COVID-19 death and BCG vaccination programs worldwide

Dallal Bashi, Y. H., Jirjees, F. J., & Al-Obaidi, H. J. (2020). COVID-19 death and BCG vaccination programs worldwide. *Tuberculosis and respiratory diseases*. https://doi.org/10.4046/trd.2020.0063

**Published in:**
*Tuberculosis and respiratory diseases*

**Document Version:**
Publisher's PDF, also known as Version of record

**Queen's University Belfast - Research Portal:**
[Link to publication record in Queen's University Belfast Research Portal](https://www.qub.ac.uk)

**Publisher rights**
Copyright 2020 the authors.
This is an open access Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits use, distribution and reproduction for non-commercial purposes, provided the author and source are cited.

**General rights**
Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

**Take down policy**
The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Download date: 27. Apr. 2021
COVID-19 Death and BCG Vaccination Programs Worldwide

Feras J. Jirjees, Ph.D.1*, Yahya H. Dallal Bashi, Ph.D.2*, and Hala J. Al-Obaidi, Ph.D.2
1College of Pharmacy, University of Sharjah, Sharjah, United Arab Emirates, 2School of Pharmacy, Queen’s University Belfast, Belfast, UK

Several clinical trials are being conducted worldwide to investigate the protective effect of the bacillus Calmette-Guérin (BCG) vaccine against death in healthcare providers who are working directly with coronavirus disease 2019 (COVID-19) patients. Clinical studies suggested that certain live vaccines, particularly the BCG vaccine, could reduce the mortality due to other diseases caused by non-targeted pathogens, most probably through the nonspecific effects (heterologous effects). By the end of May 2020, the available information on the COVID-19 pandemic indicated the great effect of the BCG vaccine in reducing the number of COVID-19 death cases. The occurrence of death due to COVID-19 was found to be 21-fold lower in countries with a national BCG vaccination policy than in countries without such a policy, based on the medians of COVID-19 death case per 1 million of the population in these two groups of countries (p<0.001, Mann-Whitney test). Therefore, it can be concluded that the early establishment of a BCG vaccination policy in any country is a key element in reducing the number of COVID-19 and tuberculosis death cases.

Keywords: COVID-19 Pandemic; BCG Vaccine; COVID-19 Death Cases; Coronavirus; COVID-19 Mortality

Introduction

By the end of December 2019, a new viral infection that mainly affects the human lower respiratory tract was first detected in China and quickly spread out to all over the world within a few weeks. This novel virus is type 2 severe acute respiratory syndrome coronavirus (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19). COVID-19 is a highly contagious disease that has rapidly spread worldwide and has been announced as a pandemic by the World Health Organization (WHO). More than 5.7 million individuals worldwide were infected, and approximately 358,000 death cases were reported by 28 May2. There are many factors that might cause the large variations in the prevalence and death rate of COVID-19 among countries. One of these factors is whether a country enacts vaccination prevention programs against serious infectious diseases, such as tuberculosis (TB). Although TB and COVID-19 are caused by two different microorganisms, both infect the lower respiratory tract and are transmitted via small respiratory droplets coughed or sneezed by an infected patient. In addition, any of these two diseases are known to be a deadly infection for people with weak immunity system. Epidemiological data on the global prevalence of COVID-19 indicated that countries with bacillus Calmette-Guérin (BCG) vaccination policies have lower rate of death related to COVID-19 than in countries without such a policy3,4.

Vaccine for Mycobacterium tuberculosis and the Immune System

TB is caused by bacterial infection of *Mycobacterium tuberculosis* to the human body through mainly the pulmonary route. This *Mycobacterium* species is present in the air...
The BCG vaccine is typically administered shortly after birth to protect infants and children from serious forms of TB, particularly to prevent pulmonary TB. In brief, the immune response induced in newborns after BCG vaccination typically starts with the recognition of BCG by neutrophils, macrophages, and dendritic cells at the inoculation site. This is followed by the activation of the adaptive immune system via migration of dendritic cells to the lymph nodes, resulting in the activation of mycobacteria-specific CD4+ and CD8+ T cells, which secrete high amounts of interferon (IFN)-γ and granzymes (serine proteases enzymes released within cytotoxic T cells and natural killer cells for inducing apoptosis to eliminate cells that have become cancerous or infected with bacteria or viruses). This subsequently leads to the activation of B cells and the generation of plasma and memory T cells in addition to the production of antigen-specific antibodies in response to the presence of BCG antigens. These antibodies help protect the body against TB infection. Some evidence also shows that BCG vaccine induces non-specific cross-protection via improved innate immune responses against microorganisms other than the TB-related pathogen. Recently, it was found that IFN-γ-dependent manner to optimally prime CD4+ and CD8+ T cell immunity and to induce much stronger immune responses. Moreover, BCG vaccine is associated with low hospitalization rates for other respiratory infections not related to TB.

