ORIGINAL ARTICLE

Association between BCG vaccination and tuberculosis diagnosis: analysis by life stage and clinical characteristics

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ABSTRACT

Objective: To determine the association between BCG vaccination status and tuberculosis diagnosis across different life stages and clinical features in patients treated at the Dirección de Redes Integradas de Salud (DIRIS) Lima Sur from 2019 to 2022.

Materials and Methods: This cross-sectional study used secondary data from the Sistema de Información Gerencial de Tuberculosis (SIGTB). A census sampling approach was employed, incorporating records from 2019 to 2022. Absolute and relative frequencies were calculated, and Chi-square (χ^2) tests were used for comparisons. Logistic regression analysis was conducted to evaluate associations among variables, and Odds Ratios (OR) were computed.

Results: The study included a total of 8,298 participants. No significant association was found between BCG vaccination and the occurrence of extrapulmonary tuberculosis (EPTB) (OR = 0.92; 95% CI = 0.81–1.05; p = 0.232) or pulmonary tuberculosis (PTB) (OR = 1.02; 95% CI = 0.99–1.05; p = 0.215). These findings suggest that BCG vaccination does not confer a clear protective effect in the analyzed population. However, when stratified by age, BCG vaccination demonstrated a significant protective effect against EPTB in children under five years old (OR = 0.23; 95% CI = 0.13–0.42; p < 0.001).

Conclusions: No statistically significant association was identified between BCG vaccination and the presence of either EPTB or PTB, indicating that its protective effect remains inconclusive in the general study population. Nevertheless, stratified analysis by age demonstrated a significant protective effect of BCG vaccination against EPTB specifically in children under the age of five.

Keywords: Tuberculosis; *Mycobacterium tuberculosis*; BCG Vaccine; Tuberculosis, Pulmonary (Source: MeSH)

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Asociación entre la vacunación BCG y el diagnóstico de tuberculosis: un enfoque por etapas de vida y sus características clínicas

RESUMEN

Objetivo: Determinar la asociación entre el estado vacunal BCG y el diagnóstico de tuberculosis por etapas de vida y características clínicas en pacientes atendidos en la Dirección de Redes Integradas de Salud (DIRIS) Lima Sur entre el periodo 2019-2022.

Materiales y métodos:
Estudio transversal que empleó datos secundarios del Sistema de Información Gerencial de Tuberculosis (SIGTB). Se realizó un muestreo censal de los registros correspondientes al periodo 2019-2022 en el sistema SIGTB. Se utilizaron frecuencias absolutas y relativas, y la prueba de Chi-cuadrado (χ2) para comparaciones. Para determinar la asociación entre variables, se utilizó la prueba de regresión logística y se elaboró un modelo con Odds Ratio ajustado (ORa). El modelo se ajustó por edad categorizada.

Resultados: El estudio incluyó a 8 298 participantes. No se encontró una asociación significativa entre la vacunación con BCG y la presencia de tuberculosis extrapulmonar (TBEP) (OR = 0,92; IC 95 % = 0,81-1,05; p = 0,232) ni con la tuberculosis pulmonar (TBP) (OR = 1,02; IC 95 % = 0,99-1,05; p = 0,215). Estos hallazgos sugieren que la vacunación no tiene un efecto protector claro en la población analizada. Al estratificar por edad, se observó que la vacunación con BCG solo protegió significativamente contra la TBEP en niños menores de 5 años (OR = 0,23; IC 95 % = 0,13-0,42; p < 0,001).

Conclusiones: No se identificó una asociación estadísticamente significativa entre la vacunación con BCG y la presencia de TBEP o TBP, lo que indica que su efecto protector no es concluyente en la población general estudiada. Sin embargo, al realizar un análisis estratificado por edad, se observó que la vacunación con BCG presentó un efecto protector significativo contra TBEP únicamente en niños menores de 5 años.

Palabras clave: Tuberculosis; *Mycobacterium tuberculosis*; Vacuna BCG; Tuberculosis pulmonar (Fuente: DeCS)

INTRODUCTION

The World Health Organization (WHO) estimates that one-third of the global population is infected with Mycobacterium tuberculosis, the bacillus responsible for tuberculosis (TB), resulting in approximately 3 million deaths annually (1). TB is associated with high morbidity and mortality, and accumulating evidence indicates a significant burden of morbidity and mortality due to the sequelae of TB (1, 2). In response to the TB epidemic, the WHO proposed the "End TB Strategy," which aims for a 95.0% reduction in TB mortality by 2035 (1, 3–5).

