New Variant of SARS-CoV-2: What's the Concerns?

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Potential consequences of new variants

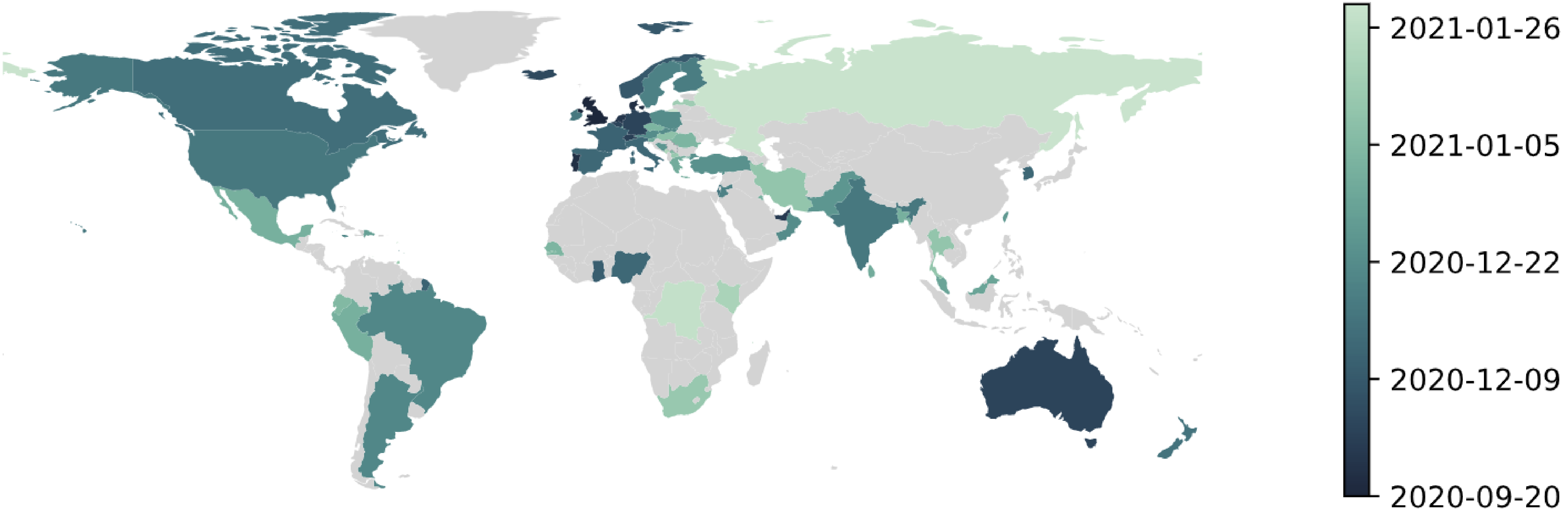
- **Ability to spread more quickly in people.**
- **Ability to cause either milder or more severe disease in people.**
- **Ability to evade natural or vaccine-induced immunity.**
- **Ability to evade detection by specific diagnostic tests.**
  - Most commercial polymerase chain reaction (PCR) tests have multiple targets to detect the virus, such that even if a mutation impacts one of the targets, the other PCR targets will still work.

There are 4 variants of concern

- **VOC 202012/01** (B.1.1.7), first detected in Kent England
- **VOC 202012/02** (B.1.351), first detected in South Africa
- **VOC 202101/02** (P.1), first detected in Brazil
- **VOC 202102/02** (B.1.1.7 cluster with E484K mutation), first detected in South West England has been detected in 23 cases.

