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Variances in BCG protection against COVID-19 mortality: A global assessment

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ABSTRACT

The BCG vaccine is known to impart nonspecific immunological benefits alongside conferring protection to tuberculosis in endemic regions. It is also known to protect against bladder cancer and other respiratory tract infections. During the coronavirus disease 2019 (COVID-19) pandemic, the BCG vaccine has gained attention due to its role in conferring protective immunity. We demonstrate the potential immunological protective mechanisms that play a role against COVID-19. We conduct a global assessment of the countries that have the highest and lowest mortality rates determined by an a priori methodology. Lastly, we discuss the potential limitations of incorporating BCG vaccines as potential strategies against COVID-19 and provide recommendations regarding their use in ongoing and future epidemics.

1. Introduction

Bacillus Calmette-Guérin (BCG) vaccine is a live attenuated Mycobacterium bovis that was developed to combat Tuberculosis (TB) infections in the early 20th century [1,2]. One of the most widely used vaccines globally, BCG, is administered at once at birth with immune correlates of protection suspected to extend to adulthood [3]. Countries like France, Germany, and Spain stopped mass BCG immunization as the prevalence of TB decreased in these countries. In contrast, countries like China, Russia, and Ukraine continue to administer BCG mass immunization [1]. BCG is the only licensed vaccine for TB and is traditionally administered at the time of birth. Evidence supports that BCG vaccination is effective in preventing adult pulmonary tuberculosis (TB), which is caused by Mycobacterium tuberculosis. Numerous prospective trials and recent retrospective studies show that BCG provides immunity against pulmonary TB for up to 50 years [3]. The activation of the bystander B and T cells independent of antigens could be one of the mechanisms by which BCG provides non-specific immunity, known as heterologous immunity [4]. Secondly, the innate immune cells could be activated and reprogrammed by BCG, establishing trained innate immunity [4]. The hypothesis that BCG vaccination provides heterologous immunity against COVID-19 is currently under investigation. We find that COVID19 mortality may be associated with BCG vaccination as countries like South Korea, Japan, being ones with an active BCG vaccination policy, have a lower COVID-19 mortality rate than countries with no active BCG vaccination policy such as the USA and Italy. Whether BCG, a century-old vaccine that was first used in 1921, is one of the contributing factors to reduced COVID-19 mortality is a subject of interest. Our ecological study not only sheds light on the differences of BCG vaccinations on COVID-19 mortality but also how the vaccine may confer with protective immunity against other pathogens [4].

2. Materials and methods

An a-priori methodology was used to identify the top ten and bottom ten countries according to the death rate (Fig. 1). The death rate was taken as the relative number of COVID-19 deaths within a population per unit of time. The daily counts of COVID-19 cases and deaths globally

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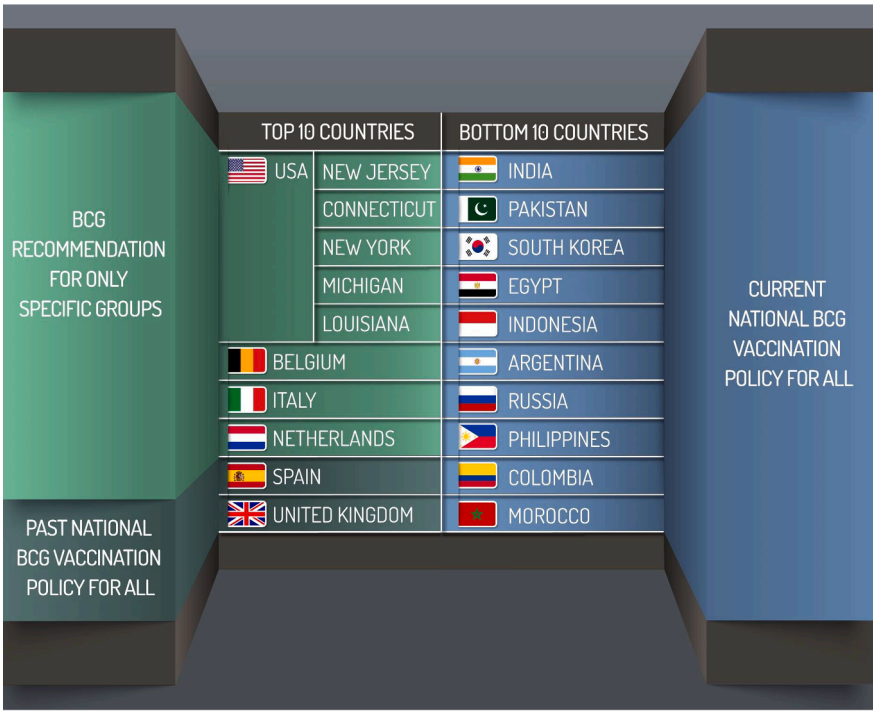
a



