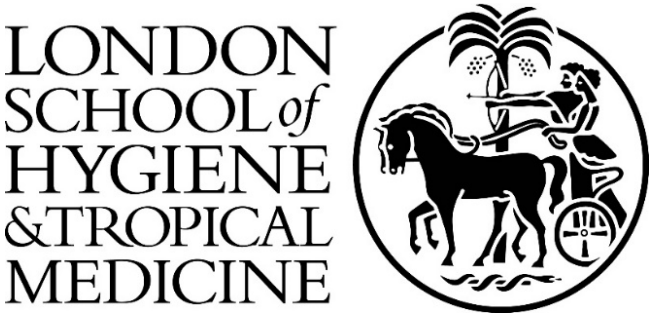

Evaluating the sequelae of pulmonary tuberculosis in Gambian children and adolescents

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Declaration

I, Esin Esin Nkereuwem, hereby declare that the work presented in this thesis is my original work and constitutes my own independent research. Where information has been derived from other sources, I have acknowledged and referenced them appropriately within the thesis.

Esin Esin Nkereuwem

Date: 18th November 2024

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Abstract

Pulmonary tuberculosis (pTB) remains a significant public health challenge, particularly in low- and middle-income countries such as The Gambia, where the disease burden is substantial. Despite advancements in treatment, the long-term health impact on children and adolescents who survive the disease is often not fully addressed. This dissertation evaluates the sequelae of pTB in Gambian children and adolescents, focusing on both physical and psychosocial outcomes while identifying key factors contributing to these outcomes.

This research employed a combination of cross-sectional, longitudinal cohort, and qualitative study designs. The first objective involved assessing lung function and health-related quality of life (HRQoL) in children and adolescents previously diagnosed with and treated for pTB. The findings revealed that a significant proportion of these children suffer from impaired lung function, most commonly manifesting as restrictive lung disease. This impairment was strongly associated with declines in HRQoL, particularly in physical functioning, with children and their caregivers reporting substantial challenges in daily activities. These physical impairments are not isolated issues but are closely linked to the overall well-being of the individuals.

The second objective was to conduct a review of existing literature on paediatric post-TB lung disease (PTLD). The review found that there were critical gaps in the current research, especially the lack of standardised definitions and measurement tools for PTLD. This makes it difficult to compare findings across studies and hinders the development of practical guidelines for clinical practice, especially for younger children who are frequently excluded from research due to diagnostic challenges. The review also emphasised the need for more focused research on this vulnerable population to better understand the long-term impacts of pTB.

The third objective of the research was to determine the prevalence and pattern of residual respiratory impairments at the completion of pTB treatment and to describe how these impairments evolve over a 12-month period. The results showed that over half of the participants had impaired lung function immediately after treatment, and these impairments persisted—and in some cases worsened—over the subsequent year. Several key risk factors were identified, including older age at diagnosis, undernutrition, and the presence of fibrosis on chest X-rays. These factors were significant predictors of long-term respiratory health outcomes, underscoring the need for targeted interventions for at-risk groups.

The fourth objective of the study explored the psychosocial dimensions of surviving pTB through qualitative interviews. The research revealed that the physical sequelae of pTB are accompanied by social and emotional challenges, including stigma, social isolation, and disruptions to education and future aspirations. These challenges are not just secondary to the disease but are deeply connected to its physical effects, further complicating the recovery process and impacting the

overall quality of life of TB survivors. The findings suggest that the stigma associated with ongoing symptoms, such as chronic coughing, often leads to significant social withdrawal and emotional distress, which in turn worsens the physical health challenges faced by these young survivors.

Overall, these findings underscore the multifaceted and interconnected impact of pTB on young people, highlighting the urgent need for a comprehensive approach to TB management. Such an approach should extend beyond just achieving microbiological cure to include long-term care strategies that address both the physical and psychosocial challenges faced by TB survivors. The implications of this research are significant for public health policy in The Gambia and similar settings, as integrating post-TB care into national TB programmes has the potential to improve the overall health outcomes of children and adolescents recovering from TB, ensuring that their recovery is holistic and sustainable.

Acknowledgements

This thesis would not have been possible without the unwavering support of my supervisors, Prof Beate Kampmann and Dr Toyin Togun. Your expertise, patience, and encouragement have guided me through every challenge. I am fortunate to have had you both as mentors, and your dedication to my success has been instrumental in my growth. I am also thankful to my advisory board members, Prof Ginny Bond and Dr Schadrac Agbla. Your timely guidance played a crucial role in shaping this research. Prof Andrew Bush, thank you for your support during my time at Imperial and beyond.

The Childhood TB Research Team has been the backbone of this project: Abdoulie Tunkara, Dr Amie Secka, Dr Aunty Nyima Fofana, Awa Baldeh, Bernice-Helen Ameh, Dr Bintou Njai, Fatou Sanyang, Fatoumatta Jah, Isatou Sanneh, Kumba Badjan, Lamin Mari, Lisa Jallow, Dr Madikoi Danso, Aunty Marie, Martina Boakarie, Maryama Jawara, Sr Monica Genekah, Muhammed Lamin Jatta, Saffiatou Jarju, Sarjo Koita, Dr Sheila Owusu, Sheriff Kandeh, Suleiman Dibba, and Uma Masterton. Your hard work and collaboration made this research possible, and I am proud to have worked with such a committed team. I also extend my gratitude to Dr Abdou K Sillah, Dr Mariama Sonko, and the entire Adult TB Team for their support throughout this project.

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I am grateful to the Gambia National TB Programme for their collaboration, with special thanks to Wandifa Samateh, Muhammed Lamin Darboe, and the Leprosy and Tuberculosis Inspectors in Western Regions 1 and 2. Your commitment to improving TB care in The Gambia was vital to the success of this research.

To the children and their caregivers who participated in this research, your courage and willingness to share your experiences were the true heart of this project. This research is dedicated to you, with the hope that it will lead to better care and brighter futures for all children affected by TB.

Finally, to my beloved family—Oluwatosin, Nathan, and Anna—your love and support have been my foundation. Tosin, your patience and encouragement were my greatest comfort. To my little ones, your smiles brightened even the toughest days. To my parents and siblings, your unwavering belief in me has been my driving force. I am forever grateful to each of you.

Thank you, Abba.

List of Publications

Below is a list of research articles, letters, and commentaries published from my PhD research work.

1) **Nkereuwem E,** Agbla S, Sallahdeen A, Owolabi O, Sillah AK, Genekah M, Tunkara A, Kandeh S, Jawara M, Saidy L, Bush A, Togun T, Kampmann B. Reduced lung function and health-related quality of life after treatment for pulmonary tuberculosis in Gambian children: a cross-sectional comparative study. *Thorax* 2023;78(3):281-287.

2) **Nkereuwem E,** Owusu SA, Edem VF, Kampmann B, Togun T. Post-tuberculosis lung disease in children and adolescents: a scoping review of definitions, measuring tools, and research gaps. *Paediatr Respir Rev* 2024: S1526-0542(24)00055-1.

3) **Nkereuwem E**, Agbla S, Jatta ML, Masterton U, Owolabi O, Edem VF, Kampmann B, Togun T. Childhood TB sequel: evaluating respiratory function after treatment for pulmonary tuberculosis in a prospective cohort of Gambian children – a study protocol. *BMC Pulm Med* 2023; 23:387.

4) **Nkereuwem E,** Agbla S, Njai B, Edem VF, Jatta ML, Owolabi O, Masterton U, Jah F, Danso M, Fofana AN, Samateh W, Darboe ML, Owusu SA, Bush A, Kampmann B, Togun T. Post-tuberculosis respiratory impairment in Gambian children and adolescents: a cross-sectional analysis. *Pediatr Pulmonol* 2024;59:1912-1921.

5) **Nkereuwem E,** Kampmann B, Togun T. Making a case for investing in post-tuberculosis lung health in children. *Lancet Respir Med* 2022;10(6):536-537.

6) **Nkereuwem E,** van der Zalm MM, Kampmann B, Togun T. “Yes! We can end TB,” but remember the sequelae in children. *Lancet Respir Med* 2024;12(5):348-350.

7) Nkereuwem O, **Nkereuwem E**, Owolabi O, Johm P, Egere U, Mortimer K, Kampmann B, Togun T. Perspectives of TB survivors and policymakers on post-TB disability. *Public Health Action* 2023;13(1):17-22.

8) **Nkereuwem E,** Edem VF, Owolabi O, Genekah M, Owusu SA, McCollum ED, Kampmann B, Togun T. Impact of race-neutral GLI global reference equations on spirometry interpretation in healthy Gambian children. *IJTLD Open* 2024;1(9):418-421.

9) **Nkereuwem E,** Edem VF, Agbla S, Owolabi O, Jatta ML, Njai B, Masterton U, Genekah M, Jah F, Owusu SA, Saidy L, Samateh W, Darboe ML, Kampmann B, Togun T. Respiratory outcomes in children and adolescents treated for pulmonary tuberculosis in The Gambia: a prospective study. Status: not yet submitted.

10) **Nkereuwem E,** Nkereuwem O, Jallow AO, Owolabi J, Gibba A, Jawara F, Manneh Z, Opoku A, Bond V, Togun T, Kampmann B. “I live with pain, it cannot go away”: a qualitative study exploring the lived experiences of childhood and adolescent pulmonary tuberculosis survivors in The Gambia. Status: submitted.

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Table of Abbreviations

BMI	Body Mass Index
CALHIV	Children and Adolescents Living with HIV
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
CXR	Chest X-Ray
ECOWAS	Economic Community of West African States
EDCTP	European and Developing Countries Clinical Trial Partnerships
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GBA	Greater Banjul Area
HDT	Host Directed Therapy
HIV	Human Immunodeficiency Virus
HRQoL	Health-Related Quality of Life
ISSF	Institutional Strategic Support Fund
LLN	Lower Limit of Normal
LMIC	Low-and-Middle-Income Country
LRTI	Lower Respiratory Tract Infection
LSHTM	London School of Hygiene and Tropical Medicine
LTBI	Latent Tuberculosis Infection
MRC	Medical Research Council
Mtb	*Mycobacterium tuberculosis*
NLTP	National Tuberculosis and Leprosy Control Programme
pTB	Pulmonary Tuberculosis
PTLD	Post-Tuberculosis Lung Disease
TB	Tuberculosis
WHO	World Health Organization

List of Contributors

I, Esin Nkereuwem, designed the objectives of my PhD studies and took lead responsibility for the quality of the data utilised throughout this thesis. This responsibility included data curation, cleaning, integration, and validation. I also performed all analyses and wrote all sections of the thesis, including the manuscripts, incorporating valuable input from my supervisors and PhD advisory committee members. Other specific contributors to the work in this thesis are listed below.

Name	Position and Institution	Contribution
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Virginia Bond	Professor of Anthropology Public Health, Department of Global Health and Development, Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine London, UK.	PhD Advisor. Provided guidance and advice on qualitative study methods.
Wandifa Samateh	Programme Director, National Leprosy and Tuberculosis Control Programme, Kanifing, The Gambia.	Collaborator. Provided access to the Gambia National Leprosy and Tuberculosis Control Programme treatment centres.
Muhammed L Darboe	Monitoring and Evaluation Officer, National Leprosy and Tuberculosis Control Programme, Kanifing, The Gambia.	Collaborator. Provided access to the Gambia National Leprosy and Tuberculosis Control Programme data.
Andrew Bush	Professor, Centre for Paediatrics and Child Health, Imperial College London, London, UK	Collaborator. Provided training on paediatric spirometry.
Lindsay Zurba	Founder and Training Manager, Education for Health Africa, South Africa	Provided training and support on paediatric spirometry.
Oluwatosin Nkereuwem	Senior Social Scientist, MRC Unit The Gambia at the London School of	Collaborator. Provided expert knowledge and guidance on

	Hygiene and Tropical Medicine, The Gambia.	the qualitative study design, methodology, and fieldwork.
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Sheila Agiewaa Owusu	PhD Fellow, MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine, The Gambia.	Screened titles and abstracts, reviewed full texts of relevant articles, and extracted data during scoping review.
Njilan Johnson	Programme Manager, Vaccines and Immunity Theme, MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine, The Gambia.	Project Logistics and budgetary support.
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Matthew Quaife	Assistant Professor in Health Economics, London School of Hygiene and Tropical Medicine (LSHTM), London, UK.	PhD Upgrading Examiner

Training and activities undertaken during the PhD

In addition to the activities specific to each of the objectives covered in Chapters 3 to 6, below is a list of the specific training and activities I undertook during the PhD.

Training	**Institution**
Training/clinical observership in paediatric spirometry	Royal Brompton Hospital, London
Training in paediatric spirometry with a certificate of competence	Pan-African Thoracic Society
Methods in Epidemiologic, Clinical, and Operations Research (MECOR) course Level 2 & 3	Pan-African Thoracic Society
Qualitative and Mixed Methods in International Health Research course	Institute of Tropical Medicine, Antwerp
Activities	**PhD Objective**
Application for ethics approvals	Objectives 1, 3, and 4
Clinical assessment of study participants	Objectives 1, 3
Performing spirometry on study participants	Objectives 1, 3
Quality assessment and quality control of spirometry data	Objectives 1, 3
Training and supervision of the research teams	All objectives
Design of data collection instruments	All objectives
Data analysis	All objectives
Writing up findings	All objectives
Overall coordination of all aspects of the research	All objectives

Thesis outline

This PhD thesis is divided into three parts and comprises seven chapters presented in the ***research paper style***. Part 1, which includes Chapters 1 and 2, provides the background and objectives of the research. Part 2, which comprises Chapters 3, 4, 5, and 6, consists of analytical chapters presented as research papers. Finally, Part 3, which is Chapter 7, presents a general discussion, the future direction for research, and recommendations. An overview of the outline is provided below.

PART 1: BACKGROUND

Chapter 1 introduces the global, regional, and local burden of childhood tuberculosis (TB). It discusses the current TB treatment outcomes, highlighting their limitations in measuring the long-term effects of TB. The concept of post-TB lung disease (PTLD) is introduced, along with an overview of its definition and measurement tools. The chapter also emphasises the lack of data on paediatric PTLD and sets the stage for the scientific rationale behind the PhD research.

Chapter 2 of the thesis provides an overview of the aim, hypothesis, and objectives of the PhD research. It also presents an overview of the different methodologies used throughout the research. There is no overall methods section because the methods used to address each PhD objective differs. Detailed methods to achieve each objective are thus presented in the respective chapters within the included research papers and the accompanying supplementary materials.

PART 2: ANALYTICAL CHAPTERS

Chapter 3 of this thesis addresses the first objective of my PhD, which was to describe the lung function and health-related quality of life in children under 15 years who had previously been diagnosed with pulmonary TB at the MRC Unit The Gambia at London School of Hygiene and Tropical Medicine between 2014 and 2019. This chapter is presented as a published research paper:

Research Paper 1: ***Nkereuwem E,*** *Agbla S, Sallahdeen A, Owolabi O, Sillah AK, Genekah M, Tunkara A, Kandeh S, Jawara M, Saidy L, Bush A, Togun T, Kampmann B. Reduced lung function and health-related quality of life after treatment for pulmonary tuberculosis in Gambian children: a cross-sectional comparative study. Thorax 2023;78:281-287.*

Chapter 4 of the thesis addresses the second objective of my PhD, which was to systematically review the existing literature on paediatric post-tuberculosis lung disease (PTLD) with the aim of identifying the definitions, measurement instruments, and research gaps in paediatric PTLD. This chapter is presented as a research paper that has been accepted for publication:

Research Paper 2: ***Nkereuwem E,*** *Owusu SA, Edem VF, Kampmann B, Togun T. Post-tuberculosis lung disease in children and adolescents: a scoping review of definitions, measuring tools, and research gaps. Paediatr Respir Rev 2024: S1526-0542(24)00055-1.*

Chapter 5 addresses the third objective of my PhD, which was to measure the prevalence and pattern of residual respiratory impairment at pTB treatment completion among Gambian children and adolescents and to prospectively describe the evolution of these sequelae. This chapter includes one published research paper and one paper that is being prepared for submission to a journal:

Research Paper 3: ***Nkereuwem E,*** *Agbla S, Njai B, Edem VF, Jatta ML, Owolabi O, Masterton U, Jah F, Danso M, Fofana AN, Samateh W, Darboe ML, Owusu SA, Bush A, Kampmann B, Togun T. Post-tuberculosis respiratory impairment in Gambian children and adolescents: a cross-sectional analysis. Pediatr Pulmonol 2024; 59:1912-1921.*

Research Paper 4: ***Nkereuwem E,*** *Edem VF, Agbla S, Owolabi O, Jatta ML, Njai B, Masterton U, Genekah M, Jah F, Owusu SA, Saidy L, Samateh W, Darboe ML, Kampmann B, Togun T. Respiratory outcomes in children and adolescents treated for pulmonary tuberculosis in The Gambia: a prospective study. Status: not yet submitted.*

Chapter 6 of the thesis focuses on the fourth and final objective of my PhD research, which was to explore the perceptions and lived experiences of children and adolescent TB survivors and gain an in-depth understanding of the social dimensions of the post-TB phenomenon. This chapter is presented as a research paper that has been submitted to the *BMC Public Health* journal.

Research Paper 5: ***Nkereuwem E,*** *Nkereuwem O, Jallow AO, Owolabi J, Gibba A, Jawara F, Manneh Z, Opoku A, Bond V, Togun T, Kampmann B. "I live with pain, it cannot go away": a qualitative study exploring the lived experiences of childhood and adolescent pulmonary tuberculosis survivors in The Gambia. Status: submitted.*

PART 3: GENERAL DISCUSSION, CONTRIBUTION OF THE PHD TO LITERATURE, AND DIRECTION FOR FUTURE RESEARCH

Chapter 7 of the thesis summarises the main findings from the four analytical chapters. It discusses their interconnectedness, highlights the conceptual and methodological contributions to the literature, and discusses its limitations. Additionally, this chapter highlights the implications of the PhD research for programme and policy and presents direction for future research. Finally, the chapter ends with concluding remarks.

PART 1: BACKGROUND

Chapter 1: Introduction

1.1 Global burden of childhood tuberculosis

Tuberculosis (TB) is a communicable bacterial disease caused by the *Mycobacterium tuberculosis* (*Mtb*) complex. It remains a significant global public health threat and is the leading cause of death from a single infectious agent.[1] According to the World Health Organization (WHO), an estimated 10.6 million people fell ill with TB worldwide in 2022, resulting in 1.3 million deaths[1] This translates to roughly 29,000 new TB cases and over 3,000 deaths every day. Despite significant progress in combating TB over the past decade, the disease continues to disproportionately affect low- and middle-income countries (LMICs).[2]

The most common site of TB infection is the lungs, with pulmonary TB (pTB) accounting for over 85% of all TB cases each year.[3] The disease is transmitted through inhalation of airborne droplets from an infectious person.[4] When inhaled, the bacteria typically settle in the lungs, where they can either cause active TB disease or remain dormant under strict immune control.[5] This dormant state, known as latent TB infection (LTBI), does not cause any symptoms but can progress to active TB disease if the immune system becomes weakened.[6]

West Africa bears a heavy burden of TB, with several countries in the region classified as *high TB burden* by the WHO, characterised by an incidence greater than 100 cases per 100,000 population.[1] The region as a whole contributes around 7% of the global TB burden.[1] The Gambia is one of these *high TB-burden* countries, with an estimated annual incidence of 145 cases per 100,000 population.[1] Thus, TB remains a significant public health concern in the country. Furthermore, the free movement agreement of the Economic Community of West African States (ECOWAS) allows for migration across borders within the region.[7] This mobility presents a potential challenge as individuals with undiagnosed or incompletely treated TB may unknowingly spread the infection into new areas.[7,8]

The global trend of TB notification has steadily increased since 2010 at an average rate of about 2.1% annually.[1] Despite being affected by the COVID-19 pandemic in 2019 and 2020, the increase resumed in 2022 (Figure 1). However, this progress has been uneven, particularly concerning the proportion of TB cases notified among children. Estimates suggest that of the 1.3 million children under 15 years who contracted TB in 2022 worldwide, only approximately 600,000 were notified.[1]

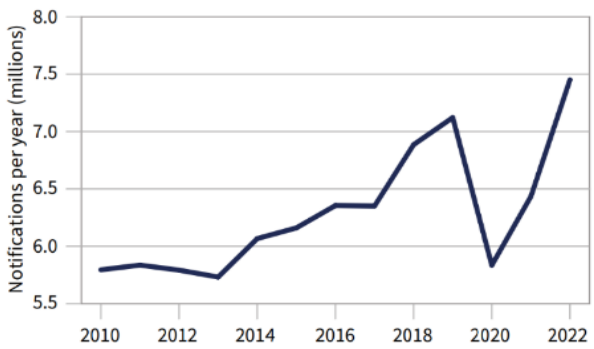

Figure 1: Global trend in case notifications of people newly diagnosed with TB, 2010 – 2022.
Image source: World Health Organization, 2023[1]

Despite childhood TB accounting for an estimated 12% of global TB cases and 16% of annual TB-

related deaths,[1] diagnosing pTB in children is challenging due to difficulties in obtaining sputum or other respiratory samples.[9] Even when these samples are successfully obtained, microbiological tests such as *Mtb* culture or Xpert MTB/RIF Ultra are less likely to yield positive results because childhood TB is frequently paucibacillary.[10] Consequently, many childhood TB diagnoses are made presumptively based on clinical and radiological features without laboratory confirmation.

Children and adolescents are particularly vulnerable to TB. Malnutrition and human immunodeficiency virus (HIV) infection, which is widespread in many low- and middle-income countries (LMICs), weaken a child's immune system, making them more susceptible to TB.[11,12] Adolescents also have an even greater susceptibility to TB due to biological changes during puberty, increased social interaction, potential nutritional deficiencies, and reactivation of undiagnosed childhood infections.[13]

Furthermore, the clinical presentation of pTB varies across the different paediatric age groups. Younger children with less developed immune systems often show primarily lymph node involvement.[14] In contrast, adolescents may have pTB presentations resembling those of adults, including radiographic features such as cavitations in the lungs.[13] Older adolescents over 15 years also contribute substantially to the disease burden, often exhibiting a combination of features that reflect their transitional stage between childhood and adulthood.[15] It is crucial to recognise these distinct presentations of paediatric TB, as they have significant implications for diagnosing and managing the disease in this unique population. Understanding these distinctions is also essential for effective treatment strategies and better tools for assessing TB and its long-term effects in children.

1.2 Childhood tuberculosis in The Gambia

The Gambia National Leprosy and Tuberculosis Control Programme (NLTP) coordinates all TB-related services and activities in the country.[16] Through a network of strategically located diagnostic and treatment centres, the Gambia NLTP ensures nationwide access to TB care. There is a higher concentration of these centres in the Greater Banjul Area (GBA) because this region, which includes urban, peri-urban, and rural areas, contributes more than 70% of all notified TB cases in the country.[17] At the service level, all TB programme activities are fully integrated with the public healthcare sector.[16] Additionally, TB treatment services are exclusively accessible via the Gambia NLTP and are provided free of charge.

Diagnosing childhood TB in The Gambia is a huge challenge.[18-20] Despite children under 15 years of age contributing an estimated 15% of the country's TB burden, The Gambia, like many other countries, only detects a small fraction of these cases.[16] Since 2016, when the Gambia NLTP

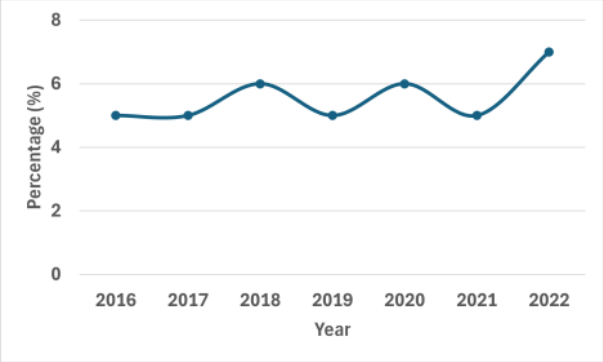

Figure 2: % new TB cases aged below 15 years in The Gambia, 2016 – 2022[1]

began consistently reporting age-disaggregated TB data, annual notifications have continued to hover around 6% of the total reported TB cases annually (Figure 2).[1] Only 175 out of an estimated 390 new cases of childhood TB in 2022 were reported.[1] This gap can be attributed to the inherent difficulties in diagnosing TB in children. While typically diagnosed within specialised TB services, opportunities to integrate case identification into broader child health services are often missed.[21] Moreover, the disease can mimic other common childhood illnesses like bacterial or viral lower respiratory tract infections (LRTIs) and is further masked by malnutrition, both of which are widespread issues in The Gambia.[11,22-24] These factors all contribute to the under-diagnosis of childhood TB in The Gambia, highlighting the need for improved diagnostic tools and strategies specifically tailored for this vulnerable population.

Treatment for drug-sensitive or drug-resistant childhood TB in The Gambia follows the WHO guidelines and uses a standardised course of anti-tuberculosis medication.[25,26] The duration of treatment varies depending on drug sensitivity and disease severity, usually lasting from six to nine months. Anti-tuberculous treatment is provided free of charge at designated Gambia NLTP facilities, and the national data shows that a significant proportion of reported cases, including an estimated 84% of the total 2500 cases annually, complete treatment.[1]

Although treatment is free, it is important to note that TB care involves more than just medication. Several economic and social factors create a significant burden, especially for low-income families who are already suffering from the debilitating effects of TB.[27] These factors include, but are not limited to, hidden costs associated with TB care, such as transportation costs, loss of income due to illness or time spent seeking care, the need for nutritious food, etc.[28,29] Many of these challenges persist even after the period of TB treatment. Therefore, recognising and addressing these factors is crucial to improving treatment success and overall health outcomes for TB patients, regardless of age.

1.3 Tuberculosis treatment outcomes

Successful treatment for pTB has traditionally been divided into two categories: *cured,* when there is no longer bacteriological evidence of TB infection at the end of treatment, and *treatment completed,* when the patient has shown clinical improvement even without bacteriological confirmation of cure at treatment completion (Table 1).[30] Up to 88% of individuals treated for their first episode of TB will achieve treatment success, leading to an increasing number of TB survivors, estimated to be about 155 million as of 2020.[31,32]

Table 1: Classification of treatment outcomes for drug-sensitive TB patients. Source: World Health Organization, 2014[30]

Outcome	Definition
Cured	A PTB 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 before starting or during the course of treatment
Lost to follow-up	A TB patient who did not start treatment or 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 cases for whom the treatment outcome is unknown to the reporting unit
Treatment success	The sum of cured and treatment completed

While successful treatment is crucial, a growing body of evidence suggests that many adult pTB survivors continue to experience chronic health problems up to three years after apparently successful treatment.[33-37] The clinical spectrum of these long-term consequences is extensive, including airway diseases (such as TB-associated obstructive lung disease and bronchiectasis), parenchymal abnormalities (such as cavitation, parenchymal destruction, and fibrotic changes, as well as aspergillus-related lung disease), chronic pleural disease, and pulmonary vascular complications characterised by pulmonary hypertension.[38]

Studies have shown that adult pTB survivors are two to four times more likely to have abnormal spirometry compared to those without a history of TB.[34,36,39] Additionally, these survivors often report persistent respiratory symptoms and a poorer overall health-related quality of life (HRQoL).[34,36,37] Furthermore, research has established a connection between previously treated pTB and an increased risk of death. Mortality rates for adult TB survivors are reported to be as much as three times higher than those of the general population, with these excess deaths primarily caused by TB-associated cardiovascular and respiratory complications.[40,41] This trend is worrying, as even in high-income countries, pTB survivors have mortality rates three to six times higher than those of the general population.[40-42]

The emerging data challenges our current understanding of what constitutes successful treatment for TB. While treatment success is important, it seems that it may not be enough to ensure long-

term lung health and does not necessarily mean that the individual will have a healthy life after TB.[43] Therefore, the traditional assessments done after completing treatment may not be sufficient.

Despite this growing evidence of health issues in adult pTB survivors, post-tuberculosis lung disease (PTLD) is not widely recognised as a significant health challenge, especially in the younger population.[38] Even though children and adolescents account for at least 12% of estimated TB cases each year, there is still a lack of understanding about the burden and clinical spectrum of paediatric PTLD. This knowledge gap is concerning.

The importance of including children in PTLD research is rooted in the critical nature of lung development.[44] Beginning in utero and spanning the first two decades of life, this period is vital for establishing optimal lung function.[44] Any insults occurring during this time, such as pTB disease, have the potential to permanently alter the trajectory of a child's lung function, leading to an increased risk of respiratory morbidity and mortality throughout their life (Figure 3).[45-47] This is especially important since children have a longer life course ahead of them. Therefore, recognising and addressing PTLD in children is essential, as this period of development makes them particularly vulnerable to long-term consequences following TB treatment.[48]

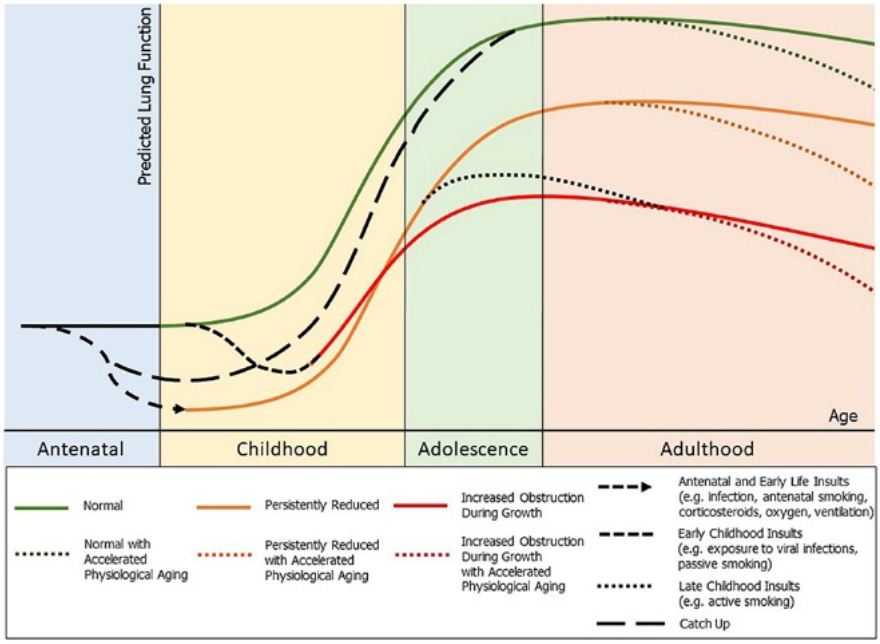

Figure 3: Potential lung function trajectories throughout life. Image source: Gibbons et al. 2020[49]

Accurate diagnosis and prompt, effective treatment are crucial for managing childhood TB.[50] However, it is equally important to address the critical gap in understanding the long-term effects of the disease on children. Investigating the prevalence and nature of post-TB sequelae in children and adolescents is needed in order to understand these long-term effects.[48] This understanding will help us develop comprehensive TB care strategies that extend beyond achieving a cure. These

strategies would focus on mitigating the potential aftermath of the disease and ensuring a child's overall health trajectory is not negatively impacted.[51]

1.4 Paediatric post-tuberculosis lung disease

The sequelae of TB have historically been overlooked, as national TB programmes focus mainly on completing treatment and achieving a cure without considering the long-term well-being of patients.[43] Unlike most respiratory infections, TB can cause permanent damage to the lungs. After apparently successful treatment, pTB can progress from a treatable communicable disease to a chronic, non-communicable disease across the life course.[51,52]

Several longitudinal studies have demonstrated that lower respiratory tract infections (LRTI) during infancy are linked to reduced lung function in later childhood and adulthood.[53-56] These findings, combined with data from adult pTB survivors, suggest that early-life pTB may impact respiratory health in children and adolescents, potentially leading to similar or more severe adverse outcomes following treatment completion. However, at the start of this PhD, there was very little data on the long-term effects of pTB in children and adolescents.

In recent years, there has been growing awareness of the long-term consequences of pTB. This renewed emphasis has led to the convening of two International Post-TB Symposiums.[51,57] The first and second symposiums took place in Stellenbosch, South Africa, in 2019 and 2023, respectively. During these meetings, the focus was on discussing research priorities for post-TB, reaching a consensus on terminologies and definitions, and proposing a toolbox for future measurement of PTLD. These symposiums brought together patients, clinicians, and researchers to advocate for individuals experiencing post-TB complications and to identify areas where more information is needed. Their goal was to address the challenges associated with post-TB sequelae in both research and clinical practice, including developing standardised definitions and guidelines.[51]

During the 2023 symposium in Stellenbosch, experts proposed a definition for paediatric PTLD as follows: "*evidence of chronic respiratory impairment in a child previously treated for pulmonary tuberculosis, where active TB and other chronic lung diseases are ruled out*."[57] This definition provides a valuable framework for research studies to accurately assess the burden of PTLD in children and report their findings in a way that is comparable to other studies.

Although this framework may be helpful, defining paediatric PTLD is particularly challenging for many reasons. Children and adolescents represent a wide spectrum of the TB disease.[48] Infants are more prone to developing systemic illnesses such as miliary TB, while younger children usually develop predominantly lymph node TB.[14] In contrast, older children and adolescents tend to develop adult-type disease with more extensive respiratory impairment.[13] These differences in

disease presentations make it more challenging to have a cross-cutting definition that equally captures the age-specific phenotypes of pTB.[58]

Based on available evidence, primarily from adult studies, the clinical presentation of PTLD is heterogeneous, ranging from a complete absence of symptoms to severe illness.[38] The pathology can affect different parts of the lungs, including the airways, parenchyma, pleura, and pulmonary vascular compartment, either alone or in combination (Table 2).[38,51] Multiple patterns of pathology can be seen within a single patient and across different areas of the lung.[38] Currently, there is no clinically validated tool for describing or scoring the severity of the structural pathology of PTLD. However, the changes in chest X-rays or computed tomography (CT) scans may show residual cavitation, bronchiectasis, fibrotic changes, anatomical distortion, and destroyed lung tissue.[34,59-61] Additionally, there is a high burden of residual inflammatory changes observed after pTB treatment, and these lesions appear to change over time, suggesting an ongoing inflammation.[62,63]

Table 2: Clinical patterns of post-tuberculosis lung disease. Source: Allwood et al. 2020[51]

Compartment	Clinical patterns	Suggested definition
Airways	Tuberculosis-associated obstructive lung disease	Airway obstruction (FEV_1/FVC ratio <0.7 OR <LLN) thought primarily related to small airway disease
	Bronchiectasis	CT definition – evidence of airway dilatation > diameter of adjacent vessel, or non-tapering, or CXR definition – evidence of ring shadows and tramlines
Parenchyma	Cavitation	A gas-filled space either within an area of pulmonary consolidation or surrounded by a thin wall
	Parenchymal destruction	Extensive destruction of lung tissue, with a gas-filled space/collapsed parenchyma occupying the volume of ≥1 lobe
	Fibrotic change	Areas of parenchymal scarring with associated volume loss
	Aspergillus-related lung disease	Evidence of aspergilloma on imaging or chronic pulmonary aspergillosis on imaging and blood testing
Pleura	Chronic pleural disease	Evidence of pleural thickening on CXR or CT imaging
Pulmonary vascular	Pulmonary hypertension	Elevated pulmonary artery pressures, as estimated using Doppler echocardiography or measured at right heart catheterisation
PTLD = post-tuberculosis lung disease; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; LLN = lower limit of normal; CT = computerised tomography; CXR = chest X-ray		

1.5 Measuring paediatric post-tuberculosis lung disease

During the first International Post-TB Symposium in 2019, various methods and approaches were proposed for measuring PTLD.[51] These methods constitute a comprehensive "toolbox" for evaluating core disease parameters, such as self-reported symptoms, clinical measures, lung function, radiological imaging, HRQoL, disease behaviour patterns, and the socioeconomic impact of the disease (see Table 3).[51] This toolbox also includes a list of co-exposures and co-morbidities considered essential for measurement in PTLD due to their potential to influence the presentation and severity of the disease.

Table 3: Post-TB lung disease measurement toolbox. Source: Allwood et al. 2020[51]

Category	Clinical patterns	Suggested definition
Post-TB lung disease measurement	Self-reported symptoms	Shortness of breath, cough, sputum, wheeze, chest pain, haemoptysis, fatigue
	Clinical measures	Observations: respiratory rate, oxygen saturation, heart rate, BMI; Investigations: arterial blood gas
	Lung function	Pre- and post-bronchodilator spirometry; Lung volumes; Gas transfer
	Radiology	CXR parameters; CT parameters
	Functional capacity	Submaximal tests: 6-minute walk, sit to stand; Maximal tests: incremental shuttle, cardiopulmonary exercise testing
	Health-related quality of life	Respiratory focused; General tools; Tool for economic analyses (WHO TB patient cost surveys)
	Disease behaviour	Evidence of cor pulmonale: pedal oedema, echocardiography (pulmonary artery pressures); Evidence of exacerbations: exacerbation rate, hospitalisation rate; Microbiology: colonising/infecting organisms, including bacteria/mycobacteria/ viruses/fungi
	Socio-economic consequences	Mental health symptom screen; TB-related stigma; self-reported disability related to TB; Socio-economic information and patient costs (direct and indirect): WHO TB patient cost surveys
Factors influencing disease or outcomes	Co-exposures	Respiratory exposures: smoking, substance abuse, biomass exposure, occupational exposures; Environmental exposures: alcohol use, socio-economic situation
	Comorbidities	Preceding/concurrent respiratory disease: silicosis, COPD, other Immunosuppression: HIV, diabetes mellitus, other; Other comorbidities: cardiovascular disease, other

TB = tuberculosis; BMI = body mass index; CXR = chest X-ray; CT = computed tomography; WHO = World Health Organization; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus

The measurement tools and items recommended at the Symposium are primarily based on studies involving adults and often require standardisation and quality control.[51] However, these tools designed for adults may not always be suitable for children due to differences in physiology, disease presentation, and developmental stages. Additionally, tools that rely on self-reported data, such as symptom questionnaires and HRQOL assessments, or those that require specific physical manoeuvres like spirometry and functional capacity tests, may not be suitable or may produce unreliable results in very young children due to limitations in communication and cooperation.[64,65]

It is important to acknowledge that many high-burden TB settings have limited resources and lack access to several of these tools. For example, even though lung function testing is an important tool in the PTLD toolbox, many of these settings do not have access to essential equipment such as spirometers.[66] While the importance of lung function testing in children and adolescents cannot be overstated, we must recognise the challenges posed by limited resources in these settings.

Furthermore, the reference equations commonly used to interpret lung function and functional capacity tests are based on data from healthy populations in high-income countries with low TB prevalence.[67] This raises concerns about the accuracy of these equations for children in low-income settings with high TB prevalence and other co-exposures. Using reference equations from non-TB endemic populations could result in misinterpretation of lung function data, leading to potential misclassification of respiratory impairments in children who have undergone TB treatment.[68]

Radiological assessments are an essential part of diagnosing PTLD, but they come with their own challenges. The scoring systems used for adults may not work well for children, as they have different patterns of TB manifestation and healing.[69,70] Moreover, interpreting chest X-rays for children requires specialised expertise, as normal developmental changes can mimic pathological findings and vice versa.[71]

Furthermore, the socioeconomic effects of PTLD, including its impact on education and family dynamics, are often not thoroughly examined in adult studies. Specific findings related to children, such as extended periods of absence from school, learning difficulties, and social isolation, which can have lasting impacts on their development and well-being, are not taken into account in tools that are centred on adults.[28,29]

While achieving universal standardisation across all tools might not be feasible, the need for standardisation and quality control remains paramount.[51] It is crucial to either adapt these existing tools to meet the unique needs of the paediatric population or develop new tools specifically for

children. This would enable the accurate measurement of PTLD and other dimensions of the disease in the paediatric population. This adaptation or development process should take into consideration the unique physiological, developmental, and context-specific factors affecting children in TB-endemic regions.[67,72] By doing so, we can ensure that the tools used are both accurate and relevant, ultimately leading to better diagnosis, treatment, and management of PTLD in children and adolescents.

1.6 Rationale for the PhD studies

Despite significant progress in the global effort to combat TB, the disease continues to disproportionately affect children and adolescents in LMICs.[2] The Gambia, a low-income country in West Africa, is also grappling with childhood TB as a significant public health concern.[1] While ensuring successful treatment is crucial, there is a substantial gap in our understanding of the long-term effects, or sequelae, of paediatric pTB.[33,38] These sequelae can impact a child's health and well-being for many years.

The current approach to pTB treatment outcome classification focuses solely on achieving microbiological cure or treatment completion, overlooking the critical aspect of post-TB complications.[30,43] These post-TB complications may include chronic respiratory symptoms, impaired lung function, abnormal chest radiological findings, and reduced functional capacity.[34-36,38] The disease also has detrimental effects on the HRQoL as well as socioeconomic consequences for TB-affected individuals and their households.[34,36,51]

Unlike in adults, the understanding of PTLD in children and adolescents is currently limited.[51] Thus, this PhD research focuses on thoroughly examining the consequences of pTB in Gambian children and adolescents. This research aims to measure the prevalence, pattern, and evolution of PTLD among this population, identify the factors that contribute to its development, and understand how PTLD impacts their long-term health and well-being.

This thesis offers valuable insights specific to the Gambian context. Understanding the scope of the problem, the risk factors involved, and its impact on children's lives is crucial for informing evidence-based interventions. These interventions may include strategies for early identification and management of PTLD, as well as potential modifications to follow-up care plans to mitigate the risk of long-term complications.

This PhD thesis aims to enhance our overall understanding of the sequelae of paediatric pTB. By studying this population, we can gain valuable insights into the impact of childhood pTB on a vulnerable population in a West African context. This knowledge will ultimately inform the development of more effective strategies for the prevention, diagnosis, and treatment of pTB and its consequences in children and adolescents, not just in The Gambia but across West Africa and beyond.

Chapter 2: The PhD aim, hypothesis, objectives and methodology

2.1 Aim

The overarching aim of this research is to describe long-term adverse physical and psycho-social outcomes associated with pulmonary tuberculosis in children and adolescents, to describe the evolution of these sequelae, and to determine the epidemiological risk factors associated with these sequelae.

2.2 Hypotheses

1. Children and adolescents previously treated for pulmonary tuberculosis have reduced lung function and lower health-related quality of life scores compared to those without previous tuberculosis disease.
2. Children and adolescents in The Gambia continue to experience impaired respiratory health, characterised by respiratory symptoms, abnormal chest X-rays, and reduced lung function, even after successful treatment for pulmonary tuberculosis.
3. Post-tuberculosis respiratory impairment evolves over the course of 12 months after completing treatment for pulmonary tuberculosis.
4. There are social dimensions associated with the post-tuberculosis phenomenon.

2.3 Specific objectives

The four specific objectives of the PhD research are:

1. To describe the lung function and health-related quality of life (HRQoL) in children younger than 15 years who were previously diagnosed with pulmonary tuberculosis at the MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine (LSHTM) between 2014 and 2019.

2. To systematically review the existing literature on paediatric post-tuberculosis lung disease (PTLD) with the aim of identifying definitions, measurement instruments, and research gaps in paediatric PTLD.

3. To measure the prevalence and pattern of residual respiratory impairment at pulmonary tuberculosis treatment completion among Gambian children and adolescents and to prospectively describe the evolution of these sequelae.

4. To explore the perceptions and lived experiences of child and adolescent TB survivors and gain an in-depth understanding of the social dimensions of the post-TB phenomenon.

2.4 Methodology

During my PhD, I utilised a wide range of established research methodologies to effectively address the four objectives described above. The research papers provide detailed descriptions of

the methodologies and statistical techniques used. These research methodologies can be divided into four components, as outlined below:

2.4.1 Cross-sectional comparative study design

I utilised a **cross-sectional comparative study design** to achieve Objective 1 of my PhD research. The goal was to describe lung function and health-related quality of life (HRQoL) in children previously diagnosed with pTB at the MRC Unit The Gambia at LSHTM. The MRC Unit The Gambia at LSHTM runs a comprehensive childhood TB research programme to evaluate preventive, screening, and novel diagnostic approaches in childhood pTB. Using the register in our dedicated childhood TB research clinic, I identified children diagnosed with confirmed or unconfirmed pTB between January 2014 and December 2019 in the Greater Banjul Area (GBA).[18,73] Additionally, I included a comparison group of age-matched children and adolescents living in the same household as the cases but who had never previously been diagnosed with pTB. In the Gambian context, a household is defined as a group of people who eat from the same pot and live in the same building.[74] The GBA of The Gambia runs a successful contact tracing and prophylaxis programme with a high uptake of isoniazid preventive treatment, exceeding 78%.[75] The contact tracing programme provided the epidemiological framework for recruiting this study's post-tuberculosis cases and household comparison group.