Date of earliest_B.1.1.7 detected

Countries reported	93

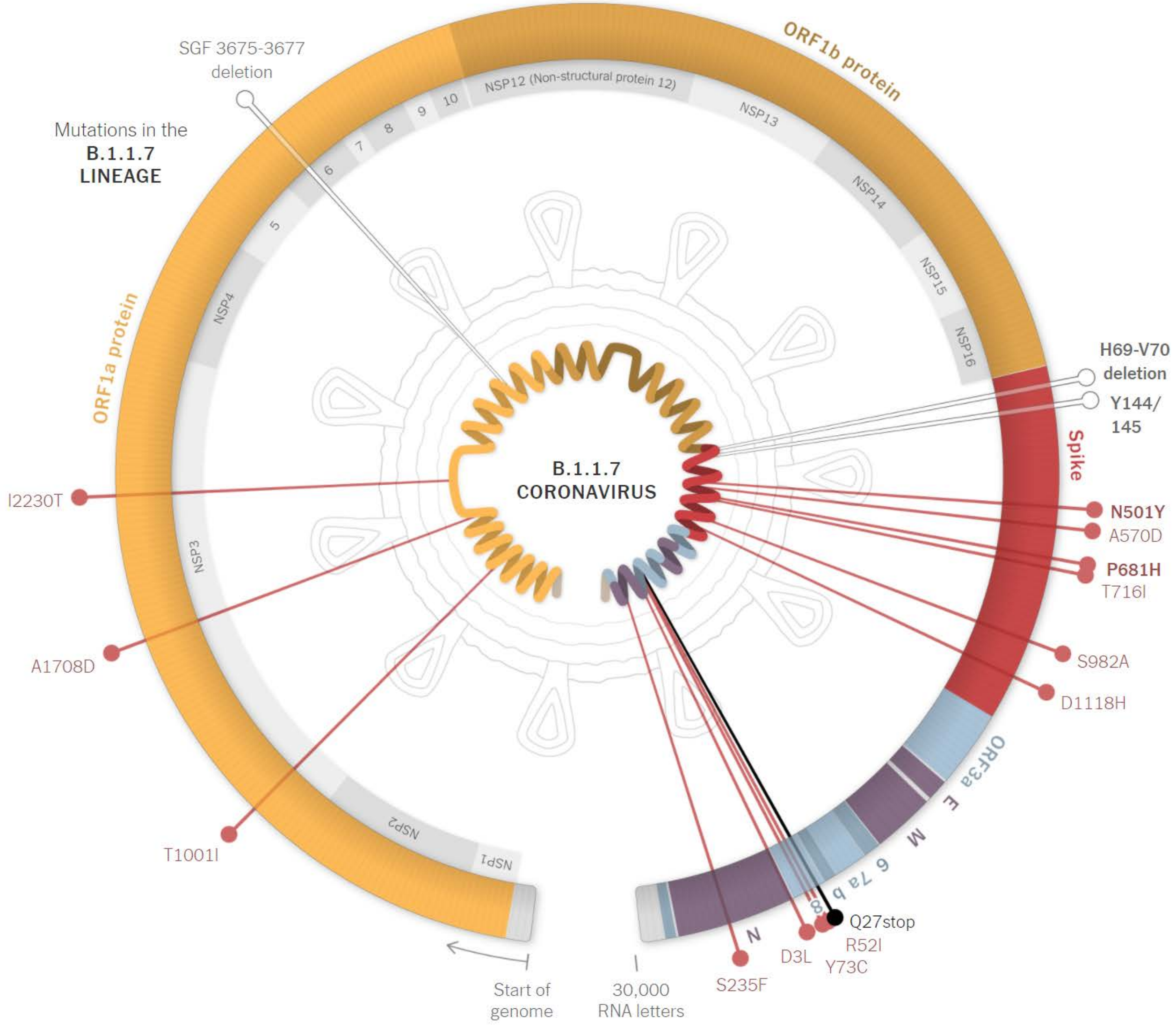


https://cov-lineages.org/

VOC 202012/01 (B.1.1.7)

- **Genomic profile**

Gene	amino_acid	actual_nucleotide
S Gene	H69_V70del	21765_21770del
	Y144del	21991_21993del
	N501Y	23063A>T
	A570D	23271C>A
	P681H	23604C>A
	T716I	23709C>T
	S982A	24506T>G
	D1118H	24914G>C
ORF1ab	T1001I	3267C>T
	A1708D	5388C>A
	I2230T	6954T>C
	3675-3677del	11288_96del
ORF8	Q27*	27972C>T
	R52I	28048G>T
	Y73C	28111A>G
N Gene	D3L	28280_2delinsCTA



