

Allergy / Early View

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Childhood BCG vaccination seems to selectively protect adult males from COVID-19 infection

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To the Editor,

Many studies have suggested a beneficial, non-specific effect of the now 100-year-old Bacille Calmette-Guérin (BCG) vaccine on child mortality due to a reduction in neonatal sepsis and respiratory tract infections as well as protection against various specific viral diseases.¹⁻⁶ Two mechanisms have been demonstrated by which non-specific protection against unrelated pathogens is thought to occur: (i) epigenetic training of macrophages and natural killer (NK) cells and (ii) heterologous T helper 1 (Th1) and Th17 immune responses.⁷ In the first wave of the COVID-19 pandemic, some countries had a substantially lower mortality and morbidity due to SARS-CoV-2. Early on, some ecological studies concluded that BCG vaccination might be one of the underlying causes of the observed difference between countries, while others did not find such a correlation.^{3, 4, 8, 9} We used a case-control design to investigate whether BCG vaccination during childhood affects the risk of COVID-19-infection in adults. The study was conducted in East Germany at a time of the COVID-19 pandemic before the so-called 'variants of concern' emerged in our region. We took advantage of a federally imposed contact tracing system in Germany to selectively include uniformly defined close contacts of COVID-19-infected persons thereby having a comparable risk of COVID-19-transmission. Close contacts were considered cases if they had a positive SARS-CoV-2-PCR test and/or if SARS-CoV-2-specific antibody testing—which was performed at least three weeks after contact—returned a positive result. BCG vaccination status was individually assessed under consideration of vaccination certificates and additional

supportive parameters by a medical professional (Appendix [S1](#)). 800 persons were invited (response rate 28.9%). Due to rigorous BCG vaccination policy in East Germany until the year 1990, age-adjusted analysis could not be conducted for older age groups due to the lack of BCG-non-vaccinated participants. 147 of 190 included individuals from 17 to 46 years of age were therefore selected for final analysis to form three age groups (17–26, 27–36 and 37–46). There were 87 females (59.2%) and 60 males (40.8%) (Table [1](#)). Likelihood ratio tests performed to test for interaction by sex and age yielded a P value of 0.015 and 0.79, respectively, indicating that the association between BCG status and COVID-19 infection was modified by sex but not by age. Therefore, a final model of the relationship between BCG vaccination and COVID-19 infections was fitted that included age as a confounder and sex as an effect modifier. BCG vaccination status was associated with a lower likelihood of COVID-19 infection for men but not for women (ORs 0.13 and 1.04, respectively). For men, we found a highly significant association with 95% CIs ranging from 0.04 to 0.48 ($p = 0.002$), while for women, 95% CIs ranged from 0.40 to 2.71 ($p = 0.938$) (Table [2](#)). Grossly, we observed comparatively more infected BCG-non-vaccinated males and fewer infected BCG-vaccinated males than females which resulted in a roughly balanced distribution of COVID-19 infections between males and females in our study (OR: 1.06, 95% CI 0.53–2.09 $p = 0.876$). BCG vaccination might differentially affect men by turning them from a natural state of being at higher risk of COVID-19 infection to a state of being at lower risk compared with women.

TABLE 1. Descriptive analysis and crude associations of primary exposure/potential confounders with COVID-19 infection

Variable		n (%)	Infected	Non-infected	OR (95% CI) ^a	p ^b
BCG status	Non-vaccinated	48 (32.7)	22	26	1	
	Vaccinated	99 (67.3)	33	66	0.59 (0.29–1.21)	0.143
Age	17–26 years	55 (37.4)	20	35	1	
	27–36 years	63 (42.9)	22	41	0.94 (0.44–2.00)	0.870
	37–46 years	29 (19.7)	13	16	1.42 (0.57.3.55)	0.451
Sex	Male	60 (40.8)	22	38	1	
	Female	87 (59.2)	33	54	1.06 (0.53–2.09)	0.876

^a Odds ratios and 95% confidence intervals included within brackets.
^b p values were derived by logistic regression models (Wald test), values <0.05 were considered significant.

