Post-tuberculosis lung damage in Malawian adults

Thesis submitted in accordance with the requirements of the Liverpool School of Tropical Medicine

for the degree of Doctor of Philosophy by Dr Jamilah Meghji

Feburary 2019

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

This work was only possible thanks to the hard work and enthusiasm of the 'LAT' study team – Beatrice, Malumbo, Hygiene & Rabecca. What a joy it was to be surrounded by their laughter, good cheer, and determination during my time in Malawi!

The academic support I have received from my supervisors, Bertie & Kevin, over the past four years has been invaluable, but I am equally grateful for their generosity of spirit, and the twinkle in the eye that they both seem to carry. I hope that I have learnt something of their conviction that research can and must work for those in greatest need.

I am grateful for the time and thought that our collaborators have given to this project over its duration. The work has been all the richer, and much more enjoyable, for their contributions.

To my PhD colleagues in Malawi, who provided laughter, encouragement, and adventures aplenty, and to friends at home who stayed in touch and sent snail-mail throughout my time away, I send thanks.

For my very wonderful grandparents & parents & siblings – without whose guidance and support I wouldn't have managed any of this – I count my lucky stars.

And lastly to our patients in Malawi, who gave their time and energy to this study in the hope that it would help others like them, I owe a huge debt. I hope that one day they will see the benefit of the work we've completed together.

SUPERVISORS AND COLLABORATORS

SUPERVISORS:

Professor S. Bertel Squire, Liverpool School of Tropical Medicine

Professor Kevin Mortimer, Liverpool School of Tropical Medicine

Professor Liz Corbett, London School of Hygiene & Tropical Medicine

COLLABORATORS:

Role	Collaborator	Institution
Systematic Review	Hope Simpson (HS)	London School of Hygiene & Tropical Medicine, UK
Radiology	Dr Elizabeth Joekes (EJ)	Royal Liverpool University Hospital, UK
	Dr Joe Jacob (JJ)	University College London, UK
	Dr Harmien Zonderland (HZ)	Retired from Amsterdam Academic Medical Centre, University of Amsterdam, The Netherlands
Spirometry	Lindsay Zurba (LZ)	Spirometry Training Services, Africa
Aspergillus serology	Professor David Denning	National Aspergillosis Centre, University of Manchester, UK
	Dr Bayu Wilopo (BW)	National Aspergillosis Centre, University of Manchester, UK
Qualitative work	Dr Stefanie Gregorius	Liverpool School of Tropical Medicine, UK
Statistics & epidemiology	Professor Maia Lesosky	University of Cape Town, SA
	Dr Peter MacPherson	Liverpool School of Tropical Medicine, UK
Local supervision of cohort	Dr Andrew McCallum	Liverpool School of Tropical Medicine, UK
	Rebecca Nightingale	Liverpool School of Tropical Medicine, UK
	Dr Sarah Rylance	Liverpool School of Tropical Medicine
Clinical care of cohort	Dr Peter Banda (PB)	Queen Elizabeth Central Hospital, Malawi / Malawi College of Medicine, Malawi
	Dr Jamie Rylance (JR)	Malawi Liverpool Wellcome Trust, Malawi / Liverpool School of Tropical Medicine, UK

ABBREVIATIONS

Abbreviations listed in alphabetical order	
ART	Antiretroviral treatment
ATS	American Thoracic Society
BMI	Body Mass Index
BOLD	Burden of Obstructive Lung Disease study
CAP	Community Acquired Pneumonia
CLD	Chronic lung disease
COPD	Chronic obstructive pulmonary disease
CXR	Chest x-ray
ERS	European Respiratory Society
EQ5D3L	EuroQol quality of life score
FEV_1	Forced expiratory volume in 1-second
FVC	Forced vital capacity
GLI-2012	Global Lung Initiative, 2012
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GXP	Xpert MTB/Rif assay (Cephaid, Sunnyvale, California)
HIV	Human immunodeficiency virus
HRCT	High resolution computerised tomography
IGRA	Interferon gamma release assay
ILD	Interstitial lung disease
LMIC	Low and middle income countries
LTBI	Latent TB infection
MDR	Multi-drug resistant
MMP	Matrix metalloproteinase
MTB	Mycobacterium tuberculosis
MUAC	Mid-upper arm circumference
NCD	Non-communicable diseases
NHANES III	3rd National Health & Nutrition Examination Survey, 1988-1994
NTM	Non-tuberculous mycobacteria
NTP	National Treatment Programme
PTB	Pulmonary tuberculosis

PTLD	Post-TB lung damage
QECH	Queen Elizabeth Central Hospital
SGRQ	St George's Respiratory Questionnaire
TB	Tuberculosis
TIMPS	Tissue inhibitors of metalloproteases
TST	Tuberculin skin test

ABSTRACT

TITLE: Post-tuberculosis lung damage in Malawian adults
AUTHOR: Dr Jamilah Meghji

INTRODUCTION:
Pulmonary tuberculosis (PTB) remains an important risk factor for chronic lung disease (CLD) in sub-Saharan Africa (sSA), but our understanding of the nature of post-TB lung damage, its evolution over time, and the associated morbidity remains limited. This information is needed to inform clinical care and health system approaches to the management of those surviving PTB disease.

METHODS:
A general review of the literature on CLDs in sSA, TB disease and epidemiology, and post-TB lung damage and its associated morbidity were completed, followed by a systematic review of the prevalence and pattern of post-TB structural lung pathology.

Primary data presented in this thesis were drawn from two studies based in urban Blantyre, Malawi. The first was a cross-sectional survey of respiratory abnormalities amongst adults in the community which was completed as part of the Burden of Obstructive Lung Disease (BOLD) initiative. The second was a prospective cohort study of HIV-positive and negative adults completing treatment for PTB which aimed to describe a) the prevalence of respiratory pathology at TB treatment completion using symptoms, quality of life scores, spirometry and high-resolution CT imaging, and b) the relationships between post-TB lung damage at treatment completion and adverse outcomes over 1-year of follow-up.

RESULTS:
The systematic review identified 39 studies of variable quality describing post-TB structural lung damage. A lack of prospective data, and data from sSA and HIV-positive groups was noted. Few studies related structural damage to symptoms, spirometry, or morbidity.

The BOLD data estimated a high burden of respiratory symptoms and abnormal spirometry amongst adults aged ≥18 years in urban Blantyre: 11.8% reported ≥1 symptom, and 4.8% had airway obstruction. The prevalence of the low-FVC pattern of abnormal spirometry varied according to the reference range used for standardisation, from 9.0% (local reference range) to 38.6% (NHANES III reference range).

A considerable burden of residual lung pathology was seen amongst 405 adults completing treatment for PTB in Blantyre: 60.7% had ongoing weekly/monthly respiratory symptoms, and 34.2% of participants had abnormal spirometry at PTB treatment completion. Participants had a median of 1.4 lobes of abnormal parenchyma on CT imaging. Moderate-severe bronchiectasis was seen in 44%, and 9.6% had ≥1 'destroyed' lobe. The burden of pathology was lower in HIV-positive vs. HIV-negative adults, but patterns of abnormality were similar. The odds of ongoing respiratory symptoms or an impaired quality of life at 1-year were over three-fold higher amongst those with both extensive structural damage and abnormal spirometry at PTB treatment completion.

CONCLUSION:
Post-TB lung damage is a common but neglected form of CLD amongst both HIV-positive and negative adults in Malawi, and occurs against a high background prevalence of respiratory symptoms and abnormal spirometry in the community. Severe forms are associated with considerable ongoing morbidity including persistent symptoms and reduced quality of life. Further work is required to understand the range of patterns of post-TB lung damage, and their relationship with long-term outcomes such as respiratory exacerbations and mortality. However, this is a neglected population and interventions to maximise their health following PTB treatment completion are required.

1 INTRODUCTION

In this brief introductory chapter, the context and rationale for the body of work presented in this thesis is described followed by an outline of the content of each of the chapters.

1.1 MALAWI

Malawi is a land-locked country in sSA with an estimated population of 18 million people.[1] 48% of the population was aged under 15 years in 2016.[2] Rapid growth is ongoing as a result of high total fertility rates (4.4 children per woman), and falling under-5 mortality rates (234 deaths/1000 live births in 1992 vs. 63 deaths/1000 live births in 2015-16). Forecasts based on the 1998 Malawi population census predict that growth will continue at a rate of 3.2-3.4% per annum through to 2023, with the largest increases expected in young and older adults.[3] Malawi remains largely rural, with 82% of men and 81% of women living in rural areas.[2] However, in keeping with patterns seen across sub-Saharan Africa, rural to urban migration is ongoing and urban populations are expanding. Blantyre is the second city in Malawi. It is located in the densely populated Southern region, and has an estimated population of over 1 million, many of whom live in rapidly growing informal settlements around the city centre. The city is situated in the Shire highlands, in a hilly area, and sits at an altitude of 780 – 1612m from sea level.

Malawi is an economically vulnerable country. Agriculture is the dominant sector but suffered heavy blows due to flooding in 2014/15 and drought in 2015/16. Energy shortages hamper growth, with electricity access available to only 4% of rural and 49% of urban households, and frequent supply shortages seen in recent years.[2] Inflation stabilized from 218% in 2016 to 12.3% in 2017 as a result of good harvests,[4] but poverty remains widespread and is particularly marked in rural areas where wealth indices are low. The Gross national income (GNI) per capita was $320 in Malawi in 2016, compared to the UK where the GNI was $42,370 in the same year.[1] Although 91% of households in urban areas fall into the highest two national wealth quintiles, it must be noted that this is a relative measure and that even these 'wealthy' households have limited resources and expenditure. The proportion of men and women who were employed in the week prior to the 2016 Demographic Health Survey (DHS) was 73% and 54% respectively in urban and rural areas. Educational attainment throughout the country remains low – only 26% of women and 36% of men aged 15-49 years have at least some secondary education, and 72% of women and 83% of men are literate.[2]

The burden of tuberculosis (TB) is high in Malawi, and is addressed by a strong and well-functioning TB National Treatment Programme (NTP). The most recent TB prevalence survey in 2014 reported a national prevalence of microbiologically confirmed PTB of 452/100,000 (95% CI: 312-593), and smear positive PTB of 220/100,000 (95% CI: 142-297). Nationally, 16,959 confirmed cases of TB disease were notified in 2016, of which 53% were HIV co-infected.[5] TB treatment services in Malawi are

decentralized – treatment registration and monitoring is provided by TB officers within local health centres, with referral to hospitals only as required. TB diagnostics are largely limited to sputum smears in community settings, with XPert MTB/RIF and chest radiography available only at tertiary centres on referral. Sputum culture is routinely performed at the National Reference Laboratory for retreatment cases, but is not generally available for new cases. In most settings TB management is provided separately to other medical services. Drugs are provided free of charge to patients on a 2-weekly basis during the first 2-month intensive phase of treatment, and monthly thereafter, in order to support compliance and regular review. Direct observation of treatment is not performed on site, but all patients are asked to appoint a guardian to sign for medications as they are taken in the home setting. In the event of a patient not attending for follow up, health centres are mandated to follow individuals in the community using the contact details provided. Treatment success (patients classified as having treatment cure or completion) was reported for 81% amongst new / relapsed TB cases registered during 2015.[5] That is, 4 out of 5 patients registered for TB treatment in Malawi are thought to survive to treatment completion, with microbiological cure or clinical resolution confirmed. 0.4% of new cases and 4.8% of retreatment cases were documented to have MDR in the national drug resistance survey in 2010-11.[6]

Malawi has a generalized HIV epidemic with an estimated national prevalence amongst those aged 15-49 years of 11.2% (10.5-11.9%) in women and 7.1%(6.7-7.5%) amongst men in 2016.[7] Estimated annual incidence is 4.15/1000 population for adults aged 15-49 years. Data from Blantyre, obtained through a recent self testing programme, suggest a peak prevalence amongst those aged 40-49 years of 22.5% (95% CI 19.4%– 25.8%).[8] However Malawi is a country with a strong and forward looking HIV strategy: it was the first country to adopt Option B+ whereby all pregnant women are provided with antiretroviral treatment (ART) at diagnosis which is continued for life, and an early adopter of the 'Test & Treat' strategy with early initiation of ART for all individuals receiving a positive HIV diagnosis. ART uptake is correspondingly high. Anti-retroviral drugs are provided free to all patients, and the current first line regimen includes tenofavir, lamivudine and efavirenz, and can be used concurrently with standard TB treatment. Co-trimoxazole is also provided free of charge to all patients. CD4 counts are varyingly performed in patients at HIV diagnosis. Viral loads are not yet widely available and whilst recommended for those who develop TB disease and are already HIV positive and on ART with good compliance, to investigate for treatment failure, this is not routinely done. Isoniazid Preventative Therapy (IPT) was not in programmatic use for the majority of this study, but was introduced in December 2017.

1.2 POST-TUBERCULOSIS LUNG DAMAGE

Non-communicable diseases (NCDs) are a key driver of morbidity and mortality worldwide: The Global Burden of disease studies estimate that chronic diseases were responsible for 69% of all deaths

(38.3/54.9 million) globally in 2013,[9] and 61.5% (1.47 /2.39 billion) of all disability adjusted life years lost worldwide in 2016.[10] Cancer, cardiovascular diseases, chronic respiratory disease, and diabetes have been highlighted as areas of concern, and target 3.4 of the Sustainable Development Goals (SDG) demands a one-third reduction, relative to 2015 levels, in the probability of dying between 30 years and 70 years of age from these diseases by 2030. Progress to date has, however, remained slow – the effect of NCDs is felt disproportionately by those living in low and middle income countries (LMICs), and rates of decline are stagnating in many of these countries such that they are likely to miss this SDG target by tens of years.[11]

The ongoing high burden of chronic lung diseases (CLDs) in LMICs is of particular concern. Many known risk factors for respiratory disease are poverty associated and common in these settings. These include limited in utero growth as a result of poor maternal health, recurrent respiratory infections in childhood, and exposure to indoor and outdoor air pollution, tobacco smoke, HIV infection, and TB disease across the life course. Despite the widespread nature of these risk factors, data on the epidemiology, nature and outcomes of respiratory disease in these settings remains limited, such that the development of health services for prevention and management is extremely challenging.

Residual lung damage after pulmonary tuberculosis may be a particularly important but neglected type of chronic lung disease in many LMICs. Despite many years of concerted effort, WHO estimates suggest that there were 10.4 million incident cases of active tuberculosis (TB) disease in 2016, one quarter of which occurred in the African region, where TB remains a disease of young adults and the majority of incident cases are seen in those aged 15-44 years.[12] Amongst those started on treatment for drug sensitive disease globally, it is thought that >80% survive with treatment cure / completion. TB management programmes have traditionally discharged these 'TB survivors' from health services as 'cured' at the end of standard short-course therapy, with no ongoing follow-up, but evidence for lasting post-TB sequelae amongst this group is growing. This is particularly evident for individuals who have completed treatment for pulmonary tuberculosis disease (PTB) who appear to be at increased risk of persistent abnormal spirometry after treatment completion, with significantly increased odds of residual airway obstruction and spirometric restriction demonstrated in several systematic reviews.[13-15]

Despite growing concerns that post-TB lung damage may be a key form of chronic respiratory pathology in LMICs, our knowledge of this condition remains limited: few studies have attempted to comprehensively characterise post TB lung pathology, to describe the evolution of damage over time, or to measure its associated morbidity and mortality. Data on the nature and impact of post-TB lung damage amongst HIV infected adults and those living the sub-Saharan African (sSA) setting are particularly scarce.

This PhD was completed in response to the need to address the high burden of CLDs in LMICs, and the indication that post-TB lung damage may be an important but neglected contributor to CLD in this setting. Its overall aim was to review and document the current body of literature on post-TB lung damage, and to establish a representative cohort of adults completing PTB disease in sSA amongst whom the prevalence, pattern and impact of post-TB lung damage could be measured, and placed in the context of the community burden of CLD.

1.3 THESIS STRUCTURE

This thesis starts with a broad review of the literature that summarises the scientific context for the novel work described in the following chapters. In Chapter 2 the burden of NCDs in sSA and Malawi in particular, the epidemiology and clinical management of tuberculosis disease, mechanisms of tuberculosis related lung damage, and the nature and impact of post-TB lung damage are reviewed. Approaches to the measurement of lung damage and patient centred outcomes in CLDs are discussed. Chapter 2 identified a need for a systematic review of the literature on the prevalence and pattern of structural post-TB lung damage, which was done and is presented in Chapter 3.

Chapter 4 describes a population-based cross-sectional study of chronic symptoms and spirometry amongst adults in urban Blantyre which was done to understand the burden of chronic respiratory disease amongst 'well' adults in the community in Blantyre, and provide a comparator for the cohort study described in Chapter 5.

Chapter 5 is the centrepiece of this thesis and describes a prospective cohort study of adults completing treatment for pulmonary TB in Blantyre. This study measured the prevalence and pattern of post-TB lung pathology amongst HIV-positive and negative adults at TB treatment completion, and its evolution over a 1-year follow up period, and explored the association between severe residual lung damage and patient outcomes.

Finally, Chapter 6 is a general discussion that draws together the findings of all the Chapters and outlines implications for future research and policy.

The three chapters (3, 4 and 5) that describe the novel work of this thesis are written as standalone studies in accordance with the relevant PRISM and STROBE guidelines, each with introduction, methods, results, discussions and conclusions sections. Although this makes for long individual chapters – particularly Chapter 5 – it is hoped that this consistent approach and alignment with international reporting guidelines will be helpful to the reader.

2 LITERATURE REVIEW

This Chapter provides a broad review of the literature on NCDs and TB, and summarises the scientific context for the novel work described in later sections of this thesis.

Literature describing the burden and patterns of chronic lung disease (CLD) in sSA is scarce. A general overview of this literature is given here, with a focus on Malawi.

In contrast, the body of literature on tuberculosis is vast – although the *Mycobacterium tuberculosis* organism was not discovered by Robert Koch until 1882, the disease has been present for centuries and there exists a great catalogue of pure science, clinical and public health work describing the condition. In this introduction I have focused mainly on the literature most relevant to TB related respiratory damage, including brief overviews of the epidemiology, diagnosis and management, and current understandings of the mechanisms of TB-related lung damage. Existing data on the nature of post-TB lung damage (PTLD) and its associated morbidity are outlined, and gaps in our knowledge highlighted. Lastly, potential approaches to the measurement of post-TB lung damage in resource poor settings, which have informed the work described in subsequent chapters, are discussed.

2.1 CHRONIC LUNG DISEASE IN SUB-SAHARAN AFRICA

Non-communicable diseases (NCDs) are widely recognized as leading causes of morbidity and mortality worldwide – the Global Burden of Disease study 2013 estimated 38.3 million (95% CI: 37.2 – 29.4m) NCD related deaths in 2013, with 4.2 million (95% CI: 4.0 – 4.7m) of these attributed to chronic lung diseases. The importance of tackling high burden NCDs has been enshrined in the Sustainable Development Goal target 3.4, which requires a one-third reduction, relative to 2015 levels, in the probability of dying between 30 years and 70 years of age from cancers, cardiovascular diseases, chronic respiratory diseases, and diabetes by 2030.

2.1.1 RISK FACTORS FOR CHRONIC LUNG DISEASE IN SSA

At the time of starting this PhD few data were available on the burden of CLDs in the sSA region, but many acknowledged risk factors for chronic respiratory damage are known to converge here. These include poverty-related in-utero and early childhood exposures, biomass fuel exposure, a rapidly increasing prevalence of smoking, chronic HIV-infection, and of course a persistently high incidence of pulmonary tuberculosis.[16]

There is strong evidence of in-utero and early childhood exposures constraining lung growth in the early years of life. Many risk factors for reduced growth are poverty-associated and common in low resource settings, including maternal malnutrition, maternal smoke and pollution exposure, fetal

prematurity and intrauterine growth restriction, and early childhood lower respiratory tract infections.[17] Longitudinal studies suggest that children with impaired lung development as a result of these factors go on to have lower lung function in adulthood.[17] The broad impact of these insults on general health may explain the association between low FVC volumes and mortality which has been observed amongst asymptomatic adults,[18] and the higher and earlier incidence of cardiac and metabolic comorbidities experienced by young adults with impaired lung function, as they age. [19]

It is thought that 1/3 of the world's population use solid fuel combustion for cooking, heating and lighting. The majority of these individuals live in low and middle income countries (LMICs): data from Malawi suggest that even in urban settings, individual level exposures to pollutants released by biomass used including $PM_{2.5}$ and CO frequently exceed WHO recommended ranges.[20] Biomass fuel exposure has been associated with childhood respiratory tract infections, chronic obstructive pulmonary disease (COPD), and respiratory malignancy, and is thus a major risk factor for CLDs in sSA. The growing prevalence of tobacco use in sSA is of also concern: a 2009 review of tobacco use in Kenya, the Gambia, Uganda and Liberia found a prevalence of current smoking of between 5-54% depending on the population sampled, with male dominance noted throughout.[21] Tobacco consumption in many LMICs is increasing, and it has been estimated that by 2030, 70% of global tobacco related deaths will occur in developing countries.[22] Uptake of tobacco monitoring and prevention policies in many of these regions have however been slow.[23] Malawi remains particularly vulnerable – its economy remains reliant on exports of tobacco crop, and perhaps in relation to this Malawi has only limited cigarette taxation, no smoke-free policies, no health warnings on tobacco products, and no tobacco advertising bans in place.[22]

HIV infection is known to increase the incidence of severe respiratory tract infection across all age groups, and in advanced immunosuppression is associated with opportunistic respiratory infections such as *Pneumocystis jirovecii* (PCP), *Cryptococcus neoformans*, and *Histoplasma capsulatum*.[24] Chronic HIV infection has also been associated with CLDs – increased odds of airway obstruction and accelerated rates of lung function decline have been demonstrated in HIV-positive western cohorts, as well as a high incidence of pulmonary hypertension[25]. It has been suggested that this is the result of immune activation and subsequent immune senescence caused by chronic HIV-disease, both directly and through associated chronic/recurrent bacterial and viral infections.[26] High rates of obliterative bronchiolitis have been detected amongst adolescents with vertically acquired HIV in sSA, with the same underlying mechanism postulated here.[27]

2.1.2 BURDEN OF CHRONIC LUNG DISEASE IN SSA

Despite the presence of multiple risk factors for CLD in sSA, and the resulting suspicion of a high burden of disease in this setting, few robust data on the epidemiology of disease in this region were available until the start of The Burden of Obstructive Lung Disease (BOLD) initiative in 2005.[28] This was a multi-

country programme of work primarily designed to measure the prevalence of chronic obstructive pulmonary disease (COPD) amongst adults >40-years around the world, using standardized community sampling approaches, questionnaires, and spirometry procedures in multiple study sites, with centralized quality control and data analyses.

Data for the first 12 sites was published in 2007, and included findings from Cape Town, South Africa where the prevalence of moderate-severe airway obstruction was found to be particularly high at 19.1%, compared to prevalence estimates of 5.9 – 14.3% from sites in Western Europe and North America.[29] This finding sparked much concern, and resulted in BOLD studies being initiated at several other African sites for comparison.

In fact, data from Tunisia, Morocco, Nigeria, and Malawi have shown a much lower prevalence of obstruction than that seen in Cape Town – the estimated population prevalence of obstruction ≥GOLD stage II (FEV_1/FVC ratio<0.7 and FEV_1 <80%) was 7.9% in Morocco and 4.2% in Tunisia,[30 31] and the prevalence of any obstruction (FEV_1/FVC ratio<0.7) was 6.7 – 8.7% in Nigeria,[32] 8.7% in rural Malawi and 4.2% in urban Malawi.[33 34] The dominant pattern of abnormality observed across these sites was instead a low FVC pattern, or a picture of reduced lung volume. If standardized against a Caucasian American population using the National Health and Nutrition Examination Survey III (NHANES III) reference ranges, the population prevalence of reduced FVC was estimated at 70.4 – 72.8% in Nigeria, 38.6% in urban Malawi, and 34.8% in rural Malawi.[33-35] These findings suggest that it is small lungs, rather than obstructed airways, which is the dominant deficit in the African setting.

There remains much debate about the underlying cause of this low FVC pattern. It is possible that black African populations have lower 'normal' lung volumes compared to Caucasian Americans due to genetic differences. However, some have argued that optimal lung volumes are likely similar across ethnic groups, with the low lung volumes observed in the African setting reflecting widespread in utero or early childhood exposures which have prevented optimal lung development.[36] This will be discussed in greater detail below.

Although the burden of airway obstruction may be lower across sSA than initially suspected, where obstruction is seen, exposures other than tobacco may be important risk factors in this setting. Never-smokers made up 1/3 of those with airway obstruction across 14 of the earliest BOLD study sites,[37] and many had high exposures to biomass fuel and occupational dusts. An association between poverty and obstructive FEV_1/FVC ratios has been demonstrated both within and between populations from 14 LMIC sites, which is independent of smoking.[38]

Outside of these BOLD studies, there have been few large-scale robust efforts to document patterns of CLDs across the sSA region. Existing data are therefore focused largely on clinical symptoms and spirometry deficits, with little attention paid to the structural lung pathology underlying these

abnormalities and the specific respiratory diagnoses they relate to. If mortality related to CLDs in sSA is to be reduced, further work in this area is required.

2.1.3 BURDEN OF CHRONIC LUNG DISEASE IN MALAWI

As highlighted in the introduction above, much of the primary data presented in this thesis is drawn from Malawi, and a more detailed description of existing data on the burden of CLDs in Malawi is therefore given below.

- URBAN MALAWI

Data from the BOLD study completed in urban Blantyre in Malawi in 2014 were analysed as part of this PhD, and are presented in detail in Chapter 4 of this thesis. In summary, this study showed that amongst an age and gender stratified sample of 1059 adults from Chilomoni district of urban Blantyre, 11.8% (SE 1.2%) reported respiratory symptoms including cough, sputum production, exertional breathlessness, or wheeze. 72.8% (749/1029) of participants completed ATS standard spirometry, amongst whom 4.3% (SE 1.1) of men and 4.1% (SE 1.1) of women were found to have post-bronchodilator obstruction, and 38.6% were found to have a reduced FVC pattern of deficit using NHANES III reference ranges.[34] Increasing age and lower socioeconomic situation (SES) were associated with airway obstruction in multivariate models, whilst a low FVC pattern was more common in those with a reduced BMI. No associations were demonstrated between HIV status, biomass exposure, smoking or self-reported previous TB disease, and either pattern of abnormal spirometry.

- RURAL MALAWI

Data from two further studies have examined the burden of respiratory symptoms and spirometric deficits amongst adults in rural Malawi, and confirm a high background burden of chronic respiratory symptoms / impairment within the general Malawian population

Recently published findings from a community based prevalence survey in a rural area in southern Malawi (Chikwawa) showed that amongst 1481 adults aged over 18 years, 12.6% reported at least one respiratory symptom, with cough in 11.1%, regular sputum production in 2.6%, and breathlessness and wheeze both reported by 1.6% of participants.[33] Self-reported previous TB (reported by 3.2% of the cohort) was associated with increased odds of respiratory symptoms (OR 2.50, 95% CI 1.04 – 15.58). The prevalence of airway obstruction was 8.7% (95% CI 7.0-10.7%) and a low FVC pattern of deficit was seen in 34.8% (95% CI 31.7-38.0) using NHANES III reference ranges. Female gender, increasing age, and previous TB disease were associated with lower FEV1 and FVC volumes. Smoking was associated with lower FEV_1 volumes. Biomass exposure was reported by 99.8% of the study

population, and directly measured in 1144 study participants, but in multivariable models neither particulate matter ($PM_{2.5}$) nor carbon monoxide (CO) levels were associated with either FEV_1 or FVC.

Figures from a second rural study available for Malawi are rather higher – a population proportion sampling approach was used to select 5670 households from 27 clusters defined by local health centres in Dowa and Ntchisi in central Malawi in 2014/15. A total of 15795 adults ≥15 years old were interviewed from across these households, and 22.5% reported some combination of chronic cough, shortness of breath, or wheeze within the last 12months.[39] Out of those patients reporting chronic respiratory symptoms, only 18% (648/3554) had a respiratory diagnosis recorded in their health passport (including bronchitis, COPD, asthma or lower respiratory tract infection), highlighting the unmet need for chronic respiratory services in this setting.

Variation in the burden of symptoms reported by these studies may relate to the format of the questions used and duration of time over which symptoms were recorded, but all confirm the finding of a high burden of chronic respiratory symptoms and perhaps respiratory pathology within the general population in Malawi.

- NATIONAL DATA

The final source of data on the burden of chronic respiratory pathology in Malawi comes from the National TB prevalence survey, which was completed in 2014 and included 31,579 adults ≥15 years.[40] This study was focused on collecting data relevant to the diagnosis of TB, rather than chronic respiratory pathology. As such, questionnaires focus on current symptoms, in comparison to the BOLD questionnaires used in the studies above, which ask about symptoms experienced in recent months. Nevertheless, amongst adults included in the prevalence survey, current cough for at least 2 weeks was reported by 3.7%, and any TB symptoms (including cough, breathlessness, night sweats, fever or weight loss) for 1 week by 8.6% of participants. The overall prevalence of ever-smoking was 16%, with much higher rates of current smoking amongst men (18.1%) compared to women (3.6%).

In addition to symptom data, the national prevalence survey included imaging with chest x-ray (CXR) for all survey participants, whether symptomatic or not. Images were read by 1 radiologist and 1 physician in the field and classified according to the categories defined below (Table 1), with central re-reads performed for 10% of the normal images and the majority of the abnormal images, for quality control. On initial field review, 95.8% of patients were thought to have normal CXRs, and only 4.2% had abnormal CXRs. This proportion of those suspected of having abnormal films was higher in men than women (4.4 vs. 2.4%). The majority of abnormal scans were attributed to TB disease (76.4%, 1016/1330). However, the accuracy of this field interpretation is likely limited: rereading of 10% of the normal films led to 5.3% of them being reclassified as abnormal, and over half of the abnormal films were reclassified as normal on central review, and sub-optimal image quality was noted in the survey

report[40] Given these limitations, and the difficulty in using the case definitions employed to differentiate between signs of acute and old PTB, these data are likely of limited use in understanding the population burden of chronic structural lung damage and post-TB lung damage specifically in Malawi. No other population or survey level imaging data from Malawi were identified on review of the literature.

Table 1: CXR classification in National TB prevalence survey (n=31,561)

Field Category	Description of category (verbatim, from the NTP manual)	Field reading results, n (%)	Central re-reading results
Normal	No abnormality detected	30,231 (95.8%)	3627 re-read Normal: 3434 (94.7%) TB: 49 (1.4%) Other lung disease: 66 (1.8%) Cardiac disease: 35 (1.0%) Other: 10 (0.0%) Non interpretable: 33 (1.0%)
Abnormal – TB related	CXR images that showed abnormalities usually with pulmonary TB. Eg. Cavitation, apical involvement, parenchymal opacities with or without pleural effusion, parenchymal opacities with mediastinal or hilar lymph node enlargement, isolated lymphadenopathy, diagonal parenchymal involvement, miliary parenchymal mottling, and involvement of typical tubercular sites such as apices and upper segments of lower lobes plus isolated pleural effusion and pneumothorax.	1016 (3.2%)	1168 re-read Normal: 586 (50.2%) TB: 273 (23.4%) Other lung disease: 189 (16.2%) Cardiac disease: 72 (6.2%) Other: 20 (1.7%) Non interpretable: 28 (2.4%)
Abnormal – not TB related	CXR images that were significantly abnormal but the radiologist is certain that the cause is non-tubercular. Eg. Emphysema, classic bronchiectasis, classic lobar consolidation with air bronchograms (bacterial pneumonia), spiculated or stellate masses (malignancy), canon ball metastases or other vascular abnormalities.	312 (1.0%)	
Non-interpretable	CXR images where significant abnormality existed but the radiologist was not sure whether the cause is tubercular or non-tubercular. Eg. Non-homogeneous opacities, bizarre patterns.	2 (0.0%)	N/a

2.2 TUBERCULOSIS EPIDEMIOLOGY AND MANAGEMENT

As mentioned above, pulmonary tuberculosis (PTB) remains one of a series of risk factors for chronic lung damage which may be encountered over the life course in the sSA setting. The relationship between PTB and CLD is the central focus of this thesis, and a brief overview of the epidemiology, clinical presentation and management of tuberculosis disease is therefore given below.

2.2.1 MYCOBACTERIUM TUBERCULOSIS

Discovered in 1882 by Dr Robert Koch, *Mycobacterium tuberculosis* (MTB) is an aerobic bacterium with a thick lipid rich cell wall, and a slow dividing time of 15-20 hours. Humans are the only known reservoir

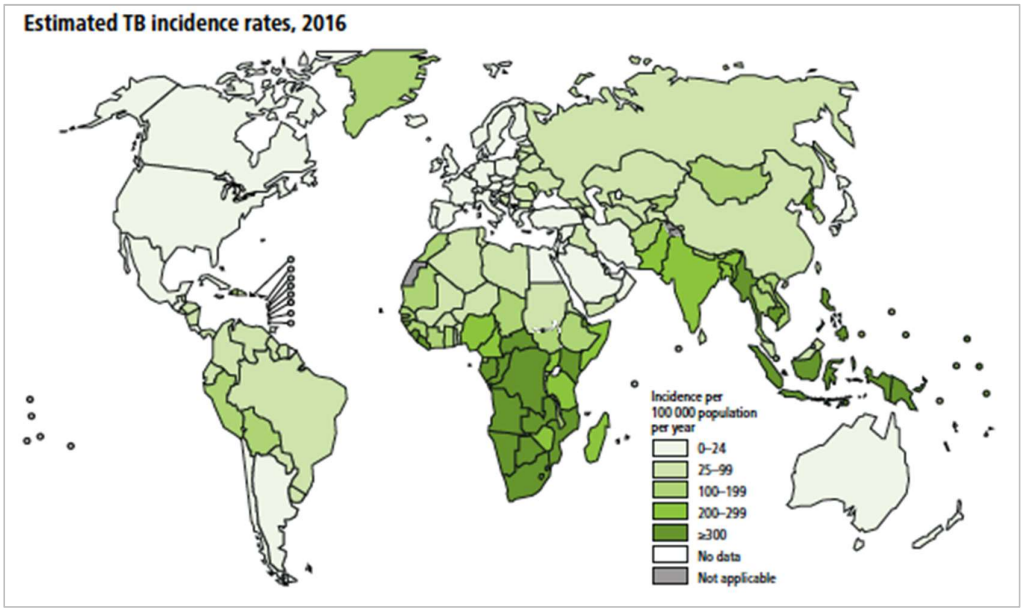
of the organism. It is a respiratory transmitted infection, spread between individuals in air droplets inhaled into the lungs.

2.2.2 EPIDEMIOLOGY

WHO estimates suggest that there were 10.4 million incident cases of active TB disease in 2016, with 30 high TB burden countries accounting for 87% of all incident cases, and the largest number of cases seen in India, China, the Philippines and Pakistan. It is thought that 10% of incident TB cases (range 8-12%) in 2016 occurred among people living with HIV, with the proportion of HIV co-infection cases highest in the African region (30% HIV co-infection, range 24-35%).

Incidence rates of TB disease vary widely between countries (Figure 1), with the rate across the WHO African region thought to lie at 254/100,000 (Range 227-284). Globally, TB incidence rates are falling, but progress is slow with an average rate of decline between 2000-2016 of 1.4%.

Figure 1: Global estimates of TB incidence rates*, per 100,000 population



*Estimates of incident cases drawn from National TB Prevalence survey data and TB notification rates in high and middle income countries with well performing national surveillance programmes, with adjustment for estimated underreporting and under diagnosis based on expert opinion and ancillary data.