Diagnosing TB is complex because of its varied clinical presentations and the absence of pathognomonic symptoms (6). Age is a significant determinant in TB epidemiology, influencing clinical presentation, disease progression, and therapeutic efficacy. These variations are primarily linked to age-related immunological changes (7, 8).

Age-associated changes in the composition and function of lung cells are characterized by increased inflammation and oxidative stress, which impair pulmonary homeostasis and increase susceptibility to M. tuberculosis infection (8).

Age-specific social patterns may contribute to differing risks of tuberculosis transmission among age groups, as seen in other respiratory diseases (7, 9, 10). In general, there is a need to understand the driving mechanisms behind significant age disparities in the burden of tuberculosis; this information is valuable for planning control measures (7). Achieving these aims requires a more equitable deployment of existing interventions and the development of new tools for the prevention, diagnosis, and treatment of tuberculosis (11).

As a preventive measure, the bacilli Calmette-Guérin (BCG) vaccine, an attenuated vaccine capable of inducing an adaptive immune response, was developed and is considered a cornerstone of global efforts to combat tuberculosis (12, 13). Each year, more than 90.0% of newborns worldwide receive the BCG vaccine; in the Americas, coverage reaches approximately 95.0% to prevent active TB (14–16). BCG is administered to newborns within hours or days after birth, and its protective effects against tuberculous meningitis and miliary tuberculosis exceed 70.0%, while protection against pulmonary tuberculosis (PTB) averages 52.0% (14, 16).

Key questions remain regarding the efficacy of the BCG vaccine in preventing TB, particularly its protection against PTB (17). Studies have yielded variable results, with some reporting high levels of protection and others showing little to none. Factors such as exposure to environmental mycobacteria, timing of vaccination, and the rigor of diagnostic criteria may contribute to this variability (17).

There is limited information on its impact across different life stages. These uncertainties hinder global TB control efforts and the development of new vaccines. In this context, this study aimed to determine the association between BCG vaccination status and TB diagnosis by life stage and clinical characteristics in patients attending the Dirección de Redes Integradas de Salud Lima Sur (DIRIS Lima Sur) between 2019 and 2022.

MATERIALS AND METHODS

Study design

This study employed a cross-sectional design and utilized secondary data from the Sistema de Información Gerencial de Tuberculosis (SIGTB). This system collects clinical and epidemiological data on tuberculosis at the national level. For our analysis, we focused specifically on data from the DIRIS Lima Sur, including participants who received a tuberculosis diagnosis between 2019 and 2022.

Participants

The initial population consisted of 8,325 registered individuals. We conducted census sampling. After applying the inclusion and exclusion criteria, 8,298 participants remained (Figure 1), all of whom had a registered diagnosis of tuberculosis in the Tuberculosis Control Program at health facilities within DIRIS Lima Sur during the study period.

Variables of interest

The dependent variable was tuberculosis diagnosis. A case was defined as any person diagnosed with TB, classified for analysis as pulmonary (PTB) or extrapulmonary (EPTB), with a positive result by smear microscopy, culture, or rapid molecular test, and registered in the SIGTB by the health facility, regardless of whether treatment was initiated (18). The independent variable was BCG vaccination status (vaccinated or not vaccinated) as recorded in the SIGTB. No cases of concurrent PTB and EPTB were reported.

Inclusion and exclusion criteria

The inclusion criteria were patients with a confirmed diagnosis of PTB or EPTB registered in the SIGTB of DIRIS Lima Sur between January 2019 and December 2022, regardless of whether treatment was initiated (see appendices). A patient was classified as "vaccinated" if their record indicated BCG immunization, as evidenced by a documented scar or a vaccination entry in the SIGTB. We excluded patients whose records in the SIGTB had more than 20.0% missing data for the main variables, as well as those who attended health facilities not registered in the SIGTB during the study period.

Data collection

We requested the variables of interest from the Portal de Transparencia del Estado Peruano. The information was specifically obtained from the Programa de Control de Tuberculosis data via the SIGTB. These data were linked with the HIS, NETLAB (from the Instituto Nacional de Salud), and Noti TB (from the Centro Nacional de Epidemiología, Prevención y Control de Enfermedades) systems. All procedures complied with data protection and confidentiality standards. The database was obtained under Information Note No. D000441-2023-DGIESP-DPCTB-MINSA. Variables were recoded to align with the study's objectives.

