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Short Communication

# TB infection and BCG vaccination: are we protected from COVID-19?

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ABSTRACT

*Objectives:* The incidence of emerging coronavirus disease 2019 (COVID-19) disease is variable across the different parts of the world. Apart from travel patterns, other factors determining this difference may include host immune response. The aim of this study was to assess the effect of tuberculosis (TB) endemicity and Bacille Calmette-Guerin (BCG) coverage on COVID-19.
*Study design:* This was a cross-sectional study.
*Methods:* We reviewed available data regarding TB incidence, BCG coverage (as per the World Health Organization), and COVID-19 incidence of 174 countries. We divided the countries into four cohorts depending on annual TB incidence and BCG coverage.
*Results:* Countries with high TB incidence had lower COVID-19 than countries with low TB incidence. Similarly, countries with high BCG coverage had lower incidence of COVID-19, suggesting some protective mechanisms in TB-endemic areas. However, the ecological differences and different testing strategies between countries could not be accounted for in this analysis.
*Conclusion:* Higher TB incidence and BCG coverage were found to be associated with lesser incidence of COVID-19. This outcome paves the way for further research into pathogenesis and immune response in COVID-19.


The coronavirus disease 2019 (COVID-19) pandemic has affected countries across the globe but in a differential manner. Apart from traveling patterns, probable hypotheses postulated for the same have been temperature differences and the presence of Bacille Calmette-Guerin (BCG) vaccination in the immunization schedule of various countries.[1,2] Because BCG vaccination is commonly practiced in countries with higher tuberculosis (TB) burden, an apparent confounding factor for the same would be the presence of latent TB infection in the community. It is imperative to differentiate whether the decreased SARS-CoV-2 infection is related to BCG vaccination or latent TB, as it might give an insight regarding the pathogenesis of the disease. In this study, we evaluated the relationship of BCG coverage and TB incidence of 174 countries affected, with their COVID-19 incidence and case fatality rate (CFR).

This was a retrospective cross-sectional study and population data of all the countries affected by COVID-19 (174 countries), the number of cases, and the deaths due to COVID-19 as on 1st April 2020 were sorted from online platforms.[3–5] The TB incidence data were obtained from the world TB registry as available on the World Health Organization (WHO) website (after prior permission).[4] The data were managed and analyzed using Stata 14.0 statistical software. We stratified the countries based on TB incidence (low/high, low defined as <50 cases per 100,000 population) as well as BCG coverage (low/high, low defined as ≤60% coverage as per the WHO, or BCG not part of the immunization schedule of the country). A comparison of the distribution of quantitative variables between two categories of population density and TB incidence were made using the Wilcoxon rank-sum test.

As of 1 April 2020, the USA had a maximum reported COVID-19 cases (n = 163,199), while Libya, Papua New Guinea, Syria, Timor-Leste, Sierra Leone, and Saint Vincent and Grenada had the least (n = 1). Maximum deaths occurred in Italy (n = 12,430), while 62 countries reported no mortality. After stratifying the countries into four groups, i.e., low TB/low BCG (group 1), low TB/high BCG (group 2), high TB/low BCG (group 3), and high TB/high BCG (group 4), COVID incidence (per 100,000 population) and CFR (per 100 population) were analyzed. The median incidence (per 100,000

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**Table 1**
COVID-19 incidence (per 100,000 population) and case fatality rate (per 100 population) in relation to annual TB incidence (per 100,000 population) and BCG coverage of the country.

| Characteristic | Group 1 (low TB incidence, low BCG coverage) N = 38 | Group 2 (low TB incidence, high BCG coverage) N = 60 | Group 3 (high TB incidence, low BCG coverage) N = 5 | Group 4 (high TB incidence, high BCG coverage) N = 71 | *P*-value |
|---|---|---|---|---|---|
| COVID-19 incidence (per 100,000) | 46.60 (1.36–749.06) | 4.30 (0.005–132.51) | 0.04 (0.02–17.61) | 0.43 (0.01–85.46) | <0.001 |
| COVID-19 case fatality rate (per 100) | 1.42 (0–11.7) | 1.43 (0–25.0) | 0 (0–28.5) | 0 (0–33.3) | 0.09 |

Data are represented in terms of median (range).
Data were taken from the World Health Organization website, Global Tuberculosis Report, and https://www.worldometers.info/coronavirus.
BCG, Bacille Calmette-Guerin; COVID-19, coronavirus disease 2019; TB, tuberculosis.

population) of COVID-19 was 46.6 in group 1, 4.3 in group 2, 0.04 in group 3, and 0.43 in group 4, with a significant difference ($P < 0.05$) among all the groups except group 3 and group 4 ($P = 0.1$) Table 1. The median CFR was 1.42 in group 1, 1.43 in group 2, and 0 in group 3 and group 4, without any significant difference between the groups.

Our analysis demonstrated that high-TB-burden countries had a lower incidence of COVID-19, irrespective of the BCG vaccine status of the country. On the other hand, in low-TB-burden countries, BCG vaccine might confer protection against COVID-19. This probable relationship between TB and COVID-19 may be explained by cross-immunity between *Mycobacterium* species and COVID-19, which may be conferred by either latent or previous TB infection or BCG vaccination. Various vaccines including the BCG can produce positive non-specific immune effects leading to enhanced response against other non-mycobacterial pathogens such as the vaccinia virus. Another possible explanation is that COVID-19 and TB share the common Th1 immune pathway, and it seems plausible that latent TB infection or a past TB infection could lead to a better immune response to SARS-CoV-2.[6,7] As mentioned earlier, BCG vaccination for COVID-19 may have a protective role in low-TB-burden countries, thus suggesting a role of BCG vaccination as prophylaxis to individuals at high risk of COVID-19 and its complications in these countries. A clinical trial with this intent is already underway (https://clinicaltrials.gov/ct2/show/NCT04327206). This analysis has several limitations as the countries are in different stages of the disease, and it may be premature to infer the effect of TB endemicity on COVID-19 incidence. Second, the administrative strategies to prevent transmission of infection also vary significantly between countries. Some countries have resorted to aggressive testing and abandoning all social get-togethers, while others have not. It might have affected the exact incidence of disease, thus affecting our study outcomes. The number of countries in group 3 was low; thus, finding the BCG effect in high-TB-burden countries is not possible. We were also not able to account for the ecological differences between the countries while analyzing these data sets. The countries vary in the form of the age structure of the population, economic status, social practices between various subpopulations, and hygiene practices. All these factors may contribute to the variable occurrence of COVID-19. The United Kingdom (UK) has reported a significant proportion of deaths due to COVID-19 in minority populations such as blacks and Asians, which are more likely to have received BCG vaccination or had a history of previous TB, but the data on their duration of stay in the UK have also not been analyzed so far. Another issue is that the protection provided by BCG vaccine may also wane with age and thus predisposing the elderly population to a higher risk of disease. Finally, it is crucial to understand that these data only provide a correlation rather than a causal association, suggesting the need for prospective evaluation.

We conclude that there might be an association of low BCG coverage and low TB incidence with poor outcomes in COVID-19. Future research into the pathogenesis of COVID-19 may further improve our understanding of TB and COVID-19 relationship.

## Author statements

### *Ethical approval*

Ethical approval was not deemed necessary as this was an analysis of publically available data. WHO data was used after obtaining prior permission.

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### *Competing interests*

None declared.

### *Authors' contribution*

All the authors have contributed equally.

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