WHO estimates of global TB related deaths are drawn from a combination of vital registration data, mortality surveys, and modelling based on TB incidence and case-fatality rates, and suggest that TB remains the 9th leading cause of death worldwide, responsible for 1.3 million (range: 1.2-1.4m) deaths amongst HIV-negative and 374,000 (range: 325-427,000 deaths) amongst HIV-positive people in 2016. Mortality rates are again unevenly distributed, with 85% of TB deaths seen in the WHO Africa and South-East Asia regions. The average case fatality rate (the number of TB deaths, divided by the

number of incident cases) for TB was 16% globally in 2016, but remains >20% in the majority of countries in the WHO African region.[12]

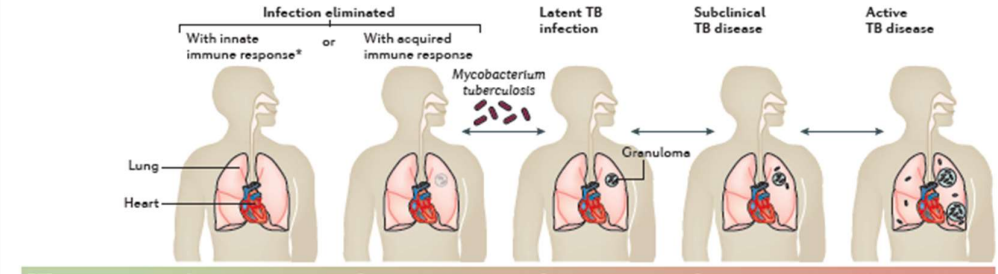
Global estimates suggest that tuberculosis prevalence remains higher in men than women, with a ratio of between 1.3 to 2.1 across the WHO regions,[12 41] and evidence of reduced access to available health care services amongst men in many resource-poor settings.[42 43] Estimates of TB incidence in the African region suggest that the majority of cases are seen in young adults, between the ages of 15 – 44years.[12] Modelling studies, which include primary tuberculin skin test (TST) data from 37 countries, suggest that 23% of the global population or 1.7 billion people had latent TB infection in 2014.[44]

Of note - tuberculosis is a disease driven by social determinants, with risk factors for transmission, development of active disease, and poor access to treatment common amongst those living in poverty.[45] Significant declines in disease and mortality were seen in the early 20th century as a result of economic growth, improvement in working conditions, and public health interventions to improve nutrition, housing and sanitation, even prior to the arrival of anti-tuberculosis chemotherapy in the 1940s.[46] However, the HIV epidemic of the late 1980s and 90s, ongoing funding limitations, and challenges providing public health services during the dissolution of the Soviet Union led to an upsurge in cases and TB mortality, such that the WHO declared tuberculosis a global emergency in 1993.[47] Perhaps the most striking feature of the TB epidemic which is seen today is how gradual progress has been, since then.

2.2.3 SPECTRUM OF TUBERCULOSIS DISEASE

For public health and clinical purposes, TB disease is classically thought of as either 'latent' or 'active'. However, in reality TB disease is likely a spectrum based on the balance between mycobacterial burden and the host immune response (Figure 2).

Figure 2: Schematic to illustrate the spectrum of TB disease, from MTB exposure to active pulmonary disease[48]



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

On entering the lung, the MTB organism is phagocytosed by the alveolar macrophage, but evades destruction by preventing fusion of the phagosome with the lysosome, and rather begins to replicate. Over time, the organism gains access to the lung parenchyma, either through translocation of infected macrophages across the alveolar epithelium, or by direct movement of the mycobacteria into the lung tissue. As infected dendritic cells and inflammatory monocytes are recognized by the pulmonary lymph nodes, the host T-cell response is triggered, T and B cells are recruited, and granuloma form at the site of infection.

In the context of a competent immune response the mycobacterial burden is contained, granuloma remain intact and a controlled state – or latent TB infection – is established. Individuals remain asymptomatic, and are not infective but typically have evidence of an acquired T-cell response to infection which is evident on Tuberculin skin test (TST), or serum Interferon gamma release assay (IGRA).

If the host immune response is inadequate and the bacterial burden increases, the granuloma may fail to contain the infection, resulting in dissemination of mycobacteria within the respiratory tract or through the blood stream to other organs. Early in this process, individuals may remain asymptomatic with 'subclinical' disease – several population based prevalence surveys have found that up to half of those with prevalent culture-positive disease identified on screening are clinically asymptomatic.[49] However, in the absence of treatment, the mycobacterial burden grows leading to symptomatic pathology and active disease. In the absence of TB treatment, mortality from active disease is invariably high with case fatality rates estimated at 70% for smear positive and 20% for smear negative HIV uninfected adults.[50]

In those with latent infection, the lifetime risk of progression to active disease or 'reactivation' is thought to lie between 5 – 15%,[51] with the highest risk seen in the early years after infection. Whilst it is clear that reactivation is more common in those with compromised immunity,[52] for example those with HIV co-infection in whom the risk is as high as 10% per year, investigation into the contribution of mycobacterial factors and host genetic susceptibility / immune response to reactivation rates are ongoing.[53] Neither of the LTBI tests – TST or IGRA – are able to predict future development of active disease.[48]

The symptoms associated with active TB disease depend on the site of mycobacterial dissemination and replication. The most common manifestation of disease is pulmonary tuberculosis, with extrapulmonary tuberculosis (EPTB) disease accounting for only 8-24% of notified cases across the WHO regions in 2016.[12] Respiratory symptoms of PTB disease include cough, sputum production, haemoptysis, chest pain and breathlessness. Constitutional symptoms of active disease include weight loss, fever and night sweats.

2.2.4 DIAGNOSIS OF TUBERCULOSIS DISEASE

Tests of the adaptive T-cell immune response – TST and IGRA –are used to determine whether an individual has previously encountered the MTB pathogen, and are markers of pathogen exposure only. In the Mantoux TST, 0.1ml of tuberculin (a purified protein derivative of MTB) is injected intradermally in to a patient's forearm and the extent of the resulting skin induration is used to quantify the host immune response to this protein. For IGRA assays, a whole blood sample is taken and mixed with antigens derived from MTB, and either the number of cells producing interferon-gamma (IFN-g) or the amount of IFN-g produced is measured. Both of these assays are expected to be positive if an individual has previously encountered MTB and has a host immune reaction which is 'primed' to the pathogen, whether or not they currently carry the infection. As such, these tests are unable to differentiate between latent and active disease.

Detection of active TB disease instead relies on four main technologies – imaging techniques, microscopy, culture, and molecular methods – the sensitivity and specificity of which are shown in Figure 3.

Culture remains the gold standard for detection of active TB disease, liquid media are increasingly used in the automated BACTEC Mycobacteria Growth Indicator Tube (BACTEC MGIT) system.[54] Although sensitivity of culture is high, and isolation of the MTB organism allows drug sensitivity testing for resistant disease, samples take 10-21 days to be processed, and culture is usually only available in central reference or research laboratories such that wide spread use in low and middle income settings remains limited. In practice, TB management services in these settings remain largely reliant on smear microscopy with direct visualization of mycobacteria using either conventional microscopy, or the more sensitive fluorescence microscopy. Smear microscopy is a technique that is more easily decentralized, and can be performed on the same day, but requires investment in quality control to maintain standards. Sensitivity remains much lower than that of culture.

The emergence of molecular techniques in recent years has significantly changed practice. The Xpert MTB/RIF assay is an automated cartridge based nucleic acid amplification test, which can be performed on sputum and other biological samples, with a 2-hour turn around period. It is expensive assay, costing around $17,000 for the initial unit and $10 for each single-test cartridge used, but sensitivity is higher than that of sputum smear testing, and includes concurrent assessment of Rifampicin resistance. WHO authored a policy update in 2013, conditionally recommending the use of XPert MTB/RIF as the first-line diagnostic test in all adults and children with suspected active TB disease, particularly in those with HIV co-infection.[55] By the end of 2016, 28/48 high TB burden countries had national algorithms including Xpert MTB/RIF as the initial diagnostic test for all TB suspects.[12]

The lipoarabinomannan (LAM) urinary assay is the first truly point-of-care test for advanced TB disease to have emerged in recent years. LAM is a component of the *M.tuberculosis* cell wall, and is found in the urine of those who have disseminated TB disease with renal involvement. It has been shown to have high sensitivity for TB disease in those with advanced HIV infection and CD4 counts <100 cells/uL, in whom disseminated disease is more common.[56] It is currently recommended by WHO as a diagnostic tool in HIV infected adults with CD4 counts <100 cells/u, or those with unknown counts. A recent multicentre randomized control trial demonstrated a mortality benefit when LAM was used as a screening tool for disseminated TB disease amongst HIV-infected adults admitted to hospital with low CD4 counts, severe anaemia, or clinically suspected TB disease.[57]

Use of chest x-ray as a stand-alone diagnostic tool has been somewhat limited to date. Until recently radiography was available largely in secondary and tertiary health care settings only, and sensitivity / specificity of chest imaging for active TB disease was limited by reader inconsistency. However, increasing use of Computer Aided Diagnostics (CAD), which rely on automated reading and interpretation of images, will allow standardized interpretation and may improve performance in coming years, and if used together with digital CXR, may make the use of chest radiographs for decentralized screening and diagnosis increasingly feasible.

Figure 3: Diagnostic tools for active TB disease, reviewed by WHO[48]

Test	Assay principle	Use	Sensitivity (%)	Specificity (%)	TAT*	Target setting[‡]	Year endorsed
Imaging techniques							
Chest X-ray	Imaging of the lungs	Active TB disease screening	87 (using TB abnormality as a threshold)	69 (using TB abnormality as a threshold)	Same day	Secondary and tertiary centres	Included in the WHO guidelines for many years
Microscopy							
Conventional sputum smear microscopy	Direct visualization of mycobacteria using light microscopy	Active TB disease diagnosis	32–94	50–99	Same day	Peripheral and reference laboratories	Included in the WHO guidelines for many years
LED fluorescence smear microscopy[§]	Direct visualization of mycobacteria using fluorescence microscopy	Active TB disease diagnosis	52–97	94–100	Same day	Peripheral and reference laboratories	2011
Culture-based techniques							
Liquid culture with DST	Mycobacterial culture on liquid media	• Active TB disease diagnosis • Drug resistance	• 89 (among smear-positive and culture-positive) • 73 (among smear-negative and culture-positive)	>99	10–21 days	Reference laboratory	2007
Antigen detection techniques							
LAM lateral flow assay[§]	Antigen detection	Active TB disease diagnosis in HIV-positive individuals	• 44 (all) • 54 (in HIV-positive individuals)	• 92 (all) • 90 (in HIV-positive individuals)	Same day	Peripheral laboratory	2015 (conditional recommendations in selected groups)
Molecular techniques (nucleic acid amplification tests)							
Xpert MTB/RIF[§,‖]	NAAT (qPCR)	• Active TB disease diagnosis • Drug resistance (rifampicin)	• 98 (smear-positive and culture-positive) • 67 (smear-negative and culture-positive) • 95 (rifampicin resistance)	• 99 (smear-negative and culture-negative) • 98 (rifampicin resistance)	Same day	District or sub-district laboratory	2010

TAT: Turn around time

2.2.5 EMPIRICAL TB TREATMENT

It is worth noting that in the context of imperfect diagnostics, clinicians in both high and low burden settings have long initiated empirical treatment for TB disease where there is reasonable clinical suspicion of disease, but no microbiological or pathological confirmation. Thresholds for empirical treatment are known to vary widely between settings, with factors such as the background prevalence of tuberculosis, presence of HIV co-infection, patient stability, access to clinical investigations, probability of a one-off patient encounter, and perhaps the individual physicians own training and risk perceptions influencing the decision to start treatment.[58] As such, the accuracy of clinical judgements in the diagnosis of pulmonary TB disease are likely to vary widely between regions.

Some evidence of accuracy of clinical diagnosis can be drawn from a recent meta-analysis of 5 studies, which compared the accuracy of the 2007 WHO algorithm for the clinical diagnosis of smear negative pulmonary TB, with sputum culture confirmed disease as the gold standard. This study showed a pooled sensitivity of 69% (66-72%) and specificity of 69% (66-72%) for the algorithm, against culture, suggesting that when formal guidelines are followed the accuracy of clinical diagnosis is likely limited.[59] A wider spectrum of accuracy is likely in real-life settings where the algorithm is likely incompletely followed and clinical judgements may vary. Previous work from Malawi has shown that amongst 352 smear-negative patients registered for treatment in Lilongwe – prior to the introduction of molecular diagnostics – approximately 1/3 were shown to have microbiologically confirmed PTB disease when extensively investigated, 1/3 show clinical behaviour very similar to that of those with microbiologically confirmed PTB and are thought likely to have true smear negative disease, and the remaining patients with likely non-TB diagnoses had a very high mortality,[60] suggesting that at least in this time and in this setting, rates of false positive diagnosis amongst smear negative patients were perhaps limited.

2.2.6 ACTIVE CASE FINDING

Despite ongoing investments in TB health services, improvements in diagnostics, and the use of empirical treatment as deemed appropriate, it is clear that there remains a diagnostic gap: in addition to the 6.3 million new and relapse TB cases reported globally in 2016, it is thought that there were an additional 4.1 million unreported cases of active disease.[12] Post-mortem studies suggest a high prevalence of undiagnosed TB disease amongst unwell patients dying in hospital, with up to 45% of TB cases identified amongst HIV-infected adults remaining undiagnosed at time of death.[61]

A 2008 systematic review of 58 observational studies investigating barriers to treatment for TB disease identified substance / alcohol abuse, poverty, low access to health care facilities, rural residence, old age, and poor knowledge about TB as risk factors for treatment delays. Health system capacity / approach limitations were also highlighted as barriers to prompt diagnosis and treatment initiation,

with patients with smear negative or EPTB disease, or who used traditional or private practitioners first experiencing longer delays.[62] Recurrent visits to the same health care provider for investigation was a widespread issue, together with the stigma associated with a TB diagnosis and its association with HIV disease.

This diagnostic gap poses a public health challenge as it facilitates onwards transmission of disease from infectious untreated individuals, and is also detrimental to the health of the individual patient. Active case finding aims to address this gap, with screening of either whole communities in high TB incidence settings or specific high risk populations for active disease, in order to decrease time to treatment and minimize ongoing disease transmission. In various settings, it has been shown to decreased incident disease,[63] and has been endorsed by the WHO End-TB strategy as a means to promote early diagnosis and treatment.[64]

2.2.7 TUBERCULOSIS TREATMENT

Although MTB was discovered in 1882, the advent of anti-tuberculosis drug therapy came only in the 1940s when streptomycin and para-aminosalicylic acid (PAS) were shown to be effective. In fact the discovery of the four first-line drugs which continue to form the backbone of modern short-course TB treatment dates back to the same period: Pyrizinamide was discovered in the late 1940s, isoniazid in 1951, ethambutol in 1961, and the rifamycins in 1956.[65]

WHO currently recommends six-months of therapy for drug sensitive disease, with an initial 2-month 'intensive' phase of treatment with rifampicin, isoniazid, pyrazinamide, and ethambutol, followed by a 4-month 'continuation' phase with with rifampicin and isoniazid alone. Whilst extension of therapy beyond 6-months is not recommended for any patients by WHO, various national guidelines advocate a further prolonged continuation phase in those with extensive disease or cavitation, or persistently positive microbiology.[66] Traditionally the response to drug treatment is thought to be biphasic, with early killing of replicating bacteria, followed by slower killing of a subpopulation of slowly dividing or sequestered 'persistent' organisms. Although the majority of smear positive patients are seen to have converted to become culture negative by the end of the intensive treatment phase, trials conducted to date which have attempted to shorten treatment regimens to less than 6-months have failed, with increasing rates of relapse seen.[66]

Combination therapy has long been used in TB treatment to minimize the risk of drug resistance and treatment failure. Drug resistance in MTB is conferred by mutations, rather than acquisition of new DNA,[48] which are thought to occur at a spontaneous rate of approximately 1 mutation every 10^7 - 10^{10} divisions for each of the four first-line drugs. Using these four drugs in combination, the chances of any single organism developing resistance to all four drugs is thought to be minimal. In addition, each of the drugs has a different mode of action, with rifampicin having the most marked bactericidal effect.

2.2.8 DRUG RESISTANT DISEASE

Drug resistance can be detected by phenotypic culture-based approaches, as well as molecular based methods to detect the genetic mutations. WHO estimates from 2016 suggest that globally, 4.1% of new cases (95% CI 2.8 – 5.3%), and 19% of retreatment cases (95% CI; 9.8 – 27%) had rifampicin resistant (RR) tuberculosis disease, or multidrug resistant (MDR) where resistance to both isoniazid and rifampicin are detected. It is thought that 6.2% (95% CI: 3.6 – 9.5%) of these organisms are extensively drug resistant (XDR), with additional resistance to a fluoroquinolone (Eg. levofloxacin or moxifloxacin) and to at least one of the three injectable second line drugs (Amikacin, capreomycin or kanamycin). The countries with the highest numbers of cases of MDR / RR disease, accounting for 47% of the overall burden, are China, India and Russia.[12]

Treatment regimens for MDR-TB require a larger number of drugs delivered for a prolonged period, with use of individualized regimens based on drug-susceptibility testing. Traditionally, treatment regimens lasting at least 20-months were recommended. However in 2016, based on the results of the STREAM trial which demonstrated comparable effects of 9-month treatment regimen compared to the 20-month treatment regimen within rigorous clinical trial conditions,[67] the WHO now recommends a 9-12month treatment regimen for MDR disease using 7 drugs for the initial 4 months, followed by 4 drugs for at least a further 5 month period.[68] Despite this reduced duration, pill burdens and drug side effects experienced during treatment for resistant disease are often profound.

2.2.9 TREATMENT OUTCOMES

TB treatment outcomes are classified according to standard WHO definitions (Table 2). In drug sensitive disease treated with standard short course therapy, 'treatment success' was reported for 83% of cases treated in 2015.[12] Programmatic data suggest that outcomes are much worse in the context of drug resistance with only 54% of patients with MDR/RR-TB and 30% of those with XDR-TB achieving treatment success.

Table 2: WHO TB treatment outcome definitions[69]

Outcome	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
Treatment completed	A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
Died	A TB patient who dies for any reason 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.

There remains some controversy over when TB treatment outcomes should be defined. Standard WHO treatment outcomes which are assigned at the point of treatment completion have been criticised for their failure to include relapse after this time point as a type of treatment failure, particularly in the context of MDR treatment.[70] However, the inclusion of relapse within standard outcome definitions would require ongoing follow-up of all TB patients for at least 1-year following treatment completion. With current resource constraints this may prove challenging – or impossible - for many National TB treatment programmes in resource-poor settings, and as such treatment outcome definitions continue to be determined at the point of treatment completion.

2.2.10 RECURRENT TB DISEASE

Recurrent TB disease after successful treatment completion can be the result of either endogenous reactivation following inadequate initial treatment, or exogenous reinfection. Rates of relapse are thought to be highest soon after completion of the initial TB treatment episode. A systematic review of 15 early tuberculosis trials found relapse rates of between 3 - 8% across the studies, with 78% of relapse episodes occurring within the first 6-months following completion of the initial TB treatment regimen,[67] and 91% occurring within the first 1-year.

A recent population based retrospective cohort study of 1869 individuals who had been successfully treated for smear positive TB in Cape Town, South Africa between 1996-2008 used molecular strain typing to differentiate between relapse and reinfection, and confirmed the early dominance of the former. Within this study, 10.9% of individuals experienced a recurrent episode of smear positive TB disease during follow-up, with a median time to disease of 21 months. Amongst those with recurrent disease for whom sputum samples were available for both disease episodes, 49% were identified as relapse and 51% recurrence. Reinfection accounted for only 20% of cases within the first year after the initial treatment episode, but 66% of recurrent cases thereafter.[71]

There remains some uncertainty about the extent of lasting immunity conferred by an initial TB disease episode.[73] Ongoing latent infection is thought to confer some protection against progression to active disease following re-exposure amongst HIV-negatives, but the same pattern has not been demonstrated amongst HIV positives.[74] An episode of active TB disease may also confer lasting protection, as it is increasingly thought that cells involved in the innate immune response become 'trained' at both the mucosal level within the lung and through their development within the bone marrow after an episode of active disease,[75 76] such that a more effective innate immune response is mounted on subsequent exposures.[77]

2.2.11 IMPACT OF HIV CO-INFECTION

HIV co-infection, seen in approximately 10% of incident TB cases globally in 2016, impacts both TB epidemiology, and clinical presentation, diagnosis and management.

HIV infection leads to impairment of T-cell dependent immune responses early in disease, and in more advanced stages reduces the total number of CD4 T-cells,[48] such that the ability of the host immune response to contain MTB infection is reduced. As such, the risk of developing active TB disease from both exogenous infection, and endogenous reactivation of latent infection rises in HIV co-infected adults.[78] This increased risk manifests early in HIV disease, with some studies showing a doubling of risk within the first 1-year following HIV seroconversion.[79] Annual risks of reactivation of latent to active TB disease are estimated at 10% per year in HIV infected adults, in contrast to the 10% lifetime risk quoted for HIV-negative individuals.[80]

Patients with HIV co-infection are more likely to develop EPTB or disseminated disease than HIV-negative individuals, particularly at lower CD4 counts.[81] Whilst pulmonary disease remains the most common pattern of TB disease in both groups, its appearance on chest radiographs at lower CD4 counts has been widely documented as 'atypical' with more individuals showing non-cavitatory infiltrates, miliary disease, pleural effusions, or even normal appearances, compared to HIV negative adults.[81-83] In the context of active PTB disease, HIV positive individuals are more likely to be smear-negative.[84]

Clinical management of drug sensitive TB disease in those with HIV co-infection relies on the same drug regimens presented above, for the same 6-month duration. Introduction of antiretroviral treatment (ART) amongst ART-naïve HIV-infected patients with concurrent TB disease is known to increase the risk of developing an immune reconstitution inflammatory syndrome (IRIS), particularly within the first 3-months pf TB treatment and amongst those with CD4 counts <100 cells/mm^3.[78] However, despite this risk, early introduction of ART within 2 weeks of TB treatment initiation has been shown to significantly reduce mortality, except in the context of TB or cryptococcal meningitis, and is therefore widespread practice in resource poor settings today.[85]

Given the increased risk of reactivation from latent to active TB disease in the context of HIV infection, WHO guidelines currently recommend the use of isoniazid preventative therapy (IPT) in HIV infected individuals with no evidence of active disease, regardless of CD4 count and TST result, for at least 36 months in settings of high TB incidence and transmission.[86]

2.2.12 INTERNATIONAL TARGETS

Despite the ongoing challenges to the prevention, diagnosis, and management of TB outlined above, target 3.3 of the Sustainable Development Goals includes an explicit objective to end the epidemic of

multiple infectious diseases, including tuberculosis, by 2030. The WHO End TB strategy published in 2015 sets out the indicators and targets required to meet this ambitious objective. The central pillars of this agenda include a focus on health systems with integrated, patient-centred approaches to treatment and prevention, social and political action to address key social determinants of disease, and recognition of the urgent need for research to provide new tools or diagnosis and treatment of disease.[64] Much progress is required however, if this objective is to be met. In the foreseeable future it is likely that high rates of TB transmission and active disease will persist.

2.3 TUBERCULOSIS RELATED LUNG DAMAGE: MECHANISMS & DETERMINANTS

As can be seen from the above, globally there remains an ongoing high burden of active TB disease, with a concentration in resource poor settings. Although mortality remains high, over 80% of individuals successfully complete first-line treatment for drug sensitive disease,[12] and it is on this group of individuals that this PhD was focused. Crucial to understanding the nature of the residual lung pathology that they may be left with, after treatment, is some appreciation of the mechanisms and drivers of the TB-related lung damage during disease.

Research into the immune mechanisms underlying TB related lung damage has been limited by the lack of an accurate animal model for disease, with no non-human primates or other models which completely mimic the TB related pathology seen in humans, and limited opportunities to perform biopsies of sites of infection and disease within the infected human lung. However, our current understanding suggests that much of the pulmonary pathology seen is a result of the host immune response to infection which causes both tissue destruction and aberrant healing mechanisms, and is influenced by a combination of pathogen, environmental and host factors. An overview of existing literature on the mechanisms of TB related lung damage and drivers of this pathology is presented below.

2.3.1 MECHANISMS OF LUNG DAMAGE

- GRANULOMA FORMATION

Within the lung, MTB is phagocytosed by the alveolar macrophage but resists destruction by preventing fusion of the phagosome with the acidic lysosome,[87] and instead initiates replication. Initiation of an inflammatory cascade follows, and together with other inflammatory cells (T-cells, B-cells, NK cells, granulocytes) localised granulomata are formed at sites of infection within the lung.[87] Impairment of alveolar macrophage phagosomal proteolysis in HIV-infected adults in the early years

of ART treatment has been demonstrated, and likely contributes to the increased risk of TB disease amongst HIV-infected populations.[88]

Granulomata are highly organised structures that form within the lung, with alveolar macrophages – many of which differentiate into foamy macrophages with high lipid content – at the core and a fibrous coating / density of lymphocytes found more peripherally. It is in many ways the balance of the immune response at the level of the granuloma which determines the extent of tissue destruction: in some cases, stable granulomata which 'wall off' mycobacteria with no ongoing lung tissue destruction are seen, whilst in others ongoing activity with necrosis occurs at the core of the lesion with extensive destruction of alveolar tissue. Diverse granuloma stages and behaviours can be seen within the lung of a single infected individual, suggesting that immune responses mediating their formation and the MTB response is highly localised,[87] and perhaps accounting for the heterogeneous patterns of residual lung damage seen even within a single patient in different lung lobes.

- LUNG DESTRUCTION WITH CAVITATION

Cavitation with connection to the airways is in the interest of the MTB organism as it allows spread of disease through expectoration of caseous material that contains live organisms. However, the process through which lung cavities are formed remains unclear. Classically, they have been thought to be the result of caseation and alveolar destruction at the core of granulomata with rupture through the wall of an adjacent airway. However, other data suggest that cavities arise from areas of lipoid pneumonia which form in the lung, distinct from granulomata.[89] The role of Matrix Metalloproteinases (MMPs) in this process of lung destruction is increasingly recognised. MMPs are a group of enzymes responsible for the degradation of extra-cellular matrix components. Upregulation of MMP genes with increased secretion of MMP in the lung has been shown in the context of TB disease, with a lack of corresponding increase in the levels of the tissue inhibitors of metalloproteases (TIMPS), producing a local environment in which fibrin collagens and elastin in the lung are destroyed.[90]

- ABERRANT HEALING WITH FIBROSIS

Changes in lung architecture which are seen following TB disease are not due to tissue destruction alone, but also related to aberrant healing with architectural distortion and fibrosis / parenchymal scarring. Whilst less important for disease transmission during active TB disease, these processes may be highly relevant in producing residual pathology and ongoing disability after disease resolution. Data on the processes underlying these healing responses are less extensive, but it has been hypothesised that dysregulation of fibrogenic cytokines including TNF-a, TGF-ß and IL-1ß (which is implicated in the fibrosis seen in idiopathic pulmonary fibrosis) may be associated with higher levels of lung fibrosis in response to TB disease.[89]

- AIRWAY DAMAGE WITH BRONCHIECTASIS

Tuberculosis is a well-known cause of bronchiectasis, but literature on the mechanisms underlying the airway damage it produces are scarce: the TB immunology research community has historically focused more on mechanisms underlying TB related parenchymal changes such as fibrosis and cavitation, perhaps because these are more readily visible on chest x-ray and due to the public health importance of cavitation for TB transmission. However, calls for increasing research into the causal mechanisms of bronchiectasis and heterogeneity of airway damage in response to an infective insult are ongoing within the respiratory community.[91 92] It is possible that much of the bronchiectasis seen in the context of TB infection is related to the remodelling described above, and is 'traction' bronchiectasis, but it is possible that TB disease causes local and systemic inflammation which may lead to airways pathology independently of this architectural distortion.

2.3.2 DETERMINANTS OF LUNG DAMAGE

- MYCOBACTERIAL FACTORS

Animal models suggest that MTB strains differ in their virulence, the immune responses they trigger, and how they respond to oxidative stress. However, there are no data from human studies demonstrating a link between MTB strain type and disease phenotype at the individual or population level, such that the relationship between mycobacterial strain and localised lung pathology remains unclear.[93] Calls for increasing systems biology approaches that investigate genotypic diversity and environmental exposures together to better understand this process are ongoing.

Of note, it cannot be assumed that a single individual is exposed to a single MTB organism which behaves in a uniform way through the lung. it has been suggested that even within a genetically homogeneous mycobacterial population in a single human host, phenotypic diversity may exist in distinct granulomata in the lung, and may account in part for the diverse patterns of lung pathology seen within a given individual.[94] The presence of mixed strain infections and genetic diversity between respiratory samples taken from individual hosts has also been reported in autopsy studies, suggesting that there may be genotypic diversity within a single host also.[95] The impact of these variations on the nature and extent of lung damage seen is not clear.

- ENVIRONMENTAL EXPOSURES

The potential for an environmental exposure to modify the pulmonary reaction to MTB is clearly demonstrated in the context of silica exposure. Amongst male gold miners in South Africa silicosis has been shown to be both a risk factor for incident TB disease,[96] and associated with slower / incomplete resolution of imaging after miliary TB disease.[97] The hypothesis is that the already inflammatory / pro

fibrotic environment which is seen in the lung with silicosis compounds the local immune response triggered by TB, to give a more marked effect.

As mentioned above, smoking is a common exposure in resource poor settings and likely has a direct effect on lung development and decline, but its relationship with TB related lung damage is less clear. Smoking is thought to increase the incidence of TB disease. Perhaps the largest epidemiological study supporting this was a case-control study comparing the prevalence, in India, of ever-smoking and causes of death in 45,000 deceased adult males compared to 35,000 controls, published in 2003.[98] This study showed a relative risk of tuberculosis related death of 4.5 (95% CI 4.0-5.0) amongst urban ever-smokers compared to never-smokers, and a similar ratio of 4.2 (3.7-4.8) amongst rural ever vs. never smokers. The prevalence of current/previous TB disease amongst living ever smokers within the same population was noted to be higher than that amongst never smokers suggesting that this increased mortality in smokers may be due to increased TB incidence in this group, as well as worse outcomes amongst those with disease. A dose-response ratio was observed, with a higher prevalence of current/previous TB disease amongst those with a greater intensity of cigarette or bidi[1] use, perhaps suggesting a causal relationship between smoking and TB disease. In vivo murine studies have demonstrated increased susceptibility to MTB disease following cigarette smoke exposure, and cellular studies suggest alterations in macrophage, neutrophil and T-cell behaviour / differentiation with cigarette smoke exposure,[99] such that there is a plausible but as yet unconfirmed biological mechanism underlying this relationship. However, despite these data suggesting increased susceptibility to TB disease amongst smokers, and our existing understanding of smoking as an independent risk factor for COPD, no literature on the influence of smoking on the residual lung damage which persists after TB disease itself has been identified.

Bacterial co-infection may be another key factor influencing the host immune response to MTB infection. The lung is no longer thought of a sterile site, but one that is colonised by a range of bacterial, fungal, and viral organisms. The relationship between the prevalence, diversity, and burden of the lung microbiome and both tuberculosis disease / tissue responses remains largely unclear: the influence of the pulmonary microbiota on the rate of progression to active TB disease, its impact on the local immune response to mycobacterial infection, and its relationship to residual lung pathology remain poorly defined. Because the pulmonary microbiome is an exposure that changes over time, it is possible that the microbiome seen in the lung both prior to diagnosis, and the changes that occur during treatment in response to antibiotic pressure from the TB treatment (especially from the rifamycins, which have a broad spectrum of activity) are important in determining treatment response and sequelae.[100]

[1] Hand rolled cigarette widely smoked in South Asia, typically made of unprocessed tobacco wrapped in leaves

- HOST FACTORS

Literature on the relationship between host genetic polymorphisms and localised immune responses / lung pathology seen with TB infection are sparse. However, genetic polymorphisms are well known to be linked to the prevalence and progression of other respiratory conditions including COPD, and a role in determining the response to TB disease has been hypothesised.[89]

HIV co-infection is well known to be a key determinant of the extent and patterns of TB related lung damage: as described above imaging appearances during active disease are related to the degree of immune function, with classic findings of upper zone cavitation / fibrosis seen in those with preserved immune function, and atypical often more subtle features of airspace opacification / effusions / lymphadenopathy seen in those with advanced immune suppression.[83] A recent study has demonstrated different sputum MMP profiles between HIV infected and HIV negative TB patients, with higher levels of MMP-1 seen in HIV negatives with extensive cavitation on chest x-ray,[101] suggesting that differential MMP responses may be one mechanism underlying these differences.

- DURATION OF THE HOST IMMUNE RESPONSE

Recent imaging studies have used Positron Emission Tomography and Computerized Tomography (PET-CT) imaging to demonstrate ongoing areas of high metabolic activity with increased 18F-fluorodeoxyglucose (FDG) uptake suggestive of high glucose metabolism within lung lesions, even after completion of TB treatment. A prospective cohort study of 99 HIV-negative patients completing TB treatment in Cape Town demonstrated marked diversity in the treatment response of lung lesions between and within individuals: at the point of treatment completion, 72% of individuals still had lesion(s) with moderate-high intensity uptake on PET, with 28% of those cured showing at least one lung lesion with increased FDG uptake compared to baseline imaging. Amongst 50 patients re-imaged 1-year after TB treatment completion, only 8 of whom were diagnosed with recurrent disease, the majority had incomplete resolution of their metabolic activity. Patterns of imaging in those with ongoing high FDG uptake were largely consistent with TB related disease rather than other causes.[102] These data confirm the heterogeneity of response to TB treatment between lung lesions within individuals as above, and suggest that TB related metabolic activity continues long after TB treatment completion.

The reason for this remains unclear - the relationship between sputum MTB-RNA tested by GeneXpert and PET lesion intensity within the study above was weak only ($p=0.08$), but it remains possible that persistent viable mycobacteria drive ongoing metabolic activity within lung lesions after treatment completion. The current 6-month duration of standard short course treatment for a first episode of pulmonary tuberculosis was determined by acceptable rates of disease relapse / recurrence after cessation of therapy, rather than a measure of the timing of sterilisation of disease, and rates of

recurrence within 2 years of treatment completion for an initial episode are variably quoted as 2.6-9.7% within multi-site trials.[102] It may be the case that a significant number of patients do not achieve sterilisation with current short course TB treatment, and the ongoing high metabolic activity seen in lung lesions even after PTB treatment completion is a response to persistent, viable mycobacteria. Regardless of the reason for these ongoing lesions – whether this be a feature of persistent mycobacterial disease or an aberrant and protracted host immune response to disease that has been sterilised – the persistence of inflammation beyond the point of treatment completion is a key factor which may influence the patterns of residual post-TB lung damage, and their evolution over time.

2.4 POST-TB LUNG DAMAGE: NATURE & SEVERITY

Just as our understanding of the mechanisms driving TB related lung damage are incomplete, so our understanding of the nature of the residual lung damage that persists after treatment completion remains limited. Existing data on the patterns, prevalence, and evolution of post-TB lung damage are outlined below.