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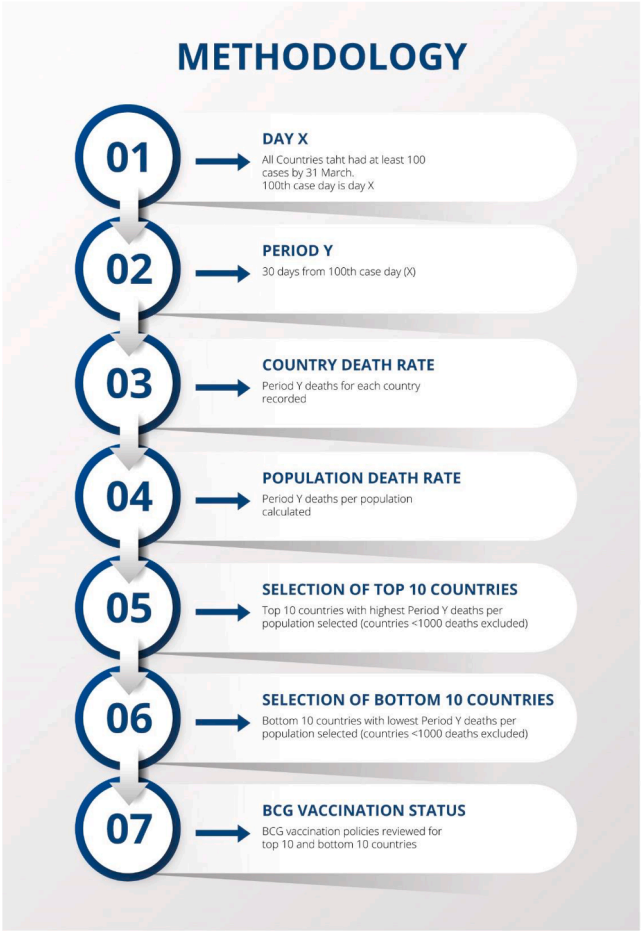

Fig. 1. 1 a and b. Global assessment of countries according to death rate per population and BCG vaccination policies. An a priori methodology was established to tabulate countries according to descending death rates per population. The top and bottom 10 countries were identified and the BCG vaccination policies were identified.

were obtained by the World Health Organization Coronavirus disease situation dashboard. For every country until 31 March, which had at least 100 confirmed cases, a tabulated list was arranged with the total deaths within that population from day X. Day X was taken as the day at which at least 100 confirmed cases were recorded. Defined as day Y, the total deaths were then identified in the next 30 days since day X. The death rates were arranged in descending order, and countries greater than 5,000,000 km^2 were further analyzed by state or province. The states or provinces whereby the death rates per population were in the top or bottom ten were also taken as "countries" for our study.

3. Results

The top 10 countries were identified according to the death rates per population. Deaths were obtained in the first 30 days after at least 100 confirmed cases were identified before March 31, 2020. The top 10 countries had BCG recommendations for only specific groups. However, the bottom ten countries had current national BCG vaccination policies for all at birth. The findings are summarized in Fig. 1.

