

EMERGENCE AND SPREAD OF THE 501Y.V2 NEW VARIANT OF SARS-CoV-2

Prof Tulio de Oliveira & Dr Richard Lessells for the Network for Genomic Surveillance South Africa



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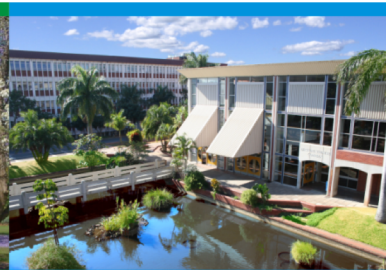
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NELSON R MANDELA SCHOOL OF MEDICINE



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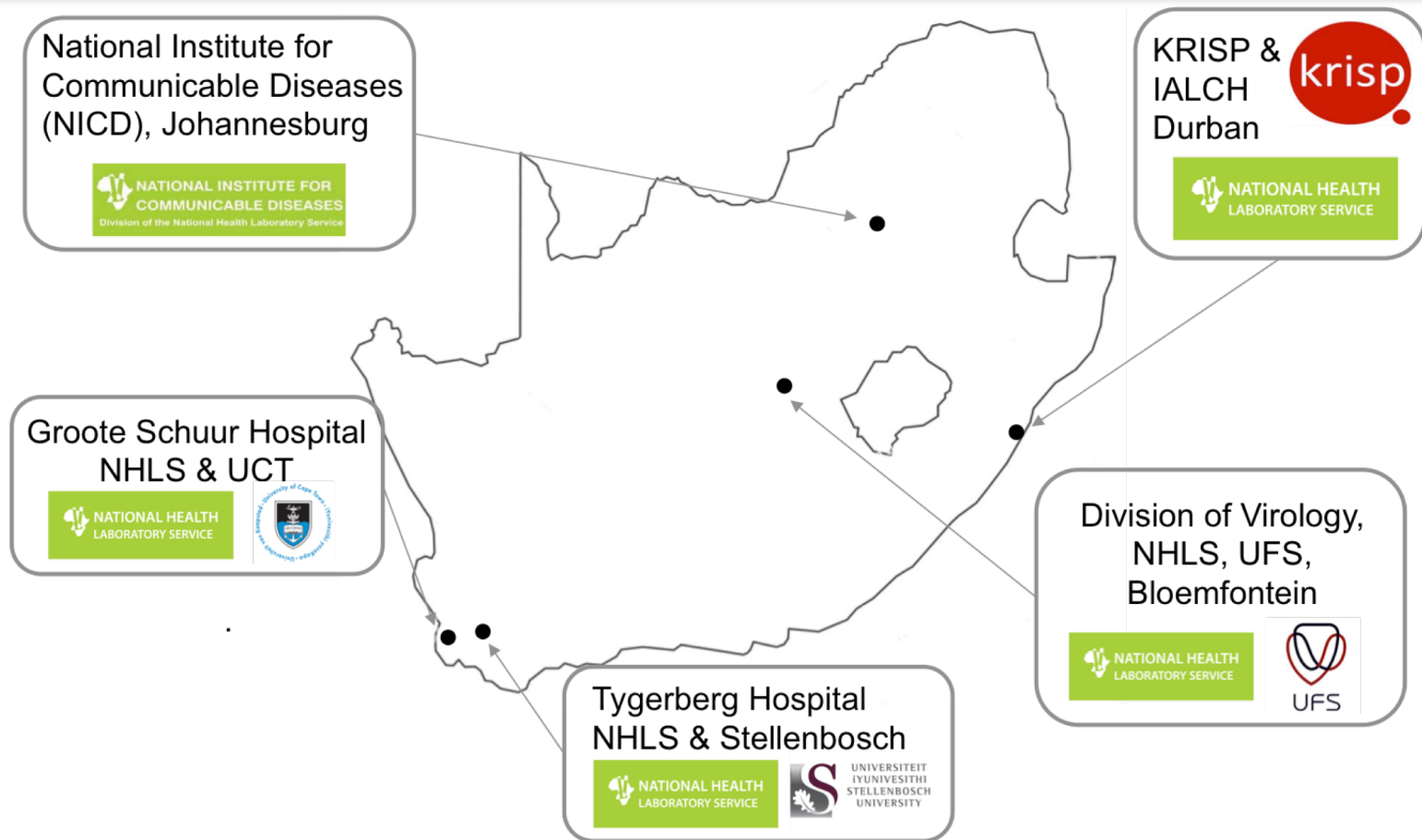
UKZN INSPIRING GREATNESS

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

- Used to discover the virus that caused 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 the host-virus interactions

~470 000 genomes produced and shared globally - 3150 in South Africa

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



science & innovation

Department:
Science and Innovation
REPUBLIC OF SOUTH AFRICA

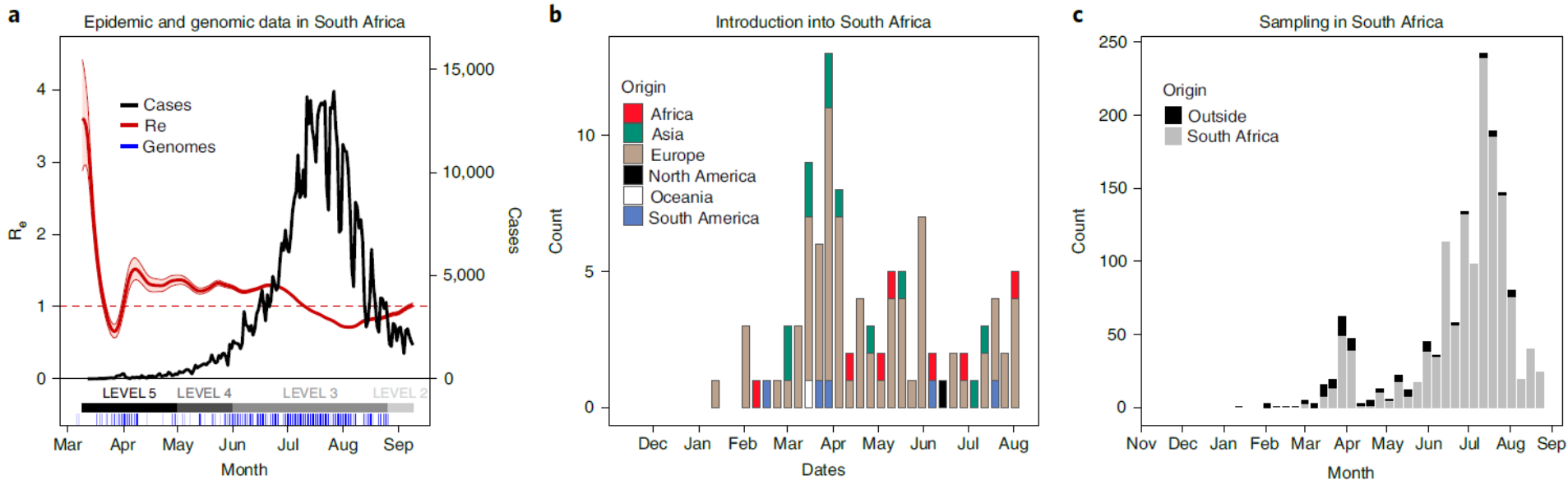
Supported by the DSI and the SA MRC
Msomi N, Mlisana K, *et al.* Lancet Microbe 2020



