CHILDHOOD TUBERCULOSIS EPIDEMIOLOGY IN URBAN CENTRAL ETHIOPIA: DEATH PREDICTORS, DISEASE DETERMINANTS, AND UNFAVORABLE TREATMENT OUTCOMES

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List of original papers

This dissertation work is based on the three original papers listed below.

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III. **Burusie A**, Enquesilassie F, Salazar-Austin N, Addissie A. **The magnitude of unfavorable tuberculosis treatment outcomes and their relation with baseline undernutrition and sustained undernutrition among children receiving tuberculosis treatment in central Ethiopia**. Heliyon. 2024; 10(6):e28040. Doi: 10.1016/j.heliyon.2024.e28040. PMID: 38524586; PMCID: PMC10957419.

Acronyms and abbreviations

1HP	A 1-month regimen of daily rifapentine with isoniazid
3HP	A 3-month regimen of weekly rifapentine plus isoniazid
4R	A 4-month regimen of daily rifampicin
3RH	A 3-month regimen of daily isoniazid plus rifampicin
6/9H	A 6- or 9-month daily monotherapy of isoniazid
AFB	Acid-fast bacilli
aHR	Adjusted hazard ratio
AM	Alveolar macrophages
aOR	Adjusted odds ratio
aRR	Adjusted risk ratio
ART	Antiretroviral treatment
BCG	Bacillus Calmette-Guerin
BMI	Body mass index
CAD	Computer-aided detection software
CD4+	Cluster of differentiation-4+
CD4+8	Cluster of differentiation-8+
CDC	Centers for Disease Control and Prevention
CFR	Case fatality ratio
cHR	Crude Hazard ratio
CI	Confidence interval
CNS	Central nervous system
cOR	Crude odds ratio
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
cRR	Crude risk ratio
CSF	Cerebrospinal fluid
CXR	Chest X-ray
DM	Diabetes mellitus
DOT	Directly Observed Treatment

DOTS	Directly Observed Treatment, Short-course
DST	Drug-susceptibility testing
EPTB	Extra-pulmonary tuberculosis
HBCs	high burden countries
HIV	Human immunodeficiency virus
IFN-γ	Interferon gamma-gamma
IGRA	Interferon-γ release assay
IL-2/-10/-12	Inter-leukin-1/-10/-12
IPT	Isoniazid preventive therapy
IRB	Institutional Review Board
LAM	lipoarabinomannan
LF-LAM	lateral flow- lipoarabinomannan
LTBI	Latent tuberculosis infection
MAC	Mycobacterium avium complex
MAM	Moderate acute malnutrition
mCOR	Matched crude odds ratio
MDGs	Millennium Development Goals
MDR/RR-TB	Multi-drug resistance or Rifampicin resistant tuberculosis
MDR-TB	Multi-drug resistant-tuberculosis
mORadj	Matched adjusted odds ratio
MPs	Macrophages
MTB	Mycobacterium tuberculosis
MTB/RIF®	Mycobacterium tuberculosis and rifampicin resistant
MTBC	Mycobacterium Tuberculosis Complex
MUAC	Mid-upper-arm circumference
mWRDs	Molecular WHO-recommended rapid diagnostic tests
NNS	Number needed to screen
NTM	Non-tuberculous Mycobacteria
PHs	Proportional hazards
PTB	Pulmonary tuberculosis
SAM	Severe acute malnutrition

SDG	Sustainable Development Goal
SDH	Social determinants of health
SPH	School of Public Health
TB	Tuberculosis
TBM	Tuberculosis meningitis
Th1/2	T helper type-1/-2
TPT	Tuberculosis preventive treatment
TST	Tuberculin skin test
US	United States
W4SS	WHO-recommended four-symptom screen
WH/L	weight-for-height/length
WHO	World health organization

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Abstract

Background: Limited evidence exists on the epidemiology of childhood tuberculosis (TB) in Ethiopia. Even though the TB treatment success rate is one of the most important global metrics for assessing the implementation of the End TB Strategy, little is known about the magnitude and determinants of unfavorable TB treatment outcomes that affect TB treatment success rates among children in Ethiopia. Additionally, despite Ethiopia's high national BCG coverage and studies showing the vaccine's effectiveness against TB meningitis (TBM), the disease remains a persistent problem.

Objectives: To describe the epidemiology of drug-susceptible TB and identify predictors of TB death, identify determinants of TB disease, assess the magnitude and predictors of unfavorable TB treatment outcomes, and evaluate the effectiveness of BCG vaccine against TBM among children aged 16 and under in Urban Central Ethiopia.

Methods and materials: This study was conducted across healthcare facilities in Addis Ababa, Adama, and Bishoftu from September 25 to June 24, 2022. A retrospective cohort design was used to address the following specific objectives: describing TB epidemiology, identifying predictors of death, and assessing the magnitude and determinants of unfavorable treatment outcomes. Additionally, 1:1 matched case-control and 1:4 unmatched case-control designs were used to identify determinants of TB disease and assess BCG vaccine effectiveness against TBM, respectively. Sample sizes were statistically determined. Thirty-two healthcare facilities—26 in Addis Ababa, three in Bishoftu, and three in Adama—were randomly selected. All children treated for TB at these facilities were included in the descriptive epidemiology and predictors of death analyses, as well as in the study on unfavorable treatment outcomes. In the matched case-control study, cases (children with TB) were randomly selected from treated children identified through TB registries. Controls (children never diagnosed with TB) were sequentially chosen from the same facilities. Data on TB cases were collected through TB record reviews and phone interviews with parents or caregivers. Data on controls were obtained through face-to-face interviews with parents or caregivers. Descriptive epidemiology was presented using relative frequency tables and graphs. Statistical analyses included Cox proportional hazards regression (challenged with extended Cox regression) to compute adjusted hazard ratios (aHR) for death predictors, conditional logistic regression for matched adjusted odds ratios (mORadj) of TB

disease determinants, log-binomial analysis for risk ratios (aRR) of unfavorable outcomes, and unconditional logistic regression for adjusted odds ratios (aOR) to assess BCG vaccine effectiveness against TBM. This study was approved by the Institutional Review Board of the College of Health Sciences, Addis Ababa University (protocol number: 057/19/SPH).

Results: Data from 640 children aged 16 years and under who underwent treatment for TB were analyzed. Among them, 80 (12.5%) were under two years old, and a resurgence occurred starting from around 12 years of age. Most of the enrolled children, 557 (87.0%), had no known household TB contact. Out of 519 children with an identified place of stay, 396 (76.3%) were attending school or daycare before being diagnosed with TB. Thirty-six (5.6%; 95% confidence interval (CI) = 4.0–7.7%) of the 640 children died during the course of TB treatment. Among those who died, nine (25%) were under two years old. Factors such as HIV infection (aHR = 4.2; 95% CI = 1.9–9.3), undernourishment (aHR = 4.2; 95% CI = 2.2–10.48), age below 10 years (aHR = 4.1; 95% CI = 1.7–9.7), and relapsed TB (aHR = 3.7; 95% CI = 1.1–13.1) increased the likelihood of death during TB treatment.

Children not vaccinated with BCG at birth or within two weeks of birth (mORadj = 2.11; 95% CI = 1.28–3.48), those who lived with a TB-sick family member (mORadj = 4.28; 95% CI = 1.95–9.39), those who lived with a smoking family member (mORadj = 3.15; 95% CI = 1.07–9.27), and HIV-infected children (mORadj = 8.71; 95% CI = 1.96–38.66) were more likely to develop TB than their counterparts. A post-estimation analysis indicated that children who were BCG-vaccinated at birth or within two weeks of birth had a lower risk of TB than their unvaccinated counterparts until the age of 15, but there was no difference found between the two groups when they turned 16.

Out of 640 children, 42 (6.6%; 95% CI = 4.8–8.8%) had unfavorable TB treatment outcomes, with 31 (73.8%; 95% CI = 58.0–86.1%) occurring after the first two months of treatment initiation. Children under ten years old (aRR = 2.69; 95% CI = 1.56–4.61), those with relapsed TB (aRR = 3.19; 95% CI = 1.79–5.70), undernourished children at TB diagnosis (aRR = 2.68; 95% CI = 1.53–4.71), and HIV-infected children (aRR = 2.62; 95% CI = 1.50–4.59) had a higher risk of unfavorable TB treatment outcomes than their counterparts. However, among children who completed the first two months of TB treatment, relapsed TB was not significantly associated (aRR = 2.81; 95% CI = 0.96–8.22) with unfavorable outcomes, while the remaining

factors retained significance. No significant association was detected between BCG vaccination and the risk of TBM (aOR = 0.46; 95% CI = 0.11–1.84).

Conclusions: Most children contract TB from the community, with morbidity resurging around age 12, possibly due to waning BCG vaccine effectiveness. Despite a pooled global death rate of 0.9% in treated childhood TB patients, the death rate in Urban Central Ethiopia is high. Risk factors for death and unfavorable outcomes include being under 10, suggesting redefining the high-risk age category from 5 to 10 years. BCG vaccination is protective of childhood TB but wanes with age. Second-hand smoking increases childhood TB risk, underscoring the need for public health policies to reduce children's exposure to tobacco smoke. HIV remains a significant morbidity and mortality risk factor, raising concerns about the coverage and efficacy of TB preventive treatments. The rate of unfavorable TB treatment outcomes aligns with the WHO's milestone, staying below 10%, but nearly three-quarters of these outcomes occur during the continuation phase, highlighting the need for extended risk-focused follow-up. Undernutrition persisting into the continuation phase of TB treatment predicts unfavorable outcomes, indicating the need for nutritional interventions throughout both the intensive and continuation phases of childhood TB treatment. BCG was not found to significantly protect against TBM compared to other types of TB combined.

Recommendations: Expand TB contact tracing in children to include school communities and maintain universal newborn BCG immunization. Consider legislation against smoking in households with children. Include children under 10 as a high-risk group for TB-related death in TB guidelines. Evaluate the coverage and effectiveness of TB preventive therapy intervention in HIV-infected children. Children under 10, those who are HIV positive, and undernourished children should be carefully assessed, treated, monitored, and provided with necessary support, regardless of the phase of TB treatment they are in. This study recommends conducting larger studies to assess the effectiveness of BCG vaccination against TBM compared to other types of TB.

Keywords: Childhood TB; epidemiology; survival; disease determinants; treatment outcomes

1. Introduction

1.1. Background of the study

Tuberculosis (TB) is primarily caused by Mycobacterium TB (MTB) [1], spreading through inhalation of droplets from TB patients [2-4]. TB primarily affects the lungs, which is known as pulmonary TB (PTB), but it can also damage almost all other organs and tissues of the body, causing extra-pulmonary TB (EPTB). EPTB accounts for 15-20% of all TB patients [5-8], rising to 50% among those co-infected with human immunodeficiency virus (HIV) [8]. In children, up to 80% of TB cases are PTB. EPTB in children most commonly affects the lymph nodes (67%), followed by the meninges (13%), the pleura (6%), miliary TB (5%), and skeletal TB (4%) [9].

MTB is estimated to infect nearly a quarter of the global population [10, 11]. Approximately 5-10% of MTB-infected persons develop active TB disease during their lifetime [12], while the vast majority of people who are exposed to MTB remain in an asymptomatic [13, 14]. Active TB disease, also called clinical TB, can develop immediately after the first infection, known as primary disease, or many years later by endogenous reactivation or re-infection [15]. Over 90% of TB cases in children under 15 years old develop within a year after infection [16].

If left untreated, the case fatality rate for smear-positive PTB in human immune-deficiency virus (HIV)-negative individuals is 70% and 20% for culture-positive smea-negative TB in 10 years, independent of age group up to 50 years [17]. With multidrug chemotherapy, TB can be cured in 95% of patients [18]. Treatment failure is mainly due to non-adherence to TB treatments and drug resistance [19, 20].

In 1993, the World Health Organization (WHO) declared TB a global public health emergency [21], prompting the publication of an annual global TB report since 1997 [22]. The report is based on data submitted by more than 200 nations and territories, representing more than 99% of the global population and TB patients [23]. However, Childhood TB reports were included in the WHO annual global TB report for the first time in 2012, marking a significant delay of 15 years [24].

A country's TB burden, indicating TB's impact, was defined from 1998 to 2015 as having 100 or more TB patients per 100,000 people [25]. From 2016 to 2020, the WHO introduced high-burden lists for TB/HIV co-infection and multidrug-resistant TB (MDR-TB) [26]. Ethiopia and Kenya exited the high MDR/RR-TB list in 2021 [27]. These lists aim to focus efforts on the End TB Strategy and the Sustainable Development Goals (SDGs), targeting TB eradication by 2030 [27].

Since declaring TB a global public health emergency in 1993 [21], WHO has developed three successive TB control strategies: DOTS (Directly Observed Treatment, Short-course) (1994-2005) [28], Stop TB (2006-2015) [29], and End TB (2016-2035) [30]. Before these, a vertical TB control approach (1948-1963) was successful in developed countries but less effective in resource-poor settings [31]. The DOTS Strategy was introduced in reaction to a resurgence of the global TB epidemic in the 1990s [32]. The forehead culprit of the resurgence of TB was the pandemic of HIV infection, which resulted in a larger pool of susceptible persons who were far more likely to progress to active (contagious) TB after contracting MTB [32, 33]. DOTS' global targets aimed to detect 70% of estimated TB patients and cure 85% of sputum-positive patients under treatment by the year 2000 [29]. Unfortunately, the DOTS targets were not met even in 2005, with a global case detection rate of 60% and a treatment success rate of 84% [34]. Despite reducing TB morbidity and mortality [35], the improvements were insufficient [36], prompting the development of the Stop TB Strategy [26].

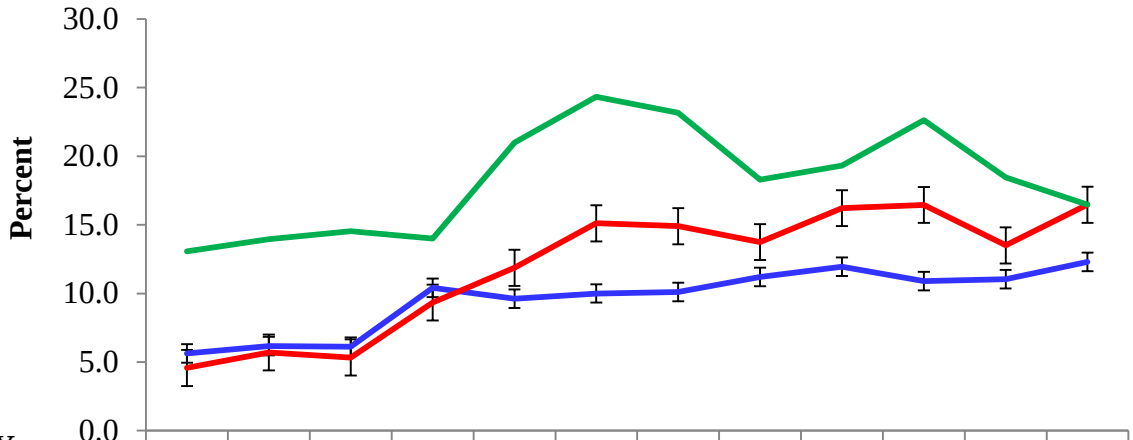
Stop TB, retaining DOTS at its core, addressed the social determinants of TB [35] and challenges like HIV-associated TB, multidrug-resistant TB, private-sector and community involvement, and the need for better diagnostics [26]. However, it fell short with global TB prevalence declining by 42% instead of the targeted 50% by 2015 as compared to the baseline of 1990 [26]. The shortfall was due to the lack of an effective strategy to prevent TB reactivation among the billions infected with MTB [37]. The SDGs later spurred innovations in TB control [38], leading to the development of the End TB Strategy [30].

The WHO End TB Strategy aims for "a world free of TB — zero deaths, disease, and suffering due to TB" by 2035 [30]. Both the SDGs and the End TB Strategy share the goal of ending the global TB epidemic [30, 38], defined as avhieving a TB incidence rate of less than 10 new cases per 100,000 population per year [39]. The End TB Strategy outlines three high-level indicators

with targets for 2030 and 2035, and milestones for 2020 and 2025. The indicators are: (1) the absolute number of TB deaths per year; (2) the TB incidence rate per 100,000 persons per year; and (3) the percentage of TB-affected households experiencing catastrophic costs due to TB disease. Additionally, there are 10 operational indicators to monitor the implementation of the strategy, including a TB treatment success rate milestone of over 90% by 2025 [39]. The global TB treatment success rate for children under 15 was 88% in both 2019 and 2020, indicating an unfavorable outcome rate of 12% [40]. The aim is to reduce the unfavorable outcome rate to below 10% to achieve the 90% milestone set for 2025 [30].

Globally, an estimated 10.6 million people developed TB in 2022, with 12% of them being children aged 0-14 years, surpassing the 2021 estimate of 10.3 million, where 11% were children [41]. In 2022, TB caused an estimated 1.30 million deaths globally (16% were children), [41], a decrease from the 1.4 million recorded in 2021 (14% were children) [40]. Between 2015 and 2022, the global death toll from TB decreased by 19%, falling much short of the WHO's End TB Strategy target of a 75% reduction by 2025. Similarly, the decrease in TB incidence rate during the same period was only 8.7%, well below the WHO's target of a 50% reduction by 2025 [41]. Ethiopia has been among the high TB burden countries (HBCs) from 1998 to 2025 [24, 26, 40]. In Ethiopia, TB deaths in 2021 were 27% lower than the 2015 figure of 29,000 [26] but did not meet the End TB Strategy's of 35% reduction target [30]. The TB case-fatality ratio (CFR) of the country in 2021 was 15% [42], far above the 2025 milestone of a maximum of 5% [39].

According to WHO's global TB report, child (age below 15 years) TB cases escalated from 0.5 million (5.6% of all cases) in 2011 [24] to 1.2 million (11% of all cases) in 2021 globally [40]. The proportion of child TB deaths to total TB-related deaths increased from from 4.6% in 2011 [24] to 14.0% in 2021 (13.5% when considering TB deaths among HIV-positive individuals) [40]. Data synthesis from WHO reports [43] indicates a rising proportion of new childhood TB cases from 2012 to 2022. Since 2015, children have accounted for a growing share of TB deaths compared to total TB deaths across all age groups, with their contribution to mortality consistently surpassing their contribution to incidence. The analysis also uncovers a fluctuating trend in the child TB case fatality ratio (CFR) above the 2011 baseline (Figure 1).



Year	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Incidence share of childhood TB (%)	5.6	6.2	6.1	10.4	9.6	10.0	10.1	11.2	11.9	10.9	11.0	12.3
Death share of childhood TB (%)	4.6	5.7	5.3	9.3	11.9	15.1	14.9	13.7	16.2	16.4	13.5	16.5
Childhood TB case fatality ratio (%)	13.1	14.0	14.5	14.0	21.0	24.3	23.2	18.3	19.3	22.6	18.5	16.5

Figure 1. Trends in Childhood TB Incidence and Mortality Shares, and Case Fatality Ratio: a synthesis from WHO Global TB Reports, 2012-2022 [43]

The term "children" can refer to different age groups depending on the publication, even within WHO documents. In the WHO's global TB report documents, "children" refers to individuals under 15 years old [40, 44, 45]. However, in the WHO consolidated guidelines on TB, "children" are defined as those under 10 years old, while individuals aged 10 to 19 are classified as adolescents [46, 47]. Other studies have different definitions: some consider children to be individuals under 18 years old [48, 49], others under 19 years old [50], and yet others under 15 years old [51]. Therefore, in this dissertation, the specific age group will be clearly specified whenever the term "children" is used.

1.2. Statement of the problem

Diagnosing TB in children, particularly in those under two years of age is challenging [52]. However, the introduction of GeneXpert MTB/RIF® (Xpert) has significantly improved TB diagnosis in this age group [51]. Xpert offers superior sensitivity and specificity compared to microscopy [51, 53, 54]. Since late 2015, the GeneXpert MTB/RIF® (Xpert) has been gradually implemented as the primary tool for TB diagnosis in Ethiopia [55]. However, few studies on

childhood TB epidemiology have been conducted since the introduction of Xpert. As a result, there is a lack of an updated understanding of the landscape of childhood TB epidemiology.

According to the WHO global TB report, approximately 20,000 children under the age of 15, making up 11.6% of all TB patients, fell sick of TB in 2017 in Ethiopia [56]. However, country-level death figures for childhood TB are not provided in the global TB reports [40, 45, 56] nor does Ethiopia have studies that provide the national childhood TB death figures. A study by Ramos et al. noted a 4.1% mortality rate among children undergoing TB treatment at a rural hospital in southern Ethiopia from 1998 to 2015 but did not identify predictors of death [57]. In contrast, other studies have reported lower death rates (less than 1%) among children diagnosed and treated for TB [58, 59], indicating a possible variability in outcomes that needs further investigation. Evidence indicates undernutrition is associated with an increased risk of TB mortality in adults [60, 61]. However, childhood TB studies in Africa, including Ethiopia, have often overlooked studying the effect of malnutrition on deaths from childhood TB [59, 62-71]. Risk-factor targeted intervention reduces mortality rates among children receiving TB treatment [72-74].

Childhood TB is a major public health problem [41] that remains understudied in Ethiopia. Studies reveal that the Bacillus Calmette-Guerin (BCG) vaccine is less effective in protecting against TB near the equator, which includes Ethiopia [75, 76]. However, studies on childhood TB have not specifically assessed the effectiveness of the BCG vaccine in these regions [77]. The duration of BCG vaccine efficacy against childhood TB remains debated, with some studies suggesting protection lasts for 10 to 20 years post-vaccination [78-80], while recent meta-analyses indicate significant protection only in children under five years old [81]. Additionally, while some studies have identified passive cigarette smoking as a risk factor for TB in children [82, 83] there is a lack of research evaluating passive smoking as a risk factor for TB among Ethiopian children [77, 84].

Ethiopia achieved an 86% treatment success rate for all-age new TB patients in 2021, but there is no documentation of a treatment success rate specific to childhood TB [42]. Monitoring the TB treatment success rate is a crucial global indicator for tracking the implementation of the WHO's End TB Strategy [30]. Previous studies have often classified transfer-out patients as experiencing unfavorable outcomes [65, 66, 69], which may not accurately reflect reality, as

these patients could indeed be cured or have completed TB treatment. Additionally, while unfavorable treatment outcomes such as death are more prevalent in the initial weeks of TB treatment, they can also occur during the continuation phase following the intensive phase [85]. However, previous childhood TB studies in Ethiopia have seldom distinguished between predictors of unfavorable TB treatment outcomes across the two TB treatment phases.

BCG is known to be 73% effective against TB meningitis (TBM) [86]. However, despite high national BCG vaccine coverage and an 81% BCG scar rate in Ethiopia [87], TBM remained prevalent in the country [88, 89]. In recent years, there has been a paucity of literature on the epidemiology of TBM [90].

1.3. Rationale of the study

Childhood TB remains a significant public health issue and an insufficiently studied area in Ethiopia [91]. Research has highlighted GeneXpert's superior diagnostic accuracy for both pulmonary and extrapulmonary TB in children [92]. Therefore, conducting both descriptive and analytic epidemiology of childhood TB based on more valid data generated in the Xpert era is crucial. Such studies provide an updated understanding of the current landscape of childhood TB epidemiology, aiding informed decision-making for TB intervention and control.

Existing studies provide some insights into childhood TB but are limited in scope and detail. There is lack of studies that explore the predictors of death among children on TB treatment [57]. These gaps highlight the need for comprehensive studies to identify risk factors and to develop risk-focused interventions aimed at minimizing TB deaths in children undergoing TB treatment.

Additionally, there is a lack of specific research on the effectiveness of the Bacillus Calmette-Guerin (BCG) vaccine near the equator, where Ethiopia is located. Studies on passive cigarette smoking as a risk factor for childhood TB development in Ethiopian children are also scarce. This study aims to address these gaps by assessing the determinants of childhood TB.

Furthermore, this study is important because it addresses the lack of evidence on the magnitude of TB treatment success rates among children, involving multiple healthcare facilities in Urban Central Ethiopia. It also aims to fill the knowledge gap regarding the risks of unfavorable treatment outcomes during different phases of TB treatment. Identifying context-based predictors

of unfavorable outcomes, such as death, treatment failure, and loss to follow-up [93], is imperative for targeted interventions aimed at maximizing successful treatment outcomes [94].

1.4. Significance of the study

This study's updated data on the epidemiological landscape of childhood TB is crucial for formulating effective public health interventions and policies. A comprehensive understanding of TB determinants in children, along with areas requiring urgent attention, is essential for informed decision-making in TB prevention and control strategies. Identifying childhood TB diasese determinants is vital for developing targeted interventions aimed at reducing TB incidence rates among vulnerable children. Additionally, this study is significant as it identifies context-specific predictors of unfavorable treatment outcomes, providing critical insights for designing risk-focused interventions. Risk-based interventions minimize magnitude of unfavorable outcomes and ensure higher rates of successful TB treatment in children. Ultimately, risk-focused measures reduce the burden of childhood TB and improve health outcomes for those affected.

Overall, this dissertation fills significant gaps in the understanding of childhood TB in Urban Central part of Ethiopia and offers actionable insights for decision-makers, policymakers, and healthcare providers.

1.5. Literature review

TB remains a significant public health challenge worldwide, especially in low- and middle-income countries. Ethiopia is among the 30 high TB burden countries, which together account for 87% of global TB cases. Children constitute a considerable portion of the TB-affected population. In 2022 alone, children aged 0-14 years accounted for 1.3 million TB cases (12% of global incidents) and over 200,000 deaths (16% of global TB deaths) [41]. This literature review provides a foundational overview of TB pathogenesis and characteristics, aiming to synthesize existing research on the epidemiology of childhood TB, focusing on predictors of death, determinants of the disease, and unfavorable treatment outcomes.

1.5.1. Pathogenesis of TB

Pathogenic Mycobacteria: Mycobacterium TBComplex (MTBC) and Non-tuberculous Mycobacteria (NTM)

MTB, Mycobacterium bovis, and Mycobacterium africanum constitute the MTBC, sharing high genetic similarities despite slight phenotypic variations [95]. Among them, MTB stands out as the primary pathogen, responsible for 97–99% of human TB cases [5]. Mycobacterium bovis predominantly causes TB in both cattle and humans, particularly manifesting as intestinal TB in the latter, while Mycobacterium africanum is relatively uncommon, mainly isolated from TB patients in West Africa [96, 97]. NTM, also known as atypical Mycobacteria or environmental Mycobacteria, and Mycobacterium avium complex (MAC) are two other pathogenic Mycobacteria that cause opportunistic infections, particularly in immunosuppressed individuals [97].

Characteristics of MTB

The MTB is a rod-shape bacterium with a width of 0.2–0.5 x 10^{-6} meter and a length of 2-4 x 10^{-6} meter, which allows it to pass through the narrowest airways to reach alveolar macrophages in the remote parts of the lungs easily [98]. MTB is an acid-fast bacillus (AFB) and has a lipid-rich cell wall formed of mycolic acid; hence the name mycobacterium, a fatty substance that makes the bacteria immune-resistant and aids in drug resistance [99].

Mechanisms and Factors Influencing TB Transmission

TB is spread from one sick person to another through the air by droplet nuclei, particles 1–5 mm in diameter that contain MTBC [100]. Droplet nuclei are generated when people with pulmonary or laryngeal TB cough, sneeze, speak, or sing. They can also be produced by aerosol therapies, sputum induction, aerosolization during bronchoscopy, manipulation of lesions, or processing of tissue or secretions in the hospital or laboratory [101]. Droplet nuclei, which contain two to three MTB organisms, are so small that air currents in any interior environment can keep them airborne for extended periods of time, making them effective vehicles for TB transmission [101]. The likelihood of MTB transmission is determined by four factors: (1) the number of organisms expelled into the air; (2) the concentration of organisms in the air determined by the volume of

the space and its ventilation; (3) the length of time an exposed person breathes the contaminated air; and (4) presumably the immune status of the exposed individual [102].

MTB survival and Replication in Alveolar Macrophages

MTB's ability to survive in intracellular environments (to live inside other cells such as macrophages) is key to its pathogenesis [103]. When MTB is inhaled into the lungs, it is engulfed (phagocytized) by alveolar macrophages (AM) [104], which is a sort of innate (non-specific) immune response [105]. The phagocytized bacilli undergo intracellular replication by inhibiting the body's immunological defense mechanism of phagosome-lysosome fusion, which otherwise would break down and kill the bacterium [106]. MTB's sulfatides are virulence factors of the bacilli that allow it to evade phagolysosome fusion as well as prevent phagocyte activation [107]. Therefore, MTB survives intracellularly via inhibiting phagosomal maturation, resisting lysosomal acidification, and inhibiting macrophage apoptosis (a process that favors mycobacterial death) [108, 109]. When macrophages fail to suppress multiplication of or destroy the bacilli, the viable bacilli multiply within their intracellular habitat (macrophages). The macrophages then burst dead and release the replicated bacilli, and those liberated bacilli will infect other populations of macrophages, and the cycle goes on [3]. The bacilli infect a variety of monocyte-derived and tissue-resident macrophages, dendritic cells, and neutrophils when infected alveolar macrophages migrate into the lung interstitium. Children often exhibit immature innate immune responses, which can affect the efficacy of phagocytosis and bacterial clearance [79].

Granuloma Formation and Bacilli Dissemination

The AM produces chemokines [110], which are signal proteins to initiate an inflammatory immune response [111]. The chemokines pull a swarm of immune cells, also known as white blood cells or leukocytes, such as neutrophils, monocyte-derived macrophages, and natural killer cells, from the circulation to the infection site to form a granuloma that surrounds and walls off the infected macrophages and the released bacilli, preventing the bacilli from spreading [112]. At this point, the person is asymptomatic, and depending on the host's immune strength and the bacilli's virulence balance, the TB bacteria may be completely eliminated from the body (calcified granuloma), may persist dormant inside the granuloma forever or until reactivation to

active TB (called secondary TB), or become an incipient or subclinical infection [103, 113, 114]. However, in people who lack the immunity to control and restrict MTB in granulomas, the infection rapidly develops into active primary TB, with clinical signs and symptoms that start manifesting [103, 113, 115, 116]. Primary TB often develops within less than two years of the initial infection [117], and it affects approximately 5% of MTB-infected people [118]. About 5% of MTB-infected persons develop TB during their lifetime by reactivation of their latent TB infection (LTBI) [118]. The majority (90%) of infected persons remains TB infected as a result of a successful adaptive immune response, with outcomes ranging from sterilized infection to subclinical disease, but there is no means to distinguish between people who sterilized their infection and those who harbor viable bacilli [103].

Infected macrophages in the midst of the granuloma lose their lipid content as they necrotize (die), creating caseation (cheese-like structure) [119] where extracellular multiplication of the bacilli occurs [120]. The macrophage-rich caseum in the middle of a granulomatous lesion in the lung parenchyma is referred to as the Ghon focus [121]. The Ghon focus is commonly found subpleural, majorly in the top half of the lower lobe or the lower part of the middle or upper lobe [122]. Through hemogenous and lymphatic dissemination, TB can drain from the Ghon focus to the neighboring hilar lymph nodes and cause caseation there as well, a combination known as the Ghon complex [123]. The Ghon complex can fibrose and calcify, and it frequently produces scar tissue. This calcified Ghon structure is referred to as the Ranke complex [124].

Despite the ability of alveolar macrophages to phagocytose and potentially destroy MTB bacilli [125], paradoxically, they also provide a favorable niche for bacterial multiplication [104]. This intricate interplay between MTB and host cells exemplifies the complex pathogenesis underlying TB infection. The hallmark of TB disease pathophysiology is an adaptive immune response of granuloma formation by host-pathogen interactions [126], and its formation by MTBC is controversial as an immune system protection or an MTBC survival strategy in hosts [95]. On the one hand, tuberculous granuloma restricts the growth of MTB as the activated macrophages surround and kill the bacilli [127]. On the other hand, granulomas provide a protective shelter for the bacteria, allowing them to remain latent until a chance for reactivation and dissemination occurs [128]. The mycolic acids in MTB's cell wall stimulate the development of human monocyte-derived macrophages into foamy macrophages (FMs), which are lipid-rich. When the

foamy macrophages necrotize, they release their lipids into the granuloma, providing nutrients for MTB multiplication in the granuloma [129]. As the TB disease takes over the immune system, the center of the solid granuloma begins to necrotize, forming a necrotic granuloma, allowing the dormant bacilli to resurrect as the necrotic center becomes larger centrifugally and liquifies, creating a caseous granuloma [119]. The caseous center of the granuloma eventually ruptures into the lung airway, releasing extracellular free MTB bacilli into the airways to be breathed into the atmosphere and facilitating infection transmission [130, 131].

Adaptive Immunity response to TB

T lymphocytes, particularly Cluster of differentiation-4+ (CD4+) and Cluster of differentiation-8+ (CD8+) T cells, are central players in the adaptive immune response against MTB in children. CD4+ T cells orchestrate the immune response by secreting cytokines such as interferon-gamma (IFN-γ), which activates macrophages to enhance bacterial killing [120]. By boosting phagosomal maturation and acidity, IFN-γ encourages macrophages to kill intracellular MTB [132]. CD8+ T cells, on the other hand, directly lyse infected cells and contribute to the containment of bacterial dissemination [133]. MTB may be cleared by the innate or adaptive host immune response, persist as a latent infection, or proceed to primary active disease after initial exposure [114, 134]. A significant aspect of the adaptive response is the formation of granulomas, structures that aim to contain the infection. But children have a lower frequency of TB-specific IFN-γ producing T cells, which are crucial for effective granuloma formation and maintenance [135].

Spectrums of TB Infection Outcomes

The MTB infection outcome spectrum has recently been broadened from the classical binary at opposite ends of the spectrum, LTBI and active TB disease [114, 136], to five by the addition of two new intermediate states, incipient and subclinical TB, and one initial state, eliminated TB infection [114]. Individuals with eliminated TB infection state no longer have viable MTB bacilli in their body, but immunological markers of earlier infection may still exist [114]. Positive tuberculin skin test (TST) or interferon-γ release assay (IGRA) readings can occur in some people who have eliminated the pathogen through innate or acquired immune responses but still have a substantial memory T-cell response. Such a person will not benefit from LTBI

treatment [134]. It is estimated that one-quarter of TB-infected people self-clear within 10 years of infection, and 73% do so over time [137].

LTBI, which recently the term TB infection has mostly replaced it [47, 138], is a non-infectious condition characterized by persistent infection with viable TB bacilli but no clinical, radiological, or microbiological evidence of active TB disease [139-141]. If the MTB is not eliminated from the body, the bacteria persist in a quiescent or latent state inside macrophages or granulomas but can be detected indirectly by TST or IGRA-positive tests, which show T-cell responses against MTB antigens [134, 142]. These tests imply LTBI based on a T- cell response to TB or TB-like antigens; hence, there is no direct means to validate LTBI or its microbiological load [142, 143].

Incipient TB is a new concept that represents a non-infectious state that follows LTBI (and can be reversed to LTBI) with evidence of T-cell reactivation biomarkers that herald a high likelihood of progressing to active TB within a half-year to a year but has not yet induced clinical symptoms, radiographic abnormalities, or microbiologic evidence consistent with active TB disease [114, 144]. Incipient TB is also referred to as a period of slow metabolic activity and bacilli replication, but there has been no validated test for diagnosing it so far [114].

Patients with subclinical TB do not have clinical TB symptoms, or the symptoms are unrecognized, but they are culture-positive (though often smear-negative due to the low bacillary burden) or have a radiologic abnormality [114, 134]. Subclinical TB patients are contagious, spreading the bacilli to others, and 50% of those with subclinical disease do not show symptoms after 5 years [145]. TB infection, incipient, and subclinical TB all share the absence of clinically active TB disease-related symptoms and a very low mycobacterial burden [146]. However, unlike non-infectious LTBI and incipient TB, subclinical TB patients are infectious and can spread TB infection to others [147].

Active PTB patients have symptoms such as unremitting coughing, fever, night sweats, and weight loss [148], and the diagnosis is usually confirmed with a sputum smear, culture, or Molecular tests [148, 149]. Individuals with subclinical or active PTB should follow one of the approved active TB treatment regimens, which consist of an intense phase with four drugs followed by a longer continuation phase with two drugs [134].

1.5.2. TB Infection diagnosis and Treatment

Diagnosis of TB Infection

The term "TB infection" is now being used to better depict the continuum from TB bacilli inhalation to active TB disease development than the previously used term, LTBI [150]. One of the critical interventions required to end the TB epidemic is the rapid detection and successful treatment of TB infection [150-153] as persons with TB infection serve as the “seedbeds” of TB in the community [154]. TST and IGRA (QuantiFERON®-TB Gold In-Tube and T-SPOT®.TB) are the two WHO-approved tests for diagnosing TB infection [140].

TST and IGRA are both tests that show the body's immunological response to MTB infection [134, 135]. There is no gold standard test for detecting MTB infection in individuals [142], and neither the TST nor the IGRA indirect tests can distinguish between TB infection and incipient TB [144]. BCG vaccination lowers TST specificity (TST is cross-reactive with the previous BCG vaccine), making IGRA a preferable test [155]. However, when BCG is given at birth, it has a limited influence on TST specificity since its effect fades over time [156]. As a result, a history of BCG vaccination has a minimal effect on the interpretation of TST results later in life (such as after 10 years of BCG injection); so, as per WHO’s recommendation, BCG vaccination is used to choose between TST and IGRA testing [140].

The IGRA test works on the same idea as the TST (evaluation of cytokine release by sensitized lymphocytes). IGRA is an in vitro whole blood test that detects T-cell release of IFN-γ, a cell-mediated immune response produced after stimulation with antigens specific to the MTBC (with the exception of BCG sub-strains and NTM) [1, 157, 158]. Only two MTB antigens (ESAT-6 and CFP-10), which are missing in Mycobacterium bovis, BCG, and most environmental mycobacteria, are employed to stimulate lymphocytes, making IGRA more specific than TST [142]. According to some studies, whereas IGRA predicts TB infection progression to active illness better than TST [153], it is not superior in identifying TB infection [159].

TSTs are less expensive and less technically demanding to perform than IGRAs. IGRA requires a cut into the vein (phlebotomy) to withdraw blood, which can be difficult, particularly in very young children; nonetheless, results can be known within 24 hours. TST can be performed in the field, but it necessitates a cold chain and two trips to a health care facility [140]. According to a

meta-analysis study, TST sensitivity is higher than QFT-GIT sensitivity (82% versus 73%) in immune-competent children under the age of 15, whereas TST and QFT-Gold in Tube both have 98% specificity in non-BCG-vaccinated children, but TST has a lower specificity than QFT-GIT (82% versus 98%) in BCG-vaccinated children [160]. The sensitivity of both IGRA and TST to detecting TB infection is low in a variety of immunosuppressed individuals [160, 161]. Hence, the WHO strongly recommends that TST or IGRA TB infection testing is not a requirement for initiating TB preventive treatment (TPT) in people living with HIV or children under the age of five who have been exposed to household TB contacts [140].

Treatment of TB Infection (TPT) in Children

TPT, also known as TB chemoprophylaxis, involves administering one or more anti-TB drugs to individuals with TB infection to prevent progression to active TB disease [162]. TPT is generally mandatory for young children (under 5 years old), while it is suggested for older children and adults under specific conditions [47, 140]. Given that only an estimated 5-10% of TB infection patients will develop active TB in their lifetime, universal treatment of TB infection is not cost-effective [12, 14]. TPT is recommended only for those at high risk of developing active TB [30, 140]. Before starting TPT, it is crucial to rule out subclinical or active TB [163].

WHO Recommendations for High-Risk Groups

The WHO strongly recommends TPT for high-risk individuals, including:

- **HIV-Infected Individuals**: Adolescents (10-19 years old) and adults with HIV should receive TPT as part of comprehensive HIV care, including those on antiretroviral treatment (ART), pregnant women, and those previously treated for TB, regardless of immunosuppression level or TB infection test availability.
- **Infants and Children**: Infants under one year living with HIV in contact with TB should receive TPT if active TB is ruled out based on an appropriate clinical evaluation or according to national guidelines. Children over one year (inclusive) with HIV should also receive TPT in high TB transmission settings as defined by national authorities. Children under 5 years in household contact with confirmed PTB patients should receive TPT if active TB is ruled out, even without TB infection testing [140, 164].

Efficacy of TPT

A meta-analysis revealed that TPT reduces the risk of progression from TB infection to active TB disease in HIV patients by 36-48%, though its long-term effectiveness in high-reinfection settings is unclear [165]. In medium-burden settings, 6 months of isoniazid in HIV-infected patients with positive TST significantly lowers TB risk over 7 years [166].

TPT Regimens and Safety

Recommended TPT regimens include 6 or 9 months of daily isoniazid (6/9H), 3 months of weekly rifapentine plus isoniazid (3HP), or 3 months of daily rifampicin plus isoniazid (3RH). Alternatives include 1 month of daily rifapentine with isoniazid (1HP) or 4 months of daily rifampicin (4R) [164]. In a randomized controlled trial (RCT) with participants aged 12 and above, those treated with 3HR showed better adherence and lower hepatotoxicity rates than those on 9H, while maintaining equal effectiveness [167] . An RCT with children under 18 years old found that the 3R regimen was equally effective and safe compared to the 9H regimen. However, the 3R regimen exhibited superior adherence [168]. In Ethiopia, Isoniazid preventive therapy (IPT) is administered for six months as TPT to children under 5 years old who have been in close contact with an infectious TB patient and to HIV-infected children, once active TB has been excluded [169, 170].

Implementation Challenges and Performance

The concern is that MDR-TB (which accounts for 3-4% of new cases and 18% of previously treated cases) poses a major threat to TPT program [42, 45]. In 2021, only 59% of HIV-positive individuals and 32% of children under 5 in household contact with TB patients received TPT globally; however, Ethiopia reported higher performance rates, achieving 64% and 76%, respectively [42].

1.5.3. Pulmonary TB Disease Screening

The WHO recommends systematic screening for PTB disease, which is defined as the systematic identification of individuals at risk for TB disease development in a predetermined target group

through the assessment of symptoms and the use of rapid tests, and examinations [138]. So far, no screening approach for EPTB has been developed [171].

Global and Regional TB Screening

In 2021, around 40% of estimated TB incident patients worldwide and in Ethiopia 27% of incident cases were not notified [42]. Early TB disease detection and treatment reduces the likelihood of poor treatment outcomes, health complications caused by late intervention, and the negative social and economic repercussions of TB. Furthermore, it aids in the reduction of community-level TB disease prevalence by breaking the MTB transmission chain.

WHO Recommendations

Beyond identifying TB disease, screening can also identify TB infection in individuals, allowing them to benefit from TPT once TB disease has been ruled out, thus removing the danger of progression to TB disease [138]. The WHO recommends that a target screening test should have an overall sensitivity of 90% and a specificity of 70% in order to detect or rule out PTB in those being screened [172].

Screening Algorithms and Tools

Various screening algorithms are available, depending on the group being screened (e.g., the general population, persons living with HIV (PLHIV), people with other risk factors for TB, children) and the availability of tests [171]. The WHO-recommended TB screening tools include:

1. **Four-Symptom Screen (W4SS)**
2. **Chest X-ray (CXR)**
3. **C-reactive Protein (CRP)**
4. **Molecular WHO-recommended Rapid Diagnostic Tests (mWRDs)** [138].

The reference benchmark for evaluating the accuracy of the various TB screening procedures is culture [51, 173].

Four-Symptom Screen (W4SS)

Since 2011, WHO has recommended W4SS for PLWHIV, which comprises any one of the following: current ≥ 2 week cough, fever, night sweating, or weight loss [174]. Screening for TB in HIV-positive children using one or more of cough, fever, poor weight growth, or TB close contact (W4SS for children) had a pooled sensitivity of 61% and a specificity of 94%, and in TB contacts, it had a pooled sensitivity of 89% and a pooled specificity of 69% [175]. One or more of cough, fever, or decreased playfulness symptom screening in children aged under five years, inpatient, or outpatient had sensitivity ranging from 64% to 76% and specificity from 37% to 77% [175]. For those with a positive W4SS, confirmatory testing with a WHO-recommended molecular rapid diagnostic test such as Xpert MTB/RIF is performed [138].

Chest X-ray (CXR)

CXR can be employed as a standalone screening modality or in conjunction with symptom screening, either in parallel or serially [176]. When paired with W4SS, a CXR can be effective in outpatients on ART [177]. However, it has limitations such as low sensitivity (67%) [178], lack of radiologists, and high variability in detecting TB abnormalities [179]. There is hope that computer-aided detection (CAD) software for automated interpretation of digital CXR images will facilitate non-subjective interpretations [138, 180, 181].

C-reactive Protein (CRP)

CRP is a non-specific acute-phase protein that rises in response to bacterial infections such as active TB [182]. It can be measured on capillary blood collected through a finger prick [183]. CRP shows comparable sensitivity but greater specificity than W4SS [177] and improves sensitivity when used together with W4SS regardless of HIV status [183]. For PTB screening in HIV-positive outpatients, CRP (threshold 8 mg/L) shows high sensitivity (82%) and specificity (82%) [184]. WHO recommends using CRP in addition to W4SS for TB screening in all PLHIV in high TB burden areas [138].

Molecular WHO-recommended Rapid Diagnostic Tests (mWRDs)

GeneXpert MTB/RIF is a widely used mWRD that detects MTB's genetic material and rifampicin resistance in less than 2 hours from various specimens like sputum, lymph node

tissue, cerebrospinal fluid, pleural fluid, and gastric lavage [185]. It requires minimal technical effort and should be accessible to all with presumptive TB before considering its use as a screening tool, given its significant resource implications [138].

1.5.4. TB disease diagnosis

To confirm TB disease, MTB bacilli must be identified or isolated from a clinical sample using smear microscopy for acid-fast bacilli (AFB), mycobacterial culture, or molecular tests [149]. Clinically diagnosed TB refers to PTB cases diagnosed based on signs and symptoms combined with X-ray abnormalities or TB-suggestive histology, as well as EPTB cases not confirmed by laboratory testing [186].