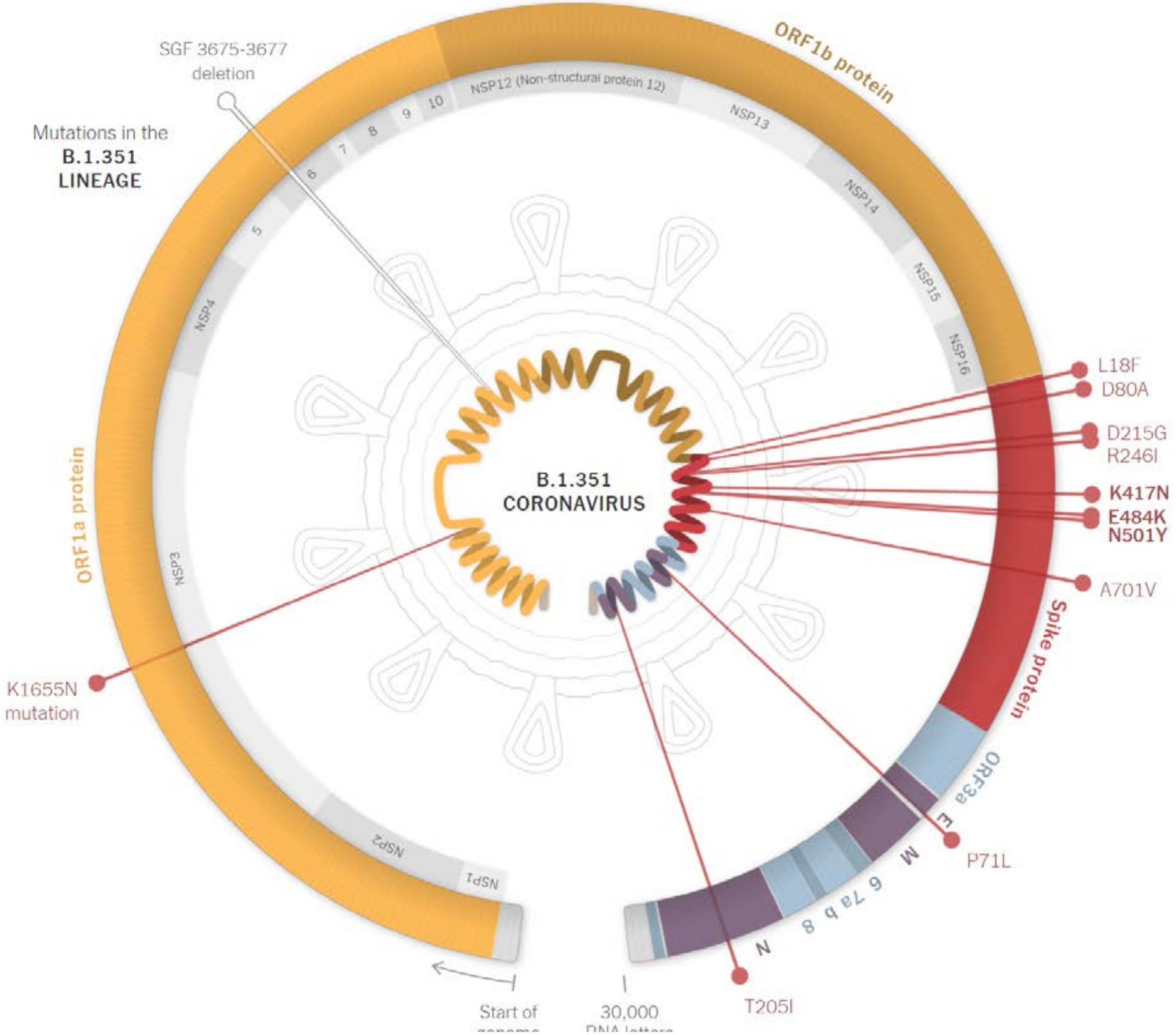
VOC 202012/02 (B.1.351)

- Also Known as **501Y.V2 (South Africa)** was first identified in South Africa in December 2020.

