

Could BCG Vaccine be used to Protect against COVID-19

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Abstract

Background: A new coronavirus, called SARS-CoV-2, was identified in Wuhan, China, in December 2019. The SARS-CoV-2 spread very rapidly, causing a global pandemic, Coronavirus Disease 2019 (COVID-19). A few pharmaceutical companies and pathologists have been trying to come up with a cure in the form of a vaccine but in vain. It has been seen that universal BCG vaccination has been effective in prevention from and to reduce severity of COVID-19.

Materials and methods: A pilot study was conducted on Pakistani population using an online survey. A questionnaire acquiring data regarding BCG vaccination and COVID-19 status and symptoms experienced was generated using Google forms. Statistical analysis was performed using SPSS version 23. Simple descriptive analysis was conducted to access the correlation between universal BCG vaccination and COVID-19.

Results: This pilot study consisted of 50 participants who were suffering or had suffered from COVID-19, 39 of which were BCG vaccinated. Statistical analysis revealed that there is no significant correlation between universal BCG vaccination and COVID-19.

Conclusion: Universal BCG vaccination has shown to have no significant impact on COVID-19. Further research including a bigger sample size is needed to support or decline this finding.

Keywords: COVID-19; Universal BCG vaccination

Introduction

The COVID-19 caused by the novel Coronavirus (SARS-CoV-2) that started from China in December 2019 has affected all countries in the world very rapidly. To limit the spread of this disease governments of all countries had taken measurements, they had implemented social distancing and quarantined those with disease. Citizens had strictly been advised to stay at home. Attempts for creating vaccines for novel Coronavirus (COVID-19) are progressing, yet it is probably not going to be accessible in

the near future [1]. In the absence of particular treatment, the analysts are investing other likely preventive and restorative choices. Now a days there has been a buzz about the defensive impact of Bacille Calmette-Guerin (BCG) vaccine against COVID-19. BCG is an attenuated strain gotten from a confine of Mycobacterium bovis utilized generally over the world as an immunization for Tuberculosis (TB). Numerous countries including China and Japan are having a universal BCG vaccination strategy in new born babies [2]. BCG was initially evolved by Albert Calmette and Camille Guerin in the beginning of the twentieth century. First utilized in quite a while in 1921, BCG is presently one of the most generally utilized vaccines in newborn children and youngsters, in whom its fundamental utility is in the anticipation of tuberculous meningitis and tuberculosis [3]. A study in Guinea-Bissau found that kids inoculated with BCG were seen to have 50% decrease in overall mortality, which was ascribed to the vaccine's effect on lessening respiratory illnesses and sepsis [4]. Significantly, BCG is additionally utilized as adjuvant immunotherapy for patients with non-muscle-intrusive bladder cancer [5]. There is a proof from the previous epidemics that brace the hypothesis that BCG vaccination can ensure against DNA and RNA viral infections like herpes and influenza and other malady for example asthma [6]. These perceptions have offered backing to the chance of BCG vaccine providing assurance against this novel corona virus known as COVID-19, which is related with fever and serious respiratory disease. A researcher observed that there might a connection between the administration of BCG in every nation and the degree to which the spread of COVID-19 occurs [7]. Researchers are going to start a clinical trial of BCG vaccine on this illness soon, in light of the proposed gainful impact of BCG [8]. In Indonesia, a randomized placebo-controlled trial was done. BCG given month to month continuously for 3 months fundamentally decreased frequency of intense upper respiratory disease among people aged more than 65 years [9]. In a preliminary among Native Americans, BCG vaccine given during adolescence showed adequacy in preventing tuberculosis as long as 60 years after inoculation demonstrating the durability of this protection [10]. The basis of the feasible utilization of BCG vaccine against COVID-19 lies in its Non-Specific Effects (NSEs) over the immune system [11]. BCG vaccination altogether increases the discharge of pro-inflammatory cytokines specially IL-1B which has been appeared to play an imperative role in

antiviral immunity [12]. BCG could prompt to antigen-independent initiation of bystander B and T cells a mechanism that has been named heterologous immunity. Ultimately BCG could lead to long term triggering and reprogramming of innate immune cells.