Although national BCG vaccination programs are available in most countries apart from Western European countries and North American countries, such as the United States and Canada, TB remains a life-threatening disease with 1.5 million deaths in 2018 worldwide; moreover, it is estimated that 10 million people suffer from TB globally, with most cases occurring in eight countries: India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa. The main reason for that is the efficacy of BCG vaccine in preventing pulmonary TB by 50% in average. This means that BCG vaccine can reduce the risk of TB and its progression to active TB. Likewise, COVID-19 death records in those countries were less than 6 per 1 million of population. Yet, BCG vaccine does not provide complete protection against TB owing to many factors, such as genetic differences among the populations, environmental changes, exposure to specific strains of TB or other bacterial, and the TB strains used to manufacture the vaccine. These factors also include genetic differences between the strains being cultured and the choice of growth medium.

In addition, the duration of protection by BCG is not clearly known, as published data showed an inconsistent protective effect of the BCG vaccine. One study found that in a given population, the protective effect of BCG against TB could decrease after 15 years and probably disappeared after 20 years, whereas another study in Native Americans immunized in the 1930s found evidence of protection even at 60 years after immunization, with only a slight waning in efficacy.

In 2018, 153 countries were considering the BCG vaccine as a standard childhood immunization program, and there are only 113 countries with a BCG coverage of ≥90% of the population. Recently, several published articles stated that to a certain extent, countries with national BCG vaccine policies have less COVID-19 death rates than countries without such a policy.

### Published Information about the Proposed Role of BCG in Activating the Immune System against COVID-19

The BCG vaccine typically enhances the immune system capability to fight off pathogens, by interacting immune cells receptors with different pathogen associated molecular patterns, such as peptidoglycans, cell wall proteins, lipopolysaccharides, mycolic acids and glycoproteins which locate at the pathogen cell membrane and preserve molecular signatures of bacteria and viruses as well. Following this reaction, a series of biological stimulations take place including the production and secretion of pro-inflammatory cytokines as described in section 2. In particular, the BCG vaccine was found to be also defending against viral infections which affect the respiratory tract. In this context, it was found that mice who vaccinated with BCG prior to be infected with the Influenza virus have mild lung damage and lower Influenza load in their blood compared to those did not vaccinated and this was referred to either an earlier antibody secretion or the nonspecific cell-mediated immunity.

In an experimental laboratory setting, the BCG vaccination exhibited the capability to reduce the level of the yellow fever vaccine (an attenuated viral strain) viremia in human monocytes and this was correlated with induction of cytokine responses (especially interleukin [IL]-1β). In a randomized placebo-controlled pilot study, healthy volunteers received either placebo vaccine (n=20) or live attenuated BCG vaccine (n=20). After 14 days, all participants received intramuscular injection of trivalent influenza vaccine. Antibody responses against that influenza vaccine strain were
Table 1. Effect of BCG vaccination policy on the number of COVID-19 death cases in countries with more than 10,000 confirmed COVID-19 cases as per the WHO situation report on 28 May 2020

