Review Article

Does Bacille Calmette–Guérin Vaccination Provides Protection against COVID-19: A Systematic Review and Meta-analysis

Daisy Khera, Ankita Chugh[1], Sameer Khasbage[2], Surjit Singh[2]

Departments of Pediatrics, [1]Dentistry and [2]Pharmacology, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India

Abstract

Background: Lower morbidity and mortality in few geographic locations on the globe suffering with SARS-CoV-2 has been associated with the existing or previously followed long-standing Bacille Calmette–Guérin (BCG) vaccination policy among infants. However, does it hold true that today after years of BCG vaccination, few adults have better prognosis or is it just confounding due to differential disease burden, population density, testing facilities, or improper reporting. The purpose was to evaluate and correlate this effect systematically. **Methods:** Detailed electronic search for randomized controlled trials (RCTs) and observational studies in PubMed, Cochrane Library, and ClinicalTrials.gov for eligible studies was performed. **Results:** One hundred and fourteen studies were yielded on search strategy and 28 observational studies were finally included for analysis. From our results, we can say that BCG vaccination causes a decrease in COVID-19 incidence and mortality. However, these results must be interpreted cautiously as lot of confounding factors were present in included studies, which can affect the outcome. **Conclusion:** The evidence of BCG vaccination for the protection against COVID-19 cannot be ruled out as evidence from many studies support the hypothesis, but the evidence of well-conducted RCTs and observational studies can strengthen the evidence.

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Keywords: BCG, COVID 19, morbidity, mortality

Introduction

COVID-19 pandemic that began in December 2019 from a localized city, Wuhan, China, has spread worldwide to become a global threat and is still showing dubious patterns in terms of its spread and severity of infectivity. It has become a dynamic situation with many answers yet to be found. Whether any existing vaccine can provide an innate or trained immunity was a matter of concern.

Bacille Calmette–Guérin (BCG) vaccination in wide use among infants for prevention against tuberculous meningitis and disseminated tuberculosis since 1921 is known to offer heterologous protection against other diseases, especially of respiratory origin.[1] Nations in the world that do not have universal BCG vaccination policy (BCGVPC), like Italy and USA, have had higher COVID-19 mortality than countries with long-standing universal BCG vaccination programs, such as South Korea and Japan.[2] Even the countries that withdrew universal BCG vaccination program, due to decrease in the incidence of tuberculosis, have reported increased number of cases and deaths due to COVID-19, compared to the ones that retained BCG as a part of at-birth vaccination policy.[3] This geographical variation triggered anxiousness about the mechanism by which this trained immunity enhances body's innate response. BCG may lead to heterologous immunity with antigen-independent mechanism of B and T cells stimulation. It could also cause long-term activation, programming, and memory of natural killer cells. Hence, metabolic and epigenetic changes induced by this live vaccine might cause decreased viral load of SARS-COV-2, thus decreasing severity.

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Address for correspondence: Dr. Ankita Chugh, Department of Dentistry, All India Institute of Medical Sciences, Jodhpur - 342 005, Rajasthan, India.
E-mail: ankitamody@gmail.com

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Most scientists speculate that protection by BCG vaccination against COVID-19 is due to nonspecific effects of BCG vaccine. On the contrary to obvious correlation between SARS-CoV-2 and BCG, many believe the variations in epidemiological data are influenced by various factors such as burden of disease, differing phases of the pandemic in various countries, testing rates, and other demographic differences. Hence, these are prone to confounders and bias and vested political and economic concerns are at stake. Other reasons presented by authorities not accepting this correlation are an implausible and questionable theory that how BCG vaccine administered decades back can alleviate severity of COVID in today's elderly.[4]

However, conclusion drawn from many observational studies of reduced mortality rates of COVID-19 in countries having universal BCGVPC compared to that of the countries without it cannot be negated completely. A thorough and systematic evaluation of the COVID data available from both set of nations is the aim of this review.

Methods

Electronic search in PubMed, Cochrane Library, and ClinicalTrials.gov for eligible studies was performed on August 17, 2020, with restriction to English language. Bibliography search was done for the included articles to find other studies.

Search strategy was synthesized using the terms SARS-CoV-2, COVID-19, and BCG vaccination. Two authors independently assessed the articles for inclusion and exclusion criteria and extracted data. All types of studies except case reports and case series were included. Any discrepancy was resolved with the help of the third author. We were unable to perform meta-analysis of all outcomes for the included studies as the outcomes were not similar across studies. Many of the studies have studied only correlation and not the number of events with regard to mortality rates. However, we performed meta-analysis to provide pooled estimate of correlation of mortality with BCGVPC from 4 studies which had given the correlation (r) values.

