

ORIGINAL ARTICLE

EFFECTIVENESS OF BCG VACCINATION AGAINST SARS-COV-2

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Background: Bacillus Calmette-Guerin (BCG) vaccine is weakened *Mycobacterium bovis* based preparation that provides protective effects and immunotherapy against many ailments and may be tested against SARS-COV-2. Herein, we compare the prevalence of COVID-19 in countries with and without mandatory BCG vaccination program along with a study to examine its incidence in doctors working at quarantine facility with and without history of prior BCG vaccination. **Methods:** For cross-sectional examination, the data was collated from worldometer.info, BCG World Atlas and COVID-19 stats at National Command and Operation Centre (NCOC), Government of Pakistan accessed on Apr 30, 2021. For a real-time analysis, total of one hundred random male and female doctors working at a COVID-19 healthcare facility in Pakistan were voluntarily selected. Chi-square test was used to perform the statistical analysis with the help of SPSS-22. **Results:** The prevalence of COVID-19 in countries with and without a mandatory BCG vaccination policy was found to be 5,512 and 75,592 cases per million, respectively, and mortality rates were 98 and 1,435 per million, respectively. Amongst our randomly selected doctors, only 28% of the BCG vaccinated doctors were affected by COVID-19 contrary to 94% of those who were unvaccinated. **Conclusions:** The incidence of COVID-19 was considerably lower in the doctors with a history of BCG vaccination supported by the evidence that the countries with a universal BCG vaccine policy had a significantly low incidence and lower mortality rate due to COVID-19.

Keywords: Bacillus Calmette-Guerin vaccine (BCG), SARS-COV-2, Tuberculosis, Coronavirus, COVID-19

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INTRODUCTION

The emergence of Corona Virus Disease 2019 (COVID-19) has infected more than 150 million people worldwide with a total of 3,179,925 casualties. Pakistan, alone has reached a total of 820,823 cases with 17,811 mortalities as of April 30, 2021. With the onset of this pandemic, vaccination is considered as the most effective preventive measure for this disease. Bacillus Calmette-Guerin (BCG) vaccine was first introduced in 1921 and has been used since then for the prevention of tuberculosis. BCG vaccines contain a live attenuated strain of *Mycobacterium bovis*, and it protects against various pathogens, some of which may be responsible for acute respiratory tract infections.¹ However, BCG activates the cross-protection that may not be associated to target the disease due to 'Trained Immunity' or innate immune memory.²

In addition to tuberculosis, BCG vaccine has also been utilized for the protection against autoimmune and inflammatory diseases.³ BCG vaccine can speed up the reactivation of the immune system.⁴ Therefore, multiple doses of BCG vaccine have been utilized previously in the treatment of bladder cancer and type-1 diabetes mellitus.⁵ Trained immunity is one of the reason, why many studies

recommend that multiple doses of BCG vaccine should be included in the clinical trials of COVID-19 vaccination.⁶ Some of the recently published studies on COVID-19 suggest that BCG vaccine is potent enough to combat this disease.^{7,8} However, a few studies do not favour the use of multiple doses of intradermal BCG vaccination.⁵

Several epidemiological studies concluded that countries with an approved policy of universal BCG vaccination had a lower incidence of COVID-19 and a lower mortality rate as compared to the countries that did not have a mandatory BCG vaccination policy.⁹⁻¹¹ The current study was carried out to provide a comparative data of selected countries with and without mandatory BCG vaccination policy and to establish the fact that 'BCG vaccination boosts immunity in health care professionals exposed to COVID-19'.

This study was conducted to assess the incidence of COVID-19 in doctors, who were previously administered BCG vaccine in their childhood and those who were not formerly administered BCG vaccine (negative control) and were dealing with COVID-19 patients in a COVID-19 healthcare facility in the city of Islamabad, Pakistan.

METHODOLOGY

The ethical approval of this study was obtained from the institutional review board at Shaheed Zulfiqar Ali Bhutto Medical University Islamabad, Pakistan. The data were compiled from worldometers.info, BCG world atlas and COVID-19 stats at National Command and Operation Centre (NCOC), Government of Pakistan [accessed on April 30, 2021].

