Tuberculosis-associated respiratory impairment and disability in children and adolescents: a systematic review

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Summary

Background While the immediate effects of pulmonary tuberculosis are well-documented, respiratory impacts persisting beyond treatment, particularly in children and adolescents, are less understood. This systematic review aimed to evaluate the current evidence on tuberculosis-associated respiratory impairment and disability in children and adolescents following tuberculosis treatment.

Methods We searched MEDLINE, Embase, CENTRAL, Global Index Medicus, and preprints from January 1, 2004, to December 5, 2024, to identify studies enrolling children (0–9 years old) or adolescents (10–19 years old) who completed treatment for microbiologically confirmed or clinically diagnosed pulmonary tuberculosis. Eligible studies measured at least one tuberculosis-associated respiratory impairment or disability outcome. Data were analyzed descriptively and stratified into three age groups based on median age of tuberculosis diagnosis: <5 years, 5–10 years, and >10 years. This study was prospectively registered (PROSPERO CRD42024529906).

Findings We identified 117 studies reporting tuberculosis-associated respiratory impairment or disability outcomes. Of those, five met our inclusion criteria, as over 80% of the identified studies excluded children and adolescents. Following tuberculosis treatment, children and adolescents exhibited significant respiratory impairments. In children <5 years of age, impairment included reduced tidal volume and peak tidal expiratory flow. Among those 5–10 years, approximately 40% exhibited abnormal lung function post-treatment, increasing to 65% in adolescents >10 years. Disability was frequently reported, with 35–50% of children and adolescents experiencing respiratory symptoms and children <10 years showing reduced growth metrics and a diminished quality of life.

Interpretation Even after successful tuberculosis treatment, children and adolescents can experience respiratory impairments and disability that may reduce their quality of life, ability to participate in activities, and growth potential. The epidemiology and clinical manifestations of these impairments vary by age, reflecting distinct biological and behavioural differences. Future research should prioritize these younger populations to ensure their unique needs and challenges are adequately represented.

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Research in context

Evidence before this study

In adults, up to 60% of tuberculosis survivors experience tuberculosis-associated respiratory morbidity, but its impact on children and adolescents remains poorly understood. We conducted a systematic review of tuberculosis-associated respiratory morbidity in children and adolescents, searching MEDLINE, Embase, CENTRAL, Global Index Medicus, and Europe PMC preprints from January 1, 2004, to December 5, 2024, without language restrictions. Comprehensive terms for 'tuberculosis,' 'impairment,' and 'disability' were used. Eligible studies were assessed for risk of bias using an adapted version of the ROBINS-E tool for observational studies.

Added value of this study

Of the 117 studies identified in our systematic search, only five—all published in 2023 and 2024—reported outcomes separately for participants under 19 years. Like adults, children and adolescents experience significant respiratory morbidity, with reduced tidal volume and peak tidal expiratory flow in children <5 years, abnormal lung function in 40% of children 5–10 years, and up to 65% of adolescents >10 years. Disability was also frequently observed, with 35–50% of children and adolescents experiencing respiratory symptoms and children <10 years of age exhibiting reduced growth metrics and a diminished quality of life.

Implications of all the available evidence

Children and adolescents can experience substantial and persistent respiratory impairments and disabilities following successful tuberculosis treatment, underscoring the critical need for early diagnosis and treatment in this population. However, limited geographic representation, variability in study design, outcome measures, timing of assessments, diagnostic certainty, and considerations of confounders complicate efforts to draw conclusions. These findings underscore the need to include younger populations in studies, establish standardized definitions and tools, and improve reporting on diagnostic certainty and disease severity. Addressing these gaps is critical to improving long-term health outcomes and informing future interventions for these populations.

Introduction

Tuberculosis remains a significant global health challenge, affecting over 10 million people annually, including more than 1 million children under 15 years of age.[1] While the immediate impacts of pulmonary tuberculosis are well-documented, there is increasing attention on the long-term consequences of this disease on respiratory health.[2] Tuberculosis-associated respiratory impairment and disability, also known as post-tuberculosis lung disease, results from the complex interplay of bacterial, host, and environmental factors.[3] Data from adult populations suggest that, despite completing treatment, up to 60% of tuberculosis survivors experience respiratory morbidity post-treatment.[4,5] However, the epidemiology and clinical characteristics of tuberculosis-associated respiratory morbidity in children and adolescents remain poorly understood.[6]

A previous review estimated that 1–49% of children and adolescents who survive pulmonary tuberculosis develop respiratory sequelae, marked by persistent symptoms and radiographic abnormalities.[7] However, no formal pulmonary function testing was done in the six included studies reporting these outcomes in the review. Several studies in this review also compared different treatment regimens and intermittent therapy, raising questions about whether the observed respiratory sequela was due to tuberculosis itself or inadequate treatment. Additionally, the results were aggregated for children and adolescents without considering the varied spectrum of disease and severities that occur in childhood and adolescence.[3,8]

Children >2 years are at higher risk for severe, disseminated pulmonary tuberculosis, while those aged 2–10 typically develop less disease that is concentrated in the intrathoracic lymph nodes but can extend to the lung parenchyma.[8,9] By adolescence (10–19 years), the clinical presentation shifts towards adult-type tuberculosis, with higher bacillary loads, greater parenchymal involvement, and the development of cavities and fibrosis.[10] As these clinical manifestations evolve throughout the life course, it is likely that the epidemiology and clinical features of tuberculosis-associated respiratory impairment and disability also change, with distinct phenotypes potentially emerging within different age groups.[3] Consequently, extrapolating data from adults or combining data between age groups is inappropriate, given the significant differences in tuberculosis presentation.