VOC 202012/02 (B.1.351)

Genomic profile

Gene	amino_acid	actual_nucleotide
S Gene	L18F	21614C>T
	D80A*	21801A>C
	D215G*	22206A>G
	R246I	22299G>T
	K417N*	22813G>T
	E484K*	23012G>A
	N501Y*	23063A>T
	A701V*	23664C>T
	242-244del	
ORF1ab	T265I	1059C>T
	K1655N*	5230G>T
	K3353R	10323A>G
	3675-3677del	11288_96del
ORF3a	Q57H	25563G>T
	S171L	25904C>T
E Gene	P71L*	26456C>T
N Gene	T205I*	28887C>T



VOC 202101/02 (P.1)

- Also known as **501Y.V3** or **B.1.1.28** or Brazilian lineage.
- The variant was first reported in Japan, in four people who contracted P.1 on a trip to Brazil.
- The lineage emerged in late 2020 in Manaus, the largest city in Brazil’s Amazon region. It quickly became the predominant variant there and in several other South American cities.

Genomic characterisation of an emergent SARS-CoV-2 lineage in Manaus: preliminary findings

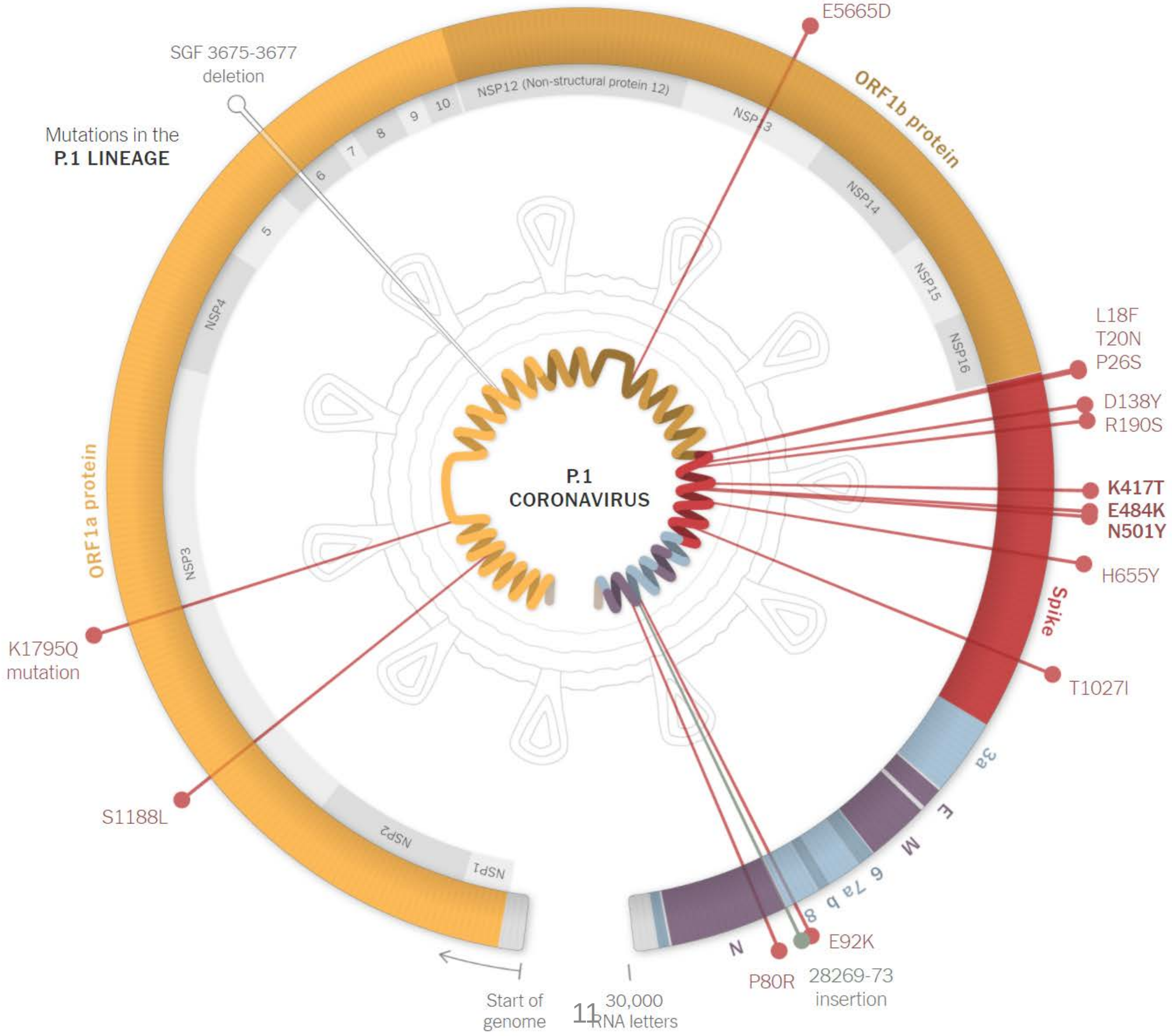
Genomic characterisation of an emergent SARS-CoV-2 lineage in Manaus: preliminary findings

