Impaired lung function in adolescents with pulmonary tuberculosis during treatment and following treatment completion

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eClinicalMedicine
2024;67: 102406
Published Online 3 January 2024
https://doi.org/10.1016/j.eclinm.2023.102406

Summary

Background Little is known about post-tuberculosis lung disease in adolescents. We prospectively assessed lung function in adolescents with microbiologically confirmed pulmonary tuberculosis during treatment and after treatment completion.

Methods In a prospective study, we enrolled adolescents diagnosed with microbiologically confirmed tuberculosis and healthy tuberculosis-exposed household controls, between October 2020 and July 2021 in Cape Town, South Africa. Spirometry, plethysmography, diffusion capacity lung function tests and 6-min walking test (6MWT) were completed according to international guidelines 2 months into treatment and following treatment completion. Abnormal lung function was defined as abnormal spirometry (z-score < –1.64 for forced expiratory volume in 1 s (FEV_1) and/or forced vital capacity (FVC) and/or FEV_1/FVC), plethysmography (total lung capacity (TLC) < 80% of predicted, residual volume over TLC of >45%) and/or diffusion capacity (DLCO z-score < –1.64).

Findings One-hundred adolescents were enrolled; 50 (50%) with tuberculosis and 50 (50%) healthy tuberculosis-exposed controls. Of the 50 adolescents with tuberculosis, ten had multidrug-resistant tuberculosis. Mean age of the group was 14.9 years (SD 2.7), 6 (6.0%) were living with HIV and 9 (9.0%) were previously treated for tuberculosis. Lung function improved over time; during treatment abnormal lung function was found in 76% of adolescents with tuberculosis, compared to 65% after treatment completion. Spirometry indices were lower in adolescents with tuberculosis compared to controls, both at 2 months and after treatment completion. Plethysmography in adolescents with tuberculosis showed that air-trapping was more common during treatment than in controls (12% vs 0%, respectively, p = 0.017); which improved following treatment completion. Adolescents with tuberculosis both during and after treatment completion walked a shorter distance than controls.

Interpretation Adolescents with tuberculosis have impaired lung function even after treatment completion. It is crucial to include adolescents in trials on the prevention and treatment of tuberculosis-associated respiratory morbidity.

Funding EDCTP, National Institute of Health, Medical Research Council, BMBF.

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Keywords: Tuberculosis; Adolescents; Morbidity; Lung health; Post-tuberculosis

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Research in context

Evidence before this study

Despite microbiological cure achieved in most adults, a substantial proportion experience respiratory morbidity after completion of tuberculosis treatment. Despite the high burden of tuberculosis in adolescents, who typically develop adult-type disease, there are limited data on respiratory morbidity in adolescents after successful tuberculosis treatment. A recent systematic review and meta-analysis on the magnitude, and factors associated with, post-tuberculosis lung disease in low- and middle-income countries identified 8 studies which included adolescents, but data were not specifically reported for adolescents as a subgroup.

Added value of this study

This is the first study to comprehensively assess lung function in adolescents with tuberculosis during anti-tuberculosis treatment and after treatment completion. Our data show that two thirds of the adolescents with tuberculosis had abnormal lung function after treatment completion, defined as abnormal spirometry (forced expiratory volume in 1 s (FEV_1) and/or forced vital capacity (FVC) and/or FEV_1/FVC < z-score −1.64), plethysmography (total lung capacity (TLC) < 80% of predicted, residual volume (RV) over TLC of >45%) and/or diffusion capacity (DLCO < −1.64). Adolescents with TB had a significant increased odds of having impaired spirometry lung function compared to controls during treatment and after treatment completion. After treatment completion, plethysmography showed a higher RV and a slightly higher RV/TLC ratio in adolescents with tuberculosis compared to controls. Diffusion capacity was similar between groups. Adolescents with tuberculosis walked a shorter distance during the 6-min walking test during treatment and after treatment completion. The lung function of the local control group was also lower than expected according to international reference ranges.

Implications of all the available evidence

Post-tuberculosis disease outcomes are not yet routinely included in global tuberculosis programmes, although there is substantial tuberculosis-associated morbidity. Our data suggest that a large proportion of adolescents with microbiologically confirmed tuberculosis have impaired lung function following successful treatment completion. Strategies are required to identify individuals at risk for respiratory morbidity and interventions are needed to improve lung health after tuberculosis. Moreover, our data shows that it is crucial to include adolescents in studies that investigate prevention and treatment of tuberculosis-associated respiratory morbidity.

Introduction

There is increased awareness that life after pulmonary tuberculosis is associated with respiratory morbidity. Data from adults suggest that despite microbiological cure achieved in the majority of individuals with pulmonary tuberculosis, a substantial proportion of adults experience respiratory morbidity after treatment completion.[1–3] A recent systematic review and meta-analysis showed that 59% of individuals that had spirometry after treatment completion had abnormal lung function, with 22% having obstruction, 23% having restriction and 15% mixed pattern.[4] To date, disaggregated data on tuberculosis-associated respiratory morbidity in adolescents are lacking and only limited number of adolescents have been included in adult studies.[5,6]

The incidence of tuberculosis increases during adolescence after a nadir in primary school-aged children. Each year an estimated 850,000 adolescents develop tuberculosis disease, with an estimated 90% living in low- and middle-income countries.[7,8] Adolescents who develop tuberculosis often present with 'adult-type' pulmonary tuberculosis that is sputum microscopy smear-positive, indicating severe disease.[7] The risk for adolescents to develop tuberculosis-associated respiratory morbidity, similar to adults, is therefore substantial.[4,9,10]

