

## BCG Protection Against COVID-19: Is it Reality or Illusion?

Inas K. SHARQULE , Khalifa E. SHARQULE 

**Ethics Committee Approval:** Not applicable.

**Conflict of interest:** The authors declare that they have no conflict of interest.

**Funding:** None.

**Informed Consent:** Not Applicable.

**Cite as:** Sharquie IK, Sharquie KE. BCG protection against COVID-19: Is it reality or illusion?. Medeniyet Med J. 2021;36:80-2.

The COVID-19 pandemic (caused by the SARS-CoV-2 virus) has caused over 1.6 million deaths globally in 2020<sup>1,2</sup>. Early responses to address this crisis have involved the development of vaccines and rearranging existing drugs. Interestingly, however, some epidemiological studies linked Bacillus-Calmette-Guérin (BCG) - one of the world's oldest vaccines - to the protection of humans against nonspecific pathogens such as SARS-CoV-2<sup>3</sup>. It comprises an attenuated, less virulent strain of Mycobacterium bovis, and years of data support its protective efficacy against tuberculosis, ie: its intended target. Nonspecific targets that BCG elicits protective effects ranging from Mycobacteria that causes leprosy through to non-mycobacterial prokaryotes including Staphylococcus aureus, and viruses including respiratory syncytial virus (RSV)<sup>4-6</sup>, and those causing viral warts<sup>7-8</sup> and recurrent aphthous stomatitis<sup>9</sup>. BCG vaccine has been associated with a reduction in respiratory tract infections of vulnerable patient groups including neonates and the elderly, which has raised hopes that BCG may offer protection against COVID-19 during the second wave of epidemics<sup>3</sup>.

### Epidemiological and clinical evidence of BCG-mediated protection against nonspecific pathogens

Although little specific evidence suggested that BCG protected against the coronaviruses that caused the 2003 severe acute respiratory syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) epidemics (SARS-CoV-1 and MERS-CoV, respectively), several observations suggested that it might offer protection against COVID-19. Countries routinely conducting mass vaccination programmes that included BCG have seen significantly lower mortality rates from COVID-19 than countries that administer the vaccine on a case-by-case basis following a positive Mantoux test result<sup>3,10-12</sup>. One study suggested that case-by-case BCG vaccinating countries (Italy, the USA, the Netherlands, Belgium) had 265 cases per million population compared with 60 in low-income countries that applied mass vaccinations<sup>13</sup>.

**Received:** 24 January 2021

**Accepted:** 2 February 2021

**Online First:** 26 March 2021

**Corresponding Author:**

**I.K. Sharquie**

**ORCID:** 0000-0002-4953-7365

University of Baghdad,

College of Medicine,

Department of Microbiology &

Immunology,

Baghdad, Iraq

✉ iksharquie@yahoo.com -

inasksharquie@comed.uobaghdad.edu.iq

**K.E. Sharquie**

**ORCID:** 0000-0002-0265-2040

University of Baghdad,

College of Medicine,

Department of Dermatology,

Baghdad, Iraq



Although one study did not prove a protective effect of BCG against COVID-19<sup>14</sup>, the authors acknowledged that their observations may be confounded by reporting biases. Generally, opinion leaders believe that continued investigation is required until a consensus is reached<sup>3,10,11</sup>. Data from several eagerly awaited randomised clinical trials will determine how BCG affects COVID-19 infection. The BCG-CORONA (the Netherlands) and BRACE (Australia) placebo-controlled trials are studying the effects of BCG on 1500 and 10,078 healthcare workers, respectively exposed to COVID-19 patients<sup>15-17</sup>. Additionally, a study in the USA reported a statistically significant reduction in the number of COVID-19 disease related to hospital admissions in BCG-vaccinated participants (although the authors did not indicate when they were vaccinated)<sup>18</sup>. This suggests that BCG vaccination deployment may reduce COVID-19 cases, hospitalisations, and deaths, a view shared by many opinion leaders.

### **How BCG mediates protection against nonspecific pathogens**

There are several mechanisms for this putative protective effect. BCG reportedly triggers a form of nonspecific innate immune cell memory by epigenetic reprogramming - known as trained memory. PBMCs from vaccines stimulated with nonspecific pathogens produce elevated levels of proinflammatory cytokines IFN- $\gamma$ , TNF- $\alpha$ , and IL-1 $\beta$ , which were also linked to the protection of T-cell- and B-cell-deficient BCG-vaccinated SCID mice against non-mycobacterial pathogens<sup>19</sup>. This process was accompanied by methylation of these genes<sup>19</sup>. Additionally, BCG-recipients subsequently vaccinated with the yellow fever vaccine had lower levels of viremia than those not unvaccinated which was also correlated with epigenetic reprogramming within proinflammatory cytokine genes<sup>20</sup>. Taken all together, these findings strongly implicate the presence of trained memory in BCG-mediated protection against nonspecific pathogens.

Adaptive immunity may also be playing a role. A clinical trial showed that BCG vaccination followed by influenza vaccination increased antibody titres against the latter (correlating with the protective efficacy), suggesting that it may increase B-cell responses against nonspecific respiratory viral pathogens in some settings in 2009<sup>21</sup>. Additionally, the elevated proinflammatory cytokines driven by BCG were postulated to increase heterologous responses of CD4+ and CD8+ Th1 and Th17 cells<sup>10,22</sup>. If such responses are directed against SARS-CoV-2, it would be likely to have protective effects.

