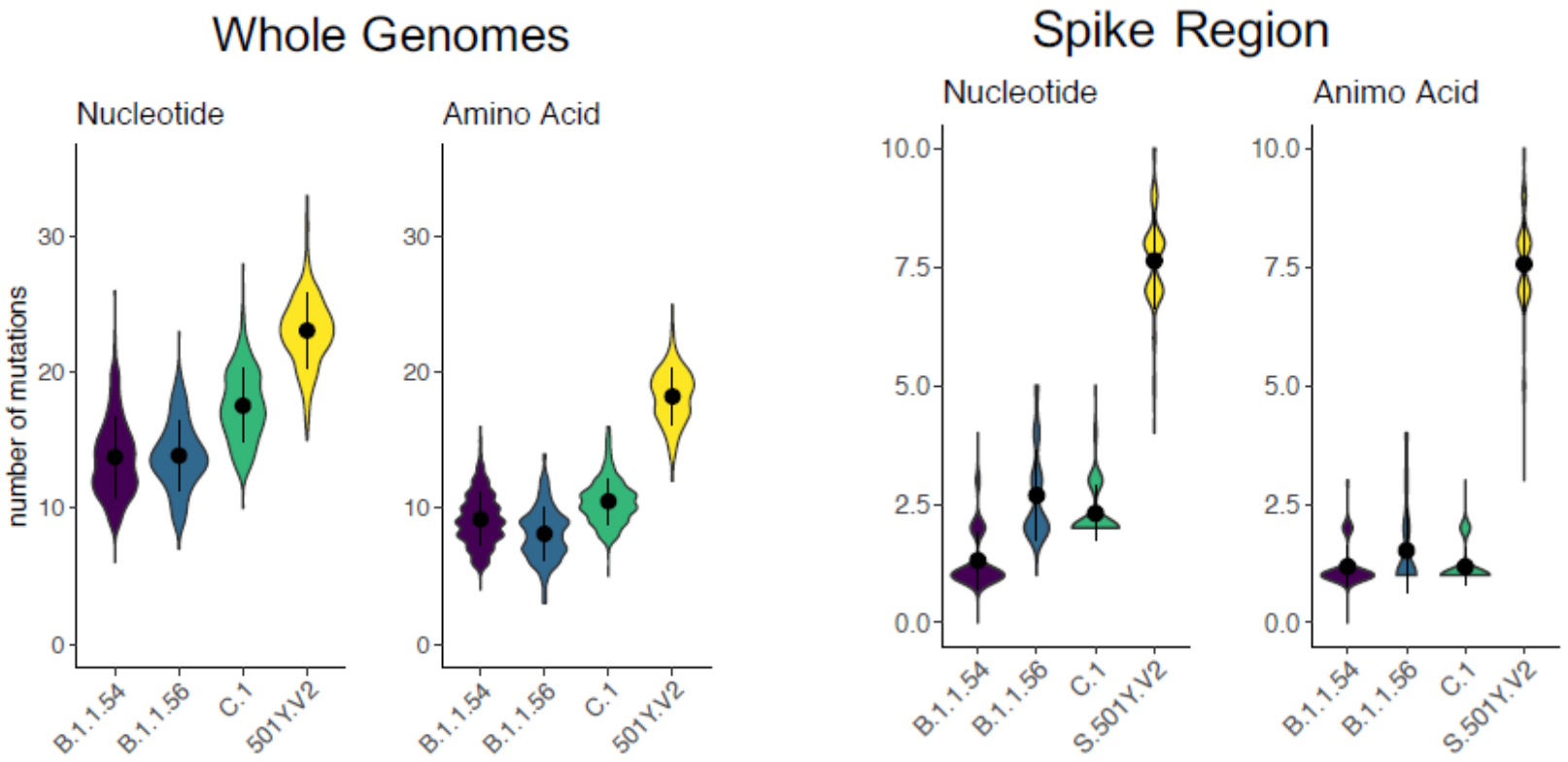
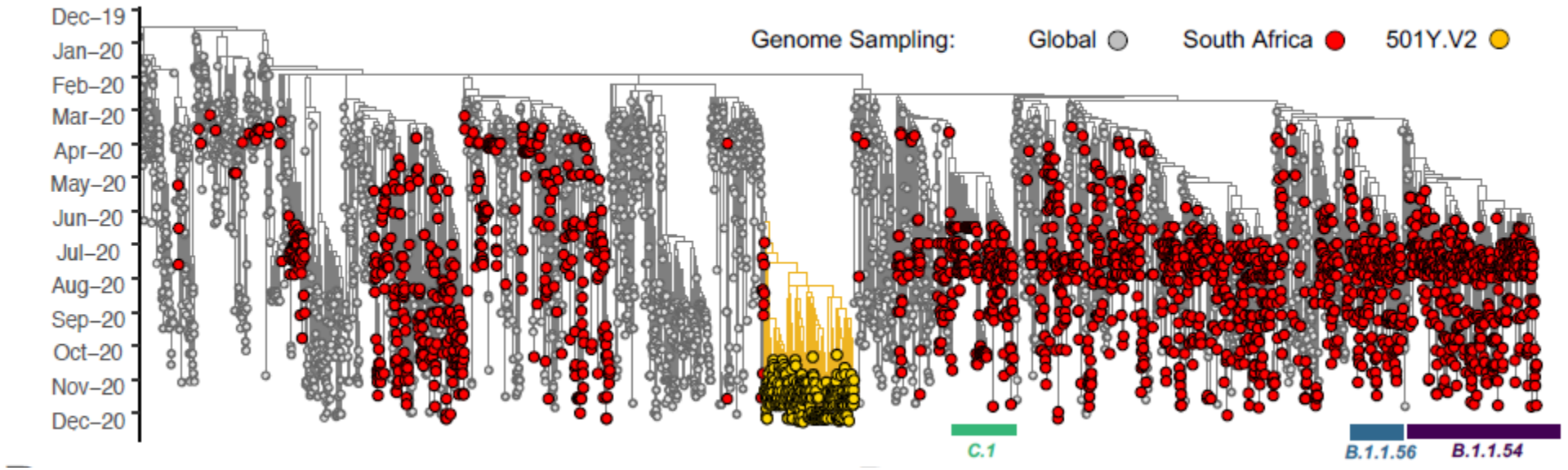
Genomic characteristics of 501Y.V2



High number of non-synonymous mutations, particularly in spike protein

Tegally H, *et al*. Nature 2021 (in press)

Phylogenetic analysis



On phylogenetic tree, 501Y.V2 separate from three main wave 1 lineages (C.1, B.1.1.54 & B.1.1.56)

Tegally H *et al*. Nature 2021 (in press)