Respiratory infections during early life can profoundly impact lung function trajectories as lung development spans childhood and adolescence, leaving the respiratory system particularly vulnerable in these critical stages.[11,12] Tuberculosis during childhood and adolescence can, therefore, have a profound impact on long-term respiratory health.[3] A nuanced understanding of tuberculosis-associated respiratory impairment—characterized by lung function outside the normal z-score range (representing the 5th to 95th percentile of a healthy population)—and respiratory disability—which includes chronic symptoms like persistent cough, limitations in daily activities compared to peers, and growth impairments—is crucial. Such understanding is vital for

effectively managing this condition, advocating for necessary resources, and ensuring the inclusion of children and adolescents in studies aimed at identifying treatment and prevention strategies. Thus, this study aimed to systematically review the current evidence on tuberculosis-associated respiratory impairment and disability in children and adolescents following treatment completion and identify gaps in knowledge.

Methods

Search strategy and selection criteria

We systematically searched MEDLINE, Embase, CENTRAL, Global Index Medicus, and preprints through Europe PMC from January 1, 2004, to December 5th, 2024, using a broad search strategy developed with an academic librarian (Table S1). We chose these dates to reflect contemporary estimates of tuberculosis-associated respiratory morbidity. This review was reported according to PRISMA guidelines and prospectively registered in PROSPERO (CRD42024529906).[13]

Two reviewers (KR and SL) independently screened the titles, abstracts, and full texts, achieving consensus at each stage. Uncertainties regarding inclusion or exclusion were resolved by a third reviewer (JRC). Studies were included if they met the following criteria: were original research papers published in any language; used a cohort, cross-sectional, or trial study design; included participants with pulmonary tuberculosis, microbiologically confirmed or clinically diagnosed according to established criteria for childhood intrathoracic tuberculosis[14]; and reported at least one outcome of interest related to tuberculosis-associated respiratory impairment or disability in children or adolescents (see below). Children were defined as those 0–9 years of age, and adolescents as those 10–19 years of age.

Studies were excluded if they did not present outcomes separately for participants under 19 years of age, to ensure that results relevant to children and adolescents could be extracted and analyzed consistently. Studies were also excluded if they included fewer than 10 participants, included only participants with a self-reported history of tuberculosis diagnosis or treatment (e.g., from population-based questionnaires), or diagnosed past tuberculosis solely through radiological findings. Additionally, studies that only included participants with severe complications requiring surgical intervention or home ventilation were excluded to avoid selection bias toward severe impairment or disability.

Data extraction

Using a standardized form, one reviewer (KR) extracted data from the full-text articles, while another (SL) cross-checked the extracted data. The extracted data consisted of study characteristics, including enrollment period, country, population, inclusion criteria, and follow-up period; characteristics of the study population, including age, sex, height, weight, HIV status, tobacco and biomass exposure; details regarding tuberculosis disease, including diagnosis method, treatment regimen, and drug susceptibility; and outcome data, including the measure of tuberculosis-associated respiratory impairment or disability and the time from treatment initiation or completion to outcome measurement. We contacted the corresponding authors to address uncertainties or clarify missing information. Any clarifications or additional data provided were incorporated.

Outcomes

Our primary outcome focused on two aspects of tuberculosis-associated respiratory morbidity: (1) impairments in respiratory function and structure and (2) chronic respiratory symptoms and/or disability, defined as limitations in daily activities, including growth impairments, restrictions in participation, and reduced health-related quality of life. These outcomes were selected based on the terminology used by the WHO International Classification of Functioning, Disability, and Health (ICF), which offers a standardized language and framework for describing health and health-related states.[15]

Quality assessment

We evaluated the risk of bias in the included studies using an adapted version of the ROBINS-E tool for observational studies.[16] Two reviewers (KR and JRC) independently assessed each study across six domains: (1) confounding, (2) measurement of exposure, (3) selection of participants, (4) post-exposure interventions, (5) missing data, and (6) measurement of outcomes (Table S2). Using modified ROBINS-E tool algorithms, we assigned a risk of bias rating—low, medium, high, very high, or uncertain—to each domain. Any disagreements were resolved through discussion. As there is no detailed guidance for providing an overall risk of bias for each study, we did not assign an overall risk rating; instead, we considered the implications of such biases within our discussion.

Statistics

Due to the small number of studies identified and their heterogeneity, we performed a narrative synthesis without a meta-analysis. Based on the data available and known differences in clinical phenotypes across age groups, we stratified our synthesis into three age groups by median age at tuberculosis diagnosis: <5 years, 5–10 years, and >10 years. Study characteristics and key outcomes are summarized in tables and graphs.

Ethics

This study did not require specific ethical approval.

Role of funding source
Funding for this study was provided by the Robert E. Leet & Clara Guthrie Patterson Trust (USA) and the Canadian Institutes of Health Research. The funders had no role in the study design, data extraction, analysis, interpretation, or manuscript preparation.

Results

Of the 13,895 unique studies identified, 117 reported on tuberculosis-associated respiratory impairment or disability. Of those, only five met the inclusion criteria[17–21]; 94 did not include children or adolescents, 16 did not present outcomes separately for participants under 19 years of age, one included fewer than ten children or adolescents, and one study investigating lung disease in adolescents living with HIV did not present results stratified by tuberculosis history (Fig. 1).

