Global Journal of Medicine & Public Health

Decoding the BCG and COVID-19 connection: an empirical analysis

*Nand Lal Mishra[1], Alka Chauhan[1], Pankaj Kumar Patel[1], Bishwajeet Besra[1], Sampurna Kundu[*1]*

GJMEDPH 2020; Vol. 9, issue 3
[1]International Institute for Population Sciences, Deonar, Mumbai-88, India

***Corresponding author**
Sampurna Kundu, MPhil Research Scholar
International Institute for Population Sciences, Deonar, Mumbai-88, India
sampurna34@gmail.com

Conflict of Interest—none

Funding—none

ABSTRACT

Background

Bacillus Calmette-Guérin (BCG) vaccination offers protection against tuberculosis (TB), an infectious disease caused by the *Mycobacterium tuberculosis* bacterium. TB generally affects the lungs and can prove fatal. There is evidence that BCG vaccination has non-specific immune-boosting effects that protect against other pathogens including *Candida albicans* and *Staphylococcus aureus*. During the early months of the COVID-19 pandemic, the list of countries most affected bore a resemblance to the list of countries that do not have universal BCG vaccination policy. In this study, we explore the possible association between BCG vaccine policy and SARS CoV-2 attributable mortality.

Methods

We obtained cumulative counts of cases and deaths attributed to SARS CoV-2 from the WHO COVID-19 Dashboard, collated details of BCG vaccination policy from the BCG World Atlas and extracted data on BCG coverage for the past 30 years from WHO. We applied multivariate log-linear regression models to examine the association of deaths per 1 million population attributed to SARS CoV-2 and BCG vaccination policy and coverage.

Results

A significant association between the absence of universal BCG vaccination and the higher death rate was found even after controlling for other variables including median age, hospital beds and days since 100th case. The present study does not, however, find any significant association between BCG vaccination coverage and mortality attributed to SARS CoV-2 across the countries where the BCG immunization has been administered since or before 1990 and where BCG coverage falls within the range 35– 99% of the population.

Conclusion

These results support the prevailing view that the connection between BCG immunization and COVID-19 mortality is correlation rather than causation and is likely due to confounding factors within profoundly affected populations.

Keywords: SARS CoV-2, Bacillus Calmette-Guerin (BCG) vaccine, Vaccination policy

INTRODUCTION

The entire world is suffering from the pandemic caused by the spread of SARS CoV-2, a novel coronavirus. SARS Cov-2 causes COVID-19, a disease that can result in pneumonia. The first COVID-19 outbreak was reported in December 2019 in Wuhan, China[1] and in less than four months – the time at which strict lockdowns began in many European and North American cities – its aggressive spread had led to infections in more than 2.6 million people and more than 182,000 deaths across 213 countries of the world.[2] With over half of the world's population still experiencing lockdowns by the end of 2020, with serious socioeconomic consequences,[3,4] governments across the globe are trying to reduce the spread. A case fatality rate of 3–15% is recorded worldwide, with continuous surveillance and a growing bank of

available treatments.[5,6] Likelihood of death and severity of symptoms are associated with age and comorbidities, factors which can vary considerably across and even within countries.[7] Outbreak control measures such as social distancing and country or state lockdowns have had a substantial impact on SARS CoV-2 attributable morbidity and mortality, as have the timeliness with which lockdowns were or were not implemented; but measures, as well as their success, have varied considerably across countries.[8]

There have been some striking differences in how the pandemic has behaved in different countries. For instance in Italy and Spain, where social and physical contacts were strongly curtailed in the first half of 2020, mortality attributed to SARS CoV-2 is still high. In contrast, Japan and South Korea had some of the earliest cases, did not impose such strict measures on close social interactions, and saw mortality remain relatively low through 2020[9], though both were seeing upticks in cases as this paper went to press.