2.4.1 SPIROMETRIC DEFICITS

Much of the interest in post-TB lung damage to date has focused on the residual spirometric deficits that persist after TB disease. Three reviews of papers investigating this relationship have been published since 2011. The first by Erlich et al. included 8 epidemiological studies from South Africa that investigated the relationship between PTB and lung function parameters – this was not a systematic review, the methods of literature selection are not clearly described, and the studies included varyingly reported on FEV1, FVC, and patterns of spirometric deficits.[15] However, amongst them, a reduction in FVC in conjunction with an obstructive FEV/FVC ratio – that is a mixed pattern of spirometric deficit – was the most common picture seen, and the OR for airway obstruction following TB disease treatment was 2.6-8.9. In 2013 Allwood et al. performed a systematic review of English language studies describing the relationship between PTB and airway obstruction only - they identified 19 studies for inclusion, 3 of which were from South Africa and 1 from Lesotho, with no data from elsewhere on the African continent.[13] The three large population-based surveys included here (BOLD, PLATINO & PREPCOL) again confirmed a significant association between previous PTB and airway obstruction (OR 1.37 – 2.94). Finally, Byrne et al. performed a systematic review of studies describing the relationship between PTB and airway obstruction or bronchiectasis. The search strategy used here was somewhat unusual in that it identified only studies containing the MESH term 'respiratory tract disease' in addition to tuberculosis, and it is perhaps for this reason that it identified only 9 studies describing airway obstruction, with 1 study from South Africa and none from other African countries. However, again, the positive association between previous TB and airway obstruction was confirmed.[14]

Although none of these reviews were able to perform meta-analyses to measure the overall strength of association between TB disease and residual spirometric deficits due to the heterogeneity of studies included, their findings have been reinforced by more recent findings from the large multi-centre Burden of Obstructive Lung Disease (BOLD) study. Here, spirometry data were collected from age and gender standardised populations from 19 sites around the world with measurements taken from 14,050 individuals. Early publications from the BOLD network showed that across the 14 original country sites, a surprising 23.6% (302/1282) of adults ≥40 years identified as having airway obstruction with FEV1/FVC ratio<LLN for age were never smokers,[37] with a particularly high prevalence of moderate to severe airway obstruction (19.1%) seen in Cape Town where 11.9% of patients reported previous PTB disease.[103] A subsequent individual level regression analysis of data from all BOLD study sites investigated the relationship between self-reported previous TB disease (defined as a positive answer to the question "Has a doctor or other health care provider ever told you that you have tuberculosis?") and residual obstruction or restriction amongst adults ≥40 years, showed that amongst the low-middle income sites, the adjusted OR for obstruction was 3.11 (95% CI: 2.30–4.21) with a similarly high aOR for spirometric restriction of 3.19 (95% CI: 1.70–5.99) in those who had had previous TB compared to those who had not. Heterogeneity was marked for the low FVC estimates (I^2 79%) compared to the obstruction data (I^2 0%), for unclear reasons, but the pattern of findings was similar when continuous spirometric data were used: previous TB was associated with both decreased FEV1/FVC (β=−3.43, 95% CI −5.05–−1.80) and decreased FVC (β=−0.15, 95% CI −0.23–−0.06).[104] These analyses were controlled for age, sex, BMI and pack-years of smoking, but were not standardized or stratified for HIV status. They are restricted to adults ≥40years, and rely on self-reported previous TB to define exposure, but the scale of this study and the strengths of the associations seen very much support the influence of TB disease on long term spirometric outcomes. [104]

These data then include both individual clinical studies and large population level surveys, studies that have defined TB exposure using both self-report and microbiological / clinical diagnosis, and both cohort and cross-sectional studies. All have been consistent in identifying increased odds of both obstruction and spirometric restriction following treatment for TB disease.

Reduced FEV_1 volumes are known to predict mortality both amongst those with COPD, and the general population, with causes including respiratory failure as well as cardiovascular disease.[105] Recent data suggest that the FVC may be an additional, or even more important, driver of mortality even in the absence of persistent symptoms or an underlying diagnosis of lung pathology.[18 106] Whilst the studies on which these findings are based draw largely on data from non-TB populations in high resource settings, it is plausible that a comparable increase in mortality may be seen in relation to spriometric deficits in the post-TB population also.

2.4.2 STRUCTURAL PATHOLOGY

Whilst there has been much focus on spirometric deficits remaining after TB disease, no systematic reviews of residual structural lung damage were found in the literature prior at the time of starting this PhD. A systematic review was therefore completed as part of this PhD, and was published in 2016 (PLoS ONE 11(8): e0161176. Doi: 10.1371/journal.pone.0161176). Findings from this review are presented in Chapter 3 below, and are not therefore presented here.

2.4.3 RELATIONSHIP BETWEEN IMAGING AND SPIROMETRY

The majority of the studies of post-TB lung damage to date have measured lung pathology using either imaging or spirometry only, rather than focusing on the relationship between these parameters. The limited number of studies describing the relationship between these parameters are described below.

- CHEST X-RAY STUDIES

In her cross sectional study of 127 non-smoking adults who had previously completed PTB treatment 6-18 months previously in Mexico city, Baez Saldana demonstrated a negative correlation between post-TB spirometric values (absolute and % predicted FEV1 and FVC) and the total extent of pathology (any pattern) seen on chest x-ray (range 0-20).[107] For each unit increase in the radiology score, a decrease in FVC of 2.48% predicted (95% CI: -3.45 to -1.50%) and in FEV1 of 2.92% (95% CI: -3.87 to -1.97%) was observed. Amongst the cohort, the dominant patterns of abnormal spirometry were obstruction in 24% and restriction in 17%, and 97% of patients had some degree of radiographic abnormality including parenchymal fibrosis, bronchiectasis, and emphysema, but the relationship between these various imaging patterns and the spirometric deficits seen were not described, and dominant clinical disease phenotypes such as COPD or bronchiectasis were not allocated.

De la Mora also performed a cross sectional study in Mexico, inviting patients who has completed TB treatment in the past 3-years to attend for assessment, and comparing imaging findings in patients with (n=24) and without (n=46) fixed airway obstruction on spirometry following treatment completion. Those with airway obstruction had more lung quadrants affected by fibro-cavitatory changes, residual lung cavities, and mediastinal retraction/deviation on chest x-ray than those without.

In the prospective cohort study of 92 patients with biopsy / microbiologically proven TB pleural effusions conducted by Lai et al. in Taiwan, it was shown that at 6 and 12 months after the start of anti-TB treatment, patients with residual pleural thickening of at least 10mm seen on chest x-ray had lower FVC than those without thickening (FVC 73.6% vs. 81.4% at 6m, $p<0.01$ / 75.4% vs. 83.2% at

12m, p<0.01), although it should be noted that the extent of the pleural thickening seen was not recorded, and despite the reduction these FVC volumes are only marginally reduced.[108]

- CT IMAGING STUDIES

Three studies were identified which related details of CT imaging findings to spirometric abnormalities amongst individuals with pulmonary TB disease.

The first study recruited 595 patients with 'destroyed lung' - parenchymal tissue destruction and anatomical distortion following TB disease – who were identified from 21 hospitals in Korea at unspecified times following PTB treatment, and compared their imaging and spirometry findings. The median age of the cohort was 65 years and traction bronchiectasis was seen in 80% (333/419) of imaged patients. Amongst this group of patients, those with more lobes destroyed had lower % predicted FEV1 and FVC volumes.[109]

In their study of 101 adults self-presenting to hospital in India with symptoms and a history of previous TB disease, Panda et al. showed a high prevalence of spirometric deficits (1% pure obstruction, 40% restrictive, 35% mixed deficit) with 55% of patients having an FEV1<60% predicted. The extent of fibrosis, cavitation, and bronchiectasis were higher in patients with severe FEV1 limitation (<60% predicted), but summary measures of the extent of any radiological abnormality across the lung were not associated with spirometry results.[110]

Lastly, Lee et al investigated 97 patients who were found to have had spontaneously healed PTB within an ongoing population-based cohort study of 8697 adults in Korea, based on radiological sequelae of PTB seen on chest x-ray, and a positive IGRA blood test. These patients had a higher prevalence of airway obstruction compared to the rest of the population (13.4% vs. 7.4%, p<0.05). CT imaging and spirometry in this group showed that amongst the 82 patients with a positive IGRA, both the total number of lobes affected by TB sequelae and the extent of emphysema, were positively associated with the presence of spirometric airway obstruction (p=0.0461 & p=0.0084).[111]

Findings from these studies are consistent in suggesting that more extensive structural pathology is correlated with a greater extent of spirometric abnormality following PTB disease, and that fibrocavitatory disease, bronchiectasis, emphysema, and pleural thickening dominate. However, we still have little understanding of whether these patterns vary between those with spirometric obstruction or restriction, or whether there are distinct phenotypes of post-TB lung damage who have had heterogeneous responses to the lung insult of TB disease.

2.4.4 IMPACT OF HIV CO-INFECTION

Imaging data from the point of TB diagnosis consistently show that HIV infection modifies the pattern of chest x-ray changes seen in the context of active TB infection, and that HIV positivity is associated with less marked cavitatory lung damage and 'atypical' imaging appearances.[83] However, there is a remarkable paucity of data on the relationship between HIV infection and post-TB lung damage.

Only two studies reporting on the relationship between HIV infection and patterns of residual spirometric impairment following TB disease were identified, both of which suggest no statistically significant association between HIV and ongoing spirometric deficits: Hnidzo et al showed no difference in the lung volumes observed amongst HIV infected / uninfected gold miners with the same number of previous episodes of TB disease in South Africa,[112] and Mbatchou et al. showed no univariate association between HIV infection and lung function impairment following TB treatment amongst 296 adults treated for PTB in Cameroon within the preceding 3-years.[113]

Only one imaging study which included disaggregated imaging data for both HIV-infected (n=12) and uninfected (n=98) patients following PTB treatment completion was identified.[114] In this study in Thailand, all patterns of radiographic abnormality were more common in HIV-negative compared to HIV-positive adults following TB treatment completion, however differences were statistically significant for reticular fibrotic change only which was seen in 70% (69/98) of HIV negative and 25% (3/12) of HIV positive patients.

Given the well documented 'atypical' findings seen on chest imaging in HIV infected adults at TB diagnosis, the lack of evidence for differences in the nature / severity of post-TB lung damage between HIV-positive and negative groups is surprising. Data from high-income settings suggest that HIV disease is directly associated with increased odds of airway obstruction, and a more rapid decline in lung function over time,[25] independently of TB disease, and it may be the case that reduced amounts of TB-related lung damage amongst HIV-infected adults is somewhat offset by the direct impact of HIV-disease on the lung. However, further investigation of these relationships is required. Factors such as the timing of ART initiation and the degree of immune-compromise at the time of TB disease must be considered.

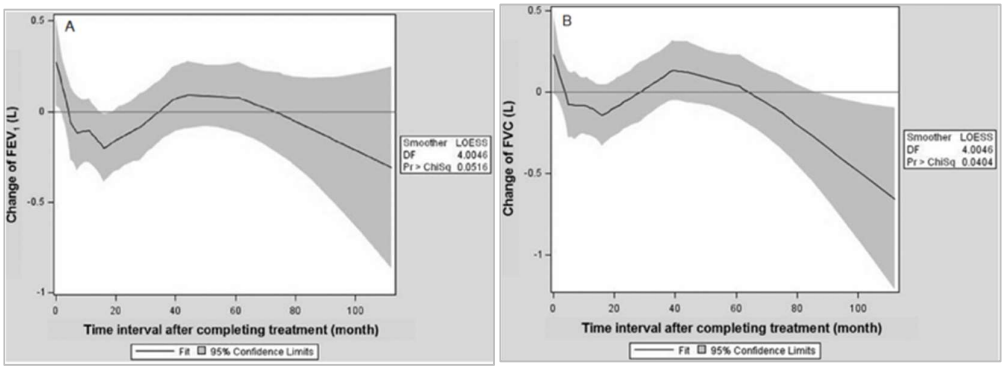
2.5 POST-TB LUNG DAMAGE: CHANGE OVER TIME

There are few prospective data tracking lung function or imaging after TB treatment completion, and as such we have a limited understanding of how post-TB lung damage evolves over time. Only two studies aiming to map changes in spirometry over time after PTB treatment were identified. In his

study amongst male adult gold miners in South Africa, Hnidzo et al. compared the spirometry measurements taken at varying intervals from a clinical / radiological / microbiologically defined episode of TB disease.[112] Improvement was seen from 13-18 months from TB treatment completion, with 'stabilisation' at an average reduction of 153ml in absolute FEV1 and 96ml in absolute FVC volumes after this point. When FEV1 was considered as % predicted rather than an unstandardized volume, the % predicted loss seems to increase with time from disease episode resulting in more obstruction over time. However, these are cross-sectional data from different individuals at different time points from TB disease treatment rather than true prospective data tracking change in spirometry in the same individuals over time and were obtained from a very specific population of male gold miners with concurrent occupational exposures such that they cannot be extrapolated.

In a smaller study of 115 patients who had performed 162 pulmonary function tests within 5-years of TB treatment completion identified from a tertiary referral hospital in Taiwan, Chung et al used their data to construct partial models predicting lung function over time, controlling for age, weight and height. The median age across the cohort was 59.3 years. These models suggest a biphasic relationship with nadir lung function at 18-months after treatment completion (Figure 4), but again it should be noted that the number of repeated measures included into these models was limited, the sample size small, and 26% of the cohort had had at least 1 non-tuberculous mycobacteria isolate, such that again data from this study cannot be extrapolated.

Figure 4: Predicted change in FEV_1 and FVC over time from TB treatment completion (Chung et al.)



Only one imaging study with repeated chest imaging after PTB treatment completion was identified – this was based in Romania and used repeat chest x-rays to determine the proportion of retreatment patients who had cavitation at the start of treatment, the end of treatment, and 6-months after this. Although the study findings suggested a resolution of cavitation over time, with prevalence falling from 84% (36/43) at treatment initiation to 68.8% (22/32) 6-months after treatment completion, the study was limited by marked loss to follow up and a limited highly selective sample population.[115] Given the limited amount of prospective imaging and spirometry data available, the extent of respiratory recovery or ongoing decline experienced after PTB disease remains unclear, and the heterogeneity of responses within the patient population poorly defined. Understanding this change

over time will be key to understanding outcomes of those surviving PTB treatment, and determining whether / what ongoing support patients require.[116]

2.6 POST-TB LUNG DAMAGE: MORBIDITY & MORTALITY

Perhaps of greatest relevance to patients is the impact that any residual post-TB lung damage may have on their lives and livelihoods. Existing data on the relationship between post-TB lung damage and outcomes including impairment of quality of life, persistent respiratory symptoms, reduced functional capacity, rates of ongoing respiratory exacerbation and hospitalization, and mortality are presented below. Also, of relevance in low-resource, high TB prevalence settings are the risks of TB retreatment associated with symptomatic post-TB lung damage, and the financial impact of disease. Existing data on the relationship between PTLD and these outcomes are also reviewed.

2.6.1 MORBIDITY

Only 7 studies describing the morbidity related to post-TB lung damage measured using spirometry or imaging were identified – the majority included cross sectional data, and reported on a single measure of morbidity only (Table 3).

Table 3: Spirometry / imaging studies reporting patient centred outcomes in relation to spirometric or imaging deficits

Study	Location	Patient population	Exposure	Outcome	Findings
Imaging studies					
Godoy et al. [117]	Brazil	18 patients, completing MDR TB treatment	Extent of CXR damage	6-minute walk distance	100% (3/3) of those with Grade III damage failed to reach expected distance, compared to 64% (7/11) of those with Grade I damage (no statistical comparison between groups)
Banu Rekha et al. [118]	India	198 patients who had first episode of PTB median 16.5yrs previously	Extent of CXR Pathology	SGRQ score	No statistically significant difference in symptoms, activity, impact, or overall SGRQ score between in those with ≤2 vs. >2 CXR damaged zones on imaging
Rhee et al.[109]	Korea	595 patients with ≥1 destroyed lung lobe following previous PTB	Number of lobes destroyed on CXR	Respiratory exacerbation rate	Number of exacerbations per year increases with number of lobes destroyed.
Panda et al. [110]	India	105 patients completing PTB treatment, first episode	CT imaging findings	Any dyspnoea (mMRC1-4)	Positive correlation between extent of fibrosis, bronchiectasis, nodules, summary pathology scores, and presence of dyspnoea.
Ryu et al. [119]	Korea	169 patients with TB destroyed lung (median 25-50% of the lung destroyed) at median 31m post-treatment completion	N/a	Hospitalisation Pneumonia Death, all cause Death, respiratory	64% (108/169) hospitalised 57% (96/169) pneumonia episode 28% (47/169) died, all cause 68% (32/47) of deaths respiratory No comparison group, median 31m follow up.

Spirometry studies					
Baez Saldana et al.[107]	Mexico	127 patients, median 11 (6-18m) post treatment completion	FEV1 & FVC	MRC dyspnoea scores	Negative correlation between MRC dyspnoea scores and FEV1 and FVC values (absolute & % predicted) in univariate analyses
Pasipanodya et al. [120]	USA	105 patients completing PTB treatment	FEV1, FVC, Ratio, MEF25-75	SGRQ scores	Negative correlation between symptom, activity, impact and total SGRQ scores and all spirometric measures

SGRQ: St George's Respiratory Questionnaire; MRC: Medical Research Council

Two studies investigating the relationship between post-TB lung damage and quality of life, measured using the St George's Respiratory Questionnaire (SGRQ), were identified. These were both cross sectional studies but had different findings: no relationship was demonstrated between the extent of imaging pathology and quality of life amongst 198 patients who had completed PTB treatment in India a median of 16.5 years previously in the study by Banu-Rekha et al.,[118] but a negative correlation was seen between spirometric indices and the SGRQ scores in the study by Pasipanodya in the USA which measured these parameters at the time of TB treatment completion.[120]

Two studies investigating the relationship between the extent of PTLD and dyspnoea both showed a negative correlation, with increased breathlessness seen in those with more extensive imaging pathology or spirometric deficits.[107 110] Only one study looking at the relationship between the extent of structural pathology and the 6-minute walk test was identified – this was performed in 18 patients completing MDR TB treatment only, but suggests that there may be reduced walking distance in those with extensive pathology on x-ray.[117]

It is of note that the only two studies identified which investigated the rate of respiratory exacerbations occurring in relation to post-TB lung damage had been conducted in patients with extensive lung destruction. Ryu et al. identified 169 patients between 1994-2009 who had had TB disease a median of 25 years previously, and who now had destruction of at least half of a hemithorax on CXR or CT imaging. Patients were followed for a median of 31 months (0-172 month) and during this period 56.8%(96/169) experienced a pneumonia, 29.6%(50/169) experienced respiratory failure, and the overall mortality was 27.8%(47/169).[119] Rhee et al. recruited 595 patients with a median of 2.6 lobes destroyed, and showed the number of exacerbations experienced per year increased with the total number of lobes destroyed.[109] Both studies were vulnerable to significant selection bias given recruitment from existing hospital patients only, as well as a survival bias given patients were identified many years after the initial TB disease episode. Nevertheless, they suggest that those with extensive post-TB lung damage are at risk of recurrent respiratory exacerbations. Unfortunately no data on the risk of respiratory exacerbations amongst adults with milder forms of PTLD were identified in the literature, but the suggestion that a broad range of chronic lung pathology may increase risk of respiratory admissions in resource poor settings is supported by recent data from a case-control study of risk factors for hospitalization with pneumonia amongst adults in Blantyre, Malawi, which showed

that adults with a previous history of chronic respiratory symptoms (usual cough or sputum, breathlessness or wheeze) or respiratory diagnosis (emphysema, asthma, chronic bronchitis) were at increased odds of admission with pneumonia in this setting.[20]

None of the studies identified here reported on patient experiences of stigma, in relationship to post-TB lung disease. Previous work from Malawi has suggested that cough, HIV and TB disease are often conflated in public opinion,[43] with activities surrounding screening of patients with cough for HIV and TB disease compounding this view, with the result that chronic cough can be highly stigmatizing in this setting. It may be that this is highly relevant to patient experiences of ongoing respiratory symptoms following PTB disease.

In addition, no studies comparing the morbidity experienced in relation to post-TB lung damage between HIV-positive and HIV-negative groups were identified. HIV infected individuals are known to be at increased risk of severe acute respiratory tract infections across all age groups - the bacterial pathogens causing these infections are likely similar to those seen in HIV uninfected adults, with an additional risk of opportunistic infections also.[24] In addition, HIV is a known to be an independent risk factor for chronic airway, parenchymal, and pulmonary vascular disease, both increasing the incidence of abnormalities, and in the case of chronic airway obstruction accelerating the rate of lung function decline.[24] It is plausible that the morbidity experienced by HIV positive individuals with residual lung pathology at TB treatment completion is different from that experienced by HIV negative individuals, particularly with respect to the rate of ongoing infections and decline in lung function, and this merits further investigation.

Taken together, the data identified here do suggest that post-TB lung damage may well be associated with long-term adverse patient outcomes including impaired quality of life, ongoing breathlessness, functional impairment, and respiratory exacerbations. However, rigorous prospective data are required to confirm these results, in both HIV positive and negative groups, and will be needed to support interventions to mitigate these outcomes in this population.

2.6.2 MORTALITY

Data from both resource rich and resource poor settings suggest an increased mortality amongst adults, even after completion of treatment for active TB disease.

A recent prospective study of 10,662 adults undergoing treatment for TB disease in Vietnam, with a median 2.9 year follow up duration, showed a mortality rate of 8.9% across the duration of the study, with 60% of deaths occurring in the period after treatment completion, and an age and gender standardized mortality ratio amongst those treated for TB disease of 4.0 (95% CI: 3.7-4.2) compared to household controls.[121] Older data from a cohort of 124 Malawian adults diagnosed and treated for

PTB during 1995 who had their outcomes ascertained 6-years later showed that 46% of individuals had died in the period following treatment completion – although the majority of the cohort had advanced HIV disease, high rates of mortality were seen even amongst the HIV- uninfected group.[122]

Data from the US suggest an increased mortality in adults completing treatment for PTB, compared to those diagnosed as having latent TB infection, after treatment completion. State-wide registries from 3 states (Texas, Massachusetts & Seattle) were used to compare age, gender, ethnicity/race, nativity and HIV standardized mortality rates between adults who had completed treatment for TB between 1993-2002 and those who had received a diagnosis of latent TB infection during the same period, with a duration of follow up between 6-16 years. A total of 11135 individuals were followed over 119 772 person-years of follow up. Causes of death were not assessed, but adjusted mortality rates were 8.3/1000 vs. 1.2/1000 person-years for those treated for PTB compared to those diagnosed with latent disease, and the adjusted mortality hazard was 7.2 times higher for the PTB group compared to the latent TB infection group.[123]

Together, these studies suggest a lasting, ongoing impact of a treated TB disease episode, beyond the point of TB treatment completion. Potential mechanisms underlying this increased mortality were explored in a systematic review of the causes of death amongst TB patients after treatment completion, conducted in 2011.[124] This included 22 studies – largely retrospective, with a range of follow up from 202 days to 7 years – and showed that in low income, high prevalence settings, HIV disease especially with advanced immunosuppression, smear negative disease and malnutrition were identified as risk factors for case fatality. In wealthier countries with a lower disease burden, socioeconomic features including alcohol and drug abuse, comorbidities often associated with age (renal disease, diabetes, respiratory morbidity) and extensive or cavitatory disease on chest x-ray were associated with mortality. It is possible that residual lung damage following PTB treatment is a factor contributing to ongoing mortality in resource poor settings, but no studies directly assessing this relationship were identified in the literature.

2.6.3 RISK OF TB RETREATMENT

- RISK OF RECURRENT PTB DISEASE

The risk of incident TB disease is known to be higher in those who have already been treated for PTB, compared to those who have never been treated. A recent review of prevalence survey data used to evaluate the impact of the ZAMSTAR study[125] – a large community based intervention study of TB control strategies in 24 communities in Zambia and South Africa – showed that 18.5%(165/894) of sputum MGIT positive TB cases identified came from patients who had previously been treated for disease, that those who had been previously treated had a higher burden of cough (43% vs. 34%), and that amongst the HIV-negative individuals screened, TB disease prevalence was higher in those who

reported previous PTB compared to those that were treatment naïve (3.32/100 vs. 1.78/100 in South Africa, and 0.88/100 vs. 0.34/100 in Zambia).[126] The reasons underlying the higher prevalence of TB disease amongst adults who had previously been treated may include ongoing exposure to the same set of risk factors: individuals with repeat episodes may have a genetic milieu that increases risk for disease, patterns of social interaction that consistently increase rates of exposure, and long-standing socioeconomic conditions that compromise their ability to clear mycobacteria when exposed. As discussed above, there may also be a certain amount of disease relapse following incomplete resolution of the original infection.

However, it is reasonable to ask whether residual lung damage is a contributing factor here. Structural lung damage in which the local pulmonary immunity is disrupted may make it harder for individuals to both clear an initial episode of disease, and for them to contain mycobacteria inhaled with re-exposure. This hypothesis is perhaps supported by greater difference in TB prevalence between those that have / have not had previous PTB amongst the HIV negatives compared to HIV-positives within the ZAMSTAR prevalence data,[125] in whom we suspect residual TB related lung damage to be more marked. Other potentially supportive data for the role of structural respiratory damage in impairing the host ability to combat mycobacterial disease comes from studies in the gold mining populations of south Africa, in whom the odds of MTB disease has been shown to increase with the degree of silicosis, and and in whom NTM disease is associated with previous TB disease, focal radiological scarring, and the degree of silicosis.[96] Mechanistic work to understand the biological mechanisms through which the immune response to TB exposure is altered in the structurally damaged lung, as well as epidemiological studies to compare recurrence rates in those with / without post-TB lung damage will be required to further understand this.

- RISK OF EMPIRICAL RETREATMENT

In addition to potentially increasing the rate of true TB disease relapse or reinfection, PTLD may increase the risk of empirical or inappropriate TB retreatment. As shown above, there is a suggestion in the literature that individuals with residual lung damage following PTB treatment have a higher prevalence of ongoing respiratory symptoms. Management of persistent respiratory symptoms, which may include chronic cough and sputum production, is challenging in resource poor settings with limited access to diagnostics, and may result in empirical TB retreatment in the absence of true TB disease recurrence.

No studies investigating the performance of clinical screening tools or clinician led empirical TB diagnoses in retreatment patients were identified in the literature. Similarly, no prospective data describing the proportion of adults with chronic respiratory symptoms /persistently positive TB symptom screens following an initial episode of PTB disease, and the clinical management of these symptoms have been identified. However, data from a prospective observational study in Harare,

Zimbabwe from 2011-2013 showed that 36% (118/328) of symptomatic patients who had been started on TB retreatment for a presumed recurrent episode of TB disease infact had no microbiological evidence of disease after extensive testing with Xpert, MODS, and liquid and solid TB culture of sputum. This study also showed that of those within this group who received an X-ray 39/53 had evidence of long-term structural lung pathology including bronchiectasis and atelectasis. It may be the case that some of these individuals had residual lung damage from a previous episode of disease, which let to ongoing chronic respiratory symptoms and may have resulted in empirical retreatment.[127]

Given the recent calls to increase our focus on active case finding for recurrent TB disease amongst patients who have already had an episode of disease as a means of better controlling transmission[128], better understanding of the impact of chronic symptoms on treatment decisions, and the accuracy / role of screening techniques including symptom screening / chest x-ray use in patients who have already had an episode of PTB disease is required.

2.6.4 FINANCIAL IMPACT

The high costs incurred by patients and their households, both prior to diagnosis and during TB treatment, have been well documented, even in settings where TB care is provided for 'free' within existing public health services.[129] More recently, these costs were shown to be associated with adverse patient outcomes – in a study in Lima, Peru, patients experiencing 'catastrophic' costs prior to/during treatment (defined as 20% of annual household income, and experienced by 39% of households) had an increased incidence of adverse patient outcomes (defined as death, treatment default or failure, or disease recurrence within 2-years).[130] Mitigating the economic impact of TB disease has since been included in the WHO End TB strategy, with an aim that no TB-affected family should face catastrophic costs due to TB by 2020.[64]

To date, however, there has been little attention paid to the ongoing direct / indirect costs incurred by families after TB treatment completion, with recent reviews of TB related patient costs including data from pre-diagnosis and treatment periods only.[129] It is indeed likely that out of pocket expense and loss of income are most pronounced early in TB disease, and existing data suggest that these decline towards the latter stages of treatment.[131] However, it is possible that ongoing costs persist at a low but still meaningful way beyond treatment completion in relation to residual physical morbidity or difficulty regaining employment. Global burden of disease calculations which aim to quantify the disability and quality adjusted life years (DALYs & QALYs) experienced in relation to TB disease, and which are used to calculate the cost-benefit of TB screening and prevention interventions currently consider the TB disease state to end at the point of TB treatment. However, if ongoing costs related to residual disability are widespread, this approach may require review.[9 132 133]

2.7 POST-TB LUNG DAMAGE: MEASUREMENT OF DISEASE AND OUTCOMES

As highlighted above, no comprehensive measurement frameworks or severity scores, which included multiple respiratory parameters and have been validated against patient outcomes, have been identified for post-TB lung damage. In the absence of validated measurement tools for this condition, approaches taken to the measurement of disease and outcomes in other lung diseases including bronchiectasis, COPD, and pneumonia are reviewed here. This literature has been used to guide the approach to the assessment of post-TB lung damage used in Chapter 5 below.

In addition, existing work on the measurement of chronic lung disease in Africa has identified many challenges, for example with the standardization of measurements and selection of reference ranges for comparison. These challenges will also be discussed below.

2.7.1 MEASUREMENT OF LUNG PATHOLOGY

In order to determine which aspects of post-TB lung damage may be relevant to patient outcomes, the clinical parameters included within key prognostic scores used in bronchiectasis and COPD, and the outcomes against which they have been validated were reviewed (Table 4).

Table 4: Prognostic respiratory scores / outcome validated scores

Prognostic tool	Clinical parameters included	Outcome of interest
Non-CF bronchiectasis		
FACED score Martinez-Garcia, 2013[134]	Age >70 yrs mMRC dyspnoea score ≥3 FEV1 <50% predicted >2 lobes affected on CT Chronic pseudomonas colonisation	5-year all cause mortality
Bronchiectasis severity index (BSI) Chalmers, 2014[135]	Age BMI FEV1 % predicted Previous hospital admission Previous exacerbations MRC dyspnoea score Colonisation with pseudomonas / other bacterial organism Radiological severity - ≥3 lobes / cystic bronchiectasis	Hospital admission 4-year all cause mortality
Chronic Obstructive Pulmonary Disease (COPD)		
CODEX index Almagro, 2014[136]	Charlson index of comorbidity mMRC dyspnoea score FEV1% predicted Previous severe exacerbations	3-month & 1-year all cause mortality Hospital admissions
BODE score Celli, 2004[137]	FEV1 % predicted BMI MRC dyspnoea score 6-minute walking distance	1-year all cause mortality
DOSE score Jones, 2009[138]	MRC dyspnoea score FEV1% predicted Current smoking Previous exacerbation frequency	Clinical COPD questionnaire score Current respiratory failure (SO2<92%) Current 6-minute walk distance Health care use / hospitalisation

ADO score Puhan, 2009[139]	Age MRC dyspnoea FEV1 % predicted	3-year all cause mortality

Each of these prognostic scores was noted to include multiple respiratory parameters to capture disease severity, based on the finding that individual measures of respiratory disease have poor prognostic power. The use of multiple parameters to characterize respiratory disease is further supported by the increasing focus on disease phenotyping across parameters within the literature for many of these disease conditions.[142 143]

Spirometry was a widely used measure of respiratory impairment, with imaging parameters appearing as a key feature in bronchiectasis prognostic scores. The degree of breathlessness was found to have prognostic relevance in both COPD and bronchiectasis, and age, BMI, and comorbidities were relevant for outcome in various scores. Several of these scores include the number of previous respiratory exacerbations as a predictor of long term outcome. Measurement of this parameter is unlikely to be appropriate in the assessment of post-TB lung damage, given our interest in new pathology caused by the recent TB episode rather than long standing progressive disease. Similarly, although respiratory colonization with pseudomonas / other pathogens is a strong predictor of outcome in bronchiectasis, the availability of respiratory culture is limited in many resource poor settings including Malawi, such that measurement of this parameter is unlikely to be feasible.

2.7.2 INTERPRETATION OF SPIROMETRY DATA

From this review it is clear that measurement of spirometry is key to the assessment of PTLD. However, several controversies exist in the approach taken to standardizing spirometry data and defining patterns of deficit, and the literature on these issues will be reviewed here.

- SELECTION OF THE REFERENCE RANGE

When presenting spirometry data, it is important to describe how far from normal the volumes measured are. Conventionally this is achieved by standardising FEV_1 and FVC volumes, relative to the normal values which might be expected from a patient of that age / height / gender. However, there is much debate over which reference population these 'normal' values are drawn from, and whether standardized data should be presented as a % predicted values or z-scores. Four different sets of reference ranges for 'normal' lung volumes are available for use in the Malawian setting: NHANES III Caucasian, NHANES III African American, GLI-2012, and local Malawian reference ranges.[34 144 145] The populations from which these reference ranges were derived, key features about the models used to generate 'normal' curves, and the normal values available for each of these reference ranges are outlined below (Table 5). Of note – all of these reference ranges are derived from cross sectional data

from individuals of different ages, rather than prospective cohort data following individuals up over time to truly document change with increasing age, so all are subject to a cohort effect.

Table 5: Comparison between spirometry reference ranges

Reference range	Derivation	Model	Available parameters
NHANES III Caucasian (Hankinson, 1999)[144]	898 male / 1383 female Caucasians, aged 8-80yrs. Asymptomatic lifelong non-smokers	Model includes age and standing height. Mean values of FEV1 and FVC derived for 2yr age and 2cm height intervals 2 linear models for each gender generated, for young /older adults (cut point at 20yrs for males / 18 yrs female)	Predicted & LLN values for: FEV1, FEV6, FVC, PEF, FEF25-75, FEV1/FVC
NHANES III African American (Hankinson, 1999)[144]	1027 male / 1481 female African-Americans, aged 8-80yrs. Asymptomatic lifelong non-smokers	Includes a correction term for lower observed lung volumes, and marginally lower FEV1/FVC ratio in African Americans.	Predicted & LLN values for: FEV1, FEV6, FVC, PEF, FEF25-75, FEV1/FVC
GLI-2012 (Quanjer, 2012)[145]	Asymptomatic life long non-smokers with data available on sex, age, height, self-reported ethnicity, and spirometry, aged 3-95yrs (31,856 males / 42,331 females) Regression performed separately for 4 groups: Caucasian, Black, SE Asian, NE Asian, and final model includes adjustment for each of these. An 'other' category added, averaging the results of these groups. Data for black adults derived from 4 African American cohorts including 1520 males / 2025 females	Height (to 1dp) and age (to 1dp) standardised Single curve generated for all age groups, using a spline African American scores lower than Caucasian scores: FEV1 -13.8-14.7% FVC -14.4-15.5% Ratio -0.6-0.8%	Z-scores & LLN values for: FEV1, FEV6, FVC, PEF, FEF25-75, FEF 75, FEV1/FVC
Local Malawi reference ranges (unpublished)[34]	Post-bronchodilator spirometry from healthy non-smokers 242 males / 383 females Urban Blantyre, 2013-2014	Height and age (rounded to 0dp) standardised	Predicted & LLN values for: FEV1, FEV6, FVC PEF, FEF25-75, FEV1/FVC

Much of debate surrounding which of these reference ranges to use centres on the role of ethnicity in determining normal lung function. The relationship between ethnicity and lung volumes is highly confounded by socioeconomic situation (SES) and the associated early life exposures – that is, low SES is independently associated with ethnicity within / between countries, and is also an independent predictor of lung volumes. Because SES is not reported in the large prediction models used to generate the reference ranges above, and as few studies have compared lung volumes across ethnically similar individuals from diverse socioeconomic backgrounds, or ethnically diverse individuals from similar socioeconomic and environmental backgrounds, it has proved difficult to identify the independent impact of these variables on lung function.[36]

Theoretical arguments against an ethnically driven variation in lung volumes, and therefore against using ethnic corrections for lung volume standardisation are based on the premise that 'normal' lung

volumes have presumably evolved to be maximally efficient for the body's function, and that there is no biological reason why this efficient fixed point should differ between ethnic groups. Some have argued that rather than being data driven, the assumption of different 'normal' volumes between ethnic groups is deeply rooted in 19th century writings on slavery and concepts of the racial 'inferiority' of black individuals.[146] In addition, many argue that the notion of distinct and homogenous categories of ethnicity and race is a social rather than biological construct – the genetic heterogeneity between black individuals in Africa is marked, and there are likely to be many distinct genetic sub categories within this 'ethnic' group, which cannot be captured in simple ethnicity corrections. In addition, even if we accept that there is one universal set of norms for lung volumes, use of the Caucasian reference ranges described above to represent these norms assumes that the populations from whom these reference ranges were derived lived in optimal environments for the development of lung function, but we have no data on the SES or maternal health of individuals included in these derivation cohorts on which to base this assumption.

Theoretical arguments in favour of using ethnic corrections may include that different ethnic groups have widely observed different body characteristics: it is possible that these are genetic / endogenous and have evolved over time in response to long-term differences in environment to become 'norms', and variation in 'normal' lung volumes may be one such characteristic. In addition, many note that there is much less variation in the FEV1/FVC ratio between ethnicities than the variation seen in the FEV1 and FVC volumes themselves, suggesting that perhaps it is the ratio which is the efficient 'fixed point' to which we have all evolved, with variation in absolute lung volumes around this.

