

## RESEARCH ARTICLE

# Convergence between global BCG vaccination and COVID-19 pandemic

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## Abstract

The novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has kept the whole world in tenterhooks due to its severe life-threatening infectious disease, COVID-19. The virus is distinct from its cousins, SARS-CoV and MERS-CoV in terms of severity of the infection. The obligated killing properties of the SARS-CoV-2 virus is mediated by its unique structure. Efforts for developing vaccines for COVID-19 are ongoing, but it is unlikely to be available in the immediate future. Due to the absence of precise treatment, the investigators are discovering other effective, protective, and healing choices. However, the lower than a predictable number of SARS-CoV-2 cases in countries with fragile health systems is mystifying. Recently, there has been a buzz about the protective effect of Bacille Calmette-Guérin (BCG) vaccine in COVID-19 through long-term boosting of trained immunity. Based on **epidemiological correlations**, we link up that BCG vaccination adopted by different countries might influence the SARS-CoV-2 transmission patterns and/or COVID-19 associated mortality through the vaccine's capacity to confer heterologous protection. A number of clinical studies are underway to investigate this possibility but even if they prove effective-many questions will remain. Moreover, responsible **stewardship of the BCG** vaccine in the context of the COVID-19 epidemic is directly needed.

## KEYWORDS

BCG vaccination, correlation data, COVID-19, severity variation, trained immunity

## 1 | INTRODUCTION

At the end of 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, China.<sup>1</sup> A few weeks later, in January 2020, a series sequencing analysis from lower respiratory tract samples identified a novel virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as a causative agent for that observed pneumonia cluster.<sup>2</sup> The 2019 novel coronavirus or the SARS-CoV-2 as it is now called, is rapidly spreading from its origin in Wuhan City, China to the rest of the world.<sup>3</sup> SARS-CoV-2 has been declared as a public health emergency of international concern by the World Health Organization (WHO).<sup>4</sup> On 11th March 2020, the WHO Director-General, Dr Tedros Adhanom Ghebreyesus, named the

disease caused by the SARS-CoV-2 as “COVID-19” and subsequently declared it a pandemic due to the widespread infectivity and high contagion rate.<sup>5</sup> Patients contracting the severe form of the disease constitute approximately 15% of the clinically diagnosed cases.<sup>6</sup> The new coronavirus has become a worldwide health threat<sup>7</sup>: up to 08 June 2020, COVID-19 has caused the death of 406 552 individuals worldwide and infected more than 7 114 524.<sup>8</sup> Human coronaviruses typically cause respiratory and enteric infections.<sup>9</sup> Clinical features and risk factors are highly variable, making the clinical severity range from asymptomatic to fatal.<sup>10</sup>

Initially, the coronavirus belongs to a family of viruses that may cause various symptoms such as pneumonia, fever, breathing difficulty, and lung infection.<sup>11</sup> The SARS-CoV-2 infection mainly

presents flu-like symptoms such as fever, cough, and asthenia, similar to other coronaviruses.<sup>12</sup> Susceptibility seems to be associated with age, biological sex, and other health conditions.<sup>13</sup> Although severe lung injury has been described at all ages, in some high-risk individuals, such as the elderly or those affected by multimorbidities, the virus is more likely to cause severe interstitial pneumonia, acute respiratory distress syndrome and subsequent multiorgan failure, which are responsible for severe acute respiratory failure and high death rates. Typically, affected individuals display a variable extent of dyspnoea and radiological signs.<sup>14</sup>

The SARS-CoV-2 is a novel RNA virus, with a typical crown-like appearance under an electron microscope due to the presence of spike glycoprotein on its envelope.<sup>15</sup> The SARS-CoV-2 virus belongs to the same family as SARS-CoV-1 and Middle East respiratory syndrome coronavirus.<sup>16</sup> There are four genera of CoVs:  $\alpha$ -coronavirus,  $\beta$ -coronavirus probably present in bats and rodents; while  $\delta$ -coronavirus and  $\gamma$ -coronavirus probably represent avian species.<sup>10,16,17</sup> These viruses are common in animals worldwide, but very few cases have been known to affect humans. The sources of SARS-CoV2 may be combined natural and zoonotic origin. Two conditions that can reasonably clarify the origin of SARS-CoV2 are: (a) natural selection in a lower animal host before zoonotic transmission; and (b) natural selection in human beings succeeding zoonotic transmission.<sup>10,17</sup> In response to the outbreak, the Chinese Centre for Disease Control and Prevention (China CDC) dispatched a rapid response team to accompany health authorities of Wuhan city to conduct epidemiological and etiological investigations. The WHO confirmed that the outbreak of the coronavirus epidemic was associated with the Huanan South China Seafood Marketplace, but no specific animal association was identified.<sup>18</sup> Scientists immediately started to research the source of the new coronavirus, and its genome sequence of COVID-19.<sup>19</sup> This virus blow-out quickly throughout China within a month. After infecting and causing the death of thousands of persons in China, the virus has spread, reaching Italy and other European countries and the United States<sup>20-22</sup> with the number of confirmed new cases currently increasing every day.

