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# A tale of two variants…

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***COVID-19 Actuaries Response Group – Learn. Share. Educate. Influence.***

**Summary**

This bulletin discusses the emergence of two new variants of SARS-CoV-2 in the UK and South Africa. Mutation of SARS-CoV-2 is common and has been under ongoing monitoring by scientists since the first genome was sequenced and released in January 2020. However, the two new variants, which share a common mutation, show cause for concern. Scientists studying these variants believe increased transmission risk is plausible but are not yet clear on the impact on severity of the disease, reinfection risk and importantly, the efficacy of vaccines.

## New variants of SARS-CoV-2 emerge

During the last couple of weeks two new variants of SARS-CoV-2 (the virus responsible for COVID-19) were announced in the United Kingdom (UK) and South Africa (SA).

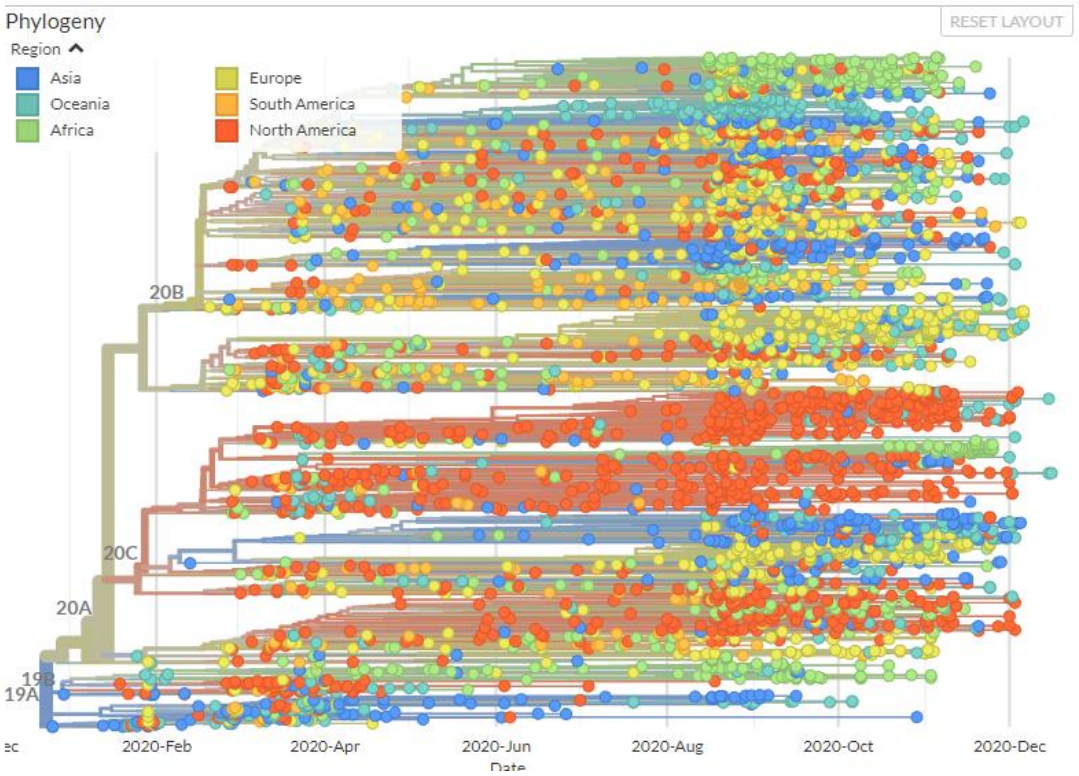
- Public Health England (PHE) first announced the UK were investigating a new variant of the virus (later classified as B.1.1.7 lineage). As at 13 December 2020, 1,108 cases were identified in the South and East of England.
- On 18 December 2020, the Minister of Health of SA, together with scientists, also announced the emergence of a new variant of the virus. Similar to the UK, the variant was identified via genomic surveillance of the virus (it was labelled 501.V2). A pre-print paper was released on 21 December 2020.

## Mutations, variants and strains

Viruses, by their nature, mutate. These **mutations** are changes to the genetic material of the virus. SARS-CoV-2 has been mutating just as other viruses do. Most SARS-CoV-2 mutations make no material difference to its behaviour. However, we know seasonal flu changes materially enough each year to warrant a new vaccination. So how do we know when the mutation change is material enough?

