20 January 2021

Mutations and variants of COVID-19 and their consequences

Dana Holt

Outlined below are the findings of the UK and South African variants of COVID-19, discussing the effect of mutations and how they may affect the efficacy of the vaccines. Whether the introduction of these new variants are the cause of the recent surge in cases and deaths in the United Kingdom will also be discussed.

A mutation can generally be defined as being a random change in the genetic material of an organism, which occurs during replication. When DNA viruses (such as herpesviruses and poxviruses) replicate, the number of 'mistakes' are minimised during translation due to its double stranded nature [14]. However, in single stranded, RNA viruses (such as the novel coronavirus), mutations can occur up to 1000 times more often [1,2,14], which is why we are seeing new variants COVID-19 earlier than some may have expected. Not all mutations provide a selective advantage for the virus. Usually, they are neutral or even harmful to the virus [3,4].

There are thousands of variants circulating the world. Of these, experts are focussing their attention on mainly three of these:

- A UK Variant: B.1.1.7 (also known as VOC-202012/01)
- A South Africa Variant: B.1.351
- A Brazil Variant: P.1 [6]

Scientists have now been able to trace the new UK variant (B.1.1.7) back to September 2020, when the cases of COVID-19 in London rapidly increased [6]. Of the 23 known mutations, eight of them occur in the spike protein and six are "silent" [14,15]. These are illustrated in **Figure 1** and **Figure 2**, showing several base deletions and substitutions which have resulted in changes to the RNA sequence [3,5]. There are indications that the N501Y spike protein mutation has increased the binding strength of angiotensin-converting enzyme 2 (ACE2) [8,9]. There is no evidence to suggest that the spike protein mutation results in more severe infections, however, the N501Y has been thought to have made the virus more transmissible [3,4]. Public Health England believe the new strain is between 30% and 50% more transmissible although it could be as high as 70% [7]. The UK New and Emerging Respiratory

Virus Threats Advisory Group (NERVTAG) has evidence to suggest that the viral load has increased by a factor of three, although there is no reason to believe that there is a causal relationship between binding strength and transmissibility [8].

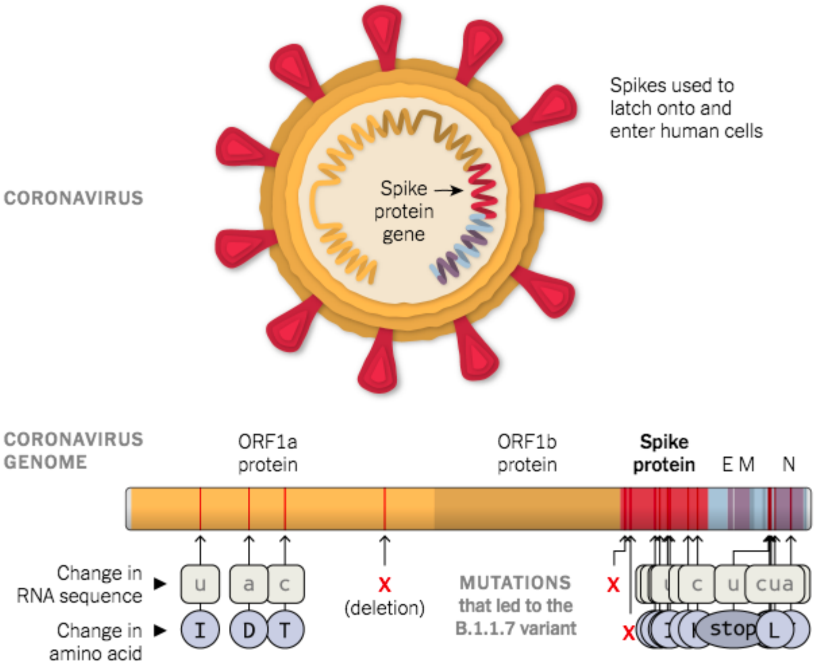

Figure 1 - Diagram showing mutations leading to B.1.1.7 variant; Source: Andrew Rambaut et al., Covid-19 Genomics Consortium U.K. [5]

Another notable mutation in the B.1.1.7 lineage, 69-70del, is defined by the loss of two amino acids and can cause the evasion of an immune response in immunocompromised people [14]. This may affect vaccine efficacy as the mutation affects the protein spikes.

The variant, 501.V2, first emerged in South Africa and has now spread to at least 12 countries. Among other mutations, this variant contains an E484K and a K417N mutation which affects the shape of the SARS-CoV-2 spike protein [15]. Scientists are referring to the E484K as an “escape mutant” as it is able to evade some of the antibodies produced by the vaccine, bypassing immune protection [4,15]. It also has the N501Y spike mutation, like the B.1.1.7 lineage, which affects binding strength, making it easier to establish infection [15]. These three mutations to the spike protein affect the receptor binding domain, possibly contributing to the increased transmissibility [19]. **Figure 2** and **Figure 3** show the mutations exhibited by both the B.1.1.7 lineage and the B.1.351 lineage.

