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SARS-CoV-2 escape mutants and protective immunity from natural infections or immunizations

Di Caro A, Cunha F, Petrosillo N, Beeching NJ, Ergonul O, Petersen E, Koopmans MPG

1. European Society for Clinical Microbiology and Infectious Diseases (ESCMID), Emerging Infections Task Force. ESCMID, Basel, Switzerland.
2. Laboratory of Microbiology, National Institute for Infectious Diseases "Lazzaro Spallanzani", Rome, Italy.
3. Department of Molecular Medicine, San Matteo Hospital, University of Pavia, Pavia, Italy.
4. Department of Infectious Diseases, Coimbra Hospital and University Center, Coimbra, Portugal.
5. European Society for Clinical Microbiology and Infectious Diseases (ESCMID), International Affairs Subcommittee, Basel, Switzerland.
6. Clinical and Research Department, National Institute for Infectious Diseases "Lazzaro Spallanzani", Rome, Italy.
7. Tropical and Infectious Disease Unit, Royal Liverpool University Hospital and Liverpool School of Tropical Medicine, Liverpool, UK.
8. Koç University Research Center for Infectious Diseases, Istanbul, Turkey
9. Institute for Clinical Medicine, Faculty of Health Science, University of Aarhus, Denmark.
10. Viroscience department, ErasmusMC, WHO collaborating centre, Rotterdam The Netherlands

* Corresponding author

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Updates of detections of spike gene mutations for each GISAID clade are posted daily on the “CoVariants” website, together with geographic maps of their proportional distribution, and visualised through collaboration with Nextstrain. The current version of the Nextstrain data visualisation software allows switching between GISAID and PANGO lineage designations, and the WHO is working on a unifying system for nomenclature.

Three recently detected SARS-CoV-2 lineages (B.1.1.7, B.1.351, and P.1), have been scrutinized because they are unusually divergent and each possesses a unique constellation of mutations of potential biological importance, several of which are in the gene coding for the Spike protein. In addition, some viral genomes of the B.1.1.7 lineage have been observed that acquired the E484K mutation which is thought to be linked to immune evasion.

Cell binding and functional immunity
Mutations that cause conformational changes in the spike protein receptor binding domain (RBD), and which affect binding to key host tissue receptors, are expected to impact on infectivity. For the above variants, there is some evidence that the binding affinity is increased, and that there may be a selective advantage increasing transmissibility. A recent study plotted the binding affinity to ACE2 of all RBD mutations against their incidence in the population and showed a strong correlation between the two. It also showed how further evolution might increase binding affinity even further. Such mutations are also considered to have the most important impact on the effects of neutralizing antibodies. One study found that binding by polyclonal serum antibodies is affected by mutations in three main epitopes in the RBD. The most important site is E484, where neutralization by some convalescent and vaccinee sera is reduced >10-fold by several mutations, including one in emerging viral lineages in South Africa (B. 1.351, also named 501.V2) and Brazil (B.1.1.28.1, also named P1). A study using VSV pseudovirus expressing different variants of the SARS-CoV-2 spike protein found that VSV pseudoviruses with spike containing K417N-E484K-N501Y-D614G and full B.1.351 mutations were less easily neutralized with 2.7 and 6.4-fold lower neutralizing antibody titres respectively, when compared to the non-variant VSV pseudovirus used in this study.

While some of these observations are reason for concern, the field is very young, and careful evaluation of the effects is needed, for instance on the impact of emergence of variants on vaccine
efficacy. In addition to neutralising and binding antibodies, SARS-CoV-2 infection also elicits a vast repertoire of T cell responses and dominant epitopes had the capacity to bind multiple HLA allelic variants [22]. A further study by the same authors found that “CD4+ and CD8+ T cell responses in convalescent COVID-19 subjects or COVID-19 mRNA vaccinees are not substantially affected by mutations found in the SARS-CoV-2 variants” [23]. A major limitation of that study is that all donors were recruited in California and had no known exposure to the escape variants first found in the UK, South Africa or Brazil. Therefore, we do not know if T cell responses elicited by previous SARS-CoV-2 infection or immunisation with the present “1st generation” vaccines will be protective against infections with escape mutants.

