NERVTAG paper

Brief note on SARS-CoV-2 B.1.351

Authors: Peter Horby, Wendy Barclay, Ravi Gupta, Catherine Huntley

SAGE meeting date: 28 January 2021

Summary

1. **There is epidemiological evidence to suggest that variant B.1.351 is associated with increased transmission (medium confidence). Further information is needed to confirm this finding.**

2. **There is a single piece of evidence that suggests that B.1.351 may be associated with increased severity (low confidence).**

3. **At this time, the available evidence suggests that B.1.351 has reduced neutralisation with convalescent plasma. The clinical impact of this reduction in neutralisation remains unclear.**

4. **At this time, the available evidence suggests that B.1.351 has reduced neutralisation with postvaccination serum. The clinical impact of this reduction in neutralisation remains unclear.**

5. **At this time, the available evidence suggests that B.1.351 may be associated with loss of activity of single monoclonals targeting the RBD and the N-terminal domains. Activity of combination monoclonals in clinical development appears largely unaffected.**

Background

6. B.1.351 (also known as VOC 202012/02 or 501Y.V2), was first identified in South Africa. It includes nine changes in the spike protein: one group of four substitutions and a deletion in the N-terminal Domain (NTD) and another group of three substitutions in the RBD (K417N, N501Y, and E484K). [1]

Transmissibility

7. There is some evidence to suggest that B.1.351 is associated with increased transmissibility.

8. B.1.351 has shown rapid epidemiological growth in an area (Nelson Mandela Bay) with reported high levels of seropositivity. [2]

9. A model of the epidemic trajectory in South Africa (incorporating data on cases, deaths, and population demographics) showed that, without changes to the circulating pathogen or underlying population, a subsequent 'second wave' should be precluded by accumulated immunity. The occurrence of a 'second wave' despite these findings suggests increased transmissibility, immune escape, or a combination of the two. [3]

a. If an assumption of complete cross protection between variants is made, the model suggests that B.1.351 is 1.50 (95% CrI:1.20-2.13) times as transmissible as previously circulating variants.

b. If an assumption that the transmissibility of the new variant is the same as previous variants is made, the model suggests the new variant evades 21% (95%CrI: 11-36) of previously acquired immunity.

10. There is epidemiological evidence to suggest that variant B.1.351 is associated with increased transmission (medium confidence). Further information is needed to confirm this finding. Increased transmission could arise from increased transmissibility, immune escape, or a combination of the two.

Severity

11. There is a single piece of evidence that suggests that B.1.351 may be associated with increased severity (low confidence).

12. One study found some evidence of an increase in the delay-adjusted case fatality ratio since the arrival of the new variant in a single Province (Western Cape), though the authors report substantial uncertainty. [3]

Susceptibility and Immunity

13. There is some evidence that the variant B.1.351 variant is associated with antigenic escape from naturally, monoclonal or vaccine acquired immunity. Preliminary evidence suggests the E484K change, as well as the combination of substitutions present on the RBD in this variant, are associated with antigenic escape. The clinical significance of these findings remains unclear.

Natural infection

14. There is some evidence to suggest that individuals who have been previously infected with SARS-CoV-2 may show reduced ability to neutralise the B.1.351 variant.

15. In vitro data showed weaker neutralisation of pseudoviruses with E484K substitution with polyclonal serum. [4]

16. One study assessed the neutralisation ability of polyclonal sera derived from individuals infected with SARS-CoV-2 (n=44) against pseudovirus containing only the three RBD mutations present in B.1.351, as well as against B.1.351 pseudovirus. When assessed against the RBD triple mutant, 27% of samples lost all neutralisation activity. When assessed against B.1.351 pseudovirus, 48% had no detectable neutralisation activity. Three individuals retained high neutralisation titers against B.1.351, all of whom had previously experienced severe disease. [1]

17. In a live virus neutralization assay, a study of the neutralising antibody response of convalescent plasma from six donors infected in the first wave against live B1.351 virus showed reduced neutralisation of the new variant, with one complete loss of neutralisation activity. [5]

18. A further study showed that B.1.351 pseudovirus is markedly (~11-33 fold) more resistant to convalescent plasma relative to the wild type (D614G). 16 out of 20 samples showed >2-fold loss in potency against B.1.351, with the loss of plasma neutralising activity largely attributable to E484K. [6]

19. Three studies of small numbers of human polyclonal sera show reduced neutralisation against the B1.351 variant, using either live or pseudo virus. The clinical impact of this reduction remains unclear.