For a real-time analysis, a COVID-19 healthcare facility of a tertiary care hospital operating with a compliance to standard operating procedures (SOPs) of World Health Organization (WHO) was selected. Informed consent was obtained from all of the participants of this study and access to this facility was obtained with all implemented ethical considerations and standard biosafety procedures.

A total of one hundred doctors, who were assigned to take care of more than 500±50 COVID-19 positive patients for 6 months at a tertiary care hospital in Pakistan were included in this study. The sample size was similar to that used in previously published studies related to COVID-19.^{12,13} A similar sample size was also calculated according to the sample size calculator to calculate vaccine effectiveness for studies related to COVID-19 where the predicted vaccine effectiveness was 90%, the desired precision width was 30%, and considering that the attack rate of the virus was 30% as suggested by WHO.

The BCG vaccination cards of the healthcare workers were obtained after consent and the evaluation of BCG vaccination scar was performed. Those without the preceding records were confirmed through mantoux test. These doctors were observed for nosocomial infection of SARS Cov-2 despite employment of PPEs with a strict compliance.

Doctors in direct contact with the patients were included in this study while nursing staff, phlebotomists, sanitary workers, infectious waste management personnels, management staff and sample transporters of the hospital were excluded. The individuals with any known health conditions like diabetes, hypertension, pulmonary diseases, rheumatoid arthritis and obesity were also excluded. Only the primary data recorded was analyzed.

All information of the respondents was obtained after proper certification of the Bioethics and Biosafety Committee of the healthcare facility. Chi-square test was used to perform the statistical analysis with the help of SPSS-22. The confidence interval was established at 95% and $p < 0.05\%$ was deemed as statistically significant.

RESULTS

A total of one hundred health care workers, who were assigned to take care of more than 500 COVID-19 positive patients at a tertiary care hospital in Pakistan were included in this study. Out of these 100 individuals, 29 male healthcare workers and 21 female healthcare workers had a prior history of BCG vaccination in their childhood while 30 male and 20 female healthcare workers were never administered BCG vaccine (Table-1).

Doctors were assessed for COVID-19 for a period of six months. Data compiled from 1 to 30 April 2021 revealed that 28% of the doctors who had received a BCG vaccine in their childhood still were affected by COVID-19. Contrary to this, 94% of the workers who were not vaccinated with BCG vaccine in their childhood suffered from SARS COV-2 hospital-acquired infection. The immunized doctors who tested positive for COVID-19 were asymptomatic; however, some alongwith all of the unimmunized individuals, exhibited mild fever, malaise, dry cough, headache and shortness of breath (Table-2).

Countries with and without a universal BCG vaccine policy alongwith their respective prevalence of COVID-19 cases and mortality rate per million are tabulated as Table-3 and 4, and the data has been dichotomized.

Table-1: Total number of immunized and unimmunized doctors included in the study

	Male	Female	Total
Total Participants	59	41	100
Immunization			
Immunized with BCG Vaccine	29	21	50
Unimmunized with BCG Vaccine	30	20	50
Infected			
Immunized infected	8	6	14
Unimmunized infected	28	19	47
Total Infected	36	25	61

Table-2: Association of BCG Vaccine with COVID-19

Vaccine		COVID			p	Unadjusted Odds Ratio	Adjusted Odds Ratio	95% CI for Odds Ratio
		Yes	No	Total				
No	Count [n (%)]	47 (94)	3 (6)	50	<0.001	40.29	44.58	11.46–173.44
	Within COVID-19 (%)	77	7.7	50				
Yes	Count [n (%)]	14 (28)	36 (72)	50				
	Within COVID-19 (%)	23	92.3	50				
Total	Count (n)	61	39	100				
	Within COVID-19 (%)	100	100	100				