| No. | Country      | Total COVID-19 cases | Total COVID-19 death cases | Case per 1 million | Death per 1 million |
|-----|--------------|----------------------|---------------------------|-------------------|-------------------|
| 1   | Belgium      | 57,849               | 9,388                     | 4.991             | 810               |
| 2   | Spain        | 238,278              | 29,037                    | 5.096             | 621               |
| 3   | UK           | 269,131              | 37,837                    | 3.696             | 557               |
| 4   | Italy        | 231,732              | 33,142                    | 3.833             | 548               |
| 5   | France       | 146,122              | 28,608                    | 2.239             | 438               |
| 6   | Sweden       | 35,727               | 4,266                     | 3.538             | 422               |
| 7   | Netherlands  | 45,950               | 5,903                     | 2.682             | 345               |
| 8   | Ireland      | 24,841               | 1,639                     | 5.031             | 332               |
| 9   | USA          | 1,675,258            | 98,889                    | 5.061             | 299               |
| 10  | Switzerland  | 30,713               | 1,654                     | 5.349             | 191               |
| 11  | Canada       | 87,902               | 6,799                     | 2.329             | 180               |
| 12  | Germany      | 180,458              | 8,450                     | 2.154             | 101               |
| 13  | Denmark      | 11,512               | 568                       | 1.987             | 98                |
| 14  | Austria      | 16,543               | 668                       | 1.837             | 74                |
| Median No. | Belgium | 72,876               | 7,625                     | 3.543             | 338               |

BCG countries

| No. | Country          | Total COVID-19 cases | Total COVID-19 death cases | Case per 1 million | Death per 1 million |
|-----|------------------|----------------------|---------------------------|-------------------|-------------------|
| 15  | Ecuador          | 38,471               | 3,313                     | 2.181             | 188               |
| 16  | Portugal         | 31,596               | 1,369                     | 3.099             | 134               |
| 17  | Peru             | 135,905              | 3,983                     | 4.122             | 121               |
| 18  | Brazil           | 411,821              | 25,598                    | 1.937             | 120               |
| 19  | Panama           | 11,728               | 315                       | 2.718             | 73                |
| 20  | Mexico           | 78,023               | 8,597                     | 6.05              | 67                |
| 21  | Romania          | 18,791               | 1,229                     | 9.97              | 64                |
| 22  | Turkey           | 160,979              | 4,461                     | 1.909             | 53                |
| 23  | Chile            | 86,943               | 890                       | 4.548             | 47                |
| 24  | Dominican Republic | 16,068             | 485                       | 1.481             | 45                |
| 25  | Kuwait           | 24,112               | 185                       | 5.646             | 43                |
| 26  | Russia           | 387,623              | 4,374                     | 2.656             | 30                |
| 27  | Serbia           | 11,300               | 241                       | 1.293             | 28                |
| 28  | Poland           | 22,825               | 1,038                     | 6.03              | 27                |
| 29  | UAE              | 32,532               | 258                       | 3.289             | 26                |
| 30  | Belarus          | 39,858               | 219                       | 4.218             | 23                |
| 31  | Iran             | 143,849              | 7,627                     | 3.76              | 16                |
| 32  | Colombia         | 24,104               | 803                       | 4.74              | 16                |
| 33  | Ukraine          | 22,811               | 679                       | 5.22              | 16                |
| 34  | Saudi Arabia     | 80,185               | 441                       | 2.303             | 13                |
| 35  | Qatar            | 50,914               | 33                        | 17.672            | 11                |
| 36  | Argentina        | 13,933               | 501                       | 3.08              | 11                |
| 37  | South Africa     | 27,403               | 577                       | 4.62              | 10                |
significantly enhanced in BCG group compared to the placebo group. Enhanced pro-inflammatory leukocyte responses and modulation of cytokine responses against unrelated pathogens were observed.

Likewise, the BCG vaccine might probably induce such a mechanism in the human body against COVID-19 which could result in reducing both the COVID-19 death rate and the severity of cases.

COVID-19 Pandemic

COVID-19 was first reported in Wuhan City, Hubei Province, China in December 2019, and the disease spread rapidly in China and globally in less than 5 weeks. Coronaviruses are a family of viruses that commonly exist in nature and can infect humans, causing pneumonia, kidney failure, damage in the digestive tracts, and even death. Currently, the novel COVID-19 is spreading more quickly than other known coronaviruses.

COVID-19 is mainly transmitted between people via close contact or respiratory droplets coughed or sneezed by COVID-19–infected people. The high incidence of COVID-19 could probably be caused by the spreading of the virus via asymptomatic infected individuals. The initial site of COVID-19 infection is not yet defined, and its pathogenesis is still under investigation. Because COVID-19 is a respiratory disease, the lungs of most COVID-19 patients appear to be affected. The common symptoms of COVID-19 are fever, cough, fatigue, sore throat, and shortness of breath.

