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RESEARCH ARTICLE

Effect of BCG Vaccination on Tuberculosis and Its Severity in Children from a High-Burden Setting in Pakistan: A Hospital-Based Study

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ABSTRACT

Background: Tuberculosis (TB) remains a major public health issue in children in high-burden countries like Pakistan. The Bacille Calmette-Guérin (BCG) vaccine is administered at birth to protect against severe forms of TB, but its efficacy in high-burden settings is variable. This study evaluated the association of BCG vaccination with TB occurrence, severity, and disease classification in children from Lahore, Pakistan.

Methods: This hospital-based study analyzed routine data from 550 children younger than 15 years with presumptive TB at Gulab Devi Teaching Hospital (December 2022–March 2024). TB status was determined using a composite reference standard. BCG vaccination status was based on history and scar examination. Multivariable Poisson regression with robust variance estimation was used to calculate adjusted relative risks (aRR) and 95% confidence intervals (CI), adjusting for age group, sex, nutritional status, and history of TB contact.

Results: Of 550 children, 297 (54.0%) were BCG-vaccinated. TB was diagnosed in 322 (58.5%). BCG vaccination was not significantly associated with TB diagnosis (aRR 0.89, 95% CI 0.77-1.02, p=0.10), severe TB (aRR 0.95, 95% CI 0.81-1.11, p=0.52), pulmonary versus extrapulmonary TB (aRR 0.78, 95% CI 0.48-1.26, p=0.31), or confirmed versus unconfirmed TB (aRR 0.94, 95% CI 0.79-1.15, p=0.62). Independent risk factors for TB diagnosis included age 10 years or older (aRR 1.68, 95% CI 1.38-2.04, p<0.0001), female sex (aRR 1.25, 95% CI 1.07-1.47, p=0.005), and severe acute malnutrition (SAM; aRR 1.35, 95% CI 1.15-1.58, p<0.0001). SAM was strongly associated with severe TB (aRR 2.28, 95% CI 1.82-2.85, p=0.001).

Conclusions: In this high-burden setting, BCG vaccination showed no significant protective effect against TB occurrence or severity. Older age, female sex, and SAM were the primary risk factors. These findings underscore the urgent need for improved vaccination strategies, nutritional interventions, and next-generation vaccines to advance pediatric TB control toward Sustainable Development Goal 3.3.

Keywords: BCG vaccine, tuberculosis, children, severe acute malnutrition, Pakistan.

Introduction

Tuberculosis (TB) remains a major cause of morbidity and mortality in children, particularly in high-burden countries[1]. Globally, an estimated 1.2 million children and young adolescents (aged <15 years) developed TB in 2024, resulting in approximately 174,300 TB-related deaths among children (accounting for 14.2% of all TB deaths)[1]. Pulmonary TB (PTB) accounts for the majority of cases, however, young children are at markedly elevated risk of severe disseminated forms, including miliary TB and tuberculous meningitis, which carry high case-fatality rates when undiagnosed or untreated. Alarmingly, an estimated 43% of children with TB remain undiagnosed or untreated, underscoring persistent gaps in case detection and access to care[1]. The United Nations Sustainable Development Goals (SDGs), specifically SDG 3.3, target ending the TB epidemic by 2030, aiming for an 80% reduction in incidence and a 90% reduction in deaths compared to 2015 levels[2]. However, global progress remains slow, with only a modest decline in the TB incidence rate observed between 2023 and 2024[1]. In Pakistan, the fifth-highest TB-burden country globally (contributing 6.3% of cases), the incidence remains high, and mortality reductions lag, hindering SDG achievement[1].

