Citizen science initiative points at childhood BCG vaccination as a risk factor for COVID-19

Running title: Childhood BCG vaccination: a COVID-19 risk factor

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Abstract

Current results do not provide conclusive evidence on the effect of BCG vaccination on COVID-19 alone or in combination with other factors. To address this limitation, in this study we used a citizen science initiative on the COVID-19 pandemic to collect data worldwide during October 2-30, 2020 (1,233 individuals) in a structured way for analyzing factors and characteristics of affected individuals in relation to BCG vaccination. For the first time, the results of our study suggested that vaccination with BCG may increase the risk for COVID-19 at certain age, particularly in individuals vaccinated at childhood. A reasonable explanation for this effect is the activation of certain innate immunity mechanisms associated with inflammatory reactions, which should be considered when analyzing the risks associated with this global pandemic. These factors should be considered when analyzing the risks associated with this global pandemic.

Keywords: COVID-19; Humans; Pandemics; BCG Vaccine; Risk Factors; Citizen Science; severe acute respiratory syndrome coronavirus 2; Vaccination; Innate immunity

Introduction

The pandemic of coronavirus disease 19 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represents a health, social, economic and scientific challenge. Early identification of risk factors for COVID-19 disease morbidity and mortality is necessary during the pandemic to develop treatment strategies and interventions with priority for those at highest risk. Citizen science plays a key role in addressing these challenges trough monitoring, assessment and control of COVID-19 (Pearse, 2020).

The Bacille Calmette-Guérin (BCG) vaccine against tuberculosis has been associated with non-specific pleiotropic protective effects against other infections, and significant reductions in all-cause morbidity and mortality (Escobar et al., 2020; Giamarellos-Bourboulis et al., 2020). Regarding COVID-19, it has been proposed that trained innate immunity or heterologous T cell responses induced by BCG vaccination may reduce disease incidence, morbidity and severity (Giamarellos-Bourboulis et al., 2020; Mantovani and Netea, 2020; Kubota et al., 2020; Curtis et al., 2020; Jirjees et al., 2020; Wickramasinghe et al., 2020; Levi et al., 2020). However, considering the limitations of ecological studies, analyses of the links between BCG vaccination and COVID-19 incidence and mortality have shown no correlation (Hensel et al., 2020), negative correlation (Singh et al., 2020), or changes in correlation patterns as the pandemic progresses (Kubota et al., 2020). Other factors that have been proposed to affect SARS-CoV-2 infection and disease morbidity and mortality include ABO blood group (higher and lower susceptibility to infection in individuals with A and O blood groups, respectively) (Wu et al., 2020; Hodžić et al., 2020), age (older age associated with COVID-19 severity and mortality) (Ho et al., 2020), antibody levels against glycan Galα1-3Galβ1-(3)4GlcNAc-R (α-Gal) present in midgut

microbiota (lower antibody levels associated with higher disease severity) (Urra et al., 2020), and sex (male patients appear to be at higher risk of mortality) (Ritter and Kararigas, 2020).

Some evidence also suggests a higher COVID-19 susceptibility among BCG vaccinated individuals. Recently, a COVID-19 outbreak occurred among crew members of the U.S.S. Theodore Roosevelt. Infection spread quickly in this group of predominantly young males (mean age 27 years), because transmission was facilitated by close-quarters conditions. In total, 26.6% of the crew (1271 of 4479) tested positive for SARS-CoV-2 infection by PCR. Nearly half of those who tested positive for the virus never had symptoms, 23 (1.7%) were hospitalized, 4 (0.3%) received intensive care, and 1 died (Kasper et al., 2020). This represents a very low hospitalization rate. Vaccination with BCG is not officially recommended in the U.S.A. (BCG Vaccine, 2020) and is not part of routine navy healthcare (https://www.med.navy.mil/directives/ExternalDirectives/6224.8C.pdf). By contrast, a study on COVID-19 associated hospitalizations among U.S. health care personnel, a group where BCG vaccination was considered on an individual basis (BCG Vaccine, 2020), found that 27.5% (i.e., 100 times more) received intensive care (Kambhampati et al., 2020).

These results do not provide conclusive evidence on the effect of BCG vaccination on COVID-19 alone or in combination with other factors. To address this limitation, in this study we used a citizen science initiative on the COVID-19 pandemic to collect data in a structured way for analyzing factors and characteristics of affected individuals in relation to BCG vaccination.