On 20th March 2020, WHO Director-General said that the "greatest concern" was COVID-19 spreading in countries with fragile health systems.<sup>23</sup> Although countries like Bangladesh, India, Philippines, Thailand, and Nepal have reported their first confirmed cases of the SARS-CoV-2 virus in late January, widespread community spread has not been reported. Contrary to such justified expectations/predictions, on 13 March 2020, the WHO declared Europe as the epicenter of the COVID-19 pandemic with Italy having the worst hit. In the United Kingdom (UK), London is the worst affected. Similarly, in the United States of America, New York City is the most affected. However, in later 23 May 2020 South America (particularly Brazil) has become a new epicenter. Meanwhile, COVID-19 has not yet hit the Middle East and North Africa as hard as the rest of the world.<sup>24</sup>

Early evidence from the current COVID-19 pandemic suggests that the disease intensity and case fatality rate vary in different parts of the world.<sup>25</sup> A better understanding of the epidemiological

characteristics of COVID-19, as to why people living in certain nations are more susceptible, would help us effectively control this pandemic. These understandings might putatively support vaccine development for COVID-19 treatment. These differences are attributed to differences in cultural norms, mitigation efforts, and health infrastructure.<sup>26</sup> These national differences in COVID-19 impact can be explained by the different national policies with respect to Bacille Calmette-Guérin (BCG) childhood vaccination. BCG is a vaccine-derived from the live attenuated strain of *Mycobacterium bovis* for the vaccination against tuberculosis (TB) that is given to infants intradermally shortly after birth in high-risk regions. The WHO recommends neonatal BCG vaccination in countries with a high incidence of TB, with BCG being one of the safest and most widely distributed vaccines worldwide.<sup>27</sup> Even though we are still in the midst of the coronavirus pandemic, the disproportionately smaller number of cases reported from disadvantaged/low-income countries remains puzzling. Here we hypothesize that general BCG vaccination policies adopted by different countries might have impacted the transmission patterns and/or COVID-19 associated morbidity and mortality.

## 2 | MATERIALS AND METHODS

The inclusion and exclusion criteria for this study: (a) collected data of total numbers of COVID-19 infected population and death from every country in the world based on COVID-19 dashboard by the Centre for Systems Science and Engineering at Johns Hopkins University (<https://coronavirus.jhu.edu/map.html>), WHO (<https://covid19.who.int/> and [worldometers.info/coronavirus/](http://worldometers.info/coronavirus/)) on 05 June 2020. (b) Sorted these data from BCG vaccinated countries that followed universal BCG vaccination policy to nonvaccinated countries, and (c) examined the thirteen topmost countries associated with COVID-19 infection and death. Comparison studies were performed on the number of cases and deaths of COVID-19 people in BCG vaccinated countries with nonvaccinated countries. The Student's *t* test, statistical analysis also performed accordingly.

## 3 | RESULTS

We compare a large number of countries' BCG vaccination policies with the morbidity and mortality for COVID-19. Interestingly, countries in absence of universal policies of BCG vaccination like the United States, Italy, Nederland, France have been found more severely exaggerated compared to countries having universal and long-standing BCG policies. The countries without such universal policies on BCG vaccination are among the worst hit by COVID-19 infection. Many other countries including China, Korea, Bangladesh, India, Japan, and the Russian Federation, have mandatory childhood BCG vaccines against TB. These countries have so far, a relatively low per capita death rate from COVID-19 compared to countries that have no mandatory BCG vaccines (United States, Spain, France, Italy, the Netherlands).