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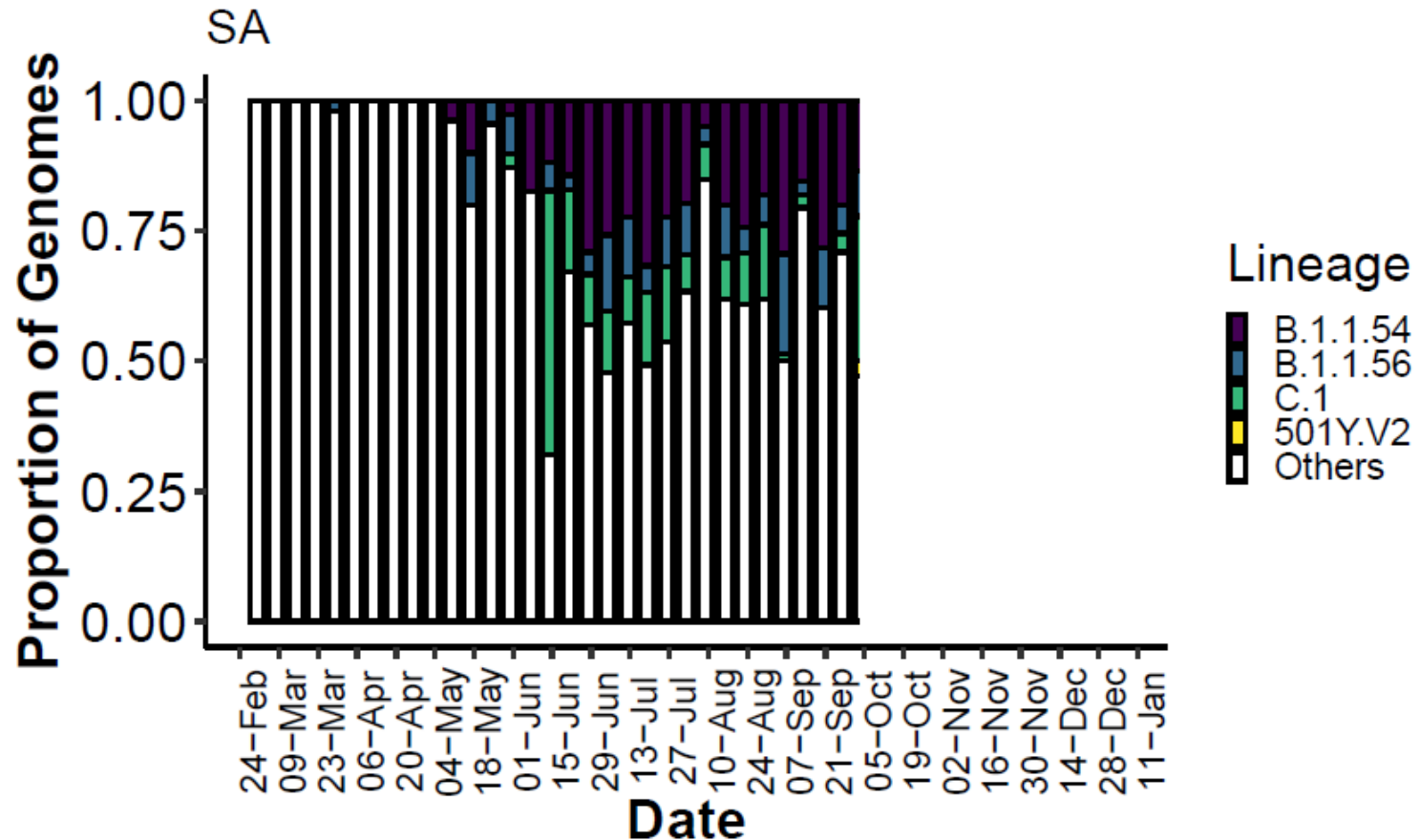


Introductions and local transmission of SARS-CoV-2 (first wave)



Tegally H *et al.* Nature Med 2021

Multiple lineages circulating in South Africa through first wave



In the first wave, we had multiple lineages circulating
(Three lineages responsible for ~42% of sampled cases)

November 2020 – Eastern Cape

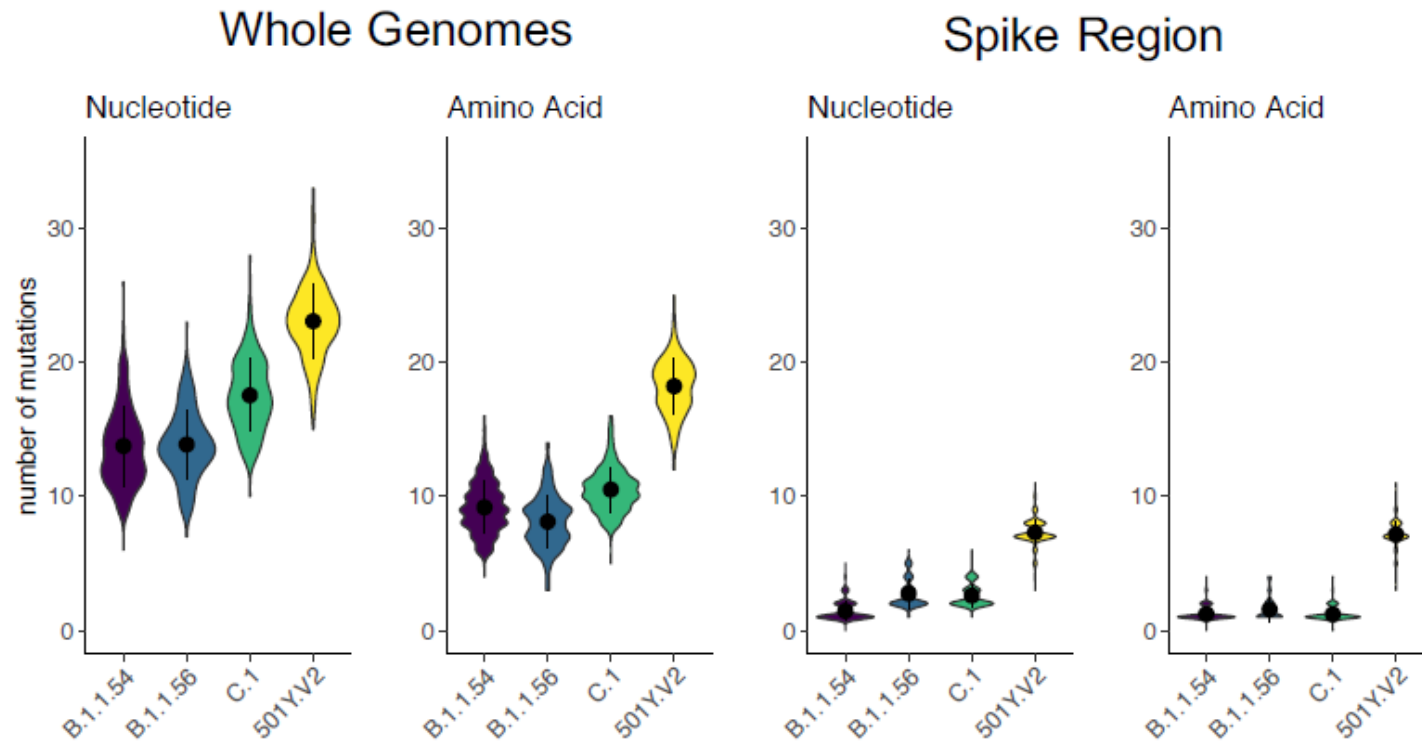


Greenacres Hospital was among the Netcare hospitals in South Africa where doctors spotted an unexplained spike in cases in October. Samantha Reinders for The New York Times

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
- Also concerned that clinical spectrum of disease was different
- Contacted us – “Is this a different strain?”

