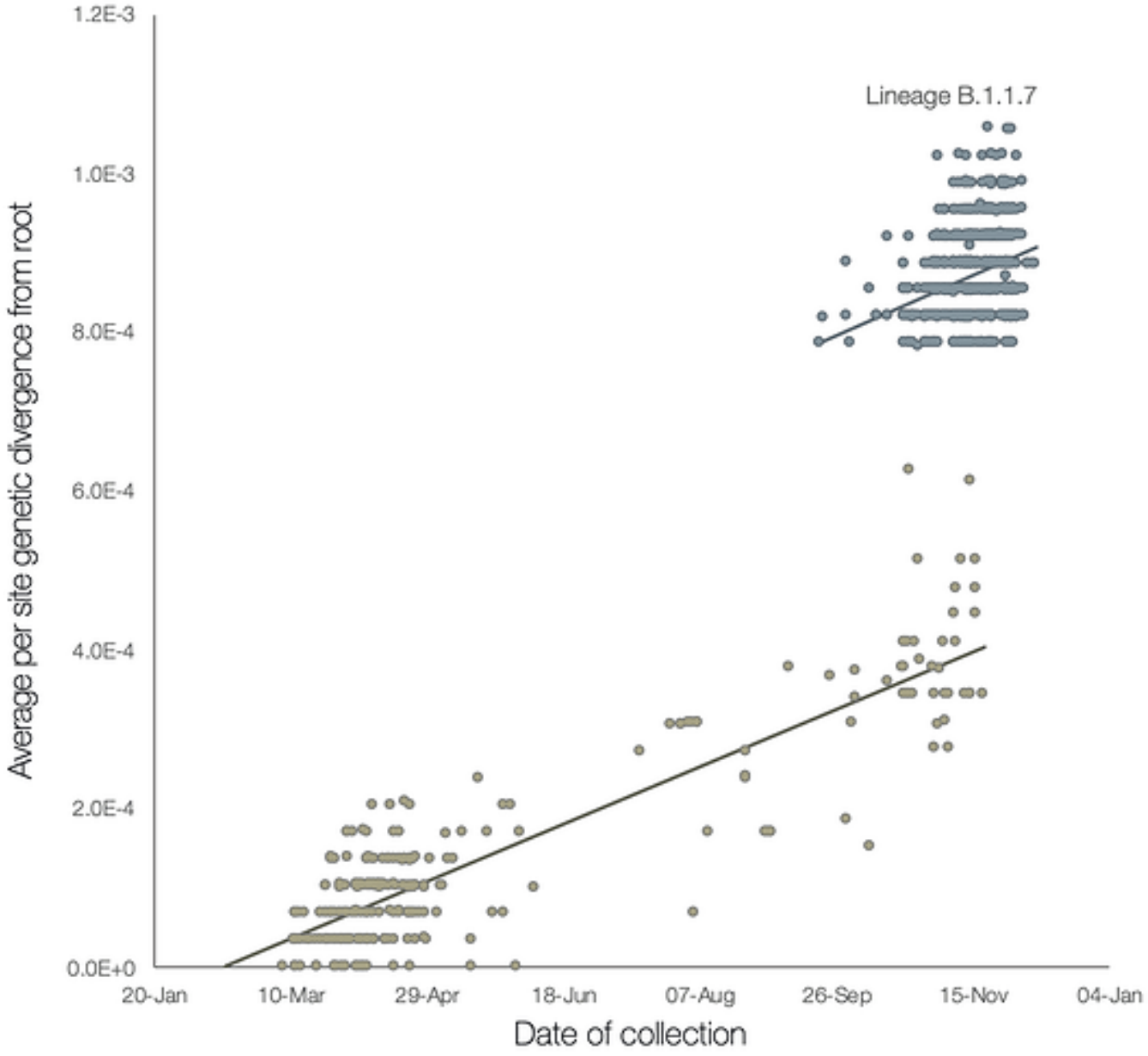
SARS-CoV-2 variants in the United Kingdom and Republic of South Africa

