

Original Article

Does the Bacillus Calmette–Guérin vaccine provide protection from COVID-19?

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ABSTRACT

Objective: The novel coronavirus pandemic is ravaging throughout the world. It has infected more than 1.2 million people and killed more than 64,000. Frantic research is underway to find prevention and cure. Of late, Bacillus Calmette–Guérin (BCG) has been speculated as a possible protection from COVID-19. We sought to investigate the evidence behind the claim.

Material and Methods: Data were collected regarding the total number of COVID-19 cases per million and total number of COVID-19 deaths per million in various countries. The BCG vaccination policies of these countries were also obtained.

Results: It was seen that the countries with no universal BCG policy had a mean 1272.9 (median 795) cases per million and 80.7 deaths (median 18) per million population. On the contrary, the countries with a universal BCG vaccination policy had a mean 131.2 (median 40) cases per million and 4 deaths (median 1) per population. The difference is highly significant ($P < 0.001$).

Conclusion: The data strongly support the hypothesis that BCG may offer protection from COVID-19. Heterologous protection offered by BCG through production of trained immunity, epigenetic reprogramming of monocytes, non-specific activation of NK cells, and increase of pro-inflammatory cytokines (particularly, tumor necrosis factor [TNF]-alpha and interleukin 1 beta) production may be the mechanism behind its cross-protection against the novel coronavirus.

Keywords: Novel coronavirus, Severe acute respiratory syndrome coronavirus-2, COVID-19, Bacillus Calmette–Guérin, Tuberculosis

INTRODUCTION

The recent COVID-19 pandemic has been ravaging relentlessly around the world. A total of 1,202,715 people have been infected and 64,734 people have been killed by the novel coronavirus.^[1] As such tremendous research is underway to find prevention or cure. Recently, there has been considerable interest on whether Bacillus Calmette–Guérin (BCG) vaccine provides any immunity to COVID-19.^[2] We sought to study whether there is in fact any significance to the claim that BCG provides immunity to COVID-19. Furthermore, it must be remembered that BCG is in fact a strain of *Mycobacterium* species (live-attenuated strain obtained from *Mycobacterium bovis*). Hence, we also tried to study that whether it is specifically BCG that is providing the immunity, or is it the *Mycobacteria* species (for example, latent or subclinical *Mycobacterium tuberculosis*), in general, that is providing the protection against COVID-19?

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MATERIAL AND METHODS

Data on the “total number of COVID-19 cases per 1 million population” and “total number of COVID-19 deaths per 1 million population” of different countries were obtained from an online source.^[1] Data on the “BCG policy,” “incidence of TB/1,000,000 population,” and the “income group according to World Bank data” of these countries were obtained from another online source. Countries with a total case fatality 20 (on the date of the study) were included.^[3]

The countries were divided into two groups: Group A containing the countries “where universal BCG policy is in practice at present” and Group B containing the countries “where universal BCG policy is not practiced at present.” We compared the “total number of COVID-19 cases per 1 million population” as well as the “total number of deaths per 1 million population” between Groups A and B to look for any statistical significance. Subsequently, we divided the countries with “no universal BCG policy” into two groups: Group C containing the countries where “universal BCG policy was previously present, but has now been stopped” and Group D containing the countries where “universal BCG policy was never present.” The number of COVID-19 cases per 1 million population in Group C and Group D was compared to look for any statistically significant difference. Similarly, the number of deaths per million was also compared between Groups C and D. Eventually, we grouped all the countries into two groups: The first group (Group E) comprising “countries where incidence of tuberculosis is $\leq 20/1,000,000$,” i.e., countries with low incidence of tuberculosis and the second group (Group F) comprising nations “where the incidence of tuberculosis is $>20/1,000,000$,” i.e. countries with higher incidence of tuberculosis). We compared the “total number of COVID-19 cases per 1 million population” as well as the “total number of deaths per 1 million population” between Groups E and F.

Statistical analysis

The data in the two groups were tested for statistical significance using the Mann–Whitney U-test. An online software was used to analyze the data available at http://www.statskingdom.com/170median_mann_whitney.html.

RESULTS

At the time of the study, 50 countries had a total COVID-19 deaths of ≥ 20 . Out of these, 21 countries do not have a universal BCG vaccination policy at present, whereas 29 countries have it. Out of the 21 countries with no universal BCG policy, 20 countries are from high-income group and one country is from upper middle-income group. Out of the 29 countries with universal BCG vaccination, 7 are from high income, 15 are from upper middle, and 7 are from lower middle-income group. The countries where universal

BCG vaccination is not practiced have a mean COVID-19 positive cases of 1272.9 (standard deviation 1557.9) per 1 million population with a median of 795. The countries where universal BCG vaccination is practiced have a mean COVID-19 positive cases of 131.1 (standard deviation 208.7) per 1 million population with a median of 40. The difference is statistically significant ($P < 0.001$) [Figure 1a]. The countries where universal BCG vaccination is not practiced have a mean COVID-19 deaths of 80.7 (standard deviation 180.8) per 1 million population with a median of 18. The countries where universal BCG vaccination is practiced have a mean COVID-19 positive deaths of 4 (standard deviation 7.6) per 1 million population with a median of 1. The difference is statistically significant ($P < 0.001$) [Figure 1b].