2.4.2 Scoping review of the empirical literature on paediatric post-tuberculosis lung disease

To address Objective 2 of my PhD research, which was to identify definitions, measurement instruments, and gaps in the existing research on paediatric PTLD, I conducted a **scoping review** following the guidance framework described by the *Joanna Briggs Institute*.[76] I searched five electronic databases for peer-reviewed articles published from January 1, 2000, to March 1, 2021, that examined PTLD in unique paediatric or mixed populations. Research Paper 2, which addresses this objective, outlines the scoping review methods and is presented in Chapter 4.

2.4.3 Cross-sectional and longitudinal cohort study designs

To address Objective 3 of my PhD, which aimed to measure the prevalence and pattern of residual respiratory impairment at pulmonary TB treatment completion among Gambian children and adolescents, and to prospectively describe the evolution of these sequelae, I used both **cross-sectional** and **longitudinal cohort designs**. I prospectively enrolled all eligible and consenting children and adolescents at treatment completion for pulmonary TB in the GBA of The Gambia over 15 months (April 2022 to July 2023). Then, I followed up with each of them six months and one year later, during which I assessed their respiratory health and measured how these impairments, if present, evolved over the 12 months. In Paper 3, presented in Chapter 5, I provided a detailed **cross-sectional description and analysis** of participants enrolled in the prospective cohort, with an emphasis on the proportion of them having residual respiratory impairment at pTB

treatment completion. In Paper 4, also presented in Chapter 5, I measured the prevalence of these respiratory parameters at each 6-month visit and examined the evolution of these respiratory impairments over the one-year post-TB period.

2.4.4 Embedded qualitative design

To explore the perspectives and lived experiences of the childhood pTB survivors, I employed a **qualitative study design,** which was embedded within the larger quantitative study described in Section 2.4.3 above – **QUAN(qual) design**. I adopted an interpretative phenomenological approach[77] to gain a comprehensive, 'emic' understanding of how children, adolescents, and their caregivers perceive and describe the post-TB phenomenon. I used facilitator-guided group discussions and in-depth interviews to collect qualitative data. I employed an inductive process to analyse and interpret the patterns across the dataset to address Objective 4 of my PhD. Paper 5 in Chapter 6 of my thesis presents a detailed description of this methodology.

2.5 Ethics

I have obtained the following approvals for the research studies conducted during my PhD and included in this thesis:

1. **Objective 1**: The Gambia Government/MRC Joint Ethics Committee (Project ID/Ethics ref: 17747; Date: November 5, 2019, Appendix 11) and the LSHTM Observational/Interventions Research Ethics Committee (LSHTM Ethics Ref: 17747; Date: November 5, 2019, Appendix 12).
2. **Objective 3**: The Gambia Government/MRC Joint Ethics Committee (Project ID/Ethics ref: 22613; Date: January 18, 2022, Appendix 13) and the LSHTM Observational/Interventions Research Ethics Committee (LSHTM Ethics Ref: 22613; Date: January 19, 2022, Appendix 14).
3. **Objective 4**: The Gambia Government/MRC Joint Ethics Committee (Project ID/Ethics ref: 28229; Date: November 22, 2023, Appendix 15) and the LSHTM Observational/Interventions Research Ethics Committee (LSHTM Ethics Ref: 28229; Date: January 9, 2024, Appendix 16).

All study participants aged 18 years and older, as well as caregivers of participants under 18 years, provided informed consent to participate. Assent was obtained from participants under 18 years old. There were no exceptional circumstances which required informed consent to be provided to participants under 18 years old. All personal identifiers were removed from the analysed data.

2.6 Funding

The research work presented in this thesis was funded by a Wellcome Trust Institutional Strategic Support Fund (ISSF) administered through a Global Clinical Research Fellowship from the Imperial College London (grant number: PS3456_WMNP) and a Career Development Fellowship from the

EDCTP2 Programme, supported by the European Union (grant number: TMA2020CDF-3197 – Childhood TB Sequel). The Wellcome Trust ISSF Fellowship spanned from July 1, 2019, to December 31, 2020, and the EDCTP Fellowship spanned from July 1, 2021, to October 31, 2024. These fellowships aim to support early- and mid-career researchers by providing opportunities to develop research expertise and skills.

PART 2: ANALYTICAL CHAPTERS

Chapter 3: Lung function and health-related quality of life after treatment for pulmonary tuberculosis in Gambian children (Research Paper 1)

3.1 Overview of Chapter

This chapter addresses the first objective of my PhD, which was "*to describe the lung function and health-related quality of life (HRQoL) in children younger than 15 years who were previously diagnosed with pulmonary tuberculosis at the MRC Unit The Gambia at LSHTM between 2014 and 2019.*"

This chapter also tests the following hypotheses:

- *Children and adolescents previously treated for pulmonary tuberculosis have reduced lung function and lower health-related quality of life scores compared to those without previous tuberculosis disease.*

The research paper addressing the objective in this chapter was published in *Thorax* with the following full bibliographic information:

Nkereuwem E, Agbla S, Sallahdeen A, Owolabi O, Sillah AK, Genekah M, Tunkara A, Kandeh S, Jawara M, Saidy L, Bush A, Togun T, Kampmann B. Reduced lung function and health-related quality of life after treatment for pulmonary tuberculosis in Gambian children: a cross-sectional comparative study. *Thorax* 2023; **78**:281-287. https://doi.org/10.1136/thorax-2022-219085.

The supplementary material accompanying the research paper in this chapter is included in Appendix 6.

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Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	449227	**Title**	Dr
First Name(s)	Esin Esin		
Surname/Family Name	Nkereuwem		
Thesis Title	Evaluating the sequelae of pulmonary tubeculosis in Gambian children and adolescents		
Primary Supervisor	Professor Beate Kampmann		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	BMJ Thorax		
When was the work published?	September 2022		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION E

Student Signature	[redacted]
Date	1 September 2024

Supervisor Signature	[redacted]
Date	2 September 2024

Original research

Reduced lung function and health-related quality of life after treatment for pulmonary tuberculosis in Gambian children: a cross-sectional comparative study

Esin Nkereuwem ,[1,2] Schadrac Agbla,[3,4] Azeezat Sallahdeen,[1] Olumuyiwa Owolabi,[1] Abdou K Sillah,[1] Monica Genekah,[1] Abdoulie Tunkara,[1] Sheriff Kandeh,[1] Maryama Jawara,[1] Lamin Saidy,[5] Andrew Bush ,[6,7] Toyin Togun ,[1,2,8] Beate Kampmann [1,2,9]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/thorax-2022-219085).

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ABSTRACT

Background Post-tuberculosis (post-TB) lung disease is an under-recognised consequence of pulmonary tuberculosis (pTB). We aimed to estimate the prevalence of residual lung function impairment and reduced health-related quality of life (HRQoL) in children after pTB treatment completion.

Methods We conducted a cross-sectional comparative study of children aged less than 15 years at TB diagnosis who had completed treatment for pTB at least 6 months previously with a comparator group of age-matched children without a history of pTB. Symptoms, spirometry and HRQoL measured with PedsQL scale were collected. Variables associated with lung function impairment were identified through logistic regression models.

Results We enrolled 68 post-TB cases (median age 8.9 (IQR 7.2–11.2) years) and 91 children in the comparison group (11.5 (8.0–13.7) years). Spirometry from 52 (76.5%) post-TB cases and 89 (94.5%) of the comparison group met the quality criteria for acceptability and repeatability. Lung function impairment was present in 20/52 (38.5%) post-TB cases and 15/86 (17.4%) in the comparison group, p=0.009. Previous pTB and a history of chronic cough were significantly associated with the presence of lung function impairment (p=0.047 and 0.006 respectively). Forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and FEV_1/FVC *z*-scores were significantly lower in the post-TB cases compared with the comparison group (p= <0.001, 0.014 and <0.001, respectively). The distribution of the self-reported physical health score, and parent-reported physical, emotional, psychological, social and total HRQoL scores were significantly lower in the post-TB cases compared with the comparison group.

Conclusions Previous TB in children is associated with significantly impaired lung function and HRQoL.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pulmonary tuberculosis (pTB) is associated with lung function impairment in adult TB survivors.

WHAT THIS STUDY ADDS

⇒ Childhood pTB is associated with significantly increased odds of having impaired lung function, and significantly lower health-related quality of life scores, beyond 6 months after treatment completion.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This suggests that a more holistic approach, which takes into account the physical and psychosocial effects of the disease, is needed to better define the outcomes of pTB treatment in children.

INTRODUCTION

In 2020, an estimated 1.1 million children below 15 years developed tuberculosis (TB) worldwide, with paediatric disease accounting for approximately 11% of the 9.9 million new cases.[1] The global annual numbers of TB cases in children have been on the rise, increasing from about 1 million in 2017 to 1.2 million in 2019, with the vast majority of these cases affecting the lungs.[1]

Traditionally, successful treatment for TB has been classified as either *cured* if there is no longer bacteriological evidence of TB in the last month of treatment, or *treatment completed* if the patient has clinically improved in the absence of bacteriological confirmation of cure at the end of treatment.[2] Up to 85% of persons who are treated for the first TB episode will achieve treatment success.[3 4] However, while emerging data derived almost exclusively from adult patients with TB suggest a high burden of residual morbidity after TB treatment, there is a huge knowledge gap regarding the post-TB outcomes in children.[5]

Many adult survivors who had pulmonary TB (pTB) develop chronic physical and psychosocial consequences such as persistently abnormal spirometry and reduced health-related quality of life (HRQoL).[5 6] Adult pTB survivors have been shown to have twofold-to-fourfold higher odds of persistently abnormal spirometry compared with those without previous TB disease.[7–9] Similarly, studies have documented persistence of respiratory symptoms, and reduced HRQoL despite successful

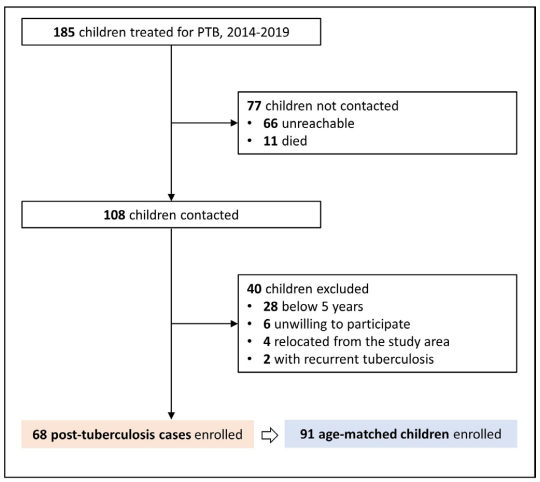

Figure 1 Study flowchart for selection of study participants. PTB, pulmonary TB.

completion of treatment for TB in adults.[10 11] However, although a growing literature describes multiple post-TB morbidities in adults, the actual burden of each of these illnesses in children remains poorly described. More so, even though pTB accounts for at least 80% of all estimated TB cases that occur in children, post-TB lung disease (PTLD) remains an under-recognised health challenge in children, especially in regions of the world with high TB burden.[5 7]

Lung development begins in utero and continues into early adulthood before declining from about 20–25 years of age.[12 13] Consequently, early insults to the lungs have been shown to affect lung growth and development adversely.[14] This has the potential to accelerate decline in lung function, and increase risk of chronic respiratory illnesses in later life, with consequent reduction in the HRQoL.[12 15] Several longitudinal studies have shown that lower respiratory tract infections (LRTI) during infancy are associated with reduced lung function in later childhood and adulthood.[16–19] Furthermore, a longitudinal study in HIV-infected adolescents in South Africa suggested a correlation between prior history of TB or severe LRTI and decline in lung function.[20]

Based on these findings, we hypothesised that previously treated TB may be associated with persistently impaired lung function in children, and that children might experience similar or more severe adverse outcomes after completion of TB treatment. In this cross-sectional comparative study in The Gambia, we investigated the prevalence of residual lung function impairment in children after pTB treatment completion and compared their lung function and HRQoL to a comparison group of age-matched children without previous TB disease, who grew up in the same environment.

METHODS

Study design

We conducted a cross-sectional comparative study at the childhood TB research clinic of the Medical Research Council Unit The Gambia at the London School of Hygiene & Tropical Medicine (MRCG at LSHTM), The Gambia. The MRCG at LSHTM has a long-standing collaboration with the Gambia National Leprosy and Tuberculosis Control Programme, and routinely contributes to the childhood TB diagnosis and case notification.[21–23]

Post-TB cases

Using our childhood TB registry, we identified children who were diagnosed with confirmed or unconfirmed pTB at MRCG at LSHTM between January 2014 and December 2019 in the Greater Banjul Area (GBA).[23 24] The GBA in The Gambia has a successful contact tracing and prophylaxis programme with a high isoniazid preventive treatment uptake of greater than 78%.[21] The contact tracing programme provided the epidemiological framework for the recruitment of the post-TB cases and household comparison group in this study. These were children who had presented with symptoms suggestive of pTB following community-based contact tracing of sputum smear adults or following referral from peripheral health facilities. Unconfirmed TB was defined as presence of at least two of the following: symptoms and signs suggestive of TB, chest radiograph consistent with TB, close TB exposure and positive response to TB treatment; confirmed TB was defined by bacteriological confirmation of *Mycobacterium tuberculosis* (culture, Xpert MTB/RIF assay or both) from at least one respiratory specimen.[25] At the time of TB diagnosis, from this cohort, we included children who were 15 years old or younger at the time of TB diagnosis and had successfully completed their anti-tuberculous therapy with a documented standard treatment outcome of *cured* or *treatment completed* not less than 6 months before the date of enrolment.[2] In this paper, we have referred to these children as *post-TB cases*. Children were excluded if they were younger than 5 years old at enrolment (as they are often unable to perform spirometry reliably), unwilling to participate or if they had relocated from the study area. We also excluded children who were currently receiving treatment for recurrent pTB.

Comparison group

We enrolled a comparison group which comprised children who were age-matched as closely as possible to the cases, and who lived in the same household as the cases but had never previously been diagnosed with pTB. We aimed to enrol at least two children into the comparison arm for each post-TB case enrolled from the household. In the context of this study, a household was defined as a group of individuals eating from the same pot and living in the same building.[26] There were no children with signs and symptoms of active TB in the comparison group at the time of the study visit. We excluded all children with known chronic lung disease. All children who fulfilled the eligibility criteria for the comparison group were included in the study.

Procedures

During a screening telephone call with the family, we invited all children who were eligible for enrolment as post-TB cases for a study visit. We also invited all other children in the same household, who met our enrolment criteria for the comparison group, to attend with the post-TB case. During the study visit, we obtained demographic and clinical information for each child. Clinical and laboratory data relating to previous TB disease were collected from the participants' medical records at the MRCG at LSHTM childhood TB research clinic. We calculated anthropometric measurements, including height-for-age and body-mass-index-for-age z-scores using the WHO 2007 reference standards.[27] Stunting was defined as a height-for-age z-score less than −2 SD for age and sex.

Table 1 Participant characteristics, stratified by prior tuberculosis status

	Post-TB cases (n=68)	Comparison group (n=91)	P value
Age, years, median (IQR)	8.9 (7.2–11.2)	11.5 (8.0–13.7)	0.001*
Age at TB diagnosis, years, median (IQR)	6.5 (3.7–9.3)	–	–
Time since TB treatment completion, months, median (IQR)	19.2 (10.2–44.4)	–	–
Sex			
Female	32 (47.1)	34 (37.4)	0.259†
Male	36 (52.9)	57 (62.6)	
BCG scar present	60 (90.9)	82 (92.1)	0.789†
Stunted	13 (19.1)	6 (6.6)	0.032†
Underweight	17 (25.0)	19 (20.9)	0.521†
Comorbidities			
HIV infection	9 (13.2)	0	0.002†
Asthma	3 (4.4)	0	0.081†
Non-TB LRTI in preceding 12 months	6 (8.8)	1 (1.1)	0.036†
Allergies	6 (8.8)	4 (4.4)	0.196†
Exposure to environmental tobacco smoke	25 (36.8)	30 (33.0)	0.563†
Household biomass smoke exposure	66 (97.1)	89 (97.8)	0.333†
Type of TB diagnosis			
Confirmed	24 (35.3)	–	–
Unconfirmed	44 (64.7)	–	–

Data are presented as n (%) unless otherwise indicated.
*P value based on the non-parametric Somers' D measure, accounting for clustering.
†P values obtained from fitting a univariable mixed effect logistic regression where prior TB status is the dependent variable.
LRTI, lower respiratory tract infection; TB, tuberculosis.

Table 2 Clinical and respiratory parameters, stratified by prior tuberculosis status

	Post-tuberculosis cases	Comparison group	P value
Self-reported clinical and respiratory symptoms*	n=68	n=91	
Cough, n (%)	21 (30.9)	20 (22.0)	0.176†
Sputum, n (%)	8 (11.8)	7 (7.7)	0.397†
Wheeze, n (%)	6 (8.8)	9 (9.9)	0.819†
Easy fatigability, n (%)	15 (22.1)	10 (11.0)	0.095†
Chest pain, n (%)	17 (25.0)	15 (16.5)	0.105†
Failure to gain weight, n (%)	19 (27.9)	13 (14.3)	0.026†
Any respiratory symptom, n (%)	35 (51.5)	34 (37.4)	0.068†
Child self-report quality of life	n=63	n=89	
Physical health, median % (IQR)	68.8 (56.3–93.8)	81.3 (62.5–100)	0.016‡
Emotional functioning, median % (IQR)	80.0 (60.0–90.0)	80.0 (60.0–80.0)	0.538‡
Social functioning, median % (IQR)	90.0 (80.0–100)	90.0 (80.0–100)	0.333‡
School functioning, median % (IQR)	70.0 (60.0–90.0)	80.0 (60.0–90.0)	0.221‡
Psychosocial health, median % (IQR)	80.0 (70.0–86.7)	80.0 (70.0–90.0)	0.676‡
Total score, median % (IQR)	73.9 (65.2–89.1)	78.3 (67.4–89.1)	0.215‡
Parent-report quality of life	n=63	n=82	
Physical health, median % (IQR)	87.5 (68.8–93.8)	100 (87.5–100)	<0.001‡
Emotional functioning, median % (IQR)	80.0 (70.0–100)	90.0 (80.0–100)	0.001‡
Social functioning, median % (IQR)	100 (90.0–100)	100 (100–100)	0.019‡
School functioning, median % (IQR)	80.0 (60.0–100)	80.0 (60.0–100)	0.347‡
Psychosocial health, median % (IQR)	73.3 (80.0–93.3)	90.0 (80.0–96.7)	0.004‡
Total score, median % (IQR)	82.6 (71.7–93.5)	91.3 (82.6–97.8)	<0.001‡
Spirometry	n=52	n=86	
FEV_1 *z*-score, mean (SD)	−1.52 (−0.99)	−0.83 (−0.84)	<0.001‡
FVC *z*-score, mean (SD)	−1.32 (1.02)	−0.87 (0.89)	0.014‡
FEV_1/FVC ratio *z*-score, mean (SD)	−0.54 (0.91)	−0.03 (0.81)	0.001‡
Abnormal spirometry, n (%)	20 (38.5)	15 (17.4)	0.009†
Pattern of spirometry			
Normal, n (%)	32 (61.5)	71 (82.6)	0.029§
Obstructive, n (%)	1 (1.9)	2 (2.3)	
Restrictive, n (%)	19 (36.4)	13 (15.1)	

*Question read as follows: 'Have you had any of the following occurring often or repeatedly in the last 6 months?'.
†P values obtained from fitting a univariable mixed effect logistic regression where prior TB status is the independent variable.
‡P value based on the non-parametric Somers' D measure, accounting for clustering.
§P values obtained from fitting a univariable mixed effect logistic regression where prior TB status is the dependent variable.
FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; TB, tuberculosis.

Lung function measures

Lung function testing was performed on all study participants by a trained technician using the Easy on-PC portable spirometer (ndd Medical Technologies, Zurich, Switzerland). Spirometry was performed according to the American Thoracic Society (ATS)/European Respiratory Society guidelines.[28] Before daily data collection, ambient temperature, humidity and altitude were recorded. Afterwards, the spirometer was calibrated using a 3 L syringe to ensure measured volumes within 3% of syringe volume. Briefly, up to eight forced exhalations were performed while sitting. The procedure was repeated for all participants after receiving a bronchodilator (BD), salbutamol via a spacer device. We included only spirometry traces that met the ATS quality criteria in the analysis. Each flow volume was reviewed for acceptability and repeatability by two independent reviewers who were unaware of the results from each other. In cases of discordance, the two clinicians agreed on a consensus result. The *z*-scores for the highest forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were recorded and used for analysis. Data were standardised using the Global Lung Initiative 2012 (GLI-2012) African American reference ranges.[29] The GLI-2012 African American reference ranges have been previously validated among African children.[30] Lung function impairment was defined as the presence of abnormal spirometry measurement classified as either obstructive, possible restriction or mixed obstruction–restriction pattern.[31] Obstructive pattern was defined by a post-BD FEV_1/FVC ratio below the lower limit of normal (LLN) for height, age and sex. Possible restriction was defined by post-BD FVC below the LLN for the height, age and sex, with a normal FEV_1/FVC ratio.

HRQoL

We measured the HRQoL using the generic PedsQL V.4.0 instrument.[32] The PedsQL 4.0 has age-appropriate versions for children aged 2–18 years. It contains 23 items in four scales: physical health (8 items), emotional functioning (5 items), social functioning (5 items) and school functioning (5 items). A psychosocial health score (combined score of the emotional, social and school functioning subscales) and a total scale score can be computed. Items are scored on a 5-point Likert scale from 1 'Never a problem' to 5 'Almost always a problem', with a 1-week

Table 3 Factors associated with lung function impairment in all children

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	aOR (95% CI)	P value
Post-TB case	4.2 (1.5 to 12.0)	0.009	3.9 (1.1 to 15.1)	0.047
Age ≥10 years	2.4 (0.8 to 7.9)	0.516	3.0 (0.7 to 12.1)	0.121
Male	1.0 (0.3 to 3.5)	0.915	0.7 (0.2 to 2.2)	0.504
BCG scar present	3.1 (0.4 to 25.7)	0.291	–	–
Stunted	11.0 (1.3 to 92.0)	0.001	4.3 (0.6 to 31.4)	0.147
Underweight	5.7 (1.2 to 27.1)	0.004	3.2 (0.9 to 12.2)	0.080
Comorbidities				
HIV infection	17.0 (1.9 to 151.2)	0.016	2.0 (0.1 to 49.6)	0.671
Asthma	1.5 (0.1 to 16.9)	0.739	–	–
Non-TB LRTI in preceding 12 months	1.5 (0.3 to 8.6)	0.634	–	–
Allergies	1.5 (0.4 to 6.4)	0.574	–	–
Respiratory symptoms*				
Cough	4.2 (1.1 to 15.8)	0.002	19.0 (1.6 to 226.0)	0.006
Sputum	3.2 (0.5 to 20.5)	0.195	0.1 (0.1 to 1.9)	0.137
Wheeze	1.1 (0.2 to 7.2)	0.902	–	–
Easy fatigability	2.6 (0.7 to 10.1)	0.207	–	–
Chest pain	1.9 (0.4 to 8.6)	0.009	4.7 (0.8 to 29.4)	0.096
Failure to gain weight	3.6 (1.5 to 9.0)	0.011	7.1 (0.8 to 66.9)	0.087
Any respiratory symptom	2.8 (0.7 to 11.6)	0.014	0.1 (0.01 to 1.3)	0.094
Exposure to environmental tobacco smoke	1.1 (0.1 to 13.3)	0.935	–	–

Data are presented as n (%) unless otherwise indicated.
*Question read as follows: 'Have you had any of the following occurring often or repeatedly in the last 6 months?'.
aOR, adjusted OR; LRTI, lower respiratory tract infections; TB, tuberculosis.

recall period. The responses are collected from the child and the parent independently, and answers are transformed into a 0–100 scale, with a higher score representing a better HRQoL. The PedsQL has been shown to have a high reliability and validity among children with chronic health conditions.[33 34]

The PedsQL instrument was in English Language. It was administered by staff who had been trained in its use and are proficient in English but also speak the local languages. Interviewers administered the instrument in any of the local languages that the subject felt most comfortable with. The children and their parents were interviewed separately.

Table 4 Time since tuberculosis treatment and type of tuberculosis diagnosis, stratified by spirometry outcome in post-tuberculosis cases

	Normal spirometry (n=32)	Abnormal spirometry (n=20)	P value
Time since TB treatment completion (months)			
<12 months	11 (34.4)	7 (35.5)	0.878*
12 to <24 months	9 (28.1)	4 (20.0)	
>24 months	12 (37.5)	9 (45.0)	
Type of TB diagnosis			
Confirmed	13 (40.6)	7 (35.0)	0.774†
Unconfirmed	19 (59.4)	13 (65.0)	

*P value obtained from Cochran-Armitage test for trend.
†P value obtained from Fisher's exact test.
TB, tuberculosis.

Statistical analysis

We used a convenience sample of all reachable and eligible post-TB cases from our childhood TB registry as described above, as well as all eligible children who were willing to be enrolled into the comparison group. Means (SD), medians (IQR) and proportions were used as appropriate to describe the burden of respiratory pathology using clinical and respiratory parameters, by prior TB status of the children. We assessed the association between prior TB status and those clinical and respiratory parameters using the mixed effects logistic and the Somers' D statistic as appropriate to account for clustering between post-TB case and apparently healthy children within the same households. The Somers' D statistic is a rank-based measure of association, that can accommodate clustered data.[35] We investigated the association between prior TB status and abnormal lung function with a priori defined clinical data using univariable mixed effects logistic regressions. We then fitted a multivariable logistic regression model which incorporated variables with p values<0.20 in the univariable model. We also compared the distributions of the HRQoL scores between the post-TB cases and comparison group. Among the post-TB cases, we investigated the association between time since TB treatment completion, or the type of TB diagnosis, and abnormal lung function using the χ^2 test for trend and Fisher's exact test, respectively. ORs with 95% CI were reported. We investigated possible interaction between post-TB case and each of the covariates in the multivariable logistic regression, but no evidence of interaction was found. Data were analysed using Stata/SE V.17.0 (StataCorp, College Station, Texas, USA).

Role of funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

RESULTS

Participant characteristics
A total of 185 children were identified from the childhood TB registry to have been diagnosed and treated for pTB from 2014 to 2019. Of these, families of 108 children were contacted, of whom 40 children were ineligible for enrolment because they were below 5 years of age (n=28), unwilling to participate (n=6), had relocated from the study area (n=4) or were ill with a recurrent pTB (n=2). Overall, 68 post-TB cases and 91 children in the comparison group were enrolled between 13 January 2020 and 3 March 2021 (figure 1). The number of children enrolled as post-TB cases and comparison group from each household are shown in online supplemental material table 1.

The demographic characteristics of the study participants are detailed in table 1. The post-TB cases had a median age of 8.9 years (IQR 7.2–11.2) compared with 11.5 years (IQR 8.0–13.7) in the comparison group, which was statistically significant but thought not to be clinically important. The median age at TB diagnosis was 6.5 years (IQR 3.7–9.3), and the median duration since completion of TB treatment was 19.2 months (IQR 10.2–44.4). A higher proportion of the post-TB cases were stunted compared with the comparison group (13/68, 19.1% in post-TB cases vs 6/91, 6.6% in comparison group, p=0.032). A history of non-TB LRTI in the preceding 12 months was more commonly reported in the post-TB cases than in the comparison group (6/68, 8.8% in the post-TB cases vs 1/91, 1.1% in the comparison group, p=0.036). The prevalence of HIV infection among the post-TB cases was 13.2%. Three (4.4%) post-TB cases had been previously diagnosed with asthma. There were no children living with HIV or asthma in the comparison group. We found no significant differences in the distribution of exposure to environment tobacco smoke or household biomass smoke exposure between post-TB cases and the comparison group (table 1).

Chronic respiratory symptoms and HRQoL
More than half (35/68, 51.5%) of the post-TB cases reported one or more recurrent respiratory symptom(s) in the preceding 6 months compared with about one-third (34/91, 37.4%) of the comparison group. The most common reported symptom in both groups was cough (21/68, 30.9% in the post-TB cases and 20/91, 22.0% in the comparison group). Furthermore, the post-TB cases were more likely to report failure to gain weight compared with the comparison group (19/68, 27.9% in the post-TB cases vs 13/91, 14.3% in the comparison group, p=0.026, table 2).

Post-TB cases had lower median percentage scores on the self-reported physical functioning scale of the PedsQL (68·8%) compared with the comparison group (81.3%), p=0.016. More so, the post-TB cases had lower median percentage scores compared with the comparison group in five out of six of the parent-reported PedsQL scales (table 2).

Lung function impairment
The spirometry data from 52 (76.5%) post-TB cases and 86 (94.5%) of the comparison group met the quality criteria for acceptability and repeatability. The mean *z*-scores for the FEV_1, FVC and FEV_1/FVC ratio were significantly lower in the post-TB cases compared with the comparison group (p<0.001, p=0.014 and p=0.001, respectively). The proportion of children with impaired lung function was significantly higher in the post-TB cases (20/52, 38.5%) compared with the comparison group (15/86, 17.4%), p=0·009. Restrictive pattern abnormalities were the most common in both post-TB cases (19/52, 36.4%) and comparison group (13/15, 15.1%). There were no study participants with mixed obstructive–restrictive pattern (table 2).

Factors associated with lung function impairment
Compared with the comparison group, there was strong evidence for abnormal lung function in post-TB cases, after controlling for prespecified sociodemographic and clinical covariates (adjusted OR (aOR) 3.9, 95% CI 1.1 to 15.1, p=0.047, table 3). A self-reported history of frequent or repeated cough in the preceding 6 months was found to be associated with abnormal lung function among the children in this study (aOR 19.0, 95% CI 1.6 to 226.0, p=0·006).

Among the post-TB cases, there was no evidence of association between time since TB treatment completion, or the type of TB diagnosis, and presence of abnormal lung function (table 4).

DISCUSSION
We compared the lung function measurements and HRQoL between former childhood TB cases who were at least 6 months post-treatment completion and a comparison group of age-matched children who had never been previously diagnosed with pTB disease and lived in the same household. The post-TB cases had more than threefold increased odds of lung function impairment, predominantly of the restrictive type, compared with the comparison group. Similarly, post-TB cases had significantly lower self-reported physical HRQoL scores when compared with the comparison group.

To our knowledge, this is the first study describing the prevalence and pattern of lung function impairment associated with pTB treatment completion in children. The finding of a high burden of post-TB lung function impairment is consistent with findings in adults from previous literature which suggest that pTB survivors had twofold-to-fourfold increased odds of abnormal spirometry compared with healthy controls.[7–9] Our findings are similar to data in adolescents living with HIV which showed that prior pTB was associated with low FEV_1 and FVC, suggesting a similar or possibly higher population burden of these post-TB pulmonary sequelae in children.[20]

Published evidence in adolescents has shown that the effect of HIV on lung function was reduced after adjusting for previous pTB infection.[20] Similarly, adults living with HIV have been found to have no different or less extensive lung damage following TB compared with HIV-negative adults, even when they have had similar duration of TB.[10 36] Likewise, in our study, HIV infection was not significantly associated with lung function impairment among all children. These findings suggest that pTB may be associated with reduced lung function, even in people living with HIV. However, we acknowledge that the small number of children living with HIV among the sample population (with none in the comparison group) suggest that these findings need to be interpreted with caution.

The substantial burden of chronic respiratory symptoms and abnormal lung function (prevalence 17.4%) among the apparently healthy comparison group in this study is alarming. This is possibly due to the potential effect of frequent respiratory infections, or exposure to environmental factors such as tobacco smoke and biomass smoke exposure on lung function in children. Evidence in the literature has documented abnormal

spirometry in as high as 16.5% of children aged 6–8 years who were exposed to open fire cooking.[37] Similarly, early-life LRTI has been shown to be associated with impaired lung function later in life.[19] Our findings warrant further investigation to explore the prevalence and risk factors of impaired lung function in the apparently-healthy population, who nevertheless experiences frequent occurrences of early-life LRTI and a high level of exposure to biomass smoke in the household due to cooking on open fires.[38]

Our data show that pTB is associated with a reduction in all domains of the HRQoL in the longer term. In the present study, the post-TB cases self-reported primarily impaired physical functioning, while their parents reported an impairment across five out of six HRQoL domains. Adverse physical and psychosocial consequences are well recognised outcomes of pTB.[39] While studies have shown that HRQoL improves during standard treatment for TB,[40–43] our data suggest that many children may have reduced HRQoL long after treatment completion, although we only report a snapshot, given that we have no pre-TB measurements. Moreover, the discrepancy between the self-reported and parent-reported HRQoL scores are not unexpected. Parents and caregivers are known to perceive their child's ailment as more problematic.[34] Our data support the need to assess the HRQoL as an outcome measure after treatment completion and beyond, preferably using a more qualitative approach.[40]

The combination of spirometry and HRQoL measures as tools to assess health and well-being after TB treatment represents a strength of this study, as this further highlights the association between previous TB and long-term physical and psychosocial well-being.[44] A limitation of our study is that spirometry alone cannot be relied on to make inference about the presence of restrictive lung function abnormalities. This often requires diagnostic confirmation by measuring the total lung capacity, which was not possible in our setting.[31] Second, as the lung function was not assessed prior to TB disease, we cannot currently confirm a causal relationship between the disease and impaired lung function, although further prospective work is currently ongoing. Third, a single spirometry measurement may not fully reflect the evolution of the lung function, which has been shown to change over time after treatment completion for TB.[10] This is especially so in children whose lungs are still undergoing developmental changes.[12 13] Fourth, our participant recruitment required prior attendance of the MRCG at LSHTM childhood TB research clinic, with a potential for selection bias away from those who were diagnosed elsewhere.

In conclusion, previous pTB in children was associated with reduced spirometric *z*-scores, and HRQoL scores compared with age-matched peers without a history of TB. Post-TB cases had greater than threefold increased odds of having abnormal lung function compared with the comparison group. Longitudinal studies to further characterise the evolution of symptoms and lung volumes after TB treatment completion in children are needed to help define and further characterise PTLD in children. Finally, we recommend a more holistic approach to define TB treatment outcome which considers the evaluation and management of sequelae, especially in children, to improve health and well-being across the life course. Anti-tuberculous chemotherapy leads to a bacteriological cure, but is far from the complete answer to tuberculous disease in children.

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Chapter 4: Identifying the definitions, measurement instruments, and research gaps in the literature on paediatric post-tuberculosis lung disease (Research Paper 2)

4.1 Overview of Chapter

This chapter addresses the second objective of my PhD, which was "*to systematically review the existing literature on paediatric post-tuberculosis lung disease (PTLD) with the aim of identifying definitions, measurement instruments, and research gaps on paediatric post-tuberculosis lung disease.*"

As of the time of the thesis submission, the scoping review paper addressing this chapter's objective had been accepted for publication in the *Paediatric Respiratory Reviews*. The complete bibliographic information and authorship order are shown below:

Nkereuwem E, Owusu SA, Edem VF, Kampmann B, Togun T. Post-tuberculosis lung disease in children and adolescents: a scoping review of definitions, measuring tools, and research gaps. *Paediatr Respir Rev* 2024: S1526-0542(24)00055-1. https://doi.org/10.1016/j.prrv.2024.07.001.

The supplementary material accompanying the scoping review paper in this chapter is included in Appendix 7.

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SECTION A – Student Details

Student ID Number	449227	**Title**	Dr
First Name(s)	Esin Esin		
Surname/Family Name	Nkereuwem		
Thesis Title	Evaluating the sequelae of pulmonary tubeculosis in Gambian children and adolescents		
Primary Supervisor	Professor Beate Kampmann		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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SECTION E

Student Signature	[redacted]
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4.2 Research Paper 2

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Paediatric Respiratory Reviews xxx (xxxx) xxx

Contents lists available at ScienceDirect

Paediatric Respiratory Reviews

Review

Post-tuberculosis lung disease in children and adolescents: A scoping review of definitions, measuring tools, and research gaps

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Educational aims

The reader will come to appreciate:

- Understand that the literature available on post-tuberculosis lung disease (PTLD) in children and adolescents lacks a consistent terminology or definition.
- Evaluate the various methods and tools used to measure PTLD in the current literature and identify the inconsistencies in the measurement techniques employed.
- Understand that the literature on post-TB research in children and adolescents has several gaps that need to be addressed.

ARTICLE INFO

Keywords:
Childhood tuberculosis
Post-tuberculosis lung disease
Respiratory impairment
Sequelae

ABSTRACT

Tuberculosis (TB) survivors, especially children and adolescents, can develop chronic respiratory problems called post-tuberculosis lung disease (PTLD). We conducted a scoping review to identify the current knowledge gaps on PTLD definitions, measuring tools, and research specific to this age group. We searched MEDLINE, EMBASE, Global Health, CINAHL, and Web of Science for studies published between January 1, 2000, and March 1, 2024, and identified 16 studies.

Our review found that no consistent definition of PTLD was used in the studies, and the measurement tools used varied widely. Moreover, there was a lack of research on children under five years old, who are disproportionately affected by TB. Also, symptom screening tools designed for adults were frequently used in these studies, raising concerns about their accuracy in detecting PTLD in children and adolescents.

Several critical research gaps require attention to improve our understanding and treatment of PTLD. Firstly, the use of inconsistent definitions of PTLD across studies makes it challenging to compare research findings and gain a clear understanding of the condition. Therefore, we need to include an objective measurement of respiratory health, such as a comprehensive post-TB lung function assessment for children and adolescents. It is also crucial to determine the optimal timing and frequency of post-TB assessments for effective PTLD detection. Furthermore, we need more knowledge of the modifiable risk factors for PTLD. The scarcity of prospective studies makes it difficult to establish causality and track the long-term course of the disease in children and adolescents. Finally, current approaches to PTLD management often fail to consider patient-reported outcomes and strategies for social support. Addressing these

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research gaps in future studies can improve our understanding and management of paediatric PTLD, leading to better long-term health outcomes for this vulnerable population.

INTRODUCTION

The burden of chronic lung diseases attributable to tuberculosis (TB) is growing worldwide [1]. It is estimated that between 1 % and 49 % of paediatric pulmonary tuberculosis (pTB) survivors experience sequelae characterised by persistent respiratory symptoms, radiographic abnormalities, or impaired lung function [2]. While the diagnosis of TB in children remains a challenge, over 80 % of newly diagnosed children started on treatment each year will achieve a microbiological cure, thus adding to this growing pool of TB survivors [3,4].

Emerging evidence suggests that similar to adults, these childhood and adolescent pTB survivors are also susceptible to the long-term consequences of pTB [5–7]. This residual respiratory impairment, known as post-tuberculosis lung disease (PTLD), can manifest beyond six months after treatment completion and have a significant impact on overall health and well-being [6]. It is now evident that the impact of pTB extends beyond the initial infection and treatment period [8].

However, our understanding of PTLD in children and adolescents remains incomplete. Paediatric pTB differs significantly from adults [9]. Children and adolescents have developing lungs that are susceptible to insults [10,11]. Moreover, PTLD is particularly concerning in this younger population as they have a longer lifespan ahead of them. Furthermore, drug-resistant pTB often requires longer treatment and is associated with prolonged illness and an increased risk of lung damage [7,12]. Consequently, children who contract TB face the potential to carry the detrimental effects of the disease for an extended period. Therefore, it is crucial to understand, correctly define, and mitigate the long-term consequences of pTB in children and adolescents, especially given the improving survival rates [13].

Several co-morbidities affect lung function and may potentially influence the development and progression of PTLD. HIV infection in children and adolescents has been linked to pulmonary complications and a higher prevalence of lung function impairment. Consequently, TB/HIV co-infected children and adolescents may be susceptible to more severe respiratory sequelae [14,15]. Similarly, as post-COVID-19 disorders account for substantial lung health consequences, it is reasonable to assume that a TB and COVID-19 co-infection may be associated with worse outcomes [16].

Host factors such as genetics, nutritional status, and hereditary conditions like cystic fibrosis, as well as environmental exposure to pollutants and crowded living conditions, may play a critical role in exacerbating lung damage and altering the overall course of TB-associated respiratory morbidity [17–19]. Therefore, it is essential to consider and address these in studies measuring PTLD in children.

During the second International Post-Tuberculosis Symposium, a definition for paediatric PTLD was proposed as *'evidence of chronic respiratory impairment in an individual previously treated for pulmonary tuberculosis in whom active tuberculosis is excluded, and in whom no other cause of chronic lung disease is the predominant cause.'*[20] Although this definition aimed to standardise the literature, its practical implementation remains unclear. There are still several unanswered questions about paediatric PTLD, such as *what to measure*, *when to measure*, and *which tools to use for the measurement*. Therefore, we conducted a scoping review to evaluate the current state of evidence regarding the definition and measurement of paediatric PTLD in the literature. Additionally, we sought to report the research gaps identified in the few published studies.

METHODS

Scoping review questions

In this scoping review, we sought to answer the following questions: 1) What are the different terms and definitions used in the literature to describe paediatric PTLD? 2) What tools are used to measure paediatric PTLD in the literature? 3) What are the research gaps in the literature regarding paediatric PTLD?

Search strategy

We conducted a literature search across five databases, which included MEDLINE, EMBASE, Global Health, CINAHL, and Web of Science. To ensure a comprehensive search, we followed a three-step strategy recommended by the Joanna Briggs Institute [21]. First, we conducted a preliminary search of MEDLINE and Web of Science on January 18, 2024, using the key search concepts "Paediatric," "Post-TB," and "Sequel." After analysing the text words in the title and abstract of the retrieved papers, as well as the indexing terms, we refined the initial search strategy by including additional key concepts. Our librarian provided input to develop and refine the search strategy, which is available in Supplementary Material Table 1.

In the second step, we conducted a full search on March 27, 2024, across all five included databases using the refined search strategy from the first step. We adapted the search strategy to fit the search terminologies for each database. In the third step, we searched the reference list of the included papers from the database search for additional sources not previously retrieved.

Inclusion criteria

We included studies that fulfilled the following criteria: 1) studies that included children and adolescents aged $\leq$19 years, including mixed population studies. This was because we anticipated a lack of publications specifically focused on paediatric populations; 2) Sequelae measured after pTB treatment completion; and 3) observational studies and clinical trials. Considering the limited number of studies in the field, we did not exclude any studies based on the language of publication. However, we only considered studies published from January 1, 2000 to March 1, 2024. We extended the search to March 1, 2024, to include up-to-date evidence on paediatric post-TB sequelae. We excluded systematic reviews, study protocols, journal commentaries, and conference papers.

Study selection

We imported the retrieved articles into Endnote 21 (Clarivate Analytics) for the de-duplication of records. Subsequently, we exported the records to Rayyan, a web-based application for screening review articles [22]. Two reviewers (EN and SAO) independently screened the titles and abstracts for relevance using the eligibility criteria. We exported the records that met the

eligibility criteria to Endnote for full-text retrieval, screening, and extraction. One reviewer (EN) screened the full text of the records to ensure their suitability for full data extraction, while the other reviewer (SAO) verified all decisions. Final decisions regarding the eligibility of articles were made through consensus. A third member of the review team (VFE) was consulted to resolve disagreements when the two initial reviewers failed to reach a consensus. All decisions were based on consensus.

Data extraction and collation

We used a data extraction template to extract relevant information from the articles included in the study. The template was adapted from the JBI data extraction tool specifically designed for scoping reviews. Before initiating data extraction, two members of the review team piloted the template on five randomly selected articles and refined it based on feedback. One reviewer (EN) extracted data from the articles, while another reviewer (SAO) cross-checked the full-text articles to ensure the extracted variables were correct.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination of this research.

Analysis

We used descriptive statistics to summarise the extracted data and presented the results as tables and charts. We evaluated each study to see if it aligned with the current definition of paediatric PTLD. To assess the "*evidence of chronic respiratory impairment*", we rated each study using the ten parameters proposed in the PTLD measurement toolbox to determine how it would perform compared to the current definition [17]. Each parameter received a score of one if the authors reported measuring it. The minimum score was zero if no parameter was measured, and a maximum of ten if all parameters were measured. We presented the measuring tools for pulmonary sequelae based on the classification of toolboxes for post-TB assessment proposed in the clinical standards for PTLD [23]: 1) Clinical assessment; 2) radiological assessment; 3) lung function assessment; and 4) other tools that may have been used for functional evaluation to assess the health and well-being following TB treatment completion.

We followed a thematic analytic approach to identify the research gaps in each included study [24]. This approach involved three stages: 1) coding of the findings from each study while examining for meaning and content; 2) reorganising the codes into categories; and 3) examining and comparing the categories for similarities and differences to allow clear identification of themes arising from the data.

Role of the funding source

The funder of the research had no role in the design, selection, data collection, data analysis, data interpretation, or writing of the report of this scoping review.

RESULTS

The initial search yielded 887 articles, as shown in Fig. 1. After removing duplicates, 666 articles were retrieved and reviewed for inclusion. After full-text screening, 16 articles were included in the analysis.

Characteristics of the included studies

Table 1 gives a detailed summary of the studies included in the review. The studies were conducted in 13 countries across four continents, with publication dates ranging from 2005 to 2024. Most studies (n = 9) were conducted in sub-Saharan Africa, with ten studies coming from high-burden TB countries. The primary language of publication was English for all the studies. The review included four retrospective [25–28], seven cross-sectional [6,12,29–33], and five prospective studies [5,7,34–36].