Given this complexity, the selection of which reference range to use is largely a judgement based on the intended purpose of the data collected, and the impact of over/under estimation of abnormality which would result. In the BOLD study described in Chapter 4 below, the main aim was to compare general findings in the Malawian population with those of other populations, in other settings, and the widely used NHANES III Caucasian reference range was therefore chosen for ease of comparison. However, in the cohort study presented in Chapter 5 below, the main aim was to describe differences within a Malawian cohort, rather than with reference to an external group. A reference range with maximal sensitivity to differences between Malawian individuals was therefore required. As will be discussed in Chapter 4, infact the NHANES III has high expected lung volumes and tends to classify a large proportion of Malawian as having abnormally small lungs, such that it has limited discriminative ability between individuals in this setting.[34] In theory the Malawian reference range would be ideal for an internal comparison, but confidence in the predictive models used to derive this range is limited: the R^2 values for FEV_1 and FVC in males and females within the model ranged from 0.31-0.45, suggesting that the 'fit' of the predictive models for this population is poor and explains only between 31-45% of the variation in the true lung volumes observed. Use of these equations to derive normal values is therefore unlikely robust. Finally, both the GLI and NHANES III African-American equations

are derived from US based African American populations, and set the expected age/height standardised lung volumes rather lower than NHANES III Caucasian reference range. These therefore provide more conservative estimates of abnormality, and are likely to make identification of those with clearly limited lung volumes from within this cohort more robust. The GLI equations are more widely used and employ z-scores / LLN values, such that they take into account the distribution of observed data in the reference population, as well as the mean predicted value.[145] 'Normal' values derived from GLI-2012 'Black' reference group were therefore selected for use for all primary data analysis within the cohort study described in Chapter 5 below.

- MEASURING DISEASE SEVERITY: Z-SCORES VS. % PREDICTED VALUES

Whilst use of % predicted scores to interpret the severity of spirometry deficits is widespread in clinical practice, it is in some ways statistically flawed – although this approach takes into account the predicted mean value for a group of patients of a specific height, age and gender, it does not account for the expected variation around this normal value for a given group. In contrast, z-scores are measures which are standardised according to the data distribution seen within the reference population: a reading which is 1 z-score away from the 'expected' value is the equivalent of 1 standard-deviation from the mean. Because they take into account both the mean 'normal' estimate, and the expected variation within the reference group for any individual, z-scores are perhaps statistically more appropriate measures of severity.

Whilst % predicted scores were used for the BOLD data analysis presented in Chapter 4 below, in keeping with the methods used by BOLD studies in other settings, analysis of data collected from the post-TB cohort described in Chapter 5 instead used z-scores.

- DEFINING PATTERNS OF ABNORMALITY

Spirometry data are most accurately presented as continuous variables, with % predicted values or z-scores used as a measure of abnormality. However, for ease of interpretation and in keeping with clinical practice, spirometry results are instead often classified into those that are normal / abnormal, and into patterns of deficit.

A fixed FEV1/FVC ratio of 0.7 has been classically used as the cut off to define airway obstruction in the literature. However, this ratio is known to vary with age, with a non-linear decline from early adulthood even amongst normal 'well' individuals. Use of a fixed ratio cut off of 0.7 therefore tends to underdiagnose obstruction in younger patients, and over diagnose in older patients. In addition, although average ratio values remain constant at a given age / height across all ethnicities (except SE Asians), the expected scatter of values varies between ethnicities and age groups and use of a fixed ratio does not account for this. Similarly, absolute % predicted cut offs have been used to define 'abnormal' FEV_1 or FVC volumes. However, these are controversial: as explained above, % predicted

values ignore variation in the distribution of data around the average reading for patients of a given age / height, and as such are misleading measures of abnormality. Perhaps related to this, the % predicted cut points at which lung volumes are considered abnormal vary widely between patient guidelines and are poorly supported by relationships with patient outcomes (Table 6).[147]

Table 6: FEV1 severity classification, amongst those with reduced FEV1/FVC ratios

	ATS/ERS	GOLD 2017	GLI 2012
Mild	≥70%	≥80%	>60%
Moderate	60-69%	50%≤≤FEV1<80%	40-60%
Mod-Severe	50-59%		
Severe	35-49%	30%≤≤FEV1<50%	<40%
Very severe	<35%	<30%	

Instead of using fixed % predicted values and a constant FEV_1/FVC ratio to define abnormality across the whole population, lower limit of normal (LLN) values which take into account both the location and spread of data can be used to define abnormality at the individual level.[148] A LLN cut off of 5% or the 5th percentile can be used to identify measurements which are greater than 1.64 standard deviations or z-scores away from the mean in a reference population of individuals with the same age / height / gender. Classifying all measurements which fall outside of this range as abnormal accepts a false +ve rate of 5% for all patients, whereby 5% of a normal population would be mistakenly classified as having abnormally low readings. The result of using the LLN cut offs for abnormality rather than fixed % predicted cut offs is that where 'normal' data have wider spread amongst patients of a given age / gender / height, fewer people are classified as abnormal. This is particularly relevant for older age groups where the spread of data tends to be wider, standard deviations are larger, and the LLN is lower than the 80% fixed cut off used in GOLD, such that fewer older individuals will be classified as having abnormal lung volumes if the LLN approach is used.[145]

- DESCRIBING PATTERNS OF DEFICIT

Spirometry alone is capable of detecting airway obstruction, as this defined by the presence of a reduced FEV_1/FVC ratio alone. Use of the term 'obstructed' to describe those with a low ratio on spirometry is likely an appropriate reflection of underlying lung pathology. However, use of the term 'restriction' to describe spirometry readings where the FEV_1/FVC is preserved but FVC volume reduced is likely misleading as true restrictive pathology is defined by a reduced total lung capacity (TLC), and diagnosis therefore requires formal measurement of lung volumes, rather than spirometry alone. In the context of post-TB lung damage in particular, it is not possible to make assumptions about the degree to which a low FVC measurement represents a low TLC and true underlying restrictive pathology: the true prevalence of restrictive pathology within this cohort is not known and the positive predictive value of a low FVC for this is therefore unclear. In addition, a reduced FVC can be the result of severe obstruction with gas trapping causing increased residual volumes (RV) / reduced expired

volumes, whilst in others the presence of a normal/slightly high ratio with proportionately reduced FEV1 and FVC may be caused by submaximal inspiratory or expiratory effort rather than true underlying lung pathology. For all of these reasons, use of the terms 'restriction' to describe those with a low FVC is likely misleading within this patient group, and the term 'low FVC' may be more accurate. In keeping with this, it is not possible to define a group with mixed disease using spirometry only within this group – both restrictive and obstructive pathologies can cause reduction in FVC, such that it is not possible to determine the degree of restrictive pathology in a patient who is obstructed, using spirometry alone.

- MEASURING REVERSIBILITY

Reversibility describes a proportional change in lung volumes in response to bronchodilation, but the definition of this varies between guidelines with different denominators used for calculation: the ATS/ERS guidelines suggest that any change in volume is measured in reference to the best pre-bronchodilator FEV1 value, whilst the GLI-2012 guidelines suggest use of the FEV1 predicted value (Table 7). However, both of these measures use changes in % predicted values and absolute volumes to define reversibility, and as the ATS/ERS classification is more widely recognised, this definition was considered more appropriate for use in further analyses presented here.

Table 7: Reversibility criteria

	ATS/ERS 2005	GLI-2012
None	n/a	Increase <9% of FEV1 predicted AND <200ml increase
Indeterminate	n/a	Increase 9-12% of FEV1 predicted OR >200ml increase
Clear	>200ml increase AND Increase >12% of baseline FEV1 value	Increase >12% of FEV1 predicted

2.7.3 SCORING OF CXR & CT IMAGING DATA

Only one CXR scoring system designed and validated specifically for a post-TB population was identified on review of the post-TB lung damage literature presented above, and in the systematic review which will be described in Chapter 3 below. In their cross-sectional study of 127 Mexican adults who had completed PTB treatment a median of 11 months previously, Baez-Saldana et al. developed a simple imaging severity score, whereby the lung fields of each image were divided into quadrants, scored from 0(normal) to 5(severe abnormality), and then these scores summed across the lung fields. This severity score was found to be negatively correlated with absolute and % predicted values of FEV1 and FVC following PTB disease. Unfortunately, this scoring system applies to CXR imaging only, is relatively broad and simple, and does not measure specific patterns of parenchymal, airway and other pathology seen. It was therefore not felt to be appropriate for use in the analyses to be performed in the cohort study of post-TB patients presented in Chapter 5 below, and it was felt necessary to

generate new scoring system instead. The chronic lung disease most closely related to post-TB lung damage in which imaging appears to play a key role in prognostication / management is bronchiectasis, and approaches to the measurement of lung damage in bronchiectasis are therefore reviewed below.

The two radiological scoring systems for bronchiectasis severity in widest use at the time of starting this project were the Bhalla and Reiff scores. The Bhalla score was developed in 1991 to measure structural abnormalities in patients with cystic fibrosis, and the Reiff score subsequently developed in 1995 to quantify the pattern, severity and distribution of damage in patients with bronchiectasis with a range of aetiologies, with the BRICS scoring tool developed during the course of this study.[149 150] (Table 8)

Table 8: Existing CT bronchiectasis scoring systems

Name of score	Variables measured	Options
Reiff, 1995[149]	Extent of involvement	0: Absent 1: ≤1 BP segment 2: ≥ 2 BP segments
	Severity of dilatation	0: Normal 1: Lumen < 2x vessel diameter 2: Lumen 2-3 x vessel diameter 3: Lumen >3 times vessel diameter
	Severity of bronchial wall thickening	0: normal 1: 0.5x vessel diameter 2: 0.5-1 x vessel diameter 3: >1 x vessel diameter
	Type of bronchiectasis	Cylindrical Varicose Cystic
	Dominant site	Central Peripheral Mixed
	Lobar distribution	Widespread (5-6 lobes) Predominant UK Predominant ML Predominant LL Both ML and LL equally involved
Bhalla, 1991	Severity of dilatation	0: Normal 1: Lumen slightly >vessel diameter 2: Lumen 2-3 x vessel diameter 3: Lumen >3 times vessel diameter
	Peribronchial thickening	0: Absent 1: Wall thickness = vessel diameter 2: Wall thickness 1-2x vessel diameter 3: Wall thickness >2x vessel diameter
	Extent of bronchiectasis involvement	0: Absent 1:1-5 BP segment 2: 6-9 BP segments 3: >9 BP segments
	Extent of mucus plugging	As above
	Extent of sacculations / abscesses	As above
	Generation of bronchial divisions with Bx / plugging	0: Absent 1: Up to 4th generation 2: Up to 5th generation 3: Up to 6th generation / distal
	Number of bullae	0: Absent 1: Unilateral (not >4) 2: Bilateral (not >4) 3: >4
	Emphysema	0: Absent 1: 1-5 BP segments

		2: >5 BP segments
	Collapse / consolidation	0: Absent 1: Subsegmental 2: Segmental
BRICS, 2017[150]	Bronchial dilatation	0: Absent 1: Lumen slightly >vessel diameter 2: Lumen 2-3 x vessel diameter 3: Lumen >3 times vessel diameter
	Number BP segments with emphysema	0: Absent 1: 1-5 BP segments 2: >5 segments

Variations of these scores have been used in multiple studies investigating patient outcomes in relation to imaging measures of bronchiectasis severity (Table 9). The patient cohorts included in these studies were different to the likely post-TB population in the Malawian context: all were based in resource rich settings, the aetiology of bronchiectasis was different / diverse, average ages were higher, and patients were mostly recruited from specialist respiratory units / hospitals at which they were being seen for respiratory symptoms. Despite these differences, is it plausible that similar parameters may be clinically relevant to outcomes amongst post-TB patients in resource poor settings. Reviewing these studies, the parameters most consistently associated with adverse patient parameters were: the numbers of lobes affected by bronchiectasis, the overall radiographic extent of bronchiectasis, the severity of airway dilatation, and the extent of bronchial wall thickening and emphysema. These imaging features were therefore all included in the CT scoring tool designed for use in the cohort study of this PhD (Chapter 5).

Table 9: Studies investigating patient outcomes in relation to imaging appearance, amongst patients with bronchiectasis

Study	Study design	Patient population / inclusion criteria	CT scoring method	Patient centred outcome	Imaging features associated with outcome
Sheehan 2002[151]	Prospective cohort Median 28m follow up (6-74m) Single centre UK (1991 – 1999)	N=48 Chronic sputum production, 2x HRCTs with PFTs within 2m of each	Modified Bhalla score	Change in FEV1 between scans	Univariate: baseline bronchiectasis extent, bronchial wall thickening, airway plugging score Multivariate – bronchial wall thickening only
Onen 2006[152]	Prospective cohort with 4yr follow up Single centre Turkey (2000-2005)	N = 98 Mean age 68yrs 75% non-smokers, 28% previous PTB Previous respiratory admission, both HRCT and PFT results available	Radiographic extent of disease (1/2/3) – based on BP segments affected & pattern	All cause mortality 16 deaths (16% mortality) – all were respiratory	Univariate & multivariate: radiographic extent of disease
Martinez Garcia 2007[134]	Prospective cohort 2yr follow up Single centre Spain (2003-2005)	N=76 Mean age 70yrs Non smokers only, 20% post-TB CT Bx affecting more than 1 lobe or with cystic pattern, in a stable phase	Modified Bhalla score	Rate of FEV1 decline	Univariate & multivariate: no Imaging features (overall score, presence of cylindrical or cystic disease) were statistically significant predictors of FEV1 decline

Loebinger 2009[153]	Prospective cohort 14yr follow up Single centre UK (1994-2007)	N=91 Mean 51yrs (SD 12yrs) 56% idiopathic, 22% post infection 77% never smokers Clinically diagnosed Bx, confirmed on CT imaging	Modified Bhalla score	All cause mortality 27 deaths (30% mortality) - 70% were respiratory	Univariate model - Bx extent, dilation severity, wall thickness, large airway plugging, mosaicism, emphysema Multivariate model, CT variables only – bronchial wall thickness, emphysema Multivariate model, all covariates – no CT features significant
Martinez-Garcia 2013[154]	Retrospective cohort 5yr follow up 7 centres Spain (Dec 2005)	N=819 Mean age 59yrs CT diagnosis of Bx, and clinical symptoms	Number of lobes affected	All cause mortality 20% mortality – 43% respiratory	Univariate & multivariate: number of lobes affected significant
Goeminne 2013[155]	Prospective cohort Mean follow up 5.2yrs Single centre Belgium (2006-2012)	N=245 Median age 68yrs 'Clinically significant' Bx, with CT confirmation	Number of lobes involved + worst pattern seen	All cause mortality 20% mortality – 58% from respiratory cause	Multivariate: number of lobes affected significant
Chalmers 2014[135]	Prospective cohort 4yr follow up Single centre UK (2008-2012)	N=608 78% aged 50-79yrs 14% post TB CT diagnosis of Bx, and clinical symptoms	Modified Reiff score Score ≥3 used as cut off (3 lobes /cystic Bx) – as per AUC / Youden's index	All cause mortality 62 deaths (10% mortality) Exacerbation frequency Hospital admissions Quality of life	Univariate: radiological severity ≥3 associated with admissions and weakly associated with quality of life Multivariate: radiological severity score ≥3 associated with hospital admissions
Bedi 2017[150]	Cross sectional study Single centre UK (2006-2013)	N=184 Median age 65 years CT diagnosis of Bx and clinical symptoms, idiopathic / post infective aetiology. Limited smoking history only.	Bhalla & modified Reiff scores	FEV1<50% Sputum purulence Hospital admissions	Multivariate: severity score for bronchial dilatation associated with FEV1<50%, BP segments with emphysema associated with sputum purulence and hospital admissions

Bx: bronchiectasis; BP: Bronchopulmonary segment

2.7.4 MEASUREMENT OF QUALITY OF LIFE

Quality of life emerged as a key outcome measured in the existing literature on PTLD, and that from other chronic lung diseases. The most widely used tool for the measurement of respiratory related quality of life is the St George's Respiratory Questionnaire (SGRQ). Developed in the UK in 1992, the SGRQ is standardized health-related quality of life assessment tool designed specifically for use in patients with chronic respiratory disease.[138] It includes 50 items with 76 weighted responses, with a focus on respiratory symptoms and their physical and psychosocial impact.[156] It has been shown to be reliable and valid across multiple chronic respiratory pathologies including COPD and bronchiectasis. The long form of the questionnaire, which asks about the frequency of symptoms over the preceding 3-months has been shown to have superior psychometric properties to versions which ask about

symptoms over a shorter duration of time. The questionnaire generates data on individual questions, which are combined and weighted using a standard algorithm to generate a symptom, activity, impact, and summary score. Each of these four scores ranges from 0 (no symptoms) to 100 (maximal symptoms), such that a lower score indicates a superior quality of life. The mean total score amongst healthy individuals with no history of respiratory disease is quoted at 6 (IQR: 5-7) in the original SGRQ manual.[156]

In the literature review above, only 2 studies which had used the SGRQ to assess health related quality of life following PTB disease were identified. In a 2007 study by Pasipanodya et al., SGRQ results amongst 106 patients from multiple ethnic backgrounds who had completed at least 5-months of treatment for culture confirmed PTB were compared with those of patients diagnosed with latent TB infection (LTBI) within the same health care unit in Texas, USA (n=207). Comparison was also made between the SGRQ and the Medical Outcome Study (MOS) questionnaire (a well validated general HRQoL questionnaire that includes data on physical function, general health, and other aspects of physical / emotional wellbeing) in 50 patients to assess construct / content validity of the SGRQ in this post-TB population. Study findings suggested that the SGRQ was a valid quality of life measure within this patient group: those who had been treated for PTB had higher SGRQ scores than those with LTBI; both the SQRQ total and sub-scores were correlated with age standardized pulmonary function results including FEV1, FVC, FEV1/FVC ratio in both the PTB and LTBI groups; and the SGRQ and MOS scores were highly correlated, except for the symptom score, which is perhaps unsurprising given the respiratory focus of the SGRQ/ the more general focus of the MOS. An additional finding of interest was that differences in scores between PTB and LTBI groups persisted even when controlling for spirometry, which suggests that the SGRQ may capture aspects of quality of life outside of pure respiratory pathology/ physiology. Of note, the data suggested some cultural variation in results, with higher scores observed amongst White American compared to foreign-born / non-white participants in the same setting.[157]

Only one other study, investigating the relationship between structural lung damage and quality of life using the SGRQ in a post-TB population was identified in the literature. In this cross-sectional study in India, lung function, CXR and the SGRQ were preformed in 198 patients who had been treated for TB a mean of 16.5 years previously [118]. The symptom, activity, impact, and overall SGRQ scores were slightly higher in those with abnormal CXRs, more pathology on CXR (damage of >2 vs. ≤2 CXR zones) or worse FEV1 scores (≤80% predicted vs. >80% predicted), but these differences were generally not statistically significant.

Of note – whilst not respiratory focused, the EQ-5D-3L is a short quality of life questionnaire that assesses 5 domains of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), together with a measure of self-reported general health reported on a Visual Analogue Scale (VAS) scaled from 0-100, which has previously been validated for use amongst TB

patients in Malawi.[158 159] It is quick to complete and provides a broader assessment of general quality of life than the SGRQ, can be used for post-hoc validation of the SGRQ, and importantly can be used for cost-effectiveness analyses, and as such is used in the cohort study described in Chapter 5 below.

2.7.5 MEASUREMENT OF FUNCTIONAL CAPACITY

The most widely used sub-maximal test of functional capacity is the six-minute walking test (6MWT). This is a self-paced test with patients asked to walk continuously along a 30m flat corridor for a 6-minute period, following standardized instructions. It is considered a sub-maximal exercise test in that whilst it does push patients to their peak oxygen requirement (VO_2 peak) it requires lower ventilation than a cardio-pulmonary exercise test. The primary outcome of the test is the total distance covered by the patient in the 6-minute study window (6-minute walking distance, 6MWD). Exercise intensity is known to be a key predictor of the 6-minute walking distance and reflects the 'effort' put into the test.[160] This is calculated as the % of maximum heart rate reached – or the end of test heart rate divided by the maximum heart rate, with the latter approximated as (220 – patient age).

Models which have sought to design prediction equations for the 6MWD using parameters such as height, age, sex, and weight have been limited in their ability to explain the observed variation in walking distance achieved between patients.[160] A 2014 ERS / ATS review found that at a single time point, the walking distance has been shown to have only weak to moderate correlation with health related quality of life measures and pulmonary function measures (FEV1, FVC, diffusing capacity of the lung for carbon monoxide (DLCO)) across multiple forms of chronic lung disease.[161] In fact, the main value of the walking distance has been shown to be is its correlation with long-term adverse patient outcomes over time including mortality and hospitalization, and therefore its prognostic implications. The minimum important distance for the 6MWD reported in the literature – that is, the change in distance walked which is observed over time and likely clinically meaningful – is thought to be approximately 30-metres.[161]

Only one study in which 6-minute walk tests were performed in post-TB patients was identified in the literature: this was conducted in Brazil and included 18 patients treated for MDR TB only, amongst whom no statistically significant relationship was demonstrated with the extent of pathology seen on CXR.[117] No accepted norms or cut offs for the 6MWD were identified within the literature for the post-TB population.

2.7.6 DEFINITION OF ACUTE RESPIRATORY EXACERBATIONS

Challenges in defining respiratory exacerbation in chronic lung disease are widely recognized – no biomarkers for exacerbation are available, and objective confirmation of a deterioration in patients symptoms is often difficult.[162] Some of the most commonly used definitions of infective exacerbations

in bronchiectasis and COPD are outlined below (Table 10). These chronic respiratory conditions were chosen as both airway obstruction and bronchiectasis were expected to be common in the post-TB population. Although fibrotic change was also thought likely, the pattern and nature of this was felt likely to be different to the fine reticular change often observed in the interstitial lung diseases, and definitions of exacerbations seen in the latter were therefore not reviewed.

Table 10: Potential definitions of acute respiratory event or respiratory exacerbation

Source	Definition
Bronchiectasis	
Pasteur et al., 2010[163] British Thoracic Society	A change in one or more of the common symptoms of bronchiectasis (increasing sputum volume or purulence, worsening dyspnoea, increased cough, declining lung function, increased fatigue/malaise) or the appearance of new symptoms (fever, pleurisy, haemoptysis, requirement for antibiotic treatment).
Hill et al, 2017[164] EMBARC working group	A deterioration in three or more of the following key symptoms for at least 48 h: cough; sputum volume and/or consistency; sputum purulence; breathlessness and/or exercise tolerance; fatigue and/or malaise; haemoptysis AND a clinician determines that a change in bronchiectasis treatment is required.
COPD	
Wedzicha et al, 2007[165]	An acute worsening of respiratory symptoms associated with a variable degree of physiological deterioration
GOLD, 2007	An event in the natural course of the disease characterized by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD
GOLD 2017[166]	An acute worsening of respiratory symptoms that result in additional therapy

These definitions have been developed largely for use in resource rich settings, and amongst patients with pre-existing diagnoses of chronic respiratory disease who may be well informed about their respiratory health. The features included within these definitions include change in symptoms, change in physiology, a time-frame over which these changes were observed, and health seeking with a change in clinical management. Reporting of each of these parameters may be problematic in resource poor settings or when dealing with a patient population with limited education or health literacy. Symptom descriptions may vary / be less precise, ascertainment of time frames may be challenging, and issues around health service access may influence health seeking.[165] Medical documentation is often more limited in these settings, such that events are difficult to ascertain from health records. In such contexts, simpler definitions are required.

2.7.7 MEASUREMENT OF FINANCIAL IMPACT

As explained above, adults completing treatment for PTB may continue to experience economic costs as a result of persistent morbidity and ongoing health service use. No validated tools for the measurement of post-treatment costs were identified on review of the literature, but at the start of this PhD the STOP-TB partnership were in the process of developing a cost questionnaire for TB patients.[167] This questionnaire includes questions on both direct and indirect patient costs: direct costs include the medical expenses (Eg. investigation and medication costs) and non-medical expenses (Eg.

transport, accommodation, food) incurred by patients and their households through the process of health care seeking, whilst indirect costs relate to lost income due to time away from work during health care seeking. This tool was therefore used as the basis for data collected in Chapter 5 below.

Of note, recall bias in the reporting of income and expenditure, particularly when data are collected some months after the event have been widely reported in the economic literature. 'Dissaving' is an alternate concept recently proposed in the literature, as a more reliable measure of patient and household costs – it includes the use of savings, selling of assets, and borrowing of money by the household to cover health related costs or lost income, and is thought to be the final consequence of catastrophic costs. It may be more memorable than income levels or expenditure, [168] and is therefore also included in Chapter 5 below.

2.8 SUMMARY

Despite the WHO declaration of TB as a global emergency in the 1990s, there remain an estimated 10.4 million incident cases of TB disease per year, with incidence rates of 254/100,000 population per year in the African region. Although incidence rates are falling, progress is slow with an average rate of decline of only 1.4% per year. Despite the ambitious targets set out in the SDGs and the end-TB strategy, TB disease is therefore likely to remain a pressing public health priority in the decades ahead.

In recent years, much emphasis has been placed on reducing TB related mortality – national surveillance systems are mandated to report predominantly on microbiological and mortality outcomes, with little focus on morbidity. However, in 2015 treatment success rates of up to 83% of registered cases of drug sensitive disease were reported, suggesting that by far the majority of individuals treated for TB disease survive to 6-months with either microbiological cure or clinical recovery. Given these numbers, some focus on the long-term outcomes of survivors is warranted.

We now have good evidence that PTB disease leads to lung damage which persists after completion of treatment. These data are particularly strong when residual damage is measured using spirometry – the odds of airway obstruction in those who have had previous PTB compared to those who have not are 1.37 – 8.9 higher in numerous studies, with 1.70 - 5.99 times higher odds of restrictive spirometry demonstrated within the BOLD studies. However, there have been limited attempts to describe the structural pathology underlying abnormal spirometry after PTB disease, there is an absence of prospective data describing the evolution of pathology over time, and we have few data on the relationship between residual post-TB lung damage and ongoing morbidity. Whilst there is some suggestion that those with more extensive residual damage may be at risk of reduced quality of life, impaired functional capacity, and increased respiratory exacerbations in long term, these data are far from robust. The relationship between post-TB lung damage and mortality, risk of recurrent TB disease / empirical retreatment, and ongoing economic impact are poorly defined. Lastly, there

remain many gaps in our understanding of post-TB lung damage amongst those who are HIV co-infected, who account for 30% of TB cases in the African region.

A key challenge for future work in this area is the lack of consistency in terminology used between studies when describing post-TB lung damage, and the lack of validated tools for measurement of both disease and outcomes. Consensus agreement on the terminology and measurement tools to be used for future work in this area are required, but a comprehensive understanding of what this damage looks like and how it behaves is first needed.

Finally, the population in Malawi may be particularly vulnerable to the effects of post-TB lung damage. Almost 17,000 new cases of TB disease are reported annually, and over half of TB patients at HIV co-infected. The population is economically vulnerable with limited educational opportunities, and there is a high burden of background respiratory impairment on which the additional insult of PTB disease is experienced, with 11.8 – 22.5% of adults reporting respiratory symptoms and over 40% of adults having abnormal spirometry using NHANES III reference ranges. In this setting, the impact of residual post-TB lung damage and any disability related to this may be profound.

3 SYSTEMATIC REVIEW OF POST-TB STRUCTURAL LUNG DAMAGE

3.1 INTRODUCTION

As highlighted in the literature review above, the majority of large studies seeking to describe post-TB lung damage to date have focused on describing the prevalence of residual abnormal spirometry: 3 reviews and data from the international BOLD studies have provided strong evidence that PTB disease is associated with increased odds of persistently abnormal lung function after treatment completion. However, no comparable reviews of the patterns of structural lung damage were identified in the literature. In response to this a systematic review of the prevalence and patterns of post-TB structural lung damage was completed, and was published in 2016 (PLoS ONE 11(8): e0161176. Doi: 10.1371/ journal.pone.0161176).[169] The findings of this review, which was updated in January 2018, are presented below.

3.2 METHODS

3.2.1 SYSTEMATIC REVIEW PROTOCOL, JULY 2016

The original review protocol was designed in accordance with PRISMA guidelines, and was registered with the National Institute of Health Research (NIHR) Prospero register (CRD42015027958) with the stated research question of "What is the prevalence and pattern of imaging defined (CT or CXR) respiratory pathology in adults, following treatment for pulmonary TB disease?".

Only studies in which unselected consecutive participants with pleural, miliary, or pulmonary TB had been recruited, where CXR or CT had been performed after the completion of a full medical TB treatment regimen, and where the prevalence of abnormal imaging or the severity of residual structural lung damage had been reported were included. Studies describing the prevalence of radiological abnormalities amongst a subset of patients completing PTB treatment, for example those with confirmed airway obstruction or ongoing symptoms, were excluded to avoid selection bias. Cohort studies, cross-sectional studies and randomised control trials (RCTs) were eligible for inclusion. There were no limits on publication date. Only studies published in English were included.

Original literature searches were conducted in Medline, Pubmed, Scopus, Web of Science, and the Cochrane Library using the search terms shown in Table 1. Reference lists from published reviews and reference and citation lists of papers meeting inclusion criteria were reviewed to identify additional articles.

Table 1: Template for literature search: Pulmonary, pleural or military tuberculosis AND [CXR imaging OR CT imaging]

Criteria	Search terms
Pulmonary, pleural, or miliary tuberculosis	“Tuberculosis, pulmonary”[MESH] OR “tuberculosis, miliary[MESH] OR “tuberculosis, pleural”[MESH] OR "pulmonary TB" OR "pulmonary tuberculosis"
CXR Imaging	“thoracic radiography"[MESH] OR “chest x-ray" OR "chest radiograph" OR "CXR"
CT imaging	“computed tomography”[MESH] OR "CT" OR "comput* tomography"

The title and abstract of all identified studies were screened by two independent reviewers (JM & HS). Full text review was performed on all selected articles. Studies restricted to paediatric populations, in whom PTB has a varied presentation, or patients with non-HIV related immunosuppression (chemotherapy, malignancy etc.) where imaging was likely to be affected by comorbidities, were excluded. Data from the control arms of trials of adjuvant immunomodulatory therapies, in which patients received medical TB treatment only, were included. A standardized data extraction form was used to determine the primary outcome of interest, which was the prevalence of abnormal imaging after TB treatment. Information was collected on the patterns of imaging pathology, study characteristics, participant characteristics, treatment regimens, and the modality and timing of thoracic imaging (Table 2). The proportion of studies that presented a measure of association between imaging findings and other clinical parameters including spirometry, functional capacity, respiratory symptoms, or health-related quality of life was recorded.

Table 2: Study data extracted

Category	Data collected
Study characteristics	Author Year of publication Country Study design Study dates (month/year)
Patient characteristics	Pattern of TB disease – pleural, pulmonary, miliary First episode / retreatment Microbiological evidence for disease Drug sensitivity of organism HIV status of participants Treatment outcome Participant age Other inclusion / exclusion criteria used
TB treatment received	Duration of treatment Treatment regimen
Imaging findings	Timing of imaging, post treatment completion Imaging modality – CXR / CT imaging Number of imaging readers Definitions of imaging findings used % prevalence of the following: overall normal / abnormal imaging, cavitation, bronchiectasis, fibrosis, lung destruction, pleural thickening, other Severity scores used Severity score results
Associated outcomes	Patient centred outcomes measured (Symptoms, health related quality of life, functional capacity) Lung function measured Relationship of associated factors to imaging described

Disagreements in study selection and data extraction were resolved by discussion. Subgroup analyses were conducted to explore the effect of different manifestations of disease (pleural vs. pulmonary), imaging modality (CXR vs. CT), and multidrug-resistant (MDR) disease on the primary outcome.

Study quality was determined using a modified version of the Newcastle-Ottowa score,[170] which included assessment of selection bias, adequacy of follow-up, the accuracy with which baseline TB disease and treatment completion were determined, the quality and standardisation of imaging interpretation, and the exclusion of those with structural lung disease preceding TB-disease. Whilst there is no formal recommendation for multiple readers in radiology research, this is the norm in the imaging literature, as the amount of variation between readers can be used by to quantify levels of 'uncertainty' in imaging interpretation. It was therefore felt to be an important marker of study quality and was included in our evaluation. A maximum score of 5 was possible for cohort studies, and 4 for cross-sectional studies where no follow-up was required (Table 3)

Table 3: Modified Newcastle-Ottowa score for assessment of study quality

Study characteristic	Study performance	Score
Selection of study cohort	Truly representative of the average TB patient in the community* Somewhat representative of the average TB patient in the community Selected groups No description of the derivation of the cohort	1
Assessment of exposure	Secure record of TB disease and treatment* Structured interview recording of TB disease and treatment Written self report of TB disease and treatment No description of how exposure ascertained	1
Demonstration that outcome not present at start	Imaging performed prior to TB diagnosis, with exclusion of those with prevalent lung disease* Statement of exclusion of those with known preceding lung disease	1
Assessment of outcome	Independent blind assessment by 2 readers with definitions of imaging findings (severity score or individual features) given* 1 reader only No description of readers, or no definitions given	1
Adequacy of follow-up[§]	≤20% of those starting treatment & surviving lost to follow up, with subjects lost unlikely to introduce bias* Loss to follow up >20% of those who survived treatment No statement on follow-up	1

*Studies awarded a point only when this highest standard achieved for each study parameter
[§]Only applicable to cohort studies in which patient follow-up required

3.2.2 SYSTEMATIC REVIEW UPDATE, JANUARY 2018

The search above was repeated for the period from June 2016 - January 2018, in order to ensure up to date findings. Because during the course of the PhD it became clear that the term 'sequelae' is frequently used in the literature to denote residual morbidity following TB disease, including lung pathology, an additional search using this term was performed in January 2018 (Table 4).

Table 4: Template for additional literature search: Pulmonary, pleural or military tuberculosis AND [sequel*]

Criteria	Search terms
Pulmonary, pleural, or miliary Tuberculosis	"Tuberculosis, pulmonary"[Mesh] OR "tuberculosis, miliary[Mesh] OR "tuberculosis, pleural"[Mesh] OR "pulmonary TB" OR "pulmonary tuberculosis"

Respiratory sequelae	sequel*

This update was performed in Pubmed only and was again limited to English language publications, with article review and data extraction performed by one reviewer (JM) only.

3.3 RESULTS

3.3.1 ARTICLES IDENTIFIED

The initial search performed in July 2016 identified 10,740 articles, with 6909 articles remaining after removal of duplicates. Title and abstract review identified 309 articles for full text review, of which 277 were excluded for reasons including non-consecutive patient recruitment (n=48), imaging prior to treatment completion (n=162), and failure to report the absolute prevalence or severity of residual lung damage (n=35). Reference and citation searches identified 5 further articles for inclusion, giving a total of 37 articles. Repetition of this search for the period from June 106 to January 2018 identified an additional 192 articles, with no duplicates. Only 13 new articles were left after title and abstract review, of which none remained for inclusion after full text review.

The additional search performed using the term 'Sequel*' in January 2018 identified 288 articles, with 52 of these remaining after abstract / title review. Six of these were duplicates of papers already identified by the two searches above, and were therefore discarded. Full texts were reviewed for 37 or the remaining 46 articles, and 2 of these were thought to be eligible for inclusion.

A summary of the reasons for exclusion across these three sections of the review is given in Table 5, and the PRISMA diagram for the initial and updated searches given in Figure 1. The total number of articles identified which provide data on the prevalence and pattern of post-TB structural lung damage was 39.

