

# BCG vaccination provides protection against COVID 19: A Systematic review and meta-analysis

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## Systematic Review

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## Abstract

**Context:** 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 BCG vaccination policy amongst infants. But does that 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.

**Evidence acquisition:** Detailed electronic search for randomised controlled trials and observational studies in PubMed, Cochrane database and clinicaltrials.gov for eligible studies was performed. We performed a meta-analysis to provide pooled estimate of correlation of mortality with BCG vaccination policy from 4 studies.

**Results:** 114 number of 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. But 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 protection against COVID-19 can't 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.

## Introduction

COVID 2019 pandemic that began in December 2019 from a localized city, Wuhan in China has spread worldwide to become a global threat and is still showing dubious patterns in terms of its spread and severity of infectivity. A successful vaccine for it in the near future is also not certain. 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.

BCG vaccination in wide use among infants and neonates for prevention against tuberculous meningitis and disseminated tuberculosis since 1921 is known to offer heterologous protection against other diseases especially of respiratory origin.[1] Many non-specific antiviral effects of the BCG vaccination resulted in decreased viral load, thus causing a reduction in respiratory tract infections in children. Nations in the world that do not have universal BCG vaccination policy, like Italy and USA, have had higher COVID 19 mortality than countries with long-standing universal BCG vaccination programs, like 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. So metabolic and epigenetic changes induced by this live vaccine might cause decreased viral load of SARS-COV-2, thus resulting in decrease severity of COVID-19.

Most scientists speculate that protection offered by BCG vaccination against COVID-19 is due to non-specific effects of BCG vaccine. On the contrary to obvious correlation between SARS-CoV-2 and BCG many believe the variations in epidemiological data is influenced by various factors like burden of disease, differing phases of the pandemic in various countries, testing rates and other demographic differences. So these are prone to confounders and bias and vested political and economic concerns are at stake. Other reason 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]

But conclusion drawn from many observational studies of reduced mortality rates of COVID-19 in countries having universal BCG vaccination policy 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

The "PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)" statement was used for reporting of systematic review. The study protocol was registered with "PROSPERO (International Prospective Register of Systematic Reviews)" database (CRD42020204466).

Electronic search in PubMed, Cochrane database and clinicaltrials.gov for eligible studies was performed on 17<sup>th</sup> August, 2020. Bibliography search was done of included articles to find other studies. Language restriction was applied as only studies published in English were included. No publication restriction was applied.

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. All types of studies like RCT as well as observational were included in review. Case reports and case series were not part of review. Any discrepancy in the inclusion were resolved with the help of third author. Two authors independently extracted the data like study patient characteristics, design of study, groups and outcomes. We were unable to perform meta-analysis of all outcomes for 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 BCG vaccination policy from 4 studies which had given the correlation (r) values.

## Results

### Evidence from studies

We did an extensive database search of PubMed, Medline and Cochrane for relevant studies. PRISMA flowchart is shown in Figure 1. A total of 28 studies were included. The studies in which correlation between COVID-19 mortality and morbidity with BCG vaccination was analysed were included.

**Mortality Benefit:** The characteristics and outcome data of studies [2,5-31] is represented in Table 1. Various studies have estimated the mortality and cases in BCG vaccination policy countries in comparison to non BCG vaccination policy. According to Miller et al death per million was significantly less in higher income countries with BCG vaccination policy (BCGVPC) compared to non-BCG vaccination policy countries (non BCGVPC). Covian et al stated that there was statistically significant decrease in mortality (deaths per million) with BCG vaccination in COVID-19 patients. Similarly, Dayal et al showed that countries with past BCG vaccination program had less case fatality rates compared to countries with no BCG vaccination program. Ebina et al exhibited that there was significant decrease in median mortality per million population of COVID-19 in BCGVPC. Gursel et al showed mortality benefit of BCG vaccination in COVID-19 patients. Hegarty et al also showed that death rate from COVID-19 was lower in BCGVPC than non BCGVPC. 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 less than 95% vaccination coverage versus greater than 95% coverage. But significant difference was observed in European and American countries for COVID-19 mortality. Berg et al found that there was negative correlation i.e. decrease mortality in BCGVPC. Similar negative correlation was shown in Escobar et al and Li et al. Klinger et al elaborated negative correlation between deaths per million in COVID-19 to BCG vaccination policy. The results were similar in study by Macedo et al.