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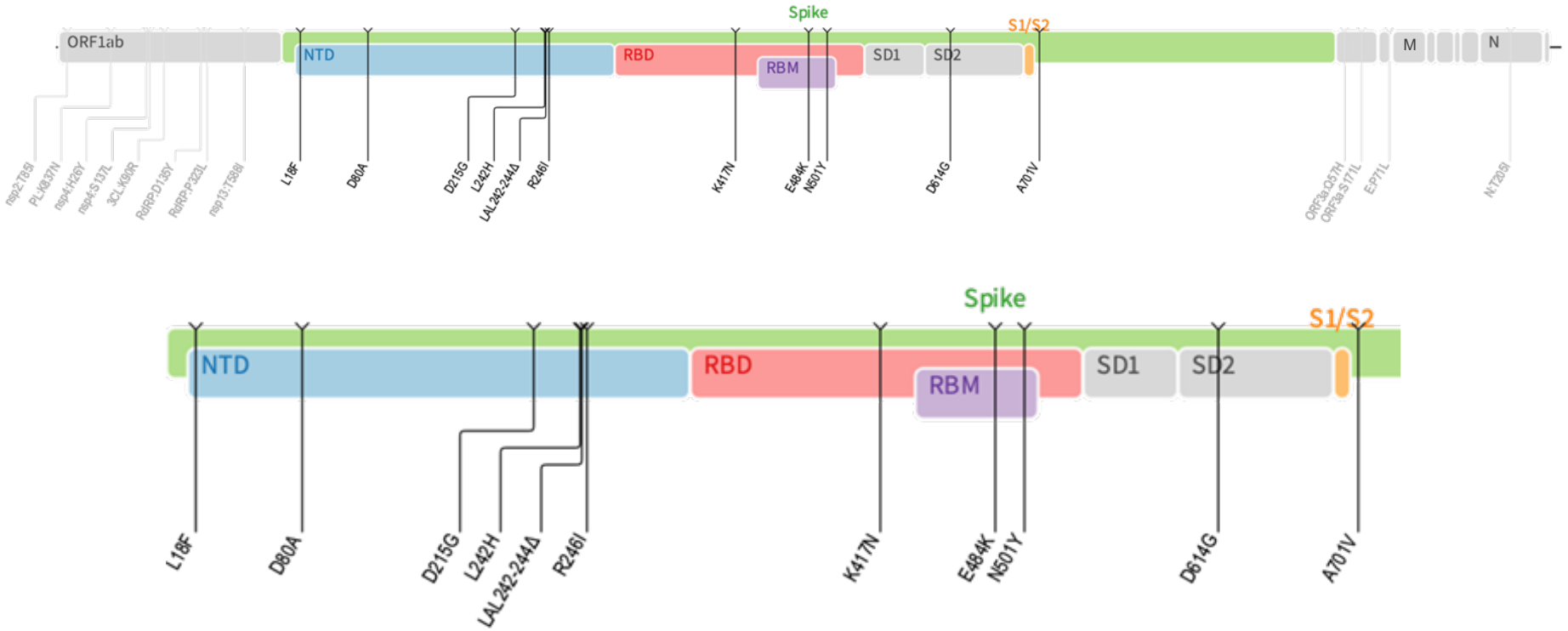
Genomic map of 501Y.V2



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

https://covdb.stanford.edu/

Structural analysis of spike mutations

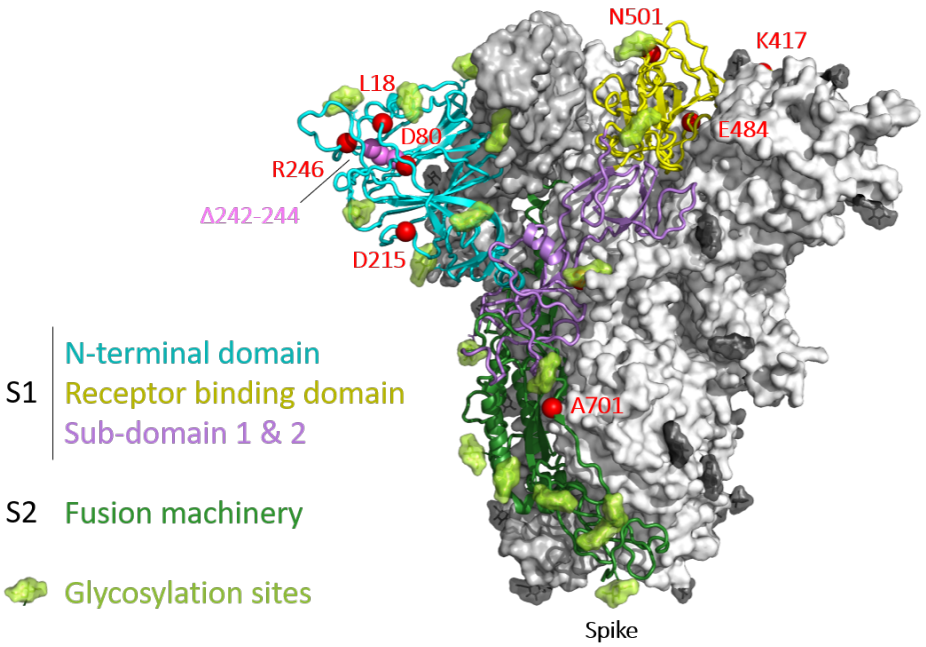


Image: Kurt Wibmer, NICD & NGS-SA

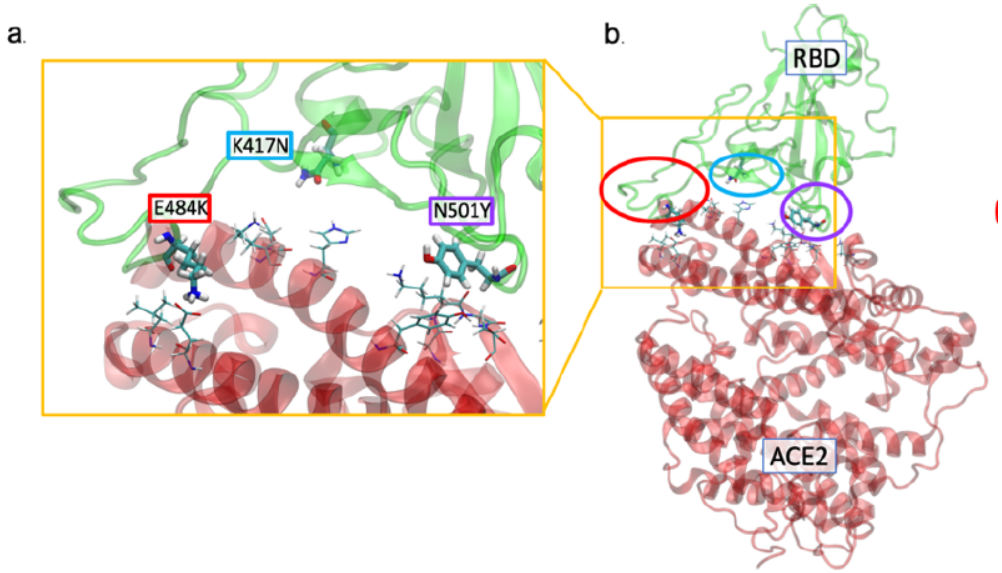
The **spike protein** attaches to the **ACE2 receptor** on host cells - each of the three petals of the spike protein carries a 'hook', called the **receptor-binding domain** (**RBD**) which is what directly interacts with hACE2