22 December 2020


Lineage B.1.1.7
Average per site genetic divergence from root
1.2E-3
1.0E-3
8.0E-4
6.0E-4
4.0E-4
2.0E-4
0.0E+0
20-Jan
10-Mar
29-Apr
18-Jun
07-Aug
26-Sep
15-Nov
04-Jan
Date of collection

United Kingdom - background

- A distinct phylogenetic cluster (named lineage B.1.1.7) has been growing rapidly over the past 4 weeks and spreading across the UK.
- B.1.1.7 has an unusually large number of genetic changes, particularly in the spike protein; this specific variant is referred to as Variant Under Investigation (VUI) 20212/010.
- UK officials informed WHO via IHR on 14 December of a new virus variant that includes several mutations, including the N501Y mutation. WHO held a call with UK officials and ECDC on 16 December and WHO informed Member States on 18 December.
- 1439 total confirmed cases in the UK as of 16 December.
- UK is working directly with the SARS-CoV-2 Virus Evolution Working Group.

Preliminary genomic characterisation of an emergent SARS-CoV-2 lineage in the UK defined by a novel set of spike mutations: https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563

United Kingdom - VUI 2020 12/01

- VUI 2020 12/01 has a larger than usual number of mutations.
- Three of these mutations have potential biological effects that have been described previously to varying extents:
  - Mutation **N501Y** is one of six key contact residues within the receptor-binding domain (RBD) and has been identified as increasing binding affinity to human and murine ACE2.
  - The **spike deletion 69-70del** has been described in the context of evasion to the human immune response but has also occurred a number of times in association with other RBD changes.
  - Mutation **P681H** is immediately adjacent to the furin cleavage site, a known location of biological significance.

- Representative sequences have been submitted to GISAID.

gene	nucleotide	amino acid
ORF1ab	C3267T	T1001I
	C5388A	A1708D
	T6954C	I2230T
	11288-11296 deletion	SGF 3675-3677 deletion
spike	21765-21770 deletion	HV 69-70 deletion
	21991-21993 deletion	Y144 deletion
	A23063T	N501Y
	C23271A	A570D
	C23604A	P681H
	C23709T	T716I
	T24506G	S982A
	G24914C	D1118H
Orf8	C27972T	Q27stop
	G28048T	R52I
	A28111G	Y73C
N	28280 GAT->CTA	D3L
	C28977T	S235F

Frequently asked questions

- Does it make you sicker?
- Do I run a bigger risk of infecting loved ones?
- Will the vaccine still work?
- Is the virus going to continue to mutate?
- How do we control this new variant?

United Kingdom – preliminary findings / ongoing work

- Preliminary genetic analyses and modelling studies suggest an increased transmissibility associated with this virus. Studies are underway to determine if the increased spread is associated with the virus variant or changes in people's behavior over the past several months, or a combination of both.

- Clinical severity for this variant is being investigated – no systematic data available at present.

- Few virus isolates available and more viruses being isolated. Neutralization (sera incl. from vaccinated individuals used) and fitness experiments planned; results expected over holidays/early January 2021. Virus will be shared with companies and countries once sufficient quantities have been grown.