In severe COVID-19 cases, high levels of pro-inflammatory cytokines (IL-2, IL-7, IL-10, granulocyte colony-stimulating factor, IFN-γ–induced protein 10, monocyte chemotactic protein 1, macrophage inflammatory protein 1A, and tumor necrosis factor α), a phenomenon known as cytokine storm, were observed. This cytokine storm can lead to inflammation-induced lung damage with serious complications, such as pneumonia, respiratory failure, shock, and even death.

Currently, paracetamol as an antipyretic/analgesic agent as well as empirical antibiotics for co-infections are common treatment options used to manage COVID-19 cases in hospitals worldwide.

Both the incidence and death rates of COVID-19 in the United States and most European countries (which should have robust healthcare systems) were higher than those in other developed countries with good healthcare systems, such as Singapore, Japan, Korea, and Hong Kong, and also higher than that in developing countries that might not have well-established healthcare systems.

Based on BCG data of the last 40 years published by WHO, countries with more than 10,000 confirmed COVID-19 cases were classified as BCG and non-BCG countries in this review article. Till 28th of May 2020, the WHO data revealed that the incidence of COVID-19 (cases per 1 million of population) in countries with a national BCG vaccination policy is 3.6-fold lower than that in countries without such a policy, based on

| No. | Country      | Total COVID-19 cases | Total COVID-19 death cases | Case per 1 million | Death per 1 million |
|-----|--------------|-----------------------|----------------------------|--------------------|--------------------|
| 38  | Bahrain      | 10,052                | 15                         | 5,907              | 9                  |
| 39  | Philippines  | 15,588                | 921                        | 142                | 8                  |
| 40  | Egypt        | 20,793                | 845                        | 203                | 8                  |
| 41  | Japan        | 16,719                | 874                        | 132                | 7                  |
| 42  | Afghanistan  | 13,659                | 246                        | 351                | 6                  |
| 43  | Pakistan     | 64,028                | 1,317                      | 290                | 6                  |
| 44  | Indonesia    | 24,538                | 1,496                      | 90                 | 5                  |
| 45  | Republic of Korea | 11,402      | 269                        | 222                | 5                  |
| 46  | Singapore    | 33,249                | 23                         | 5,683              | 4                  |
| 47  | India        | 163,799               | 4,706                      | 120                | 3                  |
| 48  | Bangladesh   | 40,321                | 559                        | 245                | 3                  |
| 49  | China        | 84,547                | 4,645                      | 59                 | 3                  |
| Median                     | 31,596               | 845                        | 977                | 16                 |

COVID-19, coronavirus disease 2019; WHO, World Health Organization; BCG, Bacillus Calmette-Guérin.

*BCG vaccination policy has been stopped in 2009, BCG vaccination covered approximately 80% of newborns between 1985 and 2007.* †BCG vaccination covered <27% of newborns every year. ‡BCG policy covered less than 40% between 2004–2012 and stopped in 2016. §BCG vaccination covered 76% in 1980 and approximately 90% of newborns from 2013 to 2018.
the medians of the two groups (Table 1). Regardless of the number of countries used in this comparison, the number of COVID-19 cases is also higher by two-fold in countries without a national BCG vaccination policy than in countries with such a policy, based on the medians of the two groups (Table 1).

In this context, another research group found that the reported number of COVID-19 cases are very low in the countries with universal BCG vaccination policies compared to countries without such a policy21.

**BCG Vaccination and COVID-19 Death Occurrence**

In general, the death rate of COVID-19 in each country is mainly related to the age and health conditions (such as cardiovascular diseases, diabetes, and weak immune system) of COVID-19 patients32,33. Moreover, the numbers of COVID-19 death cases varied among non-BCG countries (Table 1). For example, the number of COVID-19 death cases in Germany is 4.4-fold lower than that in the United Kingdom. This can be further expressed as one death case per 21 COVID-19 cases in Germany, whereas in the United Kingdom the number was one death case per seven COVID-19 cases. This might be attributed to the differences between Germany and the United Kingdom in terms of healthcare settings and actions taken by governments to minimize the spreading of COVID-19.