Diagnostic Methods for Childhood TB

1. **Rapid Molecular Tests**

The WHO strongly recommends specific and rapid molecular tests, such as Xpert MTB/RIF or Xpert Ultra, as initial diagnostic tests for MTB and rifampicin resistance detection in people with TB signs and symptoms, rather than smear microscopy or culture and phenotypic DST for both PTB and EPTB [149, 187]. To confirm EPTB bacteriologically, invasive specimen collection via biopsy or fine needle aspiration is required, followed by the use of Xpert MTB/RIF or Xpert Ultra tests. [187, 188]. These tests have high specificity for detecting TB across most specimen types, except for TBM and tuberculous pleuritis [189]. Despite their effectiveness, in 2021, globally only 38% of notified TB cases were tested with rapid diagnostics at the time of diagnosis, with no specific report for Ethiopia [42].

2. **Sputum Smear Microscopy**

Until recently, most patients suspected of having TB were diagnosed by sputum smear microscopy for AFB [25]. This method is inexpensive, simple, rapid, and specific but only positive in about half of patients with active TB [190]. The sensitivity of the test is substantially lower in children and patients with HIV infection [191] , making it less effective for meeting the WHO's end-TB strategy [30].

3. **Mycobacterial culture**

Mycobacterial culture involves growing bacteria in nutrient-rich media and is considered the gold standard for MTB detection and drug susceptibility testing (DST) [192]. However, due to MTB's slow growth, sputum cultures can take up to four weeks on liquid medium and eight weeks on solid media to report results [192, 193]. Culture is essential for confirming drug susceptibility and monitoring treatment success, especially for second-line drugs in multidrug-resistant TB (MDR-TB) patients [190]. This method requires highly skilled professionals and advanced infrastructure, typically available only in regional reference laboratories [190].

4. **Lateral flow lipoarabinomannan (**LF-LAM)

The detection of the lipoarabinomannan (LAM) antigen, a component of mycobacterial cell walls, in the urine of a person with active PTB or EPTB has emerged as a potential point-of-care diagnostic for TB [194]. LF-LAM assays have a short turnaround time (25 minutes) but low sensitivity, making them unsuitable as universal TB diagnostic tests [149, 195]. However, they have higher sensitivity for identifying TB in people with advanced HIV disease (WHO clinical stages 3 and 4) or in patients with low CD4+ cell levels (<200 cells/ml), and are strongly recommended by the WHO for use in these subgroups [149, 196].

In Ethiopia, microscopy is used to diagnose TB at the primary healthcare facility level, and specimens are transported to nearby hospital laboratories for GeneXpert testing. Mycobacterial culture and first-line-/second-line-LAM are only performed at regional and national referral laboratories [170].

1.5.5. Challenges of diagnosing TB disease in children

Diagnosing TB in children presents several challenges primarily due to the paucibacillary nature of the disease, which results in low sensitivity of smear microscopy examinations. Additionally, children often struggle with sputum expectoration, making sample collection difficult. The lack of rapid molecular tests, particularly in low-income countries, and the non-specific signs and symptoms of TB further complicate the diagnosis of PTB in this population [51, 197, 198].

The primary obstacle in accurately detecting MTB bacilli in children is the paucibacillary nature of the disease [199]. Consequently, TB diagnosis and treatment in children largely depend on a

combination of contact history, clinical signs and symptoms, radiological abnormalities suggestive of TB, and microbiological test results [52, 200-202].

Microbiological tests like Xpert MTB/RIF assay show similar performance in HIV-infected and HIV-uninfected children. However, in the context of severe immunodeficiency, such as HIV infection, clinical and radiologic features of TB are less specific [51, 203]. Additionally, immunodeficiency decreases the sensitivity of immunologic tests for TB infection [204]. For children with suspected PTB, the WHO strongly recommends using Xpert or Xpert Ultra as the initial diagnostic test for TB and rifampicin resistance detection on respiratory samples (sputum, nasopharyngeal aspirate, gastric aspirate), or stool, rather than smear microscopy, culture, and phenotypic DST [47].

When using expectorated or induced sputum samples, Xpert demonstrates pooled sensitivities and specificities of 62% and 98%, respectively, and 66% and 98%, respectively, when using gastric lavage samples. Xpert's sensitivity is 36-44% higher than that of microscopy. Given that young children often swallow their sputum, stool-based MTB testing with Xpert MTB/RIF, which has a sensitivity of 68.2% and nearly 100% specificity [205], it has been listed as a testing option in recent WHO guidelines [149]. The sensitivity and specificity of Xpert for detecting rifampicin resistance in children are 86% and 98%, respectively [51].

In older children (over 10 years) and adolescents, the clinical presentations and diagnostic approach to PTB are similar to those in adults. They typically present with persistent cough, weight loss, night sweats, and fever, and radiographic findings often include cavitary lesions [206, 207]. In contrast, younger children with TB disease exhibit clinical signs such as fever, prolonged cough (over 2 weeks), weight loss, and failure to thrive [16, 52, 198].

EPTB signs vary by the affected organ. TB lymphadenitis commonly presents as initially painless and hard swelling that can form abscess-draining sinuses [5]. Central nervous system TB (TB meningitis) can manifest as altered mental status, cranial nerve palsies, headaches, vomiting, or seizures. Spinal TB (tuberculous spondylitis or Pott's spine) can lead to vertebral collapse and a kyphotic deformity known as Gibbus deformity [5, 52].

1.5.6. Overview of epidemiology of childhood TB

The epidemiological landscape of pediatric TB is influenced by various factors such as socioeconomic status, household TB exposure, and regional prevalence rates [16]. The burden of childhood TB often mirrors that of adult TB; where adult TB is prevalent, childhood TB is also likely to be significant. Conversely, in regions with a lower TB burden, childhood TB incidence is typically lower [208, 209].

TB in Children versus Adults

Children are less contagious than adults due to the paucibacillary nature of TB in this age group [210], which has historically led to it being overlooked in TB control initiatives [24]. Despite this, children represent a significant portion of TB morbidity and mortality, especially in resource-limited settings [211, 212]. TB infections acquired in childhood contribute to the future pool of TB cases, highlighting the need for attention comparable to that given to adult TB [210]. Children born in other countries contribute one-third of TB among people under the age of 18 in wealthy nations such as the United States (US) [213].

Global and National Statistics

In 2012, when childhood TB was first included in the WHO global report, there were an estimated 530,000 new cases in children under 15, making up 6% of overall TB cases [214]. By 2021, the estimated number of children with TB had increased to approximately 1.2 million, accounting for 11% of all TB cases, while adult men and women accounted for 56.5% and 32.5% of cases, respectively [40]. However, children made up only 7% of the total notified TB cases that year [42]. In Ethiopia, in 2021, children represented 10% of all notified TB cases, whereas adult men and women accounted for 51% and 39%, respectively [42].

TB Mortality and Incidence in Children

In 2021, children under 15 accounted for 14% of all HIV-negative TB deaths and 11% of TB incidence globally [40]. In 2020, these figures were 16% for HIV-negative TB deaths and 11% for TB incidence [45]. This suggests that children contribute a higher percentage to total TB mortality than they do to the total TB incidence. Unfortunately, recent reports for Ethiopia do not

provide specific figures on the national-level proportion of TB mortality among children [40, 44, 45].

Sites of TB Disease in Children

The lungs are the most commonly affected site of TB in children, accounting for up to 80% of all cases [48, 215, 216]. Among extra-pulmonary TB (EPTB) cases, TB of the lymph nodes is the most frequent (67%), followed by TB meningitis (TBM) at 13%, most common in children under three years old, pleural TB at 6%, miliary TB at 5%, and osteoarticular (bone/joint) TB at 4% [215]. Children are more likely to develop EPTB compared to adolescents and adults, who are more prone to PTB, "adult type" disease [16].

Key Age Group for Childhood TB Impact

Children under five are more susceptible to developing TB disease and have higher rates of severe or disseminated forms such as TBM [16, 198, 217]. This age group constitutes half of all childhood TB cases [218]. A modeling study indicated that 80% of TB-related deaths occur in children under five, and 96% of children under 15 who died from TB had not received treatment. [219].

1.5.7. Determinants of Childhood TB disease development

Understanding the determinants of childhood TB disease development is crucial for effective prevention and control strategies. Key determinants include BCG vaccination, HIV infection, young age, undernutrition, and close contact with a patient who has PTB.

BCG Vaccination:

BCG vaccination is a critical factor in the prevention of TB in children. Developed in 1921 from live attenuated Mycobacterium bovis by Albert Calmette and Camille Guérin at the Pasteur Institute, the BCG vaccine has been in use for nearly a century [220]. Administered intradermally [78], the dosage varies with age: 0.05 ml for newborns under one year and 0.1 ml for individuals older than one year [221]. WHO-approved BCG strains include the French Pasteur strain 1173 P2, the Danish strain 1331, the Glaxo strain (Copenhagen 1077), and the Tokyo strain 172, which account for over 90% of global BCG use [222]. The absence of a prior

MTB infection is associated with improved efficacy of the BCG vaccine against TB [223]. To prevent pre-vaccination exposure to MTB, the WHO recommends administering a single dose of BCG to newborns at birth or as soon as possible thereafter in regions with high TB prevalence [222]. Following this guideline, Ethiopia's Expanded Program on Immunization (EPI), initiated in 1980, schedules BCG vaccination at birth [224, 225]. Worldwide, 157 countries, including Ethiopia, have universal BCG vaccination policies. In contrast, countries like the United States, Italy, and Belgium have selective BCG vaccination policies [156].

The presence of a BCG scar at the injection site (typically the right upper arm) serves as a sensitive (surrogate) marker of BCG vaccination, usually forming weeks to months after the injection [226]. Over 90% of children vaccinated within the first week of life develop this scar [227, 228]. Undernourished children are less likely to develop a BCG scar compared to well-nourished children [229]. Several factors influence BCG vaccine-associated injection site reactions, including the BCG strain type (with children vaccinated with the Russian strain being less likely to develop a scar compared to those vaccinated with the Danish strain) [230] and the administration technique (not forming a post-injection wheal) [231]. However, the absence of a BCG scar does not indicate a lack of protection or the need for revaccination [221]. Studies have shown that children with BCG scars have better survival rates (lower all-cause mortality) and fewer hospitalizations than those without scars, suggesting that the BCG vaccine provides non-TB-specific clinical benefits [232-235]. Despite this, there is no significant association between the size of the BCG scar and the vaccine's effectiveness in preventing TB [236].

The vaccine's efficacy has been debated, with some studies suggesting limited effect [237-239] and while others report significant protection, particularly against severe forms of TB such as miliary TB and TB meningitis [79, 80, 240]. The efficacy of BCG also varies by geographic location, showing better protection at higher latitudes compared to regions near the equator, where Ethiopia is located, possibly due to the prevalence of NTM [75, 76, 241]. The duration of BCG vaccine effectiveness varies significantly between studies. An early meta-analysis found that BCG efficacy could last up to ten years following newborn vaccination [242]. An RCT in Great Britain involving 14-15-year-old children who were TST-negative at the start found that the BCG vaccine was 84% effective during the first five years and 77% effective over the first 20 years of follow-up [243]. Another meta-analysis later indicated that BCG vaccination provides

protection against both pulmonary and extrapulmonary TB for up to 10-15 years [78]. A population-based retrospective cohort study in Norway involving individuals aged 12 to 50 showed that vaccine efficacy was significant up to 9 years (61%), and 10-19 years (58%), excluding TB episodes in the first two years. However, efficacy was not significant after 20 years [80]. Recent meta-analyses suggest that BCG protects against TB in children under five but not in adolescents or adults [81].

Regarding BCG strains, some studies suggest that the Russian strain is less effective than the Danish and Japanese strains, with the latter two inducing higher proportions of MTB-specific polyfunctional IFN-γ, TNF-α, interleukin-2 (IL-2), and CD4+ T cells [244, 245]. However, other studies indicate no significant difference in efficacy between BCG strains, and there is no global consensus on the best strain to use [222, 223, 246]. Ethiopia uses the Danish strain [247], which has the highest rate (99%) of scar formation at the injection site [230].

HIV infection:

HIV infection significantly increases the risk of developing TB in children. Meta-analyses indicate that HIV-infected children have a 5- to 8-fold higher risk of TB incidence compared to their HIV-uninfected peers [248, 249]. The impact is more pronounced in infants, who face a 24-fold higher risk of TB if HIV-infected [250]. HIV infection also substantially increases the risk of TB-related death; a minimum of a 6-fold increased risk was reported in Ethiopia's study [251]. HIV infection compromises immune function, thereby increasing susceptibility to TB [252-254]. Children in advanced (severe) stages of HIV infection, particularly WHO clinical stages-3 and -4, are five times more likely to develop TB than children in non-severe stages [248]. However, antiretroviral therapy (ART) can reduce the risk by up to 70% [248]. A meta-analysis also identified that HIV infection and extra-pulmonary TB are highly associated [255].

Under 5 years of Age:

Those under five years of age are particularly vulnerable, with recent meta-analysis indicating, children under the age of five have a significantly higher risk of progression to TB disease than older children, such as those aged 5 to 9 years, 10 to 14 years, and 15 to 18 years. However, TB-infected children under the age of one year and under the age of five have a similar risk of developing TB within two years of infection (18% and 19%, respectively) [249]. Older children

and adolescents have a lower risk, with a 9% progression rate within two years post-infection [171].

Undernutrition:

Undernutrition is another significant determinant of TB development in children. An RCT found that a nutrition intervention for household contacts of TB patients reduced TB incidence by 39% (all types of TB) to 48% (microbiologically confirmed pulmonary TB) over a two-year follow-up period [256]. A case-control study in South India reported that children with a weight-for-age ratio at or below 70% of the expected value were more likely to develop active TB [82]. Furthermore, an experimental study discovered that 1,25-dihydroxy-vitamin D3 (1,25D), the active metabolite of photosynthesized vitamin D, enhances the maturation and activation of human monocytes and macrophages. This enhancement protects the macrophages against virulent tubercle bacilli [257].

Close Contact with TB Patients and Crowdness:

Children in close contact with pulmonary TB (PTB) patients are at a higher risk of developing TB. A meta-analysis found that household contact increases the risk by approximately four times compared to community peers [258]. Crowded living conditions further exacerbate this risk, as demonstrated in studies from Bangladesh and other regions [259]. The case-control study in Bangladesh showed that children who slept in less crowded rooms (two or less than two persons per room) had had a lower chance of developing TB [260].

Passive Smoking:

Passive smoking (exposure to second-hand smoking) is also one of the factors that increase the risk of developing TB disease in children [82, 261, 262].

Chronic illnesses:

Although not age-specific, a cohort study in Taiwan identified several chronic conditions—diabetes mellitus (DM), end-stage renal disease, liver cirrhosis, and chronic obstructive pulmonary disease—as risk factors for developing pulmonary TB (PTB) [263]. Another study from Britain, which included participants of all ages, found that malignancies and steroid use were also associated with a higher risk of TB [264]. A meta-analysis further corroborated that DM is linked to a two- to four-fold increased risk of active TB [265]. DM compromises both innate and adaptive immune responses, facilitating primary infection with MTB or reactivation of latent TB [266]. The risk of TB-diabetes comorbidity is particularly high in patients with poor glycemic control [267]. Each of these factors impacts the immune response and overall susceptibility to TB.

MTB Strain Type:

The strain type of MTB also matters in TB disease development as it influences the innate immune response [268]. The East Asian/Beijing genotype was independently associated with a shorter duration of illness before presentation and drug-resistant TB than the Euro-American genotype [269].

Genetic Susceptibility:

A retrospective cohort study in North Carolina revealed that the risk of developing active childhood TB is higher in blacks than whites [270]. With regard to infection rate too, blacks are more readily infected with MTB than whites [271, 272]. One justification for that, according to a systematic review, is that the capacities of skin to synthesize vitamin D post-ultraviolate B were significantly higher in whites than in black subjects [272]. The risk of progressive TB disease can be enhanced by genetic as well as acquired defects in host immune response pathways. Mutations in the genes for either the IFN-γ receptor or the IL-12 receptor, which lead to the absence of receptors on cell surfaces and thereby a functional defect, were identified as causing susceptibility to mycobacterial infection [273, 274].

Helmnthic Infectation:

One way that the human body defends itself from MTB is through the induction of a potent T-helper type-1 (Th1) immune response by tubercle bacilli infection, which in turn produces IFN-γ that activates phagocytic host cells to kill the bacilli [275]. However, T-helper type-2 (Th2) responses induced by helminth co-infections impair Th1 immune responses, and thereby limiting MTB control. The other mechanism by which helminth co-infection increases susceptibility, disease progression, and severity in TB is by enhancing arginase-1 activity, which is associated with increased lung inflammation [276].

1.5.8. Severe forms of childhood TB

Advanced TB disease in children under the age of 15 is often identified by the presence of cavities or bilateral disease on CXR. Severe EPTB is defined by the presence of miliary TB or TBM, indicating disseminated TB disease, at any age [277]. Additionally, EPTB forms other than lymphadenopathy (involving peripheral nodes or isolated mediastinal masses without airway compression) are classified as severe TB in children under 15 years [278]. The term "miliary" TB refers to the visual resemblance of disseminated lesions to millet seeds. These lesions are 1-2 mm yellowish nodules, histologically identified as granulomas. When these nodules appear in the lung, the radiographic pattern is termed "miliary" [101].

TBM is particularly severe and has high mortality and morbidity rates. A meta-analysis reported that, even with treatment, the risk of death from TBM in children is around 20% [279, 280], Furthermore, survivors face a greater than 50% risk of neurological sequelae, such as hearing loss [281], cognitive impairment, motor deficits, optic atrophy (visual impairment), and other cranial nerve palsies [280]. TBM occurs more frequently in children under five years old [16, 282].

TBM progresses through three stages [283, 284]. The initial stage, lasting more than one week, is marked by nonspecific symptoms such as low-grade fever, headache, irritability, lethargy, malaise, vomiting, photophobia, listlessness, and poor weight gain or loss. Infants may exhibit developmental delays, a bulging anterior fontanel, fever, cough, altered awareness, and convulsions [284]. Neck stiffness is uncommon in stage I [284, 285], making early diagnosis challenging due to the vague symptoms. A history of contact with an active TB patient is found

in about 50% of cases [286]. Stage II is characterized by lethargy, neck rigidity, positive meningeal signs, hypertonia, seizures, vomiting, and localized neurological deficits. Hydrocephalus, increased intracranial pressure, encephalitis with disorientation or movement disorders, speech impairment, and cranial nerve involvement (notably the sixth cranial nerve in 30%-50% of cases) are also observed, along with vision loss. Most diagnoses are made at this stage [284].

Diagnosing TBM using acid fast staining of CSF has a very poor sensitivity, less than 10% [287-289]. To diagnose TBM, MTB CSF culture has a sensitivity of 65%, and GeneXpert has a sensitivity of 60% [290].

BCG immunization can minimize the risks of severe disease and mortality from TB [171, 242]. A meta-analysis of case-control studies estimated BCG efficacy against TBM and miliary TB to be 73% and 77%, respectively [86]. A study shows there was no rise in TBM incidence after universal mandatory BCG immunization was replaced by vaccination of high-risk children [288]. [291]. Evidence from a ten-year retrospective study on TB in Ethiopia indicates that TBM accounts for 2.2% of all TB cases in children under 15 years old [89].

1.5.9. Treatment of TB disease

Effective multi-drug TB treatment was available since the 1970s [21]. Drug-susceptible TB is highly treatable [186]; cure rate of drug-susceptible TB in children is 95% - 100% [9]. The discovery of the etiology of TB by Robert Koch was the turning point towards finding a cure for TB disease [292]. Before the advent of effective chemotherapies, TB patients were cared for in sanatoriums, isolated medical facilities situated in high-altitude regions, providing fresh air and nutritious diets [293]. The development of anti-TB drugs in the mid-twentieth century led to a substantial decline in TB rates in Europe and North America until the 1980s, when the HIV epidemic triggered resurgence [294]. Improved living conditions, better nutrition, education, reduced poverty—collectively known as social determinants of health—and possibly sanatorium isolation all contributed to the significant reduction in TB cases and deaths well before the introduction of chemotherapy, which later accelerated the decline [295]. Streptomycin, introduced in 1945 but no longer had a first-line treatment marked the beginning of anti-TB drug

therapy. Subsequently, isoniazid, ethambutol, and rifampicin were developed in the 1950s, 1960s, and 1970s, respectively, and remain foundational to TB treatment today [292].

To determine an appropriate treatment approach, drug-susceptible TB is categorized as severe or non-severe. Non-severe TB includes peripheral lymph node TB, intra-thoracic lymph node TB without airway obstruction, simple TB pleural effusion or paucibacillary, non-cavitary TB limited to a single lung lobe, and without a miliary pattern [186]. The WHO recommends a minimum 6-month treatment for patients with new or relapsed drug-susceptible PTB and all forms of EPTB, excluding TBM and osteoarticular TB, in its guidelines from 2010, 2017, and 2022 [186, 296, 297].

In Ethiopia's drug-susceptible TB treatment guidelines, the intensive phase spans two months and consists of rifampicin, isoniazid, pyrazinamide, and ethambutol, following WHO recommendations. Rifampicin and isoniazid are continued for four months. TBM and osteoarticular TB require 12 months of treatment, including two months of intensive phase and 10 months of continuation phase with the same medications [170].

Per the 2022's WHO consolidated guidelines, children and adolescents aged 3 months to 16 years with non-severe TB should undergo a 4-month treatment regimen, comprising two months of intensive treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by two months of continuation treatment with isoniazid and ethambutol [186].

Serious adverse events in children are rare with recommended TB treatment regimens [298]. Isoniazid-induced pyridoxine deficiency can lead to peripheral neuropathies, especially in severely malnourished or HIV-positive children on ART, warranting daily supplementary pyridoxine doses [299]. In HIV-positive or malnourished children being treated for TB, a daily dose of 5–10mg of supplementary pyridoxine is recommended [298]. Though TB-drug-associated hepatotoxicity is uncommon in children, caregivers should be educated on early hepatotoxicity symptoms and liver function testing may be necessary [52].

Most children with TB experience improvement after a few weeks of anti-TB medication. However, lack of symptom resolution or worsening symptoms, persistent weight loss, and positive sputum smear after two months of treatment may indicate treatment failure, often due to

poor adherence. Treatment failure, more prevalent among HIV-positive children, suggests MDR-TB and necessitates thorough evaluation [298].

1.5.10. Predictors of unfavorable TB treatment outcomes in children

Treatment success is frequently referred to as a favorable outcome, whereas unfavorable TB outcomes include loss to follow-up, treatment failure, and death [300]. One of the key global indicators for monitoring the implementation of the WHO's End TB Strategy is the treatment success rate [30]. The global treatment success rate for children under the age of 15 was 88% in 2019 as well as in 2020, implying that the rate of unsuccessful (unfavorable) outcomes was 12% [40]. The goal is to achieve a treatment success rate of more than 90% by 2025, which means keeping unfavorable outcomes below 10% [30]. Although unfavorable outcomes are more common in the first few weeks of TB treatment, they can also occur during the continuation phase of TB treatment, which follows the first two months of an intensive phase of treatment [85].

Predictors of Unfavorable TB Treatment Outcomes in Children

1. **Child's Age**

Several studies have identified age as a significant predictor of TB treatment outcomes. Children under five years old, particularly those under two, are at higher risk of unfavorable outcomes compared to older children. A seven-year retrospective cohort study in South Africa found that children under 2 years had an increased hazard of death compared to 10–14 year-olds [59]. Similarly, studies in Nigeria and Lagos State indicated that the treatment success rate was significantly lower in younger children, emphasizing that younger age is a risk factor for unfavorable outcomes [67, 301]. However, a cross-sectional study in Benin reported no significant difference in treatment outcomes between children aged 0–4 and those aged 5–14 years [302].

2. **HIV infection**

HIV infection is a well-documented predictor of poor TB treatment outcomes. HIV-infected children have a higher risk of mortality and lower rates of treatment success compared to their HIV-negative peers [59, 303]. Studies in Benin and Nigeria reported significantly lower

successful treatment outcomes in HIV-positive children [301, 302]. Additionally, meta-analyses and retrospective studies from Ethiopia confirmed that HIV-infected children are more likely to have unfavorable outcomes [66, 69, 304, 305]. In contrast, some studies from Nigeria and the Congo found no significant difference between HIV-positive and HIV-negative children [67, 306].

3. **Commorbidities like Diabetes**

A prospective study in Tanzania and a meta-analysis have shown that diabetes increases the risk of treatment failure and death in TB patients [307]. A meta-analysis study also witnesses the same by reporting that diabetes comorbidity increases failure and death outcomes in TB patients [308].

4. **Undernutrition**

Undernutrition significantly increases the risk of unfavorable TB treatment outcomes in children. Even more than a decade old studies were reporting undernutrition is predictor of unfavorable TB treatment outcomes [309, 310]. A 2022 multicenter prospective cohort study conducted in India found that undernutrition at the start of TB treatment is associated with higher rates of treatment failure, relapse, and mortality [311].

5. **Treatment Adherence and History**

A cross-sectional study in Ethiopia showed more than 85% adherence to TB treatment was an independent predictor of treatment success in children under 15 years of age [70]. There is also a meta-analysis of interventional studies on adherence that has demonstrated the children in intervention arms had significantly higher rates of treatment success [312].

Previous TB treatment has been identified as a risk factor for mortality and poor outcomes. Studies in Nigeria, Pakistan, and Thailand indicated that children with a history of TB treatment had higher rates of unsuccessful outcomes compared to newly treated cases [85, 313, 314]. A meta-analysis of Ethiopian studies also showed that the success rate among children who had a previous history of TB treatment was significantly lower than that of newly treated cases [304]. Conversely, a study in Bhutan found no significant association between retreatment and unfavorable outcomes [315].

6. **TB Disease Severity and Type**

In a retrospective study in Nigeria and China, severe forms of TB, such as disseminated or miliary TB disease, were identified as predictors of unfavorable TB treatment outcomes [85, 316]. TBM was also identified as associated with an increased risk of death [317].

7. **Other predictors**

Other factors influencing TB treatment outcomes include male sex [65, 298, 299], rural residence [300, 302], and cigarette smoking [312]. Additionally, the presence of a BCG scar has been associated with a lower risk of mortality in patients with PTB, as found in a prospective study in Gambia [318]. Studies also identified smear positive-pulmonary TB [71, 313, 319], male sex [65, 301, 320], and rural residence [313, 321] predictors of unfavorable TB treatment outcome in children.

Studies in Ethiopia, same as some studie of other coontries, often classify transfer-out patients as having poor or unfavorable outcomes [65, 69], which may not be the case in reality because transfer-out patients may actually be cured or have their treatment completed.

1.6. Dissertation Theoretical/ Conceptual frameworks

This dissertation is predominantly grounded in the model of social determinants of health. Social determinants of health (SDH) lack a single, universally accepted definition, but they generally refer to the various conditions and pathways through which societal factors impact health, potentially modifiable through informed action [322]. According to the WHO, SDH encompass the conditions in which individuals are born, grow, work, live, and age, along with the broader set of forces and systems shaping these conditions [323]. The WHO further elaborates that these determinants include the social environment, physical environment, health services, and structural and societal factors, which collectively contribute to health inequities [324]. The Centers for Disease Control and Prevention (CDC) adds that SDH include essential resources such as food supply, housing, economic and social relationships, transportation, education, and healthcare, whose distribution across populations determines the length and quality of life [325].

Literature quantifies the impact of different health determinants: healthcare accounts for 25%, biological factors 15%, physical and environmental factors 10%, and socioeconomic determinants 50% [326].

Studies revealed that there are multiple factors that enhance the development of TB disease. Even though variability by statistical significance exists between literatures, the risk factors for developing TB disease identified by one or another include: BCG unvaccination, HIV infection, younger age group mainly during the first five years of age, undernourishment, close contact with PTB patients, exposure to an overcrowded environment, exposure to smoking, compromised immunity of the host, virulence of the bacteria, genetic susceptibility of the host, and infection with helminths. Being unvaccinated with BCG is further identified as a risk factor for severe forms of TB, namely, TBM and military TB. TB is curable with proper treatment, but certain conditions can impede recovery, leading to unfavorable outcomes such as death, loss of follow-up, or treatment failure. Despite conflicting reports on the importance of specific factors, common risk factors include lack of BCG vaccination, undernutrition, younger age, exposure to secondhand cigarette smoking, drug-resistant TB, severe forms of TB, poor adherence to treatment, and previous history of TB disease, as depicted in the conceptual framework below (Figure 2).

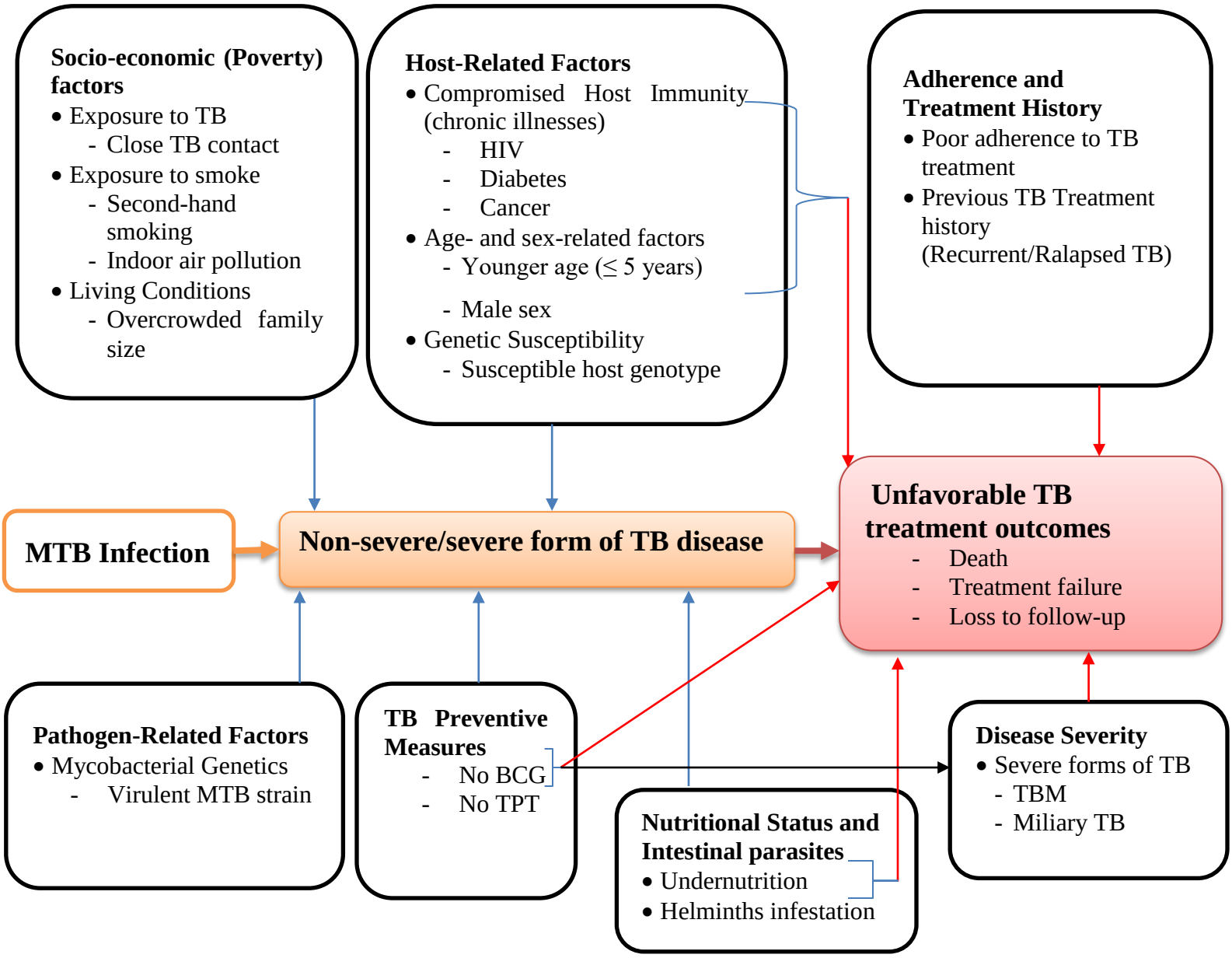


Figure 2. Conceptual framework of risk factors for TB disease and unfavorable treatment outcomes in children (developed from a literature review) [40, 67, 81, 85, 94, 248, 249, 256, 258, 261, 269, 273, 276, 303, 310, 311, 327-330]

2. General and specific objectives

2.1. General objective

- To describe the epidemiological patterns of childhood TB, identify predictors of TB-related deaths, assess determinants of TB disease, and identify predictors of unfavorable TB treatment outcomes among children aged 16 years or younger in urban areas of Central Ethiopia.

2.2. Specific objectives

- To describe the socio-demographic patterns of childhood TB and identify predictors of mortality among children aged 16 years or younger undergoing TB treatment in Urban Central Ethiopia.
- To identify determinants of TB disease development in general and in relation to BCG vaccination in children in Urban Central part of Ethiopia.
- To assess the magnitude of unfavorable treatment outcomes and estimate their relationship with baseline and sustained undernutrition among children aged 16 years or younger receiving TB treatment in Urban Central Ethiopia.
- To assess effectiveness of BCG vaccine against TB meningitis compared to all other forms of TB combined in Urban Central Ethiopia.

3. Methods and materials

3.1. Study areas and period

This dissertation study was conducted within healthcare facilities situated in Addis Ababa city, as well as Adama and Bishoftu towns in Central Ethiopia. These three urban research areas are positioned around 9° N and 39° E [331].

Addis Ababa serves as the capital and largest city of Ethiopia. As per the 2007 census, the total population of Addis Ababa was 2,738,248, with an annual population growth rate of 2.1% between 1994 and 2007. Within this population, there were approximately 656,233 individuals under the age of 15, with 195,932 aged 0–4, and 209,532 and 250,769 aged 5–9 and 10–14, respectively [332]. Utilizing the geometric population projection model, the city's total population in 2023 was estimated to reach 3,818,428, with over 915,103 individuals under the age of 15 [333]. However, this projection is likely an underestimate due to significant recent migration to the city [334].

According to the Addis Ababa City Health Bureau's first six-month performance report for 2017, healthcare facilities in Addis Ababa include 109 public health facilities (95 health centers and 14 hospitals), along with over 771 private or non-governmental healthcare facilities. Among these, there are 36 hospitals, four non-governmental hospitals, 31 non-governmental clinics, and over 700 clinics at various levels. TB treatment, which is for free, is available at 163 of these facilities, predominantly at governmental healthcare institutions [335].

Adama town, another study site, is located in the Oromia region, approximately 100 kilometers southeast of Addis Ababa. Its total population was 222,035 in 2007, with a 2.9% annual population growth rate [332]. Using a geometric population projection method, the population was estimated to be around 350,806 in 2023 [333]. There are approximately seven healthcare facilities providing TB treatment services in Adama: one public hospital and six health centers.

The third study site, Bishoftu town, also in the Oromia region, is halfway between Addis Ababa and Adama. In 2007, its total population was 100,114 [332]. Assuming a 2.9% population

growth rate, the population in 2023 was predicted to be around 158,176 [333]. Bishoftu had one public hospital, one military hospital, and five health centers providing TB treatment service.

Adama and Bishoftu are larger urban areas than other twons within a 100-kilometer radius of Addis Ababa. Residents in these areas have easy access to telephones for phone interviews. Their proximity to Addis Ababa is assumed to facilitate access to advanced diagnostic procedures, reducing the likelihood of TB misdiagnosis.

The study included data from children treated for TB disease between June 6, 2014, and February 16, 2022. For the case-control study, data from control participants were collected between June 1, 2022, and June 24, 2022.

3.2. Study designs

A retrospective cohort study design was used to provide the descriptive epidemiology of childhood TB, identify predictors of death among children treated for TB, and assess the magnitude and predictors of unfavorable TB treatment outcomes. Additionally, 1:1 matched case-control design and 1:4 unmatched case-control designs were employed to identify determinants of TB disease and assess the effectiveness of the BCG vaccine in preventing TBM specifically compared to all other forms of TB collectively in children, respectively.

3.3. Source and study population

All children aged 16 or under diagnosed with drug-susceptible PTB or EPTB TB and initiated on TB treatment were the source population for this study. The study population was children aged 16 or under diagnosed with with drug-susceptible PTB or EPTB TB and initiated on TB treatment in the study facilities. Children transferred to the study healthcare facilities after commencing TB treatment at another facility were excluded due to unavailability of baseline data such as nutritional status at treatment initiation. Children who were initially diagnosed with TB and started on TB treatment but later had their diagnosis changed to a different medical condition, regardless of how close they were to completing TB treatment, were also excluded from the study.

For the matched case-control study, cases, controls, and matching criteria were defined as follows:

Cases: The cases were children aged 16 and under who were diagnosed with PTB or EPTB and treated as drug-suceptible TB. The patients (cases) who were treated for drug-suceptible TB and whose outcomes were known between May 1, 2015, and June 15, 2022, were extracted from the TB registers.

Controls: The controls were children who had never been diagnosed with PTB or EPTB based on verbal reports from their parents or caregivers (i.e., the controls were not diagnosed with TB at an age when their equal-age cases had been diagnosed with TB). Furthermore, controls were screened during data collection to ensure they were free of potential TB symptoms listed in the WHO [174] and Ethiopia's TB national guidelines [336] such as prolonged cough for ≥ 2 weeks, fever, night sweets, weight loss, and the extra-pulmonary site or organ-specific TB symptoms such as cervical or axillary lymphadenopathies, spinal deformity (kyphosis or gibbous), and signs of meningeal irritation (neck stiffness, seizure). The controls were drawn from the same birth cohort as the cases, minimizing potential biases related to varying BCG vaccination coverage and the use of possibly different BCG vaccine strains across years. To determine the age of a control for recruitment during the interview, the case's age at the time of TB diagnosis was used to ensure alignment within the same birth cohort. These controls were selected from children receiving treatment for non-TB illnesses or attending non-ill visits for health promotion or preventive services, such as the Expanded Program on Immunization (EPI), vitamin A supplementation, and reproductive health counseling at the same healthcare facilities as the cases. This approach aimed to ensure that the controls represented a population-based sample.

Matching: TB-sick children were matched 1:1 by age and study facilities with children who had never experienced TB. Age was chosen as a matching variable with the premise that it is a strong confounder. In the investigation assessing the effectiveness of the BCG vaccination against TBM, the cases were children diagnosed with TBM, and the controls were children diagnosed with any TB type other than TBM.

3.4. Study variables

The outcome variable for the objective assessing predictors of death through survival analysis was the time-to-death (measured in months) of a child on TB treatment. The end-of-follow-up periods for the 6 and 12-month regimens were 6 and 12 months, respectively. Independent variables included the child's BCG vaccination status at birth or within 15 days (vaccinated or not vaccinated), age, sex, HIV status (HIV-negative or -positive), TB treatment history (whether the case was new or a relapse), nutritional status at the start of TB treatment (normal or undernourished), and nutritional status two months after TB treatment initiation (normal or undernourished).

In the matched case-control study investigating the factors influencing TB, the dependent variable was whether the child had ever been diagnosed with TB disease, categorized as either "yes" or "no", reported by the parent or guardian. The primary independent variable was the child's BCG vaccination status at birth or within two weeks after birth. Control variables included sex, HIV status, presence of a cigarette-smoking family member living with the child, and prior or concurrent household TB patient contact.

For the study that aimed to examine predictors of unfavorable treatment outcomes in childhood TB, the dependent variable was the child's TB treatment outcome, categorized as “favorable” or “unfavorable”. Independent variables encompassed the child’s age, sex, baseline nutritional status at TB treatment initiation, nutritional status sustained two months post-treatment initiation, HIV status, TB treatment history, and BCG vaccination status within 15 days of birth.

The outcome variable in the study evaluating the efficacy of BCG vaccination in preventing TBM was the occurrence of TBM in patients, categorized as either “yes” or “no”.

3.5. Operational definitions

Drug-susceptible TB (DS-TB): “A bacteriologically confirmed or clinically diagnosed case of TB without evidence of infection with strains resistant to rifampicin and isoniazid” [186].

New TB: “patients that have never been treated for TB or have taken anti-TB drugs for less than one month” [170].

Relapsed TB: "Patients who were declared cured or had their most recent treatment course completed and recently have been diagnosed with recurrent TB" [170].

Under nutrition: In this study, severe acute malnutrition and moderate acute malnutrition were classified as under nutrition.

Normal, moderate acute malnutrition (MAM), and severe acute malnutrition (SAM): The nutritional status of each child was evaluated using various indices, including the Body Mass Index (BMI)-for-age-z-score, Weight-for-Height/Length (WH/L)-z-score, mid-upper-arm circumference (MUAC), or Weight-for-Age percentile, depending on their age appropriateness and data availability. Essential measurements such as weight, height (or length for children under two years old), age, and MUAC, used for determining nutritional statuses, were extracted from TB treatment registers. In cases where a child's height or length measurements were absent in the registers, the weight-for-age chart, developed by CDC for children aged 2 to 20 years, was employed to identify underweight. The cutoff values used to distinguish between normal, MAM, and SAM are detailed in Table 1.

Table 1. Indices used to assess the nutritional status of childhood TB patients (≤ 16 years old) in Urban Central Ethiopia, 2014–2022

Option	Child age	Index	Cutoffs for nutritional status		
			Normal	MAM	SAM
Option 1 [337]	5-18 years	BMI-for-age-z-score	$-2 \leq z \leq +1$	$-3 \leq z < -2$	$z < -3$
Option 2 [338]	0 – 59 months	WH/L-z-score	$-2 \leq z \leq +1$	$-3 \leq z < -2$	$z < -3$
Option 3 [337]	6 -59 months	MUAC	≥ 125mm	115 – 125mm	< 115mm
	5-9 years	MUAC	≥ 145mm	135 – 145mm	< 135mm
	10-14 years	MUAC	≥ 185mm	160 – 185mm	< 160mm
Option 4 [339]	2 – 20 years	CDC weight-for-age percentile	5^{th} -95^{th}	$<5^{th}$ is underweight	

Favorable and unfavorable TB treatment outcomes: Children undergoing TB treatment were broadely categorized into either favorable or unfavorable outcomes following the guidelines established by the WHO [340].

Favorable (successful) outcome: Children who were cured or completed their treatment defined as smear or culture conversion to negative or clinical improvement on anti-tubercular treatment

Unfavorable outcome: Composite outcome of death, treatment failure, or lost to follow-up of children who were treated for TB disease

The WHO definitions of unblended treatment outcomes for drug-susceptible TB are as follows [340]:

Cured: A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion

Treatment completed: A TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable

Treatment failed: A TB patient whose sputum smear or culture is positive at month 5 or later during treatment

Died: A TB patient who dies for any reason during the course of treatment

Lost to follow-up: A TB patient whose treatment was interrupted for 2 consecutive months or more

Not evaluated: A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as patients for whom the treatment outcome is unknown to the reporting unit

3.6. Sample size

We used the sample size determination formula for the Cox proportional hazards model that compares the survival curves of two groups [341].

The formula is written as follows:

$$n_1 = \frac{mk}{kP_E + P_C} \quad , \qquad n_2 = \frac{m}{kP_E + P_C}$$

$$m = \frac{1}{k}\left(\frac{kHR + 1}{IHR - 1}\right)^2 \left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2$$

Where,

m = total expected number of events (deaths) across both exposed and control groups

k = the ratio of participants in the exposed (BCG vaccinated) group to the control (BCG unvaccinated) group

P_E = Probability of failure in an exposed group over time

P_C = Probability of failure in the control group over time

HR = Assumed hazard ratio for the exposed group versus the control group

α = Level of significance (probability of type one error).

β = Type-two error probability

$1-\beta$ = Test power

Thus, with a significance level of 5% and a standard normal distribution value of 1.96, achieving a power of 80% with a cut-off point for a 20% error at 0.84 [342], a postulated hazard ratio of 0.5 for death among children vaccinated with BCG compared to those unvaccinated, and based on previous studies where the probability of failure in exposed control groups equals 0.08 and 0.24, respectively [232], and using k=4 with an assumption that 81% of the population had scars and 19% did not [87], the total sample size required would be 628 cases of TB (502 BCG vaccinated versus 126 not vaccinated).

For the case-control study, a formula to determine the sample size for individually matched studies with 1:1 matching [343] was employed to compute the required number of cases.

The formula is: $N= \{[Z_{\alpha/2}(1+\Psi) + 2Z_{\beta}(\Psi)^{1/2}] / (\Psi-1)\}^2/[k(\Psi+1)\pi_p(1-\pi_p)]$

Where $k = 1/[1+(\Psi-1)\pi_p]$, and

N = is the required number of cases

$Z_{\alpha/2}$ = the generic value of Z that corresponds to a probability of type I error (α)

Z_β = the generic value of *Z* that corresponds to a probability of *type II error (β)*

Ψ = expected odds ratio

π_p = *prevalence of exposure to BCG scar*

Because BCG scar is a sensitive marker of BCG vaccination [226], we used its proportion in the population to calculate our sample size. Taking $Z_{\alpha/2}$ of 1.96 for 5% significance level (α), Z_β of 0.84 for 80% power, and assuming 81% of children are exposed to BCG scar [87], the required number of cases to detect an odds ratio of 2.00 was calculated to be 256. As a result, the total number of cases and controls became 512, yielding 256 matched case-control pairs.

The unmatched case-control research included all children with TBM and used a case-to-control ratio of 1:4.