Scientists sequence the virus genome and track changes. Various common mutations might be identified as a particular **variant**. Once the observable behaviour of the virus is meaningfully affected it might be identified as a new **strain**. So where do the recently announced SARS-CoV-2 developments come in?

Scientists have been monitoring SARS-CoV-2 mutations essentially since the first genome sequence was shared on 10 January 2020. The chart below shows the "family tree" of SARS-CoV-2. Dots represent sampled virus genomes and the family tree on the left stretches back to its unsampled origin (where there was a single variant of the virus that infected humans). Through continuous mutations we now have (on the right) many different variants present the world over.




(Source: https://nextstrain.org/ncov/global )

Using techniques such as this allows scientists to estimate when the virus first emerged into humans. Similarly, patterns can be monitored as different mutations transmit globally. It also aids our understanding of reinfection (when genetically different virus is detected in the same person).

**The spike protein**

The SARS-CoV-2 virus has spikes emanating from its surface which allow it to connect to the human (or indeed animal) cells. The spike proteins (seen in red in Figure 1) are important for how the virus enters the host's cells and so how the virus behaves and how successfully it infects individual cells. This is why scientists are particularly interested in mutations affecting the spike protein.

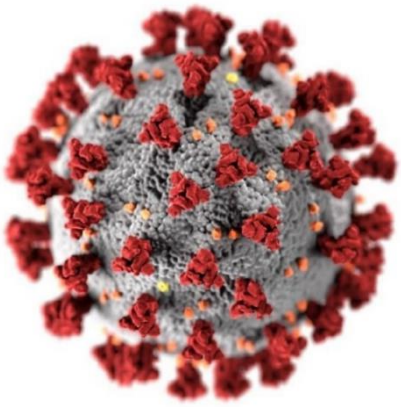


*Figure 1: Representation of the SARS-CoV-2*

**D416G: A spike protein mutation**

The D416G mutation is a previous example of such a mutation to the spike protein that has been recognised by researchers as having the potential to increase infectivity of the SARS-CoV-2. Genome monitoring of virus samples showed that variants with this mutation became more common over time since it was first identified in May 2020.

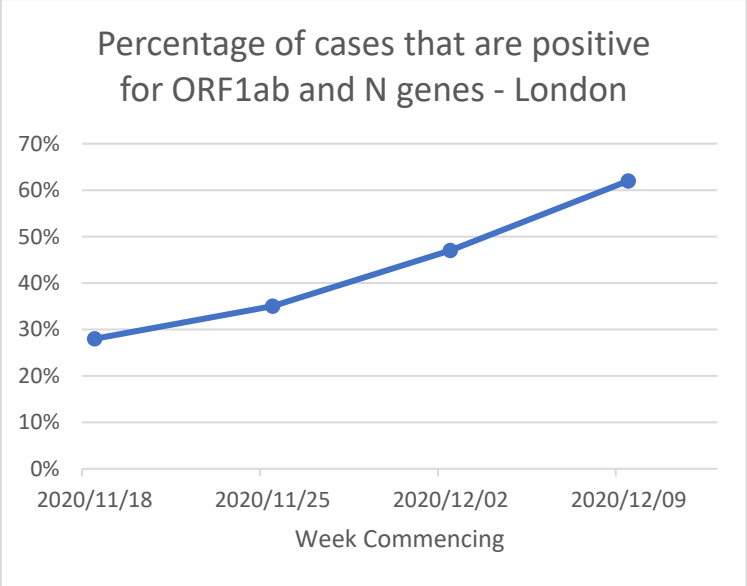
Before we look more closely at the two new variants, it is worth noting these variants came about independently, even though they share a common mutation (N501Y).

**The UK Variant (B.1.1.7)**

B.1.1.7 has been analysed and has been observed to account for a significant proportion of cases in parts of England (mainly South and East). It has an unusually large number of genetic changes. There are 3 main mutations in the spike area that could be significant:

- Mutation N501Y: may assist with binding to the human cell.
- Mutation 69-70del: might assist with evading the human immune response but also may be involved in binding.
- Mutation P681H is near a site of biological significance.