Material and Methods

Survey characteristics, data transformation and statistical analysis

A questionnaire was conducted during October 2-30, 2020 containing 10 qualitative questions (sex, blood group, country of residence, BCG-vaccination, COVID-19 diagnostic, hospitalization

with COVID-19, PCR test, antibody test, symptomatic, consent), 2 quantitative questions (age, duration of symptoms) and one space for free text (symptoms description) (total 13 questions) was circulated via e-mail and social networks (i.e., Facebook, Twitter, LinkedIn, Instagram). Relative to BCG vaccination and COVID-19, the following seven questions were included in the survey (Table 1): (i) have you been vaccinated with BCG? (Yes, No, Maybe), (ii) have you been diagnosed with COVID-19? (Yes, No). (iii) have you been hospitalized with COVID-19? (Yes, No), (iv) duration of symptoms (days), (v) were you positive to the PCR test? (Yes, No, No PCR test), (vi) were you positive to the antibody test? (Yes, No, No antibody test), (vii) main symptoms in case you have been diagnosed with COVID-19 (free text) (Supplementary Data). The following additional or grouping variables were added to the survey results: Blood group class (A or O; B or AB; Unknown); Age class (41; <41); COVID-19 cases per 100,000 inhabitants (>1000 or <1000, calculated after data downloaded from the ECDC at https://www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide, accessed on 02 November 2020); Region (Africa; Russia and Belarus; Central and North Europe; Mediterranean Western Europe; Southeastern Europe; America other than North; North America; Other); Symptoms duration (short if <15 days; long if >14 days); Any test positive (Yes if either PCR or antibody tests positive; No if both negative or not attempted); Symptoms score (High, Low); Symptomatic (Yes if symptoms reported, No if no symptoms reported with any test positive). By 31 October 2020 we had obtained 1267 responses, of which 1233 agreed in the use and publication of this anonymous information for the study. Respondents belonged to 48 countries and included 782 females and 447 males, with a mean age of 40.4 years (SD 14.22; range 3-84). Sample size of completed and approved

responses was calculated as 1215 for a population size of 1 million, 99% confidence level and 3.7% margin of error (https://www.surveymonkey.com/mp/sample-size-calculator/).

We designed a binomial generalized linear model with a logit link function to test the statistical effect of categorical (Sex; Blood group; BCG vaccination; high/low number of COVID-19 cases per 100,000 inhabitants; Region) and continuous predictors (Age) on the probability of having been diagnosed with COVID-19 (dependent variable). We used a stepwise backward strategy to obtain the final model. Homogeneity among additional binary variables was analyzed using a Fisher's exact test and comparisons between numerical groups were done with Mann-Whitney's U test. The significance level was set at $p<0.05$. We used SPSS statistical software.

The data that support the findings of this study are available in the Supplementary Data.

Results and Discussion

Our results identify BCG vaccination as a risk factor for COVID-19

The significant effects resulting from the backward selection of the model where age, BCG vaccination and COVID-19 cases per 100,000 inhabitants, which influence the likelihood of being diagnosed with COVID-19 (Table 2). Sex, blood group and region were not retained by the model. Childhood BCG vaccination increased the likelihood of being diagnosed with COVID-19 fivefold in COVID-19 low-incidence countries and threefold in high-incidence countries (Figure 1). Moreover, BCG vaccinated subjects were three times more likely to have a positive SARS-CoV-2 PCR or blood test ($p < 0.0001$) and were also seven times more likely to have been hospitalized due to COVID-19 ($p < 0.0001$). However, BCG vaccination had no effect on symptoms development nor on symptoms duration ($p > 0.05$).

BCG vaccination may constitutes a risk factor for COVID-19

The results of our study suggested that BCG vaccination constitutes a risk factor for COVID-19, and raised the question of why is BCG vaccination not only not protective but increases disease risk?

Children are usually vaccinated with a number of adjuvant-containing formulations, which may decrease their relative susceptibility to COVID-19 (Castagnoli et al., 2020). Exposure to BCG can reprogram or train the innate immune system for trained immunity-mediated response to secondary stimuli (Rusek et al., 2018). Nevertheless, based on current evidence, BCG vaccination during childhood does not protect against SARS-CoV-2 infection in adults, likely due to the limited long-lasting trained immunity induced by BCG and/or the probable abrogated effect of other vaccines (Hamiel et al., 2020). In fact, as recently published (Mantovani and Netea, 2020), myeloid cells (e.g. monocytes and dendritic cells) associated with the immune response to BCG have a relatively short-life in the vascular system. However, recent results support a role for epigenetic reprogramming of bone marrow myeloid progenitor hematopoietic stem cells in the long-lasting trained innate immunity in response to BCG (Cirovic et al., 2020).