The RBD is the main target for **neutralizing antibodies (NAbs)** elicited during SARS-CoV-2 infection

The remaining neutralizing activity seems to be targeted at the N-terminal domain of the spike protein

Piccoli L *et al*. Cell 2020
Chi X *et al*. Science 2020
McCallum M *et al*. bioRxiv 2021

Spike RBD mutations enhance binding to ACE2



The RBD mutations are all at key sites interacting with hACE2

N501Y and E484K increase binding affinity to hACE2

Dynamic modelling suggests that mutations lead to significant conformational changes – could have effect on hACE2 binding and NAb binding

Starr T, *et al*. Cell 2020
Nelson G *et al*. bioRxiv 2021

E484 is a key neutralizing epitope

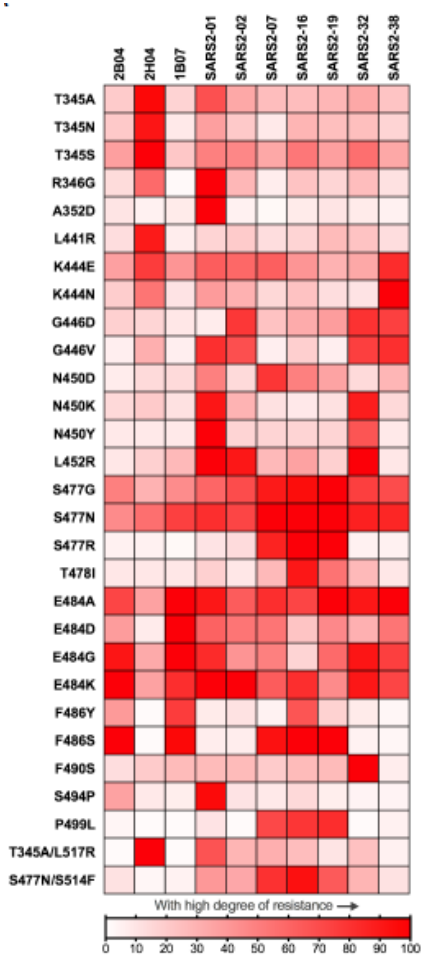
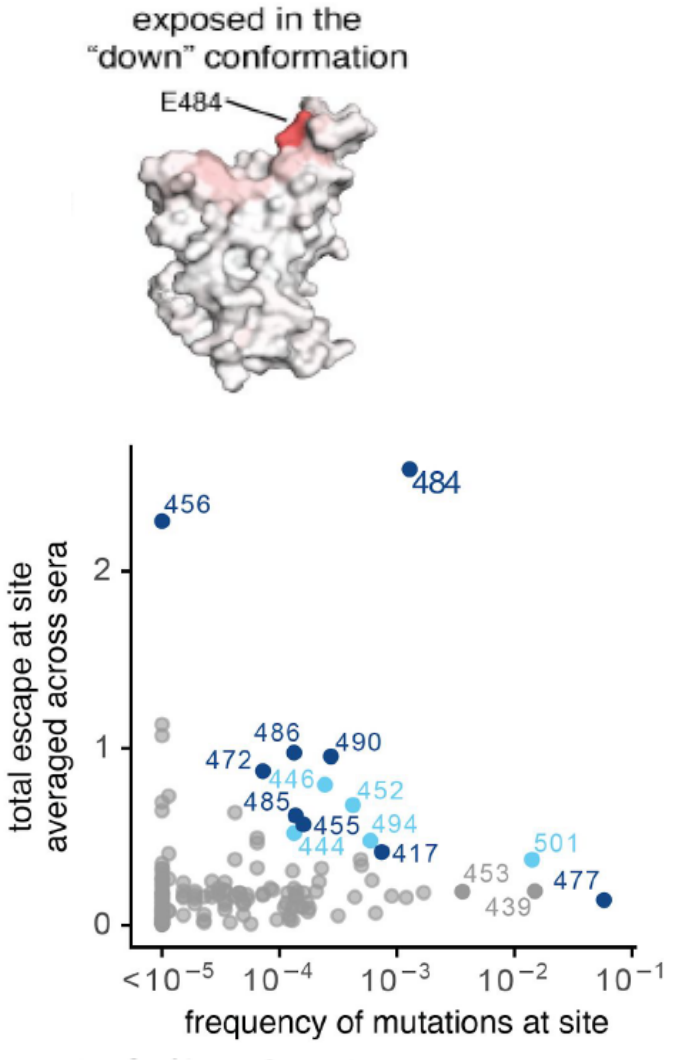


Image from Liu et al.

- Residues E484-F486 of the receptor-binding domain RBD are a hotspot for binding of neutralizing antibodies (NAbs)
- In several *in vitro* studies using a range of different monoclonal antibodies (mAbs), E484K emerged as an immune escape mutation
- E484K shown to confer broad cross-resistance to mAbs

Baum A, *et al*. Science 2020
Greaney AJ, *et al*. Cell 2020
Weisblum Y, *et al*. eLife 2020
Liu Z, *et al*. Cell 2020

Comprehensive mapping confirms importance of E484 mutations in immune escape



- Bloom laboratory - complete mapping of RBD mutations that reduce binding by polyclonal serum Abs confirms E484 as key site for immune escape
- Binding reduced in 9 of 11 convalescent serum samples
- Mutations at E484 caused the largest drops in neutralization