Results

Evidence from studies

A total of 28 studies were included [Figure 1]. The studies in which correlation between COVID-19 mortality and morbidity with BCG vaccination was analyzed were included.

Mortality benefit

The characteristics and outcome data of studies[2,5-31] are represented in Tables 1 and 2. According to Miller *et al*., death per million was significantly less in higher income countries with BCGVPC compared to non-BCGVPC countries. Hensel *et al*. also showed lower mortality due to COVID-19 with BCGVPC compared to no or past BCGVPC, but did not achieve statistical significance. Analysis done by Goswami *et al*. interpreted that no significant difference occurred in COVID-19 mortality in BCG vaccination countries with <95% vaccination coverage versus >95% coverage. However, significant difference was observed in European and American countries for COVID-19 mortality. A negative correlation, i.e. decreased mortality in BCGVPC, was shown by many.[5,9,16,17]

Number of cases

Miller *et al*. evaluated that cases per million were significantly less in higher income countries with BCGVP compared to non-BCGVP. Hegarty *et al*. demonstrated that COVID-19 cases in BCGVPC were significantly lower as compared to non-BCGVPC. Madan *et al*. interpreted that countries having greater BCG coverage had lesser incidence of COVID-19. Furthermore, interestingly, they compared TB incidence with COVID-19, high TB incidence resulted in lower COVID-19 cases. Samrah *et al*. showed that significantly more asymptomatic patients had received BCG vaccine than symptomatic ones. Weng *et al*. exhibited that patients with BCG vaccination were less hospitalized for COVID-19 than no BCG vaccination. However, contrary results were also observed. Hamiel *et al*. study findings showed that there was no significant difference in cases of COVID-19 in BCG-vaccinated patients and patients who were not BCG vaccinated.

From the above results, we can say that BCG vaccination causes a decrease in COVID-19 incidence and mortality. However, these results must be interpreted very cautiously as there are lot of confounding factors too in various studies, which can affect the outcomes.

Only four studies have reported correlation values. Pooled correlation revealed a significant negative correlation of COVID-19 mortality with BCG vaccination (random effect pooled $r = -0.48$ [95% confidence interval = −0.61 to −0.35]) [Figure 2].

Discussion

A number of observational studies have reported inverse correlation between BCG vaccination program and SARS-CoV2 infections.

Miller *et al*.[2] found that countries with higher income having a current universal BCG program (55 countries) had fewer deaths per million people. Higher income countries without a universal BCG program (5 countries) had a greater number of deaths. The number of cases per million inhabitants was 4 times higher in the higher income countries without a universal BCG program. Berg *et al*.[5] in their analysis showed that mandated BCG vaccination is associated with decreased incidence of COVID-19. They controlled for age, gross domestic product per capita, density and size of population, rate of migration, and other cultural factors in their study.

Sala *et al*.[22] employed multiple regression analysis to control for potential confounders and found that BCGVPC is associated with reduction in both incidence and mortality due to COVID-19. Shet *et al*.[26] used linear regression

