UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

Hôpitaux Universitaires Genève

Last update, January 10, 2021

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Currently two new variants of SARS-CoV-2 are circulating that are internationally observed with great attention; **these are the variant named VOC 202012/01 or lineage B.1.1.7, first identified in the UK, and another variant named 501Y.V2 or lineage B1.351, first identified in South Africa**. These variants are associated with a rebound of the pandemic, particularly in the UK and South Africa, but a causal link needs further investigation and confirmation. The origin of these two variants remains unexplained for the moment. The number of new mutations accumulated by the B.1.1.7 is unusual and unexpected; the apparent lack of intermediates suggests a long period of undetected replication and evolution, which may be explainable by intra-host-evolution such as a long chronic infection or spread in an area with poor monitoring systems.

The preliminary results of these two variants highlight the presence of several combined mutations (Table 1). Both variants share a mutation, N501Y, within the RBD of the spike protein, which, *in vitro* and in animal models, results in a greater affinity for human ACE2 receptor (1–3). This enhanced interaction may account, in part, for the assumed 56% to two-fold higher transmission rate of the B.1.1.7 (4,5), and the elevated transmission rate observed for the B1.351(6). In addition, one pre-print reported a higher viral load in samples from patients with B.1.1.7 compared to previously circulating SARS-CoV-2 (7). Notably, with the time from symptom onset and additional associated data are not available for the samples, thus it cannot be excluded that the observed differences in viral load are due to sampling bias. Personal communication following meetings about B.1.1.7 state that the virus grows slightly better in respiratory cells than a previous variant, potentially explaining higher viral loads.

At this time the regions where the variant circulate in the UK experience an uncontrolled outbreak and an overwhelming occupation rate of hospital beds. Currently data suggests that, for B.1.1.7, there is no increase in the severity of the disease, neither in terms of an increase in the hospitalisation rate, nor in terms of the risk of re-infection or mortality at 28 days(8) – in fact, based on available epidemiological data, hospitalization rate was lower for the UK variant, but given the small dataset and the size of the difference, it did not meet the threshold for statistical significance (Chi-squared test p=0.162). These data are extrapolated from a small initial dataset and must be interpreted with caution. One case report described a re-infection with B.1.1.7. in a dialysis patient, with more severe disease during the 2nd episode (29). No data is currently available regarding the severity B1.351. A single paper suggests a slight and significant increase in the number of infections in the under 20 age group for B.1.1.7(9), and anecdotal reports suggest greater transmission among the youth for B1.351 (10), but no conclusions should be drawn from this data yet, given the limited data and multiple risks of bias. Private communications following meetings about B.1.1.7. state that no difference in the age pattern has been observed.

Concerning vaccination and antigenicity, for the time being no data is available regarding resistance of these variants to immunity induced by vaccination or previous exposure to other strains. No neutralisation data are currently published or publicly available. Several in vitro data seem to suggest that the presence of certain mutations, notably at the level of the 69/70 deletion or the E484 mutation, reduce the neutralisation of the virus by polyclonal serums. The main reason for this is that these two sites at the RBP level are believed to be more strongly involved in antibody binding. Similarly, in vitro data suggests that a number of these mutations may reduce binding affinity of specific monoclonal antibodies (Table 1). Resistance to specific

monoclonal antibodies or resistance due to a single mutation is unlikely to significantly affect neutralizing activity of polyclonal sera, indeed the N501Y mutation found in both strains has been shown not to result in any significant decrease of neutralizing activity of polyclonal sera from subjects given the BNT162b2 vaccine(11); but the combination of several such mutations will have unpredictable effects. Notably, no single mutation identified so far would be sufficient to abolish neutralizing activity, and thus we can expect that current vaccines and exposure to other variants will still provide protection, although said protection may be reduced to an unknown extent. In vivo and clinical data is needed to reach any firm conclusions. Private communications following meetings about B.1.1.7. state that neutralization activity against the UK variant is still seen in convalescent plasma from patients exposed to other variants, although no relative quantification of activity was given.