Greaney A, *et al*. Cell Host Microbe 2020

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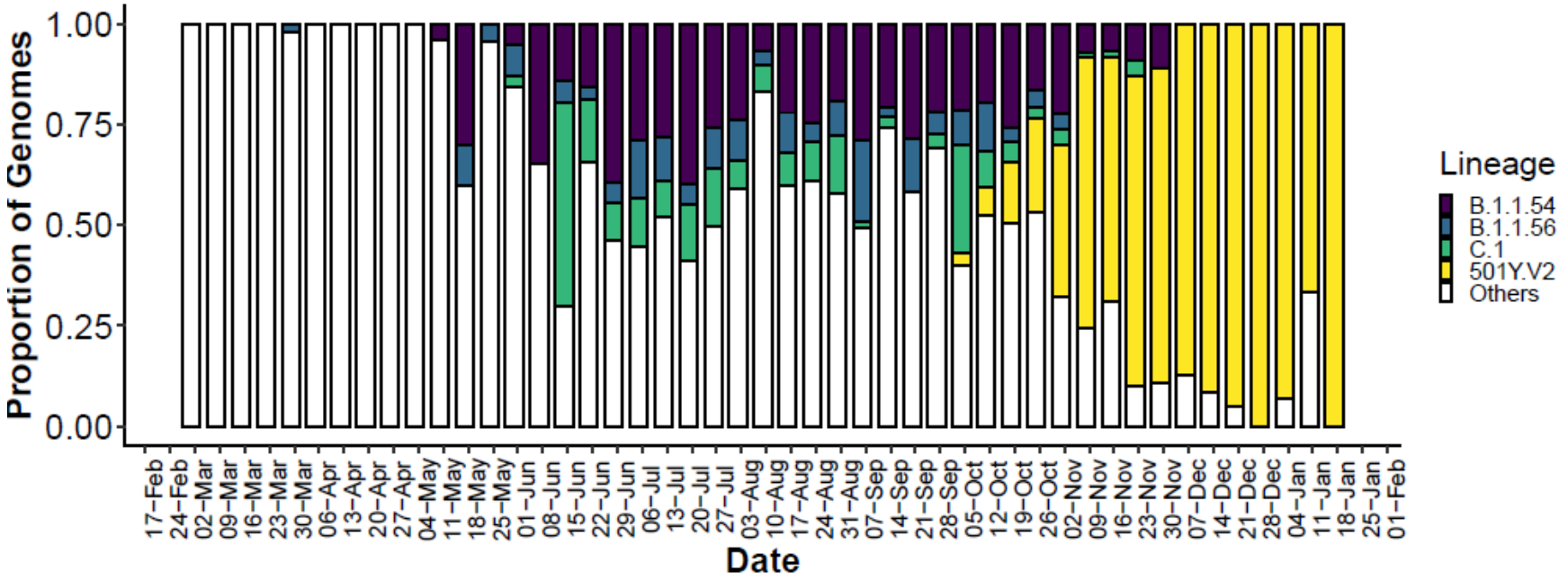
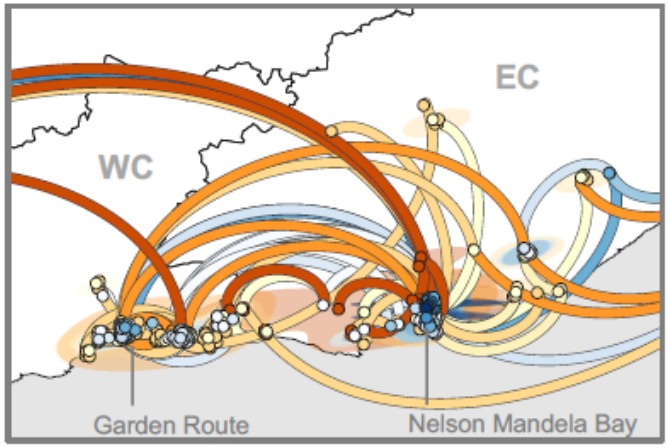
Distribution of SARS-CoV-2 lineages

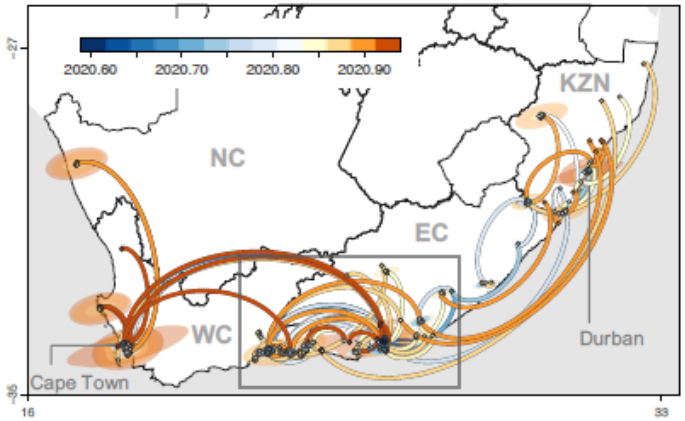
South Africa



Data from **3324 sequences** from all 9 provinces, collected up to 19 Jan

501Y.V2 emerged in Nelson Mandela Bay





Our analysis suggests that this lineage emerged in Nelson Mandela Bay then spread to other districts in EC, to Western Cape and to multiple locations in KZN

Analysis suggests emergence early August (mid July – end August 2020, 95% highest posterior density)

We have detected this lineage in **>700 genomes** collected **8 Oct – 19 Jan** originating from:

- >30 different health facilities in 3 districts of WC
- >30 different health facilities in 3 districts of EC
- >30 different health facilities in 7 districts of KZN
- 5 different health facilities in 2 districts of NC

Tegally H *et al*. Nature 2021 (in press)

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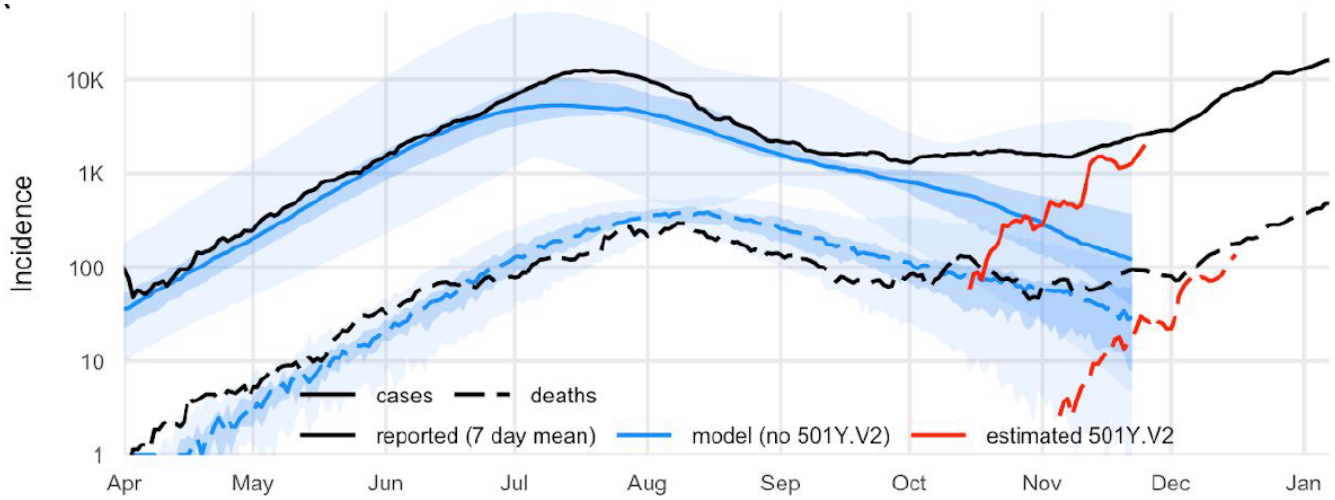
Increased transmissibility of 501Y.V2 – preliminary estimates