The five included studies reported on tuberculosis-associated respiratory impairment and disability outcomes in children and adolescents in South Africa (n = 3)[17,18,21] and The Gambia (n = 2)[19,20] (Fig. 2). Two of the five studies were published in 2023[17,19] and three in 2024[18,20,21]; three were prospective cohort studies,[17,18,21] and two were cross-sectional.[19,20] Four studies included comparison populations without tuberculosis,[17–19,21] and three only included participants with drug-susceptible tuberculosis.[19–21] (Table 1). One included study was

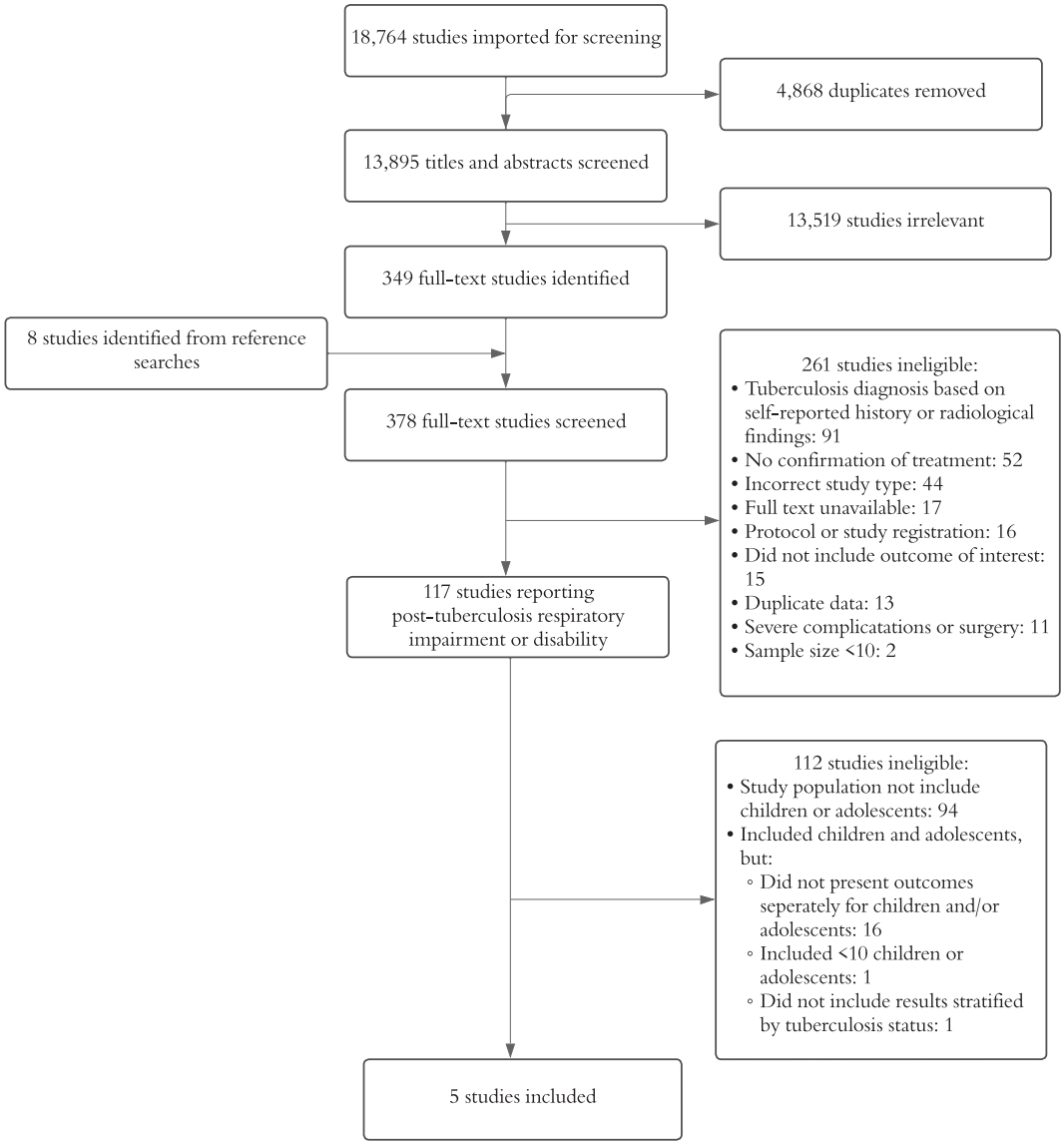

Fig. 1: PRISMA flowchart of selected studies.

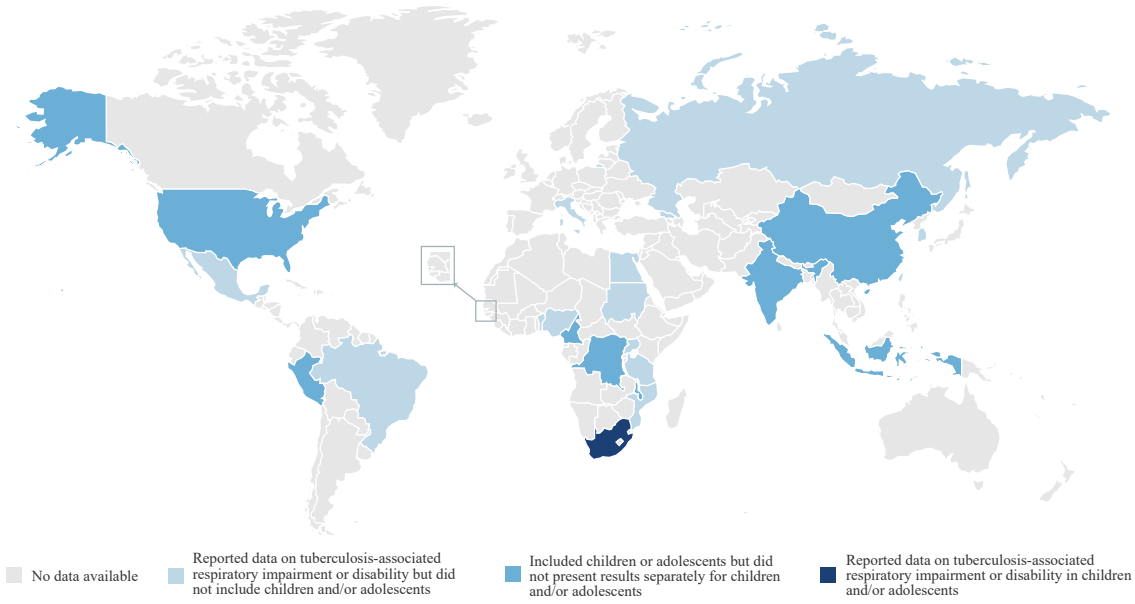

Fig. 2: Countries with studies reporting data on post-tuberculosis respiratory impairment and disability in children and/or adolescents.

published as a research letter and reported limited data.[21] To address this limitation, we contacted the corresponding author, who provided additional data that have been incorporated into our results.