Vaccines

20. 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. [7]

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.

21. A study showed that the immune sera of both human subjects (n=8) and non-human primates (n=12) that received two doses of the Moderna vaccine showed lower neutralisation against B.1.351 pseudovirus. In humans, pseudovirus containing full B.1.351 mutations resulted in a 6.4-fold GMT reduction compared to D614G pseudovirus. Despite this, all evaluated human sera remained able to fully neutralise. [8]

22. A further study showed that the immune sera of 12 Moderna vaccinees (two doses on days 0 and 28, sample collected on day 43) and 10 Pfizer vaccinees (two doses on days 0 and 21, sample collected on or after day 28) lost neutralisation activity against B.1.351 pseudovirus. This loss ranged from slight to substantial, with a mean loss of neutralising activity of 8.6 fold for Moderna, and 6.5 fold for Pfizer. The loss of neutralisation activity was principally attributed to E484K. [6]

23. Three studies have shown that immune sera from mRNA vaccinees show small reductions in neutralisation activity against B.1.351 pseudovirus. The clinical significance of these reductions remains unclear.

Drugs and Therapeutics

24. In vitro data shows that B.1.351 pseudovirus is refractory to neutralisation by most NTD 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. Some combinations of mAbs, including REGN10933+REGN10987 and COV2-2196+COV2-2130 are seemingly unaffected. [6]

25. 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]). [9, 10]

26. Initial data shows weaker neutralisation of B.1.351 by several monoclonal antibodies, with the E484K thought to be a key mediator of this effect. Combinations of mAbs may still be effective.

27. At the current time, evidence suggests that B.1.351 is associated with significant loss of activity of single monoclonals targeting the RBD and the N-terminal domains. Activity of combination monoclonals in clinical development is largely unaffected.

Diagnostic assays

28. There is currently no evidence to suggest that B1.351 would affect the performance of diagnostic assays.

References:

[1] C. K. Wibmer, F. Ayres, T. Hermanus, M. Madzivhandila, P. Kgagudi, B. Lambsen, M. Vermeulen, K. van den Berg, T. Roussow and M. Boswell, “SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma,” *bioRxiv [preprint],* 2021.

[2] . H. Tegally, E. Wilkinson, M. Giovanetti, A. Iranzadeh, V. Fonseca, J. Giandhari and et al., “Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa,” *bioRxiv,* 2020.

[3] C. Pearson, T. W. Russell, N. G. Davies, A. J. Kuckarski and CMMID COVID-19 working group, “Estimates of severity and transmissibility of novel South Africa SARS-CoV-2 variant 501Y.V2,” *Preprint,* 2021.

[4] A. J. Greaney, A. N. Loes, K. H. Crawford, T. N. Starr, K. D. Malone, H. Y. Chu and J. D. Bloom, “Comprehensive mapping of mutations to the SARS-CoV-2 receptor-binding

domain that affect recognition by polyclonal human serum antibodies," *bioRxiv [preprint],* 2021.

[5] S. Cele, I. Gazy, L. Jackson, S.-h. Hwa and et al, "Escape of SARS-CoV-2 501Y . V2 variants from neutralization by convalescent plasma," *[preprint],* 2021.

[6] P. Wang, L. Liu, S. Iketani, L. Yang, Y. Guo and et al., "Increased Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7 to antibody neutralization," *bioRxiv [preprint],* 2021.

[7] Z. Wang, F. Schmidt, Y. Weisblum, F. Muecksch, C. O. Banres, S. Finkin, D. Schaefer-Babajew, M. Cipolla, C. Gaebler, J. A. Lieberman and Z. Yang, "mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants," *bioRxiv [preprint],* 2021.

[8] K. Wu, A. P. Werner, J. Moliva, M. Koch and et al., "mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants," *bioRxiv [preprint],* 2021.

[9] A. Baum, B. O. Fulton, E. Wloga, R. Copin, K. E. Pascal, V. Russo, S. Giordano, K. Lanza, N. Negron, M. Ni, Y. Wei, G. S. Atwal and A. J. Murphy, "Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies," *Science,* vol. 369, no. 6506, pp. 1014-1018, 2020.

[10] Eli Lilly and Company, "Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) of Bamlanivimab," 2020.