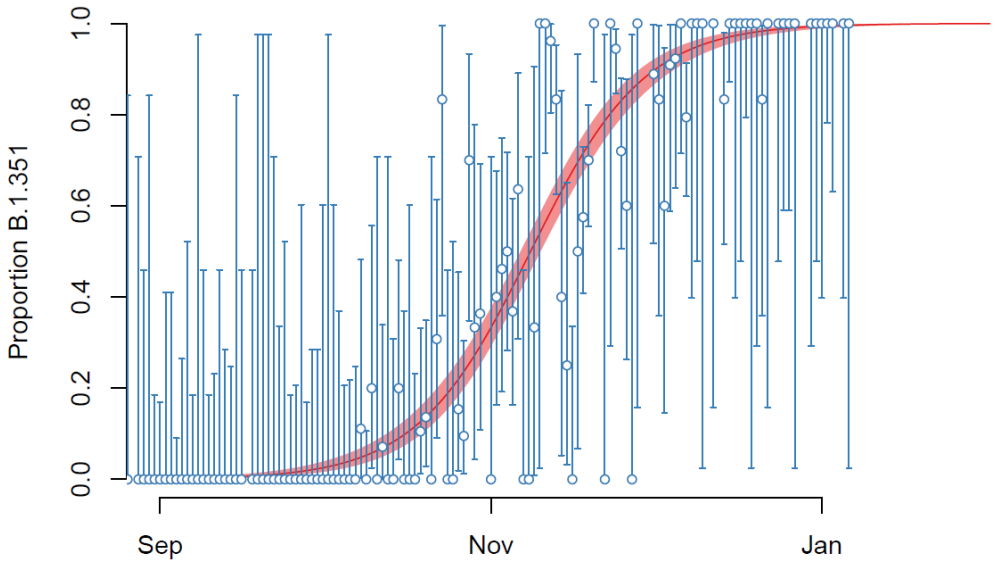
CMMID, LSHTM (Carl Pearson et al.)
CovidM: age-structured mathematical model

501Y.V2 - **1.50 (95%CrI 1.20-2.13) times as transmissible** as previously circulating lineages

BUT, same effect could be explained by 501Y.V2 evading 21% (95% CrI 11-36%) of previously acquired immunity, without any increased transmissibility

https://cmmid.github.io/topics/covid19/sa-novel-variant.html

Increased transmissibility of 501Y.V2 – preliminary estimates



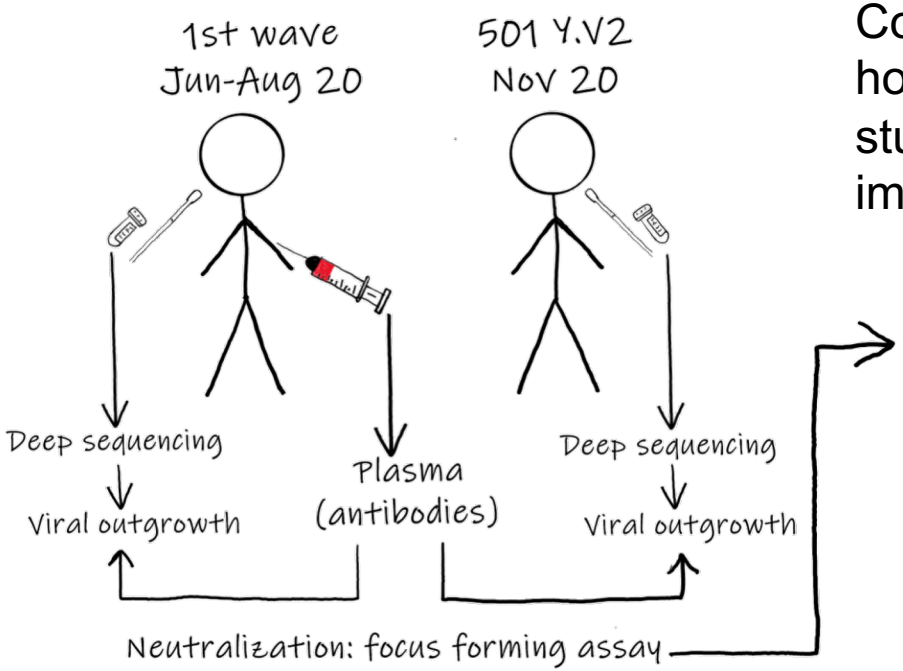
Christian Althaus (Bern), Tanja Stadler (ETH Zurich) – unpublished data
Genomic modelling

501Y.V2 - **48%** (95%CI 43%-53%) or **67%** (95%CI 60%-74%) increase in transmissibility, assuming generation time of 5 or 7 days respectively

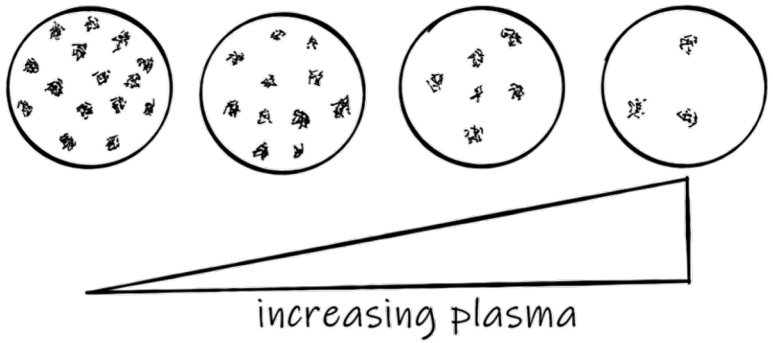
This analysis does not consider immune escape

501Y.V2 escape from convalescent plasma

Live virus neutralization assay



Convalescent sera collected from hospitalized cases in prospective cohort study investigating SARS-CoV-2 immune responses

