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A Systematic Review of BCG and tie-in to coronavirus disease: A Point of Contention for Global Health?

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ABSTRACT

Background: COVID-19, a pandemic that started in December 2019 from the city of Wuhan in China. BCG (Mycobacterium Bovis Bacillus Calmette-Guérin) is a live attenuated vaccine used for tuberculosis (TB) that. The BCG vaccine became a part of the 'National Tuberculosis Control Program (NTCP)' in India in 1962. The BCG vaccine is given to all children in India, preferably within the first year after birth. However, as per CDC recommendations in the US, BCG is only considered for very select cases, for e.g. children who have a negative TB test and who are continually exposure to adults with TB disease. It induces epigenetic and metabolic alterations at promoter sites of genes encoding inflammatory cytokines such as IL-1,IL-6 and TNF that improve the innate immune response to the subsequent infections by trained immunity. This may be useful in management of COVID-19.

Method: We conducted a literature review searching databases like Cochrane, PubMed, Google scholars, CINAHL, LILACS, UpToDate, Scopus, EMBASE, WOS, and Science Direct. We used the following keywords: COVID 19, SARSCoV2 and BCG vaccines. We included case reports, case series and cohort (retrospective and prospective).

Results: The global trend suggested an inverse association between BCG vaccination policy and COVID-19 mortality. Countries with current BCG vaccination had lower deaths and was negatively associated with COVID-19 deaths per million Patients with BCG vaccination were more likely to experience myalgia and less likely to require hospital admission. BCG is known to elicit non-specific immune effects through the induction of the innate immune responses and the enhanced production of IL-1β and help combat COVID-19 like respiratory infections.

Conclusion: If the BCG vaccine is proven to provide non-specific protection to bridge the gap before a disease-specific vaccine is developed, this would be an important tool in the response to COVID-19 and future pandemics.

Keywords
COVID-19, BCG vaccine, Viral infections.

Introduction
COVID-19, a pandemic that started in December 2019 from the city of Wuhan in China. It is caused by SARS-CoV-2 i.e. severe acute respiratory syndrome Coronavirus-2, which has spread to over 210 countries and territories and caused a total of 162 million cases worldwide with 3.36 million deaths, as of 15th May 202. It involves common symptoms like fever, dry cough, tiredness, some GIT symptoms like diarrhea and other symptoms that include joint pains, headache, rash and many more.

BCG (Mycobacterium Bovis Bacillus Calmette-Guérin) is a live attenuated vaccine used for tuberculosis (TB). It is given to infants right after their birth in some countries where there is a higher incidence of TB. The BCG vaccine became a part of the 'National Tuberculosis Control Program (NTCP)' in India in 1962. The BCG

vaccine is given to all children in India, preferably within the first year after birth. However, as per CDC recommendations in the US, BCG is only considered for very select cases, for e.g. children who have a negative TB test and who are continually exposure to adults with TB disease.

The BCG vaccine contains an attenuated strain of Mycobacterium bovis, which is clinically and radiographically indistinguishable from M. tuberculosis. The live attenuated vaccine organism can replicate and produce immunity in the host but does not cause illness. The BCG vaccine has also shown to boost the innate immune response to other non-specific infections. It induces epigenetic and metabolic alterations at promoter sites of genes encoding inflammatory cytokines such as IL-1,IL-6 and TNF that improve the innate immune response to the subsequent infections by trained immunity [3,4].

In addition to protection against TB, BCG vaccine has been routinely used to treat bladder cancer [1,2] and enhance protection against unrelated pathogens. An example includes in 1927, Swedish children who received BCG vaccination at birth had a lower mortality rate than children who were not vaccinated which may have been due to nonspecific immunity [4].

There are many other examples that are witnesses of the protective effect of BCG vaccination in respiratory infections, which may suggest that it can have a protective effect against COVID-19 infection [4].

Aim
To review the application of BCG vaccination to prevent and attenuate SARS-2-COVID-19 infections in countries where COVID-19 vaccines are not available.

Objectives
To review the differences in BCG vaccination status between US and India.
To review the application of BCG vaccination to prevent COVID-19 infections, in countries where COVID-19 is not available.
To create recommendations for possible use of the BCG vaccine in emergency management plans for future waves of the COVID-19 pandemic.