Out of the 21 countries with no universal BCG vaccinations policy, 15 countries had universal BCG vaccination policy in the past but have stopped the practice at present (Group C); five countries never had universal BCG (Group D) and data were not available about one country (San Marino). The difference in the “number of cases per 1 million” between Group C and Group D was not statistically significant ($P = 0.8$). Similarly, the difference in the “number of deaths per 1 million” between Groups C and D was also not statistically significant ($P = 0.2$).

Out of the 50 countries included in the study, the incidence of tuberculosis is $\leq 20/1,000,000$ population in 29 countries (Group E) and $>20/1,000,000$ population in 21 countries (Group F). The difference between the “total number of cases per million population” in Group E and Group F was statistically significant ($P < 0.001$) [Figure 1c]. Besides, “the total number of deaths per million population” between Groups E and F was also statistically significant ($P < 0.001$) [Figure 1d and Table 1].

DISCUSSION

The study shows that there are a significantly lower number of cases as well as deaths in countries where universal BCG policy is being practiced. Hence, it can be possibly concluded that BCG vaccination provides a cross-protection against COVID-19. However, a detailed study into the epidemiological parameters of the countries which had universal BCG vaccination policy in the past (but have stopped universal BCG as of now) revealed enigmatic result. The earliest to stop universal BCG was Sweden which stopped it in 1975.^[3] It means that almost all people aged >45 years in Sweden have received BCG vaccination in their childhood. In fact, most of these countries have stopped universal BCG vaccination around the 1990s which means that most of the people aged around 30 years or more (in these countries) have received BCG vaccination in their childhood. France is one of the last countries to have stopped universal BCG in the year 2007.^[3]

Table 1: Number of COVID-19 cases per million population and number of COVID-19 deaths per million population in the different groups of countries.

Group	Criterion (UBV)	Number of countries	Number of cases per million population			Number of deaths per million population		
			Mean	SD	Median	Mean	SD	Median
A	UBV given	29	131.2	208.7	40	4	7.6	1
B	UBV not given	21	1272.9	1557.9	795	80.7	180.7	18
C	UBV given previously but stopped at present	15	1002.5	970.9	718	32.9	50.6	16
D	UBV never given	5	947.6	597.9	795	75	85.6	68
E	Countries with TB incidence of $\leq 20/1,000,000$	29	980.6	1408.4	567	60.6	156.5	15
F	Countries with TB incidence of $> 20/1,000,000$	21	99.9	179.9	25	2.6	4.1	1

UBV: Universal BCG vaccination, BCG: Bacillus Calmette–Guérin, TB: Tuberculosis

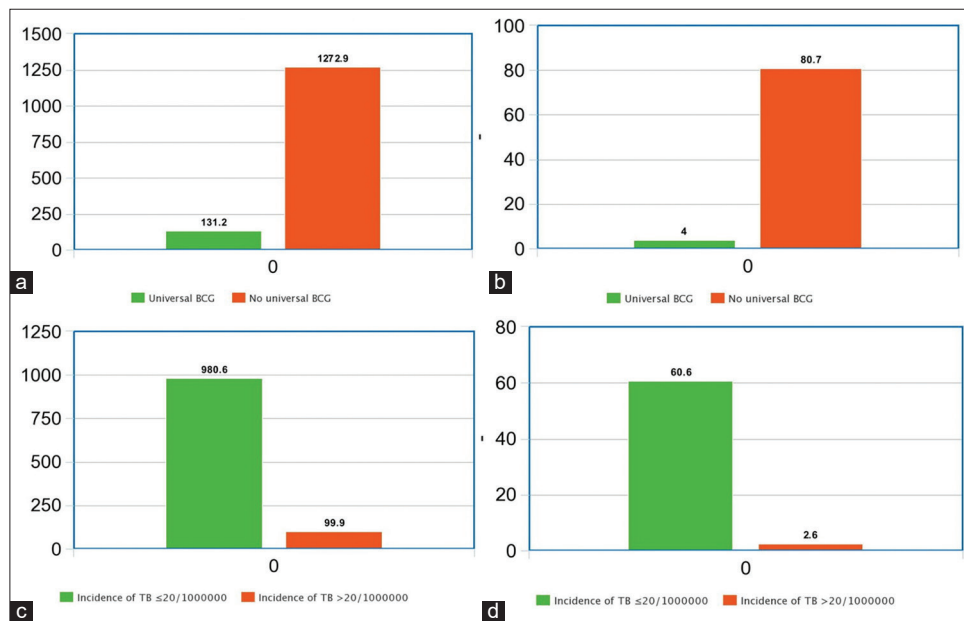


Figure 1: (a) Mean number of cases per million in countries with universal Bacillus Calmette–Guérin (BCG) versus those without. (b) Mean number of deaths per million in countries with universal BCG versus those without. (c) Mean number of cases per million in countries with tuberculosis (TB) incidence of 20/1,000,000. (d) Mean number of deaths in countries with TB incidence of 20/1,000,000.