Eleven studies were conducted with participants of different age groups, including children, adolescents, and adults [12,25–27,29–31,33–36]. Conversely, the remaining five studies [5–7,28,32] recruited only children and adolescents, with only two [5,32] including participants younger than five years old. Thus, the studies included in this review had a limited representation of younger children.

Four studies [6,32,35,36] included only participants diagnosed with drug-sensitive TB (DSTB), while one study [12] included only those with drug-resistant TB (DRTB). Three studies [5,7,26] examined a mixed population with both DSTB and DRTB, while the remaining eight studies [25,27–31,33,34] did not specify the type of TB in the enrolled population.

In the studies reporting HIV prevalence among the investigated population, data ranged from <1 % [5,12,32] to 100 % [29]. The study that reported 100 % HIV prevalence [29] enrolled only children and adolescents aged 10 to 19 years living with HIV.

Terminologies and definitions for pulmonary sequelae of TB

None of the reviewed literature presented a unified definition of PTLD. Furthermore, there was an inconsistency in the terminologies used across the studies. The most frequently encountered descriptive phrase was *sequelae of pulmonary TB* [12,25,26,28]. Various terminologies, such as post-TB *lung function impairment* [31], *lung damage* [33,35], *chronic respiratory symptoms* [25], *TB-associated complications* [32], and pulmonary impairment after TB (PIAT) [34] were used without explicit definitions.

When assessing how the evidence of chronic respiratory impairment aligned with the current paediatric PTLD definition and proposed toolbox, one study [35] scored a 10/10, and two [12,34] scored an 8/10. Most studies [5–7,26,27,29] scored between 5/10 and 7/10. The study [28] with the lowest rating (0/10) did not use any of the parameters proposed in the toolbox. Rather, the authors only stated that the children experienced pulmonary sequelae of TB without mentioning how it was assessed (Fig. 3).

Measuring tools for pulmonary sequelae of TB

Clinical assessment

In most studies (n = 10), self-reported symptoms were the primary approach for evaluating patients following TB treatment (Fig. 2). One study [5], which particularly focused on wheezing in children under five years of age, used a previously described and validated tool that depends on a combination of parental reports and health worker-ascertained wheezing [37,38].

Several studies used pre-validated tools for the purpose of screening symptoms or conducting broader clinical assessments. These tools included the Modified Medical Research Council (mMRC) Dyspnoea Scale [29,34], the COPD Assessment Test (CAT) [29], as well as the St. George's Respiratory Questionnaire (SGRQ) [35] and the International Multidisciplinary Programme to Address Lung Health and TB in Africa (IMPALA) questionnaire for lung health in Africa across the life course [30].

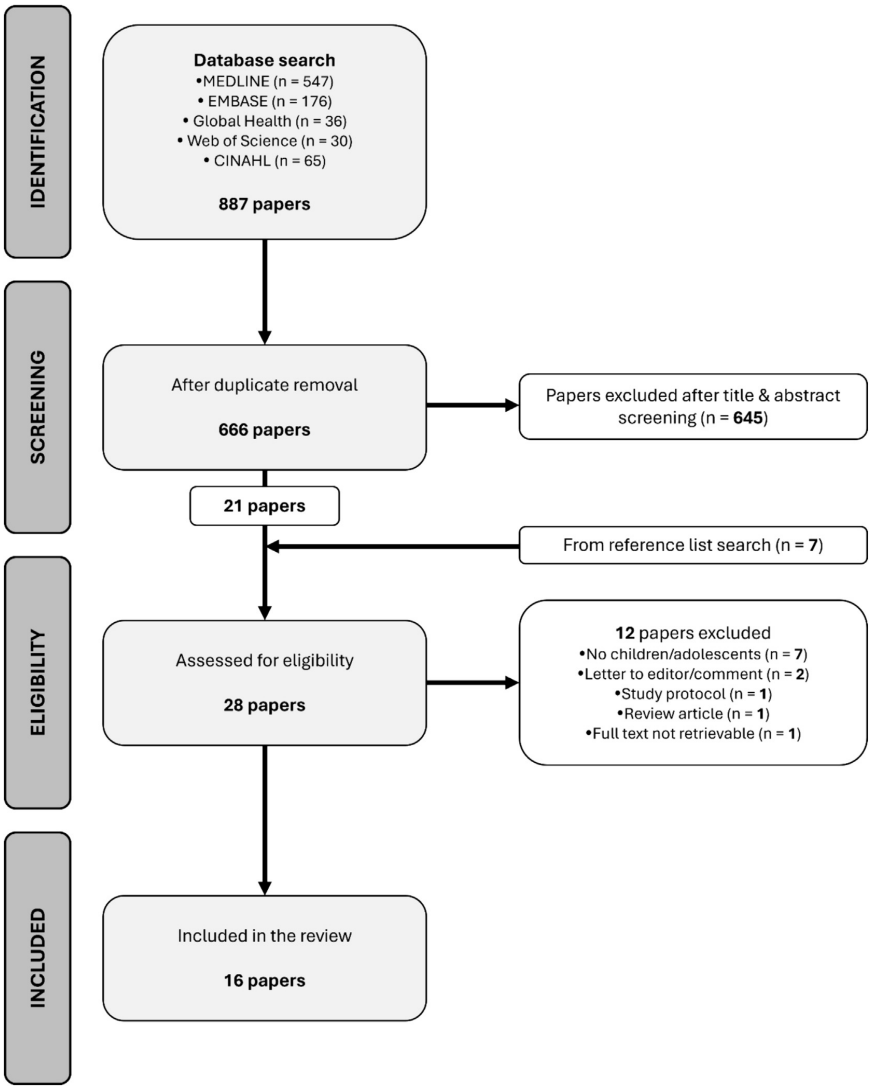

Fig. 1. Study flowchart.

The definition of chronic respiratory symptoms varied across studies. Some studies defined chronic symptoms as those lasting for more than two weeks [33], more than four weeks [30], or occurring two or more times [5]. Additionally, several studies did not mention the screening scales or duration used to define the symptoms.

In addition to symptom screening, many studies included other assessments, such as anthropometric measurements [5,6,26,35] and socioeconomic status [12,35].

Radiologic assessment

Seven studies used chest X-ray (CXR) imaging for post-TB assessment (Fig. 2) [12,25,32–36]. Of these, five studies utilised pre-validated tools for CXR assessment [12,35,36], while one study [33] remained unclear about their method for abnormality classification. Additionally, two studies [25,32] did not provide specific details on the criteria or rationale for using CXRs.

On the other hand, five studies utilised CT scans for post-TB assessment [25,27,29,32,35], and three studies provided a detailed explanation of the specific criteria or indications for its use [27,29,35]. Moreover, one study defined PTLD solely based on the presence of abnormal findings on both CXR and CT scans [25].

Lung function assessment

Ten studies [6,7,12,26,27,29,31,34–36] measured lung function using spirometry, nine of which reported performing both pre-bronchodilator and post-bronchodilator tests (Fig. 2). In addition,

Table 1
Characteristics of the included studies.

Study	Year of publication	Country	Study design	Age of participants (years)	Proportion of participants that are children & adolescents (n/N)	Proportion of participants that are HIV +	Type of TB in participants	Timing of post-TB assessment
Binegdie *et al.* [25]	2015	Ethiopia	Retrospective	≥12	18*/134	?	?	?
Gandhi *et al.* [34]	2015	India	Prospective	≥14	59*/146	?	?	?
Snène *et al.* [28]	2016	Tunisia	Retrospective	≤18	46/46	?	?	?
Mbatchou *et al.* [31]	2016	Cameroun	Cross-sectional	≥15	?/269	18%	?	Within 3 years post-treatment
Byrne *et al.* [26]	2017	Peru	Retrospective	10 to 70	20#/177	?	DSTB+DRTB	Within 12 months and 36 months post-treatment for DSTB & DRTB respectively
Attia *et al.* [29]	2018	Kenya	Cross-sectional	≥10	52^/427	100%	?	?
van Kampen *et al.* [33]	2018	Uganda	Cross-sectional	≥15	109*/798	?	?	?
Katoto *et al.* [30]	2018	DRC	Cross-sectional	≥15	121@/441	?	?	?
Singla *et al.* [12]	2018	India	Cross-sectional	≥1	1~/46	0%	DRTB	?
Soñano-Arandes *et al.* [32]	2019	Catalonia	Cross-sectional	<2	134/134	0%	DSTB	Within 2 years post-treatment
Meghji *et al.* [35]	2020	Malawi	Prospective	≥15	17^/405	60%	DSTB	At 6-months and 12-months post-treatment
Dias *et al.* [27]	2022	Brazil	Retrospective	≥14	?/54	11%	?	?
Ravindranath *et al.* [36]	2022	India	Prospective	≤65	26~/130	?	DSTB	?
Nkereuwem *et al.* [6]	2023	The Gambia	Cross-sectional	5 to 18	68/68	13%	DSTB	Beyond 6-months post-treatment
Martinez *et al.* [5]	2023	South Africa	Prospective	≤5	96/96	<1%	DSTB+DRTB	At 6 months, 12 months, then annually for the first 5 years of life
van der Zalm *et al.* [7]	2024	South Africa	Prospective	10 to 19	50/50	6%	DSTB+DRTB	At treatment completion and 12 months later

*≤24 years; #<18 years; ^≤19 years; @≤35 years; ~≤15 years; n = number of participants including paediatric age-group; N=total number of study participants with previous pulmonary tuberculosis; DSTB: drug-sensitive tuberculosis; DRTB: drug-resistant tuberculosis;? = not stated.

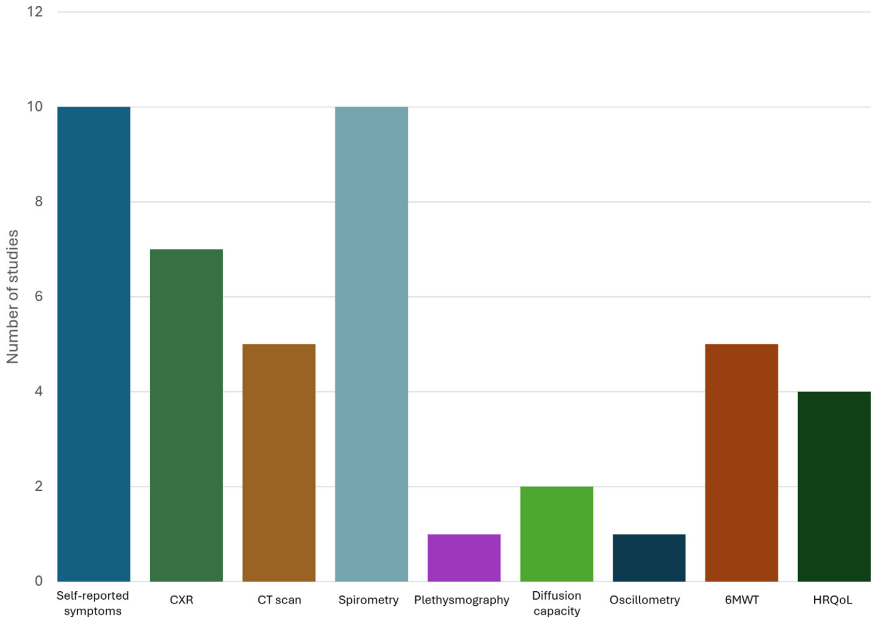

Fig. 2. Number of included studies that used each measuring tool for post-TB assessment; CXR: chest X-ray; CT: computerised tomography; 6MWT: six-minute walk test; HRQoL: health-related quality of life.

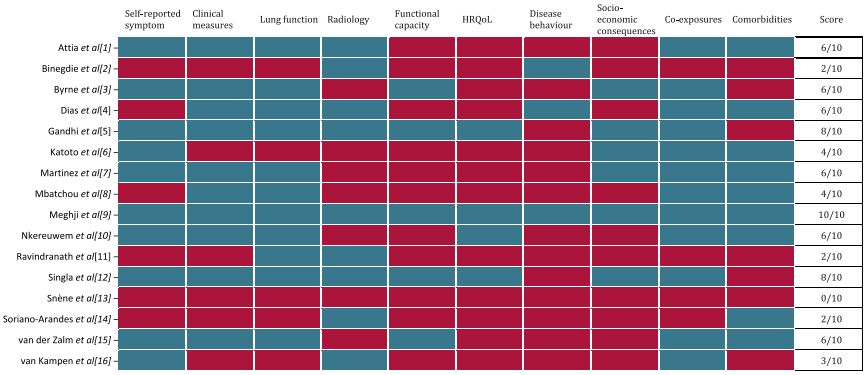

Fig. 3. Summary of how each study assessed evidence of chronic respiratory impairment based on the parameters in the PTLD toolbox proposed during the First International Post-TB Symposium.[17] Each parameter was assigned a score of one. Red: parameter was not assessed; Green: parameter was assessed; HRQoL: health-related quality of life. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

two studies [7,12] performed a more comprehensive lung function measurement, including plethysmography and diffusion capacity.

One of the two studies [5] which enrolled children under five years old conducted comprehensive lung function measurements. The measurements included tidal breathing, oscillometry, fractional exhaled nitric oxide [FeNO], multiple breath washout [MBW] and lung clearance index [LCI]. This was also the only study in the review that measured pre-TB lung function.

Other measurements

Other tests were conducted to assess the post-TB health status, including the six-minute walk test (6MWT) [7,12,26,34,35] and measurement of the health-related quality of life using pre-validated tools (Fig. 2) [6,12,34,35].

Timing of measurement

The frequency of post-TB assessments and measurements varied significantly across different research studies. Two of the five studies that used a prospective design had fixed time points for post-TB testing, either at treatment completion, six months, or 12 months after enrolment [7,35]. Another prospective study, which was a birth cohort, had a pre-determined schedule for follow-up at six months, 12 months, and annually thereafter, irrespective of when the children contracted TB during the study (Table 1) [5].

Similarly, the timing of enrolment relative to the date of treatment completion also varied across different studies. One study enrolled subjects at least six months post-treatment but conducted the assessments at varied time points depending on when the participants were recruited, with a median duration of 19.2 months post-TB treatment completion [6]. All other studies had different time points for enrolment, such as within one year [26] and within three years of TB treatment completion [26,31]. However, there was little mention of how much of the observed respiratory health impairment could be attributed to other lung diseases during this post-TB period.

As cited in one study [30], the inclusion of participants did not consider the time since their previous TB as there was no evidence of a relationship between the time since treatment completion and the onset or peak of lung function impairment [6].

Identified research gaps

The research gaps which were identified from the included studies following a thematic analytic approach were grouped into four themes as follows (Fig. 3):

Comprehensive pulmonary function assessment

The studies included in this review highlighted the critical importance of including children and adolescents in research on TB-associated respiratory morbidity [6,7]. The studies suggested that future research should not only rely on symptom assessments but also incorporate pulmonary function measurement to diagnose PTLD accurately [7,26,33]. However, limited resources might also restrict comprehensive pulmonary function assessments in some settings. Therefore, more accessible, and cost-effective tools are needed to identify children and adolescents at risk of PTLD [7,31].

Modifiable risk factors and sequelae

Several studies highlighted the importance of investigating modifiable risk factors for developing PTLD. The most frequently highlighted factors included host factors such as malnutrition [5–7,12,26,29,31,34,35], co-morbid illnesses such as HIV [5–7,27,29,32,35], mycobacterial drug susceptibility [5,7,12,26], and environmental factors such as exposure to indoor pollution [5–7,26,29,30,35], tobacco smoke [5–7,26,27,29,31,33–35], and overcrowding [5,35]. Some studies also suggested exploring the impact of pre-treatment illness duration on respiratory outcomes [26,33,36], emphasising the need for early diagnosis. Other studies highlighted the need to investigate how the relationship between these host factors, environmental determinants, and pathogen characteristics could be harnessed as potential targets for intervention [35]. Furthermore, studies investigating the effectiveness of early TB diagnosis and host-directed therapies should also consider the burden of PTLD as a secondary outcome [35].

Prospective studies and exposure assessment

Most of the cross-sectional or retrospective studies [6,12,26,27,29–31,33] considered other exposures or illnesses that could independently affect respiratory health. However, these studies had a limited ability to establish temporality due to the snapshot nature of the study design. They suggested the need to conduct prospective studies that aim to capture lifetime exposure to various other risk factors which could affect respiratory health [6,30,31,33]. Additionally, prospective studies are required to establish causality, as well as characterise the evolution of symptoms and lung volumes after treatment [6,33].

The five prospective studies [5,7,34–36] included in the review demonstrated a temporal association between previous TB and respiratory outcomes while accounting for these other illnesses and exposures. Furthermore, one prospective [7], one cross-sectional [6], and one retrospective [26] study included a non-TB comparison group to account for these co-exposures and strengthen the association between previous pTB and poor respiratory outcomes.

Long-term impact, follow-up, and social support

Given the long-term impact of TB on quality of life, it was proposed that patient-reported outcomes be incorporated to assess quality of life beyond treatment completion, potentially by using qualitative approaches [6,34]. Long-term follow-up is important to understand the full impact of TB on patients' physical, functional, and socio-economic well-being [12]. Moving beyond a focus on bacteriological cure, future efforts should integrate medical management and social support programmes into national TB control strategies to address the post-treatment sequelae [12,34]. A more holistic approach to TB treatment outcomes is needed, emphasising the evaluation and management of sequelae, especially in children, to improve long-term health and well-being [5–7,33,34]. This approach would consider TB care a continuum, beginning with primary prevention and ending with post-TB care where needed [13].

DISCUSSION

Our review identified a lack of consistency in the definition and description of PTLD across research studies. Although there is now a proposed definition for paediatric PTLD, this inconsistency hinders a clear understanding of the condition and makes it challenging to compare studies. Consequently, the tools and methods used to measure PTLD differed significantly across studies, thus adding complexity to the comparison of results. Considering these identified research gaps, which require further attention in future studies, it remains to be determined how the proposed definition of paediatric PTLD holds up in clinical and research contexts.

In evaluating children and adolescents with PTLD, it is crucial to consider socioeconomic factors like poverty, limited healthcare access, and malnutrition, as they can worsen symptoms and hinder recovery [26]. As such, combining standardised tools with open-ended caregiver interviews which assess the social determinants of health may help improve the accuracy of PTLD evaluation and intervention planning.

A particularly concerning finding was the limited representation of younger children below five years old in the reviewed studies. This age group carries a significant burden of childhood TB and is likely to live the longest with the potential detrimental effects of the disease [9]. This gap in research on younger children might be attributed to the limited access to or absence of age-appropriate tools for measuring PTLD in this age group [39]. For instance, oscillometry, which can measure airway resistance in young children, was employed in only one of the studies we reviewed [5]. For very young children who may have difficulty with subjective assessments, keeping track of their weight and height can be a valuable indicator of overall health and identify any growth deficits related to PTLD [5]. Additionally, investigating lung-specific biomarkers holds promise for objectively assessing the severity of PTLD in the future [20].

It is worth noting that the symptom screening tools used in these studies were initially designed for adults with chronic obstructive pulmonary disease (COPD) and may not be completely accurate when used on children [40]. This transfer of tools intended for adults to children raises concerns regarding their precision and effectiveness in detecting symptoms unique to younger age groups.

The importance of lung function testing in children and adolescents, who face the longest post-TB period, cannot be overstated. However, the reality that many high-burden TB settings lack access to essential lung function testing equipment, like spirometers, is acknowledged [41]. There is also the ongoing question of what reference ranges to use for tools like spirometry [42]. All of these highlight the need to develop and validate alternative, age-appropriate tools for diagnosing PTLD in resource-limited settings. As more evidence becomes available, there may be a need to standardise recommendations for using radiographic or lung function tests in clinical settings [43].

Beyond the challenge of appropriate tools, there are also uncertainties regarding the optimal timing for assessing children post-TB treatment to ensure PTLD is adequately captured. As there is no previous documentation of the specific timeframe for the onset or peak of respiratory sequelae among pTB survivors, the ideal frequency of post-TB assessments remains unclear [17,20]. However, a cross-sectional or retrospective design makes it even more challenging, as several other confounders could alter lung function, not necessarily the previous TB.

Adding PTLD care to TB services could potentially lead to an increase in the overall cost of TB services. This could be due to the need for extra resources for diagnosing and managing PTLD, as well as the need for specialised healthcare providers and supportive care services. However, addressing paediatric PTLD can significantly reduce the long-term burden on healthcare systems and improve the HRQoL of TB survivors. Effectively managing PTLD can help identify and treat TB re-infection or relapse earlier and prevent complications and hospital readmissions, ultimately resulting in cost savings for healthcare systems. An economic evaluation of TB care as a continuum, where national TB programmes assess all patients at the end of TB treatment and then decide which TB patients require long-term follow-up based on their findings, should be carefully considered to ensure the sustainability of comprehensive care while managing cost implications [43].

The review exposed several important research gaps. Firstly, there is an over-reliance on symptom assessment for PTLD diagnosis. This method might miss a significant portion of cases, particularly as respiratory symptoms do not always correlate with lung function [44]. Secondly, research is needed into modifiable co-exposures such as malnutrition, HIV infection, indoor air pollution, smoking (active, passive or maternal), non-TB respiratory tract infections like COVID-19, and overcrowded living conditions [29]. Thirdly, the limited number of prospective studies hinders our ability to establish causality and understand the long-term course of PTLD [6,30].Finally, there is a gap in incorporating patient-reported outcomes and social support strategies into PTLD management [12].

CONCLUSION

In conclusion, this review underscores the urgent need for further research on PTLD in children and adolescents, particularly younger children below five [13,45]. Future research should focus on establishing a standardised definition for PTLD, developing and validating age-appropriate tools for diagnosis, and determining the optimal timing and frequency for post-TB assessments [13,20]. It is crucial to tackle the issue of limited access to lung function testing equipment in high-burden settings. By addressing these research gaps, we can significantly improve our understanding and management of PTLD in children, ultimately leading to better long-term health outcomes for this vulnerable population.

FUTURE RESEARCH DIRECTIONS

- Longitudinal research studies are needed to characterise the epidemiology and assess the evolution of respiratory function in children and adolescents after TB treatment.
- Future research is needed to identify modifiable risk factors contributing to the development of PTLD.
- It is necessary to assess the feasibility of adding post-TB clinical assessment to routine care for children and adolescents treated for TB.

Data availability

All data relevant to the study are included in the article or uploaded as Supplementary Information.

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.prrv.2024.07.001.

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Chapter 5: Prevalence, pattern, and evolution of post-tuberculosis respiratory impairment among children and adolescents in The Gambia (Research Papers 3 & 4)

5.1 Overview of Chapter

This chapter addresses the third objective of my PhD, which was "*to measure the prevalence and pattern of residual respiratory impairment at pulmonary tuberculosis treatment completion among Gambian children and adolescents, and to prospectively describe the evolution of these sequelae"*.

This chapter also tests the following hypotheses:

- *Children and adolescents in The Gambia continue to experience impaired respiratory health, characterised by respiratory symptoms, abnormal chest X-rays, and reduced lung function, even after successful treatment for pulmonary tuberculosis.*
- *The post-tuberculosis respiratory impairment evolves over the course of 12 months after completing treatment for pulmonary tuberculosis.*

This chapter was divided into two research papers to adequately address the third PhD objective and test the hypotheses. The first paper was published in *Pediatric Pulmonology*. As of the time of the thesis submission, the second research paper addressing this chapter's objective is being prepared for submission to a journal. The complete bibliographic information and intended authorship order are shown below:

Nkereuwem E, Agbla S, Njai B, Edem VF, Jatta ML, Owolabi O, Masterton U, Jah Fatoumatta, Danso M, Fofana AN, Samateh W, Darboe ML, Owusu Shelia, Bush A, Kampmann B, Togun T. Post-tuberculosis respiratory impairment in Gambian children and adolescents: a cross-sectional analysis. *Pediatr Pulmonol.* 2024; 59:1912-1921. https://doi.org/10.1002/ppul.27009.

Nkereuwem E, Edem VF, Agbla S, Owolabi O, Jatta ML, Njai B, Masterton U, Genekah M, Jah F, Owusu SA, Saidy L, Samateh W, Darboe ML, Kampmann B, Togun T. Respiratory outcomes in children and adolescents treated for pulmonary tuberculosis in The Gambia: a prospective study. Status: not yet submitted.

This chapter is supplemented by the full protocol paper, published in *BMC Pulmonary Medicine* and included in Appendix 1. The supplementary materials accompanying the two research papers in this chapter are included in Appendix 8 and Appendix 9, respectively.

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Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	449227	**Title**	Dr
First Name(s)	Esin Esin		
Surname/Family Name	Nkereuwem		
Thesis Title	Evaluating the sequelae of pulmonary tubeculosis in Gambian children and adolescents		
Primary Supervisor	Professor Beate Kampmann		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Pediatric Pulmonology		
When was the work published?	April 2024		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceptualised and designed the study; I developed the data collection tools; I led the data acquisition and performed the data analysis and interpretation; I wrote the original draft of the manuscript and incorporated feedback from the co-authors; I gave the final approval for the version to be published.

SECTION E

Student Signature	[redacted]
Date	1 September 2024

Supervisor Signature	[redacted]
Date	2 September 2024

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ORIGINAL ARTICLE

WILEY

Post-tuberculosis respiratory impairment in Gambian children and adolescents: A cross-sectional analysis

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Abstract

Background: Although post-tuberculosis lung disease (PTLD) is a known consequence of pulmonary tuberculosis (pTB), few studies have reported the prevalence and spectrum of PTLD in children and adolescents.

Methods: Children and adolescent (≤19 years) survivors of pTB in the Western Regions of The Gambia underwent a respiratory symptom screening, chest X-ray (CXR) and spirometry at TB treatment completion. Variables associated with lung function impairment were identified through logistic regression models.

Results: Between March 2022 and July 2023, 79 participants were recruited. The median age was 15.6 years (IQR: 11.8, 17.9); the majority, 53/79 (67.1%), were treated for bacteriologically confirmed pTB, and 8/79 (10.1%) were children and adolescents living with HIV. At pTB treatment completion, 28/79 (35.4%) reported respiratory symptoms, 37/78 (47.4%) had radiological sequelae, and 45/79 (57.0%) had abnormal spirometry. The most common respiratory sequelae were cough (21/79, 26.6%), fibrosis on CXR (22/78, 28.2%), and restrictive spirometry (41/79, 51.9%). Age at TB diagnosis over ten years, undernutrition and fibrosis on CXR at treatment completion were significantly associated with abnormal spirometry (p = .050, .004, and .038, respectively).

Conclusion: Chronic respiratory symptoms, abnormal CXR, and impaired lung function are common and under-reported consequences of pTB in children and adolescents. Post-TB evaluation and monitoring may be necessary to improve patient outcomes.

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KEYWORDS
childhood tuberculosis, lung function, post-tuberculosis, respiratory impairment, sequelae, spirometry

1 | INTRODUCTION

Tuberculosis (TB) continues to impose a significant global health burden, with 10.6 million new cases and 1.6 million deaths reported in 2022.[1] Even though up to 85% of persons treated for new pulmonary TB (pTB) achieve treatment success, the issues of potentially long-lasting consequences for the health and well-being of TB survivors have recently gained increasing attention.[2–5] Emerging evidence from mostly adult studies has suggested that people previously treated for pTB continue to experience long-term respiratory impairment even years after successful treatment, leading to substantial post-TB morbidity and mortality.[6–9] Therefore, it is equally important to evaluate respiratory health and overall well-being after TB treatment in children and adolescents who are in a critical period of their lung development.[10]

A few published pediatric studies also suggest that children treated for pTB continue to experience ongoing respiratory health challenges, even after completing treatment and being declared cured.[11–13] Childhood pTB survivors have more frequent respiratory symptoms, significantly lower lung volumes, and more than three-fold increased odds of lung function impairment compared to healthy, age-matched children who had never been treated for TB.[11] Furthermore, a recent prospective birth cohort study highlighted persistent respiratory symptoms and growth impairment in post-TB survivors, emphasizing the long-term impact of early-life pTB on child health.[12]

Based on the still scarce existing literature, between 1% and 49% of pediatric TB survivors have post-TB respiratory sequelae characterized by persistent respiratory symptoms, radiological sequelae, or abnormal spirometry.[11–14] Moreover, the current definition of post-TB lung sequelae in the literature is quite heterogeneous, leaving room for subjectivity. There is need for a comprehensive minimum case definition for pediatric post-TB lung disease (PTLD) that captures the different disease phenotypes and can be useful in research and clinical practice.[2] Additionally, more data are needed to ascertain the long-term burden of PTLD.[2,11]

As proposed during the first international post-TB symposium, we defined pediatric PTLD as chronic respiratory impairment measured using chronic or recurrent respiratory symptoms, abnormal chest X-ray (CXR), and abnormal spirometry occurring alone or in combination.[2] The Gambian *Childhood TB Sequel* study set out to define the spectrum of PTLD in Gambian children and adolescents at treatment completion and assess the evolution of PTLD over the 12 months posttreatment.[15] Our aim in this paper is to describe the baseline characteristics of the *Childhood TB Sequel* cohort. We aimed to describe their respiratory symptoms, CXR findings, and spirometry characteristics and to identify the factors associated with abnormal respiratory function after TB treatment.

2 | METHODS

2.1 | Study design and participants

We conducted a cross-sectional descriptive analysis of participants at enrollment into the *Childhood TB Sequel* study, an ongoing prospective cohort study in the Western Regions of The Gambia.[15] Using the treatment registers at the 20 Gambia National Leprosy and Tuberculosis Control Programme (NLTP) clinics in the Western Regions 1 and 2, where the majority of the notified TB cases in The Gambia are treated,[16] we identified children and adolescents aged 19 years and below in the final month of antituberculous therapy for bacteriologically confirmed or clinically diagnosed (unconfirmed) pTB. Following successful outcome classification as *cured* or *treatment completed* by the Gambia NLTP, these children and adolescents were referred to our study clinic for screening and enrollment. We consecutively enrolled all eligible children and adolescents who presented within 6 weeks of treatment completion, following informed consent from their parents/legal caregivers and assent from children aged >7 years.

2.2 | Procedures

Study visits were conducted at the childhood TB research clinic of the Medical Research Council Unit The Gambia at the London School of Hygiene & Tropical Medicine (MRCG at LSHTM). Clinical information, including current self- or parent-reported symptoms derived from the St George's Respiratory Questionnaire,[17] recent and previous TB history were recorded during the enrollment visit. We also obtained a self-reported smoking history and environmental exposure to tobacco smoke and biomass fuel. Anthropometric measurements were calculated using the WHO 2007 reference standards.[18] Underweight and stunting were defined as body-mass-index-for-age (BAZ) and height-for-age z-scores (HAZ) less than −2 SD for age and sex, respectively.

A CXR was performed for each subject and interpreted by two independent clinicians (EN and BN) experienced in pediatric pTB. The clinicians were unaware of the symptoms or spirometry results of the subjects before CXR interpretation. Where there were disagreements in the presence or type of radiological abnormality, a third reader (ANF) was used to resolve discrepancies.

We performed spirometry for all children above 4 years using an Easy on-PC portable spirometer (ndd Medical Technologies, Zurich, Switzerland). Spirometry was performed by trained and experienced technicians and followed the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines.[19] The z-scores for the Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 s (FEV_1) and the FEV_1/FVC ratio were calculated using the African American reference ranges of the Global Lung Function Initiative 2012 (GLI-2012) reference equations, which has shown to be best fit for the Gambian population.[20] The pattern of spirometry was defined using the 2022 ERS/ATS guideline.[21]

All children diagnosed with TB in The Gambia are routinely tested for HIV. For participants whose HIV status was unknown, we did a rapid HIV test followed by a confirmatory test (PCR for children below 18 months or HIV ELISA for children ≥18 months) if the rapid test was positive.

2.3 | Statistical methods

Every year, an average of 90 incident TB cases in children and adolescents are notified in the Western Regions 1 and 2 of The Gambia. Consistent with previous results in our population, we assumed a population prevalence of abnormal lung function of 38.5%,[11] and a finite population size of 90 in 1 year, a sample size of 73 allowed us to estimate the prevalence of respiratory impairment with a margin of error of less than 5% with 95% confidence.

For the analysis, we included only participants who could perform spirometry. Additionally, based on previously reported data, we classified self-reported illness duration into two categories: ≤4 weeks and >4 weeks.[22] Medians (IQR) and proportions were used as appropriate to describe the baseline, clinical and respiratory characteristics. We used Chi-square, Fisher's exact, or Mann-Whitney U tests to compare between groups as appropriate. Using univariable logistic regressions, we investigated the association

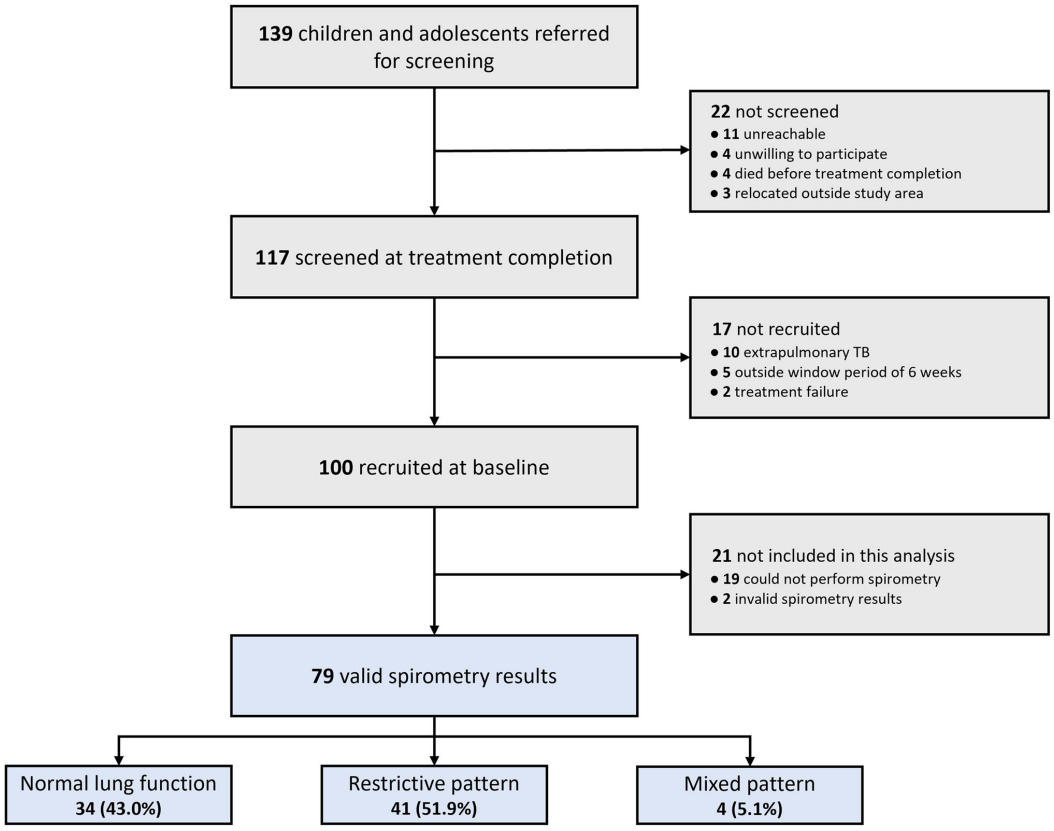

FIGURE 1 Study flowchart and spirometry outcomes. Obstructive pattern: postbronchodilator (post-BD) FEV_1/FVC ratio z-score below the lower limit of normal (LLN); Restrictive pattern: post-BD FVC z-score below LLN; Mixed: post-BD FVC z-score and FEV_1/FVC z-score below LLN; LLN = −1.64. The 19 children who could not perform spirometry were all aged below 5 years.

between post-TB respiratory impairment defined by abnormal spirometry and a priori defined pre- and post-TB treatment characteristics. We then fitted a multivariable logistic regression model incorporating variables with $p < .10$ from the univariable model. We reported odds ratios with 95% CI. Data were analysed using Stata/SE V.17.0 statistical software.

2.4 | Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

3 | RESULTS

A total of 139 children and adolescents were referred from the NLTP clinics to our Childhood TB research clinic during their last month of antituberculous therapy. After completion of treatment, 117 participants were screened, of whom 17 were ineligible for enrollment because they had a previous diagnosis of extrapulmonary TB alone without pTB ($n = 10$), were 6 weeks past the end of treatment ($n = 5$), or had treatment failure ($n = 2$). The study enrolled 100 children and adolescents between March 2022 and July 2023, of whom 79 had valid spirometry results (Figure 1). The characteristics of the participants who were not included in the analysis are shown in Supporting Information S1: Table 1.

3.1 | Participant characteristics

The baseline characteristics of the participants are detailed in Table 1. The median age was 15.6 years (IQR: 11.8, 17.9), 41/79 (51.9%) were female, and 8/79 (10.1%) were living with HIV. The median self-reported duration of illness before commencing TB treatment was 4.0 weeks (IQR: 3.0, 5.0). Although most participants (97.5%) had never smoked, the majority (74.7%) reported exposure to environmental tobacco smoke and cooking with biomass fuels (94.9%).

Except for age, the confirmed and unconfirmed participants had similar demographic characteristics. The confirmed TB group was significantly older, with a median age of 17.0 years (IQR: 13.1, 18.0) compared to 12.3 years (IQR: 8.1, 14.0) in the unconfirmed TB group.

TABLE 1 Participant characteristics and spirometry result at TB treatment completion stratified by prior tuberculosis diagnosis.

	Total ($n = 79$)	Unconfirmed TB ($n = 26$)	Confirmed TB ($n = 53$)
Age, years	15.6 (11.8, 17.9)	12.3 (8.1, 14.0)	17.0 (13.1, 18.0)
Female	41 (51.9)	11 (42.3)	30 (56.6)
HIV infection	8 (10.1)	5 (19.2)	3 (5.6)
Asthma	1 (1.3)	1 (3.9)	0
Sickle Cell Anemia	3 (3.8)	3 (11.5)	0
Ever smoked	2 (2.5)	1 (3.9)	1 (1.9)
Exposure to environmental tobacco smoke	59 (74.7)	18 (69.2)	41 (77.4)
Household biomass exposure	75 (94.9)	25 (96.2)	50 (94.3)
More than one previous TB	2 (2.5)	1 (3.9)	1 (1.9)
Self-reported duration of TB illness before treatment, weeks	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)
Time since TB treatment completion, weeks	1.2 (0.8, 2.4)	1.2 (0.4, 2.4)	1.2 (0.8, 2.4)
Spirometry			
FEV_1 z-score	−1.51 (−2.82, −0.96)	−1.55 (−3.29, −0.63)	−1.51 (−2.55, −1.11)
FVC z-score	−1.84 (−2.92, −1.07)	−1.59 (−3.66, −0.83)	−1.87 (−2.58, −1.29)
FEV_1/FVC z-score	0.20 (−0.68, 0.79)	0.02 (−1.12, 0.61)	0.29 (−0.51, 0.84)
Abnormal spirometry	45 (57.0)	13 (50.0)	32 (60.4)
Pattern of spirometry			
Normal	34 (43.0)	13 (50.0)	21 (39.6)
Restrictive	41 (51.9)	11 (42.3)	30 (56.6)
Mixed	4 (5.1)	2 (7.7)	2 (3.8)

Note: Data are *n* (%) or median (IQR).

3.2 | Lung function impairment at TB treatment completion

The median FEV_1 and FVC z-scores were −1.51 (IQR: −2.82, −0.96) and −1.84 (−2.92, −1.07), respectively. Forty-five participants (57.0%) had abnormal spirometry; the most common type of abnormality was the restrictive pattern seen in 41/79 (51.9%), followed by the mixed pattern in 4/79 (5.1%) (Table 1). Using the GLI race-neutral reference equations resulted in significantly lower median FEV_1 and FVC z-scores compared to the African American reference equations, resulting in 15 additional participants having abnormal spirometry (Table 2, Supplementary Material). The clinical characteristics and CXR results of the 15 participants whose spirometry was 'normal' with the African American and 'abnormal' with the race-neutral equations, respectively, are shown in Table 3 of the Supplementary Material.

3.3 | Clinical and respiratory parameters at TB treatment completion

Twenty-eight (35.4%) of the participants reported one or more chronic or recurrent respiratory symptom(s) present at the completion of TB treatment (Table 2). The most common symptom was cough in 21/79 participants (26.6%), followed by sputum production in 14/79 participants (17.2%). Participants experienced similar respiratory symptoms irrespective of their spirometry results.

At treatment completion, 8/79 (10.1%) participants were stunted, while 21/79 (26.6%) were underweight. More participants in the abnormal spirometry group were underweight, with a median BMI-for-age z-score of −1.65 (−2.41, −0.91) compared to −0.68 (−1.40, −0.30) in the normal spirometry group, $p < .001$.

TABLE 2 Clinical and respiratory parameters measured at TB treatment completion stratified by spirometry outcome.

	Total ($n = 79$)	Normal spirometry ($n = 34$)	Abnormal spirometry ($n = 45$)	p value
Confirmed TB	53 (67.1)	21 (61.8)	32 (71.1)	.470
Self-reported symptoms*				
Any respiratory symptom	28 (35.4)	9 (26.5)	19 (42.2)	.163
Cough	21 (26.6)	7 (20.6)	14 (31.1)	.318
Sputum	14 (17.2)	4 (11.8)	10 (22.2)	.373
Shortness of breath	9 (11.4)	4 (11.8)	5 (11.1)	.999
Wheeze	5 (6.3)	1 (2.9)	4 (8.9)	.384
Clinical observations				
Height-for-age z-score	−0.74 (−1.40, −0.06)	−0.76 (−1.34, −0.37)	−0.65 (−1.56, 0.43)	.593
BMI-for-age z-score	−1.25 (−2.06, −0.47)	−0.68 (−1.40, −0.30)	−1.65 (−2.41, −0.91)	<.001
Stunted	8 (10.1)	2 (5.9)	6 (13.3)	.455
Underweight	21 (26.6)	4 (11.8)	17 (37.8)	.011
Oxygen saturations, %	99 (99, 100)	99 (99, 100)	99 (99, 100)	.741
Chest X-ray findings, $n = 78$				
Abnormal chest X-ray	37 (47.4)	9 (26.5)	28 (63.6)	.001
Pattern of abnormality				
Fibrosis	22 (28.2)	5 (14.7)	17 (38.6)	.024
Volume loss	7 (9.0)	0	7 (15.9)	.017
Bronchiectasis	6 (7.7)	0	6 (13.6)	.033
Parenchymal infiltrates	4 (5.1)	1 (2.9)	3 (6.8)	.628
Cavity	3 (3.9)	0	3 (6.8)	.253
Consolidation	2 (2.6)	0	2 (4.6)	.502
Pleural effusion	2 (2.6)	0	2 (4.6)	.502
Collapse	1 (1.3)	0	1 (2.3)	.999

Note: Data are *n* (%) or median (IQR).

*Symptoms present if the self-reported frequency is at least a few days per month.

TABLE 3 Factors associated with abnormal lung function at TB treatment completion among participants who performed spirometry.

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*p* value	aOR (95% CI)	*p* value
Pre-TB characteristics				
Age at TB diagnosis >10 years	3.1 (1.0, 9.5)	.047	4.3 (1.0, 18.4)	.050
Male	0.9 (0.4, 2.1)	.769	-	-
HIV positive	0.9 (0.8, 1.1)	.462	-	-
Exposed to environmental tobacco smoke	0.6 (0.2, 1.8)	.403	-	-
Exposed to household biomass	1.3 (0.2, 10.1)	.774	-	-
Confirmed TB diagnosis	1.5 (0.6, 3.9)	.383	-	-
Self-reported duration of TB illness before treatment >4 weeks	1.5 (0.6, 3.8)	.439	-	-
Time since TB treatment completion >4 weeks	1.3 (0.3, 5.8)	.739	-	-
Posttreatment characteristics				
Self-reported symptoms				
Cough	1.7 (0.6, 4.9)	.297	-	-
Sputum production	2.1 (0.6, 7.5)	.235	-	-
Shortness of breath	0.9 (2.3, 3.8)	.928	-	-
Wheeze	3.2 (0.3, 30.2)	.306	-	-
Clinical observations				
Stunted	2.4 (0.5, 13.0)	.290	-	-
Underweight	4.6 (1.4, 15.2)	.014	8.3 (2.0, 35.2)	.004
Chest X-ray findings				
Fibrosis	3.7 (1.2, 11.3)	.024	3.6 (1.1, 12.0)	.038
Parenchymal infiltrates	2.4 (0.2, 24.3)	.454		

Of the 78/79 (98.7%) participants who had CXRs available, 37/78 (47.4%) had abnormal CXRs at treatment completion. There was a good inter-reader agreement for the presence of radiological sequelae (kappa: 0.62), with only 18 CXRs requiring a third reader. The most common abnormality was fibrosis, seen in 22/78 (28.2%), followed by volume loss seen in 7/78 (9.0%) and bronchiectasis in 6/78 (7.7%), Figure 2. The frequency of radiological sequelae was significantly higher in the abnormal spirometry group (28/45, 63.6%) compared to the normal group (9/34, 26.5%), $p = .001$.