Statistical analysis

Descriptive analysis was performed by tabulating categorical variables in terms of absolute and relative frequencies. For numerical variables, measures of central tendency and dispersion (mean ± standard deviation [SD] or median ± interquartile range [IQR]) were used. The χ^2 test compared sociodemographic characteristics between participants with PTB and those with EPTB. A logistic regression model was used to assess the association between the outcome variable (PTB vs. EPTB) and the main exposures (BCG vaccination status and age strata), reporting odds ratios (ORs) with 95% confidence intervals (95% CI) for both crude and adjusted models. Statistical significance was set at $p < 0.05$. Data cleaning and analysis were conducted in Stata v16 (StataCorp LLC, College Station, TX, USA).

Ethical considerations

This study was approved by the Institutional Research Ethics Committee of the Faculty of Human Medicine at Universidad de San Martín de Porres. We used the anonymized secondary SIGTB database, and all data were handled to preserve anonymity and confidentiality. The present research work is registered in the Portal de Proyectos de Investigación en Salud (PRISA) of the Instituto Nacional de Salud del Perú, with code EI00000003100.

RESULTS

During the 2019-2022 study period, a total of 8,325 confirmed participants with diagnostic criteria for tuberculosis were identified in the registry. After applying the exclusion criteria, 8,298 participants were included in the analysis (Figure 1).

Sociodemographic and clinical features

Out of a total of 8,298 participants, the results show that the largest proportion was male (n = 5,086; 61.3%). The mean age of the study population was 35.5 years (SD ± 17.4). Most participants were of Peruvian nationality (n = 8,157; 98.3%), and the locality with the highest prevalence of TB cases was Villa El Salvador, with 1,954 cases (23.6%).

Regarding health coverage, 89.9% (n = 7,453) of participants had some insurance, with Seguro Integral de Salud (SIS) being the most common, covering 88.1% (7,294 of the 7,453 insured participants).

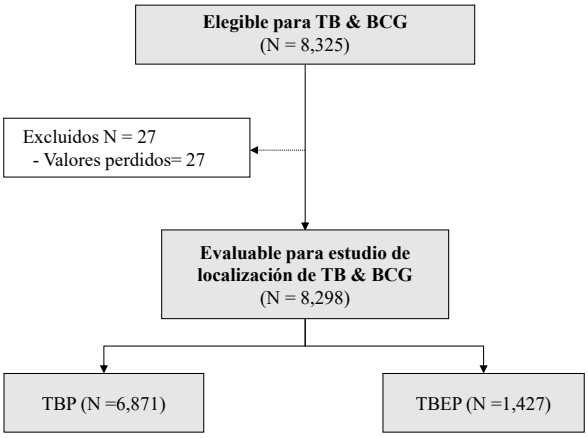


Figure 1. Flowchart depicting the study participants' selection process

Regarding comorbidities recorded in the SIGTB, diabetes was the most prevalent (11.1 %; n = 918), followed by human immunodeficiency virus (HIV) infection (6.1 %; n = 507) and cancer (0.8 %; n = 68). The frequencies of harmful habits self-reported by participants showed a prevalence of alcohol consumption of 12.3 %, followed by drug use (10.1 %) and smoking (8.2 %).

The results show that a history of contact with TB is more frequent in patients with PTB (18.1%) compared to those with EPTB (14.0%), with a statistically significant difference ($p = 0.002$). In terms of age group distribution, most cases were found in the adult group aged 18–59 years (75.6%; 1,078 of 1,427), with significant differences between the PTB and EPTB groups ($p = 0.001$). These results suggest that PTB is more common in young and middle-aged adults, with a higher prevalence of previous TB contact compared to EPTB. The results are described in Table 1.

Disease features and diagnosis

The findings regarding tuberculosis disease indicate that the most prevalent TB pattern is drug-sensitive TB (n = 7,038; 84.8 %), followed by drug-resistant TB (n = 1,260; 15.2 %). The analysis shows that drug-resistant TB is more frequent in pulmonary TB (PTB) compared to extrapulmonary TB (EPTB), with a statistically significant difference ($p < 0,001$).