**Number of Cases:** Miller et al evaluated that cases per million was significantly less in higher income countries with BCGVPC compared to Non-BCGVPC. Similar results were obtained by Covian et al. According to Goswami et al there was significant difference in incidence of COVID-19 cases in BCGVPC with less than 95% coverage versus greater than 95% coverage. Hegarty et al demonstrated COVID-19 cases in BCGVPC were significantly lower as compared to Non-BCGVPC. Also, Hensel et al stated the similar results regarding COVID-19 cases. Madan et al interpreted that countries having greater BCG coverage had lesser incidence of COVID-19. Also interestingly they compared TB incidence with COVID-19, high TB incidence resulted in lower COVID-19 cases. Samrah et al showed significantly more asymptomatic patients had received BCG vaccine than symptomatic ones. Weng et al exhibited that patients with BCG vaccination were less hospitalised for COVID-19 than no BCG vaccination. Berg et al obtained a negative correlation between COVID-19 cases and BCG vaccinated status which was statistically significant. Similar negative correlation was shown by Li et al. Klinger et al and Macedo et al also demonstrated significant negative correlation between cases per million and 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 above results we can say that BCG vaccination causes a decrease in COVID-19 incidence and mortality. But 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 significant negative correlation of COVID-19 mortality with BCG vaccination [Random effect Pooled  $r = -0.48$ (95% CI = -0.61 to -0.35)] (Figure 2).

## Discussion

A number of observational studies have studied the correlation between BCG vaccination and COVID 19 incidence and mortality. Many of them have reported inverse correlation between BCG vaccination program and SARS-C oV2 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 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 his 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. Escobar et al found a strong correlation between the BCG index, a measure of the extent of universal BCG vaccination implementation in a country and mortality attributed to COVID 19 in various European countries with similar social background. Sala et al[22] employed multiple regression analysis to control for potential confounders and found that BCG vaccination policy is associated with reduction in both incidence and mortality due to COVID 19. Shet et al[26] used linear regression model to adjust for confounders like 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. Toyoshimo et al, Urashima et al, Ozdemir et al, Sharma et al also found that COVID-19 mortality rate was significantly lower in BCG-vaccinated countries versus no such programs. [21, 24, 28, 29]

There are few studies which were unable to 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 was 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 like age, comorbidities like diabetes mellitus, cardiovascular diseases, gross domestic product, hospital beds and number of beds as per 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 can't be drawn from this study. In the study by Hamiel et al, there was no difference in the incidence of COVID 19 among the BCG vaccinated population versus non vaccinated population.[12] In this study the population were different with regard to age group, as BCG vaccinated were born between 1979-81 and unvaccinated were from 1983-85. Whole population data with regard to vaccination was not used. It is like a sub-group study, hence increasing chances of alpha error. In addition, the severity 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, authors misinterpreted the results as the countries with past or present BCG vaccination policy revealed less number of cases and death as compared to Non BCGVPC. 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 current scenario (dated 21<sup>st</sup> September 2020), India have 5487580 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 percent. Similarly, South Africa has case fatality rate of 2.4 percent (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 revealed a significant negative correlation of BCG vaccination with COVID-19 mortality. Pooled data was taken from Escobar et al, Klinger et al, Li et al and Urashima et al. Rest of the studies did not report the r values.

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. Most importantly, unless we have robust evidence from randomised controlled trials (RCT), we cannot conclude that BCG vaccination can prevent COVID-19 or reduce mortality associated with COVID-19. But it is difficult to prove the current hypothesis with RCTs. Therefore, the evidence of well conducted observational studies can strengthen the evidence. Though, it cannot be concluded that BCG vaccination provides protection against COVID-19 or reduces the mortality, but the evidence from many studies do support the hypothesis.

## Declarations

**Conflicts of interest:** None

## References

1. Colditz GA, Berkey CS, Mosteller F, Brewer TF, Wilson ME, Burdick E, et al. The efficacy of bacillus Calmette-Guerin vaccination of newborns and infants in the prevention of tuberculosis: meta-analyses of the published literature. *Pediatrics*. 1995 Jul;96(1 Pt 1):29-35.
2. Miller A, Reandelar M, Fasciglione K, Fasciglione K, Roumenova V, Li Y, et al. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. [preprint]. *medRxiv*. doi: <https://doi.org/10.1101/2020.03.24.20042937>. 2020.
3. Maheshwari N, Jain A. Is There a Rationale for Using Bacillus Calmette-Guerin Vaccine in Coronavirus Infection? *Viral Immunol*. 2020 Aug 26.
4. Rajarshi K, Chatterjee A, Ray S. BCG vaccination strategy implemented to reduce the impact of COVID-19: Hype or Hope? *Med Drug Discov*. 2020 Sep;7:100049.
5. Berg M, Q Y, Salvador C, Melani I, Kityama S. Mandated Bacillus Calmette-Guérin (BCG) vaccination predicts flattened curves for the spread of COVID-19. [preprint]. *medRxiv*. <https://doi.org/10.1101/2020.04.05.20054163>. 2020.
6. Covian C, Retamal-Diaz A, Bueno SM, Kalergis AM. Could BCG Vaccination Induce Protective Trained Immunity for SARS-CoV-2? *Front Immunol*. 2020;11:970.
7. Dayal D, Gupta S. Connecting BCG Vaccination and COVID-19: Additional Data. [preprint]. *medRxiv*. <https://doi.org/10.1101/2020.04.07.20053272>. 2020.
8. Ebina-Shibuya R, Horita N, Namkoong H, Kaneko T. National policies for paediatric universal BCG vaccination were associated with decreased mortality due to COVID-19. *Respirology*. 2020 Jun 18.
9. Escobar LE, Molina-Cruz A, Barillas-Mury C. BCG vaccine protection from severe coronavirus disease 2019 (COVID-19). *Proc Natl Acad Sci U S A*. 2020 Jul 28;117(30):17720-6.
10. Goswami R, Mittal D, Goswami R. Interaction between malaria transmission and BCG vaccination with COVID-19 incidence in the world map: A cross-sectional study. [preprint]. *medRxiv*. <https://doi.org/10.1101/2020.04.03.20052563>. 2020.

