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Efficacy of BCG vaccination on incidence, severity and clinical progression of COVID-19: A BCG-REVAC population analysis

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ABSTRACT

Background: Can vaccination with Bacille Calmette-Guérin prevent clinical progression of COVID-19? Data from the BCG-REVAC trial was archived in a database, creating an excellent opportunity to link it to notified cases of COVID-19 to evaluate the efficacy of BCG against incidence, severity and clinical progression to severe COVID-19 when given at birth day, at school age as a first dose or as a second dose.

Methods: This study was conducted in the population of the BCG-REVAC cluster randomisation trial including 354,403 schoolchildren, aged 7 to 14 years, from 767 schools from two cities, Salvador and Manaus. Cases of COVID-19 from the System for Notification of Infectious Diseases and the System for Notification of Severe Respiratory Illnesses were record linked to BCG-REVAC population. The exposure was Vaccination or revaccination obtained by the BCG-REVAC. The outcomes of interest in this study were incidence COVID-19; incidence of severe COVID-19; and clinical progression of COVID-19. This project was approved by the Ethics Committee of the Institute of Collective Health, Federal University of Bahia, Brazil.

Results: The neonatal dose and a first dose of BCG at school age protect against the incidence of severe COVID-19 in multivariate models, whose efficacies were 30 % (95 %CI:1–51) and 64 % (95 %CI: 22–84), respectively. The neonatal dose showed an effect on severe clinical progression of symptomatic COVID-19 disease in COVID-19 infected subjects 39 % (95 %CI:11 % - 58 %).

Conclusion: Even 23 years after BCG vaccination and revaccination of school-age children our results suggesting a protective effect of BCG first dose against incidence of severe COVID-19 in infected individuals, a smaller effect of the neonatal dose and no effect of the second dose at school age.

1. Background

Can vaccination with *Bacille Calmette-Guérin* (BCG) prevent clinical progression of COVID-19? There is some evidence that BCG vaccination has a non-specific effect, decreasing frequency or severity of non-tuberculous respiratory diseases, including COVID-19 [1–7]. The biological plausibility of this non-specific effect is based on the concept of trained immunity [8–10]. Although in clinical trials, the non-specific protection by BCG against viral infections and reduction of viremia is shown to be associated with regulation of IL-1β, a key cytokine in the mechanism of the immune response [8,10,11] there is no clear understanding of how and in which situations BCG vaccination protects

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against infections and severity of disease.

There is evidence of an impact of BCG vaccination on the occurrence and severity of COVID-19 infections but it appears contradictory [7,8]. It is likely that the question needs to be defined more precisely, in terms of features of the BCG (age at vaccination, time since vaccination, region) and COVID-19 (incidence, clinical progression) and this requires further specific research [5].

In a systematic review that evaluated the results of clinical trials of BCG vaccination for protection against COVID-19, it was shown that six trials reported a beneficial effect of BCG vaccination against the disease, however with a low level of evidence. On the other hand, a negative effect of BCG on protection against Coronavirus was also observed in four trials [12].

In Brazil, a country with a high incidence of tuberculosis, universal BCG vaccination is recommended at birth [13,14]. A large community trial of the efficacy against tuberculosis of a second dose of BCG at school age (BCG-REVAC) was conducted in the early 2000s, with a population of over 300,000 schoolchildren. Brazil has an effective system of notification of infectious diseases, which includes notification of positive COVID-19 tests and of severe respiratory illness. Data from the BCG-REVAC trial were archived in a database, creating an excellent opportunity to link it to notified cases of COVID-19 to evaluate the efficacy of BCG against incidence, severity and clinical progression to severe COVID-19 when given at birth, at school age as a first dose or as a second dose (revaccination).

2. Methods

2.1. Study question

Does BCG vaccination at birth, school age, as a first or as second dose have an effect on incidence, severity and clinical progression of COVID-19 in a population who did not receive COVID-19 vaccination?

2.2. Study population and data sources

This study was conducted in the population of the BCG-REVAC cluster randomisation trial including 354,403 schoolchildren aged 7 to 14 years from 767 schools from two cities, Salvador and Manaus aimed to investigate efficacy of BCG vaccination on incidence of tuberculosis. The design of the BCG REVAC trial and its primary findings regarding to efficacy of tuberculosis are described in previous publications [15–17]. We assume that follow-up losses (deaths and migrations) were the same in both trial arms before the onset of pandemic. Currently, after 22 years of follow-up, this population is aged between 30 and 38 years.