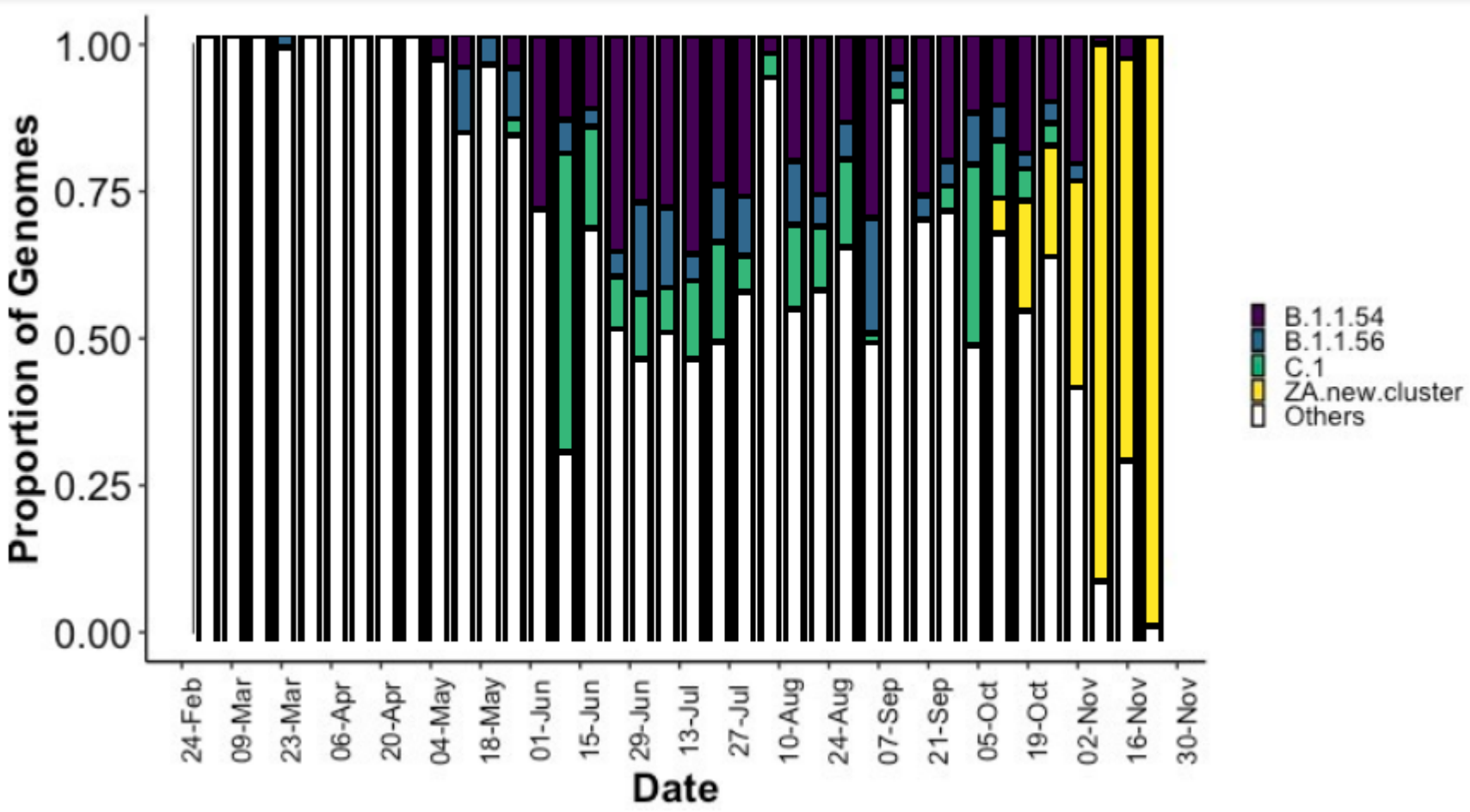
- Spike deletion 69-70del results in S gene target failure by PCR; this is used in the UK as a proxy indicator for this new variant. Most PCR assays in use worldwide use multiple targets and therefore the impact of the variant on diagnostics is not anticipated to be significant.