Despite similarity in tuberculosis pathogenesis with adults, adolescents face unique challenges associated with their age and developmental stage, such as growth and behavioural aspects which can affect the developing lungs of adolescents and influence the impact of tuberculosis on lung health. Adolescence is an important period for lung growth which continues until early adulthood.[11] Any respiratory disease, including tuberculosis, can potentially interfere with normal lung growth processes during this stage. Tuberculosis during adolescence could therefore negatively affect the ability to reach full lung potential.[11] Furthermore, adolescents may be more susceptible to engage in behaviours that can exacerbate the impact of tuberculosis on their growing lungs, such as smoking, delayed health seeking behaviour resulting in more severe disease. With the combination of the high tuberculosis burden, severity of tuberculosis disease, behavioural aspects, and the critical period in lung development, adolescents may have more tuberculosis-associated respiratory morbidity compared to adults. With longer life expectancy after tuberculosis compared to adults, adolescents may contribute substantially to the overall disability burden caused by tuberculosis.[9,10]

Multiple studies in adults have shown that spirometry alone underestimates residual respiratory morbidity.[5,12] In adults who experienced at least one

pulmonary tuberculosis episode, air trapping and impaired diffusion capacity were more common than restrictive lung disease, which would have been missed by evaluating lung function using spirometry alone.[12] Therefore comprehensive assessment of lung function is needed in order to accurately assess the burden of respiratory morbidity in adolescents. In this study, we aimed to investigate the impact of pulmonary tuberculosis on adolescent lung health and compared this to tuberculosis-exposed healthy adolescent controls.

Methods

Study design and setting

This was a prospective, longitudinal, observational study. Study eligibility and recruitment has been described elsewhere.[13] In brief, 50 adolescents aged 10–19 years, with and without HIV co-infection, with newly diagnosed microbiologically confirmed (sputum Xpert® MTB/RIF-positive, Xpert Ultra-positive or *Mycobacterium tuberculosis* culture-positive) pulmonary tuberculosis were enrolled from October 2020 through July 2021 in Cape Town, South Africa. Fifty tuberculosis-exposed, healthy and not previously treated for tuberculosis, adolescent controls from the same households were recruited, as a local control group for lung function measurements. Some households contributed to more than one control while others did not contribute any controls. Adolescents with both drug-susceptible and multidrug-resistant (i.e., *M. tuberculosis* resistant to both isoniazid and rifampicin) tuberculosis disease or exposure (control group) were included.

The study was approved by the health ethics research committee of Stellenbosch University (N19/10/148) and was conducted in accordance with South African Good Clinical Practice guidelines. Written consent was obtained for adolescents 18–19 years and both written consent from parents/guardians and assent were obtained for adolescents 10–17 years.

Study procedures

Adolescents with microbiologically confirmed tuberculosis were enrolled within the first 14 days of tuberculosis treatment and followed up 2 months later and again 12 months following enrolment. Tuberculosis treatment was given according to the National Tuberculosis program within routine care services. Healthy tuberculosis-exposed controls from the same household underwent study procedures, including lung function measurements, at enrolment only. Controls were carefully assessed to exclude tuberculosis disease. Demographic and clinical data, including clinical examination, were collected at enrolment. Microbiological samples were collected and analysed at the National Health Laboratory Service. Body Mass Index for age z-scores (BAZ) and height for age z-scores were calculated using the World Health Organization anthropometry calculator.

All adolescents had chest X-rays (CXR; posterior-anterior and lateral) at enrolment. Severe disease on CXR was defined as tuberculosis affecting more than one lobe, the presence of cavities, miliary pattern, complex pleural effusion or intrathoracic lymph node disease with significant airway obstruction or bilateral airway narrowing. CXRs were read by a tuberculosis expert (HSS).

Lung function assessment was done at Tygerberg Hospital Lung Function Laboratory by a qualified technologist. Due to hospital infection control protocols, the first full lung function was completed 2 months following initiation of anti-tuberculosis treatment and repeated after treatment completion, 12 months later. Measurements included spirometry pre- and post-bronchodilation, plethysmography and diffusion capacity. Spirometry was done using the Jaeger full MasterScreen (Jaeger™ Corp. Germany, 2011, system V532.0.5 CD-Version 5.72.1.77). Forced Expiratory Volume in 1 s (FEV_1), Forced Vital Capacity (FVC) and the FEV_1/FVC ratio was measured, including post-bronchodilation using 400 µg of salbutamol to assess reversibility. Lung function measurements were completed according to European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines.[14] A minimum of three, and up to eight attempts were carried out per participant. Acceptability and repeatability were assessed and the best value of three attempts was used for analysis. We included only lung function measurements that met the ERS/ATS quality criteria for acceptable and repeatable measurements.[14] Body plethysmography was done to measure total lung capacity (TLC), Functional Residual Capacity (FRC), residual volume (RV), RV/TLC ratio and airway resistance (Raw). Diffusion capacity was done using the single breath technique to measure lung diffusion capacity for carbon monoxide (DL_{CO}). Diffusion capacity was done in a limited number of adolescents because the gasses were out of stock for long periods during the COVID-19 pandemic. Global lung initiative (GLI) reference ranges were used to calculate z-scores, using the ethic reference category "other" which has previously been shown to be the best fit for the South African population.[15,16] A 6-min walk test (6MWT) was done according to ATS guidelines, measuring distance walked in metres and desaturation incidents.[17,18]

While we aimed to assess all participants at 12 months following enrolment, following treatment completion, there was some variability in the timing of this visit due to logistical issues, in part due to successive waves of COVID-19 and associated restrictions.

Statistical analysis

We compared baseline socio-demographic characteristics and reported symptoms at enrolment between adolescents with tuberculosis and controls using t-tests or Wilcoxon rank-sum tests for continuous variables and

Pearson's χ^2 or Fisher's exact tests categorical variables, based on the distribution of the data. We visually assessed normality using histograms and Q–Q plots and used the Shapiro–Wilk test to statistically assess whether the data were normally distributed and used Levene's test to assess homogeneity of variance. We used a Fisher's exact test wen the expected value of cells was below 5 in 80% of cells or when the expected value in a cell was below 1. Standardized z-scores for the different lung function measurements were reported as medians and interquartile ranges (IQRs). The median difference and 95% confidence interval (95% CI) was estimated between adolescents with tuberculosis (at month 2 and following treatment completion) and tuberculosis-exposed healthy controls. We also compared the lung function measurements of adolescents with tuberculosis at 2 months to that following treatment completion, using a repeated measures ANOVA for categorical variables and a paired t-test or Wilcoxon signed-rank test for continuous variables. The normality of difference assumption for the paired t-test was assessed visually using a histogram and Q–Q plot.