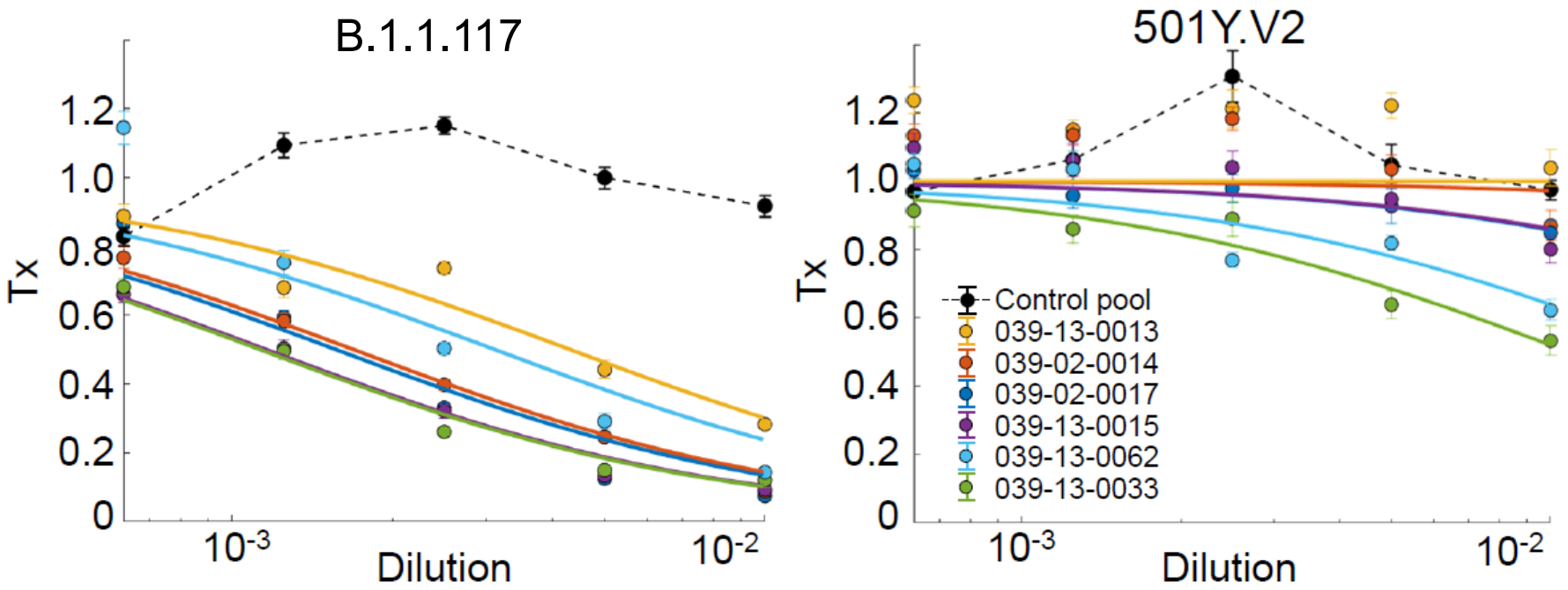


Highlights the importance of strong research collaborations – ability to rapidly link genotype to phenotype

Cele S, *et al*. medRxiv 2021
Karim F, *et al*. medRxiv 2020

501Y.V2 escape from convalescent sera

Live virus neutralization assay (Sigal Lab, AHRI)



Neutralization of the 501Y.V2 virus strongly attenuated, with IC_{50} 6- to 200-fold higher relative to that for the B.1.1.117 virus

Cele S, *et al*. medRxiv 2021

501Y.V2 and risk of re-infection

Novavax vaccine trial – placebo arm

- Phase 2b trial NVX-CoV2373 - 4400 adults
- Antibody testing at enrolment (anti-spike IgG) – 31% positive

	N	Any symptomatic COVID-19		Moderate-severe COVID-19	
		n	% (95% CI)	n	% (95% CI)
Seronegative	1494	58	3.9 (3.0-5.0)	35	2.3 (1.6-3.2)
Seropositive	674	26	3.9 (2.5-5.6)	16	2.4 (1.4-3.8)

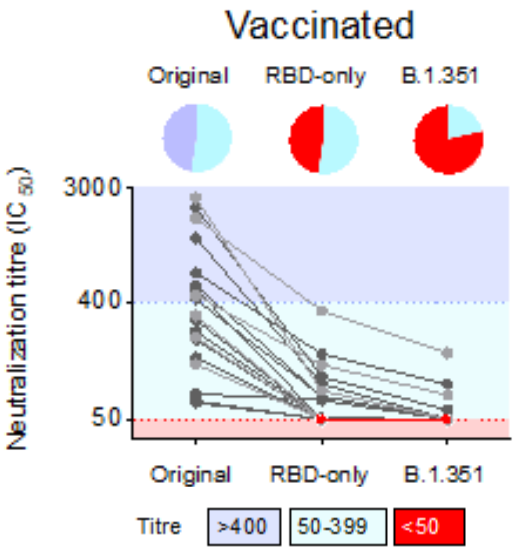
- Results suggest prior infection offers no protection from re-infection – need caution given risk of bias (e.g. differential risks of exposure seropositive vs. seronegative participants)

https://www.novavax.com/sites/default/files/2021-02/20210202-NYAS-Novavax-Final.pdf

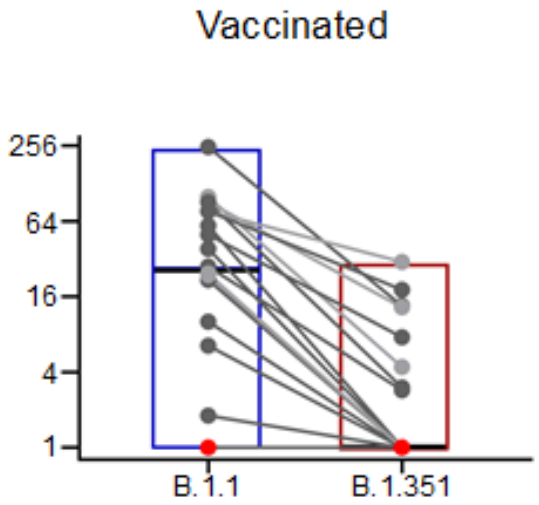
501Y.V2 escape from vaccinee sera

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

Pseudovirus assay



Live virus assay

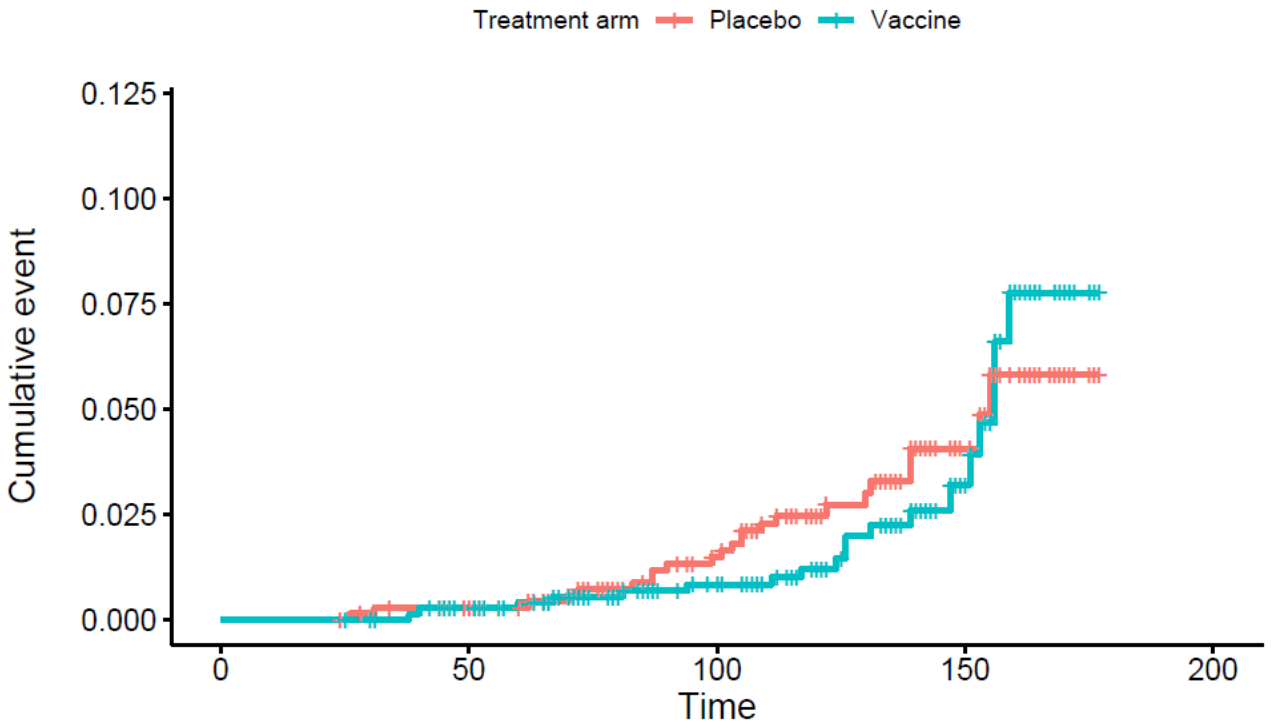


15/19 (79%) in pseudovirus assay and 11/19 (58%) in live virus assay had no detectable neutralization