Key barriers to progress in Pakistan include suboptimal Bacille Calmette-Guérin (BCG) vaccination coverage and efficacy in real-world settings, compounded by widespread malnutrition affecting 35–40% of children. Malnutrition markedly exacerbates TB susceptibility, disease progression, and treatment failure, with 63,000 undernourished TB cases reported in 2024[3]. The BCG vaccine, administered at birth in endemic regions, is the only licensed vaccine against TB and aims to protect against severe TB in infancy. However, its efficacy varies widely (0-80%) and is significantly diminished by factors such as severe acute malnutrition (SAM), high environmental mycobacterial exposure, differences in circulating *Mycobacterium tuberculosis* strains, host genetics, and waning immunity over time, limitations that are particularly pronounced in high-burden settings like Lahore, Pakistan[4-6]. Recent systematic reviews and individual-participant data meta-analyses confirm moderate protection (approximately 18% overall, with up to 37% in children under 5 years) against pediatric TB, but this wanes with age and is less effective against PTB in older children[6-8].

Additional risk factors, including household TB contact, SAM, female sex, older age, and socioeconomic deprivation, interact synergistically to drive the pediatric TB burden in resource-limited settings[9,10]. These multifactorial influences highlight the inadequacy of relying solely on neonatal BCG vaccination and underscore the urgent need for context-specific evidence to guide integrated control strategies. Despite Pakistan's high national BCG coverage (reported at 96%), real-world effectiveness in malnourished, high-transmission populations remains poorly characterized.[11] This hospital-based study, therefore, aims to evaluate the association of BCG vaccination status with TB occurrence, disease severity, and classification (pulmonary versus extrapulmonary, confirmed versus unconfirmed) among Pakistani children younger than 15 years. By addressing this evidence gap through rigorous multivariable analysis, we seek to inform comprehensive TB control strategies that integrate enhanced vaccination efforts with targeted interventions to address modifiable risk factors and accelerate progress toward SDG 3.3[2].

Methods

STUDY DESIGN AND POPULATION

This study used hospital routine data from 550 children aged <15 years with presumptive TB who presented and were assessed at the Gulab Devi Teaching Hospital, Lahore, Pakistan, from December 2022 to March 2024. Children were classified using a composite reference standard (CRS) as confirmed TB (microbiologically positive on gastric aspirate, sputum, stool, or bronchial lavage), unconfirmed TB (based on contact history, clinical or radiological findings in the absence of positive microbiology), or no TB (unlikely TB)[12]. Confirmed and unconfirmed TB cases were taken as TB cases, and anti-tuberculosis treatment (ATT) was initiated. Furthermore, children were classified as PTB, and extrapulmonary TB (EPTB), including tuberculous meningitis, abdominal TB and peripheral lymph node TB, based on the site involved. Further, TB cases were evaluated for severe and non-severe disease using WHO criteria[13]. Nutritional status was assessed and classified according to WHO criteria as Severe

Acute Malnutrition (SAM), moderate acute malnutrition (MAM) and normal[14]. Vaccination history was taken from the parent or guardian, and the BCG scar was observed. Children with a vaccination history and/or a BCG scar were considered BCG-vaccinated. A history of contact with a person with TB was defined as contact within the last 2 years. The study was ethically approved by the ethical review board of Gulab Devi Teaching Hospital, Lahore, Pakistan.

OUTCOME

The primary outcome of this study was each child's TB status, defined as a binary variable. Children were classified as either having TB (which includes both confirmed and unconfirmed TB cases) or not having TB (no TB). Secondary outcomes were disease severity, confirmed TB (determined by microbiological evidence from samples such as gastric aspirate, sputum, stool, or bronchial lavage), unconfirmed TB (based on contact history, clinical or radiological findings in the absence of positive microbiology), and TB site (pulmonary or extrapulmonary). Children who did not meet either criterion were considered unlikely to have TB and were categorized as no TB.

EXPOSURE VARIABLES

The primary exposure variable was BCG vaccination status, categorized as either vaccinated (presence of a vaccination history and/or a BCG scar) or unvaccinated. Other factors included age, divided into two groups: children younger than 10 years and those aged 10 years or older; sex, classified as male or female; and nutritional status, rigorously assessed according to WHO criteria and grouped as SAM, MAM, or normal nutritional status. In addition, TB contact history was recorded, defined as whether the child had been exposed to a person with TB within the preceding two years. These predictors were selected based on their established or potential influence on TB risk and were systematically included in both univariate and multivariable Poisson regression analyses to determine their relationship with TB status.