The absolute number and proportion of adolescents with tuberculosis and controls with an abnormal FEV_1, FVC, FEV_1/FVC were described and compared using Pearson's χ^2 or Fisher's exact tests, as was the number of participants with an obstructive, restrictive, or mixed pattern, and those with air-trapping. An abnormal FEV_1, FVC or FEV_1/FVC was defined as a z-score less than the predicted lower limit of normal (LLN; similar to z-score < –1.64). Airflow obstruction was defined as a post-bronchodilator FEV_1/FVC ratio of less than the predicted LLN, with an FVC higher than the predicted LLN. A restrictive pattern on spirometry was defined as a normal FEV_1/FVC in combination with an FVC less than the predicted LLN or as restrictive disease (using plethysmography) if the TLC was less than 80% of predicted. Air-trapping on plethysmography was defined as an RV/TLC of greater than 45%. A low DL_{CO} was defined as values of less than LLN. Abnormal lung function was defined as FEV_1 <–1.64 z-score, FEV_1/FVC < –1.64 z-score, FVC < –1.64 z-score, TLC <80% of predicted, RV/TLC< 45% and DLCO < –1.64 z-score. Odds ratios (OR), with 95% CI were calculated for lung function patterns using logistic regression.

In order to assess the impact of important risk factors for poor lung health on lung function measurements, we did separate sensitivity analyses excluding adolescents who (i) smoked tobacco, (ii) had tuberculosis previously, (iii) had multidrug-resistant tuberculosis, and (iv) were living with HIV. Analyses were conducted in Stata (v15.1, StataCorp, College Station, TX, USA).

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

A total of 100 adolescents were included; 50 (50%) adolescents with pulmonary tuberculosis, including 10 with multidrug-resistant tuberculosis (20%) and 50 (50%) controls. Of the 100 participants, one (1%) was a screening failure and one (1%) control was diagnosed with tuberculosis after enrolment and both were excluded from analyses because study procedures were not done according to study protocol (Fig. 1).

Forty-seven (47%) adolescents were male and 6 (6%) were living with HIV (Table 1). Adolescents with tuberculosis were older (mean 16.4 years (standard deviation (SD) 2.0) vs mean 13.4 years (SD 2.5), p < 0.001), had a lower BAZ (median –1.04 (IQR –2.03, –0.31) vs 0.23 (IQR 0.-0.86, 0.67), p = 0.003), and more often smoked (36% vs 12%, p = 0.005) than controls. Household smoke exposure was common in 68% of all adolescents. Nine (18%) adolescents with tuberculosis had a previous history of tuberculosis. The most commonly reported symptoms among those with tuberculosis were cough (n = 42, 84%), wheeze (n = 20, 40%), loss of appetite (n = 21, 42%), and loss of weight (n = 39, 78%). Thirty-eight (74%) adolescents with tuberculosis had adult-type disease on CXR; one CXR was reported as normal.

A total of forty-nine controls had lung function measurements done at enrolment, of whom 4 (8%) did not meet quality criteria for acceptability and repeatability during the spirometry and were excluded from analyses.

Of the forty-eight adolescents with tuberculosis seen at 2-month assessment, 6 (13%) did not meet quality criteria (Fig. 1). Final lung function measurement was done following treatment completion, 12 months later. Forty-one (85%) adolescents with tuberculosis had repeat lung function measurements following treatment completion; 4 (10%) did not meet quality criteria. The median time between treatment initiation and post treatment assessment was 13.3 months (IQR 11.7, 14.3). Of the ten adolescents with multidrug-resistant tuberculosis, eight (80%) came for the post-treatment assessment, of whom two (25%) were still on anti-tuberculosis treatment; they were included in the analysis. The other 39/41 (95%) adolescents had completed treatment. One adolescent died, which was unrelated to tuberculosis.

To demonstrate a difference in spirometry between healthy adolescents (assumed to have a FEV1/FVC ratio of 100%; SD: 15%), and adolescents with pulmonary tuberculosis disease (assumed to have a ratio of 90%), with 80% power and an alpha of 0.05, we needed 36 healthy controls and 36 adolescents with pulmonary tuberculosis at each time-point.

Spirometry

At month 2, pre- and post-bronchodilation spirometry z-scores for FEV_1, FVC and FEV_1/FVC, were lower in

