Should Bacillus Calmette–Guérin (BCG) vaccine be used in the prophylaxis of COVID-19?

Authors: Daisy Sanchez-Mostiero, M.D., Abigail F. Melicor, M.D.
Date of Review: 01-APRIL-2020 (version 3)
Last Updated: 30-APRIL-2020 (version 3)

KEY FINDINGS

> At present, there is no sufficient evidence to support the use of BCG vaccine as prophylaxis for COVID-19.

- Bacillus Calmette Guerin (BCG) vaccine is an attenuated microorganism derived from bovine tubercle bacillus and is being given to prevent severe tuberculosis. It may enhance production of antibodies and pro-inflammatory cytokines such as interleukin (IL)-1β and tumor necrosis factor (TNF).
- BCG may lead to increased CD4 and CD8 T-cell activity on subsequent viral infection.
- Ecological studies on the effect of BCG vaccination policy on COVID-19 outcomes have conflicting results and are prone to bias from confounders.
- There is insufficient evidence on the efficacy and safety of BCG vaccine for COVID-19 prophylaxis.
- Five clinical trials are ongoing in healthcare workers to evaluate the efficacy and safety of BCG vaccine in preventing COVID-19 and its severe symptoms.
- WHO does not recommend the use of BCG vaccine as prophylaxis against COVID-19.
- Adverse events of BCG vaccine range from mild local cutaneous reactions to systemic adverse events such as abscess, lymphadenopathy and osteomyelitis.

RESULTS

Available ecological studies have conflicting results. Majority of the studies have reported decreased incidence, mortality rates and case fatality rates for countries with BCG vaccination policy but did not factor into their analysis other variables that may affect COVID-19 outcomes such as population characteristics, level of testing, healthcare systems, control measures, burden of disease and stage of epidemic. In contrast, one study reported BCG coverage from 1981-1985 as proxy of coverage in 34-39-year-old cohort had no significant effect on crude growth rate and case fatality rates at the same stage of the epidemic (tenth day after cumulative cases exceeded 100 in a country).

There are **no completed clinical trials** on BCG vaccine as prophylaxis for COVID-19. However, there are five ongoing clinical trials (1 in Australia, 1 in Netherlands, 1 in United States of America, 1 in Egypt, 1 in Colombia) investigating safety and efficacy of BCG vaccination in healthcare workers. Characteristics of these trials are summarized in Table 2.

CONCLUSION

Presently, there is insufficient evidence regarding the use of BCG vaccine as prophylaxis to COVID-19. The results of ongoing clinical trials are needed.

Declaration of Conflict of Interest

No conflict of interest

REFERENCES

1. Zimmermann, P., Curtis, N., *The influence of BCG on vaccine responses – a systematic review.* 2018. SSN: 1476-0584 (Print) 1744-8395 (Online) Journal homepage: http://www.tandfonline.com/loi/ierv20
2. Angelidou, A., Diray-Arce, J., Conti M., et al*., BCG as a Case Study for Precision Vaccine Development: Lessons from Vaccine Heterogeneity, Trained Immunity, and Immune Ontogeny.* Front Microbiol, 2020. 11(11):332. DOI: 10.3389/fmicb.2020.00332
3. Moorlag, SJCFM., Arts, RJW., Crevel, R van., Netea, MG.*Non-specific effects of BCG vaccine on viral infections.* Clinical Microbiology and Infection 25 (2019) 1473-1478.https://doi.org/10.1016/j.cmi.2019.04.020
4. Clothier, HJ., Hosking, L., Crawford, NW., et al, *Bacillus Calmette-Guérin (BCG) vaccine adverse events in Victoria, Australia: analysis of reports to an enhanced passive surveillance system. Drug Saf* 2015. 38(1):79-86. DOI: 10.1007/s40264-014-0248-6
5. Deeks, SL., Clark, M., Scheifele, DW., et. al. *Serious adverse events associated with bacille Calmette-Guérin vaccine in Canada.* Pediatr Infect Dis J 2005. 24(6):538-541. DOI: 10.1097/01.inf.0000164769.22033.2c
6. Miller A., Reandelar MJ., Fasciglione K., Roumenova V., Li Y., Otazu G. *Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study.* MedRxiv 2020. DOI: 10.1101/2020.03.24.20042937
7. Hegarty PK., Zafirakis H., Kamat A., Dinardo A. *BCG vaccination may be protective against COVID-19.* 2020 cc doi: 10.13140/RG.2.2.35948.10880
8. Dolgikh S. *Further Evidence of a Possible Correlation Between the Severity of Covid-19 and BCG Immunization.* MedRxiv 2020. DOI: 10.1101/2020.04.07.20056994
9. Dayal, D., Gupta, S. *Connecting BCG Vaccination and COVID-19: Additional Data.* MedRxiv 2020. DOI:10.1101/2020.04.07.20053272.
10. Li Y, Zhao S, Zhuang Z, Cao P, Yang L, He D. *The correlation between BCG immunization coverage and the severity of COVID-19.* 2020. DOI: 10.2139/ssrn.3568954
11. World Health Organization. Bacille Calmette-Guérin (BCG) vaccination and COVID-19 Scientific Brief. Retrieved on Aplrl 27, 2020 from https://www.who.int/news-room/commentaries/detail/bacille-calmette-gu%C3%A9rin-(bcg)-vaccination-and-covid-19.

12. ClincalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT04328441, Reducing Health Care Workers Absenteeism in Sars-Cov-2 Pandemic Through Bacillus Calmette-Guérin Vaccination, A Randomized Controlled Trial (BCG-CORONA); 2020 March 31 [cited 2020 March 31]. Available from: https://clinicaltrials.gov/ct2/show/NCT04328441

13. ClincalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT04327206, BCG Vaccination to Protect Healthcare Workers Against COVID-19 (BRACE); 2020 March 31 [cited 2020 March 31]. Available from: https://clinicaltrials.gov/ct2/show/NCT04327206

14. ClincalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT04350931, Application of BCG Vaccine for Immune-prophylaxis Among Egyptian Healthcare Workers During the Pandemic of COVID-19; 2020 April 17 [cited 2020 April 30]; [about 4 screens]. Available from: https://clinicaltrials.gov/ct2/show/NCT04350931

15. ClincalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT04362124, Performance Evaluation of BCG Vaccination in Healthcare Personnel to Reduce the Severity of SARS-COV-2 Infection; 2020 April 24 [cited 2020 April 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT04362124

16. ClincalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT04348370, BCG Vaccine for Health Care Workers as Defense Against COVID 19 (BADAS); 2020 April 16 [cited 2020 April 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT04348370

Table 1. Characteristics of included studies

No.	Title/Author	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes	Key findings
1	Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y, Otazu G	Cross-sectional	USA	Countries affected with COVID-19 with more than 1 million inhabitants	BCG vaccination policy	No BCG vaccination policy	Mortality rate	Lower mortality rates were reported for countries with BCG vaccination policy. Variability of mortality rates was noted for middle-high income countries with BCG vaccination policy.
2	BCG vaccination may be protective against COVID-19 Hegarty PK, Zafirakis H, Kamat A, Dinardo A	Cross-sectional	USA	Countries affected with COVID-19 (n=178)	BCG vaccination policy	No BCG vaccination policy	COVID-19 incidence Mortality rate	Countries with BCG vaccination program incidence: 38.4 per million mortality rate: 4.28 per million Countries without BCG vaccination program incidence: 358.4 per million mortality rate: 40 per million
3	Further Evidence of a Possible Correlation Between the Severity of Covid-19 and BCG Immunization Dolgikh S	Cross-sectional	--	Countries affected with COVID-19	BCG vaccination policy	No BCG vaccination policy	COVID-19 cases per capita COVID-19 mortality per capita	Italy, Spain, France, USA had severe COVID-19 disease compared to mild COVID-19 cases in Taiwan, Germany, many East European jurisdiction Vaccination level of different countries were correlated with the reported impact of COVID-19 on countries grouped according to mortality per capita (m.p.c.), which is a measure of epidemic impact. Countries in which the m.p.c. is <1 have universal immunization program (UIP) against tuberculosis Countries in which m.p.c. <10 have ongoing UIP against tuberculosis or has limited use (Canada, Norway). Countries who had never had a UIP or significant BCG immunization program have m.p.c. greater than or near 100. Time of cessation of UIP/BCG and the m.p.c. value of COVID-19 impact showed a significant correlation. The later the cessation of UIP/BCG, the lower the m.p.c. This, however, was not observed in Australia. Thus, further studies are suggested. UIP/BCG offered at an older age age (UK and possible France) have m.p.c. rates between 65-100. Portugal, Spain, Canada have regional variations in UIP/BCG.