STATISTICAL ANALYSIS

Data analysis for this study involved a systematic approach to summarizing and comparing baseline characteristics and evaluating associations with TB outcomes. For continuous variables such as age, the mean and standard deviation (SD) were calculated to provide a measure of central tendency and variability within the study population. Categorical variables, including sex, nutritional status (normal, MAM, or SAM), BCG vaccination status, and history of TB contact, were summarized using frequencies and percentages to depict the distribution of these characteristics among participants.

To assess whether there were significant differences in categorical variables between groups (such as BCG vaccinated versus unvaccinated children), the chi-square test was employed. In cases where expected cell counts were small, Fisher's exact test was used as an alternative, providing an exact p-value for small sample sizes.

The association between baseline characteristics, including BCG vaccination status, and TB outcomes was estimated using generalized linear models. Specifically, models with a Poisson distribution and robust variance estimation were utilized to calculate both crude relative risks (RR) and adjusted relative risks (aRR), each accompanied by 95% confidence intervals (CI). Multivariable models were constructed to adjust for potential confounders that could influence the relationship between exposure variables and TB status. These confounders were specified a priori and included age group (children younger than 10 years vs. those 10 years or older), sex, nutritional status (normal, MAM, SAM), and history of TB contact within the previous two years. By including these variables in the model, the analysis aimed to isolate the effect of each predictor on TB risk while controlling other factors.

Statistical significance was determined using a two-sided p-value threshold of less than 0.05. All statistical analyses were conducted using Stata version 18.0 (Stata Corp, College Station, TX, USA).

Results

BASELINE CHARACTERISTICS

A total of 550 children aged <15 years were included. Table 1 shows their baseline characteristics stratified by BCG vaccination status. Overall, 297 (54.0%) children were BCG-vaccinated and 253 (46.0%) were unvaccinated. The mean age was similar between groups (10.0 ± 3.7 years vs 10.3 ± 3.3 years). BCG-vaccinated children were more likely to be female (54.5% vs 45.5%). Nutritional status and history of household TB contact were comparable between the vaccinated and unvaccinated groups.

Table 1. Baseline characteristics of children by BCG vaccination status (n=550)

Characteristic	BCG Vaccinated (n=297)	BCG Unvaccinated (n=253)	Total (n=550)
Age (in years)			
Mean (SD)	10.0 (3.7)	10.3 (3.3)	10.2 (3.5)
Age group (years)			
< 10 years	111 (37.4%)	84 (33.2%)	195 (35.5%)
≥ 10 years	186 (62.6%)	169 (66.8%)	355 (64.5%)
Sex			
Male	135 (45.5%)	83 (32.8%)	218 (39.6%)
Female	162 (54.5%)	170 (67.2%)	332 (60.4%)
Nutritional status			
Normal	124 (41.8%)	126 (49.8%)	250 (45.5%)
Moderate acute malnutrition (MAM)	76 (25.6%)	44 (17.4%)	120 (21.8%)
Severe acute malnutrition (SAM)	97 (32.7%)	83 (32.8%)	180 (32.7%)
History of TB contact			
No	210 (70.7%)	189 (74.7%)	399 (72.5%)
Yes	87 (29.3%)	64 (25.3%)	151 (27.5%)

TB DIAGNOSIS AND ASSOCIATED FACTORS

Figure 1 shows how TB classification is distributed among BCG-vaccinated and BCG-unvaccinated children in the study population (n=550). Overall, the proportion diagnosed with TB is similar in both groups.