Further, the top ten and bottom ten countries were screened for the incidence of tuberculosis (TB), education index, and percentage of the population aged 65 and above. The top 10 countries had a lower incidence of TB, with only three countries with an incidence of >5 per 100,000 people, including Spain, Belgium, and the United Kingdom, identified in Table 1. The overall poverty headcount ratio was low in the top 10 countries and was in direct correlation with the lower rates of incidence in the countries. All the countries in the top 10 had BCG national policies for specific groups. The education index was high in the top 10 countries, between 0.790 till 0.894. However, 16–25% of the total population in the top 10 countries was aged 65 years and above. Approximately 90–98% of the children aged 12–23 months were given the measles vaccine in 2019.

The bottom 10 countries had BCG vaccination policies for all that corroborate with the higher incidence of TB, ranging from 12 to 554 per 100,000 people, tabulated in Table 2. The poverty headcount ratio was variable in the bottom ten states/nations. The incidence of TB was higher in correlation to the poverty index. The education index was consistently lower than in the top 10 countries except for South Korea. The bottom 10 countries had fewer percentages of the population aged 65 and above except South Korea and Russia. The other countries within the bottom 10 had a 4–11% population in the older age groups. With the exceptions of Pakistan and the Philippines, the immunization of measles was comparable to the top 10 countries.

4. Discussion

Poverty is widely recognized as a contributing factor to TB, with a higher global prevalence in South-East Asia (44%), Africa (24%), and the Western Pacific (18%). Poverty, housing quality, and undernutrition are frequently cited as determinants for higher incidences of TB both among and within these countries. Over 10 million cases were diagnosed in 2018, and the 153 countries are administering BCG vaccine as standard practice in childhood immunization programs, the coverage of which is >90% in 113 countries [5]. Previously, studies have reviewed the incidence of COVID-19 cases in countries where BCG was mandated and compared with countries that did not. While there may be ecological bias, our findings were standardized by taking the death rates in the first wave of the pandemic. While it is certain that the testing rates and the rates of incidence were higher in larger countries with better health infrastructures, we reviewed the confirmed cases and deaths in the first 30 days, thereby accounting for the differences in such factors. BCG vaccination is recommended in countries in TB-endemic countries, and clinical trials are underway to determine the efficacy of BCG on the immune system when immunized later in life. The rates of measles-immunized children were comparable across the top and bottom ten countries, with recent attention given to the potential protective effects of measles, mumps, and rubella (MMR) vaccine in COVID-19.

Senoo et al. reviewed the morbidity and mortality rates among the Organization for Economic Co-operation and Development (OECD) at different stages of the pandemic and the differential impact of BCG implementation [6]. The methodology had the limitation of not accounting for different stages across the pandemic but was able to demonstrate similar findings to our study in favor of BCG vaccination policies and the trends of the COVID-19 pandemic [6]. Another study conducted by Pathak et al. accounted for different stages of the pandemic at three different time points with findings similar to ours showing correlation of BCG vaccination policies with lower COVID-19 mortality rates [7]. Pandita et al. and Mohapatra et al. note the lower incidence of COVID-19 in countries with routine vaccination programs, citing nonspecific effects (NSEs) of BCG vaccination in TB-endemic countries [8,9]. However, identify the difficulty of ascertaining BCG vaccination policies on the dynamics of the COVID-19 pandemic citing the multifactorial nature of the early stages and minimal accounting of confounding factors [10,11]. A study reviewed the contribution of confounding factors with the incidence of TB being a significant contributor explaining the differences in the COVID-19 mortality burden [12]. Further, a cohort of 6,201 healthcare workers (HCWs) of whom 29.6% had been vaccinated for BCG and 68.9% had not been. There was a significant correlation among a history of BCG vaccination of HCWs with lower incidence, seroconversion assessed by anti-SARS-CoV-2 IgG levels as well as lower self-reported symptoms [13].