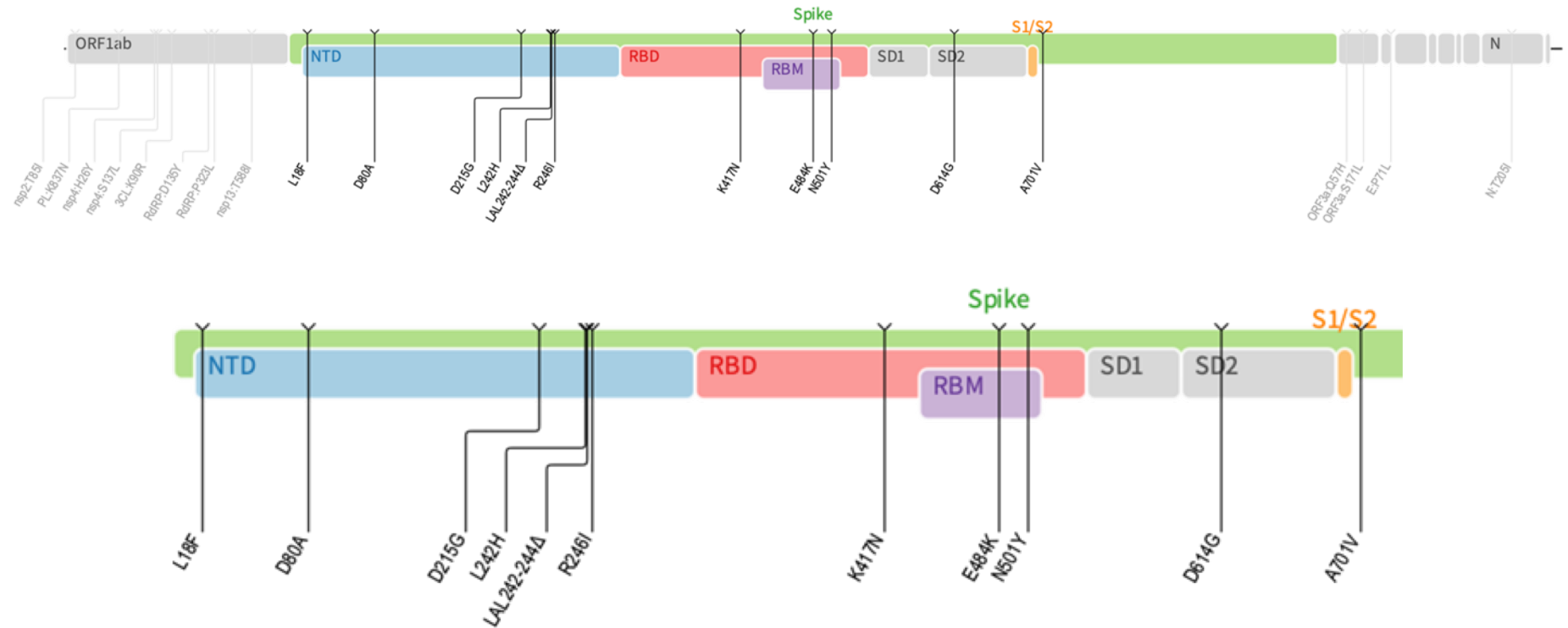
Genomic characteristics of 501Y.V2



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

Tegally H *et al.* medRxiv 2020

Genomic map of 501Y.V2

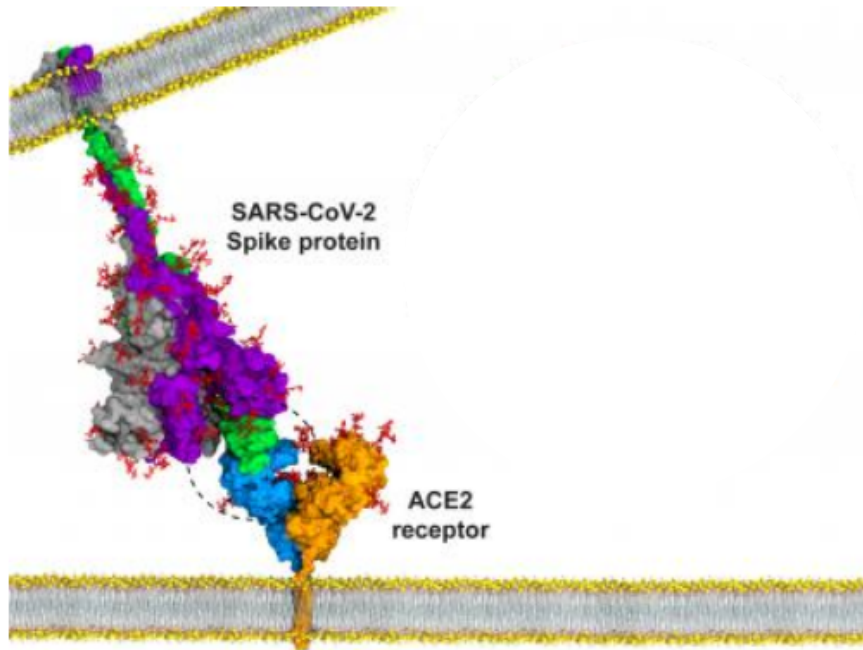


Three mutations in spike receptor-binding domain & cluster of mutations in N-terminal domain