Method
A systematic search was conducted for research articles on BCG and COVID-19 from December 2019 through. Five primary databases were used, Pub-Med, Google Scholar, WHO, ResearchGate, and Science Direct. The search strategy used the keywords, coronavirus, COVID-19, BCG, BCG outcome, COVID vaccine and their combinations.

Data Screening and eligibility
The final review articles fulfilled the following criteria:
1. Healthy Patients with no prior chronic inflammation, immunocompromise or illness
2. Full text, peer-reviewed articles (Meta-analysis, case-studies and case series, systematic reviews, randomized controlled trials).
3. Articles in English.
4. Patients with >70 years aged patients, taking immunomodulators, history of cancer, history of chemotherapy and if in combination with other medications were excluded.

Articles that did not have patient data, studies limited to pregnant patients, and those limited to specific co-morbidities and organ dysfunctions were excluded to avoid selection bias. In doing so, we had 8 articles for the final review (Table 1).

Selected articles were independently reviewed by two authors. All disagreements were resolved with a discussion between the two authors.

Our review included studies from various countries from across the globe. The studies used have been listed in Table 1. We tabulated the information using Microsoft Excel. Referencing was done according to guidelines using Endnote.

This study did not require ethical approval as data was obtained from already available databases, and patients were not directly involved.

Results
After reviewing 182 articles, we finalized eight articles for the literature review (Table 1). Netea et al. suggested the importance of trained immunity as a fundamental characteristic of host defense of multicellular organisms. Pollard et al. explained that augmenting trained immunity could be specifically useful in attenuating life-threatening infections during the first few vulnerable months of life, particularly in high mortality settings, such as the current COVID-19 pandemic A similar perspective was shared by Goodridge et al., who suggested that the induction of a super-protective state that could be used for a period of increased susceptibility to infections, such as during the neonatal period, or during the current pandemic. Moreover, considering the ACTIVATE trial which studied the effect of BCG on influenza A, we specifically wanted to look at the application of boosting one's trained immunity to provide protection against COVID-19 infections. Ana Paula et al. are also conducting a clinical trial to study the effectiveness of the BCG virus to reduce incidence of SARS-CoV-2 infection in Brazil.

Escobar et al. suggested that the global trend suggested an inverse association between BCG vaccination policy and COVID-19 mortality [4]. Patients with BCG vaccination was more likely to experience myalgia and less likely to require hospital admission. As per Weng et al, BCG is known to elicit non-specific immune effects through the induction of the innate immune responses and the enhanced production of IL-1β and help combat COVID-19 like respiratory infections [5].