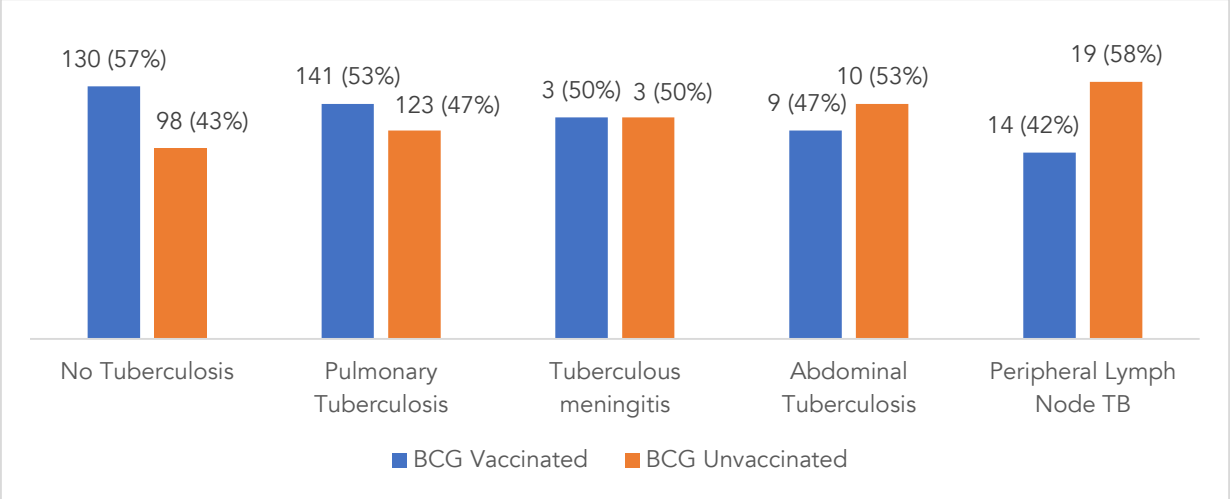

Figure 1: Number (%) of children with TB classification by their BCG vaccination status (n=550)

Of the 550 children, 322 (58.5%) were diagnosed with TB and 228 (41.5%) were not (Table 2). In both univariate and multivariable analyses, BCG vaccination was not significantly associated with TB diagnosis (aRR 0.89, 95% CI 0.77–1.02; p=0.10). Factors independently associated with TB diagnosis were aged ≥10 years (aRR 1.68, 95% CI 1.38–2.04; p<0.0001), female sex (aRR 1.25, 95% CI 1.07–1.47; p=0.005), and SAM (aRR 1.35, 95% CI 1.15–1.58; p<0.0001). History of TB contact was not associated with TB diagnosis.

Table 2: Comparison of baseline characteristics of children aged <15 years who had TB with those who did not have TB: univariate and multivariate analyses (n=550)

Characteristic	TB (n=322)	No TB (n=228)	RR (95% CI)	aRR (95% CI), p-value
Age group (years)				
< 10 years	77 (23.9%)	118 (51.8%)	Reference	Reference
≥ 10 years	245 (76.1%)	110 (48.2%)	1.75 (1.45-2.11)	1.68 (1.38-2.04), <0.0001
Sex				
Male	107 (33.2%)	111 (48.7%)	Reference	Reference
Female	215 (66.8%)	117 (51.3%)	1.32 (1.13-1.54)	1.25 (1.07-1.47), 0.005

Characteristic	TB (n=322)	No TB (n=228)	RR (95% CI)	aRR (95% CI), p-value
Nutritional status				
Normal	127 (39.4%)	123 (53.9%)	Reference	Reference
MAM	63 (19.6%)	57 (25.0%)	1.03 (0.84-1.27)	0.98 (0.80-1.21), 0.87
SAM	132 (41.0%)	48 (21.1%)	1.44 (1.24-1.68)	1.35 (1.15-1.58), <0.0001
History of TB contact				
No	233 (72.4%)	166 (72.8%)	Reference	Reference
Yes	89 (27.6%)	62 (27.2%)	1.01 (0.86-1.18)	1.05 (0.90-1.23),0.52
BCG vaccinated				
No	155 (48.1%)	98 (43.0%)	Reference	Reference
Yes	167 (51.9%)	130 (57.0%)	0.92 (0.80-1.06)	0.89 (0.77-1.02), 0.10