3.7. Sampling methods

Healthcare facilities providing TB diagnosis and treatment services were selected through a random sampling process, with stratification in the Addis Ababa, Adama, and Bishoftu areas. In Addis Ababa, three hospitals were randomly chosen from a total of six governmental hospitals, and 23 governmental health centers were selected randomly from a pool of 95 centers offering TB treatment services. In Adama, one government hospital and two health centers were randomly selected from the five facilities providing TB services. Similarly, in Bishoftu, one hospital and two health centers were randomly chosen from the available options. This sampling strategy resulted in a total of 32 healthcare facilities being included in the study. All children treated for TB in these facilities who met the inclusion criteria were included in the study of descriptive epidemiology childhood TB pattern and predictors of TB death.

For the matched case-control study, the sampling frame comprised a list of 524 childhood TB patients whose BCG vaccination status known and entered into SPSS software. The cases were thus ransdomly selected from this sampling frame. Controls were sequentially selected at triage from the same healthcare facilities where the cases were treated. TB diagnosis in children is challenging and often delayed [344]. Thus, to avoid enrolling unrecognized early-stage active TB patients or sub-clinical (asymptomatic but infectious) or misdiagnosed TB cases as controls, the

controls were recruited after the cases' TB treatment outcomes were determined. Delaying control recruitment allows for more time for an unrecognized or subclinical TB to manifest clearly, lowering the risk of misclassification bias. Similarly, it minimizes the chance of enrolling in misdiagnosed TB, which would later be changed to another medical diagnosis.

In the TB treatment outcomes study, data from all children who were analyzed for the survival analysis study were included.

To assess the efficacy of BCG vaccination against TBM, all TBM patients were selected, and four controls for each case were randomly chosen from a list of all other TB types using SPSS software.

3.8. Survey instruments and data collection

The content of the TB register was utilized to generate a checklist and extract data. This checklist was augmented with a structured questionnaire (see Annex-1) to gather additional information that could not be captured solely through the checklist. This included data such as BCG vaccination status, the child's schooling, presence of a smoking family member living with the TB-sick child, and the existence of a TB-sick individual in the household prior to or during the child's illness and TB diagnosis. Telephone interviews were conducted with parents or caregivers to collect these data, as they did not have designated fields in the TB register. Oral reports of BCG vaccination status were considered reliable, given that the only vaccine administered via injection at birth or within two weeks of delivery in Ethiopia is the BCG vaccine [225].

To accommodate the language abilities of the study participants, the data collection tool was translated into Amharic (see Annex-2a and -2b) and Afan Oromo (see Annex-3a and -3b). For some patients, data collection extended until the completion of their TB treatment or until their treatment outcome was determined, with further data collection carried out from May 10, 2022, to June 15, 2022, depending on the date when the treatment outcome was recorded in the TB treatment register.

3.9. Data management and analysis

EpiData version 3.1 was utilized for data entry, followed by data export to Stata version 14 for cleaning and subsequent analysis. Descriptive statistics were employed, including frequency tables and a line graph.

To assess the proportional hazards (PH) assumption, a log-log graphical test was conducted initially. Independent variables demonstrating parallel curves for their categories were considered for inclusion in the Cox PH survival analysis model. Additionally, a statistical goodness-of-fit test was performed to supplement the graphical assumption test. Variables with p-values exceeding 0.05 were deemed to satisfy the PH assumption and were included in the Cox PH model. In instances where log-log curves crossed within variable categories, disaggregated analysis was conducted, separately examining survival functions for times below and above the crossing point. Variables with ambiguous graphical test results but positive goodness-of-fit results were treated as time-varying in the extended Cox model to accommodate any potential violations of the PH assumption. Initially, a single covariate Cox PH model was executed to identify variables with p-values ≤ 0.20 for crude hazard ratio (cHR), serving as candidates for the final multivariable Cox PH model. Model selection between the Cox PH and extended Cox models was determined via the log likelihood ratio test. Covariates with p-values < 0.05 for adjusted hazard ratio (aHR) were reported as independent predictors of death in children undergoing TB treatment. Confidence intervals (CI) at the 95% level were provided for both crude HR and aHR. Since BCG vaccination status was collected through phone interviews, data for some children whose surrogates could not be reached by phone was likely missing. Therefore, a missing data analysis was conducted to justify the use of the complete case analysis method. This involved comparing the distribution of outcome variables and independent variables between children with and without recorded BCG vaccination status. Chi-square tests were used to determine if there were statistically significant differences in these distributions. If the missing data analysis showed no statistically significant differences, it was assumed that using the complete case analysis method would be valid and provide unbiased estimates [345].

For the matched case-control study, a conditional logistic regression model was employed to assess associations, calculating matched crude odds ratios (mCOR) with corresponding 95% CI. Variables with p-values ≤ 0.2 during bivariate analysis were selected as candidates for multivariable analysis. Variables achieving a p-value < 0.05 for the matched adjusted odds ratio

(mORadj) were reported as significant determinants of TB disease, odds ratios being calculated from discordant pairings.

To evaluate the duration of BCG vaccination effectiveness in preventing TB disease, predictive probabilities were calculated for vaccinated and unvaccinated groups using a multivariable unconditional logistic regression model. These probabilities were then plotted against the children's ages.

The association between clinical characteristics and unfavorable TB outcomes was estimated using log-binomial regression. Variables with a p-value ≤ 0.2 for crude risk ratio (cRR) in bivariate analysis were considered for inclusion in the multivariable model. Significant predictors of unfavorable TB treatment outcomes were identified as variables with p-values < 0.05 for their adjusted risk ratios (aRR). To mitigate the impact of multicollinearity, separate multivariable models were developed for the child's nutritional status at the onset of TB treatment and two months later, at the initiation of the continuation phase. The effects of these statuses on TB treatment outcomes were examined independently.

Finally, the relationship between BCG vaccination and the risk of TBM was assessed using unconditional logistic regression, computing both crude odds ratios (cOR) and adjusted odds ratios (aOR). A P-value of < 0.05 was used to determine a significant association.

3.10. Data quality assurance

To ensure data quality, the data collection tool was pre-tested and revised before actual data collection began. Clinical nurses and health officers received training to extract data and conduct the questionnaire. Additionally, the principal investigator ckecked the completed checklists for correctness and completeness and conducted follow-up phone call with parents or guardians to verify the accuracy of the data. EpiData was used for data entry to minimize errors, as it includes built-in checks based on variable definitions. For instance, numeric fields only accept numbers with a specified pre-defined number of decimal places created during quesfile formation, and date fields do not accept invalid dates. Additional checks, such as “must to enter”, “legal ranges” for numeric variables, “label blocks” for categorical variables, and skip patterns, were implemented to reduce data entry errors further. Finally, the dataset in EpiData from was

imported into Stata for further cleaning. This process involved computing frequencies to detect missing values and identifying outliers applying ascending and descending pattern analyses. These steps ensured the accuracy and reliability of the collected data.

3.11. Ethical considerations

This study was approved by the Institutional Review Board (IRB) of Addis Ababa University's College of Health Sciences under protocol number 057/19/SPH. Letters of support were obtained from the Addis Ababa City Administration and the Oromia Regional State's Health Bureaus, granting access to the healthcare facilities involved in the study. Access to TB registration data and permission to contact the patients' parents or caregivers were subsequently granted by the medical directors of the involved healthcare facilities.

Before conducting the phone interviews, informed oral consent was obtained from the parents or guardians of the children who had been treated for TB. Additionally, assent was sought and obtained from children aged 8 years and older, ensuring their willingness to provide their data through their parents or guardians. A similar approach informed consent and assent was applied during face-to-face interviews with the children selected as controls. The parents and older children were assured that their de-identified data would not be shared with anyone and that only a summary of all individuals' data, with no personal identification, would be published to inform decision-makers and improve childhood TB prevention and control activities.

Participation was emphasized as important and voluntary, and participants were assured that no harm would result from declining participation. The consent and assent processes were thoroughly documented using forms annexed as -4a, -4b, -7a, and -7b. These ethical protocols were rigorously followed to ensure the rights and well-being of the participants throughout the study. The careful consideration of ethical standards underscores the commitment to conducting the research with integrity and respect for all the participants.

4. Summary table of study objectives and methods

The dissertation work outlined by the specific objectives, including the associated designs, study populations, estimated sample sizes, sampling procedures, data collection tools, and analytic methods, has been summarized below (Table 2).

Table 2. Summary of the dissertation work on childhood TB in central Ethiopia, organized by the specific objectives and accompanying methods

Specific Objective	**Study Design**	**Study Population**	**Sample Size**	**Sampling procedure**	**Data Collection Tools**	**Method of Analysis**
1. Assessing epidemiologic patterns and predictors of death of children on TB treatment	Retrospective cohort	Children treated for TB disease	502 BCG vaccinated, 126 without BCG, A total of 628	All childhood TB patients in the selected healthcare facilities	Checklist and questionnaire	Descriptive and extended Cox challenged Cox PH regression
2. Identifying determinants of TB disease development	Matched case-control	Children with and without TB disease	256 cases, 256 controls	Simple random sampling for case selection and sequential for control	Checklist and questionnaire	Conditional logistic regression
3. Identifying predictors of unfavorable TB treatment outcome	Retrospective cohort	Children receiving TB treatment	502 BCG vaccinated, 126 without BCG, 628 total	All childhood TB patients in the selected healthcare facilities	Checklist and questionnaire	Log-binomial
4. Assessing effectiveness of BCG vaccine against TBM than other types of TB	unmatched case-control	Children with TB disease	22 cases, 88 controls	Simple random sampling for control selection and all patients of TBM	Checklist and questionnaire	Binary logistic regression

5. Results

5.1. Descriptive epidemiology of childhood TB patients

5.1.1. Socio-demographic characteristics of childhood TB patients

A total of 650 children aged 16 years and younger who were initially treated for TB were identified from the TB registers. Successful phone interviews were conducted with 534 (83.4%) of the children's families or guardians. During the interviews, the caregivers or guardians of 10 (1.9%) children reported that further investigation revealed their children's illnesses were lymphoma, brain stem glioma, and Crohn's disease rather than TB. Consequently, these 10 children were excluded, leaving 640 included in the analysis: 524 (81.9%) children who could be reached by phone and 116 (18.1%) children who could not be reached by phone.

Of the 640 children included, 368 (57.5%) were female. The mean (standard deviation) age of the patients was 10.0 (5.4) years. Four hundred and fifty-five children (71.1%) were residents of Addis Ababa. Among the 519 children with a known daytime spending place, 376 (72.4%) were in school (including kindergarten), and 20 (3.9%) were in daycare, together accounting for 76.3% of the total TB-sick children involved in the study. However, 123 (23.7%) were spending time at home when they were diagnosed with TB, of which 111 (90.2%) did not attend school (kindergarten) because they were not of school age (< 4 years).

One hundred and ninety-eight (52.7%) of those enrolled in school were in grades one through six. Two hundred and fifty-two (67.0%) were attending a public school at the time of the TB diagnosis. One hundred and sixty-five mothers (32.6%) and 98 fathers (20.1%) of the children had no formal education. Out of the total number of children, 560 (87.5%) were diagnosed with and treated for TB after 2015, when GeneXpert MTB/RIF® was introduced (Table 3).

Table 3. Socio-demographic characteristics of childhood TB patients (≤16 years old) and their families in Urban Central Ethiopia, 2014-2022

Characteristics	Category	Frequency (%)
Sex (n=640)	Male	272 (42.5)
	Female	368 (57.5)
Age in years (n=640)	Mean (standard deviation) = 10.0 (5.4)	
Region of residence (n=640)	Addis Ababa city adminstration	455 (71.1)
	Oromia	165 (25.8)
	SNNPR	9 (1.4)
	Amhara	8 (1.3)
	Other regions	3 (0.5)
Where child was spending at the time of TB diagnosis (n=519)	In school (including kindergarten)	376 (72.4)
	At home	123 (23.7)
	At daycare	20 (3.9)
Child's education (n=376)	Kindergarten	40 (10.6)
	Grade 1 to 6	198 (52.7)
	Grade 7 to 8	81 (21.5)
	Grade 9 to 10	57 (15.2)
The type of school the child was attending (n=376)	Public	252 (67.0)
	Private	124 (33.0)
Mother's education (n=506)	Didn't attend formal school	165 (32.6)
	Grade 1 to 6	66 (13.0)
	Grade 7 to 8	50 (9.9)
	Grade 9 to 12	115 (22.7)
	Diploma	31 (6.1)
	Degree and above	35 (6.9)
	Mother was not alive	44 (8.7)
Father's education (n=487)	Didn't attend formal school	98 (20.1)
	Grade 1 to 6	57 (11.7)
	Grade 7 to 8	50 (10.3)
	Grade 9 to 12	129 (26.5)
	Diploma	40 (8.2)
	Degree and above	62 (12.7)
	Father was not alive	51(10.5)
Year the child diagnosed with TB (n=640)	2014	13 (2.0)
	2015	67 (10.5)
	2016	69 (10.8)
	2017	112 (17.5)
	2018	102 (15.9)
	2019	106 (16.6)
	2020	107 (16.7)
	2021	64 (10.0)

5.1.2. Clinical characteristics of the childhood TB patients

Six hundred and seventeen (96.4%) of the children were newly diagnosed with TB. Three hundred and sixty-seven (57.3%) of them had EPTB, while the remaining 273 (42.7%) had PTB, with 159 (24.8%) being pulmonary-negative and 114 (17.8%) pulmonary-positive. Among the EPTB patients, 210 (57.3%) had TB lymphadenitis, 26 (7.1%) had pleural TB, 25 (6.8%) had osteoarticular TB, 24 (6.5%) had intestinal TB, and 22 (6.0%) had TBM.

Out of the 273 PTB patients, 120 (44.0%) were diagnosed using GeneXpert MTB/RIF®, 196 (71.8%) using sputum smear microscopy, and 43 (15.8%) using both tests. One hundred and thirteen (20.8%) of all TB patients underwent GeneXpert examination, revealing MTB in 84 (63.2%) cases; among them, 79 (59.4%) showed no rifampicin resistance (RR), while 5 (3.8%) had indeterminate RR. MTB was not detected in the remaining 49 (36.8%) patients tested with GeneXpert. Thirteen (9.8%) of the 133 GeneXpert tests were performed on non-sputum samples such as lymphoid discharge, cerebrospinal, pleural, or peritoneal fluids. Of the 196 PTB patients, 67 (34.5%) tested positive with sputum smear microscopy.

When TB treatment commenced, 194 children (30.3%) were undernourished; among them, 109 (17.0%) had MAM, and 85 (13.3%) had SAM. Only 13 (6.7%) of the undernourished children received nutritional assistance in the form of a plump nut or plump sup. Of the 629 children who survived for two or more months after starting TB treatment, 116 (18.4%) were undernourished: 77 (12.2%) had MAM and 39 (6.2%) had SAM.

During the intensive phase of treatment, 18 children (2.8%) missed at least one dose (not shown in the table). All 640 children had known HIV status, and 85 (13.3%) were living with HIV. BCG vaccination status was known for 524 (81.9%) of the children, with 315 (60.1%) receiving the vaccine within two weeks of birth. Among the 524 children, 56 (10.7%) were living with a family member who smoke cigarettes. Among the 640 children, 557 (87.0%) had no prior or concurrent known sick family member with TB living with them, while 78 (12.2%) had at least one known household contact with PTB; among these, 77 (12%) had smear-positive contacts and 1 (0.2%) had a smear-negative contact. Only 16 (20%) of the 80 children under the age of two had household contact with PTB (Table 4).

Table 4. Miscellaneous characteristics of childhood TB patients (≤16 years old) in Urban Central Ethiopia, 2014-2022

Characteristics	Category	Frequency (%)
TB treatment history (n=640)	New	617 (96.4)
	Relapse	23 (3.6)
TB type (n=640)	Extra-pulmonary	367 (57.3)
	Pulmonary-negative	159 (24.8)
	Pulmonary-positive	114 (17.8)
Extra-pulmonary TB type (n=367)	TB lymphadenitis	210 (57.2)
	Pleural TB	26 (7.1)
	TB of the spine or bone	25 (6.8)
	Intestinal TB	24 (6.5)
	TB meningitis (CNS TB)	22 (6.0)
	TB peritonitis	12 (3.3)
	Other	1 (0.3)
	Not recorded	47 (12.8)
GeneXpert MTB/RIF® result (n=133)	MBT detected, RR not detect	79 (59.4)
	MTB detected, RR indeterminate	5 (3.8)
	MBT not detected	49 (36.8)
Sputum smear result (n=194)	Positive	67 (34.5)
	Negative	127 (65.5)
Child's nutritional status at the time of TB treatment start (n=640)	Normal	446 (69.7)
	MAM	109 (17.0)
	SAM	85 (13.3)
Child received nutritional support (n=194)	Yes (plump nut or plump sup)	13 (6.7)
	No	181(93.3)
Child's nutritional status if survived to two months after starting TB treatment (n=629)	Normal	513 (81.6)
	MAM	77 (12.2)
	SAM	39 (6.2)
Child's HIV status (n= 640)	Positive	85 (13.3)
	Negative	555 (86.7)
BCG vaccination at birth or within 15 days of birth (n=524)	Received	315 (60.1)
	Not received	209 (39.9)
A smoking family member living with the child (n=524)	Yes	56 (10.7)
	No	468 (89.3)
A previous or concurrent household TB contact (n=640) in child's age	No household TB contact	557 (87.0)
	Pulmonary-positive	77 (12.0)
	Pulmonary-negative	1 (0.2)
	EPTB	5 (0.8)
Prior or concurrent TB type in household in a child under the age of two (n=80)	Pulmonary-positive	16 (20.0)
	Pulmonary-negative	0 (0.0)
	EPTB	2 (2.5)

5.1.3. Childhood TB disaggregated by age

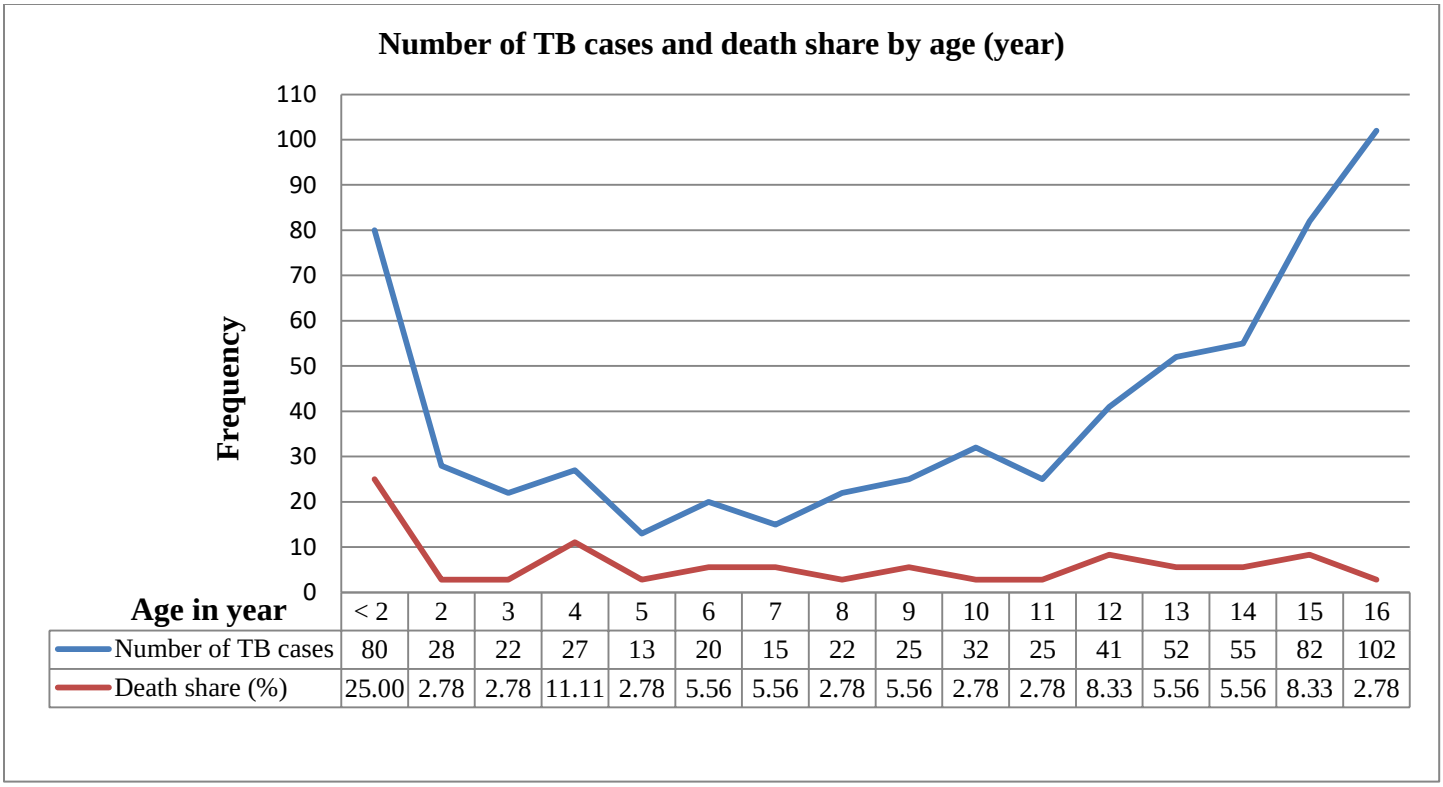
Eighty (12.5%) of children diagnosed with TB were under the age of two, while 157 (24.5%), 94 (14.7%), 205 (32%), and 184 (28.8%) were under the age of five, between five and nine, ten to fourteen, and fifteen to sixteen years old, respectively. Children under the age of two accounted for 25.0% of all deaths. Children aged 0-4, 5-9, 10-14, and 15-16 years accounted for 41.7%, 22.2%, 25.0%, and 11.1% of all deaths, respectively. Out of the 640 children who initiated TB treatment, 36 (5.6%; 95% CI = 4.0–7.7%) died during the treatment (Table 5). Five (0.8%) patients were recorded as lost-to-follow-up on TB registers, but their deaths were confirmed through phone interviews with their caregivers, thus counted as died outcome. Except for one death, all occurred within six months of initiating TB treatment. The remaining 604 patients (94.4%; 95% CI, 92.3–96.0%) were censored (i.e., cured, treatment completed, or treatment failed).

Table 5. Number of TB patients and proportion of deaths by age group among children undergoing TB treatment in Urban Central Ethiopia, 2014-2022

Age (years)	**Number of TB patients (%), n=640**	**Proportion of deaths (%), n= 36**
Under 2	80 (12.5)	9 (25.0)
0-4	157 (24.5)	15 (41.7)
5 -9	94 (14.7)	8 (22.2)
10-14	205 (32.0)	9 (25.0)
15-16	184 (28.8)	4 (11.1)
Over death rate = 36/640 (5.6%; 95% CI = 4.0 – 7.7%)		

The following line graph illustrates the age-related pattern of TB disease frequency and the proportion of TB deaths attributed to each age group out of the total TB deaths (i.e., 36). Following a decline after the age of two, the number of TB patients began to rise again around the age of 12 and reached its peak at the age of 16.

Upon examining the percentage share of deaths by age for children who died while undergoing TB treatment, we observed that children under two years old had the highest share (25%). Furthermore, the death share appeared stable, remaining below 10% for practically all ages from two years and beyond (Figure 3).



Age in year	< 2	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Number of TB cases	80	28	22	27	13	20	15	22	25	32	25	41	52	55	82	102
Death share (%)	25.00	2.78	2.78	11.11	2.78	5.56	5.56	2.78	5.56	2.78	2.78	8.33	5.56	5.56	8.33	2.78

Figure 3. Distribution of childhood TB cases and proportion of death by age in Urban Central Ethiopia, 2014-2022

5.2. Predictors of death among children on TB treatment

5.2.1. Missing data on BCG vaccination status

The BCG vaccination status of 116 (18.1%) of the children involved in the study was missing due to a lack of a phone contact address for interview purposes. Consequently, it was examined whether the children with missing BCG vaccination status was associated with any of the covariates included in the multivariable analysis and with the outcome variables. None of the factors showed a significant association ($P \geq 0.05$) with missing values for BCG vaccination status (Table 6). Therefore, we proceeded with a complete-subject analysis to assess predictors of death among children undergoing TB treatment.

Table 6. The missing data regarding BCG vaccination status and its relationship with other covariates and outcome variables

Characteristics	**BCG status known (n=524)**	**BCG status missing (n=116)**	**P-value for Chi-square**
Age less than 10 years (%)	209 (39.9)	42 (36.2)	0.46
Female sex (%)	300 (57.3)	68 (58.6)	0.79
HIV positive (%)	63 (12.0)	22 (19.0)	0.05
Undernutrion at baseline (%)	154 (29.4)	40 (34.5)	0.28
Relapse TB (%)	20 (3.8)	3 (2.6)	0.78*
Died outcome (%)	29 (5.5)	7 (6.0)	0.83
Unfavourable treatment outcomes (%)	35 (6.7)	7 (6.0)	0.80

*p-value for Fisher's exact test

5.2.2. Multivariable analysis of predictors of death among children on TB treatment

The log-log plot satisfied proportional hazards (PH) assumptions for sex, nutritional status at the start of TB treatment, nutritional status two months later, age category, TB treatment history, and an interaction term of BCG vaccination with age category. However, the graphical assumption test for HIV status showed diverging curves, indicating ambiguity regarding PH. Nevertheless, all covariates, including HIV status, passed the PH assumption test with a p-value greater than 0.05 on the goodness-of-fit test. To resolve the discrepancy between the graphical and statistical assumption tests for HIV status, both standard Cox PH models and extended Cox PH models were fitted. Ultimately, the Cox PH model was chosen as the best-fit model since there was no significant difference in the outputs of the two models based on the likelihood ratio (LR) test statistics for model selection (likelihood ratio chi-squared (1) = 0.93; p-value = 0.33). Additionally, the PH Cox model exhibited greater precision. Furthermore, the fitted extended Cox model revealed that the Cox regression coefficient estimate for the time-varying covariate, HIV status times the log of survival time, was not statistically significant (a = -0.72; 95% CI = -2.25–0.80; p-value = 0.35), suggesting that the risk of death did not significantly differ over time between HIV-positive and HIV-negative children receiving TB treatment (Table 7).

Table 7. Extended Cox regression multivariable survival analysis with HIV status as a time-varying covariate in children treated for TB in Urban Central Ethiopia, 2014-2022.

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_t	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
main						
sex	-.2420028	.3806474	-0.64	0.525	-.988058	.5040523
HIVs	2.192465	.9081607	2.41	0.016	.4125025	3.972427
nutbase	1.564997	.3978817	3.93	0.000	.7851627	2.34483
agecat	1.392363	.4422378	3.15	0.002	.525593	2.259133
tbcat	1.307612	.6429427	2.03	0.042	.0474673	2.567756
BCG_agecat	-.298251	.5153482	-0.58	0.563	-1.308315	.7118129
tvc						
HIVs	-.7252251	.7774439	-0.93	0.351	-2.248987	.7985369

HIVs = HIV status, nutbase = baseline nutritional status, agecat = age category, tbcat = TB category, tvc = time varying covariate

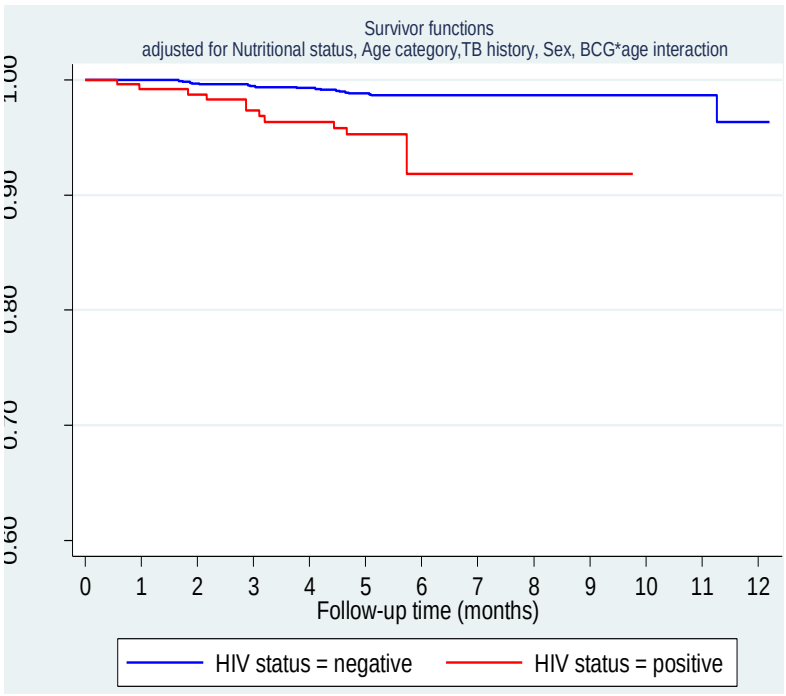
In the multivariable model, HIV-positive children were four times more likely than HIV-negative children to die from TB (adjusted Hazard Ratio (aHR) = 4.21; 95% CI = 1.90–9.32). Similarly, undernourished children at the start of TB treatment were four times more likely to die than their adequately nourished counterparts (aHR = 4.21; 95% CI = 2.21–10.48). Children under the age of ten were four times as likely as those aged ten and older to die (aHR = 4.06; 95% CI = 1.70–9.67). Children with relapsed or retreated TB were also more than three times more likely to die from the disease than children with new TB (aHR = 3.71; 95% CI = 1.05–13.11). No statistically significant effect modification (interaction) was found between BCG vaccination and age categories labeled as under ten years and ten years or older (aHR = 0.76, 95% CI = 0.28–2.08) (Table 7).

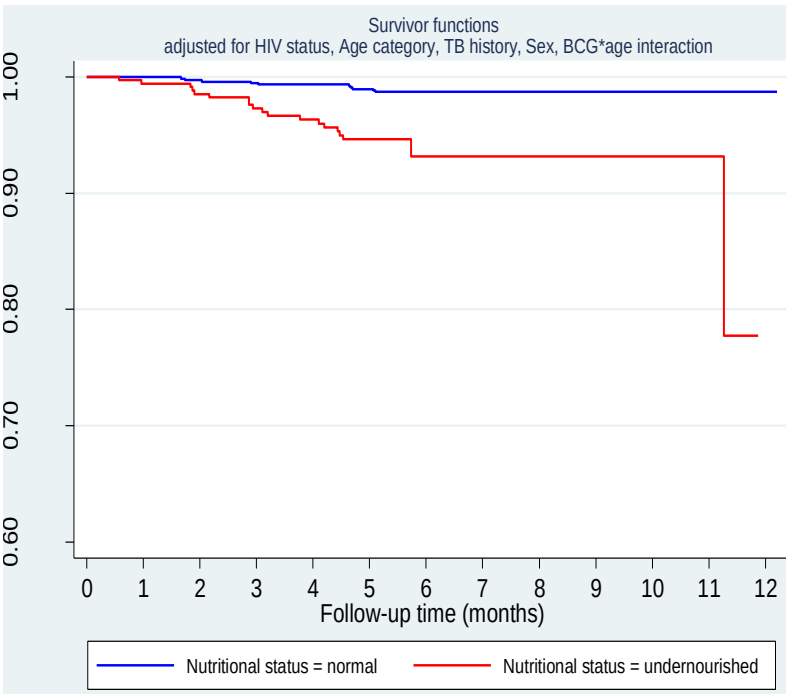
Table 8. Cox proportional hazards survival analysis with single and multivariable covariates in children treated for TB in Urban Central Ethiopia, 2014-2022

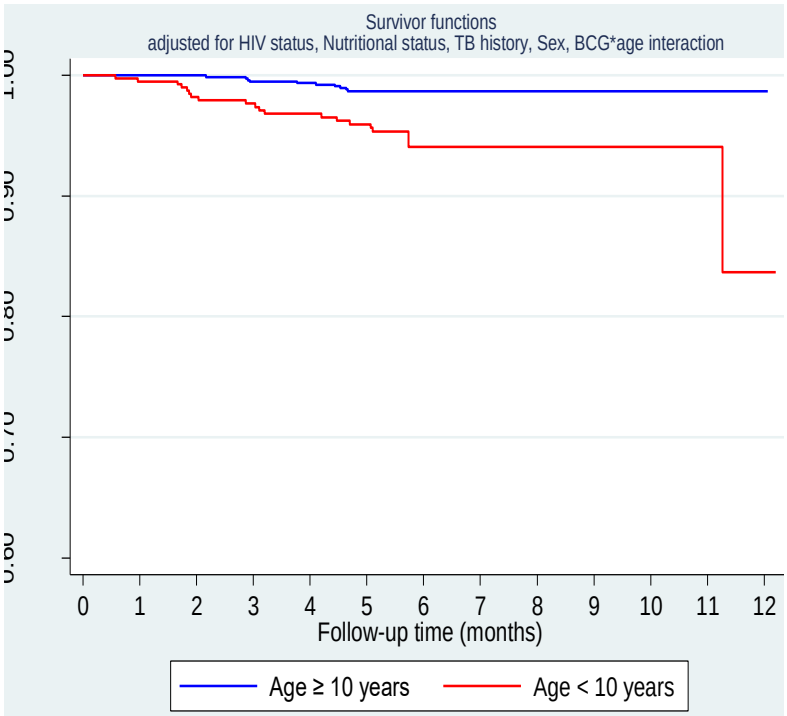
Characteristics		Deaths/n (%)	cHR (95% CI)	p-value	aHR (95% CI)	p-value
Sex	Male	20/272 (7.35)	1.00		1.00	
	Female	16/368 (4.35)	0.58 (0.30 - 1.13)	0.110	0.78 (0.37- 1.64)	0.506
Child's HIV status	Negative	23/555 (4.14)	1.00		1.00	
	Positive	13/85 (15.30)	3.98 (2.02 - 7.87)	0.000	4.21 (1.90 - 9.32)	0.000*
Nutritional status at TB treatment start	Normal	15/446 (3.36)	1.00		1.00	
	Undernourished	21/194 (10.82)	3.31 (1.70 – 6.42)	0.000	4.81 (2.21 - 10.48)	0.000*
Age category	≥ 10 years	13/389 (3.34)	1.00		1.00	
	< 10 years	23/251 (9.16)	2.74 (1.39 – 5.42)	0.004	4.06 (1.70 - 9.67)	0.002*
TB treatment history	New	33/617 (5.35)	1.00		1.00	
	Relapse (or retreatment after lost to follow up)	3/23 (13.04)	2.59 (0.79 – 8.47)	0.115	3.71 (1.05 - 13.11)	0.041*
BCG*age category	Aged ≥10 and BCG vaccinated	23/464 (4.96)	1.00		1.00	
	Aged <10 or BCG unvaccinated or both	6/60 (10.00)	2.17 (0.88 – 5.36)	0.092	0.76 (0.28 - 2.08)	0.590

*Statistically significant at p-value < 0.05

The survival curve drived from the multivariable Cox regression model showed that HIV-negative children consistently had higher survival probabilities than HIV-positive children. Similarly, children who were normally nourished, aged ten or older, and those with new TB had better survival rates than their counterparts. Panel of Cox-adjusted survival curves for covariates that were independent predictors of death in children treated for TB are shown below (Figure 4).







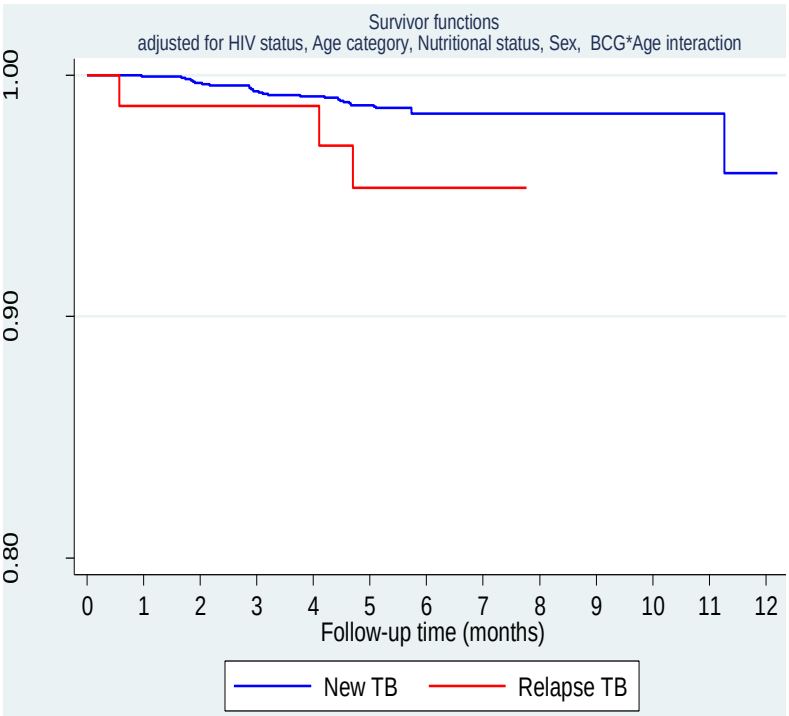


Figure 4. Panel of Cox-adjusted survival curves for categories of HIV status, age category, nutritional status, and TB treatment history in children treated for TB in Urban Central Ethiopia

The effects of BCG vaccination statuses clearly violated the graphical assumption test by displaying crossing log-log curves at a survival time of around three months, slightly beyond the natural logarithm of one month (Figure 5).

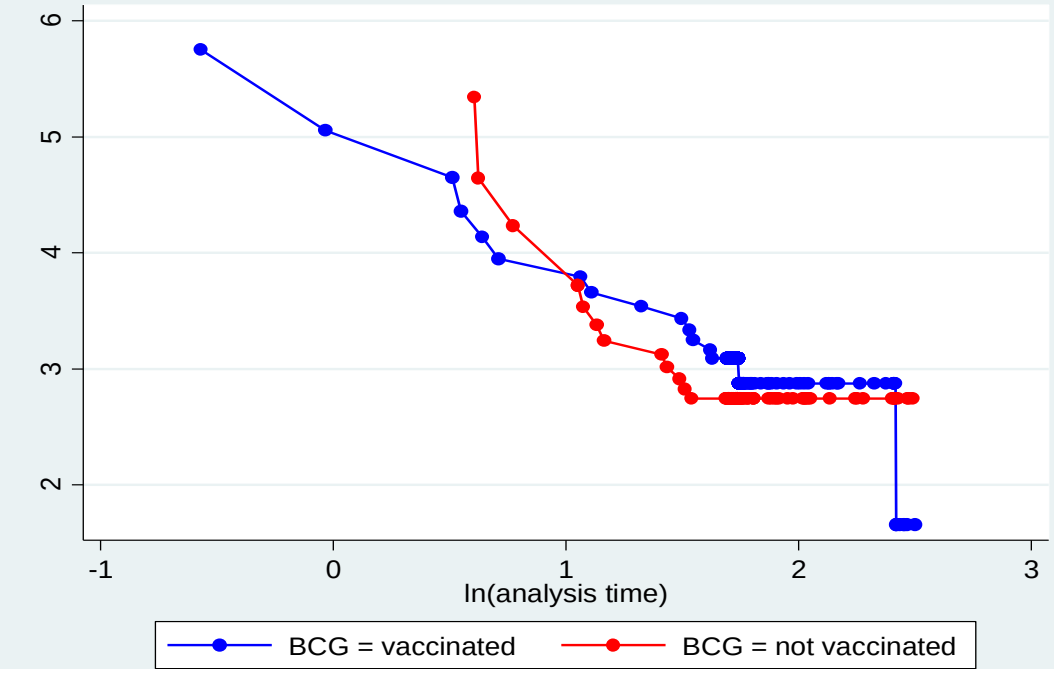


Figure 5. Test of the proportional-hazards assumption for BCG vaccination status

Disaggregated analyses for either time period, i.e., before and after three months, demonstrated no significant difference in survival between vaccinated and unvaccinated children. The hazard ratio (HR) for unvaccinated children starting TB treatment was 0.42 (95% CI = 0.13–1.36) in the first three months after treatment initiation and 1.22 (95% CI = 0.46–3.29) after the first three months.

EPTB, smear-negative TB, and smear-positive TB were responsible for 18 (50.0%), 15 (41.7%), and three (8.3%) of the deaths, respectively. Meningitis-TB claimed five lives, accounting for 27.8% of EPTB-related deaths and 13.9% of all TB deaths.

5.3. Determinants of childhood TB disease

5.3.1. Characteristics of childhood TB cases and the controls

The study examined 256 patients with TB (cases) and 256 individuals who had never been diagnosed with TB (controls). A TB diagnosis was confirmed through sputum smear microscopy and X-rays in 63 (24.6%) patients, while GeneXpert/RIF was used in 52 (20.3%) patients. The remaining 141 (55.1%) cases were clinically diagnosed based on a high index of suspicion and TB-suggestive imaging.

Of the cases, 126 (49.2%) were male, and of the controls, 119 (46.5%) were male; the rest were female. The mean age of the cases was nine years, while that of the controls was ten years. A total of 180 (70.3%) cases and 180 (70.3%) controls were selected from Addis Ababa. Due to recent demarcation changes, some settlements previously part of Addis Ababa were relocated to the Oromia region, and vice versa. However, they continue to receive healthcare services from their original facilities, resulting in differences in the distribution of cases and controls across the regions.

Ninety-nine (38.7%) cases were not vaccinated with BCG, compared to 58 (22.7%) controls. Exposure to household TB contact was reported in 43 (16.8%) cases and only 10 (3.9%) controls. In households with cases, 22 (8.6%) had a cigarette smoker, whereas only six (2.3%) of the control households did. HIV infection was present in 22 (8.6%) cases and three (1.2%) controls. The largest household size among cases was 30, originating from a foster center where multiple children shared a room, while among controls, it was 9 (Table 8).

Table 9. Characteristics of cases at the time of TB diagnosis and that of controls at time of survey in a study conducted in Urban Central Ethiopia, 2022

Characteristics	**Category**	**Cases (%) N=256**	**Controls (%) N=256**
Sex	Male	126 (49.2)	119 (46.5)
	Female	130 (50.8)	137 (53.5)
Age in years at TB diagnosis for cases and at survey for controls	Mean (standard deviation); median	8.96(5.5); 10	10.3(5.3); 10
Study site	Addis Ababa city	180 (70.3)	180 (70.3)
	Adama town	26 (10.2)	26 (10.2)
	Bishoftu town	50 (19.5)	50 (19.5)
Nutritional status	Normal	176 (68.8)	248 (96.9)
	Undernourished	80 (31.2)	8(3.1)
BCG vaccination within two weeks of birth	Yes	157 (61.3)	198 (77.3)

	No	99 (38.7)	58 (22.7)
Child's Education	Kindergarten	23 (13.2)	40 (19.6)
	Grade 1-6	98 (56.3)	86 (42.2)
	Grade 7-8	34 (19.5)	38 (18.6)
	Grade 9-12	19 (10.9)	40 (19.6)
Household family member sick with TB	Yes	43 (16.8)	10 (3.9)
	No	213 (83.2)	246 (96.1)
Cigarette smoking family member	Yes	22 (8.6)	6 (2.3)
	No	234 (91.4)	250 (97.7)
HIV status	Positive	22 (8.6)	3 (1.2)
	Negative	234 (91.4)	61 (23.8)
	Unknown	0 (0)	192(75.0)
Household size	Minimum; Maximum; mean; median	2; 30; 5.2; 4	2;9; 4.7 ;5

5.3.2. Mutivariable analysis of determinants of TB disease in children

A total of 256 case-control pairings were analyzed. Regarding BCG vaccination, 66 (25.8%) pairings were discordant, with cases not vaccinated for BCG while controls were, and 25 (9.8%) were discordant in the opposite scenario. In 42 (16.4%) discordant pairings, cases had household TB contact while controls did not, whereas in 9 (3.5%) pairings, the opposite was true. For cigarette smoking, 21 (8.2%) cases had lived with a smoking family member while controls had not, and 5 (2.0%) cases had never lived with a smoking family member while controls had. Additionally, 21 (8.2%) discordant pairings occurred when cases were HIV-positive and controls were not, while 2 (0.8%) occurred vice versa.

In the multivariable analysis, the odds of being unvaccinated for BCG at birth or within two weeks after birth were more than twice as high (mORadj = 2.11, 95% CI = 1.28–3.48) among TB patients compared to those who had never had TB. Our study also found that children who lived with a family member who had TB were significantly more likely to develop TB disease (mORadj = 4.28, 95% CI = 1.95–9.39) than children who had no TB patient contact in the family. Similarly, children who lived with a smoking family member were significantly more likely to develop TB than children who did not (mORadj = 3.15, 95% CI = 1.07–9.27). Furthermore, TB patients had more than eightfold higher odds of HIV infection than non-TB groups (mORadj = 8.71, 95% CI = 1.96–38.66). However, household size (as a continuous covariate) showed no statistically significant association with the development of TB disease (mORadj = 1.04, 95% CI = 0.96–1.12). Sex had a bivariate p-value of 0.544, which did not meet

the threshold of less than or equal to 0.2 required for inclusion in the multivariable model (see Table 9).

Table 10. Multivariable conditional logistic regression for determinants of TB disease development among children in Urban Central Ethiopia, 2022

Cases	Controls		mCOR (95% CI)	p-value	mORadj (95% CI)	p-value
	Male	Female				
Male	56 (21.9%)	70 (27.3%)	1.11 (0.78-1.59)	0.544		
Female	63 (24.6%)	67 (26.2)	1.00			
	No BCG	BCG received				
No BCG	33 (12.9%)	66 (25.8%)	2.64 (1.67-4.18)	0.000*	2.11(1.28-3.48)	0.003**
BCG received	25 (9.8%)	132 (51.6%)	1.00		1.00	
	Household TB contact	No household TB contact				
Household TB contact	1 (0.4%)	42 (16.4%)	4.67 (2.27-9.59)	0.000*	4.28 (1.95-9.39)	0.000**
No household TB contact	9 (3.5%)	204 (79.7%)	1.00		1.00	
	Smoker family	No smoker family				
Smoker family	1 (0.4%)	21 (8.2%)	4.20 (1.58-11.14)	0.004*	3.15 (1.07-9.27)	0.037**
No smoker family	5 (2.0%)	229 (89.5%)	1.00		1.00	
	HIV infected	HIV uninfected or unknown				
HIV infected	1 (0.4%)	21 (8.2%)	10.50 (2.46-44.78)	0.001*	8.71 (1.96-38.66)	0.004**
HIV uninfected	2 (0.8%)	232 (90.6%)	1.00		1.00	
Household size			1.05(0.99-1.13)	0.118*	1.04 (0.96-1.12)	0.339

*Included in the multivariable model **Statistical significant at p-value < 0.05

5.3.3. Postestimation analysis of probability of TB in BCG vaccinated versus unvaccinated children

Apart from a narrow difference observed in children under one year old and around the age of 15, the difference in the predictive probability of developing TB between BCG-vaccinated and unvaccinated children was wider and significantly lower for the vaccinated group up to the age of 15, as evidenced by the non-overlapping 95% CI of the groups' predictive probabilities. However, the contrast in the likelihood of developing TB between the vaccinated and unvaccinated groups diminished around the age of 15, and by the age of 16, it had reached a point of no significant difference, as indicated by the overlapping CI (Figure 5).