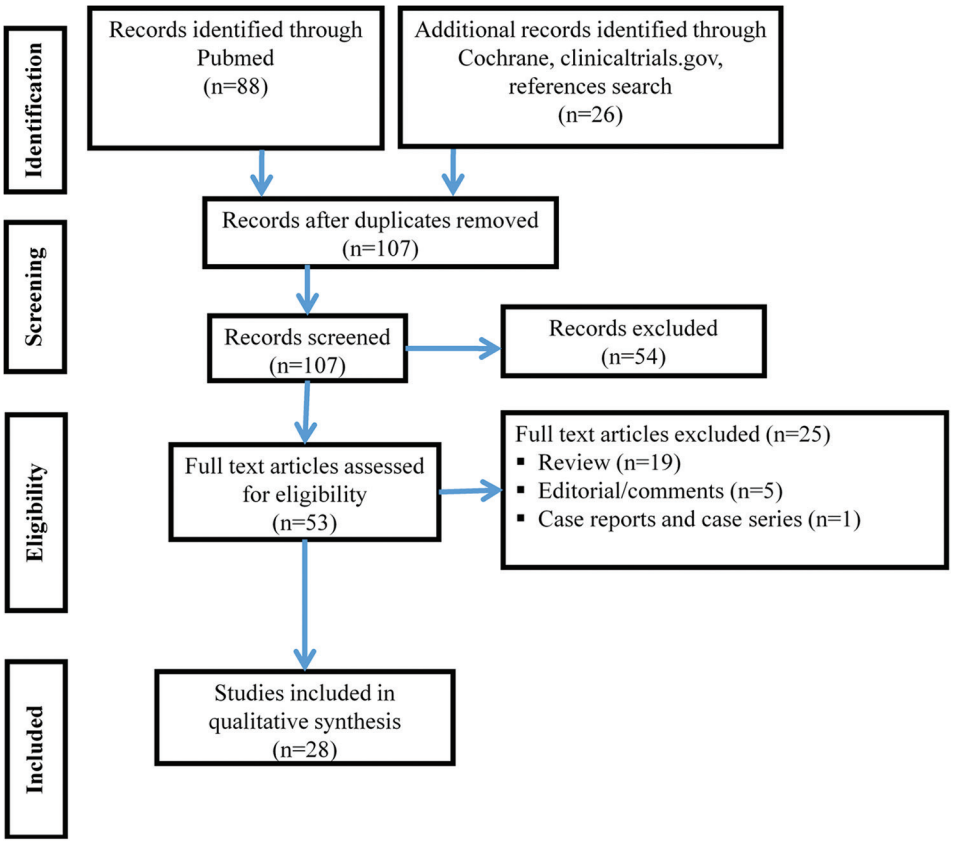

Figure 1: PRISMA flow diagram of study selection for systematic review

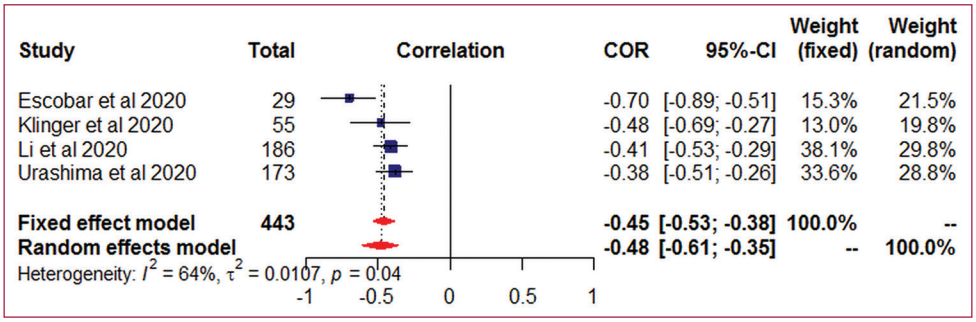

Figure 2: Pooled analysis of correlation of countries with Bacille Calmette-Guérin vaccination policy versus mortality

model to adjust for confounders such as GDP per capita and proportion of elderly and assessed the association between BCG vaccination and mortality with COVID-19. Mortality per million population was 5.8 times less in countries with BCG vaccination programs versus countries without any BCG vaccination policies. Dayal *et al*.[7] in their study observed a significant decrease in mean case fatality rate with BCG vaccination. Goswami *et al*.[10] found that in US and European world, countries with greater coverage of population with BCG vaccine resulted in significant decrease in mortality in comparison to countries with population having poor BCG coverage. Hegarty *et al*.[13] found that incidence and mortality in countries with BCG vaccination was much lower than the countries without such a program. Similar results with significantly lower mortality were reported.[21,24,28,29]

There are few studies which could not establish a correlation of BCG vaccination with COVID-19. Hensel *et al*. included countries performing more than 2500 COV-2 tests per million population in their analysis and found no significant association between numbers of COVID-19 cases per million population with BCG vaccination. Kirov *et al*.[15] performed linear regression for cofactors and COVID-19 cases and mortality and significant correlation was observed with income level and median age but not with BCG policy. Szigeti *et al*. were unable to establish correlation between COVID-19 case fatality rates and the period of introduction of universal BCG vaccination programs.[27] Meena *et al*. adjusted for confounding variables such as age, comorbidities such as diabetes mellitus, cardiovascular diseases, gross domestic product, hospital beds, and number of beds as per

Table 1: Studies evaluating the effect of Bacillus Calmette-Guerin vaccination in COVID-19 included in systematic review