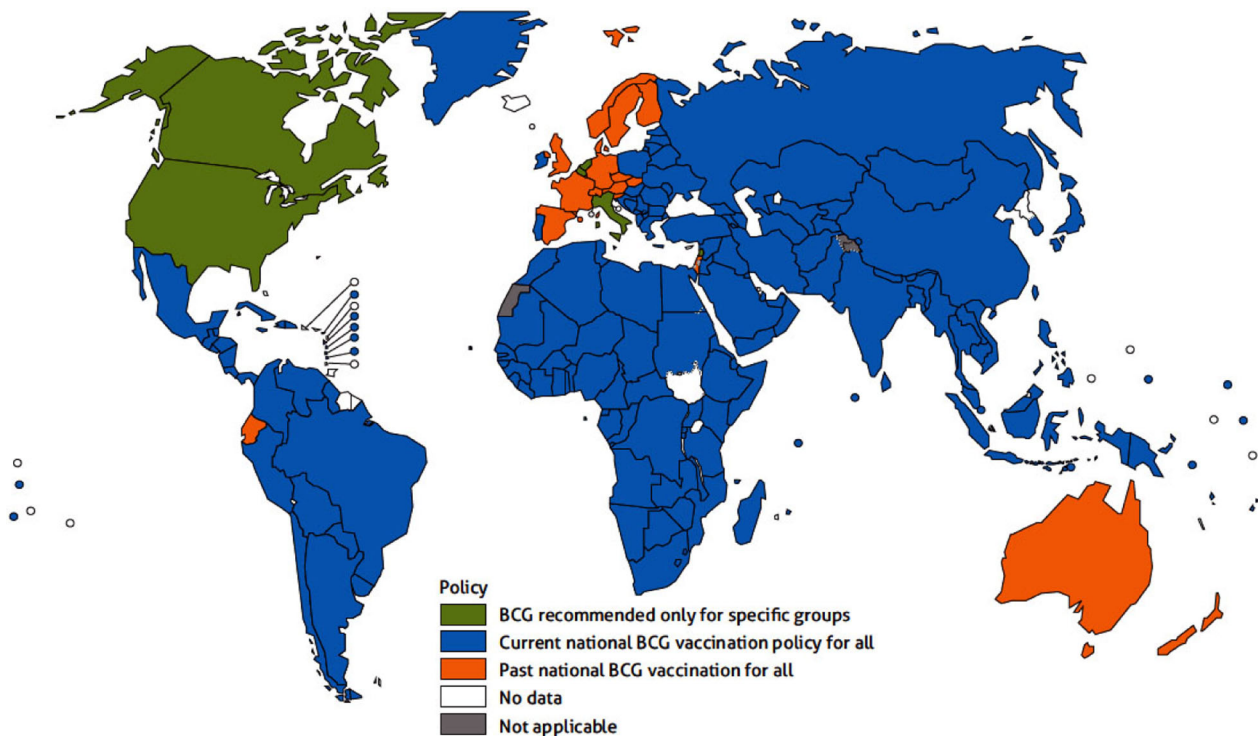
Interestingly, the BCG vaccine strain used in Japan, Brazil, and Russia is one of the original strains, while further modified BCG strains are used for vaccination in European countries. Countries that have a late start of universal BCG policy had high mortality, consistent with the idea that BCG protects the vaccinated elderly population.<sup>27</sup> We also noticed that BCG vaccination also reduced the number of reported COVID-19 cases in a country. The combination of reduced morbidity and mortality makes BCG vaccination a possible new tool in the fight against COVID-19.<sup>28</sup>

An epidemiological data summarizes national policies on BCG vaccination (Figure 1) and COVID-19 hotspots (Figure 2). Among 213 countries for which data were collected, 154 recommended universal BCG vaccination, the top 13 reported having had a national BCG policy for everyone in the past, and the remaining six countries had policies of selective vaccination for at-risk individuals in high-risk groups (Figure 1). According to date on 05 June 2020, the COVID-19 deaths/million are 327, 590.1, 823.9, 580.3, 557.1 (Figure 3A) and rate of deaths/total infected cases are 5.8, 16.2, 14.1, 11.3, 14.4 in BCG nonvaccinated countries like United States, UK, Belgium, Spain, and Italy, respectively (Figure 3B) where 337.3, 198.7, 159.4, 152.7, 142.7 (Figure 3A) and 6.6, 8.5, 5.5, 2.7, 4.3 (Figure 3B) in BCG vaccinated countries like Ireland, Ecuador, Brazil, Peru, and Portugal, respectively (Table 1 in details). These data suggest that the rate of deaths per total infected cases is higher in BCG nonvaccinated countries than in vaccinated countries. It can be argued that observation/correlation does not mean causation. These data are observational and based on a single time-point and that there may be

several confounding issues such as limited testing and reporting in many countries. In addition, the protective effect of BCG is found in the incidence and mortality of COVID-19 between countries with and without a BCG vaccination program.<sup>29</sup> It might be concluded that countries with a national program of whole population BCG vaccination appear to have a lower incidence and death rate from COVID-19. Similar results have also been found from other studies that epidemiological analyses of COVID-19 incidence might correlate to nation-based BCG vaccination policies.<sup>29,30</sup> The observations of these studies indicate a higher COVID-19 related morbidity and mortality in those countries which do not have a current or recent, universal BCG vaccination policy. However, we cautiously visualized the data and found that these epidemiological studies are based on hypothesis-generating only.