Early in the pandemic, such disparities saw the emergence of articles on pre-print sites[10-16] that suggested a link between countries' COVID-19 caseloads and level of Bacillus Calmette-Guérin (BCG) vaccination coverage. Such papers suggested that BCG vaccination might confer long-lasting protection against SARS Cov-2 and thus COVID-19 morbidity and mortality. There is experimental evidence from both animal and human studies that the BCG vaccine – developed for and used to prevent tuberculosis (TB), an infectious disease caused by the *Mycobacterium tuberculosis* bacterium – might have non-specific immune-boosting effects. Although these effects have not been well characterized and their clinical relevance is unknown[17,18] it is tempting to hypothesize and investigate how BCG might work against SARS Cov-2. These ecological studies are crude in several ways, however, including their selection of variables, statistical methods applied, how they adjust for confounders, and epidemic time lag.[19] Thus, it would be more appropriate to use continuous scale data to produce a more accurate estimation of the impact of BCG immunization coverage on morbidity and mortality attributed to SARS CoV-2[16] along with adjusting for major confounders. In this study, attempts have been made to analyze the true association of BCG vaccination coverage and mortality attributed to SARS CoV-2.

METHOD AND MATERIALS

The SARS CoV-2 attributable counts for cumulative cases and deaths were obtained from the official WHO COVID-19 Dashboard (https://covid19.who.int/) on June 19, 2020, at 10:00 AM GMT. National population, along with the median age for the year 2020 and the number of hospital beds available per 1,000 people were retrieved from the United Nations World Population Prospects 2019 and the World Bank Open Data respectively. Details on BCG immunization policies across the nations were collated from the BCG World Atlas[20] and were verified by matching with WHO data on BCG immunization coverage available since 1980. On the basis of the collected information, we categorized countries into two groups: countries that follow a universal BCG immunization programme and those that do not have a national BCG policy or have a BCG vaccination programme for specific population groups only. Finally, we collated data on annual BCG immunization coverage among 1 year old children for the last 30 years (1989 to 2018) from the WHO Global Health Observatory. From this, we estimated the current share of each country's population aged 1– 30 years who received the BCG vaccination at age 1 year and from this generalized estimates for the whole population. Here, we assumed that deaths among the population aged below 30 are independent of being BCG immunized at age 1.

Multivariate log-normalized linear regression models were run on the data we compiled to assess the association of BCG vaccination with number of deaths per 1 million population attributed to SARS CoV-2, adjusted for the other covariates including median age of the population and number of hospital beds per 1,000 people. As the arrival of the epidemic across countries varied and was dependent on many factors, we included the number of days since the 100th SARS CoV-2 positive case was reported (as of Apr 19, 2020) to realign the countries on a comparable epidemic timeline. Model 1 explains the association of log-normalized deaths per 1 million with the presence and absence of universal BCG vaccination policy, whereas

model 2 examines the association of the former with BCG immunization coverage across the countries where universal BCG vaccination is administered. A total of 103 countries were considered for the analysis, where cumulative cases were found to be more than 400. Among these 103 countries, 72 countries have followed universal BCG vaccination policy for at least three decades and 28 have either BCG vaccination policy for specific groups or no policy at all. For three countries, status was unknown. Analysis was carried out using STATA 14 software. If BCG vaccination policy helps in reducing COVID-19 mortality, we hypothesize that the BCG coverage should reduce mortality attributed to COVID-19 in countries where universal BCG immunization is administered.

RESULTS

The distribution of log-normalized cases and deaths per 1 million population attributed to SARS CoV-2 by the countries following universal and specific (or no) BCG vaccination policies infers a strong relationship between BCG coverage and COVID-19 morbidity/mortality. Countries that do not have BCG coverage or where coverage is limited to specific groups observed 7.3 (IQR=1.4) and 3.7 (IQR=2.3) median cases and deaths per 1 million population, respectively. Countries following universal BCG vaccine coverage observed 5.0 (IQR=2.2) and 1.1 (IQR=1.9) median cases and deaths per 1 million: substantially lower than those of the first group (Fig 1).

