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# Bacille Calmette-Guérin (BCG) vaccine and potential cross-protection against SARS-CoV-2 infection — Assumptions, knowns, unknowns and need for developing an accurate scientific evidence base

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ABSTRACT

After a century of controversies on its usefulness in protection against TB, underlying mechanisms of action, and benefits in various groups and geographical areas, the BCG vaccine is yet again a focus of global attention- this time due to the global COVID-19 pandemic caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Recent studies have shown that human CD4+ and CD8+ T-cells primed with a BCG-derived peptide developed high reactivity to its corresponding SARS-CoV-2-derived peptide. Furthermore, BCG vaccine has been shown to substantially increase interferon-gamma (IFN-g) production and its effects on CD4+ T-cells and these non-specific immune responses through adjuvant effect could be harnessed as cross protection against severe forms of COVID-19.The completion of ongoing BGG trials is important as they may shed light on the mechanisms underlying BCG-mediated immunity and could lead to improved efficacy, increased tolerance of treatment, and identification of other ways of combining BCG with other immunotherapies.


## Introduction

It has been more than a hundred years since Jean-Marie Camille Guérin and Albert Calmette developed the Bacille Calmette–Guérin (BCG) vaccine for preventing tuberculosis (Towey, 2015). After a century of controversies on its usefulness in protection against TB, underlying mechanisms of action, and benefits in various groups and geographical areas (Lienhardt and Zumla, 2005; Locht and Lerm, 2020), the BCG vaccine is yet again a focus of global attention- this time due to the global COVID-19 pandemic caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). As of 26 January 2021, there have been over 98.8 million confirmed cases of COVID-19, including 2,124,193 deaths,

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## Non-specific BCG cross-protection

The BCG vaccine contains live attenuated *Mycobacterium bovis*, and is known to induce both humoral and adaptive immunity, activating both non-specific and cross-reactive immune responses in the host (Moorlag et al., 2019). Combined, these non-specific adjuvant effects of BCG could effectively mount responses to other pathogens, including viruses (Moorlag et al., 2019; Uthayakumar et al., 2018). It has also been used for treating bladder cancer for the past 40 years although the specific mechanisms of action remain unknown (Sfakianos et al., 2021). Previous studies have documented associations between BCG vaccination and reductions in the incidence of respiratory tract infections among children and adults, and all-cause mortality in children(Moorlag et al., 2019; Uthayakumar et al., 2018). Furthermore, the vaccine has been reported to exert antiviral effects in experimental models; reduce viremia in an experimental human model of viral infection; protecting against experimental infection with yellow fever vaccine strain, and enhancing immune responses to other vaccines such as influenza vaccine (Arts et al., 2018). Many of these broad-spectrum protective effects have been attributed to trained immunity, the epigenetic and metabolic reprogramming of innate immune cells (Arts et al., 2018; Moulson and Av-Gay, 2020). Based on these reports and epidemiological observations, the potential for BCG vaccination to induce (partial) protection against SARS-CoV-2 infection and prevent serious disease was thus deemed plausible and logical in what was a desperate global situation (Escobar et al., 2020; Patella et al., 2020). A pressing question arose: Does prior BCG vaccination reduce host susceptibility to SARS-CoV-2 infection and/or significantly reduce COVID-19 severity and mortality rate?

## Observations on COVID-19 epidemiology and BCG vaccination

Before the advent and recent rollout of COVID-19-specific vaccines, the desperate search to find interventions which could prevent the high mortality rates, especially in the elderly and those with co-morbidities, sparked off a global debate on the potential use of BCG for management or prevention of COVID-19 (Brooks et al., 2021; Charoenlap et al., 2020; Escobar et al., 2020; Klinger et al., 2020; Lindestam Arlehamn et al., 2020; Junqueira-Kipnis et al., 2020; Kinoshita and Tanaka, 2020; Riccò et al., 2020; ten Doesschate et al., 2020; Yitbarek et al., 2020). Due to the sense of urgency in addressing the rapidly-progressing pandemic, there were calls to roll out BCG vaccine for protection against SARS-CoV-2 (De Wals et al., 2020; Kangbai et al., 2021; Malik et al., 2020; Salman and Salem, 2020). There are also concerns about the lack of any convincing data on the effectiveness of BCG in preventing serious disease due to SARS-CoV-2 infection. An additional concern was that indiscriminate BCG use would create a shortage and compromise routine immunization programs (Chimoyi et al., 2020; Kumar and Meena, 2020; Kuroda, 2020; Riccò et al., 2020).