2.3. Cases of COVID-19

Cases of COVID-19 in the study population were ascertained if they were notified from January 1, 2020 to August 3, 2021 to the *System for Notification of Infectious Diseases* (SINAN-COVID-19) or *System for Notification of Severe Respiratory Illnesses* (SIVEP-GRIPE). *SINAN-COVID-19* consist of compulsory notification by health units of positive tests for COVID-19 (RT-PCR or rapid test). The notification form has a field for clinical outcome where stay in an Intensive Care Unit and death can be reported. SIVEP-GRIPE was initially developed to notify Influenza-like-illness and later expanded to include Covid −19. The notification form has fields for information on hospitalization, stay in ICU and death.

Both SINAN-COVID and SIVEP-GRIPE were updated daily during the period of the study [18]. Subjects in the BCG-REVAC population not linked to SINAN-COVID nor SIVEP-GRIPE were considered as control subjects without COVID-19 infections during the study period.

2.4. Linkage process

Cases of COVID-19 from the *System for Notification of Infectious Diseases* (*SINAN-COVID)* and the *System for Notification of Severe Respiratory Illnesses (SIVEP-GRIPE)* were record linked to the BCG-REVAC population. The linkage of the data set from the different record systems was carried out by the Center for Integration of Data and Knowledge for Health (CIDACS) in a strict data protection environment and according to ethical and legal rules, using the CIDACS-RL-record linkage tool that uses the method of combining indexing algorithms and search [19–21]. Name, date of birth, sex and municipality of residence were used as matching variables between databases. The quality of the linkage process was assessed based on a manual review of a sample of peers. The sensitivity of the linkage between BCG-REVAC and SINAN-COVID and SIVEP-GRIPE in Salvador was 97.9 % and specificity of over 98.9 %. For the linkage between BCG-REVAC and SINAN-COVID and SIVEP-GRIPE in Manaus, sensitivity was about 100 % and specificity of over 99.1 %.

2.5. Outcomes: Incidence COVID-19, incidence of severe COVID-19 and clinical progression of COVID-19

The outcomes of interest in this study were incidence COVID-19 (comparative analysis between COVID-19 or not COVID-19 in population BCG-REVAC); incidence of severe COVID-19 (comparative analysis between severe COVID-19 or not COVID-19 in population BCG-REVAC); and clinical progression of COVID-19 (comparative analysis between severe COVID-19 or not severe COVID-19).

2.6. Exposure: BCG vaccination

At recruitment into BCG-REVAC trial, intradermal BCG vaccination status was ascertained through the examination of the left or right upper arm for the presence or absence of a BCG vaccine scar (and reading the childhood vaccination card when available). Children without scar at recruitment were presumed having not to have been vaccinated at birth; children with a scar at recruitment were presumed having received BCG at birth. Children from both groups were randomly allocated to intervention (BCG at school age) or control (no vaccination). Vaccination or revaccination by the BCG-REVAC trial team was noted in the database [15].

Subjects in the BCG-REVAC population were therefore classifiable into 4 groups: 1. no BCG; 2. BCG at birth only; 3. BCG at school age but not at birth; and 4. BCG both at birth and at school age. For this analysis of efficacy of BCG vaccination on incidence of COVID-19, incidence of severe COVID-19 and clincal progession of COVD-19, we used the BCG vaccination status obtained from the BCG-REVAC community trial database [15–17].

2.7. Statistical analyses

We conducted time-to-event analysis considering COVID-19 cases (date of notification) and severe COVID-19 cases (date of entry in intensive care unit (ICU)) as events in two different nested study populations. Population A) the entire BCG-REVAC trial population and Population B) the subpopulation of BCG-REVAC subjects reported in the surveillance system that were at least once tested positive for COVID-19 during the study period.

The efficacy analysis of the population A including all BCG-REVAC subjects aims to estimate the effect of BCG on incidence of COVID-19 and incidence of severe COVID-19. By contrast, the analyses in the populations B aim to estimate this effect on clinical progression in infected individuals separately. For both populations we used a dynamic cohort set up with late onset of exposure: for analyses with population A subjects enter the cohort at time of BCG-REVAC randomisation but enter at risk at the date of the first COVID case registered in Brazil (26 February 2020). For the analysis with population B, the person enters at risk for clinical progression at the date of confirmed COVID-19 infection (register of date of notification). We defined the date for clinical

progression as the day of ICU hospitalization due to severe clinical COVID-19 disease. We fitted models in two different randomized subpopulations of the BCG REVAC to estimate the effect of the vaccination: analysis 1 including all subjects with one BCG scar at school age aimed to estimate the effect of a second BCG dose at school age and analysis 2 including all subjects without BCG scar at school age aimed to estimate the effect of a first BCG dose.