Furthermore, we computed Pearson's correlation coefficient to measure the degree of mutual associations between standardized (log-normalized) deaths per 1 million population and selected confounding factors: median age, hospital beds per thousand people and days since the 100th case was reported. Results indicate significant positive association of standardized death rate with median age (r=0.579, p<0.001), number of days since 100th case (r=0.419, p<0.001) and hospital beds (r=0.305, p<0.005). Standardized deaths per 1 million population are positively correlated with the number of hospital beds available per 1,000 people (Table 1).

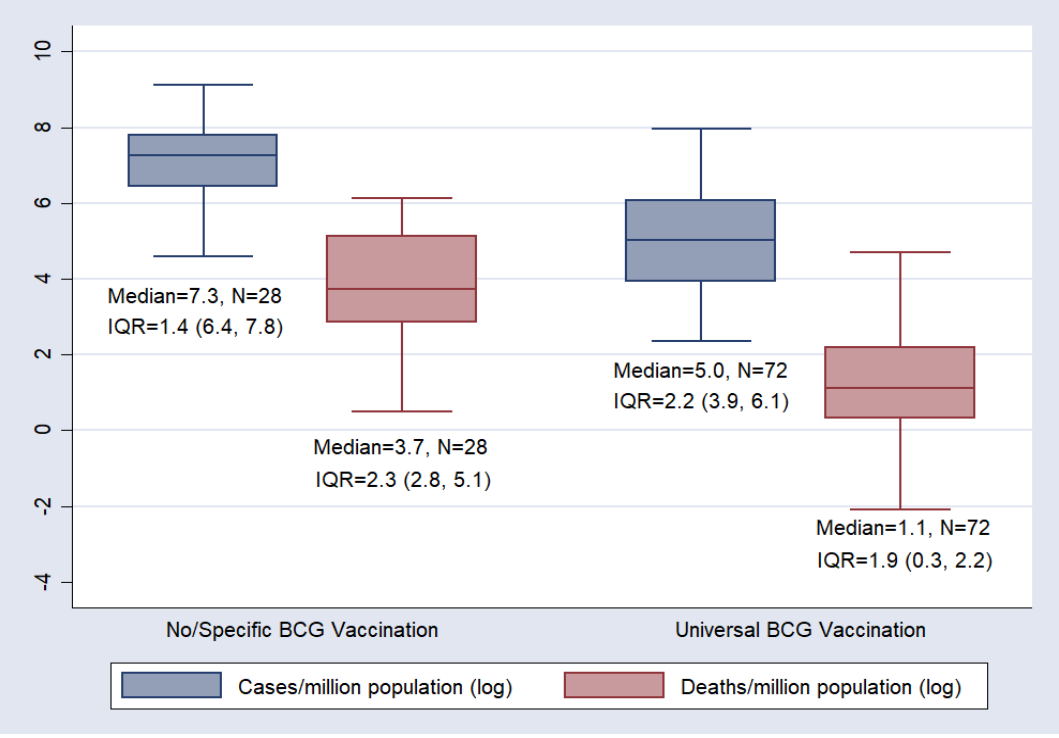

Fig 1: Log-normalized cases and deaths per 1 million population attributed to SARS CoV-2 by the two groups of countries following universal and specific (or no) BCG vaccination policy.

Table 1: Log-normalized multivariate linear regression models of deaths per 1 million population attributed to SARS CoV-2 and BCG immunization policy and coverage adjusting for other covariates (coefficients are exponentiated estimates of the parameters).

