

Rapid Reviews COVID-19

Review 1: "Circulating SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity"

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RR:C19 Evidence Scale rating by reviewer:

- **Reliable.** The main study claims are generally justified by its methods and data. The results and conclusions are likely to be similar to the hypothetical ideal study. There are some minor caveats or limitations, but they would/do not change the major claims of the study. The study provides sufficient strength of evidence on its own that its main claims should be considered actionable, with some room for future revision.

Review:

The preprint entitled, "Circulating SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity," underlines the significance of developing new vaccines or reformulating current vaccines capable of cross-neutralization of emerging variants of SARS-CoV-2. The results of this study provide adequate evidence that BNT162b2 and mRNA-1273 vaccines are only protective of a few circulating SARS-CoV-2 variants through humoral immunity.

The global emergence of several variants of SARS-CoV-2 has raised concern due to its mutations of the spike protein– the main target of vaccine-elicited neutralizing protein. Hence, it is crucial to understand the effectiveness of current vaccines against these variants to prevent re-infection and intervene in the progression of the pandemic. The study finds that ACE2 receptor-binding domain (RBD) mutations containing K417N/T, E484K, and N501Y, predominantly found in P.1 and B.1.351 variants, have reduced neutralization in all subjects of their cohort, despite whether the subject was fully vaccinated or not. These results are consistent with previous findings of increased antibody resistance to P.1 and B.1.351 in convalescent and vaccine sera. This investigation, however, provides new insight into the effectiveness of current mRNA vaccines, as some previous reports used non-naturally occurring single mutations or combinations of mutations noted in this study. The study also highlights the importance of the 2-dose vaccine regimen to provide detectable neutralization of SARS-CoV-2 as demonstrated by the reduced neutralization in one-dose subjects for both BNT162b2 and mRNA-1273 vaccines. The implications of this study suggest the need for new vaccines that elicit broader neutralizing antibodies against emerging strains and supports the reformulation of existing vaccines to impede the pandemic.

One of the strengths of this manuscript is it positions itself well within current literature and discusses the limitations of previous studies, and addresses limitations of its own, such as the modeling capabilities of pseudovirus as it only describes the ACE2-dependent entry step of SARS-CoV-2. Therefore, the study cannot suggest the overall immunological impact of the mutations outside of the spike proteins. Moreover, cellular immunity and its associated T-cell responses are not investigated in this study.

Although the manuscript provides insight into the effectiveness of current vaccines against new variants of SARS-CoV-2, some limitations should be addressed in the scope of subsequent studies. The number of subjects enrolled in the cohort of this study is rather small with only 47 individuals. 42 of those individuals are below the age of 45. Thus, the small cohort may not produce representative data for those of older age. The total number of individuals fully vaccinated with two doses in this cohort is 26. All in all, the small cohort may render the power of the study.