Rapid Reviews COVID-19

Review 1: "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:

- **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.

Summary of the Report:

This report from Israel, which has led the world in providing COVID-19 vaccine to its population, is an attempt to answer a critically important question, which is the extent to which the COVID-19 vaccine (specifically the BNT162b2 mRNA vaccine) protects against variants of the SARS-CoV-2 virus that are “of concern.” Prior in vitro studies examining the ability of antibodies present in vaccinated individuals to neutralize such variants have produced mixed results, while a T-cell study did not find evidence of a reduction in the response to the variants examined. As new variants of SARS-CoV-2 develop and spread, in some instances becoming dominant, the ability of one or more such variants to “escape” vaccine-induced protection is of critical importance with regard to the deployment of COVID-19 vaccines, the possible need to re-formulate such vaccines, and the possible need to provide “booster” doses to vaccinated individuals.

The study compared the distribution of SARS-CoV-2 variants in partially vaccinated and fully vaccinated individuals to the distribution of variants in unvaccinated individuals. The authors found that among partially vaccinated individuals, there was an increased odds of being infected with the B.1.1.7 variant and that among fully vaccinated individuals, there was an increased odds of being infected with the B.1.351 variant of SARS-CoV-2, compared to unvaccinated individuals. The authors point to these results, taken to gather with the results of in vitro studies of SARS-CoV-2 neutralization, as evidence that such in vitro studies are a “good proxy for real-life protection” against variants of SARS-CoV-2. At the same time, the authors acknowledge that their study did not allow for the calculation of the effectiveness of the mRNA Covid-19 vaccine being used in Israel against infection with the various SARS-CoV-2 variants and that while “breakthrough cases among vaccine recipients

may be disproportionately caused by one or more variants of concern, vaccination efforts are, thus far, producing their desired effect on the rate of COVID-19."

Specific Comments

Assuming these results can be replicated elsewhere, this study provides important information regarding the possibility that variants of the SARS-CoV-2 virus can escape vaccine-induced protection. The results regarding partially vaccinated individuals (i.e. those who have not received or not had time to respond to a second dose of the vaccine) are also relevant to the discussion about extending the interval between the first and second doses of an mRNA Covid-19 vaccine in order to give a larger proportion of the population one dose of the vaccine sooner.

It is important to note, as alluded to above, that this study did not provide estimates of the effectiveness of either one or two doses of the BNT162b2 mRNA vaccine against infection with SARS-CoV-2 or against various levels of severity of resulting Covid-19 illnesses (e.g. effectiveness in preventing hospitalization ICU admission, and death). The report does not provide any information regarding what proportion of the infections caused by the various variants of SARS-CoV-2 resulted in a COVID-19 illness or in COVID-19 of various levels of severity. Thus, it is possible that the Covid-19 vaccine being used in Israel is still providing a high level of effectiveness and protection against severe cases of Covid-19, despite the circulation of one or more variants of concern of SARS-CoV-2.

Conclusions

The protection against SARS-CoV-2 infection and resultant Covid-19 illnesses induced by the BNT162b2 mRNA Covid-19 vaccine may differ, depending on which variant of SARS-CoV-2 is circulating and causing infection, reinforcing the need for close monitoring of the variants that are circulating and further studies of the performance of Covid-19 vaccines under "real-world" conditions, including studies of vaccine effectiveness, particularly against the more severe forms of Covid-19. If one or more variants of SARS-CoV-2 that can escape vaccine-induced protection begin to circulate, it may become necessary to formulate and administer booster or subsequent doses of vaccines formulated to ensure protection against such variants. In the meantime, continued use of the currently approved Covid-19 vaccines is a key component of the strategy for reducing the risk of Covid-19 illnesses, hospitalizations, and deaths in the U.S. and elsewhere.