Exposure variables	Pearson correlation coefficients	Model 1: BCG vaccination policy	Model 2: BCG vaccination coverage
Median age	0.579***	0.11*** [0.07, 0.15]	0.13*** [0.08, 0.18]
Hospital beds[+]	0.305***	-0.07* [-0.15, 0.001]	-0.1* [-0.19, -0.01]
Days since 100[th] case	0.419***	0.02 [-0.01, 0.04]	0.00[NS] [-0.03, 0.03]
BCG policy[#]	NA	-1.81*** [-2.44, -1.18]	NA
BCG coverage	0.107[NS]	NA	-0.001[NS] [-0.03, 0.02]
Constant	NA	-0.79[NS] [-2.28, 0.69]	-1.94[NS] [-4.29, 0.41]
R-square value	NA	0.57	0.34
No. of observations	69– 98	98	69

*[+]Per 1000 population, [#]dichotomous variable with categories coded 0 (reference category) as countries following no or specific BCG vaccination policy and 1 as countries following universal BCG vaccination policy; ***p<0.001, **p<0.01, *p<0.05; [NS]: not significant; NA: Not applicable and [ ]: 95% confidence interval.*

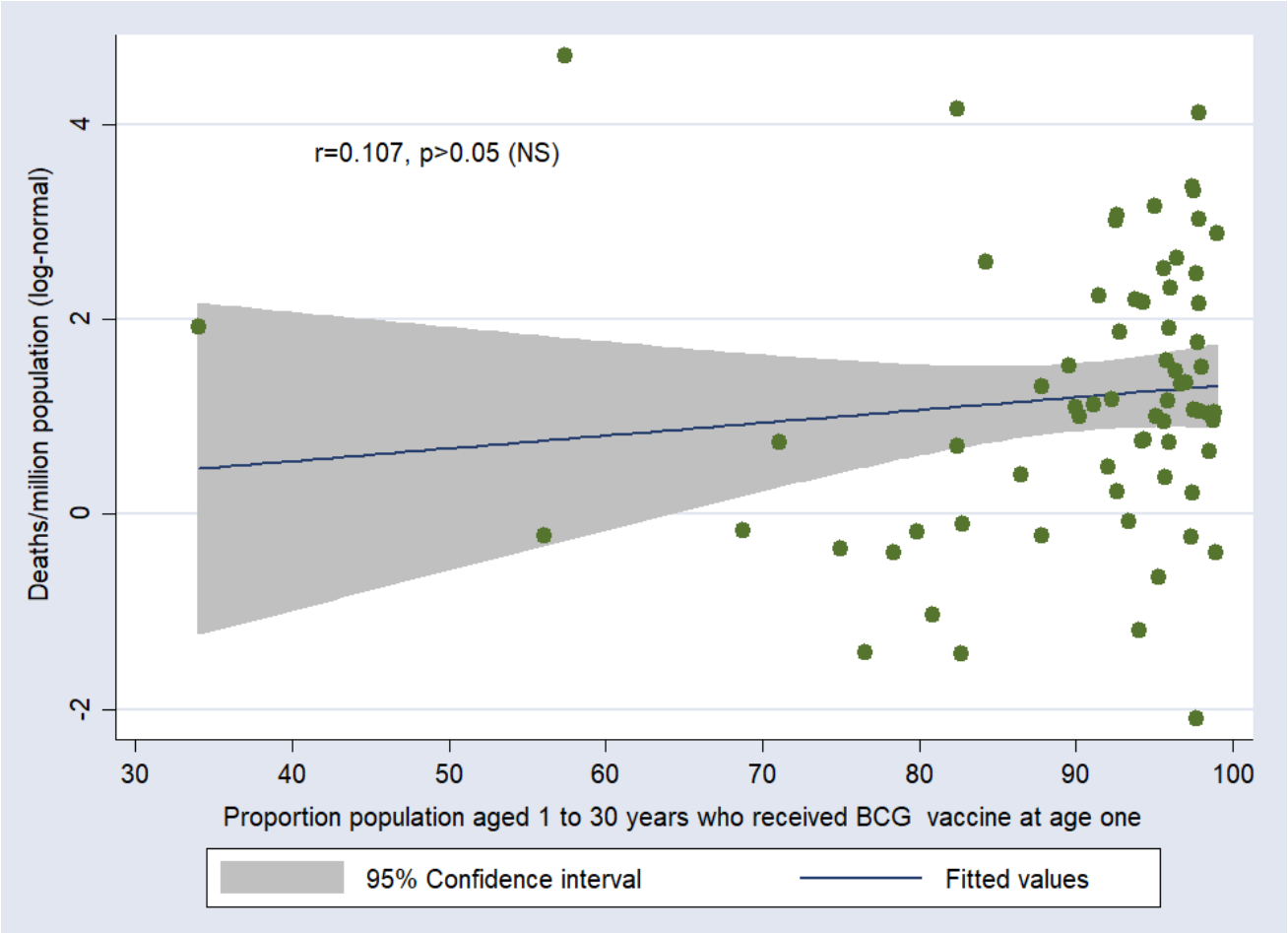

Fig 2: Association between SARS CoV-2 attributable deaths per 1 million population (log-normalized) and BCG vaccination coverage across countries that follow universal BCG vaccination policy.

The results from multivariate log-linear regression analysis, with standardized deaths per 1 million population as the outcome variable and BCG policy as the exposure variable of interest (Fig 2), show a statistically significant association between the absence of universal BCG vaccination and higher standardized death rate, even after controlling for other variables including median age, hospital beds and days since the 100th case (Table 1).

However, this result could also be due to plausible alternative explanations. To further verify this, we plotted the log-normalized deaths per 1 million population by proportion of the population aged 1– 30 years who would have received BCG vaccination at the age of 1 year for the countries that follow universal BCG vaccination. Results (r=0.107, p>0.05) suggest that there is no significant association between universal BCG coverage and SARS CoV-2 attributable deaths (See Fig 3).

To test our hypothesis, we performed multivariate log-linear regression analysis for the countries following universal BCG policy, with standardized deaths per 1 million population as the outcome variable and BCG immunization coverage as exposure variable of interest, controlled for the previously included confounding factors (Fig 3). We see that even here, results verified that there is no significant association between standardized death rate attributed to SARS Cov-2 and BCG immunization coverage. Hence, these findings reject the hypothesis.