TB: Tuberculosis; RR: Relative Risk; aRR: Adjusted relative risk; CI: confidence interval; MAM: moderate acute malnutrition; SAM: severe acute malnutrition

SEVERITY OF TB

Figure 2 shows that, among children diagnosed with TB, severe TB accounts for the majority of cases in both BCG-vaccinated and BCG-unvaccinated groups. Overall, the distribution of TB severity appears similar by BCG status, suggesting no clear difference in severity patterns between vaccinated and unvaccinated children in this cohort.

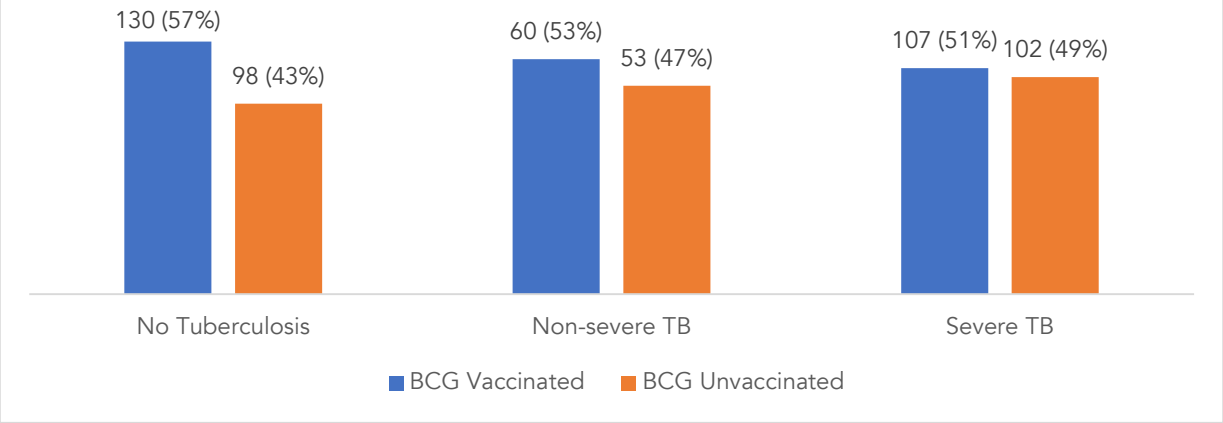

Figure 2: Number (%) of children with severity of TB by their BCG vaccination status (n=550)

Among the 322 children with TB, 209 (64.9%) had severe TB and 113 (35.1%) had non-severe TB (Table 3). BCG vaccination was not associated with severe TB in multivariable analysis (aRR 0.95, 95% CI 0.81–1.11; p=0.52). The only factor strongly and independently associated with severe TB was SAM (aRR 2.28, 95% CI 1.82–2.85; p=0.001). Age, sex, and history of TB contact were not significantly associated with severity.

Table 3: Comparison of baseline characteristics of children aged <15 years who had severe TB with those who did not have severe TB: univariate and multivariate analyses (n=322)

Characteristic	Non-severe (n=113)	Severe (n=209)	RR (95% CI)	aRR (95% CI) p-value
Age group (years)				
< 10 years	32 (28.3%)	45 (21.5%)	Reference	Reference
≥ 10 years	81 (71.7%)	164 (78.5%)	1.15 (0.93-1.41)	1.08 (0.88-1.33), 0.45
Sex				
Male	48 (42.5%)	59 (28.2%)	Reference	Reference
Female	65 (57.5%)	150 (71.8%)	1.27 (1.04-1.53)	1.18 (0.97-1.44), 0.09
Nutritional status				
Normal	76 (67.3%)	51 (24.4%)	Reference	Reference
MAM	31 (27.4%)	32 (15.3%)	1.26 (0.92-1.75)	1.22 (0.88-1.68), 0.23
SAM	6 (5.3%)	126 (60.3%)	2.38 (1.92-2.95)	2.28 (1.82-2.85), 0.001
History of TB contact				
No	76 (67.3%)	157 (75.1%)	Reference	Reference
Yes	37 (32.7%)	52 (24.9%)	0.87 (0.71-1.06)	0.92 (0.75-1.12), 0.40
BCG vaccinated				
No	53 (46.9%)	102 (48.8%)	Reference	Reference
Yes	60 (53.1%)	107 (51.2%)	0.97 (0.83-1.14)	0.95 (0.81-1.11), 0.52

