Review of: "Association of BCG vaccination policy and tuberculosis burden with incidence and mortality of COVID-19"

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This article tests the hypothesis that BCG vaccination and TB infection are associated with fewer COVID-19 cases and deaths, and concludes that this hypothesis should hold even after accounting for many confounding factors.
First, the authors should focus on the closely related work of Takahashi (2020):Role of latent tuberculosis infections in reduced COVID-19 mortality: Evidence from an instrumental variable method analysis - PMC (nih.gov). He investigated the hypothesis that latent tuberculosis infection (LTBI) was associated with lower COVID-19 mortality using the instrumental variable method to avoid the effect of unknown cofounding factors. The results showed with robust statistical support that LTBI was also associated with reduced COVID-19 mortality.

-General Comments-

1) Statistical problem: multicollinearity

They analyzed two types of estimation equations, one with both BCG Policy and TB Incidence as the independent valuable and the other with BCG Policy only as the independent variable. Let us examine Table 4 and Table 5, where the estimation results of growth factor analysis are reported. Comparing the p-values of estimates of BCG Policy variable provides that the p-values of BCG Policy only models more than 20 times greater than those of two independent variables models. This phenomenon typically indicates that there is a serious multicollinearity problem, and that the t-test does not work correctly. This is the reason why the coefficient estimates for TB Incident in the bivariate model become insignificant.

2) About dependent variable

Note that COVID-19 cases/deaths are detected by testing symptomatic or asymptomatic patients. Thus, these numbers will also depend on the frequency of COVID-19 testing, which varies widely from country to country. Accordingly, using the case fatality rate (CFR), defined as the ratio of the number of COVID-19 deaths per million people to the number of COVID-19 infections per million people, is more suitable.

3) Role of latent tuberculosis infection

Many countries with a relatively high incidence of TB infection, including Japan, require BCG vaccination during early childhood and most citizen of these countries also have LTBI, which is highly immunoprotected because of elicited innate

immune responses. In fact, TB infection leads to LTBI in 90%-95% of cases, while 5%-10% of individuals develop active TB disease. Furthermore, regional data reported by WHO indicate that the number of LTBI far exceeds the number of TB infections. This fact suggests that LTBI also play an important role in the mortality reduction of COVID-19, as Takahashi (2020) statistically demonstrated.

-Final evaluation-

The paper should be evaluated based on how much new knowledge it adds to the previous studies, especially Takahashi (2020). Based on the above comments, we must conclude that the contribution of this paper is unfortunately slight.