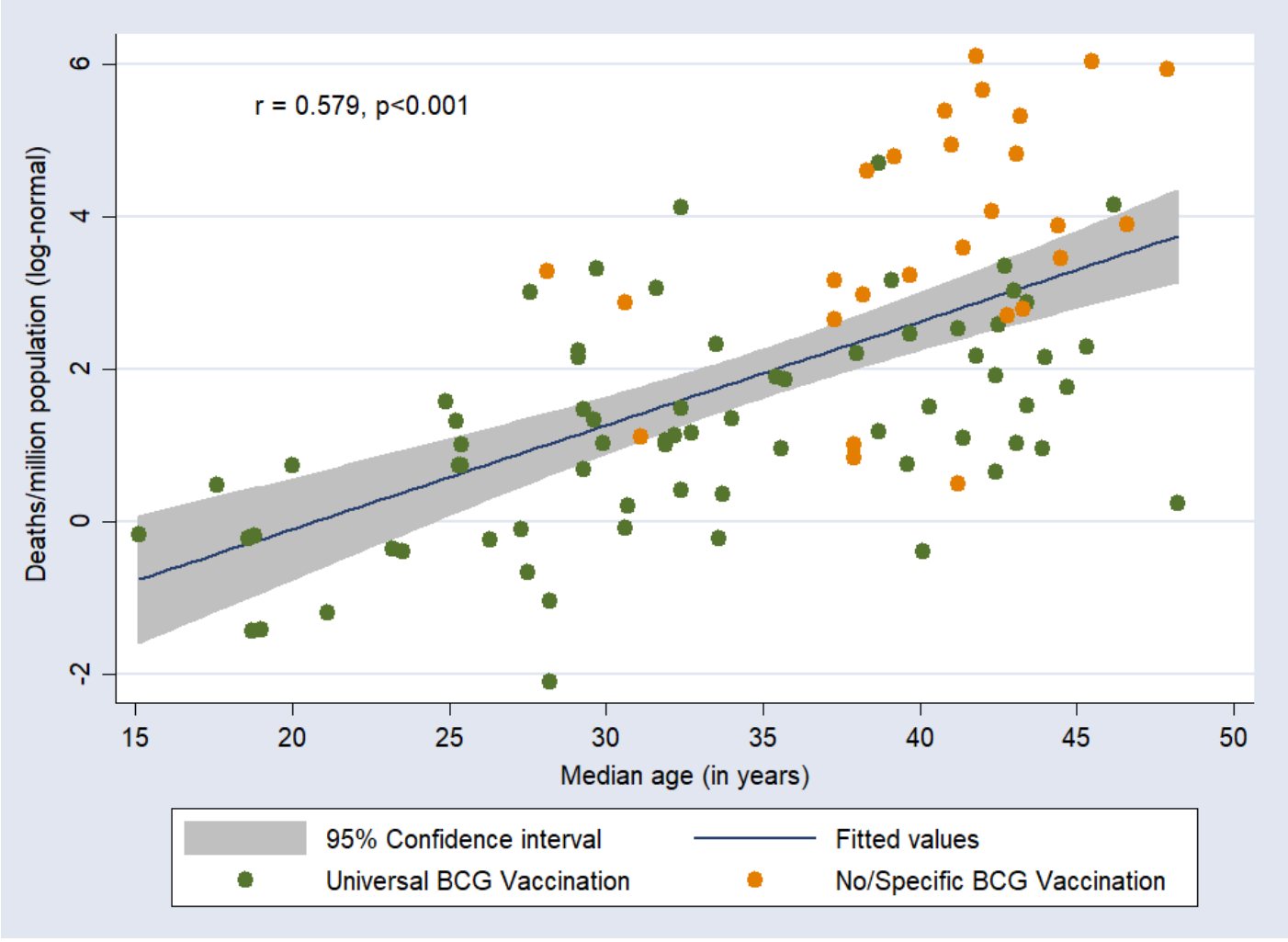

Fig 3: Association between national SARS CoV-2 attributable deaths per 1 million population (log-normalized) and median age by the two groups of countries with universal and specific (or no) BCG vaccination policy.

We observed a statistically significant association of median age ($p<0.001$) with death rates attributable to attributable to SARS CoV-2 in both of the models. We plotted a two-way graph of log-normalized deaths per 1 million against the median age of the population (Fig 3). There was a clear division between countries in terms of the death rate by BCG usage policy, establishing population age and associated comorbidities as a major confounding variable. It infers that apparent differences in SARS CoV-2 death rates of two groups are most likely linked with other factors and are not linked to the BCG vaccination policy or coverage present in the country.

DISCUSSION

This study aimed to determine if there is any association between BCG vaccine coverage and mortality attributed to SARS CoV-2. We have considered two group of countries throughout the study: one group recommends BCG vaccination only for specific groups or does not recommend vaccination at all, while the other group has universal BCG vaccination policy. Early studies suggested a statistically significant association between universal BCG vaccination policy and reduced mortality associated with SARS-CoV-2.[10-16] Unlike our analysis, most of these studies did not take into account the extent of BCG coverage (percentage of the population vaccinated) nor did they account for potential confounding effects such as the age structure of the population, medical care capacity, or the timing and progression of the epidemic.

In our study, the two models have been selected based on BCG policies to provide clarity on vaccination coverage and to help suggest where further research is needed. The first model (Fig 2), which considers both groups, shows a statistically significant association between BCG vaccination and deaths per 1 million attributed to SARS CoV-2. Also, it has been observed that countries with no BCG vaccine coverage or group-specific coverage have had a higher median number of cases as well as a higher number of deaths per 1 million. This model seems to be legitimate when we look at countries such as Japan, South Korea and Iran which have universal BCG vaccine coverage as well as low deaths in the early stages of the pandemic and compare these with countries including the USA, Italy and Spain which have not had a universal BCG vaccine policy in last four decades and experienced high SARS CoV-2 mortality.[9] While it is easy to jump to conclusions from the results of the first model, which considers both groups, it has been worthwhile to accommodate the second model, which takes into account only the group with universal BCG vaccine coverage. This second model takes into account a continuous outcome variable, i.e., the percentage of BCG coverage ($n=70$, mean=90.3, and SD=11.5). This model does not have statistically significant BCG vaccination coverage with regard to its association with SARS CoV-2 attributable deaths. This presents a potential paradox.

