

LETTERS

Childhood Bacille Calmette-Guérin vaccination seems to selectively protect adult males from COVID-19 infection

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.

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

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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

^aOdds ratios and 95% confidence intervals included within brackets.

^bp 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.

^aOdds ratios and 95% confidence intervals included within brackets.

^bp values were derived by logistic regression models (Wald test), values <0.05 were considered significant.

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.

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