As such, every French citizen >13 years of age must have received BCG vaccination, but even then France ranks 4th in the total number of cases per million population (only after Italy, Spain, and the US).^[1] The study also shows that the “total number of cases” as well as “the total number of deaths” per million are significantly lower in countries with a high incidence of tuberculosis. It must be remembered that not all countries with a high incidence of tuberculosis are practicing universal vaccination (for example, Ecuador has an incidence of 52/1,000,000, but has no universal BCG policy) and not all countries with low incidence of tuberculosis have stopped giving universal BCG (for example, Hungary, Ireland, Greece, etc.).^[3] In fact, no significant difference in COVID-19 parameters was observed between countries where was never a universal BCG policy versus countries which have recently stopped

universal BCG. Surprisingly, COVID-19 infection rates and death rates were significantly lower in countries with a higher incidence of tuberculosis, irrespective of whether universal BCG is given there or not.

BCG provided heterologous or non-specific immunity against a host of non-mycobacterial disease conditions such as viral infections and sepsis.^[4] In a study in West Africa, Kristensen *et al.* found that BCG provided increased survival in children than could be attributed to the protection against only tuberculosis.^[5] BCG has been shown to induce T-cell-independent protection against secondary infections with *Candida albicans* or *Schistosoma mansoni* in mice.^[6] BCG is also known to produce non-specific protective effects through innate immunity-dependent mechanisms in malignancies such as bladder cancer, melanoma, leukemia, and lymphoma.^[6] Kleinnijenhuis

et al. found that BCG induces epigenetic reprogramming of monocytes, thereby resulting in an increase of pro-inflammatory cytokines (particularly, TNF-alpha and interleukin-1 beta) production in response to non-related pathogens. They concluded that BCG produces sustained changes in immune system, leading to a non-specific response to infections both at the level of innate trained immunity and heterologous Th1/Th17 responses.^[7] BCG also causes the activation of NK cells, leading to increased production of pro-inflammatory cytokine in response to mycobacteria and other unrelated pathogens. It has previously been shown that BCG provides non-specific protection against *C. albicans* in mice at least partially through NK cells. BCG produces an increase in inflammatory mediators from monocytes in healthy volunteers, which correlated with parallel changes in a histone modification associated with gene activation. Hence, these non-specific (or heterologous) effects show that BCG induces trained immunity that protects against unrelated pathogens.

Whether other mycobacterial infections (for example, latent or subclinical tuberculosis) provide any cross-protection against COVID-19 or other unrelated infections are a matter of conjecture. The medical literature is excessively scanty in that regard. However, Tarancon *et al.* found that MTBVAC, genetically modified form of *M. tuberculosis*, is able to produce trained immunity.^[8] Baldrige *et al.* showed that during an infection with *Mycobacterium avium*, there is an increased proliferation of long-term repopulating hematopoietic stem cells, a response that requires increased interferon-gamma (IFN γ) signaling.^[9] Khader *et al.* noted that innate immune cells, namely, myeloid cells and NK cells undergo functional adaptation (trained immunity) after infection (with *M. tuberculosis*) or vaccination with BCG.^[10] Besides, it is well known that various infections like malaria can also induce a state of hyperresponsiveness that is functionally equivalent to the induction of trained immunity. For example, herpesvirus latency increases resistance to the bacterial pathogens *Listeria monocytogenes* and *Yersinia pestis* by increased production of IFN γ and systemic activation of macrophages.^[6]

Limitations

The health-care system, COVID-19 testing rate, and age profile of the populations of the different countries may be confounding factors. The strain of BCG used in each country was not taken to consideration. Different countries may be at different stage of the pandemic at the time of writing the article. Hence, the infection and death rates may increase in some countries in future.

CONCLUSION

From the study, it is concluded that cross-protection against COVID-19 by the BCG vaccination is a very strong possibility

and hence it must be properly explored through randomized controlled trials. Besides, a prevalence of mycobacterial infections (either by BCG or by latent/subclinical/clinical tuberculosis) may also possibly contribute to some protection against COVID-19.

Declaration of patient consent

Patient's consent not required as the patient's identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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