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NUMBER 006-04: Effects of BCG vaccination on COVID-19

Based on information as of 25 December 2020

Rapid Policy Brief Number: 006-04 - **Effects of BCG on COVID-19**

1	**RAPID POLICY BRIEF NUMBER: 006-04**
2	**RESEARCH DOMAIN: COVID-19 AND PREVENTION**
3	**TITLE:** Effects of BCG vaccination on COVID-19
4	**DATE OF PUBLICATION: 02/16/2021**
5	**BACKGROUND** Coronavirus disease 2019 (COVID-19) was first identified in Wuhan, China, in December 2019. By 25 December 2020, over 77.5 million people had been infected with SARS-Cov2, the virus that causes COVID-19, and over 1.7 million people had died[1]. In 2019, over 10 million people worldwide fell ill with tuberculosis (TB) and more than 1.4 million people died of TB[2]. Bacille Calmette-Guerin (BCG) vaccine has been used for close to a century to prevent TB. Several countries around the world have a mandated BCG vaccination program at birth while others only give BCG for high-risk individuals. BCG is known to have non-specific effects on other diseases and has also been used as treatment for bladder cancer [3]. Several studies have suggested that BCG could be protective against SARS-CoV-2 infection and COVID-19 and thus the evidence presented here originates from a systematic review of literature on the association of BCG vaccination and COVID-19 cases or deaths.
6	**SEARCH STRATEGY / RESEARCH METHODS** PubMed and WHO COVID-19 databases were systematically searched between 10 December and 23 December 2020 using a combination of the following search terms: COVID, COVID-19, SARS-CoV-2, Bacille Calmette-Guerin, Bacillus Calmette-Guerin, and BCG. In addition, we searched reference lists of potentially eligible studies and related reviews obtained from the two databases. We included studies of any design published in English between 01 December 2019 and 23 December 2020, which reported data on COVID-19 in people vaccinated or injected with BCG for any condition. The search yielded 167 studies in PubMed, 145 in the WHO COVID-19 database, and 15 from reference lists. After screening and removal of duplicates, 41 studies met the inclusion criteria. Of the 42 included studies, 1 was specifically conducted in Africa (Nigeria) and 1 was published as pre-prints with no peer-review yet. We provide a descriptive analysis of the findings.
7	**SUMMARY OF GLOBALLY PUBLISHED LITERATURE RELATED TO THE SUBJECT** Twenty-one studies identified as epidemiological studies, 1 case report, and the rest as either observational, cohort studies or ecological studies. Two studies were identified that use intravesical BCG for the treatment of bladder cancer[3, 4]. A few patients receiving BCG developed COVID-19 with favourable outcomes and it was concluded

that even though the patients are high risk for developing COVID-19, BCG did not have any effect on COVID-19 outcomes.

There were several epidemiological or ecological studies that analysed data from several countries around the world with or without mandated BCG vaccination programs [5-26]. Data on COVID-19 and BCG vaccination programs were collected from several sources including online case reporting and government databases. Results from these studies showed that, generally, countries with current or most recent BCG vaccination programs reported fewer COVID-19 case and death rates compared to countries with no BCG vaccinations or countries that ceased BCG vaccination several decades ago.

There were also several retrospective observational, cohort studies or case reports describing the effects of BCG vaccination on COVID-19 outcomes [27-43]. In summary, data from these studies indicated that BCG was associated with either fewer cases of COVID-19, less severity of COVID-19, fewer COVID-19-compatible symptoms, or lower death rates. Analyses by a few studies reported no association between BCG vaccination and case numbers, deaths or disease severity [10, 29, 32, 37].

Overall, several of the studies have shown that BCG may be protective against COVID-19 severity and mortality. This may be attributed to the "trained immunity" associated with the wider immune response associated with BCG [8].

| 8 | **SUMMARY OF AFRICA-SPECIFIC LITERATURE ON THE SUBJECT** |

Of the studies identified, only one was specifically conducted in Africa (Nigeria) [9], and the rest of the studies presented global data with some African countries included. Data from the study on Africa suggest that lower BCG vaccination coverage was associated with higher COVID-19 cases and deaths. In a meta-analysis study of 160 countries, it was reported that North African countries (and some Middle East countries) with >70% coverage in BCG vaccination still showed high rates of SARS-CoV-2 infections [13].

| 9 | **POLICY FINDINGS** |

- The studies show that BCG vaccination may be protective against severe COVID-19.
- BCG vaccination may also reduce mortality from COVID-19
- Intravesical BCG for bladder cancer treatment did not have any effect on COVID-19
- Countries with mandated BCG vaccination programs have lower infection and fatality rates compared to countries with no mandated BCG vaccination programs

	In conclusion, people with history of BCG vaccination seems to have less severe COVID-19 and less likely to die. Epidemiological studies suggest that countries with mandated BCG vaccination programs have lower rates of infections and mortality associated with COVID-19
10	**ONGOING RESEARCH IN THE AFRICAN REGION** Several studies including clinical trials are ongoing around the world including several African countries to properly address the effects of BCG vaccination on SARS-CoV-2 infection and COVID-19 outcomes [11, 44]
11	**AFRO RECOMMENDATIONS FOR FURTHER RESEARCH** BCG vaccination at birth or other high-risk groups for tuberculosis and further preventive and management of COVID-19 need to continue while data on whether BCG vaccination is protective against COVID-19, especially in Africa, become available.