COVID-19 death cases (per 1 million of the population) in countries with more than 10,000 confirmed COVID-19 cases were also reviewed and reported (Table 1). The occurrence of COVID-19 death is 21-fold lower in countries with a national BCG vaccination policy than in countries without the policy, based on the medians of COVID-19 death case per 1 million of population in these two groups of countries (p < 0.001, Mann-Whitney test). Moreover, the odds ratio for COVID-19 death in countries with BCG vaccination program was found to be 0.15 (95% confidence interval [CI], 0.14–0.16). In particular, the highest reported values of COVID-19 death case per 1 million of population in a non-BCG country and a BCG country were 810 (in Belgium) and 188 (in Ecuador), respectively (Table 1, Figure 1).

Moreover, a median of one death case per 10 cases of COVID-19 was reported in non-BCG countries, compared with one death case per 37 cases of COVID-19 in BCG countries. Furthermore, the number of COVID-19 death cases in BCG countries was nine times lower than that in non-BCG countries, based on the medians of COVID-19 death cases in these two groups of countries (Table 1).

However, the race, age, health conditions, and location of COVID-19 patients, as well as the number of population per country and actions taken by governments, might affect the occurrence of COVID-19 death. In particular, the presence of a national BCG vaccination policy appeared to have a great impact on reducing the rate of COVID-19 death in a given country. For example, the COVID-19 death case per 1 million of population in Spain (a non-BCG country) is 4.6- and 89-fold higher than that in Portugal and Japan (BCG countries),

![Figure 1. Summary of coronavirus disease 2019 (COVID-19) death case per million of population in countries with more than 10,000 COVID-19 cases in the presence and absence of Bacillus Calmette-Guérin (BCG) vaccination policies, as per the World Health Organization situation report on 28 May 2020.](https://doi.org/10.4046/trd.2020.0063)
respectively (Table 1). This can also be further expressed as one death case per 23 in Portugal and per 19 in Japan (BCG countries), whereas in Spain (a non-BCG country) the number was one death case per eight cases of COVID-19. Furthermore, Japan and India had already established national BCG vaccination policies in 1951 and 1962, respectively, and experienced seven and three COVID-19 death cases per 1 million of population in 2020, respectively.34,35

These findings were in line with those recently published by Hegarty’s team (2020), who generally reported a mean COVID-19 death rate of 4.28 per 1 million of population in countries with national BCG vaccination policies compared with 40 per 1 million of population in countries without such policies; they also indicated that a booster dose of BCG vaccine between 7 to 14 years after the first vaccination did not lead to better outcomes compared with single-dose vaccination.3 In this context, Miller’s research team (2020) also found that the presence of established BCG vaccination policy correlated with a reduced COVID-19 death rate in a given country. However, this does not clearly prove that BCG vaccine would enhance defences in older adults.4 Another research group was also indicated that the data in the literature can suggest a possible inverse correlation between BCG immunization and the number of COVID-19 cases and severity.36 At the same time, it was recommended to do not use the BCG for preventing or managing COVID-19 with no direct evidence from clinical trials.47 Therefore, several countries started clinical trials on the BCG vaccine as it could be a potential prophylactic treatment until producing the appropriate COVID-19 vaccine.

Variations in the number of COVID-19 death cases among countries without a national BCG vaccination policy can also be explained by their history of BCG vaccination coverage. For example, in Denmark, BCG vaccination was neither mandatory nor recommended from 1975; however, BCG vaccination was started in 1946 and was recommended until the early 1980s, and BCG vaccination coverage for children born in 1965 was 60%.38 In Germany, according to the Robert Koch Institute’s national tally, BCG vaccination was more common in East Berlin than in West Berlin, covering 94.2% and 16.5% of the population, respectively.39 In addition, 621 COVID-19 death cases per 1 million of population were reported in Spain, where BCG vaccination was introduced in 1965 and stopped in 1981. Finally, 134 COVID-19 death cases per 1 million of population were reported in Portugal, where a BCG vaccination program was also introduced in 1965.27

On the other side, there are debates about the association of the presence of active BCG vaccination programs with the COVID-19 related prevalence and mortality rate.40,41 These studies actually denying any association between COVID-19 incidence rates and the presence of active BCG vaccination policies. But there is no disagreeing for a relation with the COVID-19 mortality rate as described in this review. However, BCG vaccination programs might be not a magical resolution for COVID-19, as there are many other factors, in addition to these programs need years to develop human protection immunity to reduce consequence of SARS-CoV-2 virus infections. This review highlights the possibility of the protective role of BCG in the context of COVID-19 which can also ex-