Nuno R. Faria[1,2,3], Ingra Morales Claro[3,4], Darlan Candido[2,3], Lucas A. Moyses Franco[3,4], Pamela S.

A recent study reported on a cluster of cases in Manaus, the largest city in the Amazon region, in which the P.1 variant was identified in 42% of the specimens sequenced from late December.

In this region, it is estimated that approximately 75% of the population had been infected with SARS-CoV2 as of October 2020.
However, since mid-December the region has observed a surge in cases. The emergence of this variant raises concerns of a potential increase in transmissibility or propensity for SARS-CoV-2 re-infection of individuals.

gene	amino_acid	actual_nucleotide
S Gene	L18F	21614C>T
	T20N	21621C>A
	P26S	21638C>T
	D138Y	21974G>T
	R190S	22132G>T
	K417T	22812A>C
	E484K	23012G>A
	N501Y	23063A>T
	H655Y	23525C>T
	T1027I	24642C>T
orf1ab	-	733T>C
	-	2749C>T
	S1188L	3828C>T
	K1795Q	5648A>C
	-	11288_96del
	-	12778C>T
	-`	13860C>T
	E5665D	17259G>T
orf8	E92K	28167G>A
	-	28263insAACA
N Gene	P80R	28512C>G
	-	28877A>T
	-	28878G>C