#### 4 | DISCUSSION

BCG is well known for its ability to induce a heterologous immunomodulatory effect on nonrelated conditions, a mechanism which is well understood and documented in the infectious disease literature.<sup>31</sup> There is evidence with a low to moderate risk of bias that BCG vaccination prevents respiratory infections (pneumonia and influenza) in children and the elderly. This heterologous immunomodulatory effect has been shown to last up to 1 year following vaccination.<sup>32</sup> Trained immunity inducing agents reprogram bone marrow hematopoietic stem cells and multipotent progenitors



**FIGURE 1** BCG vaccination policy by country. Source: The BCG World Atlas 2nd Edition, <http://www.bcgatlas.org/>, accessed 23 July 2019. BCG, Bacille Calmette-Guérin

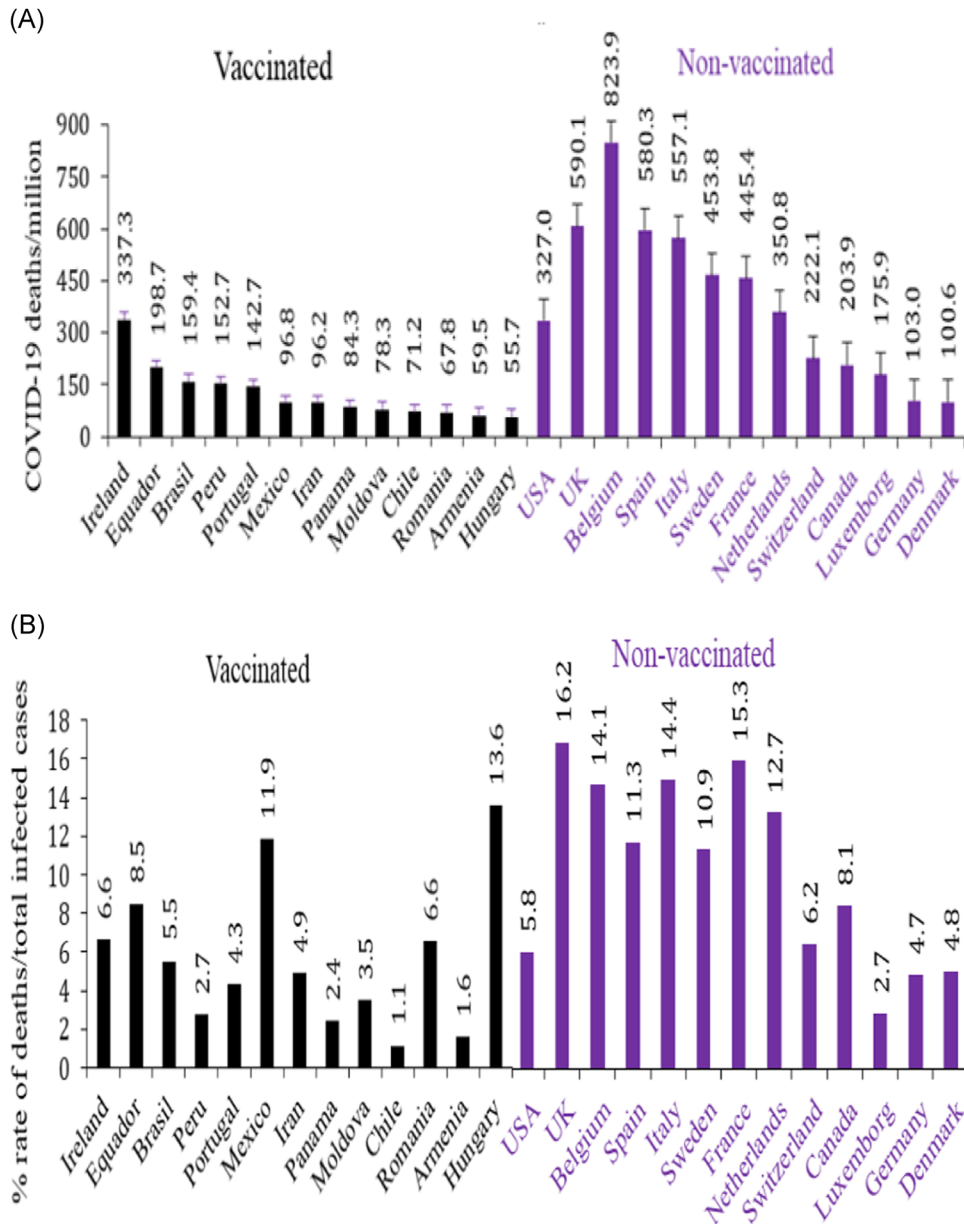


**FIGURE 2** Global distribution of COVID-19 cases. Source: COVID-19 Dashboard by the Centre for Systems Science and Engineering at Johns Hopkins University. <https://coronavirus.jhu.edu/map.html>