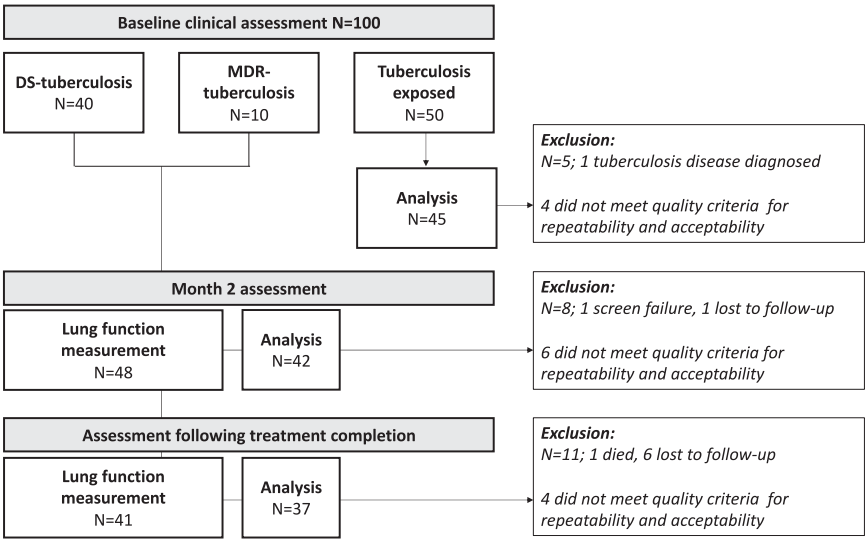


***Fig. 1:* Flowchart of study participants**. **Legend**: A total of 100 adolescents, 50 with pulmonary tuberculosis and 50 healthy tuberculosis-exposed controls, were enrolled into the study. Adolescents exposed to tuberculosis were only assessed at baseline. Adolescents with drug-susceptible or multidrug-resistant tuberculosis were enrolled at baseline (<2 weeks on treatment) and lung function was done both 2 months and following treatment completion. Lung function that did not meet quality criteria for repeatability and acceptability according to ERS/ATS guidelines were removed from the data-analysis, but if they had an acceptable quality lung function measurement at the next visit this data was analyzed. **Abbreviations**: DS, drug-susceptible; MDR, multidrug-resistant.

adolescents with tuberculosis compared to controls (Table 2, Fig. 2). There was an improvement of FEV_1 and FVC following treatment completion in adolescents with tuberculosis compared to month 2 assessment (Table 2, Supplemental Figure S1). However, after treatment completion, all values except for FVC, remained lower in adolescents with tuberculosis compared to controls. There was an increased odds of having an abnormal FEV_1, FVC or FEV_1/FVC ratio in adolescents with tuberculosis compared to controls during treatment and for FEV_1 and FEV_1/FVC after treatment completion (Table 3).

Plethysmography

Plethysmography initially showed a lower vital capacity in adolescents with tuberculosis than controls (median difference –0.70, 95% CI –1.10, –0.33), which improved after treatment completion (median difference 0.24, 95% CI –0.38, 0.85) (Table 2). TLC was initially slightly lower in adolescents with tuberculosis than controls (median difference 0.39, 95% CI –0.03, 0.88) with an overall higher RV and RV/TLC ratio (Table 2, Fig. 3). After treatment completion, the TLC and RV/TLC ratio was similar to controls, with a higher RV in adolescents with tuberculosis (median difference –0.46, 95% CI –0.70, –0.19). Airway resistance (Raw) was higher in controls compared to those with tuberculosis, which did not change in adolescents after treatment completion (median difference 0.11, 95% CI 0.02, 0.17). Overall, there was some improvement of plethysmography indices in those with tuberculosis after 2 months of treatment compared to after treatment completion (Table 2, Supplemental Figure S2).

Air-trapping, defined as an RV/TLC ratio of more than 45%, was more frequent in adolescents with tuberculosis compared to controls (12% versus 0% respectively, p = 0.017) (Table 3). The proportion of adolescents with tuberculosis who had air-trapping decreased after treatment completion. Restrictive lung disease was seen in 31% of adolescents with tuberculosis compared to 18% of controls (OR 2.1, 95% CI 0.8, 5.7), which improved after treatment completion to 19% (OR 1.1, 95% CI 0.4, 3.3). Mixed lung function patterns were seen in adolescents with tuberculosis and not in controls.

Diffusion capacity

Diffusion capacity was similar between individuals with tuberculosis after 2 months of treatment and controls (median difference 0.54, 95% CI –1.16, 2.09) (Table 2, Supplementary Figure S3). This remained comparable after treatment completion. In total, 36% of adolescents with tuberculosis and 14% of controls had an abnormal diffusion capacity after 2 months of treatment (OR 3.4, 95% CI 0.6, 19.4) and 27% after treatment completion had an abnormal (OR 2.3, 95% CI 0.4, 13.2) (Table 3).

Six-minute walking test

Adolescents with tuberculosis walked a median distance of 405 m [IQR 360,445] during the 6MWT, while

	All (n = 100)	Controls (n = 50, 50%)	Adolescents with tuberculosis disease (n = 50, 50%)	p-value
	N[a] (%)	N[a] (%)	N[a] (%)	
Demographics				
Male	47 (47%)	28 (56%)	19 (38%)	0.071
Age (years), mean [SD]	14.9 (2.7)	13.4 (2.5)	16.4 (2.0)	<0.0001
HAZ, median [IQR]	−0.69 [−1.32, 0.45]	−0.76 [−1.51, −0.02]	−0.48 [−1.34, 0.14]	0.551
BAZ, median [IQR]	−0.37 [−1.47, 0.04]	0.23 [−0.86, 0.67]	−1.04 [−2.03, −0.31]	0.003
Household smoke exposure	68 (68%)	37 (74%)	31 (62%)	0.198
Cooking				1.000
Paraffin	0 (0%)	0 (0%)	0 (0%)	
Coal	3 (3%)	2 (4%)	1 (2%)	
Electric	97 (97%)	48 (96%)	49 (98%)	
Heating source				
Paraffin	7 (7%)	3 (6%)	4 (8%)	0.500
Coal	4 (4%)	3 (1%)	1 (2%)	0.617
Electric	81 (81%)	43 (86%)	38 (76%)	0.308
Active smoking	24 (24%)	6 (12%)	18 (36%)	0.005
Living with HIV	6 (6%)	1 (2%)	5 (10%)	0.204
Previous tuberculosis	9 (9%)	0 (0%)	9 (18%)	0.003
Underlying comorbidities (not HIV or previous or current tuberculosis)	3 (3%)	2 (4%)	1 (2%)	1.000
Presenting signs and symptoms				
Cough	44 (44%)	2 (4%)	42 (84%)	
Wheeze	20 (20%)	0 (0%)	20 (40%)	
Fever	7 (7%)	0 (0%)	7 (14%)	
Loss of appetite	21 (21%)	0 (0%)	21 (42%)	
Decreased energy	2 (2%)	0 (0%)	2 (4%)	
Loss of weight	40 (40%)	1 (2%)	39 (78%)	
Chest X-rays				
Normal chest X-ray[b]	44 (45%)	43 (88%)	1 (2%)	
Adult type disease	NA	NA	37 (74%)	

Abbreviations: SD, standard deviation; BAZ, BMI for age z-score; BCG, Bacillus Calmette–Guérin; BMI, body mass index; cm, centimetre; CXR, chest x-ray; HIV, human immunodeficiency virus; IQR, interquartile range; kg, kilogram; WAZ, weight for age z-score. **Legend**: p-values were calculated using Pearson's Chi square or Fisher's exact tests for categorical variables, and t-tests and rank sum tests for continuous variables. [a]Unless otherwise indicated. [b]2 missing, 1 in the adolescents with tuberculosis and 1 in the control group.