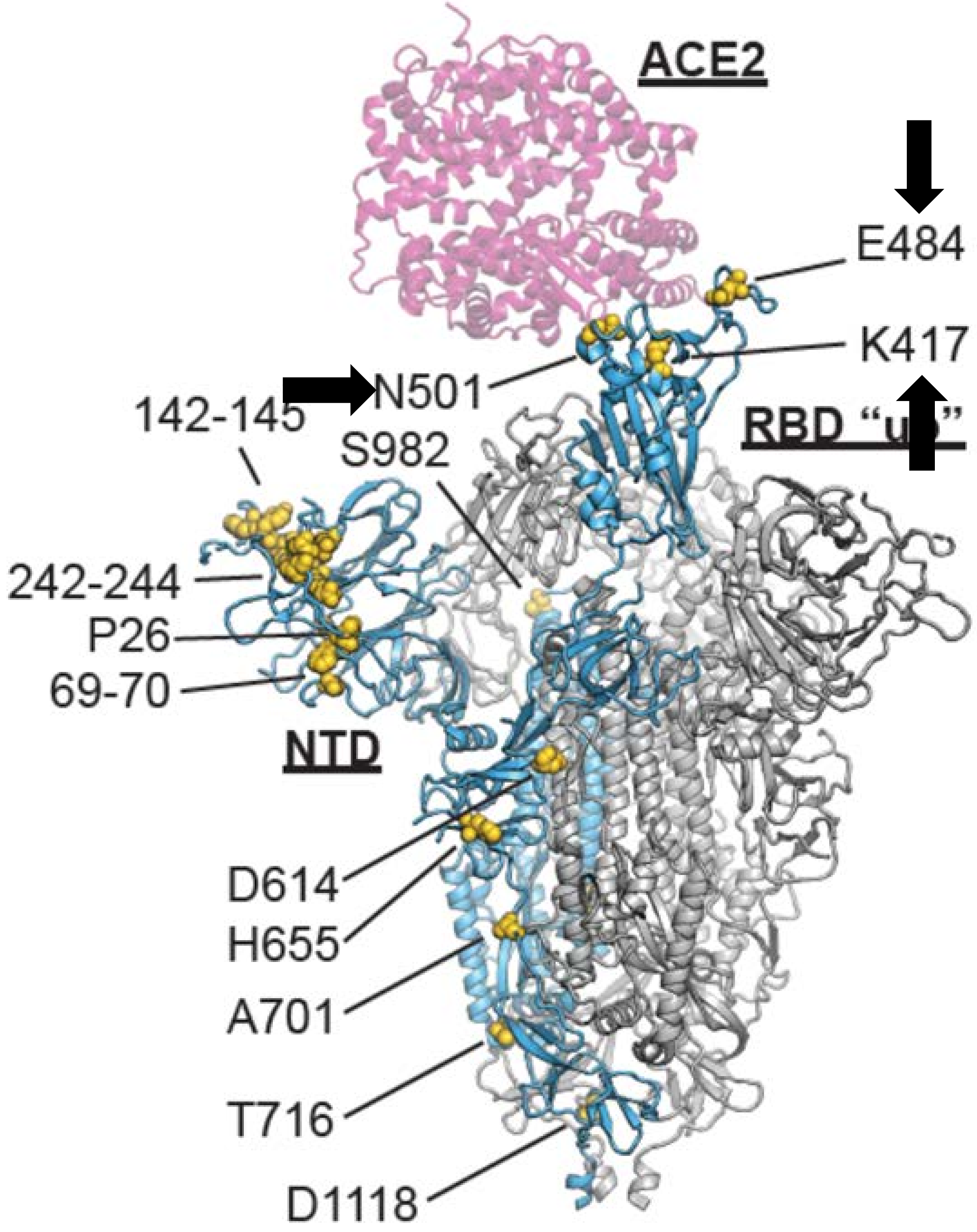


VOC 202102/02 (B.1.1.7 cluster with E484K)

- Through routine scanning of variation in VOC 202012/01 (B.1.1.7) a small number of B.1.1.7 sequences (33 of 258504 sequences as of 11 February 2021), had acquired the spike protein mutation E484K.
- The cluster (VOC 202102/02 (B.1.1.7 cluster with E484K)) has the mutations previously described for VOC 202012/01 (B.1.1.7) with the addition of **E484K** in spike gene**, L730F in orf1ab**, and **A173V, A398T in N gene** in all cases
- E484K is a mutation of concern with regards to antigenic change and receptor binding avidity, and is potentially more concerning when combined with N501Y.
- E484K is associated with increased binding to human ACE2, though it is unclear what impact this has on virus phenotype.
- Finally, E484K is associated with multiple variants of concern including the **B.1.351 and P.1 lineages**, as well as being identified as **a long-term adaptation** in several different immunocompromised patient studies.

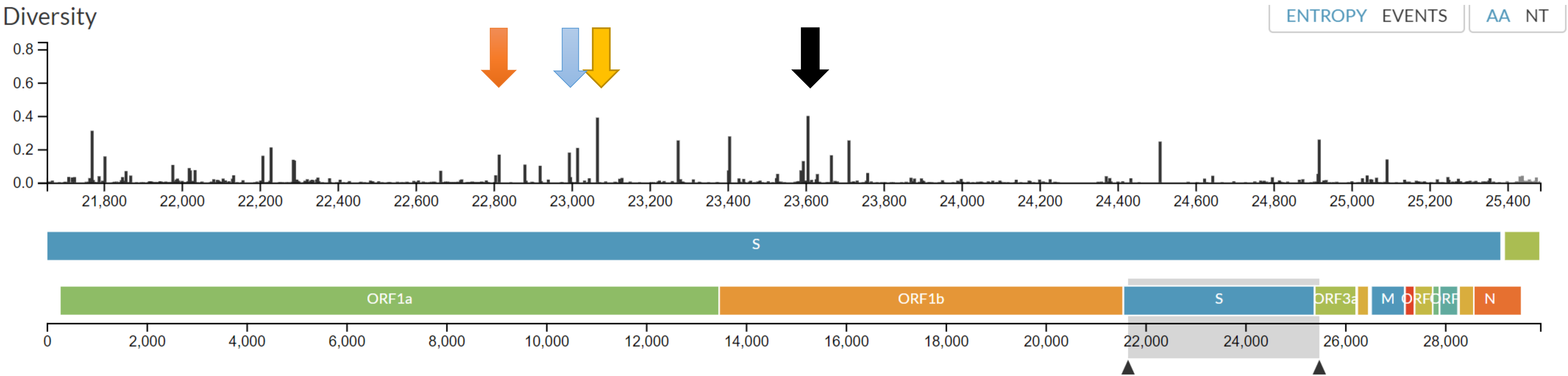
Important Mutations in the three VOCs

N501Y: **B.1.1.7, B.1.351, P1**
K417N: **B.1.351, P1**
E484K: **B.1.351, P1**



https://nextstrain.org/ncov/global?c=gt-S_21511=nimg&25435=xamg&452

	AA change	ENTROPY
➡	**N501Y**	0.389
➡	**E484K**	0.207
➡	**K417N**	0.0167
➡	**D614G**	**0.399**