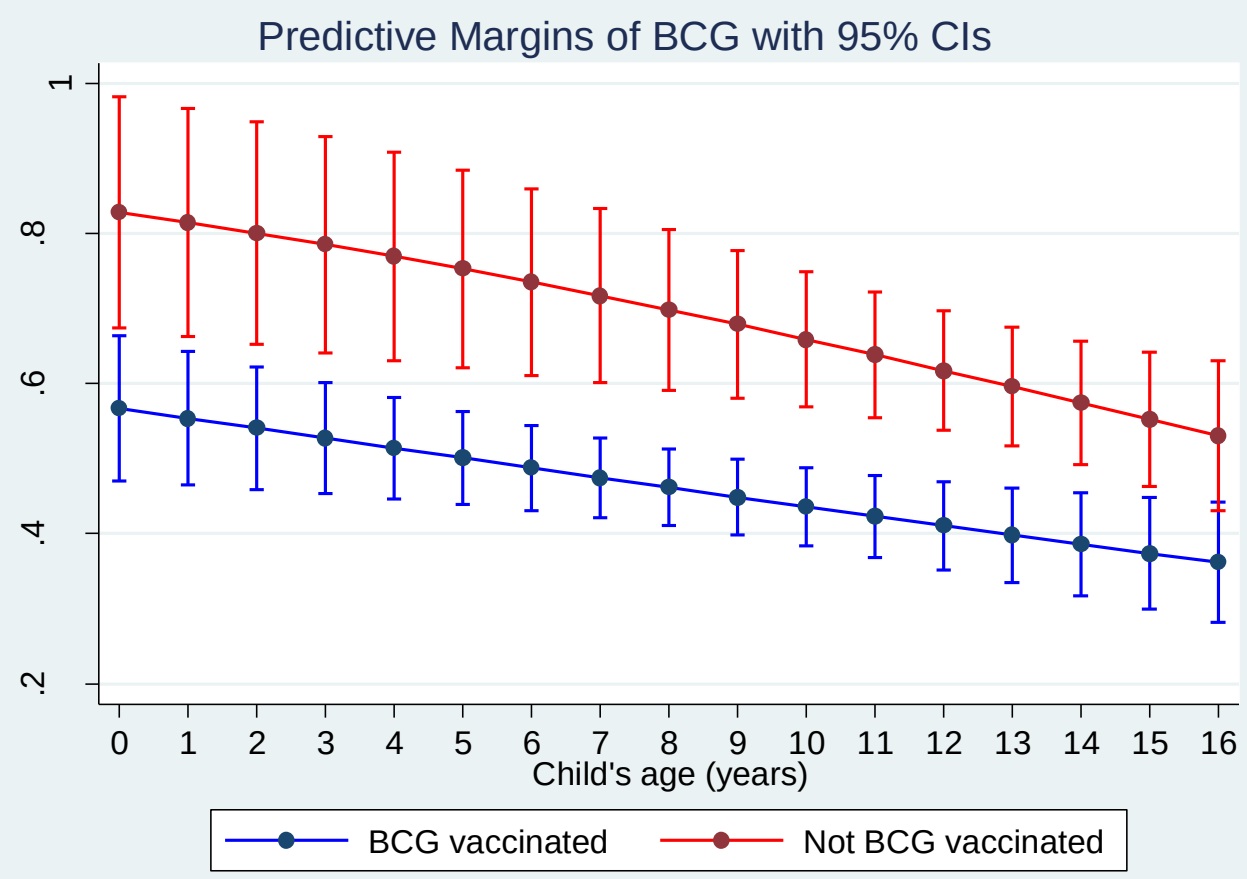


Figure 6. Predictive probability of developing TB disease among BCG vaccinated and unvaccinated children in Urban Central Ethiopia, 2022

5.4. Unfavorable TB treatment outcome in children

5.4.1. Characteristics of study participants assessed for TB treatment outcome

For the investigation of TB treatment outcomes in children, we analyzed a cohort of 640 children undergoing treatment for drug-susceptible TB. Among these, 157 (24.5%) were aged 0–4 years, 94 (14.7%) were aged 5–9 years, 205 (32%) were aged 10–14 years, and 184 (28.8%) were aged 15–16 years. Female patients comprised 368 (57.5%) of the total childhood TB cases. A flow diagram illustrating the study's examination of predictors for unfavorable treatment outcomes among children receiving TB treatment is presented below (Figure 6).

Figure 7. Finding predictors of unfavorable treatment outcome among children receiving TB treatment in Urban Central Ethiopia

5.4.2. Magnitude of unfavorable TB treatment outcome among children

Of the 640 children treated for drug-susceptible TB, 42 (6.6%; 95% CI = 4.8–8.8%) experienced an unfavorable TB treatment outcome. Among these, 36 (5.6%) died, and 6 (0.9%) encountered treatment failure. Conversely, 598 (93.4%; 95% CI = 91.2–95.2%) achieved a favorable treatment outcome, with 106 (16.5%) being cured and 492 (76.9%) completing their treatment. Out of the 42 individuals with unfavorable outcomes, 11 (26.2%; 95% CI = 13.9–42.0%) occurred during the intensive phase, while 31 (73.8%; 95% CI = 58.0–86.1%) transpired during the continuation phase of TB treatment. Of the total 31 deaths, 11 (30.6%; 95% CI = 16.3–48.1%) happened during the intensive phase, and 25 (69.4%; 95% CI = 51.9–83.7%) took place during the continuation phase of TB treatment (Table 10).

Table 11. Treatment outcomes among children with TB, Urban Central Ethiopia, 2014-2022

Treatment outcome (n=640)	**Frequency (%)**	95% CI
Unfavorable	42 (6.6)	4.8 – 8.8%
Died	36 (5.6)	4.0 – 7.7%
Treatment failed	6 (0.9)	0.3 – 2.0%
Favorable	598 (93.4)	91.2 – 95.2%
Cured	106 (16.5)	13.8 – 19.7%
Treatment completed	492 (76.9)	73.4 – 80.1%
Unfavorable outcome during intensive phase (n=42)	11 (26.2)	13.9 – 42.0%
Unfavorable outcome during continuation phase (n=42)	31 (73.8)	58.0 – 86.1%
Died during intensive phase (n=36)	11 (30.6)	16.3 – 48.1%
Died during continuation phase (n=36)	25 (69.4%)	51.9 – 83.7%

Note on transferred out patients' TB treatment outcomes

The principal investigator, in collaboration with the TB focal persons from the transferring out facilities, conducted follow-ups with nine patients who had been transferred out and assessed their TB treatment outcomes via telephone. Subsequently, it was verified one patient as cured, as reported by both the TB focal person at the receiving health facility and the child's parent. Unfortunately, one patient passed away after being transferred to a tertiary hospital for advanced treatment, according to the child's parent. The remaining seven patients were classified as treatment completed. Among these, one treatment outcome was confirmed by the TB focal person at the receiving hospital, while the remaining six were reported by the parents.

5.4.3. Overall predictors of unfavorable TB treatment outcome among children

In an unadjusted analyses, significant association was not found between BCG vaccination and unfavorable TB treatment outcomes (RR = 1.00; 95% CI = 0.52–1.93). In a multivariable analysis, sex was not found to be significantly associated with unfavorable treatment outcomes (aRR = 0.61; 95% CI = 0.34–1.01). Notably, undernourished children at the TB treatment start (aRR = 2.68; 95% CI = 1.53–4.71) exhibited a significantly higher risk of unfavorable outcomes compared to their normally nourished counterparts. Similarly, children aged less than 10 years (aRR = 2.69; 95% CI = 1.56–4.61) had a significantly increased risk compared to those aged 10 or older. In addition, HIV-infected children (aRR = 2.62; 95% CI = 1.50–4.59) had a significantly higher risk compared to HIV-uninfected children, and relapsed TB patients (aRR = 3.19; 95% CI = 1.79–5.70) also had a higher risk compared to new TB patients (Table 11).

Table 12. A multivariable log-binomial model demonstrating predictors of unfavorable treatment outcome in children receiving TB treatment, Urban Central Ethiopia, 2014-2022

Characteristics	**TB treatment outcomes**		**cRR (95% CI)**	**p-value**	**aRR (95% CI)**	**p-value**
	Unfavorable (%)	**Favorable (%)**				
BCG vaccination (n=524)						
Vaccinated	21 (6.7)	294 (93.3)	1.00			
Not vaccinated	14 (6.7)	195 (93.7)	1.00 (0.52-1.93)	0.989		
Sex (n=640)						
Male	23 (8.5)	249 (91.5)	1.00			
Female	19 (5.2)	349 (94.8)	0.61 (0.34-1.10)	0.100*	0.67 (0.40-1.13)	0.132
Nutritional status at treatment start (n=640)						
Normal	19 (4.3)	427 (95.7)	1.00			
Undernourished	23 (11.9)	171 (88.1)	2.78 (1.55-4.00)	0.001*	2.68 (1.53-4.71)	0.001**
Age category (n=640)						
≥ 10 years	16 (4.1)	373 (95.9)				
< 10 years	26 (10.4)	225 (89.6)	2.52 (1.40-4.60)	0.003*	2.69 (1.56-4.61)	0.000**
HIV status (n=640)						
Negative	28 (5.0)	527 (95.0)				
Positive	14 (16.5)	71 (83.5)	3.26 (1.80-5.95)	0.000*	2.62 (1.50-4.59)	0.001**
TB category(n=640)						
New	38 (6.2)	579 (93.8)				
Relapse	4 (17.4)	19 (82.4)	2.82 (1.10-7.25)	0.031*	3.19 (1.79-5.70)	0.000**

* Selected for multivariable model ** Significant at 5% significance level

5.4.4. Predictors of unfavorable TB treatment outcomes in children during the continuation phase

Among the 629 (98.3%) children who survived two months or more on TB treatment, 116 (18.4%) were undernourished. Among them, 15 (12.9%) experienced unfavorable treatment outcomes, while 101 (87.1%) had favorable treatment outcomes. In a separate multivariable model that analyzed the effect of persistent undernutrition into the continuation phase of TB treatment, it was found it significantly increased the risk of unfavorable TB treatment outcomes (aRR = 3.76; 95% CI = 1.90–7.33). Additionally, being younger than 10 years old (aRR = 2.60; 95% CI = 1.31–5.15) and having HIV infection (aRR = 2.26; 95% CI = 1.11–4.59) were identified as significant risk factors for unfavorable outcomes during the continuation phase. However, being a relapsed TB patient (aRR = 2.81; 95% CI = 0.96–8.12) did not continue to increase the risk of unfavorable outcomes after the initial two months of TB treatment (Table 12).

Table 13. A multivariable log-binomial model that shows the effect of sustained under nutrition on TB treatment outcomes among children receiving TB treatment in Urban Central Ethiopia, 2014 - 2022

Characteristics	**TB treatment outcomes (n=629)**		**cRR (95% CI)**	**p-value**	**aRR (95% CI)**	**p-value**
	Unfavorable (%)	**Favorable (%)**				
Sex						
Male	16 (6.0)	249 (94.0)	1.00			
Female	15 (4.1)	349 (95.9)	0.68 (0.34 – 1.36)	0.275		
Nutritional status after the first two months of treatment start						
Normal	16 (3.1)	497 (96.9)	1.00		1.00	
Undernourished	15 (12.9)	101 (87.1)	4.15 (2.11 – 8.14)	0.000*	3.76 (1.90 – 7.43)	0.000**
Age category						
≥ 10 years	14 (3.6)	373 (96.4)	1.00		1.00	
< 10 years	17 (7.0)	225 (93.0)	1.94 (0.97 – 3.87)	0.059*	2.33 (1.18 – 4.60)	0.015**
HIV status						
Negative	21 (3.8)	527 (96.2)	1.00		1.00	
Positive	10 (12.3)	71 (87.7)	2.81 (1.34 – 5.88)	0.001*	2.26 (1.11 – 4.59)	0.024**
TB category						
New	28 (4.6)	579 (94.4)	1.00		1.00	
Relapse	3 (13.6)	19 (86.4)	2.96 (0.97 – 8.99)	0.056*	2.81 (0.96 – 8.22)	0.059

5.5. Effectiveness of BCG vaccination against TBM

When comparing the characteristics of children with TBM and those with non-TBM TB, it was found that their mean ages (standard deviation) were 5.6 (±5.1) years and 9.9 (±5.3) years, respectively. Among the children with non-TBM TB, males accounted for 47 (53.4%) of the cases, whereas among those with TBM, males comprised 13 (59.1%) of the cases. Regarding HIV status, one child (4.6%) with TBM was HIV-positive, while 11 (12.5%) of the children with non-TBM TB were HIV-positive. Concerning BCG vaccination status, three children (15.0%) with TBM were unvaccinated, compared to 30 (38.0%) with non-TBM TB. Eighteen (90%) of the children with TBM were delivered in a health institution, while 51 (65.4%) of the children with non-TBM TB were born in a health facility. In the study, 5 children (22.7%) with TBM died, compared to 5 children (5.7%) without TBM (Table 13).

Table 14. Characteristics of children on TB treatment who were TBM and non-TBM TB patients

Characteristics		**TBM (%)**	**Non-TBM TB (%)**
Age in years	Mean (sd)	5.6 (5.1)	9.9 (5.3)
	Median (IQR)	3.8 (1.5-12.0)	12 (5.4-15.0)
Sex	Male	13 (59.1)	47 (53.4)
	Female	9 (40.9)	41 (46.6)
HIV status	Negative	21 (95.4)	77 (87.5)
	Positive	1(4.6)	11(12.5)
BCG vaccination	Yes	17 (85.0)	49 (62.0)
	No	3 (15.0)	30 (38.0)
Delivery place	Home	2 (10.0)	27 (34.6)
	Health institution	18 (90.0)	51 (65.4)
Outcome	Died	5 (22.7)	5 (5.7)
	Survived	17 (77.3)	83 (94.3)

sd = standard deviation; IQR = interquartile range

After adjusting for the child's age and delivery place, being BCG unvaccinated was not found to be associated with the development of TBM in children (aOR = 1.06; 95% CI = 0.14–7.93). However, according to this model, it was observed that, on average, for each additional year in a child's age, the odds of developing TBM decrease by 15% (aOR = 0.85; 95% CI = 0.77–0.95) (Table 14). The model demonstrated a good fit, as indicated by a likelihood ratio chi-square value of 15.0 with a corresponding p-value of 0.00. Additionally, the p-value for the Hosmer-Lemeshow goodness of fit test was 0.24, reaffirming that the model was fit.

Table 15. Association between TB meningitis and BCG vaccination among children on TB treatment

Characteristics		**TBM Compared to Other TB Forms**			
		cOR (95% CI)	**p-value**	**aOR (95% CI)**	**p-value**
BCG	unvaccinated	0.29 (0.08-1.07)	0.62	1.06 (0.14-7.93)	1.00
	vaccinated	1.00		1.00	
Mean age in years		0.86 (0.74-0.94)	0.00	0.85 (0.77-0.95)	0.00
Sex	Male	1.00			
	Female	0.80 (0.31-2.05)	0.63		
HIV status	Negative	1.00			
	Positive	0.33 (0.04-2.73)	0.31		
Delivery place	Home	1.00			
	Health institution	4.8 (1.03 -22.08)	0.05	3.30 (0.34-32.51)	0.31

6. Discussion

As one of its objectives, this study has described the epidemiology of childhood TB and identified the predictors of death in children who were on TB treatment in Urban Central Ethiopia between 2014 and 2022. In regards to this, the four main findings are that: healthcare facilities in central Ethiopia had a high child TB death rate, 5.6%, with children under two years old disproportionately affected; HIV, undernutrition at TB treatment initiation, persistent undernutrition throughout the initiation phase, relapse, and young age all increased the risk of death; BCG vaccination status at birth or within two weeks after birth did not influence death; and community transmission might be more important than household transmission among children of all ages.

The WHO's End TB strategy includes a monitoring indicator that sets a target TB CFR at 5% or lower by 2025 for all countries. The CFR is calculated by dividing the number of TB deaths, as reported through a national vital registration system, by the estimated number of incident TB cases, and includes untreated TB deaths in its numerator [39]. Therefore, if the target for the CFR, which includes untreated TB deaths, is set at 5%, the TB death rate among treated patients is ideally expected to be much lower than 5%.

However, this study observed a notably high CFR, with the highest impact on children under the age of two. A meta-analysis, incorporating data from Ethiopia too, reveales that in scenarios where most children received TB treatment, the pooled CFR is 0.9% (95% CI: 0.5%, 1.6%) [58], thus reinforcing the conclusion that observed death rate in this study is notably high. The line graph in our result showed that the proportion of TB deaths was higher among children in the first two years of life, and this is consistent with the literature [207]. The higher death rate in younger children could be explained by the fact that infants' immune systems are immature, making them more likely to die from TB [346].

This study's death rate (5.6%; 95% CI = 4.0–7.7%) is significantly higher than that of an earlier study done in eight hospitals in eastern Ethiopia (1.0%; 95% CI = 0.6–1.5) [65] and in all TB service-providing facilities in Sidama zone, southern Ethiopia (3%; 95% CI = 2.5-3.5%) [68]. The eastern Ethiopia study did not involve TBM patients, which may explain the lower death

rate observed, as TBM has a 20% case fatality rate on average [280]. TBM accounted for nearly 14% of all TB deaths in the current study.

The death rate in the current study is higher when compared to the death rates of other African studies: South Africa (0.8%; 95% CI = 0.7–0.9%) and the Democratic Republic of the Congo (1.4%; 0.4–3.6%). The lower death rates in both studies, however, were likely to be understated due to the larger proportion of loss to follow-up: 7% in the Congo [306] and 6% in South Africa [59], which could be due to deaths. In the current study, however, patients recorded as lost to follow-up on the programmatic TB register were confirmed dead by phone call from their parents or caregivers.

The death rate in this study is significantly lower than in a study conducted in rural southern Mozambique (10.7%; 95% CI = 8.7–12.8). One possible explanation for the higher death rate in the Mozambique study is that the majority of the patients, 62%, were HIV co-infected, and nearly half, 49.6%, were under the age of five [63], compared to a smaller proportion of patients being HIV co-infected, 13.3%, and being under the age of five, 24.5%, in this study. People who are TB-HIV co-infected have a higher risk of death than those who are not HIV-infected, even if they are on anti-retroviral therapy, and younger children also have a higher risk of death than their older counterparts [58].

Other African countries' death rates, Kenya (4%; 95% CI = 4.11-4.63%) and Malawi (9.5%; 95% CI = 6.4 -13.4%), are comparable to this study's findings, despite having higher TB-HIV co-infection rates, 28.0% for Kenya and 32.6% for Malawi. On the other hand, TBM rates were lower in both the Kenya and Malawi studies, at 1% and 1.4% of all TB patients, respectively [62, 64]. A Nigerian study also found a comparable death rate (6.0%; 95% CI = 4.2–8.4%) despite a higher HIV co-infection rate, 26.7%. However, it appears that Nigeria's death rate was understated, as the proportion of patients that were lost to follow-up (possibly due to deaths) was high, 15.0% [67].

The current study found that HIV is an independent predictor of death, which aligns with a recent meta-analysis finding [58]. Similar to this study’s findings, Hesseling et al. reported in South Africa that undernutrition at the time of diagnosis predicts mortality, but their study was limited to HIV-positive children. They did not assess the effect of nutritional status after two

months of treatment, which remained a significant predictor in this study [347]. Consistent with this study's findings, studies in Sidama Zone, Ethiopia [68], rural southern Ethiopia [57], Kenya [62], South Africa [59], and Nigeria [67] found that a younger children were at a higher risk of death, whereas studies in Congo [306] and an older study in South Africa by Hesseling et al. [347] did not find this association. Consistent with this study's findings, re-treatment was found associated with death in studies conducted in South Africa [59].

The fact that only one in eight (12.2%) of all children and 20% of children under 2 years old had known previous or concurrent household PTB patient contact suggests that the children were infected with TB from outside of home sources, from the community. This is consistent with the findings of Martinez et al. [348]. School community screening is not part of Ethiopia's TB contact tracing and screening strategy [170] , yet it is an environment where children spend a significant amount of time.

At the start of TB treatment, 21.7% of children under the age of five (not shown in a table) experienced undernutrition, which is higher than the national prevalence of 10% in 2016 [349] and 7% in 2019 [350]. Even two months after starting TB treatment, the rate of undernutrition among children under five (12.6%, not shown in a table) remained higher than national figures. A lack of studies examining the deaths of children on TB treatment and their association with malnutrition on the African continent, where malnutrition rates are the highest in the world [351], reveals a gap in childhood TB research.

This study also assessed the association of the BCG vaccine with deaths from TB in children. While BCG vaccination status did not show association with death in this study, evidences show BCG-vaccination prevents TB-associated deaths [352, 353]. The discrepancy could be due to the possibility of the family of a deceased child positively reporting that the child had been vaccinated, in fear of a blame, which might hide the effect of BCG in this study. The WHO recommends all healthy newborns receive a single dose of the BCG vaccine at birth or as soon as possible thereafter to protect the child before exposure occurs [221]. The Ethiopian EPI, which began in 1980, also calls for BCG vaccination at birth, with the option to administer it to children up to one year old [225]. BCG coverage in Addis Ababa was 97.5%, 94.6%, and 96.3% in 2011, 2016, and 2019, respectively, while coverage in urban Ethiopia was 81.6%, 88.8%, and 88.8% during the same periods [349, 350, 354]. To avoid the effect of prior infection before

vaccination, which could mask the effect of the vaccine, this study assessed BCG vaccination status at birth or within 15 days [223].

The line graph in the result showed a relatively low number of TB patients treated between the ages of two and 11 years, followed by an increasing pattern afterward. This could be attributed to the impact of the BCG vaccine, which is effective in preventing TB for up to ten years and then fades [78]. However, infants' immune systems are immature, making them more likely to develop TB disease regardless of BCG vaccination [346].

This study confirmed that being unvaccinated for BCG, exposure to a household TB patient, exposure to a cigarette-smoking family member, and being HIV-infected were determinants of childhood TB disease development in Urban Central Ethiopia. This finding, therefore, will aid in the development of risk-factor-based intervention strategies to prevent and control TB [355], as well as serve as a foundation for future research on childhood TB. The finding that BCG vaccination protects against TB disease is consistent with previous studies [79-81, 240, 356]. BCG vaccination activates CD4+ and CD8+ T lymphocytes, increasing IFN-γ production, which enhances anti-mycobacterial action in macrophages [357].

This study's finding also consistent with prior studies showing that close contact with a TB patient increases the risk of childhood TB disease development [264, 327, 358, 359], even if the child was vaccinated for BCG at birth [83]. Additionally, the current study found that living with a smoking family member increases the risk of TB disease development in children, which is consistent with prior individual studies [82, 262] and a meta-analysis [261]. In contrast, a study in Taiwan found no association between second-hand smoke exposure and TB [360] possibly due to the lack of TB contact in the households of its study participants, which might otherwise interact with second-hand smoke and increase the risk.

HIV infection, a well-established risk factor for TB in children < 15 years [248], was also identified as a risk factor for TB in the current study, though the interval estimation was imprecise. In adults, Isoniazid preventive therapy with ART prevents TB in diverse HIV and TB subgroups, supporting its broad use among people living with HIV [361]. A meta-analysis in Africa found IPT prevents TB in HIV-positive children not on ART, but its benefit for those on ART is inconclusive [362]. The lack of association of TB with total household size in our study

contradicts findings from studies in Thailand and Bangladesh [83, 327]. This disparity could be explained by the fact that our study measured household size, whereas those two studies measured the number of people living in a single room in a house. We found no association between sex and TB in children, but the debate over whether adult males are more likely than adult females to contract TB due to confounding factors such as smoking, alcohol, and drug use or due to female hormones inhibiting TB disease development independently continues [363].

This study also assessed the magnitude and predictors of unfavorable TB treatment outcomes among children treated for drug-susceptible TB. Approximately one in every fifteen (6.6%; 95% CI = 4.8–8.8%) children treated for TB experienced unfavorable TB treatment outcomes. The WHO's End TB recommends a milestone of over 90% for a successful TB treatment outcome rate by 2025 which translates to an unsuccessful or unfavorable outcome rate of less than 10% [30]. Based on this, the unfavorable outcome rate of 6.6% in our study can be considered has meet the set milestone.

Similar percentages of unfavorable outcomes were reported in studies conducted in Botswana (6.9%) [94], Pakistan (4.8%) [364], and Kenya (8.0%) [62], which defined unfavorable outcomes as including death, loss to follow-up, and treatment failure, as this study did. A study in Ethiopia that involved the country's two largest regions, Oromia and Amhara, also reported a similar magnitude of unfavorable outcomes when transfer out was considered (4.0%; 95% CI = 3.9–4.9%) and when it was not considered (7.8%) as unfavorable outcomes [329].

However, a higher percentage of unfavorable TB treatment outcomes were reported in studies conducted in eastern Ethiopia (11.4%; 95% CI = 10.0–12.9%) [65], Addis Ababa, Ethiopia (14.5%; 95% CI = 11.5–17.9%) [69], South Africa (14.1%; 95% CI = 13.7–14.5%) [59], and Mozambique (16.4%; 95% CI = 14.0–18.9%) [63]. The higher percentage could be explained by counting transfer outs as an unfavorable outcome.

Despite not including transfer outs as an unfavorable outcome, the percentages of unfavorable treatment outcomes in a study conducted in Ethiopia's Tigray region (11.3%; 95% CI = 9.2–13.6%) and Pakistan (11.1%; 95% CI = 9.7%–12.6%) were higher than those in our study. This difference could be explained by a higher proportion of under-five-year-old children in the

Tigray study (30%) [71] and the Pakistan study (66.6%) [321] compared to this study (24.5%). Younger children are more at risk of unfavorable treatment outcomes [71, 93, 94, 301, 320, 329].

Furthermore, the Balochistan province of Pakistan, where the study was conducted, shares a long porous border with war-torn Afghanistan, which hosts a large number of refugees. Consequently, the province experiences poor-quality healthcare services, high levels of poverty, and malnutrition [365], all of which contribute to the rise in the magnitude of unfavorable TB treatment outcomes in the setting.

The higher proportions of unfavorable outcomes reported by Adejumo et al. (21.3%; 95% CI = 17.9 - 25.0%) and Adamu et al. (47.5%; 95% CI = 41.7 - 53.3) in their studies conducted in Nigeria may be attributed to the higher proportion of HIV-TB co-infection in their study populations, 29% and 33.3%, respectively[67, 85], compared to this stud's, (13.3%).

The timing of the higher proportion of deaths in this study contrasts with that observed in a study at a large tertiary hospital in Nigeria. In Nigeria, the majority of deaths (over 75%) occurred during the intensive phase of treatment [85], whereas this proportion of deaths occurred later during the continuation phase in this study. Because the tertiary hospital served as a referral center for terminally ill patients, the early death rate might have been inflated, resulting in a higher proportion of unfavorable outcomes during the intensive phase than the continuation phase [85, 366].

Many studies on childhood TB treatment outcomes did not consider the effect of undernutrition on TB treatment outcomes [59, 62, 63, 65, 71, 93, 94, 313, 329]. However, a few studies examining the effect of undernutrition reached similar conclusion to this one's: undernutrition is a risk factor for unfavorable treatment outcomes [310, 366]. People with low BMI have reduced cytokines, which are crucial for resisting TB bacilli multiplication in the body, putting them at risk of developing TB [367].

Prior research compared children on TB treatment who were under the age of five to those who were five or older and found that younger children are at higher risk of unfavorable outcomes [58, 93, 94, 301, 320]. In this study, it was found that children under 10 years old were also more likely to have an unfavorable treatment outcome than those aged 10 or older.

The finding that HIV infection is a risk factor for unfavorable TB treatment outcomes aligns with many other studies [59, 62, 65, 85, 94, 301, 366]. Relapsed TB was another risk factor identified in this study, with similar findings reported by other studies [85, 93, 94, 313]. However, in this TB treatment phase-disaggregated analysis, relapsed TB was not found to retain its significance in increasing the risk of unfavorable treatment outcomes after the intensive phase of TB treatment (during the continuation phase of TB treatment), unlike other factors such as age under 10 years, HIV infection, and sustained undernutrition, which demonstrated a significant effect during the continuation phases of TB treatment.

Few studies have conducted treatment phase-disaggregated analysis of predictors of unfavorable treatment outcomes in children. However, a multicenter study across five health facilities in India showed that failure to increase BMI is linked to unfavorable TB treatment outcomes in adults aged 18 and older [311]. In contrast to other studies' finding male sex as a risk factor for unfavorable outcomes [65, 301], this study did not identify sex as a risk factor for TB. There are also studies that found no link between the demographic or clinical characteristics of childhood TB patients and treatment outcomes [306, 315]. BCG vaccination status was not found to be associated with TB treatment outcomes in this study, as it was in studies in Pakistan [364] and Uganda [366].

The lack of an association between BCG vaccination status and TBM should be interpreted with caution because most children with TBM who are unvaccinated may die before being diagnosed and admitted to hospital [280], introducing survivor bias into this study.

7. Validity and generalizability

7.1. Internal validity

Bias

To ensure the internal validity of our study on the epidemiology of childhood TB in Urban Central Ethiopia, we implemented several measures to minimize potential biases and enhance the validity of our findings.

To mitigate selection bias and provide a comprehensive understanding of TB deaths among children, we included healthcare facilities across all levels. This ranged from tertiary hospitals managing critical TB patients at higher risk of death to primary healthcare facilities overseeing ambulatory TB cases at lower risk of death. In our case-control study design, we took particular care to minimize selection bias by accurately characterizing cases and selecting an appropriate control group representative of the population at risk of TB.

However, it's important to acknowledge a potential limitation regarding the representation of BCG-vaccinated controls. Since BCG vaccination reduces the risk of certain infections, including TB, BCG-vaccinated individuals may visit healthcare facilities less frequently due to lower illness rates [368]. This could lead to a lower representation of BCG-vaccinated controls in our study sample compared to the general population, potentially biasing the association between BCG vaccination and TB disease by overestimating the effect of BCG. To reduce this bias, we included control subjects who visited healthcare facilities for non-illness-related reasons, such as immunizations, vitamin A supplementation, and reproductive health counseling.

Furthermore, we implemented rigorous data collector training and quality control measures to enhance the internal validity of our study. However, it's important to acknowledge the potential threat of non-response bias due to missing contact information. Despite this, the even distribution of BCG vaccination status among missing data across the analyzed covariates and outcome categories suggests that the missing data are likely to be completely at random, minimizing the risk of bias in our findings [345].

Chance

To minimize the influence of random variability, sample sizes for each objective were statistically calculated, aiming to reduce the potential for random error. By carefully determining sample sizes, we sought to enhance the precision of our findings and thereby lower the risk of internal validity threats stemming from chance fluctuations

Confounding

Confounding variables, such as age and HIV infection were acknowledged as potential influencers of TB disease development in children.To control for these confounders; rigorous measures were implemented, including individual age matching and multivariable regression analysis. While these strategies were effective in minimizing the influence of confounding, it's important to note that residual confounding may still exist. Factors not accounted for in the study, such as genetic predispositions, could still impact the observed associations. Therefore, while our findings provide valuable insights into the epidemiology of childhood TB, cautious interpretation is warranted to account for the potential influence of confounding variables.

Overall, while we implemented various measures to enhance internal validity, it's essential to interpret our findings with caution and acknowledge the potential limitations inherent in observational epidemiological studies.

7.2. External validity/Generalizability

The findings of this study can be applied to similar populations of children in different settings. However, some conclusions may not be generalizable to specific contexts. For example, the risk associated with second-hand smoking is not relevant in populations consisting exclusively of non-smokers, as the threat of TB disease development from second-hand smoke is absent. Therefore, in such settings, the impact of smoking on the development of TB disease does not apply. Similarly, in populations with high coverage of TB preventive treatment, close contact with TB patients may not be a practically significant risk factor.

8. Strengths and limitations

8.1. Strengths

One of the strengths of this study lies in supplementing the TB register review with phone interviews, allowing for the capture of additional data not available in the registers and confirming existing ones.

Furthermore, this study uniquely assessed the effect of persistent undernutrition two months after TB treatment initiation on mortality and the impact of BCG vaccination. This adds valuable insights, particularly in the context of Africa, where such assessments are rare.

In this study, the mean age of cases (8.96 years) appeared to be younger than that of controls (10.3 years). This seeming age disparity, contrary to individual matching, is explained by recording patients' ages at TB diagnosis and obtaining controls' ages after treatment outcome determination. This approach is strength, as it allowed sufficient time for clinical signs of potentially undetected TB in the controls to manifest, avoiding the misclassification bias of unrecognized TB cases being labeled as controls. Additionally, it facilitated the elimination of cases misdiagnosed as TB who later discontinued TB drugs due to a change in diagnosis [369].

To ensure valid statistics, transfer-out patients were traced via phone and categorized based on plausible treatment outcomes rather than simply classifying their outcomes as unsuccessful without further investigation into their actual treatment outcomes. This approach enhances the internal validity of the study's findings.

8.2. Limitations

The study has some limitations that should be considered. Firstly, it was unable to determine the statistics of disseminated or milliary TB due to the absence of this data in the TB registers and the technical nature of the terminologies, making validation with parents or caregivers challenging during phone interview too.

Another limitation is the reliance on phone calls to ascertain BCG vaccination status, which may have been subject to social desirability bias of falsely reporting the child is vaccinated, potentially leading to an underestimation of the protective effect of the BCG vaccine on deaths from TB.

Additionally, the study's reliance on secondary data meant that certain TB risk factors, such as diabetes, were not recorded. As a result, the association between diabetes and TB in children could not be assessed.

HIV testing is required for TB patients in Ethiopia [336]. However, the unknown HIV status of a significant proportion of controls poses another limitation. Categorizing these controls as HIV-negative may have led to an overestimation of the association between HIV infection and TB disease. However, given the low HIV prevalence among children, HIV prevalence among persons aged 15 to 19 is as low as 0.1%, in Ethiopia [370], the likelihood of having HIV-positive children among the 192 unknown status controls would be too small to influence the findings.

Furthermore, the study did not assess the effect of malnutrition as a risk factor for TB due to difficulty in determining the temporal relationship between malnutrition and TB onset. Similarly, the study did not include diabetes or pre-diabetes data for both cases and controls, despite the known increased risk of TB associated with these conditions.

Lastly, the study did not investigate whether deaths occurred at home or in inpatient settings, which could have provided valuable insights for guiding appropriate follow-up care during the continuation phase of TB treatment. These limitations should be considered when interpreting the study's findings.

9. Conclusions

The study highlights that most children contract TB from the community, with a resurgence in morbidity observed around age 12, possibly due to declining BCG vaccine effectiveness as children approach adolescence. Given that a majority of TB-infected children spend significant time in crowded settings like schools or daycare centers, and only a fraction has contact with a TB-infected family member, there is a clear need for TB screening mechanisms in these environments.

In light of the WHO's End TB goal to achieve a case-fatality ratio of 5% or lower by 2025, and a pooled global death rate of 0.9% in treated childhood TB patients, the observed death rate among children undergoing TB treatment in Urban Central Ethiopia, particularly affecting those under two years old, is high. Age below 10 years is a significant risk factor for childhood TB death and unfavorable treatment outcomes, suggesting a need to revise TB guidelines and expand the high-risk age category for TB mortality from 5 years to 10 years. The finding that BCG vaccination did not significantly impact the survival of children treated for TB should be interpreted cautiously, considering the potential social desirability bias in reporting positive vaccination status by parents of children who died from TB.

BCG vaccination was found to be effective in preventing childhood TB, but its effectiveness wanes as children approach adolescence. Exposure to second-hand smoke was associated with an increased risk of childhood TB. This implies the need to maintain universal newborn vaccination in Ethiopia and to consider legislation against smoking in households with children.

Despite advancements in HIV treatment and universal TB preventive treatment interventions aimed at reducing TB incidence in HIV-infected children, HIV infection remained a significant risk factor for childhood TB morbidity and mortality. This necessitates an evaluation of TB preventive treatment intervention coverage and efficacy in children with HIV infection.

While the proportion of unfavorable TB treatment outcomes in central Ethiopian children remained below the WHO's 10% threshold, a significant portion occurred during the treatment continuation phase, requiring stringent follow-up during this phase, similar to the directly

observed treatment (DOT) intervention during the intensive phase. The finding that unresolved undernutrition persists as an independent predictor of unfavorable outcomes into the continuation phase of TB treatment underscores the critical importance of addressing undernutrition throughout the entire course of TB treatment.

The lack of distinct effectiveness of BCG to TBM while it is generally effective in preventing childhood TB highlights the need for alternative TBM preventive measures.

10. Recommendations

Recommendations for the Ministry of Health:

- **Expand TB Contact Tracing and Screening**: Enhance Ethiopia's TB contact tracing and screening strategy by incorporating reverse contact tracing, which includes close contacts within the school community of a TB sick child.
- **Adjust High-Risk Age Category**: Extend the high-risk age category for childhood TB mortality from 5 years to 10 years. This adjustment will ensure interventions are comprehensive and focused on a broader age group at high risk, enhancing the effectiveness of TB control efforts.
- **Maintain Universal BCG Immunization**: Continue the policy of universal BCG immunization for newborns in Ethiopia.
- **Reduce Exposure to Second-Hand Smoke**: Implement comprehensive public health policies to reduce children's exposure to tobacco smoke. These should include anti-smoking legislation and public awareness campaigns to minimize the risk of childhood TB and protect children's health.
- **Enhance Nutritional Support and TB Care**: Improve the nutritional status of children undergoing TB. Children under 10, those who are HIV positive, and undernourished children should be carefully assessed, treated, monitored, and provided with necessary support, regardless of the phase of TB treatment they are in.
- **Evaluate TPT Programs**: Conduct evaluations of TB Preventive Therapy (TPT) programs, as HIV remains a significant risk factor for TB morbidity and mortality.

Recommendations for Researchers:

- **Study the Resurgence of TB in Adolescents**: Investigate the reasons behind the resurgence of childhood TB as children approach adolescence to develop targeted interventions for this age group.
- **Examine TB and DM Comorbidity**: Future studies should incorporate aspects not covered by this study, such as the comorbidity of TB and DM, to understand how DM may influence TB disease development and treatment outcomes in children.

- **Assess BCG Effectiveness Against TBM**: Conduct larger studies to evaluate the effectiveness of BCG vaccination against TBM compared to other forms of TB.
- **Evaluate TPT Coverage and Efficacy**: Investigate the coverage and duration efficacy TPT in children who received TPT to enhance understanding of its long-term benefits and optimize treatment protocols.
- **Malnutrition and helminthic infestations on TB incidence**: Further research is recommended to investigate the impact of reducing malnutrition and helminthic infestations on TB incidence.