RR: Relative Risk; aRR: Adjusted relative risk; CI: confidence interval; MAM: moderate acute malnutrition; SAM: severe acute malnutrition

PULMONARY VERSUS EXTRAPULMONARY TB

Among children with TB, 264 (82.0%) had PTB and 58 (18.0%) had EPTB (Table 4). BCG vaccination was not associated with the site of TB disease (aRR for PTB 0.78, 95% CI 0.48–1.26; p=0.31). No other baseline characteristics were significantly associated with PTB versus EPTB in the adjusted model.

Table 4: Comparison of baseline characteristics of children aged <15 years who had pulmonary TB with those who had extrapulmonary TB: univariate and multivariate analyses (n=322)

Characteristic	PTB (n=264)	EPTB (n=58)	RR (95% CI)	aRR (95% CI), p-value
Age group (years)				
< 10 years	59 (22.3%)	18 (31.0%)	Reference	Reference
≥ 10 years	205 (77.7%)	40 (69.0%)	0.70 (0.42-1.16)	0.72 (0.43-1.21), 0.22
Sex				
Male	85 (32.2%)	22 (37.9%)	Reference	Reference
Female	179 (67.8%)	36 (62.1%)	0.81 (0.50-1.32)	0.85 (0.52-1.39), 0.52
Nutritional status				
Normal	99 (37.5%)	28 (48.3%)	Reference	Reference
MAM	50 (18.9%)	13 (22.4%)	0.94 (0.52-1.70)	0.96 (0.53-1.74), 0.89
SAM	115 (43.6%)	17 (29.3%)	0.58 (0.33-1.03)	0.62 (0.35-1.10), 0.10
History of TB contact				
No	190 (72.0%)	43 (74.1%)	Reference	Reference
Yes	74 (28.0%)	15 (25.9%)	0.91 (0.53-1.57)	0.95 (0.55-1.64), 0.85
BCG vaccinated				
No	123 (46.6%)	32 (55.2%)	Reference	Reference
Yes	141 (53.4%)	26 (44.8%)	0.75 (0.47-1.21)	0.78 (0.48-1.26), 0.31

PTB: pulmonary Tuberculosis; EPTB: Extrapulmonary Tuberculosis; RR: Relative Risk; aRR: Adjusted relative risk; CI: confidence interval; MAM: moderate acute malnutrition; SAM: severe acute malnutrition

CONFIRMED VERSUS UNCONFIRMED TB

Of the 322 children with TB, 210 (65.2%) had microbiologically confirmed TB and 112 (34.8%) had unconfirmed TB (Table 5). BCG vaccination status was not associated with microbiological confirmation (aRR 0.94, 95% CI 0.79–1.15; p=0.62). Female sex (aRR 1.16, 95% CI 0.96–1.40; p=0.04) and SAM (aRR 1.35, 95% CI 1.10–1.65; p<0.001) were independently associated with confirmed TB.