Madhi S, *et al*. medRxiv 2021

Impact of NAb escape on vaccine efficacy

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

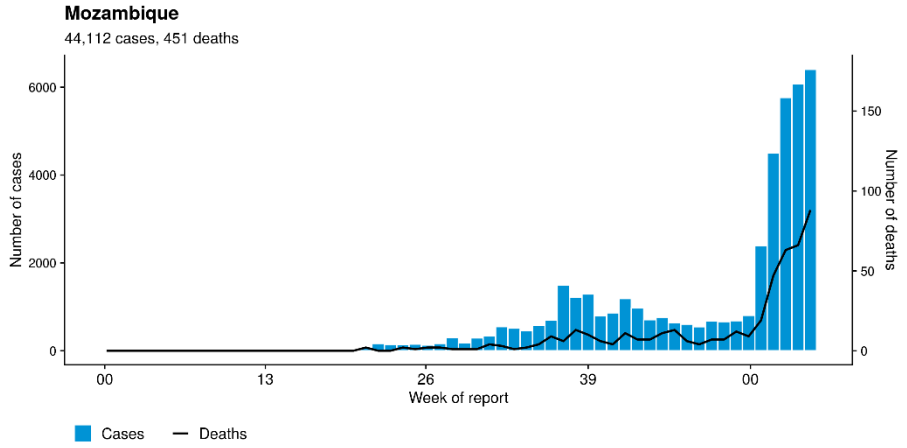


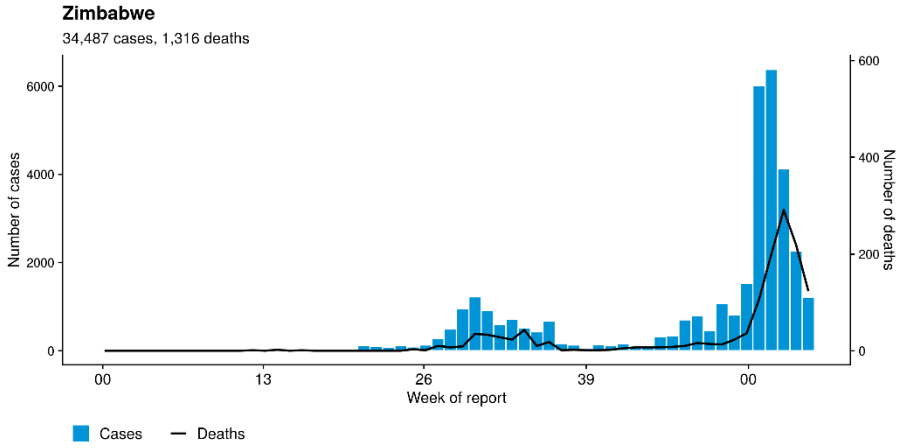
39/41 (95%) of lab-confirmed cases with sequence were due to 501Y.V2

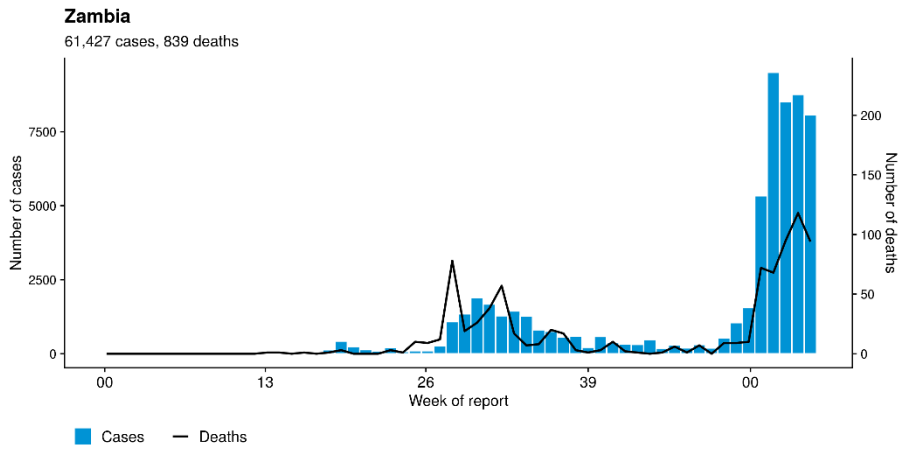
Vaccine efficacy 21.9% (95%CI -49.9, 59.8) against symptomatic COVID-19 - all cases mild/moderate