3.4 | Factors associated with lung function impairment

Following the univariable logistic regression, age at pTB diagnosis, posttreatment weight status, and presence of fibrosis on CXR at the end of treatment showed a $p < .10$ and were subsequently included in the multivariable analysis. Multivariable logistic regression was then performed and showed that age older than ten years at pTB diagnosis, being underweight, and having fibrosis on CXR at treatment completion were strongly associated with abnormal post-TB spirometry ($p = .050$, .004, and .038, respectively). There was no significant relationship between any self-reported symptom and abnormal spirometry at TB treatment completion (Table 3).

3.5 | Correlation of respiratory symptoms, radiological sequelae and lung function impairment at TB treatment completion

Figure 3 shows the subsets of presentations of respiratory impairment, which characterized the 78 participants who had symptom screening, spirometry, and CXR done. The single most common respiratory impairment was an abnormal spirometry seen in 44/78 (56.4%) participants. The largest combination of respiratory impairments was abnormal spirometry and CXR (17/78, 22%), while the least common subset was participants with respiratory symptoms and abnormal CXRs (1/78, 1%).

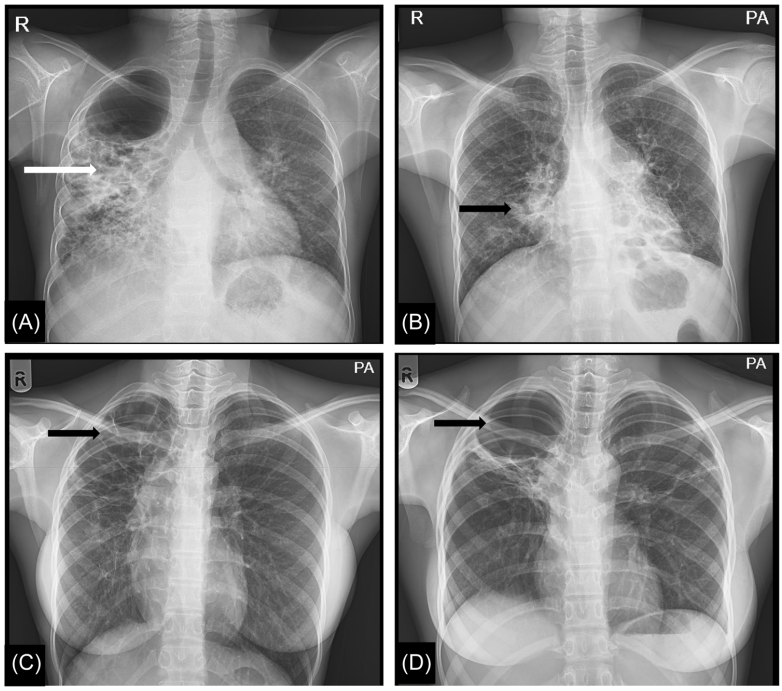

FIGURE 2 Chest X-ray imaging from participants with severe radiological abnormalities. (A) Bronchiectasis (arrow) with volume loss on the right. (B) Fibrosis (arrow). (C) Fibrosis with bronchiectasis (arrow) in the right upper zone. (D) Fibrosis with volume loss and cavitation (arrow) in the right upper zone.

4 | DISCUSSION

Our findings indicate that more than half of children and adolescents have impaired spirometry at TB treatment completion. Additionally, several of these TB survivors have abnormal CXR and continue to experience respiratory symptoms at this stage. Furthermore, age above 10 years at pTB diagnosis, undernutrition and fibrosis on CXR at treatment completion were strongly associated with impaired spirometry after TB. Notably, the majority of children and adolescents with respiratory abnormalities had either an abnormal CXR or abnormal spirometry.

Our study provides compelling evidence of the respiratory consequences of childhood and adolescent TB, building upon previous research in the same geographical area.[11] Moreso, the high proportion of children with abnormal spirometry in our study corroborates recently published data from South Africa, which found that up to 65% of adolescent TB survivors had abnormal spirometry at treatment completion. These studies indicate that TB has a detrimental effect on the lung function of young individuals, which is still present at treatment completion. We aim to track the longitudinal changes in spirometry within this cohort over time to assess its evolution.

The most frequently observed symptom in this cohort was chronic or recurrent cough, which is similar to what is commonly reported in the literature.[6,9,11,13,23] Similar to previous published post-TB studies in adults and children, we also found fibrosis to be the most common radiological sequelae and restrictive spirometry pattern as the most common lung function abnormality.[6,11,14,23] However, despite CXR and spirometry identifying more than two-thirds of all children with respiratory sequelae, there was minimal overlap between symptoms, CXR appearance and abnormal lung function. This finding is unsurprising since persistent post-TB symptoms correlate poorly with lung function.[24] The wide range of phenotypes observed in our study emphasizes the need for comprehensive post-TB assessments in children and adolescents.

The association between a low BMI at TB treatment completion and impaired lung function, as seen in our study, has been previously reported.[9] Low BMI is known to predict lung function decline in adults.[25] As proper nutrition is vital for supporting lung health, we expect the effects of undernutrition to be even more pronounced in children. This finding underscores the significance of addressing malnutrition during TB treatment, which we hope will improve lung health and treatment outcomes.[26]

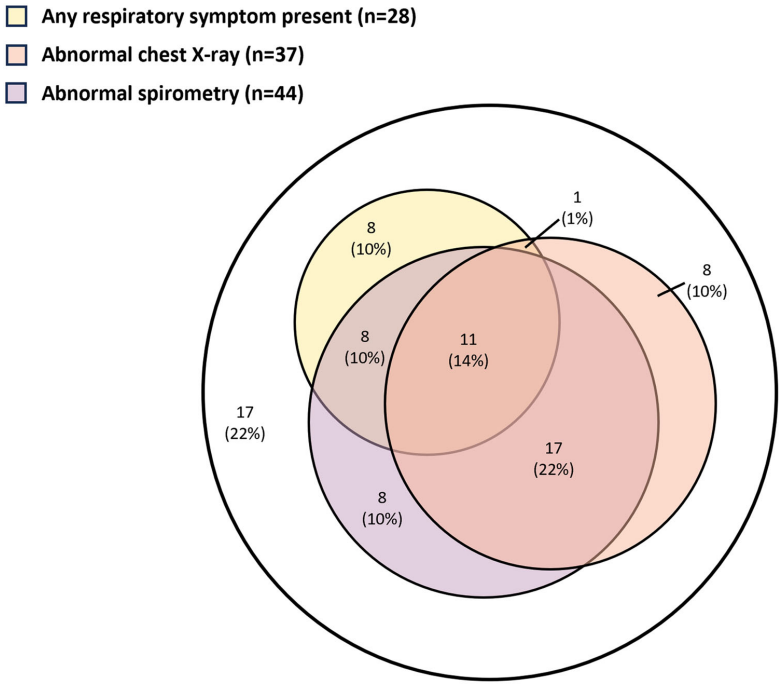

FIGURE 3 Relationship between the outcomes at treatment completion among 78 participants aged 5 years and older using symptom screening, spirometry, and chest X-ray.

Defining pediatric PTLD and assessing its severity presents several challenges.[2] First, relying on self- or parent-reported symptoms may be subject to recall bias.[27] Second, the interpretation of CXR can exhibit variability between clinicians.[28,29] Third, the disease characteristics differ with age, with adolescents often displaying a disease pattern more akin to adults.[30] The diversity in the presentation of childhood and adolescent TB implies that the definition of PTLD may also vary across the pediatric age spectrum. Given these challenges, incorporating an objective assessment such as lung function measurement using spirometry alongside other metrics can enhance diagnostic precision. Nonetheless, due to limited accessibility to spirometry, alternative proxies such as posttreatment anthropometric measurements and CXR findings become valuable tools for evaluating lung function in the post-TB pediatric population. Furthermore, since CXRs cannot reliably differentiate the radiological patterns of PTLD, more elaborate radiological imaging, such as CT scans, should be considered where indicated and available.[31]

A notable strength of our study is being one of the first to document post-TB characteristics in children and adolescents. Additionally, including older adolescents further strengthens the study, as this age group is often excluded from both childhood and adult TB studies. However, the lack of pre-TB anthropometry measurements and CXR data represents a study limitation, hindering our ability to directly compare and fully assess the impact of nutritional status and radiological severity of pTB on post-TB lung health. The absence of a comparison group may also be considered a limitation, especially considering that our previous study reported a substantial burden of chronic respiratory symptoms and impaired lung function among children and adolescents without TB.[11] Moreover, it is important to acknowledge that it might be too early to fully capture post-TB effects within 6 weeks of TB treatment completion. For these reasons, we are conducting a longitudinal follow-up of this cohort to observe how these characteristics evolve over time.

In conclusion, we found that a high proportion of childhood and adolescent TB survivors continue to have any or all of chronic respiratory symptoms, abnormal CXR, or impaired lung function after completing treatment. These findings underscore the necessity for ongoing monitoring to improve the health and well-being of children and adolescents who have been treated for TB. In the absence of spirometry, we recommend symptom screening, anthropometry, and CXR as a minimum. Additionally, nutritional support during treatment may improve post-TB respiratory outcomes in children and adolescents.

AUTHOR CONTRIBUTIONS

Esin Nkereuwem: Conceptualization; investigation; funding acquisition; writing—original draft; methodology; writing—review and

editing; formal analysis; data curation; project administration; supervision. **Schadrac Agbla**: Formal analysis; writing—review and editing. **Bintou Njai**: Data curation; writing—review and editing. **Victory Fabian Edem**: Writing—review and editing. **Muhammed Lamin Jatta**: Data curation; writing—review and editing. **Olumuyiwa Owolabi**: Writing—review and editing; project administration; data curation. **Uma Masterton**: Writing—review and editing; project administration; data curation. **Fatoumatta Jah**: Writing—review and editing; project administration; data curation. **Madikoi Danso**: Writing—review and editing; project administration; data curation. **Aunty Nyima Fofana**: Writing—review and editing; project administration; data curation. **Wandifa Samateh**: Writing—review and editing. **Muhammed Lamin Darboe**: Writing—review and editing. **Sheila Ageiwaa Owusu**: Writing—review and editing. **Andrew Bush**: Writing—review and editing. **Beate Kampmann**: Conceptualization; funding acquisition; writing—original draft; methodology; supervision; writing—review and editing. **Toyin Togun**: Conceptualization; funding acquisition; writing—original draft; methodology; writing—review and editing; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request.

ETHICS STATEMENT

This study involved human participants and was approved by The Gambia Government/MRC Joint Ethics Committee (Ethics Ref: 22,613) and the Observational/Interventions Research Ethics Committee of the London School of Hygiene and Tropical Medicine (Ethics Ref: 22,613–2). Participants gave informed consent to participate in the study before taking part.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	449227	**Title**	Dr
First Name(s)	Esin Esin		
Surname/Family Name	Nkereuwem		
Thesis Title	Evaluating the sequelae of pulmonary tubeculosis in Gambian children and adolescents		
Primary Supervisor	Professor Beate Kampmann		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	The Lancet Respiratory Medicine
Please list the paper's authors in the intended authorship order:	Esin Nkereuwem, Victory Fabian Edem, Schadrac Agbla, Olumuyiwa Owolabi, Muhammed Lamin Jatta, Bintou Njai, Uma Masterton, Monica EL Genekah, Fatoumatta Jah, Sheila Owusu, Lamin Saidy, Wandifah Samateh, Muhammed Lamin Darboe, Beate Kampmann, Toyin Togun

Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceptualised and designed the study; I developed the data collection tools; I led the data acquisition and performed the data analysis and interpretation; I wrote the first draft of the manuscript and incorporated feedback from the co-authors.

SECTION E

Student Signature	[redacted]
Date	1 September 2024

Supervisor Signature	[redacted]
Date	2 September 2024

5.3 Research Paper 4

Title Page

Respiratory outcomes in children and adolescents treated for pulmonary tuberculosis in The Gambia: a prospective study

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Summary

Background

The long-term consequences of pulmonary tuberculosis in children and adolescents who are successfully treated have yet to be clearly defined. We aimed to describe the temporal trends in respiratory outcomes over 12 months in Gambian children and adolescents treated for pulmonary tuberculosis and to investigate the associated risk factors.

Methods

Children and adolescents younger than 19 years who were treated for pulmonary tuberculosis were prospectively enrolled at the time of treatment completion and followed up at six and 12 months. During the study visits, participants underwent symptom screening, chest X-ray, and spirometry.

Findings

Between April 1, 2022, and July 31, 2023, we prospectively enrolled 79 participants. The median age of participants was 15·6 years (IQR 11·8–17·19), and eight (10%) were living with HIV. Lung function impairment was seen in 57% (95% CI 45–68) at baseline, 62% (95% CI 50–73) at month six, and 59% (95% CI 47–71) at month 12. Although there was a modest improvement in the forced vital capacity (FVC) and the chest X-rays, the frequency of respiratory symptoms and lung function impairment remained similar over the 12-month follow-up period. Abnormal baseline spirometry (aOR 31·2 [95% CI 6·6 – 146·6]; p<0·001), being stunted at baseline (OR 15·7 [95% CI 1·2 – 211·5]; p=0·037), and fibrosis on the chest X-ray (OR 6·5 [95% CI 1·0 – 41·2]; p=0·046) were independent predictors for abnormal spirometry at month six. Abnormal baseline (aOR 13·3 [95% CI 3·4 – 52·1]; p<0·001) spirometry was a strong predictor of abnormal 12-month spirometry.

Interpretation

Respiratory impairment persists up to 12 months after treatment completion. Assessing children and adolescents at treatment completion is crucial to identify those requiring further follow-up and intervention.

Funding

EDCTP.

Keywords

Childhood tuberculosis; post-tuberculosis; impairment; sequelae; lung disease; spirometry.

Introduction

Tuberculosis remains a significant public health concern, with children and adolescents accounting for an estimated 12% of the 10·6 million new cases reported in 2022.[1] Despite this unacceptably high disease burden, up to 88% of newly notified cases of drug-sensitive tuberculosis are successfully treated.[1] This improvement in treatment outcomes has led to an increasing number of tuberculosis survivors, estimated to be 155 million (95% uncertainty interval: 138 million-171 million) as of 2020.[2]

A growing body of evidence has shown that even after successful treatment, children and adolescents experience a substantial burden of post-tuberculosis respiratory complications.[3-5] A recent systematic review of six studies on post-treatment pulmonary outcomes among 985 children and adolescents estimated that between 1% and 49% had sequelae, including persistent coughing, wheezing, and radiological sequelae.[6] Cross-sectional studies in children and adolescents have shown that previous tuberculosis is linked to impaired lung function six months or more after treatment.[4] It is now evident that young tuberculosis survivors may face long-standing consequences that can affect their quality of life and respiratory health.

Adult pulmonary tuberculosis survivors often continue to experience lingering respiratory symptoms up to two years after treatment despite some improvement in their lung function.[7, 8] A recent longitudinal study among 50 adolescents with pulmonary tuberculosis found that lung function improved during and after treatment.[5] However, data on the long-term course of respiratory health in children following treatment for tuberculosis is still scarce. This highlights a critical gap in our understanding of how paediatric pulmonary tuberculosis impacts long-term health and well-being.[9]

To address this gap, our study evaluated changes in respiratory health outcomes over 12 months following the completion of treatment for pulmonary tuberculosis in a cohort of children and adolescents in the Gambia. We used spirometry to measure the prevalence and pattern of lung function impairment at both six and 12 months post-treatment. Additionally, the study aimed to identify factors associated with poorer respiratory outcomes.

Methods

Study design and participants

In this prospective longitudinal study, children and adolescents aged 19 years and below who were being treated for pulmonary tuberculosis in the Greater Banjul Area of The Gambia were identified through the National Leprosy and Tuberculosis Programme (NLTP) treatment clinics and approached for study participation.[10]

At tuberculosis diagnosis, all participants were classified as either bacteriologically confirmed or clinically diagnosed (unconfirmed) pulmonary tuberculosis based on the Gambia NLTP national guidelines.[11] Individuals who were classified as *cured* or *treatment completed* at tuberculosis treatment completion, according to the WHO treatment outcome definition,[12] were recruited within six weeks of their successful treatment outcome. Individuals who relocated outside the study area after completing treatment or developed recurrent pulmonary tuberculosis were excluded at the time of enrolment or during follow-up. This cohort's baseline demographic and respiratory characteristics have been previously described.[13]

We obtained written informed consent and assent from all study participants. This study was approved by The Gambia Government/MRC Joint Ethics Committee (Ethics Ref: 22,613) and the Observational/Interventions Research Ethics Committee of the London School of Hygiene and Tropical Medicine (Ethics Ref: 22,613–2).

Procedures

We assessed individuals at treatment completion, six months, and 12 months after treatment completion. At treatment completion, we collected information on recent and previous tuberculosis, tobacco smoke, and biomass fuel exposure. During each study visit, participants underwent screening for current respiratory symptoms, physical examination, chest X-ray, and lung function test using spirometry.[10] We calculated the body-mass index-for-age (BAZ) and height-for-age *z*-scores (HAZ) using the WHO 2007 reference standards.[14] Underweight and stunting were defined as BAZ and HAZ less than -2 SD for age and sex, respectively.

We performed posteroanterior chest X-rays for each participant at each study visit. Two experienced clinicians independently reviewed the X-rays and determined if they were normal or abnormal. If any abnormalities were found, they also identified the type and location of the lesion. The clinicians were unaware of the participants' symptoms or spirometry results before interpreting the chest X-ray. Any disagreements in the presence or type of lesion were resolved by a third reader.

We conducted lung function tests in line with the American Thoracic Society (ATS)/European Respiratory Society guidelines.[15] We used an Easy on-PC portable spirometer (ndd Medical Technologies, Zurich, Switzerland). Each participant performed a minimum of eight forced exhalations while seated. Only spirometry results meeting the ATS quality criteria were considered for analysis. We calculated the *z*-scores for the best forced expiratory volume in 1 s ($z\text{FEV}_1$), the forced vital capacity ($z\text{FVC}$), and the $z\text{FEV}_1/\text{FVC}$ ratio using the Global Lung Function Initiative 2012 (GLI_{2012}) African American reference equation.[16] This reference equation has been shown to be the most suitable for this population.[17] The classification and

severity of lung function were determined using the 2022 ERS/ATS guideline.[16] The $z\text{FEV}_1$ or zFVC severity were categorised as follows: normal if >-1·65, mild if between -1·65 and -2·5, moderated if between -2·51 and -4·0, and severe if <-4·0.

Children and adolescents exhibit varying lung function measurements due to physiological changes and cognitive development.[18] Therefore, close attention is necessary when conducting serial spirometry measurements in this age group to prevent misinterpretation of these changes. To account for this variability, we calculated a conditional change score for the $z\text{FEV}_1$, which is defined as a change in lung function greater than expected in healthy children and adolescents (Panel).[16, 18] Changes within ±1.96 change scores were considered within the normal limits.

Panel: **Calculation of conditional change score**

The change score was calculated as follows: $\frac{z\text{FEV}_{1t2}-(r \times z\text{FEV}_{1t1})}{\sqrt{1-r^2}}$

where $z\text{FEV}_{1t1}$ and $z\text{FEV}_{1t2}$ are the forced expiratory volume in 1 s z-score at the initial and second time-points, respectively, and r is defined as: $0.642 - 0.04 \times time\ (years) + 0.020 \times age\ at\ t_1$.

Statistical analysis

On average, 90 cases of pulmonary tuberculosis in children and adolescents are notified in Western Regions 1 and 2 of The Gambia. Assuming a population prevalence of abnormal lung function of 38·5%[4] and a finite population size of 90 in one year, a sample size of 73 allowed us to estimate the prevalence of impaired lung function at each time point with a margin of error of less than 5% with 95% confidence.[10]

We calculated the proportion of children with impaired lung function and abnormal respiratory parameters at baseline, six and 12 months, along with the corresponding 95% confidence intervals. To assess the evolution of respiratory parameters over time, baseline data were then compared with the 6-month and 12-month data using mixed effects logistic regression to account for repeated measurements.

Participants were stratified by lung function outcome at six months and 12 months, and their characteristics were compared. We used the Student's t-test or Wilcoxon rank-sum test for continuous variables and Pearson's $\chi 2$ or Fisher's exact tests for categorical variables based on the distribution of the data. We investigated the association between the participants' baseline characteristics and abnormal lung function with a priori-defined clinical data using backward stepwise elimination logistic regressions incorporating variables with p values <0·20 in the

univariable model. We reported the results as ORs with 95% Cis. The data were analysed using Stata/SE 18·0 statistical software.

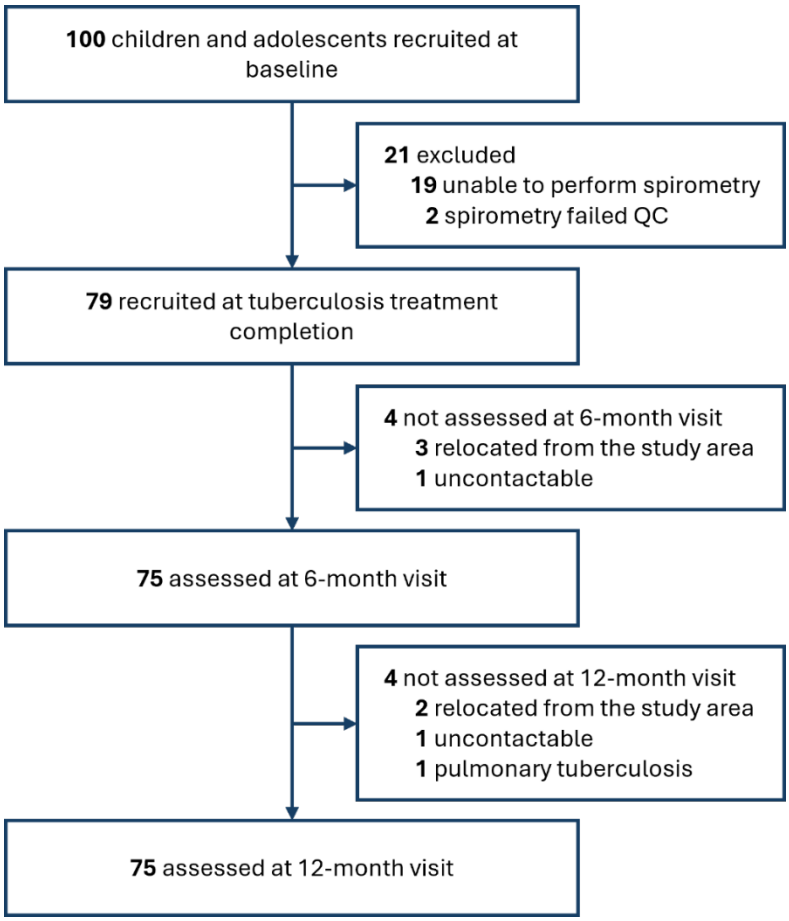
Role of the funding source

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

Results

Between April 1, 2022, and July 31, 2023, 117 children and adolescents who received treatment for pulmonary tuberculosis were screened for eligibility. Out of the 100 participants recruited at treatment completion, 79 (79%) had valid spirometry at baseline and were prospectively enrolled for follow-up at six months and 12 months (Figure 1). Of these, three participants missed their 6-month visit, two missed their 12-month visit, and one missed both follow-up visits. One participant was diagnosed with pulmonary tuberculosis after the 6-month visit and was excluded from further participation in the study.

Figure 1: Participant flow diagram



* QC: quality control

The participants were followed up for a median of 177 days (IQR 173–182) at six months and 355 days (350–361) at 12 months. 41 (52%) participants were female and 38 (48%) were male. The median age was 15·6 years (IQR 11·8–17·9). Eight (10%) participants were living with HIV. Although the majority (97%) had never smoked, 59 (75%) were exposed to environmental tobacco smoke, and 75 (95%) were exposed to biomass. Additionally, one (1%) had a history of asthma, and three (4%) had a history of sickle cell anaemia. Pulmonary tuberculosis was confirmed in 53 (67%) of the participants, and only 2 (3%) had a history of more than one previous episode of the disease (Table 1).

Table 1: Participant characteristics

	All participants (n=79)
Age, years	15·6 (11·8 – 17·9)
Age group, years	
<5	2 (3%)
5 to <10	13 (16%)
10 to <15	23 (29%)
≥15	41 (52%)
Sex	
Female	41 (52%)
Male	38 (48%)
Co-morbidities	
HIV infection	8 (10%)
Asthma	1 (1%)
Sickle Cell Anaemia	3 (4%)
Ever smoked	2 (3%)
Environmental exposures	
Environmental tobacco smoke	59 (75%)
Household biomass exposure	75 (95%)
Type of tuberculosis diagnosis	
Confirmed tuberculosis	53 (67%)
Unconfirmed tuberculosis	26 (33%)
≥ Two previous tuberculosis episodes	2 (3%)
Follow-up visit, days	
Month 6	177 (173 – 182)
Month 12	355 (350 – 361)

On average, the frequency of respiratory symptoms decreased from 35% (95% CI 25%–47%) at treatment completion to 24% (15%–35%) at six months and 21% (13%–32%) at 12 months. However, this decrease was not statistically significant (p=0·11). Cough and sputum production were the most reported symptoms throughout the follow-up period (Table 2).

Table 2: Clinical and respiratory parameters measured at baseline, 6-month, and 12-month study visits

Parameter	Treatment completion (n=79)	6-month visit (n=75)	12-month visit (n=75)	*p*-value*
Self-reported symptoms				
Any respiratory symptom	28 (35%)	18 (24%)	16 (21%)	0·11
Cough	21 (27%)	13 (17%)	13 (17%)	0·26
Sputum	14 (18%)	5 (7%)	7 (9%)	0·10
Shortness of breath	9 (11%)	5 (7%)	9 (12%)	0·44
Wheeze	5 (6%)	3 (4%)	4 (5%)	0·37
Anthropometry				
Height-for-age *z*-score	-0·74 (-1·42, 0·06)	-0·67 (-1·44, 0·03)	-0·63 (-1·38, 0·14)	0·69
Stunted	9 (11%)	8 (11%)	8 (11%)	0·68
BMI-for-age *z*-score	-1·25 (-2·02, -0·47)	-1·28 (-1·84, -0·55)	-1·25 (-2·17, -0·57)	0·09
Underweight	20 (25%)	18 (24%)	21 (28%)	0·20
Chest X-ray (n=78/75/74)				
Abnormal	37 (47%)	26 (35%)	28 (38%)	**0·05**
Fibrosis	22 (28%)	19 (25%)	21 (28%)	0·47
Volume loss	7 (9%)	8 (11%)	8 (11%)	0·17
Bronchiectasis	6 (8%)	6 (8%)	6 (8%)	0·99
Parenchymal infiltrates	4 (5%)	4 (5%)	4 (5%)	0·90
Cavity	3 (4%)	2 (3%)	3 (4%)	0·80
Consolidation	2 (3%)	2 (3%)	1 (1%)	0·69
Pleural effusion	2 (3%)	1 (1%)	0 (0%)	0·60
Spirometry (n=79/74/74)				
Abnormal spirometry	45 (57%)	46 (62%)	44 (59%)	0·61
Pattern of abnormal spirometry				
Possible restriction	41 (52%)	38 (51%)	36 (49%)	0·55
Obstruction	0	4 (5%)	5 (7%)	
Mixed	4 (5%)	4 (5%)	3 (4%)	
zFEV_1	-1·51 (-2·82, -0·96)	-1·66 (-2·46, -1·35)	-1·60 (-2·40, -1·09)	0·08[#]
*z*FVC	-1·84 (-2·92, -1·07)	-1·82 (-2·69, -1·11)	-1·69 (-2·38, -1·31)	**0·02**
zFEV_1/FVC	-0·22 (-0·66, 0·83)	-0·01 (-1·02, 0·73)	-0·02 (-0·68, 0·97)	0·35
Abnormal *z*FEV_1	36 (46%)	37 (50%)	35 (47%)	0·73
Abnormal *z*FVC	45 (57%)	42 (57%)	41 (55%)	0·84
Abnormal *z*FEV_1/FVC	4 (5%)	8 (11%)	8 (11%)	0·20
Change in lung function				
Conditional change score	-	-0·04 (-0·93 to 0·45)	-0·08 (-1·13 to 1·24)	0·55
Significant decline in *z*FEV_1	-	7 (10%)	7 (10%)	0·59

* p-values from mixed effects logistic regression accounting for repeated measurements

Similarly, there was a significant drop in the frequency of abnormal chest X-ray findings over the 12 months from 47% (95% CI 36%–59%) at treatment completion to 35% (24%–47%) at six months and 38% (27%–50%) at 12 months (p=0·05). Fibrosis remained the most prevalent radiologic abnormality at all study time points (Table 2).

Spirometry results were valid for 79 participants at enrolment, 74 participants at month six, and 73 participants at month 12 visits, respectively. Lung function was abnormal in 57% (95% CI: 45–68) of participants at baseline, 62% (95% CI 50%–73%) at six months, and 59% (47%–71%) at 12 months. There was no significant change in the frequency of abnormal spirometry across the 12-month follow-up period (p=0·61). The most frequently occurring pattern of abnormality was the restrictive pattern (52% at baseline, 51% at six months, and 49% at 12 months (Table 2).

The median *z*FEV$_1$ worsened from -1·51 (IQR -2·82, -0·96) at enrolment to -1·66 (-2·44, -1·35) at six months, and then improved to -1·59 (-2·40, -1·09) at 12 months (p=0·08, Figure 2a). Conversely, the median *z*FVC improved steadily from -1·84 (-2·92, -1·07) at enrolment to -1·82 (-2·69, -1·11) at six months. A further improvement to -1·68 (-2·37, -1·31) was observed at 12 months (p=0·02, Figure 2b). There was a modest improvement in the severity of lung function impairment over the follow-up period. At 12 months compared to baseline, significantly fewer participants were classified as having severe or moderate impairment, and more participants were classified as having mild impairment or normal lung function based on the *z*FEV$_1$ and the *z*FVC (Figure 2c and Figure 2d).

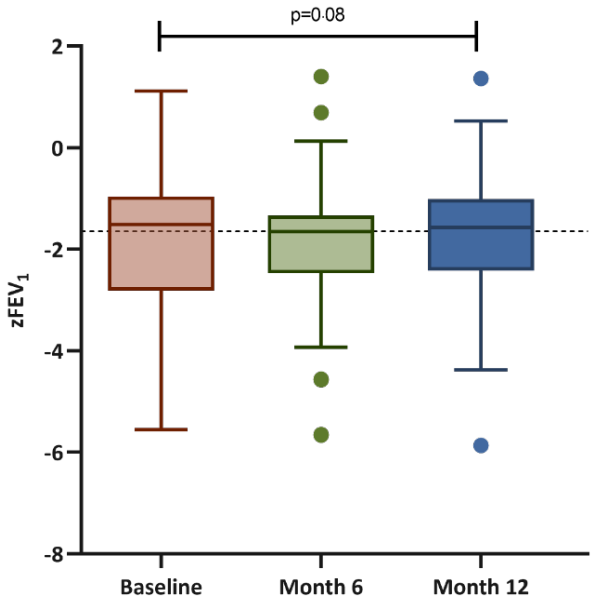
After adjusting for the predicted longitudinal changes in lung function, the median observed change scores for zFEV$_1$ at six months (-0·41, -0·93 to -0·45) and 12 months (-0·07, -1·13 to 1·24) were within the expected normal variability limits of ±1·96. However, there was a significant decline in *z*FEV$_1$ outside the normal limits in seven (10%) participants at six months and 12 months (Table 2).

A significantly higher number of participants with abnormal spirometry at month-6 were underweight at baseline (p=0·003), had an abnormal baseline chest X-ray (p=0·001), or had abnormal baseline spirometry (p<0·001) compared to those with normal month-6 spirometry (Supplementary Table 1). Similarly, participants with stunted growth (p=0·04), underweight (p=0·007), or abnormal spirometry at baseline (p<0·001) were more likely to have abnormal month-12 spirometry (Supplementary Table 2).

Using backward stepwise regression, we found that stunting at baseline (aOR 15·8 [95% CI 1·2 – 211·5]; p=0·04), fibrosis on baseline chest X-ray (aOR 6·5 [95% CI 1·0 – 41·2]; p=0·05), and abnormal baseline spirometry (aOR 31·2 [95% CI 6·6 – 146·6]; p<0·001) were the most significant predictors of abnormal spirometry at six months (Table 3). The only variable

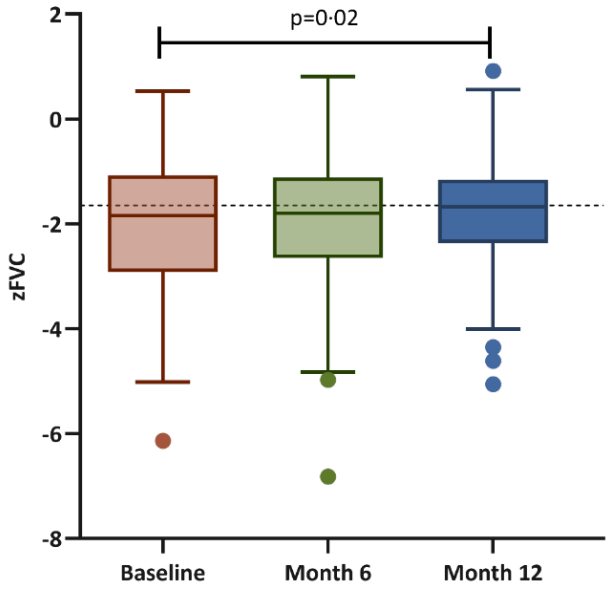
identified as a significant predictor of abnormal 12-month spirometry was abnormal baseline spirometry (aOR 13·3 [95% CI 3·4 – 52·1]; p<0·001).

Figure 2a: Temporal changes in $zFEV_1$ across three study visits over 12 months



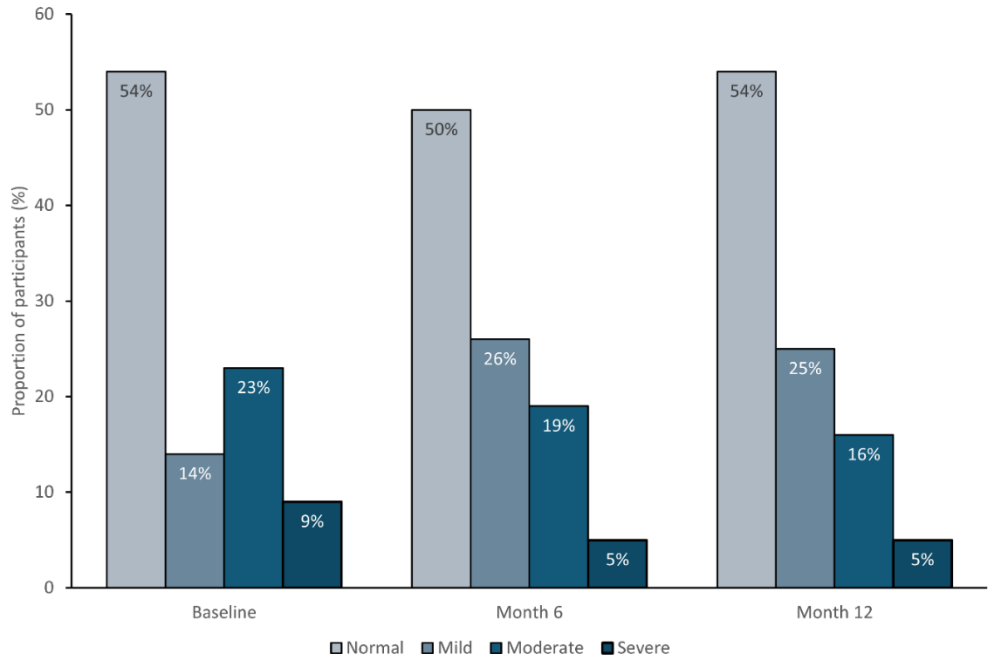
$zFEV_1$: forced expiratory volume in one-second z-score

Figure 2b: Temporal changes in zFVC across three study visits over 12 months



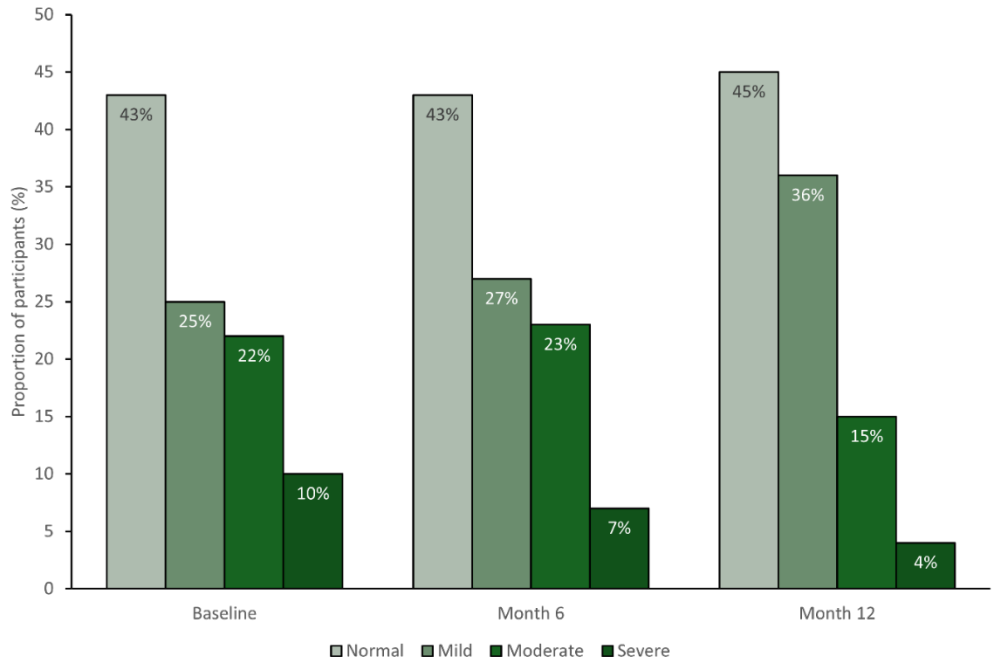
zFVC: forced vital capacity z-score

Figure 2c: Lung function ($zFEV_1$) impairment severity classification



Bars showing the proportion of participants classified into each category of severity of $zFEV_1$; $zFEV_1$: forced expiratory volume in one-second z-score

Figure 2d: Lung function (zFVC) impairment severity classification



Bars showing the proportion of participants classified into each category of severity of zFVC; $zFVC$: forced vital capacity z-score

Table 3: Predictors of abnormal spirometry at 6 months and 12 months

Abnormal spirometry at Month 6		
Parameter	**aOR (95% CI)**	***p*-value**
Stunted	15·7 (1·2, 211·5)	**0·037**
Fibrosis on baseline chest X-ray	6·5 (1·0, 41·2)	**0·046**
Abnormal spirometry	31·2 (6·6, 146·6)	**<0·001**
Abnormal spirometry at Month 12		
Parameter	**aOR (95% CI)**	***p*-value**
Female	4·0 (1·0, 16·3)	0·054
Stunted	11·4 (0·7, 198·8)	0·10
Underweight	7·4 (0·6, 97·9)	0·13
Abnormal spirometry	13·3 (3·4,52·1)	**<0·001**

Discussion

In this prospective longitudinal cohort study in The Gambia, we documented the serial changes in children and adolescents at baseline, six months, and 12 months after receiving treatment for pulmonary tuberculosis. Over the follow-up period, we observed modest improvements in the *z*FVC and reduced frequency of respiratory symptoms and chest X-ray abnormalities. However, over 50% of the participants had reduced lung function up to 12 months after treatment completion. Having abnormal baseline spirometry was independently associated with increased odds of lung function impairment at 12 months.

The prevalence of lung function impairment at 12 months (59%; 95% CI 47%–71%) was similar to baseline (57%; 95% CI 45%–68%), suggesting that pulmonary tuberculosis can have persistent detrimental effects on lung health even after completing the appropriate treatment.[4] However, on average, *z*FVC values showed improvement over time, particularly in individuals with abnormal lung function. This pattern of partial recovery has been observed in adults before.[5, 7, 19] While most of the changes observed in lung function were within the limits of expected normal variability, up to 10% of the individuals experienced a significant decline at six and 12 months. This is particularly concerning because reduced FEV_1 and FVC have been linked to increased mortality.[20, 21]

At 12 months after treatment completion, respiratory symptoms did not fully resolve in 21% of participants. This finding is similar to studies in adults, where persistent symptoms were reported in as many as a third of tuberculosis survivors up to three years after completing treatment.[7, 8] While the presence of symptoms does not always correlate with lung function,[22]

chronic symptoms like cough can be stigmatising,[23] often leading to repeated hospital visits and unnecessary empirical tuberculosis retreatment.[24]

Our study demonstrates a significant, albeit modest (p=0·05) decrease in the frequency of abnormal chest X-rays over the 12-month follow-up period. This finding aligns with expectations, as certain chest X-ray abnormalities associated with tuberculosis are expected to resolve over time.[7] However, it is important to acknowledge that other findings, such as bronchiectasis or fibrosis, may persist.[25]

Our findings demonstrate that spirometry at treatment completion can predict persistent abnormal lung function in children and adolescents 12 months later. This highlights the importance of post-tuberculosis spirometry for this age group. However, we acknowledge the limited access to spirometry in high-burden settings.[26] Despite this, evidence suggests that assessing lung function remains crucial for identifying children at risk of lasting lung function impairment. Therefore, until further data emerges, screening at treatment completion and providing follow-up care for those with abnormalities is a safe approach.

Importantly, this study is one of the first to prospectively track changes in lung function after completing tuberculosis treatment. However, the lack of pre-tuberculosis data, such as anthropometry and chest X-rays, makes it difficult to identify earlier predictors for poor outcomes at 12 months. Radiological severity of the disease might correlate with lung function at both treatment completion and later follow-up, which would allow for risk assessment at an early stage. Additionally, we did not have pre-tuberculosis pulmonary function tests that could serve as a benchmark for future comparison. However, by enrolling children and adolescents prospectively, we were able to assess the temporal changes in respiratory symptoms, chest X-rays, and lung function. The observed changes suggest a causal relationship with the tuberculosis disease.

In summary, this study has found that lung function impairment, abnormal chest X-rays, and respiratory symptoms persist for many months after completing treatment for pulmonary tuberculosis. Our data highlight the importance of assessing children and adolescents after treatment to identify those requiring further follow-up and intervention. Understanding the extent and evolution of post-tuberculosis respiratory issues in children and adolescents will help determine the optimal timing for interventions and ensure a thorough assessment of their post-tuberculosis respiratory health.

Contributors

EN, BK, and TT contributed to the study design and oversaw the study planning and implementation. VFE, OO, MLJ, BN, UM, MG, FJ, SO, FS, and LS contributed to the study planning and implementation. EN, VFE, and SA analysed the data. EN, VFE, SA, BK, and TT contributed to the data interpretation. All authors provided input into the manuscript and approved the final manuscript. EN had full access to all the data in the study, was responsible for the overall content as the guarantor, and had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

The authors declare no conflict of interest.

Data sharing

Data are available upon reasonable request.

Acknowledgements

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Chapter 6: Perceptions and lived experiences of childhood and adolescent pulmonary tuberculosis survivors in The Gambia (Research Paper 5)

6.1 Overview of Chapter

This chapter addresses the fourth objective of my PhD, which was "*to explore the perceptions and lived experiences of child and adolescent TB survivors and gain an in-depth understanding of the social dimensions of the post-TB phenomenon*".

This chapter tests the following hypotheses:

- *There are psycho-social dimensions associated with the post-tuberculosis phenomenon*.

The research paper addressing this chapter's objective has been submitted to the *BMC Public Health* Journal. The complete bibliographic information and authorship order are shown below:

Nkereuwem E, Nkereuwem O, Jallow AO, Owolabi J, Gibba A, Jawara F, Manneh Z, Opoku A, Bond V, Togun T, Kampmann B. "I live with pain, it cannot go away": a qualitative study exploring the lived experiences of childhood and adolescent pulmonary tuberculosis survivors in The Gambia. Status: submitted.

The supplementary material accompanying the research paper in this chapter is included in Appendix 10.

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SECTION A – Student Details

Student ID Number	449227	**Title**	Dr
First Name(s)	Esin Esin		
Surname/Family Name	Nkereuwem		
Thesis Title	Evaluating the sequelae of pulmonary tubeculosis in Gambian children and adolescents		
Primary Supervisor	Professor Beate Kampmann		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
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Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceptualised and designed the study; I developed the data collection tools; I led the data acquisition and performed the data analysis and interpretation; I wrote the first draft of the manuscript and incorporated feedback from the co-authors.