through epigenetic and metabolic changes, resulting in a more robust response in differentiated innate immune cells, following an encounter with a pathogen. Interestingly, the BCG vaccine has the potential to induce epigenetic reprogramming of the innate immune system, conferring protection against experimental infection with an attenuated yellow fever virus vaccine strain<sup>33</sup> and to enhance immune responses to other vaccines in general including influenza vaccination.<sup>34</sup> In epidemiological studies, neonatal BCG vaccination is associated with a reduction in all-cause child mortality by 30%, widely thought to be related to a reduction in rates of neonatal sepsis and pneumonia.<sup>27</sup> In mouse models, BCG was found to induce a trained immune response to avian influenza A (H7N9), however, it was not associated with a clinical difference in survival, clinical scores, or pulmonary inflammation.<sup>35</sup> Interestingly, BCG is also an effective immunotherapy in oncology. For example, intravesical BCG therapy is used for the treatment of nonmuscle invasive bladder cancer, being a standard of care to achieve a reduction in tumor progression and recurrence.<sup>36,37</sup> Children vaccinated with BCG suffer less from other respiratory illnesses; it could protect against asthma and autoimmune diseases such as type 1 diabetes.<sup>38</sup> The ability for BCG vaccination to induce a trained immune response to nonrelated pathogens raises the exciting possibility that it may have a role in protecting against the COVID-19 virus.

Given the widespread inconsistencies in collecting data relating to COVID-19 between countries, consideration of the stage of the COVID-19 pandemic in each country, differences in testing rates, isolation policies, national disease burden, and demographics all must

to take into consideration. So, these need to be interpreted with a mathematical explanation with all parameters. Moreover, the association between BCG vaccination and prevalence and mortality of COVID-19 in different countries is difficult to confirm and validate due to broad differences between countries such as socioeconomic status, availability, and sensitivity of diagnostic tests and the criteria for testing, time of arrival of the pandemic, demographic structure, and national control strategies to limit the spread of COVID-19. Thus, the WHO released a scientific brief cautioning against indiscriminate use of BCG in COVID-19 until appropriate evidence from ongoing clinical studies becomes available.<sup>30</sup> In our study, the several variables like the difference in testing strategies, demographics, nation's ability to respond to the pandemic, prevalence of comorbidities, and different stages of the pandemic across various countries might have a significant impact on these associations/correlations and are necessarily interpreted carefully. Calculation of our studies have summarized the correlation between BCG vaccination policy and COVID-19 morbidity and mortality across countries in Table 1. The calculation of the study indicates a significant correlation between BCG vaccination and COVID-19 frequency of cases and/or mortality, where countries with universal BCG vaccination policies showed fewer cases and/or deaths. The significant correlation is maintained on the basis of GDP per capita, population density and size, geographic region, net migration rate, and other factors. We also found that the most significant confounding factor is low COVID-19 incidence and deaths where countries adopted BCG policy and suggest that BCG vaccination may be a protecting factor.



**FIGURE 3** Comparison of the number of SARS-CoV-2 deaths/million and percentage rate (% rate). SARS-CoV-2 deaths/million if deaths/total infected people between countries that have provided a national BCG vaccination program and those that did not have or have stopped their national BCG vaccination programs (A) and percentage rate if deaths/total infected people between vaccinated counties and nonvaccinated counties (B) on 05 June 2020. BCG, Bacille Calmette-Guérin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Vaccines provide protection to a particular pathogen by inducing effector mechanisms directed to that pathogen. Since the introduction of the BCG vaccine in 1921, an increasing body of evidence has demonstrated its ability to exert a range of nonspecific effects (NSEs) beneficial for a range of other conditions.<sup>39,40</sup> The BCG, live attenuated vaccine can protect against unrelated pathogens, some of which cause acute respiratory tract infections.<sup>39</sup> BCG has the ability to train the innate immune system to generate an immune memory-like response against secondary infections, a process also termed “trained immunity” which helps in faster recognition triggering a quicker inflammatory response.<sup>33,41</sup> In innate immune cells, of the “trained immunity,” BCG

induces histone modifications and epigenetic reprogramming at the promotor sites of genes encoding inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor.<sup>41</sup> This trained immunity also offers protection against a variety of pathogens (*Salmonella*, *Shigella*, malaria, respiratory viruses, etc) other than *M. tuberculosis*, and forms the basis of its use in bladder cancer, melanoma, etc. However, this NSE is mostly short-lived and wanes soon after the primary BCG stimulus is cleared from the body. By the mechanism of the NSEs, the BCG vaccine has shown to reduce the mortality in children. Though a few observational studies suggest that the NSEs may last till adulthood, but the overall evidence is still inadequate and is of low quality.<sup>41,42</sup>