12 **References**

1.   WHO, *Coronavirus disease (COVID-19) pandemic: Numbers at a glance.*
      https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (Accessed 25 December
      2020), 2020.
2.   WHO, *Global tuberculosis report 2020.*
      https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf (Accessed 25
      December 2020), 2020.
3.   Akan, S., et al., *COVID-19 infection threat in patients with high-risk non-muscle invasive bladder
      cancer receiving intravesical BCG therapy.* Int J Clin Pract, 2020: p. e13752.
4.   Karabay, O., et al., *Investigation of the frequency of COVID-19 in patients treated with intravesical
      BCG.* Rev Assoc Med Bras (1992), 2020. **66Suppl2**(Suppl 2): p. 91-95.
5.   Berg, M.K., et al., *Mandated Bacillus Calmette-Guerin (BCG) vaccination predicts flattened curves
      for the spread of COVID-19.* Sci Adv, 2020. **6**(32): p. eabc1463.
6.   Ebina-Shibuya, R., et al., *Current national policies for infant universal bacille Calmette-Guerin
      vaccination were associated with lower mortality from coronavirus disease 2019.* Clin Exp Vaccine
      Res, 2020. **9**(2): p. 179-182.
7.   Escobar, L.E., A. Molina-Cruz, and C. Barillas-Mury, *BCG vaccine protection from severe
      coronavirus disease 2019 (COVID-19).* Proc Natl Acad Sci U S A, 2020. **117**(30): p. 17720-17726.
8.   Gursel, M. and I. Gursel, *Is global BCG vaccination-induced trained immunity relevant to the
      progression of SARS-CoV-2 pandemic?* Allergy, 2020. **75**(7): p. 1815-1819.
9.   Hassan, Z., M.J. Hashim, and G. Khan, *Population risk factors for COVID-19 deaths in Nigeria at
      sub-national level.* Pan Afr Med J, 2020. **35**(Suppl 2): p. 131.
10.   Hensel, J., et al., *Protection against SARS-CoV-2 by BCG vaccination is not supported by
      epidemiological analyses.* Sci Rep, 2020. **10**(1): p. 18377.
11.   Islam, M.Z., M.K. Zahan, and M.A.A. Al-Bari, *Convergence between global BCG vaccination and
      COVID-19 pandemic.* J Med Virol, 2020.
12.   Jirjees, F.J., Y.H. Dallal Bashi, and H.J. Al-Obaidi, *COVID-19 death and BCG vaccination programs
      worldwide.* Tuberc Respir Dis (Seoul), 2020.
13.   Joy, M., et al., *Is BCG associated with reduced incidence of COVID-19? A meta-regression of global
      data from 160 countries.* Clin Epidemiol Glob Health, 2021. **9**: p. 202-203.
14.   Kumar, A., et al., *Global impact of environmental temperature and BCG vaccination coverage on
      the transmissibility and fatality rate of COVID-19.* PLoS One, 2020. **15**(10): p. e0240710.
15.   Lerm, M., *On the relationship between BCG coverage and national COVID-19 outcome: could
      'heterologous' herd immunity explain why some countries are better off?* J Intern Med, 2020.
      288(6): p. 682-688.
16.   Li, W.X., *Worldwide inverse correlation between Bacille Calmette-Guerin immunization and
      COVID-19 morbidity and mortality.* Res Sq, 2020.
17.   Lindestam Arlehamn, C.S., A. Sette, and B. Peters, *Lack of evidence for BCG vaccine protection
      from severe COVID-19.* Proc Natl Acad Sci U S A, 2020. **117**(41): p. 25203-25204.
18.   Macedo, A. and C. Febra, *Relation between BCG coverage rate and COVID-19 infection worldwide.*
      Med Hypotheses, 2020. **142**: p. 109816.
19.   Miller, A., et al., *Correlation between universal BCG vaccination policy and reduced mortality for
      COVID-19.* medRxiv, 2020.
      https://www.medrxiv.org/content/10.1101/2020.03.24.20042937v2.full.pdf.
20.   Miyasaka, M., *Is BCG vaccination causally related to reduced COVID-19 mortality?* EMBO Mol
      Med, 2020. **12**(6): p. e12661.

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21. Ogimi, C., et al., *Association between live childhood vaccines and COVID-19 outcomes: a national-level analysis.* medRxiv, 2020.