<https://covdb.stanford.edu/>

Importance of spike glycoprotein and receptor-binding domain

Virus



Human cell

The **spike protein** attaches to the **ACE2 receptor** on host cells

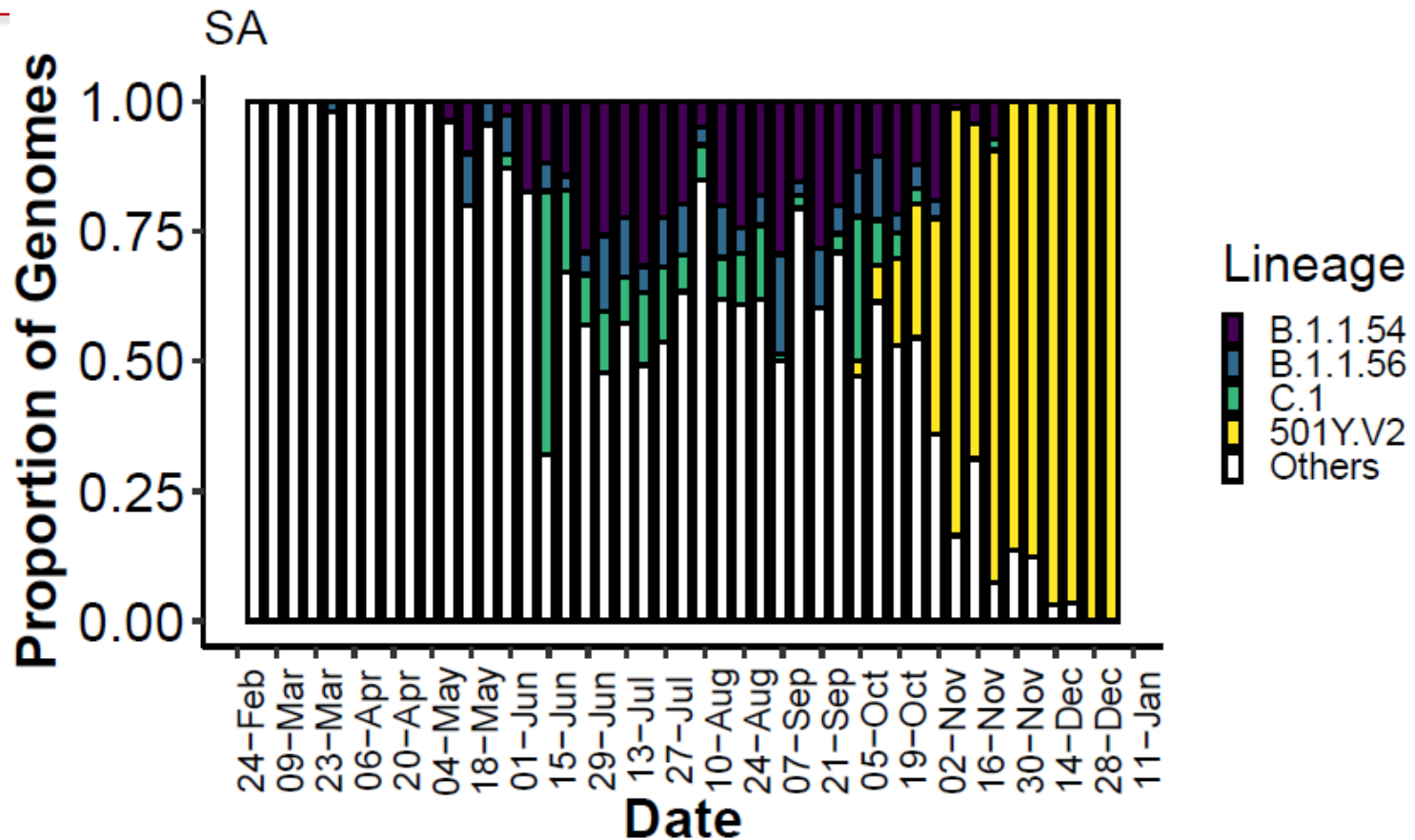
Each of the three petals of the spike protein carries a 'hook', called the **receptor-binding domain (RBD)** which is what directly interacts with ACE2

The RBD is also the main target for **neutralizing antibodies**

Mutations may therefore affect ACE2 binding and/or neutralization

Image courtesy of: <https://www.sciencemuseumgroup.org.uk/blog/coronavirus-the-spike/>

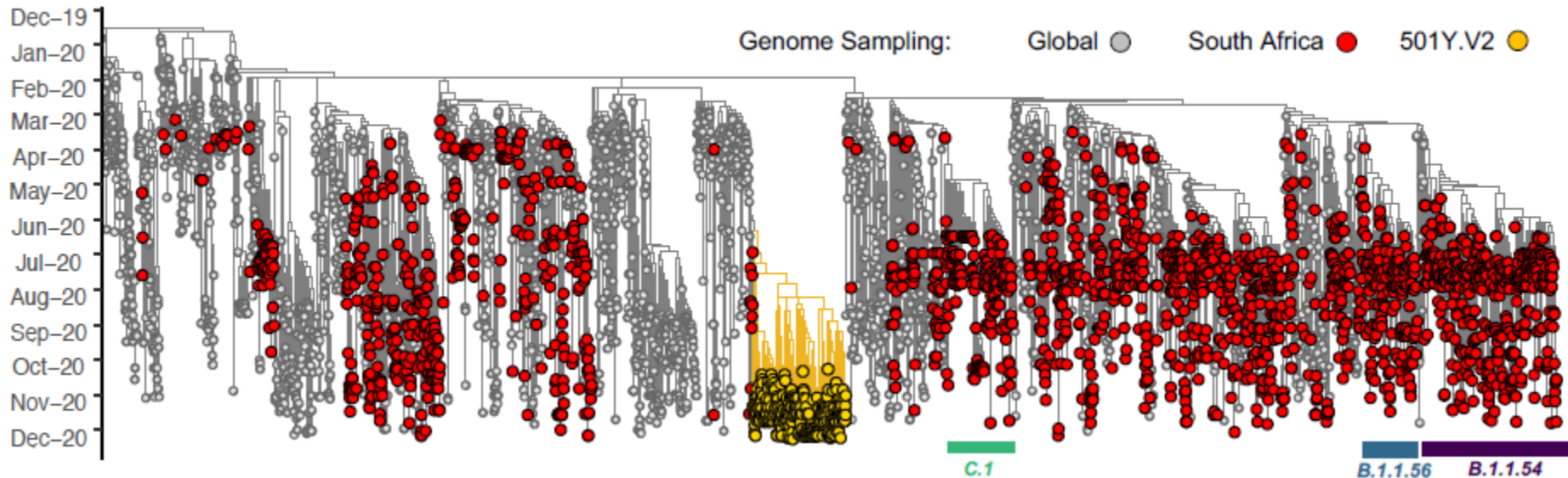
501Y.V2 becomes dominant lineage Nov-Dec



By early November, 501Y.V2 accounted for >80% of cases in the sampled locations (EC, WC and KZN)

Tegally H *et al.* medRxiv 2020

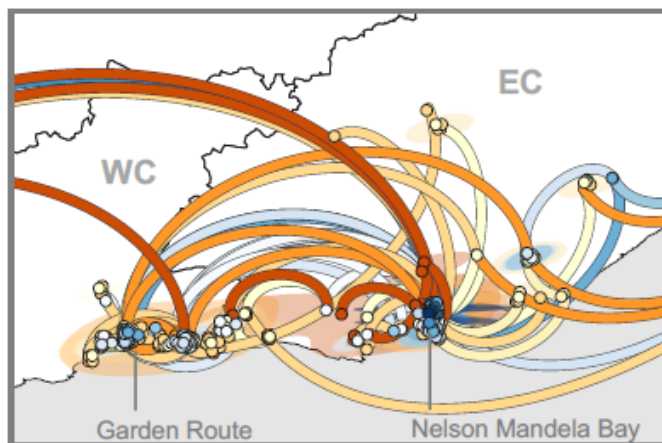
Phylogenetic analysis



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.* medRxiv 2020

New lineage emerged in NMA and spread rapidly to Western Cape and KZN



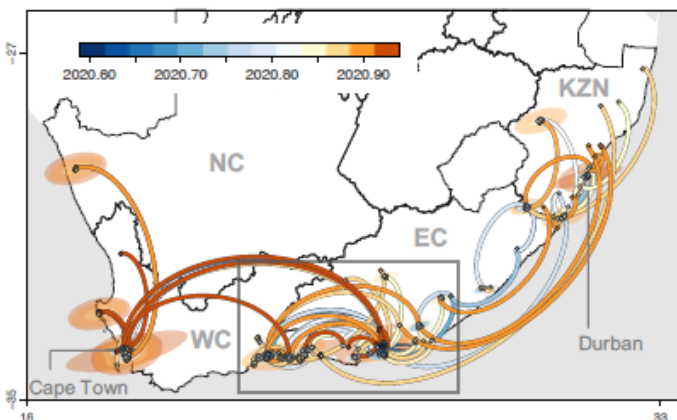
Our analysis suggests that this lineage emerged in Nelson Mandela Bay then spread to other districts in EC, to Western Cape and to multiple locations in KZN