Table 2. Registered COVID-19–BCG vaccine related clinical trials

| No. | Clinical trial                                                                 | Country     | No. of participants |
|-----|--------------------------------------------------------------------------------|-------------|---------------------|
| 1   | BCG vaccine for health care workers as defense against COVID 19 (BADAS)         | USA         | 1,800               |
| 2   | Application of BCG vaccine for immune-prophylaxis among Egyptian healthcare workers during the pandemic of COVID-19 | Egypt       | 900                 |
| 3   | Reducing health care workers absenteeism in COVID-19 pandemic through BCG vaccine | Netherlands | 1,500               |
| 4   | Using BCG vaccine to protect health care workers in the COVID-19 pandemic       | Denmark     | 1,500               |
| 5   | BCG vaccination to protect healthcare workers against COVID-19                  | Australia   | 4,170               |
| 6   | Performance evaluation of BCG vaccine in healthcare personnel to reduce the severity of SARS-COV-2 infection | Colombia   | 1,000               |
| 7   | BCG vaccination for healthcare workers in COVID-19 pandemic                     | South Africa | 500                 |
| 8   | Efficacy of BCG vaccination in the prevention of COVID19 via the strengthening of innate immunity in health care workers (COVID-BCG) | France     | 1,120               |
| 9   | COVID-19: BCG as therapeutic vaccine, transmission limitation, and immunoglobulin enhancement (BATTLE) | Brazil     | 1,000               |
| 10  | BCG vaccine in reducing morbidity and mortality in elderly individuals in COVID-19 hotspots | India      | 2,175               |
| 11  | Prevention, efficacy and safety of BCG vaccine in COVID-19 among healthcare workers | Mexico     | 908                 |
| 12  | Bacillus Calmette-Guérin vaccination to prevent COVID-19                        | Greece      | 900                 |

COVID-19, coronavirus disease 2019; BCG, Bacillus Calmette-Guérin.
plain why there are 12 registered BCG-coronavirus clinical trials. Therefore, there is a real need to wait for the results of clinical trials.

**Recent COVID-19 BCG-Related Clinical Trials**

Many clinical trials are being conducted to determine whether BCG vaccine can reduce the frequency and severity of COVID-19 symptoms. Currently, there are 12 clinical trials in 12 countries, all of which are registered in the official website of clinical trials; these studies are aimed to evaluate the protective effect of BCG vaccine against COVID-19 in healthcare workers (Table 2).

**Conclusion**

It can be concluded that the presence of a national BCG vaccination policy in a given country could potentially offer a beneficial protective effect against TB and other nonspecific infectious diseases. Likewise, BCG could be one of the reasons of low the number of COVID-19 death cases or lower the severity of COVID-19 cases in the same country as per the WHO data till 28th of May 2020. According to the records, the BCG vaccine might also play a role in decreasing the incidence of COVID-19 in countries with a BCG national vaccination program. However, the available WHO information on BCG vaccination policies in different countries covers only the last 40 years. In BCG countries, most COVID-19 death cases occurred in people aged ≥50 years, which indicate that BCG vaccine may offer indirect protection or herd immunity in these countries.

This review found that the probability of death due to COVID-19 could be lower in individuals born in countries that adopt BCG vaccination policy (i.e., individuals vaccinated with BCG shortly after birth) than in those born in countries without a BCG vaccination policy.

Finally, investigating into the effect of BCG vaccine on individuals with COVID-19 in the clinical trial setting might be a helpful approach to confirm whether BCG is effective in managing the current COVID-19 pandemic and the anticipated second wave of this infection in the coming winter. Meanwhile, these studies are needed, especially in the absence of a marked vaccine against COVID-19 and in the presence of records and reports which support the role of the BCG vaccine in activating the human immunity system against respiratory viral infections.

**Authors’ Contributions**

Conceptualization: Jirjees FJ. Methodology: Jirjees FJ, Dallal Bashi YH. Formal analysis: Dallal Bashi YH. Data curation: Dallal Bashi YH, Jirjees FJ, Al-Obaidi HJ. Software: Dallal Bashi YH. Validation: Dallal Bashi YH, Jirjees FJ. Investigation: Jirjees FJ, Dallal Bashi YH, Al-Obaidi HJ. Project administration: Jirjees FJ. Supervision: Jirjees FJ. Visualization: Dallal Bashi YH, Al-Obaidi HJ. Writing - original draft preparation: Jirjees FJ, Dallal Bashi YH. Writing - review and editing: Jirjees FJ, Dallal Bashi YH, Al-Obaidi HJ. Approval of final manuscript: all authors.