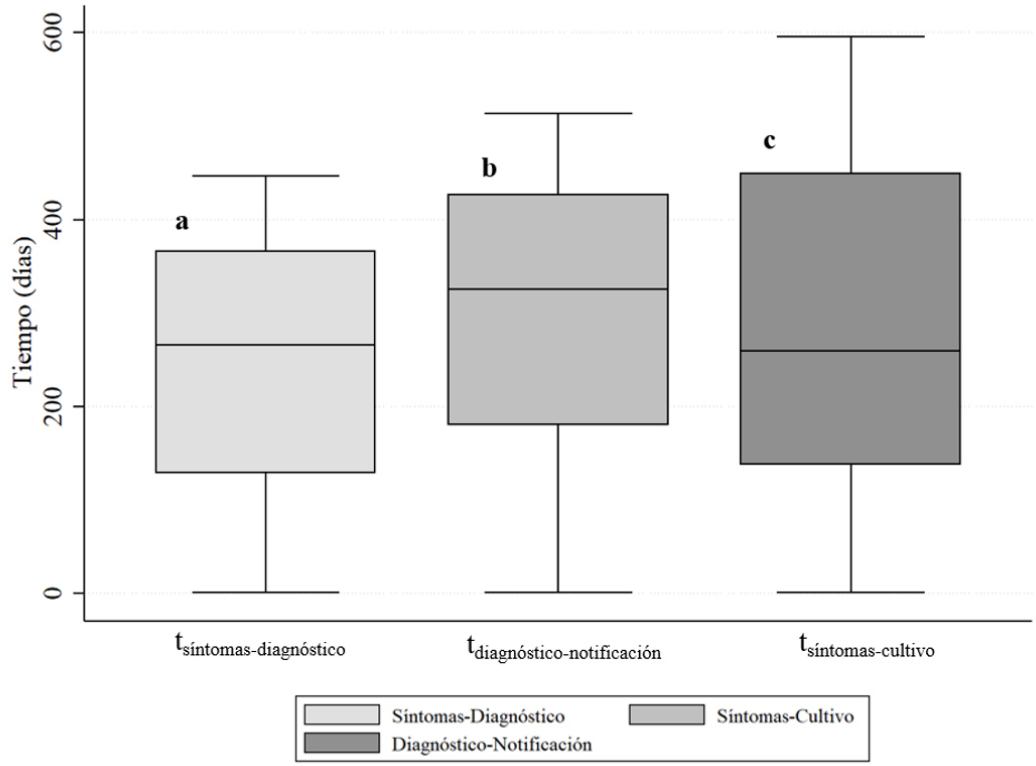
Regarding the times related to TB diagnosis, according to the data provided by the SIGTB program and after adjusting the variables (excluding missing, negative, and outlier values), the mean time from symptom onset to diagnosis was 247.3 days (SD ± 125.5). The mean time from diagnosis to notification was 290.0 days (SD ± 170.2). The mean time from symptom onset to culture collection was 303.9 days (SD ± 130.5), which was significantly longer in patients with PTB. This delay may reflect a more extended period required for microbiological diagnostic confirmation of this form of the disease (Figure 2).

Regarding the criteria used for the diagnosis of the form of TB, the microbiological criterion (positive smear microscopy) was the most commonly used for the diagnosis of PTB (77.6 %; n = 4,942), compared to the radiological criterion compatible

Table 1. Summary of the demographic and clinical characteristics of the study population. Participants are categorized into extrapulmonary tuberculosis (EPTB) and pulmonary tuberculosis (PTB) (n = 8, 298)