Table-3: Countries without a universal BCG vaccine policy

Country	Total Cases	Cases/Million	Deaths/Million
France	5,592,390	85,520	1,594
Finland	86,613	15,612	165
Italy	4,009,208	66,391	1,996
Sweden	967,678	95,326	1,379
Slovenia	239,339	115,112	2,041
Mean	2,179,046	75,592	1,435

Table-4: Countries with a universal BCG vaccine policy

Country	Total Cases	Cases/Million	Deaths/Million
Pakistan	820,823	3,658	79
Bangladesh	756,955	4,559	69
India	18,762,976	13,487	150
Indonesia	1,662,868	6,027	164
Philippines	1,028,738	9,286	155
Afghanistan	59,745	1,507	66
China	90,655	63	3
Mean	3,311,823	5,512	98

DISCUSSION

This study aimed to assess the comparative immunity of doctors against COVID-19. Most of these doctors were previously immunized with a BCG vaccine, while the others had no prior immunization with a BCG vaccine throughout their life. Though, WHO has not yet recommended the use of BCG vaccine for the prevention or treatment of COVID-19 still, it has been thought to enhance immunity.¹⁴⁻¹⁶ Clinical trials are under progress, where doctors in contact with COVID-19 patients are being administered BCG vaccine to evaluate the effects of this vaccine concerning prevention against COVID-19.¹⁷

The results of this study support previously published literature, which suggests that a reduced rate of mortality and morbidity due to COVID-19 disease is observed in the countries where a universal BCG vaccination policy has been implemented.¹⁸⁻²⁰

As of 30 April 2021, a total of 151,240,576 cases of COVID-19 have been reported with 3,182,092 recorded casualties at a rate of 408.2 casualties per million population. Incidence of COVID-19 in BCG vaccinated countries and in countries without a universal BCG vaccine policy was 5,512 cases per million and 75,592 cases per million, respectively. Moreover, the death rates due to COVID-19 in BCG vaccinated countries and in countries without a universal BCG vaccine policy was 98 per million and 1,435 per million, respectively. Pakistan, individually has a total number of 820,823 cases with a gross occurrence of 3,658 cases per million with a mortality rate of 79 deaths per million. According to Global health observatory data repository provided by WHO 91% 1-year-olds in Pakistan are BCG vaccinated in 2020. Another study suggested that 80% of the population was BCG vaccinated.²¹

BCG vaccination is a part of vaccination policy. However, countries like Finland, France, Italy and Sweden require an approval of parents before administration of vaccine and it is not mandatory for all individuals to get vaccinated. If the parents are unwilling to get the vaccine the vaccine is not administered to their children. According to Global health observatory data repository provided by WHO no data for BCG vaccination in 1-year-olds is available for Slovenia, Italy, Finland and France which indicates uncertainty about vaccination. Similarly according to the Global health observatory data repository provided by WHO 26% of 1-year-olds in Sweden are BCG vaccinated.

The dichotomized data of crude case fatality rate (CFR) (deaths/incidence) was 1.33% for BCG and 2.24% for non BCG administering countries. A comparison of total cases from a few randomly selected countries with and without a universal BCG vaccine policy till 30 April 2021, suggests that the average of COVID-19 cases was lower in countries with a universal BCG vaccine policy. Furthermore, the average of the total number of deaths per million was higher in countries without a universal BCG vaccine policy.

This is further strengthened with the statement that BCG vaccines are manufactured under different conditions across the globe generating divergent formulations.^{22,23} A study carried out in Guinea Bissau suggested that BCG vaccinated children have a lower mortality rate of around 50%. Furthermore, it was also noticed that the overall mortality rate was lowered due to the administration of BCG vaccine as it reduced the possibility of respiratory infections and sepsis.²⁴

This study supports the results from previously published studies that the randomly selected countries that do not administer BCG vaccine had a higher number of COVID-19 cases and a higher mortality rate per million individuals. Contrary to this finding, the countries where BCG vaccination policy was in place and the vaccine was administered had a lower mortality rate per million and the total number of cases per million were lower. These findings supported that BCG vaccination might have a potential role in reducing the average of COVID-19 cases and mortality rate in the population under study.