Table 1: **Characteristics of study participants at baseline.**

controls walked a median of 428 m [IQR 390,480] (median difference 30, 95% CI 0, 60) (Table 2). Desaturation was uncommon among both adolescents with tuberculosis (n = 4, 10%) and controls (n = 1, 2%, p = 0.192). After treatment completion, there was no improvement in distance walked in adolescents with tuberculosis (Table 2, Supplementary Figure S4).

Abnormal lung function, assessed as a combination of spirometry, plethysmography and diffusion capacity was seen in 58% of controls compared to 76% of adolescents after 2 months of treatment (OR 2.3, 95% CI 0.9, 5.9), and 65% after tuberculosis treatment completion (OR 1.3, 95% CI 0.5, 3.3).

Sensitivity analysis

Sensitivity analyses excluding important risk factors for lung health (smoking, previous tuberculosis, and multidrug-resistant tuberculosis) did not change our findings (Supplementary Tables S1–S4).

Discussion

This is the first study to prospectively and comprehensively assess lung health in adolescents with tuberculosis during treatment and following treatment completion. Our findings indicate that a substantial portion of adolescents with microbiologically confirmed tuberculosis have impaired lung function even after treatment completion, which was lower compared to healthy controls from the same household and setting and lower compared to international reference ranges.

The fact that adolescents with tuberculosis after successful treatment have overall lower lung function compared to their peers is concerning because this might mean that they will not be able to reach their full potential when they reach adulthood, with the subsequent risk of developing chronic lung disease early on in life. Studies have shown that even mild or subclinical impairment of lung function is associated with increased risk of cardio-respiratory events later in life.[19]

	Controls	Adolescents with tuberculosis disease		Difference between controls at baseline and adolescents with tuberculosis at 2 months[a]	Difference between controls at baseline and adolescents with tuberculosis after treatment completion[a]	p-value for difference between adolescents with tuberculosis at 2 months and following treatment completion[b]
	Baseline	2 months	Following treatment completion	Median difference (95% CI)	Median difference (95% CI)	p-value
Spirometry	N = 45	N = 42	N = 37			
Pre-bronchodilation						
FEV_1, z-score	−1.04 [−1.61, −0.39]	−2.08 [−3.15, −1.05]	−1.90 [−3.04, −0.69]	1.14 (0.52, 1.77)	0.89 (0.21, 1.61)	0.0001
FVC, z-score	−0.97 [−1.74, −0.26]	−1.86 [−2.95, −0.95]	−1.44 [−2.67, −0.55]	0.97 (0.37, 1.57)	0.58 (−0.06, 1.25)	<0.0001
FEV_1/FVC, z-score	−0.04 [−0.55, 0.52]	−0.77 [−1.53, 0.36]	−0.82 [−1.88, −0.04]	0.63 (0.15, 1.12)	0.72 (0.25, 1.33)	0.343
MEF_{25}, z-score	−0.21 [−0.85, 0.25]	−1.19 [−2.95, −0.15]	−1.19 [−2.56, 0.11]	1.04 (0.34, 1.69)	0.94 (0.21, 1.70)	0.165
Post-bronchodilation						
FEV_1, z-score	−0.71 [−1.57, −0.06]	−1.67 [−2.84, −0.54]	−1.52 [−2.72, −0.27]	1.10 (0.49, 1.81)	0.81 (0.10, 1.52)	0.0003
FVC, z-score	−0.84 [−1.82, −0.33]	−1.91 [−3.15, −0.94]	−1.31 [−2.77, −0.54]	0.91 (0.27, 1.57)	0.40 (−0.24, 1.08)	<0.0001
FEV_1/FVC, z-score	0.65 [0.17, 1.11]	−0.23 [−0.73, 0.67]	−0.34 [−1.38, 0.87]	0.71 (0.29, 1.13)	0.74 (0.16, 1.41)	0.551
MEF_{25}, z-score	0.27 [−0.30, 1.09]	−0.51 [−2.36, 0.60]	−0.43 [−1.90, 0.75]	1.01 (0.35, 1.78)	0.75 (0.13, 1.61)	0.177
Plethysmography	N = 45	N = 42	N = 37			
FRC, z-score	−0.25 [−0.66, 0.28]	−0.31 [−1.07, 0.32]	0.18 [−0.39, 0.71]	0.13 (−0.28, 0.55)	−0.31 (−0.69, 0.05)	0.032
TLC, z-score	−1.43 [−1.76, −0.95]	−1.66 [−2.63, −0.88]	−1.43 [−2.07, −0.74]	0.39 (−0.03, 0.88)	0.13 (−0.27, 0.52)	0.253
IC, z-score	−1.53 [−2.02, −0.80]	−1.66 [−2.73, −1.10]	−1.99 [−2.62, −1.25]	0.44 (−0.02, 0.88)	0.49 (0.05, 0.91)	0.639
RV, z-score	−0.23 [−0.54, 0.13]	0.23 [−0.34, 0.86]	0.34 [0.00, 0.58]	−0.40 (−0.73, −0.07)	−0.46 (−0.70, −0.19)	0.404
RV/TLC, z-score	0.31 [0.00, 0.76]	1.22 [0.40, 1.54]	0.98 [0.16, 1.63]	−0.70 (−1.10, −0.33)	−0.55 (−0.92, 0.13)	0.045
VC, z-score	−1.89 [−2.47, −1.06]	−2.55 [−3.42, −1.57]	−1.99 [−2.98, −0.94]	0.72 (0.18, 1.32)	0.24 (−0.38, 0.85)	0.0002
Resistance, kPa*s/L	0.56 [0.42, 0.63]	0.44 [0.35, 0.55]	0.42 [0.35, 0.48]	0.08 (0.02, 0.16)	0.11 (0.02, 0.17)	0.823
Diffusion capacity	N = 14	N = 22	N = 22			
DLCO, z-score	−0.34 [−1.12, 0.80]	−0.30 [−1.89, 0.77]	−0.49 [−1.65, 0.49]	0.54 (−1.16, 2.09)	0.30 (−0.85, 1.64)	1.000
6MWT	N = 45	N = 42	N = 29			
Distance (m)	428 [390, 480]	405 [360, 445]	390 [340, 420]	30 (0, 60)	54 (20, 80)	0.531
Desaturation (%)	1 (2%)	4 (10%)	0 (0%)	0.192[c]	1.000[c]	0.162