All five studies were at elevated risk of bias due to confounding; four were classified as having a medium risk[17–19,21] and one as having a high risk of bias due to confounding,[20] primarily due to insufficient consideration of potential confounders (Table 2). Two studies were rated as having a medium risk of bias in the measurement of exposure due to a low proportion of participants with microbiologically confirmed tuberculosis.[17,19] However, it is important to note that both studies enrolled young children and followed established criteria for clinical tuberculosis diagnosis.[14] One study was rated as having a medium risk of bias in post-exposure interventions and measurement of outcomes due to an extended time interval between tuberculosis treatment completion and the assessment of outcomes.[19] Three studies were rated as having a medium risk of bias due to missing data, as outcome data were available for <90% of enrolled participants.[18,19,21]

All five studies reported at least one respiratory impairment outcome (Table 3). The outcomes varied considerably across studies and included measures of tidal breathing, spirometry, plethysmography, diffusion capacity, and chest x-ray findings.

One study, the Drakenstein birth cohort study, evaluated tuberculosis-associated respiratory impairment in children <5 years. This study included 1068 children, of whom 96 (9.0%) developed tuberculosis during 5 years of follow-up.[17] Of those, 13.0% (13/96) had confirmed tuberculosis. Follow-up assessments unrelated to tuberculosis were conducted at six weeks and one year of age and then annually until 5 years of age. Respiratory outcomes were presented separately for children diagnosed with tuberculosis between 0 and 1 year and 1–4 years of age. Children diagnosed between 0 and 1 year showed a reduced time to peak tidal expiratory flow (–2.4%, 95% CI –4.9, –0.2) and increased fractional exhaled nitric oxide (2.9 ppb, 95% CI 0.6, 5.2) at age 5, compared to children who remained tuberculosis-free at the age of 5. In contrast, children diagnosed between 1 and 4 years exhibited a reduced tidal volume (–9.3 ml, 95% CI –14.9, –3.8) and time to peak tidal expiratory flow (–2.7%, 95% CI –5.5, 0.0) at age 5 compared to those who remained tuberculosis-free.[17]

Two studies evaluated tuberculosis-associated respiratory impairment in children with a tuberculosis diagnosis between 5 and 10 years.[19,21] The first was a cross-sectional study that included 68 children who completed tuberculosis treatment, of which 24 (35.3%) had confirmed tuberculosis. The comparator population comprised 91 children from the same household without a history of tuberculosis. Outcomes were assessed at a median of 19.2 months (IQR 10.2, 44.4) after tuberculosis treatment completion. Among children with a history of tuberculosis, 38.5% (20/52) had abnormal spirometry, with 36.4% (19/52) showing possible restrictive disease. Among the comparator population, 17.4% (15/91) had abnormal spirometry, of which 15.1% (13/91) had possible restrictive disease.[19]

The second, a prospective cohort, included 69 (41%) children with microbiologically confirmed drug-susceptible pulmonary tuberculosis, 70 (41%) with clinically diagnosed pulmonary tuberculosis, and 30 (18%) with non-tuberculosis lower respiratory tract infections.[21] Spirometry outcomes were assessed at

Author (Year)	Study design	Enrollment period	Country	Total study N	Study population	Comparison population	TB population characteristics								
							Total TB N	Mircobiologically confirmed TB, %	Drug resistance, %	Prior TB, %	Male, %	Median age at diagnosis[a] (IQR)	Living with HIV, %	Exposed to tobacco smoke, %
Martinez (2023)	Prospective birth cohort	2012–2015	South Africa	1068	Children (0–5 yoa) enrolled in a prospective birth cohort	Children who remained healthy over the follow-up period	96[a]	13.0	1.0	5.0[d]	55.2	1.1 (0.5, 2.9)	0.0	38.5[c]
Nkereuwen (2023)	Cross sectional	2014–2019	The Gambia	159	Children and adolescents (5–15 yoa) treated for PTB	Children from the same household	68	35.3	0.0	0.0	52.9	6.5 (3.7, 9.3)	13.2	36.8
Gray (2024)	Prospective cohort	2015–2022	South Africa	169	Children and adolescents (5–15 yoa) with microbiologically confirmed clinically diagnosed PTB	Children (5–15 yoa) with non-TB lower respiratory tract infections	139	41.0	0.0	8.0[e]	51.0[e]	9.8[e] (7.4, 11.5)	11.0[e]	Unk
Nkereuwen (2024)	Cross sectional	2022–2023	The Gambia	79	Children and adolescents (≤19 yoa) treated for PTB	–	79	67.1	0.0	2.5	48.1	15.6 (11.8, 17.9)	10.1	74.7
van der Zalm (2024)	Prospective cohort	2020–2021	South Africa	100	Adolescents (10–19 yoa) with, microbiologically confirmed PTB	Healthy TB exposed adolescents from the same household	50	100.0	20.0	18.0	38.0	16.2 (2.0)[b]	10.0	24.0[f]

PTB, pulmonary tuberculosis; yoa, years of age; Unk, unknown. [a]95 pulmonary, 1 disseminated tuberculosis (tuberculosis meningitis). [b]Mean (SD) age. [c]Maternal antenatal smoking. [d]5% of children had two tuberculosis episodes. [e]Of all 169 children and adolescents included in the study, regardless of tuberculosis diagnosis. [f]Actively smoking.