22. Sharma, A., et al., *BCG vaccination policy and preventive chloroquine usage: do they have an impact on COVID-19 pandemic?* Cell Death Dis, 2020. **11**(7): p. 516.

23. Singh, B. and e. al., *Epidemiological determinants of acute respiratory syndrome coronavirus-2 disease pandemic and the role of the bacille-calmette-guerin vaccine in reducing morbidity and mortality.* J. Pure Appl. Microbiol. ; (14): 1007-1016, 20200423, 2020.

24. Urashima, M., et al., *BCG Vaccination and Mortality of COVID-19 across 173 Countries: An Ecological Study.* Int J Environ Res Public Health, 2020. **17**(15).

25. Wassenaar, T.M., G.S. Buzard, and D.J. Newman, *BCG vaccination early in life does not improve COVID-19 outcome of elderly populations, based on nationally reported data.* Lett Appl Microbiol, 2020. **71**(5): p. 498-505.

26. de Chaisemartin, C. and L. de Chaisemartin, *BCG vaccination in infancy does not protect against COVID-19. Evidence from a natural experiment in Sweden.* Clin Infect Dis, 2020.

27. Aksu, K., T. Naziroglu, and P. Ozkan, *Factors determining COVID-19 pneumonia severity in a country with routine BCG vaccination.* Clin Exp Immunol, 2020. **202**(2): p. 220-225.

28. Goenka, M., et al., *Seroprevalence of COVID-19 Amongst Health Care Workers in a Tertiary Care Hospital of a Metropolitan City from India.* J Assoc Physicians India, 2020. **68**(11): p. 14-19.

29. Hamiel, U., E. Kozer, and I. Youngster, *SARS-CoV-2 Rates in BCG-Vaccinated and Unvaccinated Young Adults.* JAMA, 2020. **323**(22): p. 2340-2341.

30. Hidvegi, M. and M. Nichelatti, *Bacillus Calmette-Guerin vaccination Policy and Consumption of Ammonium Chloride-Enriched Confectioneries May Be Factors Reducing COVID-19 Death Rates in Europe.* Isr Med Assoc J, 2020. **22**(8): p. 501-504.

31. Levi, M., et al., *Letter in response to article in journal of infection: Impact of routine infant BCG vaccination on COVID-19.* J Infect, 2020.

32. Luciani, M., et al., *Coinfection of Tuberculosis Pneumonia and COVID-19 in a Patient Vaccinated with Bacille Calmette-Guerin (BCG): Case Report.* SN Compr Clin Med, 2020: p. 1-4.

33. Madan, M., et al., *TB infection and BCG vaccination: are we protected from COVID-19?* Public Health, 2020. **185**: p. 91-92.

34. Matsuba, I., et al., *Survey of the current status of subclinical coronavirus disease 2019 (COVID-19).* J Infect Chemother, 2020. **26**(12): p. 1294-1300.

35. Moorlag, S., et al., *Safety and COVID-19 Symptoms in Individuals Recently Vaccinated with BCG: a Retrospective Cohort Study.* Cell Rep Med, 2020. **1**(5): p. 100073.

36. Noval Rivas, M., et al., *BCG vaccination history associates with decreased SARS-CoV-2 seroprevalence across a diverse cohort of healthcare workers.* J Clin Invest, 2020.

37. Patella, V., et al., *The bacillus Calmette-Guerin vaccination allows the innate immune system to provide protection from severe COVID-19 infection.* Proc Natl Acad Sci U S A, 2020. **117**(41): p. 25205-25206.

38. Samrah, S.M., et al., *COVID-19 outbreak in Jordan: Epidemiological features, clinical characteristics, and laboratory findings.* Ann Med Surg (Lond), 2020. **57**: p. 103-108.

39. Weng, C.H., et al., *Bacillus Calmette-Guerin vaccination and clinical characteristics and outcomes of COVID-19 in Rhode Island, United States: a cohort study.* Epidemiol Infect, 2020. **148**: p. e140.

40. Wickramasinghe, D., et al., *Correlation between immunity from BCG and the morbidity and mortality of COVID-19.* Trop Dis Travel Med Vaccines, 2020. **6**: p. 17.

41. Sharma, A.K., et al., *Characteristics and Outcomes of Hospitalized Young Adults with Mild Covid -19.* J Assoc Physicians India, 2020. **68**(8): p. 62-65.

42. Kinoshita, M. and M. Tanaka, *Impact of Routine Infant BCG Vaccination on COVID-19.* J Infect, 2020. **81**(4): p. 625-633.

43. Ozdemir, C., U.C. Kucuksezer, and Z.U. Tamay, *Is BCG vaccination affecting the spread and severity of COVID-19?* Allergy, 2020. **75**(7): p. 1824-1827.
44. ClinicalTrials.gov, https://clinicaltrials.gov/ct2/results?cond=COVID&term=BCG&cntry=&state=&city=&dist= (Accessed 25 December 2020), 2020.

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