Abbreviations: 95% CI, 95% confidence interval; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; MEF_{25}, maximum expiratory flow at 25% FVC; FRC, functional residual capacity; TLC, total lung capacity; IC, inspiratory capacity; RV, residual volume; VC, vital capacity; DLCO, diffusing capacity of the lungs for carbon monoxide; 6MWT, 6 Minute Walking Test; m, meters. **Legend:** Unless otherwise indicated. [a]Hodges-Lehmann median difference. [b]p-values were calculated using a repeated measures ANOVA for categorical variables and a paired t-test or Wilcoxon signed-rank test for continuous variables. [c]p-values were calculated using Pearson's Chi square or Fisher's exact tests for categorical variables.

Table 2: **Functional assessment of controls at baseline and adolescents with tuberculosis disease at follow-up.**

As a result, these adolescents are at risk of permanent long-term cardio-respiratory morbidity.

Comprehensive lung function assessment showed that only one third of the adolescents with tuberculosis had normal lung function after treatment completion. Restrictive lung disease was the most frequently observed disease pattern, which is similar to what is commonly reported in most adult studies[4] and a recent study from the Gambia in young children (median age 9 years).[20] Published data on restrictive lung disease after tuberculosis are heterogenous which can be partly explained by studies assessing restrictive lung disease using spirometry only. Assessment of lung volumes and a TLC below LLN are formally required to determine restrictive disease. While restriction was most common, the proportion of adolescents with restrictive disease decreased following treatment completion. This is in line with findings from other studies that suggest a decrease of restrictive disease seen over time with an increase in proportion of obstructive disease.[3,4,12]

Similar to studies conducted in adults, our study revealed the presence of air-trapping in a subset of adolescents after treatment completion, indicating possible small-airway disease.[12] In contrast to some adult data, our findings demonstrated an improvement of air-trapping and potential small-airway disease, over time. It remains uncertain whether our assessment of lung function was conducted prematurely, potentially overlooking further progression of small-airway disease in the adolescents at a later stage or if there is further improvement expected over time. To answer this question, long-term follow-up of these adolescents is needed until lung function has stabilized.

There were no differences in diffusion capacity between adolescents with tuberculosis and the control group. Abnormal diffusion capacity is a common finding in adult studies, with some research reporting

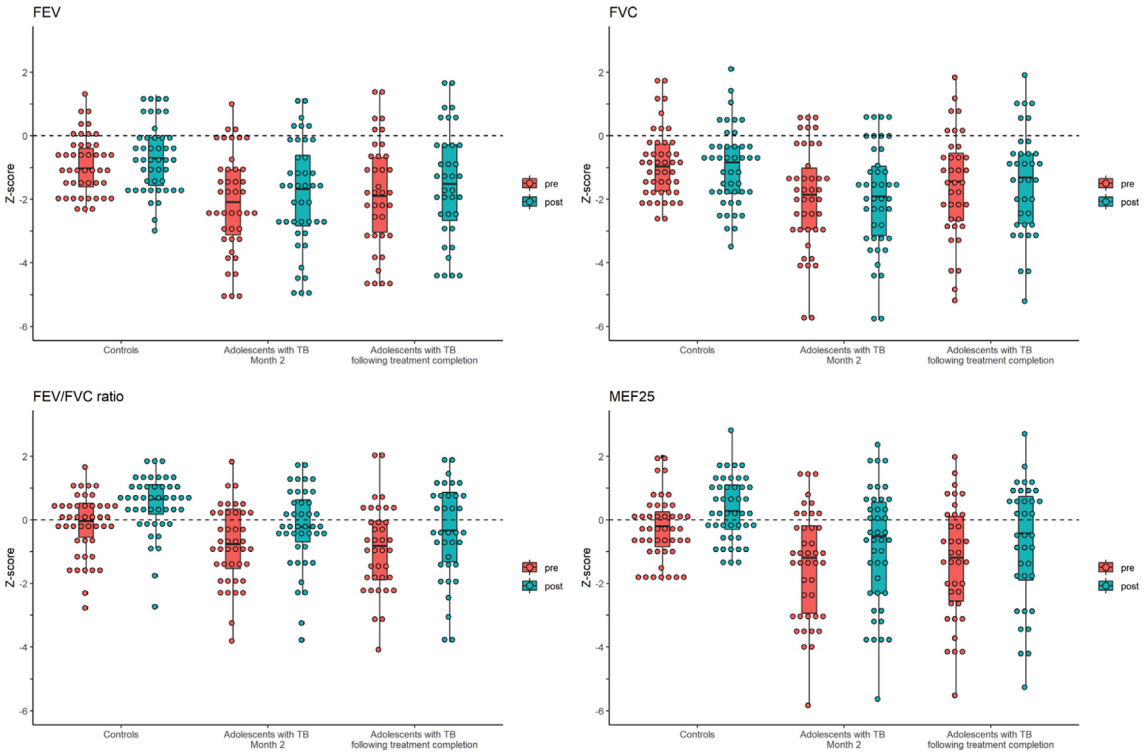


Fig. 2: **Spirometry lung function measurements in controls at baseline and adolescents with tuberculosis disease at month 2 and following treatment completion. Abbreviations**: FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; MEF_{25}, maximum expiratory flow at 25%. Pre = pre bronchodilation (in red). Post = post bronchodilation (in green). The boxplot indicates the median, interquartile range, range and outliers of the Z-score. The dots indicate the individual Z-scores. Outliers are defined as values that are outside of the expected range, e.g., data points that are below the minimum (lower quantile—1.5*interquartile range) or above the maximum (upper quantile + 1.5*interquartile range) values.