4.1. Innate immunity in SARS-CoV-2

Davids et al. conducted a study in Africa to compare 2 BCG strains, namely BCG Japan and BCG Denmark. It showed that a more robust proliferation of CD4+ and CD8+ T cells was induced by BCG Japan. Also, there was a lower secretion of Th2 cytokines (IL-4) and higher secretion of Th1 cytokines (interferon-γ, TNF-α, and IL-2) by BCG Japan compared with BCG Denmark [14]. Another study conducted in Mexico showed that BCG Japan induced higher levels of IL-1α, IL-1β, IL-6, and IL-24 compared to BCG Denmark. These studies suggest that BCG Japan produces multiple types of inflammatory cytokines in peripheral blood lymphocytes and is more efficient for the same when compared to BCG Denmark [15].

4.2. Immune correlates of protection

After intradermal injection of BCG vaccination, local neutrophils, macrophages, and dendritic cells at the site of inoculation begin the immune response through the interaction of different pattern recognition receptors such as toll-like receptors-2 (TLR-2) and 4 (TLR-4) with pathogen-associated molecular patterns (PAMPs), including peptidoglycan, arabinogalactan, and mycolic acids present on the bacterium cell wall. Other cell receptors that can recognize BCG PAMPs include nucleotide-binding oligomerization domain (NOD)-like receptors (such as NOD2), found in the cytoplasm of innate immune cells. Besides, C-type lectins (such as DC-specific intercellular adhesion molecule-3-grabbing non-integrin) participate in the recognition and internalization of BCG, which results in dendritic cells maturation and migration and expression of costimulatory molecules such as CD40, CD80, CD83, and CD86 [16]. Moreover, antigen 85, present in BCG's cell wall, stimulates the production of proinflammatory factors such as TNF-alpha (tumor necrosis factor-alpha), interleukin (IL) 1-beta, and IL-6, which promotes the activation of immune cells.

4.3. Trained immunity

In 2011, Netea et al. proposed for the first time the concept of "trained immunity," described as a less specific response to a secondary infection mediated by innate immune cells (monocytes/macrophages and NK cells), either to the same pathogen or a different one (cross-

Table 1
Top 10 countries selected by the Day Y deaths rate. Only countries with more than 1000 deaths till day Y were further screened for deaths per population. The incidence of tuberculosis (per 100,000 people) was calculated in 2018 by the World Health Organization. The education index is calculated using Mean Years of Schooling and Expected Years of Schooling, reported by the United Nations Development Programme as of 15 December 2013. The population, aged 65 and above, was reported by the World Bank based on estimates of age/sex distributions by the United Nations Population Division's World Population Prospects in 2019. The percentage of children aged 12–23 months who were given measles vaccine was reported by WHO and UNICEF in 2019. *A State (note the capital "S") is a self-governing political entity that can be used interchangeably with a country. A nation, however, is a tightly-knit group of people who share a common culture. The top 10 " countries" also include states or provinces for countries with an area greater than 5,000,000 km^2.