Looking at this situation, we cannot assertively claim that BCG has no association with the incidence of COVID-19 cases. Certain underlying elements need to be explored. Many developed nations do not have universal BCG vaccine policy[20] in place as TB is no longer considered to be a serious public health threat in these countries; they have advanced healthcare infrastructure and better access to medical facilities compared with developing countries.[21] At the same time, developed nations are at a different stage of the demographic transition and also have a different age structure as well as a different pattern of comorbidities.[22] These confounding factors can be attributed to the results coming from the first model, where universal BCG policy seems to be working to reduce mortality.[23,24]

Another peculiar and less explored aspect that could be the cause of this apparent paradox is the as yet unexplored effects of the BCG vaccine in suppressing symptoms arising due to SARS CoV-2 infection and ultimately giving rise to a higher number of asymptomatic patients within a population. It may also be possible that the vaccine prevents the progression of the disease after infection, since at present, only persons with severe symptoms tend to receive PCR tests in many countries. This hypothesis requires additional empirical corroboration, however. Studies show that asymptomatic cases could be anywhere between 4–75% of the people testing positive for SARS CoV-2.[25,26]

Controlling for other covariates such as geographical locations, environmental factors such as temperature and humidity, ethnicity and age-structure, the prevalence of comorbidities including cardiovascular disease, chronic respiratory disease, diabetes, standards of medical care, preparedness of the local health system, spread control measures such as social distancing and access to improved hand hygiene, underreporting of cases, testing ability and so on might seem relevant in the current situation yet it is difficult to establish the relevance of the confounders without results from well-designed randomized clinical trials. Two clinical trials addressing this question are underway and the WHO will evaluate the evidence when it is available. Meanwhile, in the absence of evidence, WHO does not recommend BCG vaccination for the prevention of COVID-19.[27]

LIMITATIONS

This study carries all the common constraints of an ecological study. Our findings are prone to significant bias from several unmeasured confounders such as the difference in timing and stages of the pandemic across nations and uncounted deaths as the result of under-testing. We used annual BCG immunization coverage among 1 year old children from 1989–2018 to estimate the current share of the population aged 1–30 years who were vaccinated at age 1 year and have generalized the figures for the whole population, which may be crude. The multivariate log-linear regression is limited in terms of included number of observations and covariates. Thus, our findings need to be interpreted with caution and verified by randomized clinical trials.

CONCLUSION

The present study finds no significant association between BCG vaccination coverage and mortality attributed to SARS CoV-2 across the countries where BCG immunization has been administered since or before 1990 and where BCG coverage varies between 35–99%. However, like other studies, our analysis also yields a significant positive association between higher SARS CoV-2 attributable mortality and the absence of universal vaccination across 103 countries. Further investigations suggest that this may be a coincidence caused by confounding factors such as age structure and comorbidity patterns of profoundly affected populations. Recently, WHO has also stated that there is no evidence that the Bacille Calmette-Guérin vaccine (BCG) protects people against infection with the SARS Cov-2 virus.[27]