Table 1: **Characteristics of included studies.**

baseline and months 1, 3, 6, and 12 months after treatment initiation for those diagnosed with tuberculosis, and at baseline and months 1 and 3 for those with non-tuberculosis lower respiratory tract infections. At 6 months after treatment initiation, 39.3% (33/84) of participants with tuberculosis had abnormal post-bronchodilator spirometry. When participants were stratified by diagnostic certainty, 46.0% (21/46) with microbiologically confirmed tuberculosis and 32% (12/38) with clinically diagnosed disease had this outcome. At 12 months post-treatment initiation, 36.4% of participants with tuberculosis had abnormal post-bronchodilator spirometry; this outcome was found in 45% (17/38) with microbiologically confirmed tuberculosis and 25% (7/28) with clinically diagnosed disease. Restriction was the most common spirometry pattern observed among those with abnormalities. In contrast, 33.0% (4/12) of participants with non-tuberculosis lower respiratory tract infections demonstrated abnormal spirometry at their 3-month follow-up assessment.

The two remaining studies evaluated tuberculosis-associated respiratory impairment in adolescents with a median age >10 years.[18,20] The first, a cross-sectional study conducted at a median of 1.2 weeks (IQR 0.8, 2.4) after tuberculosis treatment completion, included 79 participants who had completed treatment for tuberculosis.[20] Abnormal spirometry was observed in 57.0% (45/79) of all participants, 60.4% (32/53) of those with microbiologically confirmed tuberculosis, and 50.0% (13/26) of those with clinically diagnosed tuberculosis. Restrictive pattern was the most common spirometry abnormality observed, affecting 51.9% (41/79) of participants overall, 56.6% (30/53) of those with microbiologically confirmed tuberculosis, and 42.3% (11/26) of those with clinically diagnosed disease.

The second was a prospective cohort which assessed outcomes at a median of 13.3 months (IQR 11.7, 14.3) after treatment initiation in 100 adolescents, 50 (50.0%) with confirmed tuberculosis and 50 (50.0%) healthy, tuberculosis-exposed adolescents of similar age from the same household.[18] This study found 60% (22/37) of adolescents who had confirmed tuberculosis had abnormal spirometry, compared to 36% (16/45) of the controls. When results from plethysmography, diffusion capacity, and spirometry were combined, 65% (24/37) of adolescents with confirmed tuberculosis exhibited abnormal lung function, compared to 58% (26/45) of controls.[18]

Four studies also reported at least one chronic respiratory symptom or disability outcome, including anthropometric measurements, reduced health-related quality of life assessments or functional limitations measured by the 6-min walk test (Table 4).

Children <5 years diagnosed with tuberculosis had a higher risk of wheezing or recurrent wheezing, regardless of the timing of tuberculosis, and lower height-for-age z-scores (HAZ) compared to those without tuberculosis.[17]

	Confounding	Measurement of exposure	Selection of study participants	Post-exposure intervention	Missing data	Measurement of outcome
Martinez (2023)	Medium	Medium	Low	Low	Low	Low
Nkereuwen (2023)	Medium	Medium	Low	Medium	Medium	Medium
Gray (2024)	Medium	Low	Low	Low	Medium	Medium
Nkereuwen (2024)	High	Low	Low	Low	Low	Low
van der Zalm (2024)	Medium	Low	Low	Low	Medium	Low

Table 2: **Risk of bias among included studies.**

In children with a median tuberculosis diagnosis age between 5 and 10 years, 51.5% (35/68) reported respiratory symptoms compared to 37.4% (34/91) of children from the same household without a history of tuberculosis.[19] A greater proportion of children with a history of tuberculosis were stunted (HAZ < –2, 19.1% [13/68] vs. 6.6% [6/91]) and underweight (weight-for-age z-score [WAZ] < –2, 25.0% [17/68] vs. 20.9% [19/91]). These children also had significantly lower parent-reported quality-of-life scores.[19]

Among adolescents with a median tuberculosis diagnosis age >10 years, 35.4% (28/79) of participants in one study reported chronic respiratory symptoms, and 26.6% (21/79) were underweight.[20] Conversely, the other study found no significant difference in the 6-min walk distance (390 m [95% CI 340, 420] vs. 428 m [95% CI 390, 480]) between adolescents with and without a history of tuberculosis.[18]

Discussion

In this systematic review, we identified five studies that evaluated tuberculosis-associated respiratory impairment and disability in children and adolescents at varying ages and time points following tuberculosis treatment. The findings emphasize that, even after successful tuberculosis treatment completion, children and adolescents may experience significant respiratory impairments. These include reduced tidal volume and peak tidal expiratory flow in children <5 years of age. Among those aged 5–10 years, approximately 40% exhibited abnormal lung function, increasing to approximately 65% in adolescents >10 years of age. Furthermore, disability was frequently reported, with an estimated 35–50% of children and adolescents experiencing respiratory symptoms and children <10 years of age exhibiting reduced growth metrics and diminished quality of life.