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Appendices

Annex-1. English version of checklist and questionnaire for a study on childhood tuberculosis (TB) in Urban Central Ethiopia, 2022

Participating child:

A case: A child diagnosed with any type of drug-susceptible TB

A control: A child who never had TB disease and currently no symptoms of active pulmonary TB (PTB) [in children aged 5 years and older no current ≥2 weeks cough, fever, night sweating, and weight loss; in children under five years old, no cough, fever, and decreased playfulness]; for extra-pulmonary TB, one of the symptoms for PTB, except cough, or symptoms manifested depending on the affected site or organ [cervical, axillary lymphadenopathy; deformity of the spine which may manifest as kyphosis (gibbus) in its severe form; focal neurological deficit, headache, seizure, meningeal signs such as nucheal rigidity]

Questionnaire's code: _____ Interview date (dd/mm/yy): ____ / _____ / _____ (E.C) Interviewer code: _____			
Instruction: circle the option or fill in the blank space as required			
Question code	Questions	Coding categories	Skip
Section one: Socio-demographic and basic information data			
101	Health facility name		
102	Unit TB Number (*skip for a control*)		
103	Region of the child	1. Addis Ababa 2. Oromia → 105 3. SNNPR → 105 4. Amhara → 105 5. Other (specify)_____ →	

104	If the child was living in Addis Ababa, which sub-city?	1. Addis Ketema 2. Arada 3. Kirkos 4. Lideta 5. Yeka 6. Gullele 7. Bole 8. Kolfe Keranio 9. Nifas Silk Lafto 10. Akaki Kality 11. Lemi Kura	
105	Zone of the child (For a child who came outside of Addis Ababa for treatment)		
106	Phone number of the child's family *(skip for a control)*		
107	Sex of the child	1. M = Male 2. F = Female	
108	Age of the child at TB diagnosis in completed years/ age at interview for a control	Years	
109	TB most at risk group	1. Diabetes 2. Homeless 3. Refugee 4. Other congregated setting 5. TB case contact 6. Not recorded	
110	Phone number of contact person *(skip for a control)*		
111	Linked to TB service by *(skip for a control)*	1. Self 2. HP = Health Post/community 3. PHF = Public Health Facility 4. PPM HF = Private Public Mix Health Facility	
Section two: laboratory investigations and , TB category *(skip this section for a control)*			
201	Xpert MTB/ RIF as initial diagnosis done?	1. Y = Yes 2. N = No →	203
202	Xpert MTB/ RIF result?	1. TB = MBT detected, rifampicin resistance not detected 2. RR = MTB detected, rifampicin resistance detected 3. TI = MTB detected, rifampicin resistance indeterminate 4. N = MBT not detected 5. I = Invalid/no result /error	

203	Sputum smear result	1. P = Positive 2. N = Negative 3. U = Not done/result not available 4. NA = Not applicable	
204	Category	1. N = New 2. R = Relapse 3. F = Treatment after failure 4. L = Treatment after loss to follow-up 5. T = Transfer in 6. O = Other	
205	Type of TB	1. Pulmonary/Positive → 2. Pulmonary/Negative → 3. Extra-pulmonary 4. Both Pulmonary & Extra-pulmonary (disseminated)	301 301
206	If extra-pulmonary TB, what type?	1. TB lymphadenitis 2. TB of the spine (spondylitis), bone or joints 3. TB meningitis (CNS TB) 4. TB peritonitis 5. Pleural TB 6. Miliary TB 7. Other(specify) _____ 8. Not recorded	
Section three: Baseline nutritional assessment and status			
301	Weight at the start of treatment	☐ Kg	
302	Height at start of treatment	☐ Cm	
303	MUAC at the start of treatment	☐ Cm	
304	Nutritional status at baseline	1. Normal 2. MAM = Moderate Acute Malnutrition 3. SAM = Severe Acute Malnutrition	
Section four: Intensive phase treatment *(skip this section for a control)*			
401	Intensive phase drugs [new P/Pos, p/Neg, & extra pul = 2(RHZ) + E] [Relapse, lost, failure = 3(RHZ) + E]	1. 2 (RHZ) + E 2. 3 (RHZ) + E	
402	Intensive phase drug dose	☐ Tabs	
403	Treatment started date	DD/MM/YY:_____/_____/_____	
404	Intensive phase treatment monitoring chart Days: the number of days TB doses missed (*count "X" or "?" marks*) NB:"√" indicates each day the patient receives DOT treatment	☐ doses/days missed	
Section five: TB/HIV Co-infection or HIV infection for a control			

501	HIV test offered	1. Y = Yes 2. N = No	
502	HIV test performed	1. Y = Yes 2. N = No	
503	Target population category	1. I = General population 2. E = Orphan and vulnerable child (OVC) 3. F = Child of PLHIV 4. C = Mobile/Daily laborers 5. D = Prisoners 6. H = Other MARP (specify) _____	
504	HIV test result	1. P = Positive 2. N = Negative →	601
505	CPT started date in E.C *(skip for a control)*	DD/MM/YY: _____/_____/_____	
506	Enrolled in HIV care date in E.C *(skip for a control)*	DD/MM/YY: _____/_____/_____	
507	ART started date in E.C (skip this section for a control)	DD/MM/YY: _____/_____/_____	
Section six: Drug resistant TB (skip this section for a control)			
601	Presumptive Drug Resistance (DR)	1. Y = Yes 2. N = No →	701
602	Drug susceptibility test (DST) result	1. No RR = no resistance at least to rifampicin → 2. RR TB = resistance to rifampicin only 3. MDR TB = resistance to both rifampicin and INH 4. Pre-XDR = MDR + (either fluoroquinolone or injectable resistance) 5. XDR = MDR + (fluoroquinolone and injectable resistance) 6. XXDR/TDR/CDR	701
603	If Drug Resistant (DR)-TB confirmed linked to	Name of HF:	
604	Date DR TB started in E.C	DD/MM/YY: _____/_____/_____	
Section seven: crowdedness and TB case contacts			
701	Total household (HH) and/or close contacts	Number:	
702	Total contacts screened for TB	Number:	
703	Total TB diagnosed among contacts	Number:	
704	Total under 5 contacts	Number:	
705	Total under 5 contacts screened for TB	Number:	

706	Total under 5 contacts screened negative	Number:	
707	Total under 5 put on Isoniazid protective therapy (IPT)	Number:	
Section eight: Follow up sputum results, and Nutritional Assessment and Status *(skip this section for a control)*			
801	2nd month sputum result	1. Smear positive 2. Smear negative 3. Unknown (not done) 4. Not applicable (NA) b/e EPTB or P/Negative → 804	
802	5th month sputum result	1. Smear positive 2. Smear negative 3. Unknown (not done)	
803	6th month sputum result	1. Smear positive 2. Smear negative 3. Unknown (not done)	
804	Weight at the end of 2nd Month (Kg)	Kg	
805	MUAC at the end of 2nd Month (cm)	cm	
806	Nutritional status at end of 2nd month	1. Normal 2. MAM = Moderate Acute Malnutrition 3. SAM = Severe Acute Malnutrition	
807	Continuation phase drug	1. 4 (RH) 2. 10 (RH) 3. 5(RH) + E	
808	Continuation phase dose	tabs	
809	Continuation phase treatment monitoring chart weekly attendance: Number of missed doses	doses/days missed	
Section nine: TB treatment outcome and nutritional intervention *(skip this section for a control)*			
901	TB treatment outcome	1. Cured 2. Completed 3. Lost to follow up 4. Not evaluated 5. Moved to DR-TB register 6. Dead 7. Other (specify) _____	
902	Date TB treatment outcome assigned in EC	DD/MM/YY/: _____/_____/_____	
903	Type of nutritional treatment	1. RUTF or Plumpy nut 2. RUSF or Plumpy sup 3. No nutritional treatment → 907	
904	Nutritional treatment started date in EC	DD/MM/YY/: _____/_____/_____	
905	Outcome of nutritional treatment	1. Recovered/Cured 2. No change	

		3. Other (specify) _____	
906	Date nutritional outcome assigned in EC	DD/MM/YY/: _____/_____/_____	
907	TB treatment adherence support provided at?	1. Health facility 2. Health post 3. Not describe	
908	Remarks	_____	
Section ten: BCG vaccination history and TB diagnosis delay [call and ask for a case and face-to-face interview for a control]			
1001	Where was the child born?	1. At home 2. Health post 3. Health center 4. Governmental hospital 5. Private clinic 6. Private hospital 7. Other (specify) _____	
1002	Was the child vaccinated for BCG vaccine at birth? (was the child vaccinated within 15 days after birth)	1. Yes 2. No →	1004
1003	Does the child have BCG scar on his/her arm?	1. Yes 2. No	
1004	How many days after the child showed signs of illness was the first time he/she was taken to the health facility?	After_____ days	
1005	What kind of health facility was the first time the child was taken ill?	1. Health Center 2. Governmental hospital 3. Private clinic 4. Private hospital 5. Other (specify) _____	
1006	Was the child diagnosed with tuberculosis at the health facility where he/she first went or was it somewhere else? (referred for further investigation and diagnosis) *(skip this for a control)*	1. Diagnosed at first visited health facility 2. Referred to another health facility for further investigation	
1007	How many days after the child was taken to a health facility did he/she diagnosed with TB? *(skip this for a control)*	After _____days	
Section eleven: Child education, family education, and smoking history			
1101	What was his/her school situation right before the child became ill?	1. Used to go to school 2. Used to stay at day care 3. Used to stay at home →	1104
1102	If the child went to school, what grade was the child attending before he/she became ill?	1. Kindergarten 2. Grade 1 to 6 3. Grade 7 to 8	

		4. High school	
1103	If the child went to school before he/she got sick, what was the school type?	1. Governmental school 2. Private school	
1104	What was the educational status of the child's mother when the child was sick?	1. Didn't go to school 2. Grade 1 to 6 3. Grade 7 to 8 4. Grade 9 to 12 5. Diploma 6. Degree 7. Masters and above 8. Mother was not alive	
1105	What was the educational status of the child's father when the child was sick? (record father's current educational status if the child is a control)	1. Didn't go to school 2. Grade 1 to 6 3. Grade 7 to 8 4. Grade 9 to 12 5. Diploma 6. Degree 7. Masters and above 8. Father was not alive	
1106	Was there a family member who smokes cigarette and was living with child?	1. Yes 2. No →	1108
1107	If there was anyone in the family who smokes, what was the relationship with the child?	1. Father 2. Mother 3. Brother/sister 4. Other (specify) _____	
1108	Was there domestic animal living overnight in the same house the family live in?	1. Yes 2. No →	End
1109	If "yes" to Q806, which type of domestic animal lives in the living house?	1. Sheep 2. Goat 3. Cow/ox/calf 4. Two or all of the above 5. Other (specify) _____	
109ext1	Did another family member become sick with TB before or after the child was diagnosed with TB if a case child, and any other disease if a control child?	1. Yes 2. No	
109ext2	What type of TB did that other family member get?	1. Pulmonary positive 2. Pulmonary negative 3. Extra pulmonary	
109ext3	What is the relationship of a person with TB to the child?	1. Mother 2. Father 3. Brother/sister 4. Grandparent 5. House servant 6. Other (specify) _____	

Annex-2a. Amharic version of checklist and questionnaire for a study on childhood tuberculosis (TB) in Urban Central Ethiopia, 2022 (cases)

Questionnaire's code: _____ Interview date (dd/mm/yy): ____ / _____ / _____ (E.C)			
Instruction: encircle the option or fill in the blank space as required			
Question code	Questions	Coding categories	Skip
Section one: Socio-demographic and basic information data			
101	Health facility name		
102	Unit TB Number		
103	Region of the child	1. Addis Ababa 2. Oromia → 105 3. SNNPR → 105 4. Amhara → 105 5. Other (specify)_____ → 105	
104	If the child was living in Addis Ababa, which sub-city?	1. Addis Ketema 2. Arada 3. Kirkos 4. Lideta 5. Yeka 6. Gullele 7. Bole 8. Kolfe Keranio 9. Nifas Silk Lafto 10. Akaki Kality 11. Lemi Kura	
105	Zone of the child (For a child who came outside of Addis Ababa for treatment)		
106	Phone number of the child's family		
107	Sex of the child	1. M = Male 2. F = Female	
108	Age of the child at TB diagnosis in completed years	_____ years	
109	TB most at risk group	1. Diabetes 2. Homeless 3. Refugee 4. Other congregated setting 5. TB case contact 6. Not recorded	
110	Phone number of contact person		
111	Linked to TB service by	1. Self 2. HP = Health Post/community 3. PHF = Public Health Facility 4. PPM HF = Private Public Mix Health	

		Facility	
Section two: laboratory investigations and , TB category			
201	Xpert MTB/ RIF as initial diagnosis done?	1. Y = Yes 2. N = No →	203
202	Xpert MTB/ RIF result?	1. TB = MBT detected, rifampicin resistance not detected 2. RR = MTB detected, rifampicin resistance detected 3. TI = MTB detected, rifampicin resistance indeterminate 4. N = MBT not detected 5. I = Invalid/no result /error	
203	Sputum smear result	1. P = Positive 2. N = Negative 3. U = Not done/result not available 4. NA = Not applicable (EPTB or smear negative TB)	
204	Category	1. N = New 2. R = Relapse 3. F = Treatment after failure 4. L = Treatment after loss to follow-up 5. T = Transfer in 6. O = Other	
205	Type of TB	1. Pulmonary/Positive → 2. Pulmonary/Negative → 3. Extra-pulmonary 4. Both Pulmonary & Extra-pulmonary (disseminated)	301 301
206	If extra-pulmonary TB, what type?	1. TB lymphadenitis 2. TB of the spine (spondylitis), bone or joints 3. TB meningitis (CNS TB) 4. TB peritonitis 5. Pleural TB 6. Intestinal TB 7. Other(specify) _____ 8. Not recorded	
Section three: Baseline nutritional assessment and status			
301	Weight at the start of treatment	☐ Kg	
302	Height at start of treatment	☐ cm	
303	MUAC at the start of treatment	☐ cm	
304	Nutritional status at baseline	1. Normal	

		2. MAM = Moderate Acute Malnutrition 3. SAM = Severe Acute Malnutrition	
Section four: Intensive phase treatment			
401	Intensive phase drugs [new P/Pos, p/Neg, & extra pul = 2(RHZ) + E] [Relapse, lost, failure = 3(RHZ) + E]	1. 2 (RHZ) + E 2. 3 (RHZ) + E	
402	Intensive phase drug dose	☐ tabs	
403	Treatment started date	DD/MM/YY:_____/_____/_____	
404	Intensive phase treatment monitoring chart Days: the number of days TB doses missed (*count "*X*" or "*?*" marks*) NB:"√" indicates each day the patient receives DOT treatment	☐ doses/days missed	
Section five: TB/HIV Co-infection			
501	HIV test offered	1. Y = Yes 2. N = No	
502	HIV test performed	1. Y = Yes 2. N = No	
503	Target population category	1. I = General population 2. E = Orphan and vulnerable child (OVC) 3. F = Child of PLHIV 4. C = Mobile/Daily laborers 5. D = Prisoners 6. H = Other MARP (specify) _____	
504	HIV test result	1. P = Positive 2. N = Negative →	601
505	CPT started date in EC	DD/MM/YY: _____/_____/_____	
506	Enrolled in HIV care date in EC	DD/MM/YY: _____/_____/_____	
507	ART started date in EC	DD/MM/YY: _____/_____/_____	
Section six: Drug resistant TB			
601	Presumptive Drug Resistance (DR)	1. Y = Yes 2. N = No →	701
602	Drug susceptibility test (DST) result	1. No RR = no resistance at least to rifampicin → 2. RR TB = resistance to rifampicin only 3. MDR TB = resistance to both rifampicin and INH 4. Pre-XDR = MDR + (either fluoroquinolone or injectable resistance) 5. XDR = MDR + (fluoroquinolone and injectable resistance) 6. XXDR/TDR/CDR	701
603	If Drug Resistant (DR)-TB confirmed linked to	Name of HF: ☐	

604	Date DR TB started in EC	DD/MM/YY: _____/_____/_____	
Section seven: crowdedness and TB case contacts			
701	Total household (HH) and/or close contacts	Number: ☐	
702	Total contacts screened for TB	Number: ☐	
703	Total TB diagnosed among contacts	Number: ☐	
704	Total under 5 contacts	Number: ☐	
705	Total under 5 contacts screened for TB	Number: ☐	
706	Total under 5 contacts screened negative	Number: ☐	
707	Total under 5 put on Isoniazid protective therapy (IPT)	Number: ☐	
Section eight: Follow up sputum results, and Nutritional Assessment and Status			
801	2nd month sputum result	1. Smear positive 2. Smear negative 3. Unknown (not done) 4. Not applicable (NA) b/e EPTB or P/Negative → 804	
802	5th month sputum result	1. Smear positive 2. Smear negative 3. Unknown (not done)	
803	6th month sputum result	1. Smear positive 2. Smear negative 3. Unknown (not done)	
804	Weight at the end of 2nd Month (Kg)	☐ Kg	
805	MUAC at the end of 2nd Month (cm)	☐ cm	
806	Nutritional status at end of 2nd month	1. Normal 2. MAM = Moderate Acute Malnutrition 3. SAM = Severe Acute Malnutrition	
807	Continuation phase drug	1. 4 (RH) 2. 10 (RH) 3. 5(RH) + E	
808	Continuation phase dose	☐ tabs	
809	Continuation phase treatment monitoring chart weekly attendance: Number of missed doses	☐ doses/days missed	
Section nine: TB treatment outcome and nutritional intervention			
901	TB treatment outcome	1. Cured 2. Completed 3. Lost to follow up	

		4. Not evaluated 5. Moved to DR-TB register 6. Dead 7. Other (specify) _____	
902	Date TB treatment outcome assigned in EC	DD/MM/YY/: _____/_____/_____	
903	Type of nutritional treatment	1. RUTF or Plumpy nut 2. RUSF or Plumpy sup 3. No nutritional treatment →	907
904	Nutritional treatment started date in EC	DD/MM/YY/: _____/_____/_____	
905	Outcome of nutritional treatment	1. Recovered/cured 2. No change 3. Other (specify) _____	
906	Date nutritional outcome assigned in EC	DD/MM/YY/: _____/_____/_____	
907	TB treatment adherence support provided at	1. Health facility 2. Health post 3. Not described	
908	Remarks	_____	
ክፍል አስር: የቢሲጂ (BCG) ክትባት በተመለከተና TB ህመምን ለመለየት የወሰደው ጊዜ [ደውለው ይጠይቁ]			
1001	በቲቢ የታመመው ልጅ የት ነበር የተወለደው?	1. ቤት 2. ጤና ኬላ 3. ጤና ጣቢያ 4. የመንግስት ሆስፒታል 5. የግል ክሊኒክ 6. የግል ሆስፒታል 7. ሌላ (ይጠቀስ) _____	
1002	ልጁ እንደ ተወለደ ወይም ተወልዶ በ15 ቀን ውጥ የBCG ክትባት ተሰጥቶት ነበር?	1. አዎ 2. አይ →	1004
1003	ልጁ ክትባት የተወጋበት እጅ ቦታ ላይ የBCG ክትባት ጠባሳ አለበት?	1. አዎ 2. አይ	
1004	ልጁ የህመም ምልክት ማሳየት ከጀመረ ከስንት ቀን በኋላ ነው ወደ ህክምና ቦታ የተወሰደው?	ከ_____ ቀናት በኋላ	
1005	መጀመሪያ የተወሰደበት ህክምና ተቋም የትኛው አይነት ነበር?	1. ጤና ጣቢያ 2. የመንግስት ሆስፒታል 3. የግል ክሊኒክ 4. የግል ሆስፒታል 5. ሌላ (ይገለጽ) _____	
1006	ልጁ በቲቢ በሽታ መታመሙ የታወቀው	1. መጀመሪያ የታየበት ቦታ	

	እዚያው መጀመሪያ የወሰዳችሁበት ጤና ተቋም ውስጥ ነው ወይስ ሌላ ቦታ ሪፈር ተብሎ ነው?	2. ሌላ ቦታ ለተሻለ ምርመራ ሪፈር ተብሎ ነው የታወቀው	
1007	መጀመሪያ ወደ ህክምና ተቋም ከወሰዳችሁት ከስንት ቀን በኋላ ነው በሽታው ቲቢ መሆኑ የታወቀው?	ከ _____ቀናት በኋላ	
ክፍል አስራ-አንድ: የልጁ እንዲሁም የቤተሰቡ ትምህርት ሁኔታና የቤተ-ሰብ ሲጋራ የማጨስ ሁኔታ			
1101	ልጁ ከመታመሙ በፊት ውሎው የት ነበር?	1. ትምህርት ቤት 2. ህጻናት ማቆያ 3. ቤት →	1104
1102	ውሎው ትምህርት ቤት ከሆነ ከመታመሙ በፊት ስንተኛ ክፍል ይማር ነበር?	1. ሚለ-ህጻናት 2. 1 – 6 ክፍል 3. 7 – 8 ክፍል 4. 9ኛ ወይም ከዚያ በላይ	
1103	ውሎው ትምህርት ቤት ከነበረ፣ ሲማርበት የነበረው ትምህርት ቤት ምን አይነት ነበር?	1. የመንግስት 2. የግል	
1104	የልጁ በታመመበት ወቅት የእናቱ የትምህርት ደረጃ ምን ነበር?	1. አልተማረችም 2. ከ 1ኛ እስከ 6ኛ ክፍል 3. ከ 7ኛ እስከ 8ኛ ክፍል 4. ከ 9ኛ እስከ 12ኛ ክፍል 5. ዲፕሎማ 6. ዲግሪ 7. ማስተርስ ወይም ከዚያ በላይ 8. እናት በህይወት አልነበረችም	
1105	የልጁ በታመመበት ወቅት የአባቱ የትምህርት ደረጃ ምን ነበር?	1. አልተማረም 2. ከ 1ኛ እስከ 6ኛ ክፍል 3. ከ 7ኛ እስከ 8ኛ ክፍል 4. ከ 9ኛ እስከ 12ኛ ክፍል 5. ዲፕሎማ 6. ዲግሪ 7. ማስተርስ ወይም ከዚያ በላይ 8. አባት በህይወት አልነበረም	
1106	ከልጁ ጋር ከሚኖሩት የቤተ-ሰብ አባላት ውስጥ ሲጋራ የሚያጨስ ሰው ነበር እንዴ?	1. አዎ 2. አይ →	1108
1107	ከቤተ-ሰብ አባል ውስጥ የሚያጨስ ሰው ካለ ከልጁ ጋር ያለው ዝምድና ምንድነው?	1. አባት 2. እናት 3. ወንድም/እህት 4. ሌላ (ይጠቀስ) _____	
1108	ከእናንተ ጋር አንድ ላይ እቤት ውስጥ	1. አዎ	

	የምታሳድሩት የቤት እንስሳ ነበር እንዴ?	2. አይ →	109ext1
1109	እቤት ውስጥ የምታሳድሩት የቤት እንስሳ ከነበረ ምን አይነት እንስሳ ነው?	1. በግ 2. ፍየል 3. ላም/በሬ/ጥጃ 4. ሌላ (ይጠቀስ) ----------	
109ext1	ልጁ ከመታመሙ በፊት ወይም ከታመመ በኋላ ቲቢ የታመመ ሌላ የቤተሰብ አባል ነበረ?	1. አዎ 2. አይ →	አበቃ
109ext2	የታመመ የቤተሰብ አባል ከነበረ በምን አይነት ቲቢ ነበር የታመመው?	1. በሳምባ/አክታው ውስጥ የተገኘ 2. በሳምባ/አክታው ውስጥ ያልተገኘ 3. ከሳምባ ውጭ በሆነ ቲቢ	
109ext3	በቲቢ የታመመው ሰው ከልጁ ጋር ያለው ዝምድና ምን ነበር?	1. እናት 2. አባት 3. ወንድም/እህት 4. አያት 5. የቤት ሰራተኛ 6. ሌላ (ይገለፅ) _____	

ለሰጡኝ መረጃ አመሰግናለሁ!

Annex-2b. Amharic version of checklist and questionnaire for a study on childhood tuberculosis (TB) in central Ethiopia, 2022 (controls)

ከዚህ በፊት በቲቢ በሽታ ታመው ለማያውቁ ብቻ የሚሞላ መጠይቅ

ቀን (ቀን/ወር/አመት): ____ / _____ / _____ (ዓ.ም)			
መመሪያ: አማራጮችን ይክበቡበት ወይም በተሰጠው ባዶ ቦታ ላይ መልሱን ይፃፉ			
መለያ	ጥያቄ	ኮድ _____	እለፍ
ክፍል አንድ: ሶሾ-ዲሞግራፊና መሰረታዊ መረጃ			
000	ልጁ ምን የህመም ምልክት ኖሮት ነው እዚህ ሀኪም ቤት የመጣው? (ከአንድ በላይ መልስ ሊኖረው ይችላል)	1. ትኩሳት 2. ተቅማጥ 3. ተውከት 4. የሆድ ቁርጠት 5. ሳል 6. ራስ ምታት 7. የምግብ ፍልጎት መቀነስ 8. የሰውነት ክብደት መቀነስ 9. ሌሊት ማላብ 10. ሌላ ምልክት ከሆነ እዚህ ይፃፍ---------- 11. ምንም የህመም ምልክት የለውም (ለምሳሌ	

		ለክትባት የመጣ/ች)	
101	የጤና ተቋሙ ስም		
103	የሚኖርበት ክልል የት ነው?	1. አዲስ አበባ 2. ኦሮሚያ → 105 3. ደቡብ → 105 4. አማራ → 105 5. ሌላ (ጥቀስ)_____ → 105	
104	አዲስ አበባ ከሆነ፣ክፍለ-ከተማው የት ነው?	1. አዲስ ከተማ 2. አራዳ 3. ቂርቆስ 4. ልደታ 5. የካ 6. ጉለሌ 7. ቦሌ 8. ኮልፌ 9. ንፋስ ስልክ ላፍቶ 10. አቃቂ ቃሊቲ 11. ለሚ ኩራ	
105	ከአዲስ አበባ ውጭ ከሆነ የት ዞን ነው?		
107	የልጁ/የልጅቷ ፆታ?	1. ወንድ 2. ሴት	
108	እድሜ (ያጠናቀቀው/ችው አመት)	አመት	
109	ለቲቢ በሽታ ተጋላጭ የሚያደርገው ነገር ምን አለ?	1. ስኳር ታማሚ ነው 2. ቤት አልባ ነው (ጎዳና ተዳዳሪ) 3. የስደተኛ መጠለያ የሚኖር ነው 4. ሌላ የተጨናነቀ ቦታ (ዩኒቨርሲቲ፣ እስር ቤት፣ ህፃናት ማሳደጊያ ወዘተ) የሚኖር 5. ቲቢ ከታመመ ሰው ጋር ግንኙነት ነበረው 6. የታወቀ ነገር የለም	
111	ልጁን ወደዚህ ህክምና ተቃም እንድታመጡት ማን መከራችሁ?	1. በራሳችን ነው የመጣነው 2. የጤና ኤክስቴንሽን 3. ሌላ የመንግስት ጤና ተቋም ሪፈር አድርጎን 4. የግል ጤና ተቋም ሪፈር አድረጎን	
ክፍል ሶስት: የስነ-ምግብ ሁኔታ ግምገማ			
301	የልጁ ኪሎ አሁን ላይ ስንነት ነው?	ኪሎ ግራም	
302	የልጁ ቁመት ስንት ነው?	ሴንቲ ሜትር	

303	MUAC (የማእከላዊ ክንድ ዙሪያ)	☐ ሴንቲ ሜትር	
304	Nutritional status at baseline (በተመራማሪው የሚሞላ)	1. Normal 2. MAM = Moderate Acute Malnutrition 3. SAM = Severe Acute Malnutrition	
ክፍል አምስት: ቲቢ እና ኤች.አይ.ቪ			
501	HIV እንዲመረመር/እንድትመረመር ተጠይቃችሁ ታውቃላችው?	1. አዎ 2. አይ	
502	HIV ተመርምሮ/ተመርምራ ያውቃል/ታውቃለች?	1. አዎ 2. አይ	
503	ለቲቢ ተጋላጭ ማህበረሰብ ምደባ	1. I = መደበኛ ህዝብ 2. E = ቤተ-ሰብ አልባ ልጅ 3. F = ቤተ-ሰብ የኤች.አይ.ቪ የተጠቃበት 4. C = የቀን ሰራተኛ 5. D = የህግ ታራሚ 6. H = ሌላ የተጋለጠ (ግለፅ) _____	
504	የኤች.አይ.ቪ ምርመራ ውጤት	1. P =ፖዘቲቭ 2. N = ኔጋቲቭ → 701 3. አይታወቅም → 701	
505	CPT የጀመረበት ቀን	ቀን/ወር/አመት: _____/_____/_____	
506	ወደ ኤች.አይ.ቪ ክትትል የገባበት ቀን	ቀን/ወር/አመት: _____/_____/_____	
507	ፀረ-ኤች.አይ.ቪ የጀመረበት ቀን	ቀን/ወር/አመት: _____/_____/_____	
ክፍል ሰባት: የተፋፈገ ሁኔታ እና ከቲቢ ታማሚ ጋር ግንኙነት			
701	አንድ ቤት ውስጥ የምትኖሩት የቤተሰብ ብዛት ስንት ነው?	☐	
702	ሳል፣ለሊት ማላብ፣የምግብ ፍላጎት እና የሰውነት ክብደት መቀነስ ምልክት ያለው ሰው ቤት ውስጥ አለ?	☐ ከሌለ ዜሮ ፃፍ	
703	ባለፉት ሁለት አመታት ውስጥ አንድ ቤት ውስጥ ከምትኖሩት የቤት ሰብ አባል ውስጥ በቲቢ በሽታ የታመመ ሰው አለ?	☐ ከሌለ ዜሮ ፃፍ	
704	ከአምስት አመት በታች ህፃን ቤት ውስጥ ሰንት አለ?	☐	
705	ሳል፣ሌሊት ማላብ፣ የምግብ ፍላጎት ወይም የሰውነት ክብደት መቀነስ ምልክት ያለው ከአምስት አመት በታች ህጻን ቤት ውስጥ አለ?	☐ ከሌለ ዜሮ ፃፍ	
707	የቲቢ በሽታ መከላከያ (INH) የሚወስድ ከአምስት አመት በታች ህፃን ቤት ውስጥ	☐ ከሌለ ዜሮ ፃፍ	

	አለ?		
ክፍል አስር: የቢሲጂ (BCG) ክትባት በተመለከተና ህመምን ለመለየት የወሰደው ጊዜ			
1001	ይሄ ልጅ የት ነበር የተወለደው?	1. ቤት ውስጥ 2. ጤና ኬላ 3. ጤና ጣቢያ 4. የመንግስት ሆስፒታል 5. የግል ክሊኒክ 6. የግል ሆስፒታል 7. ሌላ (ይጠቀስ) _____	
1002	ልጁ እንደ ተወለደ ወይም ተወልዶ በ15 ቀን ውስጥ የBCG ክትባት ተከትቦ ነበር?	1. አዎ 2. አይ	1004
1003	ልጁ ክትባት የተወጋበት እጅ ክንድ ላይ የBCG ክትባት ጠባሳ አለበት? *(መኖር አለመኖሩን በመመልከት አረጋግጥ)*	1. አዎ 2. አይ	
1004	ልጁ የህመም ምልክት ማሳየት ከጀመረ ከስንት ቀን በኋላ ነው ወደ ህክምና ቦታ የመጣው?	ከ_____ ቀናት በኋላ	
1005	መጀመሪያ የተወሰደበት ህክምና ተቋም የትኛው አይነት ነበር?	1. ጤና ጣቢያ 2. የመንግስት ሆስፒታል 3. የግል ክሊኒክ 4. የግል ሆስፒታል 5. ሌላ (ይገለጽ) _____	
1007	መጀመሪያ ወደ ህክምና ተቋም ከወሰዳችሁት ከስንት ቀን በኋላ ነው ህመሙ የታወቀው?	ከ _____ቀናት በኋላ	
ክፍል አስራ-አንድ: የልጁ እንዲሁም የቤተሰቡ ትምህርት ሁኔታና የቤተ-ሰብ ሲጋራ የማጨስ ሁኔታ			
1101	ልጁ ውሎው የት ነው?	1. ትምህርት ቤት 2. ህጻናት ማቆያ 3. ቤት 4. ስራ	
1102	ውሎው ትምህርት ቤት ከሆነ ስንተኛ ክፍል ነው?	1. ሚለ-ህጻናት 2. 1 – 6 ክፍል 3. 7 – 8 ክፍል 4. 9ኛ ወይም ከዚያ በላይ	
1103	ውሎው ትምህርት ቤት ከነበረ፣ ሲማርበት የነበረው ትምህርት ቤት ምን አይነት ነበር?	1. የመንግስት 2. የግል	
1104	የልጁ የእናቱ የትምህርት ደረጃ ምን ምንድርን ነው?	1. አልተማረችም 2. ከ 1ኛ እስከ 6ኛ ክፍል	

		3. ከ 7ኛ እስከ 8ኛ ክፍል 4. ከ 9ኛ እስከ 12ኛ ክፍል 5. ዲፕሎማ 6. ዲግሪ 7. ማስተርስ ወይም ከዚያ በላይ 8. እናት በህይወት የለችም	
1105	የልጁ የአባቱ የትምህርት ደረጃ ምንድርን ነው?	1. አልተማረም 2. ከ 1ኛ እስከ 6ኛ ክፍል 3. ከ 7ኛ እስከ 8ኛ ክፍል 4. ከ 9ኛ እስከ 12ኛ ክፍል 5. ዲፕሎማ 6. ዲግሪ 7. ማስተርስ ወይም ከዚያ በላይ 8. አባት በህይወት የለም	
1106	ከልጁ ጋር ከሚኖሩት የቤተ-ሰብ አባላት ውስጥ ሲጋራ የሚያጨስ ሰው ነበር እንዴ?	1. አዎ 2. አይ →	1108
1107	ከቤተ-ሰብ አባል ውስጥ የሚያጨስ ሰው ከነበረ ከልጁ ጋር ያለው ዝምድና ምንድነው?	1. አባት 2. እናት 3. ወንድም/እህት 4. ራሱ ልጁ 5. ሌላ (ይጠቀስ) _____	
1108	ከእናንተ ጋር አንድ ላይ እቤት ውስጥ የምታሳድሩት የቤት እንስሳ አለ እንዴ?	1. አዎ 2. አይ →	109ext1
1109	እቤት ውስጥ የምታሳድሩት የቤት እንስሳ ከነበረ ምን አይነት እንስሳ ነው?	1. በግ 2. ፍየል 3. ላም/በሬ/ጥጃ 4. ሌላ (ይጠቀስ) ----------	
109ext1	ከቤተሰብ ውስጥ በቲቢ የታመመ የቤተሰብ አባል ቤታችሁ ውስጥ ነበር?	1. አዎ 2. አይ →	አበቃ
109ext2	በቲቢ የታመመ የቤተሰብ አባል ከነበረ በምን አይነት ቲቢ ነበር የታመመው?	1. በሳምባ/አክታው ውስጥ የተገኘ 2. በሳምባ/አክታው ውስጥ ያልተገኘ 3. ከሳምባ ውጭ በሆነ ቲቢ	
109ext3	በቲቢ የታመመው ሰው ከልጁ ጋር ያለው ዝምድና ምን ነበር?	1. እናት 2. አባት 3. ወንድም/እህት 4. አያት 5. የቤት ሰራተኛ 6. ሌላ (ይገለፅ) _____	

ለሰጡኝ መረጃ አመሰግናለሁ!

Annex-3a. Afan Oromo version of checklist and questionnaire for a study on childhood tuberculosis (TB) in central Ethiopia, 2022 (cases)

Questionnaire's code: _____ Interview date (dd/mm/yy): ____ / _____ / _____ (E.C)			
Instruction: encircle the option or fill in the blank space as required			
Question code	Questions	Coding categories	Skip
Section one: Socio-demographic and basic information data			
101	Health facility name		
102	Unit TB Number		
103	Region of the child	1. Addis Ababa 2. Oromia 3. SNNPR 4. Amhara 5. Other (specify)_____	 105 105 105 105
104	If the child was living in Addis Ababa, which sub-city?	1. Addis Ketema 2. Arada 3. Kirkos 4. Lideta 5. Yeka 6. Gullele 7. Bole 8. Kolfe Keranio 9. Nifas Silk Lafto 10. Akaki Kality 11. Lemi Kura	
105	Zone of the child (includes for a child who came outside of Addis Ababa for treatment)		
106	Phone number of the child's family		
107	Sex of the child	1. M = Male 2. F = Female	
108	Age of the child at TB diagnosis in completed years	Years	
109	TB most at risk group	1. Diabetes 2. Homeless 3. Refugee 4. Other congregated setting 5. TB case contact 6. Not recorded	
110	Phone number of contact person		

111	Linked to TB service by	1. Self 2. HP = Health Post/community 3. PHF = Public Health Facility 4. PPM HF = Private Public Mix Health Facility	
Section two: laboratory investigations and , TB category			
201	Xpert MTB/ RIF as initial diagnosis done?	1. Y = Yes 2. N = No →	203
202	Xpert MTB/ RIF result?	1. TB = MBT detected, rifampicin resistance not detected 2. RR = MTB detected, rifampicin resistance detected 3. TI = MTB detected, rifampicin resistance indeterminate 4. N = MBT not detected 5. I = Invalid/no result /error	
203	Sputum smear result	1. P = Positive 2. N = Negative 3. U = Not done/result not available 4. NA = Not applicable (EPTB or smear negative)	
204	Category	1. N = New 2. R = Relapse 3. F = Treatment after failure 4. L = Treatment after loss to follow-up (L) 5. T = Transfer in (T) 6. O = Other	
205	Type of TB	1. Pulmonary/Positive → 2. Pulmonary/Negative → 3. Extra-pulmonary 4. Both Pulmonary & Extra-pulmonary (disseminated)	301 301
206	If extra-pulmonary TB, what type?	1. TB lymphadenitis 2. TB of the spine (spondylitis), bone or joints 3. TB meningitis (CNS TB) 4. TB peritonitis 5. Pleural TB 6. Miliary TB 7. Other(specify) _____ 8. Not recorded	
Section three: Baseline nutritional assessment and status			
301	Weight at the start of treatment	____ Kg	
302	Height at start of treatment	____ Cm	
303	MUAC at the start of treatment	____ Cm	

304	Nutritional status at baseline	1. Normal 2. MAM = Moderate Acute Malnutrition 3. SAM = Severe Acute Malnutrition	
Section four: Intensive phase treatment			
401	Intensive phase drugs [new P/Pos, p/Neg, & extra pul = 2(RHZ) + E] [Relapse, lost, failure = 3(RHZ) + E]	1. 2 (RHZ) + E 2. 3 (RHZ) + E	
402	Intensive phase drug dose	☐ Tabs	
403	Treatment started date	DD/MM/YY:_____/_____/_____	
404	Intensive phase treatment monitoring chart Days: the number of days TB doses missed (*count "*X*" or "*?*" marks*) NB:"√" indicates each day the patient receives DOT treatment	☐ doses/days missed	
Section five: TB/HIV Co-infection			
501	HIV test offered	1. Y = Yes 2. N = No	
502	HIV test performed	1. Y = Yes 2. N = No	
503	Target population category	1. I = General population 2. E = Orphan and vulnerable child (OVC) 3. F = Child of PLHIV 4. C = Mobile/Daily laborers 5. D = Prisoners 6. H = Other MARP (specify) _____	
504	HIV test result	1. P = Positive 2. N = Negative →	601
505	CPT started date in EC	DD/MM/YY: _____/_____/_____	
506	Enrolled in HIV care date in EC	DD/MM/YY: _____/_____/_____	
507	ART started date in EC	DD/MM/YY: _____/_____/_____	
Section six: Drug resistant TB			
601	Presumptive Drug Resistance (DR)	1. Y = Yes 2. N = No →	701
602	Drug susceptibility test (DST) result	1. No RR = no resistance at least to rifampicin → 2. RR TB = resistance to rifampicin only 3. MDR TB = resistance to both rifampicin and INH 4. Pre-XDR = MDR + (either fluoroquinolone or injectable resistance) 5. XDR = MDR + (fluoroquinolone and injectable resistance) 6. XXDR/TDR/CDR	701

603	If Drug Resistant (DR)-TB confirmed linked to	Name of HF:	
604	Date DR TB started in EC	DD/MM/YY: _____/_____/_____	
Section seven: crowdedness and TB case contacts			
701	Total household (HH) and/or close contacts	Number:	
702	Total contacts screened for TB	Number:	
703	Total TB diagnosed among contacts	Number:	
704	Total under 5 contacts	Number:	
705	Total under 5 contacts screened for TB	Number:	
706	Total under 5 contacts screened negative	Number:	
707	Total under 5 put on Isoniazid protective therapy (IPT)	Number:	
Section eight: Follow up sputum results, and Nutritional Assessment and Status			
801	2nd month sputum result	1. Smear positive 2. Smear negative 3. Unknown (not done) 4. Not applicable (NA) b/e EPTB or P/Negative ➔804	
802	5th month sputum result	1. Smear positive 2. Smear negative 3. Unknown (not done)	
803	6th month sputum result	1. Smear positive 2. Smear negative 3. Unknown (not done)	
804	Weight at the end of 2nd Month (Kg)	Kg	
805	MUAC at the end of 2nd Month (cm)	Cm	
806	Nutritional status at end of 2nd month	1. Normal 2. MAM = Moderate Acute Malnutrition 3. SAM = Severe Acute Malnutrition	
807	Continuation phase drug	1. 4 (RH) 2. 10 (RH) 3. 5(RH) + E	
808	Continuation phase dose	Tabs	
809	Continuation phase treatment monitoring chart weekly attendance: Number of missed doses	doses/days missed	
Section nine: TB treatment outcome and nutritional intervention			

901	TB treatment outcome	1. Cured 2. Completed 3. Lost to follow up 4. Not evaluated 5. Moved to DR-TB register 6. Dead 7. Other (specify) _____	
902	Date TB treatment outcome assigned in EC	DD/MM/YY/: _____/_____/_____	
903	Type of nutritional treatment	1. RUTF or Plumpy nut 2. RUSF or Plumpy sup 3. No nutritional treatment →	907
904	Nutritional treatment started date in EC	DD/MM/YY/: _____/_____/_____	
905	Outcome of nutritional treatment	1. Recovered/cured 2. No change 3. Other (specify) _____	
906	Date nutritional outcome assigned in EC	DD/MM/YY/: _____/_____/_____	
907	TB treatment adherence support provided at	1. Health facility 2. Health post 3. Not describe	
908	Remarks	_____	
Kutaa 10: Talaallii BCG fudhachuu ilaalchiseefi dhukubichi TB osoo hin beekkamin hanga ture [Bilbilatoo gaafadhaa]			
1001	Mucaan TBn qabame kun eessatti dhalate?	1. Manatti 2. Keellaa fayyaatti 3. Buufta fayyaatti 4. Hospitaala mootummaatti 5. Kiliinikii dhuunfatti 6. Hospitaala dhuunfatti 7. Kan biraat (ibsi) _____	
1002	Gaafadhalate san ykn dhalatee guyyaa 15 keessatti talaalli BCG fudhatee jiraa?	1. Eeyyeen 2. Lakki →	1004
1003	Harka talaalli waraanname san irratti godaanisa BCG ni qabaa ?	1. Eeyyeen 2. Lakki	
1004	Mucaan erga guyyaa meeqa mallattoo dhibee muul'iseen booda mana yaalaa geeffame?	Guyyaa_____ booda	
1005	Akkuma dhibameen yeroo duraatiif mana yaalaa akkamiittit geeffame?	1. Buufata fayyaa 2. Hospitaala 3. Kiliinika dhuunfaa 4. Hospitaala dhuunfaa 5. Kan biroo (ibsi) _____	
1006	Dhukkuba TBn akka qabame kan beekkame iddoodhuma calqaba laallame kanatti moo iddoo biraatti fudhatameet?	1. Bakkuma calqaba deemetti beekkame 2. Iddoo biraatti fudhaneet beekkame	

	(Kara biraatti riifarii godhamee ture?)		
1007	Mana yaalaa guyyaa fudhatame irraa eegalee hanga dhibeen isaa TB ta'uu beekkamutti guyyaa meeqa fudhate?	guyyaa_____	
Section eleven: Haala barnoota mucaa akkasumas kan warra fi sigaaraa xuuxuu maatii			
1101	Mucaan osoo hin dhibamin dura oolman isaa eessa ture? (Mana barumsaa yoo jennu oolmaa daa'immaniis ni dabalata)	1. Mana barnoota 2. Kunuunsa daa'immanii (daycare) yoo wagga 4 gedi ta'e 3. Mana oola ture →	1104
1102	Yoo kan mana barumsaa deemaa ture ta'e dhibamuu isaatiin dura kutaa meeqa barata ture ?	1. Oolmaa daa'immanii (KG) 2. kutaa 1 - 6 3. kutaa 7 - 8 4. kutaa 9 ykn isaa ol	
1103	Yoo kan baratu ture, mana barumsaa akkamiitti barata ture?	1. Mana barumsaa mootummaa 2. Mana barumsaa kan dhuunfaa (private)	
1104	Yommuu mucaan dhibamu sana sadarkaan barnootaa hadhaa isaa meeqa ture?	1. Hin barannee 2. Kutaa 1 hanga 6 3. Kutaa 7 hanga 8 4. Kutaa 9 hanga 12 5. Diploomaa 6. Digriii 7. Mastarsii ykn isaa ol 8. Haati lubbuun hin jirtu	
1105	Yommuu mucaan dhibamu sana sadarkaan barnootaa abbaa isaa meeqa ture?	1. Hin barannee 2. Kutaa 1 hanga 6 3. Kutaa 7 hanga 8 4. Kutaa 9 hanga 12 5. Diploomaa 6. Digriii 7. Mastarsii ykn isaa ol 8. Abbaan lubbuun hin jiru	
1106	Maatii keessaa namni sigaaraa xuuxu kan mucaa wajjin mana tokko keessa jiraatu jiraa?	1. Eeyyeen 2. Lakki →	1108
1107	Yoo namni sigaaraa xuuxu mana keessa kan jiraatu ta'e firoomni mucaa TBn dhibame wajjin qabu maalinni?	1. Abbaadha 2. Haadha 3. Obboleessa/obboleettidha 4. Kan biraat(Ibsi) _____	
1108	Mana keessa jiraachaa turtan keessa loon/horii ni bulchitu ture?	1. Eeyyeen 2. Lakki →	109ext1
1109	Mana keessa jiraattan keessa loon/horiin kan bulu yoo ta'e loon akkamiitu mana keessa bulaa ture?	1. Hoolaa 2. Re'ee 3. Sa'a/jabbii/qotiyyoo 4. Kan biraa(ibsi) _____	

109ext1	Mucaan kun osoo hin dhibamnin duras ta'e isa booda maatii keechaa namni dhibee TBtiin qabame jira ture?	1. Eeyyeen 2. Lakki →	Dhume
109ext2	Yoo namni qabame ture ta'e, gosa TB isa kamiin qabame?	1. Kan sombaa posativii 2. Kan sombaa nagatiivii 3. Sombaan ala	
109ext3	Namni TBn qabamee ture kun firoomni inni mucaa TB dhukumsate wajjin qabu maali?	1. Haadha 2. Abbaaa 3. Obboleessa/obboleettii 4. Akkoo/akaakayyuu 5. Hojjettuu manaa 6. Kan bira (ibsi) _____	

Odeeffannoo naaf laattaniif baay'ee galatoomaa!