Table 5: Comparison of baseline characteristics of children aged <15 years who had confirmed TB with those who had unconfirmed TB: univariate and multivariate analyses (n=322)

Characteristic	Confirmed TB (n=210)	Unconfirmed TB (n=112)	RR (95% CI)	aRR (95% CI), p-value
Age group (years)				
< 10 years	47 (22.4%)	30 (26.8%)	Reference	Reference
≥ 10 years	163 (77.6%)	82 (73.2%)	1.09 (0.89-1.33)	1.04 (0.85-1.26), 0.4
Sex				
Male	61 (29%)	46 (41.1%)	Reference	Reference
Female	149 (71%)	66 (58.9%)	1.22 (1.01-1.47)	1.16 (1.00-1.4), 0.04
Nutritional status				
Normal	70 (33.3%)	57 (50.9%)	Reference	Reference
MAM	37 (17.6%)	26 (23.2%)	1.07 (0.83-1.39)	1.02 (0.76-1.36), 0.63
SAM	103 (49%)	29 (25.9%)	1.42 (1.18-1.7)	1.35 (1.1-1.65), <0.001
History of TB contact				
No	159 (75.7%)	74 (66.1%)	Reference	Reference
Yes	51 (24.3%)	38 (33.9%)	0.84 (0.69-1.03)	0.86 (0.68-1.05), 0.10
BCG vaccinated				
No	103 (49%)	52 (46.4%)	Reference	Reference
Yes	107 (51%)	60 (53.6%)	0.96 (0.82-1.13)	0.94 (0.79-1.15), 0.62

TB: Tuberculosis; RR: Relative Risk; aRR: Adjusted relative risk; CI: confidence interval; MAM: moderate acute malnutrition; SAM: severe acute malnutrition

Discussion

This hospital-based study of 550 children with presumptive TB in a high-burden setting in Pakistan demonstrates that BCG vaccination was not associated with reduced risk of TB diagnosis, disease severity, or disease site. Instead, older age (≥10 years), female sex, and SAM emerged as the main independent risk factors for TB. These findings underscore the multifactorial nature of paediatric TB and align closely with evidence from other endemic regions, further emphasizing the limitations of relying solely on current neonatal BCG vaccination strategies in high-transmission, resource-limited settings[6-8].

BCG vaccination status showed no statistically significant protective association with TB diagnosis, severe disease, PTB versus EPTB, or microbiological confirmation in our cohort. Although BCG vaccination has been reported to provide protection against severe disseminated forms of TB, such as tuberculous meningitis and miliary TB, particularly during early childhood[15-17], its protective efficacy is known to decline with increasing age and varies considerably across populations and epidemiological settings[4,6,7,18]. The lack of significant protection observed in this study may reflect the well-recognized heterogeneity in BCG effectiveness and could be influenced by multiple factors, including high environmental mycobacterial exposure in Pakistan, differences in circulating *Mycobacterium tuberculosis* strains, host genetic susceptibility, malnutrition and other host-related factors, waning immunity over time, and geographical variation[6-8]. Recent 2025 meta-analyses, including individual-participant data analyses, confirm that overall protection against infection is modest (approximately 18%), with even lower effectiveness in high-incidence settings such as ours[6,8]. In addition, BCG vaccination coverage in this cohort was modest, with only 54% of children classified as vaccinated. This highlights the limitations of relying solely on neonatal BCG vaccination for pediatric TB control in high-burden settings.

A major finding of the study was the significant association between older age (≥10 years) and TB diagnosis. Children aged ≥10 years had a substantially higher risk of TB compared with younger children, which may reflect cumulative exposure to infectious contacts, increased social interaction, and waning immunity from neonatal BCG vaccination over time[6,7,9]. Previous studies and meta-analyses have similarly demonstrated reduced BCG effectiveness in older children and adolescents, particularly against PTB[6,7,9]. However, in the subgroup analysis comparing PTB and EPTB, no significant difference was observed between age groups, indicating that age influenced overall TB occurrence rather than the site of disease involvement[6,7].

Malnutrition, particularly SAM, emerged as the strongest and most consistent risk factor across analyses. SAM was independently associated with TB diagnosis, severe TB, and microbiologically confirmed TB, similar to other studies[16,19-21]. This finding is biologically plausible, as malnutrition impairs both innate and cell-mediated immunity, increasing susceptibility to infection and progression to severe disease[16]. The markedly higher proportion of SAM among severe TB cases highlights the synergistic relationship between undernutrition and TB severity. However, despite a higher proportion of SAM among PTB cases than among EPTB cases, this difference did not reach statistical significance, suggesting that malnutrition increases overall disease burden rather than determining disease site.

