

Tuberculosis endemicity and BCG vaccination: Protection against COVID-19

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Abstract

The coronavirus disease 2019 (COVID-19) has affected different countries in a differential manner. The host susceptibility and host factors are important parameters for this variability. This study aimed to assess the effect of tuberculosis (TB) endemicity and Bacille Calmette-Guerin (BCG) coverage on COVID-19. Available data regarding TB incidence, BCG coverage (as per the World Health Organization), and COVID-19 incidence of 168 countries as of 19th September 2021 was

collected. Countries were divided into four cohorts based upon annual TB incidence and BCG coverage and COVID-19 incidence and case fatality rates were compared using the Kruskal-Wallis test. Countries with low TB incidence and low BCG coverage had the highest COVID-19 incidence per lac population. However, no significant difference was seen in COVID-19 cases fatality rate. Higher TB incidence and BCG coverage were associated with lesser incidence of COVID-19. This result paves the way for research into pathogenesis and host immune response in COVID-19.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic had its origin in Wuhan, China and had rapidly spread across the globe to be declared a pandemic soon. Even today, it continues to remain a significant health care issue affecting most of the countries across the globe. Despite its spread across the world, there has been a differential pattern of spread, suggesting some environmental or host factors might be contributing to the transmission and severity of illness [1]. Several studies have assessed the role of various environmental factors, including temperature and humidity, in the transmission of SARS-CoV-2. Similarly, among the host factors, childhood vaccination against tuberculosis in the form Bacille Calmette-Guerin (BCG) has been studied and is hypothesized to confer protection from COVID-19 [2]. BCG vaccination in childhood leads to activation of cell-mediated immunity and provides protection from tuberculosis. Childhood vaccination with BCG has been hypothesized to be protective from COVID-19 due to non-specific immune response including innate and cell-mediated immune response. In contrast to the adaptive immunity, based on the antigen-specificity, innate immune cell populations may exhibit heterologous memory responses triggered upon microbial exposure. Establishing the role of BCG in providing protection from COVID-19 will pave way for further research into its role as immunomodulator. The endemicity of tuberculosis has also been thought to be associated with a lesser incidence of COVID-19. These two factors may lead to better trained adaptive immunity and need further studies. Several studies have assessed these parameters; however, most of them are limited by the fact that they were conducted in the early part of the pandemic, wherein the extent of disease transmission was yet to be seen well [2,3]. In this epidemiological study, we evaluated the relationship between TB endemicity and BCG vaccination coverage of the affected countries and the COVID-19 incidence and mortality to identify if they confer protection from COVID-19.

Methods

This was an ecological study evaluating the relationship of BCG vaccination and TB infection with COVID-19 epidemiology. We used the online platforms for data collection for all the countries affected by COVID-19 for whom population data, number of COVID-19 cases and deaths due to COVID-19 was available as of 19th September 2021 since the first case of COVID-19 in those countries [4-6]. The incidence of tuberculosis and BCG coverage data in these countries were obtained from the TB registry as maintained by World Health Organization (WHO) on its website [5]. We included 168 countries in our analysis as complete data including COVID-19 incidence, tuberculosis incidence and BCG vaccination coverage were available only for them. The countries were classified based upon the incidence of tuberculosis (less than or more than 50 cases per 100,000 population) as well as BCG coverage (low or high). Low BCG coverage was defined as <60% coverage as per the WHO, or BCG not being part of the routine immunization schedule of the country. Based upon these two parameters, the countries were divided into 4 subgroups: low TB/ low BCG (group 1, 37 countries), low TB/ high BCG (group 2, 58 countries), high TB/ low BCG (group 3, 5 countries), and high TB/ high BCG (group 4, 68 countries). All the data were extracted on an excel spreadsheet by two investigators (TKB and SM) and the Stata 14.0 statistical software was used for statistical analysis. The distribution of quantitative variables between the two categories of tuberculosis incidence and BCG coverage were compared using the Kruskal-Wallis test.