Author and year (study design)	Institution/Country of study conduct	Study interventions and control; study population characteristics	Study outcomes/Limitations
Miller *et al*., 2020[2] (observational)	NYIT College of Osteopathic Medicine, New York Institute of Technology, Old Westbury, New York, USA	Countries with BCG vaccination policy (BCGVPC) versus without BCG vaccination policy (non-BCGVPC). COVID-19 patients: Middle high- and high-income countries=BCG policy (*n*=55 countries) Middle high- and high-income countries=No BCG policy (*n*=5 countries)	DPM in middle high- and high-income countries with BCG versus no BCG policy: 0.78±0.40 versus 6.39±7.33 (mean±SEM); (*P*=8.64e-04, Wilcoxon rank sum test) CPM inhabitants in middle high- and high-income countries with BCG versus no BCG policy: 59.54±23.29 versus 264.90±134.88 (mean±SEM); (*P*=0.0064, Wilcoxon rank sum test) CPM Inhabitants low-income levels countries (18): 0.32±0.09 Limitations: Under reporting in low-income countries, more RCT required with BCG for COVID-19
Berg *et al*., 2020[5] (observational)	Johns Hopkins University Center for Systems Science and Engineering	Countries: BCG mandated policy versus non-BCG mandated policy Two categories of BCG policy countries status Current versus combined (past and none) Past versus none	Growth rate COVID-19 cases: Negative correlation of COVID-19 cases with BCG vaccination: b=−0.039, *P*<0.001 No significant correlation in growth rate of case between past versus none BCG policy: b=−0.009, *P*=0.610 Growth rate of Death due to COVID-19: Significant negative correlation of death rate with BCG vaccination: b=−0.059, *P*<0.001 No significant correlation in growth rate of deaths between past versus none BCG policy: b=−0.007, *P*=0.772 Limitations: Underreporting of cases, confounding factor cultural dimensions
Covián *et al*., 2020[6] (observational)	Millennium Institute on Immunology and Immunotherapy, Santiago, Chile	Countries with BCGVPC versus non-BCGVPC Countries with BCG vaccination policy (*n*=22) versus countries without BCG policy (*n*=16)	CPM inhabitants: Significant difference between BCG and non-BCG DPM inhabitants: Significant difference between BCG and non-BCG Limitations: Amount of testing, social distancing measures, demographic distribution of country
Dayal and Gupta 2020[7] (observational)	Postgraduate Institute of Medical Education and Research, Chandigarh, India	No BCG policy countries versus past BCG policy countries Two categories: High COVID-19 burden countries (high CFRs) (*n*=12) versus countries with BCG revaccinations (*n*=12)	CFR: Between two groups: 5.2% versus 0.6%, *P*<0.0001 Limitations: Not representing true CFR, oversimplification of interpretation
Ebina-Shibuya *et al*., 2020[8] (observational)	National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, USA	BCGVPC versus past BCG vaccination countries versus non-BCGVPC Two categories: CRC (*n*=27) and CNRC (*n*=23)	Median (IQR) mortality/1 million population: CRC versus CNRC: 2.1 (0.7-8.0) versus 42.6 (13.1-139.3), Mann-Whitney *P*<0.001 Median (IQR) mortality: Never recommended countries > previously recommended countries: 46.5 (56.6-260.5) >2.1 (0.7-8.0) Limitations: Selection bias in the study participants
Escobar *et al*., 2020[9] (observational)	Virginia Polytechnic Institute and State University, Blacksburg, VA	BCGVPC versus past or non-BCGVPC in socially similar European countries (*n*=22) and America (US vs. Latin America)	BCG index and COVID-19 mortality: Negative correlation: R^2=0.49, *P*<0.00001 BCG index and COVID-19 mortality in socially similar European countries: First month of pandemic: R^2=0.88; $P=8\times10^{-7}$. Means a 10% increase in BCG index was directly proportional to 10.4% reduction in COVID-19 deaths Limitations: Sampling biases, more RCT needed Strength: Potentially confounding factors (e.g., stage of the COVID-19 epidemic, development, rurality, population density, and age structure were adjusted)
Goswami *et al*., 2020[10] (observational)	All India Institute of Medical Sciences, New Delhi, India	BCG vaccination <95% Coverage countries versus BCG vaccination >95% coverage countries From 166 countries: COVID-19 cases: 412,637; COVID-19 deaths: 18,559	COVID-19 incidence: No difference in European and American countries having >95% BCG coverage (*P*=0.28) COVID-19 mortality less in European and American countries having >95% BCG coverage (*P*=0.017) COVID-19 incidence less in African and Asia and Australasian countries with >95% coverage (*P*<0.0008) COVID-19 mortality: No difference in African and Asia and Australasian countries (*P*=0.068) Limitations: Screening of other parasitic diseases, underreporting of cases, socioeconomics factor

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Table 1: Contd...