Annex-3b. Afan Oromo version of checklist and questionnaire for a study on childhood tuberculosis (TB) in central Ethiopia, 2022 (controls)

Gaaffii namoota kanaan dura dhukkuba TBtiin qabamanii hin beekneef guuttamu

Guyyaa (guyyaa/ji'a/waggaa): ____ / _____ / _____ (A.L.I)			
Ajaja: Filannoo sirrii ta'e irratti geengessi ykn iddoo duwwaa kennamerratti deebii barreessi			
Lakk.	Gaaffii	koodii _____	Irra ce'i
Kutaa tokko: Sooshoo-diimoogiraafifi oddeffanno bu'uraa			
000	Mucaan maal mallattoo dhibee maal waan qabuuf mana yaalaa dhuftan? (mallattoo dhibee tokkoo ol guutuun ni dands'ama)	1. Nafa oo'isuu 2. Gedi-teechisuu 3. Ol jechisiisuu (hoqii) 4. Garaa muruu 5. Ukaa 6. Bowwoo mataa 7. Fedhii nyaata dhabuu 8. Ulfina qamaa hir'isuu 9. Halkan dafqisiisuu 10. Kan biroo (ibsi)---------- 11. Mallatoo dhibee tokkoo hin qabu (Fknf yoo talaalliif dhufe)	
101	Maqaa mana yaalaa		
103	Naannoo mucaan keecha jiraatu?	1. Finfinnee 2. Oromiyaa → 3. Naannoo kibbaa → 4. Amaara → 5. kab biroo (ibsi)_____ →	 105 105 105 105

104	Finfinee, kutaa magaalaa kam?	1. Aaddis katamaa 2. Araadaa 3. Qirqoos 4. Lidataa 5. Yakkaa 6. Gullallee 7. Boolee 8. Kolfee 9. Nifaas silk laaftoo 10. Aqaaqii Qaallittii 11. Lammii Kuraa	
105	Finfinee ala yoo ta'e, godina kam?		
107	Saala mucaa?	1. Dhiira 2. Dhalaa	
108	umrii (waggota xumureen)	Waggaa	
109	Dhukkuboota dhibee TBtiif saaxilan ni qabaa?	1. Dhibee sukkaaraa 2. Karaarra jiraata 3. Iddoo buqqaatonni jiraatan 4. Iddoo walitti baa'inaan jiraatan (Yunivarsiitii, Mana hidhaa, giddu-gala daa'imman warra hin qabne itti guddisan) keessa jiraata 5. Nama TBn dhibame wajjin wal-qunnamtii qaba 6. Wanti beekamu hin jiru	
111	Mucaa akka gara mana yaalaa fiddan eenyutu isin gorse?	1. Ofumaaf dhufne 2. Eksteenshinii fayyaa 3. Mana yaalaa mootummaa birootii riifarii godhamneet 4. Mana yaalaa dhuunfatii riifarii godhamneet	
Kutaa sad: Madaallii haala nyaataa wajjin walqabate			
301	Ulfinni mucaa meeqa?	Kiiloo-giraama (Kg)	
302	Dheerinna mucaa	Seentiimeetira (cm)	
303	Hamma sarkaanfiraansii giddu-gala harkaa (mid-upper arma circumference)	Seentiimeetira (cm)	
304	Nutritional status at baseline (kan qorataadhaan guuttamu)	1. Normal 2. MAM = Moderate Acute Malnutrition 3. SAM = Severe Acute Malnutrition	
Kutaa shan: TB/HIV Co-infection			
501	Mucaan qorannoon HIV akka godhamuuf gaafatamtanii beektuu?	1. Eeyyeen 2. Lakki	
502	Mucaa qorannoon HIV godhameefii beekaa?	1. Eeyyeen 2. Lakki	
503		1. I = Ummata waliigalaa	

	Ramaddii kutaa uummataa saaxilamaa	2. E = Mucaa warri irraa du'e 3. F = Mucaa warri HIVdhaan jalaa qabame 4. C = Hojjetaa guyyaa 5. D = Mana hidhaa kan jiru 6. H = Saaxilamaa gosa biroo (ibsi) _____	
504	Bu'aa qorannoo HIV	1. P = Pozatiivii 2. N = Nagatiivii → 3. Hin beekamu →	 701 701
505	Guyyaa CPT eegle	Guyyaa/ji'a/waggaa: _____/_____/_____	
506	Guyyaa hordoffii HIV keessa seene	Guyyaa/ji'a/waggaa: _____/_____/_____	
507	Guyyaa dawaa HIV eegale	Guyyaa/ji'a/waggaa: _____/_____/_____	
Kutaa torba: crowdedness and TB case contacts			
701	Maatiin mucaa mana keessa nama meeqa taatanii jiraattu?	☐	
702	Namni ukaa, halkan dafqisiisuu, fedhii nyaata hir'atuu fi mallattoo hir'ina ulfina qaamaa qabu mana keessa ni jiraa?	☐ Yoo hin jiraannee "0" guuti	
703	Waggoota lamaan darban keessaatti namni mana keessaa dhukuba TBtin qabame jiraa?	☐ Yoo hin jiraannee "0" guuti	
704	Da'imti umriin waggaa shani gedii meeqatu mana keesss jira?	☐ Yoo hin jiraannee "0" guuti	
705	Daa'imti waggaa shani gedii ukaa, halkan dafqisiisuu, fedhii nyaata hir'atuu fi mallattoo hir'ina ulfina qaamaa qabu mana keessa ni jiraa?	☐ Yoo hin jiraannee "0" guuti	
707	Daa'imti dawaa ittisa TB (INH) Fudhachaa jiru mana keessa jiraa?	☐ Yoo hin jiraannee "0" guuti	
Kutaa 10: Talaallii BCG fudhachuu ilaalchiseefi dhukubichi TB osoo hin beekkamin hanga ture [Bilbilatoo gaafadhaa]			
1001	Mucaan kun eessatti dhalate?	1. Manatti 2. Keellaa fayyaatti 3. Buufta fayyaatti 4. Hospitaala mootummaatti 5. Kiliinikii dhuunfatti 6. Hospitaala dhuunfatti 7. Kan biraat (ibsi) _____	
1002	Gaafadhalate san ykn dhalatee guyyaa 15 keessatti talaalli BCG fudhatee jiraa?	1. Eeyyeen 2. Lakki →	 1004
1003	Harka talaalli waraanname san irratti godaanisa BCG ni qabaa ?	1. Eeyyeen 2. Lakki	
1004	Mucaan erga guyyaa meeqa mallattoo dhibee muul'iseen booda mana yaalaa geeffame?	Guyyaa_____ booda	

1005	Akkuma dhibameen yeroo duraatiif mana yaalaa akkamiittit geeffame?	1. Buufata fayyaa 2. Hospitaala 3. Kiliinika dhuunfaa 4. Hospitaala dhuunfaa 5. Kan biroo (ibsi) _____	
1006	Dhukkuba TBn akka qabame kan beekkame iddoodhuma calqaba laallame kanatti moo iddoo biraatti fudhatameet? (Kara biraatti riifarii godhamee ture?)	1. Bakkuma calqaba deemetti beekkame 2. Iddoo biraatti fudhaneet beekkame	
Kutaa kudha-tokko: Haala barnoota mucaa akkasumas kan warra fi sigaaraa xuuxuu maatii			
1101	Mucaan osoo hin dhibamin dura oolman isaa eessa ture? (Mana barumsaa yoo jennu oolmaa daa'immaniis ni dabalata)	1. Mana barnoota 2. Kunuunsa daa'immanii (daycare) yoo wagga 4 gedi ta'e 3. Mana oola ture →	1104
1102	Yoo kan mana barumsaa deemaa ture ta'e dhibamuu isaatiin dura kutaa meeqa barata ture ?	1. Oolmaa daa'immanii (KG) 2. kutaa 1 - 6 3. kutaa 7 - 8 4. kutaa 9 ykn isaa ol	
1103	Yoo kan baratu ture, mana barumsaa akkamiitti barata ture?	1. Mana barumsaa mootummaa 2. Mana barumsaa kan dhuunfaa (private)	
1104	Yommuu mucaan dhibamu sana sadarkaan barnootaa hadhaa isaa meeqa ture?	1. Hin barannee 2. Kutaa 1 hanga 6 3. Kutaa 7 hanga 8 4. Kutaa 9 hanga 12 5. Diploomaa 6. Digriii 7. Mastarsii ykn isaa ol 8. Haati lubbuun hin jirtu	
1105	Yommuu mucaan dhibamu sana sadarkaan barnootaa abbaa isaa meeqa ture?	1. Hin barannee 2. Kutaa 1 hanga 6 3. Kutaa 7 hanga 8 4. Kutaa 9 hanga 12 5. Diploomaa 6. Digriii 7. Mastarsii ykn isaa ol 8. Abbaan lubbuun hin jiru	
1106	Maatii keessaa namni sigaaraa xuuxu kan mucaa wajjin mana tokko keessa jiraatu jiraa?	1. Eeyyeen 2. Lakki →	1108
1107	Yoo namni sigaaraa xuuxu mana keessa kan jiraatu ta'e firoomni mucaa TBn dhibame wajjin qabu maalinni?	1. Abbaadha 2. Haadha 3. Obboleessa/obboleettidha 4. Kan biraat(Ibsi) _____	
1108	Mana keessa jiraachaa turtan keessa loon/horii ni bulchitu ture?	1. Eeyyeen 2. Lakki →	109ext1

1109	Mana keessa jiraattan keessa loon/horiin kan bulu yoo ta'e loon akkamiitu mana keessa bulaa ture?	1. Hoolaa 2. Re'ee 3. Sa'a/jabbii/qotiyyoo 4. Kan biraa(ibsi) _____	
109ext1	Mucaan kun osoo hin dhibamnin duras ta'e isa booda maatii keechaa namni dhibee TBtiin qabame jira ture?	1. Eeyyeen 2. Lakki →	Dhume
109ext2	Yoo namni qabame ture ta'e, gosa TB isa kamiin qabame?	1. Kan sombaa posatvii 2. Kan sombaa nagatiivii 3. Sombaan ala	

Odeeffannoo naa kennitaniif galatoomaa

Annex-4a. Parental information sheet (English version)

Title of the project: "Childhood tuberculosis: Epidemiology, Role of BCG vaccine in preventing severe forms and unfavorable treatment outcomes in central Ethiopia"

Principal investigator: Abay Burusie

Supervisor: Prof. Fikre Enquesilassie, Dr. Adamu Addissie

Coordinating Office: Addis Ababa University, School of Public Health

Introduction: Thank you very much for willing to talk with me. My name is _____. I am here with you/calling to you from (health facility name where the TB patient had follow up) on behalf of **Mr. Abay Burusie** who is doing his PhD dissertation on a topic entitled "Childhood tuberculosis (TB): Epidemiology, Role of BCG vaccine in preventing severe forms and unfavorable treatment outcomes in central Ethiopia" to collect data. Magnitude of childhood TB is escalating from time to time in spite of high BCG vaccine (which is supposed to decrease the risk of infection as well as developing TB) coverage in Ethiopia. Furthermore, what makes this study important is a new TB diagnostic test named gene-expert which has higher sensitivity and specify than the previously implemented acid fast bacilli test has been introduced currently. This newly introduced TB diagnostic test thus will help to estimate more accurate epidemiology of the disease.

Purpose of the Research: The objective of this research is to assess the current epidemiology of childhood TB and significance of BCG vaccine in preventing severe forms and unfavorable TB treatment outcomes. This research undertaking is a doctor of philosophy (PhD) degree partial fulfillment research work.

Procedure and participation: The study is a restrospective follow up study of those who were following TB treatment. However, there will be a retrospective exposure assessment of children who have not yet experienced TB disease so far and whom we call them controls to compare them with the exposure history of children who have already developed the disease and are called cases. This phone call is to earn more information than we found on the TB unit register of the cases. For the control who will be recruited from the same health facility where the case had

follow up, the interview will not take more than 15 minutes. Similarly, the cases will be interviewed for the same length of time as controls. Participation of your child is very important to answe the purposes of the study stated above and to develop useful evidence that will improve strategy of prevention and management TB in children. The information that we need about the child includes; socio-demographic charcteristics like age, sex, schooling and BCG vaccination history and presence of vaccine scar, TB disease history, contact history with TB case, exposure to crowded environment if he/she is selected as control and additionally for the cases, at the end of follow up, TB treatment outcome and if there is emergency of new TB case after him/her in the household.

Confidentiality: To establish secured confidentiality of research datathe original data will be locked in cabinets until the data analysis carried out and no person shall access except the PI and the supervisor for data checking and cleaning purpose. The information you provided will not be disclosed in the way it identifies the child's personal characteristics and privacy. Using the information you provided about the child for any other purpose than the parent/surrogate consented for is unethical. After the research defense and final work is approved by the school of public health and academic commission and the University senate, the original data questionnaire will be incinerated in secure manner.

Benefit: The research does not have a short term financial, health care and capacity building benefit to the research participant as an individual or as a group but in the long run it will help the concerned organization and policy makers to have a policy consideration and direction and formulation of strategy and design childhood TB program that will help combat childhood TB better based on the recommendations and the findings.

Risks: The proposed research does not elicit any inhuman treatment of research participants and any physical harm, social discrimination, psychological trauma and economic loss caused by merely involving in the study.

Inducement, Incentive and Compensation: This research project does not support any form of inducement, coercion and incentive. However, when study participants that will serve as controls come to health facility only for the purpose of this research, compensation will be given for transportation.

Results Dissemination: The principal investigator is primarily responsible to disseminate the finding of this research to relevant stakeholders. Moreover, dissemination will be ensured through publishing the finding in scientific, peer reviewed reputable journals.

Right to Refuse or Withdraw: If you do not want your child to participate in the study, you have full right to decline or withdraw from the study any time after the initiation of interview. Declining to take part in the study from the beginning or withdrawing any time after sometime of involvement for any reason, will not have effect on the quality or type of services that should be rendered to your child. You are not expected to give justification for deciding that you child should not take part in the study

Person to Contact: The child's paraent/surrogate has the right to ask information that is not clear about the research context and content before and or during the research work. To ensure that the study will not bring about any harm to child, the research proposal has been evaluated for ethical sanity and approved by Institutional Review Board of College of Health Sciences, Addis Ababa University. In case of any concern that is not clarified satisfactorily by the data collector, you can contact the principal investigator or his supervisor or Institutional review board of College of Health Sciences, Addis Ababa University through their contact address indicated below.

1. **Principal Investigator name and address:** Abay Burusie, Mobile: 0912239390, E-mail: babaynanaty@gmail.com
2. **Supervisor's name and address (diceased):** Professor Fikre Enquesilassie, Mobile: 0911242547, E-mail: fikreens@yahoo.com
3. **Supervisor's name and address:** Dr. Adamu Addissie, Mobile: 0911404954, E-mail: adamuaddissie@gmail.com
4. **Addis Ababa University, College of Health Sciences:** IRB chair person name: Dr. Adamu Addissie, email: chs@aau.edu.et, IRB telephone: 0118961396

Annex-4b. Parental Informed Consent form (English version)

Title of the project: "Childhood tuberculosis: Epidemiology, Role of BCG vaccine scar in preventing severe forms and unfavorable treatment outcomes in central Ethiopia"

I have been well awared of that this research undertaking is a postgraduate degree partial fulfilment of research dissertation which is fully supported and coordinated by Addis Ababa University School of Public Health and the designated principal investigator is **Mr. Abay Burusie**. I have been fully informed in the language I understand about the research project objectives that are to assess epidemiology of childhood tuberculosis and significance of BCG vaccine scar in preventing severe forms and unfavorable TB treatment outcomes in central part of Ethiopia.

I have been informed that all the information I shall provide to the interviewer about my child/the child I am surrogate to, will be kept confidential. I understood that the research has no any harm to the child. I also knew that, being on the behalf of the child, I have the right to withhold information, skip questions to answer or to withdraw from the study any time. I have acquainted nobody will impose me to explain the reason of withdrawal. I have been also enlightened there would have no effect at all in the child's health benefit or other administrative effect that he/she ought to get from the health care facility.

I have been assured that the right to ask information that is not clear about the research before and or during the research work and whom to contact for explanation when doubt is arosed.

Addis Ababa University, College of Health Sciences IRB Secretary Office Tel. 0115512876

Principal Investigator's Name: Abay Burusie Mobile: 0912239390

Supervisor's Name and address: Dr. Adamu Addissie Mobile: 0911404954

This consent form is read to me in the language I comprehend and I understood the condition stated above. Therefore, I am willing and confirm my child's participation by giving oral consent.

I agree to participate in the study: Yes □ continue the interview

No □ terminate the interview

Annex-5a. Parental information sheet (Amharic version)

ለጥናት ተሳታፊ የተዘጋጀ የጥናቱ መረጃ

የጥናቱ ርዕስ፡ <u>የህፃናት ‹ቲቢ› በሽታ፤ ስርጭት፣ የከፉ አይነት ‹ቲቢን› ና የማይደገፉ የ‹ቲቢ› ህክምና ውጤቶች ላይ የቢ.ሲ.ጂ ክትባት አስተዋፆ በመአከላዊ ኢትዮጲያ</u>

ዋና ተመራማሪ፡ <u>አባይ ቡሩሴ</u>

የተመራማሪው ተቆጣጣሪ፡ <u>ፕ/ር ፍቅረ እንቁስላሴ</u>

አስተባባሪ ቢሮ፡ <u>አዲስ አበባ ዩኒቨርሲቲ፣ጤና ሳይንስ ኮሌጅ</u>

<u>መግቢያ</u>፡- ሊያነጋግሩኝ ፈቃደኛ ስለሆኑ በጣም አመሰግናለሁ። ስሜ ---------- እባላለሁኝ፣ እዚህ የመጣሁት፣ በአዲሰ አባባ ዩኒቨርስቲ የጤና ሳይንስ ኮሌጅ፡ ሕ/ሰብ ጤና አጠባበቅ ትምህረት ክፍል በ **አቶ አባይ ቡሩሴ** የሚደረግ ምርምር በስልክ መረጃ ለመሰብሰብ ነው። ይህ ጥናት ለፒ.ኤች ዲ ዲግሪ ከፊል ማሟያ ሲሆን የሚያጠናው የህፃናት ‹ቲቢ› በሽታ፤ ስርጭት፣ የከፉ አይነት ‹ቲቢን› ና የማይደገፉ የ‹ቲቢ› ህክምና ውጤቶች ላይ የቢ.ሲ.ጂ ክትባት አስተዋፆ በመአከላዊ ኢትዮጲያ በሚል ርዕስ ላይ ነው። የህጻናት ‹ቲቢ› መጠን ከጊዜ ወደ ጊዜ እየጨመረ የመጣ በሽታ ሲሆን፣ የበሽታውን መስፋፋት ይበልጥ የከፉውን አይነት ይገታል ተብሎ የሚሰጠው የቢ.ሲ.ጂ ክትባት ምንም እነኪን በሀገራችን ሽፋኑ ከፍተኛ ቢሆንም ያመጣው ለውጥ ብዙ ባለመጠናቱ ውጤታማነተቱን በሚገባ የሚያሳዩ ጥናቶች አይታዩም። በተጨማሪ በቅርብ ወቅት የ‹ቲቢን› በሽታ ለመለየት ከበፊቱ የአክታ ምርመራ የተሻለ የምርመራ አይነት ስለመጣ ትክክለኛነቱም በዚው ልክ የተሻለ የበሽታውን ስርጭትና መጠን ለማወቅ እድል ፈጥሯል።

የጥናቱ አላማ፡ የዚህ ጥናት አላማ የህፃናት ‹ቲቢ› በሽታ ስርጭቱ ምን እንደሚመስል ለማወቅና፣ የከፉ የከፉ የሚባሉትን የበሽታውን አይነቶች ለመቀነስ እንዲሁም የማይደገፉ የበሽታው ህክምና ውጤትን ለመከላከል የቢ.ሲ.ጂ ክትባት ጠባሳ መኖሩም የሚያበረክተው አስተዋፆን ለመለየት ነው።

<u>ቅደም ተከተልና ተሳትፎ</u>፡- ጥናቱ የቲቢ ህክምናን የሚከታተሉትን ህጻናት ተከታትሎ የህክምና ውጤታቸውን ማወቅ ሲሆን፣ በተጨማሪ ለማነጻጸሪያነት ከተመሳሳይ ቤት የሚመረጡና ለተለያዩ ነገሮች ተጋላጭነታቸው ከቲቢ ታማሚው ጋር ሲነጻጸር ምን እንደሚመስል የሚጠየቁበት ሁኔታ አለ። መጠይቁን

ሞልቶ ለማጠናቀቅ ከ30 ደቂቃ በላይ አይፈጅም። ነገር ግን የቲቢ ህክምና ክትትል የሚያደርጉት ተሳታፊዎች ለህክምና በሚመላለሱበት ወቅት የጤንነታቸውን ሁኔታ ለመከታተል በመደበኛው የህክምና ክትትል እንደሚደረገው ሁሉ ክብደታቸው ና ቁመታቸው የሚወሰድ ሲሆን እንዲሁም እንደ አስፈላጊነቱ የአክታ ምርመራና የቀይ የደም ሴል መጠን ክትትል ምርመራዎች ተደርገው ይመዘገባሉ። የህጻኑ በጥናቱ ውስጥ መሳተፍ እውነተኛውን በሽታው እያደረስ ያለውን የችግር መጠን ለመገመት በጣም ከፍተኛ አስተዋጾ አለው። በአጠቃላይ ሲታይ፣ የሚጠየቁት ጥያቄዎች የሚያካትቱት ስለ መሰረታው መለያ ለማሳሌ፡-እድሜ፣ጾታ፣የትምህርት ሁኔታ እና ስለ ቲቢ ህመሙ፣ ከሌላ የቲቢ ታማሚ ጋር ያለ መቀራረብ፣ እንዲሁም በክትትሉ መጨረሻ ላይ የህክምናው ውጤትን ይጨምራል።

<u>ሚስጥራዊነት</u>፡- የጥናቱ ተሳታፊ ማንነት በሌላ አካል እነዳይለይና ሚስጥሩ የተጠበቀ እንዲሆን፣ መረጃ ሲሰበሰብ የተሳታፊውን ስም መጠይቁ ላይ ከመሙላት ይልቅ በፈንታው የሚስጥር ቁጥር እንዲሞላ ይደረጋል። የተሰበሰበው መረጃ ከዋና ተመራማሪና የሱ ተቆጣጣሪ ውጪ ለሌላ ለማንም እነዳይገኝ ይቆለፍበታል። ተሳታፊው የሰጠ መረጃ መምንም መልኩ የተሳታፊውን የግል ማንነት በሚያመላክት መልኩ ማቅረብ ከስነምግባር ውጪ ስለሆነ የሚቀርበው በአጠቃላይ መልኩ የሁሉንም ተሳታፊዎች መረጃ በመጭመቅ ብቻ ይሆናል። ከላይ ከተገለጸው አላማም ውጭ መረጃውን ለሌላ ጉዳይ መጠቀም በምርምር ስነ-ምግባር የተከለከለ ነው። ጥናቱ ተሰርቶ ካለቀና እንዲሁም ለሚመለከተው አካል ቀርቦ ከጸደቀ በኋላ መረጃው የተሰበሰበበት ወረቀት እነዲቃጠል ይደረጋል።

<u>ጥቅም</u>፡- የእርስዎ ልጅ በጥናቱ ተሳታፊ መሆን በጥናቱ ላይ የተጠቀሱትን ጥያቄዎች ለመመለስና ለወደፊት የህፃናት ጤና መሻሻል ከፍተኛ አስተዋፅዖ ይኖሮዋል ተብሎ ታላቅ ግምትን ተሰጥቶታል። ሌጁ/ልጅቷ በጥናቱ በመሳተፉ/ፏ የሚሰጠው/ጣት ምንም አይነት ክፍያ የለም።

<u>ተጋላጭነት</u>፡-ጥናቱ በምንም መልኩ የጥናቱን ተሳታፊ ለአካላዊ፣ማህበረሰባዊ፣ስነ-ልቦናው ና የኑሮ /ገንዘብ ጉዳት ተጋላጭ አያደርገም። እንዲሁም መጠይቁ የህክምና ክትትል ከሚያደግ ባለሙያ ውጪ ሌላ ማንም መረጃውን/ሀሳቡን የሚሰማ ሰው በሌለበት ለብቻ የሚሞላ ይሆናል።

<u>መገፋፋት፣ማበረታቻቻ ወይም ካሳ</u>፡- ጥናቱ በሽተኞቹ በጥናቱ እንዲሳተፉ ለማድረግ ማንኛውም የመገፋፋት እንዲሁም እንደ አመቻቺ ቅድመ ሁኔታ ማበተታቻ/ጉቦ ወይም ካሳ አይሰጥም። ነገር ግን ሌላ

ወደ ጤና ተቋሙ የሚያስመጣቸው የግል ጉዳይ ሳይኖር በጥናቱ ለመሳተፍ ብቻ ተብሎ ለሚመለመሉትና ለሚጠሩት ተሳታፊዎች ያለ እቅዳቸው ላወጡት የትራንስፖርት ወጪ ይከፈላቸዋል።

<u>የጥናቱን ውጤት ማሰራጨት፡</u>- ተማራማሪው የጥናቱ ውጤት በተለያዩ መድረኮች የማሰራጨት ግዴታ አለበት። ከዛም በዘለለ ውጤቱን በአለም ኣቀፍ ታዋቂ በሆኑት ህትመቶች በማሳተም ለተጠቃሚዎች እንዲሰራጭ ይደረጋል።

<u>ያለመሣታፍ ወይም ከጥናቱ፡ የማቋረጥ መብት፡</u>- ልጆ በዚህ ጥናት እንዳይሳተፍ ከፈለጉ ያለማሳተፍ ሙሉ መብት አሎት። እንዲሁም ልጁ/ልጅቷ ባለመሳተፍዋ በጤና ተቋም በሚያገኙት ሕክምና አሰጣጥ ላይ ምንም አይነት አሉታዊ ተጽኖ አያሳድርም። በዚህ ጤና ተቋም የሚያገኙት ማንኛውም አገልግሎት እንደተጠበቀ ይሆናል። እንዲሁም ጥናቱ ውስጥ መሳተፍ ከጀመረ በኋላ እንኳን በማንኛውም ጊዜ ያለምንም ለማቋረት የምክንያት ማስረጃ በጥናቱ መሳተፍን የማቋዋረጥ መብትዎን የተጠበቀ ነው።

<u>ማግኘት የሚችሉት ሰው</u>

ማንኛውም፡ ጥያቄ፡ ካሎት፡ ከዚህ፡ በታች፡ የተጠቀሱትን፡ ሰዎች፡ ማነጋገር፡ ይችላሉ። በማንኛውም፡ ጊዜ፡ ልታነጋግሩዋቸው፡ ትችላላችሁ፡ ፡ ብኋላም ፡ ላይ፡ ማንኛውም፡ ጥያቄ፡ ካለሎት፡ የጥናቱን፡ ተመራማሪዎች፡ ከታች፡ በተጠቀሱት፡ አድራሻዎች፡ ማግኘት፡ ይችላሉ።

1. **ዋና ተመራማሪ**፡- ኣቶ፡ አባይ ቡሩሴ፡ **ሞባይል**፡- 0912239390፣ **ኢሜል**፡-babaynanaty@gmail.com
2. **የተመራማሪው ተቆጣጣሪ**፡- ዶ/ር አዳሙ አዲሴ፡ **ሞባይል**፡- 0911404954፣

ኢሜል፡-adamuaddissie@gmail.com

3. **አዲስ አበባ ዩኒቨርሲቲ፣ጤና ሳይንሶች ኮሌጅ**፣ የአይ.አር.ቢ ክፍል ሀላፊ ስም፡ ዶ/ር አዳሙ አዲሴ፣ ኢሜል ፣ chs@aau.edu.et, የአይ.አር.ቢ ክፍል ስልክ: 0118961396

Annex-5b. Parental Informed consent form (Amharic version)

የቤተሰብ የስምምነት ውል ቅጽ

ይሄ ጥናት ለፒ.ኤች.ዲ ዲግሪ ማሟያ መሆኑንና በአዲስ አበባ ዩኒቨርሲቲ ህብረተሰብ ጤና ትምህርት ቤት እውቅና ና ድጋፍ በ አቶ አባይ ቡሩሴ ዋና መሪነት እየተካሄደ መሆኑን በሚገባ ተረድቻለሁ። የጥናቱም አላማ የህጻናት ቲቢ በሽታ ስርጭትን ለማወቅ እንዲሁም ከፉ የቲቢ ህመምን ና የማይደገፉ የህክምና ውጤትን መከላከል ረገድ የቢ.ሲ.ጂ ክትባት አስተዋጾ ምን እንደሚመስል ለማወቅ መሆኑን መሚገባኝ ቋንቋ ተነግሮኝ በግልፅ ተረድቻለሁ።

በጥናቱ ተሳታፊ የሚሆነውን ልጅ በተመለከተ የምሰጠው መረጃ በሚስጥር እንደሚያዝ ተነግሮኛል። የልጁ/ጅቷ ቤተሰብ እንደመሆኔ መጠን የልጁን/ጅቷን መረጃ ሙሉ ለሙሉ ያለመስጥ ወይም ያልተመቹኝን ጥያቄዎች የመዝለል ወይም ቃለ-መጠይቁ ከተጀመረ በኋላ በመሀል የማቋረጥ መብት እንዳለኝ ተነግሮኛል። በቃለ-መጠይቁ ለመሳተፍ ፍቃደኛ አለመሆን ለልጁ የሚሰጠውን የህክምና አይትና ጥራት ላይ በምንመልኩ ተጽኖ እንደማይኖረው ተብራርቶልኛል።

ቃለ-መጠይቁ ከመጀመሩ በፊትም ሆነ ከተጀመረ በኋላ ጥናቱን በተመለከተ ግልጽ ያልሆነ ነገር ከታች በተቀመጡት አድራሻዎች ጭምር የመጠየቅ መብት እንዳለኝ ተገልጸልኛል።

አዲስ አበባ ዩኒቨርሲቲ፣ጤና ሳይንሶች ኮሌጅ የአይ.አር.ቢ ፀሀፊ ቢሮ ስልክ፡- 0115512876

የጥናቱ ዋና ተመራማሪ ስምና አድራሻ፡- አባይ ቡሩሴ **ሞባይል**፡- 0912239390

የተመራማሪው ተቆጣጣሪ ስምና አድራሻ፡- ፕሮፌሰር ፍቅረ እንቁስላሴ ሞባይል፡- 0911242547

ይህ በጥናት ለመሳተፍ ፍቃደኝነት የሚገለፅበት ቅፅ በሚገባኝ ቋንቋ ተነቦልኝ ከላይ የተገለጸውን ሁኔታ ተረድቼዋለሁ። በመሆኑም ልጁ/ጅቷ ሁኔታ መረጃ በመስጠት በጥናቱ እንዲሳተፍ/እንድትሳተፍ ፍቃደንነቴን በቃሌ አረጋግጣለሁ።

ልጁ/ልጅቷ በጥናቱ እንዲሳተፍ/እንድትሳተፍ ተስማምቻለሁ □ **አዎ** ------- ቃለ-መጠይው ይቀጥል

□ **አይ** -------- ቃለ-መጠይቁ ይቋረጥ

Annex- 6a. Parental information sheet (Afan Oromo version)

Ibsa waligaltee warraatiif

Mata-duree qorannaa: "Childhood tuberculosis: Epidemiology, Role of BCG vaccine scar in preventing severe forms and unfavorable treatment outcomes in central Ethiopia"

Qorataa adda-duree: Abbaay Burruusee

Suparviisara: Dooktar Addaamuu Aaddisee

Biroo Haala Mijeessaa: Univarsiitii Aaddis Ababaa, Mana Barumsa Papiliik Helzii

Seensa: Duraan dursee nawajjin mai'achuuf heeyyamuu keessaniif baayyeen isin galateefadha. Maqaan koo _____jedhama. As kanin dhufe/kanin isiniif bilbiluuf bakka obboo Abbaay Burruusee nama qorrannaa isaa digrii sadaffaa (PhD) mata-duree "Dhukkuba Tiibii daa'immanii: haala fafacha'insa isaa, fayiidaa talaalli isaa BCG jedhamuu gosa dhibichaa ciccimoo dhoorkuufi bu'aa yaalii isaa irratti qabu giddu-galeessa Itiyoophiyaatti" jedhamu irratti hojjechaa jiru raga sassaabuuf bakka bu'uudhaan. Hangi dhukuba Tiibii daa'immanirratti mul'atu yeroo yeroorra dabalaa deemara. Kuni ammoo bakka talaaliin BCG jedhamu kan dukkubicha ittisa jedhamu bal'inaan Itiyoophiyaa kessatti ufisa guddaa qabutti. Dabalataan qorrannaan kun kan barbaachiseef labraatooriin GeneXpert jedhamu kan dhukuba Tiibii kana sirritti addabasuun kan isa duraan fayyadamnurra caalu biyya keenya keecha waan seeneef. Kuni immoo fafacha'ins hanga dhibechaa sirritti tilmaamuuf nugargaara.

Kaayyoo qorannichaa: Kayyoon qorannoo kanaa hanga fi haala fafacha'insa Tibii, fayiidaa talaalli isaa BCG jedhamuu gosa dhibichaa ciccimoo dhoorkuufi bu'aa yaalii isaa irratti qabu addaan baafachuudha. Qorannaan kuni digrii sadaffaa isa "PhD" jedhamuuf argachuu ulaaga kuuttamuu qabu keessayis isa tokko.

Adeemsafi hirmaannaa: Qorrannan kun ijoollee dhukkuba Tiibiitiif qoricha fudhachaa jiran duuka kan bu'uudha. Hata'u malee ijoolleen hanga ammaa dhibee Tiibiitin hin qabaminis haalli isaan keessa darban kan warra dhukbsatanii wajjin walbiratti laaluuf ni qoratamu. Ijoolleen dhukubaan hin qabamin garuu kan manuma ijoollee dhibamee keessa jiraacha turan dubisuuf nama tokkoof daqiiqaa 30 caala nutti hin fudhatu. Ijoolleen dhukubichaan qabamanis daqiiqaa

kana hin caalleef dubifamu. Garuu ijoolleen Tiibiin qabaman, hordofii qoricha Tiibii fudhachuu waan qabaniif yeroo yeroon ulfinni qaama isaanii fi dheerrinni isaani kanfudhatamuu fi qorannaan akkitaafi kan dhiigaa barbachisaa ta'an kan godhamu ta'a. Kayyoo armaan alitti ibsame sana deebisuu fi ragaa dhukubicha kana ittisuuf fi yaaluu keessatti fayyidaa guddaa buusu argachuuf qorannaa kanarratti hirmaachuum mucaa keessani baayyee fayyada. Odeeffannoon mucicha dhibicha irraa bilisa ta'e irra fudhachuu barbaannu kan akka umrii isaa, saala, haala barumsaa, walitti dhufeenya nama kanaan dura dhukkuba Tiibiitiin qabame wajjin jiru, saxilama tuuta gudda keecha jiraachuu/ooluu yoo ta'u mucaa dhibichaan qabame irraa immoo dabalataa, dhuma hordoffii qorichaa irratti bu'aa yaaliiti fi namani haarofti yoo kan dhikubichaan qabame jiraatee fa'a ta'a.

Iccitii eeguu: Iccitii odeeffannoo nuuf kennamuu eeguuf jecha kooditti fayyadamna malee maqaa mucichaa uunkaa gaafichaa irratti hin barreefamu. Ragaa sassaabame kana qorataa add-dureefi suparvaayizara isaa malee namni biraa akka hin qaqabne saaxina keessatti itti hapheeffama. Ragaan mucaicha ilaalatee nuuf kennitan nama biraatiif eeyyurra akka argame ifa hin godhamu. Ragaa kana kayyoo qoranna kanaaf ala fayyadamuun safuu waan ta'eef waligaltee isin kennitaniin ala waan biraa hin olfamu. Qoranaan kun dhiyaatee falmii darbuun isaa Mana Barumsaa Pabilik Helzitiin, komishinii barumsatifi Seeneeti Univarsiitiitiin erga raggaasifamee booda waraqichi ragaan itti sassaabame akka gubatee sokkisiifamu godhama.

Faayidaa: Qorannaan kun hirmaattotaaf akka dhuunfatittis ta'ee akka waliigalaatti bu'aan mallaaqaa, kunuunsa fayyaa fi ijaarsa dandeetti inni yeroo gabaa keessatti buusu hin jiru. Garuu gara-fulduraatti bu'aan qorannoo kanaa wajjiraaleen dhimmi ilaalu fi warri polisii baasu ofitti fudhachuudhaan sagantaan ittisa Tiibii da'immanii bu'a akka fidu godhoof fayyadamuu danda'u.

Balaa: Qorannoon kun warra hirmaatu irratti balaan inni qaamarratti, hawwaasumma, saaykolojii fi diinagdee irratti fidu hin jiru.

Dhidhiibbaa, Onechiiftuu fi Kiisii: Qorannoon kun hirmaata qoranno kana irratti dhiibban, dirqisiisni akka gahus ta'ee onnechiiftuun akka kannamu hin deeggaru. Garuu, ijoolleen Tiibiin hin qabamni warraan gara mana yaalaa kana akkadhufani qorataman yemmuu taasifamu baasiin isaan geejjibaaf baasaan ni yaadame kennamaaf.

Bu’aa qorannoo raabsuu: Bu’aa qorannoo kana qamaa ilaallatuuf raabsuuf qorataan adda-dureen itti gaafatamummaa kan fudhatu yoo ta’u, rabsamuun isaa kan mirkanaa’u joornaalii sayinsaa beekkamoo ta’e irratti yoo maxanfame.

Mirga diduu ykn adda kutuu: Mucaan keessan akka qorannaa kana irratti akka hirmaatu yoo hin barbaadne mirga diduu ykn irga hirmaachuu calqabeeyuu wanni isinitti hin tolin yoo jiraate addaan kutuu mirga keessani. Diddaas ta’e addan kutuun keessan qulqulina fi gosa tajaajila mucaaf kennamuu irratti hanqinni inni fidu gonkumaa hin jiru. Mucaan keessan akka hin hirmaanneef diduun keessaniif sababii keessan ibsuun isinirraa hin eeggamu.

Nama qunamamu: Warri/guddisaan mucaa mirga wantoota qorannicha wajjin walqabatee ifa hin ta’iniif qoranichaan duras ta’ee booda mirga gaafachuu ni qabu. Qorannichii hammeenyi inni mucaa irratti fidu tokkollee akka hin jirre, karoorri qorannichaa dursamee madaallamuudhaan Boordii Itiksii Koolleejjii Fayyaat, Univarsiitii Aaddis Aababaatiin, raggasifameera. Yeroo kamiyyuu kaaffii yoo qabaattanifi deebiin funaantu ragaatiin isiniif kenname qubsaa yoo hin ta’in qorataa adda-duree ykn suparvaayizara isaa ykn Boordii Itiksii Koolleejji Faayyaa Univarsiitii Aaddis Aababaa lakkofsota armaan gadiitiin bilbiltanii dubbisuu ni dandeechu.

1. **Maqaafi laakkofsa Qorataa adda-duree**: Abbaay Burruusee, Moobaayilii: 0912239390, Imeeyilii: babaynanaty@gmai.com
2. **Maqaafi laakkoofsa suparvaayizaraa**: Dr. Addaamuu Addisee, Moobaayila: 0911404954, Immeyilii: adamuaddissie@gmail.com
3. **Univarsiitii Aaddis Aababaa, Koollejii Fayyaa**, Maqaa nama itti gaafatamaa Boordii Itiksii: Dr. Addaamuu Aaddisee, Lakkoofasa bilbila biiroo; 0118961396

Annex- 6b. Parental Informed Consent form (Afan Oromo version)

Waliigaltee warra

Mata-duree qorannichaa: "Childhood tuberculosis: Epidemiology, Role of BCG vaccine in preventing severe forms and unfavorable treatment outcomes in central Ethiopia"

Qorannoon kun kan akka digrii sadaffaatiif akka ulaaga tokkotti hojjetamaa jiruuf adda dureedhaan kan gaggeessu Obboo Abbaay Burruusee akka ta'e akkasumas Univarsiitiin Aaddis Aababaatti manni barumsaa Pabiliik Helzii akka qorannoo kana deegaruufi qindeessu irratti hubannoon gahaan naaf kennameera. Kayyichi qorrannoo kanaa haala fafacha'insa dhukkubaa Tiibii daa'immanii, fayiidaa talaalli isaa BCG jedhamuu gosa dhibichaa ciccimoo dhoorkuufi bu'aa yaalii isaa irratti qabu giddu-galeessa Itiyoophiyaatti baruuf akka ta'e afaanin ani haalaan beeku fayyadamuudhaan naaf ibsameera.

Ragaan ani mucaa kiyya ilaalchisee kennu kun akka iccitiin qabamu natti himameera. Qorannoon kun hammeenya homaatu akka mucaa kiyya hin geessifnes natti himameera. Ragaa wa'ee mucaa kiyyaa yoomun kennu wanti natti hin tolin yoo jiraatee calqabamumarraa hirmaachuu dhiisuu, yoon hirmaachuu calqabe ta'e immoo bakkan fedhetti addan kutee dhisuu akka mirga qabnu nutti himameera. Addan kutuu keenyaaf ykn hirmaachuu diduu keenyaaf wanta sababeeffanni ibsuu dirqama akka hin qabnes barreerra. Hirmaachuu baachuu keenyarraa ykn adda kutuu keenyarra kan ka'e tajaajilli mucaan mana yaalichaa irra argachuu qabu gosaa tajaajilaanis ta'ee qulqullinaan dhiibbaan nuqunnamu akka hin jirannees nuuf ibsameera.

Qorannon duras ta'e qorannoon booda wanta ifa naaf hin ta'in kamiyyuu mirga gaafachuu yeroo akkan qabuufi kanas godhuuf lakkofsota bilbilaa armaan gaditti kaayaman fayyadamuu akkan danda'u natti himameera.

Univarsiitii Aaddis Aababaa, Koolleejjii Fayya, Biroo barreessituu Boordii Itiksii Tel. 0115512876

Makaa qorataa adda-duree fi lakkofsa: Abbay Burrusee Moobaayilii: 0912239390

Maqaa suparvaayizaraa fi lakkofsa: Prof. Fiqiree inqusillasee Moobaayilii: 0911242547

Waligalteen warra armaan oliitti caqafame kun afaan nagaluun natti himaamee too hubadheera. Kanaaf, mucaan koo qorannaa kana irratti akka hirmaaatuuf heyyemuu koo jechaan ibseera.

Waliigalameera: **Eeyyeen** → Gaaffii qorannoo itti fufi

Lakki → addaan kuti

Annex-7a. Assent Information sheet (English version)

My name is _____. I am finding out what it is like for children who have TB disease and those don't have it so far.

This letter tells you what will happen if you want to help.

I will ask you questions like your age, where you live, whether you go school or not, whether you are sick or not sick of TB. I will also take your weight, height and observe your arms to check whether you were vaccinated for TB vaccine or not. For the questions you might not remember or cannot understand, your parent who is taking care after you will support you. If you are currently sick of TB, your sputum will be checked at different intervals to known how well the drugs provided to you for TB treatment are working. All those I told are routine services for children vising a hospital. I mean it is not additional duty for research purpose. The only very minor additional thing I need from you for research purpose is taking small amount of blood from you at the end of your treatment to see your red blood cell status called hemoglobin level. This information will help me write a report that can help other children. You don't have to do this if you don't want to. If you don't understand anything you can just ask me what I am doing. I won't use your real name when I write my report. If there is something you don't understand or are scared about you can talk to your parents. You get to keep a copy of this information letter and the letter that gives your permission.

Thank you for your help.

Data collectors name _____

Annex-7b. The Letter that Gives Your Permission (English version)

I have read the information letter with _____ (*data collector's name*). I understand what (*data collector's name*) is asking me to do. I will talk to *(data collector's name)* about what it is like to have or not to have TB. *(Data collector's name)* will measure my body weight, height, and assess whether there is tuberculosis vaccine induced scar on my arms or not. *(Data collector's name*) answered all my questions. (*Data collector's name*) will not use my real name when he/she writes the report. If I don't want to do this I don't have to. I can stop doing this if I want to. I get to keep a copy of the Information Letter and the Letter That Gives Permission. Accordingly, I give my willingness to participate in the study orally.

Oral assent obtained: **YES** → Continue

NO → terminate

Annex-8a. Assent information sheet (Amharic version)

የልጅ ቅድመ-ፍቃደኝነት መረጃ

ስሜ ----------ይባላል። የቲቢ ህመም በታመሙ ልጆችና እስካሁን ባልታመሙት አቻቸው መካከል ያለውን ልዩነት ለማወቅ ጥናት እያደረግን ነው። ቀጥሎ የማነበው ፅሁፍ ለመተባበር ፍቃደኛ ስትሆን የሚደረጉትን ነገሮች የሚገልፅ ነው።

ዕድሜህን፣የት አከባቢ እንደምትኖር፣እንደትማርና እንደማትማርና በቲቢ መታመም አለመታመምህን የሚመሳስሉ ጥያቄዎችን እጠይቅሀለሁ። ሌላው ክብደትህን፣ቁመትህንና የቲቢ ክትባት መውሰድ አለመውሰድህን የሚጠቁም ጠባሳ ክንዶችህ ላይ አያለሁ። የማታስታውሳቸው ወይም ለመረዳት የሚከብዱህ ጥያቄዎች ካሉ ካንተ ጋር ያሉ የቤተሰብ አባል ይረዱሀል። የቲቢ ታማሚ ከሆንክ አክታህ በየሆነ ጊዜ እየተወሰደ የምት ወስደው የቲቢ መድሀኒት እሰራና እያልሰራ መሆኑ ይመረመራል። እስካሁን የነገርኩህ ሁሉ ማንኛውም ልጅ ህክምና ፈልጎ ሀኪም ቤት ሲመጣ የሚደረግ እንጂ ለዚህ ጥናት ብቻ ተብሎ አይደለም። ስለዚህ በጥናቱ ምክንያት የተጨመሩ ጉዳዮች አይደሉም። ትንሽ በጥናቱ ምክንያት ተጨማሪ የሚሆነው፣ የቲቢ ህክማና ስትጨርስ የቀይ የደም ሴልህ መጠን ምን ደረጃ ላይ እንዳለ ለማወቅ ትንሽ ደም ከክንድ ይወሰድና ይመረመራል። ይህ መረጃ ለሌሎች ልጆች የሚጠቅም ዘገባ እንድፅፍ ይረዳኛል። ካልፈለክ ደግም አለመሳተፍ ትችላለህ። ያልተረዳከው ማንኛውም ነገር ካለህ በመሀል አስቁመክ ምን እያደረኩ እንደ ሆነ ልትጠይቀኝ ትችላለህ። ዘገባውን ስፅፍ ስምህን አልገልፀውም። የሚያስፈራ ነገር መስሎህ ከታየህ ካንተጋር ለመጣውን ቤተሰብ መንገር ትችላለህ። ይህንን ያነበብኩልህን ፅሁፍ ና ቀጥሎ የማነብልህን የስምነት ቅፅ መውሰድ ከፈለክ ቅጂውን እሰጥሀለሁ።

ሥለ ትብብርህ አመሰግንሀለሁ

የመረጃ ሰብሳቢው ስም ----------

Annex-8b. The Letter that Gives Your Permission (Amharic version)

የልጅ ፍቃደኝነት መስጫ ቅፅ

የቅድመ-ፍቃደኝነት መረጃውን ከ ----------(የመረጃ ሰብሳቢው ስም) ጋር አምብበናል። ----------(የመረጃ ሰብሳቢው ስም) ምን እንዳደርግ እንደፈለገ ተረድቻለሁ። ከ ----------(የመረጃ ሰብሳቢው ስም) ጋር ስለ ቲቢ በሽታ እናወራለን። እንዲሁም ----------(የመረጃ ሰብሳቢው ስም) የሰውነት ክብደቴን፣ቁመቴን ይለካል/ትለካለች እንዲሁም ክንዶቼ ላይ የ ቲቢ ክትባት ጠባሳ መኖር ለመኖሩ ይታያል። የቲቢ ታማሚ ከሆነኩ የመድሀኒቱን ውጤታማነት ለማወቅ እንደ አስፈላጊነቱ አክታ ይወሰዳል። በተጨማሪ የቀይ የደም ሴል መጠኔን ለማወቅ የቲቢ ህክምና እንደጨረስኩ ትንሽ ደም ከክንዴ ላይ ለምርመራ ይወሰዳል።.----------(የመረጃ ሰብሳቢው ስም) የጠየኩትን ጥያቄዎች ሁሉ መልሶልኛል። በዚህ የምርምር ውጤት ዘገባ ውስጥ ስሜ አይጠቀስም። አለመሳተፍ ከፈለኩ መተው እችላለሁ። መሳተፍ ከጀመርኩ በኋላ እንኳን ካልተስማማኝ ማቋረጥ እችላለሁ። የዚህን ስምምነት ፅሁፍ ከፈለኩ ቅጂውን መውሰድ እችላለሁ። በዚሁ መሰረት በጥናቱ ለመሳተፍ ፍቃደኛ መሆኔን የቃል ፍቃድ ሰጥቻለሁ።

የቃል ፍቃድ ተሰጥቷል: **አዎ** → መጠይቁን መሙላት ቀርል

አይ →አቋርጥ

Annex-9a. Assent information sheet (Afan Oromo version)

Ibsa Heeyyemamummaa Ijoollee

Maqaan koo ----------jedhama. Ijoollee dhukuba tiibiitiin dhibamaniifi kan hin dhibamin jidduu garaagarumaa jiru qorachaa jirra. Kanatti aansee ibsa siif dubbisu yoo ati heeyyamamaa taate wantoota qidhamaniidha.