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

**Funding**

No funding to declare.

**References**

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet 2020;395:470-3.
2. World Health Organization. Coronavirus disease (COVID-19): situation report - 130 [Internet]. Geneva: World Health Organization; 2020 [cited 2020 May 29]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200529-covid-19-sitrep-130.pdf?sfvrsn=bf7e7f0c_4.
3. Hegarty PK, Kamat A, Zafirakis H, DiNardo A. BCG vaccination may be protective against Covid-19. Preprint at https://doi.org/10.13140/RG.2.2.35948.10880 (2020).
4. Miller A, Reandelar MJ, Fasigilione K, Roumenova V, Li Y, Otazu GH. Correlation between universal BCG vaccination policy and reduced mortality for COVID-19. Preprint medRxiv at https://doi.org/10.1101/2020.03.24.20042937 (2020).
5. British Lung Foundation. Tuberculosis. London: British Lung Foundation; 2020 [cited 2020 Apr 25]. Available from: https://www.blf.org.uk/support-for-you/tuberculosis.
6. Luca S, Mihaescu T. History of BCG vaccine. Maedica (Bucur) 2013;8:53-8.
7. Covian C, Fernandez-Fierro A, Retamal-Diaz A, Diaz FE, Vasquez AE, Lay MK, et al. BCG-induced cross-protection and development of trained immunity: implication for vaccine design. Front Immunol 2019;10:2806.
8. Tanner R, Villarreal-Rumos B, Vordermeier HM, McShane H. The humoral immune response to BCG vaccination. Front
9. Bosteels C, Neyt K, Vanheerswynghels M, van Helden MJ, Sichien D, Debeuf N, et al. Inflammatory type 2 cDCs acquire features of cDC1s and macrophages to orchestrate immunity to respiratory virus infection. Immunity 2020;52:1039-56.

10. de Castro MJ, Pardo-Seco J, Martínón-Torres F. Nonspecific (heterologous) protection of neonatal Bacillus Calmette-Guerin vaccination against hospitalization due to respiratory infection and sepsis. Clin Infect Dis 2015;60:1611-9.

11. Global tuberculosis report 2019 (WHO/CDS/TB/2019.15) [Internet]. Geneva: World Health Organization; 2019 [cited 2020 May 1]. Available from: https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1.

12. Mangtani P, Ngoupdop-Djomo P, Keogh RH, Trinder L, Smith PG, Fine PE, et al. Observational study to estimate the changes in the effectiveness of bacillus Calmette-Guerin (BCG) vaccination with time since vaccination for preventing tuberculosis in the UK. Health Technol Assess 2017;21:1-54.

13. Colditz GA, Brewer TF, Berkley CS, Wilson ME, Burdick E, Fineberg HV, et al. Efficacy of BCG vaccine in the prevention of tuberculosis: meta-analysis of the published literature. JAMA 1994;271:698-702.

14. Fine PE. Variation in protection by BCG: implications of and for heterologous immunity. Lancet 1995;346:1339-45.

15. Venkataseswamy MM, Goldberg MF, Baena A, Chan J, Jacobs WR Jr, Porcelli SA. In vitro culture medium influences the vaccine efficacy of Mycobacterium bovis BCG. Vaccine 2012;30:1038-49.

16. Abubakar I, Pimpin L, Ariti C, Beynon R, Mangtani P, Sterne JA, et al. Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette-Guerin vaccination against tuberculosis. Health Technol Assess 2013;17:1-372.

17. The SAGE Working Group on BCG Vaccines and WHO Secretariat. Report on BCG vaccine use for protection against mycobacterial infections including tuberculosis, leprosy, and other nontuberculous mycobacteria (NTM) infections [Internet]. Geneva: World Health Organization; 2017 [cited 2020 May 1]. Available from: https://apps.who.int/immunization/sage/meetings/2017/october/1_BCG_report_revised_version_online.pdf.

