NERVTAG paper
Brief update on SARS-CoV-2 variants [New text in red]

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1. In recent months several SARS-CoV-2 variants with a large number of mutations have been identified that are concerning since they appear to have rapid epidemiological growth. This rapid growth may relate to biological properties of the virus that confer a competitive advantage over other virus variants.

2. The UK (B.1.1.7; VOC 202012/01) variant appears to have increased transmissibility compared to other variants and has grown quickly to become the dominant variant in much of the UK. It possesses several changes in the spike glycoprotein but change N501Y is thought to be a possible major determinant of the increased transmissibility. There is no evidence that this variant is associated with changes in disease severity or antigenic escape from naturally, monoclonal or vaccine acquired immunity. [1,2]

    a. Data from the UK's national COVID-19 Infection Survey (CIS), a representative sample of households with longitudinal follow up, shows that the B1.1.7 variant leads to higher infection rates, but is not particularly adapted to any age group. Between 21 December 2020 and 2 January 2021, there was no evidence of variation by age group in the percentage of positives that showed S-gene target failure (SGTF) and those that did not. [3]

    b. Earlier data had reported lower ct values in SGTF versus non-SGTF samples. [4] [5]. The CIS found that these earlier differences in ct values have been lost and by mid-January ct values in SGTF were similar to non-SGTF. This suggests early findings of lower ct values in SGTF may have been due to SGTF being predominantly early infections during the early stages of emergence. [3]

    c. New data from 19.01.2021 demonstrates the immune sera of 16 Pfizer vaccinees (21 days after second dose) have equivalent neutralisation titres to both the B1.1.7 variant and the Wuhan Reference Strain. [6]

    d. New data have been reported on VOC B.1.1.7 disease severity. See separate SAGE paper.

3. A different variant (VOC 202012/02, 501Y.V2) has shown rapid epidemiological growth in South Africa. It possesses the N501Y substitution and well as an E484K substitution. The rapid growth could be related to increased transmissibility, antigenic escape or both. There are reasons to be concerned about the possibility of antigenic escape:

a. In vitro data showing weaker neutralisation of viruses with the E484K substitution with polyclonal serum. [7]

b. In vitro data showing that variants with the E484K substitution show weaker neutralisation with some monoclonal antibodies (bamlanivimab – Eli Lily; REGN10933 – Regeneron [also K417E]). [8,9].

c. New data from 19.01.2021 shows reduced plasma neutralising activity against SARS-CoV-2 pseudovirus variants encoding E484K, N501Y, or combined K417N:E484K:N501Y (the triple combination present in the South African variant) in a cohort of 20 volunteers who received either the Moderna (n=12) or Pfizer (n=6) vaccine, 8 weeks after the second dose. [10]

   i. There was a 1-3 fold decrease in neutralising activity against E484K, a 1.3-2.5 fold decrease in neutralising activity against N501Y, and a 1.1-3 fold decrease in neutralising activity against K417N:E484K:N501Y.

   ii. In the same study, neutralisation by 14 out of 17 vaccine-elicited monoclonal antibodies was reduced in E484K or N501Y mutations.

d. New data from 19.01.2021 reported that the 501Y.V2 lineage had high levels of resistance to convalescent sera (n=44).48% of sera had no detectable neutralisation activity when assessed against the 501Y.V2 virus. [11]

e. Rapid epidemiological growth in an area (Nelson Mandela Bay) with reported high levels of seropositivity. [12]

4. Viruses in the lineage B.1.1.28 have emerged in Brazil with the E484K substitution, without (VUI 202101/01) and with the N501Y (VUI 202101/02). Data are limited but there may be rapid growth of these variants (low confidence). VUI 202101/02 has been identified in Manaus which is experiencing a rapid growth in numbers of COVID hospitalisations. SARS-CoV-2 seroprevalence in Manaus has previously been reported to be high [13]. If present, this rapid growth could be related to increased transmissibility, antigenic escape or both. There are reasons to be concerned about the possibility of antigenic escape:

   a. In vitro data showing weaker neutralisation of viruses with the E484K motif with polyclonal serum. [7]

   b. In vitro data showing that variants with the E484K substitution show weaker neutralisation with some monoclonal antibodies (bamlanivimab Eli Lily, >100 fold; REGN10933 Regeneron, 25-fold [also K417N, 7-fold]). [8,9]

   c. Data showing reduced plasma neutralising activity against SARS-CoV-2 variants encoding E484K, N501Y, or K417N:E484K:N501Y in vaccinees, as described in section 2. [10]

   d. Identification in an area (Manaus) with rapid growth in COVID hospitalisations and previously reported high levels of seropositivity. [12]

5. A small number of South African and Brazilian and other genomes with the E484K substitution have been identified in the UK as of 12 January 2021 (50-100 genomes).

6. Variants with the combined N501Y and E484K substitutions have been shown to have enhanced ACE2 receptor binding. [12,14]

Conclusion

7. The emergence and spread of SARS-CoV-2 virus variants which may have either increased transmissibility or antigenic escape or both is a significant concern.

8. The following actions should be considered:

    a. Minimising spread of these and other variants by reducing overall infection transmission in the UK.

    b. Minimising introduction of VOCs into the UK by enhanced border measures.

    c. Enhanced case detection, contact tracing and quarantine related to any viruses with the E484K substitution in order to minimise spread.

    d. Conduct of neutralisation assays to assess antigenic properties of variants with the E484K substitution.

    e. The determination of additional substitutions of concern (e.g. K417N/E) and systemic genomic surveillance and phenotypic evaluation of these substitutions.

    f. A review of vaccine development pipelines with a view to accelerated antigenic update if needed.

    g. A review of monoclonal antibody formulations with a view to accelerated monoclonal update if needed.

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