TABLE 2. Odds ratios of COVID-19 infection in the final model

Variable	Fully adjusted ORs of COVID-19 infection (95% CI) ^a	p ^b
BCG status (vaccinated vs non-vaccinated)		
Male	0.13 (0.04–0.48)	0.002
Female	1.04 (0.40–2.71)	0.938
Sex (females vs males)		
Non-vaccinated	0.29 (0.08–1.00)	0.050
Vaccinated	2.32 (0.92–5.81)	0.074
Age category		
17–26	1	
27–36	1.27 (0.55–2.94)	0.584
37–46	2.54 (0.88–7.32)	0.084

Note

Due to effect modification of BCG status by sex for the odds of COVID-19 infection, specific odds ratios are presented for the effect of BCG status on COVID-19 infections for males and females and the effect of sex on COVID-19 infections for BCG vaccinated and BCG-non-vaccinated.

- ^a Odds ratios and 95% confidence intervals included within brackets.
- ^b p values were derived by logistic regression models (Wald test), values <0.05 were considered significant.

Bacille Calmette-Guérin vaccination status did not seem to affect COVID-19-related symptoms (fever, shortness of breath, joint pains, fatigue, dry cough and loss of smell), and no correlation between impact of symptoms on state of health and BCG vaccination status was found (overall estimate and conducted separately for males and females and two age groups [≤ 30 and >30 years of age] using chi-squared test and Fisher's exact test as appropriate, Appendix [S1](#)).

A cross-sectional study conducted in Los Angeles found evidence of a protective effect of BCG vaccination but did not mention results from sex-stratified analysis.¹⁰ BCG vaccination was never part of the US routine vaccination programme. A case-control study from Canada evaluated COVID-19-related health outcomes for BCG-vaccinated and BCG-non-vaccinated born between 1956 and 1976 and did not find evidence of a protective effect from BCG vaccination.¹¹ Participants in the present study tended to be much younger limiting

comparability.

Epidemiological investigations of sex-dependent differences in non-specific effects of BCG vaccination are scarce. A randomized trial (RCT) found that non-specific effects of BCG vaccination concerning all-cause mortality and morbidity in the neonatal period differed between males and females in the first weeks of life.⁵ A case-control study on children <5 years of age in Guinea-Bissau found a protective effect of BCG vaccination against acute lower respiratory tract infection, especially caused by respiratory syncytial virus, that was most marked in girls.² In contrast, a case-control study conducted in Kenya found a statistically significant reduction in community-acquired pneumonia in BCG-vaccinated males (study population: 15–54 years of age), while no effect was present in women.⁶ The longevity of non-specific effects of BCG vaccination is not clear; however, monocytes stimulated with the TLR4 ligand lipopolysaccharide a year after BCG vaccination showed an increased expression of pattern recognition receptors such as CD14, toll-like receptors (TLR4) and mannose receptor correlating with increase in pro-inflammatory cytokine production. Similarly, heterologous immune responses with Th1 expressing IFN- γ and Th17 expressing IL-17 and IL-22 upon stimulation remained highly elevated a year after BCG vaccination.⁷

The impact of BCG vaccination on systemic inflammation and cytokine responses to re-stimulation has been investigated by Koeken, Netea and collaborators. Higher pre-vaccination levels and lower post-vaccination levels of inflammatory proteins were found in males. Ex vivo PBMC-derived cytokine production upon re-stimulation (14 and 90 days after vaccination) was then investigated, and strong sex-dependent correlations with baseline (pre-vaccination) circulating inflammatory protein levels were found. High levels of pre-vaccination inflammatory proteins were associated with increased IFN- γ production upon re-stimulation in males.¹²

Very recently, homology between several SARS-CoV-2 peptides and peptides from BCG has been demonstrated. In a recent in vitro experiment, CD4⁺ and CD8⁺ cells primed with BCG-derived peptides developed enhanced reactivity to their corresponding homologous SARS-CoV-2-derived peptides. BCG-vaccinated individuals exhibited across all peptides showed a trend towards increased TNF and INF- γ responses in CD4⁺ and CD8⁺ T cells. Crucially, the participants had been BCG-vaccinated years before stimulation.¹³

In light of sex dependencies with respect to IFN- γ release after BCG vaccination and the recent evidence for T cell cross-reactivity between BCG and SARS-CoV-2-derived peptides, a mechanism involving heterologous immune responses mediated by Th1 cells could be hypothesized.