Gene	Nucleotide	Amino Acid
ORFab	C3267T	T1001I
	C5388A	A1708D
	T6954C	I2230T
	11288-11296 deletion	SGF 3675-3677 deletion
Spike	21765-21770 deletion	HV 69-70 deletion
	21991-21993 deletion	Y114 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

Figure 2 - Non-synonymous mutations and deletions inferred to occur on the branch leading to lineage B.1.1.7 lineage. [16]

Gene	Nucleotide	Amino acid
ORF1ab	C1059T	T2651
	G5230T	K1655N
	C8660T	H2799Y
	A10323G	S2900L
	G13843T	K3353R
	C14408T	D4527Y
	C17999T	P4715L
Spike	C21614T	T5912I
	A21801C	L18F
	A22206G	D80A
	G22299T	D215G
	G22813T	R246I
	G23012A	K417N
	A23063T	E484K
	A23063T	N501Y
	G23664T	D614G
ORF3a	G25563T	A701V
	C25904T	S171L
E	C26456T	P71L
N	C28887T	T205I

Figure 3 - Shows Mutations of the B.1.351 lineage [19]

Figure 4 and **Figure 5** show the countries where both the UK and South African variants are prevalent. As shown the VUI 202012/01 originated in the United Kingdom but it is now spreading further, with 185 cases in Denmark, and 85 cases in the Netherlands (17/01/2021) [11]. As for the South African variant, it is shown that the United Kingdom has a significant amount of cases, with only South African numbers exceeding the UK's cases. It should be noted that the data will not completely accurate as not all countries have the same access to resources. For example, low income countries (LICs), which are economically challenged are unable to carry out as much testing as more developed countries. Another potential source of error is in people who are asymptomatic with the new variant, as these people are unlikely to be added in the statistics. After all, each country has limited test resources so not everyone can be tested.

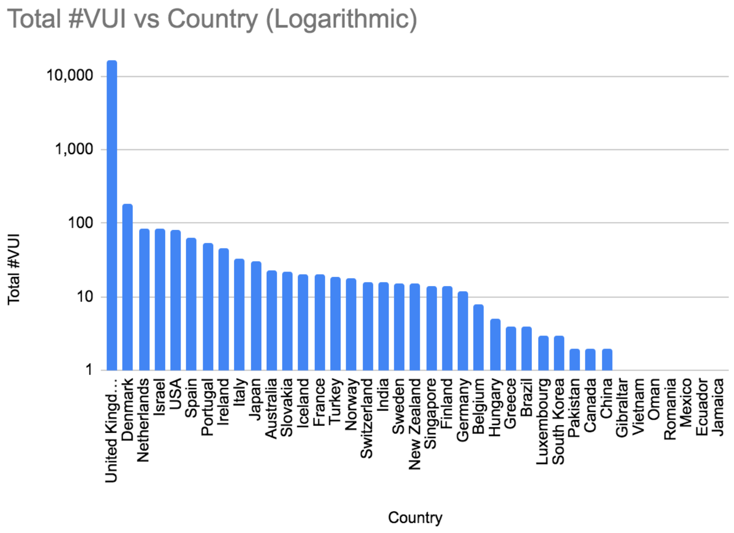

Figure 4 - shows a comparison of countries with the VUI 202012/01 (UK) variant

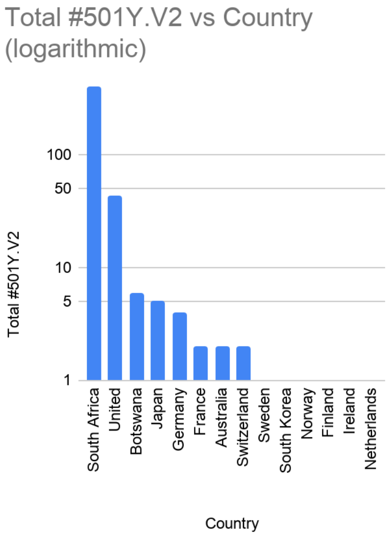

Figure 5 - shows a comparison of countries with the 501Y.V2 (South African) Variant; Data source from GISAID [11,12]

The specific cause of the significant number of mutations is unknown but it is theorised that it occurred due to prolonged infection in a single patient rather than through selection pressures from ongoing vaccination programmes. Other less likely explanations are that the mutations could have occurred via animal hosts or through circulation in countries with little sequencing coverage [3].