SECTION E

Student Signature	[redacted]
Date	16 November 2024

Supervisor Signature	[redacted]
Date	16 November 2024

6.2 Research Paper 5

Title

"I live with pain, it cannot go away": a qualitative study exploring the lived experiences of childhood and adolescent pulmonary tuberculosis survivors in The Gambia

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Abstract

Background

Childhood and adolescent tuberculosis (TB) survivors often face long-lasting physical and psychosocial challenges even after successful treatment. This study explored the lived experiences of these survivors in The Gambia, focusing on the ways the disease has shaped their health and daily lives.

Methods

This was a qualitative study conducted using the phenomenological approach. A purposive sampling method was used to select 33 children and adolescent TB survivors who were part of an ongoing quantitative Childhood TB Sequel Study. Data were collected using facilitator-guided group discussions and art-based research methods during participatory workshops as well as semi-structured, face-to-face interviews. Data were analysed thematically to identify key experiences and challenges faced by survivors after completing TB treatment.

Results

The study identified four major themes: 1) physical health challenges, 2) psychosocial challenges, 3) disrupted education and academic setbacks, and 4) shifting career aspirations. Participants reported persistent physical symptoms such as fatigue, breathlessness, and chest pain, which limited their daily activities and led to a feeling of frustration. Psychosocial challenges included isolation and stigma, often exacerbated by fears of judgement. However, social support from family, teachers, and friends played a crucial role in helping participants navigate these struggles. Educational disruptions due to frequent absences resulted in lower academic performance and delayed progress. While some participants experienced diminished career aspirations, others were inspired by their experience with TB to pursue healthcare roles.

Conclusions

The findings emphasise the multifaceted impact of TB on young survivors, highlighting the need for comprehensive support systems that address not only their physical health but also their psychosocial and educational needs. Social support networks, particularly from family, played a crucial role in mitigating the negative effects of TB. The study underscores the importance of developing targeted interventions to improve long-term outcomes for childhood and adolescent TB survivors.

Keywords

Childhood tuberculosis; post-tuberculosis; lived experiences; sequelae

Background

Tuberculosis (TB) remains a significant public health challenge globally, consistently ranking among the top ten causes of death [1]. The impact on children under 15 years is particularly alarming, as it is a leading cause of death from a single infectious disease [1]. Notably, at least 80% of these childhood TB cases affect the lungs. Fortunately, treatment outcomes for children are generally favourable, with over 85% achieving treatment success after their first episode [1, 2].

Traditionally, successful treatment of pulmonary TB has been classified as either "cured" or "treatment completed"[3]. However, unlike many respiratory illnesses, TB has the potential to cause permanent lung damage, effectively transforming it from a treatable infectious disease into a chronic, non-communicable condition [4, 5]. This shift highlights a critical gap in the current definitions of successful TB treatment outcomes, which do not account for the long-term consequences of the disease—consequences that may be more prevalent than currently recognised [6].

Emerging research has highlighted multiple dimensions of the long-term effects of pulmonary TB in adults [7-13]. Even after completing treatment, many adult pulmonary TB survivors continue to face ongoing physical health challenges, often necessitating repeated hospital visits [7, 9, 10, 14]. Moreover, there is growing evidence of adverse psychological and socioeconomic impacts among adult pulmonary TB survivors and their households [8, 11-13].

The physical and psychosocial burdens associated with post-TB lung disease (PTLD) are also evident in children and adolescents. For example, childhood pulmonary TB significantly increases the odds of impaired lung function and is linked to lower health-related quality of life [15]. However, the full extent and spectrum of these aftereffects, as well as their impact on the lived experiences of childhood TB survivors, remain insufficiently explored [16]. There is a need for a more comprehensive and in-depth understanding of the social dimensions of the post-TB experience, which could provide crucial insights for addressing PTLD among childhood and adolescent TB survivors.

This study aimed to explore the perceptions and lived experiences of childhood TB survivors, seeking to gain an in-depth, 'emic' understanding of the social dimensions of life after TB. We employed qualitative methods, which are particularly well suited to addressing questions related to experience, meaning, and perspectives from the standpoint of pulmonary TB survivors [17]. Specifically, we sought to understand how survivors of childhood and adolescent pulmonary TB perceived and described different dimensions of the post-TB phenomenon and to explore how this experience impacted their daily lives.

Methods

Study design

This qualitative study used an interpretative phenomenological approach (IPA) to allow the participants to share their post-TB lived experiences and their interpretations of the various dimensions of these experiences [18]. This study was embedded within a larger quantitative *Childhood TB Sequel* study – QUAN(qual) design [19]. The *Childhood TB Sequel* is a prospective cohort study in the Western Regions of The Gambia that seeks to explore and characterise the multidimensional sequelae of pulmonary TB among Gambian children and adolescents. Participants were enrolled after TB treatment and prospectively followed up for 12 months, during which each participant had three study visits [19]. We obtained separate written informed consent and assent for the qualitative study. Participation in the qualitative study had no impact on the individual's participation in the *Childhood TB Sequel* study.

Participant selection

Only participants who attended all three *Childhood TB Sequel* study visits were eligible to participate in the qualitative arm of the study. The *Childhood TB Sequel* included children and adolescents aged 19 years and below who had completed treatment for drug-sensitive pulmonary TB (DS-TB) with an outcome of "cured" or "treatment completed". Specifically, we invited children and adolescents aged ten years and above, as well as caregivers of children below ten years, to participate in the qualitative study. Participants were purposively sampled to represent the *Childhood TB Sequel* study population. The participants were approached in person during their study visits or contacted by phone to participate in the qualitative study.

Data collection

We collected data using facilitator-guided group discussions and in-depth interviews (IDIs).

Group discussions

We held three participatory workshops during which facilitator-guided group discussions were conducted. The workshops were held separately for children and adolescents aged 10 to under 15 years, adolescents aged 15 and above, and caregivers of children aged under 10 years (see Supplementary Material). These workshops aimed to facilitate discussions among the childhood TB survivors and their caregivers, allowing them to share common experiences and express their meanings of the TB and post-TB experience.

We invited between 10 and 20 caregivers, children, and adolescents from each group to participate in the workshops. Caregivers were encouraged to accompany the children and younger adolescents. The workshops were conducted in a neutral location with a dedicated play area for the children to ensure a comfortable and relaxed environment.

The study team present during each workshop comprised a female social scientist (ON) with an MPH experienced in conducting group discussions among children and adolescents, a male MD (EN) with training and experience in designing and conducting qualitative research, and six research assistants (two female and four male) who all hold bachelor's degrees in social science or public health and have field experience in conducting group discussions and interviews.

During each workshop, the discussions were guided by a lead facilitator (ON) and the social science research assistants. The group sessions began as a large group with some icebreakers and introductions before the participants were invited to engage in age-appropriate activities in small groups, followed by individual and group debrief sessions. Each smaller group activity was facilitated by a pair of social science research assistants and had a similar structure (see Supplementary Material). These activities included art-based research methods (collages, body mapping, and drawing), games, role-playing, and storytelling [20]. The activities during these workshops were guided by a flexible discussion guide targeted at addressing the study's objectives.

Participants were given materials such as magazines, newspapers, scissors, and colourful pens to create individual collages and drawings representing their past experiences, present selves, and future aspirations (Figure 1). The facilitators introduced the method to encourage storytelling and interaction among participants. After creating their collages, participants shared and discussed them with the group, using the collages as a means to reflect on their lives and experiences. During the body mapping exercise, participants gathered around a large outline of the human body and were encouraged to colour the areas where they felt symptoms, pain, or discomfort. The end result was a collective image that vividly illustrated the locations of discomfort experienced by participants through different colours.

The workshops were audio-recorded using encrypted devices, and the researchers took notes to capture any non-verbal cues during the discussions. The workshop lasted about two hours for caregivers of children aged five to under ten years, about three hours for children aged ten to under 15 years, and three hours for adolescents aged 15 years and above. The workshops were moderated in English and accompanied by one of the research assistants proficient in the commonly spoken local languages who served as an interpreter.

In-depth interviews

Following each age group's workshop, IDIs were conducted with purposively selected children, adolescents, and caregivers who had participated in the workshops. The aim was to select respondents with maximum variability to ensure a wide range of perspectives. Four primary caregivers of children aged under ten, four adolescents aged ten to under 15 years, and four adolescents aged 15 years and older were invited for the IDIs (see Figure 2).

Figure 1. Participants making collages (participatory workshop, May 2024)

The social science field workers conducted the IDIs in English or the local language preferred by the participants. Interviews were conducted face-to-face with four caregivers and 11 adolescents. Each interview lasted approximately 32 minutes on average. We used a semi-structured interview guide, which was developed based on a previous qualitative study conducted among adolescent and adult TB survivors in The Gambia (see Supplementary Material) [21]. However, the guide remained open to revisions, reflecting insights from the group discussions and preceding IDIs, including emerging themes and ideas. The questions in the guide were intentionally broad, with additional prompts encouraging the respondent to share their experiences. We continued the interviews until data saturation was achieved and no further emerging themes were identified.

Data analysis

The group discussions and interviews were recorded using an encrypted device, and the researcher took notes to capture any nonverbal cues. Social science field staff performed verbatim, word-for-word transcription of the audio recordings independently in pairs. A third person assessed each pair of transcripts for similarity and accuracy. The information obtained from the group discussions was used to refine the structured guides for the IDIs.

Although we had a framework of pre-specified themes based on previous qualitative work [21], we used an inductive approach to refine these themes and for subtheme generation [22]. Two researchers initially familiarised themselves with the transcripts to analyse the data. They then

independently coded a subset of the data before collaboratively refining their coding approach and impressions of emerging themes. To enhance trustworthiness, the entire research team reviewed the organisation of these codes and provided additional input. Both researchers then coded the remaining transcripts independently, organising the codes into subthemes while considering the context to inform the thematic interpretation. Subsequently, all the researchers collaboratively refined the interpretive decisions.

Researchers' perspectives and reflexivity

Before conducting the workshops, the study team met regularly to discuss and document their personal and professional perspectives, as well as their initial impressions of the interview process and potential themes. This practice continued after each workshop and during the interviews and data analysis. The coders also participated in these reflexive practices to ensure an open, honest, and reflective approach to theme and sub-theme generation. The two lead researchers (EN and ON) shared a collective motivation to better understand the qualitative dimensions of post-TB lung health and to identify the participants' experiences, and this research interest was disclosed to the participants.

Results

Characteristics of the sample

The recruitment of participants is summarised in Figure 2. Twenty-five caregivers, ten adolescents aged 10 to <15 years, and 16 adolescents aged ≥15 years and older participated in the group discussions. The caregivers were predominantly mothers (n=10), with a median age of 40.0 years (IQR 23.0 to 46.0). The younger group of adolescents consisted of six boys and four girls, with a median age of 12.5 years (IQR 11.8 to 13.1), while the group of adolescents aged 15 years and older included seven boys and nine girls, with a median age of 17.8 years (IQR 16.7 to 18.1).

The qualitative data revealed a complex and deeply intertwined set of experiences among childhood and adolescent TB survivors, touching on physical, psychosocial, educational, and career-related challenges. These themes and sub-themes highlight the intricate relationship between the physical and emotional aspects of the disease, illustrating its broad and enduring impact on participants' lives.

Physical health challenges

Participants consistently reported a decline in physical fitness following TB treatment, significantly affecting their daily activities. This decline was evident in reduced physical capacity, the persistence of debilitating symptoms, and difficulties in performing routine chores and engaging in recreational activities.

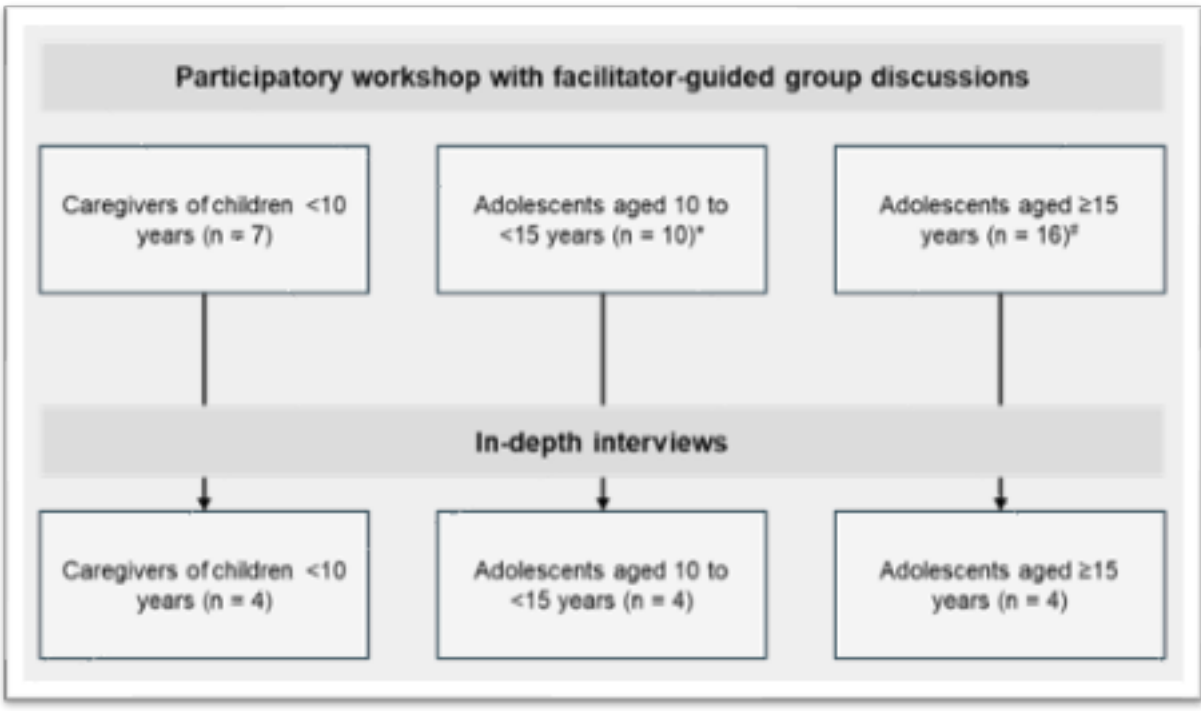

Figure 2. Participants in the research. **Nine caregivers were also present at this workshop (two mothers, four fathers, one grandmother, and two siblings); #Nine caregivers were also present at this workshop (three mothers, two fathers, and four siblings)*

Physical activity limitations

A noticeable reduction in the ability to perform physical activities, especially in sports and exercise, was a common experience among participants. They often felt weaker and less capable, which hindered their participation in activities they once enjoyed, leading to frustration and a sense of loss.

For instance, one participant reflected,

> *"TB affected my sports life. This year, I could not participate in inter-house sports. When I ran a short distance, I easily got tired. The strength that I had for sports before is completely different now"* (17-year-old male).

Similarly, another mentioned:

> *"Before I got sick, I usually played football normally. But when I got sick, I wanted to play football, but I could not. When I'm not feeling well, when my people are running at the field, I tell my coach that I cannot run… If my chest is hurting, then I will sit down. When it's time to play, he will put me inside to play. Even at that, after a while, I sit"* (9-year-old male).

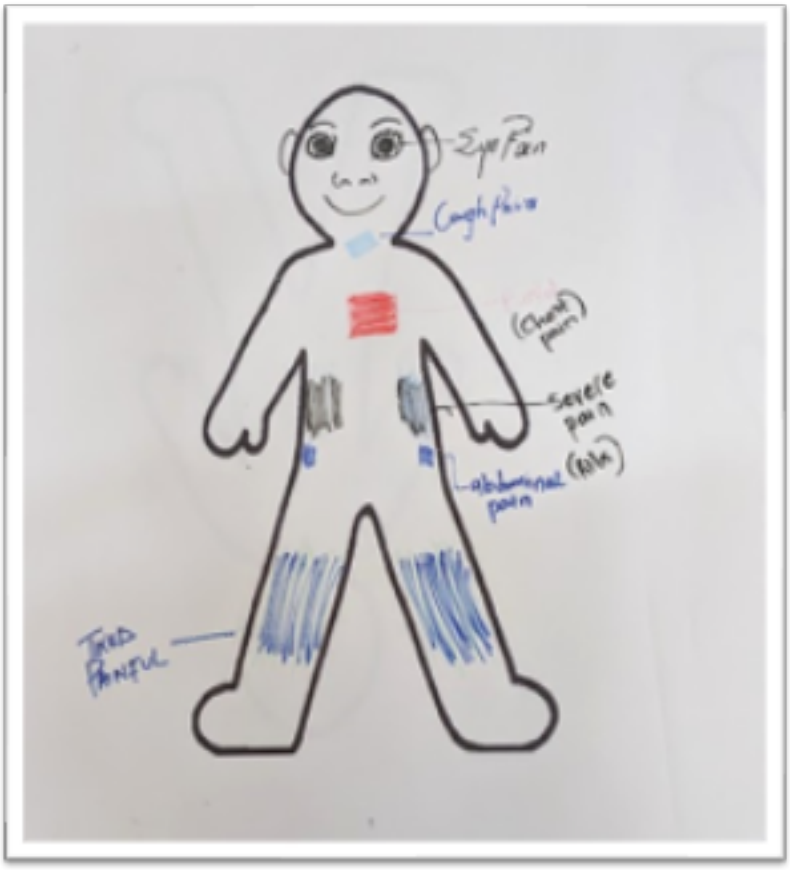

Figure 3. Body mapping created by participants showing the areas of predominant physical symptoms they experienced (facilitatory workshop, May 2024)

The body-mapping exercise, where participants illustrated their physical symptoms on images of a person, further underscored these challenges, vividly depicting the areas of their bodies most affected by the disease (Figure 3).

Persistent symptoms

Chronic symptoms, including persistent coughing, chest pain, and fatigue, continued to trouble participants even after the completion of TB treatment. These symptoms not only caused ongoing discomfort but also required frequent hospital visits, serving as a constant reminder of the disease's lasting impact. As one participant described,

> *"Now it's better, but the pain is still there. Sometimes I tell my sister I live with pain. I think this pain is part of me now. It cannot go away. Yeah, but still, you just have to push yourself"* (18-year-old female).

Caregivers echoed these concerns, with one noting:

> *"The recurrent cough and breathlessness worry me a lot"* (caregiver of a 12-year-old male).

Challenges in performing daily chores

The physical limitations extended to household chores, where participants found themselves struggling with tasks that had previously been routine. This difficulty in managing daily responsibilities exacerbated their feelings of frustration and helplessness.

One caregiver observed:

> *"What has changed in her life is, her productivity has reduced, in terms of work that she does. She can't do her work as she wishes"* (caregiver of an 11-year-old female).

Another participant shared,

> *"For me … I do cooking, I do laundry sometimes, but most of the time if I do it, then I will have chest pain"* (18-year-old female).

Impact on recreational activities

Engagement in recreational activities also declined, with many participants feeling unable to join in games or social events. This lack of participation contributed to feelings of isolation and a loss of social connection. One participant recalled,

> *"Before I got sick, I usually played football normally, but when I got sick, I wanted to play football but I could not"* (9-year-old male).

Another echoed this sentiment, stating:

> *"When I am playing, I get easily tired. Sometimes, when my friends call me to play with them, I would sometimes respond no"* (11-year-old female).
>
> *"Sometimes he will be at one place, even if other kids are playing, he will not participate. He can't go for football, sometimes he will be sitting alone and feeling sad"* (caregiver of an 11-year-old male).

These experiences highlight the significant impact that TB has had on their physical health and social lives, extending far beyond the period of active treatment.

Psychosocial challenges

The psychosocial impact of TB on participants was equally profound, deeply influencing their emotional well-being, social interactions, and self-perception. The following sub-themes capture the range of psychosocial experiences reported after TB treatment.

Emotional and Social Support

Support from caregivers, particularly mothers, was crucial during and after TB treatment. This support provided both emotional comfort and practical assistance, helping participants navigate the challenges of their illness. Teachers and classmates also played supportive roles, enhancing participants' sense of being cared for and valued.

The participants shared,

> *"During the period of my sickness, my parents, both of them, and the doctors helped me. I'm grateful to them for their help"* (12-year-old male).
>
> *"When I was sick, I did not think I would get better. Now, I am on my feet, going to work and doing—thanking my mum, who also supported me in everything. I was even saying that all my neighbours who thought I would not get better—I'm now better"* (18-year-old female).

Another reflected on the broader support network:

> *"The time I was sick, my classmates, all of them, came and visited me. Every time they would come. Some of my teachers would call and ask me: 'So, how are you feeling now?' I would say I'm fine. 'We miss you in school.' I wished to attend school, but I was not strong enough"* (18-year-old female).

Triggers and memories

Despite the support they received, participants frequently encountered emotional triggers that brought back painful memories of their illness. Encounters with classmates who had progressed in school or reminders of missed events often led to feelings of sadness and loss.

> *"I used to think the disease would return. I feel like it will come back, and it gets me scared"* (17-year-old male).

Another participant recalled a distressing moment:

> *"When I was done with the treatment, when everything was clear, they told me I was negative. I burnt [my treatment card] immediately... So after some weeks, I got a call to come back (for the research). That day, I don't know how I was feeling. Many things were going through my mind. I felt sad"* (18-year-old male).

Self-esteem and isolation

The experience of illness, coupled with the academic setbacks and physical limitations that followed, took a significant toll on participants' self-esteem. Many felt inadequate or embarrassed due to their inability to engage in normal activities, leading to social withdrawal.

> *"It has affected the way I think. I think about death a lot... I am usually alone. No one visits me. People run away from me, so I see myself as somebody who is dead. That disturbs me a lot psychologically"* (17-year-old male).

The stigma associated with TB often led to isolation, with participants distancing themselves from social interactions out of fear of judgment or rejection. *"I like to sit and chat with my friends, but I can't,"* a 13-year-old male participant admitted, revealing the loneliness that came with their condition.

Secrecy and disclosure

Many participants chose to keep their TB diagnosis a secret, revealing it only to close family members. This secrecy persisted even after treatment, driven by fears of stigma and potential rejection.

> *"Only my mum and my sister knew. I didn't feel like telling others because maybe they would distance themselves from me"* (18-year-old female).

Another participant explained that *"none of my friends knew I was sick. Among my family, only my parents knew, not even my younger siblings"* (17-year-old female). Their decision to maintain secrecy reflected concerns about how others might perceive them if their illness was known.

Disrupted education and academic setbacks

The illness significantly disrupted participants' educational experiences, adversely affecting both their academic performance and school attendance.

Participants frequently reported a decline in their academic performance, which they attributed to frequent absences and difficulty concentrating on schoolwork. The physical and emotional burden of their illness made it challenging to keep up with their studies, leading to noticeable drops in their grades and overall academic standing.

One participant shared, *"When I go to school, I don't concentrate"* (16-year-old female), while another reflected:

> *"My school performance has also dropped. From grade one to five, I was in the first position. Five to six grades, I dropped to the second position"* (17-year-old male).

A caregiver of an 11-year-old female observed, *"She is someone who tries a lot. But now her performance at school is reducing... because of her health."*

Frequent absenteeism emerged as a significant issue, with participants often too ill to attend school regularly. This inconsistent attendance not only disrupted their learning but also delayed their educational progress, sometimes forcing them to repeat grades.

> *"I got TB when I was in grade eight. I wasn't going to school at the time TB was disturbing me. After my treatment, I decided to go to school but I was told that I should repeat grade eight"* (12-year-old male).
>
> *"Sometimes he does not go to school because walking long distances disturbs him. Sometimes when he had an attack at school, the teacher will allow him to go home to take his medication"* (caregiver of a 12-year-old male).

Extended absences from school and the advancement of their classmates to higher grades left participants feeling isolated and disconnected. This sense of exclusion was further exacerbated by visits from friends who recounted school activities they missed.

"I feel left behind. I was so behind... They were all going to school, I'm staying at home" (18-year-old female).

"It affected my schooling because my schoolmates, whom I was on the same level with, all left me behind" (12-year-old male).

These experiences illustrate the emotional toll of being left out, compounding the challenges participants faced in their educational journey.

Shifting career aspirations

The experience of TB had a profound impact on participants' career aspirations, influencing their future plans and ambitions. For some, the illness dampened their enthusiasm for their original career goals, while others found renewed purpose in pursuing a career in healthcare.

The physical and emotional challenges participants faced during their illness led many to reassess and shift their career aspirations. Some lowered their ambitions or chose not to pursue further education or professional goals, reflecting the significant impact on their future plans:

"I wanted to be an accountant... and I wanted to do football, but since my TB came, all that was away. I cannot do sports now because I usually get tired easily, and breathing becomes a problem when I jump or sometimes run. My breathing is a problem, especially my ribs—they disturb me a lot. My mum says it's not healthy, so it's better I focus on being an accountant" (18-year-old female).

"I really wanted to be a nurse, but after I got sick, I lost all hope. I even dropped out of school" (18-year-old female).

Additionally, the uncertainty and setbacks experienced during their illness led some participants to lose enthusiasm for their initial career plans. The physical limitations and emotional toll of TB caused them to reconsider or abandon their original ambitions.

"Although I don't use to pass science that much, I always used to tell my mum that one day, I will be a doctor... but the time I was sick, I gave up on that" (18-year-old female).

Conversely, for a few participants, the experience of dealing with TB strengthened their resolve to enter the healthcare field. The desire to help others who might be suffering from similar health issues became a motivating factor in their career choices.

"Even though it's still affecting me somehow, I still want to be a nurse. I don't think this will stop me from doing that" (18-year-old female).

Another participant, who had once hoped to return to sports, ultimately decided to focus on their education and future career, stating, *"I lose hope in that area... I am focusing more on my education now"* (AD 010). The collage exercise, where participants used images and clippings to

express how TB affected their lives and influenced their future aspirations, further illustrated this shift in focus (Figure 4 and Figure 5).

Figure 4. Collage created by an 18-year-old female demonstrating negative emotions experienced during and after treatment but also showing a shift in focus and hope in the future

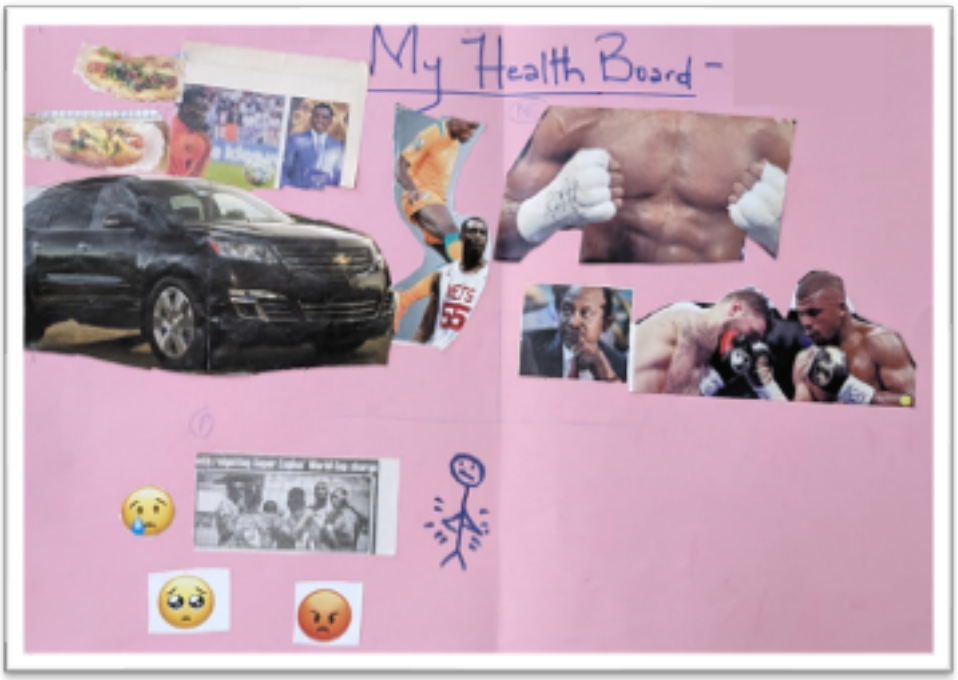

Figure 5. Collage created by a 16-year-old male demonstrating negative emotions due to his inability to participate in sport/physical activity but also showing renewed strength and desire to bounce back

Discussion

This study provides a comprehensive understanding of the lasting impact of childhood and adolescent TB on survivors in The Gambia, revealing how the disease affects not only their physical health but also their psychosocial well-being, educational progress, and future aspirations. The findings highlight the intricate interplay between these domains, demonstrating that the challenges faced by TB survivors are both multifaceted and deeply interconnected. Physically, survivors frequently reported ongoing symptoms; psychosocially, the stigma associated with TB led to social isolation, withdrawal, and a decline in self-esteem, compounded by academic setbacks. Despite these challenges, some participants demonstrated resilience, developing a newfound interest in healthcare careers, underscoring the complex ways in which the TB experience can shape young survivors' life trajectories.

A significant finding of this study is the persistence of physical health challenges among TB survivors, with many reporting ongoing symptoms that continued to affect their daily lives long after treatment had ended [23]. These physical impairments were not just residual effects of the disease but barriers that hindered their ability to engage in activities they once enjoyed [6, 24]. This aligns with findings from other studies in low- and middle-income countries (LMICs), where TB survivors often experience prolonged physical limitations due to the disease [9, 10]. This underscores the need for improved healthcare infrastructure and post-treatment support in high-burden LMICs to mitigate the long-term physical impacts of TB [25].

The psychosocial impact of TB, especially the stigma associated with the disease, emerged as a significant barrier to social reintegration [26]. Participants frequently reported feelings of isolation and withdrawal, driven by a fear of judgment and discrimination. This stigma exacerbated the psychological burden on survivors, leading to a decline in self-esteem and a sense of alienation. These findings resonate with global literature on TB, where stigma is consistently identified as a major challenge for survivors [24, 26]. However, the study also revealed resilience among some participants, who expressed a renewed commitment to pursuing careers in healthcare. The collage exercise was particularly illuminating, allowing participants to visualise their future aspirations, many inspired by a desire to help others [27]. This transformation of adversity into motivation is a testament to the capacity of young survivors to find meaning and purpose in their experiences, even in the face of significant social stigma [28, 29].

Social support was crucial in helping survivors manage the challenges of TB recovery. Family members, teachers, and classmates offered encouragement, emotional support, practical assistance, and encouragement that made survivors feel valued. These findings highlight the

role of social networks in fostering resilience, aiding recovery and mitigating the negative effects of illness [30].

Educational disruptions were another major consequence of TB, with participants frequently reporting declines in academic performance and frequent absences from school. The physical and emotional toll of TB made it difficult for survivors to maintain their academic standing, resulting in lower grades and, in some instances, the need to repeat classes. These findings align with broader research on chronic illnesses, where prolonged absence from school often leads to long-term academic disadvantages [31, 32]. These educational challenges influenced participants' future aspirations, with some expressing diminished career goals due to setbacks experienced during and after TB treatment [33]. Yet, for others, the disruption of their education became a catalyst for rethinking life goals, leading to a desire to pursue careers in healthcare or other fields where they felt they could make a meaningful contribution [34]. This duality in the impact of TB on educational and career aspirations underscores the complex ways in which illness can shape a young person’s future.

Despite the valuable insights gained, several limitations should be acknowledged. The reliance on caregivers to provide information about younger participants may have introduced bias, as caregivers' interpretations might not fully capture the children's true experiences [35]. Additionally, while the qualitative design and relatively small sample size limit the generalisability of the findings, the intent was to define and explore the post-TB phenomenon from the perspectives of children, adolescents, and their caregivers. The rich, contextualised data generated through this approach are meant to offer transferability, allowing researchers to apply the findings to similar contexts or populations, where applicable [36]. The interpretive phenomenological approach, while valuable for exploring subjective experiences, also carries the risk of researcher bias influencing the analysis [18]. Furthermore, conducting interviews in both English and local languages presented translation challenges that may have affected the nuance and accuracy of the data.

Conclusions

In conclusion, this study offers a nuanced view of the long-term impact of TB on childhood and adolescent survivors in The Gambia. The findings emphasise the importance of holistic support systems that address not only the physical but also the emotional, social, and educational needs of TB survivors. Future research should continue to explore these interconnected challenges, with an emphasis on developing interventions that improve long-term outcomes. Comparative studies across different contexts could also provide valuable insights into how resource availability and healthcare infrastructure influence the recovery and reintegration of TB

survivors. By addressing these challenges, we can better support TB survivors in their journey towards a healthier and more fulfilling life.

List of abbreviations

DS-TB	Drug-sensitive tuberculosis
IDI	In-depth interview
IPA	Interpretative phenomenological approach
IQR	Inter-quartile range
LMIC	Low-and-middle income countries
PTLD	Post-tuberculosis lung disease
TB	Tuberculosis

Declarations

Ethics approval and consent for publication

Ethical approval for the qualitative study was obtained from The Gambia Government/MRC Joint Ethics Committee (Reference 28229) and the LSHTM Observation/Interventions Research Ethics Committee (Reference 28229).

Consent for publication

Not applicable

Availability of data and materials

Anonymised interview transcripts are available from the corresponding author on request.

Competing interests

The authors declare no competing interests.

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Author contributions

EN, ON, VB, TT, and BK contributed to the study design. EN and ON oversaw the study planning and implementation. EN, ON, AOJ, JO, AG, FJ, ZN, and AO contributed to data collection. EN, ON, AOJ, and JO analysed the data. AG, FJ, ZM, and AO contributed to the data interpretation. All authors provided input into the manuscript and approved the final manuscript. EN and ON had

full access to all the data in the study, were responsible for the overall content as the guarantor, and had final responsibility for the decision to submit the manuscript for publication.

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PART 3: GENERAL DISCUSSION, CONTRIBUTION TO LITERATURE AND DIRECTION FOR FUTURE RESEARCH

Chapter 7: General discussion, contribution of the PhD to literature, and direction for future research

7.1 Overview

Children with TB disease face not only the immediate risk of severe illness and death but also the risk of long-term respiratory issues even after apparently successful treatment.[1,51,57] As diagnosis and treatment coverage for new cases of paediatric pTB continue to improve, national TB programmes are increasingly confronted with the challenge of managing the growing number of childhood TB survivors who continue to experience the lasting effects of the disease.[31] While the End TB Strategy rightly focuses on diagnosing and treating 90% of people who develop TB by 2027,[78] it is equally crucial to prioritise the effective assessment and management of children with post-TB sequelae. These long-term consequences are often overlooked but should be taken seriously, particularly in children who have many years of life ahead of them.[51,57]

This thesis aimed to explore the long-term adverse physical and psycho-social outcomes associated with pTB in Gambian children and adolescents, describe the evolution of these sequelae, and identify the epidemiological risk factors associated with these outcomes. To achieve this aim, the thesis had four specific objectives: 1) To describe the lung function and HRQoL in children younger than 15 years who were previously diagnosed with pTB at the MRC Unit The Gambia at LSHTM between 2014 and 2019; 2) To systematically review the existing literature on paediatric PTLD with the aim of identifying definitions, measurement instruments, and research gaps in paediatric PTLD; 3) To measure the prevalence and pattern of residual respiratory impairment at pTB treatment completion among Gambian children and adolescents and to prospectively describe the evolution of these sequelae; and 4) To explore the perceptions and lived experiences of child and adolescent TB survivors and gain an in-depth understanding of the social dimensions of the post-TB phenomenon.

In this final chapter, I summarise the main findings from the four analytical chapters and discuss their interconnectedness. I then explore the contributions of the PhD research to existing literature and the implications of the findings for policy and practice. Finally, I highlight the limitations of the individual studies and suggest directions for future research.

7.2 Summary of findings

This thesis provides a comprehensive evaluation of the sequelae of pTB in Gambian children and adolescents, highlighting the multifaceted and interconnected nature of the disease's impact. The findings are drawn from a series of objectives, each contributing to a deeper understanding of the physical and psychosocial consequences of pTB.

The first Objective, which assessed lung function and HRQoL among children and adolescents who completed treatment for pTB, revealed significant long-term health impairments.[79] Compared

to their age-matched peers without a history of pTB, the post-TB group had more than three-fold increased odds of lung function impairment. This impairment predominantly manifested as restrictive lung disease, characterised by reduced lung volumes, which aligns with findings from previous studies in adults and adolescents, particularly those living with HIV.[80] The observed restrictive pattern may reflect underlying fibrosis or other structural lung changes resulting from TB.[52]

Furthermore, the impact of pTB extended beyond measurable lung function abnormalities. Affected children were found to have significantly lower HRQoL scores, indicating a substantial decline in their overall well-being.[37,79] This decline was most pronounced in self-reported physical functioning, while parents observed impairments across multiple HRQoL domains, including emotional and social well-being. The discrepancy between child and parent reports may reflect differences in perceptions of illness and its impact, with parents possibly more attuned to subtle changes in their child's health and behaviour.[81]

Additionally, the substantial burden of respiratory symptoms and abnormal spirometry in the seemingly healthy comparison group raises further concerns. It suggests that environmental factors, such as exposure to biomass smoke and frequent respiratory infections, might contribute to subclinical lung damage, highlighting the need for broader public health interventions.[82]

The scoping review (Objective 2) conducted as part of this thesis identified several critical gaps in the literature on paediatric PTLD.[83] A major concern was the lack of consistent and/or standardised clinical definition and measurement approaches for paediatric PTLD, which varied widely across studies. This inconsistency hinders the comparability of research findings and complicates the synthesis of evidence necessary to inform clinical practice and policy. Although a proposed definition for paediatric PTLD exists,[57] its application in clinical and research settings remains uncertain, especially given the diverse clinical presentations of the disease.

The review also revealed a significant underrepresentation of younger children, especially those under five years old, in existing studies. This age group is especially vulnerable to lower respiratory tract insults and their long-term consequences, yet they are often excluded from research due to the lack of age-appropriate diagnostic tools.[49,84,85] The limited use of techniques such as oscillometry to assess lung function in young children points to a broader issue of inadequate diagnostic capabilities, especially in resource-limited settings.[66,85] Furthermore, the review emphasised the importance of considering socio-economic determinants, such as poverty, limited access to healthcare, and malnutrition, which can exacerbate the severity of PTLD and complicate recovery. Incorporating these factors into future research and clinical assessments could enhance the accuracy of PTLD diagnoses and improve the planning of effective interventions.

The prospective longitudinal study presented in Chapter 5 (Objective 3) of this thesis provides a nuanced understanding of the evolution of respiratory impairments in children and adolescents

following pTB treatment. At the baseline assessment, immediately after treatment completion, more than half of the participants exhibited impaired lung function, as indicated by abnormal spirometry results.[86] This high prevalence of lung function impairment persisted, with minimal improvement observed at the six and twelve-month follow-ups. The study identified several key risk factors associated with poor lung outcomes, including older age at TB diagnosis, undernutrition, and the presence of fibrosis on post-TB chest X-rays (CXR). These factors strongly predicted persistent lung function impairment, underscoring the need for targeted interventions for at-risk groups.

The findings also highlighted the complex and heterogeneous nature of post-TB respiratory sequelae. While chronic or recurrent cough was the most commonly reported symptom, there was notable variability in the types of respiratory abnormalities observed. Some children showed significant improvements in lung function over time, particularly in forced vital capacity (FVC), suggesting partial recovery in some cases. However, a concerning subset of participants experienced a decline in lung function, with up to 10% showing significant deterioration at follow-up assessments. This finding is particularly alarming, given the established link between reduced lung function parameters, such as FEV_1 and FVC, and increased mortality risk.[87,88] The study also documented a significant, albeit modest, reduction in abnormal CXR findings over time, indicating that while some radiological abnormalities may resolve, others, such as fibrosis or bronchiectasis, persist.[89]

The qualitative exploration under the fourth objective provided valuable insights into the experiences of children and adolescents after TB treatment. Participants described a range of physical, psychosocial, and educational challenges that significantly affected their daily lives. The physical health impacts included reduced physical fitness, persistent symptoms such as coughing and fatigue, and difficulties performing everyday activities, including household chores and school-related tasks. These physical limitations often lead to feelings of frustration and helplessness. The psychosocial dimension revealed a deep-seated stigma associated with TB, contributing to social isolation and withdrawal. Many participants reported a decline in self-esteem, exacerbated by academic setbacks such as repeating classes and missing significant school events. The emotional toll was compounded by the tendency to keep their TB diagnosis a secret, even from friends, due to fear of judgment and discrimination. Despite these challenges, some participants found motivation in their experiences, with a few expressing a newfound interest in pursuing careers in healthcare to help others facing similar struggles. This shift in career aspirations underscores the profound impact of TB on shaping the future outlook and aspirations of young survivors.

7.3 Interconnectedness of findings

The interconnectedness of the findings from this thesis reveals a complex interplay of clinical, psychological, and socio-economic factors that interact to shape the post-TB experience of children and adolescents in The Gambia. This interaction is evident across the four specific objectives, revealing how each aspect contributes to a comprehensive understanding of paediatric PTLD.

To begin with, the clinical outcomes observed in Objective 1, such as the high prevalence of lung function impairment and reduced HRQoL, are closely linked to the findings in Objective 3, which tracked the longitudinal changes in respiratory health. The persistence of abnormal spirometry and symptoms like chronic cough up to 12 months post-treatment suggests that the physiological damage caused by TB can be long-lasting. This chronicity is further evidenced by the observation that initial spirometric abnormalities at treatment completion were strong predictors of continued impairment, suggesting that the disease's impact extends well beyond the immediate post-infection period. The correlation between undernutrition and lung function decline, identified in both Objectives 1 and 3, underscores the critical role of nutritional status in respiratory recovery, highlighting the need for integrated nutritional and medical care.

In Objective 2, the review of existing literature underscored the inconsistencies in definitions and measurement tools for PTLD, complicating the comparison of study results and the establishment of universally applicable treatment guidelines. This lack of standardisation directly impacts clinical practice, as observed in Objective 3, where variability in diagnosing and measuring PTLD complicates the assessment of disease progression and recovery. The absence of a standardised approach hampers the ability to provide tailored interventions and complicates efforts to monitor the efficacy of treatments across different settings and populations. Moreover, the underrepresentation of younger children in PTLD studies, highlighted in Objective 2, points to a significant gap in our understanding of the disease's impact on this vulnerable group. This gap was also apparent in Objectives 1 and 3, where we limited our assessment to children aged five years and above. The lack of lung function data in this younger population limited the ability to fully characterise the disease's long-term effects on them.

The psychosocial dimensions explored in Objective 4 reveal a critical layer of the interconnectedness of the research findings, highlighting how social and emotional challenges compound the physical sequelae of TB. The qualitative data indicated that survivors often experience a decline in physical fitness, persistent symptoms, and difficulties in performing daily activities, which contribute to a sense of frustration and helplessness. These physical challenges, as identified in Objectives 1 and 3, are closely intertwined with psychosocial issues, as the stigma associated with ongoing symptoms, such as chronic coughing, frequently leads to social isolation

and withdrawal. This stigma exacerbates the psychological burden on young TB survivors, further impacting their self-esteem and sense of belonging.

Moreover, the findings showed that the illness disrupts educational and career aspirations, with some participants lowering their ambitions due to the setbacks experienced during and after treatment. This impact on future outlooks illustrates how the physical and psychosocial effects of TB are interdependent, shaping survivors' overall life trajectories. Interestingly, while some survivors faced diminished aspirations, others found motivation in their experiences, with a few expressing a desire to enter healthcare professions. This duality underscores the complex interplay between the physical, emotional, and social consequences of TB, where the disease can both limit and inspire future career choices.

Finally, the findings from this thesis collectively underscore the necessity of a holistic approach to TB management that addresses not only the medical and nutritional needs but also the psychosocial and socio-economic factors.[90] The psychosocial challenges identified in Objective 4, such as stigma and altered career aspirations, are deeply intertwined with the clinical and socio-economic contexts explored in Objectives 1, 2, and 3. The persistence of symptoms and physical limitations, coupled with social stigma, can significantly impact self-esteem and future aspirations, illustrating the multifaceted nature of post-TB sequelae. This comprehensive understanding of the impacts of TB highlights the need for integrated care models that encompass psychological support, social services, and educational interventions alongside conventional medical treatment.[90] A longer-term vision is required to address these needs, as care for TB patients does not stop when medications are finished. Such a multidisciplinary approach is crucial for improving the long-term quality of life and well-being of TB survivors, facilitating a more holistic recovery and better integration into society.

7.4 Contribution of the PhD research to literature

This PhD research contributes significantly to the understanding of paediatric PTLD, particularly in the context of The Gambia. The findings expand the current knowledge base by providing a comprehensive evaluation of both clinical and psychosocial dimensions of PTLD in children and adolescents. The contributions are discussed under three main headings: *Methodological Innovations*, *Conceptual Contributions,* and *Advocacy*, with specific references to the Objectives and Chapters.

7.4.1 Methodological innovations

A comprehensive framework for assessing PTLD

The methodological framework developed in this thesis, detailed in Chapters 3, 5, and 6, provides an essential tool for accurately assessing the prevalence and severity of PTLD. By integrating clinical assessments with psychosocial evaluations, the study provides a holistic understanding of

PTLD, as outlined in Objectives 1, 3, and 4. This comprehensive framework allows for a more detailed evaluation of both physical and psychological outcomes, thereby enhancing the accuracy of PTLD diagnosis and management. The framework sets a new standard for future research in the field, ensuring a more thorough understanding of PTLD's multifaceted impacts.