The South African variant B.1.351

The B.1.351 lineage is present in 90% of recent infections for which sequence data was generated in South Africa, and has been associated with increased transmissibility [24]. Press reports indicate that it also may predominate in Botswana, Zimbabwe, Zambia, Namibia and Malawi [25]. An increasing number of cases have been detected with the B.1.351 variant in different parts of the UK, which is believed to represent second and third generation cases, as those infected had no known links to South Africa [26], and by now, B.1.351 variant viruses have been found in more than 50 countries. The Novavax COVID-9 vaccine was reported to be somewhat less effective in preventing infection in a second trial in South Africa, where the SARS-CoV-2 variant B.1.351 is prevalent. In the South Africa trial of over 4,400 people, the vaccine was 60% effective in people that were HIV negative [27], compared to 89.3% effective at preventing COVID-19 in participants in its Phase 3 clinical trial in the UK [28]. Protective efficacy was reduced further to 49.4% in South African cases infected with the B.1.351 variant [25]. In a Phase 3 trial including 44,000 people, a single dose of the Johnson and Johnson, JNJ, vaccine showed an overall protective 66% efficacy. However, the contrasting efficacy of 72% efficacy in the US arm of the trial versus 57% in South Africa supports the concept of immune escape/resistance of the B.1.351 variant, as seen following the Novavax vaccine [29]. A recent study from South Africa found that effective neutralization by immune sera after B.1.351 infections inhibited first wave (non- B.1.351) virus, providing preliminary evidence that vaccines based on variant sequences could work against other circulating SARS-CoV-2 lineages [30]. However, it remains to be seen to what extend emergence of new variants affects vaccine efficacy as results from separate trials are difficult to compare.
The Brazilian variant P1

The P.1 lineage was first discovered in Manaus, Brazil, where it accounted for 42% of genomes sampled in December 2020, having been absent in samples collected there between March and November 2020 [14]. A study from Brazil found that 76% of the population had been infected with SARS-CoV-2 by October 2020 [31]. The sharp increase in the number of COVID-19 hospital admissions seen in Manaus in January 2021 (3,431 in Jan 1–19, 2021, vs 552 in Dec 1–19, 2020) indicates that immunity obtained during infection in mid to late 2020 was not fully protective [32]. Little is known about the transmissibility of the P.1 lineage, but it shares several independently acquired mutations with the B.1.1.7 (N501Y) and the B.1.325 (K417N/T, E484K, N501Y) lineages first detected in the UK and South Africa, which seem to have increased transmissibility [13]. By now, the variant has been detected in 25 countries.

Vaccine upgrades and the future of immunisation against SARS-CoV-2

Moderna is exploring how their vaccine could be updated to incorporate sequences coding for the new variants of the spike protein [33]. Novavax is working on a booster and/or combination bivalent vaccine in response to the B.1.351 variant in South Africa [34]. BioNTech is looking to authorize “a new version of the Pfizer-BioNTech vaccine that would be better able to head off the variant in South Africa” [25]. Studies estimating the ability of vaccines to reduce transmission of different viral lineages continue to be essential [35]. A challenge will be when to decide to change the vaccine composition, as the dispersal is not uniform globally. Also, regulators are studying the regulatory process needed for vaccine updates.

Conclusion

The global expansion of SARS-CoV-2 and the continued circulation in partially immune populations has led to emergence of variants with some adaptive changes leading to increased transmissibility and/or decreased sensitivity to neutralising antibodies. The expanding number of people with immunity to SARS-CoV-2, following natural infection or immunisation, and the inequality of access to and/or application of interventions and vaccines is likely to create further immune pressure on the virus. Thus, the strategy by vaccine manufacturers to foresee the need for “second generation” vaccines covering the new mutants is reassuring. From a public health perspective, it is likely that we will need repeated immunisation rounds, like those already in place for influenza, with annual vaccines tailored to new variants. The challenge with SARS-CoV-2 is the global scale of
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