A couple of nations had never had an all-inclusive BCG strategy. The purpose behind not inoculating was because of low TB rate and the likelihood to hold utilization of the tuberculin skin test in order to evaluate TB infections. In thoughts for the potential protection BCG vaccine against different irresistible diseases including CoV-2 disease, Australia, which suspended its all-inclusive BCG immunization during the 1980's, is right now testing whether the BCG vaccine can shield health care workers from CoV-2 or decrease COVID-19 related symptoms. Given our present comprehension on BCG vaccine's nonspecific immunotherapeutic mechanisms and by inspecting current epidemiological information, the aim of this study is to identify a potential relationship between the universal BCG vaccine policies and the morbidity and mortality related to COVID-19 infection in Pakistan.

Materials and Methods

Study design: Cross sectional descriptive analysis.

Sample size: 50

Study setting: Islamabad, Pakistan.

Methodology

It is a pilot study done on Pakistani population to assess the correlation between universal BCG vaccination and COVID-19. This study is a questionnaire based cross sectional study. A standardized questionnaire was prepared for this study. The study was conducted through Google forms. These forms were sent *via* a link to the participants through WhatsApp. The link was active from June 2020 to July 2020. Before filling the questionnaire, consent was given by the participants. They were also informed about the purpose of the study. The questionnaire consisted of demographic information, time of diagnosis of COVID-19, their current COVID-19 status, test for confirmation of diagnosis, medical history and administration with BCG vaccine as a child. They were also asked about the symptoms faced due to Coronavirus. The study sample was calculated 50.

Inclusion criteria

- All people who have been tested positive for COVID-19
- All patients who recovered from COVID-19
- Both genders included
- All age groups included

Exclusion criteria

- People who have not been tested for COVID-19
- People who have been tested negative for COVID-19

Data analysis

The questionnaire data was entered in SPSS version 23. Descriptive analysis and *chi-square* test was run to assess the significant difference between BCG vaccination and COVID-19.

Results

A pilot study was conducted on 50 participants who were infected by coronavirus. Results were calculated by running *chi-square* test, simple descriptive analysis and cross-tabulation. All the participants were the citizens of Pakistan, most of them were from Punjab (n=35) (70%), 26% (n=13) were from federal area and 4% (n=2) belonged to Khyber Pakhtunkhwa. Among them 25 were females and 25 were males (Figure 1). Majority of the participants (38%, n=19) belonged to the age group of 31-45 years while only 4% (n=2) were older than 60 years of age. Among the participants, 20% (n=10) were health care workers and the rest belonged to different fields. Around 84% of the participants (n=42) were diagnosed with COVID-19 less than 3 months ago.

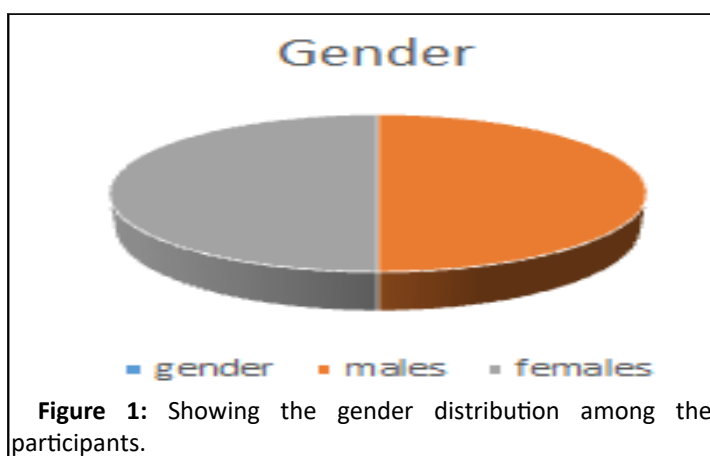


Figure 1: Showing the gender distribution among the participants.

During our study period, COVID-19 status of 86% (n=43) of the participants was negative while 14% (n=7) were still infected from the virus.

Age: Majority of the participants (n=19) belonged to the age group of 31-45 years, 17 belonged to the age group of 15-30 years, 12 belonged to age group of 46-60 years and only 2 were older than 60 years of age (Figure 2).

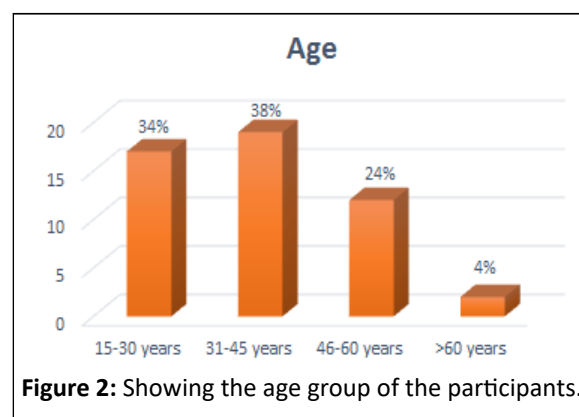


Figure 2: Showing the age group of the participants.