**TABLE 1** COVID-19 infected cases per million population with BCG vaccinated and nonvaccinated countries on 05 June 2020

Country	Country with National BCG Immunization Coverage					Country with no National BCG Immunization Coverage							
	Total cases	Total deaths	%	Case/1 M pop	Deaths/1 M Pop	Pop in M	Country	Total cases	Total deaths	%	Case/1 M pop	Deaths/1 M pop	Pop in M
Brazil	614 941	34 021	5.53	2894.51	160.14	212.451	United States	1 872 660	108 211	5.78	5659.90	327.06	330.8647
Russia	440 538	5376	1.22	3018.83	36.84	145.9302	UK	283 079	39 987	14.13	4171.47	589.25	67.86077
India	226 770	6363	2.81	164.44	4.61	1379.011	Spain	240 660	27 133	11.27	5147.42	580.34	46.75354
Peru	183 198	5031	2.75	5562.03	152.75	32.93724	Italy	234 013	33 689	14.40	3870.04	557.14	60.46781
Turkey	167 410	4630	2.77	1986.54	54.94	84.2722	France	189 569	29 068	15.33	2904.67	445.39	65.26352
Iran	164 270	8071	4.91	1957.63	96.18	83.91258	Germany	184 472	8635	4.68	2202.25	103.09	83.76527
Chile	118 292	1356	1.15	6191.90	70.98	19.1043	Canada	95 269	7717	8.10	2525.82	204.60	37.71812
Mexico	105 680	12 545	11.87	819.65	97.30	128.9331	Belgium	58 767	9548	16.25	5072.21	824.09	11.58608
S Arabia	93 157	611	0.66	2679.04	17.57	34.77253	Netherlands	47 148	6009	12.74	2752.00	350.74	17.13225
Pakistan	89 249	1838	2.06	404.65	8.33	220.5563	Sweden	41 883	4562	10.89	4148.98	451.92	10.09478
China	84 171	4638	5.51	58.48	3.22	1439.324	Switzerland	30 913	1921	6.21	3573.73	222.08	8.650074
Quarter	63 741	45	0.07	2270.136	16.03	2.807805	Israel	17 562	291	1.66	1909.41	31.64	9.19759
Bangladesh	57 563	781	1.36	349.78	4.75	164.5692	Austria	16 805	670	3.99	1866.65	74.42	9.002749
Belarus	45 981	253	0.55	4865.95	26.77	9.449534	Bahrain	13 296	21	0.16	7837.64	12.38	1.69643
Ecuador	40 966	3486	8.51	2324.62	197.81	17.62268	Denmark	12 011	582	4.85	2074.16	100.50	5.790777

Abbreviations: BCG, Bacille Calmette-Guérin; M, million; pop, population; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Sources: Countries with topmost infected cases with SARS-COV-2 were included. Coronavirus related statistics were based on data obtained from <https://www.worldometers.info/coronavirus/> (According to the latest update on 05 June 2020, 12:59 GMT) and <https://coronavirus.jhu.edu/map.html>.

The COVID-19 pandemic has prompted an urgent need for novel vaccination or means of reducing disease morbidity and mortality in the global community. BCG vaccine's heterologous beneficial effect against non-TB infections is well known.<sup>43</sup> Thus, researchers want to test whether the TB vaccine could have a similar effect against the new coronavirus, either by reducing the risk of being infected or by limiting the severity of the symptoms. It has been postulated that patients with comorbidities such as diabetes and hypertension which are treated with angiotensin-converting enzyme (ACE) inhibitors are at higher risk for developing the severe disease due to COVID-19.<sup>44</sup> Patients on ACE inhibitors have greater expression of ACE receptors which have been shown to be the entry point into human cells for COVID-19 virus. This leads to the corollary that any drug or vaccine which has the potential to increase the level of ACE may help downregulate the expression of ACE2 receptors, thereby having some beneficial effect on the host immune system against COVID-19. Earlier animal studies have shown that ACE-like activity increased with inflammation induced by BCG suppressed the induction of the inflammatory response in both lungs and spleen.<sup>45</sup> The BCG vaccine does not directly protect against the coronavirus but provides a boost to the immune system which may lead to improved protection and a milder infection.<sup>45</sup> However, in COVID-19 cases, some patients have also suffered extreme immune responses, with the uncontrolled production of proinflammatory cytokines as called cytokine storm. In this case, BCG might help to better orchestrate this inflammatory immune response and acts as a "military exercise in peacetime" so that the body can "fight the enemy effectively in wartime".<sup>46</sup> The basis of the possible use of the BCG vaccine against COVID-19 can be explained via its common characteristic NSEs as "trained immunity" over the immune system. The NSEs of BCG are mostly facilitated by potentiating trained immune response through epigenetic mechanisms. These epigenetic changes within the innate cells act as de novo enhancers to boost the immune response against a secondary challenge.<sup>31,34,36</sup>