The emergence of new variants may have an effect on vaccine efficacy, although scientists are confident that the developed vaccines, such as the Pfizer-BioNTech vaccine, will not be completely useless as they are designed to attack several parts of the virus, not just the mutated spike proteins [6,10]. Experts have assured the public that the vaccine can be modified to accommodate the new variants in a matter of weeks [6].

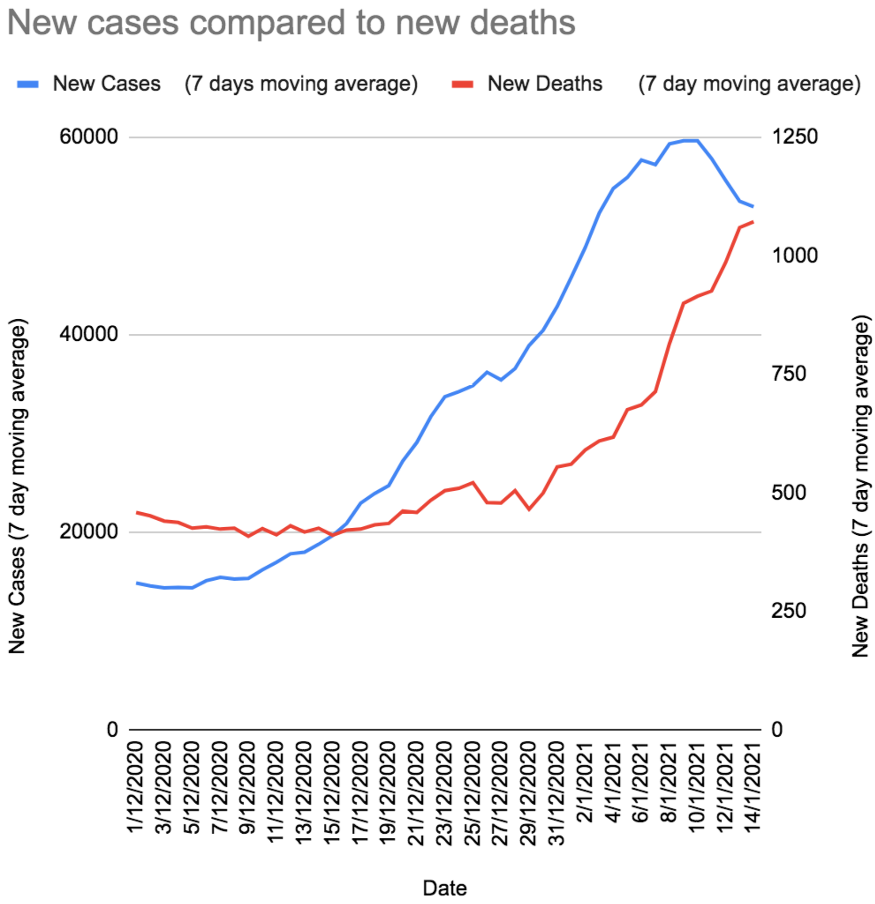

Figure 6 - Graph showing rise in UK COVID-19 deaths and cases since December 2020

Data sourced from worldometers [18]

The question of how dangerous these variants are, is prevalent in the news. Whilst there is no information suggesting that the infection is more severe, there is evidence showing increased transmissibility, leading to more hospitalisations. This has resulted in health services in affected countries being strained and there is concern for how they will cope. The death rates in the United Kingdom have been rising, as shown by **Figure 6**, which is possibly alarming for vulnerable groups and the elderly. Although the cases appear to be declining, hospital admissions will inevitably continue to rise in the short-term due to the length of time for symptoms to become severe. The new, emerging variants may not be entirely to blame for the sudden surge in cases and deaths. Other causes could include less UVC light compared to previous months. UV light is said to be effective at inactivating viruses [20]. Another alternative cause could be increased breaching of restriction as the general public grow tired of following the government guidelines, especially in December during Christmas, leading to an increased infection rate due to lack of social distancing. Despite these possible contributions to growing infection, there is significant evidence that the new variants are a main factor to the sudden increase in cases. Experts are still confident in the vaccines working, although their efficacy may be reduced due to mutated spike proteins [8].

To conclude, whilst these variants are more transmissible, there is no evidence to suggest that they are any more harmful to the individual although, increased infection rates could overwhelm the health services. The reliability and extent of the data presents challenges towards understanding the spread and impact of both the B.1.1.7 and the B.1.351 lineages of COVID-19. Scientists will continue to investigate these and other new variants, such as the P.1 lineage and experts are confident that alterations to vaccines can be made quickly after learning the magnitude of any new variants [6].