Top 10 countries	Da X = 100th case day	Day Y = 30 days from X (Y = X + 30)	Number of cases on Day Y	Number of deaths till date Y	Population (in millions)	Day Y deaths per population*	Incidence of TB per 100,000 people*	Poverty headcount ratio at $1.90 a day (% of the population)	Education Index*	Population aged 65 and above (% of the total population)	Immunization of measles (% of children ages 12–23 months)
New Jersey	Mar 16	Apr 15	67,874	3156	8.88	355	3	1.0	0.890	16	90
Connecticut	Mar 19	Apr 18	16,464	1086	3.57	304	3	1.0	0.890	16	90
New York	Mar 7	Apr 6	1,306,089	4758	19.45	244	3	1.0	0.890	16	90
Michigan	Mar 19	Apr 18	25,246	2308	9.99	231	3	1.0	0.890	16	90
Louisiana	Mar 15	Apr 14	21,951	1013	4.65	217	3	1.0	0.890	16	90
Spain	Mar 3	Apr 2	102,136	9053	46.72	193	9	0.9	0.794	20	98
Belgium	Mar 7	Apr 6	19,691	1447	11.42	126	9	0.1	0.812	19	96
Italy	Feb 24	Mar 25	69,176	6820	60.43	112	7	2.0	0.790	23	94
Netherlands	Mar 7	Apr 6	17,851	1766	17.23	102	5	0.1	0.894	20	94
United Kingdom	Mar 6	Apr 5	41,907	4313	66.49	64	8	0.1	0.860	16	91

protection), and independent of T and B cell responses [17]. It has been demonstrated that after BCG vaccination, peripheral blood monocytes display a rise in H3K4me3 histone modification (epigenetic reprogramming), triggering proinflammatory cytokine production (through the transcription of the genes tnfα, il6, and tlr4), and improving microorganism recognition by pattern recognition receptors (PRRs) such as TLRs, C-type lectins receptors, NOD-like receptors, and RIG-I-helicases. When these "trained monocytes" are subsequently exposed to a second infection, the microorganism would be recognized by these PPRs, driving to a cytokine burst [16,18].

4.4. Heterologous immunity

BCG causes a Th1-type proinflammatory cytokine production and activates innate immunity arbitrating antimycobacterial responses. Still, other T-cell populations could also respond in a heterologous manner. Kleinnijenhuis et al. measured BCG vaccination's effect on heterologous Th1 and Th17 responses showing C. Albicans and S. aureus boosted IL-17 and IL-22 production at two weeks and one-year post-immunization in BCG-vaccinated adults; compared with the control group, CD8+ Bordetella pertussis-specific T cells were found in BCG-vaccinated HIV-exposed but uninfected infants in South Africa [19]. Due to BCG vaccination, the heterologous T-cell response might improve trained innate immunity even after multiple weeks of immunization and provide heterologous protection from infections once trained innate immunity fades [20].

4.5. BCG vaccination efficacy in other illnesses

Bladder cancer therapy, specifically the non-muscle-invasive forms of bladder cancer (NMIBC), uses BCG bacterial intravesical instillation following transurethral resection of tumors (TURBT) as a standard treatment. BCG therapy usually involves an induction regimen consisting of a 6-week course of 2–19 × 108 colony forming units (CFUs) of BCG in normal saline to be instilled through a catheter into an empty bladder, 2–3 weeks after the TURBT, followed by a maintenance treatment of intravesical BCG instillations for six weeks, every three months during 1–3 years [21,22]. Innate and adaptive immune responses are part of the BCG mechanism of action. TURBT causes urothelial damage; in these areas, BCG bacteria adhere to the damaged bladder mucosa, where, following its binding via α5β1 integrin receptors, it enters the malignant urothelial cell. After internalization, a primary innate immune response involves cytokine release of TNF-α, IFN-γ, IL-2, IL-6, IL-8, and IL-12; this release activates neutrophils, T lymphocytes, BCG-activated killer cells, and natural killer cells, eliminating malignant urothelial cells with the internalized BCG bacteria. After induction therapy, BCG-induced immune response slowly decreases. Thus the need for maintenance therapy to heighten the immune cell response and cytokine levels [22].