		PTB	EPTB	Total	p
	n	6, 871	1, 427	8, 298	
Men	n (%)	4,337 (63.1)	749 (52.5)	5, 086 (61.3)	0.000
Women	n (%)	2,534 (36.9)	678 (47.5)	3, 212 (38.7)	
Age (years)	mean (±SD)	35.5 (±17.4)	34.2 (±17.6)	35.3 (±17.4)	0.010
< 5 years	n (%)	32 (0.5)	9 (0.6)	41 (0.5)	0.001
5 to 12	n (%)	107 (1.6)	21 (1.5)	128 (1.5)	
13 to 17	n (%)	514 (7.5)	153 (10.7)	667 (8.0)	
18 to 29	n (%)	2,643 (38.5)	556 (39)	3,199 (38.6)	
30 to 59	n (%)	2,751 (40.0)	522 (36.6)	3,273 (39.4)	
> 60	n (%)	824 (12)	166 (11.6)	990 (11.9)	
Epidemiology					
Peruvian	n (%)	6,763 (98.4)	1,394 (97.7)	8,157 (98.3)	0.049
Locality					0.002
Chorrillos		1,048 (15.3)	205 (14.4)	1,253 (15.1)	
Lurín		196 (2.9)	42 (2.9)	238 (2.9)	
Pachacamac		421 (6.1)	86 (6.0)	507 (6.1)	
San Juan de Miraflores		1,546 (22.5)	263 (18.4)	1,809 (21.8)	
Santiago de Surco		366 (5.3)	107 (7.5)	473 (5.7)	
Villa El Salvador		1,598 (23.3)	356 (25)	1,954 (23.6)	
Villa María del Triunfo		1,575 (22.9)	333 (23.3)	1,908 (23.0)	
Others		121 (1.7)	35 (2.4)	156 (1.9)	
Seguro integral de Salud	n (%)	6,031 (87.9)	1,263 (88.7)	7,294 (88.1)	0.021
History of TB contact [7, 655]	n (%)	1,151 (18.1)	182 (14.0)	1,333 (17.4)	0.002
Medical history					
Harmful habits	n (%)				0.000
Smoking [7,016]		511 (9)	61 (4.6)	572 (8.2)	
Alcoholism [7,018]		781 (13.8)	85 (6.3)	866 (12.3)	
Drug addiction [8,023]		739 (11.2)	67 (4.8)	806 (10.1)	
Comorbidities	n (%)				0.000
Cancer		50 (0.7)	18 (1.3)	68 (0.8)	
Diabetes		827 (12)	91 (6.4)	918 (11.1)	
HIV		373 (5.4)	134 (9.4)	507 (6.1)	
Others		5,621 (81.8)	1,184 (83)	6,805 (82)	

TB: tuberculosis, **EPTB**: extrapulmonary tuberculosis, **PTB**: pulmonary tuberculosis, **SD**: standard deviation, **HIV**: human immunodeficiency virus
Data are summarized as counts (n, %) or means (±SD), unless stated otherwise.
A p-value of **<0.05** is considered statistically significant.
Values in parentheses indicate the total number used for frequency calculations and the applicable statistical tests (Chi-square or Student's t-test).
If no parentheses are present, the total study population (n = 8,298) is referenced.
Certain variables only present the most frequent category.
Comorbidities are identified based on SIGTB criteria and are self-reported.
The "Others" category includes Punta Hermosa, Punta Negra, San Bartolo, Pucusana, and Barranco (excluded due to frequency <1%).



a. Time from symptom onset to diagnosis (in days) based on recorded dates in the TB nominal information system (SIGTB) for both variables.
b. Time from diagnosis to culture sampling (in days).
c. Time from symptom onset to culture sampling (in days).

* Mean values (±SD) can be found in Table 2.

Figure 2. Box-and-whisker plots illustrating time intervals related to diagnosis recorded in the SIGTB system

with tuberculosis (35.7 %; n = 463) for the diagnosis of EPTB. Regarding the results of participants diagnosed with EPTB, 95.7% (n = 1,186) had a negative smear microscopy result, and 88.7% (n = 456) had a negative culture result (Table 2).

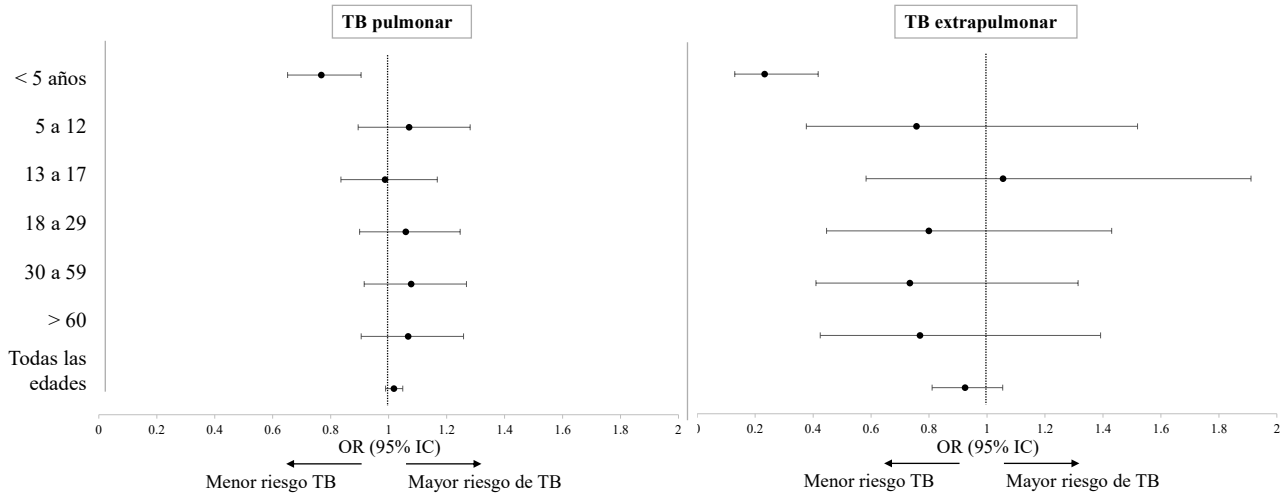
Association of BCG vaccination and tuberculosis diagnosis