South Africa - background

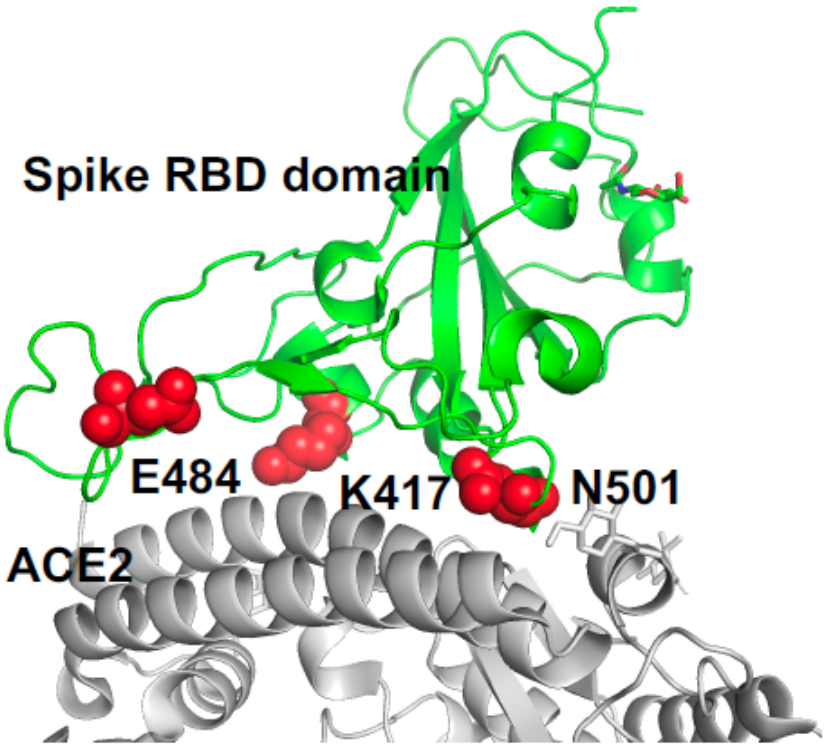
- 501.V2 Variant is characterized by multiple mutations in the spike protein, including three mutations at key residues in the receptor-binding domain (K417N, E484K and N501Y); Representative sequences have been submitted to GISAID.
- This lineage spread rapidly to multiple areas within the Eastern Cape Province and along the coastal region into Western Cape and KwaZulu-Natal Provinces, rapidly becoming the dominant circulating lineage in those locations.
- 501.V2 was detected in 196 genomes collected 15 Oct – 25 Nov.
- According to the researchers, there are multiple lines of evidence to suggest that this lineage may be associated with increased transmissibility.
- Virus isolation is ongoing. Neutralization experiments planned.
- While both variants have one common change (501Y), the virus variants reported from South Africa and the UK are different and sequence analysis revealed that they originated separately.
- South Africa is working directly with the SARS-CoV-2 Virus Evolution Working Group.

Press release: https://sacoronavirus.co.za/2020/12/18/new-covid-19-variant-identified-in-sa/