Author and year (study design)	Institution/Country of study conduct	Study interventions and control; study population characteristics	Study outcomes/Limitations
Gursel and Gursel 2020[11] (observational)	Middle East Technical University, Ankara, Turkey	BCGVPC versus non-BCGVPC Countries with at least 1000 COVID-19 cases were included	COVID-19 Cases/million: Countries with BCG versus no BCG program: $P<0.0001$ Deaths/million: Countries with BCG versus no BCG program: $P<0.0058$ and $P<0.0001$ Deaths/million: Countries ($n=5$) ceased BCG 2 decades back versus countries ($n=8$) ceased BCG 3-4 decades back: $P=0.0109$
Hamiel *et al*., 2020[12]	Tel Aviv University, Tel Aviv, Israel	BCG patients ($n=297,340$) versus non-BCG patients ($n=301,600$) Previously vaccinated patient's versus nonvaccinated Men tested (%): BCG versus non-BCG: $n=1509$ (49.2) versus $n=1458$ (50.8) ($P=0.29$)	Positive test results: n (%) BCG versus non-BCG: 361 (11.7) versus 299 (10.4) ($P=0.09$) Men positive (%): BCG versus non-BCG: 181 (50) versus 152 (51) ($P=0.87$) Limitations: Immigrants vaccine status more minority age groups (4.9% and 4.6% of the older and younger)
Hegarty *et al*., 2020[13] (observational)	USA	BCGVPC versus non-BCGVPC Total=178 countries BCG program: $n=131$ No BCG program: $n=21$ Unknown status: $n=26$	COVID-19 Incidence: BCG versus no BCG: 38.4/million versus 358.4/million Death rate: BCG versus no BCG: 4.28/million versus 40/million CFR: BCG versus no BCG: 0.13% versus 0.33% Limitations: Limited testing and reporting
Hensel *et al*., 2020[14] (observational)	Metastasis Research Center, University of Texas MD Anderson Cancer Center, Houston, TX, USA	BCGVPC versus non-BCGVPC Total=78 countries BCG program: 69% No BCG program: 8% Past BCG program: 23%	COVID-19 Cases/1 million inhabitants: BCG policy versus no or past BCG policy: Significantly less with BCG policy Percent mortality: BCG policy versus no or past BCG policy: significantly less with BCG policy High CoV-2 testing countries: BCG policy ($n=21$) versus no BCG policy ($n=6$) versus past BCG policy ($n=17$): ANOVA, $P=0.17$ Limitations: Faulty case reporting, lack of reporting, socioeconomic barriers, other comorbidities, adherence to vaccination
Kirov 2020[15] (observational)	Bristol-Meyers Squibb, USA	BCGVPC versus non-BCGVPC 1=current universal policy 2=used to recommend, not anymore 3=never had universal policy	Pearson correlation Median age and infection rates: $R=0.774$ BCG policy and the infection rates: $R=0.521$ Start date of BCG vaccination and infection rates: $R=0.21$ Limitations: Other confounders such as B.P., public policies and time from first infection not included; need more RCTs
Klinger *et al*., 2020[16] (observational)	The Hebrew University of Jerusalem, Israel	BCGVPC versus non-BCGVPC Total countries: 55 COVID-19 outcomes: DPM and CPM. Adjusted confounders such as lifespan, age, GDP, and population size	BCG administration: Negative correlation DPM ≥0.5 and DPM ≥2: $r=-0.48$ ($P=0.00056$) and $R=-0.47$ ($P=0.00084$) Negative correlation: CPM ≥0.5 and CPM ≥2: $R=-0.38$ ($P=0.0091$) and $r=-0.35$ ($P=0.017$) Limitations: Different countries with variable demographic parameters mask protective effect of BCG, results driven by small number of influential countries
Li 2020[17] (observational)	University of Oxford	BCGVPC versus non-BCGVPC Correlation of COVID-19 deaths and different demographic and socioeconomic factors	COVID-19 DPM: Correlation with median age $r=0.48$, $P=4.8e-4$ and per capita GDP: $r=0.55$, $P=4.14e-5$; and negatively correlates with BCG vaccination rate: $r=-0.63$, $P=9.9e-7$ Negative correlation between BCG vaccination rates and COVID-19: Cases: $r=-0.338$, $P=0.0082$ and death: $r=-0.411$, $P=0.0011$ Limitations: Old age as a confounder