rates as high as 80%.[12] The exact mechanisms behind the reduced diffusion capacity are not yet fully understood, however, one hypothesis is that changes occur in the vasculature of the broncho-vascular bundle in and around the small airways.[12] Due to limited numbers our study cannot confirm or exclude the possibility of

	Controls (n = 45)	Adolescents with tuberculosis		Adolescents with tuberculosis vs controls	
		Month 2 (n = 42)	Following treatment completion (n = 37)	Month 2	Following treatment completion
	n (%)	n (%)	n (%)	OR (95% CI)	OR (95% CI)
Abnormal lung function[a]	26 (58%)	32 (76%)	24 (65%)	2.3 (0.9–5.9)	1.3 (0.5–3.3)
Abnormal FEV_1[b]	11 (24%)	25 (60%)	21 (58%)	4.4 (1.8–11.4)	4.1 (1.6–10.4)
Abnormal FVC[b]	13 (29%)	23 (55%)	17 (46%)	3.0 (1.2–7.2)	2.1 (0.8–5.2)
Abnormal FEV_1/FVC[b]	3 (7%)	10 (24%)	12 (32%)	4.4 (1.1–17.2)	6.7 (1.7–26.1)
Obstructive[c]	3 (7%)	3 (7%)	5 (14%)	1.1 (0.2–5.7)	2.2 (0.5–9.8)
Restrictive pattern (spirometry only)[d]	13 (29%)	16 (38%)	10 (27%)	1.5 (0.6–3.7)	0.9 (0.3–2.4)
Restrictive disease[e]	8 (18%)	13 (31%)	7 (19%)	2.1 (0.8–5.7)	1.1 (0.4–3.3)
Mixed[f]	0 (0%)	7 (17%)	7 (19%)	0.005[i]	0.003[i]
Airtrapping[g]	0 (0%)	5 (12%)	3 (8%)	0.017[i]	0.052[i]
Abnormal diffusion capacity[h]	2/14 (14%)	8/22 (36%)	6/22 (27%)	3.4 (0.6–19.4)	2.3 (0.4–13.2)

Abbreviations: FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; TLC, total lung capacity; RV, residual volume; 95% CI, 95% confidence interval. [a]Defined as FEV_1< −1.64 z-score, FEV_1/FVC < −1.64 z-score, FVC < −1.64 z-score, TLC <80% of predicted, RV/TLC > 45% and DLCO < −1.64 z-score. [b]Defined as a measurement of <1.64 z-score. [c]Defined as having a FEV/FVC < −1.64 z-score and an FVC ≥ −1.64 z-score. [d]Defined as having a FEV/FVC ≥ −1.64 z-score and an FVC < −1.64 z-score. [e]Defined as having a FEV/FVC ≥ −1.64 z-score and an FVC < −1.64 z-score and TLC <80% of predicted. [f]Defined as a FEV/FVC < −1.64 z-score and an FVC < −1.64 z-score. [g]Defined as RV/TLC >45%. [h]Defined as DLCO < −1.64 z-score. [i]p-values were calculated using Pearson's Chi square or Fisher's exact tests for categorical variables.

Table 3: **Lung function patterns in controls at baseline and adolescents with tuberculosis disease at follow-up.**

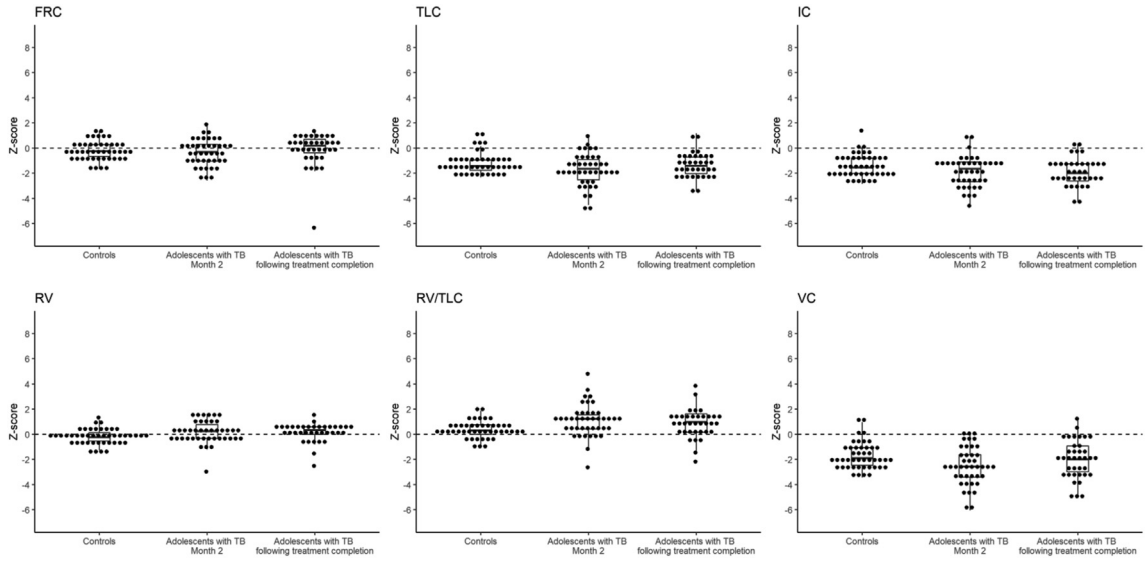


Fig. 3: **Plethysmography lung function measurements in controls at baseline and adolescents with tuberculosis disease at month 2 and following treatment completion**. **Abbreviations**: FVC; FRC, functional residual capacity; TLC, total lung capacity; IC, inspiratory capacity; RV, residual volume; VC, vital capacity; TB, tuberculosis. The boxplot indicates the median, interquartile range, range and outliers of the Z-score. The dots indicate the individual Z-scores. Outliers are defined as values that are outside of the expected range, e.g., data points that are below the minimum (lower quantile—1.5*interquartile range) or above the maximum (upper quantile + 1.5*interquartile range) values.

diffusion abnormalities in adolescent tuberculosis survivors. Overall, our findings indicate that spirometry alone may fail to detect lung function abnormalities. Therefore, additional lung function tests including plethysmography and diffusion capacity should be considered to fully assess overall lung health outcomes.