As the effect seen in the present study was limited to COVID-19 infection with no influence on symptoms, instantaneous defence mechanisms such as pattern recognition receptors suitable to prevent infection differentially expressed by BCG-vaccinated males might play a

role but cannot be elucidated from the evidence currently available.

Adjustment for confounding factors other than age and sex was impeded by the study's limited sample size. Analysis of effect modification by age was affected by the strong correlation between age and BCG vaccination status in our study population, limiting any inferences about the longevity of the effect of BCG vaccination of COVID-19 infections. Notwithstanding these limitations, we believe that this study contributes to the emerging picture of a protective effect of childhood BCG vaccination on COVID-19 infection at a time, at which many countries struggle to scale up COVID-19 vaccination programmes. The selective protective effect on males found in this study could broaden the understanding of COVID-19 infection dynamics with possible use to implementation of COVID-19-related public health measures. Urgently needed further research will be challenging as increasing COVID-19 vaccine coverage will obscure the protective effect of BCG vaccination.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

Supporting Information



Filename	Description
all15186-sup-0001-AppendixS1.zip application/ .zip, 132.7 KB	Appendix S1

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Appendix S1

Childhood BCG vaccination seems to selectively protect adult males from COVID-19 infection

Supplementary methods

Study population. Individuals ≥ 16 years of age from Rostock city who were registered with the Rostock public health authority (Gesundheitsamt Rostock) after a close contact to an individual infected with COVID-19 (with or without developing a COVID-19 infection subsequently) were eligible to participate. To standardize contact tracing within the country the following events were classified as “close contacts” (associated with a high risk of transmission) by the German federal government agency responsible for disease control and prevention, the Robert Koch institute (RKI): Cumulative, face-to-face contact ($<1,5$ meters of physical distance) of at least 15 minutes without a protective mask; direct contact with secretions or body fluids; exposure to a likely relevant concentration of aerosols; Medical staff in contact (≤ 2 meters) with a confirmed case without a protective masks (<https://www.rki.de>). As a public health measure these close contacts were submitted into mandatory 14-day quarantine.

Over the course of two recruitment rounds in August and December 2020 800 participants were contacted by mail to receive an invitation letter, information sheet, informed consent form and a questionnaire. The questionnaire was developed with the evasys web-based platform V8.1 (evasys GmbH, Luneburg, Germany) which allowed completion either in written form or online. The questionnaire comprised questions on demographics, BCG vaccination status, kind and intensity of contact and COVID-19 related symptoms. Participants were asked to self-assess the impact of COVID-19 related symptoms on their state of health (i.e. no impact, some illness without being bedridden, bedridden for more than a day, symptoms leading to hospital admission). Participants were invited to the Institute of Medical Microbiology, Virology and Hygiene, University Medicine Rostock, for a blood sample and evaluation of their BCG vaccination status.

Ethical considerations. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the University Medicine Rostock (Registration number A 2020-0136). All participants provided written informed consent before the survey forms and blood samples were collected.

BCG vaccination status. Participants were asked to report: If BCG vaccination was recorded on a vaccination certificate and, if so, indicate the year of vaccination (typically, BCG vaccine was administered between day 1-3 of birth); If they had any personal memory of the vaccination process; If BCG vaccination was reported to them by a close relative; At visit, participants were checked for

the presence of a typical scar on the left upper arm or left thigh. If available, official vaccination documents were checked for records of BCG vaccination. BCG vaccination status was then assessed under consideration of the history of the BCG vaccination program in East and West Germany as depicted in Figure 1. If BCG vaccination status was inconclusive participants were excluded from analysis.

Figure 1: Flowchart representing the classification of BCG vaccination status in the study.

