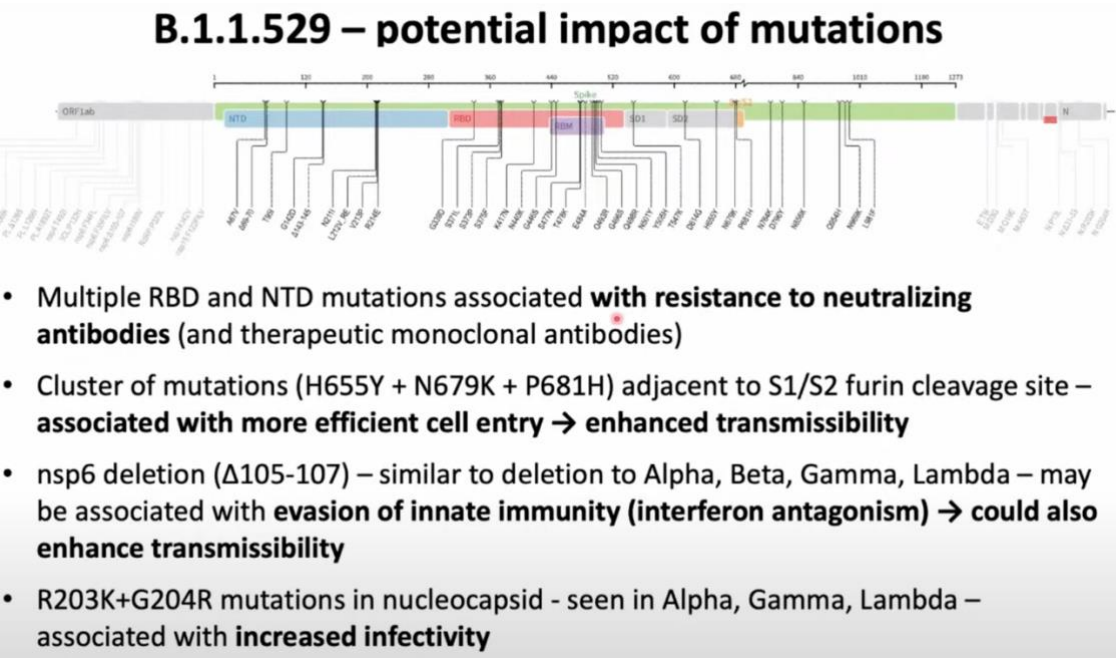
Omicron Scientific Update – Monday 29th November 2021

Success of surveillance and open communication.
We all owe a debt of gratitude to the viral surveillance experts in Botswana and South Africa who last week identified this very heavily mutated variant by whole genome sequencing, and openly disseminated their early findings of rapid spread. If you wish to hear their presentation of these findings, which have informed the swift decision making by WHO and governments around the world, it is here: https://www.youtube.com/watch?v=Vh4XMueP1zQ



The South African team extended their data from viral sequencing by interrogating viral PCR testing data across South Africa, using the presence of a false-negative "drop-out" of one of the primer pairs as a proxy for presence of one of the signature deletions in the Omicron spike sequence.