Table 1

Author name	DOI	Title of article	Methodology	Outcomes of study	Recommendations for public health
Netea et al.	https://dx.doi.org/10.1016%2Fj.cell.2020.04.042	Trained Immunity: a Tool for Reducing Susceptibility to and the Severity of SARS-CoV-2 Infection	Perspective Article	Inducing trained immunity can lead to increased defence against COVID-19 patients and a decrease in inflammation	Trained immunity, as an epigenetic memory of inflammatory encounters, is a fundamental characteristic of host defence of multicellular organisms, including mammals. The impact of trained immunity, and more generally of epigenetic rewiring in various processes of priming, adaptation or tolerance during disease, warrants further studies.
Pollard et at.	http://dx.doi.org/10.1136/archdischild-2015-310282	Non-specific effects of vaccines: plausible and potentially important, but implications uncertain	Review Article	Current immunobiological perspectives and the widespread use of vaccine adjuvants to stimulate the immune system and enhance vaccine immunogenicity are evidence that there can be NSIE of vaccines, even though our understanding of the importance, magnitude, and duration of impact remains inadequate.	Interventions designed to augment non-specific resistance to life-threatening infections during the first few vulnerable months of life, particularly in high mortality settings, merit further investigation.
Escobar et al.	https://doi.org/10.1073/pnas.2008410117	BCG vaccine protection from severe coronavirus disease 2019 (COVID-19)	Review Article	We found that COVID-19 mortality in the states of NY, Illinois, Louisiana, Alabama and Florida was significantly higher than states from BCG-vaccinated countries (Pernambuco, Rio de Janeiro, and Sao Paulo in Brazil, Mexico State and Mexico City in Mexico).	The consistent association between BCG vaccination and reduced severity of COVID-19 observed in these and other epidemiological explorations is remarkable, but not sufficient to establish causality between BCG vaccination and protection from severe COVID-19.
Goodridge et al.	https://doi-org.echo.louisville.edu/10.1038/nri.2016.43	Harnessing the beneficial heterologous effects of vaccination	Review Article	Positive heterologous effects mediated by innate and/or adaptive immune mechanisms could be leveraged to confer broader protection against a range of pathogens.	If a super-protective state could be induced by vaccination, even if only for a brief window of exquisite infectious susceptibility, such as in the neonatal period, imprint improvements in health could be realized.
Activate trial	https://clinicaltrials.gov/ct2/show/NCT03296423	Bacillus Calmette-Guerin Vaccination to Prevent Infections of the Elderly (ACTIVATE)	Clinical Trial	Primary Outcomes Measures: Time to First Infection	Volunteers previous vaccinated by BCG developed significantly greater tigers against hem agglutinin A of the influenza A virus whereas their circulating monocytes were more potent to produce IFNgamma7.
Ana Paula et al.	https://doi.org/10.1186/s13063-020-04822-0	BCG revaccination of health workers in Brazil to improve innate immune responses against COVID-19: A structured summary of a study protocol for a randomised controlled trial	Phase 2 Trial	The primary objective is to verify the effectiveness and safety of the BCG vaccine to prevent or reduce incidence of severe acute respiratory syndrome coronavirus-2 infection in the city of Goiania (Brazil) among HW previously vaccinated with BCG and also its severity and mortality during the pandemic of the disease.	Based on the results of the trial, when available, the BCG vaccine could be used to improve innate immunity against symptomatic infection due to COIVD or even severity of infection due to COVID-19.
Weng et al	doi:10.1017/S0950268820001569	Bacillus Calmette–Guérin vaccination and clinical characteristics and outcomes of COVID-19 in Rhode Island, United States: a cohort study	Cohort Study	Patients with BCG vaccine was more likely to experience myalgia and less likely to require hospital admission.	Recent ecological studies comparing countries with and without universal BCG vaccination policies found that BCG vaccination appears to significantly reduce mortality associated with COVID-19 and mandatory BCG vaccination was associated with a flattening of the curve in the spread of COVID-19.
O'Neill et al	https://doi.org/10.1038/s41577-020-0337-y	BCG-induced trained immunity: can it offer protection against COVID-19?	Review Article	They proposed that trained immunity induced by BCG could be used to protect against COVID-19	One could finally envisage using trained immunity as an important tool against emerging pathogens. BCG (or other stimuli that induce trained immunity) could be rapidly tested and eventually used at the beginning of a pandemic, bridging the 1-2-year period until a specific vaccine can be developed.

Ecological studies done by O'Neill et al. have suggested that countries and regions that mandate BCG vaccination for the population have a lower number of infections and a reduced mortality from COVID-19. Countries with current BCG vaccination had lower deaths and was negatively associated with COVID-19 deaths per million [6].

Discussion

The BCG vaccine has been shown to lower mortality rates due to non-specific immunity in the past. In this review, we looked specifically at the effect that BCG vaccination had on the mortality and morbidity due to COVID-19 and tried to find explanations for the same. This review highlights the importance of increasing the population's innate immunity or tolerance to numerous different infections.

We found that some studies showed the negative association between BCG vaccination and COVID-19 deaths. As of May 14, 2021, the total number of cases in US are 32.9M 585,000 deaths, whereas India has 24.4M cases and 266,000 deaths. This result was unexpected, considering the lower compliance with mask-wearing in India, vaccine hesitancy and the significantly higher population density in India. This is in line with Escobar et al' observation of the adequate control of COVID in BCG vaccinated countries like Brazil and Mexico. Therefore, we would like to put forward the possibility that the BCG vaccine confers immunity against the SARS-CoV-2 virus.