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

We have detected this lineage in **>500 genomes** collected **8 Oct – 15 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

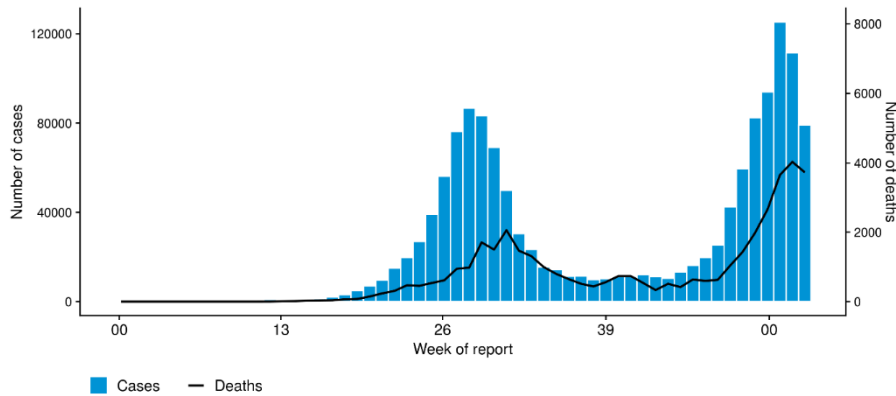
New data to be analysed from Gauteng & Free State – similar picture of 501Y.V2 dominance



Regional spread?