Though the epidemiological association between BCG and COVID-19 is striking, it does not prove a causal relationship unless tested in well-designed clinical trials.<sup>47</sup> Also, we should not forget that the NSEs of the BCG vaccine have not been well-studied in human beings and their clinical relevance is unknown.<sup>48,49</sup> Therefore, in the absence of evidence, the BCG vaccination for the prevention of COVID-19 cannot be recommended. The result of the ongoing randomized clinical trials (RCTs) shall guide us further. Several clinical trials have been recently launched to ascertain whether BCG may indeed offer protection against COVID-19, including in healthcare workers (Table 2). It is noted that BCG strains that appear to be associated with lower COVID-19 mortality (eg, BCG Japan and BCG Russia) are both early strains, whereas BCG Denmark, which seems to induce less protection against COVID-19.

The sole maker and supplier of BCG, Merck & Co, Inc the United States is the only source of BCG to many other countries around the world. Due to the increasing global demand for BCG treatment and as the only source of OncoTICE BCG (is indicated for the treatment of primary or concurrent carcinoma-in-situ of the urinary bladder) in many countries, Merck anticipates this shortage to continue

throughout 2020.<sup>50</sup> Although the producer of BCG has increased its manufacture of BCG by more than 100% and is manufacturing the vaccine to the completest extent of their producing capacity, the company is not able to sustain the cumulative worldwide demand of BCG since it is a lengthy and complex production process. This has led to supply constraints and a BCG shortage.<sup>50</sup> The COVID-19 treatment may also be affected by global shortages of the BCG vaccines.

It has already been proved that the BCG is a lifesaving preventive tool against TB-related morbidity and mortality. In many high TB burden countries, BCG has routinely been administered to new-borns since the 1970s. Therefore, healthcare workers under 50 years of age are likely to have received BCG at birth. In these countries, healthcare workers are also commonly infected with *M. tuberculosis* (ie, have TB infection). Under these circumstances, BCG administration may lead to a strong local reaction at the injection site (similar to a strongly positive tuberculin skin test reaction). Unfortunately, as a consequence of the article by Miller et al,<sup>26</sup> some healthcare workers (and members of the general public) are now requesting revaccination as protection for themselves and vaccination of their non-BCG-vaccinated dependents, especially older children. This is understandable given the fear of COVID-19. The WHO issued a scientific brief calling for BCG to be used for neonatal BCG vaccination only in high-risk settings and not for the prevention of COVID-19. Because the correlation between BCG vaccination and COVID-19 is based on nonpeer reviewed work liable to methodological errors and inaccurate interpretation of study results. Most importantly solid evidence for prevention studies of BCS vaccine in a pandemic should be obtained from prospective RCTs, rather than retrospective studies. In this context, it is essential that some high-lighted points should be clear recommended for BCG vaccination.

(a) The first priority remains for neonatal BCG vaccination to be given to all infants in high TB burden settings. No neonate (unless clinically indicated) should leave a birthing facility without BCG vaccination. (b) Infants under 1 year of age who have not yet received BCG, require a catch-up vaccination at any health facility where BCG is available, even if they are the only infant to be vaccinated from a vial and there is a risk of wastage. (c) As the risk for TB meningitis and military TB is the highest in young children under 3 years of age, catch-up BCG, if missed at birth or thereafter, should be administered to this age group. (d) Older children (>3 years) should not routinely receive BCG if missed at birth, although we acknowledge that different countries have different guidelines regarding the upper age threshold, and the national level guidance should be followed. (e) BCG is ineffective as postexposure prevention for TB. Following documented exposure to *M. tuberculosis*, it is essential that TB preventive therapy is provided according to WHO and local TB guidelines. (f) Finally, there is currently no compelling evidence, either for or against, that BCG protects individuals from COVID-19. Outside of a clinical trial, healthcare workers (or other individuals) should therefore not receive BCG vaccination for protection against COVID-19. Healthcare workers, many of whom are at high risk of COVID-19 disease, should consider enrolling in trials, including those where BCG is used as an intervention, if feasible. Their participation would generate much-needed data regarding any potential benefit or