REFERENCES

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DS, Du B. Clinical characteristics of coronavirus disease 2019 in China. New England Journal of Medicine. 2020 Feb 28.
2. World Health Organization. Coronavirus disease 2019 (COVID-19): situation report, 95. 2020 Apr 24.
3. Maharaj S, Kleczkowski A. Controlling epidemic spread by social distancing: Do it well or not at all. BMC Public Health. 2012 Dec 1;12(1):679.
4. Fast SM, Gonzalez MC, Markuzon N. Cost-effective control of infectious disease outbreaks accounting for societal reaction. PloS one. 2015;10(8).
5. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020 Feb 15;395(10223):497-506.
6. Chang D, Lin M, Wei L, Xie L, Zhu G, Cruz CS, Sharma L. Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside Wuhan, China. Jama. 2020 Mar 17;323(11):1092-3.
7. Khafaie MA, Rahim F. Cross-Country Comparison of Case Fatality Rates of COVID-19/SARS-COV-2. Osong Public Health and Research Perspectives. 2020 Apr;11(2):74.
8. de Figueiredo AM, Codina AD, Moreira DC, Figueiredo M, Saez M, León AC. Impact of lockdown on COVID-19 incidence and mortality in China: an interrupted time series study.
9. Arab-Mazar Z, Sah R, Rabaan AA, Dhama K, Rodriguez-Morales AJ. Mapping the incidence of the COVID-19 hotspot in Iran–Implications for Travellers. Travel Medicine and Infectious Disease. 2020 Mar 14.
10. Dayal D, Gupta S. Connecting BCG Vaccination and COVID-19: Additional Data. medRxiv. 2020.
11. Gursel M, Gursel I. Is Global BCG Vaccination Coverage Relevant To The Progression Of SARS-CoV-

2 Pandemic?. Medical Hypotheses. 2020 Apr 6:109707.
12. Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y, Otazu GH. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. medRxiv. 2020.
13. Sala G, Miyakawa T. Association of BCG vaccination policy with prevalence and mortality of COVID-19. medRxiv. 2020.
14. Shet A, Ray D, Malavige N, Santosham M, Bar-Zeev N. Differential COVID-19-attributable mortality and BCG vaccine use in countries. medRxiv. 2020.
15. Singh BR, Gandharva R. Are BCG Vaccination, Population Density, Median Age and Poverty Important Determinants of COVID-19 Pandemic Spread, Morbidity and Mortality?.
16. Hegarty PK, Kamat AM, Zafirakis H, Dinardo A. BCG vaccination may be protective against Covid-19. preprint. 2020.
17. de Bree LC, Marijnissen RJ, Kel JM, Rosendahl Huber SK, Aaby P, Benn CS, Wijnands MV, Diavatopoulos DA, van Crevel R, Joosten LA, Netea MG. Bacillus calmette–guérin-induced Trained immunity is not Protective for experimental influenza a/anhui/1/2013 (h7n9) infection in Mice. Frontiers in Immunology. 2018 Apr 30;9:869.
18. Arts RJ, Moorlag SJ, Novakovic B, Li Y, Wang SY, Oosting M, Kumar V, Xavier RJ, Wijmenga C, Joosten LA, Reusken CB. BCG vaccination protects against experimental viral infection in humans through the induction of cytokines associated with trained immunity. Cell host & microbe. 2018 Jan 10;23(1):89-100.
19. Pai M. BCG Against Coronavirus, Less Hype And More Evidence, Please. Forbes. 2020 Apr 12.
20. Zwerling A, Behr MA, Verma A, Brewer TF, Menzies D, Pai M. The BCG World Atlas: a database of global BCG vaccination policies and practices. PLoS medicine. 2011 Mar;8(3).
21. Hogan DR, Stevens GA, Hosseinpoor AR, Boerma T. Monitoring universal health coverage within the Sustainable Development Goals: development and baseline data for an index of essential health services. The Lancet Global Health. 2018 Feb 1;6(2):e152-68.
22. Institute for Health Metrics and Evaluation. GBD compare.
23. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, Ji R, Wang H, Wang Y, Zhou Y. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. International Journal of Infectious Diseases. 2020 Mar 12.
24. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. Jama. 2020 Mar 23.
25. Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Eurosurveillance. 2020 Mar 12;25(10):2000180.
26. Heneghan C, Brassey J, Jefferson, T. COVID-19: What proportion are asymptomatic?. CEBM. 2020 Apr 6.
27. World Health Organization. Bacille Calmette-Guérin (BCG) vaccination and COVID-19: scientific brief, Apr 12 2020. World Health Organization; 2020.