### **CONCLUSION**

The combination of epidemiological data from the countries who apply mass vaccination backed up by strong immunological evidence that BCG vaccine protects against a wide range of nontuberculous mycobacteria, makes a strong case that BCG could help to control COVID-19. Consensus will be reached out and confirmed if the imminent further clinical trials will be carried to support this premise.

### **REFERENCES**

1. WHO. Weekly epidemiological update - 15 December 2020 [Internet]. www.who.int. 2020. Available from: <https://www.who.int/publications/m/item/weekly-epidemiological-update---15-december-2020>
2. Abdullah SF, Sharqule IK. SARS-CoV-2: A piece of bad news. *Medeni Med J*. 2020;35(2):151-60. [CrossRef]
3. Sharqule IK. BCG is a good immunotherapeutic agent for viral and autoimmune diseases: is it a new weapon against coronavirus (COVID-19)? *Electronic Journal of General Medicine*. 2020;17(6):em229. [CrossRef]
4. Setia MS, Steinmaus C, Ho CS, Rutherford GW. The role of BCG in prevention of leprosy: a meta-analysis. *Lancet Infect Dis*. 2006;6(3):162-70. [CrossRef]
5. 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. [CrossRef]
6. Stensballe LG, Nante E, Jensen IP, et al. Acute lower respiratory tract infections and respiratory syncytial virus in infants in Guinea-Bissau: a beneficial effect of BCG vaccination for girls community based case-control study. *Vaccine*. 2005;23(10):1251-7. [CrossRef]
7. Sharqule KE, Al-Rawi JR, Al-Nuaimy AA, Radhy SH.

- Bacille Calmette-Guerin immunotherapy of viral warts. *Saudi Med J*. 2008;29(4):589-93. PMID: 18382805.
8. Sharquie KE, Al-Rawi J, Noaimi A, Majly W. Tuberculin as intralesional therapy for viral warts-single-blind, split, placebo, controlled study. *Journal of Cosmetics, Dermatological Sciences and Applications*. 2016;6(5):191-8. [CrossRef]
  9. Sharquie KE, Hayani RK. BCG as a new therapeutic and prophylactic agent in patients with severe oral aphthosis. *Clin Exp Rheumatol*. 2005;23(6):914. PMID: 16396718.
  10. Moorlag S, Arts RJW, van Crevel R, Netea MG. Non-specific effects of BCG vaccine on viral infections. *Clinical microbiology and infection*. *Clin Microbiol Infect*. 2019;25(12):1473-8. [CrossRef]
  11. 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(5):507-17. [CrossRef]
  12. Charoenlap S, Piromsopa K, Charoenlap C. Potential role of Bacillus Calmette-Guérin (BCG) vaccination in COVID-19 pandemic mortality: Epidemiological and Immunological aspects. *Asian Pac J Allergy Immunol*. 2020;38(3):150-61. [CrossRef]
  13. Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y, Otazu GH. Correlation between universal BCG vaccination policy and reduced mortality for COVID-19. *medRxiv*. 2020:2020.03.24.20042937. [CrossRef]
  14. Hensel J, McAndrews KM, McGrail DJ, Dowlatshahi DP, LeBleu VS, Kalluri R. Protection against SARS-CoV-2 by BCG vaccination is not supported by epidemiological analyses. *Sci Rep*. 2020;10(1):18377. [CrossRef]
  15. Al-Kassmy J, Pedersen J, Kobinger G. Vaccine candidates against coronavirus infections. Where does COVID-19 stand? *Viruses*. 2020;12(8):861. [CrossRef]
  16. Ten Doesschate T, Moorlag SJCFM, van der Vaart TW, et al. Two Randomized Controlled Trials of Bacillus Calmette-Guérin Vaccination to reduce absenteeism among health care workers and hospital admission by elderly persons during the COVID-19 pandemic: A structured summary of the study protocols for two randomised controlled trials. *Trials*. 2020;21(1):481. [CrossRef]
  17. ClinicalTrials.gov [Internet]. BCG Vaccination to Protect Healthcare Workers Against COVID-19 (BRACE). 2020. Available from: <https://clinicaltrials.gov/ct2/show/NCT04327206>
  18. Weng CH, Saal A, Butt WWW, et al. Bacillus Calmette-Guérin vaccination and clinical characteristics and outcomes of COVID-19 in Rhode Island, United States: a cohort study. *Epidemiol Infect*. 2020;148:e140. [CrossRef]
  19. Kleinnijenhuis J, Quintin J, Preijers F, et al. Bacille Calmette-Guerin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. *Proc Natl Acad Sci U S A*. 2012;109(43):17537-42. [CrossRef]
  20. Arts RJW, Moorlag S, Novakovic B, 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(1):89-100.e5. [CrossRef]
  21. Leentjens J, Kox M, Stokman 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(12):1930-8. [CrossRef]
  22. Kleinnijenhuis J, Quintin J, Preijers F, et al. Long-lasting effects of BCG vaccination on both heterologous Th1/Th17 responses and innate trained immunity. *J Innate Immun*. 2014;6(2):152-8. [CrossRef]