Occupation: By occupation, 20%, n=10 were health care professionals, 78%, n=39 belonged to varied fields and only 2% were retired.

Diagnosis period and test conducted: 84%, n=42 participants were diagnosed in less than 3 months prior to the start of this study, 10%, n=5 were diagnosed in less than a month and 6%, n=3 were diagnosed in less than 6 months before the start of this study.

To confirm their diagnosis, 78%, n=39 of the participants used a PCR, 12%, n=6 used antibody test and 5 participants were not sure about which test was used for their diagnosis. 86% of the participants were COVID-19 negative while 14% were COVID-19 positive during our study (Figures 3 and 4).

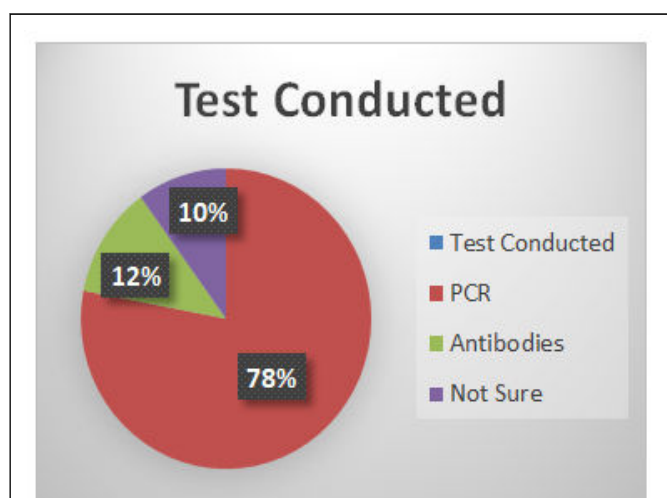


Figure 3: Showing the tests conducted for the confirmation of Coronavirus infection.

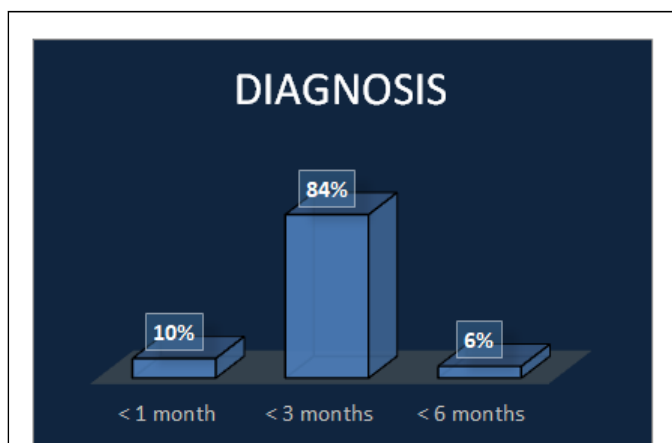


Figure 4: Showing the time at which the infection was diagnosed among the participants.

Related medical history and administration of BCG:

Regarding previous medical history, majority of the participants (72%, n=36) had no related medical history, 12%, n=6 had allergies and hypertension while only 2% of the participants had diabetes and pneumonia. 58%, n=29 participants were administered with BCG vaccine in their childhood, 8%, n=4 were not administered with BCG vaccine and 14%, n=7 were not sure if they were administered with the vaccine or not.

Symptoms

The symptoms were divided into three categories as standardized by the WHO.

Less common symptoms: Less common symptoms included sore throat, headache, and loss of taste and/or smell, aches and pains, conjunctivitis, a rash on skin or discoloration on fingers or toes and diarrhea. 39 participants (78%) who were vaccinated faced the less common symptoms while 4 unvaccinated participants (8%) faced the same symptoms. Among those who were not sure if they were vaccinated or not, 14%, n=7 faced these symptoms (Table 1).

Most common symptoms: Most common symptoms included fever, dry cough and tiredness. 39 participants (78%) who were vaccinated faced these symptoms while 4 unvaccinated participants (8%) faced the same symptoms. Among those who were not sure if they were vaccinated or not, 14%, n=7 faced these symptoms (Table 1).