BCG: Bacillus Calmette-Guerin, BCGVPC: BCG vaccination policy countries, RCT: Randomized controlled trial, SEM: Standard error of mean, CFR: Case fatality rate, CRC: Currently recommended countries, CNRC: Currently not recommended countries, IQR: Interquartile range, DPM: Deaths per million, CPM: Cases per million, GDP: Gross domestic product, COVID-19: Coronavirus disease 2019

population, but failed to find significant correlation between BCG vaccination rates and COVID-19 burden.[20] However, there is no control group in the study done by Meena *et al*. Therefore, the conclusion of no correlation cannot be drawn from this study. Hamiel *et al*. reported no difference in the incidence of COVID-19 among the BCG-vaccinated versus nonvaccinated population.[12] However, the population were different with regard to age group, as BCG vaccinated were born between 1979 and 1981 and unvaccinated were from 1983 to 1985. Whole population data with regard to vaccination were not used. It is like a subgroup study, hence increasing chances of alpha error. In addition, the severity

Table 2: Studies evaluating the effect of Bacillus Calmette-Guerin vaccination in COVID-19 included in systematic review

Author and year (study design)	Institution/Country of study conduct	Study interventions and control, study population characteristics	Study outcomes/Limitations
Macedo and Febra 2020[18] (observational)	DCBM Universidade do Algarve, Faro, Portugal	Countries with BCG vaccination policy (BCGVPC) versus without BCG vaccination policy (non-BCGVPC) BCG coverage and COVID-19 mortality after adjustment for age (*n*=125)	Pearson correlation (significant two-tailed) BCG2018 CPM: −0.396 (0.000); DPM: −0.252 (0.004) BCG2008 CPM: −0.423 (0.000); DPM: −0.282 (0.001) BCG1998 CPM: −0.380 (0.000); DPM: −0.260 (0.003) BCG1988 CPM: −0.183 (0.040); DPM: −0.129 (0.149).
Madan *et al*., 2020[19] (observational)	AIIMS, New Delhi, India	BCG coverage in COVID-19 (*n*=174) COVID-19 patients Group 1 (*n*=38) (low TB incidence, low BCG coverage) Group 2 (*n*=60) (low TB incidence, high BCG coverage) Group 3 (*n*=5) (high TB incidence, low BCG coverage) Group 4 (*n*=71) (high TB incidence, high BCG coverage)	COVID-19 Incidence (/100,000): Median (range) Group 1: 46.60 (1.36-749.06); Group 2: 4.30 (0.005-132.51) Group 3: 0.04 (0.02-17.61); Group 4: 0.43 (0.01-85.46): (*P*<0.05) COVID-19 CFR (/100): Median (range) Group 1: 1.42 (0-11.7); Group 2: 1.43 (0-25.0) Group 3: 0 (0-28.5); Group 4: 0 (0-33.3): (*P*=0.09) Limitations: Age (elderly) confounding factor, higher risk
Meena *et al*., 2020[20] (observational)	Department of Pediatrics, AIIMS, New Delhi, India	Countries with BCG vaccination policy (*n*=142). More than 100 cases of COVID-19	Countries with BCG vaccination policy (*n*=142), Weak positive correlation: Spearman rho=0.1-0.5, *P*<0.05 with CPM and DPM Limitations: Inherent Bias of observational studies
Ozdemir *et al*.,[21] (observational Study)	Institute of Child Health, Istanbul University, Istanbul, Turkey	BCG vaccinated (*n*=138) versus non-BCG vaccinated (*n*=37) Effects of BCG vaccination on COVID-19 in European countries (BCG-vaccinated countries [*n*=25], BCG-nonvaccinated countries [*n*=26])	Mean of cases per population ratio is statistically significantly lower in BCG-vaccinated countries than in BCG-nonvaccinated countries (0.0147±0.027 vs. 0.1892±0.244, respectively, *P*<0.0001) globally. Mean of deaths per population ratio is significantly lower in BCG-vaccinated versus BCG-nonvaccinated countries (0.0004±0.001 vs. 0.0113±0.020, respectively, *P*<0.0001). Mean of deaths per cases ratio is also significantly lower in BCG-vaccinated countries (3.4232±3.688 vs. 5.3429±4.830, respectively, *P*<0.05) Limitations: Did not account for confounding factors
Sala and Miyakawa[22] (ecological study)	Fujita Health University School of Medicine, Japan	BCGVPC versus non-BCGVPC Countries with populations of at least 1 million for which at least 15 days of data since the detection of the first case were available as of April the 26th (142 countries)	BCG vaccination policy and incidence of TB is associated with a reduction in both COVID-19 cases and deaths, and the effects of these two variables are additive (≈5% to 15% of total unique variance explained) Limitations: Did not exclude the effect of unknown confounding factors
Samrah *et al*. 2020[23] (cohort study)	KAUH, Jordan	BCG vaccine given (*n*=68) Hospitalized COVID-19 patients Females: 44 (54.3%) Mean age (±SD): 39.95±16.59; 84% patients receive BCG	BCG vaccination in COVID-19 patients: Symptomatic (44) versus asymptomatic (37): 33 (75%) versus 35 (94.6%), OR: −5.83 (*P*<0.017) Limitations: Small cohort, mild cases, verbal BCG confirmation no medical record reviewed, incomplete documentation of symptoms
Sharma *et al*.[24] (observational study)	Jawaharlal Nehru University, New Delhi, India	BCGVPC versus non-BCGVPC Countries with universal BCG vaccination, discontinued vaccination, and countries that never adopted BCG vaccination. Countries with over 1000 reported COVID-19 cases included	Countries without a universal BCG policy have increased incidence of COVID-19 (2810.9±497.1 [mean±SEM] per million) compared with countries with ongoing national BCG policy (570.9±155.6 [mean±SEM] per million). The incidence for countries that discontinued BCG vaccination was intermediate between these two groups (1844.67±508.89 [mean±SEM] per million) Limitations: Did not account for other confounding factors
Sharma *et al*.[25] (observational study)	PGIMER, Chandigarh, India	BCGVPC versus non-BCGVPC	Incidence of COVID-19 much lower in countries with BCG vaccination policy (11,940.98) than in countries without (44,723). Mortality percentage in BCG vaccinated countries lower (5.08%) as compared to 11% in countries without BCG vaccination program. Recovery percentage high in BCG vaccinated countries (43%) versus non-BCG countries (35%) Limitations: Did not account for confounding factors