Exploratory qualitative study on psychosocial impacts

Objective 4 involved an exploratory qualitative study, as detailed in Chapter 6, focusing on the lived experiences of children and adolescent TB survivors. This study uncovers the complex psychosocial challenges faced by these individuals, such as stigma, social isolation, and altered career aspirations. These findings are critical for grasping the full impact of TB beyond physical health, emphasising the need for supportive interventions that address the emotional and social dimensions of recovery. The qualitative insights provided by this study enrich the existing literature on TB and highlight the importance of addressing the holistic needs of survivors.

Longitudinal analysis of post-TB outcomes

The longitudinal study design employed in this research, particularly for Objective 3, offers valuable insights into the progression and persistence of PTLD features over time. Chapter 5 presents data on ongoing lung function impairments, demonstrating that these issues can persist long after treatment is completed. This longitudinal approach is pivotal in capturing the dynamic nature of PTLD and provides a critical foundation for future studies aimed at understanding the evolution of TB-related health issues. By documenting the long-term trajectory of paediatric PTLD, this research contributes to a deeper understanding of the chronic nature of TB sequelae.

Contextual adaptation and validation of diagnostic tools

Chapter 3 (Objective 2) identifies the need for locally adapted diagnostic criteria and tools. The review emphasises the importance of validating these tools within the local context to ensure accurate assessment and diagnosis of PTLD in children and adolescents. Specifically, this PhD research assessed the suitability of currently available Global Lung Function Initiative (GLI) reference equations for spirometry and found that the GLI_{2012} African American equation was the best fit for children and adolescents in The Gambia (see Appendix 7).[68] In settings like The Gambia, where existing diagnostic frameworks may not fully capture the unique needs of the paediatric population, validating these tools within the local context is particularly important for accurate diagnosis and effective management.

7.4.2 Conceptual contributions

Expanding the scope of paediatric PTLD research

This thesis expands the scope of research in PTLD by exploring the long-term effects of pTB on children and adolescents, as outlined in Objectives 1 and 3 discussed in Chapters 3 and 5. These chapters demonstrate that PTLD can result in persistent lung function impairment and a reduced

HRQoL, persisting well beyond the completion of treatment. This finding challenges the traditional emphasis on bacteriological cure as the sole indicator of recovery, highlighting the need to consider long-term outcomes as standard practice in childhood TB research.[51,57] By aligning with recent studies in adult populations,[34] this thesis underscores the importance of recognising the enduring impacts of pTB in the paediatric population.

Integrating Post-TB care into a comprehensive TB management framework

This thesis proposes a holistic approach to managing TB that integrates post-TB care as a continuous process rather than treating it as a separate entity.[58] Chapters 4 and 6, addressing Objectives 2 and 4, emphasise the importance of addressing all aspects of health outcomes, including psychosocial elements, to enhance the overall well-being of TB survivors. The qualitative findings from Objective 4 particularly highlight the intricate interplay between physical health, psychological well-being, and socio-economic factors, urging policymakers to adopt a comprehensive approach to post-TB care. This integration is vital for developing supportive interventions that cater to the multidimensional needs of paediatric TB survivors.

7.4.3 Advocacy for paediatric PTLD

This PhD research contributed to advocacy efforts for paediatric PTLD. Two commentaries[48,58] (Appendix 3 and Appendix 4) were published to mark World TB Days in 2022 and 2024, respectively. These commentaries served as a platform to raise awareness and advocate for better care for TB survivors, especially children and adolescents. Additionally, assessing the perspectives of policymakers revealed their limited awareness of post-TB sequelae (Appendix 5).[91] These publications emphasise the importance of recognising and addressing the long-term impacts of TB, highlighting the need for more funding for paediatric PTLD research as well as integrated care approaches that extend beyond the completion of treatment. By contributing to these global discussions, this research has helped to bring attention to the often-overlooked challenges faced by paediatric TB survivors.

7.5 Implications for policy and practice

The findings from this thesis highlight several critical areas for intervention and policy development. These implications span clinical practice, public health policies, and socio-economic considerations, underscoring the need for comprehensive and integrated approaches to managing paediatric PTLD. This section outlines the broader implications for global health policy, the Gambian government, healthcare providers, and local communities.

7.5.1 Implications for Global Health Policy

The absence of standardised definitions and diagnostic criteria for paediatric PTLD complicates global health initiatives. It is imperative for the WHO and other international stakeholders to establish clear guidelines that consistently define PTLD across regions. These guidelines should

emphasise integrating PTLD care into a continuous TB care model, beginning with prevention, including treatment, and extending to comprehensive post-TB care. This integrated approach ensures that PTLD is not treated as a separate entity but as part of a holistic TB management strategy, addressing the long-term impacts of the disease.

Moreover, global health policies should prioritise the inclusion of post-TB outcomes as key measures in childhood TB research. Traditional metrics often focus solely on outcomes at treatment completion, neglecting long-term health implications such as lung function impairment and reduced HRQoL. Acknowledging these outcomes will provide a more complete understanding of TB's impact and guide the development of interventions aimed at improving long-term health outcomes for survivors. Incorporating these considerations into global health agendas, such as the End TB Strategy, will strengthen international efforts to comprehensively address TB.

7.5.2 Implications for the Gambian Government and National Leprosy and Tuberculosis Programme (NLTP)

The socio-economic determinants identified in this study—poverty, limited healthcare access, and environmental exposures—highlight the need for the Gambian government to invest in public health infrastructure and socio-economic development. Enhancing access to healthcare services is crucial, especially in underserved areas. Therefore, investments should focus on equipping healthcare facilities, improving transportation networks, providing nutritional support during and after TB treatment, and ensuring the availability of diagnostic and treatment resources. Equally important is the need to engage policymakers to increase their awareness of paediatric PTLD and ensure it is adequately prioritised.

Healthcare providers and programme managers should implement comprehensive clinical follow-up systems for TB survivors. This should incorporate routine spirometry and HRQoL evaluations as part of standard care protocols. Developing locally validated reference equations for these diagnostic tools is essential to ensure accurate assessments. Furthermore, training healthcare providers to recognise and manage PTLD will enable a more integrated approach to patient care, addressing both the medical and psychosocial needs of TB survivors.

Evaluating the feasibility and cost-effectiveness of these initiatives is critical, considering the resource limitations and donor dependence of The Gambia's TB programme. Detailed assessments should determine the required resources and potential long-term benefits of comprehensive post-TB care. Such evaluations will help prioritise interventions and optimise resource allocation, potentially leveraging community health worker networks for cost-effective care delivery.

7.5.3 Implications for local communities

Local communities play a pivotal role in managing and preventing PTLD. Community-based interventions, including health education and awareness campaigns, are vital for reducing stigma

and promoting timely healthcare-seeking behaviour. These campaigns should focus on the importance of early TB diagnosis and sustained post-treatment care. Engaging local leaders and utilising culturally sensitive messaging can significantly improve the effectiveness of these initiatives.

Support systems, such as mental health services and peer support groups, are crucial for addressing the psychosocial challenges faced by TB survivors, including social isolation and altered career aspirations. One such support group is *Ex-TB Gambia*, a peer support group led by TB survivors, where members share first-hand experiences and offer encouragement to those dealing with post-TB sequelae. Empowering communities to prioritise health and well-being can result in better health outcomes and reduce the burden of PTLD. Community engagement is essential for fostering a supportive environment and encouraging TB survivors to seek and adhere to necessary treatments.

The implications of this research highlight the need for a multi-pronged approach that includes policy reforms, healthcare infrastructure improvements, and community engagement. By implementing these recommendations, stakeholders can enhance the long-term health and well-being of children and adolescents affected by TB, contributing to more effective and equitable healthcare systems in The Gambia and beyond. A coordinated, comprehensive response is essential to address the complex and multifaceted impacts of paediatric pTB and its sequelae.

7.6 Limitations

The relevant research papers from Chapter 3 to Chapter 6 of this thesis extensively discussed limitations specific to each study. In Table 1 below, I summarise the key limitations discussed in each of the research papers included in the analytical chapters.

Table 1: Summary of study limitations

Chapter (Research Paper)	Limitations
Chapter 3 (Research Paper 1)	1. The study's cross-sectional design, relying on a single spirometry measurement, may not adequately capture the dynamic changes in lung function that occur over time, particularly in growing children. Longitudinal follow-up, as conducted in our third objective, is essential for a more comprehensive understanding of post-TB lung health. 2. While spirometry was crucial for identifying restrictive lung patterns, the absence of total lung capacity (TLC) measurements limits the accuracy of these findings. Without TLC data, the true prevalence of restrictive lung disease may be underestimated. 3. Recruitment from a single research clinic (the MRCG at LSHTM) might have introduced selection bias, as children diagnosed with TB at other facilities were not included. This could limit the generalisability of the study findings.

	4. The small number of HIV-positive children in the study and the absence of HIV-positive controls restricts our ability to draw definitive conclusions about the interaction between HIV and lung function impairment in this population.
Chapter 4 (Research Paper 2)	1. A key limitation was the inconsistent use of terminology and definitions for PTLD across studies. This hindered the synthesis of findings and limited the ability to draw comprehensive conclusions. 2. The underrepresentation of children under five in the included studies restricted the generalisability of findings to the youngest age group and limited understanding of PTLD in this population. 3. Variability in study methodologies and tools complicated the synthesis of findings, particularly regarding lung function assessment and post-TB evaluation timeframes. 4. While not a primary focus, the significant variation in study quality and design among included studies highlights potential limitations in the available evidence base and may contribute to identified gaps in measurement and methodology.
Chapter 5 (Research Paper 3)	1. This study was limited by the absence of pre-treatment anthropometric and chest X-ray data. Consequently, it was challenging to accurately assess the long-term impact of TB and its treatment on lung health and nutritional status. 2. Without a comparison group of TB-free children and adolescents, it is difficult to isolate the specific effects of TB on lung function and respiratory health, especially considering the high prevalence of respiratory issues in our populations, as noted in Objective 1. 3. The lung function and respiratory health assessment was conducted relatively early in the post-treatment period. This limited the study's ability to capture the full spectrum of potential long-term lung damage associated with pTB. 4. Additionally, the reliance on self-reported symptoms introduced the possibility of recall bias, which may have affected the accuracy of symptom data and its correlation with objective lung function measures. 5. While experienced clinicians interpreted chest X-rays, inter-reader variability in assessing radiological findings remains a potential limitation. This could impact the consistency and reliability of the CXR data, particularly in identifying subtle signs of TB-related lung damage. 6. The cross-sectional design of the study provided a snapshot of post-TB health at a single time point. This prevented an evaluation of how lung function and respiratory health would evolve over time in this population. This was done in the second paper in Chapter 5.
Chapter 5 (Research Paper 4)	1. The lack of pre-TB measurements, such as height, weight, chest X-rays, and pulmonary function tests, significantly limited our ability to accurately assess the long-term impact of TB on lung health and to identify early predictors of poor outcomes. 2. The 12-month follow-up period might not be sufficiently long to capture the full spectrum of long-term changes in lung health associated with PTLD, as some sequelae may develop or resolve gradually over time. 3. The study's reliance on spirometry, while valuable, restricts its applicability to settings with limited access to this diagnostic tool, which is common in many high-burden TB countries.

	4. The absence of a comparison group of children and adolescents without TB makes it challenging to differentiate TB-related lung function impairments from those that may be present in the general population. 5. The exclusive use of chest X-rays for radiological assessment may not provide a comprehensive evaluation of lung abnormalities, as more advanced imaging techniques, such as CT scans, can offer greater detail.
Chapter 6 (Research Paper 5)	1. Relying on caregivers for information about younger participants may have introduced bias into the study. Caregivers' perceptions and interpretations of children's experiences might not have accurately reflected the children's true feelings and thoughts. 2. Participants might have felt pressured to provide socially acceptable responses during group discussions and interviews. This could have distorted their true experiences and feelings, limiting the authenticity of the data. 3. The study's qualitative design and relatively small sample size restrict the extent to which the findings can be applied to other populations and contexts. While the study provides valuable insights, caution is needed when generalising the results. 4. The interpretive phenomenological approach involves subjective interpretation, which means that researcher biases could influence the analysis and findings. Although efforts were made to minimise this through reflexivity, it remains a potential limitation. 5. Conducting interviews in both English and local languages introduced potential challenges. The process of translation and interpretation could have led to the loss of nuances in participants' expressions or the introduction of unintended biases.

7.7 Direction for future research

Based on the findings from this thesis, several critical areas for future research have emerged, each promising to deepen our understanding of PTLD and improve the quality of care for affected individuals. This section details the key directions for future research, incorporating clinical, socioeconomic, psychosocial, and interventional aspects.

7.7.1 What are the long-term outcomes and effective treatments for PTLD?

This thesis raises an important question: "*What are the long-term effects of PTLD in children and adolescents, and what treatments can effectively mitigate these effects?*" Although this research documented significant lung function impairment up to one year after TB treatment completion, there is still a need to understand how these sequelae evolve over a longer period of time. Longitudinal studies can provide valuable insights into the natural history of PTLD, identify critical periods for intervention, and assess the long-term impact of early-life TB on adult respiratory health. Furthermore, interventional studies are essential to evaluate the effectiveness of various treatment modalities and preventive strategies, including pharmacological interventions, pulmonary rehabilitation, and nutritional support, in reducing the long-term effects of PTLD. Such studies will

help establish evidence-based guidelines for the management and prevention of PTLD in this vulnerable population.

7.7.2 How can we identify predictors of PTLD and implement preventive strategies?

To effectively address PTLD, it is important to focus on prevention by identifying early predictors in children and adolescents. Future research should aim to identify specific factors—whether genetic, environmental, or related to the severity of the initial TB infection—that could signal an increased risk of developing PTLD. Understanding these predictors can help healthcare providers implement targeted interventions, such as early administration of host-directed therapies (HDT), to forestall its onset. This proactive approach is essential for reducing the long-term burden of TB-related sequelae and improving overall outcomes. Additionally, studies should explore how to incorporate these predictive measures into routine TB care to ensure that at-risk children receive the necessary preventive care and support as soon as possible.

7.7.3 How can we standardise PTLD definitions and diagnostic criteria using local resources?

There is currently a lack of consistent definitions and diagnostic criteria for PTLD in the literature. Future research should focus on developing and validating standardised criteria that can be universally applied across different settings. This standardisation is essential for improving comparability between studies and ensuring that clinical interventions are appropriately targeted. Additionally, there is a need for locally validated reference equations for existing diagnostic tools, such as spirometry, in order to ensure accurate assessments within specific populations. Research should also explore the development and validation of age-appropriate diagnostic tools, particularly for younger children who cannot perform conventional lung function tests. More easily accessible resources requiring minimal training, such as simple oscillometry devices or mobile radiography units, should be considered for use in resource-limited settings like The Gambia.

7.7.4 What is the impact of socioeconomic factors on PTLD outcomes?

Socioeconomic determinants of health (SDH) play a significant role in the prevalence and severity of PTLD. Future research should explore how factors such as poverty, limited access to healthcare, and the financial burden of TB disease impact disease outcomes. By understanding these SDHs, we can identify the barriers to effective treatment and recovery. Additionally, examining the efficacy of integrated care models that address these socio-economic factors, such as providing financial assistance and improving healthcare access, is crucial. Such research is essential for developing targeted interventions to reduce the socio-economic burdens associated with PTLD.

7.7.5 What role do co-morbidities, co-exposures, and preventive strategies play in PTLD?

Co-morbidities and co-exposures, such as HIV infection, malnutrition, and exposure to environmental pollutants, can significantly impact the course and outcomes of PTLD. Future

research should focus on understanding how these factors interact with TB to exacerbate disease severity and complicate treatment. Studies should also explore the potential benefits of targeted interventions, such as antiretroviral therapy for children and adolescents living with HIV (CALHIV) and nutritional supplements for malnourished patients. Additionally, investigating preventive measures, such as reducing exposure to indoor pollutants and improving living conditions, can inform public health policies and practices. Research should also consider the efficacy of vaccines and other preventive strategies in reducing the incidence and severity of PTLD.

7.7.6 How can psychosocial interventions and support systems be enhanced for TB survivors?

The psychosocial impact of TB, as highlighted in this thesis, includes stigma, social isolation, and altered career aspirations. Future research should focus on developing and evaluating psychosocial interventions aimed at mitigating these challenges. This could include the implementation of support groups, counselling services, and educational programmes that address stigma and promote mental health. Additionally, understanding the role of family and community support in the recovery process is crucial for designing effective psychosocial interventions. Qualitative studies exploring the lived experiences of TB survivors can provide valuable insights into the specific needs and challenges faced by this population.

7.7.7 How can we address gaps in care and follow-up in a strained healthcare landscape?

Current healthcare systems often do not have comprehensive follow-up protocols for children and adolescents who have completed TB treatment. Future research needs to look into developing and implementing systematic follow-up programmes that monitor lung function, HRQoL, and other health indicators over time. Such programmes could include regular clinic visits, home-based care, and telemedicine options to ensure continuity of care. It is also essential to assess the cost-effectiveness and feasibility of these follow-up strategies, especially in resource-limited and donor-dependent settings like The Gambia. Given the existing strain on healthcare resources and the reliance on external funding for TB care, future research must explore sustainable models that balance the need for comprehensive post-treatment support with the realities of limited financial and human resources. This includes investigating innovative funding mechanisms, optimising resource allocation, and leveraging community health worker networks to provide cost-effective follow-up care.

7.8 Dissemination

Between 2021 and 2024, I have shared and presented the research findings of this PhD. The activities are outlined in Table 2.

Table 2: Dissemination activities undertaken during the PhD Programme to share research findings (beginning with the most recent)

S/N	Title of talk and format	Organisation / Event	Audience
1	Persistence of respiratory impairment six months after completion of TB treatment in Gambian children and adolescents (**Poster presentation**)	Union World Conference on Lung Health. **Bali**. November 2024	Academics, non-governmental organisations, and donor agencies
2	Respiratory sequelae of pulmonary TB in African children & adolescents (**Oral presentation**)	Pan-African Thoracic Society & European Respiratory Society Joint Paediatric Webinar. **Virtual**. October 2024	Clinicians, nurses, academics
3	How and for how long should I follow up on the lung health of children treated for TB? (**Oral presentation**)	British Association of Paediatric TB (BAPT) Annual Conference. **London**. July 2024	Clinicians, nurses, academics
4	Lung function outcomes after TB treatment completion in Gambian children and adolescents (**Oral presentation**)	Union World Conference on Lung Health. **Paris**. November 2023	Academics, non-governmental organisations, and donor agencies
5	Evaluation of the Global Lung Function Initiative (GLI) reference equations in healthy Gambian children (**Poster presentation**)	11th European and Developing Countries Clinical Trials Partnerships (EDCTP) Conference. **Paris, France**. November 2023	Academics, non-governmental organisations, and donor agencies
6	Paediatric post-TB lung disease (**Oral presentation**)	The 2nd International Post-Tuberculosis Symposium. **Stellenbosch, South Africa**. April 2023	Clinicians, Academics, non-governmental organisations, and donor agencies
7	Reduced health-related quality of life after tuberculosis treatment in Gambian children (**Oral presentation**)	West African College of Physicians 44th & 45th Annual General and Scientific Meeting. **Virtual**. November 2021	Academics, non-governmental organisations, and donor agencies
8	Post-TB lung function impairment in Gambian children (**Poster presentation**)	The 52nd Union World Conference on Lung Health. **Virtual**. October 2021	Academic, non-governmental organisations, and donor agencies

7.9 Concluding remarks

This thesis has explored the multifaceted nature of paediatric PTLD in children and adolescents in The Gambia, highlighting the complex interplay of clinical, psychological, and socio-economic factors that shape the post-TB experience. The findings demonstrate that while significant progress has been made in managing and treating paediatric pTB, substantial gaps remain in understanding and addressing the long-term sequelae of the disease.

The thesis emphasises the high prevalence of lung function impairment and reduced HRQoL among these children and adolescents post-TB treatment. These findings are consistent with observations in the literature, suggesting that paediatric TB survivors are at a significant risk of developing chronic respiratory conditions. The persistence of respiratory symptoms and abnormal spirometry measurements up to one year after treatment completion indicates that the impacts of TB extend far beyond the bacteriological cure. This calls for a redefinition of TB treatment success to include the assessment and management of long-term health outcomes, not just the eradication of the bacteria.

Furthermore, the thesis points out critical gaps in the existing literature and clinical practice regarding the definition, measurement, and management of paediatric PTLD. The lack of standardisation in definitions and diagnostic criteria complicates the comparison of study results and the establishment of universally applicable guidelines. This thesis advocates for a unified approach to define and measure PTLD, incorporating both clinical and psychosocial dimensions to provide a holistic understanding of the disease's impact.

The qualitative exploration of the lived experiences of TB survivors adds a crucial dimension, highlighting the significant psychosocial challenges these children and adolescents face. The stigma associated with chronic symptoms, disruption to education and career aspirations, and the socio-economic burdens on families emphasise the need for integrated care models. Such models should not only address medical needs but also provide psychological support and social services to ensure comprehensive care.

In conclusion, this research contributes to the growing body of knowledge on paediatric PTLD, offering valuable insights into its prevalence, impact, and broader socioeconomic and psychological dimensions. It stresses the need for a holistic approach to TB management that includes prevention, treatment, and post-TB care, ensuring that children and adolescents receive comprehensive support throughout their recovery journey. The findings highlight the urgent need for further research, policy reform, and the implementation of integrated care models to improve the long-term health outcomes and quality of life for TB survivors in The Gambia and beyond.

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Appendices

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Appendix 1: Published protocol paper for Objective 3

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RESEARCH PAPER COVER SHEET

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SECTION A – Student Details

Student ID Number	449227	**Title**	Dr
First Name(s)	Esin Esin		
Surname/Family Name	Nkereuwem		
Thesis Title	Evaluating the sequelae of pulmonary tubeculosis in Gambian children and adolescents		
Primary Supervisor	Professor Beate Kampmann		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	BMC Pulmonary Medicine		
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SECTION E

Student Signature	[redacted]
Date	1 September 2024

Supervisor Signature	[redacted]
Date	2 September 2024

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STUDY PROTOCOL Open Access

Childhood TB sequel: evaluating respiratory function after treatment for pulmonary tuberculosis in a prospective cohort of Gambian children – a study protocol

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Abstract

Background 1.2 million children under 15 years are estimated to have developed tuberculosis (TB) in 2021. 85% of paediatric patients achieve successful treatment outcomes if treated for the first episode of TB. However, despite so-called successful treatment, TB leaves many survivors with permanently destroyed or damaged lungs. Data from prospective paediatric cohorts to establish the burden and evolution of post-TB lung disease (PTLD) are still absent. The *Childhood TB Sequel* study aims to describe respiratory consequences associated with pulmonary TB in Gambian children, describe the evolution of these sequelae, and determine associated epidemiological risk factors.

Methods We aim to recruit up to 80 subjects aged 19 years and below who have recently completed treatment for pulmonary TB. Recruitment started in April 2022 and is expected to continue until June 2024. Clinical assessment, chest X-ray, and comprehensive lung function assessment are carried out at treatment completion and again six and 12 months later.

Discussion The *Childhood TB Sequel* study will address existing research gaps to enhance our knowledge and understanding of the burden of PTLD in Gambian children. The study will also contribute to formulating a plan for post-TB evaluation and long-term follow-up strategies.

Trial registration ClinicalTrials.gov: NCT05325125, April 13, 2022.

Keywords Childhood tuberculosis, Post-tuberculosis, Impairment, Sequelae, Lung disease, Spirometry

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Background

In 2021, an estimated 10.6 million people fell ill with tuberculosis (TB), of which 1.2 million were children under 15 years [1]. Approximately 80% of these childhood TB cases affect the lungs [1]. However, from an optimistic standpoint, more than 85% of persons who receive treatment for the first episode of TB have a successful outcome, defined as smear or culture conversion to negative or clinical improvement on anti-tubercular treatment [1]. This success in treatment has resulted in about 155 million TB survivors as of 2020, of which 12% were children below 15 years of age [2].

The care for patients diagnosed with TB often ends at treatment completion without any further consultations to evaluate their health and well-being [3]. However, even after successful treatment, which is traditionally classified as either 'cured' or 'treatment completed,' [4] pulmonary TB could permanently destroy or damage the lungs and progress from a treatable communicable disease into a chronic, non-communicable illness across the life course [5]. Moreso, there is increasing evidence that TB survivors continue to experience long-term sequelae that impact their physical and mental health, households, and communities even after successful treatment [5].

Although a growing literature describes a wide range of post-TB sequelae in adults, the actual burden and spectrum of post-TB lung disease (PTLD) remain poorly described in children. Our group previously documented that 52% of childhood TB survivors continued to experience recurrent respiratory symptoms beyond six months after treatment completion [6]. We also reported significantly reduced lung volumes and health-related quality of life in the childhood TB survivors compared to a healthy comparison group. Similarly, a prospective cohort study in Cape Town, which followed children from birth until five years of age, found that children who developed TB were more likely to wheeze consistently and had reduced anthropometry and lung function parameters in the post-TB period compared to children who never had TB [7].

The impact of TB on the lungs of children may be subclinical. Hence more detailed prospective paediatric data using lung function measurements regardless of symptoms and social determinants for lung health are urgently needed to establish the burden and evolution of PTLD in children [8]. The *Childhood TB Sequel* study seeks to add to the growing body of evidence by generating data describing respiratory symptoms, radiological abnormalities and lung function impairment in children after completing pulmonary TB treatment in The Gambia. The study will also assess how abnormalities evolve over the period of 12 months after treatment completion. This study includes adolescents aged 15 to 19 who have a considerably high incidence of TB and are often neglected in childhood TB research [9].

Methods/design

Study aims

The *Childhood TB Sequel* study aims to measure the proportion of Gambian children with long-term adverse outcomes associated with pulmonary TB, to describe the evolution of these sequelae, and to determine the epidemiological risk factors associated with these sequelae.

Study setting

This study is set in the Greater Banjul Area (GBA) of The Gambia, which has mixed urban, peri-urban and rural populations [10]. In 2021, the incidence of TB in The Gambia was estimated to be 149 per 100,000 population [1]. Over 70% of all cases of TB notified in the country reside in the GBA [11]. Children aged 19 years and below comprise about 15% of all notified TB cases annually [1, 12].

After receiving a diagnosis of bacteriologically confirmed or clinically diagnosed (unconfirmed) pulmonary TB by public or private health providers, individuals are referred to their preferred Gambia National Leprosy and Tuberculosis Programme (NLTP) treatment clinic. The treatment clinics in different parts of the country are run by designated Leprosy and Tuberculosis Inspectors (LTI) who provide TB treatment, monitor treatment adherence, and assess the outcome at treatment completion. There are 20 TB treatment clinics in the GBA, which serve a population of about 700,000 [13].

Study design and participant eligibility

The *Childhood TB Sequel* is an ongoing prospective cohort study in the GBA of The Gambia. Children aged 19 years and below who are in the final month of their treatment for pulmonary TB at any of the NLTP treatment clinics in the GBA are identified for possible inclusion in the study. After treatment completion and outcome classification by the LTI, each study participant is eligible if they meet all of the inclusion criteria and none of the exclusion criteria summarised in Table 1.

Recruitment and procedures

Recruitment commenced in April 2022 and is expected to continue until June 2024. The study duration is 12 months, comprising an initial baseline (enrolment) visit and two follow-up time points at six months and 12 months from the enrolment date. A symptom screening will also be conducted via telephone at three and nine months. Table 2 shows the study time points and schedule of events (SOE). We aim to follow-up all children from baseline up to 12 months, regardless of their respiratory function.

We will evaluate clinical, radiological, spirometry and functional capacity measurements during the study visits according to the SOE in Table 2. Finally, we will

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Aged 19 years and below on the date of treatment completion	Relocate from the study area during the follow-up period
Residing within the Greater Banjul Area	Develop recurrent* pulmonary TB during the follow-up period
Previously diagnosed with either confirmed or unconfirmed pulmonary TB	
Have completed treatment with an outcome of *cured* or *treatment completed* within the preceding six weeks	
For children below 18 years, parent/caregiver willing to provide written informed consent as well as assent	

*either a true relapse or a new episode of TB caused by reinfection [4]

Table 2 Schedule of Events (SOE)

	Baseline	Month 3#	Month 6	Month 9#	Month 12	Unscheduled visit
Current symptoms	X	X	X	X	X	X
Clinical assessment	X		X		X	X
Anthropometry	X		X		X	X
Physical examination	X		X		X	X
Chest x-ray	X		X		X	ICI
Spirometry	X		X		X	ICI
6-minute walk test	X		X		X	
Respiratory sample* for Xpert MTB/RIF Ultra	ICI		ICI		ICI	ICI

* Sputum (spontaneous or induced)/nasogastric aspirate

Conducted via telephone call

ICI: if clinically indicated

characterise the changes in lung function over a period of 12 months after treatment completion.

Clinical assessment

During the enrolment visit, we will obtain relevant clinical information, which will include current self- or parent-reported symptoms derived from the St George's Respiratory Questionnaire, [14] a detailed history of the recent episode of TB for which they have just completed treatment, previous TB history, history of other known illnesses, smoking history and environmental exposure to smoking and biomass fuel. Additionally, we will conduct a general physical examination, nutritional assessment using anthropometric measurements, and detailed respiratory examination at enrolment, at six months and 12 months.

Radiological assessment

Per the SOE, we will obtain a chest X-ray (CXR) for each subject at enrolment, six months, and 12 months. Where available, radiographs obtained at TB diagnosis will also be reviewed and assessed for the classification of severity of TB disease as per the radiological case definitions [15]. The radiographs will be interpreted by two independent clinicians experienced in paediatric TB. A third reader will be used to resolve discrepancies in cases where there is a disagreement.

The radiological features of paediatric pulmonary TB are different from adults. In children, the disease is less likely to cause lung cavities commonly seen in adults and adolescents [16]. We expect the severity and typical patterns of post-TB radiological features to vary widely and to be related to the age and the radiological extent of the disease at diagnosis.

Lung function measurement

Lung function assessment will be performed for all children above four years by a trained technician using an Easy on-PC portable spirometer (ndd Medical Technologies, Zurich, Switzerland). Spirometry will be performed according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines [17]. Briefly, we will record the ambient temperature, humidity and altitude prior to daily data collection. Subsequently, the spirometer will be calibrated using a 3 L syringe to ensure that measured volumes are within 3% of the syringe volume. After assessing for contraindications, we will explain and demonstrate the procedure. We will then ask the participant to perform up to eight forced exhalations while sitting. The procedure is repeated for all participants after receiving a bronchodilator (BD), salbutamol, via a spacer device.

Two reviewers will independently assess each spirogram for acceptability and repeatability and agree on a consensus result where there is discordance. Only spirometry traces that meet the ATS quality criteria will be included in the analysis. We will then record the z-scores for the highest forced vital capacity (FVC) and forced

expiratory volume in 1 s (FEV1) and use this for the analysis. The Global Lung Function Initiative (GLI) 2012 reference equations will be used as the reference standard for spirometry data analysis, where FEV1, FVC or FEV1/FVC ratio below the lower limit of normal (LLN) will be deemed abnormal for the participants (Table 3) [18].

Functional capacity measurement

The six-minute walk test (6MWT) is a standardised measure of functional capacity or changes in functional capacity due to intervention in patients with lung disease [19]. The 6MWT will be assessed for all children above four years at the baseline, month 6, and month 12 study visits. The 6MWT will be performed according to the ATS guidelines [19]. In brief, the test will be conducted along a 30-meter-long, flat corridor with marked distances and turnaround points. Before starting the test, the participant will be requested to sit and rest for at least 10 min. After recording the baseline vital signs, dyspnoea and fatigue level will be documented using the Borg scale [20]. Afterwards, we will ask the participant to walk back and forth around the turnaround points. The objective is for the participant to walk as far as possible for six minutes, exerting themselves and taking rests as needed. At the end of six minutes, we will record the distance (in meters) covered by the participant, vital signs and fatigue level.

Outcomes and case definition

The primary outcome for this study is PTLD at enrolment, at six months and 12 months after enrolment. Post-TB lung disease, as proposed during the first international post-tuberculosis symposium, will be operationally defined as *"evidence of chronic respiratory impairment in an individual previously adequately treated for pulmonary tuberculosis in whom active tuberculosis is excluded and in whom no other cause of chronic lung disease is the predominant cause".* [5].

Evidence of chronic respiratory impairment will be assessed using self- or parent-reported chronic or recurrent respiratory symptoms derived from the St George's Respiratory Questionnaire, [14] lung function measured by spirometry, and CXR occurring alone or in combination (Table 3). The evolution and pattern of change over the 6-monthly intervals will be assessed and classified as 'improvement', 'no change' or 'deterioration' based on pre-defined minimum clinically important difference (MCID) cut-offs for the measured parameters.

Sample size

Over the past five years, the annual average notification of childhood and adolescent pulmonary TB in the GBA of The Gambia is 90. Assuming a population prevalence of the primary outcome, abnormal lung function, of 38.5%,[6] and a finite population size of 90, a sample size of 73 cases allows the estimation of the proportion of children who develop post-TB lung function impairment in one year with 95% confidence and a margin of error of less than 5%. To allow for attrition, we will aim to enrol at least 80 children and adolescents. We expect at least 28% of all enrolled children to have had microbiologically confirmed TB [21]. We aim to follow-up all children from baseline up to 12 months, regardless of their respiratory function.

Statistical analysis

The burden of children with the primary outcome, abnormal lung function, at baseline, at six months and 12 months after pulmonary TB treatment completion will be estimated (along with the corresponding 95% confidence interval) overall and stratified by confirmed versus unconfirmed pulmonary TB sub-groups. A pairwise comparison between the baseline and 6-month data and between the baseline and 12-month data will be made using McNemar's test for categorical variables and the sign rank test for continuous variables. Linear mixed effects and logistic models will be used to estimate predictors of abnormal lung function over time. The impact and form of influence of the variables will be explored graphically and by calculating proportions or quantiles depending on the nature of the data.

Ethical considerations

To ensure adherence to internationally accepted ethical standards, including the Declaration of Helsinki and the WHO Handbook for Good Clinical Research Practice, we have taken several measures in conducting our study [22]. First, the study protocol, informed consent

Table 3 Post-TB lung disease measurement parameters

Parameter	Abnormality signifying PTLD
Self- or parent-reported chronic or recurrent symptoms	Presence of any symptom
Lung function • Forced vital capacity (FVC) • Forced expiratory volume in 1 s (FEV1) • FEV1/FVC	*z*-score below the lower limit of normal (-1.64)
Chest X-ray	Presence of any TB-related abnormalities

**PTLD: post-TB lung disease*

document, and other study documents have undergone approval processes by The Gambia Government/MRC Joint Ethics Committee (Ethics Ref: 22,613) and the Observational/Interventions Research Ethics Committee of the London School of Hygiene and Tropical Medicine (Ethics Ref: 22,613–2). Additionally, study participants' parents/legal guardians must provide written informed consent, while children aged 12 years and above must provide written informed assent. To maintain the confidentiality of each participant, they are assigned a unique anonymous study identifier upon enrolment. Furthermore, we uphold transparency and accountability by submitting an annual progress report to the Ethics committee and funders.

Discussion

The lack of provision in the current Gambian TB treatment guidelines for specific post-TB monitoring or treatment of TB-related sequelae in children or adolescents, as well as the absence of estimates regarding the burden of different spectrums of PTLD, highlights the need for research on long-term sequelae and associated risk factors. The *Childhood TB Sequel* study is designed to address these gaps and contribute to the growing body of evidence in this field.

In this study, we will measure the proportion of children with PTLD at different time points: at TB treatment completion, six months, and 12 months after TB treatment. We will also document the different presentations and phenotypes of PTLD in Gambian children and adolescents. Additionally, we will describe the evolution of and track the changes in respiratory symptoms, radiological abnormalities, and lung function impairment in these children following pulmonary TB treatment completion in The Gambia.

By following the participants for at least 12 months, we aim to report lung outcomes that reflect chronicity rather than impairments associated with current TB disease. The data generated from this study will contribute to consolidating the definition of paediatric PTLD and proposing timelines for post-TB evaluation. This information will be valuable for making informed decisions and recommendations for long-term follow-up.

It is important to acknowledge certain limitations in our study. The lack of objective clinical data on the presence and extent of pre-existing comorbidities may limit our ability to attribute the sequelae exclusively to previous TB. Additionally, we have no influence over participants' adherence to anti-TB treatment, which may influence post-TB recovery [23].

In conclusion, the *Childhood TB Sequel* study aims to provide valuable data to enhance our understanding of the long-term impact of pulmonary TB on the health and well-being of Gambian children and adolescents. Through insights into respiratory symptoms, radiological abnormalities, and lung function impairment, this study will contribute to the post-TB evaluation and the development of appropriate long-term follow-up strategies.

Abbreviations

TB	Tuberculosis
PTLD	Post-tuberculosis lung disease
GBA	Greater Banjul Area
NLTP	National Leprosy and Tuberculosis Control Programme
SOE	Schedule of events
CXR	Chest X-ray
ATS	American Thoracic Society
ERS	European Respiratory Society
FVC	Forced Vital Capacity
FEV1	Forced Expiratory Volume in 1 s
GLI	Global Lung Function Initiative
LLN	Lower limit of normal
6MWT	Six-minute walk test
MCID	Minimum clinically important difference
MRC	Medical Research Council

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Authors' contributions
EN, SA, BK, and TT were involved in the conception and design of the study and the data analysis plan. EN, MLJ, UM, OO, and VFE are involved in the data collection. EN and TT wrote the first draft of the article and substantially revised it with input from all the authors. All authors read and approved the final manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
All methods will be carried out in accordance with relevant guidelines and regulations. All experimental protocols were approved by The Gambia Government/MRC Joint Ethics Committee (Ethics Ref: 22613) and the Observational/Interventions Research Ethics Committee of the London School of Hygiene and Tropical Medicine (Ethics Ref: 22613–2). Informed consent will be obtained from all subjects and/or their legal guardian(s).

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Appendix 2: Research Paper (IJTLD Open)

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Student ID Number	449227	**Title**	Dr
First Name(s)	Esin Esin		
Surname/Family Name	Nkereuwem		
Thesis Title	Evaluating the sequelae of pulmonary tubeculosis in Gambian children and adolescents		
Primary Supervisor	Professor Beate Kampmann		

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SECTION E

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LETTER

Impact of race-neutral global reference equations on spirometry interpretation in healthy children in The Gambia

Dear Editor,

Accurate interpretation of spirometry results is crucial for diagnosing and managing respiratory diseases, particularly in children. This interpretation relies on reference equations that predict lung function based on factors like age, sex, height, and, historically, race.[1] In 2012, the Global Lung Function Initiative (GLI) introduced race-specific reference equations (GLI_{2012}), aiming for standardised spirometry interpretation across populations.[2] However, these equations were primarily developed using data from healthy individuals in North America, Europe and Asia and lacked representation from sub-Saharan Africa. This raises concerns about the accuracy of these equations in interpreting lung function for all populations. The inclusion of race in spirometry equations is a topic of debate due to its potential for bias. Using race-adjusted equations in underrepresented populations can lead to incorrect diagnosis and treatment of lung diseases.[3] Relying on race-adjusted equations could also worsen already existing racial disparities in healthcare access and outcomes.[4] To address this, the GLI released new race-neutral GLI_{2022} equations, which rely only on age, sex, and height.[5] However, the impact of these revised race-neutral equations on lung function interpretation in children and adolescents from sub-Saharan Africa is yet to be described. Our objective was to evaluate the impact of the GLI_{2022} race-neutral equations on the interpretation of lung function in healthy Gambian children compared to the race-specific GLI_{2012} equations. Through this evaluation, we aimed to contribute to a more comprehensive understanding of their accuracy and their potential impact on clinical practice.

We performed a secondary analysis of spirometry data from 91 children and adolescents who participated as a healthy comparison group in a comparative study that assessed the prevalence of residual respiratory impairment in children after completion of TB treatment.[6] The participants were aged 5–18 years and resided in the Western Region of The Gambia. They had no recent respiratory tract infections, no history of smoking and no known chronic respiratory conditions. Spirometry was conducted in accordance with the ERS/ATS (European Respiratory Society/American Thoracic Society) guidelines using a calibrated portable Easy on-PC spirometer (ndd, Zurich, Switzerland).[2] We derived *z*-scores for forced expiratory volume in one second ($zFEV_1$), forced vital capacity (zFVC), and the ratio of FEV_1 to forced vital capacity (FVC) using the GLI_{2012} and GLI_{2022} reference equations.[2,5] We considered the equation a good fit if the average *z*-score and standard deviation were not significantly different from zero and one, respectively. We defined the spirometry pattern using the 2022 ERS/ATS guidelines.[7] This study was approved by the Gambian Government and MRC joint ethics committee, reference number 17747. Participants gave informed consent to participate in the study before taking part.

Of the 91 healthy children and adolescents enrolled, five (5.5%) did not meet the quality criteria for spirometry and were excluded. The median age of participants was 11.9 years (interquartile range 8.1–13.7); 34 (39.5%) were female, and 28 (32.6%) reported exposure to environmental tobacco smoke (Supplementary Table S1). The GLI_{2012} 'African American' (mean ± SD $zFEV_1$: –0.91 ± 0.87; zFVC: –0.97 ± 0.93), 'Others/Mixed' ($zFEV_1$: –1.58 ± 0.87; zFVC: –1.71 ± 1.00), and 'South-East Asian' ($zFEV_1$: –1.33 ± 0.88; zFVC: –1.23 ± 0.97) equations had a better fit for this group than the race-neutral GLI_{2022} equations ($zFEV_1$: –1.62 ± 0.75; zFVC: –1.66 ± 0.79). Conversely, the GLI_{2012} 'Caucasian' and 'North-East Asian' equations performed worst, with $zFEV_1$ and zFVC less than the GLI_{2022} estimates. However, the $zFEV_1$/FVC ratio was similar across most reference equations, except for the GLI_{2012} 'South-East Asian' equation, which showed a significantly lower mean ratio (Figure 1 and Supplementary Table S2). The proportion of participants with abnormal spirometry results varied significantly across the reference equations. The GLI_{2012} 'African American' equations had the lowest proportion (27%), whereas the GLI_{2012} 'North-East Asian' equations had the highest proportion (83%). Additionally, the GLI_{2022} equation classified 26% and 19% more as abnormal spirometry than the 'African American' and 'South-East Asian' GLI_{2012} equations, respectively (Figure 2).

Our study provides valuable insights into the challenges of applying race-neutral spirometry reference equations in Gambian children and adolescents. We observed that several GLI_{2012} equations had a better fit for this group than the race-neutral GLI_{2022} equations. Although using GLI_{2012} 'African American' and 'South-East Asian' equations resulted in fewer participants with abnormal spirometry, all reference equations classified a significant proportion of these healthy participants as abnormal. These findings align with a recent systematic review which demonstrated that healthy West African populations

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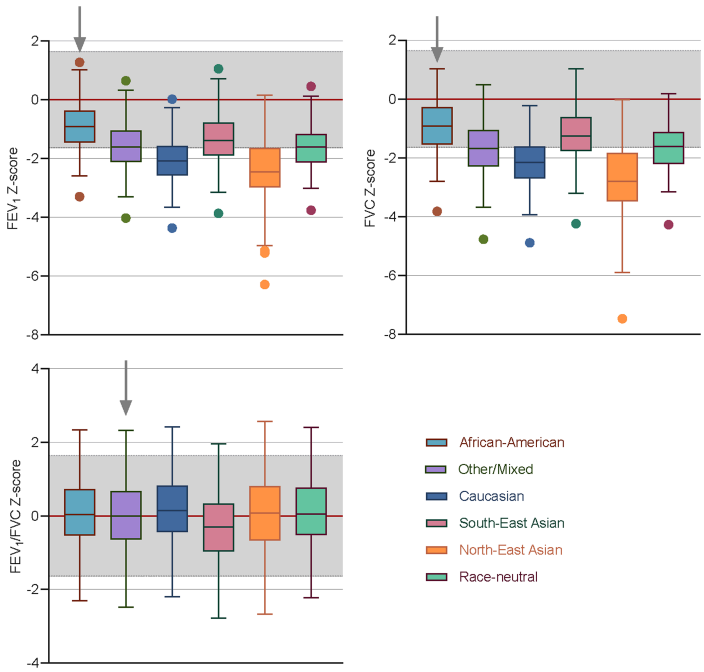

Figure 1. Distribution of *z*-scores of FEV_1, FVC, and FEV_1/FVC using the GLI_{2012} (African-American, Other/Mixed, Caucasian, South East Asian and North East Asian) reference equations and the GLI_{2022} race-neutral reference equation for the study population. The equations that resulted in the closest fit to a mean *z*-score of zero and a standard deviation of one were selected as the best fit (arrow). The shaded area is from −1.64 to +1.64 *z*-scores and represents the expected normal range for spirometry volumes. FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; GLI_{2012} = 2012 Global Lung Function Initiative.

showed a poor fit to all GLI_{2012} reference equations.[8] Furthermore, this raises important concerns regarding the suitability of the race-neutral equations for this population and highlights the need for further research into region-specific adjustments or the development of entirely new reference equations. It is worth noting that similar challenges have also been observed in other populations.[5,9] For example, there have been ongoing debates about using race-based reference equations in the United States, particularly

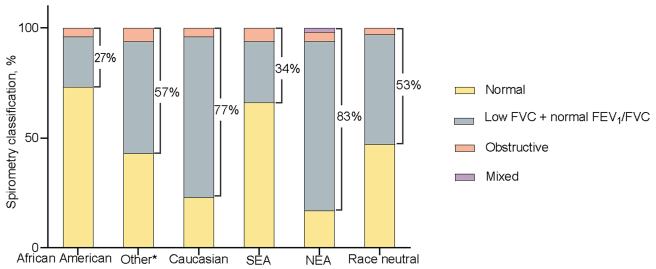

Figure 2. Stacked bar charts showing the spirometry outcome classification using the GLI_{2012} (African American, Other/Mixed, Caucasian, SEA and NEA) reference equations and the GLI_{2022} race-neutral reference equation for the study population. The proportion (%) of participants classified as abnormal using each reference equation is shown. *Or mixed race. SEA = South East Asian; NEA = North East Asian; GLI_{2012} = 2012 Global Lung Function Initiative.

for African American and Latino populations.[4] Studies have shown that race-based reference equations, such as those developed for African Americans, can result in differences in spirometry interpretation and misclassification of lung function impairment.[10] Some researchers suggest that using race-based equations may contribute to health disparities by perpetuating the notion of inherent physiological differences between races.[11] However, others argue that race-based reference equations are necessary to account for genetic and physiologic differences between populations.[12] It is a complex issue that requires further investigation and consideration of social, political, and ethical implications. Beyond genetics, various factors such as environmental exposures, nutritional deficiencies, anthropometry and socio-economic disparities likely contribute to differences in lung function.[13] For example, a study of healthy, multi-ethnic children in London, UK, found that race-specific GLI_{2012} equations described lung function in these children as normal.[14] This suggests that ethnicity may be an important factor influencing spirometry when considering local contexts and environmental factors in the interpretation of what 'normal' spirometry is.