Serious symptoms: Serious symptoms included chest pain or pressure and shortness of breath or difficulty in breathing. Among the 50 participants, 36 of them responded that they faced no serious symptoms after being infected by coronavirus, 31 of which were administered with BCG vaccine in their childhood. 3 of the participants felt chest pain or pressure, 2 of them was vaccinated and 1 of them was not vaccinated. 6 vaccinated and 1 unvaccinated participant reported that they experienced shortness of breath. 4 participants, who were not sure if they were vaccinated or also had difficulty in breathing.

Table 1: Showing symptoms faced by the patients and their vaccination status.

Less common symptoms	I am not sure	No	Yes
Aches and pains, diarrhea, headache	0	0	1 (2%)
Aches and pains, headache	0	0	4 (8%)
Aches and pains, headache, loss of taste or smell	0	0	2 (4%)

Aches and pains, sore throat	0	0	2 (4%)
Aches and pains, sore throat, diarrhea	0	0	1 (2%)
Aches and pains, sore throat, diarrhea, headache, loss of taste or smell.	0	0	1 (2%)
Aches and pains, Sore throat, diarrhea, loss of taste or smell.	1 (2%)	0	3 (6%)
Aches and pains, sore throat, headache	0	1 (2%)	0
Aches and pains, sore throat, headache, loss of taste or smell	3 (6%)	1 (2%)	8 (16%)
Aches and pains, sore throat, headache, loss of taste or smell	2 (4%)	0	4 (6%)
A rash on skin or discoloration of fingers or toes.	0	1 (2%)	0
Conjunctivitis, a rash on skin or discoloration of fingers or toes	0	0	1 (2%)
Diarrhea	0	0	1 (2%)
Diarrhea, headache, conjunctivitis	0	0	1 (2%)
Headache	0	0	2 (4%)
Headache, loss of taste or smell	0	0	1 (2%)
Loss of taste or smell	0	1 (2%)	3 (6%)
Sore throat	0	0	3 (6%)
Sore throat, headache	1 (2%)	0	1 (2%)
More common symptoms			
Fever	0	0	1 (2%)
Fever, dry cough	0	0	1 (2%)
Fever, tiredness	1 (2%)	1 (2%)	10 (20%)
Fever, tiredness, dry cough	1 (2%)	2 (4%)	19 (38%)
Tiredness	6 (12%)	0	4 (8%)
Tiredness, dry cough	0	0	3 (6%)
Severe symptoms			
Chest pain or pressure	0	1 (2%)	2 (4%)

Difficulty breathing or shortness of breath	1 (2%)	0	5 (10%)
Difficulty breathing or shortness of breath, chest pain or pressure	3 (6%)	0	1 (2%)
Difficulty breathing or shortness of breath, chest pain or pressure loss of speech or movement	0	1 (2%)	0

Discussion

A prophylactic methodology utilizing BCG vaccination against SARS-CoV-2 infection has currently been suggested due to the realized valuable off-target impacts of BCG against other infections [13]. Importantly, however, a staggering inflammatory response has been depicted to add to seriousness and mortality in certain patients with COVID-19 which raised worries that BCG vaccination, by improving innate immune responses, may have injurious impacts. The purpose of our study was to investigate whether BCG vaccination had a relation with COVID-19 infection rate and COVID-19 related symptoms in Pakistan [14]. BCG, initially created against tuberculosis, is hypothesized to create 'frontline' immunity, preparing it to react nonspecifically to certain infections with more noteworthy intensity [15]. This thought is upheld by clinical and epidemiological examinations, which indicated that BCG seemed to bring down overall mortality in children [16]. Different clinical preliminaries have demonstrated that BCG immunization emphatically decreases neonatal mortality, an impact that appeared to be because of preservation against unrelated infectious agents, bringing about fewer instances of respiratory tract infections and neonatal sepsis [17]. Spencer et al. demonstrated that BCG decreased viral load of influenza a virus in mice, an impact reliant on macrophages, while BCG vaccination likewise protected from herpes simplex infection type 2 in a controlled murine model with infant mice [18,19]. Eventually, BCG induced trained immunity manifested protective effects in a model of controlled experimental viral infections in humans. BCG, which can stay alive in the human skin for a while, triggers not just explicit memory B and T cells, yet in addition animates the innate blood cells for a delayed period. In a randomized placebo-controlled examination, it was indicated that BCG vaccination secures against experimental infection with a debilitated type of the yellow fever virus.