In addition, we used the population of the control arm of the BCG trial to estimate the effect of a neonatal dose by comparing subjects with and without BCG scar at birth. All models were multivariate Cox proportional hazards models adjusted for important predictor variables assumed to be associated with incidence and severity of COVID-19 available in the database: sex, age, socio-economic factors, race/color and comorbidity. We derived from this models multivariate hazard ratios (HR) and 95 % confidence interval by comparing subjects vaccinated and not vaccinated at birth or at school age (effect of first or second dose at school age) and with and without bcg scar at birth, resp. (effect of neonatal dose). All models were fit using robust variance estimation aimed to adjust for clustering by school. Statistical analysis was conducted using STATA.

2.8. Ethics

This project was approved by the Ethics Committee of the Institute of Collective Health (ISC), Federal University of Bahia, Brazil (Registration number 4,067,252).

3. Results

For the period analyzed, 1,148,152 cases of COVID-19 were recorded in Manaus and 235,976 cases of COVID-19 in Salvador in the SINAN-COVID and SIVEP-GRIPE information systems. Of these, 37,359 (3.25 %) and 15,841 (6.71 %) people were paired with BCG-REVAC, respectively.

Overall of 354.429 study subjects recruited in BCG-REVAC, 52,923 adults were notified with COVID-19; 14,731 (28.0 %) individuals had a scar, and were not vaccinated at school; 15,601 (29,6 %) with second dose of BCG at school age; 2743 (5.2 %) individuals had no scar, and were not vaccinated at school age and 3135 (6.0 %) had no scar and were vacinated at school age. In total, there were 314 severe cases of COVID-19 in the BCG-REVAC population, 94 (29.9 %) in the group with a second dose of BCG at school age and 81 (25.8 %) in the group without vaccination at school age; 24 (7.6 %) in the group no scar and not vaccinated at school; 12 (3.8 %) in the group no scar and vaccinated at school (Table 1).

In general, regarding cases of COVID-19, 50.5 % were male, 67.1 % were afro-descendent (black and brown), 49.4 % had between 33 and 36 years old, 30.0 % had an average family income of more than 76 (score) and 28.2 % without comorbidity; while severe cases of COVID-19, 53.8 % were female, 92.3 % were afrodescedent, 51.3 % had between 33 and 36 years old, 30.6 % had an average family income of more than 76 (score) and 79.0 % without comorbidity (Table 1).

3.1. Efficacy on incidence of COVID-19 in the REVAC population

In the univariate and multivariate analysis of the efficacy on incidence COVID-19 no protection was observed from the neonatal dose (VE = 1 %; 95 %CI: −4 % to 7 %), first (VE = 3 %; 95 %CI: −9 % - 13 %) or second (VE = 0 %; 95 %CI: −5 % - 5 %) doses at school age. (Table 2 and 5).

3.2. Efficacy on incidence of severe COVID-19 in the REVAC population

The neonatal dose and a first dose of BCG at school age protect against the incidence of severe COVID-19 in multivariate models, whose efficacies were 30 % (95 %CI:1–51) and 64 % (95 %CI: 22–84), respectively. For the second dose at school age, there was no effect observed on incidence of severe COVID-19 (Table 3 and 5).

Table 1
Characterization of the study REVAC population.