Rapid dominance of new lineage



Structural visualization of spike RBD-hACE2 complex



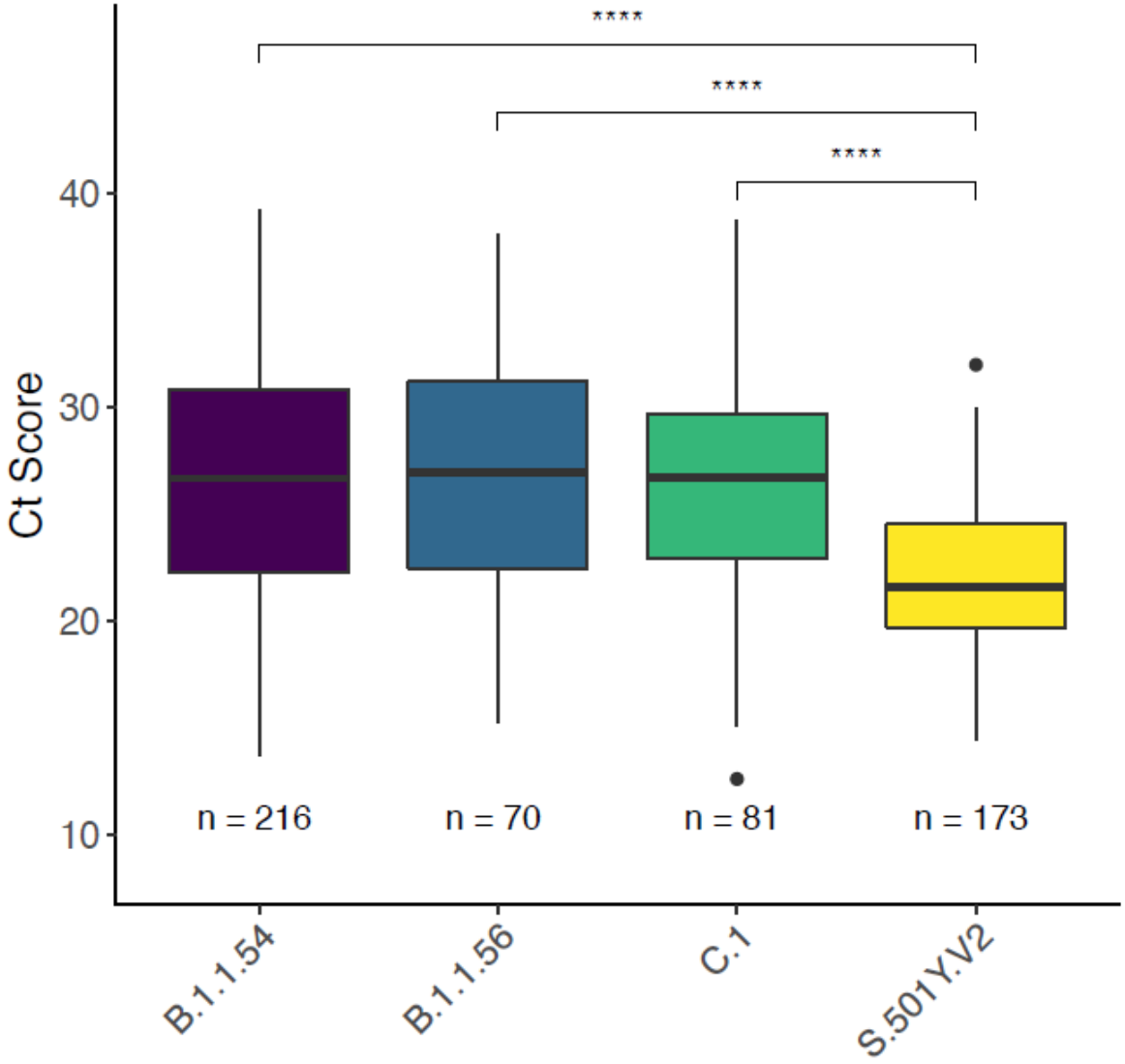
The three RBD mutations are at key residues interacting with the human ACE2 receptor and with neutralizing antibodies (NAbs)

N501Y enhances binding affinity to ACE2

E484K enhances binding affinity to ACE2 and confers resistance to class 2 NAbs

K417N would abolish key interactions with class 1 NAbs, and likely contributes toward immune evasion at this site

Growth advantage in respiratory tract?



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Summary

- Variants identified in UK and South Africa highlight the importance of sequencing of SARS-CoV-2 and sharing of sequence data internationally.
- As all viruses mutate, sequencing will identify a number of mutations; some more common than others. Many mutations have no impact on the virus itself; some may be detrimental to the virus; few may result in an advantage to the virus.
- In order to determine their impact on transmission or vaccines, experiments need to be done with live virus in advanced laboratories. Such experiments take time from weeks to several months; ongoing in UK and South Africa.
- WHO and partners are working with a group of international scientists, including the WHO Virus Evolution Working Group, from all over the world to coordinate such research efforts and assess the risk of select mutations on transmission, diagnostics and vaccines.