Bibliography

[1] Duffy, S. (2018, August 13). *Why are RNA virus mutation rates so damn high?* PLOS Journals. Retrieved January 16, 2021, from https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.3000003

[2] Brennan, J. (2017, April 25). *RNA Mutation Vs. DNA Mutation*. Sciencing. Retrieved January 16, 2021, from https://sciencing.com/rna-mutation-vs-dna-mutation-3260.html

[3] European Centre for Disease Prevention and Control, Stockholm, 2020. (2020, December 20). *Rapid increase of a SARS-CoV-2 variant with multiple spike protein mutations observed in the United Kingdom*. Retrieved January 16, 2021, from https://www.ecdc.europa.eu/sites/default/files/documents/SARS-CoV-2-variant-multiple-spike-protein-mutations-United-Kingdom.pdf

[4] CNN. (2021, January 13). Scientists fear the ‘escape mutant’ in coronavirus variant from South Africa. https://edition.cnn.com/2021/01/12/health/coronavirus-mutation-south-africa-variant/index.html

[5] Zimmer, C., & Carey, B. (2020, December 21). The U.K. Coronavirus Variant: What We Know. *The New York Times*. https://www.nytimes.com/2020/12/21/health/new-covid-strain-uk.html

[6] Roberts, M. (2021, January 14). Covid: How worrying are the UK, South Africa, and Brazil coronavirus variants? *BBC News*. https://www.bbc.co.uk/news/health-55659820

[7] Gallagher, J. (2020, December 20). New coronavirus variant: What do we know? *BBC News*. https://www.bbc.co.uk/news/health-55388846

[8] European Centre for Disease Prevention and Control. (2020, December 29). Risk related to spread of the new SARS-CoV-2 variants of concern in the EU/EEA. https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-risk-related-to-spread-of-new-SARS-CoV-2-variants-EU-EEA.pdf

[9] Fiorentini, S., Messali, S., Zani, A., Caccuri, F., Giovanetti, M., Ciccozzi, M., & Caruso, A. (2021, January 12). First detection of SARS-CoV-2 spike protein N501 mutation in Italy in August, 2020. *The Lancet Infectious Diseases*. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00007-4/fulltext

[10] Kambli, K. (2021, January 6). *Vaccines May Not be 100% Effective Against New South African Coronavirus Variant, Experts Fear*. The Weather Channel. Retrieved January 17, 2021,

from https://weather.com/en-IN/india/coronavirus/news/2021-01-06-vaccines-not-100-effective-on-south-africa-coronavirus-variant

[11] GISAID. (n.d.). *Tracking of Variants*. GISAID. Retrieved January 17, 2021, from https://www.gisaid.org/hcov19-variants/

[12] *Graphs comparing countries and variant numbers*. (n.d.). https://docs.google.com/spreadsheets/d/1XaM_ZmFx40WjNKRoLdMtOi9LMBTRRA5VcEN7AT1sSfw/edit?usp=sharing

[13] Gallagher, J. (2020, December 23). UK has 2 cases of variant linked to South Africa. *BBC News*. https://www.bbc.co.uk/news/uk-55428953

[14] Katsnelson, A. (2021, January 11). What do we know as the new SARS-CoV-2 strains gain ground worldwide. *Chemical and Engineering News*. https://cen.acs.org/biological-chemistry/infectious-disease/know-new-SARS-CoV-2/99/web/2021/01

[15] Lovett, S. (2021, January 15). The science - and mutations - behind the emerging coronavirus variants. *The Independent*. https://www.independent.co.uk/news/health/covid-variants-uk-brazil-latest-mutation-b1787483.html

[16] Rambaut, A. (2020, December). *Preliminary genomic characterisation of an emergent SARS-CoV-2 lineage in the UK defined by a novel set of spike mutations*. Virological. Retrieved January 17, 2021, from 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

[17] Thermo Fisher Scientific Inc. (2020, December 19). *Impact of the 69-70del mutation in the spike protein of SARS-CoV-2 on the TaqPath COVID-19 Combo Kit*. Retrieved January 17, 2021, from https://assets.thermofisher.com/TFS-Assets/GSD/Reference-Materials/69-70del-s-gene-mutation-eua-faq.pdf

[18] Worldometer. (n.d.). *COVID-19 coronavirus pandemic*. Retrieved January 16, 2021, from https://www.worldometers.info/coronavirus/

[19] Wikipedia. (n.d.). *501.V2 Variant*. Retrieved January 17, 2021, from https://en.wikipedia.org/wiki/501.V2_variant

[20] Philips. (n.d.). *Disinfection with the power of light*. Philips. Retrieved January 20, 2021, from https://www.lighting.philips.co.uk/products/uv-c?origin=7_gb_en_uvc~s7015I000000DWXs_ppc_____&cid=7015I000000DWXs&origin=nIVTDuxu&pcrid=489645486142|mckv|snIVTDuxu_dc|plid||slid||pgrid|118669586289|ptaid|kwd-960462505659|product||&gclid=CjwKCAiAo5qABhBdEiw