Among the 8,298 participants, 1,427 developed EPTB; of these, 1,213 (85.0%) had evidence of BCG vaccination, compared to 214 (15.0%) unvaccinated participants (Table 2). No significant association was found between BCG vaccination and the presence of EPTB (OR = 0.92; 95 % CI = 0.81-1.05; p = 0.232) nor with PTB (OR = 1.02; 95 % CI = 0.99-1.05; p = 0.215), suggesting that vaccination does not have a clear protective effect in the analyzed population. However, when stratified by age, BCG vaccination only significantly protected against EPTB in children under 5 years of age (OR = 0.23; 95% CI = 0.13-0.42; p < 0.001). BCG vaccination appears to have a protective effect in the rest of the age groups (except the 5–12 years group). However, statistical significance was only reached in the under-5 years group (Table 3, Figure 3).

Table 2. Diagnostic parameters and outcomes for study participants, categorized by pulmonary tuberculosis (PTB) and extrapulmonary tuberculosis (EPTB) (n = 8,298)

		PTB	EPTB	Total	p
	n	6,871	1,427	8,298	
TB pattern	n (%)				0.000
Drug-resistant TB		1,175 (17.1)	85 (6.0)	1,260 (15.2)	
Drug-sensitive TB		5,696 (82.9)	1,342 (94.0)	7,038 (84.8)	
BCG vaccination status					0.490
No		948 (13.8)	214 (15.0)	1,162 (14.0)	
Yes		5,923 (86.2)	1,213 (85.0)	7,136 (86.0)	
Diagnosis					
Time to diagnosis (days)	mean (±SD)	248.3 (±125.4)	242.4 (±125.7)	247.3 (±125.5)	0.102
Time to notification (days)	mean (±SD)	290.4 (±170.3)	288.5 (±169.8)	290.0 (±170.2)	0.700
Time to culture collection (days)	mean (±SD)	306.0 (±130.0)	293.9 (±132.7)	303.9 (±130.5)	0.001
Diagnostic criteria [7,655]	n (%)				0.000
Clinical		82 (1.3)	155 (12.0)	237 (3.1)	
Epidemiological		4 (0.1)	12 (0.9)	16 (0.2)	
Clinical-epidemiological		60 (0.9)	130 (10)	190 (2.5)	
Radiological		988 (15.5)	463 (35.7)	1,451 (18.9)	
Smear microscopy		4,942 (77.6)	99 (7.6)	5,041 (65.8)	
Culture		138 (2.2)	27 (2.1)	165 (2.2)	
Others		155 (2.4)	410 (31.6)	565 (7.4)	
Smear result [5,963]					0.000
1 +		1,162 (24.6)	17 (1.4)	1,179 (19.8)	
2 +		1,645 (34.8)	10 (0.8)	1,655 (27.8)	
3 +		45 (1)	14 (1.1)	59 (1)	
Negative		1,669 (35.3)	1,186 (95.7)	2,855 (47.9)	
Paucibacillary		203 (4.3)	12 (1)	215 (3.6)	
Culture result [3,494]					0.000
1 +		577 (19.4)	6 (1.2)	583 (16.7)	
2 +		1,427 (47.9)	10 (2)	1,437 (41.1)	
3 +		46 (1.5)	14 (2.7)	60 (1.7)	
Contaminated		8 (0.3)	0 (0)	8 (0.2)	
Negative		691 (23.2)	456 (88.7)	1,147 (32.8)	
< 10 colonies		198 (6.6)	25 (4.9)	223 (6.4)	
< 20 colonies		33 (1.1)	3 (0.6)	36 (1)	
Treatment outcome [7,554]	n (%)				0.000
Abandoned		526 (8.4)	59 (4.5)	585 (7.7)	
Cured		3,962 (63.5)	413 (31.4)	4,375 (57.9)	
Deceased		342 (5.5)	117 (8.9)	459 (6.1)	
Failed		34 (0.6)	4 (0.3)	38 (0.5)	
Lost to follow-up		100 (1.6)	9 (0.7)	109 (1.4)	
Treatment completed		1,250 (20)	713 (54.2)	1,963 (26)	
Treatment incomplete		24 (0.4)	1 (0.1)	25 (0.3)	