PCR-based proxy for new variant

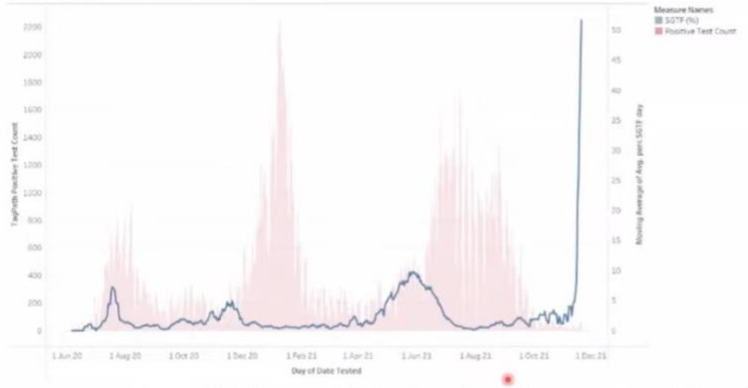
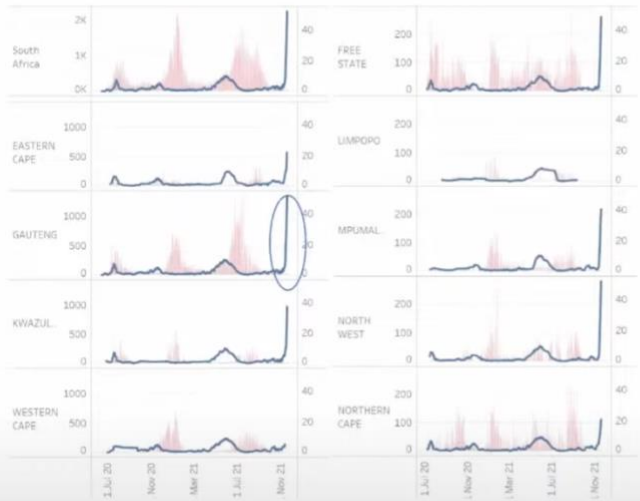


Figure 9: S-gene dropout (%) of cases with high VL (Ct value<30 for ORF or N gene). The red bars are the number of tests reporting the presence of SARS-CoV-2 (daily) on the TaqPath assay. The solid blue line is the moving median of S-gene dropout (%).
**Current (end of Nov '21) dramatically increasing trend in the proportion of SGTF (Ct value<30 for ORF or N gene)*

- Variant can be detected with one particular PCR assay (before whole genome sequencing)
- New increase in S-gene dropout noted by NHLS and private labs very recently - from mid-November
- Now rapidly increasing in most provinces

Courtesy of Lesley Scott and NHLS team

S gene target failure by province



- Rapid increase in proportion with SGTF noted across multiple provinces (caution low number of tests in most provinces)
- 77 samples with SGTF sequenced from Gauteng (samples collected 12-20 Nov) – 77/77 (100%) were B.1.1.529
- Hundreds of recently collected samples being sequenced currently by NGS-SA labs – results available by end of week (today we received 70 samples from Gauteng 67/70 were SGTF and sequencing tonight, in KZN approximately 20%).

Courtesy of Lesley Scott and NHLS team

What is absolutely clear is that this variant is overtaking Delta in almost every precinct of South Africa, and at breathtaking speed compared to the rate that Delta overtook Beta.

Given the low vaccination rates in South Africa, this points to a big jump in infectivity regardless of any evasion of vaccine-induced immunity.

The conclusion of increased infectivity also fits with Omicron carrying a unique combination of mutations in the furin cleavage sequence in the spike that parallel but goes beyond the mutation acquired in Delta that is presumed to be a key part of its enhanced infectivity. There are also mutations in nonstructural proteins that may diminish type 1 interferon-mediated innate immunity and further increase infectivity.

The combination of these two pieces of firm evidence make it certain that this variant is the most infectious yet.

Putting aside just being more infectious, the other big concern is how the spike mutations may diminish binding of vaccine-induced antibodies. There is no direct data on this yet, but it's a safe bet that it will be an equal or greater effect than the mutations in the previous South African variant (beta), given the deletions in the NTD and the 10 substitutions in the receptor binding motif of the RBD alone.

GISAID has a nice visualisation of the spike mutations here:

https://www.gisaid.org/hcov19-variants/

The density of mutations in the site1/site2 antibody region of the receptor binding domain, which are individually known to have effects on antibody binding, is extraordinary. Almost a new receptor binding surface, and very likely to diminish recognition by neutralising antibodies.