Nevertheless, community BCG vaccination raises questions regarding the stimulation of innate immunity, which may be associated with stronger inflammatory reactions and pro-inflammatory cytokine levels associated with COVID-19 severity (Huang et al., 2020). For example, when monocytes and natural killer (NK) cells from BCG-vaccinated individuals are compared to non-vaccinated controls, they display higher expression levels of toll-like receptors (TLRs) and cytokines (e.g. Tumor Necrosis Factor alpha, TNF-α and interleukin 6, IL-6) in response to various pathogens (Ifrim et al., 2014). It has been shown that the infection with SARS-CoV-2 can potentially result in the “cytokine storm syndrome (CSS)” (Horowitz et al., 2020). The CSS has been associated with the activation of the nuclear factor kappa B (NF-kB) innate immune

pathway resulting in the upregulation of proinflammatory cytokines such as TNF-α, IL-1β, IL-6 and IL-8 (Horowitz et al., 2020). Therefore, it is possible that particularly in adults after certain age and vaccinated during childhood the long-lasting trained immunity mechanisms induced by BCG may result in CSS and thus increase risk of COVID-19.

Study limitations and conclusions

The findings in this report are subject to at several limitations. Our questionnaire did not collect information on predisposing conditions other than country, age, sex, or BCG vaccination, such as obesity, which is a known risk factor for COVID-19 (Kambhampati et al., 2020). We don't know the age at BCG vaccination, although it was likely during childhood in most cases. Also, in countries that changed the vaccination schedule recently, elder people knowingly experiencing more severe disease were also BCG vaccinated. A similar risk pattern observed in both high- and low-incidence countries partially addresses this limitation. Despite collecting information from respondents of 48 countries, continents like Asia, Oceania and Africa were under-represented in our sample.

We conclude that based on results from this study, vaccination with BCG may increase the risk for COVID-19 at certain age, particularly in individuals who received the vaccine at childhood. A reasonable explanation for this effect is the activation of certain innate immunity mechanisms associated with inflammatory reactions. These factors should be considered when analyzing the risks associated with this global pandemic.

Authors' contributions

JF, OA, CG and ANL designed the study. JF, OA, LSR, CG and ANL contributed to the collection and management of the data. CG analysed the data. JF and CG interpreted the data and

wrote the manuscript. The authors listed in the COVID-BCG Collaborative Working Group contributed to data collection and systematisation. All authors revised the manuscript and approved the final version.

Declaration of interests

We declare no competing interests.

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Ethical approval

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this study was based on environmental RNA sampling. We used no individual patient data and performed no animal sampling. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data availability: The data that support the findings of this study are available in the Supplementary Data.

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Table 1. Main characteristics of respondents, depending on their BCG vaccination status.

Respondent characteristics	**BCG vaccinated (n=703)**	**Not vaccinated (n=372)**
Sex	221 Male; 480 Female, Other = 2	153 Male; 218 Female; Other = 1
Age (years, mean; range)	42.23 (3-84)	37.79 (18-80)
Blood group	488 A or O; 135 B or AB, Unknown = 80	240 A or O; 56 B or AB; Unknown = 76
Country of residence (Only countries with n > 19)	142 Mexico; 93 Belarus; 84 Russia; 81 Spain; 63 USA; 39 Romania; 30 Chile; 23 Cuba; 20 France	171 Spain; 91 Mexico; 57 Romania; 34 USA
COVID-19 diagnosed	204 Yes; 499 No	29 Yes; 343 No
Any COVID-19 test positive	188 Yes (16 only clinically diagnosed); 23 No	24 Yes (5 only clinically diagnosed); 44 No
Hospitalized with COVID-19	47 Yes; 656 No	4 Yes; 368 No
Duration of symptoms (days)	15.44 (1-90)	18.48 (3-180)

Table 2. Significant effects influencing the likelihood of being diagnosed with COVID-19.

Effect	**Degree of freedom**	**Wald statistics**	**Wald p-value**
Intercept	1	30.04	<0.0001
Age (years)	1	7.97	0.0047
BCG vaccinated (Yes, No, Maybe)	2	63.10	<0.0001
Cases/100,000 (>1000, <1000)	1	38.99	<0.0001

Figure 1. Effect of BCG vaccination on the probability of being diagnosed with COVID-19 in low-incidence and high-incidence countries.

Supplementary information. Supplementary Data. Results of the survey.