These mutations affect how the variant reacts to the polymerase chain reaction (PCR) tests for the virus. This is the common nasal/throat swab test. The PCR test reacts to three different sections of genetic material of the virus. The mutation has changed one of these enough that the test no longer detects it (but still detects a positive result based on the other two). The chart below shows what proportion of tests (in London) are responding with only positive results for the two pieces of genetic material (ORF1ab and N genes) as opposed to on all three. This gives an indication of the rapid growth of this lineage, which is a cause for concern.

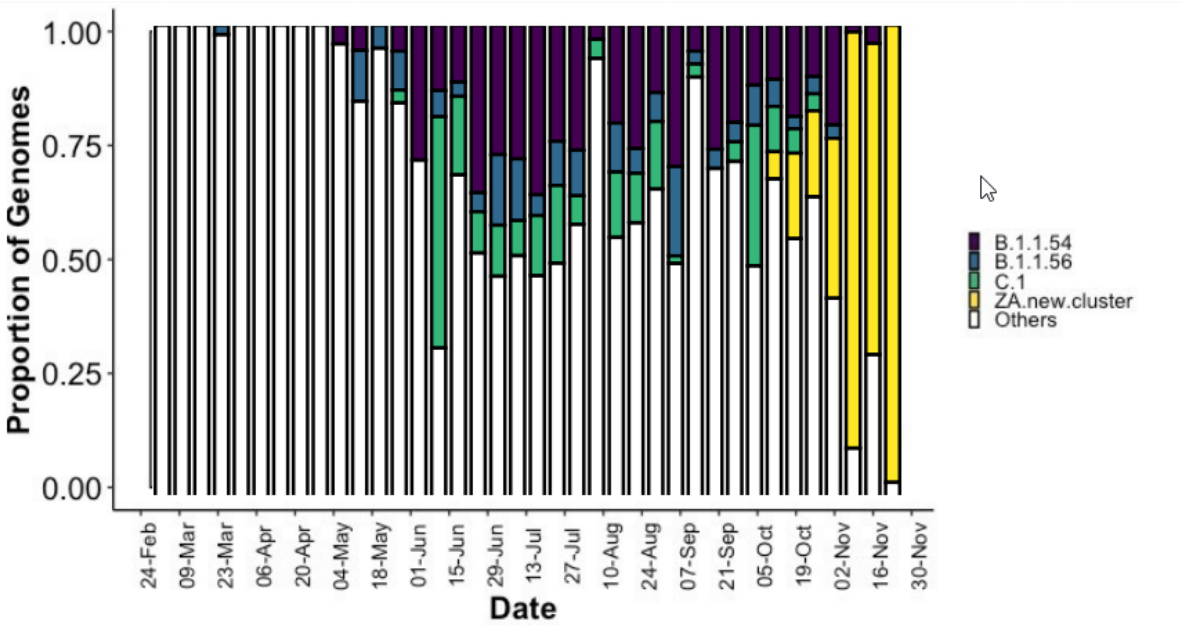



(Source: ONS Data )

**The South Africa Variant (501.V2)**

The announcement made about the SA variant contained the news that it also has more mutations than other variants observed in SA, with a number of these occurring in the spike protein. The presentation and paper identify three main mutations in the SA variant namely N501Y, E484K and K417N. The first is shared with the UK strain. The last two may assist in avoiding antibodies. For example recent research highlights how mutations at E484 is associated with resistance to neutralisation by several convalescent human sera. This is serum containing antibodies from those who have recovered from the disease.

The figure below shows the proportion of the new variant (in yellow) observed when sequencing over time. The new variant has become predominant in SA representing roughly 90% of viruses sequenced from recent random sampling.




(Source: https://www.krisp.org.za/ngs-sa/ngs-sa_updates_covid-19_analysis_narratives_reports/token/18 )