Antibody testing. At visit, a blood sample (serum) was drawn filling one 9 ml S-monovette (SARSTEDT, Nümbrecht, Germany). Samples were refrigerated at 8 °C within 60 minutes after blood draw. IgG antibody testing was done using an indirect chemiluminescent immunoassay (CLIA), the COVID-19 VIRCLIA® IgG MONOTEST (Vircell, Granada, Spain). Testing was conducted on a VIRCLIA® automated processor (Vircell) in combination with the VIRCLIA® AUXILIARY REAGENTS (Vircell) according to the manufacturer's specifications.

COVID-19 status. Participants were considered cases if they had been reported to the public health authority as the result of a positive PCR test and/or if the antibody test turned positive. Participants without a preceding positive PCR test result and with a negative antibody test result were considered controls. Antibody testing was performed at least three weeks after participants experienced symptoms.

Statistical analysis. All data analysis was carried out using Stata/IC version 15.1. Unadjusted analysis using Chi-squared tests and logistic regression models was conducted to explore the relationship between the primary outcome (COVID-19 infection) and the primary exposure (BCG vaccination status) as well as age category and sex (P values < 0.05 were considered significant, Odds ratios [RR] were accompanied by 95% confidence intervals [CI]). ORs were then adjusted for sex and age using logistic regression models. Likelihood ratio (LR) tests were used to test logistic regression models with and without interaction terms to assess effect modification. Confounders and effect modifiers were integrated into the final model using multiple regression analysis. Analysis of COVID-19 related symptoms among infected participants was conducted as an overall estimate and stratified by age [$\leq$ 30 and >30 years of age] and sex using Chi-squared test or Fisher's exact test as appropriate.

Supplementary results:

One hundred ninety participants were included for primary analysis. A total of 231 questionnaires were returned from 800 sent out questionnaires (response rate = 28.9%). Forty-one participants could not be included for analysis due to missing data on BCG status (n=11), Covid-19 status (n=22), BCG and COVID-19 status (n=6), and COVID-19-vaccination (n=2) (Figure 2). 137 birth vaccination certificates of 190 included participants were available (117 showing a record of BCG vaccination and 20 showing no record of BCG vaccination).

Figure 2: Flowchart representing total number of participants and exclusion criteria.

BCG status was highly correlated with age. Age varied from 17 to 85 years and was highly correlated with BCG vaccination status (Spearman's rank correlation coefficient: 0.54). There were no non-vaccinated participants older than 46 years. The crude odds ratio for the association between BCG status and COVID-19 infection among all 190 participants was 0.77 (95%CI 0.40-1.49, p=0.43). Due to the lack of non-vaccinated individuals in higher age groups possible confounding by age could not be accounted for. Therefore, it was decided to include only individuals up to 46 years into the further analysis of the association of interest to form three age groups (17-26, 27-36, 37-46) (n=147). Within these three age groups there were 55 infected and 92 non-infected, 99 individuals were considered vaccinated, 48 individuals were considered to be not vaccinated with BCG (27-36 years: 24 vaccinated and 31 non-vaccinated, 37-46 years: 50 vaccinated and 13 non-vaccinated, 37-46: 25 vaccinated and 4 non-vaccinated). There were 87 females (59.2%) and 60 males (40.8%). All participants were born in Germany, 85 (57.8%) in the state of Mecklenburg-Vorpommern and 62 (42.2%) in other states of Germany. Unadjusted analysis showed weak evidence of a protective effect of BCG vaccination. The crude OR for the association between BCG vaccination and COVID-19 infection for the 147 participants included in further analysis was 0.59. The odds of COVID-19 infection were therefore 41 % lower for BCG vaccinated individuals than for non-vaccinated individuals. However, the 95% CI (0.29-1.21) included 1 and the resulting p-value of 0.143 was statistically not significant. There was no significant association between age or sex and COVID-19 infection (table 1).

Age confounded the association between BCG vaccination status and COVID-19 infection. An age adjusted OR was estimated and compared to the crude OR for the association between BCG vaccination status and COVID-19 infection. The age adjusted OR showed a decrease of 15% to 0.50 (95% CI: 0.23-1.10) which was interpreted as an indication of confounding by age. Therefore, after removing the confounding effect of age, the evidence of an association between BCG vaccination

status and COVID-19 infections became stronger ($p = 0.083$). A LR test performed to test for interaction yielded a P value of 0.79, indicating no effect modification by age.

