NERVTAG paper

Brief note on SARS-CoV-2 VOC P.1

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Summary

1. **Increased transmissibility of the P.1 variant is biologically and epidemiologically plausible but at this time there is insufficient evidence to confirm or refute this.**

2. **At this time, there is insufficient evidence to assess whether variant P.1 is associated with any change in disease severity.**

3. **There are reasons to be concerned about the possibility of antigenic escape from natural and vaccine acquired immunity with variant P.1. While we are not aware of any data in the P.1 variant, there have been numerous studies of the B.1.351 variant which show varying degrees of antigenic escape from natural and vaccine-acquired immunity. Notably, both P.1 and B.1.351 share the E484K and N501Y mutations, as well as an amino acid change at position 417.**

4. **There is some evidence to suggest that variants containing the E484K change show antigenic escape from individual monoclonal antibodies.**

Background

5. Variant P.1 was first identified in Japan amongst travellers from Brazil. The P.1 lineage is a descendent of B1.1.28, and contains 17 unique amino acid changes, three deletions, four synonymous mutations, and one 4nt insertion. Three of these mutations are of known biological importance: K417T, E484K, and N501Y. [1]

Transmissibility

6. P.1 has been a 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 [2]. If present, this rapid growth could be related to increased transmissibility, antigenic escape or both.

7. Variants with the combined N501Y and E484K substitutions have been shown to have enhanced ACE2 receptor binding. [3, 4]

8. **Increased transmissibility is biologically and epidemiologically plausible, but at this time there is insufficient evidence to confirm or refute this.**

Severity

9. At this time, there is insufficient evidence to assess whether variant P.1 is associated with any change in disease severity. There is high healthcare demand and mortality in Manaus but the role of the new variant is unknown.

Susceptibility and Immunity

10. There are reasons to be concerned about the possibility of antigenic escape with variant P.1. While we are not aware of any data in the P.1 variant, there have been numerous studies of the B.1.351 variant which show varying degrees of antigenic escape from natural and vaccine-acquired immunity. Notably, both P.1 and B.1.351 share the E484K and N501Y mutations, as well as an amino acid change at position 417.

Natural infection

11. In vitro data shows weaker neutralisation of viruses with the E484K motif with polyclonal serum. [5]

12. Several studies have shown that the neutralisation ability of convalescent plasma is reduced against B.1.351 pseudovirus, and authentic virus. [6, 7, 8] The clinical impact of this reduction remains unclear.

a. One study found the reduction in convalescent plasma neutralisation of B.1.351 pseudovirus to be largely attributable to E484K. [8]

13. It is possible that the P.1 variant will show similar patterns of antigenic escape to naturally-acquired immunity to the B1.351 variant, due to similar genomic profiles, in particular the presence of E484K. However, there remains no direct evidence for antigenic escape from natural immunity in the P.1 variant.

Vaccines

14. One study showed reduced plasma neutralising activity against SARS-CoV-2 variants encoding E484K, N501Y, or K417N:E484K:N501Y (the combination present in B.1.351) in a cohort of 20 volunteers who received either the Moderna (n=12) or Pfizer (n=6) vaccine, 8 weeks after the second dose. [9]

a. 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.

15. Several studies have shown a low to moderate reduction in neutralisation activity against B.1.351 in immune sera from Moderna and Pfizer vaccinees. The clinical impact of this reduction remains unclear.

a. In one study, the loss of neutralisation activity in the immune sera of vaccinees was principally attributed to E484K. [8]

16. It is possible that the P.1 variant will show similar patterns of antigenic escape to vaccine-acquired immunity as the B1.351 variant, due to similar genomic profiles, in particular the presence of E484K. However, there remains no direct evidence for antigenic escape from vaccine-acquired immunity in the P.1 variant.

Drugs and Therapeutics

17. In vitro data shows 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]). [10, 11]

18. In vitro data shows that B.1.351 pseudovirus is refractory to neutralisation by most N-terminal domain (NTD) monoclonal antibodies (mAbs), and also to several mAbs to the receptor-binding motif on the RBD (including Ly-CoV555 and REGN10933). E484K is a key mediator of the loss of activity of mAbs that target the RBD. [8]

19. There is some evidence to suggest that variants containing the E484K change show antigenic escape from individual monoclonal antibodies.

Diagnostic assays

20. There is currently no evidence to suggest that this variant would affect the performance of diagnostic assays.

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