TB: tuberculosis, **EPTB**: extrapulmonary tuberculosis, **PTB**: pulmonary tuberculosis, **BCG**: Bacillus Calmette-Guérin.
Data are summarized as counts (n, n %) or means (±SD), unless otherwise specified.
A p-value of <0.05 is considered statistically significant.
Values in parentheses indicate the total number used for frequency calculations and the applicable statistical tests (Chi-square or Student's t-test). If no parentheses are present, the total study population (n = 8,298) is referenced.



This stratified model employs separate binary logistic regression analyses, adjusting for the variable of interest and age. Age adjustments were made within each age stratum. Odds ratios (OR, 95% CI) for each subgroup are detailed in Table 3.

Figura 3. BCG vaccination status at birth in relation to pulmonary and extrapulmonary TB incidence, stratified by age

Table 3. Association between BCG vaccination status and tuberculosis incidence by age group (n = 8,298)

	EPTB		PTB	
Characteristics	OR	p	OR	p
BCG Status				
No	ref		ref	
Yes	0.92 (0.81 - 1.05)	0.232	1.02 (0.99 - 1.05)	0.215
Age				
< 5 years	0.23 (0.13 - 0.42)	0.000	0.77 (0.65 - 0.90)	0.002
5 a 12	0.76 (0.38 - 1.52)	0.433	1.07 (0.89 - 1.28)	0.456
13 a 17	1.06 (0.58 - 1.91)	0.859	0.99 (0.84 - 1.17)	0.885
18 a 29	0.80 (0.45-1.43)	0.450	1.06 (0.89 - 1.25)	0.49
30 a 59	0.73 (0.41-1.31)	0.298	1.08 (0.92 - 1.27)	0.368
> 60	0.77 (0.42-1.39)	0.385	1.07 (0.91 - 1.26)	0.438

Data in parentheses are 95 % CIs. OR = Odds ratio

DISCUSSION

The analysis performed suggests that BCG vaccination does not have an apparent protective effect against PTB or EPTB in the general population analyzed. However, it demonstrates a protective effect in specific subgroups. Significant demographic, epidemiological, and medical differences exist between PTB and EPTB. In a study by Zhu et al. (19) conducted in China, a sex ratio (male: female) of 1.7:1 for TB was reported. In our study, this ratio was 1.6:1, with a higher prevalence observed among adults aged 18–59 years.

Comorbidities such as HIV, diabetes, and cancer were more common in EPTB, while harmful habits (tobacco, alcohol, and drugs) were more prevalent in PTB. Immune responses to M. tuberculosis infection in HIV patients may play a dual role: on the one hand, contributing to the control of the infection and, on the other, aggravating it by triggering excessive inflammation that favors pulmonary cavitation. However, previous studies in diabetic mouse models infected with tuberculosis have shown a reduction in inflammation and mortality, suggesting the need to investigate whether these findings apply to humans (20).

Regarding the diagnostic factors analyzed concerning the form of TB (pulmonary and extrapulmonary), it was documented that the time to presentation (from the onset of symptoms to the first visit to the health facility) had a mean of 247,3 days, with great variation, suggesting a considerable delay in seeking care or detecting the disease. Furthermore, in the under-5 age group, the time from symptom onset to diagnosis appears shorter than in other age groups, and times appear to be more variable in younger and older adults (21).

The mean times from diagnosis to notification and from symptom onset to culture collection were also long (21). This observation could be attributed to factors influenced by patient recall bias, the quality of medical records, or additional delays in administrative processes, making comparison with other studies difficult (21, 22). More rigorous measures for TB reporting and notification are required, as timely identification and treatment are the cornerstone of efforts to eliminate TB by 2030. It is estimated that more than 80% of adults and children at risk for M. tuberculosis infection do not complete the cascade of care (23).

