Review 1: "SARS-CoV-2 variant B.1.617 is resistant to Bamlanivimab and evades antibodies induced by infection and vaccination"

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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 manuscript by Hoffmann et al. (<https://doi.org/10.1101/2021.05.04.442663>) addresses an important topic concerning the rise of the B.1.617 lineage, the precursor to the B.617.2 "Delta" lineage, which is now the primary driver of the SARS-CoV-2 pandemic.

The present study examines: 1) the ability of B.1.617 pseudotype viruses to enter cultured cells, and the ability of soluble ACE2 and Camostat mesylate to block said entry; 2) The ability of Bamlanivimab to neutralize B.1.617 pseudotype viruses; and 3) the ability of convalescent or vaccinee plasma to neutralize B.1.617 pseudotyped virus.

The authors have found that, compared to pseudovirus bearing WT Spike protein, B.1.617 pseudovirus displays markedly higher entry efficiency in Caco-2 colorectal adenocarcinoma cells and the Calu-3 nonsmall-cell lung cancer cell line. Notably, entry efficiency in other assayed cell lines was similar, with no statistically significant difference. In addition, B.1.351 ("Beta") pseudotyped virus was also assayed and found to display similar infectivity to B.1.617 in most cells. Still, slightly higher infectivity in Calu-3 cells was noted, and a significantly higher entry rate was noted in 293T cells (human embryonic kidney cells). Such results suggest that B.1.617 is better at infecting lung and intestinal tissue than WT virus but not better than B.1.351. While showing some increased infectivity, these results apparently do not presage the apparently highly infectious derivative variants B.1.617.1 and B.1.617.2.

There was no significant difference between WT, B.1.617, and B.1.351 entry inhibition by soluble ACE2 or Camostat (a serine protease inhibitor). The use of a control virus without Spike protein lends weight to this result. This result suggests that an increased affinity does not drive the increased infectivity for ACE2.

While the paper cannot establish a reason for the increased entry of the B.1.617 pseudovirus particles into cells (although possible explanations are suggested), the authors conclusively demonstrate that the B.1.617 spike protein displays a degree of escape from neutralizing antibodies raised against WT spike.

Through measuring virus-encoded luciferase activity is fairly standard neutralization assays, the authors demonstrate that B.1.617 remains susceptible to the commercial monoclonal antibodies Casirivimab, Imdevimab, and Esetevimab. In contrast, the authors observe essentially complete escape from Bamlanivimab. Notably, B.1.351 pseudovirus escapes both Bamlanivimab and Esetevimab.

Similarly, decreased neutralizing titers are noted from both convalescent and vaccinee plasma. Notably, neutralizing titers were found to be even lower against B.1.351 pseudovirus.

This study is excellent because B.1.617 displayed concerning properties, such as a degree of immune escape and increased infectivity. Furthermore, the work is presented with appropriate controls and experiments. Although the use of real virus isolates and more complex cell culture models could improve the reliability of the results, the resulting increase in risk and difficulty would probably not be justified – given that the methods here were clearly sufficient to demonstrate increased cell entry and decreased neutralization.

Despite this, the study produced no data suggesting any reason to consider B.1.617 to be of more concern than B.1.351. In hindsight, we can see that B.1.617 continued to evolve into B.1.617.2, causing more infections than B.1.351. This study thus illustrates the need to remain vigilant and monitor other concerning strains that, for the moment, do not appear to be worse than B.1.617.2 (such as B.1.621 or C.37 “Lambda”).