Figure 1: Prisma diagram for systematic review

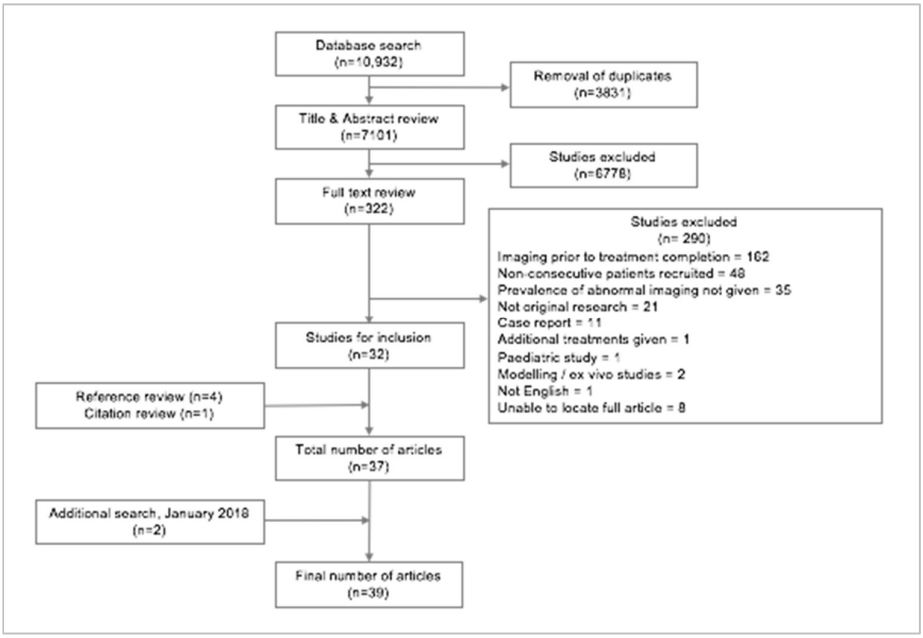


Table 5: Reasons for rejection at full-text review for the original search (July 2016), updated search (Jan 2018), and separate search with the term "sequelae"

	Original (n=309)	Update* (n=13)	Sequelae* (n=46)	Total articles receiving full text review (n=368)
Excluded				
Imaging prior to treatment completion	158	4	0	162
Prevalence of abnormal imaging not given	32	3	9	44
Non-consecutive patients recruited	44	4	14	61
Not original research	19	2	8	29
Case report/series	11	0	3	14
Additional treatments given	1	0	0	1
No treatment received	0	0	1	1
Paediatric study	1	0	0	1
Modelling / ex vivo studies	2	0	1	3
Not English	1	0	0	1
Unable to locate full article	8	0	8	16
Added				
Citation review	1	0	0	1
Reference review	4	0	0	4
Total	37	0	2	39

*One reviewer only

3.3.2 STUDY CHARACTERISTICS

Of the 39 studies identified, the majority were from the Americas (n=13), South East Asia (n=10), the Western Pacific (n=7) and Europe (n=6) (Table 6). Despite being the WHO region which contributed 25% of incident TB cases in 2016, Africa is significantly under-represented – only 2 studies were

conducted on the continent, both of which were done in South Africa, and of which 1 focused on MDR disease[171] and the other on pleural disease.[172] We did not identify any robust data on residual structural lung damage following drug sensitive pulmonary TB in Africa.

Table 6: Geographical distribution of studies, by WHO world region

WHO World Region	Total number of studies	Country (number of studies)
Americas	13	Brazil (6), Mexico (2), Martinique (1), USA (3), Canada (1)
South East Asia	10	India (7), Indonesia (2), Thailand (1)
Europe	6	Turkey (3), Spain (2), Romania (1)
Western Pacific	7	Taiwan (5), Malaysia (1), Hong Kong (1)
Africa	2	South Africa (2)
Eastern Mediterranean	1	Saudi Arabia (1)

Study publication dates spanned the period 1973-2017. Treatment regimens varied widely in the earlier studies, but even post 1995 when 'standard' first line treatment regimens were adopted, significant variation in the drugs used and treatment duration were seen. 11 studies did not specify the treatment regimen used.

There were 16 prospective cohort studies with patients recruited at TB diagnosis and imaged upon treatment completion, one prospective cohort study where imaging was performed 1 year post treatment completion[173] and one where imaging was performed 6-months after treatment completion. There were 6 cross-sectional studies, 4 of which performed imaging at various time points after treatment completion, and 9 retrospective cohort studies, which performed imaging upon treatment completion. Data from 6 RCTs were included: data from both study arms were included for two treatment regimen trials[174 175] and a study investigating the effect of Vitamin-D and L-arginine supplementation [176], but data from the control arms only were included from trials investigating prednisolone use[172 177], and a trial of *M. vaccae* immunomodulation [115]. All RCTs performed imaging at treatment completion, and 1 also performed serial imaging 6-months later[172].

Only seven studies used CT imaging to describe structural pathology. Five of these were conducted in the Americas, all were prospective cohort studies, and all performed imaging at treatment completion. Only one study of pleural disease used both CXR and CT imaging [172].

3.3.3 PATIENT CHARACTERISTICS

The total number of patients in all included studies was 4096, with disaggregated data available for 76 HIV-infected individuals only. The median number of participants per study was 56 (range 13-1080). We identified 26 studies focused on PTB, 1 on the sequelae of miliary TB, 10 restricted to pleural TB, and 2 which included patients with varying patterns of intrathoracic TB. Patients with microbiological confirmation of TB disease only were included in 22/39 studies, with 6 studies failing to describe the

baseline microbiology of patients at diagnosis. Of the studies that specified the pattern of drug sensitivity (15/39), we identified 3 studies imaging patients treated for multidrug resistant disease using CXR in South Africa,[171] India,[178] and Brazil.[117] The majority of studies did not specify whether they included patients who had completed a first or retreatment treatment regimen (25/39). Of those that did describe this, 8 studies included patients completing their first episode of treatment, 2 included retreatment patients,[115 117] and 4 included both groups. The marked heterogeneity between studies made meta-analysis of their findings inappropriate.

3.3.4 IMAGING

The majority of studies used CXR imaging only (32/39), with 6 studies using CT only, and only 1 study using both CXR and CT to image patients following pleural disease.[172] 29 studies performed imaging at TB treatment completion, 2 did not specify the timing of imaging, and the remainder imaged patients from 6m to 18yrs post completion. The approach to image reporting varied widely between studies – several studies (15/39) did not document the number of readers reviewing each image, and only 17/39 used 2-3 readers per image. In addition, many studies (11/39) did not provide definitions or a reference for the radiology terminology or scoring system used when to describe image findings.

3.3.5 STUDY FINDINGS – PULMONARY TB STUDIES

Of the 27 studies reporting the sequelae of pulmonary and miliary TB, prevalence estimates for radiographic pathology were given in 17 CXR (Table 7) and 5 CT studies (Table 8), and varied widely. Findings are summarised in Table 9 below. Twelve CXR studies reported the prevalence of cavitation (8.3-83.7%), 3 reported fibrosis (prevalence 25.0-70.4%) and 4 reported bronchiectasis (prevalence 4.3-11.2%). The CT-based studies generally reported a lower prevalence of cavitation (7.4-34.6%), and a higher prevalence of bronchiectasis (35.0-86.0%) and fibrosis (70.0-92.6%), than studies using CXR imaging.

A more diverse range of pathologies was noted on CT imaging: pleural thickening was reported in 3 studies (prevalence 0.1-50.0%, n=99), features potentially suggestive of ongoing inflammation such as nodules were seen in all 5 studies (prevalence 25.9-55.8%, n=193), consolidation was reported in 4 studies (3.7-19.2%, n=119), emphysema was seen in in 2 studies (prevalence 15.4-45.0%, n=72). Mosaicism was documented in 1 study only where it was observed in all patients with concurrent cavities (11/11) and a third of patients without cavities (3/9), and no change in prevalence was observed over the course of treatment.[179]

The prevalence of cavitation was higher in studies of re-treatment patients (68.8-83.7%), and those treated for MDR disease (51.5-69.7%), compared to those with fully sensitive, mixed, or unspecified sensitivities (8.3-49.7%). Only 1 study performed repeat imaging; this demonstrated a reduction in the

prevalence of cavitation during the 6-month follow-up period from the end of TB treatment, but the findings were limited by a small sample size and 25% loss to follow-up[115].

Table 9: Range of prevalence estimates of imaging patterns on CXR or CT following pulmonary or miliary TB

Imaging pattern	CXR imaging		CT imaging		CXR imaging in patients with MDR disease	
	Number of studies (number of patients) n=15 (3517)	% prevalence range	Number of studies (number of patients) n=5 (193)	% prevalence range	Number of studies (number of patients) n=2 (78)	% prevalence range
Normal imaging	11 (2365)	0 – 86.4%	-		2 (78)	0 – 6.1 %
Cavitation	11 (2902)	8.3 – 83.7 %	4 (173)	7.4 – 34.6 %	2 (78)	51.5 – 69.7 %
Bronchiectasis	4 (670)	4.3 – 11.2 %	5 (193)	35.0 – 86.0 %	-	-
Fibrosis	3 (551)	25.0 – 70.4 %	4 (119)	70.0 – 92.6 %	-	-
Pleural thickening	2 (1520)	6.9 – 21.2%	3 (99)	0 – 50.0 %	-	-
Nodules	-	-	5 (193)	25.9 – 55.8 %	-	-
Consolidation	-	-	4 (119)	3.7 – 19.2 %	-	-
Tree in bud			4 (166)	0 – 20.0%		
Ground glass			2 (79)	1.9 – 7.4%		
Emphysema / bullae	-	-	2 (72)	15.4 – 45.0 %	-	-
Mosaicism			1 (20)	70.0%		
Architectural distortion			1 (74)	91.0%		

A broad range of severity scores were used to quantify residual damage in 14 studies of PTB sequelae, only one of which was validated for scoring post-TB damage rather than active PTB disease (Table 10).[107]

3.3.6 STUDY FINDINGS – PLEURAL DISEASE

The only radiological feature consistently reported in studies of pleural TB sequelae was the presence of residual pleural thickening, but the thoracic area covered by this thickening was not routinely reported. Residual thickening >10mm was seen in 19.6-46.0% of patients in 5 studies (n=310) (Table 11). One study reported both CXR and CT findings following pleural TB, with mild pleural thickening >2mm seen in 50.0% (18/36) on CXR, and 60.0% (21/35) on CT[172].

Table 11: Studies of residual pleural thickening (RPT) on completion of treatment for TB pleural effusion

Imaging	Author, Year	Country	Study design	Patients	HIV status	Prevalence of pathology (%)	Quality score
CXR	Kunter, 2002[180]	Turkey	Retrospective cohort	47	Not specified	RPT>2mm: 63.8% RPT>10mm: 25.5%	2/5
CXR	Uskal, 2005[181]	Turkey	Retrospective cohort	121	Not specified	RPT>2mm: 52.1%	3/5
CXR	Wong, 2005[182]	Hong Kong	Retrospective cohort	70	Not specified	RPT>10mm: 41.4%	2/5
CXR	Barbas, 1991[183]	Brazil	Prospective cohort	44	Not specified	RPT>2mm: 52.3%	2/5
CXR	de Pablo, 1997 [184]	Spain	Prospective cohort	56	Mixed	RPT>2mm: 42.9% RPT>10mm: 19.6%	3/5
CXR	Frye, 1997[185]	America	Retrospective cohort	20	Positive	Any RPT: 65.0%	3/5
CXR	Galarza, 1995 [177]	Spain	RCT - steroid use*	60	Negative	Any RPT: 8.3%	2/5
CXR	Wyser, 1996 [172]	South Africa	RCT - steroid use*	36	Negative	RPT>2mm: 50.0%	4/5
CXR	Lai, 2009[108]	Taiwan	Prospective cohort	87	Not specified	RPT>10mm: 22.9%	4/5
CT	Wyser, 1996[172]	South Africa	RCT - steroid use*	35	Negative	RPT>2mm: 60.0%	4/5
CT	Seiscento, 2007[186]	Brazil	Prospective cohort	50	Not specified	RPT>10mm: 46.0%	3/5

*Date from study arm including steroids excluded

3.3.7 RELATIONSHIP BETWEEN IMAGING CHANGES AND OTHER RESPIRATORY PARAMETERS

Although several studies described spirometry following PTB disease, only 2 studies directly related physiological impairment to imaging findings. The first showed a statistically significant inverse correlation between both FEV_1 (forced expiratory flow in 1-second) and FVC (forced vital capacity), and the extent of radiographic abnormality on CXR in 127 adults who were a median of 11 months (IQR 6-18 months) post completion of TB treatment[107]. The second described imaging findings in patients with (n=24) and without (n=46) fixed airway obstruction on spirometry following treatment completion. Those with airway obstruction had had more previous episodes of TB (1.9+/-0.7 vs. 1.4+/-0.6, p=0.009), but had more fibrocavitatory changes evident on CXR imaging.[187]

The only study to relate imaging findings to functional capacity included 18 patients completing treatment for MDR-TB, and found a higher level of impairment amongst those with more marked radiographic damage: 64% of those with Grade I damage (7/11) failed to reach an expected 6-minute walking distance, compared to 100% of patients with Grade III damage (3/3). However, the findings of this study were limited by a small sample size and a lack of statistical testing.[117] Only one study described the relationship between imaging findings and patient quality of life. This was a cross-sectional study of 198 patients who had been treated for TB a mean of 16.5 years previously, and

found no statistically significant difference in the symptoms, activity, impact, or overall St George's Respiratory Questionnaire scores between those with pathology affecting ≤2 vs. >2 CXR zones.[188] These studies have been described in greater detail in the general thesis literature review, given above.

3.4 DISCUSSION

The key findings from this systematic review of structural lung damage in adults completing medical treatment for PTB are the high prevalence of residual structural abnormalities seen on imaging, but the lack of validated scores for the measurement of this damage. Differences in both the prevalence estimates and patterns of damage seen in CXR and CT based studies were noted, as well as the high burden of residual damage amongst those treated for MDR disease, but data from HIV-infected adults and the sSA region are limited. Few prospective studies have documented change over time or the level of morbidity experienced in relation to this residual damage.

- ### RESIDUAL STRUCTURAL LUNG DAMAGE IS COMMON FOLLOWING PTB DISEASE

Data from both the CXR and CT imaging studies suggest a high burden of residual structural pathology, which persists following PTB treatment completion. Cavitation was the feature most commonly reported on 11/15 CXR studies, perhaps in relation to the public health importance of this feature for smear positivity and ongoing transmission of disease, and was documented in 8.3 - 83.7% of cases. The range of pathologies reported on CT imaging studies was much wider, and included a high burden of both airway (Bronchiectasis: 35.0 – 86.0 %, Tree-in-bud: 0-20%) and parenchymal pathology (Fibrotic change: 70.0 – 92.6 %, consolidation: 3.7 – 19.2%, ground glass: 1.9 – 7.4%, emphysema: 15.4 – 45.0%, and mosaicism: 70.0%).

The high burden of bronchiectasis is of particular interest. Tuberculosis is a known cause of airway pathology,[189] but these data suggest that at least a third of patients completing PTB treatment may be left with this pattern of damage. This is of concern given data from resource rich settings suggesting that bronchiectasis is associated with adverse long term outcomes including reduced quality of life, increased rates of respiratory exacerbation, and mortality,[134 135 150 152-155] The high prevalence of other risk factors for bronchiectasis including HIV disease and early childhood infection in many high TB-incidence settings may compound this burden of disease,[190] and yet few imaging data from non-TB populations are available to describe the background burden of bronchiectasis in resource-poor settings, and few guidelines for clinical management have been developed for these settings. Amongst the 5 CT studies reporting the prevalence of this pathology, none were based in sSA or included HIV-

infected adults, and the extent and severity of damage was not reported. This requires further investigation.

The high prevalence of potential signs of ongoing inflammation, including tree-in-bud airway change, consolidation and ground glass infiltrate, and perhaps nodules even after treatment completion is also of note, and supports the finding of ongoing inflammatory activity documented of the PET-CT studies performed in post-TB populations and described in the literature review above.[102] The evolution of these patterns of pathology were not described in the CT studies identified in this review, such that it remains unclear whether they represent resolving inflammation or ongoing active disease. Again, this requires further investigation.

Lastly, it is of note that mosaicism – reported in one study only – had a high prevalence of 70%. Mosaicism is defined in the Fleischner guidelines as 'a patchwork of regions of differing attenuation' within the lung parenchyma,[191] with the areas of lower attenuation conventionally scored. A degree of parenchymal heterogeneity can be seen in normal individuals, with up to 20% showing mild mosaicism on inspiratory scans. What constitutes a 'normal' percentage of low attenuation in the lung tissue has been shown to vary from the apices to bases of the lung fields, and from central to peripheral regions, and is highly dependent on how complete the patient's inspiratory effort was at time of imaging, such that there are no absolute cut-offs for normal. High amounts of lung attenuation can be caused by two main groups of pathology. The first is primary small airways disease – the small airways are those with an internal diameter <2mm, between the 8th generation of the airways and the terminal bronchioles, and are only visible on CT imaging when pathologies such as primary damage with an inflammatory or constrictive bronchiolitis, involvement of the small airways in an interstitial process such as hypersensitivity pneumonitis, or involvement in a large airways process such as bronchiectasis or asthma are present. Relative lucency of parenchyma is caused by obstruction of the small airways, with gas trapping distal to the point of obstruction +/- shunting and decreased perfusion through vessels in these areas. The second situation in which the lung tissue develops low attenuation is in pulmonary hypertension, where there are regional differences in lung perfusion through pulmonary vessels and hence a 'patchy' density is seen on imaging.[192] Further studies investigating the prevalence and extent of this pattern are required – if widely seen, investigation of the cause may be warranted.

- ## THE BURDEN OF POST-TB LUNG DAMAGE IS LIKELY HIGHER FOLLOWING MDR-TB DISEASE

A limited amount of data on the residual lung damage experienced by patients treated for MDR PTB disease was identified. However, the prevalence of cavitation was higher on the two CXR studies performed in these groups (51.5-69.7%), compared to those with fully sensitive, mixed, or unspecified disease (8.3-49.7%).

This is likely a result of the longer time taken for culture conversion and treatment of multidrug resistant disease. The physical, social and economic impacts of MDR-TB disease are known to be high,[193] and the potential impact of marked residual pulmonary impairment on top of this may be significant. Globally an estimated 4.1% (95% CI: 2.8–5.3%) of new TB cases and 19% (95% CI: 9.8–27%) of previously treated cases had MDR/RR-TB in 2016,[12] and the burden of post-TB lung damage amongst this patient population requires further investigation.

- THE QUALITY OF EXISTING CT IMAGING DATA IS LIMITED

CT imaging is likely to be the more accurate modality for the measurement of structural pathology. As described here, the 5 CT studies identified in this review provide useful information about this pathology, but their findings must be interpreted with caution. The majority of these studies were completed in the Americas and were restricted to HIV-negative / HIV-unknown individuals only, and a total of 193 individuals only were included across them all. These studies largely reported on the presence of pathology, rather than its extent or severity, making it difficult to understand the importance of their findings. Finally, prevalence estimates of pathology were noted to vary widely between studies, and in the absence of standardized reporting tools, and high quality reporting systems, it is not clear whether this represents the true variation between individuals, or rather differences in the approach taken to measurement.

No validated reporting tools for chest CT imaging following PTB treatment completion were identified in this review. Rigorous and standardized approaches to the scoring of CT imaging in the post-TB population are required to allow us to more accurately document post-TB structural pathology, and to understand the heterogeneity of pathology within and between populations.

- FEW DATA ARE AVAILABLE ON THE OUTCOMES ASSOCIATED WITH STRUCTURAL DAMAGE

Few studies attempted to examine the relationship between lung damage and patient functional capacity, symptom burden, and quality of life. The available data suggest that exercise capacity may decrease with increasing extents of structural pathology, but sample sizes in the one study to assess this were low.[117] The only study relating structural pathology to quality of life was vulnerable to selection bias, and the nature of this relationship therefore remains unclear.[188] No studies identified within this review described the relationship between residual structural damage and ongoing rates of respiratory exacerbations, or mortality. As described in the literature review above, further investigation of the relationship between post-TB structural damage and long-term patient centred outcomes is required.

In addition, only two studies investigating the relationship between imaging and spirometry were identified within this review. Both were CXR studies, and whilst they suggest a correlation between the extent of abnormality / fibrocavitatory change with lung function, the relationship between imaging features such as bronchiectasis and mosaicism – which are more accurately seen on CT imaging – and lung function remains unclear. In the absence of these data, the ability of spirometry – which is a minimally invasive tool which could potentially be widely used in a decentralized fashion in resource poor settings – to detect and diagnose residual post-TB structural pathology remains unclear.

- DATA FROM SSA AND HIV-INFECTED INDIVIDUALS ARE LACKING

This review has identified a paucity of data on post-TB structural pathology from sSA and from HIV-positive patients.

It is biologically plausible, based on the high rates of respiratory co-exposures described in the literature review above, and challenges of delayed diagnosis and limited health service access seen in many parts of sSA, that post-TB lung damage may differ in both pattern and severity in this region compared to that in middle and high income settings. Collection of primary data on the nature of post-TB lung damage in sSA is required.

Whilst HIV infected adults have atypical or less extensive patterns of pathology seen on imaging at TB diagnosis,[78 81 85] patients are at risk of IRIS reactions during TB treatment, and opportunistic infections in the context of advanced HIV, both of which may alter the evolution of lung damage over the 6-month course of TB treatment. It cannot be assumed the extent of residual lung damage amongst HIV-infected adults surviving to TB treatment completion will be minimal, and direct measurement of residual pathology in the HIV-positive population is required.

- STUDY STRENGTHS AND LIMITATIONS

This study was limited by the inclusion of English language articles only. This approach was taken for pragmatic reasons, but may have introduced important bias into our findings. In addition, whilst the inclusion of studies with consecutive recruitment of patients only will have minimised bias in the prevalence estimates presented here, it may have led us to exclude important data from other studies in which alternative recruitment strategies were used. The heterogeneity of patient populations, treatment regimens, and the timing and modality of imaging meant that it was not possible to perform a meta-analysis. Interpretation of findings is limited by the highly variable quality of studies identified, the majority of which failed to specify how the radiological abnormalities reported on imaging were defined, and did not use gold-standard methods of reporting, making them vulnerable to misclassification of outcomes. Selection bias was a common issue; many studies were unclear about the reference population from which participants were drawn. The cross-sectional studies imaging

patients sometime after treatment completion consistently struggled to locate eligible patients, and were limited by survival bias.

The strengths of this review include the use of several databases with no limitation on study dates, and the use of reference and citation review to identify additional papers.

3.5 CONCLUSION

This systematic review identified a high burden of residual structural pathology amongst adults completing PTB treatment, with a wide range of features recorded on CT imaging including cavitation, fibrosis, bronchiectasis, emphysema and mosaicism, and features of ongoing inflammation. However, the quality of studies included in this review was limited, findings were mostly drawn from cross sectional data, and little information on associated morbidity was identified. A better understanding of the nature of this structural lung damage, its evolution over time, relationships with abnormal spirometry, and the associated impact on patients' lives and livelihoods is needed to guide clinical management and health-service planning.

CT imaging is able to detect a broader range of pathology than CXR, and should be the imaging modality of choice for research studies aiming to phenotype post-TB lung damage. Studies performing paired CXR / spirometry and CT imaging will be of use in determining the ability of these more accessible techniques to detect underlying structural pathology, for practical use in LMICs.

Future CT imaging studies should aim to use develop standardised scoring tools, and use high quality reporting standards. Inclusion of measures of disease extent and pattern, in addition to just prevalence, are required to allow better interpretation of the implications of findings. This is particularly relevant for findings such as bronchiectasis which appear common and may have long-term clinical implications. Specific attention is required for HIV-infected groups, those living in sSA, and those treated for MDR/RR PTB disease, for whom current data are lacking.

Table 7: Studies reporting prevalence of imaging patterns on CXR imaging following treatment for thoracic tuberculosis

Timing of imaging	Author, Year	Country	Study design	TB pattern	Participant HIV status	Treatment episode	Drug sensitivity	Number of participants	Prevalence of pathology (%)	Quality score
On completion of TB Treatment	Yu, 1995[194]	Taiwan	Prospective cohort	Pulmonary	Negative	Not specified	Mixed	22	Abnormal imaging: 13.6 %	3/5
	Al Hajjaj, 2000[195]	Saudi Arabia	Prospective cohort	Pulmonary	Not specified	Not specified	Not specified	1080	Abnormal imaging: 65.9%, Cavitation: 15.0%, Pleural thickening 6.9%, Lung destruction 52.4%	3/5
	de Valliere, 2004[171]	South Africa	Prospective cohort	Pulmonary	Mixed	Not specified	MDR	33	Abnormal imaging: 93.9 - 100%, Cavitation: 51.5% - 69.7%	2/5
	Buyukoglan, 2007 [196]	Turkey	Prospective cohort	Pulmonary	Negative	Not specified	Not specified	25	Cavitation: 28.0%	3/5
	Swaminathan, 2007 [197]	India	Prospective cohort	Miliary	Positive	Not specified	Not specified	31	Abnormal imaging: 22.6%. Lung destruction: 3.2%	3/5
	Angthong, 2011 [114]	Thailand	Prospective cohort	Pulmonary	Mixed - data disaggregated	First episode	Not specified	98 HIV+	Abnormal imaging: 84.7%, Cavitation: 11.2%, Fibrosis: 70.4%, Bronchiectasis: 11.2%	4/5
								12 HIV-	Abnormal imaging: 41.7%, Cavitation: 8.3%, Fibrosis: 25.0%, Bronchiectasis: 8.3%	
	Small, 1994 [198]	America	Retrospective cohort	Pulmonary	Positive	Not specified	Not specified	13	Abnormal imaging: 23.1%	3/5
	Menon, 2015 [199]	India	Retrospective cohort	Pulmonary, pleural, mediastinal	Not specified	First episode	Not specified	441	Abnormal imaging: 40.4, Cavitation: 21.4%, Pleural thickening: 21.2%, Fibrosis: 38.7%, Bronchiectasis: 4.3%, Mediastinal lesions: 23.6%	2/5
	Kallan, 1988 [200]	India	Cross sectional	Pulmonary	Not specified	Not specified	Not specified	119	Abnormal imaging: 100.0% , Cavitation: 42.0%, Bronchiectasis: 7.6%	1/4
	Anonymous, 1973 [175]	India	RCT–TB treatment regimens*	Pulmonary	Not specified	Not specified	Not specified	173	Cavitation: 49.7%	4/5
	Hamilton, 2008 [174]	America	RC –TB treatment regimens*	Pulmonary	Negative	Not specified	Fully sensitive	834	Cavitation: 23.3%	4/5
	Kenangalem, 2013 [176]	Indonesia	RCT–additional Vit D / L-arginine†	Pulmonary	Mixed	First episode	Mixed	77	Cavitation: 18.2%	2/5
On completion and at 6m	Corlan, 1997 [115]	Romania	RCT–additional M.vaccae†	Pulmonary	Retreatment	Mixed	Mixed	43 – CXR on completion	Cavitation: 83.7%	3/5
								32 – CXR at 6 months	Cavitation: 68.8%	
6–63 months post completion	Singla, 2009 [178]	India	Cross sectional	Pulmonary	Negative	Not specified	MDR	45	Abnormal imaging: 97.8%, Cavitation: 53.3%	1/4
14–18 years post completion	Banu Rekha, 2009 [118]	India	Cross sectional	Pulmonary	Not specified	First episode	Not specified	198	Abnormal imaging: 85.9%	1/4
5 years post completion	Lisha, 2012 [201]	India	Cross sectional	Pulmonary	Not specified	Mixed	Mixed	224	Abnormal imaging: 65.6%	2/4
0–252 months post completion	Baez-saldana, 2013 [107]	Mexico	Cross sectional	Pulmonary	Mixed	Not specified	Not specified	127	Abnormal imaging: 96.9%	2/4

*Data included from both arms

†Data included from placebo arms only

Table 8: Studies reporting prevalence of imaging patterns on CT imaging on completion of treatment for pulmonary tuberculosis

Author, Year	Country	Study design	Participant HIV status	Treatment episode	Drug sensitivity	Number of participants	Prevalence of pathology (%)	Quality score
Poey, 1997[202]	Martinique	Prospective cohort	Negative	Not specified	Not specified	27	Cavitation: 7.4%, Bronchiectasis: 85.2%, Fibrosis: 92.6%, Pleural thickening: 4.8%, Nodules: 25.9%, Consolidation: 3.7%, Ground glass pattern: 7.4%, Reticulation: 44.4%,	3/5
Long, 1998[179]	Canada	Prospective cohort	Negative	Not specified	Fully sensitive	20	Bronchiectasis: 50.0%, Fibrosis: 80.0%, Pleural thickening: 0.1%, Nodules: 55.0%, Consolidation: 15.0%, Emphysema/Bullae: 45.0%, Mosaicism: 70.0%, Tree in bud 20.0%	3/5
Bombarda, 2003 [203]	Brazil	Prospective cohort	Negative	Not specified	Not specified	20	Cavitation: 30.0%, Bronchiectasis: 35.0%, Fibrotic bands: 70.0%, Nodules: 55.0%, Consolidation: 15.0%, Mass lesions: 45%, Tree in bud: 5.0%	3/5
Lee, 2008[204]	Taiwan	Prospective cohort	Negative	First episode	Fully sensitive	52	Cavitation: 34.6%, Bronchiectasis: 44.2%, Fibrosis: 92.3%, Pleural thickening: 50.0%, Nodules: 55.8%, Consolidation: 19.2%, Emphysema/Bullae: 15.4%, Mass lesions: 7.7%, Ground glass pattern: 1.9%, Parenchymal calcification: 11.5%, Tree in bud: 0%	1/5
Capone 2017[205]	Brazil	Prospective cohort	Not specified	Not specified	Not specified	74	Cavitation: 16%, Bronchiectasis: 86%, Nodules: 48%, Parenchymal opacities: 25%, Parenchymal calcifications: 47%, Architectural distortion: 91%, Tree in bud: 5.4%	1/5

Table 10: Studies reporting severity scores of residual changes on CXR imaging performed following treatment for pulmonary TB

Author	Country	Study design	n	Participant HIV status	Treatment episode	Drug sensitivity	Timing of imaging	Source of severity score	Severity score description	Findings	Quality score
de Valliere, 2004 [171]	South Africa	Prospective cohort	33	Mixed	Not specified	MDR	On completion	Not specified	CXR split into 6 zones. Involvement of each zone scored 0-3. Total score 18.	Mean score 6.5/18	2/5
Ralph, 2010 [206]	Indonesia	Prospective cohort	152	Mixed	Not specified	Mixed	On completion	Ralph 2010 - diagnostic CXR scoring system	% lung affected + 40 if cavitation seen. Total score 140.	Median score 10/140, Range 0 - 115	3/5
Wang, 2010 [173]	Taiwan	Prospective cohort	98	Negative	Not specified	Not specified	1 year post completion	Not specified	Minimal / Moderate / Advanced fibrosis*	60.2% Minimal 14.3% Moderate 25.5% Advanced	3/5
Chen, 2011 [207]	Taiwan	Prospective cohort	51	Negative	Not specified	Not specified	On completion	McAdams & Erasmus 1995 - active TB CXR scoring system	Minimal / Extensive†	31.4% Extensive	3/5
Menon, 2015[199]‡	India	Retrospective cohort	441	Not specified	First episode	Fully sensitive	On completion	1969 National TB associate of the USA – diagnostic CXR scoring system	Minimal / Moderate / Moderately advanced / Far advanced	55.7% Minimal 22.8% Moderate 15.2% Moderately advanced 6% Advanced	2/5
How, 2014 [208]	Malaysia	Retrospective cohort	156	Mixed	Mixed	Not specified	On completion	1961 National TB association USA -diagnostic CXR scoring system [209]	Minimal / Moderate / Advanced disease¶	26.2% Minimal 60.8% Moderate 13% Advanced	2/5

Singla, 2009 [178]	India	Cross sectional	45	Negative	Not specified	MDR	6-63m post completion	1961 National TB association USA -diagnostic CXR scoring system[209]	Minimal / Moderate / Advanced disease¶	35.6% Minimal 22.2% Moderate 40.0% Advanced	1/4
Lisha, 2012 [201]	India	Cross sectional	224	Not specified	Mixed	Mixed	5 years post completion	1961 National TB association USA -diagnostic CXR scoring system [209]	Minimal / Moderate / Advanced disease¶	34.3% Minimal 13.4% Moderate 4.5% Advanced	2/4
Banu Rekha, 2009 [188]	India	Cross sectional	198	Not specified	First episode	Not specified	14 - 18 years post completion	Not specified	CXR divided into 6 zones, and zones counted	35.9% ≤2 zones 50% >2 zones	1/4
Godoy, 2012 [210]	Brazil	Cross sectional	18	Negative	Retreatment	MDR	On completion	Wilcox & Ferguson 1989 - diagnostic CXR scoring system [211]	Grade I - III#	61.1% Grade I 22.2% Grade II 16.7% Grade III	2/4
Ramos, 2009 [212]	Brazil	Retrospective cohort	37	Not specified	Not specified	Not specified	On completion	Wilcox & Ferguson 1989 - diagnostic CXR scoring system [211]	Grade I - III#	38% - Grade I 35% - Grade II 27% - Grade III	1/5
Baez-saldana, 2013 [213]	Mexico	Cross sectional	127	Mixed	Not specified	Not specified	0-252 months post completion	Created by authors for grading post-TB CXR changes & validated in study	CXR split into 4 quadrants. Involvement of each one scored 0-5. Total score 20.	Mean score 6.46/20 Standard deviation 4.14	2/4
de la Mora, 2015 [187]	Mexico	Cross sectional	70**	Not specified	Mixed	Mixed	Post completion. With CAO: 2.7+/- 4.3 yrs Without CAO: 2.3 +/- 2.1 yrs	Not specified	Number of lung quadrants with fibrocavitatory changes. Total number of cavities	With CAO: 1.8 +/-0.8 affected quadrants, 1.4 +/- 0.8 cavities Without CAO: 1.3 +/- 0.6 affected quadrants, 0.5 +/- 0.7 cavities	1/4
Kenangalem, 2013 [176]	Indonesia	RCT - Vit D / L-argenine	77	Mixed	First episode	Mixed	On completion	Ralph 2010 - diagnostic CXR scoring system	% lung affected + 40 if cavitation seen Total score 140	Papuans: Median score 6/140, Range 2-15 Non papuans: Median score 12.5/140, Range 4-20.5	2/5

* Minimal- mild - lung fibrosis <50% of RUL, no change in architecture/ clouding or lung marking or vasculature. Moderate - lung fibrosis >50% of RUL, no change in architecture/ clouding or lung marking or vasculature / lung collapse / tortuous airways / bronchiectasis. Advanced - fibrosis of whole RUL, combined with collapse, bronchiectasis and tortuous airways

†Minimal - slight to moderate density not containing cavitation with total extent not exceeding lung volume on one side above the chondro-sternal junction. Extensive - slight to moderate density extending more than total volume of one lung or equivalent in both lungs

‡Study included patients treated for pulmonary, pleural or mediastinal TB – no disaggregated data available, so all included here

¶Minimal - Unilateral or bilateral. Lesions of slight to moderate density with no cavitation. Involvement should not exceed space above 2nd chondrosternal junction and the spine of the 4th or body of 5th vertebra. Moderate - Unilateral or bilateral. Disseminated lesions of slight-moderate density may extend through total volume of 1 lung or equivalent in both lungs. Dense/confluent lesions limited to 1/3 of one lung. Total diameter of cavitation must be <4cm. Advanced - more extensive than moderate.

#Grade I - minimal change in 1 zone, with no cavities. Grade II - 2-3 zones involved, or 1 zone with cavitation. Grade III - severe involvement of >3zones, with or without cavitation

**Results stratified according to the presence of Chronic Airway Obstruction (CAO) on spirometry, as defined by a ratio of the post-bronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio <0.7, and the % predicted FEV_1< lower limit of normal: patients with CAO (n=24), without CAO (n=46). Mean and standard deviation for time since treatment and radiology findings given

4 THE BURDEN OF CHRONIC RESPIRATORY SYMPTOMS AND ABNORMAL SPIROMETRY IN URBAN MALAWI

4.1 INTRODUCTION

The systematic review presented in Chapter 3 has highlighted clear gaps in our understanding of the patterns and prevalence of post-TB lung damage in sSA. At the same time, as described in Chapter 2, data on the burden of CLDs in the African region are also lacking.

In order to provide some understanding of the background prevalence of respiratory exposures and CLD in urban Blantyre, against which PTB disease and post-TB lung damage are experienced, we did a population-level survey of respiratory symptoms and spirometry in an age and gender stratified sample of adults living in Chilomoni district of Blantyre. The study was conducted using the standardised community sampling approaches, data collection tools, and centralised quality control procedures established by the 2005 Burden of Obstructive Lung Disease (BOLD) initiative: a multi-country programme of work designed to measure the prevalence of airways disease in various global settings.[28]

Study design and data collection were led by Professor Kevin Mortimer, and data analysis and write up completed by myself as a PhD student. Findings were published in 2016 (Meghji et al. Am J Respir Crit Care Med. 2016;194(1):67-76).