Female sex was independently associated with TB diagnosis, consistent with other researchers reporting a higher incidence among girls in low- and middle-income countries[22,23]. Biological mechanisms include estrogen-driven immune shifts favoring Th2 over Th1 responses, X-linked genetic factors (e.g., TLR8), and estrogen-mediated modulation of macrophages, which may predispose females to TB[24]. Social determinants, such as indoor crowding, malnutrition, stigma, and delayed care-seeking in urbanizing settings, further amplify vulnerability[25]. Interestingly, sex was not significantly associated with disease severity or with PTB versus EPTB distribution, suggesting that, while females may have increased susceptibility to TB infection or diagnosis, the disease phenotype remained similar across sexes.

History of household TB contact was not significantly associated with TB diagnosis, severity, or disease classification in adjusted analyses. Although household exposure is a recognised risk factor for pediatric TB[9], the lack of association in this cohort may reflect underreporting of contact history, undetected community transmission, or

uniformly high background exposure in this endemic setting. Similar findings have been reported in other high-burden populations where community transmission contributes substantially to pediatric TB incidence[9].

These results have profound implications for the TB control program in Pakistan and similar high-burden settings. Our findings of suboptimal BCG coverage (54% in the cohort vs. 96% nationally) and efficacy gaps in high-risk groups indicate that neonatal BCG alone is insufficient[11]. Strategies must prioritize improving coverage, developing next-generation vaccines, and evaluating booster regimens. While earlier smaller trials suggested modest benefit from BCG revaccination in adolescents (approximately 45% efficacy against sustained infection), a large 2025 phase 2b randomized trial in South Africa found no significant protection against sustained *M.tuberculosis* infection (hazard ratio 1.04)[5,26]. This recent evidence reinforces the urgent need for novel, more effective vaccines tailored to older children and adolescents in high-burden settings. Investments in new vaccines are cost-effective, as some researchers have shown, yielding $14 in economic benefits per $1 spent through reduced treatment costs and productivity losses[11,27]. The strong association between SAM and severe TB particularly highlights the need for nutritional interventions as an integral component of TB prevention and management programs. Addressing nutritional deficits through evidence-based interventions (like zinc or vitamin D supplementation) could reduce TB incidence by 20-30% and potentially enhance vaccine immunogenicity[19,27].

Strengths of this study include its relatively large sample size from a busy tertiary care public-sector hospital serving a high-burden population, balanced demographic representation, use of a composite reference standard for TB diagnosis, and rigorous multivariable Poisson regression modelling with robust variance estimation. Limitations involve potential recall bias for BCG status (via scar/card or parental report) and contact history, as well as possible reverse causality between malnutrition and TB and reliance partly on clinical diagnosis for unconfirmed TB cases. Despite these limitations, the findings provide valuable, context-specific insights into the complex interactions among BCG vaccination, malnutrition, demographic factors, and TB outcomes among children in a high-burden setting and offer actionable evidence for policymakers.

Conclusions

In conclusion, this hospital-based study demonstrates that BCG vaccination provided no significant protection against TB diagnosis, disease severity, or disease classification in children from a high-burden setting in Pakistan. Our findings, therefore, highlight the urgent need for multifaceted approaches to pediatric TB control in high-burden settings. Beyond strengthening newborn BCG coverage, efforts must prioritize the accelerated development of more effective vaccines targeted at older children and adolescents, alongside robust nutritional support programs and systematic household contact management. Integration of these strategies, including nutritional adjuncts and novel vaccine candidates, is essential to accelerate progress toward the 2030 SDG targets for TB elimination. Future well-designed studies evaluating booster vaccination strategies in combination with nutritional interventions in endemic regions are warranted.

Conflict of Interest Statement:

All authors declare no conflicts of interest.

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