Variables	REVAC population (N=354.429)						
	Cases of COVID-19 (n=52,609)		Non cases of COVID-19 (n=301,506)		Severe cases of COVID-19 (n=314)	p-value	
	n	%	n	%	n	%	<0.000
Vaccination Status							
Scar, not vaccinated at school age	14,731	28.0	83,592	27.7	81		25.8
2nd dose of BCG at school age (intervention)	15,601	29.6	89,915	29.8	94		29.9
No scar, not vaccinated at school age	2,743	5.2	16,095	5.3	24		7.6
No scar, vaccinated at school age	3,135	6.0	18,007	6.0	12		3.8
Sex							
Female	25,889	49.2	149,412	49.5	169	53.8	0.238
Male	26,394	50.2	152,094	50.5	145	46.2	
Race/Color							
White	3,771	7.2	3,771	8.7	13	4.8	<0.001
Black	3,335	6.3	3,335	7.7	15	5.5	
Brown	33,377	64.1	33,377	77.4	238	87.8	
Yellow	2,502	4.7	2,502	5.8	04	1.5	
Indigenous	112	0.2	112	0.3	01	0.4	
Age (years)							
<33	12,952	24.6	87,858	24.8	105	33.4	<0.001
≥33 and <36	26,005	49.4	175,794	49.7	161	50.3	
≥ 36	13,340	25.3	90,463	25.5	48	15.3	
Socioeconomic (average household income)							
0 – 25	894	1.7	6,692	1.7	7	2.2	0.759
26 – 50	3,021	5.7	20,434	5.8	13	4.1	
51 – 75	9,553	18.1	64,542	18.2	63	20.1	
76 – hi	15,783	30.0	106,833	30.2	96	30.6	
*Manaus**	23,042	43.8	156,198	44.1	135	43.0	
Comorbidities							
No	14,849	28.2	14,849	98.7	248	85.5	<0.001
Yes	199	0.4	199	1.3	42	14.5	

Table 2
Efficacy of the first and second BCG dose at school age (VE in %) on incidence of COVID-19 in the REVAC population.[1]

Vaccination Status	Vaccine Efficacy *(95 %CI)*			
	N	Events (Covid 19 infection)	*Univariate Models*	*Multivariate Models*[2]
1st dose at school age	39,980	5878	-2 (−7 to 4)	3 (−9 to 13)
2nd dose at school age	203,838	30,331	2 (0 to 4)	0 (−5 to 5)

VE = Vaccine Efficacy (%).
[1] Assumption: follow-up losses (deaths and migrations) were the same in the groups compared before the start of the pandemic.
[2] Adjusted by race/color, socioeconomic, sex, age, comorbidity.

Table 3
Efficacy of the first and second BCG dose at school age (VE in %) on incidence of severe COVID-19 in the REVAC population.[1]

Vaccination Status	Vaccine Efficacy *(95 %CI)*			
	N	Event (ICU hospitalization or death due to covid-19)	*Univariate Models*	*Multivariate Models*[2]
1st dose at school age	39,980	36	56 (11 to 78)	64 (22 to 84)
2nd dose at school age	203,838	173	−11 (−50 to 18)	−21 (−70 to 13)

VE = Vaccine Efficacy (%).
[1] Assumption: follow-up losses (deaths and migrations) were the same in the groups compared before the start of the pandemic.
[2] Adjusted by race/color, socioeconomic, sex, age, comorbidity.

3.3. Efficacy on severe clinical progression of COVID-19 in the subpopulation of COVID-19 infected subjects of the REVAC population

The first dose at school age did also show a vaccine efficacy of 45 % (95 %CI: −26 % - 76 %) on this endpoint, however without statistical significance. There was no effect for the second dose at school age (Table 4). The neonatal dose showed an effect on severe clinical progression of symptomatic COVID-19 disease in COVID-19 infected subjects an effect of 39 % (95 %CI:11 % - 58 %) (Table 5).

4. Discussion

Our results pointed out the protective effect of a neonatal BCG dose and a first BCG dose at school age on incidence of severe COVID-19 disease and progression to severe clinical COVID-19 disease in COVID-19 infected individuals even 20 years after vaccination. This is an important and unique finding since other studies and trials have not been able to measure the effect of a single dose in protecting against severity of COVID-19. In contrast, the BCG revaccination at school age in a population who received neonatal BCG did not protect against incidence of COVID-19 infection or severe symptomatic COVID-19 disese nor clinical progression 20 years after vaccination.

Table 4
Efficacy of the first and second BCG dose at school age (VE in %) on severe clinical progression of symptomatic COVID-19 diseases in subjects with confirmed COVID-19 infection.[1]

Vaccination Status	Vaccine Efficacy *(95 %CI)*			
	N (Covid-19 infected indivduals)	Events (ICU hospitalization or death due to covid-19)	*Univariate Models*	*Multivariate Models*[2]
1st dose at school age	5878	30	23 (−59 to 62)	45 (−26 to 76)
2nd dose at school age	30,331	144	−2 (−42 to 26)	−4 (−51 to 29)

VE = Vaccine Efficacy (%).
[1] Assumption: follow-up losses (deaths and migrations) were the same in the groups compared before the start of the pandemic.
[2] Adjusted by race/color, socioeconomic, sex, age, comorbidity.