4.2 METHODS

An age (18–39 and >40 years) and sex stratified population-representative sample of 2,000 adults was randomly taken from an enumerated population of Chilomoni district of urban Blantyre, Malawi. Fieldworkers conducted home visits to assess eligibility and to seek informed consent between February 2013 and August 2014. Individuals were excluded if they were not permanent residents of the area, were pregnant, or were acutely unwell. Up to three repeat visits were conducted to locate initially absent residents. A target sample size of 1,200 adults completing the study, split equally between men and women, and those aged 18 to 39 years and 40 years or older, was chosen to allow stratified prevalence estimates of spirometric abnormalities with acceptable precision, in accordance with the BOLD protocol.

Standardized BOLD questionnaires about respiratory symptoms and exposures were administered in the local language, Chichewa. Questions were asked about respiratory exposures including smoking

and biomass use, but no data were collected on marijuana use. Data on previous TB disease was collected through participant self-report only, and these reports were not verified against clinic registers. Pre- and post-bronchodilator spirometry was performed according to American Thoracic Society (ATS) standards using the ndd EasyOne Spirometer (ndd Medical Technologies; Zurich, Switzerland). Anthropometric measurements and a blood sample for HIV and haematology assays were taken. Participants were given the results of the clinical observations and spirometry measurements at the point of testing. HIV test results were communicated to participants who wished to know their results. Minimal questionnaire data were collected from patients who declined to participate in the full study. Quality assurance of questionnaire and spirometry data was provided by the central BOLD coordinating centre.

Two reference ranges were used for age, gender and height standardization of spirometry data: standardization using the NHANES III reference range was used to allow comparison with other BOLD study sites, and comparison with a local reference range generated using the spirometry data from non-smoking adults with no history of respiratory disease or symptoms who were included within this study was used for internal comparison. Patterns of spirometric deficit were described using the following definitions: spirometric obstruction (FEV1/FVC ratio<0.7), moderate-severe obstruction (FEV1/FVC ratio<0.7 & FEV1<80% predicted), and Low FVC (FEV1/FVC ratio≥0.7 & FVC<80% predicted). Fixed cut offs and % predicted values were used to facilitate comparison with other BOLD studies. The term spirometric restriction has been avoided here, in light of the limitations described above.

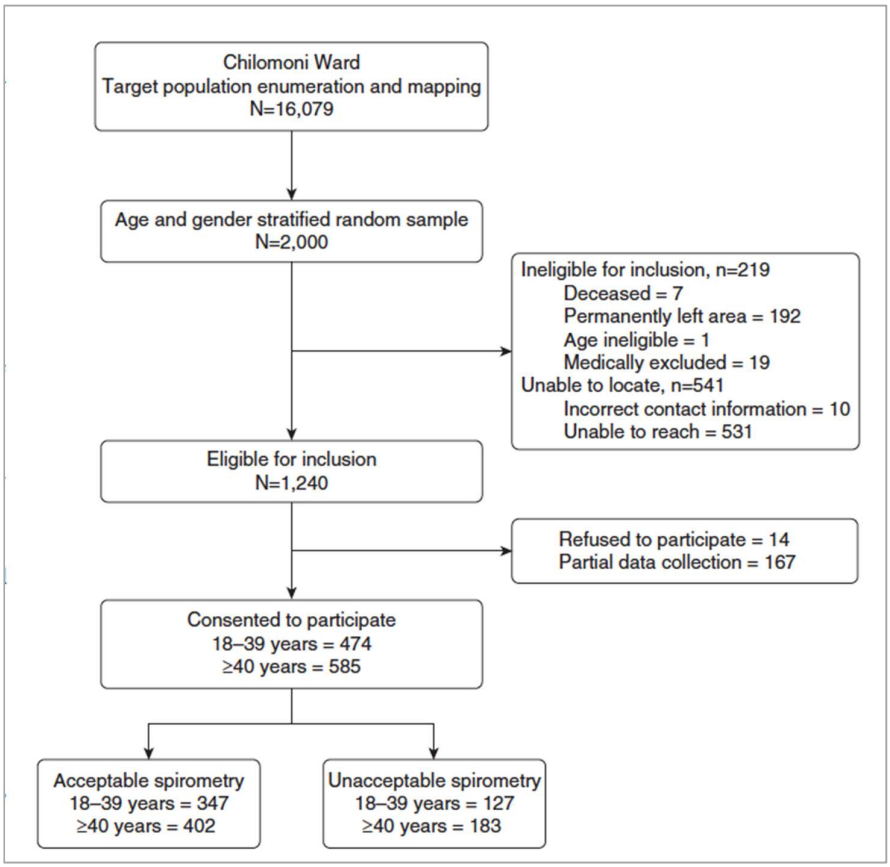
Survey weighting was used to calculate population representative prevalence estimates and develop regression models using the Svy package in Stata v12. Associations between spirometric abnormalities / symptoms and predictor variables were examined in bivariate and multivariable logistic regression models. Home ownership and household water and sanitation were used as proxy markers of socioeconomic status (SES), and no adjustments were made for multiple tests in exploratory analyses. A manual forward stepwise regression technique was used to develop multivariable models, with age and sex included a-priori, together with variables with a p-value 0.2 on bivariate analysis. Missing data were imputed using simple univariate procedures, and sensitivity analyses were used to compare results with complete case analyses. Ethical approval was given by the National Health Sciences Research Committee and the Liverpool School of Tropical Medicine Research Ethics Committee (Protocol 12.08).

4.3 RESULTS

The study flow diagram is shown in Figure 1. Of the 2000 randomly selected adults, 1469 (73.5%) were located by fieldworkers and 1240 (62.0%) were eligible for inclusion. Of eligible adults, 85.4% (1059/1240) consented to participate and completed the full questionnaire, with 70.7% (749/1059)

performing ATS standard spirometry (Figure 1). The 167 individuals who did not complete the full data questionnaire were more likely to be male (56.3% (94/167) vs. 42.1% (446/1059)) and ever-smokers (12.0% (20/167) vs 10.4% (110/1059)) compared to those contributing full data.

Figure 1: Participant recruitment flow diagram



4.3.1 PARTICIPANT CHARACTERISTICS

Mean participant age was 41.9 years (SD 15.3), and 57.9% were female. Overall 37.4% were educated to primary school level only. Although 59.3% of participants were from households that owned their own home, only 25.1% had access to flush toilets and 46.6% had a private indoor or outdoor water supply (Table 1). A total of 10.4% (110/1057) were ever smokers, with exposure was more frequently reported by men: 9.2% of men and 0.7% of women were current smokers; 12.8% of men and 1.3% of women were ex-smokers. 80.9% of those who had smoked reported <10 pack-years of exposure. Despite this study being conducted in an urban setting, 85.2% (900/1057) of the population reported use of a biomass fuel (mostly charcoal) for cooking or heating water on an open fire for ≥6 months, and 31.9% reported the use of an open fire burning wood, dung, or crop residues for heating water. Farming was the reported occupation of 29.2% of participants, even in this urban setting.

Table 1: Characteristics of participants completing full BOLD core questionnaire, including those with and without ATS standard spirometry

Variable (n)	Number (%) Mean (SD)	
Age group (n=1058)		
- 18-29	283	(26.8 %)
- 30-39	190	(18.0 %)
- 40-49	253	(23.9 %)
- 50-59	182	(17.2 %)
- 60-69	98	(9.3 %)
- 70+	52	(4.9 %)
Gender (n=1059)		
- Male	446	(42.1 %)
- Female	613	(57.9 %)
Level of education (n=1054)		
- None	59	(5.6 %)
- Primary	394	(37.4 %)
- Middle	391	(37.1 %)
- High school or college	210	(19.9%)
Years of education (n=1057)	9.29	4.35
HIV status (n=933)		
- Negative	707	(75.8 %)
- Positive	226	(24.2 %)
Self reported previous TB (n=1057)		
- No	1026	(97.1 %)
- Yes	31	(2.9 %)
Haemoglobin (g/dL) (n=936)	13.9	(1.80)
Eosinophil blood count >2% (n=927)		
- No	291	(31.4 %)
- Yes	636	(68.6 %)
BMI group (kg/m2) (n=972)		
- Underweight (BMI<18.5)	77	(7.9 %)
- Normal (18.5≥BMI<25)	568	(58.4 %)
- Overweight (25≥BMI<30)	202	(20.8 %)
- Obese (BMI≥30	125	(12.9 %)
Home ownership (n=1057)		
- Yes	627	(59.3 %)
- No	430	(40.7 %)
Access to private water supply (indoor OR outdoor tap) (n=1057)		
- Yes	492	(46.6 %)
- No	565	(53.4 %)
Household has flush toilet (n=1057)		
- Yes	265	(25.1 %)
- No	792	(74.9 %)
Smoking status (n=1057)		
- Ever	110	(10.4 %)
- Never	947	(89.6 %)
Pack years of smoking (n=1057)		
- 0 years	947	(89.6 %)
- >0 and <10years	89	(8.4 %)
- ≥10 years	21	(2.0 %)
Biomass exposure* (n=1057)		
- No	157	(14.8 %)
- Yes	900	(85.2 %)
Working in farming >3m (n=1056)		
- No	748	(70.8 %)
- Yes	308	(29.2 %)

*Use of charcoal/coal/coke or burning of wood/dung/crop residue for >6 months for cooking, or burning of wood/dung/crop residue for heating water

7.9% of the population had low BMI (<18.5 kg/m^2), 20.8% were overweight (BMI 25-30 kg/m^2), and 12.9% were obese (BMI>30 kg/m^2). The prevalence of self-reported previous TB within this cohort was 2.9% (31/1058). Data on HIV status were available for 88.1% of those who completed the core questionnaire, of whom 24.2% were HIV-infected. Haemoglobin levels were normally distributed with

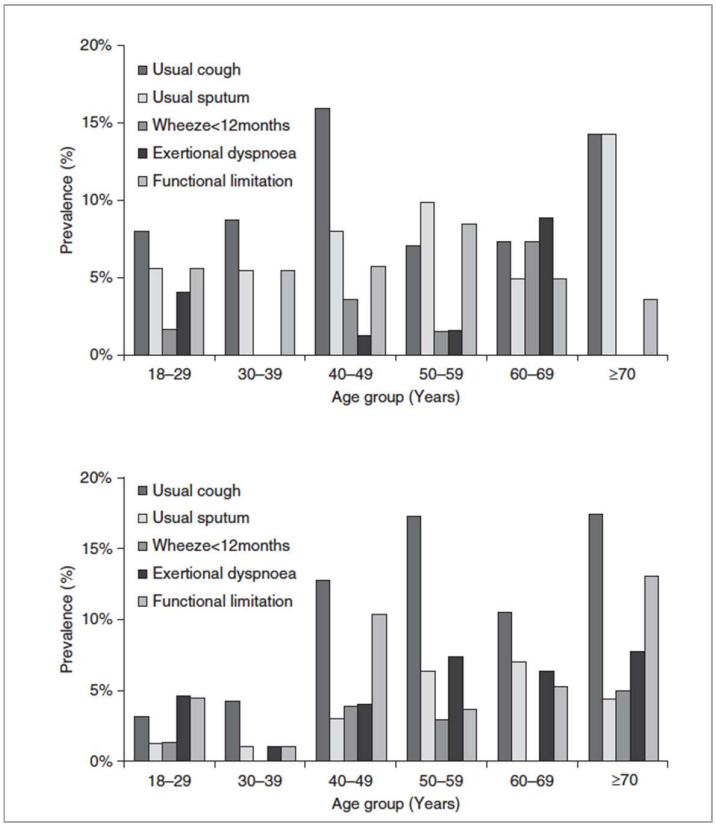
mean 13.9g/dL (SD 1.8) and range 6.7-21.4 g/dL. The median white cell count (WCC) was 5.0 (IQR: 4.1-5.9); 68.6% of participants had blood eosinophil counts exceeding 2.0% of the total WCC.

4.3.2 RESPIRATORY SYMPTOMS

Overall, 11.8% (SE: 1.2) of participants had at least one respiratory symptom, and 5.0% (SE: 0.8) reported respiratory problems interfering with their daily activities.

Cough was the most common symptom – current cough was reported by 7.5% (SE: 0.9) of participants, but chronic cough present on most days for >3 months/yr was reported by only 0.5% (SE: 0.2). Breathlessness was described by 3.6% (SE: 0.7) of participants, with 21.2% (SE: 8.5) of this group reporting severe functional impairment and stopping for breath after walking 100 yards on a flat surface (modified Medical Research Council breathlessness score = 3). Wheeze within the past year in the absence of an upper respiratory tract infection was reported by 1.4% (SE: 0.4) only. Sputum production, described as phlegm produced on most days for >3 months/yr, was the least common symptom, reported by only 0.2% (SE: 0.2) of all study participants (Table 2, Figure 2)

Figure 2: Age and gender stratified prevalence of respiratory symptoms: upper panel depicts symptom prevalence among men; lower panel depicts symptom prevalence among women. (N=1056)
The questions asked were as follows: Do you usually have a cough when you don't have a cold? (n = 1,056); Do you usually bring up phlegm from your chest? (n = 1,056); Have you had wheezing/whistling in your chest at any point in in the past 12 months, in the absence of a cold? (n = 1,007); Do you have shortness of breath when hurrying on the level or walking up a slight hill? (n = 970); and Have breathing problems interfered with your usual daily activities? (n = 1,056).

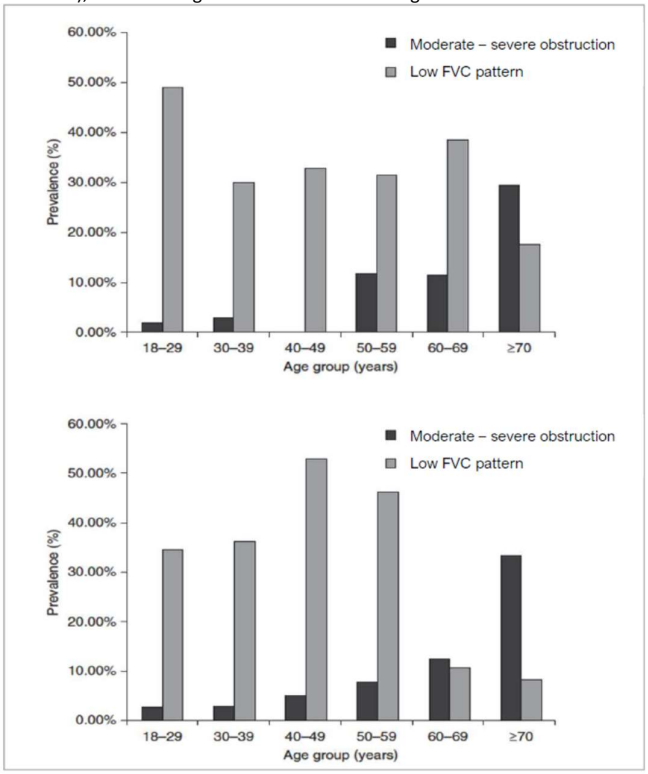


4.3.3 SPIROMETRY

Three factors were statistically significantly associated with completion of ATS standard spirometry: lower median age [41.0 years (IQR: 28-51) vs. 44.0 years, (IQR: 31-56), p<0.001], higher mean haemoglobin [14.07(SD 1.80) vs. 13.62(SD 1.76), p<0.001], and a greater average number of years of education [9.47(SD 4.20) vs. 8.85(4.65), p=0.036]. No other statistically significant differences were identified at alpha = 0.05 level between groups who did and did not complete spirometry.

Amongst the 749/1059 patients who performed ATS standard spirometry, 4.3% (SE 1.1) of men and 4.1% (SE 1.1) of women had post-bronchodilator obstruction (FEV1/FVC <0.7). A high proportion of this was at least moderate in severity: 3.2% (SE 1.0) of men and 3.9% (SE 1.0) of women had an FEV1 <80% predicted using the NHANES reference ranges, and 2.0% (SE 0.7) of men and 2.7% (SE 0.9) of women using local reference ranges. The prevalence of obstruction increased with age: any obstruction and moderate-severe obstruction were seen in 2.9% (SE 0.9) and 2.6% (SE 0.9) of 18-39 year olds, and 9.0% (SE 1.4) and 7.0% (SE 1.2) of ≥40 year olds. The number of participants in the Low FVC group was higher than that with obstruction in both genders and across age-group strata (Figure 3).

Figure 3: Age & gender stratified prevalence estimates for abnormal spirometry, amongst those completing ATS quality spirometry: upper panel depicts symptom prevalence among men; lower panel depicts symptom prevalence among women (n=749)
Moderate to severe airway obstruction ($FEV_1/FVC<0.7$ and $FEV_1<80\%$ predicted) and low FVC pattern ($FEV_1/FVC\geq0.7$ and $FVC<80\%$), defined using NHANES III reference ranges



The estimated prevalence of both the obstruction and low FVC groups were higher when NHANES III reference ranges were used, compared to local reference ranges (Table 3). This difference was particularly marked for low FVC: 38.6% (SE 2.1) were included within this category using the NHANES reference range, compared to (9.0%, SE 1.2) using locally derived reference ranges. Airway reversibility was present in 4.2% (0.8) of the cohort, but only 17.3% (SE 7.7) of those with reversibility had airway obstruction following bronchodilator.

4.3.4 FACTORS ASSOCIATED WITH RESPIRATORY SYMPTOMS

Ever smoking was positively associated with both cough and sputum production in bivariate analysis, and in multivariable analysis the odds of usual cough were 2.37 higher in current vs. never smokers (95% CI 1.12-5.02) (Table 4). The odds of regular sputum expectoration were 5.94 times higher (95% CI 1.95-18.06) in those with previous biomass exposure compared to those without. Employment in farming was positively associated with all symptoms in bivariate analyses, and the odds of exertional breathlessness remained significantly higher (OR 6.32, 95% CI: 1.87-21.32) in those employed in farming for >3 months compared to non-farmers in multivariable analysis.

Women were less likely to report cough or sputum production in bivariate analyses, and their odds of cough remained lower (OR 0.31, 95% CI 0.15-0.65) than men in multivariable analysis. Low BMI was positively associated with wheeze and sputum production in bivariate analysis, and the odds of usual sputum production remained 3.49 (95% CI 1.37 – 8.86) times higher in those with BMI<18.5kg/m^2 compared to normal weight in the multivariable model. No statistically significant relationships between symptoms and markers of SES or education persisted in multivariable models.

One-third of those with cough were HIV-infected, and a positive association was seen between cough and HIV-infection in multivariate analysis (OR 1.94, 95% CI 1.10-3.44). HIV-infection was not associated with other respiratory symptoms. Self reported previous TB was not statistically associated with any symptoms. Moderate-severe obstruction, Low FVC, or reversibility, defined using NHANES III reference ranges were not associated with respiratory symptoms (Table 5).

4.3.5 FACTORS ASSOCIATED WITH POST-BRONCHODILATOR AIRWAY OBSTRUCTION

Participant age was the factor most clearly associated with airway obstruction in bivariate and multivariable analyses, increasing in a non-linear fashion with a 10.12 times higher risk of moderate to severe obstruction (95% CI 3.54-28.93) in those aged ≥60 years compared to 18-29 year olds. This finding was also seen in the sensitivity analysis restricted to complete-case data. No association was seen between HIV-infection, ever smoking or biomass exposure and airway obstruction. Individuals

without access to private water supply had 2.44 times higher risk of moderate to severe obstruction in multivariable analysis (95% CI 1.01 – 5.88) (Table 6).

4.3.6 FACTORS ASSOCIATED WITH THE LOW FVC GROUP

BMI was strongly associated with having a reduced FVC and normal FEV_1/FVC ratio, as defined using NHANES III reference ranges: those who were underweight had 4.09 (95% CI 2.04-8.22) times higher odds of falling into this category compared to those with normal weight in the multivariable model. Older age was negatively associated with low FVC, and those aged over 60-years had 0.53 (95% CI: 0.29-0.96) times the odds of being in the low FVC category compared to the 18-29 year group. No other risk factors for a low FVC deficit were identified in the multivariable model (Table 7).

When the low FVC group was defined using local reference ranges, no clear trend in the relationship between age and reduced vital capacity emerged. The odds of being in the low FVC group were higher if underweight (OR 2.80, 95% CI 1.19-6.55) in bivariate analysis only. In multivariable analysis, previous TB was associated with higher odds of of being in the Low FVC group (OR 3.01, 95% CI 1.07-8.50).

4.4 DISCUSSION

Data from this population based cross-sectional study of non-communicable respiratory disease amongst adults in urban Blantyre, Malawi, suggested a high burden of chronic respiratory symptoms and abnormal spirometry within community. Cough was the most commonly reported symptom, and the prevalence of reduced FVC was particularly marked. Large differences were observed in the estimated prevalence of spirometric deficits using NHANES and locally defined reference ranges. No relationship between symptoms and spirometry were identified, and the role of previous TB disease in contributing to these findings remains unclear.

- #### THERE IS A HIGH BACKGROUND PREVALENCE OF CHRONIC LUNG PATHOLOGY IN MALAWI

The burden of respiratory symptoms and spirometric abnormalities seen in this 'well' outpatient population sample from urban Blantyre was high, with 11.8% (SE: 1.2) reporting at least 1 respiratory symptom, 4.2% (SE: 0.8%) noted to have an obstructive FEV1/FVC ratio on spirometry, and the prevalence of a reduced FVC pattern thought to lie between 9.0% (SE: 1.2%) – 38.6% (SE: 2.1%), depending on the reference range used. These findings are consistent with data presented above, from subsequent studies completed in rural Malawi which show a prevalence of respiratory symptoms of 12.6 – 22.5%, and abnormal spirometry in over 40% of adults.[33 39] Together, these findings suggests a high background prevalence of chronic respiratory abnormalities in the Malawian setting.

- ## LOW FVC IS THE DOMINANT PATTERN OF ABNORMALITY

The high prevalence of a reduced FVC is surprising, but has subsequently been reproduced in data from other BOLD study sites in sSA.[32] It is also of some concern, as low FVC has been shown to be associated with increased mortality, even in the absence of respiratory symptoms and a diagnosis of respiratory disease in both US and ecological studies.[18 106]

Full lung function testing and imaging were not completed within this study, such that it is not possible to determine the true cause of the low FVC seen here, but it is perhaps unlikely that this is the result of true restrictive lung pathologies which are thought to be rare. It may instead be the case that low lung volumes in resource poor settings such as Malawi are the result of impaired lung growth over the life course – early lung development is a well recognised determinant of adult lung volumes,[17] and suboptimal in-utero conditions, low birth weight, respiratory tract infections, and nutritional deficiencies which can predict adult lung health are more prevalent in resource poor settings.[214 215] The negative correlation seen between spirometric restriction and age here may represent a birth cohort effect, whereby the incidence of restriction is decreasing over time, but would also fit with earlier mortality amongst those with restriction. Prospective studies – perhaps with birth cohorts – are required to better understand the causes of low FVC in sSA, and the prognostic and public health implications of this finding.

Of note - within this data set, self-reported previous TB emerged as a strong risk factor for reduced FVC in multivariate analysis, and was associated with a three-fold increase in the odds of reduced FVC. However, this relationship was only seen when local reference ranges were used to define the low FVC group. The prevalence of previous TB was noted to be 2.9% only within this cohort – given the ongoing stigma surrounding TB disease in settings such as Blantyre,[43] there may have been some under-reporting and this figure may underestimate the true burden of previous disease within the study population. However, these data do suggest that whilst post-TB lung pathology might contribute to the burden of low FVC seen in this setting, it is unlikely to be the dominant cause.

- ## CHOICE OF REFERENCE RANGE IS IMPORTANT IN THE INTERPRETATION OF SPIROMETRY RESULTS

Data analysis for this study was complicated by the large differences in spirometry classification when local and NHANES III references were used. This was particularly marked for the low FVC pattern where prevalence estimates were 9.0 vs. 36.8% with the local vs. NHANES III ranges, compared to differences in estimates of moderate to severe obstruction which were 2.3% vs. 3.6% only.

As discussed in Chapter 2, the selection of a reference range is controversial, with genetic differences between sSA and Caucasian groups perhaps making the use of the NHANES III Caucasian range

inappropriate, and ubiquitous local exposures such as early childhood infections or maternal malnutrition limiting the ability of local reference ranges to define optimal lung function. The expected FVC values given by the Malawian reference range are clearly much lower than those given by the NHANES III range, such that more readings are considered abnormally low when the latter is used. This suggests that either the FVC volume is particularly vulnerable to either genetic differences, or to early childhood or environmental exposures which are prevalent in Malawi and drive differences in predicted norms between reference ranges.

- ## SMOKING, BIOMASS EXPOSURE AND HIV DO NOT EMERGE AS PREDICTORS OF OBSTRUCTION

It is noticeable that ever-smoking, biomass exposure, and HIV were not associated with airway obstruction within this cohort. This may be an issue of study power, given the surprisingly low prevalence of obstruction detected. However, it may also reflect a true lack of association, or limited / misclassified measurement of these exposures.

Although 10.4% of the cohort reported ever-smoking, almost 90% of these individuals had a pack year exposure of less than 10-years, such that the degree of exposure may have been too limited to impact on lung function. It should be noted that marijuana use, which may be particularly common amongst young men in Malawi, was not measured in this study, and may have been an additional but unmeasured source of respiratory damage.

The lack of association demonstrated with biomass exposure was initially thought likely to be related to misclassification, with self-reported fuel use acting as a poor measure of true exposures. However, subsequent data from a rural BOLD study conducted in Malawi failed to demonstrate any association between measured particulate matter ($PM_{2.5}$) and carbon monoxide (CO) levels with either FEV1 or FVC,[33] suggesting that this may be a true finding and that exposure to these pollutants is not a key driver of airway obstruction in this setting.

The lack of association between HIV and abnormal spirometry within these data contrast with findings from North American cohorts, which suggest an increased prevalence of airway obstruction in adults with HIV disease.[216] It has been suggested that this is the result of chronic immune activation seen in the context of HIV disease,[26] but in fact measures of HIV disease severity including CD4 count and viral load do not appear to be associated with the prevalence of abnormal spirometry,[217] and delayed time to ART does not appear to have pulmonary consequences,[218] suggesting that it may not be HIV disease itself which is driving airway obstruction in these groups but rather a high burden of associated exposures including smoking and respiratory infections. Whilst that lack of association between HIV disease and both airway obstruction and restriction in this cohort may be true, a more nuanced exploration of the relationship with time to ART and CD4 count may be helpful in confirming this.

The most consistent correlate of obstruction demonstrated in these data was lack of access to a private water supply independently associated with greater than 2-fold higher odds of airway obstruction regardless of which reference range was used. This measure is a proxy for socioeconomic situation of the individual, and is likely a marker of an individual's environmental exposures and opportunities, both historically and at the present time. The relationship between SES and obstruction is consistent with the strong socioeconomic gradients seen in other resource rich settings.[219] It is not possible to tease out the mechanism of these relationships, and it is not clear why this finding did not extent to the low FVC group, but these data do suggest that the poorest individuals are also the most vulnerable to airway obstruction in the Malawian setting.

- ## COUGH IS THE MOST COMMON SYMPTOM

Cough was the most common respiratory symptom reported, with 'usual cough' seen in 9.3% of men and 5.7% of women. The association with HIV raises the possibility that undiagnosed pulmonary tuberculosis may be responsible for part of this presentation.[125 220-223] However although current cough is one of the four symptoms included within the WHO TB symptom screening algorithm, its positive predictive value for TB disease may be low – data from the ZAMSTAR TB prevalence survey conducted in South Africa and Zambia suggest that only 2.1 - 6.0% of those with current cough were found to have culture proven TB disease,[224] suggesting that the majority of people with cough do not in fact have active TB disease. The association of chronic cough with ever smoking suggest that bronchial irritation from smoke inhalation may underlie these symptoms, and the degree to which this symptom represents chronic respiratory pathology rather than active infection is unclear.

In contrast, a low prevalence of sputum production was reported within this study, by only 4.0% of participants. Where it was seen it was associated with biomass exposure, although HIV status and previous TB exposure – both thought to be causes of bronchiectasis and potential causes of productive lung disease in this setting – were not correlated with its presence.

- ## UNDERLYING PATTERNS OF PATHOLOGY ARE UNCLEAR

No correlations were demonstrated between respiratory symptoms and spirometry results within this study, and imaging was not included, such that it is challenging to identify specific types of respiratory pathology underlying our findings.

However, a wide range of environmental exposures and host characteristics have been shown to be associated with the different respiratory symptoms and patterns of abnormal spirometry measured in this study: ever smoking, HIV status, involvement in farming, biomass exposure, BMI, and socioeconomic status have been highlighted in different multivariate models as associated with different outcomes. The diversity of these associations may suggest that, as one might expect within a large patient cohort, there are a range of pathological processes at play here. Further attempts to

define this spectrum of pathology, would be of help in guiding more nuanced diagnostic and management algorithms for respiratory disease which are specifically targeted to resource poor settings.

- ## THE ROLE OF TB IS UNCLEAR

Although previous TB was included as a covariate in many of the models constructed in this analysis, it is important to note that only self-reported disease was measured in this study – the extent to which this reflects true previous TB disease is unclear. TB is widely associated with HIV disease such that it is highly stigmatizing, and medical documentation in Malawi can be limited, such that there may have been some under-reporting of disease.

In this study, no association was observed between self-reported previous TB and airway obstruction / respiratory symptoms, and an association with low FVC was seen only when local reference ranges are used. In contrast, results from the rural BOLD study subsequently completed in Malawi, showed that self-reported TB disease (reported by 3.2% of the cohort) was in fact associated with both lower FEV_1 and FVC volumes. These differences in findings may in part be explained by the limited accuracy of self-reported previous TB disease.

Of note, many of the population-based studies of the relationship between previous TB and residual spirometric deficits described in the literature review above relied on self-reported TB disease to determine exposure. Under-reporting of previous disease and the resulting misclassification of exposure groups, will if anything, have led to underestimation of the difference in the prevalence of abnormal spirometry between groups, such that the increased odds of persistent abnormal spirometry may be even greater than estimated.

- ## STRENGTHS AND LIMITATIONS

Limitations of this study include the challenges posed by working with a mobile urban population: it was not possible to locate over 25% of the initial random sample, and 9.6% had permanently left the area between enumeration and fieldworker home visits. Few data are available on the demographics of these missing groups, and it is therefore difficult to determine how and to what extent this has biased our findings. In addition, only 71% of those who were included were able to complete adequate spirometry with fewer older individuals. As a result, the target sample size of 600 adults over and 600 adults under 40-years of age with high quality spirometry was not reached, and power to detect significant associations in the exploratory analyses was reduced.

Symptomatic individuals were not screened for pulmonary TB, and the proportion of abnormalities attributable to active TB disease, rather than background chronic lung pathology, are therefore unclear. In addition, the ability of this study to define the specific patterns of pathology underlying the

symptoms and abnormal spirometry detected is limited given the lack of imaging and measurement of total lung capacity, and given this was a cross sectional survey these data are unable to describe the impact of respiratory pathology on morbidity and mortality over time.

Lastly, in this study a stepwise approach to variable selection was used in regression analyses. In recent years there has been a move away from this approach in the literature, as it is thought that this strategy may not adequately control for confounding, and may misrepresent the causal relationships underlying the relationships being investigated.[225] The stepwise regression analyses used here are likely vulnerable to some bias, and must therefore be interpreted with some caution.

A key strength of this study was the enumeration of the target population at the start of the study, followed by age and gender stratified sampling, which allowed for population-weighted prevalence estimates to be drawn and associations to be measured. In addition, spirometry was conducted to ATS standards with careful quality control, and data on multiple respiratory exposures and comorbidities including HIV were collected.

4.5 CONCLUSION

This study provides a picture of the typical burden of respiratory abnormalities amongst 'well' community-based adults in urban Blantyre, Malawi, and sets the context for the data to be presented in Chapter 5 below. Key findings include the presence of respiratory symptoms amongst 11.8% (SE: 1.2), airway obstruction in 4.2% (SE: 0.8%), and dominant low-FVC pattern which was seen in 9.0% (SE: 1.2%) – 38.6% (SE: 2.1%) according to whether local or NHANES III reference ranges were used for standardization. Risk factors which might have been assumed to be driving abnormal spirometry in this setting, including smoking, biomass exposure and HIV infection, did not emerge as predictors, whilst low socioeconomic situation (SES) were associated with airway obstruction, and low BMI was associated with the low- FVC pattern.

