Review 2: "BNT162b2 vaccine boosts neutralizing antibodies to ancestral SARS-CoV-2 & Omicron variant in adults received 2-dose inactivated vaccine"

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RR:C19 Evidence Scale rating by reviewers:

- **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:

Immune protection in vaccinated or previously SARS-CoV-2 infected population against the newly emerged Omicron variant has reduced dramatically. There is an urgent need to seek an immunization strategy for effective protection against this new variant of concern (VOC) of SARS-CoV-2. In the manuscript by Leung et al., the investigators presented preliminary results from a trial testing specific antibody levels to SARS-CoV-2 Omicron VOC upon a boost (third) immunization with BNT162b2 mRNA-LNP COVID-19 vaccine in a population that previously received 2-dose of inactivated vaccines. Adults who received two doses of inactivated vaccines 6 months earlier were administrated a boost of a third BNT162b2 dose, and antibodies were measured 4 weeks later. The authors showed that the third dose of BNT162b2 significantly increased anti-Omicron S protein antibodies and virus neutralization. This boost immunization also dramatically increased antibody levels to the ancestral SARS-CoV-2 strain. Furthermore, the booster dose with BNT162b2 had a well-tolerated safety profile. Together with growing evidence from other studies, this work suggests that the third dose of BNT162b2 mRNA-LNP vaccine in a population previously vaccinated with two doses of inactivated COVID-19 vaccines will likely provide effective protection against the Omicron VOC-induced disease progression. Given that inactivated COVID-19 vaccines are the most widely used vaccines globally, this study and others are significant in establishing a new vaccination scheme for Omicron VOC.

The study adopted an open-label single-arm design. The single-arm design is reasonable in this research setting due to the potential ethical issues of multi-arm design. However, the open-label design can be improved. Although participants and the study staff were aware of the vaccination type, as a minimum, the outcome assessors who measured the antibody should not be aware of the study. An objective third party can perform the measurements. The primary statistical analysis method

was Wilcoxon signed-rank tests, which were the correct choice, given the before-after nature of measurement and possible data skewness.

The manuscript could be benefited from the following improvement. First, the OD values in Figure 1A should be converted to specific units of antibodies (ng/ml, BAU/ml) to compare the data with other similar studies. Second, given that neutralization activities could target NTD of S protein, it would be informative to test binding activities to NTD of the S protein. Third, the significance could be enhanced by testing whether a third dose of BNT162b2 boosts anti-S specific CD4+ and CD8+ T cell responses and, if so, what are the fold increases. Fourth, published studies suggest that a 50% PRNT50 antibody titer at ≥ 25.6 corresponds to a threshold for 50% protection. A comparison of the results from this study and other similar studies is important to further solidify this heterologous vaccination scheme.