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Bacillus Calmette–Guérin vaccination and clinical characteristics and outcomes of COVID-19 in Rhode Island, United States: a cohort study

C-H. Weng[1,2], A. Saal[2], W. W-W. Butt[2], N. Bica[2], J. Q. Fisher[2], J. Tao[3] and P. A. Chan[3]

[1]Department of Family Medicine, Brown University Warren Alpert Medical School, Providence, Rhode Island 02903, USA; [2]Providence Community Health Centers, Providence, Rhode Island 02905, USA and [3]Department of Medicine, Brown University Warren Alpert Medical School, Providence, Rhode Island 02906, USA

Short Paper

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Author for correspondence:
Chien-Hsiang Weng,
E-mail: chien-hsiang_weng@brown.edu

Abstract

Coronavirus disease 2019 (COVID-19) has resulted in a global pandemic, and there is limited data on effective therapies. Bacillus Calmette–Guérin (BCG) vaccine, a live-attenuated strain derived from an isolate of *Mycobacterium bovis* and originally designed to prevent tuberculosis, has shown some efficacy against infection with unrelated pathogens. In this study, we reviewed 120 consecutive adult patients (≥18 years old) with COVID-19 at a major federally qualified health centre in Rhode Island, United States from 19 March to 29 April 2020. Median age was 39.5 years (interquartile range, 27.0–50.0), 30% were male and 87.5% were Latino/Hispanics. Eighty-two (68.3%) patients had BCG vaccination. Individuals with BCG vaccination were less likely to require hospital admission during the disease course (3.7% *vs.* 15.8%, $P = 0.019$). This association remained unchanged after adjusting for demographics and comorbidities ($P = 0.017$) using multivariate regression analysis. The finding from our study suggests the potential of BCG in preventing more severe COVID-19.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of coronavirus disease 2019 (COVID-19) and has resulted in a global pandemic. There is limited data on effective therapies. The Bacillus Calmette–Guérin (BCG) vaccine, a live-attenuated strain derived from an isolate of *Mycobacterium bovis* and originally designed to prevent tuberculosis, has shown some efficacy against infection with unrelated pathogens [1]. A recent study suggested deaths due to COVID-19 were significantly lower in BCG-vaccinated countries when compared with BCG-non-vaccinated countries [2]. It is important for future prevention efforts to investigate this potential effect to see if BCG vaccine confers protection against more severe COVID-19.

To determine if BCG vaccination provided protection from COVID-19, we reviewed a predominately Latino/Hispanic population receiving care at the major federally qualified health centre (FQHC) in Providence, Rhode Island, United States. Ninety per cent of households in this FQHC were under the 200% Federal Poverty Level (FPL) and resided in Providence. Between 19 March and 29 April 2020, data on 120 (77.4%) out of 155 consecutive adult patients (≥18 years old) who were SARS-CoV-2 positive were available and patients were reviewed through 14 days.

We characterised patients by demographics, immunisation status, symptoms during disease course, hospitalisation and comorbid disease. The above information was self-reported and through medical record review. BCG vaccination status was determined by review of clinical charts. All the patients with mild symptoms were advised to isolate at home. Patients experiencing severe symptoms were referred to the hospitals in the same geographic areas by our triage team and clinicians using standard protocols. The clinicians in the emergency rooms were unaware of the patients' BCG status. Patients were admitted if they showed significant hypoxia which may have required more aggressive oxygen support or if they presented with signs of haemodynamic instability.

We report numbers (percentages) for binary/categorical variables and medians (interquartile ranges, IQR) for continuous variables. χ^2 tests and Wilcoxon rank-sum tests were applied to compare the statistical significances. A multivariate regression model adjusting age, sex, ethnicity, cigarette smoking history and comorbidities was applied to examine the outcome. All analyses were run using STATA 13.1 (StataCorp, College Station, TX, USA). The Providence Community Health Centers Review Committee approved the project.

Among the 120 patients, 82 (68.3%) had BCG vaccination. Median age was 39.5 years (IQR, 27.0–50.0). The BCG-vaccinated population was on average 10 years older than the

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Table 1. Characteristics and clinical outcomes of patients with Coronavirus Disease 2019 at Providence Community Health Centers

	Number (%)			
	Total patients ($N = 120$)	Patients without BCG vaccination ($n = 38$)	Patients with BCG vaccination ($n = 82$)	P value
Demographic				
Age, median (IQR), years	39.5 (27.0–50.0)	31.0 (23.0–61.0)	41.0 (29.0–49.0)	0.390
Sex				
Male	30 (25.0)	10 (26.3)	20 (24.4)	0.821
Female	90 (75.0)	28 (73.7)	62 (75.6)	
Ethnicity				
Latino/Hispanic	105 (87.5)	31 (81.6)	74 (90.2)	0.163
Non-Latino/Hispanic	9 (7.5)	3 (7.9)	6 (7.3)	
Refused	6 (5.0)	4 (10.5)	2 (2.4)	
Cigarette smoking history[a]	9 (7.5)	6 (15.8)	3 (3.7)	0.019
Symptoms during disease course				
Cough	88 (73.3)	27 (71.1)	61 (74.4)	0.701
Shortness of breath	32 (26.7)	12 (31.6)	20 (24.4)	0.407
Nasal congestion/rhinorrhoea	62 (51.7)	19 (50.0)	43 (52.4)	0.804
Myalgia	80 (66.7)	19 (50.0)	61 (74.4)	0.008
Fever	74 (61.7)	19 (50.0)	55 (67.1)	0.074
Headache	72 (60.0)	21 (55.3)	51 (62.2)	0.471
Sore throat	46 (38.3)	14 (36.8)	32 (39.0)	0.819
Vomiting/diarrhoea	47 (39.2)	19 (50.0)	28 (34.2)	0.098
Loss of smell/taste	73 (60.8)	24 (63.2)	49 (59.8)	0.722
Outcomes				
Referred to emergency room	25 (20.8)	13 (34.2)	12 (14.6)	0.014
Hospitalised	9 (7.5)	6 (15.8)	3 (3.7)	0.019
Comorbidities				
Hypertension	29 (24.2)	10 (26.3)	19 (23.2)	0.708
Diabetes	15 (12.5)	5 (13.2)	10 (12.2)	0.882
COPD or asthma[b]	10 (8.3)	7 (18.4)	3 (3.7)	0.006
Morbid obesity[c]	23 (19.2)	6 (15.8)	17 (20.7)	0.522
Chronic kidney disease	4 (3.3)	2 (5.3)	2 (2.4)	0.423
Liver cirrhosis	0	0	0	
Immunocompromised	1 (0.8)	0	1 (1.2)	0.494

