Rapid Reviews COVID-19 •

Review 1: "Delta variant and mRNA Covid-19 vaccines effectiveness: higher odds of vaccine infection breakthroughs"

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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:

Summary: Kislaya et al. present a case-case study of SARS-CoV-2 infections attributed to the Alpha and Delta variants. Using WGS and SGTF, they identified causative VOC in infections that occurred in unvaccinated, partially vaccinated, and fully vaccinated patients. The authors observed an increased rate of breakthrough infections attributed to the Delta variant. Additionally, the authors observed an increased viral load among all patients with Delta variant infections.

Overall, I think the claims are generally supported by the data and methods used. The data is important for awareness of the scientific community as it will impact public health efforts to combat the surge of Delta cases. This study further expands on the growing evidence of vaccine breakthroughs by the Delta variant. This information must be published promptly.

The authors use sound statistical analysis to determine the rate of vaccine breakthrough by Delta and Alpha SARS-CoV-2 variants among unvaccinated, partially vaccinated, and fully vaccinated individuals. The data supports the conclusion that an increased number of breakthrough infections are attributed to the Delta variant.

One weakness of the manuscript is their reliance on Ct values to determine viral load. As COVID-19 progresses, viral load changes drastically. As we do not fully understand the symptom onset/severity differences between Alpha and Delta, it is difficult to determine if this could confound the lower observed Ct values. If Delta tends to cause COVID-19 symptoms earlier, are patients more likely to get tested during a period of higher viral load? I see the citations about previous studies using Ct to estimate viral load. However, the authors are not assessing the differences between the two variants. Depending on the authors' depth of metadata on each individual, an analysis of the date of symptom onset and RT-PCR test could help position the results in more context.

Decision-makers should consider the claims in this study actionable with limitations based on the methods and data.