11. Gursel M, Gursel I. Is global BCG vaccination-induced trained immunity relevant to the progression of SARS-CoV-2 pandemic? *Allergy*. 2020 Jul;75(7):1815-9.
12. Hamiel U, Kozer E, Youngster I. SARS-CoV-2 Rates in BCG-Vaccinated and Unvaccinated Young Adults. *JAMA*. 2020 Jun 9;323(22):2340-1.
13. Hegarty P, Kamat A, Zafirakis H, Dinardo A. BCG Vaccination May Be Protective against Covid-19, 2020. <https://doi.org/10.13140/RG.2.2.35948.10880>. 2020.
14. Hensel J, McGrail D, McAndrews K, Dowlathshahi D, LeBleu V, Kalluri R. Exercising caution in correlating COVID-19 incidence and mortality rates with BCG vaccination policies due to variable rates of SARS CoV-2 testing. [preprint]. medRxiv. <https://doi.org/10.1101/2020.04.08.20056051>. 2020.
15. Kirov S. Association Between BCG Policy is Significantly Confounded by Age and is Unlikely to Alter Infection or Mortality Rates. [preprint]. medRxiv. <https://doi.org/10.1101/2020.04.06.20055616>. 2020.
16. Klinger D, Blass I, Rappoport N, Linial M. Significantly Improved COVID-19 Outcomes in Countries with Higher BCG Vaccination Coverage: A Multivariable Analysis. *Vaccines (Basel)*. 2020 Jul 11;8(3).
17. Li WX. Worldwide inverse correlation between Bacille Calmette-Guerin immunization and COVID-19 morbidity and mortality. *Res Sq*. 2020 Jul 16.
18. Macedo A, Febra C. Relation between BCG coverage rate and COVID-19 infection worldwide. *Med Hypotheses*. 2020 Sep;142:109816.
19. Madan M, Pahuja S, Mohan A, Pandey RM, Madan K, Hadda V, et al. TB infection and BCG vaccination: are we protected from COVID-19? *Public Health*. 2020 Aug;185:91-2.
20. Meena J, Yadav A, Kumar J. BCG Vaccination Policy and Protection Against COVID-19. *Indian J Pediatr*. 2020 Sep;87(9):749.
21. Ozdemir C, Kucuksezer UC, Tamay ZU. Is BCG vaccination affecting the spread and severity of COVID-19? *Allergy*. 2020 Jul;75(7):1824-7.
22. Sala G, Miyakawa T. Association of BCG vaccination policy with prevalence and mortality of COVID-19. [preprint]. medRxiv. doi: <https://doi.org/10.1101/2020.03.30.20048165>. 2020.
23. Samrah SM, AH WA-M, Ibnian AM, Raffee LA, Momany SM, Al-Ali M, et al. COVID-19 outbreak in Jordan: Epidemiological features, clinical characteristics, and laboratory findings. *Ann Med Surg (Lond)*. 2020 Sep;57:103-8.
24. Sharma A, Kumar Sharma S, Shi Y, Bucci E, Carafoli E, Melino G, et al. BCG vaccination policy and preventive chloroquine usage: do they have an impact on COVID-19 pandemic? *Cell Death Dis*. 2020 Jul 8;11(7):516.
25. Sharma AR, Batra G, Kumar M, Mishra A, Singla R, Singh A, et al. BCG as a game-changer to prevent the infection and severity of COVID-19 pandemic? *Allergol Immunopathol (Madr)*. 2020 Jul 3.
26. Shet A, Ray D, Malavige N, Santosham M, Bar-Zeev N. Differential COVID-19-attributable mortality and BCG vaccine use in countries. [preprint]. medRxiv. DOI: 10.1101/2020.04.01.20049478 2020.
27. Szigeti R, Kellermayer D, Kellermayer R. BCG protects against COVID-19? A word of caution. [preprint]. medRxiv. <https://doi.org/10.1101/2020.04.09.20056903>. 2020.
28. Toyoshima Y, Nemoto K, Matsumoto S, Nakamura Y, Kiyotani K. SARS-CoV-2 genomic variations associated with mortality rate of COVID-19. *J Hum Genet*. 2020 Jul 22.
29. Urashima M, Otani K, Hasegawa Y, Akutsu T. BCG Vaccination and Mortality of COVID-19 across 173 Countries: An Ecological Study. *Int J Environ Res Public Health*. 2020 Aug 3;17(15).
30. Wassenaar TM, Buzard GS, Newman DJ. BCG vaccination early in life does not improve COVID-19 outcome of elderly populations, based on nationally reported data. *Lett Appl Microbiol*. 2020 Jul 30.
31. Weng CH, Saal A, Butt WW, Bica N, Fisher JQ, Tao J, et al. Bacillus Calmette-Guerin vaccination and clinical characteristics and outcomes of COVID-19 in Rhode Island, United States: a cohort study. *Epidemiol Infect*. 2020 Jul 9;148:e140.