BCG vaccine, recommended by WHO, is the widely used vaccine for protection against pulmonary TB. The efficacy of the vaccine was tested in several prospective and retrospective trials. A case-control study in the UK consisting of 54,239 children aged 14–15 years reported 77% vaccine efficacy in preventing pulmonary TB incidence until up to 15 years after getting the BCG vaccine [23]. Two recent independent retrospective studies from Norway and the UK also supported a significant vaccine efficacy for at least 20 years against pulmonary TB. In addition to TB, the BCG vaccine was found to show protection against infections like influenza A virus, pandemic influenza (H1N1), and other acute respiratory tract infections, both upper and lower. Leentjens et al. reported that people with BCG vaccination developed a significantly higher hemagglutinin (HI) antibody to protect against H1N1 influenza [24]. Another study reported a significant reduction in the incidence of ALRI by 17% to 37% after receiving the BCG vaccine [25]. The BCG vaccine has also shown protection against ARTIs compared to unvaccinated counterparts, especially among the older population [26]. Furthermore, studies have shown a decrease in mortality rate from pneumonia in children who were vaccinated with the BCG vaccine. A significant reduction in hospitalization due to respiratory infections was also observed [27,28].

5. Key message

The use of the BCG vaccine varies globally, with some countries still

Table 2
Bottom 10 countries selected by Day Y deaths rate. Only countries with more than 100 deaths till day Y were further screened for deaths per population. The incidence of tuberculosis (per 100,000 people) was calculated in 2018 by the World Health Organization. The education index is calculated using Mean Years of Schooling and Expected Years of Schooling, reported by the United Nations Development Programme as of 15 December 2013. The population, aged 65 and above, was reported by the World Bank based on estimates of age/sex distributions by the United Nations Population Division's World Population Prospects in 2019. The percentage of children aged 12–23 months immunized with measles was reported by WHO and UNICEF in 2019.

Bottom 10 countries	Da X = 100th case day	Day Y = 30 days from X (Y = X + 30)	Number of cases on Day Y	Number of deaths till date Y	Population (in millions)	Day Y deaths per population*	Incidence of TB per 100,000 people*	Poverty headcount ratio at $1.90 a day (% of the population)	Education Index*	Population aged 65 and above (% of the total population)	Immunization of measles (% of children ages 12–23 months)
Pakistan	Mar 17	Apr 16	6505	124	212.22	0	265	3.9	0.372	4	75
India	Mar 15	Apr 14	10,363	377	1352.62	0	199	21.2	0.473	6	95
South Korea	Feb 20	Mar 21	8799	102	51.64	1	66	0.2	0.865	15	98
Egypt	Mar 16	Apr 15	2350	178	98.42	1	12	1.3	0.573	5	95
Indonesia	Mar 15	Apr 14	4557	399	267.66	1	316	7.2	0.603	6	88
Argentina	Mar 21	Apr 20	2839	132	44.49	2	27	0.7	0.783	11	94
Russia	Mar 19	Apr 18	36,793	313	144.48	2	54	0.1	0.780	15	98
Philippines	Mar 15	Apr 14	4932	315	106.65	2	554	6.1	0.610	5	67
Colombia	Mar 20	Apr 19	3439	153	49.65	3	33	4.5	0.602	9	95
Morocco	Mar 23	Apr 22	3209	145	36.03	4	99	1.0	0.468	7	99

having mandatory vaccine administration. At the same time, some terminated the mandatory administration policy, and some never had such a policy. Studies have shown that countries with a mandated BCG vaccine policy have a flatter curve and fewer deaths than those without such policy [29]. COVID-19 mortality was noted to be markedly higher in countries where BCG vaccination is not widely administered or is given only to high-risk groups or where it was discontinued more than 20 years ago [1]. COVID-19 mortality in different socially similar European countries was observed, indicating that every 10% increase in the BCG index was associated with a 10.4% reduction in COVID-19 mortality [1]. A study analyzing COVID-19 mortality in the first month of the pandemic surge found that countries with a BCG index of almost zero, like the Netherlands and Italy, had a high mortality rate of 75–100 per 100 million compared to the countries with a BCG Index close to 1.0, such as Ukraine and Lithuania, whose mortality rate was close to zero and close to 12.5 respectively [1]. The consistent association between BCG vaccination and reduced severity of COVID-19 observed is remarkable and hence warrants further studies and trials to be conducted.