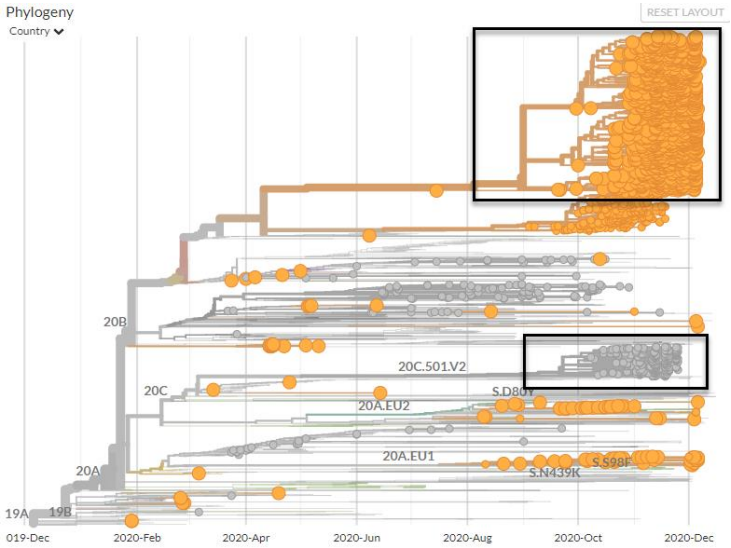
**Unusually high number of mutations**

Both new variants have a high number of mutations, indeed more than expected. There is therefore some speculation that this may have occurred as a result of one (or more) individuals being chronically infected with the virus over a long period. This could create an environment for the virus where more rapid mutation can occur, as has been seen in a previous case. Something like this could have happened independently for the SA and the UK variants.

**The N501 "family tree"**

The figure to the right contains the "family tree" of SARS-CoV-2 that contain N501 mutations. Orange dots represents genomes sampled from the UK and grey dots from SA. Branches occurring in other countries are shown but samples are hidden. The two black boxes on the right show the B.1.1.7 variant (at the top) and the 501.V2 variant (just below the middle).

(Source: nextstrain.org )




**Transmission**

When researchers studied the PCR throat swab test results for the new variant, they noticed higher viral load in the test results, meaning more virus in the samples. Similar results have been seen for the UK variant. There are also theoretical studies indicating that the N501Y mutation may aid binding and hence infection. The N501Y mutation has arisen independently in the UK and SA (and also Australia and Brazil) and even in mice. The fact that this random mutation has arisen and persisted in several settings provides an indication that this particular mutation may be useful to the virus' survival.

Given the above and with these variants becoming more prevalent in the UK and increasingly dominant in SA, it would seem to indicate a higher transmission risk of both new variants. Both the UK and SA are currently experiencing significant increase in infections during the second wave.

At the 18 December 2020 meeting of the UK's New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG), it was documented that:

- The growth rate of this variant based on genomic data is 71% (95% CI, 67% - 75%) higher than other variants.
- Correlation studies on reproduction number (R) suggests an absolute increase in R between 0.39 and 0.93.
- There is "*moderate confidence that VUI-202012/01 demonstrates a substantial increase in transmissibility compared to other variants.*"

Subsequent to this meeting the group have stated that they now have high confidence that this variant is more infectious and this was confirmed in a PHE report released on 21 December.

**Other risks**

Beyond this, not much is yet known about the corresponding disease severity of these variants. For the moment, it is assumed that the impact of being infected by the variants are similar.

There seems to be some anecdotal evidence of a younger patient profile in SA, but this increased infection amongst younger population may also be aligned to the start of summer school holidays and super-spreader events. Similarly, the latest ONS infectivity survey shows the largest increase in infections among children. Again, there is no evidence that this is linked to the new variant.

Implications for the newly developed vaccines are, again, not yet known. It is hoped and expected that vaccines remain effective. Both the UK and SA had and/or have trials for vaccines ongoing and this will doubtless be investigated.

Given the adaptation of the virus against the human immune system there are some concerns around reinfection risk but, again, not much is known at this point. The paper from SA speculates that selection due to high levels of infection and associated immunity in the region where the variant originated may have contributed to the mutation and hence the authors suggest reinfection as an area for further investigation.

**Combating the variants**

As these are variants of the SARS-CoV-2 virus, it is understood that the same preventative steps would reduce individual and collective transmission risk. Social distancing remains, on a day-to-day basis, a way in which we each can do our bit to stop the spread. However, given the likely higher transmission risk of these variants we may need to take extra care still.

With time there will be more people who have been exposed, live-with and recover-from the virus. This, in addition to the roll-out of vaccines, will put mounting pressure on the natural-selection process the virus undertakes. With this we are likely to see the emergence of more mutations that benefit the survival of the virus. We can hope that these mutations are accompanied by the survival of the host but as nature is not always so forgiving, we may also require updated vaccines to account for risk associated with the related disease.

21 December 2020