**TABLE 2** Clinical trials of BCS vaccine in COVID-19 patients worldwide

Trial ID	Study design	Intervention	Comparison group(s)	Phase	Conditions	Patients (N)	Current primary outcomes	Sponsor
Recruiting status								
NCT04328441	RCT	BCG vaccine	Placebo	3	COVID-19	1500	Healthcare workers absenteeism	UMC Utrecht
NCT04379336	RCT	BCG vaccine	Placebo comparator	3	COVID-19	500	Incidence of hospitalization	TASK Applied Science
NCT04347876	OCC	BCG vaccination	Tuberculin test	...	COVID-19	100	Pneumonia severity index	Assiut University
NCT04327206	RCT	BCG vaccine	0.9% NaCl	3	COVID-19 respiratory illness	10078	COVID-19 disease incidence	Murdoch Childrens Research Institute
NCT04414267	RCT	BCG vaccine	Placebo	4	COVID-19, COPD	900	Positive for the respiratory questionnaire related to COVID-19	Hellenic Institute for the Study of Sepsis
NCT04348370	RCT	BCG vaccine	Placebo	4	Infection viral, COVID-19	1800	Incidence of COVID-19 Infection	Texas A&M University
Not yet recruiting								
NCT04362124	RCT	BCG vaccine	Placebo	3	COVID-19	1000	Incidence of COVID-19 cases confirmed	Universidade de Antioquia
NCT04350931	RCT	BCG vaccine II	Placebo	3	COVID-19	900	Incidence of confirmed COVID-19	Ain Shams University
NCT04369794	RCT	BCG vaccine	Placebo	4	COVID-19	1000	Clinical evolution of COVID-19	University of Campinas, Brazil
NCT04373291	RCT	BCG Denmark	Saline	3	COVID-19, NSEs of vaccine	1500	Unplanned absenteeism	Bandim Health Project
NCT04384614	OCS	COVID + testing by PCR	TDR	...	COVID-19 BCG vaccination	400	Epidemiological demographic characteristics	Direction des Soins de Santé de Base
NCT04384549	RCT	BCG Vaccine	Placebo	3	Infection viral, COVID-19	1120	Symptomatic COVID-19	Assistance Publique—Hôpitaux de Paris
NCT04387409	RCT	VPM1002, rBCG vaccine	Placebo	3	Infection, respiratory tract	1200	Absenteeism due to respiratory disease	Vakzine Projekt Management GmbH
Active, not recruiting								
NCT04417335	RCT	BCG vaccine	Placebo	3	COVID-19	2014	SARS-CoV-2 related hospital admission	Radboud University

Abbreviations: COPD, chronic obstructive pulmonary disease; II, intradermal injection; NSEs, nonspecific effects; OCC, observational case-control; OCS, observational Cross-Sectional; RCT, randomized clinical trial; TDR, special program for research and training in tropical disease.

Source: <https://clinicaltrials.gov/ct2/results?cond=COVID&term=BCG&cntry=&state=&city=&dist=>.



risk of BCG vaccination in the context of COVID-19. More significantly, the BCG vaccines applied for such clinical trials should be obtained precisely for clinical research, and not from the inadequate supply existing for children in low-income countries.

## 5 | CONCLUSIONS

In the face of a global health crisis imposed by the COVID-19 pandemic, several clinical trials are still ongoing to find a cure. BCG vaccination has been proposed, through epidemiological studies, as having a role in reducing the impact of this disease. However, researchers should anticipate more BCG shortage. As well, if proven effective against COVID-19, accountable stewardship of the BCG vaccine in the context of the COVID-19 epidemic is urgently needed.

Furthermore, the more genetic screening and population-based genome-wide studies in divergent geographical regions are needed to better understand the host-pathogen interactions in a region-specific manner, which could pave the way for the genesis of more region-specific therapeutics and treatment regimens. Further research is needed to study the magnitude and duration of the NSEs of BCG vaccine on all-cause mortality before considering implications for practice and policy. This study would reflect the current evidence that the BCG vaccine protects against COVID-19. Being still in the midst of the COVID-19 pandemic, it is too early to jump to immature conclusions, where COVID-19 cases/deaths may still increase over time in some BCG-using countries. Thus, good evidence should be obtained from prospective RCTs before reflecting on practice and policy.

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## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## AUTHOR CONTRIBUTIONS

ZI designed the study. MAAB wrote, critically revised the manuscript, and proofread. KZ assisted to critically revise the manuscript. This manuscript is not under review elsewhere, and all authors read and approved the final manuscript.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from the corresponding author.

## ORCID

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