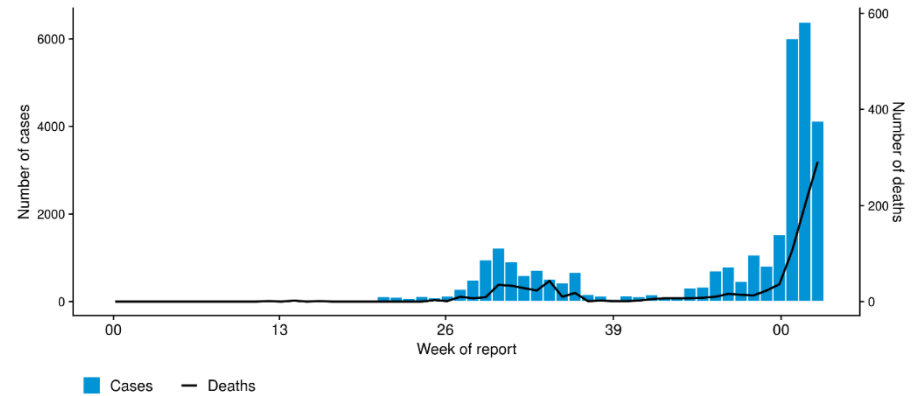
South Africa

1,423,578 cases, 41,797 deaths



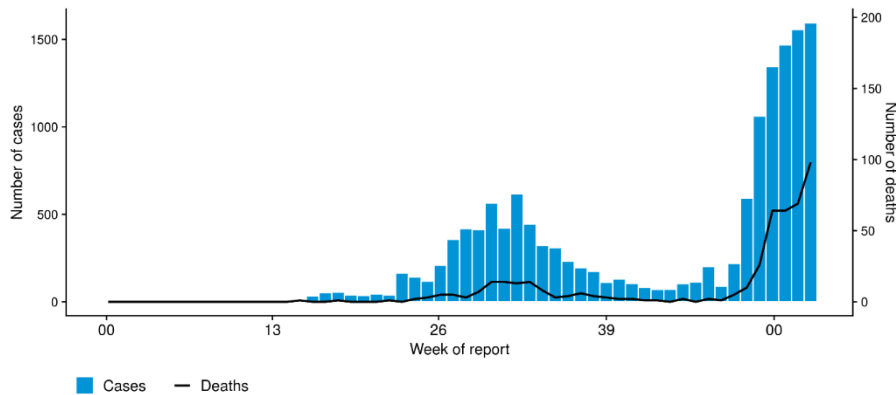
Zimbabwe

32,004 cases, 1,103 deaths



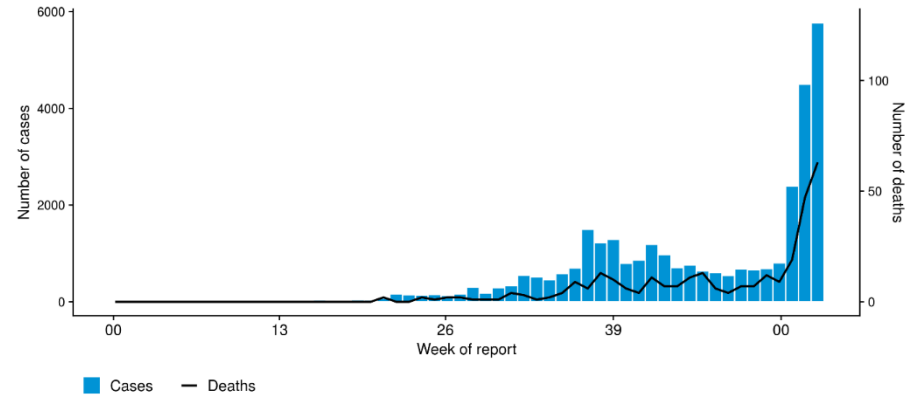
Eswatini

14,831 cases, 517 deaths



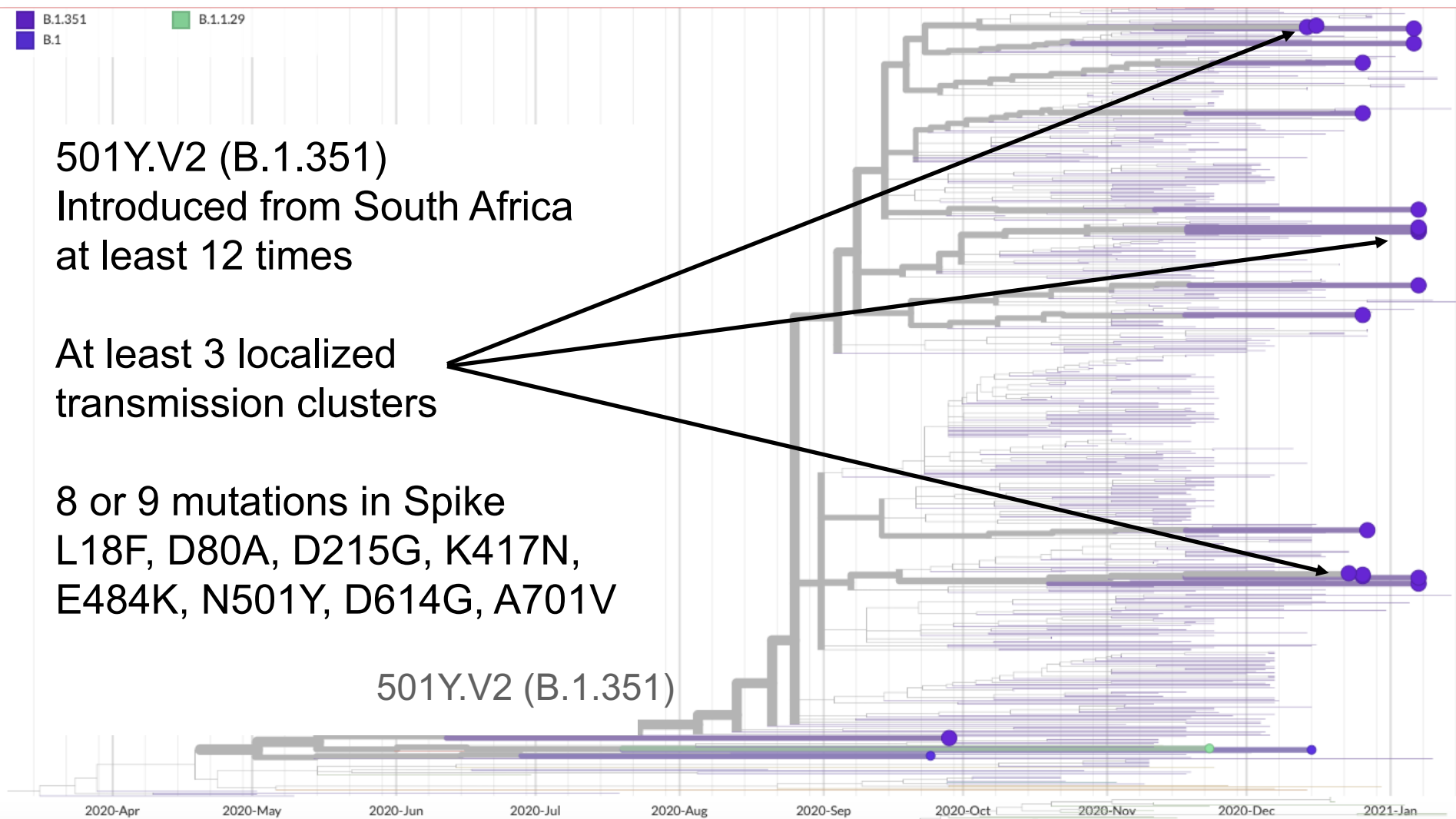
Mozambique

34,055 cases, 329 deaths

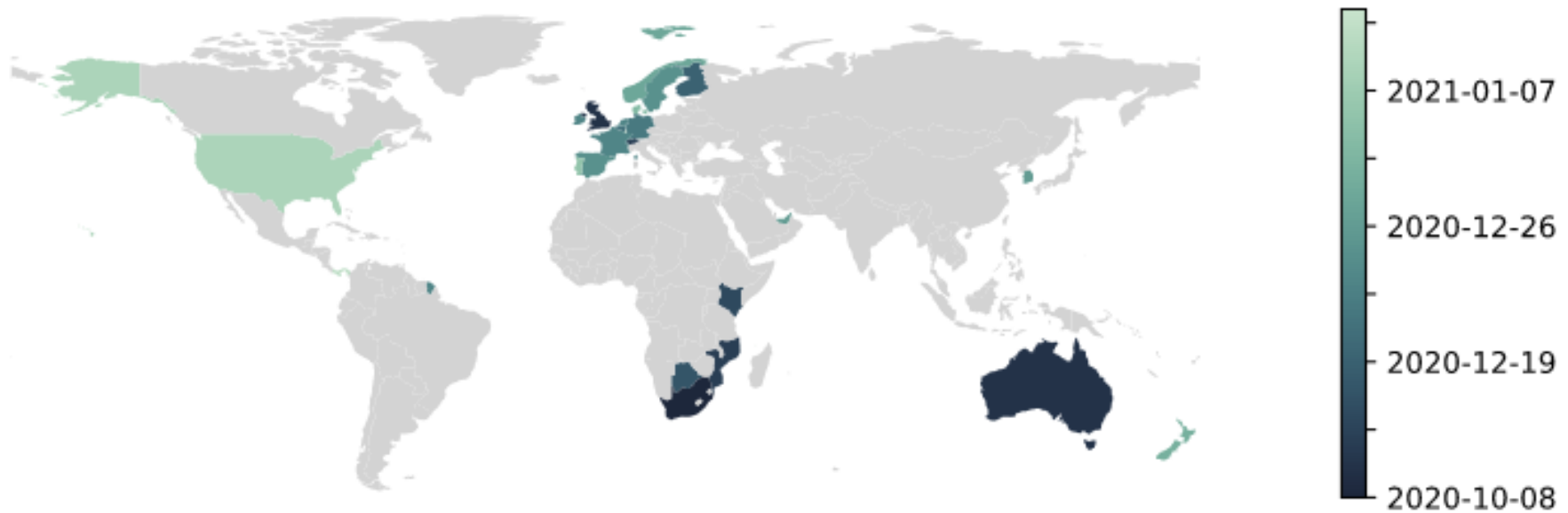


501Y.V2 variant in Mozambique

Data from Instituto Nacional de Saúde (INS)



International spread



501Y.V2 now detected in 31 countries, with evidence of local transmission in several countries

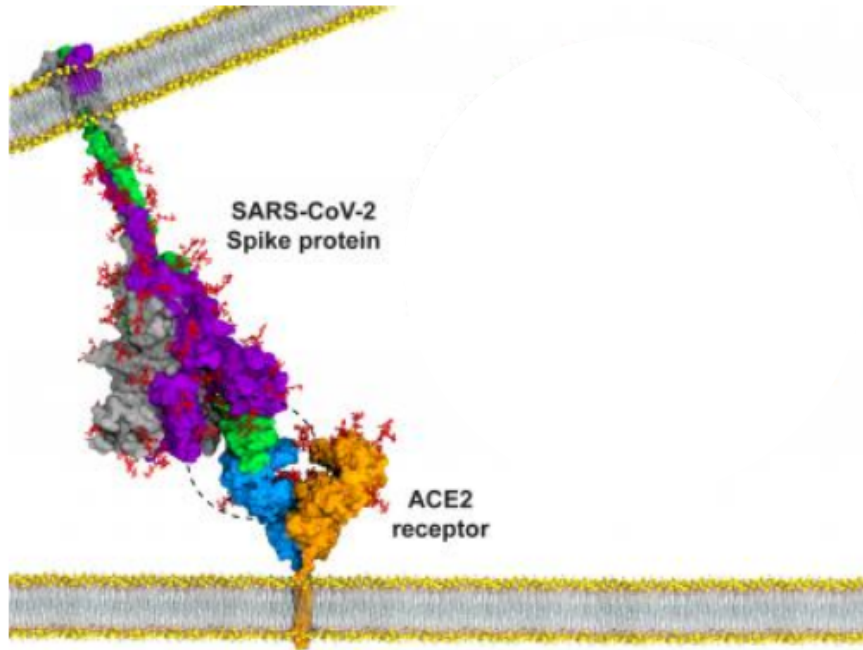
https://cov-lineages.org/global_report_B.1.351.html

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
- We detected a new lineage with multiple mutations at key sites in spike protein which could have functional significance
- Important to now link genotype to phenotype and understand full significance of mutations