This lack of protection from revaccination is consistent with two multicentre randomized double-blind placebo-controlled clinical trials designed to estimate BCG revaccination efficacy in healthcare professionals in Poland and South Africa that showed no protection by BCG revaccination against severe COVID-19 disease and hospitalization [22,23]. However, another randomized double-blind clinical trial which evaluated the occurrence of COVID-19 in 516 elderly Greek citizens revaccinated with BCG or placebo and followed for 6 months, recorded only six episodes of severe COVID-19 during the study, requiring hospitalization, of which five patients received a placebo and one person received BCG [24].

Some studies had shown that after BCG induction prototypical innate immune cells exhibit modifications in functional programming which increases responsiveness after secondary stimulation by pathogens, increasing the ability to eliminate infections. This trained immunity mechanism is explained by epigenetic reprogramming and may explain the mediation of nonspecific protective effects induced post-vaccine [25–29].

Another study that investigated the immunomodulatory effects of BCG on in vitro immune responses to SARS-CoV-2 showed that BCG modulates cytokine production and T cell phenotypes suggesting that the vaccine can suppress some of the cytokines (IL-6, TNF-alpha and IL-10) and is consistent with a protective immune response in severe cases of COVID-19 [30].

In a systematic review, regarding the analysis of the occurrence of severe COVID-19, it was interpreted that it is possible that BCG vaccination improves immune responses to SARS-CoV-2 that lead to more symptomatic diseases, while reducing those associated with to serious illnesses (hospitalization and deaths), inducing more effective viral elimination and reducing the cytokine storm [12].

An important aspect of this evaluation was the possibility of analyzing efficacy of vaccination or revaccination at school age with large randomized population decades after vaccination. A limiting factor was the lack of original observed clinical parameters, rather than information for notifications, for a better characterization of severity. A further limitation is that the estimate of the efficacy of the neonatal dose might be biased due to confounding since it was derived from a non randomized comparison of subjects with and without BCG scar at birth in the group control arm of the BCG trialtal dose by comparing.

5. Conclusion

Even 23 years after BCG vaccination and revaccination of school age children our results suggesting a protective effect of BCG first dose against incidence of severe COVID-19 in infected individuals, a smaller effect of the neonatal dose and no effect of the second dose at school age.

CRediT authorship contribution statement

Ramon Andrade de Souza: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Florisneide Rodrigues Barreto:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Carla Cristina Oliveira de Jesus Lima:** Supervision, Writing – review & editing. **Marcio Santos da Natividade:** Writing – review & editing. **Carlos Antônio de Souza Teles Santos:** Data curation, Formal analysis, Methodology, Writing –

Table 5
Efficacy of the neonatal dose (VE in %) on incidence of COVID−19 infection and incidence of severe COVID-19 disease in the control arm of the REVAC population (A) or severe clinical progression of symptomatic COVID-19 disease in subjects with confirmed COVID-19 infection (B).[1]

A) Vaccine Efficacy *(95 %CI)*						
N (BCG REVAC control arm)	Events (Covid-19 infection)	*Univariate Models*	*Multivariate Models*[2]	Events (ICU hospitalization or death due to covid-19)	*Univariate Models*	*Multivariate Models*[2]
173,744	25,828	-1 (−3 to –2)	1 (−4 to 7)	157	27 (0 to 47)	30 (1 to 51)

B) Vaccine Efficacy *(95 %CI)*			
N (Covid-19 infected indivduals)	Events (ICU hospitalization or death due to covid-19)	*Univariate Models*	*Multivariate Models*[2]
25,828	145	39 (15 to 56)	39 (11 to 58)

VE = Vaccine Efficacy (%).
[1] Assumption: follow-up losses (deaths and migrations) were the same in the groups compared before the start of the pandemic.
[2] Adjusted by race/color, socioeconomic, sex, age, comorbidity.

review & editing. **Maria Yury Ichihara:** Writing – review & editing. **Marcos Pereira:** Writing – review & editing. **Daniel Barros de Castro:** Writing – review & editing. **Bernd Genser:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Laura Cunha Rodrigues:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Maurício Lima Barreto:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Susan Martins Pereira:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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Data availability

Data will be made available on request.

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