BCG vaccination is widely used and considered safe, but its protective effect diminishes over time, thereby reducing its population impact in regions with a high TB burden (20, 24). The clinical efficacy of a vaccine is defined as the percentage reduction in disease among vaccinated individuals that is attributable to immunization and is influenced by vaccine uptake, the degree of protection, and the duration of immunity (25). IIn Peru, data from 2020 indicated that 61.1% of children under 12 months had completed the national vaccination schedule, with a notable neonatal BCG vaccination coverage of 93.5% (26, 27). In the current study, we found that 86.0% of the registered individuals had documented evidence of BCG vaccination.

Age is a key factor in evaluating the protective effect of BCG vaccination against EPTB and PTB. In our study, a significant protective association was identified only in the subgroup under 5 years of age against EPTB; however, in the other age groups, a possible protective effect was suggested, although it did not reach statistical significance. Similarly, a case-control study in England evaluated the duration of BCG protection in a low-risk school population, finding protection for at least 20 years. Unlike our study, which analyzed EPTB and PTB separately, the study in question did not specify the anatomical site of the disease (although it is presumed that most cases were pulmonary). The efficacy of BCG in the English population was 48.0% (95% CI = 17%–68%) between 10 and 15 years post-vaccination, increasing to 55.0% (95% CI = 30%–71%) between 15 and 20 years, suggesting sustained long-term protection (15).

Our study indicates a potential protective effect of BCG vaccination against EPTB across most age groups, except for adolescents aged 13–17 years. A retrospective cohort study in Norway involving more than 380,000 persons found an efficacy of 49.0% (95% CI = 26%–65%) of BCG against pulmonary tuberculosis over 40 years. Vaccine effectiveness was significant in the first 10 to 19 years (63.0%, 95% CI = 32%–80%) but declined in the following decades without statistically significant results (14, 28, 29).

Several studies indicate that the BCG vaccine offers variable protection against severe and disseminated forms of tuberculosis, with an estimated efficacy ranging from 59.0% to 80.0%. However, BCG does not effectively protect HIV-positive children, who are at a significantly increased risk of developing tuberculosis.

In HIV-infected infants not receiving antiretroviral therapy, CD4+ T-cell responses are lower and remain deficient during the first year. Furthermore, HIV-exposed but uninfected infants exhibit reduced IFN-γ responses after vaccination. These data suggest a lower immunological efficacy of BCG in populations affected by HIV (12, 25, 30).

Because disseminated disease is more common among young children and is associated with high morbidity and mortality, neonatal BCG vaccination may be cost-effective as a pediatric intervention. However, it has a limited impact on tuberculosis transmission among adults (25).

Our study has both limitations and strengths. Among the limitations is that the study variables are limited to those available in the SIGTB, so some additional factors (such as nutritional status, blood glucose values, and specific treatment regimens, among others) could not be analyzed in depth. Another limitation is the potential misclassification bias associated with vaccination status, as the criteria (BCG scar, vaccination record) may not be uniform, and exposure misclassification is possible in the absence of a visible scar.

Although the present study uses an analytical approach within a population diagnosed with tuberculosis, allowing for a detailed characterization of the disease, the main limitation is the absence of a control group of healthy individuals, which prevents comparisons regarding the risk of developing TB associated with the vaccine. Comparisons are limited to differences between pulmonary and extrapulmonary manifestations. Furthermore, the database used does not provide detailed information on the immunological status of patients prior to tuberculosis diagnosis.

Among the strengths of this study is its considerable sample size (n = 8 298). Furthermore, this is one of the first studies to investigate the association between BCG vaccination and clinical forms of tuberculosis stratified by age in Peru and in low- and middle-income countries in general.

In conclusion, no statistically significant association was identified between BCG vaccination and the presence of EPTB or PTB in the general population studied, indicating that its protective effect is not conclusive overall in this group. However, when stratified by age, BCG vaccination showed a significant protective effect against EPTB only in children under 5 years of age.

Author contributions

CALS was responsible for data curation, formal analysis, software development, supervision, validation, writing, review, and editing. DKTG participated in conceptualization, funding acquisition, project administration, resource management, visualization, and writing the original draft.

Conflicts of interest

The authors declare no conflicts of interest.

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