If significant differences in antibody reactivity are detected, antigen based rapid test sensitivity may be affected, but current data shows that the detection efficiency of rapid antigenic tests is not diminished by virus variants(12). This is unsurprising as the antigen tests generally target the N protein, and there are only 2 mutations in the N gene within B.1.1.7. and none within the B1.351. Concerning RT-PCR, most widely used tests target multiple genes, and thus have built in redundancy against mutations. Caution is needed however in single-target assays based on more variable regions, such as the S gene. B.1.1.7. in particular, possessing the deletion mutation, results in a loss of signal from spike gene amplification(13), enabling its spread to be estimated by tracking S-gene dropouts – which has suggested that the 69-70 deletion (perhaps the B.1.1.7.) may have been circulating in the USA as early as October(14). Of note, other lineages are circulating across Europe that harbour the mutation 69-70del that do not belong to lineage B.1.1.7. Thus careful evaluation of the regional circulating viral population behind such an S drop out needs to be performed by sequencing before using it as a proxy measure for circulation of a certain variant.

There is currently very little data on the South African variant, but the figures are similar in terms of transmission and reproduction rates. No other data are found for the other points.

Table 1. Mutations of new SARS-CoV-2 variants

Description of mutation (gene, mutations: effects)	**UK variant** VOC 202012/01, lineage B.1.1.7 20B/501Y.V1	**South Africa** 501.V2, lineage B.1.351 20C/501Y.V2
Spike, **N501Y**: may bind more tightly to the human angiotensin-converting enzyme 2 (ACE2) receptor (1–3,15)	Present	Present
Spike, **double deletion (69, 70):** enhances viral infectivity by two-fold (16), may lead to reduced neutralizing activity of antibodies raised against previous variants (17)	Present	Not present
Spike, **deletion 144**: confers resistance to 4A8 monoclonal antibody (18)	Present	Not present
Spike, **P681H**: adjacent to the furin cleavage site, may plausibly affect transmissibility	Present	Not present
Spike, **D614G**: already dominant world-wide (19–21)	Present	Present
Spike, **E484K**: leads to reduced neutralizing activity of antibodies raised against previous variants (22,23), may increase affinity for ACEII (24)	Not present	Present
Spike, **A570D**, **T716I**, **S982A**, **D1118H**: Unknown effects	Present	Not Present
Spike, **L18F**, **D80A**, **D215G**, **R246I**, **K417N**, **A701V**: Unknown effects	Not Present	Present
ORF1, **T1001I**, **A1708D**, **I2230T**, **triple deletion 3675-3677**: Unknown effects	Present	Not Present
ORF8, **Q27Stop**: Early stop codon likely to render ORF8 non-functional. ORF8 deletions/mutations are associated with milder clinical course and lower post-infection inflammation (25). ORF8 is involved in immune evasion by down-regulation of MHC class 1 (26–28).	Present	Not Present
ORF8, **R52I**, **Y73C**: likely irrelevant due to earlier stop codon	Present	Not Present
N, **D3L**, **S235F**: Unknown effects	Present	Not Present

Table 2. Clinical Observations for new SARS-CoV-2 variants

Variants	**UK variant** SARS-CoV-2 VOC 202012/01, lineage B.1.1.7, or 20B/501Y.V1	**South Africa** variant 501.V2, lineage B.1.351, or 20C/501Y.V2
Transmissibility	rate of transmission 56-75% higher Rt: up to 0.4 higher	Spreads more easily, but no precise data
Disease severity + Hospitalisation rate	no evidence that it causes more severe illness or increased risk of death (4,8)	no evidence that it causes more severe illness or increased risk of death

Age distribution of cases	Median age 36 y (wild-type 35 y) in small matched cohort study Small but statistically significant shift towards under 20s being infected at higher rates, caveat: may be a statistical artifact resulting from an overall increase in transmissibility(9).	Anecdotally, more young people being infected, no hard data(10)
Re-infection	No significant difference in the likelihood of reinfection (8)	No data
28-day case fatality	No statistically significant difference (8)	No data
Detection by current RT-PCR /	Causes loss of signal in the S-gene(13)	No data, unaffected?
Viral load	Decrease in RT- PCR threshold cycle (Ct) values, corresponding to an increased viral load by 1-4 orders of magnitude (7)	Reportedly higher
Detection by Ag-RDT	no report that the new variant viruses would negatively impact rapid antigen detection tests (12)	No data

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