18. Sterne JA, Rodrigues LC, Guedes IN. Does the efficacy of BCG decline with time since vaccination? Int J Tuberc Lung Dis 1998;2:200-7.

19. Briassoulis G, Karabatsou I, Gogoglou V, Tsonva A. BCG vaccination at three different age groups: response and effectiveness. J Immunol Based Ther Vaccines 2005;3:1.

20. Aronson NE, Santosham M, Comstock GW, Howard RS, Moulton LH, Rhoades EB, et al. Long-term efficacy of BCG vaccine in American Indians and Alaska Natives: a 60-year follow-up study. JAMA 2004;291:2086-91.

21. 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;48:507-17.

22. Spencer JC, Ganguly R, Waldman RH. Nonspecific protection of mice against influenza virus infection by local or systemic immunization with Bacille Calmette-Guerin. J Infect Dis 1977;136:171-5.

23. Arts RJ, MoorSl SJ, Novakov B, Li Y, Wang SY, OOSTING M, et al. BCG vaccination protects against experimental viral infection in humans through the induction of cytokines associated with trained immunity. Cell Host Microbe 2018;23:89-100.

24. Leentjens J, Kox M, Stokman R, Gerrets H, Diavatopoulos DA, van Crevel R, et al. BCG vaccination enhances the immunogenicity of subsequent influenza vaccination in healthy volunteers: a randomized, placebo-controlled pilot study. J Infect Dis 2015;212:1930-8.

25. WHO timeline - COVID-19 [Internet]. Geneva: World Health Organization; 2020 [cited 2020 May 1]. Available from: https://www.who.int/news-room/detail/27-04-2020-who-timeline---covid-19.

26. Li H, Liu SM, Yu XH, Tang SL, Tang CK. Coronavirus disease 2019 (COVID-19): current status and future perspectives. Int J Antimicrob Agents 2020;55:105951.

27. Zhao X, Zhang B, Li P, Ma C, Gu J, Hou P, et al. Incidence, clinical characteristics and prognostic factor of patients with COVID-19: a systematic review and meta-analysis. Preprint medRxiv at https://doi.org/10.1101/2020.03.17.20037572 (2020).

28. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.

29. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol 2020;38:1-9.

30. Clinical management of COVID-19 [Internet]. Geneva: World Health Organization; 2020 [cited 2020 May 1]. Available from: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected.

31. WHO vaccine-preventable diseases: monitoring system. 2019 global summary [Internet]. Geneva: World Health Organization; 2020 [cited 2020 May 1]. Available from: https://www.who.int/immunization_monitoring/globalsummary/coverages?c=PRT.

32. People with certain medical conditions [Internet]. Atlanta, GA: Centers for Disease Control and Prevention; 2020 [cited 2020 May 5]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html#asthma.

33. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020;323:1775-6.

34. Rahman M, Sekimoto M, Takamatsu I, Hira K, Shimbo T,
Toyoshima K, et al. Economic evaluation of universal BCG vaccination of Japanese infants. Int J Epidemiol 2001;30:380-5.
35. Lahariya C. A brief history of vaccines and vaccination in India. Indian J Med Res 2014;139:491-511.
36. 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;11:516.
37. 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;117:17720-6.
38. Rieckmann A, Villumsen M, Sorup S, Haugaard LK, Ravn H, Roth A, et al. Vaccinations against smallpox and tuberculosis are associated with better long-term survival: a Danish case-cohort study 1971-2010. Int J Epidemiol 2017;46:695-705.
39. Gruber C, Meinschmidt G, Bergmann R, Wahn U, Stark K. Is early BCG vaccination associated with less atopic disease? An epidemiological study in German preschool children with different ethnic backgrounds. Pediatr Allergy Immunol 2002;13:177-81.
40. Kumar J, Meena J. Demystifying BCG vaccine and COVID-19 relationship. Indian Pediatr 2020;57:588-9.
41. Ricco M, Gualerzi G, Ranzieri S, Bragazzi NL. Stop playing with data: there is no sound evidence that Bacille Calmette-Guerin may avoid SARS-CoV-2 infection (for now). Acta Biomed 2020;91:207-13.
42. ClinicalTrials.gov [Internet]. Bethesda, MD: US National Library of Medicine; 2020 [cited 2020 May 5]. Available from: https://clinicaltrials.gov/.