Importance of the spike glycoprotein and receptor-binding domain

Virus



Human cell

The **spike protein** attaches to the **ACE2 receptor** on host cells

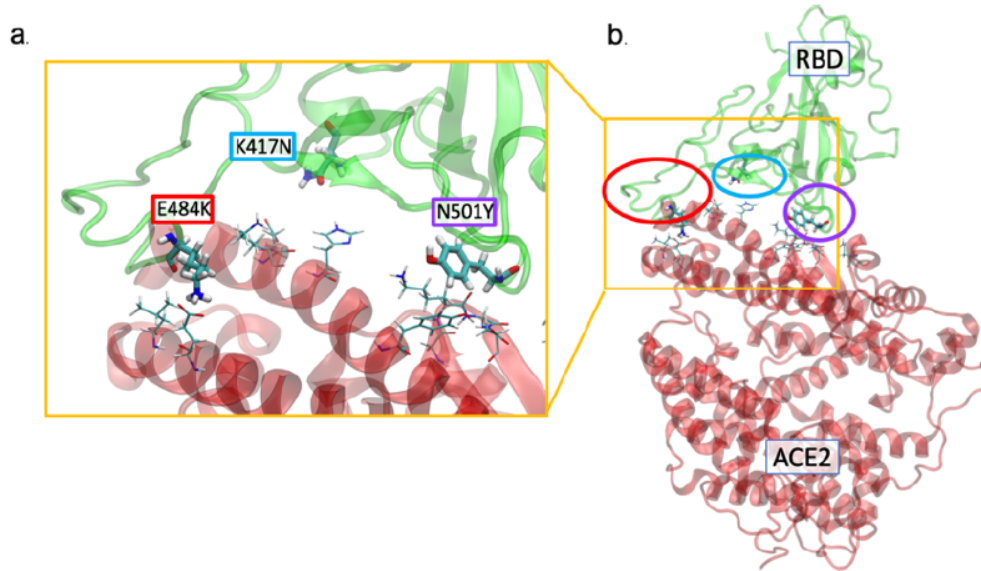
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Image courtesy of: <https://www.sciencemuseumgroup.org.uk/blog/coronavirus-the-spike/>

Spike RBD mutations enhance binding to ACE2



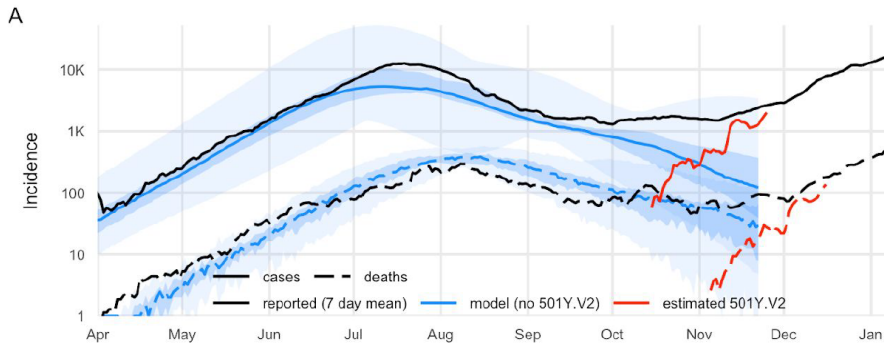
The 3 RBD mutations are all at key sites interacting with ACE2 receptor

N501Y and E484K increase binding affinity to ACE2

Plausible that this could explain increased transmissibility

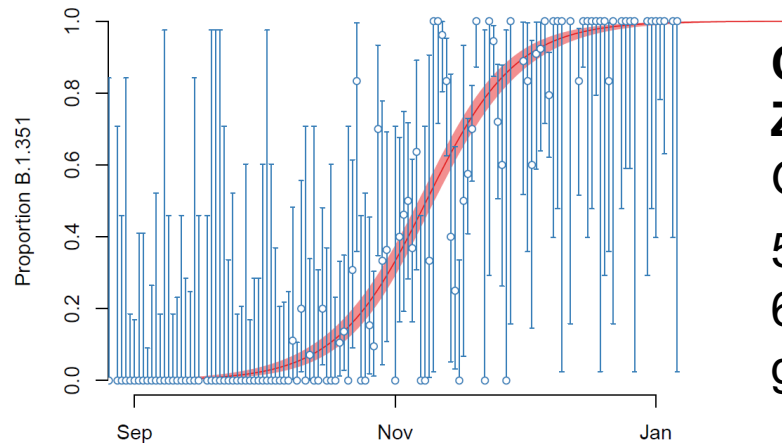
Nelson G *et al.* bioRxiv 2021

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



Christian Althaus (Bern), Tanja Stadler (ETH Zurich)

Genomic epi model

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

Neutralizing antibodies target the spike protein

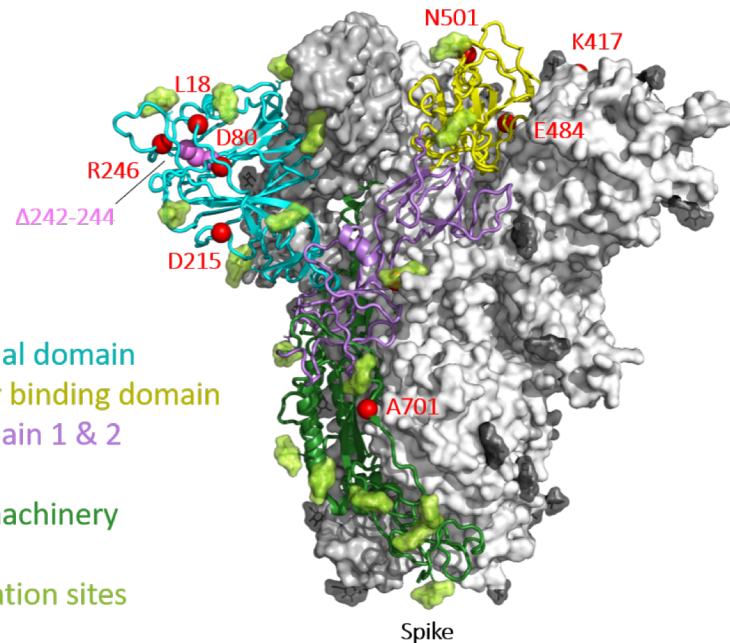


Image: Kurt Wibmer, NICD & NGS-SA

The spike receptor-binding domain (RBD) is the main target for **neutralizing antibodies (NAbs)** elicited during SARS-CoV-2 infection (~90% of the neutralizing activity present in convalescent sera)