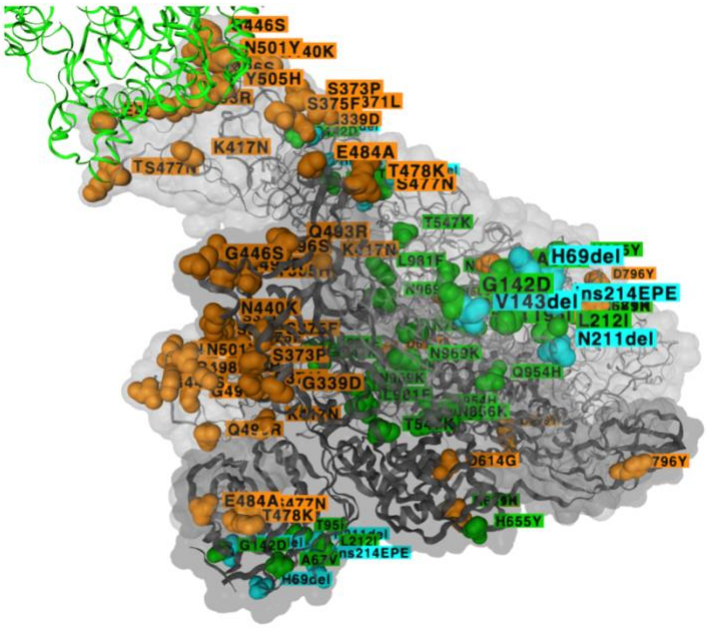
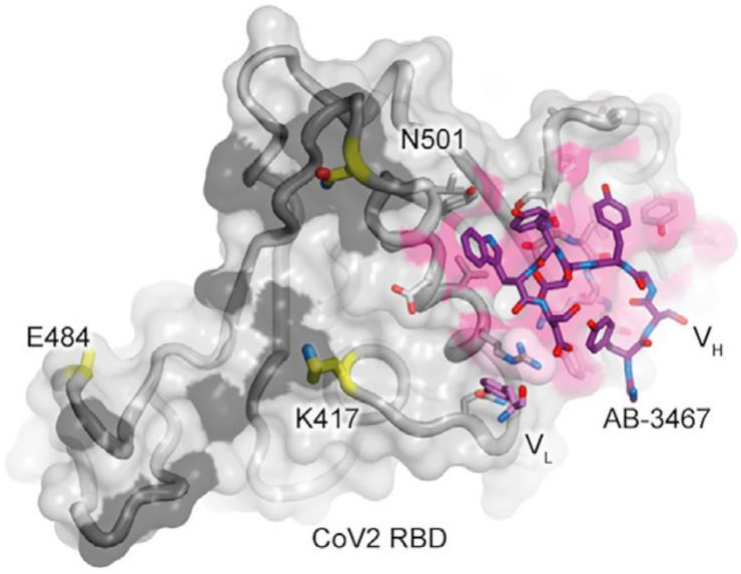


Image of CoV2 spike trimer (grey) with one of the receptor binding domains (RBD) in the up position (upper left) bound to ACE2 (green ribbon). Orange denotes Omicron substitutions known from previous experimental mutagenesis studies in the lab to have functional consequences. Note the high density of orange substitutions surrounding the ACE2 binding surface, referred to as site 1 and site 2 for neutralising antibodies. Individually, many of these substitutions are experimentally demonstrated to diminish binding of the dominant class of neutralising antibodies. How the combination of so many mutations in the RBD affects neutralising antibodies raised against the Wuhan strain RBD will need to be tested, but they are likely to have additive effects eroding antibody binding affinity.



It will take several weeks to know how these mutations affect Garvan's recent discovery of vaccine strategies to increase neutralising antibody responses against the highly conserved class 4 site on the RBD. In the structure of the RBD here, oriented as in the one above, you can see that Garvan's potent neutralising class 4 antibody AB-3467 binds in the pink area away from the site 1/site 2 mutations in Omicron (and other variants of concern) at K417, E484, and N501. But there are a cluster of unique Omicron mutations S371L, S373P, S375F that might affect binding of AB-3467 and other class 4 neutralising antibodies.