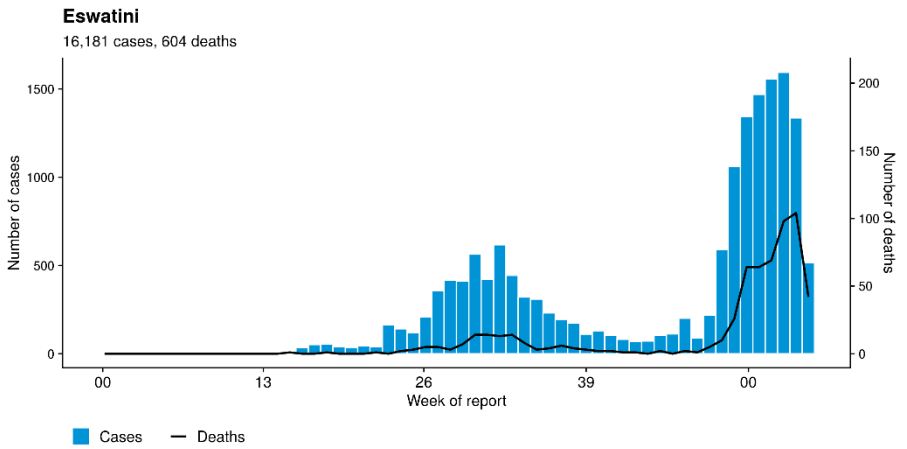
Madhi S, *et al*. medRxiv 2021

Regional COVID-19 resurgence



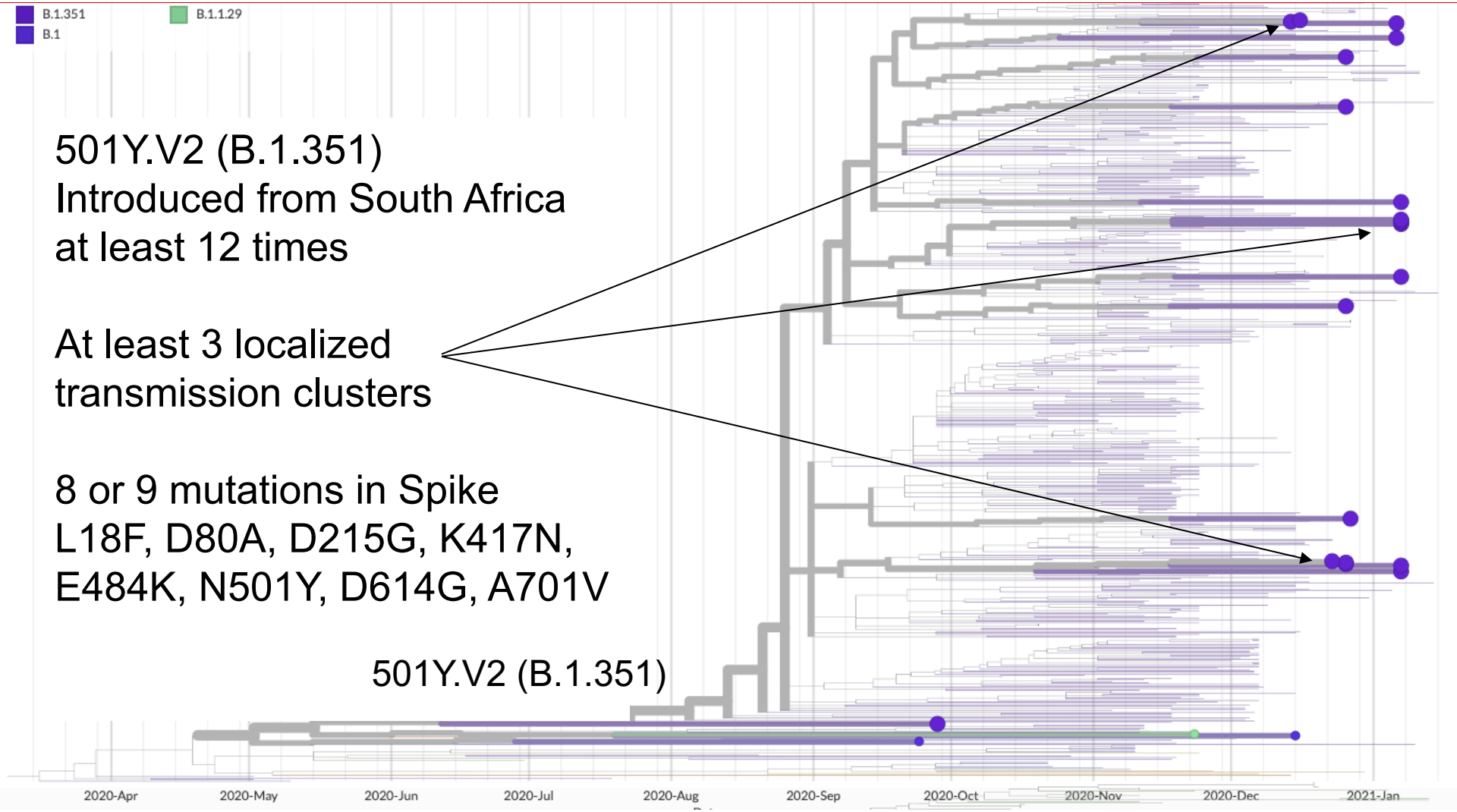




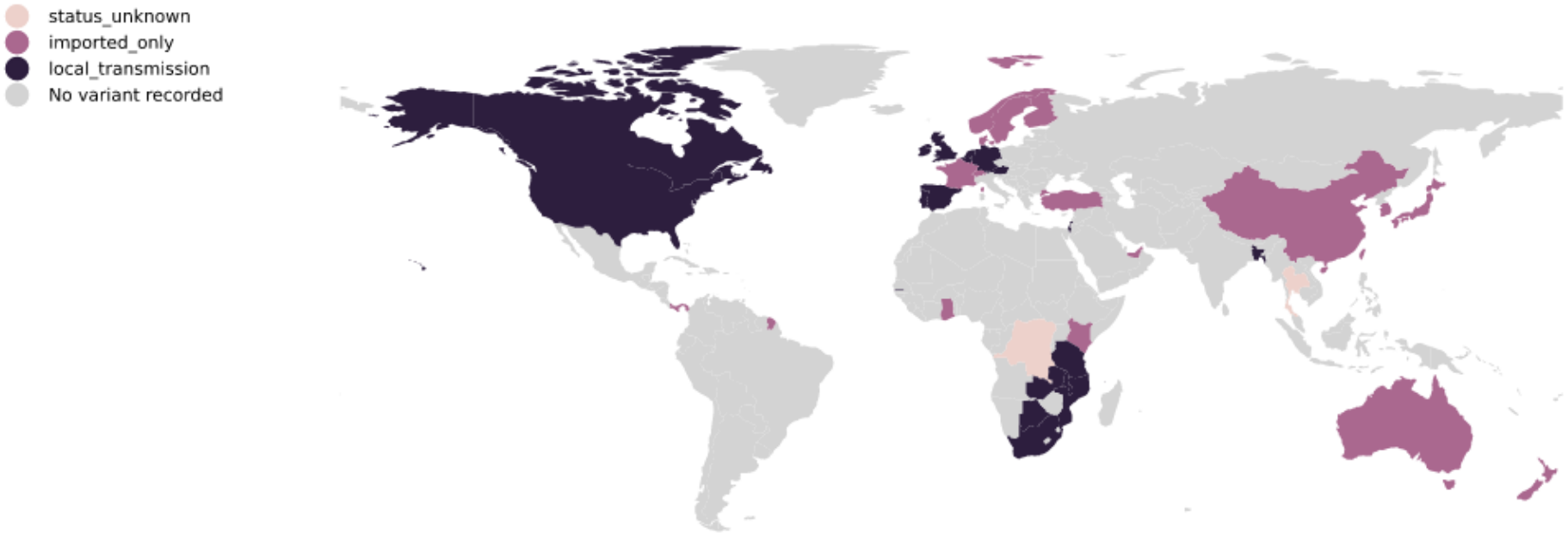


501Y.V2 in Mozambique

Data from Instituto Nacional de Saúde (INS)



International spread of 501Y.V2



501Y.V2 now reported in 40 countries (500 sequences from outside SA), with evidence of local transmission in several other countries

https://cov-lineages.org/global_report_B.1.351.html

Conclusions

- Genomic surveillance is a critical component of the epidemic response – exemplified by early detection, characterization and tracking of this new 501Y.V2 variant within and outside South Africa
- Genomic data strongly suggests 501Y.V2 has a selective advantage over other lineages, which may relate to increased transmissibility and/or immune escape
- Evidence to suggest reduced efficacy of vaccines against 501Y.V2, although some evidence that protection against severe disease remains high (Janssen Ad26.COV2.S vaccine)

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