One of the most striking findings from our review is that over 80% of studies on tuberculosis-associated respiratory morbidity published over the past two decades have excluded children and adolescents. This exclusion highlights the urgent need for research to include these younger populations to ensure they are adequately represented. Given the differences in the spectrum of tuberculosis disease, lung development, and underlying comorbidity differences between children, adolescents, and adults, age-disaggregated data are essential to fully understand the long-term impact of tuberculosis on respiratory health throughout the life course.[3,9,10]

Children <2 years are at risk for more severe forms of tuberculosis and disseminated disease.[8,10,22] In children aged 2–10 years, pulmonary tuberculosis often manifests as intrathoracic lymph node disease, which is less severe due to reduced parenchymal involvement.[8,10] As children transition into adolescence, the clinical presentation shifts towards adult-type tuberculosis, characterized by higher bacillary loads, increased lung parenchymal involvement, and more frequent cavitation and fibrosis.[10,23] Whether these clinical phenotypes, in combination with lung development, lead to different forms or risks of tuberculosis-associated respiratory morbidity remains uncertain. To clarify these associations, future studies should carefully characterize the spectrum of tuberculosis disease, including detailed information on disease severity at diagnosis and longitudinal follow-up.

Due to the paucibacillary nature of pulmonary tuberculosis in children ≤10 years of age, microbiological confirmation only occurs in 15–50% of children diagnosed.[14] Microbiological confirmation is more likely in severe episodes of tuberculosis, which, in turn, may be associated with a higher risk of tuberculosis-associated respiratory morbidity.

Indeed, South African children with clinically diagnosed pulmonary tuberculosis showed improvements in median FEV1 [forced expiratory volume]/FVC [forced vital capacity] z-scores six months after treatment completion.[21] In contrast, those with confirmed tuberculosis had decreased FEV_1/FVC at month 3, and this remained persistently low during follow-up, indicative of possible obstructive lung disease.[21] Given the lower certainty and possible severity of tuberculosis diagnosis in children with clinically diagnosed tuberculosis, future studies would benefit from stratified analyses of outcomes in children with microbiologically confirmed vs. clinically diagnosed tuberculosis.

Tuberculosis is a disease of poverty, often coinciding with risk factors such as HIV and exposure to smoke or

Median age at TB diagnosis	Measure	Author (year)	Timing of measurement[g]	Tool(s)	Outcome(s)							
<5	Lung function	Martinez (2023)[a]	At 6 weeks and 1 yoa and then annually until 5 yoa	Tidal breathing Respiratory impedance by oscillatory Fractional exhaled nitric oxide Multiple breath washout Lung clearance index	Children diagnosed with TB between 0 and 1 yoa had reduced time to peak tidal expiratory flow over total expiratory time (−2.4%, 95% CI −4.9, −0.2) and higher fractional exhaled nitric oxide (2.9 ppb, 95% CI 0.6, 5.2) at 5 yoa, compared with children who did not develop TB. Children diagnosed with TB between 1 and 4 yoa impaired tidal volume (−9.3 ml, 95% CI −14.9, −3.8) and time to peak tidal expiratory flow over total expiratory time (−2.7%, 95% CI −5.5, 0.0) at 5 yoa, compared with children who did not develop TB.							
5–10	Lung function				TB population, n/N (%)				Comparator population, n/N (%)			
					Abnormal	Restrictive	Obstructive	Mixed	Abnormal	Restrictive	Obstructive	Mixed
		Nkereuwen (2023)	Months since TB treatment completion: 19.2 (10.2, 44.4)	Post-bronchodilator spirometry	20/52 (38.5)	19/52 (36.4)[c]	1/52 (1.9)	0/52 (0.0)	15/86 (17.4)	13/86 (15.1)[c]	2/86 (2.3)	0/52 (0.0)
		Gray (2024)[e]	6 months after treatment initiation	Post-bronchodilator spirometry	33/84 (39.3)	29/84 (34.5)[c]	4/84 (4.8)	1/84 (1.2)	4/12 (33.0)	4/12 (33.0)[c]	0/12 (0.0)	0/12 (0.0)
			12 months after treatment initiation	Post-bronchodilator spirometry	24/66 (36.4)	15/66 (22.7)[c]	8/66 (12.1)	3/66 (4.5)				
					Abnormal	Restrictive	Obstructive	Mixed	Abnormal	Restrictive	Obstructive	Mixed
>10	Lung function	Nkereuwen (2024)	Weeks since TB treatment completion: 1.2 (0.8, 2.4)	Post-bronchodilator spirometry	45/79 (57.0)	41/79 (51.9)[c]	0/79 (0.0)	4/79 (5.1)	–	–	–	–
		van der Zalm (2024)	Months since TB treatment initiation: 13.3 (11.7, 14.3)	Post-bronchodilator spirometry	33/27 (60.0)[f]	10/37 (27.0)[c]	5/37 (14.0)	7/37 (19.0)	16/45 (36.0)[f]	13/45 (29.0)[c]	3/45 (7.0)	0/45 (0.0)
				Combination of plethysmography, diffusion capacity, and spirometry	24/37 (65.0)[b]	7/37 (19.0)[d]	5/37 (14.0)	7/37 (19.0)	26/45 (58.0)[b]	8/45 (18.0)[d]	3/45 (7.0)	0/45 (0.0)
									Abnormal CXR n/N (%)			
	Structural impairment	Nkereuwen (2024)	Weeks since TB treatment completion: 1.2 (0.8, 2.4)	Chest X-ray	37/78 (47.4)				–			

TB, tuberculosis; CXR, chest X-ray; aIRR, adjusted incidence rate ratio; yoa, years of age. [a]Results presented as regression coefficients. [b]Assessed as a combination of spirometry, plethysmography and diffusion capacity. [c]Possible restriction based on spirometry alone. [d]Restrictive disease defined as having an FEV/FVC ≥ −1.64 z-score and an FVC < −1.64 z-score and TLC <80% of predicted. [e]Additional data were obtained through correspondence with the study author. Comparator population measured at 3 months. [f]Pre-bronchodilator. [g]Presented as median (IQR) unless otherwise noted.