Evidence from previous laboratory and clinical experiments revealed that BCG vaccine might produce nonspecific preventive results against several viral infections in human beings.^{5,25} It has been observed that interferon-gamma (IFN- γ) was presented in a substantial quantity from CD4+ cells that prevented the mice against infection from the virus, hence, it is termed as trained immunity.²⁶ This also

emphasizes that interferon-gamma (IFN- γ) improves immuno-modulatory effects in the body as it enhances presentation and processing of antigens, augments leukocyte trafficking, entices an antiviral situation and promotes antimicrobial features.²⁷ As a consequence of BCG vaccination, pro-inflammatory cytokines like Interleukin-1 β (IL-1 β) cause nonspecific immunity against various viral agents.²⁸ The protection provided by BCG vaccination against COVID-19 is mainly due to its nonspecific effects.^{5,29}

CONCLUSION

The countries with universal BCG vaccination policy have a lower incidence of COVID-19 and a lower death rate in comparison to countries with no BCG vaccine policy. Incidence of COVID-19 was significantly lower in randomly selected doctors who had been administered BCG vaccine in their childhood in comparison to those who had never been administered the vaccine throughout their life. There is a considerable contrast in the incidence and death rate due to COVID-19 in Pakistan as compared to the countries where administration of BCG vaccine is not practiced and this possibly demonstrates enhanced recovery from the disease in Pakistani population.