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Table 2: Contd...

Author and year (study design)	Institution/Country of study conduct	Study interventions and control, study population characteristics	Study outcomes/Limitations
Shet *et al*., 2020[26] (observational study)	Johns Hopkins Bloomberg School of Public Health, Baltimore, USA	BCGVPC versus non-BCGVPC Top 50 countries reporting highest case events were included in the study. BCG using and non-BCG using countries with economies classified as low-middle-income (5), upper-middle-income (13) and high-income countries (32)	COVID-19-attributable mortality among BCG-using countries was 5.8 times lower (95% CI 1.8-19.0] than in non-BCG-using countries. Median crude COVID-19 mortality per 1 million population among countries with economies classified as LMIC, UMIC, HIC were 0.4 (IQR 0.06-0.4), 0.65 (IQR 0.2-2.2) and 5.5 (IQR 1.6-13.9), respectively Limitations: Due to testing constraints in LMICs, case ascertainment bias and a plausible rise of cases in countries with time
Szigeti *et al*.[27] (observational study)	Baylor College of Medicine, Houston, Texas, USA	BCGVPC versus non-BCGVPC Top 68 countries based on number of cases were included in the study. Countries with and without universal BCG vaccination in place before 1980	Death rate according to dpc/d (or case fatality rate)/d from onset was not different between countries without universal BCG vaccination in place before 1980, compared to those which had (P=0.258). Similarly, there was no correlation (r's=−0.03136, P=0.852) between the year of the establishment of universal BCG vaccination and the mortality rate by dpc/d Limitations: Confounders not adjusted
Toyoshima *et al*.[28] (observational study)	Japanese Foundation for Cancer Research, Tokyo, Japan	BCGVPC versus non-BCGVPC. 12,343 SARS-CoV-2 genome sequences isolated from patients in six geographic areas and identified a total of 1234 mutations by comparing with the reference SARS-CoV-2 sequence. Classified 28 countries into two groups according to the BCG-vaccination status as the routine vaccine schedules	Fatality rates was significantly lower in 11 BCG-vaccinated countries than in 17 BCG-nonvaccinated countries (4.1% vs. 8.1%, P=0.031). Frequencies of S 614G variant showed a trend of positive correlation with fatality rates (r=0.54, P=0.090) in BCG-vaccinated countries, correlation was not observed in BCG-nonvaccinated countries (r=0.19, P=0.47). The number of confirmed cases per million population was significantly lower in BCG-vaccinated countries than in BCG-nonvaccinated countries (710 vs. 2912, P=0.0012)
Urashima *et al*.[29] (ecologicalstudy)	The Jikei University School of Medicine, Tokyo, Japan	BCGVPC versus non-BCGVPC A total of 173 countries were included	BCG vaccine coverage and COVID-19 mortality: Moderately negative association (adjusted R^2=0.1457; rho=−0.29). No correlation with morbidity (adjusted R^2=0.3814)
Wassenaar *et al*.[30] (observational study)	Molecular Microbiology and Genomics Consultants, Zotzenheim, Germany	BCGVPC versus non-BCGVPC Compared countries that had introduced BCG in the 1950s (n=7) with those that had not (n=11). Total 18 countries	Whether countries had never used the vaccine, had historically used it but since ceased to do so, or were presently vaccinating with BCG did not correlate with national total number of deaths or CFR Limitations: Study design was ecological
Weng *et al*. 2020[31] (cohort study)	Federally qualified Health Centre in Rhode Island, United States	BCG vaccinated individuals (n=82) versus non-BCG vaccinated individuals (n=38) Hospitalized COVID-19 patients Males: 25 (25%); mean age (IQR) years: 39.5 (27.0-50.0)	Hospital admission rate BCG versus non-BCG: 6 (15.8) versus 3 (3.7) (P<0.019) Adverse events: Myalgia: BCG versus non-BCG: 74.4% versus 50.0% (P=0.008) One death in non-BCG Limitations: Small sample size, short time frame, unknown BCG strain and booster dose, more female and Latino/ Hispanic population