Table 2: Age and gender stratified prevalence of respiratory symptoms amongst those completing core questionnaire

Definition of restriction	Age group	Male (n=446) Prevalence (SE)	Female (n=613) Prevalence (SE)	Total (n=1059) Prevalence (SE)
Cough (Do you usually cough when you don't have a cold?)	18-29 years	8.0 % (2.4%)	3.2% (1.4%)	5.4% (1.4%)
	30-39yrs	8.7% (2.9%)	4.1% (2.0%)	6.6% (2.8%)
	40-49yrs	15.9% (3.9%)	12.7% (2.6%)	14.4% (2.4%)
	50-59yrs	7.0% (3.0%)	17.3% (3.6%)	11.9% (2.4%)
	60-69yrs	7.3% (4.1%)	10.5% (4.1%)	8.8% (2.9%)
	≥70yrs	14.3% (6.6%)	17.4% (7.9%)	15.7% (5.1%)
	TOTAL	9.3% (2.5%)	5.7% (1.0%)	7.5% (0.9%)
Sputum (Do you usually bring up phlegm from your chest?)	18-29 years	5.6% (2.1%)	1.3% (0.9%)	3.3% (1.1%)
	30-39yrs	5.4% (2.4%)	1.0% (1.0%)	3.4% (2.4%)
	40-49yrs	8.0% (2.9%)	2.4% (1.2%)	5.3% (1.6%)
	50-59yrs	9.9% (3.5%)	6.4% (2.3%)	8.2% (2.2%)
	60-69yrs	4.9% (3.4%)	7.0% (3.4%)	5.9% (2.4%)
	≥70yrs	14.3% (6.6%)	4.3% (4.3%)	9.8% (4.2%)
	TOTAL	6.3% (2.3%)	2.8% (0.6%)	4.0% (0.7%)
Wheeze (Have you had wheezing / whistling in your chest at any point in past 12m, in the absence of a cold)	18-29 years	1.6% (1.1%)	1.3% (0.9%)	1.4% (0.7%)
	30-39yrs	0	0	0
	40-49yrs	3.4% (2.9%)	3.6% (1.5%)	3.5% (1.2%)
	50-59yrs	1.4% (1.4%)	2.7% (1.6%)	2.0% (1.0%)
	60-69yrs	7.3% (4.1%)	0	3.9% (2.2%)
	≥70yrs	0	4.3% (4.3%)	2.0% (2.0%)
	TOTAL	1.5% (0.6%)	1.3% (0.5%)	1.4% (0.4%)
MRC dyspnoea II * (Do you have shortness of breath when hurrying on the level or walking up a slight hill?)	18-29 years	4.0% (1.8%)	4.6% (1.7%)	4.3% (1.2%)
	30-39yrs	0	1.0% (1.0%)	0.5% (0.5%)
	40-49yrs	1.2% (1.2%)	4.1% (1.6%)	3.0% (1.0%)
	50-59yrs	1.6% (1.6%)	7.4% (2.7%)	4.3% (1.5%)
	60-69yrs	8.8% (4.9%)	6.4% (3.6%)	7.7% (3.1%)
	≥70yrs	0	7.7%(7.4%)	3.0% (2.9%)
	TOTAL	2.3% (0.9%)	3.8% (1.0%)	3.1% (0.7%)
Any respiratory symptom† (Any of cough, sputum, wheeze without cold, exertional breathlessness as above)	18-29 years	11.2% (2.8%)	8.4% (2.2%)	9.7% (1.8%)
	30-39yrs	12.1% (3.4%)	5.2% (2.2%)	8.9% (2.1%)
	40-49yrs	20.0% (4.3%)	18.4% (3.1%)	19.3% (2.8%)
	50-59yrs	18.5% (4.8%)	27.7% (4.5%)	22.9% (3.3%)
	60-69yrs	20.6% (6.9%)	20.4% (5.8%)	20.5% (4.5%)
	≥70yrs	21.7% (8.6%)	31.3% (11.6%)	25.7% (7.0%)
	TOTAL	13.4% (1.8%)	10.2% (1.4%)	11.8% (1.2%)
Functional limitation (Have breathing problems interfered with your usual daily activities)	18-29 years	5.6% (2.1%)	4.4% (1.6%)	5.0% (1.3%)
	30-39yrs	5.4% (2.4%)	1.0% (1.0%)	3.4% (1.4%)
	40-49yrs	5.7% (2.5%)	10.3% (2.4%)	7.9% (1.7%)
	50-59yrs	8.5% (3.3%)	3.6% (1.8%)	6.2% (1.9%)
	60-69yrs	4.9% (3.4%)	5.3% (3.0%)	5.1% (2.3%)
	≥70yrs	3.6% (3.5%)	13.0% (7.0%)	7.9% (3.8%)
	TOTAL	5.7% (1.2%)	4.3% (1.0%)	5.0% (0.8%)

*Excluding 86 patients with alternative reasons for mobility impairment

†Excluding 60 patients with alternative reasons for mobility impairment & no other respiratory symptoms

Table 3: Age & gender stratified prevalence estimates for abnormal spirometry, amongst those completing ATS quality spirometry

Spirometric definition (Reference range)	Age group	Male (n=328) Prevalence (SE)	Female (n=421) Prevalence (SE)	Total (n=748) Prevalence (SE)
Post bronchodilator obstruction FEV1/FVC Ratio <0.7	18-29 years	2.0% (1.4%)	2.7% (1.6%)	2.4% (2.0%)
	30-39yrs	4.5% (2.5%)	2.9% (2.0%)	3.8% (1.7%)
	40-49yrs	0	6.7% (2.3%)	3.1% (1.1%)
	50-59yrs	12.7% (4.8%)	7.7% (3.0%)	10.9% (2.9%)
	60-69yrs	23.1% (8.3%)	15.6% (6.4%)	19.8% (5.4%)
	≥70yrs	41.2% (12.0%)	33.3% (13.6%)	37.9% (9.0%)
	TOTAL	4.3% (1.1%)	4.1% (1.1%)	4.2% (0.8%)
Post bronchodilator moderate to severe obstruction FEV1/FVC ratio <0.7 AND FEV1<80% predicted NHANES ref range	18-29 years	2.0% (1.4%)	2.7% (1.6%)	2.4% (1.0%)
	30-39yrs	3.0% (2.1%)	2.9% (2.0%)	2.9% (1.5%)
	40-49yrs	0	5.0% (2.0%)	2.3% (0.9%)
	50-59yrs	11.8% (4.5%)	7.7% (3.0%)	9.8% (2.8%)
	60-69yrs	11.5% (6.3%)	12.5% (5.9%)	12.0% (4.4%)
	≥70yrs	29.4% (11.1%)	33.3% (13.6%)	31.0% (8.6%)
	TOTAL	3.2% (1.0%)	3.9% (1.0%)	3.6% (0.7%)
Post bronchodilator moderate to severe obstruction FEV1/FVC ratio <0.7 AND FEV1<80% predicted Locally derived ref range	18-29 years	2.0% (1.4%)	2.7% (1.6%)	2.4% (1.0%)
	30-39yrs	0	0	0
	40-49yrs	0	3.4% (1.7%)	1.5% (0.8%)
	50-59yrs	7.8% (3.8%)	7.7% (3.0%)	7.8% (2.4%)
	60-69yrs	7.7% (5.2%)	6.3% (4.3%)	7.1% (3.5%)
	≥70yrs	23.5% (10.3%)	25.0% (12.5%)	24.1% (8.0%)
	TOTAL	2.0% (0.7%)	2.7% (0.9%)	2.3% (0.6%)
Low FVC FEV1/FVC Ratio>0.7, AND FVC<80% predicted NHANES ref range	18-29 years	49.0% (5.0%)	34.5% (4.5%)	41.7% (3.4%)
	30-39yrs	29.9% (5.6%)	36.2% (5.8%)	32.7% (4.0%)
	40-49yrs	32.8% (5.6%)	52.9% (4.6%)	42.0% (3.8%)
	50-59yrs	31.4% (6.5%)	46.2% (5.7%)	28.3% (4.4%)
	60-69yrs	38.5% (9.6%)	10.6% (8.7%)	39.4% (6.6%)
	≥70yrs	17.6% (9.3%)	8.3% (8.0%)	13.8% (6.4%)
	TOTAL	39.5% (3.1%)	37.7% (2.9%)	38.6% (2.1%)
Low FVC FEV1/FVC Ratio>0.7, AND FVC<80% predicted Locally derived ref range	18-29 years	13.0% (3.4%)	8.2% (2.6%)	10.6% (2.1%)
	30-39yrs	4.5% (2.5%0	4.3% (2.5%)	4.4% (1.8%)
	40-49yrs	13.4% (4.2%)	10.9% (2.9%)	12.3% (2.6%)
	50-59yrs	5.9% (3.3%)	10.3% (3.4%)	7.9% (2.4%)
	60-69yrs	15.4% (7.1%)	12.5% (5.9%(	14.1% (4.7%)
	≥70yrs	11.8% (7.8%)	0	6.9% (4.7%)
	TOTAL	10.2% (1.9%)	7.6% (1.6%)	9.0% (1.2%)
Airway reversibility FEV1 increase ≥200ml AND ≥12% following bronchodilator	18-29 years	4.0% (2.0%)	3.6% (1.8%)	3.8% (1.3%)
	30-39yrs	1.5% (1.5%)	2.9% (2.0%)	2.1% (1.2%)
	40-49yrs	7.4% (3.2%)	9.2% (2.6%)	8.2% (2.1%)
	50-59yrs	7.8% (3.8%)	6.5% (2.8%)	7.2% (2.4%)
	60-69yrs	3.8% (3.8%)	3.0% (3.0%)	3.5% (2.5%)
	≥70yrs	5.9% (5.7%)	16.7% (10.8%)	10.4% (5.7%)
	TOTAL	4.0% (1.2%)	4.4% (1.1%)	4.2% (0.8%)

Table 4: Bivariate and multivariable associations with respiratory symptoms‡ in all age groups, n=1056

Variable	Usual cough (n=103)				Usual sputum (n=51)				Exertional dyspnoea (n=35)				Wheeze (n=21)			
	Bivariate		Multivariate		Bivariate		Multivariate		Bivariate		Multivariate		Bivariate		Multivariate	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Age group																
- 18-29	1.0	-	1.0	-	1.0	-	1.0	-	1.0	-	1.0	-	1.0	-	1.0	-
- 30-39	1.24	0.56-2.71	0.97	0.44-2.17	1.05	0.36-3.00	1.12	0.38-3.12	0.11	0.01-0.82•	0.09	0.01-0.80*	Empty	-	Empty	-
- 40-49	2.96	1.55-5.65*	2.37	1.19-4.71*	1.68	0.67-4.22	1.97	0.75-5.16	0.57	0.21-1.53	0.28	0.08-1.03	2.53	0.75-8.58	1.97	0.48-8.06
- 50-59	2.37	1.20-4.70*	1.82	0.87-3.81	2.66	1.11-6.36•	3.64	1.43-9.26*	0.98	0.39-2.50	0.40	0.11-1.42	1.44	0.35-6.01	0.99	0.17-5.73
- ≥60	2.21	1.07-4.60	1.81	0.85-3.86	2.31	0.93-5.76•	2.32	0.82-6.55	1.48	0.56-3.93	0.74	0.18-3.00	2.31	0.57-9.44	1.39	0.24-7.93
Gender																
- Male	1.0	-	1.0	-	1.0	-	-	-	1.0	-	1.0	-	1.0	-	1.0	-
- Female	0.59	0.36- 0.99*	0.72	0.41-1.27	0.28	0.13-0.60•	0.31	0.15-0.65*	1.63	0.66-4.03	1.78	0.68-4.68	0.87	0.29-2.66	0.41	0.13-1.27
Years of education	0.92	0.87 - 0.97*			0.93	0.85-1.00†			0.93	0.86-1.00†			1.05	0.93 – 1.19		
Smoking status																
- Never	1.0	-	1.0	-	1.0	-			1.0	-			-	-		
- Ever	3.03	1.55 – 5.92*	2.37	1.12-5.02*	3.71	1.58–8.70•			1.16	0.32 – 4.22			0.25	0.03-1.93†		
HIV status§																
- Negative	1.0	-	1.0	-	1.0	-			1.0	-			1.0	-		
- Positive	2.12	1.19-3.78*	1.94	1.10-3.44*	1.60	0.76-3.37			0.99	0.32-3.02			0.99	0.32-3.04		
Haemoglobin (g/dL)§	0.96	0.82 – 1.13			1.26	1.03 -1.53•			0.86	0.69-1.06†			0.770	0.60-0.99•	0.74	0.58-0.94*
Eosinophil blood count >2%																
- No	1.0	-			1.0	-			1.0	-			1.0	-		
- Yes	1.25	0.67 – 2.34			1.34	0.57-3.17			0.78	0.30-1.99			1.33	0.33-5.31		
BMI (kg/m2)																
Underweight (<18.5)	1.17	0.46 – 2.97			4.33	1.71-10.95•	3.26	1.32-8.07*	1.61	0.34-7.52			6.10	1.37-27.07•	5.38	1.23-23.50*
Normal (18.5-25)	1.0	-			1.0	-	1.0	-	1.0	-			1.0	-	1.0	-
Overweight (25 - 30)	0.75	0.38-1.48			0.39	0.15-1.02†	0.37	0.15-0.91*	0.77	0.21-2.83			0.87	0.16 -4.73	1.16	0.26-5.16
Obese (≥30)	0.51	0.25-1.06†			1.41	0.46-4.31	1.15	0.31-4.30	1.75	0.56-5.51			3.59	0.61-21.00	5.47	0.93-32.38
Self reported previous TB																
- No	1.0	-			1.0	-			1.0	-			1.0	-		
- Yes	2.18	0.74-6.44†			1.79	0.38-8.33			2.61	0.55-12.47			Empty	-		
Does household own own home																
- Yes	1.0	-			1.0	-			1.0	-			1.0	-		
- No	0.87	0.51-1.47			0.71	0.35-1.47			0.72	0.30-1.74			0.44	0.14-1.45†		
Household has own water supply (indoor OR outdoor tap)																
- Yes	1.0	-			1.0	-			1.0	-			1.0	-		
- No	1.75	1.02-3.00•			1.06	0.52-2.19†			1.30	0.54-3.11			0.80	0.26-2.44		
Household has flush toilet																
- Yes	1.0	-			1.0	-	1.0	-	1.0	-			1.0	-		
- No	1.13	0.61-2.10			0.56	0.26-1.20†	0.42	0.19-0.91*	0.58	0.23-1.44			0.49	0.15-1.59		

Any biomass exposure†																
- No	1.0	-			1.0	-	1.0		1.0	-			1.0	-		
- Yes	1.39	0.62-3.15			5.46	1.85-16.25•	7.05	2.28-21.80*	0.60	0.21-1.72			0.51	0.12-2.12		
Farming >3m																
- No	1.0	-			1.0	-			1.0	-	1.0	-	1.0	-		
- Yes	2.31	1.35-3.94•			2.31	1.14-4.70•			4.30	1.80-10.31•	6.32	1.87-21.32*	2.81	0.92-8.52†		

* p<0.05

†Use of charcoal/coal/coke or burning of wood/dung/crop residue for >6 months for cooking, or burning of wood/dung/crop residue for heating water

‡Presence of respiratory symptoms ascertained using the following questions, derived from the BOLD study core questionnaire:

Usual cough: Do you usually cough when you don't have a cold?

Usual sputum: Do you usually bring up phlegm from your chest, or do you usually have phlegm in your chest that is difficult to bring up, when you don't have a cold?

Exertional dyspnea: Are you troubled by breathlessness when hurrying on the level or walking up a slight hill?

Wheeze: Have you had wheeze/whistling in your chest at any time in the past 12months? In the last 12 months have you had this wheeze or whistling only when you have had a cold? (exclude if yes to the latter question)

§Imputation of data required for 11.9% of HIV values, and 11.8% of haemoglobin values. Imputation of all other values ≤0.1

Table 5: Bivariate associations between respiratory symptoms and abnormal spirometry

Variable	Usual cough (n=103/1056)		Usual sputum (n=51/1056)		Exertional breathlessness (n=35/970)		Wheeze without cold (n=21/1056)	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Airway obstruction*								
- No	1.0	-	1.0	-	1.0	-	1.0	-
- Yes	1.11	0.44-2.80	1.64	0.60-4.51	0.98	0.20-4.83	2.99	0.73-12.33
Spirometric restriction*								
- No	1.0	-	1.0	-	1.0	-	1.0	-
- Yes	0.82	0.44-1.53	1.52	0.69-3.37	2.79	0.87-8.91	2.80	0.86-9.0.9
Reversibility								
- No	1.0	-	1.0	-	1.0	-	1.0	-
- Yes	2.28	0.80-6.52	1.91	0.40-9.08	Empty	-	2.52	0.61-10.3

*Defined using NHANES reference range

Table 6: Bivariate and multivariable associations of risk factors with post bronchodilator airway obstruction, n=749

Outcome variable	Post bronchodilator airway obstruction (FEV1/FVC ratio <0.7)				Post bronchodilator mod-severe airway obstruction, NHANES III (FEV1/FVC ratio <0.7 & FEV1<80% predicted)			
	Bivariate association		Multivariable association§		Bivariate association		Multivariable association	
Predictor variable	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Age group								
- 18-29	1.0	-	1.0	-	1.0	-	1.0	-
- 30-39	1.61	0.45 – 5.72	1.76	0.50 - 6.20	1.25	0.33-4.79	1.38	0.36-5.25
- 40-49	1.31	0.42 – 4.09	1.22	0.38 - 3.89	0.97	0.29-3.26	0.93	0.27-3.15
- 50-59	5.03	1.73 – 14.67*	5.16	1.77 – 15.03*	4.50	1.52-13.29	4.66	1.58-13.79*
- ≥60	14.33	5.18 - 39.60*	15.76	5.71 – 43.46*	9.22	3.24-26.27	10.12	3.54-28.93*
Gender								
- Male	1.0	-	1.0	-	1.0	-	1.0	-
- Female	0.97	0.46 – 2.04	1.10	0.50-2.39	1.20	0.53-2.75	1.34	0.57-3.17
Years of education (yrs)	0.88	0.82 – 0.94*			0.88	0.81-0.94*		
HIV status								
- Negative	1.0	-			1.0	-		
- Positive	1.32	0.50 – 3.44			0.93	0.30-2.89		
Self reported previous TB								
- No	1.0	-			1.0	-		
- Yes	1.28	0.28 – 5.96			1.54	0.33-7.23		
Haemoglobin (g/dL)	0.89	0.75-1.06†			0.89	0.73-1.09		
Eosinophil blood count >2%								
- No	1.0	-			1.0	-		
- Yes	1.92	0.73-5.06†			2.51	0.70-9.05†		
BMI (kg/m2)								
- Underweight (BMI<18.5)	2.08	0.64 – 6.74			2.36	0.71-7.78		
- Normal (18.5≥BMI<25)	1.0	-			1.0	-		
- Overweight (25≥BMI<30)	0.86	0.35 - 2.13			0.79	0.29-2.20		
- Obese (BMI≥30)	1.43	0.39 – 5.19			0.54	0.15-2.00		
Smoking status								
- Never	1.0	-			1.0	-		
- Ever	1.25	0.57-2.73			0.94	0.38-2.35		
Home ownership								
- Yes	1.0	-			1.0	-		
- No	1.08	0.52-2.27			1.10	0.49-2.48		
Access to private water supply (indoor OR outdoor tap)								
- Yes	1.0	-	1.0	-	1.0	-	1.0	-
- No	2.29	1.07-4.91*	2.55	1.14 – 5.71*	2.23	0.95-5.23†	2.44	1.01-5.88*
Household has flush toilet								
- Yes	1.0	-			1.0	-		
- No	1.67	0.61-4.53			1.57	0.52-4.78		
Any biomass exposure‡								
- No	1.0	-			1.0	-		
- Yes	2.55	1.00-6.50†			2.10	0.81-5.47†		
Working in farming >3m								
- No	1.0	-			1.0	-		
- Yes	1.79	0.87-3.70†			1.62	0.72-3.66		

* p<0.05 † p<0.2 ‡Use of charcoal/coal/coke or burning of wood/dung/crop residue for >6 months for cooking, or burning of wood/dung/crop residue for heating water §Multivariable model developed using variables correlated at p<0.2 level in bivariate analysis, and age group & gender as *a priori* risk factors, with imputation for missing data.

Table 7: Bivariate and multivariable associations of risk factors with reduced FVC, n=749

Outcome variable	Low FVC, NHANES III (FEV1/FVC ratio >0.7 & FVC >80% predicted)				Low FVC, local reference ranges (FEV1/FVC ratio >0.7 & FVC >80% predicted)			
	Bivariate association		Multivariable association§		Bivariate association		Multivariable association	
Predictor variable	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Age group								
- 18-29	1.0	-	1.0	-	1.0	-	1.0	-
- 30-39	0.68	0.43-1.07	0.64	0.40-1.02	0.39	0.15-1.00†	0.38	0.15-0.97*
- 40-49	1.02	0.67-1.53	1.00	0.66-1.53	1.19	0.62-2.27	1.06	0.55 – 2.05
- 50-59	0.87	0.55-1.37	0.85	0.52-1.38	0.73	0.34-1.59	0.64	0.28 – 1.48
- ≥60	0.63	0.37-1.07	0.53	0.29-0.96*	1.12	0.50-2.52	1.08	0.48 – 2.41
Gender								
- Male	1.0	-	1.0	-	1.0	-	1.0	-
- Female	0.93	0.65-1.32	0.95	0.65-1.40	0.73	0.40-1.33	0.70	0.38-1.28
Years of education (years)	1.00	0.96-1.05			0.96	0.91-1.02		
BMI (kg/m2)								
- Underweight (BMI<18.5)	3.91	1.98-7.73*	4.09	2.04-8.22*	2.80	1.19-6.55*		
- Normal (18.5≥BMI<25)	1.0	-	1.0	-	1.0	-		
- Overweight (25≥BMI<30)	1.02	0.65-1.62	1.07	0.66-1.73	1.20	0.54-2.67		
- Obese (BMI≥30)	1.37	0.77-2.44	1.58	0.85-2.96	0.92	0.41-2.03		
Haemoglobin (g/dL)	1.00	0.90-1.15			1.13	0.91 – 1.41		
Eosinophil blood count >2%								
- No	1.0	-			1.0	-		
- Yes	0.972	0.65 -1.46			1.05	0.53 – 2.07		
HIV status								
- Negative	1.0	-			1.0	-		
- Positive	1.29	0.83-1.99			1.23	0.60-2.49		
Self-reported previous TB								
- No	1.0	-			1.0	-	1.0	-
- Yes	2.34	0.89-6.18†			2.74	0.94-7.96†	3.01	1.07 -8.50*
Smoking status								
- Never	1.0	-			1.0	-		
- Ever	0.95	0.54-1.67			0.80	0.30 -2.14		
Home ownership								
- Yes	1.0	-			1.0	-		
- No	0.82	0.57-1.17			1.25	0.69-2.27		
Access to private water supply (indoor OR outdoor tap)								
- Yes	1.0	-			1.0	-		
- No	0.91	0.64-1.30			1.62	0.88-2.98		
Household has flush toilet								
- Yes	1.0	-			1.0	-		
- No	0.86	0.57-1.28			1.19	0.59-2.43		
Any biomass exposure‡								
- No	1.0	-			1.0	-		
- Yes	1.00	0.62-1.63			1.19	0.51-2.79		
Working in farming >3m								
- No	1.0	-			1.0	-		
- Yes	0.88	0.58-1.32			0.98	0.49-1.98		

* p<0.05 † p<0.2 ‡Use of charcoal/coal/coke or burning of wood/dung/crop residue for >6 months for cooking, or burning of wood/dung/crop residue for heating water §Multivariable model developed using variables correlated at p<0.2 level in bivariate analysis, and age group & gender as *a priori* risk factors, with imputation for missing data.

5 POST-TB LUNG DAMAGE IN MALAWIAN ADULTS: A PROSPECTIVE COHORT STUDY

5.1 INTRODUCTION

In Chapter 3 our limited understanding of the prevalence, patterns, and outcomes associated with post-TB lung damage was described. Despite the ongoing high incidence of TB disease in the African region where estimated incident rates remain 254/100,000 and 30% of new TB patients are HIV co-infected, a surprising lack of data from sSA and HIV-infected adults was highlighted. The prospective cohort study of post-TB lung damage amongst HIV-infected and -uninfected adults in Malawi which is presented here is a direct response to this lack of data. This work was done in urban Blantyre, and draws on the background data on the burden of respiratory abnormalities amongst community based adults in this setting which was presented in Chapter 4, for comparison.

The overarching hypothesis for this study was that a subset of both HIV-infected and -uninfected adult participants completing treatment for PTB in this setting have post-TB lung damage, which is clinically relevant, and associated with adverse outcomes. This study is presented in full in here, according to STROBE reporting recommendations.

5.1.1 AIMS & OBJECTIVES

The overall aim of this study was to determine the prevalence and pattern of post-TB lung damage amongst adults in urban Blantyre, Malawi, and to define the impact of this damage on patients' lives and livelihoods.

The specific objectives were:

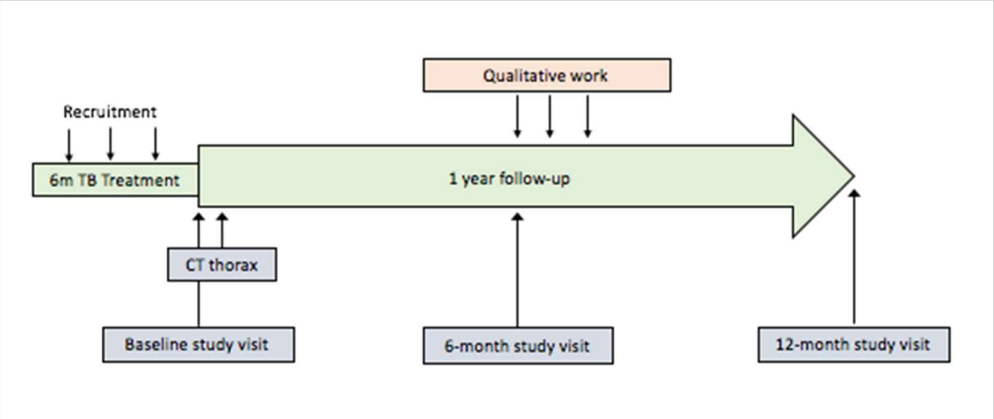
1. To determine the prevalence and pattern of post-TB lung damage in HIV infected and uninfected adults completing treatment for pulmonary tuberculosis in urban Blantyre.
2. To determine the morbidity and mortality experienced by patients in the 12-months following PTB treatment completion, and their relationship to residual post-TB lung damage.
3. To determine the ongoing costs and dissaving experienced by patients in the 12-months following PTB treatment completion.

5.2 METHODS

5.2.1 STUDY DESIGN

This was a prospective cohort study of adults aged ≥15 years completing treatment for pulmonary TB in urban Blantyre, Malawi, with a 1-year follow up period (Figure 1). Ethics approval was provided by the College of Medicine Research and Ethics Committee (COMREC) in Malawi (P.10/15/1813) and The Liverpool School of Tropical Medicine Research Ethics Committee in the UK (15.040RS).

Figure 1: Schematic for study design



5.2.2 STUDY SETTING

The PTB services and local context in Blantyre and Malawi were described in the introductory chapter of this thesis. Within this study, data were collected at three time points: at PTB treatment completion (+/- 2 weeks), and 6- and 12- months (+/- 4 weeks) after treatment completion. The baseline and 12-month study visits were performed at the local referral hospital (Queen Elizabeth Central Hospital (QECH)), whilst the 6-month visit was completed at the participant household. Screening and recruitment were completed between February 2016 – April 2017, and follow up was completed in April 2018.

5.2.3 PARTICIPANTS

- ELIGIBILITY

Adults living in urban Blantyre were eligible for recruitment to the study within the final 2-months of a first treatment course for PTB disease. All those who had been defined as having PTB by the National Treatment Programme were eligible, including both those with and without microbiological confirmation of disease (Table 1).

TB treatment outcomes were verified at the point of PTB treatment completion. Individuals with treatment success (completion or cure) were included, but those who had defaulted / failed treatment by this time point were excluded. Individuals with treatment success who remained symptomatic with a positive TB symptom screen (current cough, fever, weight loss, night sweats) at PTB treatment completion, were asked to submit a sputum sample for smear and culture, and if positive for MTB were excluded.

Table 1: inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Informed consent ≥15yrs years of age Resident of urban Blantyre Pulmonary Tuberculosis, as defined by National Treatment Programme First episode of PTB treatment Treatment completion or cure	WHO danger signs (confused or agitated, unable to walk unaided, respiratory distress, temperature >39, systolic blood pressure <90mmHg) Treatment failure / default

- RECRUITMENT

Sequential participants were recruited from 9 TB treatment centres in urban Blantyre. These were located at district health centres (n=6), the tertiary referral hospital QECH (n=1), and two small private hospitals (n=2), and were the main providers of TB services to the population.

Potentially eligible patients were identified by TB officers in these centres and referred to the central study offices at QECH for formal assessment, informed consent and enrolment by trained study staff. Consent was taken from the guardian with assent from the adolescent for those aged <18 years, in accordance with local guidelines.

Participants were recruited upstream (within the final 2 months) of treatment completion, to give multiple opportunities to identify eligible patients: during the continuation phase of treatment patients visit the TB offices monthly to collect medication, and thus each individual had 3 visits at which they could be identified (4-month visit, 5-month visit, end of TB treatment visit). The following measures were taken to maximize patient identification and referral by TB officers:

- Monthly training for TB officers, throughout the duration of the study
- Weekly visits to all TB offices by the study team to help TB officers to identify potentially eligible patients approaching the end of their TB treatment from within the NTP registers
- Weekly visits from the TB surveillance system staff
- Monthly feedback to TB Officers about patients attending for formal screening
- A financial incentive, paid at a fixed rate to all TB Officers within the network on a monthly basis, as part of the existing Hit TB / TB programme collaboration

- PARTICIPANT REIMBURSEMENT

Participants were reimbursed after each study visit to an amount deemed appropriate by the local community engagement teams / ethics committee, with adjustments made over the course of the study in line with rising costs of living. For a visit to the hospital, reimbursement was approximately 2500MK – this is the equivalent of $3.44 (Exchange rate $1 USD: 726MK, March 2017), and compares to a median monthly individual income reported across the cohort of $41.32 (IQR: $11.02- 96.42) at the point of TB treatment completion.

- PARTICIPANT FOLLOW-UP

Contact was maintained with participants between study visits with a scheduled phone call at the 3-month point. In the event of a missed study visit, home visits were conducted and the next of kin contacted in order to locate the participant.

- CLINICAL MANAGEMENT

As this was an observational study, participants were signposted to routine health services (local health centres, or QECH emergency department) if they became unwell over the course of the study. Clinical review by the study PI was only performed if the participant remained unwell with evidence of clinical deterioration after input from routine services. If participants were admitted to hospital during the follow up period, all study investigations were made available to the medical team responsible for the patient's care, but direct clinical care was not provided by the study team.

Participants with abnormal findings from investigations performed as part of this study were reviewed by the study PI during the course of follow-up if urgent clinical intervention was required. Management with locally available treatment was based on *a priori* guidelines which were drafted prior to study initiation, and included discussion with a local specialist respiratory physician (PB) as required. All participants were offered a routine one-to-one clinical review with a respiratory physician (JM, PB, JR) after their final 12-month study visit, where they received written copies of all blood results, spirometry results, and CT imaging, and findings were explained.

5.2.4 DATA SOURCES / MEASUREMENT

Questionnaire data were collected at each study visit, and investigations completed according to a pre-defined schedule summarized in Table 2 and described in detail below.

Table 2: Data collection schedule

Study visit	Questionnaire content	Investigations
Baseline visit - TB treatment completion (QECH)	Demographic details Respiratory exposures – smoking and biomass Comorbidities, including – HIV disease History of TB disease episode TB symptom screen St George's Respiratory Questionnaire Household socioeconomic status Current and pre-TB disease income / employment Baseline household dissaving	Pre and post bronchodilator spirometry EQ5D3L utility score Clinical observations 6-minute walking test Chest radiograph Non contrast HRCT chest HIV testing Blood tests – FBC +/-CD4 and plasma Sputum smear and culture (if +ve TB symptom screen)
6-month follow-up (Participant household)	TB symptom screen St George's Respiratory Questionnaire Health care use and associated costs, since baseline	Pre and post bronchodilator spirometry EQ5D3L utility score Clinical observations Sputum smear and culture (if +ve TB symptom screen)
12-month follow-up (QECH)	TB symptom screen St George's Respiratory Questionnaire Health care use and associated costs, since baseline Household dissaving, since baseline Current income / employment assessment	Pre and post bronchodilator spirometry EQ5D3L utility score Clinical observations 6-minute walking test Chest radiograph Blood tests – plasma, FBC +/- CD4 if symptomatic Sputum smear and culture (if +ve TB symptom screen)

HRCT: High resolution computerized tomography; EQ5D3L: EuroQol standardized quality of life assessment tool, using 3-options for 5-dimensions of health; QECH: Queen Elizabeth Central Hospital, Blantyre, Malawi.

QUESTIONNAIRE DATA

- ### HISTORY OF TB DISEASE

Information about the TB episode, including TB disease classification (pulmonary/extrapulmonary), treatment dates, baseline microbiology, and treatment outcome, were collected at the baseline study visit. Malawian adults carry their own inpatient and outpatient medical records in the form of a small booklet or 'health passport'. Data on TB disease and treatment were verified by review of this document where possible, as well as the TB NTP register. Cases were discussed with the TB officers in the referring health centre if required.

Patients were asked if they had received immunosuppression with steroids during TB treatment, and this was verified in the health passport.

- ### HISTORY OF HIV DISEASE

Participants were asked about their HIV status at the baseline study visit, and the health passport reviewed for a signed and dated test result or evidence of ART use. Data on the timing of diagnosis and ART initiation and concurrent co-trimoxazole use were collected for those known to be positive. Any patient who reported negative status but had not had a test within the past 1-month was retested,

as were those who reported positive status but had no documentation. Testing was performed by a trained Queen Elizabeth Central Hospital (QECH) counsellor using the Determine HIV Rapid Test (Alere), with confirmation of positive results with the Uni-Gold Recombigen HIV Rapid Test (TrinityBiotech). Participants with new positive diagnoses were referred to the ART clinic for assessment and treatment initiation as per Malawi test-and-treat guidelines.

- RESPIRATORY EXPOSURES

Data on self-reported smoking and cannabis use were collected at baseline. There are no standardized measures of cannabis exposure, and consumption volumes are difficult to ascertain given the weight per unit of purchase and consumption in Blantyre (rolled joints known as 'mbaba', or parcels known as 'bola') are unknown. The average number of mbaba smoked per day, and the total years of use were therefore recorded.

Data on self-reported individual level biomass exposure were collected, including the dominant fuel used, and information on the duration of use of specific fuels for cooking / heating water within the household. No direct measurements of particulate or biomass fuel exposure were made.

- CO-MORBIDITIES

Participants were asked about existing diagnosis of cardiac disease, respiratory disease, and diabetes with verification in the health passport where possible.

- QUALITY OF LIFE AND CLINICAL SYMPTOM DATA

Participants were asked to rank their general health on a four-point Likert scale, from poor to excellent, as a summary measure of overall health status.

The SGRQ was completed in full at each study visit. Permission was obtained for the development of a Chichewa version of the questionnaire for use in this study. Translation was performed by an official translation service, and the questionnaire reviewed / corrected by the Malawian members of the study team prior to use. Given low literacy rates in the Malawian population, a modified approach was used, with questionnaires administered by study staff who read questions and answer options to study participants in a standardized fashion and documented patient choices. The 3-month version of the questionnaire was used in this study: respiratory symptom questions referred to patient experience over the preceding 3-month period, whilst activity and impact questions referred to the current situation only. Summary scores (symptom, activity, impact, and total) scaled from 0 (optimal health) to 100 (worst health) were generated for each questionnaire completed by weighting and combining answers to the SGRQ questions according to the pre-specified SGRQ algorithm.[156]

Data on the burden of individual clinical symptoms were taken from the SGRQ, including information on the frequency of cough, breathlessness, sputum production and wheeze, and data on the severity of breathlessness.

The EQ-5D-3L was completed at each study visit with permission granted by the EuroQol group.[226] Data were collected across 5 key domains of health and function (mobility, self-care, their usual activities, issues of pain / discomfort, and anxiety or depression), and the EQ5D3L Visual Analogue Score (VAS) was completed independently by participants.

- SOCIOECONOMIC SITUATION

Data were collected from all participants on their educational level. Data on household assets (ownership of mobile phone, television, radio, landline phone, fridge, bike, motor bike, car, bank account) and household characteristics (electricity supply, water supply, toilet situation, main fuel) were collected at TB treatment completion, with verification of materials making up wall / floor / roof of households completed at the 6-month home visit. Participants were asked to report on food security within the household at each study visit.

National and urban household wealth quintiles were calculated using the indicator tool derived from the Malawi Malaria Indicator Survey, 2012 (Equity Measurement Toolkit, Social Franchising Metrics Working Group). A newer quintile tool based on the 2015-16 Malawi DHS data was released in 2018, after the start of this study, but employed different household asset / characteristic data variables and could not therefore be used retrospectively. Wealth quintiles were calculated at the start of the study and assumed to be fixed through the duration of the study.

- HEALTH SERVICE USE

Participants were asked about outpatient visits and admissions within the past 6-month period at both the 6-month and 1-year study visits. Outpatient visits to the study PI for abnormal study results were not included in this count.

Data were collected on the date, indication, location, duration, cost and management of events, and information verified in the health passport where possible. Acute respiratory events were defined as "unscheduled visits to a health care provider (outpatient or inpatient) due to a respiratory complaint (e.g. cough, breathlessness, wheeze, sputum production, haemoptysis, chest pain)".

- TB RETREATMENT

Participants were asked whether they had been initiated on TB retreatment by routine TB services, at both 6- and 12-month study visits, and health passports reviewed for evidence of this. Individuals who

were restarted on TB treatment by either routine health services, or as a result of study screening, remained within the study but aerosolizing investigations such as spirometry were omitted.

- COSTS AND DISSAVING

Data on personal and household incomes and occupations were collected for three time points: prior to TB illness, at the point of TB treatment completion, and 1-year following TB treatment completion. Information about the first two time points was collected at the baseline study visit, and data regarding the latter at the final study visit.

Participants were asked to recall any dissaving (use of savings, borrowing of money, or selling of assets to cover illness related costs) in the 1-year period prior to TB treatment completion – which included the period of illness prior to diagnosis, and the duration of treatment – at the baseline study visit. They were then asked to report on ongoing dissaving experienced following treatment completion at both the 6- and 12-month visits.

Data on the direct and indirect costs incurred by participants and guardians for each health care visit completed during the follow-up period were collected. All costs were reported by participants in Malawi Kwacha and converted into US Dollars using the exchange rate from the study mid-point (March 2017, $1 USD: 726MK). Income, cost, and dissaving questions were adapted from the STOP-TB costing questionnaire.[167]

CLINICAL OBSERVATIONS

Vital signs were recorded at every study visit. Mid upper arm circumference (MUAC) and BMI were recorded. The presence of palatal Kaposi's Sarcoma and peripheral oedema were documented by a trained research nurse.

MEASURES OF FUNCTIONAL CAPACITY

Participants were asked whether they had been unable to work in relation to health problems in the past 1-month, at both the baseline and 1-year visits. The 6-minute walk test was completed along a 30-m course in a flat hospital corridor at baseline and 1-year visits, as per ATS guidelines,[227] and the 6-minute walking distance and post-test oxygen saturation were recorded.

BLOOD TESTS

All participants had a full blood count at baseline, with a CD4 count if HIV-infected. Plasma samples were taken at both baseline and 1-year study visits, and stored locally at -80 degrees, before being shipped to the National Aspergillus Centre in Manchester, UK in batches, for measurement of Aspergillus IgG using the Bio-Rad Platelia and Bordier Aspergillus IgG ELISA kits (performed by BW).