We acknowledge that this is a proof-of-concept study. Additionally, spirometry alone cannot infer the presence of restrictive lung function abnormalities.[7] However, relying solely on spirometry reference equations to define 'normal' lung function overlooks the intricate interplay of genetic and environmental factors that influence respiratory health.[15] A holistic and patient-centred approach to managing respiratory illnesses should incorporate the evaluation of spirometry trends over time alongside a thorough clinical assessment. Importantly, spirometry reference equations should not be used as stand-alone tools for diagnosing or labelling individuals.

In conclusion, although some GLI_{2012} equations appeared to be a better fit for our sample group than the GLI_{2022} equations, our findings suggest that all existing GLI equations have the potential to misclassify spirometry results in healthy Gambian children and adolescents. This highlights the need for more nuanced and context-specific approaches to assess lung function. This should take into account not only race but also environmental and social factors that can influence lung health. By doing this, we can gain a better understanding of respiratory health disparities and develop effective strategies to address them.

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KEY WORDS: lung function; reference equation; child; adolescent; Global Lung Function Initiative; GLI_{2022}

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Supplementary Material

Impact of race-neutral GLI global reference equations on spirometry interpretation in healthy Gambian children

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Running head: GLI Global Equations in Gambian Children

Supplementary Table 1. Participant characteristics

Variable	Participants enrolled (n=86)
Age, median (IQR)	11.9 (8.1, 13.7)
Female sex	34 (39.5)
Environmental tobacco smoke	28 (32.6)
Type of cooking fuel	
Wood	58 (67.4)
Charcoal	26 (30.2)
Gas	2 (2.3)
BMI-for-age *z*-score, median (IQR)	-1.23 (-1.81, -0.46)
Height-for-age *z*-score	-0.17 (-1.01, 0.28)
Underweight	18 (20.9)
Stunted	6 (6.9)
Data are presented as n (%) unless otherwise indicated.	

Supplementary Table 2. Mean z-scores (SD) for each GLI reference equation (N=86)

Reference range	FEV_1 z-score (mean ± SD)	FVC z-score (mean ± SD)	FEV_1/FVC (mean ± SD)
GLI_{2012}			
African American	-0.91 ± 0.87	-0.97 ± 0.93	0.08 ± 0.92
Others/mixed	-1.58 ± 0.87	-1.71 ± 1.00	0.02 ± 0.96
Caucasian	-2.05 ± 0.82	-2.18 ± 0.89	0.18 ± 0.92
South-East Asian	-1.33 ± 0.88	-1.23 ± 0.97	-0.29 ± 0.96
North-East Asian	-2.43 ± 1.21	-2.80 ± 1.39	0.10 ± 1.08
GLI_{2022} race-neutral	-1.62 ± 0.75	-1.66 ± 0.79	0.12 ± 0.92
FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; SD: standard deviation.			

Comment

Making a case for investing in post-tuberculosis lung health in children

Over the past two decades, more than 66 million lives have been saved through global efforts to curb the tuberculosis pandemic.[1] With intensified efforts to improve active case finding and enable prompt diagnosis and early treatment initiation, we can expect this number to increase over the next few years. As we commemorate World TB Day on March 24, 2022, nearly 3000 children worldwide still contract this preventable disease every day.

Despite being a curable infectious disease, tuberculosis can leave behind a long shadow of physical and psychological consequences. Even after being declared cured or treatment completed, as in the current classification of tuberculosis treatment outcomes, many tuberculosis survivors still face medical and socioeconomic challenges, and often require comprehensive care to improve their physical health and quality of life.[2,3] However, patient care usually ends when tuberculosis treatment is completed, with no follow-up to assess mental health or persistence of lung damage.[2] With an estimated 155 million pulmonary tuberculosis survivors as of 2020, post-tuberculosis lung health should become an immediate research priority.[4]

Emerging data suggest that adult tuberculosis survivors have two-to-four-times increased odds of persistently abnormal lung function compared with those who have never had tuberculosis.[5] Meghji and colleagues[6] documented that about a third of adult tuberculosis survivors still reported respiratory symptoms a year after treatment completion. Additionally, there is increasing evidence of adverse socioeconomic and psychological sequelae after tuberculosis treatment.[7]

Children and adolescents are not exempt from this problem. Globally, as reported in the WHO global tuberculosis report 2021, more than one million new cases of tuberculosis occur each year in children younger than 15 years, with around 350 000 of these successfully completing anti-tuberculosis treatment. These children constitute around 12% of all tuberculosis survivors worldwide.[4] With a growing number of children surviving tuberculosis each year, we can expect to be faced with a substantial burden of paediatric post-tuberculosis lung and psychosocial sequelae, with long-lasting consequences for this younger generation.

Since all available data showing the burden of post-tuberculosis lung disease (PTLD) are from studies in adult populations, there are currently no published data on the spectrum, pattern, burden, and manifestation of PTLD in children. Lung development lasts throughout the entire first two decades of a child's life; therefore, a chronic respiratory insult such as pulmonary tuberculosis could have a long-lasting impact and leave paediatric tuberculosis survivors at risk of potentially permanent disability and increased likelihood of long-term non-communicable disease.[9]

The increasing pool of tuberculosis survivors will confront us with a unique set of health-care needs and challenges, which are not currently being addressed.[7] The first post-tuberculosis symposium, held in July, 2019, further highlighted this issue and brought together stakeholders, researchers, and tuberculosis survivors to elaborate on PTLD.[9] A consensus definition was reached for PTLD, and it was agreed that further research is necessary to determine the extent and burden of PTLD for all age groups.[10]

In this context, we postulate that the current classification of tuberculosis treatment outcomes is deficient, as it fails to capture residual effects of the disease that remain after treatment for tuberculosis is completed. It is therefore timely to revise the tuberculosis treatment outcomes and include a post-treatment review to assess for physical or psychological sequelae after tuberculosis treatment.

The World TB Day theme for 2022—Invest to End TB. Save Lives—is all encompassing and highlights the increasing need to ramp up investment. This theme is inviting us to address all aspects of tuberculosis care, including research into post-tuberculosis lung health, especially in children who have a long life-course ahead of them. Investment in a holistic approach to tuberculosis care—beyond the period of drug treatment—is needed if we wish to truly save lives.

We declare no competing interests.

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Comment

"Yes! We can end TB," but remember the sequelae in children

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As we mark World Tuberculosis Day on March 24, 2024, under the theme of "Yes! We can end [tuberculosis] TB", we need to remember that achieving zero cases and deaths is only one aspect of the battle against this tenacious disease.[1] To combat tuberculosis effectively, we need a more comprehensive approach that includes every stage of the journey, from pretreatment to life after tuberculosis.[2] This continuum of care, which incorporates post-tuberculosis assessment and care (figure), is essential to ensure that those with a history of tuberculosis, especially children and adolescents, can thrive without having debilitating sequelae.[3]

Although there has been substantial progress in the fight against tuberculosis, children and adolescents still bear a disproportionate burden of the disease; they accounted for an estimated 12% of new cases and 16% of all deaths due to tuberculosis in 2022.[4] Diagnosing tuberculosis in children remains a challenge.[1] Furthermore, many children who are eligible for preventive treatment do not receive it, for many reasons.[4] Even those children and adolescents who seem to recover from the disease are at risk of lifelong consequences, including respiratory impairment and increased risk of non-communicable diseases later in life.[5–7] These post-tuberculosis sequelae, which are often ignored by the health-care system, can greatly affect their physical, social, and economic wellbeing.[8]

Emerging scientific evidence from the past year has revealed concerning findings about post-tuberculosis lung disease in children and adolescents.[6,7,9] According to these studies, even after being successfully treated, children and adolescents can still develop chronic wheezing, cough, impaired linear growth, and reduced lung function and health-related quality of life.

Tuberculosis manifests differently in various paediatric age groups, suggesting that unique post-tuberculosis lung disease phenotypes might exist, with each group requiring tailored approaches for accurate diagnosis and effective intervention.[5,8] Additionally, the absence of biomarkers presents a substantial challenge to diagnosis and makes it difficult to compare research studies.[5] Unfortunately, we do not have a universal definition for post-tuberculosis lung disease, agreed measurement tools, or consensus on the optimal timing for assessments, all of which greatly impede our understanding and management of this condition in children and adolescents.

At the first International Post-Tuberculosis Symposium—held in Stellenbosch, South Africa, in 2019—a research definition for paediatric post-tuberculosis lung disease was proposed and later updated in 2023.[5,10] Although this development offers some hope, how the definition will be practically applied in research and clinical settings remains uncertain. There are still many unanswered questions about paediatric post-tuberculosis lung disease. For instance, how do we define it effectively for different age groups, considering their unique vulnerabilities and presentations? What parameters should be measured, and which reference ranges should be used? When and how frequently should these assessments be conducted to accurately capture the condition's dynamic nature? These questions show that we have an incomplete understanding of paediatric post-tuberculosis lung disease and its effects on the lives of children and adolescents.[8] Advocating for children and adolescents with a history of tuberculosis is essential because their lungs are still developing and they live longer with the sequelae, therefore, they have an increased likelihood of developing long-term non-communicable disease.[11]

Although primary prevention strategies to avoid contracting tuberculosis are crucial, increasing funding for post-tuberculosis research is also necessary to bridge the knowledge gap. Unfortunately, childhood tuberculosis research continues to face a substantial funding gap. In 2022, only about 50% of the US$2 billion global investment target needed for tuberculosis research was reached.[12] Even with this considerable shortfall in funding for tuberculosis research and development globally, less than 10% of annual funding investments for tuberculosis research are devoted to children and adolescents.[13] This inequity in financing childhood

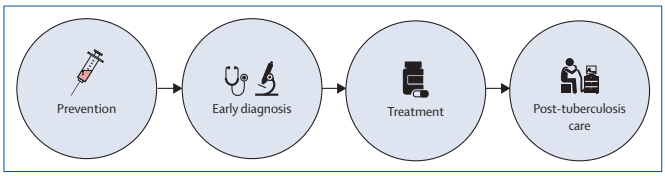

Figure: **Proposed continuum of care for children and adolescents with tuberculosis from disease prevention to post-tuberculosis care**

tuberculosis research needs to be addressed urgently. The National Institutes of Health's call in 2023 for proposals that focus on characterising post-tuberculosis lung disease in individuals living with HIV is a positive step.[14] However, we still need sustained and expanded funding to refine definitions, develop standardised tools, and identify risk factors for specific phenotypes. This investment will allow the development of targeted interventions that address the unique needs of children and adolescents with post-tuberculosis lung disease.

As we mark World Tuberculosis Day 2024, we should acknowledge the progress that has been made in the fight against this disease. However, we need to also remember that there is still a long way to go. Children and adolescents are often silently subjected to the lingering effects of tuberculosis and they deserve our unwavering attention and dedicated action. By prioritising research on paediatric post-tuberculosis morbidity, bridging the funding gap, and advocating for a continuum of care that extends beyond diagnosis and treatment, we can truly fulfil the promise of World Tuberculosis Day—a future in which every young person, with or without a history of tuberculosis, can breathe freely and thrive.

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Appendix 5: Research paper (Public Health Action)

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Student ID Number	449227	**Title**	Dr
First Name(s)	Esin Esin		
Surname/Family Name	Nkereuwem		
Thesis Title	Evaluating the sequelae of pulmonary tubeculosis in Gambian children and adolescents		
Primary Supervisor	Professor Beate Kampmann		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Public Health Action		
When was the work published?	March 2023		
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SECTION E

Student Signature	[redacted]
Date	1 September 2024

Supervisor Signature	[redacted]
Date	2 September 2024

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Perspectives of TB survivors and policymakers on post-TB disability

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BACKGROUND: An international multistakeholder participatory workshop was hosted in the Gambia, West Africa, in November 2021.

OBJECTIVES: To explore the experiences, challenges and recommendations of workshop participants on health and wellbeing after TB treatment.

METHODS: An exploratory, descriptive, qualitative approach was used for data collection through facilitator-guided group discussions. Workshop participants included adolescent and adult TB survivors, and representatives of TB advocacy groups and the policy sector. Discussions were audio-recorded and transcribed verbatim, and the data were analysed using a deductive thematic approach.

RESULTS: Overall, 38 participants (22 women) from six West African countries participated in the workshop, comprising 33 TB survivors and advocacy group representatives and 5 participants from the policy sector. Although some TB survivors noted improved ability to carry out physical activities, others continued to experience detrimental effects on their family life, social interactions, physical health and ongoing stigma. Policymakers emphasised the lack of data and clear guidelines on post-TB disability.

CONCLUSIONS: Some TB survivors continue to suffer detrimental effects of the illness even after treatment completion. However, available data on post-TB disability is inadequate to support policy adoption. Therefore, there is an urgent need for increased advocacy, awareness and research to bridge knowledge gaps.

About 10.6 million people fell ill with TB in 2021, with sub-Saharan Africa accounting for nearly one-quarter of the total number of new TB cases.[1] Among the 30 countries considered by the WHO to have a high TB burden globally, 17 are in sub-Saharan Africa, with three countries (Liberia, Nigeria and Sierra Leone) from West Africa.[1]

Recent reports by the WHO indicate that at least 85% of people who receive treatment for the first episode of TB disease achieve treatment success.[2,3] Traditionally, the outcomes for people who are successfully treated for TB are classified as either 'cured' or 'treatment completed'.[4] Although TB treatment success has resulted in more than 66 million lives saved between 2000 and 2020 globally,[3] many TB survivors continue to experience medical and psychosocial challenges that often warrant repeated hospital visits.[5]

Published data suggest that adult pulmonary TB survivors have two- to four-fold higher odds of persistently abnormal lung function than people who never previously had TB.[6–8] Other studies have documented the persistence of respiratory symptoms, and reduced health-related quality of life (HRQoL), despite successful completion of TB treatment in adults and children.[9–13] There is also increasing evidence of adverse psychosocial morbidities and persistent socio-economic impairment among TB survivors.[14]

Despite the growing data on the long-term impact of TB on lung function and physical and psychosocial wellbeing, the care of TB patients currently ceases at the time of treatment completion.[15] However, many TB survivors need continuous medical and psychosocial care beyond the completion of their anti-TB therapy, particularly children and adolescent TB survivors who still have a long life course ahead of them.[13,15,16]

This issue is increasingly being recognised, and efforts to increase awareness of post-TB disability have begun. In 2019, the first International Post-TB Symposium was held in South Africa, bringing together TB survivors, clinicians and researchers to advocate for individuals suffering from post-TB complications and to identify existing gaps in knowledge.[5,17] However, no participatory data are currently available from TB survivors or policymakers in West Africa in particular.

To begin advocacy initiatives toward increasing the awareness of post-TB lung health through active engagement with TB survivors and policymakers in West Africa, we organised an international multistakeholder participatory workshop in the Gambia in which we embedded a qualitative study.[18] Our objective was to explore and document the lived experiences and challenges of adolescent and adult TB survivors, as well as advocacy groups beyond TB treatment. We also aimed to document the perspectives and recommendations of key policy sector representatives regarding post-TB disability.

METHODS

Study design, setting and participant selection

This was an exploratory, descriptive, qualitative study on post-TB disability that was conducted during an international multistakeholder participatory workshop on post-TB lung health in West Africa. The workshop took place in The Gambia from 17 to 19 November 2021.

Participants comprised adolescent and adult TB survivors, representatives of TB advocacy groups, as

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well as policy sector representatives from six West African countries (Benin, Burkina Faso, The Gambia, Ghana, Nigeria and Sierra Leone). Authors ON and TT purposively selected and invited the participants through our established collaborative partnerships in West Africa. All participants were given information about our intention to conduct the research at the time of invitation for the workshop. The list of TB advocacy and policy organisations that participated in the workshop is provided in Supplementary Data 1.

Data collection

Primary data collection in the study was by facilitator-guided group discussions.[19] These were conducted using a semi-structured discussion guide (see Supplementary Data 2). Authors ON, EN, OO and PJ facilitated the group discussions in separate and quiet areas of the workshop venue. The workshop participants were divided into three groups: 1) adolescent TB survivors, 2) adult TB survivors and advocacy group representatives, who were further divided into two smaller groups, and 3) representatives of the policy sector. Each individual was assigned a unique identifier, which was used throughout the group discussions.

Topics explored included how persistent health problems affected family interaction, managing social interactions, physical activities, assessing healthcare support and strategies for coping with persistent health impairments due to TB. The researchers also asked probing questions during the group discussions to help clarify statements made by the participants. Generally, the probing questions used in this study were not predetermined and came from the need to seek clarity when required.

Interpreters in each group translated the conversations for non-English speaking participants. Questions were translated from English to the participant's preferred language (French, Wolof or Mandinka), and responses were back-translated into English. Each group comprised between five and 12 participants (excluding the facilitator and interpreter) with similar demographic characteristics, and three discussions were conducted per group over the course of the participatory workshop. Each group discussion lasted for 90 minutes. All group interactive sessions were recorded using an encrypted recorder.

Data analysis

Trained field assistants transcribed the recorded discussions. We used recordings and field notes to cross-check all transcripts, ensured that they were correctly translated to preserve the meaning of the participants' words and statements, and provided feedback to all field assistants.

We analysed our data using a deductive thematic approach.[20] The transcripts were read through, line by line, to identify key concepts. We then used these key concepts to develop a coding framework for data coding. The coding process involved reading the transcripts, linking and connecting texts to their representative key concepts. The key concepts were then organised into categories and sub-categories.

Ethical considerations

Ethical clearance was obtained from the Gambian Government/Medical Research Council Unit The Gambia at London School of Hygiene & Tropical Medicine Joint Ethics Committee, Banjul, The Gambia (Ref: 26573). Written informed consent was obtained from all study participants, including consent from parents/caregivers of the adolescents, and assent from the adolescents. Participants were given information about the study and the objectives, and taken through the informed consent process while registering for the workshop. Participation in the study was voluntary, and individuals could choose to attend the workshop without participating in the study. We used unique codes for each participant throughout the study to ensure data privacy and anonymity.

RESULTS

Sociodemographics of participants

Overall, 38 individuals representing different stakeholder groups from six West African countries attended the workshop, and all consented to participate in the qualitative study. The groups comprised 10 adolescents aged 13–20 years, 23 adult TB survivors and representatives of TB advocacy groups aged 21–60 years, and 5 participants from the policy sector (3 National TB Programme officers, 1 WHO staff and 1 representative of an international non-governmental organisation) (Table). Majority of the participants were female (22/38) and from the Gambia (28/38).

Themes, sub-themes and supporting quotes

Figure 1 shows the themes and sub-themes which emerged from the group discussions. From the groups with the TB survivors and advocacy group representatives, three emerging themes were 1) quality of life; 2) stigma; and 3) the need for psychosocial support (Figure 1A). The themes emerging from the group of policy sector representatives were 1) knowledge gap/inadequate data on post-TB disability to support policy adoption; 2) limited TB care package; and 3) recommendations (Figure 1B).

We present the findings from each theme and sub-theme along with supporting quotes from the participants to buttress the points made.

TB survivors and advocacy group representatives

Theme 1: Quality of life

Family life and work

All the adolescent TB survivors who participated in the discussions acknowledged that there was improvement in their general health status following TB treatment. However, the group discussions revealed that most of them reported disruptions in their relationships with family members because of their previous TB diagnosis:

> … I was isolated even after I was cured to prevent further spread of the bug. I had a private room. (Code A002)

> … everyone within the family started acting differently towards me. For example, I wasn't allowed to eat with

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The authors thank all the TB survivors, representatives of TB advocacy groups and the policy sector from West Africa who attended the multistakeholder participatory workshop and participated in this qualitative study; and the Gambia National Leprosy and Tuberculosis Control Programme (NTLP), TB PROOF (a global advocacy organisation of TB survivors), as well as the West African Regional Network for TB Control (WARN-TB) for their continuing support.

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Conflicts of interest: none declared.

TABLE Socio-demographic characteristics of workshop participants

Variables	Participants (*n* = 38)
Sex	
Female	22
Male	16
Country	
Benin	2
Burkina Faso	2
The Gambia	28
Ghana	2
Nigeria	2
Sierra Leone	2
Participating groups	
Adolescent TB survivors	10
Adult TB survivors and advocacy group representatives	23
Policy sector representatives	5

everyone. I also found out that we started fighting and getting into arguments. I now live with my uncle. (Code A001)

Similarly, the adult TB survivors acknowledged that their social participation patterns, family and work lives were negatively affected due to the illness. They emphasised the importance of family support during treatment and after treatment completion:

> … when I got TB, I was the breadwinner in my family. It was difficult for me as the head of the family to fully function in my role. It was indeed a difficult time for me and my family, even after being cured. (Code AC001)

> … I was laid off, with only 2 weeks' salary and hospital bills to pay …It was a very dark time for me and my family, my wife and children had to struggle and suffer. (Code AC004)

The discussions also revealed the negative impact of TB on the work productivity of some of the adult TB survivors, with participants discussing the challenges they faced following completion of TB treatment compared to their life before contracting TB:

> There is an assessment that is done for employees to assess their productivity and performance. Due to my struggles with TB, I wasn't able to meet up, and I was laid off. (Code AC004)

> …you won't be able to work like you used to. (Code AC007)

Social participation

The adolescent survivors said that TB negatively impacted their social interactions with others in their neighbourhood during and after their treatment. For some of the adolescents, these experiences were associated with deleterious effects on their academics and the practice of their faith; however, one adolescent TB survivor reported a positive improvement in their academic performance.

> I have lost interactions with my friends because they heard I had TB… I have improved, and I am working towards succeeding in my exams. (Code A001)

> It has affected my prayer life; I find it difficult to observe all the five daily prayers. (Code A010)

> After my treatment, I discovered I have regained the ability to focus in class and improve my grades. (Code A008)

The experience was similar among the adult TB survivors and advocacy group representatives. This group noted that they experienced reduced interaction with others in their neighbourhoods and communities due to their illness. For some participants, the experience remained the same even after treatment was completed.

> …in fact, I stopped going to church out of fear of spreading the disease. (Code AC004)

> …by the time I was cured, I had to stay back an extra year [in school] because of this illness. After my treatment, I went ahead to get two degrees. (Code AC008)

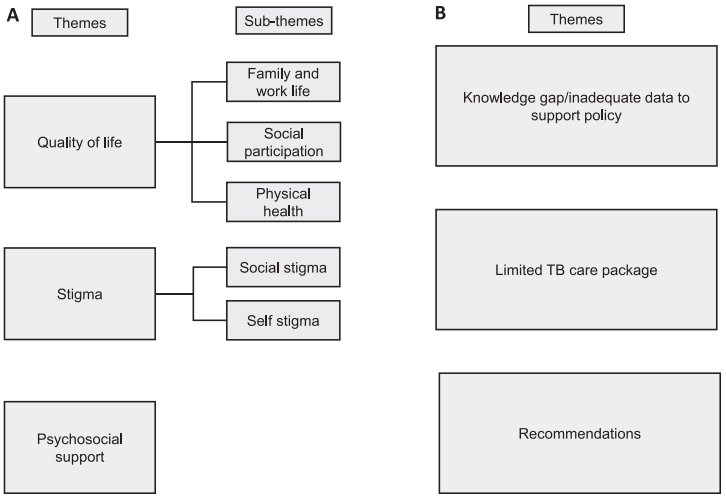

FIGURE 1: Key themes and sub-themes that emerged from the facilitator-guided group discussions with TB survivors and **A)** advocacy group representatives, and **B)** policy sector representatives.

Physical health

Several of the adolescents had high expectations and had hoped to resume their regular physical activities following completion of TB treatment. However, many said they are still experiencing persistent physical health challenges afterwards, including body pains and inability to perform regular physical activities.

> Even after my treatment, I still feel pains in my body, sometimes I run a fever. After the sickness I noticed a large change in my abilities to do physical activities, I get tired easily. (Code A001)
>
> I find myself getting tired easily. (Code A007)
>
> I used to play football a lot before with my friends, but after I got ill, I found it difficult to keep up with the energy requirements of playing football, so I have stopped. (Code A003)
>
> I used to do much physical exercise and work before TB, and after TB, I have resumed them. (Code A004)

Furthermore, although some of the adult TB survivors reported improvement in carrying out their physical activities following TB treatment, many expressed lingering and recurring health concerns similar to the adolescents, adding that there was still a need for supportive medical care following the completion of TB medication.

> … the moment I was treated and cured, all the symptoms went. (Code AC003)
>
> After TB treatment, I still produce sputum, and people start wondering whether I am still sick (Code AC021)
>
> … [after completing TB treatment] when I was pregnant I was always feeling weak and even started coughing. The side effect of the TB is always there when I undergo stress. (Code AC020)

Theme 2: Stigma

Most adolescent survivors reported that they continued to experience discrimination, labelling and ill-treatment in their local communities, which led to social isolation in some instances.

> I lost my best friend because of this sickness. She became scared of me and refused to be too close to me. (Code A006)
>
> … when my co-workers found out, they started isolating me. (Code A002)
>
> … when my father had TB, he kept it a secret from the rest of the family to avoid stigmatisation and discrimination from other members of the community and us… He went through the treatment without anyone of us knowing. (Code A010)

This perceived external stigma led many adolescents to hold onto negative beliefs about themselves even after they had finished their TB medication, thus further affecting their relationships with peers and social interactions.

> None of my friends knew I had TB. I kept it a secret from them to avoid them feeling different about me. (Code A007)
>
> I reduced going out to spend time with other people out of fear of stigma. (Code A010)

Many adult participants shared similar experiences of rejection, labelling and discrimination because of the perceived risk of transmission to other people, even after TB treatment.

> Even after I got well, some of my friends still feel uncomfortable around me or even avoid me. (Code AC004)
>
> … It was my younger brother that had TB, and I can tell first hand that the whole community stigmatised us. (Code AC014)
>
> They said I took it from somewhere and brought it into the house, they said I used to stay out for a long time, so I have gone to get it. They said I got it from the ghetto. (Code AC002)
>
> I reduced going out to spend time with other people out of fear of stigma and risk of transmitting the infection. (Code AC010)

Theme 3: Psychosocial support

Both groups emphasised the importance of psychosocial support from the community during and after TB treatment. Furthermore, they stressed the importance of awareness and proper sensitisation to achieve public acceptance. Parents, other family members and healthcare workers at TB treatment centres were mentioned as the ones who should provide continuous psychosocial support.

> …mass education of the populace to debunk myths and misconceptions about TB… Changing people's orientation about TB to help stop discrimination and stigmatisation of TB patients. (Code A009)
>
> …my mom is always trying to support me emotionally. (Code A002)

Moreover, adult TB survivors, who are now members of TB advocacy groups, felt that their experience could help others through their struggles. They did not want others to go through the same struggles they had experienced and were still experiencing.

> The doctor that treated me told me about an advocacy group and asked me to join, that he believed my story would help others going through this struggle, and that is how I joined and became an advocate. (Code AC008)

Policy sector representatives

Discussions with policymakers revealed a significant gap in knowledge about health impairment following TB treatment in adults, adolescents and children. They expressed the need for data to determine risk factors for post-TB disability, the proportion of TB survivors who develop health challenges after treatment completion and for how long. There was an emphasis on the need for evidence to make a case for adopting post-TB lung health interventions on global policy agendas.

> … If we look at the framework, there is nothing like post-TB, it is even new to me. Only research and evidence can tell us if these [problems] follow TB. (Code P004)
>
> … there isn't even sufficient evidence for it to become a policy. (Code P002)
>
> If there is evidence, people will spend on it. If it becomes a policy, the country will definitely find resources to implement it, and advocates would also find resources to pursue it. (Code P001)
>
> Even if there is sufficient evidence for it to become a policy, it might not get to the surface because most people are looking at reducing numbers, not the long-term effect. (Code P002)

Discussions also highlighted the deficiencies of the current TB care package, which was perceived as not adequately addressing the patient's needs throughout the TB treatment process, let alone afterward.

> … we do not care whether the person has eaten, what we want is that the person takes the drugs, these can result in toxic effects of the antibiotics. (Code P001)
>
> … if you look at the central level that is at the level of the ministry, TB services are being stigmatised in the sense that if recruit-

ment is being done, the lowest care of people or staff at the facility are the ones that are recruited to give services to patients that are being affected by TB …All that they do is recruit nurse attendants who are not that competent or qualified to care for people. (Code AC025)

The overwhelming recommendation from the policymakers for translating the post-TB agenda into policy was that there is a need for evidence to drive the discussions and advocacy for post-TB lung health:

… By producing clear evidence… [post-TB health] has to be assessed in terms of numbers, with representation from low and middle-income countries. The next thing is our intervention. The policy comes in guidelines, and the guidelines must be elaborate, detailed, and easy to do on a public health scale. (Code P002)

When the evidence is there, the policy drives some of these [interventions]. (Code P001)

DISCUSSION

In this study, we explored and documented the lived experiences of adolescent and adult TB survivors and advocacy group representatives, as well as the perspectives and recommendations of policymakers from six West African countries. Although TB survivors reported improvement in carrying out physical activities following treatment, some continue to experience deleterious effects on family life, social interactions, challenges in carrying out physical activities and ongoing stigma. Policymakers acknowledged that the available data on post-TB disability were inadequate to support policy adoption.

The adolescent and adult TB survivors in our study reported persistent and often disabling physical health challenges post-treatment, including continued respiratory symptoms probably due to residual lung damage. This finding is consistent with published reports suggesting chronic respiratory symptoms are often known to persist after TB treatment in adults and adolescents.[10–13]

Published evidence has shown that the economic and social problems associated with TB illness may worsen the physical post-TB comorbidities and sequelae.[21] Findings from our study support this assertion, with TB survivors reporting that their family, social and economic lives and livelihoods were adversely affected by the illness and its sequelae. A better understanding of the economic impact of TB disease beyond the end of TB treatment, and interventions to protect the livelihoods of TB survivors, should be integral components of TB control efforts.

As demonstrated in our study and confirmed by many others, TB is associated with stigma affecting TB survivors and their families, in addition to its physical consequences. Other studies have similarly reported that stigma associated with TB remains even after successful treatment when TB survivors are no longer infectious,[22] and they are often silently isolated and avoided by the community members.[23] As such, TB survivors are often motivated to get involved in TB control activities such as treatment support and combating TB-related stigma.[24] Therefore, continuous capacity building and sensitisation within and outside the health sector with the aim of educating the community to reduce the TB-related stigma are essential.[22]

It should be noted that the topic was not at all familiar to the policymakers, who highlighted the urgent need for more research to inform policy and guide decision-making for improving physical and psychosocial health, and quality of life after TB treatment. This suggests that there is a need for the development of clear evidence-based guidelines for the management of respiratory symptoms and psychosocial sequelae of TB, as alluded to in other published studies.[14,25] A positive step in this direction was the recent publication of clinical standards for post-TB lung disease by The Union.[26]

The key strength of our study is the use of a participatory approach to gain an understanding of the lived experiences of TB survivors, including adolescents. However, our study also has clear limitations: we enrolled only a small group of individuals selected from existing collaborations by invitation. Therefore, our study may not reflect the experience of a broader population of TB survivors. Nevertheless, our findings have highlighted several critical implications for TB research, policy and programmes.

In conclusion, our study shows that some TB survivors continue to suffer detrimental effects of the illness on their family life, social interactions, physical health, and ongoing stigma. Furthermore, the currently available data on post-TB disability are inadequate to support policy adoption. These findings support an urgent need for increased advocacy, awareness, and research to provide the evidence base for developing robust guidelines for the care and support of TB survivors beyond the end of treatment. Further studies and interventions on health and wellbeing after TB treatment should put into consideration the peculiarities of the needs of adolescents, especially strategies to cope with body pains, inability to perform regular physical activities and the psychosocial challenges, as seen in the discussions from this study. Furthermore, we recommend further research to investigate the burden of physical, psychosocial and economic sequelae after completion of TB treatment, risk factors and determinants of post-TB disability for early identification of TB patients at risk of developing persistent health impairment after treatment, solutions to alleviate persistent symptoms amongst TB survivors, and interventions to cushion the economic impact of post-TB disability on TB-affected households and communities. These recommendations are in line with the conclusions of the first International Post-TB Symposium that called for increased advocacy and more research on post-TB lung health,[27] and they are potential action points for the second Post-TB Symposium that is planned for 2023.

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CONTEXTE : Un atelier participatif international multipartite a été organisé en Gambie, Afrique de l'Ouest, en novembre 2021.
OBJECTIFS : Analyser les expériences, les défis et les recommandations des participants à l'atelier en matière de santé et de bien-être après un traitement antituberculeux.
MÉTHODES : Une approche exploratoire, descriptive et qualitative a été utilisée pour le recueil des données par le biais de discussions de groupe encadrées par un animateur. Les participants à l'atelier étaient des adolescents et des adultes ayant survécu à une TB, ainsi que des représentants de groupes de plaidoyer de la TB et du secteur politique. Les discussions ont été enregistrées sur support audio et transcrites textuellement, et les données ont été analysées en utilisant une approche thématique déductive.
RÉSULTATS : Au total, 38 participants (22 femmes) de six pays d'Afrique de l'Ouest ont participé à l'atelier, dont 33 représentants de groupes de plaidoyer ayant eux-mêmes survécu à une TB et 5 participants issus du secteur politique. Bien que certaines personnes ayant survécu à une TB aient constaté une amélioration de leur capacité à mener des activités physiques, d'autres ont continué à subir les effets néfastes sur leur vie familiale, leurs interactions sociales, leur santé physique et la stigmatisation permanente. Les responsables politiques ont souligné le manque de données et de directives claires sur le handicap post-TB.
CONCLUSIONS : Certaines personnes ayant survécu à une TB continuent de subir les effets néfastes de la maladie, et ce même après la fin du traitement. Cependant, les données disponibles sur le handicap post-TB sont insuffisantes pour soutenir l'adoption de politiques. Il est donc urgent de renforcer le plaidoyer, la sensibilisation et la recherche pour combler les lacunes en matière de connaissances.

Public Health Action (PHA) welcomes the submission of articles on all aspects of operational research, including quality improvements, cost-benefit analysis, ethics, equity, access to services and capacity building, with a focus on relevant areas of public health (e.g. infection control, nutrition, TB, HIV, vaccines, smoking, COVID-19, microbial resistance, outbreaks etc).

Contact: pha@theunion.org
Information on PHA: http://www.theunion.org/what-we-do/journals/pha

Supplementary Material

Perspectives of TB survivors and policymakers on post-TB disability

Oluwatosin Nkereuwem, Esin Nkereuwem, Olumuyiwa Owolabi, Penda Johm, Uzo Egere, Kevin Mortimer, Beate Kampmann, Toyin Togun

Participating TB Advocacy and Policy Sector Organisations

Policy Sector

1. Afro Global Alliance, Ghana
2. National Programme Officer for TB, World Health Organization – Gambia Country Office
3. Programme National contre la Tuberculose, Cotonou, Benin Republic
4. National Leprosy and Tuberculosis Control Programme, The Gambia

TB Advocacy Groups

1. Ghana National TB Voice Network, Accra, Ghana
2. ASSAP TB, Cotonou, Benin Republic
3. TB People, Nigeria
4. Africa Coalition against TB (ACT) – Nigeria
5. Civil Society Movement Against TB (CISMAT), Sierra Leone
6. Association des Anciens Malades de la Tuberculose (AMT), Burkina Faso
7. Ex-TB The Gambia

INTRODUCTION

Good morning, everyone. My name is_____ and here with me is our language interpreter _____ and my note taker/ assistant _____. I will be your facilitator in this group discussion today.

I would like to thank you all for consenting to be part of this workshop and to take part in this group discussion. As written in the information sheets and consenting forms we will be recording this session and taking notes for proper documentation. We promise to keep all information shared here confidential as we have maintained since the workshop started. Our unique identifier numbers will be used instead of our names to address us throughout this discussion. Thank you very much.

Day 1

Group 1: Adolescent TB survivors; Group 3: TB survivors/advocates (I)

Following the various presentations and interactive sessions today, we will like to explore our experiences following completion of TB treatment on our health-related quality of life

1. How have your experiences following the completion of TB treatment affected your family life?

(During the discussion, facilitators should explore how persistent health problems following the completion of TB treatment have affected household-incurred costs, moving house, family interaction, parenting issues, financial problems, drug, alcohol, gambling addiction or domestic violence, etc.)

2. How have persistent health problems following the completion of TB treatment affected your work life?

(During the discussion, facilitators should explore strategies adopted for coping with pressure at work or school, unemployment, exams, dependence, and finance etc.)

3. How have persistent health problems following the completion of TB treatment affected your participation in your community?

(During the discussion, facilitators should explore areas of recreation and fun, religious activities, social life, social events, friends etc.).

4. How have persistent health problems following the completion of TB treatment affected your physical health?

(During the discussion, facilitators should explore areas of nutrition and diet, lack of time due to the responsibilities of care, inactive lifestyle, sports, events, and lack of support available for emotional well-being, physical/emotional well-being, etc.).

Group 2: Policymakers

Following the various presentations and interactive sessions today, we will like to explore the policies in place to tackle post-TB lung health in specific regions or countries.

1. Why has post-TB lung health not been a policy priority?
2. How we put post-TB lung health on the policy agenda (How do we make a case for post-TB lung health)
3. How do we translate from research findings to policy regarding life after TB treatment?
4. How do we encourage discussions and advocacy for post-TB lung health?

Day 2

Following the various presentations and interactive sessions today, explore the aspect of stigma and psychosocial challenges and support following TB treatment.

1. What will you say has been your experience with social stigma and self-stigma following the completion of TB treatment?

(During the discussion, facilitators should explore areas explore forms of stigma Examples- labelling, stereotyping, social isolation, prejudice, rejection, ignorance, status loss, low self-esteem, low self-efficacy, marginalisation, or discrimination)

2. How will you say stigma has affected you following the completion of TB treatment?

(During the discussion, facilitators should explore the following areas: reluctance to seek post-TB care**;** social rejection, avoidance, and isolation**;** psychological well-being**;** poor understanding among friends and family**;** harassment, violence, or bullying**;** poor quality of life, disability, and increased socioeconomic burden**;** increased feelings of shame and self-doubt)

3. What are some of the psychosocial challenges you have faced following the completion of TB treatment?

(During the discussion, facilitators should explore the following areas: family problems**,** depression, anxiety**,** substance abuse, and violence)

4. What facility, system, structure, or individual will you consider your psychosocial support system?

(During the discussion, facilitators should encourage participants to mention as many as possible)

Appendix 6: Supplementary material for Research Paper 1 (Objective 1)

Supplementary material

Reduced lung function and health-related quality of life after treatment for pulmonary tuberculosis in Gambian children: a cross-sectional comparative study

Esin Nkereuwem[1,2] FWACP, Schadrac C. Agbla[3,4] PhD, Azeezat Sallahdeen[1] MPH, Olumuyiwa Owolabi[1] FMCPaed, Abdou K. Sillah[1] MSc, Monica Genekah[1], Abdoulie Tunkara[1], Sheriff Kandeh[1], Maryama Jawara[1] BSc, Lamin Saidy[1], Prof Andy Bush[5,6,7] MD, Toyin Togun[1,8] PhD, Prof Beate Kampmann[1,9] PhD

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Number of post-TB cases and comparison group children enrolled from each household

Supplementary Table 1 shows the number of post-tuberculosis (post-TB) enrolled along with the corresponding number of age-matched comparison group children from each household. Household 45 had two post-TB cases, and there were 13 households which did not have an eligible age-matched child for the comparison group.