Last Updated: 30/April/20

No.	Clinical Trial ID / Title	Status	Country	Population	Intervention	Comparison	Outcomes	Results
								Areas were immunization were widely used have significantly lower COVID-19 cases such as Japan, South Korea, Taiwan and Singapore with a current BCG policy which have less severe COVID-19 impacts with m.p.c. in the range of <1% or lower.
4	Connecting BCG Vaccination and COVID-19: Additional Data Dayal D, Gupta S	Cross-sectional	India	Countries affected with COVID-19	BCG revaccination policy	High disease burden of COVID-19 with no BCG revaccination policy	COVID-19 case fatality rate	Mean CFR between the two groups of countries (5.2% versus 0.6%, p value <0.0001) with an RR 0.11, (95% CI:0.09-0.14)
5	The correlation between BCG immunization coverage and the severity of COVID-19 Li Y, Zhao S, Zhuang Z, Cao P, Yang L, He D	Cross-sectional	Hongkong, China	Countries with COVID-19 cases with at least ten days data after cumulative confirmations exceed 100	BCG immunization coverage for 1980-1985 as proxy of BCG coverage among 34-39 years old cohort	No BCG immunization coverage for 1980-1985	Growth rate of confirmed cases Case fatality rate	No significant difference in the crude growth rate between countries with BCG coverage and countries without BCG coverage (p-value=0.3948, two-sample-t-test). Countries with BCG coverage had a slightly higher growth rate of 8.56 versus 7.23 (increase in cumulative number over 10 days). The group of countries with BCG coverage had higher case-fatality-rate (CFR) than those without BCG coverage (0.022 versus 0.014), but the difference is not significant (pvalue=0.06). Countries without BCG coverage may have better medical conditions and living environment, thus, the lower growth rate and case fatality rate. No significant effects of BCG coverage (1980-1985, i.e., 34-39 age cohort when they were born) on the crude growth rate and case fatality rate on the tenth day after cumulative exceeding 100 in a country. Findings remained the same after extending to 20-day range and changing the threshold to 50 cases.

Table 2. Characteristics of ongoing clinical trials

No.	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes

Last Updated: 30/April/20

1	Reducing Health Care Workers Absenteeism in Sars-Cov-2 Pandemic Through Bacillus Calmette-Guérin Vaccination, A Randomized Controlled Trial (BCG-CORONA) ClinicalTrials.gov Identifier: NCT04328441	Recruiting	Start date: 03/25/2020 Estimated primary completion date: 10/25/2020	Multicenter randomized controlled trial, placebo controlled	Netherlands	1000 nurses and physicians working at emergency rooms and wards where COVID-infected patients are treated	BCG vaccine 0.1 ml intracutaneously	Placebo: 0.1 ml of 0.9% NaCl intracutaneously	Primary: Number of days of unplanned absenteeism Secondary: Incidence of documented SARS-CoV-2 infection Incidence of severe respiratory symptoms, hospital admission, intensive care admission and death from SARS-CoV-2 infection Number of days of fever, respiratory symptoms Incidence of SARS-CoV-2 antibodies
2	BCG Vaccination to Protect Healthcare Workers Against COVID-19 (BRACE) ClinicalTrials.gov Identifier: NCT04327206 EudraCT Number: 2020-000919-69	Recruiting	Start date: 03/30/2020 Estimate primary completion date: 10/30/2020	Multicenter, open label randomized controlled trial	Australia	4000 healthcare workers in hospital sites	BCG vaccine 0.1 ml Intradermally	None	Primary: Incidence of COVID-19 disease and severe COVID-19 disease Secondary: Time to first symptom and duration of symptoms of COVID-19 Work absenteeism Hospital admission, critical care admission Need for oxygen therapy, mechanical ventilation Mortality Local and systemic adverse events to BCG
3	Application of BCG Vaccine for Immune-prophylaxis Among Egyptian Healthcare Workers During the Pandemic of COVID-19 ClinicalTrials.gov Identifier: NCT04350931	Not yet recruiting	Start date: 04/20/2020 Estimate primary completion date: 10/01/2020	Multicenter randomized controlled trial, placebo controlled	Egypt	900 healthcare workers at emergency rooms, ICUs and wards of isolation hospitals	BCG vaccine 0.1 ml Intradermally	Placebo: 0.1 ml of 0.9% NaCl intradermally	Primary: incidence of confirmed COVID-19 Secondary: Number of days of absenteeism Incidence of hospital admission Incidence of ICU admission Mortality

Last Updated: 30/April/20

4	Performance Evaluation of BCG Vaccination in Healthcare Personnel to Reduce the Severity of SARS-COV-2 Infection ClinicalTrials.gov Identifier: NCT04362124	Not yet recruiting	Start date: 04/2020 Estimate primary completion date: 06/2021	Multicenter, randomized controlled trial	Colombia	1000 healthcare workers directly involved in the care of COVID-19 patients	BCG vaccine 0.1 ml Intradermally	Placebo: 0.1 ml of 0.9% NaCl intradermally	Primary: incidence of confirmed and probable COVID-19 cases Secondary: Incidence of severe COVID-19 infection Mortality Safety of BCG vaccination (adverse events)
5	BCG Vaccine for Health Care Workers as Defense Against COVID 19 (BADAS) ClinicalTrials.gov Identifier: NCT04348370	Recruiting	Start date: 04/20/2020 Estimate primary completion date: 05/2021	Multicenter randomized controlled trial	USA	1800 healthcare workers involved in the care of suspected and confirmed COVID-19 patients with at least 25 hours per week of direct patient care	BCG vaccine 0.1 ml Intradermally	Placebo: 0.1 ml of 0.9% NaCl intradermally	Primary: incidence of COVID-19 infection Secondary: Disease severity (Covid Severity Scale Scoring)