Variant Of Concern (VOC) mutations

nt	21614 C>T	21621 C>A	21638 C>T	21767-72	21801A>C	21974 G>T	21992-4	22132 G>T	22206 A>G	22286-95	22812 A>C 22813 G>T	23012 G>A	23063 A>T	23271 C>A	23525 C>T	23604 C>A	23664 C>T	23709 C>T	24506 T>G	24642 C>T	24914 G>C
aa	L18F	T20N	P26S	HV 69-70 del	D80A	D138Y	Y144 del	R190S	D215G	LAL 242-4 del	K417N/R	E484K	N501Y	A570D	H655Y	P681H	A701V	T716I	S982A	T1027I	D1118H
B.1.1.7 UK				✓			✓						✓	✓		✓		✓	✓		✓
B.1.351 SA	✓				✓				✓	✓	N	✓	✓				✓				
B.1.1.28 Brazil	✓	✓	✓			✓		✓			R	✓	✓		✓					✓	
											RBD										

Potential consequences of VOCs

- 3- Immune evasion

Therapeutic Monoclonal Antibodies

Variants	Eli Lilly's mAb (LY-CoV555)	Regeneron's mAb Cocktail (REGN10933 and REGN10987)
B.1.1.7	Is working	Is working
B.1.351	No longer neutralizes	REGN10933 does not neutralize, REGN10987 neutralized
P.1	Probably does not neutralize	REGN10933 neutralized probably not anymore, whether REGN10987 still neutralized is unclear

Potential consequences of VOCs

- 3- Immune evasion

Influence on neutralizing activity of **convalescent sera** and **sera from vaccinated persons**

Variants	Convalescent sera	Sera from mRNA vaccinated individuals
B.1.1.7	Little loss of activity	Little loss of activity
B.1.351	Strong reduction, Loss of activity roughly 50%	Moderate reduction
P.1	Probably similar to B.1.351	Probably similar to B.1.351

- mRNA vaccines induce very high neutralizing antibody titers, even at a large drop (10x) would still have a lot of neutralizing activity stay
- For Moderna and Pfizer vaccine protection was seen after vaccination, when the neutralizing antibody titers are still very low
- Neutralizing antibodies aren't everything in the immune system

B.1.351

Novavax trial – 31% SA participants had past infection. Covid-19 incidence in:

Seronegative (no past infection) – 3.9% (58/1494; 95%CI: 3.0-5.0)

Seropositive (past infection) – 3.9% (26/674; 95%CI: 2.5-5.6)

bioRχiv

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

Constantinos Kurt Wibmer[1], Frances Ayres[1], Tandile Hermanus[1], Mashudu Madzivhandila[1], Prudence
Kgagudi[1] Bronwen E Lambson[1,2] Marion Vermeulen[3] Karin van den Berg[3,4] Theresa Rossouw[5] Michael

Convalescent sera from 44 South Africans infected in 1st wave, >90% showed reduced immunity & 48% had complete immune escape to 501Y.V2

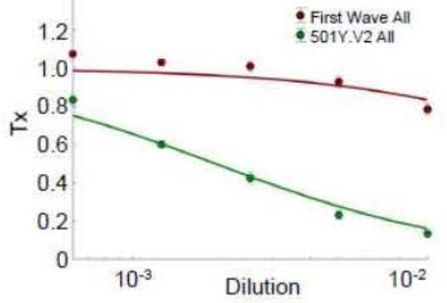
medRχiv

THE PREPRINT SERVER FOR HEALTH SCIENCES

Escape of SARS-CoV-2 501Y.V2 variants
from neutralization by convalescent plasma

Sandile Cele[1,2], Inbal Gazy[2,3,4], Laurelle Jackson[1], Shi-Hsia Hwa[1,5], Houriiyah Tegally[3], Gila Lustig[6],
Jennifer Giandhari[3] Sureshnee Pillay[3] Eduan Wilkinson[3] Yeshnee Naidoo[3] Farina Karim[1,2] Yashica

Neutralization of 501Y.V2 variant strongly attenuated, with IC50 increasing to 6 to 200-fold higher relative to 1st wave viruses



Do vaccines prevent clinically apparent SARS-CoV-2 infections with the pre-existing variants?