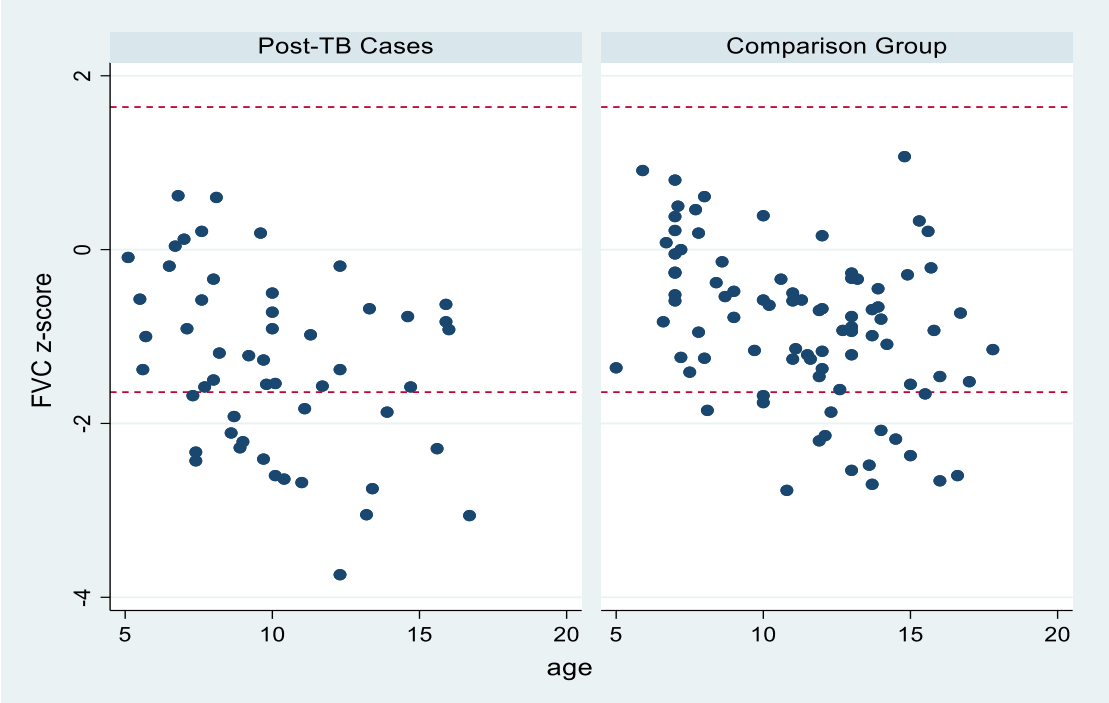
S Table 1: Post-TB cases and age-matched comparison group children from each household

Household match ID	Post-TB cases (n=68)	Comparison group (n=91)	Total (n=159)
1	1	2	3
2	1	3	4
3	1	2	3
4	1	1	2
5	1	1	2
6	1	3	4
7	1	1	2
8	1	3	4
9	1	1	2
10	1	3	4
11	1	3	4
12	1	3	4
13	1	3	4
14	1	1	2
15	1	1	2
16	1	1	2
17	1	1	2
18	1	1	2
19	1	2	3
20	1	1	2
21	1	0	1
22	1	0	1
23	1	0	1
24	1	0	1
25	1	2	3
26	1	3	4
27	1	1	2
28	1	0	1
29	1	0	1
30	1	3	4
31	1	1	2

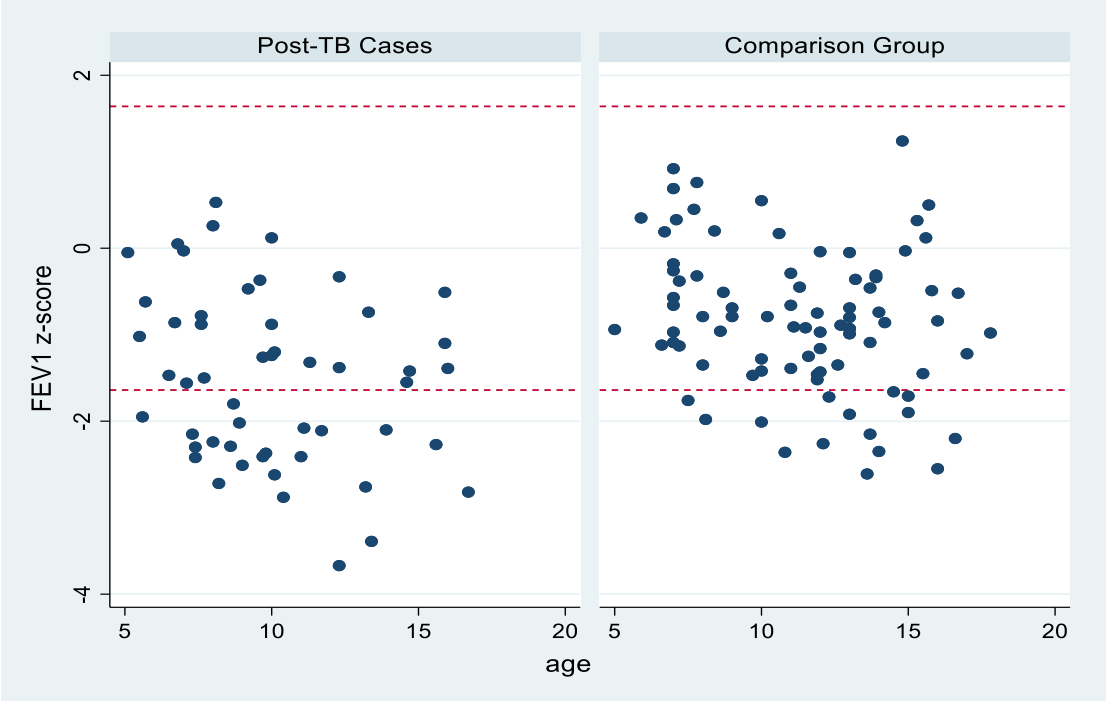
32	1	1	2
33	1	0	1
34	1	1	2
35	1	2	3
36	1	2	3
37	1	0	1
38	1	0	1
39	1	2	3
40	1	0	1
41	1	1	2
42	1	2	3
43	1	1	2
44	1	3	4
45	2	3	5
46	1	1	2
47	1	1	2
48	1	2	3
49	1	1	2
50	1	2	3
51	1	1	2
52	1	2	3
53	1	0	1
54	1	1	2
55	1	2	3
56	1	0	1
57	1	2	3
58	1	0	1
59	1	2	3
60	1	1	2
61	1	2	3
62	1	1	2
63	1	1	2
64	1	1	2
65	1	1	2
66	1	1	2
67	1	1	2

Distribution of spirometry z-scores across age

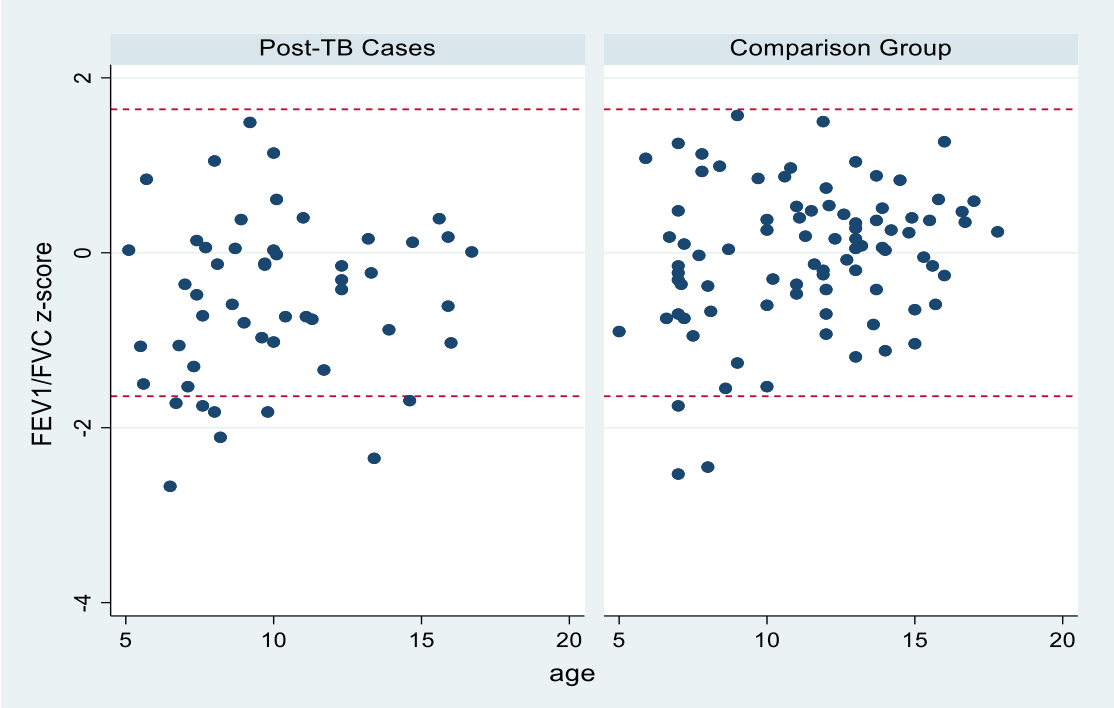
Supplementary Figures 1-3 show the scatterplots for spirometry (FVC, FEV_1, and FEV_1/FVC ratio) z-scores across age, by post-tuberculosis cases and comparison group. Scatterplots for spirometry z-scores did not show any linear trend. The spread of *z*-scores was less variable for the FEV_1/FVC ratio compared to FVC and FEV_1 *z*-scores across age. A greater proportion of *z*-scores for the post-tuberculosis cases were distributed below the lower threshold value of –1.64, compared to the comparison group (Fig. 1-3).



S Figure 1: Scatterplots for GLI_{2012} *z*-scores for FVC. Plots also demonstrate the distribution of the z-score values around 1·64 (Upper Limit of Normal) and −1·64 (Lower Limit of Normal)



S Figure 2: Scatterplots for GLI_{2012} *z*-scores for FEV_1. Plots also demonstrate the distribution of the z-score values around 1·64 (Upper Limit of Normal) and −1·64 (Lower Limit of Normal)



S Figure 3: Scatterplots for GLI_{2012} *z*-scores for FEV_1/FVC. Plots also demonstrate the distribution of the z-score values around 1·64 (Upper Limit of Normal) and −1·64 (Lower Limit of Normal)

Appendix 7: Supplementary material for Research Paper 2 (Objective 2)

Supplementary material

Post-tuberculosis lung disease in children and adolescents: a scoping review of definitions, measuring tools, and research gaps

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S1 Table: Search strategy

MEDLINE (Ovid)

Search conducted on March 27, 2024.

Search	Query	Records retrieved
#1 (Paediatric)	p?ediatric*[MeSH] or adolescen*[MeSH] or child*[MeSH]	3,477,749
#2 (Post-TB)	post-tb or post-tuberculo* or after tb or after tuberculosis or tb associated or tuberculosis associated	24,785
#3 (Sequel)	sequel* or disability or impair* or lung function or pulmonary function or lung damage or complicat*	4,858,017
	#1 AND #2 AND #3	717
Limited to: 2000 – current.		**547**

EMBASE (Ovid)

Search conducted on on March 27, 2024.

Search	Query	Records retrieved
#1 (Paediatric)	p?ediatric* or adolescen* or child*	6,026,312
#2 (Post-TB)	post-tb or post-tuberculo* or after tb or after tuberculosis or tb associated or tuberculosis associated	3,186
#3 (Sequel)	sequel* or disability or impair* or lung function or pulmonary function or lung damage or complicat*	5,858,036
	#1 AND #2 AND #3	227
Limited to: 2000 – current.		**176**

Global Health (Ovid)

Search conducted on March 27, 2024.

Search	Query	Records retrieved
#1 (Paediatric)	p?ediatric* or adolescen* or child*	688,991
#2 (Post-TB)	post-tb or post-tuberculo* or after tb or after tuberculosis or associated or tuberculosis associated	990
#3 (Sequel)	sequel* or disability or impair* or lung function or pulmonary function or lung damage or complicat*	324,357
	#1 AND #2 AND #3	36
Limited to: 2000 – current, English and French language.		**33**

CINAHL

Search conducted on March 27, 2024.

Search	Query	Records retrieved
#1 (Paediatric)	p?ediatric* or adolescen* or child*	1,307,276
#2 (Post-TB)	post-tb or post-tuberculo* or after tb or after tuberculosis or tb associated or tuberculosis associated	356
#3 (Sequel)	sequel* or disability or impair* or lung function or pulmonary function or lung damage or complicat*	1,136,640
	#1 AND #2 AND #3	**30**

Web of Science

Search conducted on March 27, 2024

Search	Query	Records retrieved
#1 (Paediatric)	p?ediatric* or adolescen* or child*	3,721,044
#2 (Post-TB)	post-tb or post-tuberculo* or “after tb” or “after tuberculosis” or “tb-associated” or “tuberculosis-associated”	1,805
#3 (Sequel)	sequel* or disability or impair* or lung function or pulmonary function or lung damage or complicat*	3,091,554
	#1 AND #2 AND #3	67
Limited to: 2000 – current.		**65**

Appendix 8: Supplementary material for Research Paper 3 (Objective 3)

Supplementary Material

Post-tuberculosis respiratory impairment in Gambian children and adolescents: a cross-sectional analysis

Esin Nkereuwem MD FWACP, Schadrac Agbla PhD, Bintou Njai MD, Victory Fabian Edem PhD, Muhammed Lamin Jatta, Olumuyiwa Owolabi MD, Uma Masterton BSN, Fatoumatta Jah , Madikoi Danso MD, Aunty Nyima Fofana MD, Wandifa Samateh, Muhammed Lamin Darboe, Sheila Owusu MD, Andy Bush MD PhD, Beate Kampmann MD PhD, Toyin Togun MD PhD

Table 1: Participant characteristics of the 21 children who were not included in this analysis stratified by prior tuberculosis diagnosis

	Total (n=21)	**Unconfirmed TB (n=17)**	**Confirmed TB (n=4)**
Age, years	3.0 (1.7, 3.9)	3.0 (1.7, 3.9)	2.9 (1.7, 4.0)
Below 5 years	19 (90.4)	15 (88.2)	4 (100)
5 to <10 years	1 (4.8)	1 (5.9)	0
10 to <15 years	0	0	0
>15 years	1 (4.8)	1 (5.9)	0
Female	9 (42.9)	6 (35.3)	3 (75.0)
HIV infection	0	0	0
Asthma	0	0	0
Sickle Cell Anaemia	0	0	0
Ever smoked	0	0	0
Exposure to environmental tobacco smoke	19 (90.5)	15 (88.2)	4 (100)
Household biomass exposure	19 (90.5)	15 (88.2)	4 (100)
More than one previous TB	0	0	0
Self-reported duration of TB illness before treatment, weeks	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	3.0 (2.5, 7.5)
Time since TB treatment completion, weeks	0.8 (0.0, 1.7)	1.2 (0.4, 2.0)	0.2 (0.0, 0.6)
Self-reported symptoms*			
Any respiratory symptom	5 (23.8)	4 (23.5)	1 (25.0)
Cough	4 (19.1)	3 (17.6)	1 (25.0)
Sputum	0	0	0
Shortness of breath	0	0	0
Wheeze	2 (9.5)	2 (11.8)	0
Clinical observations			
Height-for-age *z*-score	-0.76 (-1.82, 0.10)	-0.57 (-1.82, 0.10)	-1.27 (-2.02, -0.31)
BMI-for-age z-score	-0.71 (-1.45, -0.11)	-0.71 (-1.45, -0.11)	-0.61 (-1.92, -0.18)
Stunted	5 (23.8)	4 (19.1)	1 (25.0)
Underweight	2 (9.5)	1 (5.9)	1 (25.0)
Oxygen saturations, %	99 (99, 100)	99 (99, 100)	98 (99, 100)
Chest X-ray findings, n=20			
Abnormal chest X-ray	4 (20.0)	3 (17.6)	1 (25.0)
Pattern of abnormality			
Fibrosis	0	0	0
Volume loss	0	0	0
Bronchiectasis	0	0	0
Parenchymal infiltrates	1 (5.0)	0	1 (25.0)
Cavity	0	0	0
Consolidation	2 (10.0)	2 (12.5)	0
Pleural effusion	0	0	0
Collapse	0	0	0
Hilar adenopathy	1 (5.0)	1 (6.3)	0

Data are n (%) or median (IQR)

Table 2: Spirometry volumes and outcomes classification using the African-American versus race-neutral reference equations. The spirometry volumes were significantly lower using the race-neutral reference equation than the African-American equation. The race-neutral equation classified 15 more children and adolescents than the African-American equation as having abnormal spirometry.

	African-American	**Race-neutral**	**P-value**
FEV_1 z-score	-1.51 (-2.82, -0.96)	-2.00 (-3.14, -1.53)	<0.001
FVC z-score	-1.84 (-2.92, -1.07)	-2.24 (-3.20, -1.62)	<0.001
FEV_1/FVC z-score	0.20 (-0.68, 0.79)	0.24 (-0.69, 0.86)	0.079
Abnormal spirometry	45 (57.0)	59 (74.7)	0.019
Pattern of spirometry			
Normal	34 (43.0)	20 (25.3)	<0.001
Restrictive	41 (51.9)	55 (69.6)	
Mixed	4 (5.1)	4 (5.1)	

Data are n (%) or median (IQR)

Table 3: Clinical characteristics and chest X-ray features of the 15 participants who had 'normal' spirometry with the African American reference equation and 'abnormal spirometry with the race-neutral reference equation

	Total (n=15)
Age, years	14.3 (8.1, 17.0)
Below 5 years	0
5 to <10 years	4 (26.7)
10 to <15 years	5 (33.3)
>15 years	6 (40.0)
Female	8 (53.3)
HIV infection	2 (13.3)
Self-reported symptoms*	
Any respiratory symptom	6 (40.0)
Cough	4 (26.7)
Sputum	3 (20.0)
Shortness of breath	4 (26.7)
Wheeze	1 (6.7))
Clinical observations	
Height-for-age *z*-score	-0.94 (-1.40, -0.02)
BMI-for-age z-score	-0.61 (-1.40, -0.04)
Stunted	2 (13.3)
Underweight	3 (20.0)
Oxygen saturations, %	99 (99, 100)
Chest X-ray findings, n=20	
Abnormal chest X-ray	4 (20.0)
Pattern of abnormality	
Fibrosis	3 (20.0)
Volume loss	0
Bronchiectasis	0
Parenchymal infiltrates	1 (6.7)
Cavity	0
Consolidation	0
Pleural effusion	0
Collapse	0

Data are n (%) or median (IQR)

Appendix 9: Supplementary material for Research Paper 4 (Objective 3)

Supplementary Material

Respiratory outcomes in children and adolescents treated for pulmonary tuberculosis in The Gambia: a prospective study

Esin Nkereuwem, Victory Fabian Edem, Schadrac Agbla, Olumuyiwa Owolabi, Muhammed Lamin Jatta, Bintou Njai, Uma Masterton, Monica Genekah, Fatoumatta Jah, Sheila Owusu, Fatou Sanyang, Lamin Saidy, Wandifah Samateh, Muhammed Lamin Darboe, Beate Kampmann, Toyin Togun

Supplementary Table 1: Participant characteristics stratified by spirometry outcome at the 6-month visit

	Normal spirometry at 12 months (n=28)	**Abnormal spirometry at 12 months (n=46)**	***p*-value**
Age, years	14·6 (10·2 – 17·9)	16·2 (12·1 – 17·6)	0·46
Age group, years			
<5	1 (4%)	0	0·47
5 to <10	6 (21%)	6 (13%)	
10 to <15	8 (29%)	14 (30%)	
≥15	13 (46%)	26 (57%)	
Sex			
Female	14 (50%)	25 (54%)	0·81
Male	14 (50%)	21 (46%)	
Co-morbidities			
HIV infection	2 (7%)	6 (13%)	0·70
Asthma	0	1 (2%)	0·99
Sickle Cell Anaemia	0	2 (4%)	0·52
Ever smoked	1 (4%)	1 (2%)	0·99
Anthropometry			
Height-for-age *z*-score	-0·78 (-1·32 – -0·28)	-0·78 (-1·72 – 0·36)	0·81
Stunted	1 (4%)	8 (17%)	0·14
BMI-for-age *z*-score	-0·54 (-1·28 – -0·21)	-1·71 (-2·41 – -0·99)	**<0·001**
Underweight	2 (7%)	18 (39%)	**0·003**
Environmental exposures			
Environmental tobacco smoke	23 (82%)	33 (72%)	0·41
Household biomass	26 (93%)	45 (98%)	0·55
Type of tuberculosis diagnosis			
Confirmed tuberculosis	18 (64%)	32 (70%)	0·80
Unconfirmed tuberculosis	10 (36%)	14 (30%)	
≥ Two previous tuberculosis episodes	0	2 (4%)	0·52
Self-reported symptoms at baseline			
Cough	5 (18%)	13 (28%)	0·41
Sputum	2 (7%)	11 (24%)	0·11
Shortness of breath	3 (11%)	6 (13%)	0·99
Wheeze	1 (4%)	4 (9%)	0·64
Chest X-ray at baseline			
Abnormal	6 (21%)	28 (62%)	**0·001**

Fibrosis	3 (11%)	17 (38%)	**0·01**
Volume loss	1 (4%)	6 (13%)	0·24
Bronchiectasis	0	6 (13%)	0·08
Parenchymal infiltrates	1 (4%)	3 (7%)	0.99
Baseline spirometry			
Abnormal spirometry	4 (14%)	39 (85%)	**<0·001**
Abnormal *z*FEV_1	1 (4%)	34 (74%)	**<0·001**
Abnormal *z*FVC	4 (14%)	39 (85%)	**<0·001**
Abnormal *z*FEV_1/FVC	0	4 (9%)	0·27

Supplementary Table 2: Participant characteristics stratified by spirometry outcome at the 12-month visit

	Normal spirometry at 12 months (n=30)	**Abnormal spirometry at 12 months (n=44)**	***p*-value**
Age, years	16·0 (9·0 – 17·9)	16·2 (12·1 – 17·7)	0·57
Age group, years			
<5	2 (7%)	0	0·26
5 to <10	6 (20%)	6 (13%)	
10 to <15	6 (20%)	14 (32%)	
≥15	16 (53%)	24 (55%)	
Sex			
Female	13(43%)	25 (57%)	0·34
Male	17 (57%)	18 (43%)	
Co-morbidities			
HIV infection	3 (10%)	4 (9%)	0·99
Asthma	0	1 (2%)	0·99
Sickle Cell Anaemia	2 (7%)	1 (2%)	0·56
Ever smoked	1 (3%)	1 (2%)	0·99
Anthropometry			
Height-for-age *z*-score	-0·73 (-1·29 – -0·18)	-0·75 (-1·58 – 0·40)	0·94
Stunted	0	7 (16%)	0·13
BMI-for-age *z*-score	-0·49 (-1·34 – -0·16)	-1·71 (-2·40 – -0·88)	**<0·001**
Underweight	1 (3%)	17 (39%)	**0·001**
Environmental exposures			
Environmental tobacco smoke	22 (73%)	33 (75%)	0·99
Household biomass	28 (93%)	42 (95%)	0·99
Type of tuberculosis diagnosis			
Confirmed tuberculosis	21 (70%)	30 (68%)	0·99
Unconfirmed tuberculosis	9 (29%)	14 (32%)	
≥ Two previous tuberculosis episodes	0	2 (5%)	0·51
Self-reported symptoms at baseline			
Cough	5 (17%)	14 (32%)	0·18
Sputum	4 (13%)	10 (23%)	0·38
Shortness of breath	3 (10%)	6 (14%)	0·73
Wheeze	1 (3%)	3 (7%)	0·64
Chest X-ray at baseline			
Abnormal	11 (37%)	24 (56%)	0·15

Fibrosis	5 (17%)	16 (37%)	0·07
Volume loss	1 (3%)	6 (14%)	0·23
Bronchiectasis	0	5 (12%)	0·07
Parenchymal infiltrates	2 (7%)	2 (5%)	0.99
Baseline spirometry			
Abnormal spirometry	6 (20%)	36 (82%)	**<0·001**
Abnormal *z*FEV_1	2 (7%)	32 (73%)	**<0·001**
Abnormal *z*FVC	6 (20%)	36 (82%)	**<0·001**
Abnormal *z*FEV_1/FVC	0	3 (7%)	0·27

Appendix 10: Supplementary material for Research Paper 5 (Objective 4)

Supplementary Material

"I live with pain, it cannot go away": a qualitative study on the lived experiences of childhood and adolescent pulmonary tuberculosis survivors in The Gambia

Esin Nkereuwem*, Oluwatosin Nkereuwem*, Alpha Omar Jallow, James Owolabi, Assan Gibba, Fatoumatta Jawara, Zainab Manneh, Alex Opoku, Virginia Bond#, Toyin Togun#, Beate Kampmann#

Workshop agenda

Workshop agenda: children 5 to 10 years

Time	Activity	Details
9:00 am-9:30 am	Arrival	Register
9:30 am-10:00 am	Breakfast	
10:00 am-10:15 am	Round of introductions and how are we feeling	Open as a group by saying - How we are feeling today - One thing that we would like to tell the group about you
10:15 am-10:45 am	First activity – body mapping	Divided into groups Caregivers and their children Draw the outline of their life-size bodies on paper sheets. Then highlight, with colour pens, the parts of their bodies affected since they completed their treatment for TB.
10:45 am-11:00 am	Feedback/debrief	Led by parents/caregivers from each group Describe body mappings to the group
11:00 am-11:30 am	Second activity – drawing/painting	Introduction to drawings/paintings - Make a drawing/painting that you feel represents your child's health now. - Think about if you were to tell someone about your child, what picture would you draw/paint?
11:30 am-11:45 am	Feedback/debrief	Led by a representative from each group Tell us about your picture. - What does each picture mean to you? - What do you think your picture says about your child's health? - If you wanted to add something, but didn't, what would you have added?
11:45 am-12:00 pm	Wrap up	How did you find it? Which part of it did you particularly like?
12:00 pm-12:30 pm	Lunch/departure	

Workshop agenda: children/adolescents 10 to 19 years

Time	Activity	Details
9:00 am-9:30 am	Arrival	Register
9:30 am-10:00 am	Breakfast	
10:00 am-10:15 am	Round of introductions and how are we feeling	Open as a group, by saying - How we are feeling today - One thing that we would like to tell the group about you
10:15 am-10:45 am	First activity – body mapping activity	**Divided into groups** Draw the outline of their life-size bodies on paper sheets. Then highlight, with colour pens, the parts of their bodies affected since they completed their treatment for TB.
10:45 am-11:00 am	Feedback/debrief	**Led by representative from each group** Describe body mappings to the group
11:00 am-11:30 am	Second activity – games with dice and questions	Divided into groups
11:30 am-11:45 am	Feedback/debrief	**Led by representative from each group** Describe a summary of the group conversations and their interpretations
11:45 am-12:00 pm	Snack break	
12:00 pm-12:30 pm	Third activity – collage/drawing/painting	**Divided into groups** Introduction to collages/drawings/paintings - Make a collage/drawing/painting that you feel represents your health now. - Think about if you were to tell someone about yourself, what picture would you make/draw/paint?
12:30 am-12:45 am	Feedback/debrief	**Led by representative from each group** Tell us about your picture. - What does each picture/visual/words mean to you? - What do you think your picture says about your health? - If you wanted to add something, but didn't, what would you have added?
12:45 am-1:00 pm	Wrap up	How did you find it? Which part of it did you particularly like?
1:00 pm-1:30 pm	Lunch/departure	

Interview Topic Guides

Interview Topic Guide (adolescent)

Date	
Time	
Duration	
Location	
Participant ID	
Audio file ID	
Name of interviewer	
Name of interpreter	

Purpose: The goal of this guide is to help facilitate one-on-one interviews with children and adolescents involved in the Childhood TB Sequel study. The topic guide is aimed at exploring the lived experiences of children and adolescents after TB. This guide will be used flexibly during the discussion.

Preamble **(to be read by researcher at the start of the interview)**: Today is the (insert date [day xxth Xxx xxxx]) and it is (insert time XX:XX). This is an interview with a child/adolescent participant who is a part of the Childhood TB Sequel Study. Thank you for your time and letting me talk to you today. Today I would like to talk to you _____ (insert participant's name) about your experiences since completing treatment for TB. Before we get started, I want you to know that everything we talk about today will remain anonymous. We may write a publication or report. However, all the quotes will be anonymised to protect your identity. These reports and/or publications will not include any names or other personal information. Remember that there are no right or wrong answers and I am sincerely interested in your personal experiences in order for us to better understand how TB may affect your daily lives. May I also remind you that we are audio recording this discussion and ask that you speak loud and clear. Do you have any questions before we start?

Stage 1: Background information about the participant and family *(Note: The researcher can provide the participant with a colouring-in sheet or blank sheet of paper to draw while interviewing)*

Now we would like to ask you _____ (insert the participant's name) some questions. You can write or draw your responses. Does that sound good to you?

- Please briefly tell me about yourself *(Probes: Name, age, grade, likes, dislikes, dreams)*
- Tell me about the things that make you happy. (Probes: friends, family, playing, school etc.)
- Tell me about the things that make you sad.
- Who do you live with? *(Probes: who lives with you? Mother, father, brothers, sisters, grandmother, grandfather, aunties, uncles, cousins, etc. Does the other family live close by? Who takes care of you?*
- What have your experiences been since you started coming to MRC *(Probes: How long have you been part of the study? What makes it easy to come back? What makes it difficult to come back? What procedures do you appreciate (e.g. because it seems important), and which procedures do you fear?)*

- Who was the first person who told you that you were ill? *(Probes: Mother, Father, Grandmother, Grandfather, Sister, Brother).*
- How have you felt since you completed your treatments?

Stage 2: Lived experiences

Now, we would like to know more about your experiences since you completed your TB treatment.

- Are you going to school?
- Tell me about your school. *(Probes: What do you like about school? What don't you like about school?)*
- Are you involved in any school activities? Tell me about the activities you do in school. *(Probes: Can you run and play like other friends? Has this changed after the disease?)*
- Tell me about your teachers.
- Do you have friends at school/ community? Please tell me about your friends at school/ community.
- If you think about your siblings and friends, tell me about how they reacted when they heard you were ill. *(Probes: How did they act towards you? How were you treated compared to others? How did that make you feel? What were you not allowed to do?)*
- Please take me through a day in your life. *(Probes: from when you wake up till you go to bed. Time you wake-up, breakfast, school/day-care, activities – playing, TV, sport etc.)*
- Tell me about the days that you are feeling well. *(Probes: How does that make you feel? What do you like doing? Games you like to play)*
- Tell me about the days that you are not feeling well. *(Probes: How does that make you feel? What are you not allowed to do? are your usual activities such as sports, playing, running and/or riding a bike restricted?)*
- Please tell me about what your life was like when you were ill. *(Probes: How did that make you feel? What were you not allowed to do? Were your usual activities, such as sports, playing, running and/or riding a bike, restricted? What games did you like to play but could not because you were ill? How did it affect your concentration in class? How did it affect your school attendance? How much of school did you miss? Did you have to drop out of school?)*
- Now, please tell me about what your life is like after TB. *(Probes: How does it make you feel? What do you like doing now that you couldn't do when you were ill? How well do you get along with other children in school or at home? Are you able to go back to school? Did you have to repeat a class? How well are you performing in school?)*
- How do your siblings and friends think about you now after TB? *(Probes: How do they act towards you? How are you treated compared to others? How does that make you feel? What are you not allowed to do?)*
- Please tell me anything else you would like me to know about how TB has changed your life.

Thank you for your time.

Provide transportation refunds and refreshments.

Interview Topic Guide (caregiver)

Date	
Time	
Duration	
Location	
Participant ID	
Audio file ID	
Name of interviewer	
Name of interpreter	

Purpose: The goal of this guide is to help facilitate one-on-one interviews with caregivers of children involved in the Childhood TB Sequel study. The topic guide is aimed at exploring the lived experiences of children and adolescents after TB. This guide will be used flexibly during the discussion.

Preamble **(to be read by researcher at the start of the interview):** Today is the (insert date [day xxth Xxx xxxx]) and it is (insert time XX:XX). This is an interview with a caregiver of child/adolescent participant who is a part of the Childhood TB Sequel Study. Thank you for your time and letting me talk to you today. Today, I would like to talk to you _____ (insert caregiver's name) about your child's _____ (insert participant's name) experiences since completing treatment for TB. Before we get started, I want you to know that everything we talk about today will remain anonymous. We may write a publication or report. However, all the quotes will be anonymised to protect your identity. These reports and/or publications will not include any names or other personal information. Remember that there are no right or wrong answers and I am sincerely interested in your personal experiences in order for us to better understand how TB may affect your child's daily life. May I also remind you that we are audio recording this discussion and ask that you speak loud and clear. Do you have any questions before we start?

Stage 1: Background information about the participant and family

Now we would like to ask you _____ (insert the caregiver's name) some questions.

- Please briefly tell me about yourself *(Probes: Name, age, grade, likes, dislikes, dreams)*
- Please briefly tell me about your household. *(Probes: who lives with you? Mother, father, brothers, sisters, grandmother, grandfather, aunties, uncles, cousins, etc. Does the other family live close by? Who takes care of the child in the study?*
- Please tell me about your experience since you started coming to MRC. *(Probes: How long has your child been part of the study? What makes it easy to come back? What makes it difficult to come back? What procedures do you appreciate (e.g. because it seems important), and which procedures do you fear?)*
- Please tell me about the first time your child felt sick with TB *(Probes: Where did it hurt? Symptoms?)*
- Please tell me who was the first person to tell you that your child is sick. *(Probes: Mother, Father, Grandmother, Grandfather, Sister, Brother).*
- Please tell me about any concerns that you may have about your child's life after TB.

Stage 2: Lived experiences

Now, we would like to know more about your child's experiences since they completed their TB treatment.

- Tell me about your child's school. *(Probes: What do they like about school?, What don't they like about school?)*
- Tell me about their teachers.
- Please tell me about their friends in school and at home.
- Please take us through a typical day in the life of the child. *(Probes: from the moment the child wakes up till bedtime for the child. What time does the child wake up? Breakfast-together? School/ daycare? Dinner? Activities? TV?)*
- Please tell me about what their life was like when they were ill. *(Probes: How did that make you feel? What were they not allowed to do? Were their usual activities, such as sports, playing, running and/or riding a bike, restricted? What games did they like to play but could not because they were ill? How did it affect their school performance? How did it affect their school attendance? How much of school did they miss? Did they have to drop out of school?)*
- If you think about their siblings and friends, tell me about how they reacted when they heard your child was ill. *(Probes: How did they act towards your child? How was your child treated compared to others? How did that make you feel? What was your child not allowed to do?)*
- Now, please tell me about what your child's life is like after TB. *(Probes: What are your fears? What do they like doing now that they couldn't do when they were ill? How well do they get along with other children in school or at home? Are they able to go back to school? Did they have to repeat a class? How well are they performing in school?)*
- How do their siblings and friends think about them now after TB? *(Probes: How do they act towards your child? How are they treated compared to others? How does that make you feel? What are they not allowed to do?)*
- Tell me about the days that your child has been feeling well. *(Probes: How does that make you feel? What do they like doing? Games they like to play)*
- Tell me about the days that your child is not feeling well now. *(Probes: How does that make you feel? What are they not allowed to do? are their usual activities such as sports, playing, running and/or riding a bike restricted?)*
- Please tell me anything else you would like me to know about how TB has changed your child's life.

Thank you for your time.

Provide transportation refunds and refreshments**.**

Appendix 11: Ethics approval (MRC Unit The Gambia at LSHTM) for Objective 1

C/o MRC Unit: The Gambia @ LSHTM, Fajara
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Email: ethics@mrc.gm

The Gambia Government/MRC Joint
ETHICS COMMITTEE

Dr Esin Nkereuwem
MRCG at LSHTM, Fajara

5 November 2019

Dear Dr Nkereuwem

Study Title: Prevalence and risk factors of post-tuberculosis lung disease in children

Project ID/Ethics ref: 17747

Thank you for submitting your response to the issues raised by the Gambia Government/MRCG Joint Ethics Committee Ethics Committee. at its meeting held on 26 September 2019. the response was reviewed by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Protocol / Proposal	Study Protocol	18/08/2019	1.0
Information Sheet	Participant Information Sheet	18/08/2019	1.0
Information Sheet	Informed Consent Document	18/08/2019	1.0
Protocol / Proposal	Case Report Form	18/08/2019	1.0
Investigator CV	Beate Kampmann_CV	18/08/2019	1.0
Investigator CV	Andy Bush_CV	18/08/2019	1.0
Investigator CV	Esin Nkereuwem_CV	18/08/2019	1.0
Information Sheet	Participant Information Sheet_cases_v1.1	09/09/2019	1.1
Information Sheet	Participant Information Sheet_ controls_v1.1	09/09/2019	1.1
Protocol / Proposal	PedsQL_tool	09/09/2019	1.0
Covering Letter	SCC covering letter	09/09/2019	1.0
Protocol / Proposal	Study Protocol_v1.1	09/09/2019	1.1
Covering Letter	Ethics Committee covering letter	15/10/2019	1.0
Information Sheet	Participant Information Sheet_cases_v1.2	15/10/2019	1.2
Information Sheet	Participant Information Sheet_ controls_v1.2	15/10/2019	1.2

After ethical review

The Principal Investigator (PI) or delegate is responsible for informing the Ethics Committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment Form. Amendments must not be initiated before receipt of written favourable opinion from the Committee. An annual report should be submitted to the Committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study. At the end of the study, the PI or delegate must notify the committee using an End of Study form. All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Additional information is available at: www.lshtm.ac.uk/ethics.

With best wishes

Yours sincerely

[redacted]

Dr Mohammadou Kabir Cham
Chair, Gambia Government/MRCG Joint Ethics Committee

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Webpage:https://mrcportal.mrc.gm/Committees/SCC/SitePages/Home.aspx

Appendix 12: Ethics approval (LSHTM) for Objective 1

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
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www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Dr Esin Nkereuwem
LSHTM

6 November 2019

Dear Dr Nkereuwem

Study Title: Prevalence and risk factors of post-tuberculosis lung disease in children

LSHTM Ethics Ref: 17747

Thank you for your application for the above research project which has now been considered by the Observational Committee via Chair's Action.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Protocol / Proposal	Study Protocol	18/08/2019	1.0
Information Sheet	Participant Information Sheet	18/08/2019	1.0
Information Sheet	Informed Consent Document	18/08/2019	1.0
Protocol / Proposal	Case Report Form	18/08/2019	1.0
Investigator CV	Beate Kampmann_CV	18/08/2019	1.0
Investigator CV	Andy Bush_CV	18/08/2019	1.0
Investigator CV	Esin Nkereuwem_CV	18/08/2019	1.0
Information Sheet	Participant Information Sheet_cases_v1.1	09/09/2019	1.1
Information Sheet	Participant Information Sheet_ controls_v1.1	09/09/2019	1.1
Protocol / Proposal	PedsQL_tool	09/09/2019	1.0
Covering Letter	SCC covering letter	09/09/2019	1.0
Protocol / Proposal	Study Protocol_v1.1	09/09/2019	1.1
Covering Letter	Ethics Committee covering letter	15/10/2019	1.0
Information Sheet	Participant Information Sheet_cases_v1.2	15/10/2019	1.2
Information Sheet	Participant Information Sheet_ controls_v1.2	15/10/2019	1.2

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

[redacted]

Professor Jimmy Whitworth
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

Appendix 13: Ethics approval (MRC Unit The Gambia at LSHTM) for Objective 3

The Gambia Government/MRC Joint
ETHICS COMMITTEE

C/o MRC Unit: The Gambia @ LSHTM, Fajara
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Tel: +220 – 4495442-6 Ext. 2308
Email: ethics@mrc.gm

Dr Esin Nkereuwem

MRCG at LSHTM

18 January 2022

Dear Dr Nkereuwem

Study Title: Evaluating the sequelae of pulmonary tuberculosis in Gambian children

Project ID/ethics ref: 22613

Thank you for responding to the issues raised by the Gambia Government/MRCG Joint Ethics Committee at its meeting held on 2 December 2021.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Other	Research_Ethics_online_training_certificate	19/08/2021	1.0
Investigator CV	Esin_Nkereuwem_CV_2021	19/08/2021	1.0
Information Sheet	Informed Consent Document_v1.0	19/09/2021	1.0
Information Sheet	Participant Information Sheet_v1.0	19/09/2021	1.0
Protocol / Proposal	Protocol_EDCTP v1.0_Ethics	19/09/2021	1.0
Protocol / Proposal	Protocol_EDCTP v1.1_Ethics	06/10/2021	1.1
Information Sheet	Participant Information Sheet_v1.1	06/10/2021	1.1
Information Sheet	Informed Consent Document_v1.1	06/10/2021	1.1
Covering Letter	Cover letter to SCC_EDCTP	06/10/2021	1.0
Covering Letter	Response to Ethics Committee_EDCTP	31/12/2021	1.0
Information Sheet	Participant Information Sheet_v1.2	31/12/2021	1.2
Information Sheet	Protocol_EDCTP v1.2_Ethics	31/12/2021	1.2

After ethical review

The Principal Investigator (PI) or delegate is responsible for informing the Ethics Committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the Committee.

The PI or delegate is also required to notify the Ethics Committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form. An annual report should be submitted to the Committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study. At the end of the study, the PI or delegate must notify the Committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk. Additional information is available at: www.lshtm.ac.uk/ethics.

With best wishes

Yours sincerely

[redacted]

Dr Mohammadou Kabir Cham

Chairperson, Gambia Government/MRCG Joint Ethics Committee

C/O MRC Unit The Gambia at LSHTM
PO Box 273 Banjul, The Gambia
West Africa
Switchboard (+220) 4495442/6 Ext 2308
Fax (+220) 4495919/4496513
E-mail: ethics@mrc.gm
Intranet: http://mrcportal/Committees/SCC/SitePages/Home.aspx
Webpage:https://mrcportal.mrc.gm/Committees/SCC/SitePages/Home.aspx

Appendix 14: Ethics approval (LSHTM) for Objective 3

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
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Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Dr Esin Nkereuwem
LSHTM

19 January 2022

Dear Dr Esin Nkereuwem

Study Title: Evaluating the sequelae of pulmonary tuberculosis in Gambian children

LSHTM Ethics Ref: 22613

Thank you for your application for the above research project which has now been considered by the Observational Committee via Chair's Action.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Other	Research_Ethics_online_training_certificate	19/08/2021	1.0
Investigator CV	Esin_Nkereuwem_CV_2021	19/08/2021	1.0
Information Sheet	Informed Consent Document_v1.0	19/09/2021	1.0
Information Sheet	Participant Information Sheet_v1.0	19/09/2021	1.0
Protocol / Proposal	Protocol_EDCTP v1.0_Ethics	19/09/2021	1.0
Protocol / Proposal	Protocol_EDCTP v1.1_Ethics	06/10/2021	1.1
Information Sheet	Participant Information Sheet_v1.1	06/10/2021	1.1
Information Sheet	Informed Consent Document_v1.1	06/10/2021	1.1
Covering Letter	Cover letter to SCC_EDCTP	06/10/2021	1.0
Covering Letter	Response to Ethics Committee_EDCTP	31/12/2021	1.0
Information Sheet	Participant Information Sheet_v1.2	31/12/2021	1.2
Information Sheet	Protocol_EDCTP v1.2_Ethics	31/12/2021	1.2

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

[redacted]

Professor Jimmy Whitworth
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

Appendix 15: Ethics approval (MRC Unit The Gambia at LSHTM) for Objective 4

C/o MRC Unit: The Gambia @ LSHTM, Fajara
P.O. Box 273, Banjul
The Gambia, West Africa
Fax: +220 – 4495919 or 4496513
Tel: +220 – 4495442-6 Ext. 2308
Email: ethics@mrc.gm

The Gambia Government/MRC Joint
ETHICS COMMITTEE

Dr Esin Nkereuwem
MRCG at LSHTM

22 November 2023

Dear Dr Nkereuwem

Study Title: Exploring the lived experiences of childhood pulmonary tuberculosis survivors in The Gambia

Project ID/ethics ref: 28229

Thank you for responding to the queries raised by the Gambia Government/MRCG Joint Ethics Committee at its meeting held on 31 August 2023.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Other	Research_Ethics_online_training_certificate	12/06/2021	1.0
Investigator CV	Esin_Nkereuwem_CV_2023	17/03/2023	1.1
Protocol / Proposal	Interview Topic Guide_Adolescent_v1.0	17/07/2023	1.0
Protocol / Proposal	Interview Topic Guide_Caregiver_v1.0	17/07/2023	1.0
Covering Letter	Cover letter to SCC v1.0	17/07/2023	1.0
Protocol / Proposal	Participatory workshop agenda_adolescents_OPTIMA_v1.0	17/07/2023	1.0
Protocol / Proposal	Participatory workshop agenda_children_OPTIMA_v1.0	17/07/2023	1.0
Covering Letter	Cover letter to Ethics_ v1.0	26/10/2023	1.0
Protocol / Proposal	Protocol_OPTIMA_v1.2	26/10/2023	1.2
Information Sheet	Information Sheet_Adolescent_v1.2	26/10/2023	1.2
Information Sheet	Information Sheet_Parent_v1.2	26/10/2023	1.2
Information Sheet	Consent Form_Adolescent_v1.2	26/10/2023	1.2
Information Sheet	Consent Form_Older Adolescent_v1.1	26/10/2023	1.1
Information Sheet	Consent Form_Parent_v1.1	26/10/2023	1.1

After ethical review

The Principal Investigator (PI) or delegate is responsible for informing the Ethics Committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment Form. Amendments must not be initiated before receipt of written favourable opinion from the Committee.

The PI or delegate is also required to notify the Ethics Committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form. An annual report should be submitted to the Committee using an Annual Report Form on the anniversary of the approval of the study during the lifetime of the study. At the end of the study, the PI or delegate must notify the Committee using an End of Study Form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk. Additional information is available at: www.lshtm.ac.uk/ethics.

With best wishes

Yours sincerely

[redacted]

Dr Mohammadou Kabir Cham

Chairperson, Gambia Government/MRCG Joint Ethics Committee

C/O MRC Unit The Gambia at LSHTM
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Appendix 16: Ethics approval (LSHTM) for Objective 4

London School of Hygiene & Tropical Medicine
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Observational / Interventions Research Ethics Committee

Dr Esin Nkereuwem
LSHTM

9 January 2024

Dear Esin

Submission Title: Exploring the lived experiences of childhood pulmonary tuberculosis survivors in The Gambia

LSHTM Ethics Ref: 28229

Thank you for responding to the Observational Committee Chair's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Other	Research_Ethics_online_training_certificate	12/06/2021	1.0
Investigator CV	Esin_Nkereuwem_CV_2023	17/03/2023	1.1
Protocol / Proposal	Interview Topic Guide_Adolescent_v1.0	17/07/2023	1.0
Protocol / Proposal	Interview Topic Guide_Caregiver_v1.0	17/07/2023	1.0
Covering Letter	Cover letter to SCC v1.0	17/07/2023	1.0
Protocol / Proposal	Participatory workshop agenda_adolescents_OPTIMA_v1.0	17/07/2023	1.0
Protocol / Proposal	Participatory workshop agenda_children_OPTIMA_v1.0	17/07/2023	1.0
Covering Letter	Cover letter to Ethics_ v1.0	26/10/2023	1.0
Covering Letter	Cover letter to LSHTM Ethics_ v1.0	20/12/2023	1.0
Protocol / Proposal	Protocol_OPTIMA_v1.3	20/12/2023	1.3
Investigator CV	LSHTM CV - Toyin Togun	20/12/2023	1.0
Investigator CV	CV - Beate Kampmann	20/12/2023	1.0
Other	Ethics - Toyin Togun	20/12/2023	1.0
Other	Ethics - Beate Kampmann	20/12/2023	1.0
Information Sheet	Information Sheet_Adolescent_v1.3	20/12/2023	1.3
Information Sheet	Information Sheet_Parent_v1.3	20/12/2023	1.3
Information Sheet	Consent Form_Adolescent_v1.3	20/12/2023	1.3
Information Sheet	Consent Form_Older Adolescent_v1.2	20/12/2023	1.2
Information Sheet	Consent Form_Parent_v1.2	20/12/2023	1.2
Covering Letter	Cover letter to LSHTM Ethics_ v1.1	04/01/2024	1.1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

Professor David Leon and Professor Clare Gilbert

Co-Chairs

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

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