This information prompted the hypothesis that BCG inoculation may likewise help against disease with SARS-CoV-2, and a few huge clinical preliminaries are in progress. Epidemiological examinations appear to help this theory by revealing lower rates of infection and mortality in nations with a childhood BCG immunization program [20]. The result of our study showed insignificant correlation between BCG vaccine and COVID-19 infection (P value =0.05). So, our hypothesis that BCG vaccine causes a significant reduction of spread of coronavirus is null. Our study is similar to the study conducted by Kirov and

Szigeti et al. who also showed no correlation between BCG vaccination policy and COVID-19 infection [21,22]. WHO logical report distributed on twelfth April 2020, which expressed that there is no current proof that BCG vaccine protects against COVID-19 [23]. Strong proof ought to be created through planned assessment in RCTs [24]. Martha K berg analysis also showed that BCG vaccination is associated with flattening of the curve in the spread of COVID-19 [25]. Hansel J results are similar to MK Berg [26].

Age is a major risk factor in COVID-19 [27]. A study found that vaccination of adults >65 years of age with BCG prevented acute upper respiratory tract infection and there is an active clinical trial vaccinating adults aged >65 years with BCG to boost immunity [28]. Predominance of comorbidities, for example, diabetes, cardiovascular illness, constant respiratory sickness and malignancy are ascending in low to middle income countries. In 2019 non-insulin dependent diabetes mellitus prevalence among adults was accounted for to be 11% in Asian nations and 6% in Europe [29]. The World Health Organization gauges higher cardiovascular sickness risk in Asian areas than in European and North American regions [30]. In our study out of 50, only 6 patients had hypertension and 1 had diabetes. A study done by Moorlag SJCFMout of 266 BCG vaccinated patients only 4 hypertensive and 3 diabetic participants were present. This concluded that in COVID-19 patient's related medical history is relatively low [31].

In our study we found that BCG vaccination is not associated with severity of symptoms during the COVID-19 pandemic. In Netherland a research was done by professor of experimental internal medicine Mihai Netea and his team 5 years ago in which a group of healthy volunteers received the BCG vaccine. During COVID-19 pandemic these participants were called again to check the effect of vaccine on the symptoms attributed to coronavirus infection. Those who received the vaccine did not have more symptoms, did not become more seriously ill and did not get sick more during the first wave of COVID-19 pandemic in Netherland. The most common symptoms in our study were fever, tiredness and dry cough, similar to the study done by Moorlag SJCFM. In his study 8.3% of the participants had the incidence of extreme fatigue, common symptom of COVID-19.

BCG immunization may become viable just when a generous extent of the population is made resistant to the infection. In other words, the spread of the infection might be eased back just when there is "herd immunity" that prevents the infection

from spreading effectively over the population. Right now 3 clinical preliminaries are active and enlisting to decide whether BCG immunization ensures Health Care Workers (HCW) during the COVID-19 pandemic; BRACE is a stage III RCT, directed in Australia that will select up to 4170 HCW to decide whether the BCG vaccine lessens the frequency and seriousness of COVID-19.

Limitations

There are few limitations in our study. Firstly, the sample size in our pilot study was very small, very small number of people were willing to participate and very few of the participants were sure about being vaccinated. Secondly, most of the people in Pakistan are vaccinated with BCG so we didn't have an unvaccinated group for comparison. In all national policies, BCG is given early in life, commonly during childbirth. It is not clear whether BCG vaccination may be successful when given to grown-ups. Nor it is realized how long BCG vaccination may give immunity to COVID-19 despite the fact that it is viable against tuberculosis and lungs cancer for quite a few years. Additionally, it is unsure whether BCG may have any unfavorable impacts when given to those already infected with COVID-19.

Conclusion

There is systemic review evidence with low to moderate risk of bias that BCG vaccination prevents respiratory infections like influenza and pneumonia of all kinds and the older people as well. Our study concluded that there is no significant difference between BCG and COVID-19 and there is no evidence that BCG vaccine protects against COVID-19 up till now. More research is required to study the magnitude and span of the non-specific effects of BCG vaccine on COVID-19. Great proof ought to be acquired from prospective randomized control trials before pondering practice and strategy.

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