Gaafiwwan umrii kee, saala kee, akka barachaa turteefi hin baranne fi kankanafakkeetan sin gaafadha. Kan biraa ulfina qaama keetii, dheerinna keetifi godaannisa talaalli tiibii fudhachuu kee mu'isu yoo irree ketirra jiraate nan laala. Yoo gaaffiwwan ati hin yaadanne ykn siif hin galin jiraatan warri siyaalsisuu sifide si gargaara. Yoo dhukubsataa tiibii taate akitaa kee yeroo barbaachisaa ta'etti fudhachuudhan qorichi tiibii yaallamuuf fudhachaa jirtu hojjechaa jiruu ykn hojjechaa jiruu baachuun isaa ni qoratama. Wantoonni ati qoratamtu asiin olitti sitti hime hundinuu ijoolle yaallamuuf mana yaala dhufan hundaaf godhamu malee qorannaa kanaaf jecha qofa miti. Kanaafu sababa qorannaa kanaatiif jecha kan godhamanii miti jechuudha. Qorrannaa kanaf jecha wanti ida'amaan ati laalamtu yoo jiraate, akkuma qoricha fixxeen qoranna hanga seelii dhigaa diimaa kee laaluf harka keetirra dhiiga xiqishuun isaa fudhatamee qoratamuu qofa. Bu'aan qorannoo kana ijoollee iraa dhukuba kanarraa ittisuuf gargaaruu danda'a. Yeroo siwajjin turu keessatti wanti ifa siif hin ta'in yoo jiraate nadhaabdee maal akkan gochaa jiru nagaafachuu dandeecha. Yoon gabasa qorannoo kana barressu maqaaan kee hin barrayu. Wanti sodaate yoo jiraatte warra kee siwajjin as dhufanitti mari'achiisuu ni dandeecha. Ibsan amma siif dubises ta'ee xalayaa waligaltee itti ansee siif dubbisu yoo barbaadde garagalchaa isaa fudhachuu dandeecha.

Hirmaannaa kee hanga ammatiif sin galateefadha

Maqaa ragaa sassaabaa: _____

Annex-9b. The Letter that Gives Your Permission (Afan Oromo version)

Heeyyamamummaa ijoollee

Ibsa Heeyyamamumma _____ (*maqaa raga sassaabaa*) wajjin dubsineerra. _____ (*maqaa raga sassaabaa*)n raga maalii akka narraa barbaadu hubadhheera. Akkasumas _____ (*maqaa raga sassaabaa*) akka ulfina qamakiyyaa fi dheerinna kiyya laka'uufi fi irree kiyyarra qodaanisni talaalli tiibii fudhachuu kiyya mul'isu akka jiruuf hin jirre ni laala. Yoon dhukubsataa tiibii ta'e, qorichin tiibii yaallamuuf fudhadhu hojechaa jiraachuu isaa hordofu akkitaa kiyya yeroo barbaachisutti akka fudhatamu bareera. Dabalataan yeroon qoricha fixutti hangi seelii diimaan dhiigaa kooti hangam akka ta'e beekuuf dhiigni xiqqoon harka kiyyarraa fudhatamee akka qoratamu beekeera. - _____ (*maqaa raga sassaabaa*)n gaafiin gaafadhe hundaa naaf ibseera. Gabaasa qorannoo kana keessatti maqaan kiyya akka hin barroofne hubadheera. Yoo gaafichi natti toluu baate calqabumarraa yookiin ergan clqabee booda addan kutuu akkan danda'us beekeera. Yoon barbaade ibsa heeyyemamummaas ta'ee waraqaa heyyemamummaa kan garagalcha isaa fudhachuu akkan danda'us natti himameera. Haluma Kanaan qorannoo kanarratti hirmaachuuf heyyema afaanii kenneera.

Heeyyema kenneera: **Eeyyeen** → Gaaficha itti fufi

Lakki →addaan kuti

Annex-10. Published Original Papers/ and/ or manuscripts

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https://doi.org/10.1186/s12889-023-16183-9

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RESEARCH Open Access

Epidemiology of childhood tuberculosis and predictors of death among children on tuberculosis treatment in central Ethiopia: an extended Cox model challenged survival analysis

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Abstract

Background Childhood tuberculosis (TB) was poorly studied in Ethiopia. This study aimed to describe the epidemiology of childhood TB and identify predictors of death among children on TB treatment.

Methods This is a retrospective cohort study of children aged 16 and younger who were treated for TB between 2014 and 2022. Data were extracted from TB registers of 32 healthcare facilities in central Ethiopia. Phone interview was also conducted to measure variables without a space and not recorded in the registers. Frequency tables and a graph were used to describe the epidemiology of childhood TB. To perform survival analysis, we used a Cox proportional hazards model, which was then challenged with an extended Cox model.

Results We enrolled 640 children with TB, 80 (12.5%) of whom were under the age of two. Five hundred and fifty-seven (87.0%) of the enrolled children had not had known household TB contact. Thirty-six (5.6%) children died while being treated for TB. Nine (25%) of those who died were under the age of two. HIV infection (aHR = 4.2; 95% CI = 1.9–9.3), under nutrition (aHR = 4.2; 95% CI = 2.2-10.48), being under 10 years old (aHR = 4.1; 95% CI = 1.7–9.7), and relapsed TB (aHR = 3.7; 95% CI = 1.1–13.1) were all independent predictors of death. Children who were found to be still undernourished two months after starting TB treatment also had a higher risk of death (aHR = 5.64, 95% CI = 2.42–13.14) than normally nourished children.

Conclusions The majority of children had no known pulmonary TB household contact implying that they contracted TB from the community. The death rate among children on TB treatment was unacceptably high, with children under the age of two being disproportionately impacted. HIV infection, baseline as well as persistent under nutrition, age < 10 years, and relapsed TB all increased the risk of death in children undergoing TB treatment.

Keywords Epidemiology, Survival, Childhood tuberculosis

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Introduction

Childhood tuberculosis (TB) was first included in the World Health Organization (WHO) global report in 2012, with an estimated 0.5 million new TB patients under the age of 15, accounting for 5.7% of all TB patients in 2011 [1]. WHO estimates 1.2 million children developed TB disease in 2021, which accounts for 11% of the total TB burden [2].

WHO estimated children accounted for 4.6% and 14% of TB-related mortality globally in 2011 and in 2021, respectively, but only 5.7% and 11% of TB incidences in 2011 and 2021, respectively [1, 2]. Modeling studies suggest greater than 96% of child TB deaths occur in children not receiving treatment [3].

Ethiopia has long been one of the 22 [1] or 30 countries with a high TB burden [2, 4], ranking seventh in the world in 2021 [2]. In Ethiopia, WHO estimates that about 20,000 children under the age of 15 (i.e. 11.6% of all TB patients) become ill with TB, accounting for 9.5–14.9% of all TB patients in 2017 [4].

GeneXpert MTB/RIF® has been used as the primary tool for TB diagnosis in Ethiopia since 2015 [5]. Xpert is a more sensitive and specific test than microscopy, allowing for more accurate data generation to describe childhood TB epidemiology [6–8].

Ramos et al. discovered that 4.1% of children on TB treatment died in a rural hospital in southern Ethiopia between 1998 and 2015. However, the study did not identify predictors of death [9]. Death rates from diagnosed and treated childhood TB have been reported as less than 1% [10, 11]. To reduce the death rate among children receiving TB treatment to the greatest extent possible, we must identify the predictors of death to implement risk factor-focused interventions in addition to anti-TB treatment [12–14]. Although it has been shown in other parts of the world that the Bacillus Calmette Guerin (BCG) vaccine is effective at preventing TB deaths in children [15] and under nutrition increases the risk of death from TB in adults [16, 17], studies in Africa and Ethiopia [11, 18–27] left these factors out. The aim of this study was to describe the epidemiology of childhood TB and identify predictors of death in children with presumed drug-susceptible TB in central Ethiopia between 2014 and 2022.

Methods

Study site and period

This study was carried out in TB treatment facilities in Addis Ababa city, Adama, and Bishoftu towns. The study included data from children who were treated for TB disease between June 6, 2014, and February 16, 2022.

Study design and population

We used a retrospective cohort study design. According to Ethiopian national guidelines [28], new or relapsed pulmonary TB (PTB) patients and all forms of extra-pulmonary TB (EPTB), except TB meningitis and osteoarticular TB, are treated for at least 6 months. The intensive phase lasts two months and is treated with a combination of rifampicin, isoniazid, pyrazinamide, and ethambutol. The continuation treatment, which lasts four months, is treated with rifampicin and isoniazid. TB meningitis and osteoarticular TB are treated for a total of 12 months, including two months of the initiation phase and 10 months of the continuation phase, with the same drugs as described above.

This study included children aged 16 years and younger who had been diagnosed with PTB or EPTB, either for the first time treatment or as a relapse or retreatment, with presumed drug-susceptible TB.

Children who were transferred to the study healthcare facilities after beginning TB treatment elsewhere were excluded from the study because baseline data, such as nutritional status at the start of treatment, were unable to be obtained. Children who had switched from TB to another diagnosis despite having completed TB treatment were also excluded.

Study variables

The time-to-death (in months) of a child during TB treatment was our outcome variable. The end of follow-up periods for the 6 and 12 month regimens were 6 and 12 months, respectively.

The independent variables of this study included child's BCG vaccination status at birth or within 15 days, age, sex, HIV status, TB treatment history, TB type, nutritional status at time of TB treatment start, and nutritional status two months after TB treatment initiation.

From TB registers, we obtained patients' weight, height (length for children under the age of two), and mid-upper-arm circumference (MUAC). Body mass index (BMI)-for-age-z-score, weight-for-height/length-(WH/L)-z-score, MUAC, or weight-for-age percentile indices were used to determine the nutritional status of the children based on their appropriateness for different age groups and availability. The cutoffs for the indices for normal, moderate acute malnutrition (MAM), and severe acute malnutrition (SAM) are shown in Table 1. We used the weight for age chart developed by Centers for Disease Control and Prevention (CDC) for children aged 2 to 20 years to identify underweight when there was no height/length or MUAC measurement.

Table 1 Indices used to assess the nutritional status of childhood TB patients (≤16 years old) in central Ethiopia, 2014 to 2022

Option	Child age	Index	Cutoffs for nutritional status		
			Normal	MAM	SAM
Option 1 [29]	5–18 years	BMI-for-age-z-score	$-2 \leq z \leq +1$	$-3 \leq z < -2$	$z < -3$
Option 2 [30]	0–59 months	WH/L-z-score	$-2 \leq z \leq +1$	$-3 \leq z < -2$	$z < -3$
Option 3 [29]	6–59 months	MUAC	≥ 125 mm	115–125 mm	< 115 mm
	5–9 years	MUAC	≥ 145 mm	135–145 mm	< 135 mm
	10–14 years	MUAC	≥ 185 mm	160–185 mm	< 160 mm
Option 4 [31]	2–20 years	CDC weight-for-age percentile	5th -95th	<5th is underweight	

Sample size determination

We used the sample size determination formula for the Cox proportional hazards model that compares the survival curves of two groups [32]. The total sample size was computed to be 628 patients with childhood TB (502 BCG-vaccinated versus 126 not vaccinated). The assumptions were a significance level of 5% and a power of 80% for a normal distribution [33], a postulated hazard ratio of 0.5 for death among children vaccinated with BCG compared to those unvaccinated, the probability of death in the unvaccinated and vaccinated groups equaling 0.08 and 0.24, respectively [34], and the ratio of vaccinated to unvaccinated equaling four based on evidence that 81% of the population had BCG scars and 19% did not [35].

Sampling technique

Facilities were randomly chosen, stratifying the Addis Ababa, Adama and Bishoftu areas. From Addis Ababa, three hospitals were chosen at random from a total of six governmental hospitals, and 23 governmental health centers were chosen at random from a total of 95 centers that provide TB treatment services. The government hospital and two health centers in Adama were chosen at random from among five that offer TB services. One of Bishoftu's two hospitals and two of its four health centers were also chosen at random. As a result, the study included 32 healthcare facilities, and all children treated for tuberculosis in those facilities who met the inclusion criteria were studied.

Data collection process

The TB register's content was used to generate a checklist and extract data. A structured questionnaire was administered via phone interviews to measure variables without a space and not recorded in the registers. Trained clinical nurses and health officers extracted the data and conducted the questionnaire. The principal investigator quality checked 100% of the data for accuracy and completeness.

Data analysis

EpiData version 3.1 was used to enter data, which was then exported to Stata version 14 for cleaning and analysis. Data were described using frequency tables and a line graph. The log-log graphical proportional hazards (PH) assumption test was first performed and independent variables that demonstrated parallel curves for their categories were considered to be included in the Cox PH survival analysis model. To supplement the graphical assumption test, we ran a statistical goodness-of-fit test and variables with p-values greater than 0.05 were assumed to satisfy the PH assumption and be included in the Cox PH model. We conducted a disaggregated analysis on variables with crossing log-log curves in their respective categories, examining the survival function separately for survival times below and above the crossing point. In the final model, we challenged the Cox PH model with the extended Cox model for variables that were ambiguous with the graphical assumption test but satisfied the goodness-of-fit test. A single covariate Cox PH model was run first to identify variables with p-values less than or equal to 0.20 for crude hazard ratio (HR) as candidates for the final multivariable Cox PH model. The log likelihood ratio test was used to select the best-fit model from the Cox PH and extended Cox models. Finally, covariates with p-values less than 0.05 for the adjusted hazard ratio (aHR) were reported as independent predictors of death in children on TB treatment. The 95% confidence intervals (CI) for crude HR and aHR were also shown.

Ethical consideration

The study was approved by the Institutional Review Board of Addis Ababa University's College of Health Sciences (protocol number: 057/19/SPH). All procedures followed were in accordance with the Helsinki Declaration. Before taking part in the study, children's parents or guardians provided informed consent and older children provided informed consent to participate in the phone interview.

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Results

Socio-demographic characteristics of childhood TB patients

A total of 650 children aged 16 years and younger who were treated for TB were identified from the TB registers. A phone interview was successful with 534 (83.4%) of the children's families or guardians. During the phone interview, the caregivers or guardians of 10 (1.9%) of the children reported that further investigation revealed their children's illnesses were lymphoma, brain stem glioma, and Crohn's disease rather than TB. As a result, 640 children were included in this analysis: 524 (81.9%) children who could be reached by phone and 116 (18.1%) children who could not be reached by phone.

Of the 640 children, 368 (57.5%) were female. The mean (standard deviation) and median (inter-quartile range) ages of the patients were, respectively, 10.0 (5.4) and 12.0 (5.0 to 15.0) years. Four hundred and fifty-five children (71.1%) were Addis Ababa residents. Among the 519 children with a known daytime spending place, 376 (72.4%) were in school (including kindergarten), and 20 (3.9%) were in daycare, together accounting for 76.3% of the total TB-sick children involved in the study. But 123 (23.7%), were spending at home when they were diagnosed with TB of which 111 (90.2%) did not go to school (kindergarten) because they were not of school age (< 4 years).

One hundred and ninety-eight (52.7%) of those enrolled in school were in grades one through six. Two hundred and fifty-two (67.0%) were attending a public school at time TB diagnosis. One hundred and sixty-five mothers (32.6%) and 98 fathers (20.1%) of the children had no formal education. Of the total number of children, 560 (87.5%) were diagnosed with and treated for TB after 2015, when GeneXpert MTB/RIF® was introduced (Table 2).

Characteristics of the childhood TB patients

Six hundred and seventeen (96.4%) of the children were new TB patients. Three hundred and sixty-seven (57.3%) of the children had EPTB, while the remaining 273 (42.7%) had PTB; 159 (24.8%) pulmonary-negative and 114 (17.8) pulmonary-positive. Among the EPTB patients, 210 (57.3%) had TB lymphadenitis, 26 had pleural TB (7.1%), 25 had osteoarticular TB (6.8%), 24 had intestinal TB (6.5%), and 22 had TB meningitis (6.0%).

Of 273 PTB patients, 120 (44.0%) were diagnosed using GeneXpert MTB/RIF®, 196 (71.8%) using a sputum smear microscopy test, and 43 (15.8%) using both tests. One hundred thirteen (20.8%) of all TB patients were examined with GeneXpert, and Mycobacterium tuberculosis (MTB) was found in 84 (63.2%); 79 (59.4%) had rifampicin resistance (RR) not detected, and 5 (3.8%) had RR indeterminate. MTB was not detected in the remaining 49 (36.8%) patients who underwent GeneXpert testing.

Thirteen (9.8%) of the 133 GeneXpert tests were performed on non-sputum samples such as lymphoid discharge, cerebrospinal, pleural or peritoneal fluids.

Of 196 PTB patients, 67 (34.5%) were positive for sputum smear microscopy test.

One hundred and ninety-four children (30.3%) children were undernourished when they began TB treatment; 109 (17.0%) had MAM and 85 (13.3%) had SAM. Only 13 (6.7%) of undernourished children received nutritional assistance (plump nut or plump sup). One hundred and sixteen (18.4%) of the 629 children who survived for two or more months after starting TB treatment were undernourished: 77 (12.2%) were MAM and 39 (6.2%) were SAM.

During the intensive phase of the treatment, 18 children (2.8%), not shown in the table, had at least one dose missed.

All 640 children had known HIV status, and 85 (13.3%) were living with HIV.

The BCG vaccination status was known for 524 (81.9%) of the children, and it was discovered that 315 (60.1%) had received the vaccine within two weeks of birth.

Of the 524 children, 56 (10.7%) were leaving with a cigarette-smoking family member.

Of the 640 children, 557 (87.0%) had not had a prior or concurrently known sick family member with TB living with them, while 78 (12.2%) had had at least one known PTB sick household contact; 77 (12%) had smear positive contacts and 1(0.2%) smear negative contact. Only 16 (20%) of the 80 children under the age of two had had PTB contact in the home (Table 3).

Childhood TB disaggregated by age

Eighty (12.5%) of TB-sick children were under the age of two, while 157 (24.5%), 94 (14.7%), 205 (32%) and 184 (28.8) were under the age of five, between the ages of five and nine, ten to fourteen and fifteen to sixteen years old, respectively.

Children under the age of two made up 25.0% of all deaths. Children aged 0–4, 5–9, 10–14, and 15–16 years accounted for 41.7%, 22.2%, 25.0%, and 11.1% of all deaths, respectively. Of the 640 children who began TB treatment, 36 (5.6%; 95% CI = 4.0–7.7%) died during the treatment (Table 4). There were five (0.8%) lost-to-follow-up patients recorded on TB registers, but we confirmed their deaths through phone interviews with their caregivers and thus analyzed them as dead outcome. Except for one death, all of the deaths happened within 6 months of starting TB treatment. The remaining 604 patients (94.4%; 95% CI, 92.3–96.0%) were censored (i.e., cured, treatment completed, or treatment failed).

Table 2 Socio-demographic characteristics of childhood TB patients (≤16 years old) and their families in central Ethiopia, 2014–2022

Characteristics	Category	Frequency (%)
Sex (*n* = 640)	Male	272 (42.5)
	Female	368 (57.5)
Age summary in years (*n* = 640)	Minimum = 0.2; Maximum = 16; Mean (standard deviation) = 10.0 (5.4); Median (IQR) = 12 (5 to 15)	
Region (*n* = 640)	Addis Ababa	455 (71.1)
	Oromia	165 (25.8)
	SNNPR	9 (1.4)
	Amhara	8 (1.3)
	Other	3 (0.5)
Where child was spending at the time of TB diagnosis (*n* = 519)	In school (including kindergarten)	376 (72.4)
	At home	123 (23.7)
	At daycare	20 (3.9)
Child's education (*n* = 376)	Kindergarten	40 (10.6)
	Grade 1 to 6	198 (52.7)
	Grade 7 to 8	81 (21.5)
	Grade 9 to 10	57 (15.2)
The type of school the child was attending (*n* = 376)	Public	252 (67.0)
	Private	124 (33.0)
Mother's education (*n* = 506)	Didn't attend formal school	165 (32.6)
	Grade 1 to 6	66 (13.0)
	Grade 7 to 8	50 (9.9)
	Grade 9 to 12	115 (22.7)
	Diploma	31 (6.1)
	Degree and above	35 (6.9)
	Mother was not alive	44 (8.7)
Father's education (*n* = 487)	Didn't attend formal school	98 (20.1)
	Grade 1 to 6	57 (11.7)
	Grade 7 to 8	50 (10.3)
	Grade 9 to 12	129 (26.5)
	Diploma	40 (8.2)
	Degree and above	62 (12.7)
	Father was not alive	51(10.5)
Year the child diagnosed with TB (*n* = 640)	2014	13 (2.0)
	2015	67 (10.5)
	2016	69 (10.8)
	2017	112 (17.5)
	2018	102 (15.9)
	2019	106 (16.6)
	2020	107 (16.7)
	2021	64 (10.0)

The following line graph depicts the age-related trend of TB disease frequency and the proportion of TB deaths shared by each age from the total TB deaths (i.e., 36). After declining after the age of two, the number of TB patients began to trend upward again around the age of 12 and peaked at the age of 16.

When we looked at the death share in percentage of total death by age for children who died while on TB treatment, we noticed that children under two years old had the highest share (25%), and the death share seemed stable, remaining below 10% for practically all ages equal to and beyond two years (Fig. 1).

Predictors of death among children on TB treatment

The log-log plot satisfied PH assumptions for sex, nutritional status at the start of TB treatment, nutritional

Table 3 Miscellaneous characteristics of childhood TB patients (≤16 years old) in central Ethiopia, 2014–2022

Characteristics	Category	Frequency (%)
TB treatment history ($n=640$)	New	617 (96.4)
	Relapse	23 (3.6)
TB type ($n=640$)	Extra-pulmonary	367 (57.3)
	Pulmonary-negative	159 (24.8)
	Pulmonary-positive	114 (17.8)
Extra-pulmonary TB type ($n=367$)	TB lymphadenitis	210 (57.2)
	Pleural TB	26 (7.1)
	TB of the spine or bone	25 (6.8)
	Intestinal TB	24 (6.5)
	TB meningitis (CNS TB)	22 (6.0)
	TB peritonitis	12 (3.3)
	Other	1 (0.3)
	Not recorded	47 (12.8)
GeneXpert MTB/RIF® result ($n=133$)	MBT detected, RR not detect	79 (59.4)
	MTB detected, RR indeterminate	5 (3.8)
	MBT not detected	49 (36.8)
Sputum smear result ($n=194$)	Positive	67 (34.5)
	Negative	127 (65.5)
Child's nutritional status at the time of TB treatment start ($n=640$)	Normal	446 (69.7)
	MAM	109 (17.0)
	SAM	85 (13.3)
Child received nutritional support ($n=194$)	Yes (plump nut or plump sup)	13 (6.7)
	No	181(93.3)
Child's nutritional status if survived to two months after starting TB treatment ($n=629$)	Normal	513 (81.6)
	MAM	77 (12.2)
	SAM	39 (6.2)
Child's HIV status ($n=640$)	Positive	85 (13.3)
	Negative	555 (86.7)
BCG vaccination at birth or within 15 days of birth ($n=524$)	Received	315 (60.1)
	Not received	209 (39.9)
A smoking family member living with the child ($n=524$)	Yes	56 (10.7)
	No	468 (89.3)
A previous or concurrent household TB contact ($n=640$) in child's age	No household TB contact	557 (87.0)
	Pulmonary-positive	77 (12.0)
	Pulmonary-negative	1 (0.2)
	EPTB	5 (0.8)
Prior or concurrent TB type in household in a child under the age of two ($n=80$)	Pulmonary-positive	16 (20.0)
	Pulmonary-negative	0 (0.0)
	EPTB	2 (2.5)

status two months later, age category, TB treatment history, and an interaction term of BCG vaccination with age category. The graphical assumption test for HIV status, on the other hand, showed diverging curves, indicating that PH was ambiguous. However, all of the covariates, including HIV status, passed the PH assumption test with p-value greater than 0.05 on the goodness-of-fit test. We fit both the standard Cox PH models and the extended Cox PH to resolve the discrepancy between the graphical and statistical assumption tests for HIV status. Ultimately, we chose Cox PH as the best-fit model because there was no significant difference in the two models' outputs based on the likelihood ratio (LR) test statistics for model selection (likelihood ratio chi2 [1] = 0.93; p-value = 0.33) but the PH Cox model was more precise. Aside from the LR test and precision, the

Table 4 The number of patients and deaths by age group among TB-sick children receiving TB treatment in central Ethiopia, 2014–2022

Age (years)	Number of TB patients (%), *n* = 640	Deaths (%), *n* = 36
Under 2	80 (12.5)	9 (25.0)
0–4	157 (24.5)	15 (41.7)
5–9	94 (14.7)	8 (22.2)
10–14	205 (32.0)	9 (25.0)
15–16	184 (28.8)	4 (11.1)
Over all death rate = 36/640 (5.6%; 95% CI = 4.0–7.7%)		

fitted extended Cox model revealed that the Cox regression coefficient estimate for the time-varying covariate, HIV status times log of survival time, was not statistically significant to be preferred (α = -0.72; 95% UI = -2.25–0.80; *p*-value = 0.35), implying that the risk of death did not differ significantly over time between HIV positive and HIV negative children receiving TB treatment.

In the multivariable model, HIV positive children were four times more likely than HIV negative children to die from TB (aHR = 4.21; 95% CI = 1.90–9.32). Similarly, undernourished children at the start of TB treatment were four times more likely to die than their normally nourished counterparts (aHR = 4.21; 95% CI = 2.21–10.48). Children under the age of ten were four times as likely as those aged ten and up to die (aHR = 4.06; 95% CI = 1.70–9.67). Children with relapsed or retreated TB were also more than three times more likely to die from the disease than children with new TB (aHR = 3.71; 95% CI = 1.05–13.11). There was no statistically significant effect modification (interaction) found between BCG vaccination and age categories labeled as under ten years and ten years or older (aHR = 0.76, 95% CI = 0.28–2.08) (Table 5).

The post-Cox regression survival curve estimation revealed that the survival curve for the HIV negative children ran consistently above the curve for the HIV positive children over the course of time, indicating that the HIV negative group had a better survival probability (Fig. 2). Similarly, the survival curve for children aged ten and up remained higher than that of children under ten, indicating that older children outlive younger ones (Fig. 3). In a different multivariable Cox PH model (adjusting for gender, HIV status, age category, and TB treatment history), undernourished children were found to be significantly more likely to die than normally nourished children two months after starting TB treatment (aHR = 5.64, 95% CI = 2.42–13.14), not shown in a table.

The effects of BCG vaccination clearly violated the graphical assumption test by displaying crossing log-log curves at around survival time of three months. The time period disaggregated analyses for either time period, i.e., before and after three months, demonstrated no significant difference in survival between vaccinated and unvaccinated children; the HR for unvaccinated children starting TB treatment was 0.42 (95% CI = 0.13 − 1.36) in the first three months after treatment initiation and 1.22 (95% CI = 0.46 − 3.29) after the first three months after treatment initiation.

EPTB, smear-negative TB, and smear-positive TB were responsible for 18 (50.0%), 15 (41.7%), and three (8.3%) of the deaths, respectively. Meningitis TB claimed five lives, accounting for 27.8% of EPTB-related deaths and 13.9% of all TB deaths.

Discussion

This study describes epidemiology of childhood TB and reveals predictors of death in children who received TB treatment in central Ethiopia between 2014 and 2022. Our four main findings are that; healthcare facilities in central Ethiopia had a high child TB death rate (5.6%),

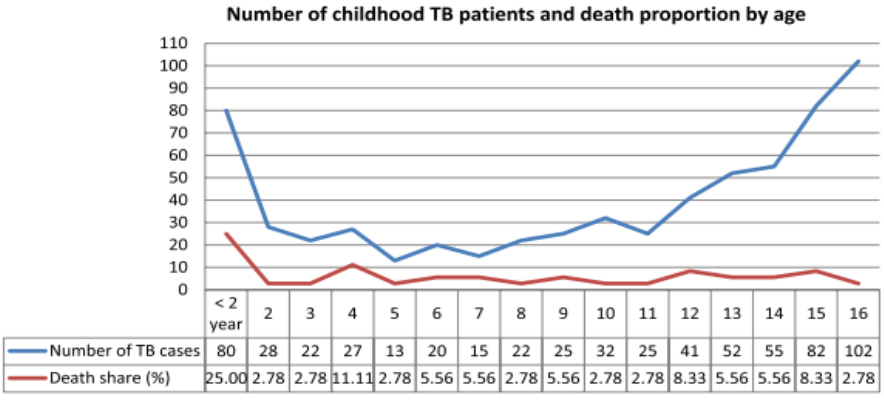

Fig. 1 The distribution of childhood TB patients and death rates by age in central Ethiopia, 2014–2022

Table 5 Cox proportional hazards survival analysis with single and multivariable covariates in children treated for TB in central Ethiopia, 2014–2022

Characteristics	Deaths/n (%)	HR (95% CI)	*p*-value	aHR (95% CI)	*p*-value
Sex					
Male	20/272 (7.35)	1.00		1.00	
Female	16/368 (4.35)	0.58 (0.30–1.13)	0.110	0.78 (0.37–1.64)	0.506
Child's HIV status					
Negative	23/555 (4.14)	1.00		1.00	
Positive	13/85 (15.30)	3.98 (2.02–7.87)	0.000	4.21 (1.90–9.32)	0.000*
Nutritional status at TB treatment start					
Normal	15/446 (3.36)	1.00		1.00	
Undernourished (MAM or SAM)	21/194 (10.82)	3.31 (1.70–6.42)	0.000	4.81 (2.21–10.48)	0.000*
Age category					
≥ 10 years	13/389 (3.34)	1.00		1.00	
< 10 years	23/251 (9.16)	2.74 (1.39–5.42)	0.004	4.06 (1.70–9.67)	0.002*
TB treatment history					
New	33/617 (5.35)	1.00		1.00	
Relapse (retreatment after lost to follow up)	3/23 (13.04)	2.59 (0.79–8.47)	0.115	3.71 (1.05–13.11)	0.041*
BCG*age category					
Aged ≥10 and BCG vaccinated	23/464 (4.96)	1.00		1.00	
Aged < 10 or BCG unvaccinated or both	6/60 (10.00)	2.17 (0.88–5.36)	0.092	0.76 (0.28–2.08)	0.590

* Statistically significant at *p*-value < 0.05

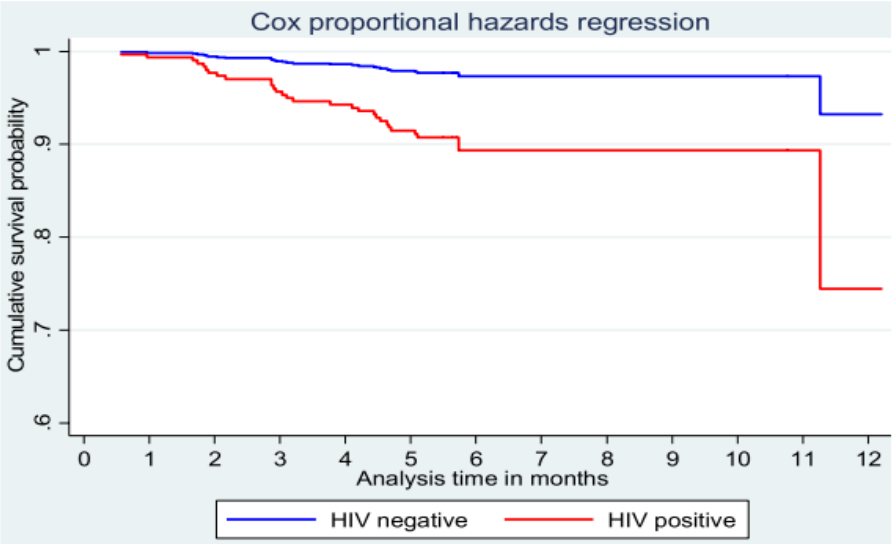

Fig. 2 Estimated survivor function in HIV-negative and HIV-positive children receiving TB treatment

with children under two years old disproportionately affected; HIV, under nutrition at TB treatment initiation, persistent under nutrition throughout initiation phase, relapse, and young age all influenced mortality; BCG vaccination status at birth or within two weeks after birth did not influence mortality; and community transmission may be more important than household transmission among children of all ages.

The line graph in our result showed that the proportion of TB deaths were higher in the first few years of life and this is consistent with the literature [36]. This could be because infants' immune systems are immature,

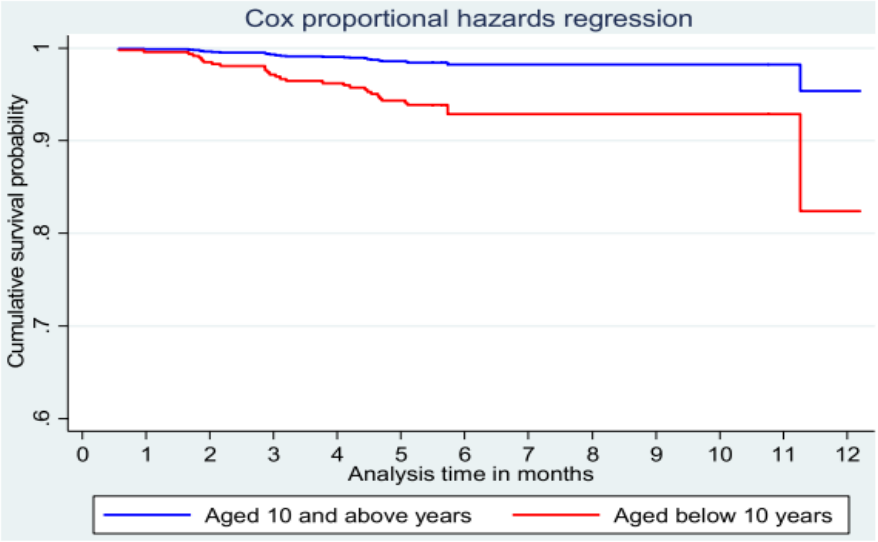

Fig. 3 Estimated survivor function for children under the age of ten and those ten and older treated for TB disease

making them more likely to die from TB irrespective of BCG vaccination [37].

Our study's death rate (5.6%; 95% CI=4.0–7.7%) is significantly higher than that of an earlier study in eastern Ethiopia (1.0%; 95% CI=0.6–1.5) [21]. The eastern Ethiopia study did involve TB meningitis patients, which may explain the lower death rate observed in its findings, as TB meningitis has a 20% case fatality rate [38]. TB Meningitis accounted for nearly 14% of all TB deaths in our study.

When we compare our study's death rate to the death rates of other African studies, we find that South Africa (0.8%; 95% CI=0.7–0.9%) and the Democratic Republic of the Congo (1.4%; 0.4–3.6) appear to have significantly lower death rates. Lower death rates in both studies, however, were likely to be understated due to larger proportion of lost to follow-up, 7% in Congo [39] and 6% in South Africa [11], which could be due to deaths. In our study, however, patients recorded as lost to follow-up on the programmatic TB register were confirmed dead by phone call from their caregivers.

The death rate in our study is significantly lower than in a study conducted in rural southern Mozambique (10.7%; 95% CI=8.7 −12.8). One possible explanation for the higher death rate in the Mozambique study is that the majority of the patients (62%) were HIV co-infected, and nearly half (49.6%) were under the age of five [19], compared to a smaller proportion of patients being HIV co-infected (13.3%) and were under the age of five (24.5%) in our study. People who are TB-HIV co-infected have a higher risk of death than those who are not HIV infected, even if they are on anti-retroviral therapy, and younger children also have a higher risk of death than their older counterparts [10].

Other African countries' death rates, Kenya (4%; 95% UI=4.11–4.63%) and Malawi (9.5%; 95% CI=6.4–13.4%), are comparable to this study's findings, despite having higher TB-HIV co-infection rates, 28.0% for Kenya and 32.6% for Malawi. On the other hand, TB meningitis rates were lower in both the Kenya and Malawi studies, at 1% and 1.4% of all TB patients, respectively [18, 20]. A Nigerian study also discovered a comparable death rate (6.0%; 95% = 4.2–8.4%) despite a higher HIV co-infection rate (26.7%). However, it appears that Nigeria's death rate was understated, as the proportion of patients that were lost to follow-up (possibly due to deaths) was high (15.0%) [23].

We discovered HIV to be an independent predictor of death, which is consistent with a recent meta-analysis finding [10].

Similar to our findings, Hesseling, et al., but it was limited to HIV-positive children, reported in South Africa that under nutrition at the time of diagnosis predicts mortality. The study did not, however, assess the effect of nutritional status after two months of treatment, which remained a significant predictor in our study [40].

Consistent with our findings, studies in Sidama Zone, Ethiopia [24], rural southern Ethiopia [9], Kenya [18], South Africa [11], and Nigeria [23] found that children of a younger age were at a higher risk of death, whereas studies in Malawi [39], and an older study in South Africa by Hesseling, et al. [40] did not. In contrast to our findings, re-treatment was not related to death in studies conducted in South Africa and Mozambique [11, 19].

The fact that only one in eight (12.2%) of all children and only 20% of those children < 2 years had a known previous or concurrent household PTB patient contact suggests that the children were infected with TB from outside sources. This is consistent with the findings of Martinez, et al. [41]. School community screening is not part of Ethiopia's TB contact tracing and screening strategy, but is where children spend a significant amount of time [28].

In this study, the percentage of under nutrition among children under the age of five (21.7%, not shown in a table) at the start of TB treatment was higher than that of the percentage of under nutrition among the population of under the age of five in Ethiopia in 2016 and 2019, which were 10% and 7%, respectively [42, 43]. The rate of under nutrition two months after starting TB treatment in children under five (12.6%, not shown in a table) is still higher than the national figures. A gap in childhood TB research is revealed by the lack of studies on the deaths of children on TB treatment and their association with malnutrition on the African continent, where malnutrition is the highest in the world [44].

We also assessed the impact of the BCG vaccine on TB-associated mortality. Although BCG had no effect on mortality in our study, there is strong evidence that it prevents TB associated deaths [15, 45]. The difference could be due to the fact that the family of a deceased child may have falsely reported that the child had been vaccinated, resulting in a biased result on the effect of BCG in our study. The WHO recommends that all healthy newborns receive a single dose of BCG vaccine at birth or as soon as possible after birth to protect the child before infection occurs [46]. The Ethiopian Expanded Program on Immunization (EPI), which began in 1980, also calls for BCG vaccination to be administered at birth. If BCG is not given at birth, it can be given to children under the age of one year [47]. BCG coverage in Addis Ababa was 97.5, 94.6, and 96.3% in 2011, 2016, and 2019, respectively, while it was 81.6, 88.8, and 88.8% in urban Ethiopia in the same order [42, 43, 48]. To avoid the effect of prior infection before vaccination, which masks the effect of the vaccine, we assessed BCG vaccination status at birth or within 15 days after birth [49].

The line graph in our result showed a relatively low number of TB patients treated between the ages of two and 11 years, followed by a significant increase at later ages. This could be attributed to the impact of the BCG vaccine, which is effective in preventing TB for up to ten years and then fades [50]. However, infants' immune systems are immature, making them more likely to develop TB disease regardless of BCG vaccination [37].

Strengths and limitations

As strength of our study, supplementing the TB register review with a phone interview allowed us to capture data not available on the registers as well as confirm some data on the register. If we had not screened by phone and excluded those who died from misdiagnosed causes, the number of TB deaths considered for this analysis would have been 40 out of 650 (6.2%; 95% CI = 4.4–8.3%) instead of 36 out of 640 (5.6%; 95% CI = 4.0–7.7%). If the misdiagnosis proportion of 1.9% of those we interviewed by phone was applied to the 116 we could not reach by phone, there would be only two children who could have been misdiagnosed, and that would have a negligible effect on our results. The other strength of our study is that, unlike other studies in Africa, we have assessed the effect of persisted under nutrition to two months after TB treatment start on mortality and that of BCG.

The limitations of this study include the inability to determine the amount of milliary TB. This was due to the fact that these data are not collected in the TB register book and could not be confirmed with caregivers due to its medical and complex nature.

The fact that BCG vaccination status was determined through a phone call and caregivers of deceased children may have been influenced by social desirability bias to report a positive response that the child had been vaccinated, was likely to obscure the true effect of the BCG vaccine on mortality from TB.

Another limitation stems from a secondary data we used, which means that TB risk factors like diabetes were not recorded, and this study was unable to measure blood sugar in children and assess the association.

Conclusions

The fact that the majority of TB-sick children spent the majority of their day in a crowded setting, such as school or daycare, and that only one in eight children had a previously or concurrently TB-sick family member with pulmonary TB suggests that schools, where children spent the majority of their day, may be a hotspot for TB transmission in children. Therefore, Ethiopia's TB contact tracing and screening strategy may need to include close contacts including those in the child's school community, where they spend a significant amount of time indoors.

The death rate among children on TB treatment was unacceptably high, affecting children under the age of two disproportionately. Focused intervention such as prevention of HIV infection, improving nutritional status of children on TB treatment, special attention for younger age children with TB, and prevention of recurrent TB should be implemented to minimize death among children on TB treatment.

The finding of BCG had no significant effect on survival should be interpreted with caution because it is likely to be prone to a potential social desirability bias of reporting positive responses on BCG vaccination by the parents in fear of a blame for children who died.

Abbreviations

aHR	adjusted hazard ratio
BCG	Bacillus Calmette Guerin
BMI	body mass index
CI	confidence interval
CNS	central nervous system
EPTB	extra-pulmonary tuberculosis
HIV	human immune-deficiency virus
HR	hazard ratio
LR	likelihood ratio
MAM	Moderate acute malnutrition
MTB	Mycobacterium tuberculosis
MUAC	mid-upper arm circumference
PH	proportional hazards
PTB	pulmonary tuberculosis
RR	rifampicin resistance
SAM	severe acute malnutrition
SPH	school of public health
TB	tuberculosis
WH/L	weight for height/length
WHO	world health organization

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Authors' contributions
AB conceived of the study. AB, FE and AA designed the study. AB, NSA, and AA cleaned and analyzed the data, and wrote the first draft of the manuscript. AB, NSA, and AA contributed to the data interpretation, critically reviewed the manuscript, and approved the final manuscript for submission.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Institutional Review Board of Addis Ababa University's College of Health Sciences (protocol number: 057/19/SPH). All procedures followed were in accordance with the Helsinki Declaration. Before taking part in the study, participants' parents or guardians provided informed consent and older children provided informed consent to participate.

Consent for publication
Not applicable.

Competing interests
Authors have no competing interests.

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Publisher's Note

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RESEARCH ARTICLE

Determinants of tuberculosis disease development in children in central Ethiopia: A matched case-control study

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Abstract

Background

The risk factors for tuberculosis (TB) disease development in children remained understudied, particularly in low-income countries like Ethiopia. The objective of this study was to identify determinants of TB disease development in general and in relation to BCG vaccination in children in central Ethiopia.

Methods

We employed a 1:1 age-matched case-control design to compare the characteristics of children who developed TB (cases) with those who did not (controls). Data were collected in healthcare facilities in Addis Ababa city, Adama, and Bishoftu towns between September 25, 2021, and June 24, 2022. Two hundred and fifty-six cases were drawn at random from a list of childhood TB patients entered into SPSS software, and 256 controls were selected sequentially at triage from the same healthcare facilities where the cases were treated. A bivariate conditional logistic regression analysis was performed first to select candidate variables with p-values less than or equal to 0.20 for the multivariable model. Finally, variables with a p-value less than 0.05 for a matched adjusted odds ratio (mORadj) were reported as independent determinants of TB disease development.

Results

The mean age of the cases was nine years, while that of the controls was 10 years. Males comprised 126 cases (49.2%) and 119 controls (46.5%), with the remainder being females. Ninety-nine (38.7%) of the cases were not BCG-vaccinated, compared to 58 (22.7%) of the controls. Household TB contact was experienced by 43 (16.8%) of the cases and 10 (3.9%) of the controls. Twenty-two (8.6%) of the cases and six (2.3%) of the controls were exposed to a cigarette smoker in their household. Twenty-two (8.6%) of the cases and three (1.2%) of the controls were positive for HIV. Children who were not vaccinated with BCG at birth or

within two weeks of birth had more than twice the odds (mORadj = 2.11, 95% CI = 1.28–3.48) of developing TB compared to those who were. Children who ever lived with a TB-sick family member (mORadj = 4.28, 95% CI = 1.95–9.39), smoking family members (mORadj = 3.15, 95% CI = 1.07–9.27), and HIV-infected children (mORadj = 8.71, 95% CI = 1.96–38.66) also had higher odds of developing TB disease than their counterparts.

Conclusions

Being BCG-unvaccinated, having household TB contact, having a smoker in the household, and being HIV-infected were found to be independent determinants of TB disease development among children.

Introduction

Mycobacterium tuberculosis (MTB) is estimated to infect nearly a quarter of the global population [1]. More than 90% of TB disease in children under the age of 15 develops within a year of infection [2].

Tuberculosis (TB)-infected children under the age of one year and under the age of five have the same chance of developing TB (18% and 19%, respectively) [3]. Children under the age of five, however, have a significantly higher rate of progression to TB disease than older children, such as those aged 5 to 9 years, 10 to 14 years, and 15 to 18 years [3].

Other than age, a number of factors have been found to increase the risk of latent TB infection developing into TB disease, which include: close contact with a TB patient [4–6]; living in a crowded household [4–6]; chronic illnesses such as HIV infection [4–6], diabetes mellitus (DM) [7–9], end-stage renal disease, liver cirrhosis, and chronic obstructive pulmonary diseases [7]; immune-compromising conditions including malignancy, steroid use, and undernutrition [6, 10, 11].

MTB strain type is also important in the development of TB disease because it influences the innate immune response [12]. The East Asian/Beijing genotype was independently associated with a shorter duration of illness before presentation compared to the Euro-American genotype [13].

Some studies have also identified passive cigarette smoking as a risk factor for TB in children [10, 14], but we lack studies that evaluate passive smoking as a risk factor for TB in Ethiopian children [15, 16].

The BCG vaccine, developed in 1921 from live attenuated Mycobacterium bovis, is known to be protective against disseminated TB disease in young children. However, there is still some disagreement about how long the BCG vaccination is effective against TB. Some studies have shown that BCG vaccination is protective against TB for 10–20 years post-vaccination, after which the effect fades [17–19]. A recent meta-analysis demonstrated that BCG only significantly protects against TB disease in children under the age of five, not in adolescents or adults [20]. Furthermore, studies reveal that the BCG vaccine is less effective in protecting against TB near the equator, which includes Ethiopia, highlighting the need for additional studies in the region to corroborate the findings [21, 22].