## Table

**Table 1: Studies evaluating the effect of BCG vaccination in COVID-19 included in systematic review**

Author & Year (Study design)	Institution/ Country of study conduct	Study Interventions Control	Study population characteristics	Study outcomes	Strengths & Limitations
Aaron 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 vs without BCG vaccination policy	<b>COVID-19 patients;</b> Middle high- and high-income countries = BCG policy (n=55 countries);  Middle high- and high-income countries = No BCG policy (n=5 countries).	<b>Deaths per million</b> in Middle high- and high-income countries with BCG vs no BCG policy: $0.78 \pm 0.40$ vs $6.39 \pm 7.33$ (Mean $\pm$ SEM); (p=8.64e-04, Wilcoxon rank sum test);  <b>Cases per million Inhabitants</b> in Middle high- and high-income countries with BCG vs no BCG policy: $59.54 \pm 23.29$ vs $264.90 \pm 134.88$ (Mean $\pm$ SEM); (p=0.0064, Wilcoxon rank sum test).  <b>Cases per million Inhabitants</b> low-income levels countries (18): $0.32 \pm 0.09$	<b>Limitations:</b> Underreporting 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 vs Non-BCG mandated policy	Two categories of BCG policy countries status  1. 1. Current versus combined (past and none) 2. 2. Past versus none	<b>Growth rate COVID-19 cases:</b> 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 vs none BCG policy: $b = -0.009$ , $P = 0.610$  <b>Growth rate of Death</b> 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 vs none BCG policy: $b = -0.007$ , $P = 0.772$ .	<b>Limitations:</b> Underreporting of cases, Confounding factor cultural dimensions.
Covian et al 2020 [6] (Observational)	Millennium Institute on Immunology and Immunotherapy, Santiago, Chile	Countries with BCG vaccination policy vs without BCG vaccination policy	Countries with BCG vaccination policy (n=22) vs countries without BCG policy (n=16).	<b>Cases per million inhabitants:</b> Significant difference between BCG and Non-BCG.  <b>Deaths per million inhabitants:</b> Significant difference between BCG and Non-BCG.	<b>Limitations:</b> Amount of testing, social distancing measures, demographic distribution of country.
Dayal et al 2020 [7] (Observational)	Postgraduate Institute of Medical Education and Research, Chandigarh, India.	No BCG policy countries vs Past BCG policy countries.	Two categories: High COVID-19 burden countries (high case fatality rates) (n=12) vs Countries with BCG revaccinations (n=12).	<b>Case fatality rate:</b> Between two groups: 5.2% vs 0.6%, p value <0.0001.	<b>Limitations:</b> Not representing true CFR, oversimplification of interpretation.
Ebina et al 2020 [8] (Observational)	National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, USA	BCG vaccinated countries vs Past BCG vaccination countries vs No BCG vaccination countries.	Two categories in terms of BCG vaccination: Currently Recommended Countries (CRC) (n=27) and Currently Not Recommended Countries (CNRC) (n=23).	<b>Median (IQR) mortality /1M population:</b> CRC vs CNRC: $2.1$ (0.7-8.0) vs $42.6$ (13.1-139.3), Mann-Whitney $P < 0.001$ . <b>Median (IQR) mortality:</b> Never Recommended Countries > Previously Recommended Countries: $46.5$ (56.6-260.5) > $2.1$ (0.7-8.0).	<b>Limitations:</b> Selection bias in the study participants.
Escobar et al 2020 [9]	Virginia Polytechnic	BCG vaccination	Potentially confounding	<b>BCG index and COVID-19 mortality:</b> Negative	<b>Strengths:</b> Confounding factors were adjusted in