Heterologous effects of adaptive immunity and trained innate immunity are the two immunological actions that have been described as the protective host response of BCG against COVID 19 [30]. To prove the benefits of BCG, clinical trials are underway. Most of these trials aim to recruit frontline health workers to demonstrate the effects of BCG on total case occurrence and the severity of COVID 19 [31]. The current epidemiological data indicates that countries with very low no. of total deaths, including South Asian Association for Regional Cooperation (SAARC) countries, adopted a mandatory BCG vaccination program [32]. In contrast, countries with a higher number of cases didn't have widespread BCG vaccination [32]. However, discrepancies exist in the above epidemiological data, and mortality due to COVID 19 depends on a no. of factors like age, comorbid conditions of patients, available health infrastructure of the region. Although case fatality could be a fair comparison of COVID-19 related deaths, it is challenging to get the exact no. or estimate of people infected with COVID-19 in a particular region as it depends on the testing facility availability, resources, climate of that region, and proportion of symptomatic to asymptomatic cases. Further, the strict lockdown measures, mandatory social distancing, and mask-wearing may have mitigated the spread of COVID-19 in a region. Also, there might be other unknown confounding factors that need consideration before making a strong conclusion regarding the effect of BCG in COVID-19. In this scenario, we need to rely on the results of BCG trials before jumping to any conclusion. Hence, we strongly support further BCG trials to be carried out to uncover the real answer to the question unless the trials are carried out by adequately informing their participants about the risk of local and systemic complications from BCG vaccination.

6. Recommendations

While preliminary data is indicative of the protective effects of BCG on COVID-19 mortality, it is pertinent to wait until randomized trials are completed. Of note, BCG vaccines are required in TB-endemic regions, and their efficacy in COVID-19 is not certain. Consequently, the use of BCG vaccines in COVID-19 may lead to shortages in supplies globally. Additionally, the current data is observed at population levels, and the lack of patient-level data incorporates confounders that may prematurely skew the findings in favor of BCG efficacy. BCG vaccines are administered at birth in TB-endemic regions, and trained immunity may not be immediately effective if BCG vaccines were administered to prevent or manage COVID-19 among infected patients. Therefore, the monitoring of protective outcomes in randomized control trials is required before the BCG vaccine may be considered an important strategy to combat COVID-19 and potential epidemics in the future.

7. Conclusion

BCG vaccination can broadly activate the human immune system to better combat SARS-CoV-2, leading to decreased incidence and milder courses, thereby reducing the burden on ICUs and hospital beds, allowing for greater global productivity. We suggest future intradermal and aerosolized investigations along with punch biopsies to evaluate immune-histological changes to understand better the benefits provided by BCG vaccination to vulnerable individuals and healthcare workers. Further studies on the safety, tolerability, immunogenicity, and efficacy of different administrative forms of BCG vaccination are recommended, which would further help us solidify the understanding of this topic.

CRediT authorship contribution statement

Zouina Sarfraz: Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Azza Sarfraz:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Krunal Pandav:** Conceptualization, Writing - original draft. **Sarabjot Singh Makkar:** Conceptualization, Writing - original draft. **Saman Hasan Siddiqui:** Conceptualization, Methodology. **Gaurav Patel:**

Visualization, Investigation. **Tania Platero-Portillo:** Data curation, Writing - original draft. **Bishnu Mohan Singh:** Data curation, Writing - original draft. **Mohamed Iburahim Haja Maideen:** Data curation, Writing - original draft. **Deepika Sarvepalli:** Data curation, Writing - original draft. **Muzna Sarfraz:** Data curation, Writing - original draft. **Jose Cardona-Guzman:** Writing - review & editing. **Marcos A. Sanchez-Gonzalez:** Writing - review & editing. **Ivan Cherrez-Ojeda:** Supervision, Validation, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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