Results

As of 19th September 2021, the USA had reported maximum cases of COVID-19 (n=42,866,805), followed by India reporting a total of 33,448,163 COVID-19 cases. The USA reported the maximum number of deaths (n=691,562), followed by Brazil and India. After stratifying the countries into four groups the incidence of COVID-19 (per 100,000 population) and case fatality rate CFR (per 100 population) were analyzed. The median (interquartile range) incidence per 100,000 population of COVID-19 was highest in group 1 at 8039.12 (4163.32-10901.71) while it was lowest in group 3 being 98.90 (87.19-120.45), with a significant between-group difference ($p < 0.00001$) (Table 1). There was no significant between-group difference in the median case fatality rate ($p = 0.11$).

Discussion

In this correlational analysis, we found that countries with a high incidence of tuberculosis had a lower incidence of COVID-19 as compared to countries with lower tuberculosis incidence. This relationship between TB and COVID-19 might be explained by the enhanced innate immune response in individuals with higher community transmission of tuberculosis due to repeated exposures and active immune systems. Various childhood vaccines, including BCG, can produce a non-specific innate immune response, leading to an enhanced response to other pathogens, including SARS viruses. Also, as the Th1 immune pathway confers protection from TB and COVID-19, the latent TB infection may be associated with a higher adaptive immune response against SARS CoV-2 [7,8]. Many countries with a low tuberculosis burden do not have BCG immunization in their routine schedule, which might be associated with increased incidence and/or severity of COVID-19 [9]. Whether the institution of BCG vaccination to boost non-specific innate and adaptive immune response will help curb COVID-19 is one question that needs to be answered yet. Whether such BCG vaccination will protect from other viruses such as influenza also needs to be studied in prospective studies. The ACTIVATE trial demonstrated that BCG vaccination in elderly individuals was associated with reduced infections, including respiratory tract viral infections [10]. Multiple studies evaluating the role of BCG for the prevention and treatment of COVID-19 are being undertaken (<https://clinicaltrials.gov/ct2/show/NCT04327206>) [11].

There have been multiple attempts at assessing the role of latent TB and BCG in prevention from COVID-19 [11,12]. However, our analysis provides up to date data on the same, especially since the pandemic has probably crossed its peak in most countries and is likely to represent the true picture around the globe till we get controlled prospective studies on BCG.

This study has several limitations as well. The reporting of COVID-19 cases and mortality varies widely between countries, affecting the exact numbers used in the analysis. Also, the testing strategies and positivity rates vary widely and will affect the number of cases reported. The effect of lockdown strategies in different countries was also not assessed. Also, since late 2020, several countries, including the USA, started vaccination against COVID-19. We did not assess the effect of the disease occurrence before and after initiation of COVID-19 vaccination. Since the initiation timing, COVID-19 vaccination coverage and type and efficacy of vaccines varied significantly between countries with time, it was not feasible to consider the effect of COVID-19 vaccination on this analysis. The number of countries with high TB incidence and low

Table 1. COVID-19 cases (per 100,000) and case fatality rate (per 100) in the countries grouped according to TB incidence and BCG coverage.

	Group 1 (low TB incidence, low BCG coverage) N. of countries =37	Group 2 (low TB incidence, high BCG coverage) N. of countries =58	Group 3 (high TB incidence, low BCG coverage) N. of countries =5	Group 4 (high TB incidence, high BCG coverage) N. of countries =68	p-value
COVID-19 cases (per 100,000)	8039.12 (4163.32-10901.71)	6561.43 (2999.49- 8874.07)	98.90 (87.19-120.45)	803.08 (283.38- 2975.74)	<0.00001
COVID-19 case fatality rate (per 100)	1.38 (0.88-1.82)	1.49 (0.88-2.41)	3.46 (1.31-5.59)	1.75 (1.24-2.75)	0.11

Data is represented in terms of median (interquartile range).

BCG vaccination rates was very small, so this group did not contribute much to the analysis. The ecological variations in the countries, including population mobility, age structure, financial status, and adherence to COVID-19 appropriate behaviour, also varied between countries and were not accounted for in our analysis. Also, elderly individuals may be at a higher risk of morbidity and mortality due to SARS-CoV-2 infection as the protection provided by the BCG vaccine may wane with age. This age effect also could not be analysed in our study.

To conclude, countries with low BCG coverage and low TB incidence had a higher incidence of COVID-19 and further research into the host factors modulating the pathogenesis of COVID-19 is needed to elucidate the role of BCG and TB infection in the occurrence of COVID-19.

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