(Observational)	Institute and State University, Blacksburg, VA	policy vs Past or Non-BCG vaccination policy in socially similar European countries (n=22) and America (US versus Latin America)	factors (e.g., stage of the COVID-19 epidemic, development, rurality, population density, and age structure were adjusted.	correlation: $r^2 = 0.49$ , $P < 0.00001$ . <b>BCG index and COVID-19 mortality in socially similar European countries:</b> First month of pandemic: $r^2 = 0.88$ ; $P = 8 \times 10^{-7}$ . Means a 10% increase in BCG index was directly proportional to 10.4% reduction in COVID-19 deaths.	analysis. <b>Limitations:</b> Sampling biases, More RCT needed.
<b>Goswami et al 2020 [10]</b> (Observational)	All India Institute of Medical Sciences, New Delhi, India	BCG vaccination <95% Coverage countries vs BCG vaccination >95% Coverage countries.	From 166 countries: COVID-19 cases: 412637; COVID-19 deaths: 18559.	<b>COVID-19 incidence:</b> No difference in European and American countries having >95% BCG coverage ( $p=0.28$ ). <b>COVID-19 mortality</b> less in European and American countries having >95% BCG coverage ( $p=0.017$ ). <b>COVID-19 incidence</b> less in African and Asia and Australasian countries with >95% coverage ( $p<0.0008$ ). <b>COVID-19 mortality:</b> No difference in African and Asia and Australasian countries ( $p=0.068$ ).	<b>Limitations:</b> Screening of other parasitic diseases, underreporting of cases, Socioeconomics factor.
<b>Gursel et al 2020 [11]</b> (Observational)	Middle East Technical University, Ankara, Turkey	BCG vaccination policy countries vs No BCG vaccination policy countries.	Countries with atleast 1000 COVID-19 cases were included.	<b>COVID-19 Cases/million:</b> Countries with BCG vs No BCG programme: $P<0.0001$ . <b>Deaths/million:</b> Countries with BCG vs No BCG programme: $P<0.0058$ and $P<0.0001$ . <b>Deaths/million:</b> Countries (n=5) ceased BCG 2 decades back vs Countries (n=8) ceased BCG 3-4 decades back: $P=0.0109$ .	
<b>Hamiel et al 2020 [12]</b> (Observational)	Tel Aviv University, Tel Aviv, Israel.	BCG patients (n=297340) vs Non-BCG patients (n=301600).	Previously vaccinated patient's vs Non vaccinated; No. of tests done: BCG vs Non-BCG: n=3064 vs n=2869; Men Tested (%): BCG vs Non-BCG: n=1509 (49.2) vs n=1458 (50.8) ( $p=0.29$ ).	<b>Positive test results:</b> No. (%): BCG vs Non-BCG: 361 (11.7) vs 299 (10.4) ( $p=0.09$ ); <b>Men positive (%):</b> BCG vs Non-BCG: 181 (50) vs 152 (51) ( $p=0.87$ ).	<b>Strengths:</b> Large samples, similar age groups, limited confounders. <b>Limitations:</b> Immigrants vaccine status more minority age groups (4.9% and 4.6% of the older and younger).
<b>Hegarty et al 2020 [13]</b> (Observational)	USA	BCG vaccination policy countries vs No BCG vaccination policy countries.	Total= 178 countries; BCG programme: n=131; No BCG programme: n=21; Unknown status: n=26.	<b>COVID-19 Incidence:</b> BCG vs No BCG: 38.4/million vs 358.4/million; <b>Death rate:</b> BCG vs No BCG: 4.28//million vs 40/million; <b>Case fatality rate (CFR):</b> BCG vs No BCG: 0.13% vs 0.33%.	<b>Limitations:</b> Limited testing and reporting.
<b>Hensel et al 2020 [14]</b> (Observational)	Metastasis Research Center, University of Texas MD Anderson Cancer Center, Houston, TX, USA.	BCG vaccination policy countries vs No BCG vaccination policy countries	Total = 78 countries; BCG programme: 69%; No BCG programme: 8%; Past BCG programme: 23%.	<b>COVID-19; Cases/1M inhabitants:</b> BCG policy vs No or Past BCG policy: significantly Less with BCG policy; <b>Percent mortality:</b> BCG policy vs No or Past BCG policy: significantly Less with BCG policy; <b>High CoV-2 testing countries:</b> BCG policy (n=21) vs No BCG policy (n=6) vs Past BCG policy	<b>Limitations:</b> Faulty case reporting, lack of reporting, socioeconomic barriers, other comorbidities, adherence to vaccination.