Many NAbs prevent the spike protein from binding to the human ACE2 receptor

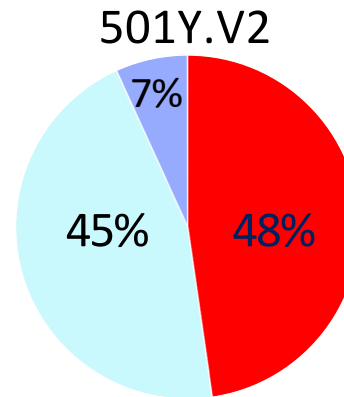
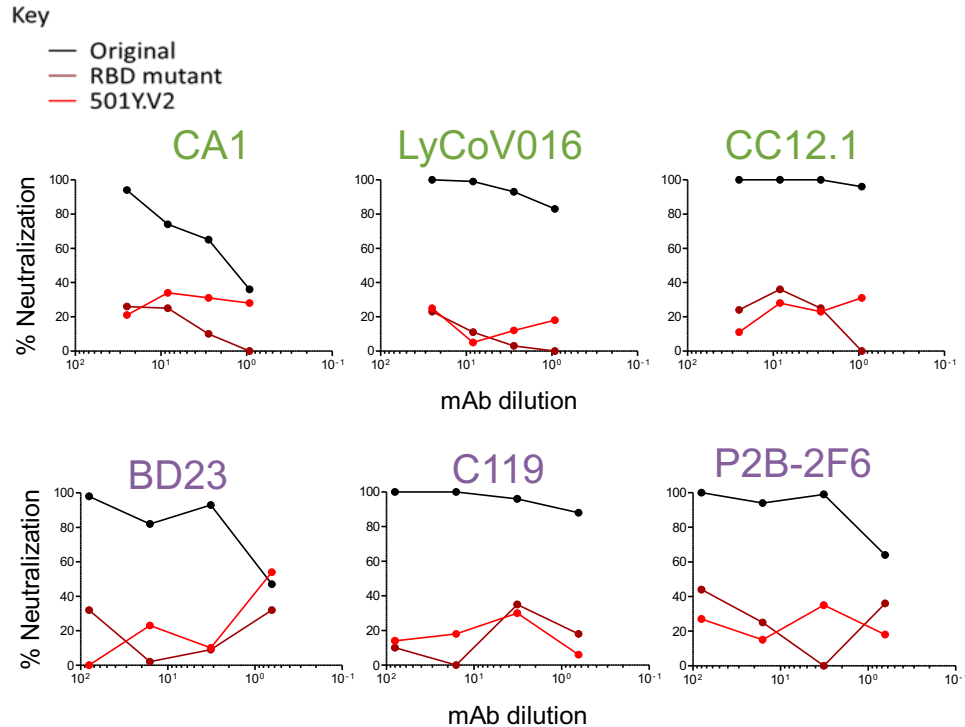
The remaining neutralizing activity seems to be targeted at the N-terminal domain of the spike protein

Piccoli L *et al.* Cell 2020

Chi X *et al.* Science 2020

McCallum M *et al.* bioRxiv 2021

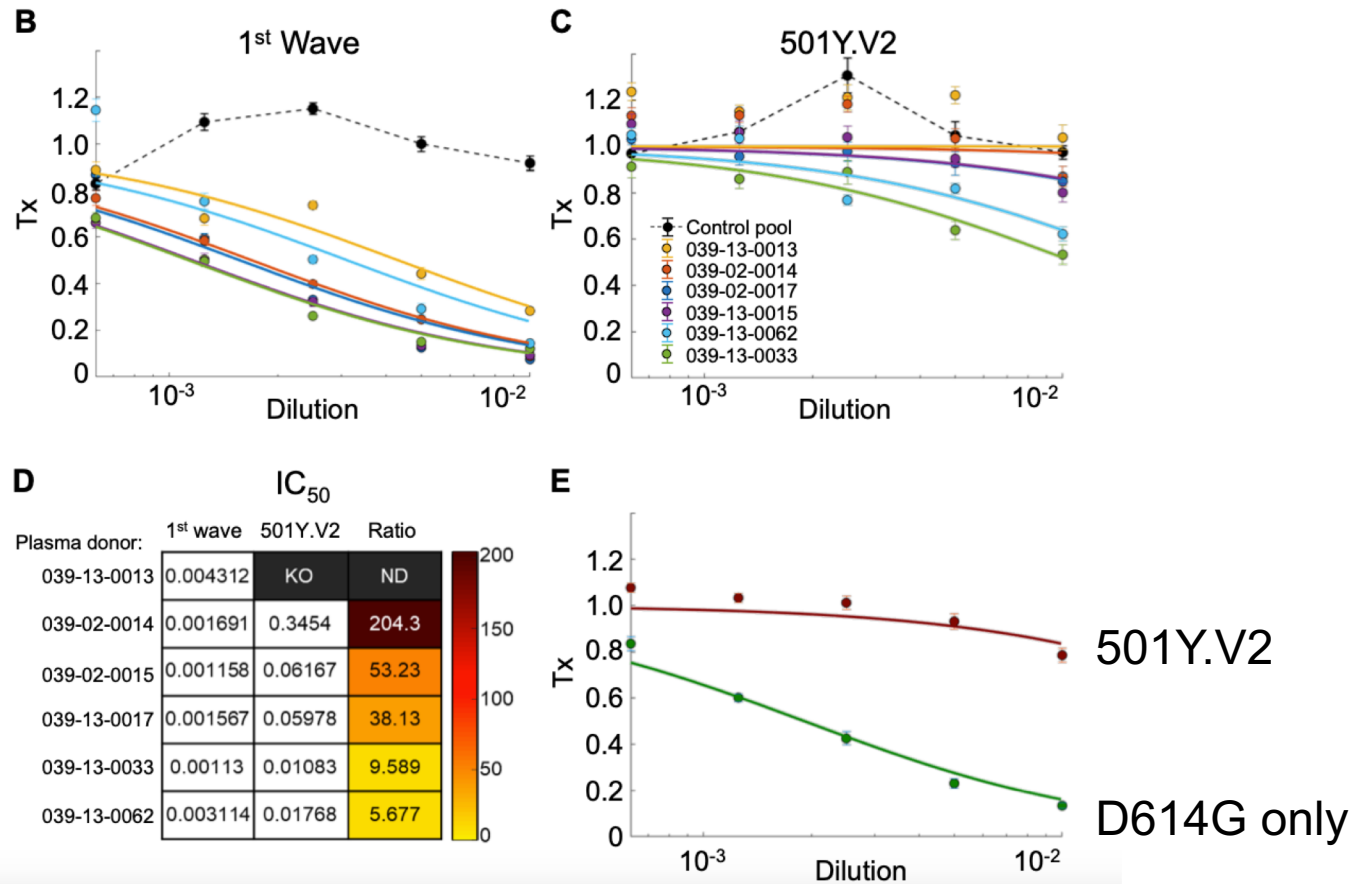
In vitro evidence of immune escape – monoclonal Abs & convalescent plasma



Convalescent donors (n=44)

Wibmer K et al. bioRxiv 2021

In vitro evidence of immune escape – convalescent plasma



SARS-CoV-2 re-infections

- Clinical reports of re-infections – a few now confirmed with genome sequencing (with 501Y.V2)
- True extent of re-infections uncertain – around 5000 putative re-infections from routine NHLS data (based on two positive PCR tests >90 days apart)
- Preliminary evidence from Novavax trial placebo arm (Prof Madhi) that rate of infection similar in Ab+ individuals cf. Ab- individuals
- Need more prospective data (cohort studies, clinical trials) to understand whether 501Y.V2 associated with increased rate of re-infection, e.g. Groote Schuur HCW cohort

Conclusions

- Strong evidence that 501Y.V2 has a selective advantage given rapid expansion and displacement of other lineages in multiple regions
- Selective advantage could be from increased transmissibility and/or immune escape (potential for re-infection)
- Much work still to be done to understand this

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