Sex modified the association between BCG vaccination status and COVID-19 infection. Adjustment for sex did not change the crude OR significantly, however for males and females markedly differing ORs were found (0.19 [95%CI: 0.05-0.69, $p= 0.005$] for males and 1.18 [95%CI: 0.47-2.94, $p= 0.876$] for females). A LR test performed to test for interaction yielded a P value of 0.015. The relationship between BCG vaccination status and COVID-19 infection thus seemed to be modified by gender with men having lower odds of acquiring a COVID-19 infection had they received a BCG vaccination compared to women.

The final model: Males had a lower risk of infection if BCG vaccinated and a higher risk if BCG non-vaccinated, compared to women. Based on the results obtained in the above investigation a final model of the relationship between BCG vaccination and COVID-19 infections was fitted that included age as a confounder and sex as an effect modifier. BCG vaccination status was associated with a lower likelihood of COVID-19 infection for men but not for women (ORs 0.13 and 1.04, respectively). For men, we found a highly significant association with 95% CIs ranging from 0.04-0.48 ($p=0.002$) while for women 95% CIs ranged from 0.40-2.71 ($p=0.938$). Likewise the effect of sex on COVID-19 infections was considered for non BCG vaccinated and BCG vaccinated participants individually. There was some evidence of a negative relationship between non-vaccinated males and females and COVID-19 infection suggesting that BCG non-vaccinated females have a lower risk of infection compared to men (and vice versa)(OR 0.29, 95%CIs 0.08-1.00, $p=0.05$). There was weak evidence of a positive relationship between BCG vaccinated males and females and COVID-19 infection suggesting that vaccinated females have a higher risk of infection compared to vaccinated men (and vice versa) (OR 2.32, 95%CIs 0.92-5.81, $p= 0.084$) (table 2).

BCG vaccination status did not seem to affect COVID-19 related symptoms or severity. All COVID-19 infected participants ($n=78$) were included to test for an association between COVID-19 related symptoms and BCG vaccination status. For all participants that reported their symptoms ($n=77$) no correlation between experiencing fever/shortness of breath/joint pains/ fatigue/dry cough/loss of smell and BCG vaccination status was found (overall estimate and conducted separately for males and females and two age groups [≤ 30 and >30 years of age] using Chi-squared test and Fisher's exact test as appropriate, P values not shown). There was some evidence of a correlation between loss of taste and BCG vaccination status among the young age group with more BCG vaccinated participants reporting loss of taste compared to non-vaccinated ($p=0.016$). However, this finding stands alone and, crucially, no correlation was seen between loss of smell and BCG vaccination status. Six participants did not report impact of symptoms on their state of health resulting in a sample size of 72. No correlation between impact of symptoms on state of health and BCG vaccination status was

131 found (overall estimate using Chi-squared: $p=0.258$; Fisher's exact test for age groups [≤ 30 and >30
132 years of age]: $p = 1.000$ and 0.734 , respectively; Fisher's exact test for males and females: $p= 0.563$
133 and 0.383 , respectively).

134

BCG vaccination certificate available ?

YES

**BCG vaccination
documented**

YES

BCG vaccinated

NO

**Born in East Germany
before 1990**

**Born in West Germany
or
Born in East Germany after
1990**

BCG vaccination

- memory/report by a close relative
- **and** scar

YES

NO

BCG non-vaccinated

RECRUITMENT

questionnaires posted (n=800)



questionnaires returned (n=231)

ELIGIBILITY

participants were excluded (n=41)

- missing data on BCG status (n=11)
- missing data on COVID-19 status (n=22)
- missing data both on BCG and COVID-19 status (n=6)
- meanwhile received COVID-19 vaccine (n=2)



included for primary analysis (n=190)

participants were excluded (n=43)

- age >46 years, due to structural absence of BCG non-vaccinated participants



included in final analysis (n=147)

INCLUDED