				(n=17): ANOVA, p = 0.17;	
<b>Kirov 2020 [15]</b> (Observational)	Bristol-Meyers Squibb, USA	BCG vaccination policy countries versus no BCG vaccination.	1 = current universal policy 2= used to recommend, not anymore 3 = never had universal policy	<b>Pearson correlation;</b> 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.	<b>Strengths:</b> All important confounding factors included. <b>Limitations:</b> Other confounders such as B.P., public policies and time from first infection not included; Need more RCTs.
<b>Klinger et al 2020 [16]</b> (Observational)	The Hebrew University of Jerusalem, Israel	BCG vaccination policy countries versus no BCG vaccination.	Total countries: 55; COVID-19 outcomes: Deaths or cases per million (DPM and CPM).	<b>BCG administration:</b> Negative correlation: DPM $\geq$ 0.5 and DPM $\geq$ 2: R = -0.48 (p-value = 0.00056) and R = -0.47 (p-value = 0.00084).  Negative correlation: CPM $\geq$ 0.5 and CPM $\geq$ 2: R = -0.38 (p-value = 0.0091) and R = -0.35 (p-value = 0.017).	<b>Strength:</b> Included confounders such as population size, Gross Domestic Product (GDP), lifespan, median age. <b>Limitations:</b> Different countries with variable demographic parameters mask protective effect of BCG, results driven by small no. of influential countries.
<b>Li et al 2020 [17]</b> (Observational)	University of Oxford	BCG vaccination policy countries versus no BCG vaccination.	Correlation of COVID-19 deaths and different demographic and socio-economic factors	<b>COVID-19 deaths per million:</b> 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.  <b>Negative correlation between BCG vaccination rates and COVID-19:</b> Cases: r=-0.338, p=0.0082 and death: r= -0.411, p=0.0011.	<b>Limitations:</b> Old age as a confounder.
<b>Macedo et al 2020 [18]</b> (Observational)	DCBM Universidade do Algarve, Faro, Portugal	BCG vaccine coverage countries vs Non BCG vaccinated	BCG coverage and COVID-19 mortality after adjustment for age (n=125)	<b>Pearson Correlation (sig. 2-tailed):</b> <b>BCG2018:</b> Cases per million: -0.396 (0.000); Deaths per Million: -0.252 (0.004). <b>BCG2008:</b> Cases per million: -0.423 (0.000); Deaths per Million: -0.282 (0.001). <b>BCG1998:</b> Cases per million: -0.380 (0.000); Deaths per Million: -0.260 (0.003) <b>BCG1988:</b> Cases per million: -0.183 (0.040); Deaths per Million: -0.129 (0.149).	
<b>Madan et al 2020 [19]</b> (Observational)	All India Institute of Medical Sciences (AIIMS), New Delhi, India	BCG coverage versus COVID-19 (n=174)	<b>COVID-19 patients;</b> 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)	<b>COVID-19: Incidence (per 100,000): Median (Range)</b> 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). <b>COVID-19: Case fatality rate (CFR) (per 100): Median (Range)</b> 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).	<b>Limitations:</b> Age (elderly) confounding factor, higher risk.
<b>Meena et al 2020 [20]</b> (Observational)	Department of Pediatrics, All India Institute of Medical Sciences,	Countries with BCG vaccination policy (n=142).	Countries with Universal BCG vaccination with more than 100 cases	Countries with BCG vaccination policy (n=142), Weak positive correlation: spearman rho = 0.1-0.5, p < 0.05	<b>Limitations:</b> inherent Bias of observational studies

	New Delhi, India			with cases and deaths per million	
<b>Ozdemir et al 2020 [21]</b> (Observational Study)	Institute of Child Health, Istanbul University, Istanbul, Turkey	BCG vaccinated (n=138) vs Non BCG vaccinated (n=37)	COVID-19 cases in the Northern Hemisphere (n = 144) and the Southern Hemisphere (n = 31), with respect to BCG vaccination status. Effects of BCG vaccination on COVID-19 in European countries [BCG-vaccinated countries (n = 25), BCG-non-vaccinated countries (n = 26)]	Mean of cases per population ratio is statistically significantly lower in BCG-vaccinated countries than in BCG-non-vaccinated countries [0.0147 ± 0.027 vs 0.1892 ± 0.244, respectively, P < .0001] globally. Mean of deaths per population ratio is significantly lower in BCG-vaccinated versus BCG-non-vaccinated 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]	<b>Limitations:</b> did not account for confounding factors <b>Strengths:</b> took hemispheric location of countries into consideration
<b>Sala et al 2020 [22]</b> (ecological study)	Fujita Health University School of Medicine, Japan	BCG vaccinated vs Non BCG vaccinated	Countries with populations of at least one million for which at least 15 days of data since the detection of the first case were available as of April the 26 <sup>th</sup> (142 countries)	BCG vaccination policy and incidence of tuberculosis 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).	<b>Limitations:</b> Did not exclude the effect of unknown confounding factors <b>Strengths:</b> employed multiple regression and principal component analysis
<b>Samrah et al 2020 [23]</b> (Cohort study)	King Abdullah University Hospital (KAUH), Jordan	BCG vaccine given (n=68).	Hospitalised 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) vs Asymptomatic (37): 33 (75%) vs 35 (94.6%), OR:- 5.83 (p<0.017).	<b>Limitations:</b> Small cohort, mild cases, verbal BCG confirmation no medical record reviewed, incomplete documentation of symptoms.
<b>Sharma et al 2020 [24]</b> (Observational study)	Jawaharlal Nehru University, New Delhi, India	BCG vaccinated vs Non BCG vaccinated	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).	<b>Limitations:</b> did not account for other confounding factors <b>Strengths:</b> analysed incidence and mortality in 5 different age groups
<b>Sharma AR et al 2020 [25]</b> (Observational study)	Post Graduate Institute for Medical Education and Research (PGIMER), Chandigarh, India	BCG vaccinated vs Non BCG vaccinated	Countries with universal BCG vaccination and those without	Incidence of COVID 19 much lower in countries with BCG vaccination policy (11940.98) 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%).	<b>Limitations:</b> did not account for confounding factors.
<b>Shet et al 2020 [26]</b> (Observational study)	Johns Hopkins Bloomberg School of Public Health, Baltimore, USA	BCG vaccinated vs Non BCG vaccinated	Top 50 countries reporting highest case events were included in the study. BCG using	COVID-19-attributable mortality among BCG-using countries was 5.8 times lower [95% CI 1.8-19.0] than in non BCG-	<b>Limitations:</b> due to testing constraints in LMICs, case ascertainment bias and a plausible rise of cases in countries with time.