DPM: Deaths per million, CPM: Cases per million, AIIMS: All India Institute of Medical Sciences, TB: Tuberculosis, BCG: Bacillus Calmette-Guerin, CFR: Case fatality rate, KAUH: King Abdullah University Hospital, PGIMER: Postgraduate Institute for Medical Education and Research, CI: Confidence interval, LMIC: Low-middle-income countries, UMIC: Upper-middle-income countries, HIC: High-income countries, IQR: Interquartile range, dpc/d: Death per case per day, BCGVPC: BCG vaccination policy countries, SEM: Standard error of mean, COVID-19: Coronavirus disease 2019

of disease and mortality were not assessed. Wassenaar *et al*. did not find any correlation between countries that had never used the vaccine, had used it previously but stopped some years back, or were currently vaccinating with BCG with COVID-19 case fatality rate.[30] However, the authors misinterpreted the results as the countries with past or present BCGVPC revealed less number of cases and death as compared to non-BCGVPC. The authors further stated that countries like India have high attack rates, though less number of deaths as deaths lag behind the number of cases. The study was done in May 2020. As per the current scenario (dated September 21, 2020), India has 5,487,580 cases and 87,909 deaths. Despite having high number of cases and adequate number of tests per million, case fatality rate in India is 1.60%. Similarly, South Africa has case fatality rate of 2.4% (total cases = 661,211 and death = 15,953), which is less as compared to US (CFR = 7,004,768/204,118 = 2.9), where BCG vaccination was never implemented. This is despite the fact that USA is much more advanced on medical and technological front than any of the other two nations.

The pooled correlation from four studies revealed a significant negative correlation of BCG vaccination with COVID-19 mortality.

There is moderate quality evidence to conclude that BCG vaccine can prevent COVID-19. One main strength of our review is that we performed a meta-analysis which showed significant protective effect of BCG vaccination. The studies included in our review are all observational studies and many of them have limitations like ignoring the fact that different countries have varying time of onset of the disease and many BCG-using countries have not yet flattened their curve. Another major limitation is that many studies have not adjusted for important confounders, such as testing rates and differences in social and economic development, population size, and age structure.

Conclusion

Most importantly, unless we have robust evidence from randomized controlled trials, we cannot conclude that BCG vaccination can prevent COVID-19 or reduce mortality associated with COVID-19. Therefore, the evidence of well-conducted observational studies can strengthen the evidence. Although it cannot be concluded that BCG vaccination provides protection against COVID-19 or reduces the mortality, the evidence from many studies do support the hypothesis.

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Conflicts of interest

There are no conflicts of interest.

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