Rapid Reviews COVID-19

Review 2: "Natural deletions in the SARS-CoV-2 spike glycoprotein drive antibody escape"

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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:

This paper shows that the deletion events in the NTD of the SARS-CoV-2 Spike protein rise independently and often, and that these deletion variants are transmitted between people (and are therefore presumably replication-competent). It is less clear from this manuscript what fitness advantage these deletions confer as they seem to have little effect on neutralization sensitivity using COVID-19 sera. However, the conclusion from this work that these mutations should be monitored is timely. The case with the immunocompromised patient that led to the RDR described here is interesting and such cases are thought to be feeding the phenotypic variation in SARS-CoV-2 leading to more fit variants.

The discussion points about these deletions affecting antigenicity and neutralization are confusing and misleading because they could be construed to suggest the variants evolve because they escape antibodies in serum. There is no evidence for that. The study shows escape for a single monoclonal chosen because it targets the RDR region, but this is not true for sera. So, it is not possible to make such broad conclusions about antigenic shifts and neutralization changes without clarifying this is not generally true. Related to the above, it would be interesting to test the RDR variant against autologous serum antibodies to determine if there is evidence of escape/antigenic variation in response to antibody pressure in that individual.

A minor note is that the neutralization data in Fig 4 could be presented more clearly using percent neutralization or NT50s.

Given there is no clear effect on serum neutralization, this suggests perhaps a replication advantage for the deleted variants. It would be interesting to test these for replication fitness changes and/or receptor affinity differences. If that is not readily doable, at least comment if this has been done for any of the other deletion variants.

Do these deletions occur equally in the background of other mutations? Or is there evidence of epistatic interactions? For example, do deletions appear in D614 and G614 background equally?

It would be helpful to describe how deletions occur in coronaviruses and also to mention if deletions are important in altering pathogenesis and/or immunity in other viruses.