			and non-BCG using countries with economies classified as low-middle-income(5), upper-middle-income(13) and high-income countries(32).	using countries. Median crude COVID-19 mortality per 1 million population among countries with economies classified as low-middle-income, upper-middle-income and high-income countries (LMIC, UMIC, HIC) were 0.4 (Interquartile Range (IQR) 0.06, 0.4), 0.65 (IQR 0.2, 2.2) and 5.5 (IQR 1.6, 13.9), respectively	<b>Strengths:</b> used a log-linear regression model after adjusting for confounders
Szigeti et al 2020 [27] (Observational study)	Baylor College of Medicine, Houston, Texas, U.S.A	BCG vaccinated vs Non BCG vaccinated	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 Death Per Case (or case fatality rate)/Days from onset (dpc/d) 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 (rs= -0.03136, p= 0.852) between the year of the establishment of universal BCG vaccination and the mortality rate by dpc/d.	<b>Limitations:</b> confounders not adjusted <b>Strengths:</b> used modified death rate as Death Per Case (i.e. case fatality)/Days (dpc/d) for the endemic of each country
Toyoshimo et al 2020 [28] (Observational study)	Japanese Foundation for Cancer Research, Tokyo, Japan	BCG vaccinated vs Non BCG vaccinated	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-non-vaccinated 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-non-vaccinated 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-non-vaccinated countries (710 vs. 2912, P = 0.0012)	<b>Strengths:</b> investigated SARSCoV-2 genome mutations, BCG-vaccination status, and HLA genotypes in 28 countries and identified significant associations of some virus genome variants with the fatality rates.
Urashima et al 2020 [29] (ecological study)	The Jikei University School of Medicine, Tokyo, Japan;	BCG vaccinated vs Non BCG vaccinated	A total of 173 countries that had data of both total COVID-19 deaths and BCG vaccine coverage were included	BCG vaccine coverage and COVID-19 mortality: Moderately negative association (adjusted R <sup>2</sup> = 0.1457; rho = -0.29). No correlation with morbidity (adjusted R <sup>2</sup> = 0.3814)	<b>Limitations:</b> study design was ecological <b>Strengths:</b> multi-linear regression model was used
Wassenaar et al 2020 [30] (Observational study)	Molecular Microbiology and Genomics Consultants, Zotzenheim, Germany	BCG vaccinated vs Non BCG vaccinated	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.	<b>Limitations:</b> did not account for confounding factors
Weng et al 2020 [31] (Cohort study)	Federally qualified health centre in Rhode Island, United States	BCG vaccinated individuals (n=82) vs Non-BCG vaccinated individuals (n=38)	Hospitalised COVID-19 patients; Males: 25 (25%); Mean age (IQR) years: 39.5 (27.0-50.0).	Hospital admission Rate: BCG vs Non-BCG: 6 (15.8) vs 3 (3.7) (p<0.019). Adverse Events: myalgia: BCG vs Non-BCG: 74.4% vs. 50.0%, (p = 0.008); 1 Death in Non-BCG	<b>Limitations:</b> Small sample size, short time frame, unknown BCG strain and booster dose, more female and Latino/Hispanic population