Netea et al. explained that this could be due to 'trained immunity'. [1] Memory characteristics in the innate immune system of vertebrates have recently been described and referred to as 'trained immunity' a process that results in a heightened reaction to secondary infections or sterile triggers of inflammation. An article by Ana Paula et al. suggested that this could be due to the activation of monocytes and innate memory NK cells, which provides a better innate immune response and reduce COVID-19 severity [7]. 'The Hellenic Institute for the Study of Sepsis' put forward the explanation that the innate immune system can recognize pathogen-associated molecular patterns (PAMPs) on pattern-recognition-receptors (PRRs) of blood monocytes and tissue macrophages. Moreover, experiments have shown that exposure to small amounts of PAMPs have prevented death upon re-exposure [8]. This explanation could even account for the increased myalgia in COVID-19 patients with a history of taking the BCG vaccine.

We would also like to explore the benefit of the BCG vaccine's ability to create trained immunity against both COVID-19 and the Influenza virus. The ACTIVATE trial explained that volunteers who were previously vaccinated with BCG developed significant greater titers against hemagglutinin A of the influenza virus. If BCG can confer trained immunity against both Influenza and COVID, it could be especially beneficial since co-infection could result in increased risk of mortality.

Limitations

In this review, we used ecological studies which could have possible confounding factors. Based on the information we found, we cannot identify a direct protective association between the BCG vaccination and immunity to COVID-19, even though there is enough evidence to suggest the same. We believe further retrospective and proactive studies should be conducted to establish a causal relationship between the two. Currently, RCTs are being conductive to identify an association between the two at University of Texas MD Anderson Cancer Center and Baylor College of medicine, which will shed more clarity on the association.

Recommendations

We would like to recommend that vaccination geared to increasing non-specific immunity in the population could be a future possibility to protect against unexpected pandemics such as the SARS-COV-2. Moreover, high efficacy vaccines like Pfizer and Moderna have not reached many 3rd-world countries yet. Keeping in mind Escobar et als' observation of the adequate control of COVID in BCG vaccinated countries like Brazil and Mexico, we recommend an interim use of the BCG vaccine to reduce mortality and morbidity due to the current COVID-19 pandemic in countries which cannot acquire the COVID-19 vaccines. Although the immunity from such vaccines might be short term, they may be especially important for the vulnerable population such as neonates and elderly aged >65.

Conclusion

If the BCG vaccine or another inducer of innate immunity provides non-specific protection to bridge the gap before a disease-specific vaccine is developed, this would be an important tool in the response to COVID-19 and future pandemics in countries where COVID-19 vaccines are not easily acquirable. However, many of the resources in the review were ecological studies with possible confounding factors. Therefore, we suggest that further research is needed to see the direct effects of BCG on COVID-19 pneumonia and other respiratory pathogens.

References

1. Netea MG, Dominguez-Andres J, Barreiro LB, et al. Defining trained immunity and its role in health and disease. Nat Rev Immunol. 2020; 20: 375-388.

2. Pollard AJ, Finn A, Curtis N. Non-specific effects of vaccines: plausible and potentially important, but implications uncertain. Arch Dis Child. 2017; 102: 1077-1081.

3. Goodridge HS, Ahmed SS, Curtis N, et al. Harnessing the beneficial heterologous effects of vaccination. Nat Rev Immunol. 2016; 16: 392-400.

4. Escobar LE, Molina-Cruz A, Barillas-Mury C. BCG vaccine protection from severe coronavirus disease 2019 (COVID-19). Proceedings of the National Academy of Sciences. 2020; 117: 17720-17726.

5. Weng C, Saal A, Butt W, et al. Bacillus Calmette–Guérin vaccination and clinical characteristics and outcomes of COVID-19 in Rhode Island, United States: A cohort study. Epidemiology and Infection. 2020; 148: E140.

6. O'Neill LAJ, Netea MG. BCG-induced trained immunity: can it offer protection against COVID-19? Nat Rev Immunol. 2020; 20: 335-337.

7. Junqueira-Kipnis AP, Dos Anjos L, Barbosa L, et al. BCG revaccination of health workers in Brazil to improve innate immune responses against COVID-19: A structured summary of a study protocol for a randomised controlled trial. Trials. 2020; 21: 881.

8. https://clinicaltrials.gov/ct2/show/NCT03296423

9. https://www.cdc.gov/tb/topic/basics/vaccines.html

10. Lahariya C. A brief history of vaccines & vaccination in India. The Indian journal of medical research. 2014; 139: 491-511. /

11. https://path.upmc.edu/cases/case746/dx.html