Early in the outbreak, it was noted that rates of SARS-CoV-2 infection and case fatality rate varied significantly in different parts of the world, being relatively higher in North America and Europe, and lower in regions such as South America, South Asia and Africa (Coronavirus Disease (COVID-19) – World Health Organization, n.d.). Epidemiological observations and ecological studies suggested that western countries that were not endemic for TB and thus did not advocate universal BCG vaccination had higher COVID-19 incidence and mortality rates, compared to low and middle-income countries with longstanding mass BCG immunization programs (http://www.bcgatlas.org/; Brooks et al., 2021; Riccò et al., 2020; Urashima et al., 2020). Most of these studies however did not consider major confounding factors such as demographics (e.g., age distribution) or how long and to what extent universal BCG vaccination was implemented. Furthermore, analyses performed in the latter half of 2020 using updated COVID-19 data have failed to show any significant association with BCG vaccination-or the lack thereof (Arlehamn et al., 2020). As of 26 January, 2021, there are at least 20 ongoing clinical trials in Africa, Australia, South Asia, North and South America and Europe, that are expected to provide more robust data on the effectiveness of BCG vaccination in modulating susceptibility to SARS-CoV-2 infection and disease (Home - ClinicalTrials.Gov, n.d.). However, to date, available evidence is relatively weak.

## BCG and cross-reactivity with SARS-CoV-2 peptides

Recent studies have shown that human CD4+ and CD8+ T-cells primed with a BCG-derived peptide developed high reactivity to its corresponding SARS-CoV-2-derived peptide (Eggenhuizen et al., 2020; Urbán et al., 2020). Peptide sensitization using BCG has been found to produce cross-reactive T-cells specific to SARS-CoV-2. They identified 8 BCG-derived peptides in silico with considerable sequence homology to either SARS-CoV-2 NSP3 or NSP13-derived peptides. Due to human leukocyte antigen (HLA) differences between individuals, not all persons develop immune responses every one of the 8 BCG-derived peptides. Overall, the study results suggest that CD4+ and CD8+ T-cells specific for BCG-derived peptides are cross-reactive to SARS-CoV-2-derived peptides. This may explain the epidemiologic observation that BCG vaccination may protect against COVID-19 disease or death by triggering cross-reactive SARS-CoV-2-specific T-cell response. While this awaits confirmation by demonstrating that SARS-CoV-2 specific T-cell clones recognize naturally processed and presented BCG – epitopes (and vice versa), 'trained immunity' imposed by BCG on the quality and quantity of cellular immune responses has been suggested, although this is often short lived and the protective role of BCG regarding clinical severe COVID-19 has been disputed (Arlehamn et al., 2020). Other, not mutually exclusive factors need to be considered: BCG vaccine has been shown to substantially increase interferon-gamma (IFN-g) production and its effects on CD4+ T cells (Flynn et al., 1993) and these non-specific immune responses could be harnessed as cross protection against severe forms of COVID-19 (Sohrabi et al., 2020; Mosaddeghi et al., 2020). Severe forms of COVID-19 have been described in patients with inborn errors of type I IFN responses (Zhang et al., 2020) or those who have autoantibodies directed against IFN (Bastard et al., 2020).

## Towards developing a better evidence base

There are currently over 20 clinical trials in progress to determine the effectiveness of BCG vaccination for prevention of SARS-CoV-2 infection or reduce the severity of COVID-19 (Home - ClinicalTrials.Gov, n.d.). Currently, at least three SARS-CoV-2 vaccines have been shown to be effective in randomized controlled trials and are licensed and approved for global roll out (Commissioner, 2021; Kim et al., 2021; Singh and Upshur, 2020). Therefore, one question arises: is there any role for BCG in COVID-19 prevention or treatment, and do the ongoing trials need to be abandoned? Based on the data reviewed and the safety and widespread use of the BCG vaccine, its low cost and easy availability, and the low priority given by vaccine manufacturers (Gupta, 2020) it is certainly reasonable to continue the trials of BCG. Furthermore, the data may provide a better understanding of the mechanisms underlying BCG-mediated immunity and could lead to improved efficacy, increased tolerance of treatment, and

identification of other ways of combining BCG with other immunotherapies. It is important that all trials of BCG are completed so that a scientific evidence base is obtained on the usefulness of BCG in the management of COVID-19.

## Author declarations

All authors declare no conflicts of interest.

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Dr. Sam-Agudu is a clinician-scientist and implementation researcher in pediatric infectious diseases. She is supported by NIH/National Institute of Child Health and Human Development (NICHD) grant R01HD089866, and by an NIH/FIC award through the Adolescent HIV Prevention and Treatment Implementation Science Alliance (AHISA), for the Central and West Africa Implementation Science Alliance (CAWISA). Dr. P.D.M.C Katoto is supported by Pitt-HRTP-SA and is a CAWISA Fellow.

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## Ethical approval

Not applicable.

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