Table 3: **Tuberculosis-associated respiratory impairments in children and adolescents.**

Median age at TB diagnosis	Measure	Author (year)	Timing of measurement[d]	Tool(s) used	Outcome(s)	
<5	Respiratory symptoms	Martinez (2023)	At 6 weeks and 1 yoa and then annually until 5 yoa	Questionnaire[b] Wheeze diagnosed on auscultation by trained study staff	Children diagnosed with TB or those with a chest X-ray suggestive of TB were at higher risk of any wheeze (aIRR 1.9 [95% CI 1.1, 3.3]) or recurrent wheezing (aIRR 2.1 [95% CI 1.2, 3.7]).	
	Growth limitations	Martinez (2023)[a]	At 6 weeks and 1 yoa and then annually until 5 yoa	Anthropometric measures	Children diagnosed with TB between 0 and 1 yoa age had lower weight-for-age z-scores (−0.5, 95% CI −0.8, −0.2) and body mass index z-scores (−0.5, 95% CI −0.83, −0.25) at 5 years, compared with children who did not develop TB Children diagnosed with TB between 1 and 4 years of age had lower length-for-age z-scores (−0.4, 95% CI −0.7, −0.1) and weight-for-age z-scores (−0.3, 95% CI −0.6, 0.0) at 5 years, compared with children who did not develop TB	
5–10					**TB population**	**Comparator population**
					Chronic respiratory symptoms, n/N (%)	
	Respiratory symptoms	Nkereuwen (2023)	Months since TB treatment completion: 19.2 (10.2, 44.4)	Study questionnaire	35/68 (51.5)	34/91 (37.4)
				Cough	21/68 (30.9)	20/91 (22.0)
				Sputum	8/68 (11.8)	7/91 (7.7)
				Wheeze	6/68 (8.8)	9/91 (9.9)
					Stunting, n/N (%)[c]	
	Growth limitations	Nkereuwen (2023)	Months since TB treatment completion: 19.2 (10.2, 44.4)	Anthropometric measures	13/68 (19.1)	6/91 (6.6)
					Underweight, n/N (%)	
					17/68 (25.0)	19/91 (20.9)
	Health related quality of life	Nkereuwen (2023)	Months since TB treatment completion: 19.2 (10.2, 44.4)	PedsQL V.4.0	**Parent-reported quality of life total score, median (IQR)**	
					82.6 (71.7, 93.5)	91.3 (82.6, 97.8)
					Child-reported quality of life total score, median (IQR)	
					73.9 (65.2, 89.1)	78.3 (64.7, 89.1)
>10					**Chronic respiratory symptoms, n/N (%)**	
	Respiratory symptoms	Nkereuwen (2024)	Weeks since TB treatment completion: 1.2 (0.8, 2.4)	St. George Respiratory Questionnaire	28/79 (35.4)	–
				Cough	21/79 (26.6)	–
				Sputum	14/79 (17.2)	–
				Shortness of breath	9/79 (11.4)	–
					Stunting, n/N (%)[c]	
	Growth limitations	Nkereuwen (2024)	Weeks since TB treatment completion: 1.2 (0.8, 2.4)	Anthropometric measures	8/79 (10.1)	–
					Underweight, n/N (%)	
					21/79 (26.6)	–
					Distance walked, m (IQR)	
	Functional limitations	van der Zalm (2024)	Months since TB treatment initiation: 13.3 (11.7, 14.3)	6-min walk test	390 (340, 420)	428 (390, 480)

TB, pulmonary tuberculosis; yoa, years of age. [a]Results presented as regression coefficients. [b]Adapted from the International Study of Asthma and Allergies in Childhood. [c]Defined as a height-for-age z-score less than −2 SD for age and sex. [d]Presented as median (IQR) unless otherwise noted.

Table 4: **Tuberculosis-associated respiratory symptoms and disability in children and adolescents.**

biofuels, which can independently contribute to respiratory morbidity.[24,25] The high prevalence of these risk factors in certain settings can result in significant background respiratory morbidity, making it difficult to attribute respiratory impairment solely to tuberculosis, particularly in high-tuberculosis burden settings. For example, van der Zalm et al. (2024) reported that 58% of healthy adolescents from the same socio-economic background as those with tuberculosis had lower-than-expected lung function,[18] underscoring the complexity of disentangling the respiratory sequelae of tuberculosis from the impact of other coexisting factors. This finding also highlights the importance of accounting for confounding factors such as passive smoking, air pollution,

recurrent respiratory tract infections, and HIV when evaluating the contribution of tuberculosis to respiratory morbidity. Furthermore, many of these exposures, such as passive smoking, not only exacerbate respiratory health outcomes but also increase the risk of tuberculosis infection and disease.[25] Thus, prevention of these exposures is necessary not only to reduce the initial risk of tuberculosis but also to reduce its subsequent respiratory consequences.

This systematic review provides a focused narrative synthesis of the existing literature on tuberculosis-associated respiratory impairment and disability in children and adolescents, exploring both impairments in respiratory function and structure and limitations in activities and quality of life. While obtaining reliable lung function in young children, especially pre-school age, can be challenging, the included studies employed comprehensive respiratory assessments conducted per international guidelines to ensure the reliability and standardization of measurements. Three studies utilized prospective, longitudinal designs to help establish temporal relationships between tuberculosis and subsequent health outcomes,[17,18,21] and four studies incorporated comparison populations, enhancing the ability to differentiate tuberculosis-related effects from other potential confounding factors.[17–19,21] Longitudinal analysis in the Drakenstein birth cohort study revealed that lung impairment following tuberculosis in early childhood was independent of premorbid lung function,[17] while both the South African child and adolescent cohorts showed lung function improvement during treatment.[18,21] These data suggest that tracking of lung function from tuberculosis diagnosis until beyond treatment completion will provide valuable insights into the recovery or decline of lung impairment over time and into adulthood —information critically needed to design and evaluate interventions and effectively support those affected.