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REFERENCES

- Aspatwar A, Gong W, Wang S, WU X, Parkkila S. Tuberculosis vaccine BCG: The magical effect of the old vaccine in the fight against the COVID-19 pandemic. *Int Rev Immunol* 2021;2021:1–14.
- de Castro MJ, Pardo-Seco J, Martinon-Torres F. Nonspecific (Heterologous) Protection of Neonatal BCG Vaccination Against Hospitalization Due to Respiratory Infection and Sepsis. *Clin Infect Dis* 2015;60:1611–9.
- Jensen KJ, Larsen N, Biering-Sorensen S, Andersen A, Eriksen HB, Monteiro I, *et al.* Heterologous immunological effects of early BCG vaccination in low-birth-weight infants in Guinea-Bissau: a randomized-control trial. *J Infect Dis* 2015;211:956–67.
- Tanner R, Villarreal-Ramos B, Vordermeier HM, McShane H. The Humoral Immune Response to BCG Vaccination. *Front Immunol* 2019;10:1317.
- Moorlag SJCFM, Arts RJW, van Crevel R, Netea MG. Non-specific effects of BCG vaccine on viral infections. *Clin Microbiol Infect* 2019;25:1473–8.
- Yamazaki-Nakashimada MA, Unzueta A, Berenise Gamez-Gonzalez L, Gonzalez-Saldana N, Sorensen RU. BCG: a vaccine with multiple faces. *Hum Vaccin Immunother* 2020;16(8):1841–50.
- Mohapatra PR, Mishra B, Behera B. BCG vaccination induced protection from COVID-19. *Indian J Tuberc* 2021;68(1):119–24.
- Gonzalez-Perez M, Sanchez-Tarjuelo R, Shor B, Nistal-Villan E, Ochando J. The BCG Vaccine for COVID-19: first verdict and future directions. *Front Immunol* 2021;12:632478.
- Urashima M, Otani K, Hasegawa Y, Akutsu T. BCG Vaccination and Mortality of COVID-19 across 173 Countries: An Ecological Study. *Int J Environ Res Public Health* 2020;17(15):5589.
- Li WX. Worldwide inverse correlation between Bacille Calmette-Guérin (BCG) immunization and COVID-19 mortality. *Infection* 2021;49(3):463–73.
- Mohamed Hussein AAR, Salem MR, Salman S, Abdulrahim AF, Al-Massry NA, Saad M, *et al.* Correlation between COVID-19 case fatality rate and percentage of BCG vaccination: is it true the vaccine is protective? *Egypti J Bronchol* 2020;14:25.
- Asghar MS, Haider Kazmi SJ, Ahmed Khan N, Akram M, Ahmed Khan S, Rasheed U, *et al.* Clinical profiles, characteristics, and outcomes of the first 100 admitted COVID-19 patients in Pakistan: A single-center retrospective study in a tertiary care hospital of Karachi. *Cureus* 2020;12(6):e8712.
- Joukar F, Yaghubi Kalurazi T, Khoshsorour M, Taramian S, Mahfoozi L, Balou HA, *et al.* Persistence of SARS-CoV-2 RNA in the nasopharyngeal, blood, urine, and stool samples of patients with COVID-19: a hospital-based longitudinal study. *Virology* 2021;18(1):134.
- Cavian 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.
- Covián C, Retamal-Diaz A, Bueno SM, Kalergis AM. Could BCG vaccination induce protective trained immunity for SARS-CoV-2?. *Front Immunol* 2020;11:970.
- Kowalewicz-Kulbat M, Loch C. BCG and protection against inflammatory and autoimmune diseases. *Expert Rev Vaccines* 2017;16(7):1–10.
- Clinical trials of BCG for COVID-19; NIH –Clinical Trials. US National Institute of Health. Retrieved April 30, 2020. <https://clinicaltrials.gov/ct2/show/NCT04327206>.
- Fu W, Ho PC, Liu CL, Tzeng KT, Nayeem N, Moore JS, *et al.* Reconcile the debate over protective effects of BCG vaccine against COVID-19. *Sci Rep* 2021;11(1):8356.
- Garzon-Chavez D, Rivas-Condo J, Echeverria A, Mozo J, Quentin E, Reyes J, Teran E. COVID-19 infection and previous bcg vaccination coverage in the Ecuadorian population. *Vaccines (Basel)* 2021;9(2):91.
- Marzoog BA, Vlasova TI. The possible puzzles of BCG vaccine in protection against COVID-19 infection. *Egypt J Bronchol* 2021;15:7.
- Butt M, Mohammed R, Butt E, Butt S, Xiang J. Why have immunization efforts in Pakistan failed to achieve global standards of vaccination uptake and infectious disease control? *Risk Manag Healthc Policy* 2020;13:111–24.
- Angelidou A, Diray-Arce J, Conti MG, Smolen KK, van Haren SD, Dowling DJ, *et al.* BCG as a case study for precision vaccine development: lessons from vaccine heterogeneity, trained immunity, and immune ontogeny. *Front Microbiol* 2020;11:332.
- Angelidou A, Conti MG, Diray-Arce J, Benn CS, Shann F, Netea MG, *et al.* Licensed Bacille Calmette-Guérin (BCG) formulations differ markedly in bacterial viability, RNA content and innate immune activation. *Vaccine* 2020;38(9):2229–40.
- Bagheri N, Montazeri H. On BCG vaccine protection from COVID-19: A Review. *SN Compr Clin Med* 2021:1–11.
- Uthayakumar D, Paris S, Chapat L, Freyburger L, Poulet H, De Luca K. Non-specific Effects of Vaccines Illustrated Through the BCG Example: From Observations to Demonstrations. *Front Immunol* 2018;9:2869.
- Rajarshi K, Chatterjee A, Ray S. BCG vaccination strategy implemented to reduce the impact of COVID-19: Hype or Hope? *Med Drug Discov* 2020;7:100049.

27. Kak G, Raza M, Tiwari BK. Interferon-gamma (IFN- γ): Exploring its implications in infectious diseases. *Biomol Concepts* 2018;9(1):64–79.
28. Netea MG, Joosten LA, Latz E, Millas KH, Natoli G, Stunnenberg HG, *et al.* Trained immunity: A program of innate immune memory in health and disease. *Science* 2016;352:aaf1098.
29. Parmar K, Siddiqui A, Nugent K. Bacillus Calmette-Guerin vaccine and nonspecific immunity. *Am J Med Sci* 2021;361(6):683–9.
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