IQR, interquartile range; COPD, chronic obstructive pulmonary disease.
[a]Cigarette smoking history: none of the nine hospitalised patients have a cigarette smoking history.
[b]COPD or asthma: among the nine hospitalised patients, two patients without BCG vaccination have COPD or asthma, no patient with BCG vaccination has COPD or asthma ($P = 0.257$).
[c]Morbid obesity was defined as a BMI of 40 or more, or 35 or more and experiencing obesity-related health conditions, such as hypertension or diabetes.

non-BCG-vaccinated population (median age 41.0 *vs.* 31.0 years, respectively, $P = 0.390$). Thirty per cent were male and 87.5% were Latino/Hispanics (Table 1). Compared to those without BCG vaccination, patients with BCG vaccination were more likely to experience myalgia during the disease course (74.4% *vs.* 50.0%, $P = 0.008$). There were no significant differences between the two groups in experiencing cough (73.3%), shortness of breath (26.7%), nasal congestion/rhinorrhoea (51.7%), fever (61.7%), headache (60.0%), sore throat (38.3%), vomiting/diarrhoea (39.2%) or loss of smell/taste (60.8%). Compared to a large case series from China [3], our overall patient population experienced symptoms at a percentage similar to a recent study from Washington State, United States [4], with more patients experiencing myalgia, headache and loss of smell/taste. The difference could reflect geographic variation or differential reporting.

COVID-19 patients with BCG vaccination were less likely to be hospitalised during the disease course (3.7% *vs.* 15.8%, $P = 0.019$). This association remained unchanged after adjusting for

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demographics and comorbidities ($P = 0.017$) using multivariate regression analysis. One patient without BCG vaccination died. The comorbidities between the two groups showed no significant differences in chronic diseases including hypertension (24.2%), diabetes (12.5%), chronic kidney disease (3.3%) and being immunocompromised (0.8%). A higher percentage of patients without BCG had a history of chronic obstructive pulmonary disease (COPD)/asthma, however, a recent study found the history of COPD was not associated with the risk of hospitalisation among COVID-19 patients [5]. Among those who were hospitalised, none had a history of cigarette smoking and there was no significant difference between the two groups in COPD/asthma ($P = 0.257$). Comparing the comorbidities among the hospitalised patients between the non-BCG- and BCG-vaccinated patients, no statistical differences were found in hypertension (83.3% *vs.* 100% respectively, $P = 0.453$), diabetes (33.3% *vs.* 66.7%, $P = 0.343$), COPD/asthma (33.3% *vs.* 0, $P = 0.257$), morbid obesity (33.3% *vs.* 33.3%, $P = 1.000$), chronic kidney disease (16.7% *vs.* 0, $P = 0.453$), none of the hospitalised patients had histories of liver cirrhosis or were immunocompromised.

In this study, patients with BCG vaccination were more likely to experience myalgia and less likely to require hospital admission. Myalgias may be related to the release of inflammatory mediators, such as interleukins (ILs) [6]. BCG is known to elicit non-specific immune effects through the induction of the innate immune responses and the enhanced production of IL-1β [1]. This may present as myalgias and help the body fight the infection. Recent ecological studies comparing countries with and without universal BCG vaccination policies found that BCG vaccination appears to significantly reduce mortality associated with COVID-19 [7] and mandatory BCG vaccination was associated with a flattening of the curve in the spread of COVID-19 [8]. These studies suggest a long-lasting protection conferred by childhood BCG vaccination against COVID-19. This duration of protection may persist for several years, as one study examining BCG vaccine protection against tuberculosis found a 50−60-year duration of protection [9]. A recent population-based study examining the cohort of Israeli adults aged 35−41 years found that the BCG vaccine may not reduce the likelihood of acquiring SARS-CoV-2 (difference, 1.3%; 95% CI −0.3% to 2.9%; $P = 0.09$) [10]. However, the lower hospitalisation rate among BCG-vaccinated patients from our prospective cohort study suggests the potential of BCG in preventing more severe COVID-19 among those who acquired SARS-CoV-2. Limitations to this study included a small sample size, short study time frame, unknown BCG strain each patient received, unknown BCG booster status, a preponderance of female patients, and a predominately Latino/Hispanic population. Future studies are needed to explore the efficacy of BCG vaccination in preventing COVID-19 disease progression.

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Author contributions.

Dr Weng had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Weng, Saal, Chan.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Weng, Chan.
Critical revision of the manuscript for important intellectual content: Weng, Butt, Chan
Administrative, technical, or material support: Weng, Saal.
Supervision: Weng, Chan.

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Conflict of interest. None.

Ethical standards. The study was approved by the Providence Community Health Centers Review Committee. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Data availability statement. The data that support the findings of this study are available on request from the corresponding author, C-H W. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

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