This review has notable limitations that reflect the constraints of the current literature. First, the limited number and relatively small sample sizes of the eligible studies restrict our ability to identify patterns and trends across different populations, age groups, and settings or to detect meaningful differences or associations, particularly in subgroup analyses. Second, with data geographically limited to children and adolescents in South Africa and The Gambia, generalizability is restricted, especially to regions with differing demographics, healthcare systems, and risk profiles. Significant heterogeneity in study design, outcome measures, and the timing of assessments further complicate efforts to draw comprehensive conclusions across studies. A universal definition, standardized measurement tools, consensus on severity grading, and optimal assessment timing are essential to enhancing our understanding and management of this condition in children and adolescents (Panel 1).

Panel 1: **Knowledge gaps and future research priorities.**

- **Inclusive research design**: Children and adolescents must be included in studies of tuberculosis-associated respiratory disability to ensure these populations are adequately represented, given the differences in epidemiology and clinical spectrum of disease across age groups. For future studies, we suggest presenting age-stratified results by the following age categories: <5, 5–10, >10 years. Furthermore, longitudinal follow-up, although not always feasible, will give additional important data on the impact of childhood tuberculosis on adult lung health.
- **Clinical spectrum and certainty of tuberculosis diagnosis:** The clinical spectrum and certainty of tuberculosis diagnosis is likely linked to the severity of tuberculosis disease, which may influence the risk of tuberculosis-associated respiratory impairment and disability. To better understand these associations, we recommend including detailed information on the clinical spectrum and diagnostic certainty, including radiological features at diagnosis and before treatment completion. Stratified analyses by confirmed vs. clinically diagnosed tuberculosis would also be of value.
- **Comparator groups**: Where possible, local comparator groups with no history of tuberculosis should be included to discern tuberculosis-associated morbidity from non-tuberculosis-associated morbidity. Local comparator groups are important also because international reference ranges may not accurately represent these populations.
- **Geographic representation**: Current evidence is limited to children and adolescents in South Africa and The Gambia. Expanding research to diverse geographic regions with varying tuberculosis and risk factor prevalence will enhance the generalizability of findings and provide a more comprehensive understanding of tuberculosis-associated respiratory impairment and disability in children and adolescents globally.
- **Lung impairment screening**: Research indicates that spirometry alone may fail to detect lung function abnormalities. Thus, additional lung function tests, including plethysmography, diffusion capacity, and oscillometry, should be considered to fully assess overall lung health outcomes, especially in populations that are unable to perform spirometry, such as preschool-aged children, the elderly and the very sick.
- **Impact on quality of life and daily activities**: The impact of tuberculosis-associated respiratory impairment and disability on health-related quality of life and daily activities among children and adolescents remains poorly understood and requires further investigation to better understand the broader implications of the disease.
- **Data harmonization:** The absence of a comprehensive universal definition and severity grading for tuberculosis-associated respiratory impairment and disability, standardized measurement tools, and a consensus on the optimal assessment timing impedes our understanding of this condition in children and adolescents. Future research should focus on establishing standardized definitions, including severity grading and determining the optimal timing and frequency of these assessments.

Key risk factors for tuberculosis-associated respiratory morbidity in children and adolescents must also be carefully considered. This includes not only factors such as active or passive smoking and vaping (both ante- and postnatally),[24] previous episodes of tuberculosis,[26] lower respiratory tract infections, and asthma,[27,28] but also HIV[29] and nutritional status,[30] and the broader context of local governments' support for tuberculosis control programs. These factors are known to affect lung health and may exacerbate the severity of tuberculosis-associated respiratory conditions. Addressing them is essential not only for accurately assessing the true burden and determinants of tuberculosis-associated respiratory morbidity in childhood and adolescence but also for ensuring the findings are interpreted in the appropriate regional and contextual framework. Moreover, understanding these factors is vital for recognizing the childhood origins of the disease and its long-term impact on lung health. Future studies should, where feasible, include local comparator populations and gather comprehensive data on environmental exposures, smoking/vaping behaviors, age, weight, sex, HIV status, and pre-existing respiratory conditions (Panel 1).

In summary, this systematic review identified five studies that evaluated tuberculosis-associated respiratory impairment and disability in children and adolescents across different ages and time points. The review revealed significant respiratory morbidity, which increased with age, underscoring the critical need for early diagnosis and treatment of tuberculosis in this population, alongside efforts to improve overall lung health in children and adolescents. Additionally, these findings emphasize the importance of including children and adolescents in studies examining tuberculosis-associated respiratory outcomes, establishing standardized definitions, tools, and assessment timing, and ensuring comprehensive reporting of tuberculosis diagnostic certainty, disease severity and confounding factors. Addressing these gaps is vital to improving long-term health outcomes and informing future interventions for younger populations.

Contributors

JRC, MMvdZ, SC, and KR conceived the study and developed the protocol. KR and SL were responsible for searching the literature and extracting data. KR and JRC conducted the risk of bias assessment. KR, JRC, SC, and MMvdZ interpreted the data. KR wrote the initial draft of the manuscript. SL, SC, MMvdZ and JRC were responsible for critical revisions of the manuscript and provided important intellectual content. KR and SL verified the underlying data, and all authors had full access to all data in the study. All authors read and approved the final version of the manuscript.

Data sharing statement

All data are available in this Article.

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Declaration of interests

JRC has received consulting fees from the World Health Organization, World Bank, and Saskatchewan Auditor's Office. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103107.

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