Rapid Reviews COVID-19

Review 3: "Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2 mRNA vaccinated individuals"

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RR:C19 Evidence Scale rating by reviewer:

- **Potentially informative.** The main claims made are not strongly justified by the methods and data, but may yield some insight. The results and conclusions of the study may resemble those from the hypothetical ideal study, but there is substantial room for doubt. Decision-makers should consider this evidence only with a thorough understanding of its weaknesses, alongside other evidence and theory. Decision-makers should not consider this actionable, unless the weaknesses are clearly understood and there is other theory and evidence to further support it.

Summary of the study:

Israel has had an effective rapid rollout of the BNT162b2 mRNA vaccine for coronavirus infectious disease 2019 (COVID-19) with more than 55% of the population vaccinated and an over 95% drop in cases across all age groups since a peak in mid-January 2021. Though this vaccine has demonstrated efficacy in preventing clinical disease (95%) and infection (85%), seven days after the second dose, the emergence of SARS-CoV-2 variants particularly the B.1.1.7, B.1.351, and P.1 strains have raised concerns about vaccine protective efficacy based on lower neutralization of recombinant virus with variant sequences by sera from vaccine recipients.

This retrospective case-control study attempted to elicit the role of variants in breakthrough infections post receipt of one and two doses of the BNT162b2 mRNA vaccine. The authors leveraged their access to the largest health care organization in Israel that insures 53% of the population. They then divide the cases (vaccinees with breakthrough) into two groups: (1) those fully immunized, 7 or more days post the second dose of the BNT162b2 vaccine; (2) those partially immunized, between 14 days after the first dose and before 7 days after the second dose. They were matched to unvaccinated controls based on similar dates of SARS-CoV-2 positive PCR, age, sex, ethnic sector, and geographic location. Complete genomic sequencing was performed for a total of 396 case-control pairs. Their results showed that the B.1.1.7 has become the predominant strain with increasing frequency over time, while the B.1.351 strain was found in only <1% of the samples. Partially immunized subjects had a significantly higher proportion of infection due to B.1.1.7 compared to the matched controls. Breakthrough infections in fully immunized cases had a higher proportion of B.1.351 (8:1).

Specific Comments:

The principal limitation of this study is in the design. Case-control studies cannot measure the incidence and so the authors stating that results showed increase incidence of variants B.1.1.7 and B.1.351 breakthrough infections is misleading. It is difficult to ascertain from a case-control study if confounding from unmatched parameters such as decreased adherence to nonpharmaceutical interventions by vaccinated subjects or other unidentified factors contribute to a higher representation of a more infectious strain (B.1.1.7) in breakthrough infections when vaccine protection may not be complete. Data from Israel show that vaccine protection against infection in the period between first and second doses of vaccine may only be 46%. In addition, due to prioritization by age/exposure risk in the vaccine roll-out, matching of vaccinated and unvaccinated controls could be inconsistent across time.

The study is also limited by selection bias since cases and controls were selected from samples available through the network and does not estimate the infection risk and hence cannot be used to estimate vaccine efficacy or lack thereof against B.1.351.

B.1.351 may be selected in fully vaccinated infected individuals, but the B.1.351 continued to stay less prevalent with increasing vaccination rates suggesting that it may not be able to overcome the increased transmissibility of the B.1.1.7. Given the rather low background rates of the B.1.351, it is difficult to draw any definitive conclusions. It is also unclear how many clinically symptomatic cases were included in the sample as they may have higher viral load and contribute more to spread than asymptomatic infections. Of note, this data was collected prior to the rather precipitous decline of cases in Israel and highlights the fact that even with the emergence of variants of concern, widespread immunization may limit the potential of such variants to cause large propagating surges in cases.

Conclusions:

This study endeavored to prove that B.1.1.7 and B.1.351 variants can overcome vaccine protection but, due to multiple intrinsic study design issues, such conclusions need to be validated in prospective trials.