Yes, quite well

	Efficacy	Endpoints (vaccine vs placebo)	Sample size
* Single dose Johnson&Johnson*	66%*	n/a	43,783
Pfizer	95%	8 vs 162	34,922
moderna	94%	11 vs 185	28,207
THE GAMALEYA NATIONAL CENTER OF EPIDEMIOLOGY AND MICROBIOLOGY	92%	16 vs 62	19,866
NOVAVAX^	89%	6 vs 56	15,000
AstraZeneca	67%	84 vs 248	17,177
sinovac#	51%	n/a	12,396

Brazilian trial
^UK trial

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Do vaccines prevent hospitalisation / severe Covid-19 with pre-existing variants?

Yes, very well

* Single dose	Efficacy – severe C-19	Severe Covid-19 (vaccine vs placebo)	Hospitalised	Sample size
Johnson & Johnson	**85%*#**	n/a	n/a	43,783
Pfizer	**90%**	1 vs 9	n/a	34,922
moderna	**100%**	0 vs 30	0 vs 9	28,207
THE GAMALEYA NATIONAL CENTER OF EPIDEMIOLOGY AND MICROBIOLOGY	**100%**	0 vs 20	n/a	19,866
NOVAVAX	**Too few**	0 vs 1	n/a	15,000
AstraZeneca	**Too few**	0 vs 3	2 vs 22	17,177
sinovac# Brazilian trial	**100%#**	n/a	n/a	12,396

#Note: number of severe cases not known

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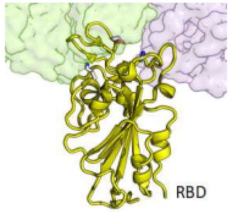
Is vaccine neutralisation impacted by 501Y.V2?

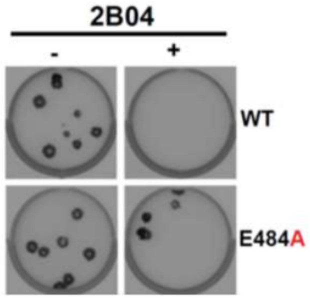
	Pseudovirion and live virus Lab assays
* Single dose Johnson & Johnson	-
Pfizer	1 to 3 fold ↓
moderna	6.4 fold ↓
THE GAMALEYA NATIONAL CENTER OF EPIDEMIOLOGY AND MICROBIOLOGY	-
AstraZeneca	3 to 86 fold↓ / ko
NOVAVAX	-
Sinopharm	1.6 fold ↓
sinovac	-

Lab assays:

- Pseudovirion mutant assay



- Live virus plaque assay



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Are vaccines clinically effective against 501Y.V2?

	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	-	-	-	-
AstraZeneca	3 to 86 fold↓ / ko	22%	-	-
NOVAVAX	-	49%	-	-
Sinopharm	1.6 fold ↓	-	-	-
sinovac	-	-	-	-

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CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

What have we learnt about vaccines & the 501Y.V2 variant…

- **Lab: all vaccine-induced antibodies less activity in neutralizing the 501Y.V2 variant – Pfizer & Sinopharm (minimum ↓) to Az (substantial ↓)**

- **Clinical studies in South Africa on mild to moderate disease**
  - Az decline in efficacy (66% → 22%), but wide 95% confidence intervals (-49 to 60%)
  - Novavax show decline in efficacy (89% → 49%)
  - No data on Pfizer, Moderna, J&J, Gamaleya, Sinovac or Sinopharm

- **Clinical studies in South Africa on severe disease and hospitalization**
  - J & J shows high efficacy (85%)
  - No data on Pfizer, Moderna, Novavax, Gamaleya, Sinovac or Sinopharm