# Figures

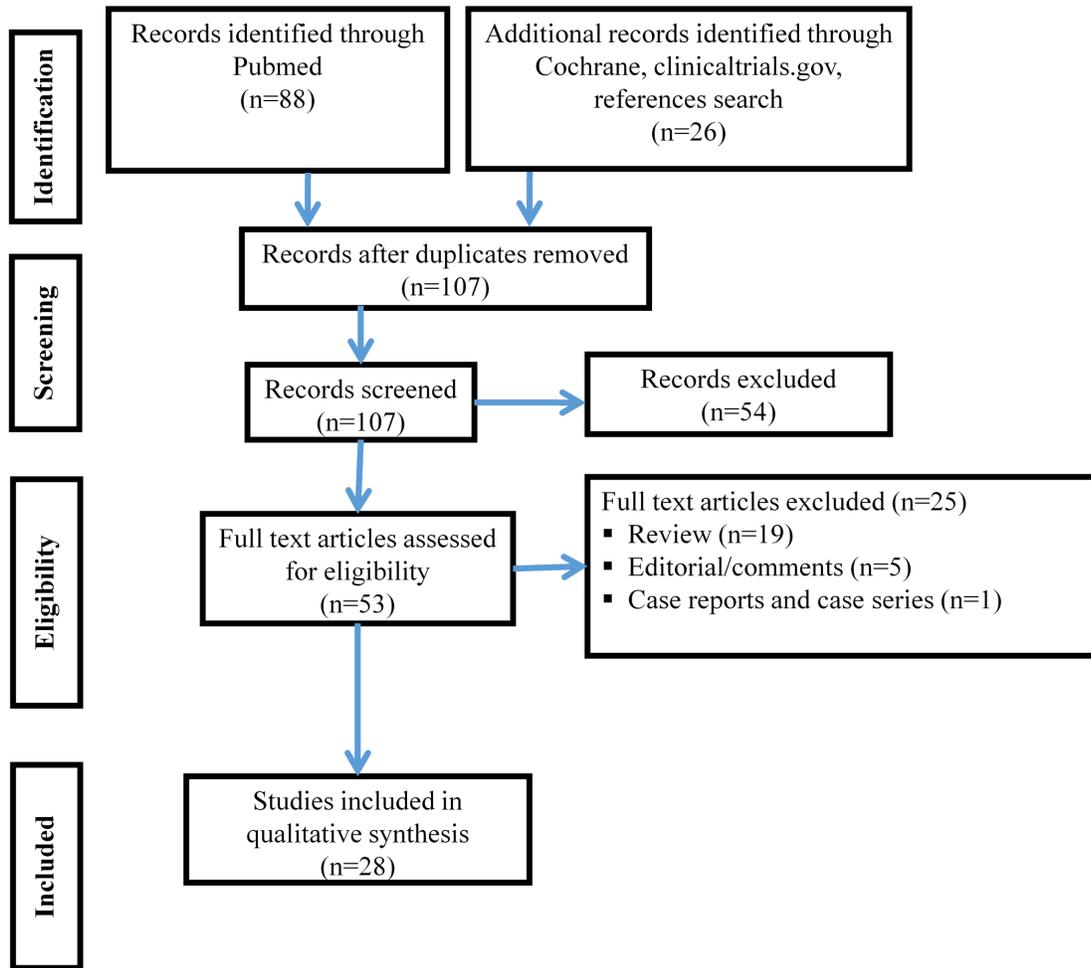
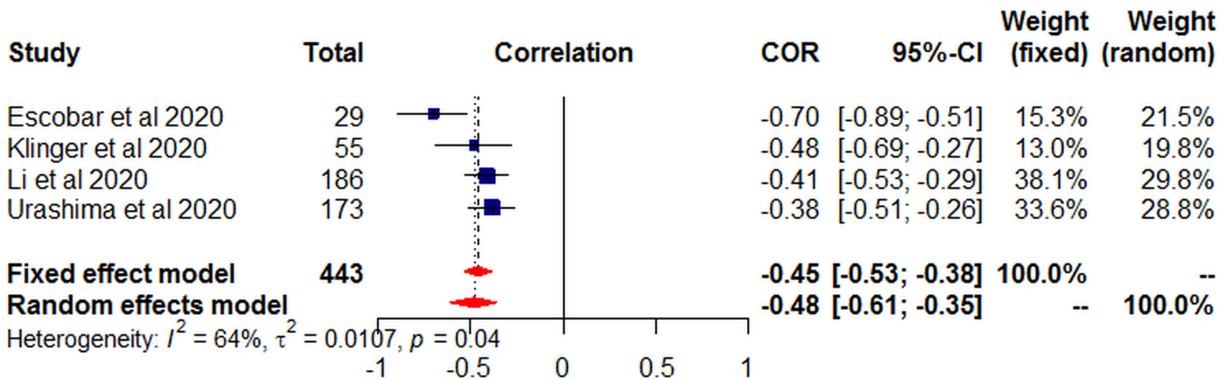


Figure 1

PRISMA flow diagram of study selection for systematic review



**Figure 2**

Pooled analysis of correlation of countries with BCG vaccination policy versus mortality