The WHO-notified BCG strains include the French Pasteur strain 1173 P2, the Danish strain 1331, the Glaxo strain 1077, and the Tokyo strain 172, which together account for about 90% of BCG vaccinations worldwide [23]. No BCG strain is demonstrably better than another

in efficacy, and there is no global consensus as to which strain of BCG is optimal for general use [23, 24]. Ethiopia administers the Danish strain [25].

Ethiopia has a long-standing and up-to-date National Implementation Guideline for Expanded Immunization Program that outlines the roles and duties of various stakeholders involved in vaccine supply, cold chain, and quality control [26] in accordance with WHO standards [27]. As a result, the Ministry of Health guarantees that potent vaccines are available at all levels. The Ethiopian Food and Drug Authority (FDA) is in charge of licensing WHO prequalified vaccinations, as well as monitoring and managing adverse occurrences. The Ethiopian Pharmaceutical and Supply Agency (EPSA) distributes vaccinations for health facilities while maintaining vaccine quality through cold chain distribution. All health facilities and stores that handle vaccines are regularly trained and supervised to use standard refrigerators (WHO PQS prequalified) to store the vaccines and must monitor and record the temperature of the vaccines in the cold chain at least twice daily, including weekends and holidays, to ensure timely action [26].

The fact that risk factors for TB disease development in children such as exposure to a household smoker have been inadequately investigated in low-income countries such as Ethiopia, as well as the ongoing debate over how long BCG protects against TB, highlights the need for additional research. We aimed to identify determinants of TB disease development in general and in relation to BCG vaccination in children in central Ethiopia.

Methods

Study design

We employed a 1:1 matched case-control design to compare the characteristics of children who developed TB disease (cases) to those who did not (controls).

Study setting and period

The study was conducted in healthcare facilities in Addis Ababa city as well as Adama, and Bishoftu towns in central Ethiopia. Adama and Bishoftu are larger urban areas located within a 100-kilometer radius of Addis Ababa, Ethiopia's capital. Residents here had easy access to telephones to be accessed for phone interviews. Being closer to Addis Ababa helps patients have readily accessible access to advanced diagnostic procedures, reducing the possibility of TB misdiagnosis.

Data were collected between June 01, 2022, and June 24, 2022, among the non-TB control study participants. Data on TB cases were obtained from TB register books and via phone interview, mostly from September 25, 2021, to December 28, 2021, not only for the purposes of this study but also to do a survival analysis of children treated for TB. Furthermore, we waited for certain cases until they finished their TB treatment or their treatment outcome was known before resuming collecting data on them from May 10, 2022, to June 15, 2022, depending on the date the treatment outcome for one was known and recorded on the TB treatment register.

Cases

The cases were children aged 16 and under who had been diagnosed with pulmonary TB (PTB) or extra-pulmonary TB (EPTB) and treated with TB drugs. The patients that were treated for TB and whose outcomes were known between May 1, 2015, and June 15, 2022, were extracted from the TB registers.

Controls

The controls were children who were born the same year as the matching cases and treated for non-TB conditions, or received health promotion or preventive services between June 1, 2022, and June 24, 2022 in the same healthcare facilities where the cases were treated for TB. The controls were individuals aged 18 and under who had never been diagnosed with PTB or EPTB based on verbal reports from their parents or caregivers. The controls were chosen from the same birth cohort as the cases, with the cases' age at the time of TB diagnosis used to estimate the age of our controls during the interview. Furthermore, controls were screened to ensure they were currently free of potential TB symptoms listed in the WHO [28] and Ethiopia's TB national guidelines [29], such as prolonged cough for $\geq$ 2 weeks, fever, night sweets, weight loss, and extra-pulmonary site or organ-specific TB symptoms such as cervical or axillary lymphadenopathies, spinal deformity (kyphosis or gibbus), and signs of meningeal irritation (neck stiffness, seizure).

Matching

Child TB patients were matched 1:1 on age and study facilities with children who had never experienced TB based. Childhood TB is difficult to diagnose and is commonly delayed [30].To avoid wrongly enrolling such unrecognized early-stage active TB or sub-clinical (asymptomatic but infectious) TB patients as controls [31], the controls were recruited after the cases' TB treatment outcomes were determined. Delaying control recruitment allow for more time for an unrecognized or subclinical TB to manifest clearly, lowering the risk of misclassification bias. Age was chosen as a matching variable with the premise that it is a strong confounder.

Study variables

The dependent variable was having ever had TB disease. The primary independent variable was BCG vaccination at birth or within two weeks after birth. Sex, HIV status, a cigarette-smoking family member living with the child, and prior or concurrent household TB patient contact were considered control variables.

Sample size determination

A formula to determine sample size for individually matched studies with 1:1 matching [32] was used to compute the required number of cases. Because BCG scar is the sensitive marker of BCG vaccination [33], we used its proportion in the population to calculate our sample size. Taking $Z_{\alpha/2}$ of 1.96 for 5% significance level (α), Z_{β} of 0.84 for 80% power, and assuming 81% of children are exposed to BCG scar [34], the required number of cases to detect odds ratio of 2.00 was calculated to be 256. As a result, the total number of cases and controls became 512, yielding 256 matched case-control pairs.

Sampling technique and data collection

The sampling frame for the random selection of cases was a list of 524 childhood TB patients entered into SPSS software and whose parents or caregivers were interviewed by phone during another study with a different objective than this one (the specifics of how and how many facilities were chosen are detailed in Burusie A. et al. [35]). Controls were selected sequentially at triage from the same healthcare facilities where the cases were treated.

We collected data from the controls using a face-to-face interviewer-administered questionnaire. We used a checklist to extract data on the cases from their TB treatment registration books. We collected the data that could not be collected using the checklist from the cases—

the information that did not have a space to fill in the TB register—by conducting a telephone interview with parents or caregivers. The following information was collected by phone interview because it did not fit into the TB registry: BCG vaccination status, child's schooling, the existence of a smoking family member living with the TB-sick child, and the presence of a TB patient in the household. Variables such as child's gender, age, nutritional status, HIV status, and household size were obtained from the patient's TB register.

The data were collected by clinical nurses and health officers.

Data analysis

We used EpiData version 3.1 to enter the data. The data was then imported into Stata version 14 for further cleaning and analysis. A conditional logistic regression model was used to assess the association using a matched crude odds ratio (mCOR) with a 95% confidence interval (CI). Variables that attained p-values less than or equal to 0.2 during the bivariate analysis were chosen as candidates for the multivariable analysis. Finally, variables with a p-value less than 0.05 for the matched adjusted odds ratio (mORadj) were reported as significant determinants of TB disease. The odds ratios were calculated from discordant pairings. We used the STROBE case-control checklist when writing our report [36].

Ethics statement

The Institutional Review Board (IRB) of Addis Ababa University's College of Health Sciences (protocol number: 057/19/SPH) approved the study. The ethical approval was originally obtained from the IRB, which was good for the period of October 22, 2020, to October 21, 2021. The ethical clearance was then renewed for another year, from May 19, 2022, to May 18, 2023.

We obtained letters of support from the Addis Ababa City Administration's and Oromia Regional State's Health Bureaus for the study's healthcare facilities. Permission to access the TB registration and contact patients' parents or caregivers was then obtained from the medical directors of the study healthcare facilities. Parents or guardians of TB-sick children (cases) gave oral consent before a phone interview was conducted. Because the interviews for the cases were conducted over the phone to ask questions such as BCG vaccination status, household TB contact, exposure to household smokers, and educational level, which were not recorded on the TB patients follow-up register book, obtaining written consent was impractical. The oral consents were documented by field notes on response and non-response counts and witnessed by the primary investigator phoning the parents as part of a data quality check.

Although it was possible to obtain written consent from controls to participate in the interview, it was a time of great instability in Ethiopia due to the civil war, and citizens used to see things with a high level of suspicion in spite of being given information on the purpose of the study, confidentiality, and the fact that their data would not be used for any other purpose than identifying predisposing factors for childhood TB and being assured of the right to refuse to participate. As a result, we were compelled to obtain oral consent because they were afraid and worried about placing their signature on a consent form. The IRB approved the oral consent.

Only the principal investigator had access to information that could identify individual participants after data collection for data quality check purposes by calling parents or guardians.

Results

Characteristics of childhood TB patients and the controls

We identified and analyzed 256 TB patients (cases) and 256 people who had never had TB (controls). Sputum smear microscopy and X-ray were used to diagnose 63 (24.6%) of TB

Table 1. Characteristics of cases at the time of TB diagnosis and that of controls at time of survey in a study conducted in central Ethiopia, 2022.

Characteristics	Category	Cases (%) N = 256	Controls (%) N = 256
Sex	Male	126 (49.2)	119 (46.5)
	Female	130 (50.8)	137 (53.5)
Age in years at TB diagnosis for cases and at survey time for controls	Mean (standard deviation); median	8.96(5.5); 10	10.3(5.3); 10
Study site	Addis Ababa city	180 (70.3)	180 (70.3)
	Adama town	26 (10.2)	26 (10.2)
	Bishoftu town	50 (19.5)	50 (19.5)
Nutritional status	Normal	176 (68.8)	248 (96.9)
	Undernourished	80 (31.2)	8(3.1)
BCG vaccination within two weeks of birth	Yes	157 (61.3)	198 (77.3)
	No	99 (38.7)	58 (22.7)
Child's Education	Kindergarten	23 (13.2)	40 (19.6)
	Grade 1–6	98 (56.3)	86 (42.2)
	Grade 7–8	34 (19.5)	38 (18.6)
	Grade 9–12	19 (10.9)	40 (19.6)
Household family member sick with TB	Yes	43 (16.8)	10 (3.9)
	No	213 (83.2)	246 (96.1)
Cigarette smoking family member	Yes	22 (8.6)	6 (2.3)
	No	234 (91.4)	250 (97.7)
HIV status	Positive	22 (8.6)	3 (1.2)
	Negative	234 (91.4)	61 (23.8)
	Unknown	0 (0)	192(75.0)
Household size	Minimum; Maximum; mean; median	2; 30; 5.2; 4	2;9; 4.7; 5

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patients, while GeneXpert/RIF was used to diagnose 52 (20.3%) of them. The remaining 141 (55.1%) patients were clinically diagnosed with a high index of suspicion and TB-suggestive imaging.

Males comprised 126 cases (49.2%) and 119 controls (46.5%), with the remainder being females. The cases had a mean age of nine years, while the controls had a mean age of ten years. One hundred eighty (70.3%) of the cases and 180 (70.3%) controls were chosen from Addis Ababa. Some settlements that were previously part of Addis Ababa were relocated to the Oromia region under the new demarcation, and vice versa. However, they continue to get health care services from the neighboring Addis Ababa-based health facility or Oromia-based health facility where they were previously served, resulting in a disparity in the number of cases and controls selected from the regions. Ninety-nine (38.7%) of the cases were unvaccinated with BCG, compared to 58 (22.7%) of the controls. Forty-three (16.8%) cases were exposed to household TB contact, whereas only 10 (3.9%) of the controls were. Twenty-two (8.6%) of the cases and six (2.3%) of the controls had a cigarette smoker in their households. Twenty-two (8.6%) of the cases and three (1.2%) of the controls were HIV-infected. The largest household size among the cases was 30, which came from a foster center where numerous children lived in the same room, whereas it was 9 among the controls (Table 1).

Determinants of TB disease in children

We analyzed 256 case-control pairings in total. Sixty-six (25.8%) of case-control pairings were discordant in the sense that the cases were not vaccinated for BCG while the controls were, and 25 (9.8%) of the pairings were discordant in the sense that the cases were vaccinated while the controls were not. The cases had household TB contact while the controls did not in 42

Table 2. Multivariable conditional logistic regression for determinants of TB disease development among children in central Ethiopia, 2022.

Cases	Controls		mCOR (95% CI)	p-value	mORadj (95% CI)	p-value
	Male	Female				
Male	56 (21.9%)	70 (27.3%)	1.11 (0.78–1.59)	0.544		
Female	63 (24.6%)	67 (26.2)	1.00			
	No BCG	BCG received				
No BCG	33 (12.9%)	66 (25.8%)	2.64 (1.67–4.18)	0.000*	2.11(1.28–3.48)	0.003**
BCG received	25 (9.8%)	132 (51.6%)	1.00		1.00	
	Household TB contact	No household TB contact				
Household TB contact	1 (0.4%)	42 (16.4%)	4.67 (2.27–9.59)	0.000*	4.28 (1.95–9.39)	0.000**
No household TB contact	9 (3.5%)	204 (79.7%)	1.00		1.00	
	Smoker family	No smoker family				
Smoker family	1 (0.4%)	21 (8.2%)	4.20 (1.58–11.14)	0.004*	3.15 (1.07–9.27)	0.037**
No smoker family	5 (2.0%)	229 (89.5%)	1.00		1.00	
	HIV infected	HIV uninfected or unknown				
HIV infected	1 (0.4%)	21 (8.2%)	10.50 (2.46–44.78)	0.001*	8.71 (1.96–38.66)	0.004**
HIV uninfected	2 (0.8%)	232 (90.6%)	1.00		1.00	
Household size			1.05(0.99–1.13)	0.118*	1.04 (0.96–1.12)	0.339

*Included in the multivariable model

**Statistical significant at p-value < 0.05

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(16.4%) discordant pairings, and the cases had no contact while the controls did in 9 (3.5%) discordant pairings. With regard to cigarette smoking, discordant pairings included 21 (8.2%) cases that had ever lived with a smoking family member but the controls had not, and 5 (2.0%) cases that had never lived with a smoking family member but the controls had. There were 21 (8.2%) discordant pairings when cases were HIV-positive and controls were not and 2 (0.8%) discordant pairings when controls were HIV-positive and cases were not. In the multivariable analysis, the odds of being unvaccinated for BCG at birth or within two weeks after birth was found to be more than twice as high (mORadj = 2.11, 95% CI = 1.28–3.48) among TB patients as in the never-had-TB groups. Our study also found that the odds of developing TB disease among those children who had household TB patient contact was significantly higher than four times the odds of developing TB disease among those who did not have household TB contact (mORadj = 4.28, 95% CI = 1.95–9.39). Likewise, children who lived with a smoking family member had significantly higher odds of developing TB than children who did not (mORadj = 3.15, 95% CI = 1.07–9.27). Furthermore, TB patients had more than eightfold higher odds of HIV infection than non-TB groups (mORadj = 8.71, 95% CI = 1.96–38.66). However, household size (as a continuous covariate) had no statistically significant association with the development of TB disease (mORadj = 1.04, 95% CI = 0.96–1.12). Sex had a bivariate p-value of 0.544, which did not meet the p-value of less than or equal to 0.2 required for inclusion in the multivariable model (Table 2).

Discussion

We confirmed that being unvaccinated for BCG, exposure to a household TB patient, exposure to a cigarette-smoking family member, and being HIV-infected were determinants of childhood TB disease development in central Ethiopia. This finding, therefore, will aid in the development of context-based intervention strategies to prevent and control TB [37], as well as serve as a foundation for future research on the subject.

Our study's finding that BCG vaccination protects against TB disease is consistent with previous studies [18–20, 38, 39]. BCG vaccination activates CD4+ and CD8+ T lymphocytes, increasing IFN-γ production which enhances anti-mycobacterial action in macrophages [40].

Our finding is also consistent with prior studies that have found that close contact with a TB patient increases the risk of childhood TB [41–44], even regardless of whether the child was vaccinated for BCG at birth [14].

In line with prior individual studies [10, 45] and a meta-analysis [46], our study also found that living with a smoking family member is associated with TB disease development in children. The lack of an association between second-hand smoke exposure and TB in Taiwan's study [47] could be attributed to the fact that its study participants did not have TB contact in their households, which could otherwise have an interaction effect with second-hand smoking.

HIV infection, a well-established risk factor for TB [4–6, 37], was also identified as one of the factors associated with TB development in children in our study, too, though the interval estimation was imprecise.

The lack of association with total household size in our study contradicts findings from studies in Thailand and Bangladesh [14, 43]. This disparity could be explained by the fact that our study measured household size, whereas those two studies measured the number of people living in a single room in a house.

We found no association between sex and TB in children. However, the debate over whether adult males are more likely than adult females to contract TB due to the confounding effect of factors such as smoking, alcohol, and drug use that expose them to TB or due to female hormones inhibiting TB disease development independently has continued [48].

In our result, the cases' mean age (8.96 years) looked to be younger than the controls' (10.3 years). The explanation for this is that the patients' ages were recorded when they were diagnosed with TB, whereas the controls' ages were obtained after the treatment outcome of the cases was determined and the matched control was chosen. This can be viewed as strength because it provided adequate time for clinical signs of potentially undetected TB in the controls, avoiding the bias of misclassifying the child with unrecognized TB as a control. This also allowed us to eliminate from our analysis any cases that were misdiagnosed as TB but later discontinued TB drugs due to a change in diagnosis [49].

The presence or absence of a BCG scar in the controls was determined during the face-to-face interview; however, identifying the presence of a BCG scars on the patients proved difficult. As a result, we based our analyses on orally reported BCG vaccination status rather than BCG scars. Oral reports of BCG vaccination status are reliable since the only vaccine provided via injection at birth or within two weeks of delivery in Ethiopia is the BCG vaccine [26].

One of our study's limitations is that the HIV status of the majority (three-fourths) of the controls was unknown, as opposed to all the cases, which had known HIV status. In Ethiopia, HIV testing is required for TB patients [29]. We included HIV-unknown controls in the HIV-negative category in our analytic strategy. There could be HIV-positive children among the HIV-status unknown controls, causing the HIV-positive distribution among cases to be incorrectly larger than among controls, leading to an overestimation of a positive association between HIV infection and TB disease. However, HIV prevalence among persons aged 15 to 19 is as low as 0.1%. In such a case, the likelihood of having HIV-positive children among the 192 unknown status controls would be too small to influence our findings [50].

The other limitation of our study is that it did not look into whether undernutrition is a risk factor for TB or not because it was difficult to determine whether undernutrition or TB occurred first in TB patients. Even though diabetes or pre-diabetes increases the risk of TB [51], we left it out of the study because we were unable to collect diabetes or pre-diabetes data for both the cases and the controls. Another limitation of our study was that we ignored

socioeconomic factors such as income level at the time of TB diagnosis since they were not feasible to quantify.

Conclusions

No BCG vaccination at birth or within two weeks of birth was one of an independent determinant of TB disease development in children. With this finding, we recommend Ethiopia maintain its universal newborn BCG immunization strategy.

We also confirmed that the odds of developing TB disease were higher in children who were exposed to a pulmonary TB patient in their homes than those who were not exposed.

Children who lived in a household with a smoker had also more odds of developing TB than their peers who had never lived in a household with a smoker. This finding might be used to argue for the inclusion of an in-house smoking prohibition in houses with children in future national tobacco control legislation.

Even in this period of antiretroviral therapy, HIV infection remained a significant risk factor for the development of tuberculosis in children.

Supporting information

S1 Dataset.
(DTA)

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Research article

The magnitude of unfavorable tuberculosis treatment outcomes and their relation with baseline undernutrition and sustained undernutrition among children receiving tuberculosis treatment in central Ethiopia

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ABSTRACT

Background: One of the global key indicators for monitoring the implementation of the World Health Organization's End Tuberculosis (TB) Strategy is the treatment outcome rate.
Objective: This study aims to assess the magnitude of unfavorable treatment outcomes and estimate their relationship with baseline undernutrition and sustained undernutrition among children receiving TB treatment in central Ethiopia.
Methods: This retrospective cohort study included children treated for drug-susceptible TB between June 2014 and February 2022. The study comprised children aged 16 and younger who were treated in 32 randomly selected healthcare facilities. A log-binomial model was used to compute adjusted risk ratios (aRR) with 95% confidence intervals (CIs).
Results: Of 640 children, 42 (6.6%; 95% CI = 4.8–8.8%) had an unfavorable TB treatment outcomes, with 31 (73.8%; 95% CI = 58.0–86.1%) occurring during the continuation phase of TB treatment. We confirmed that baseline undernutrition (aRR = 2.68; 95% CI = 1.53–4.71), age less than 10 years (aRR = 2.69; 95% CI = 1.56–4.61), HIV infection (aRR = 2.62; 95% CI = 1.50–4.59), and relapsed TB (aRR = 3.19; 95% CI = 1.79–4.71) were independent predictors of unfavorable TB treatment outcomes. When we looked separately at children who had been on TB treatment for two months or more, we found that sustained undernutrition (aRR = 3.76; 95% CI = 1.90–7.43), age below ten years (aRR = 2.60; 95% CI = 1.31–5.15), and HIV infection (aRR = 2.26; 95% CI = 1.11–4.59) remained predictors of unfavorable outcomes, just as they had in the first two months. However, the effect of relapsed TB became insignificant (aRR = 2.81; 95% CI = 0.96–8.22) after the first two months TB treatment.
Conclusions: The magnitude of unfavorable TB treatment outcomes among children in central Ethiopia met the World Health Organization's 2025 milestone. Nearly three-quarters of unfavorable TB treatment outcomes occurred during the continuation phase of TB treatment. Baseline undernutrition, sustained undernutrition, younger age, HIV infection, and relapsed TB were found to be independent predictors of unfavorable TB treatment outcomes among children receiving TB treatment in central Ethiopia.

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1. Introduction

It was estimated that approximately 1.17 million children under the age of 15 fell ill with tuberculosis (TB) in 2021 alone, accounting for 11% of all TB patients globally. Moreover, TB killed over 216,000 children, accounting for 13.5% of all TB deaths during the same year worldwide [1].

Drug-susceptible TB is highly treatable [2]. One of the global key indicators for monitoring the implementation of the WHO's End TB Strategy [3] is the treatment success rate, which includes cure and treatment completion [4]. The global treatment success rate for children under the age of 15 was 88% in 2019 as well as in 2020, implying that the rate of unsuccessful (unfavorable) outcomes was 12% [1]. The goal is to achieve a treatment success rate, also known as a favorable treatment outcome, of more than 90% by 2025, which in other words means keeping the unfavorable outcome below 10% [3]. To that end, identifying predictors of unfavorable TB treatment outcome that constitutes of death, treatment failure, and lost-to-follow-up [5] is critical for focused intervention and thus maximizing favorable treatment outcomes [6].

A plethora of studies on this topic have been conducted, and predictors of unfavorable TB treatment outcome in children have been identified. HIV infection [6–11], age under five years [5,6,8,9,12,13], relapsed TB [6,7,14], smear positive-pulmonary TB [13–15], disseminated TB [7], TB meningitis [16,17], male sex [9,11,12], and rural residence [14,18] were among the predictors identified for unfavorable TB treatment outcome in children. Previous studies, however, have typically classified transferred out patients as having a poor or unfavorable outcomes [11,19], which may not be the case in reality, because transferred out patients may actually be cured or have their treatment completed.

Although unfavorable outcomes, such as death, are more common in the first few weeks of TB treatment, they can also occur during the continuation phase of TB treatment, which follows the first two months of an intensive phase treatment [7]. However, the effect of TB treatment phase-based predictors of unfavorable treatment outcomes in children, such as sustained undernutrition, was not independently assessed in studies. This study aims to assess the magnitude of unfavorable treatment outcomes and estimate their relationship with baseline undernutrition and sustained undernutrition among children receiving TB treatment in central Ethiopia.

2. Methods

Study design, setting and population: This retrospective cohort study was conducted in 32 randomly selected healthcare facilities located in Addis Ababa city and Adama and Bishoftu towns in central Ethiopia. In Addis Ababa, we selected three government hospitals at random using the lottery approach from a pool of six that provide TB treatment services. Similarly, we selected 23 health centers at random among 95 that provided TB treatment services. Adama and Bishoftu towns each had six governmental healthcare facilities that treat TB, and we selected three (a hospital and two health centers) at random from each. Eligible participants included children aged 16 and under who were diagnosed with drug-susceptible pulmonary or extra-pulmonary TB and treated between June 2014 and February 2022.

Study variables: Our dependent variable was TB treatment outcome, which was classified as favorable or unfavorable. Our exposure variables included the child's age, sex, baseline nutritional status (nutritional status at the time of TB treatment start), sustained nutritional status (nutritional status two months later after TB treatment start), HIV status, TB treatment history (new or relapse), and BCG vaccination status at birth or within 15 days.

We extracted patients' weight, height (length for children under two years old), and mid-upper-arm circumference (MUAC) from the TB registry. Based on their appropriateness for different age groups, the nutritional status of the children was determined using the following indices:

1. the body mass index (BMI)-for-age-z-score for those 5–18 year old children [20], with cutoff point $Z < -2$ categorized as under nutrition.
2. weight-for-height/length-(WH/L) -z-score for 0–59-month-old children [21], with cutoff point $Z < -2$ categorized as undernutrition
3. MUAC for 6- to 14-year-old children, where options 1 and 2 above could not be computed due to height or length measurements not being recorded, MUAC <125 mm, <145 mm, and <185 mm were categorized as undernutrition, respectively, for children aged 6–59 months, 5–9 years, and 10–14 years old [20].
4. Where no height/length or MUAC measurement was available, we used the CDC's weight-for-age table for children aged 2–20 years and categorized the CDC weight-for-age percentile <5th percentile as undernutrition [22].

In this study, severe acute malnutrition and moderate acute malnutrition were broadly classified as under nutrition.

Operational definitions: On the basis of the World Health Organization's definition for potential TB treatment outcomes, we broadly classified those TB patients as having favorable or unfavorable TB treatment outcomes. Patients who were cured or completed their treatment were considered to have a favorable outcome, whereas those who died, had their treatment fail, or were lost to follow-up were considered to have an unfavorable treatment outcome [4].

Drug-susceptible TB (DS-TB) was defined as a bacteriologically confirmed or clinically diagnosed case of TB without evidence of infection with strains resistant to rifampicin and isoniazid [2].

Sampling technique and data collection methods: All children who were treated for TB were included in the study; children who were transferred in to the study healthcare facilities were not eligible for our study because their baseline data could not be

obtained. Patients who were transferred outs were followed via phone call to classify them under the appropriate treatment outcome rather than categorizing them all as unfavorable treatment outcome indiscriminately. Data were collected by trained health officers and nurses.

Data analysis: We analyzed the data using Stata version-14 software. We used log-binomial regression to estimate associations between clinical characteristics and unfavorable TB outcomes. In a bivariate analysis, independent variables with a *p*-value of less than or equal to 0.2 for risk ratio (RR) were chosen for a multivariable model. Finally, independent variables with *p*-values less than 0.05 for their adjusted risk ratios (aRR) were deemed significant predictors of unfavorable TB treatment outcome in children. To avoid the effect of multi-collinearity, we ran separate multivariable models for the child's nutritional statuses at the start of TB treatment and for nutritional status two months later at the start of the continuation phase of TB treatment, and we examine their effects on TB treatment outcomes.

Ethical considerations

Ethical clearance was obtained from the Institutional Review Board (IRB) of College of Health Sciences, Addis Ababa University (protocol number: 057/19/SPH).

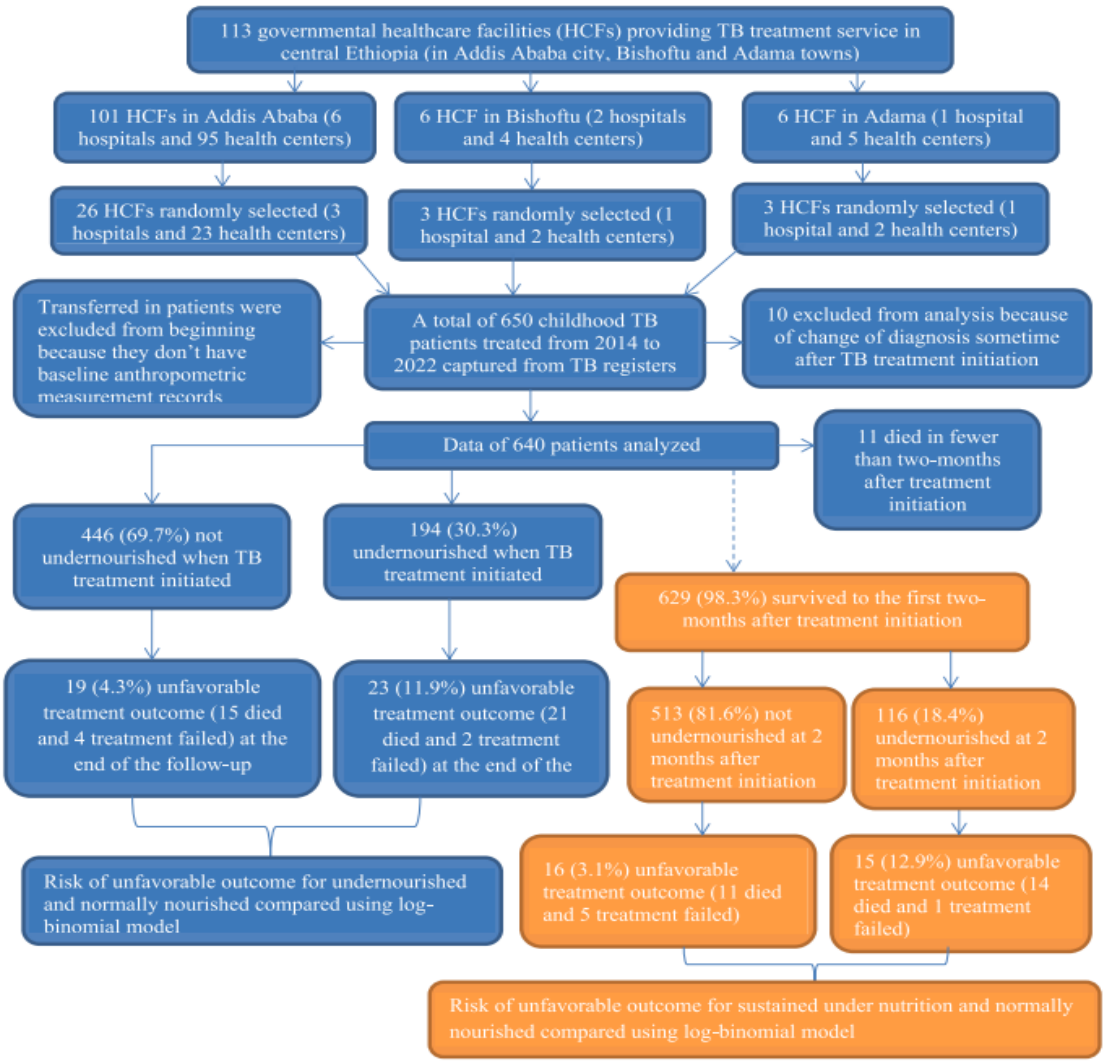

Fig. 1. Finding predictors of unfavorable treatment outcome among children receiving tuberculosis treatment in central Ethiopia.

3. Results

A flow diagram for the study on predictors of unfavorable treatment outcome among children receiving tuberculosis treatment is shown below in Fig. 1.

3.1. Socio-demographic characteristics of study participants

This study involved 640 children who were treated for drug-susceptible TB. One hundred fifty-seven (24.5%) of the children were under the age of five (0–4) years, 94 (14.7%) were between the ages of five and nine, 205 (32%) were between the ages of ten and fourteen, and 184 (28.8%) were fifteen to sixteen years old. Female patients accounted for 368 (57.5%) of all the TB patients.

3.2. Magnitude of unfavorable TB treatment outcome among children

Of the 640 children treated, 42 (6.6%; 95% CI = 4.8–8.8%) had an unfavorable TB treatment outcome; 36 (5.6%) died, and 6 (0.9%) experienced treatment failure. In contrast, 598 (93.4%; 95% CI = 91.2–95.2%) had a favorable treatment outcome, with 106 (16.5%) being cured and 492 (76.9%) being treatment completed. Out of those 42 with unfavorable outcomes, 11 (26.2%; 95% CI = 13.9–42.0%) occurred during the intensive phase and 31 (73.8%; 95% C = 58.0–86.1%) occurred during the continuation phase of TB treatment. Out of 31 total deaths, 11 (30.6%; 95% CI = 16.3–48.1%) occurred during the intensive phase, while 25 (69.4%; 95% CI = 51.9%–83.7%) occurred during the continuation phase of TB treatment (Table 1).

The principal investigator (PI), along with the TB focal persons of transferring out facilities, tracked down nine patients who had been transferred out and assessed their TB treatment outcomes over the phone. As a result, we discovered one cured patient, as reported by both the receiving health facility's TB focal person and the child's parent; one died after being transferred to a tertiary hospital for better treatment, as reported by the child's parent; and seven treatments completed and sent home (1 treatment outcome confirmed by the receiving hospital's TB focal person, but six reported by the parents).

4. Overall predictors of unfavorable TB treatment outcome among children

In our unadjusted analyses, we did not detect a significant association between BCG vaccination and unfavorable TB treatment outcome (RR = 1.00; 95% CI = 0.52–1.93) in the children. In a multivariable analysis, sex was not found to be significantly associated with unfavorable treatment outcome (aRR = 0.61; 95% CI = 0.34–1.10). Overall, undernourished children at the time TB treatment began (aRR = 2.68; 95% = 1.53–4.71) as compared to normally nourished ones, children aged less than 10 years (aRR = 2.69; 95% CI = 1.56–4.61) as compared to those aged 10 or older, HIV-infected children (aRR = 2.62; 95% CI = 1.50–4.59) as compared to HIV-uninfected children, and relapsed TB patients (aRR = 3.19; 95% = 1.79–5.70) as compared to new TB patients, all had a significantly higher risk of unfavorable TB treatment outcome in the multivariable model (Table 2).

5. Predictors of TB treatment outcomes in children during the continuation phase

Of the 629 (98.3%) children who survived two months or more on TB treatment, 116 (18.4%) were undernourished, with 15 (12.9%) having an unfavorable treatment outcome and 101 (87.1%) having a favorable treatment outcome. In a separate multivariable model analysis that disregarded the child's nutritional status at the start of TB treatment, persisted under nutrition into the continuation phase of TB treatment was found to increase the risk of an unfavorable TB treatment outcome (aRR = 3.76; 95% CI = 1.90–7.43) in children. Being younger than 10 years old (aRR = 2.60; 95% CI = 1.31–5.15) and having HIV infection (aRR = 2.26; 95% CI = 1.11–4.59) were also found to significantly increase the risk of unfavorable outcome during the continuation phase. Being a relapsed TB patient (aRR = 2.81; 95% CI = 0.96–8.22), on the other hand, did not continue to increase the risk of an unfavorable outcome after the first two months of TB treatment (Table 3).

Table 1
Treatment outcomes among children with tuberculosis, central Ethiopia, 2014–2022.

Treatment outcome (n = 640)	Frequency (%)	95% CI
Unfavorable	42 (6.6)	4.8–8.8%
Died	36 (5.6)	4.0–7.7%
Treatment failed	6 (0.9)	0.3–2.0%
Favorable	598 (93.4)	91.2–95.2%
Cured	106 (16.5)	13.8–19.7%
Treatment completed	492 (76.9)	73.4–80.1%
Unfavorable outcome during intensive phase (n=42)	11 (26.2)	13.9–42.0%
Unfavorable outcome during continuation phase (n=42)	31 (73.8)	58.0–86.1%
Died during intensive phase (n=36)	11 (30.6)	16.3–48.1%
Died during continuation phase (n=36)	25 (69.4%)	51.9–83.7%

Note on transferred-out patients' TB treatment outcomes.

Table 2
A multivariable log-binomial regression model demonstrating predictors of unfavorable treatment outcome in children receiving TB treatment, central Ethiopia, 2014–2022.

Variable	TB treatment outcomes		RR (95% CI)	*p*-value	aRR (95% CI)	*p*-value
	Unfavorable	Favorable				
BCG vaccination (n = 524)						
Vaccinated	21 (6.7)	294 (93.3)	1.00			
Not vaccinated	14 (6.7)	195 (93.7)	1.00 (0.52–1.93)	0.989		
Sex (n=640)						
Male	23 (8.5)	249 (91.5)	1.00			
Female	19 (5.2)	349 (94.8)	0.61 (0.34–1.10)	0.10[a]	0.67 (0.40–1.13)	0.132
Nutritional status at treatment start (n=640)						
Normal	19 (4.3)	427 (95.7)	1.00			
Undernourished	23 (11.9)	171 (88.1)	2.78 (1.55–4.00)	0.001[a]	2.68 (1.53–4.71)	0.001[b]
Age category (n=640)						
≥10 years	16 (4.1)	373 (95.9)				
<10 years	26 (10.4)	225 (89.6)	2.52 (1.40–4.60)	0.003[a]	2.69 (1.56–4.61)	0.000[b]
HIV status (n=640)						
Negative	28 (5.0)	527 (95.0)				
Positive	14 (16.5)	71 (83.5)	3.26 (1.80–5.95)	0.000[a]	2.62 (1.50–4.59)	0.001[b]
TB category(n=640)						
New	38 (6.2)	579 (93.8)				
Relapse	4 (17.4)	19 (82.4)	2.82 (1.10–7.25)	0.031[a]	3.19 (1.79–5.70)	0.000[b]

[a] Selected for multivariable model.
[b] Significant at 5% significance level.

6. Discussion

We assessed the magnitude and identified predictors of unfavorable TB treatment outcome among children treated for presumptive drug-susceptible TB in 32 randomly selected healthcare facilities in central Ethiopia.

We found that approximately one in every fifteen (6.6%; 95% CI = 4.8–8.8%) children treated in those healthcare facilities had unfavorable TB treatment outcome. According to the complementary rule argument, the World Health Organization's recommended 2025 goal of a successful TB treatment outcome rate over 90% can be interpreted as unsuccessful or unfavorable outcome rate of less than 10% [3]. On this basis, the unfavorable outcome rate of 6.6% in our study can be considered low.

Similar percentages of unfavorable outcome were reported in recent studies conducted in Botswana (6.9%) [6], Pakistan (4.8%) [23], and Kenya (8.0%) [24], which defined unfavorable outcome as death, loss to follow-up, and treatment failure, as we did. A study in Ethiopia that involved the country's two largest regions, Oromia and Amhara, also discovered a similar amount of unfavorable outcome when transferred out was considered (4.0%; 95% CI = 3.9–4.9%) and when it was not considered (7.8%) as an unfavorable outcome category [8].

However, a higher percentage of unfavorable TB treatment outcomes were reported in studies conducted in eastern Ethiopia (11.4%; 95% CI = 10.0–12.9%) [11], Addis Ababa, Ethiopia (14.5%; 95%CI = 11.5–17.9%) [19], South Africa (14.1%; 95% CI = 13.7–14.5%) [10], and Mozambique (16.4%; 95% = 14.0–18.9%) [25]. The higher percentage could be explained by counting transferred outs as an unfavorable outcome. Despite not including transferred outs as an unfavorable outcome, the percentages of

Table 3
A multivariable log-binomial model that shows the effect of sustained under nutrition on TB treatment outcomes among children receiving TB treatment in central Ethiopia, 2014–2022.

Variable	TB treatment outcomes (n = 629)		RR (95% CI)	*P*-value	aRR (95% CI)	*p*-value
	Unfavorable	Favorable				
Sex						
Male	16 (6.0)	249 (94.0)	1.00			
Female	15 (4.1)	349 (95.9)	0.68 (0.34–1.36)	0.275		
Nutritional status after the first two months of treatment start						
Normal	16 (3.1)	497 (96.9)	1.00		1.00	
Undernourished	15 (12.9)	101 (87.1)	4.15 (2.11–8.14)	0.000*	3.76 (1.90–7.43)	0.000**
Age category						
≥10 years	14 (3.6)	373 (96.4)	1.00		1.00	
<10 years	17 (7.0)	225 (93.0)	1.94 (0.97–3.87)	0.059*	2.33 (1.18–4.60)	0.015**
HIV status						
Negative	21 (3.8)	527 (96.2)	1.00		1.00	
Positive	10 (12.3)	71 (87.7)	2.81 (1.34–5.88)	0.001*	2.26 (1.11–4.59)	0.024
TB category						
New	28 (4.6)	579 (94.4)	1.00		1.00	
Relapse	3 (13.6)	19 (86.4)	2.96 (0.97–8.99)	0.056*	2.81 (0.96–8.22)	0.059

unfavorable treatment outcome in a study conducted in Ethiopia's Tigray region (11.3%; 95% = 9.2–13.6%) and Pakistan (11.1%; 95% CI = 9.7%–12.6%) were higher than that of our study. The difference could be explained by a higher proportion of under-five-year-old children in the Tigray study (30%) [13] and the Pakistan study (66.6%) [18] as compared to lower proportion of 24.5% in our study, and younger age children are of course more prone to unfavorable treatment outcome [5,6,8,9,12,13]. Furthermore, the Balochistan province of Pakistan, where the study was conducted, shares a long porous border with war-ravaged Afghanistan and thus was home to a large number of refugees, where healthcare services are of poor quality on top of the province's high levels of poverty and malnutrition [26], and all of these disadvantages are understandably leading to a rise in magnitude of unfavorable TB treatment outcome in the setting. The higher proportions of unfavorable outcome reported by Adejumo et al. (21.3%; 95% CI = 17.9–25.0%) and Adamu et al. (47.5%; 95% CI = 41.7–53.3) in their studies conducted in Nigeria could be attributed to the fact that their study populations had a higher proportion of HIV-TB co-infection (29% and 33.3%, respectively) than ours (13.3%) [7,27].

The timing of the higher proportion of deaths in our study and a study in a large tertiary hospital in Nigeria is reversed. The majority of deaths (more than 75%) occurred during the intensive phase of treatment in the Nigeria study [7], whereas this proportion of deaths occurred later during the continuation phase in our study. Because the tertiary hospital was serving as referral centers for terminally ill patients' care, the early death rate may have been inflated, resulting in a higher proportion of unfavorable outcome during the intensive phase than during the continuation phase [7,28].

Many studies on childhood TB treatment outcomes did not consider the effect of under nutrition on TB treatment outcome [5,6,8,10,11,13,14,24,25]. However, a few studies that looked at the effect of undernutrition came to the same conclusion as ours: undernutrition is a risk factor for unfavorable treatment outcome [28,29]. Nutritional deficiencies contribute to TB disease progression and poor outcomes, whereas nutritional support improves treatment outcomes [29].

Prior research compared children on TB treatment who were under the age of five to those who were five or older and discovered that those under the age of five are at a higher risk of unfavorable outcome [5,6,9,12,30]. In our study, we compared children less than 10 years old to those 10 and older and discovered that those under 10 years old were also more likely to have an unfavorable treatment outcome.

Our finding that HIV infection is a risk factor for unfavorable TB treatment outcome is consistent with many other studies [6,7,9–11,24,28].

Relapsed TB was another risk factor identified by our study, and similar findings have been reported by other studies [5–7,14]. However, in our TB treatment phase-focused analysis, relapsed TB was not found to retain its significance to increased risk of unfavorable treatment outcome after the intensive phase of TB treatment, i.e. during the continuation phase of TB treatment, in contrast to other factors such as age less than 10 years, HIV infection, and sustained undernutrition, which demonstrated overall significance effect as well as during the continuation phases of TB treatment. There were no other studies that conducted treatment phase-focused analysis of unfavorable treatment outcome predictors that we could find.

In contrast to other studies which discovered that male sex is a risk factor for unfavorable outcome [9,11], our study did not identify sex as a risk factor. Of course, studies that found no link between demographic or clinical characteristics of childhood TB patients and treatment outcomes exist [31,32].

We did not find BCG vaccination status was associated with TB treatment outcomes as did studies in Pakistan [23] and Uganda [28].

The study's strength is that, to obtain valid statistics, we tracked down transferred out patients by phone and assigned them to a plausible treatment outcome categorization rather than classifying their treatment outcome as unsuccessful without further investigation into their true treatment outcomes.

The limitation of this study was that it did not assessed whether the deaths occurred at home or in inpatients receiving optimal care, which could have provided useful evidence for designing appropriate follow-up for the risky group during the continuation phase as well. Additionally, due to the nature of secondary data, we were unable to obtain data that separated TB types by severity, such as miliary TB, preventing us from analyzing unfavorable outcomes based on the severity of the types of TB.

7. Conclusion

The magnitude of unfavorable TB treatment outcome in children treated for TB in healthcare facilities in central Ethiopia was contained at levels as low as the 10% milestone recommended by WHO's End TB target for 2025.

Almost three-quarters of unfavorable TB treatment outcomes in children occurred during the continuation phase of TB treatment, indicating inadequate follow-up during the continuation phase of TB treatment.

Being younger than 10 years old, having relapsed TB, being undernourished at the start of TB treatment, and having HIV infection were discovered to be overall independent predictors of unfavorable TB treatment outcome in children. Being younger than 10 years old, suffering from persistent under nutrition, and being HIV positive remained independent predictors of an unfavorable TB treatment outcome even after the child entered the continuation phase, but relapsed TB did not.

As a key message, a substantial percentage of adverse TB treatment outcomes occur during the continuation phase of TB; therefore, the continuation phase of TB treatment should receive no less medical care and support than the intensive phase. Furthermore, our study is useful because it yielded information that suggests that nutritional supplementation for children getting TB therapy, even during the continuation phase, may improve TB treatment outcomes, however more evidence from interventional trials is required.

Funding source

There was no funding received.

Ethical approval statement

Ethical clearance was obtained from the Institutional Review Board (IRB) of College of Health Sciences, Addis Ababa University (protocol number: 057/19/SPH).

Data availability statement

The dataset for this study is submitted along with the manuscript as supplementary material.

CRediT authorship contribution statement

Abay Burusie: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Fikre Enquesilassie:** Conceptualization, Funding acquisition, Resources. **Nicole Salazar-Austin:** Data curation, Formal analysis, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Adamu Addissie:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28040.

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Annex-11. DECLARATION FORM

I, the undersigned declare that this is my original work, has never been presented in this or any other university, and that all the resources and materials used for the dissertation have been fully acknowledged.

Name: Abay Burusie adere

Signature: _____

Date: Sept. 2024

Place: Addis Ababa, Ethiopia

This dissertation has been submitted for examination with my approval as university supervisor.
Name: Dr. Adamu Addissie (PhD)

Signature: _____

Date: Sept. 2024