The 6MWT is a relatively easy test to perform with limited resources and the results of the 6MWT could indicate a meaningful real-life impact on daily functioning. Our findings showed that adolescents with tuberculosis were not able to walk the same distance compared to controls during treatment and after completion, even though they were generally older and taller. However, these results should be interpreted with caution, firstly because of reduced number of tests especially after treatment completion and secondly since a poor correlation between lung function and 6MWT has been previously reported.[21,22] More data are needed in order to assess the value of the 6MWT as a lung health assessment tool in children and adolescents.

Multidrug-resistant tuberculosis has been linked to worse lung health outcomes compared to drug-susceptible tuberculosis.[4] Our findings, however, did not find significant differences between adolescents with multidrug-resistant tuberculosis and those with drug-susceptible tuberculosis. Given only 10 adolescents had multidrug-resistant tuberculosis, it is possible that the sample size was too small to detect differences. The same was the case for adolescents living with HIV. The HIV prevalence in our study was lower than numbers that have been reported in our community, which limits generalizability of our study. Most adolescents living with HIV were co-infected with tuberculosis (5 out of 6). Of the adolescents with tuberculosis and HIV, 3 were not on anti-retroviral therapy. Data from Kenya in adolescents living with HIV showed that a previous history of pulmonary tuberculosis was associated with poor lung function.[23] More prospective data are needed to investigate the impact of tuberculosis, including multidrug-resistant tuberculosis and HIV co-infection on lung health.

Of concern is the fact that a substantial proportion of the healthy adolescents had lower than expected lung function compared to international reference ranges. We used the GLI 'other' reference ranges, as this has been shown to fit our mixed South African population best,[16] however, this was not the case for our healthy adolescents. This could be partly explained by the fact that these adolescents came from lower socio-economic communities, with high household smoke exposures than the study that validated these reference ranges for the South African population. Risk factors for poor lung function are often found in lower socio-economic communities and include tobacco smoke exposure, indoor air-pollution (recurrent) respiratory infections, HIV infection and poor nutrition leading to stunting and wasting.[24–26] However, by using this group as controls, even though only at baseline, we recruited individuals with similar socio-economic circumstances to those with tuberculosis disease and so differences

between groups would likely be the result of tuberculosis rather than other confounding factors.

Our study has some limitations. First, all adolescents with tuberculosis had microbiologically confirmed tuberculosis, with mostly severe radiological disease on CXR and therefore may have represented a more severe spectrum of tuberculosis disease. Second, adolescents with tuberculosis were older, more frequently smokers compared to controls and some had a history of previous tuberculosis. Age may have impacted many aspects of lung function and risk factors for lung impairment. Previous studies have found that age, smoking and previous tuberculosis are associated with an increased risk for tuberculosis and also for lung function impairment[27–29] Although we did assess the impact of smoking and previous tuberculosis diagnoses on lung impairment in a sensitivity analysis, we did not see any change in the lung measurements when excluding participants with these risk factors. We also used age-corrected z-scores in our analyses. However, there might be residual confounding, from other risk factors, that could have affected our results and were not accounted for. Further, we aimed to see all adolescents with tuberculosis at 12 months following enrolment, and after treatment completion, there was some variability in the timing of this visit and two adolescents with multidrug-resistant tuberculosis were still on treatment. Future studies would benefit from repeat lung function measurements in control groups in order to correct for long-term tracking of lung function in adolescence.

In conclusion, these data show that lung function in adolescents with pulmonary tuberculosis is impaired even after treatment completion. Despite the increased awareness on tuberculosis-associated respiratory morbidity, global tuberculosis programs and clinical trials for new tuberculosis regimens do not currently incorporate routine assessment of tuberculosis disease outcomes. Our results show that adolescents urgently need to be included in studies investigating prevention and treatment of tuberculosis-associated respiratory morbidity; this includes the need to assess lung health as an outcome within tuberculosis treatment trials in adolescents. Conducting a comprehensive assessment of lung health, as done in this study, may not be feasible in routine care settings with limited resources, particularly in areas with a high burden of tuberculosis. Consequently, there is an urgent need for accessible and cost-effective tools that can identify children and adolescents at risk for tuberculosis-associated respiratory morbidity.

Contributors

Conceptualization: MMvdZ, JAS.
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Review of methods and interpretation of results: all authors.
Initial draft: MMvdZ, VWJ, JAS.
Writing and editing article: all authors.
Approval of final draft: all authors.

Data sharing statement

Datasets with selected aggregated data are available upon reasonable request. Proposals should be directed to JAS and MMVDZ. Individuals who request data will be asked to sign a data access agreement.

Declaration of interests

MMVDZ is supported by a career development grant from the EDCTP2 program supported by the European Union (TMA2019SFP-2836 TB lung-FACT2), the Fogarty International Center of the National Institutes of Health under Award Number K43TW011028.

JAS is supported by a Clinician Scientist Fellowship jointly funded by the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement (MR/R007942/1). BA is supported by a grant for TB Sequel Network from German Federal Ministry for Research and Education (BMBF).

Acknowledgements

The authors would like to thank the study participants and families for their participation.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102406.

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