Storage and shipment were performed with the consent of participants, ethical approval, and the necessary Material Transfer Arrangement.

SPUTUM SMEAR AND CULTURE

A TB symptom screen was performed by the study team at each study visit, and a sputum sample requested for smear and culture from those reporting any of current cough, fever, weight loss, or night sweats. Cultures were run on the BACTEC Mycobacteria Growth Indicator Tube (MGIT) system (Becton Dickson) for a maximum of 42 days, after sputum decontamination. MGIT positive samples were checked with a Ziehl-Neelson (ZN) stain to confirm the presence of a mycobacterium, and ID testing (MPT 64 antigen detection kit, SD Bioline) used to confirm the presence of *Mycobacterium tuberculosis* (MTB), with further culturing and testing as required. Whilst the TB laboratory in Blantyre was able to identify the presence of non-tuberculous mycobacteria (NTM) in sputum, further speciation was not possible on site.

SPIROMETRY

Pre- and post-bronchodilator spirometry were measured at each study visit.

All staff performing spirometry underwent a rigorous 4-day formal training course prior to the start of the study, with re-training at the study mid-point. Training was provided by a certified provider, and covered the principles underlying spirometry, ATS-standard approach to pre- and post-bronchodilator testing, basic data interpretation and quality control, and equipment maintenance.

The EasyOne spirometer was used throughout, with daily calibration using a 3L-calibration syringe. Participants were assessed for contraindications prior to testing (Table 3) – if any were detected, testing was either withheld, or rescheduled with discussion with the study PI (JM) as appropriate.

Table 3: Relative and absolute contraindications to spirometry[228]

Category	Factor identified
Absolute contraindication	Unstable angina Heart attack < 3 months Hospitalisation for cardiac problem < 3 months Chest / abdominal surgery < 3 months Detached retina / eye surgery <3 months 3rd trimester pregnancy
Relative contraindication	Tachycardia with HR >100 BP >180/110 Acute illness On TB retreatment / under investigation for active PTB recurrence

Each patient was asked to perform a minimum of 3 and maximum of 8 pre- and post-bronchodilator attempts, with the target of achieving 3 good curves for each. Where consistently poor technique / difficulty performing the test was observed, participants were asked to return on another occasion for repeat testing. Salbutamol was administered via a spacer after the pre-bronchodilator tests, using 2 x 100mcg doses from an MDI device. A minimum of 15 minutes was allowed between administration of

salbutamol and repeat spirometry. Nose clips were found to function poorly in the study population, so participants were asked to pinch their noses during testing. Disposable spirettes were used and changed for each patient. Testing was performed in the seated position. Participant age (yrs), standing height (mm), and weight (kg) were recorded at the time of testing, to allow for standardization of results. Spirometry data were stored electronically using EasyWare software.

CT IMAGING

High resolution computerised tomography imaging (HRCT) imaging was included within the study as the 'gold standard' investigation for structural lung pathology and is therefore described prior to CXR imaging throughout this chapter.

All participants were offered low dose HRCT imaging at PTB treatment completion, except for those with the following contraindications: absence of informed consent, positive pregnancy test / self-reported current pregnancy, inability to travel to imaging centre. Any patient reporting a positive TB symptom screen (cough, weight loss, fever, night sweats, haemoptysis) at the baseline study visit was asked to submit sputum, and was only booked for imaging if smear negative.

CTs were performed in batches, with 8-12 sequentially booked participants transported to the imaging centre every 1-4 weeks, depending on imaging capacity / study demand. Participants were prioritised by time from PTB treatment completion, with the aim of minimising this time interval. For logistical reasons, 2 imaging centres were used: Blantyre Adventist Hospital (BAH), Blantyre (Feb - Aug 2016) and Kamuzu Central Hospital (KCH), Lilongwe (Nov 16- May 17). Travel to the latter required a full day's round trip.

An unenhanced low dose imaging protocol was used at both scanning locations. Scans were taken of supine participants in full inspiration, with coverage from apices to bases (Appendix 2, Table 1). Scans were reconstructed using a lung algorithm only, accepting that this would give limited diagnostic quality for soft tissue. Images were stored in stored in DICOM format electronic files.

All scans were checked by the study PI (JM) within 5 days of acquisition, and participants reviewed if clinically indicated.

CXR IMAGING

Plain chest radiology was used to determine change in structural pathology over time.

CXR images were acquired from all participants with the exception of pregnant women at baseline and 1-year study visits. Digital images were taken where possible, with hard films obtained in the event of equipment malfunction, and selection of imaging modality was therefore independent of

patient characteristics. All hard copy images were 'digitalised' in order to allow for remote reporting. This was performed at the UK National Conservation Centre, in order to optimise image quality.

Images were reviewed on a weekly basis by the study PI (JM), and participants reviewed if clinically indicated.

ASCERTAINMENT OF MORTALITY

All participants were asked to provide both their own contact details and address, and those of a next of kin when registered for the study. In the event of a participant missing a study visit, attempts were made to contact them directly in the first instance. If unsuccessful, the next of kin was contacted by phone / in person to determine the participant vital status. Repeated attempts at contacting both participants and the next of kin were made, with home visits as required.

If a participant was found to have died, the approximate date and circumstances were ascertained, including whether they had been restarted on TB retreatment although formal verbal autopsies were not done.

5.2.5 DATA MANAGEMENT

Questionnaire data were collected in electronic format using Open Data Kit (ODK) software. The EQ-5D-3L questionnaire is not validated for electronic use and was therefore completed on paper using the Teleform system and converted to electronic format in batches over the course of the study. Spirometry data were stored electronically using EasyWare software. The majority of CT and CXR imaging data were directly collected and stored in DICOM format electronic files, and digital versions of hard-copy CXR films were stored as JPEG imaging files.

Data were anonymized on collection, with hard copies stored locally in a secure site at the Malawi Liverpool Wellcome Trust research centre, and electronic data stored in a secure master database held on the Liverpool School of Tropical Medicine server. Data were cleaned at the end of the study, and a final analysis-ready database saved on this central server. Consent was taken to store study data for a 10-year period from collection.

Quality control and processing of cleaned spirometry, CT and CXR data were required to generate variables for analysis. The approaches taken were informed by the issues of measurement highlighted in Chapter 2.

SPIROMETRY DATA

All spirometry tests were independently reviewed by 2 readers (JM and LZ) to identify usable curves, in accordance with CDC National Institute for Occupational Safety and Health (NIOSH) guidelines, and

the BOLD study quality control procedures.[229 230] Consensus review was used in the event of any disagreement, and data were extracted from spirometry attempts deemed to be usable at the end of this process only. Full details of the methods used for quality control and consensus reading are described in Appendix 2.

As explained in the literature review in Chapter 2, spirometry data were standardized for primary analysis using the GLI-2012 African American equations, with the aim of identifying individuals within the cohort who were left with abnormal lung function on completing PTB treatment, relative to their peers. Z-scores were used to describe the severity of impairment, and lower limit of normal (LLN) cut-off values were used to define normal / abnormal FEV_1 and FVC z-scores in order to describe patterns of deficit: the presence of obstruction was based on an FEV_1/FVC <LLN, and those without obstruction were classified as having a low FVC pattern (FVC <LLN) or a normal pattern (FVC >LLN) (Table 4). No category of mixed disease was included in the analysis.

Table 4: Classification of spirometry

Category	FEV1/FVC ratio	FEV1*	FVC
Obstruction	<LLN	n/a	n/a
Low FVC	≥LLN	n/a	<LLN
Normal	≥LLN	n/a	≥LLN

*FEV1 not directly included in diagnostic criteria, but implied through use of ratio

In order to better understand the impact of the reference range used on data findings and interpretation, spirometry data from TB treatment completion were standardised using each of the 4 reference ranges (GLI-2012, NHANES III Caucasian, NHANES III African American, Malawi), % predicted values calculated, and patterns compared. Age and gender stratified prevalence estimates for airway obstruction and low FVC were also generated using fixed FEV_1/FVC ratios and % predicted values calculated using the NHANES III reference range, in order to allow comparison to the urban Malawi BOLD study results described in Chapter 4.

As per the ATS/ERS guidelines, reversibility was defined as an increase in FEV1 of >200ml between pre- and post-bronchodilator readings, where this increase was >12% of baseline FEV1 value.

CT DATA

• CT SCORING TOOL

As discussed in the literature review in Chapter 2, no post-TB lung damage scoring tools were identified in the literature, and a dedicated tool was therefore developed for use here (Table 5). The tool was informed by the systematic review of the existing literature on post-TB lung damage above, pictorial essays of chest imaging at various stages of PTB disease, and review of image scoring systems commonly used in other chronic respiratory diseases, including bronchiectasis, COPD, and interstitial

lung diseases. It was developed by the study PI and two Europe-trained consultant radiologists: a consultant chest radiologist with predominantly UK specialist respiratory experience (JJ), and an ID radiologist with more than 10-years' experience of TB related pathology and imaging in sub-Saharan Africa (EJ).

Particular attention was paid to the selection of variables used to measure bronchiectasis and airways pathology. Established radiological criteria from the Fleischner guidelines were used for the majority of variables,[191] except for the category of 'Emphysematoid destruction' – this is a feature described in the TB literature but not mentioned in the Fleischner guidelines. Joint scoring of a training set of CT images obtained from a previous study of patients receiving TB-retreatment in urban Blantyre was used to refine the scoring tool prior to use.

Table 5: CT scoring system used for data analysis

Initial name of variable	Initial definition	Scoring options
PARENCHYMAL VARIABLES Scored at lobar level. Mutually exclusive variables, summing to 100% for each lobe.		
Parenchymal bands	Linear opacity 1-3mm thick, up to 5cm long. Usually extends to visceral pleura. May be accompanied by anatomical distortion	% of lobe (to nearest 5%)
Atelectasis	Reduced volume accompanied by increased lucency in the unaffected part of the lung. May be accompanied by displacement of fissures, bronchi, vessels.	% of lobe (to nearest 5%)
Consolidation	Homogeneous increase in lung parenchymal attenuation which obscures the margins of vessels and airway walls. An air bronchogram may be present.	% of lobe (to nearest 5%)
Ground glass opacification	Hazy increased lung opacity with preservation of bronchial and vascular margins	% of lobe (to nearest 5%)
Mosaicism	Areas of reduced lung parenchymal attenuation. Component of the mosaic attenuation pattern, where a patchwork of differing lung attenuation is seen.	% of lobe with darker areas (to nearest 5%)
Emphysema	Focal areas or regions of low attenuation usually without visible walls	% of lobe (to nearest 5%)
Emphysematoid destruction	Focal area of destruction / emphysematous change associated with features of healing TB, suggesting destruction of small airways.	% of lobe (to nearest 5%)
Cavities / cystic airspaces	Gas filled space, seen as a lucency or low-attenuation area within a pulmonary consolidation, a mass, or a nodule. Consolidation may have resolved leaving a thin wall only.	% of lobe (to nearest 5%)
Normal	Normal parenchyma, not affected by any of the pathological processes above	% of lobe (to nearest 5%)
BRONCHIECTASIS VARIABLES Scored at lobar level. Extent assessed first, with Pattern and Severity scored only if bronchiectasis seen.		
Bronchiectasis Airway lumen diameter greater than accompanying pulmonary artery outer diameter, OR Airways visible in the lung periphery, OR Lack of normal tapering	Extent	0: Absent 1: ≤1 BP segment 2: 2 BP segments 3: ≥ 3 BP segments
	Pattern (Scored only if bronchiectasis seen and 'extent' score >0)	1: Cystic (Ballooned' outline, with diameter increasing towards periphery) 2: Cylindrical (Regular and straight outline, with abrupt termination) 3: Varicose (Irregular bronchial outline, with bulbous termination)
	Severity	1: Trivial (bronchial lumen is <twice adjacent vessel diameter)

	Maximum degree of airway dilatation, to be measured by comparing diameter of airway lumen to diameter of adjacent vessel. (Scored only if bronchiectasis seen and 'extent' score >0)	2: Bronchial lumen is 2-3 times adjacent vessel diameter 3: Bronchial lumen is >3 times adjacent vessel diameter
AIRWAY VARIABLES Scored at lobar level. All variables independent of each other.		
Bronchial wall thickening	Thickening of bronchial walls	0: Absent 1: Mild 2: Moderate 3: Severe Missing: Unable to assess
Mucous plugging	Mucous seen in proximal large airways	0: Absent 1: Mild 2: Moderate 3: Severe
Tree in bud	Centrilobular branching pattern, resembling a budding tree. Most pronounced at the periphery.	0: Absent 1: Mild 2: Moderate 3: Severe
CAVITY VARIABLES Scored at lobar level. Independent of parenchymal scores. Extent scored first, with size and severity scored only if cavities seen		
Cavity Gas filled space, seen as a lucency or low-attenuation area within a pulmonary consolidation, a mass, or a nodule. Consolidation may have resolved leaving a thin wall only. Mycetoma	Extent	0: Absent 1: 1-2 cavities 2: 3-5 cavities 3: >5cavities
	Maximum size	Maximum diameter (mm)
	Mycetoma Discrete mass of hyphae, within a cavity. May have air crescent sign. May have sponge like pattern with areas of calcification.	0: Absent 1: Present
OTHER LOBAR VARIABLES Scored at lobar level		
Nodules	Rounded opacities, well or poorly-defined, >5mm, measuring up to 3cm in diameter	0: Absent 1: <5 nodules 2: ≥5 nodules 3: Miliary
WHOLE LUNG VARIABLES Scored at level of hemithorax / whole lung		
Pleural effusion	Accumulation of fluid within pleural space	0: Absent 1: Present
Pleural thickening	Pleural thickening of ≥10mm	0: Absent 1: Present
Lymph nodes	Mediastinal / hilar lymph nodes ≥10mm diameter	0: Absent 1: Present
DOMINANT PATHOLOGY Impression of reporting radiologist, after review of individual variables above		
Compatible with resolving PTB – No other pathology		
Compatible with resolving PTB, plus other diagnosis		
Resolving PTB or other diagnosis equally likely		
Not compatible with resolving PTB, other diagnosis likely		

- CT SCORING PROCESS

All CT images were independently scored by two consultant radiologists (EJ and JJ). Anonymised images were used, with no accompanying demographic or health related information. There was no pre-specification of the order of image review, but images were provided to both radiologists in the same format and in the same order in batches, over the course of the study. Neither the maximum

number of images to be read in each sitting, nor the reviewing environment (eg. quality of computer screen) were pre-specified.

CTs were scored on a lobar basis, with six lobes per scan - for scoring purposes the lingula was counted as a full lobe. Bronchial anatomy was used to define the lobes – this corresponds to fissures on the right, but on the left helps to differentiate upper and middle "lobes" or lingula which have no horizontal fissure between them. The division between the lingula and left upper lobe was drawn at the level of the lingular bronchus.

Data from the first 20 independently reported scans from within this study were reviewed by the radiologists to consolidate training. Findings were compared, discrepancies calculated, and the data and images were reviewed together in person by the radiologists to confirm that comparable approaches were being used. Re-scoring of initial data for these first 20 scans was permitted, but no subsequent changes to independently reported data were made over the course of the study. Clarification notes generated from this review, and after analysis of the full study dataset, are presented in Appendix 3, Table 2.

A live online image scoring database was created in order to facilitate efficient scoring, with safe and secure data storage, and a clear audit trail for any changes made to data. Image scores were entered directly into the database by radiologists, as images were reviewed. Default buttons for all severity and extent scores were set as 'Absent' in the database, with radiologists changing these as required. Parenchymal scores were left empty with radiologists entering scores at 5% intervals as required, and compulsory totals of 100% for each lobe. A free-text box was included for radiologists to note any queries or additional features.

- MEASUREMENT OF INTER-READER RELIABILITY

Lobar scores generated for each variable were summed across the whole lung, for each scan report produced by each reader, and these whole lung scores were then compared between readers. The following measures of inter-reader consistency were used to describe the level of discrepancy between original image readers:

- Cohen's kappa score – ordinal variables

  The kappa score accounts for the probability of agreement occurring by chance. It is generally accepted that values <0.40 indicate limited agreement, values 0.41-0.75 represent good agreement, and values >0.75 excellent agreement. A score of 1.0 indicates perfect agreement between readers.
- Weighted Cohen's kappa score – ordinal variables with multiple categories

A quadratic weighting was used here such that discrepancies between categories that are close together are less meaningful and less severely penalised that more extreme discrepancies between readers. Scores were calculated in Stata v13, using the wgt(w^2) function.

- Intra-class correlation coefficient – continuous variables

  Parenchymal scores were treated as continuous variables for discrepancy measurement. As the differences in reader reports for individual scans are of interest, rather than average reports across the cohort, a two-way fixed effects model measuring absolute agreement for individual readings was used.

• CONSENSUS REVIEW

Consensus reading was performed by a third independent reader (HZ - a senior specialist chest radiologist with 3-months experience working in sSA). This was completed at a lobar level for the most discrepant scans and variables. The method used to select scans, lobes and variables for review is described in Appendix 3.

Reviews were performed at the end of the study, and the following training was provided to support this:

- The consensus reader was provided with the imaging reporting SOP, all of the CT images which had been acquired, and all of the original reads performed by both of the primary radiologists before starting consensus reading of the required subset of scans.
- An in-person meeting with one of the original readers (EJ) was scheduled for a detailed review of these data, prior to starting consensus reviews. Meeting with the second reader (JJ) was not possible, but scoring data from this reader were reviewed to provide a perspective of the different scoring approach, in order to minimise bias.
- A discussion between the consensus reader and one of the original readers was scheduled for after the consensus reading of the first 10 scans, in order to resolve any early issues arising.

For all of the scans reviewed, the consensus reader was provided with the anonymised scores produced by both original radiologists, to inform their own decision. They were able to either choose one of the original scores or generate their own response, and the score generated by this final consensus reviewer was considered the 'final' score for each variable reviewed.

• GENERATION OF FINAL DATA SET

Original reads and consensus reads were combined to form a single 'final' data value for each variable for each scan, using the approach detailed in Appendix 2, section 3.

Where there was agreement between original readers for a given variable in a given lobe, the agreed-on score was used as the final data point. Where original readers had disagreed and a consensus

review had been performed, the consensus score was used as the final data point. Where original readers had disagreed, but no consensus read was available, the approach taken depended on the variable over which there was discrepancy: scores from the original readers were averaged for continuous variables (eg. parenchymal scores), pathology was considered to be present if either or both original readers felt it to be so for binary scores (eg. mycetoma, pleural pathology), and random selection of original reads was used for nominal variables which could not be combined (eg. bronchiectasis pattern).

- GENERATION OF FINAL VARIABLES FOR ANALYSIS

Lobar scores were summed to generate whole-lung level scores for data analysis. This approach was taken for two reasons: firstly, in order to include lobar measures, one would have to account for clustering across 'repeated measures' between lobes, because lobes within one individual are more likely similar than those between individuals, and secondly it is likely that the amount or severity of pathology across the whole lung is of greater clinical relevance than lobar pathology.

This pragmatic approach assumes that the impact or presence of pathology in all lobes has the same meaning – that is, the impact of pathology in the RUL is the same as that of pathology in the LLL. Equal weighting of all lobes (including the lingula) implies that each lobe contributes the same volume of parenchyma / pathology to the overall lung, regardless of variation in their true size.

Several new variables were derived from the data collected above. These included: lobar presence / absence scores for airway pathologies, a composite variable for 'destroyed lobes', a composite variable for atelectasis and parenchymal banding, and a % score for the total amount of abnormal parenchyma seen across the lung both with and without mosaicism. The approach taken to generate these variables is detailed in Appendix 3.

Briefly, moderate to severe airway pathology (bronchiectasis, bronchial wall thickening, tree in bud, mucus plugging, and airway narrowing) was considered present in a lobe if final score generated by averaging original reads or on consensus review was ≥2. A lobe was considered destroyed or non-functioning if ≥90% of parenchyma was occupied by atelectasis, parenchymal banding or destroyed by cavities/cystic airspaces.

CXR DATA

- CXR SCORING TOOL

A CXR scoring system was designed for use (Table 6), using terms and patterns similar to those which had been used in the CT scoring system.

Table 6: CXR scoring variables and definitions

Initial name of variable	Initial definition	Scoring options
PARENCHYMAL VARIABLES Scored at lobar level. Mutually exclusive variables, summing to 100% for each lobe.		
Parenchymal bands	Linear opacity 1-3mm thick, up to 5cm long. Usually extends to visceral pleura. May be accompanied by anatomical distortion.	% of lobe (to nearest 5%)
Consolidation / ground glass	Consolidation: Homogeneous increase in lung parenchymal attenuation which obscures the margins of vessels and airway walls. An air bronchogram may be present. OR Ground glass appearance: hazy increase in opacification with preservation of bronchial and vascular margins	% of lobe (to nearest 5%)
Cavities / cystic airspaces	Gas filled space, seen as a lucency or low-attenuation area within a pulmonary consolidation, a mass, or a nodule. Consolidation may have resolved leaving a thin wall only.	% of lobe (to nearest 5%)
Atelectasis	Reduced volume accompanied by decreased opacity in the unaffected part of the lung. Signs of volume loss should be seen, and may include: displaced hila / fissures / bronchi, narrowed rib spacing, tortuous trachea, hyper-expansion and linear vessels extending through other lung zones	% of lobe (to nearest 5%)
CAVITY VARIABLES Reported at a lobar level		
Cavity	Gas filled space, seen as a lucency or low-attenuation area within a pulmonary consolidation, a mass, or a nodule. Consolidation may have resolved leaving a thin wall only.	0 = Absent 1 = 1-2 cavities 2 = 3-5 cavities 3 = >5cavities
		Maximum diameter of largest cavity, in mm
Mycetoma	Discrete mass of hyphae, within a cavity. May have air crescent sign.	0 = Absent 1 = Present
OTHER LOBAR VARIABLES		
Nodules	Rounded opacities, well or poorly-defined, ≥5mm, measuring up to 3cm in diameter.	0 = Absent 1 = <5 2 = ≥5 3 = Miliary
Ring and tramline markings	Prominent ring -shaped opacities representing thickened airways seen end-on, or parallel lines if seen longitudinal.	0 = Absent 1 = Mild 2 = Moderate 3 = Severe (whole zone)
WHOLE LUNG VARIABLES		
Hyper-expansion	Large lung fields with flattened hemidiaphragms.	0 = Absent 1 = Present
Pleural thickening	Visible pleural thickening ≥10mm with any distribution over visceral / parietal surfaces.	0 = Absent 1 = Present
Pleural effusion	Accumulation of fluid within the pleural space, identified by blunted costophrenic angle +/- visible meniscus.	0 = Absent 1 = Present
Lymph nodes	Prominent mediastinal or hilar lymph nodes.	0 = Absent 1 = Present
Dominant pathology		
Compatible with resolving PTB – No other pathology		As per the impression of the reader
Compatible with resolving PTB, plus other diagnosis		
Resolving PTB or other diagnosis equally likely		
Not compatible with resolving PTB, other diagnosis likely		

- CXR SCORING PROCESS

Formal reporting was completed in batches in order of image acquisition / digitalisation. All films were read independently by 2 readers – one was a respiratory physician trainee (JM), and the other was a consultant radiologist (EJ). Images were scored directly into a reporting database, as described above.

All films were checked for the correct horizontal rotation (L/R sides) before reading using the location of the stomach bubble, position of the airways, and the location of the aortic knuckle. Orientation was checked against the CT report only when there was genuine concern about dextrocardia, but no other comparisons were made with the CT imaging during CXR scoring. The radiologist reporting both CT and CXR imaging for the study (EJ) reported these image types independently, at distinct times.

CXRs were scored on a zonal basis, with each lung field divided into 3 zones for reporting, giving a total of 6 zones for each film. This division was done by each reader independently for each film. The upper/middle zone boundary was drawn at the level of aortic knuckle, and the middle/lower zone boundary drawn at the bottom of the thick portion of the pulmonary artery. Where there was clear lobar collapse / volume loss of a single lobe, the collapsed area was scored as a single zone and the remainder of that hemithorax was then split into 2 further zones for scoring.

An SOP was designed and agreed by both image readers. After the first 20 X-Rays had been independently read, both readers' results were reviewed together with the original images. Imaging definitions were clarified, and scores revised within the primary data set if required. Paired reports for 24 further x-rays were reviewed by both readers together again in November 2017, to ensure a consistent approach. This allowed for clarification of imaging definitions, but no changes were made to baseline scores at this stage. The notes generated during this process are shown in Appendix 4.

- INTER-READER RELIABILITY AND CONSENSUS REVIEW

The approach to the measurement of inter-reader reliability and selection of images for consensus review was similar to that described for CT imaging above. However, no third reader was required for consensus review of CXR images: the smaller amount of time required for X-ray reading meant that the 2 to original readers were able to conduct an in-person review together for discrepant scans, and reach agreement on final scores through discussion. The approach to selecting images and variables for consensus review is detailed in Appendix 4.

- GENERATION OF FINAL DATA SET

Final scores were generated at the zonal level using an approach similar to that taken in CT reading: where there was agreement between original readers, the agreed score was used as the final score; where there was discrepancy of original reads, but a consensus review had been conducted, the consensus score was used as the final score. In the absence of agreement or consensus review, the following approaches were taken:

- Parenchymal scores – extent scores given by the original readers were averaged.
- Ring and tramline scores – severity scores given by the original readers were averaged.

- Nodule scores - significant overlap was noted between the nodule categories of <5 and ≥5 between readers, and on review this distinction was felt unlikely to be clinically useful. Nodule scores were collapsed down to give 3 categories of pathology: no nodules, non-miliary nodules (any number), or miliary pathology. If, even after collapsing the variable, there was no agreement and no consensus decision was available, data were classified as missing for this zone.
- Mycetoma – as for nodules, mycetoma data were classified as missing in the absence of agreement or consensus review
- Pleural pathology & hyper-expansion – the report provided by the more experienced reader (EJ) was used

New variables for 'absent' parenchyma (non-functioning tissue due to atelectasis, cavities or banding), and 'destroyed' zones (where 90% of a lobe appeared absent due to the above) were generated, as per the CT analysis. Atelectasis and banding were also collapsed together, and where binary scores for the presence / absence of ring and tramline change within a zone were required, only zones with an average score ≥2 were counted. For ease of analysis, and because they potentially originate from similar inflammatory aetiologies, ground glass and consolidation were combined together in analyses.

5.2.6 MINIMISING BIAS

Selection bias was minimized by including a range of health centres across Blantyre within this study, and encouraging TB officers at these centres to identify and refer all potentially eligible PTB patients to the study team for review. Our aim was to achieve sequential recruitment of eligible patients. This was supported by regular visits to each health centre to review the NTP register and identify potentially eligible patients to target for referral, regular feedback to TB officers on their referral and recruitment numbers, and the provision of training and financial incentives for TB officers throughout the recruitment period.

Financial reimbursements were provided to participants ensured that individuals from lower SES groups were able to participate. Flexibility around dates and times of study visits, including weekend reviews, allowed those who were working to attend for assessment. Results of baseline investigations performed at TB treatment completion were not communicated to the study team or participants until the end of the 1-year follow up period, unless clinically indicated, in order to avoid bias in the reporting and recording of outcome data over the course of the study. Recall bias in the reporting of health seeking and economic data was minimized by allowing a maximum of 6-months between study visits. Standardised approaches were used for the collection of quality of life, spirometry, and walking test data. Definitions of exposures and outcomes for the analysis of cohort data were established prior to data analysis, where possible.

5.2.7 VARIABLES

Exposure and outcome variables for use in the cohort analysis are described below.

EXPOSURE VARIABLES

In the absence of a validated scoring system for post-TB lung damage (PTLD), an *a priori* case definition of post-TB lung damage was established by consensus discussion prior to starting this study, in order to differentiate between individuals with marked residual lung damage at TB treatment completion, and those with mild / absent pathology (Table 7). The process through which this composite definition which includes both spirometry and CT measures of lung pathology was generated is detailed in Appendix 5.

Table 7: *A priori* definition of PTLD, for use in cohort analysis

Criteria	PTLD present
Spirometric PTLD	Airway obstruction with FEV1/FVC ratio<LLN and FEV1<LLN OR Low FVC with FEV1/FVC ratio≥0.7 and FVC<LLN
CT PTLD	Moderate-severe bronchiectasis in ≥3 lobes OR Parenchymal abnormality of ≥1/3 of the lung tissue

LLN: Lower limit of normal, as classified using GLI 2012 reference ranges

In primary analyses, individuals meeting the *a priori* definition of either spirometric or CT defined PTLD were classified as 'exposed', and those with normal measurements / abnormalities not meeting these criteria were considered to be 'unexposed'. Secondary analyses were performed using different definitions of PTLD as the exposure of interest, in order to determine which aspect of residual lung damage were the most closely related to patient outcomes. These included Spirometric PTLD, CT PTLD, or both CT and spirometric PTLD. The latter group – identifying those with both extensive structural pathology and spirometric abnormality at TB treatment completion – is likely to be the group with the most severe residual pathology.

OUTCOME VARIABLES

Five primary outcomes were recorded over the 1-year follow up period (Table 8).

Table 8: Definition of cohort study outcomes

Outcome variable	Definition
Quality of life	Prevalence of impaired quality of life (SGRQ total score >6), 1-year post TB treatment completion
Chronic respiratory symptoms	Prevalence of self-reported cough OR sputum production OR breathlessness OR wheeze occurring at least monthly (several days/ week, or most days/week), 1-year post TB treatment completion.
Acute respiratory exacerbation	Presence of ≥1 unscheduled visit to a health care provider (outpatient or inpatient) due to a respiratory complaint (cough, breathlessness, wheeze, sputum production) within the 1-year period
TB retreatment	Initiation of TB retreatment within 1-year from TB treatment completion – including those with and without microbiological evidence of disease recurrence.
Mortality	All-cause mortality within 1-year from TB treatment completion

Of note, these outcomes are altered from those specified in the original study protocol. The initial intention had been to model the SGRQ total score at 1-year as a continuous outcome, using linear regression techniques. However, the data collected for this parameter were extremely right skewed such that this approach was not feasible. The SGRQ-total score at 1-year was therefore modelled as a binary outcome in a logistic model: because no local normative data are available for the SGRQ, a cut off value of 6 was chosen, based on the mean total score quoted for a 'normal' individual with no history of respiratory disease in the SGRQ manual.[156]

Similarly, the initial plan had been to model the factors predicting the presence of regular weekly, rather than regular monthly, respiratory symptoms at 1-year post treatment completion. In fact the prevalence of weekly symptoms was low (4.1% (15/368)), such that models would have been underpowered. Factors predicting ongoing monthly symptoms, seen in 113/368 individuals (30.7%), were therefore modelled instead.

Lastly, the original data analysis plan for this study included construction of a model for incidence rates of respiratory exacerbations during the 1-year follow up, according to the person-time contributed by each participant. Within the cohort, a total of 62 participants experienced at least one unscheduled outpatient visit or admission for respiratory reasons (70 unscheduled respiratory outpatient visits across 57 individuals, and 11 unscheduled respiratory admissions across 11 individuals). This number was felt to be limited and logistic regression models exploring covariates associated with the presence / absence of at least 1 respiratory event during the follow up period were constructed instead of using person-time analyses. Models included both individuals contributing full follow-up data for the 1-year (n=364) period, or 6-months' data only (n=16), but because it is not possible to include person-time in a logistic model, these groups were not differentiated between.

5.2.8 STUDY SIZE

The sample size was calculated around the precision estimate for the binary PTLD variable at TB treatment completion. Assuming 400 participants completing baseline data collection, we anticipated being able to estimate a PTLD prevalence within the full patient cohort of between 10-50% with 5% precision and 95% confidence level (Table 9).

Table 9: Power calculation for precision estimate at recruitment

Confidence level	Precision	Prevalence	Sample size
95%	5%	10%	139
		30%	323
		50%	385

A 20% loss to follow up was assumed over the 1-year study period, leaving 320 participants remaining at study completion. Assuming a baseline prevalence of PTLD of 30%, this would leave 96 participants with PTLD in the cohort at the 1-year time point. The feasibility of detecting differences in both binary

and continuous outcomes between groups with and without PTLD, given these numbers, was assessed.

For binary outcomes: If the proportion of participants experiencing an adverse outcome (Eg. Impaired quality of life at 1-year, persistent chronic respiratory symptoms at 1-year, or ≥1 acute respiratory exacerbation over 1-year follow up) was assumed to be 30% amongst those with baseline PTLD and 10% amongst those without PTLD, this sample size would allow us to detect a difference in proportions with 80% power and 5% significance.

For continuous outcomes: A minimum of 36 individuals would be required in the smaller participant group (those with PTLD at baseline) would allow us to detect a difference 0.5 standard deviations between the means of continuous outcomes including the SGRQ total score and incidence rate of respiratory exacerbations in those with / without PTLD, and this sample size was therefore deemed sufficient.

5.2.9 STATISTICAL METHODS

All data analyses were performed in Stata v13.0 (Statacorp, 2013).

DESCRIPTIVE ANALYSES OF CLINICAL DATA

- PARTICIPANT CHARACTERISTICS

Study numbers and follow up were outlined using a consort diagram. Baseline characteristics of the cohort were then described.

- CLINICAL AND RESPIRATORY PARAMETERS

Data on the clinical symptoms, quality of life, clinical measurements, blood results, 6MWT results, spirometry findings, and imaging data at each of the study visits were reported in turn, with population level change over time described for each. Where possible, data were stratified by baseline TB microbiology or HIV status. Groups were compared using the Chi^2/Fisher's exact tests (categorical variables), Wilcoxon rank-sum tests (non-parametric continuous variables), or t-tests (continuous variables with normal distribution).

Spirometry findings were compared across reference ranges, and the age and gender stratified prevalence of obstruction and low FVC were calculated using the NHANES III Caucasian reference range for comparison with data from the Malawi BOLD study described in Chapter 4.

Sensitivity analyses were performed to determine whether time to imaging and the CT scanner used were correlated with CT imaging findings, and whether patterns of CXR change over time varied amongst those who received digital imaging at both baseline and 1-year.

- HETEROGENEITY OVER TIME

Individual level heterogeneity in the direction and magnitude of change over time were described, across parameters

- PATTERNS OF PATHOLOGY

Participant characteristics, quality of life and symptom scores, and CT imaging findings were compared between participants according to their pattern of spirometry at TB treatment completion in order to determine whether structural pathology and clinical presentation varied between groups. Comparisons were made between those with normal and abnormal spirometry, and between those with obstruction and low FVC patterns only.

DESCRIPTIVE ANALYSIS OF PARTICIPANT OUTCOME DATA

Patterns of health service use, and the incidence of TB retreatment and all-cause mortality were described.

FACTORS PREDICTING SPIROMETRIC DEFICITS

Exploratory regression analyses were conducted to identify factors predicting residual spirometric deficits at TB treatment completion and 1-year post treatment completion, and factors associated with change over time between these two time points. Models were constructed with inclusion of a pre-specified set of predictors with no reduction strategy (Table 10).

Table 10: Variables to be included in multivariate models of spirometry, for each time point

Parameter	Time point		
	TB treatment completion	Change over time	1-year post treatment completion
Spirometry outcomes	Linear regression: - Absolute FEV_1 (ml) - Absolute FVC (ml) - FEV_1/FVC ratio (%) Logistic regression: - Obstructive deficit - Low FVC deficit	Linear regression: - Change in absolute FEV_1 (ml) - Change in absolute FVC (ml)	Linear regression: - Absolute FEV_1 (ml) - Absolute FVC (ml) - FEV_1/FVC ratio (%) Logistic regression: - Obstructive deficit - Low FVC deficit
Covariates included to standardize spirometry	Age Gender Height	Age Gender Height	Age Gender Height
Covariates included for investigation	HIV and CD4 count Baseline TB microbiology BMI at TB treatment completion Ever smoking Socioeconomic status Food instability Illness duration prior to treatment	HIV and CD4 count Baseline TB microbiology BMI at TB treatment completion Ever smoking Socioeconomic status Food instability	HIV and CD4 count Baseline TB microbiology BMI at TB treatment completion Ever smoking Socioeconomic status Food instability Illness duration prior to treatment Baseline spirometry - FEV_1, FVC, ratio, or pattern of deficit Baseline CT pathology - parenchymal abnormality or bronchiectasis Events over 1-year follow up: acute respiratory exacerbation, TB retreatment

- OUTCOMES

Both linear regression models for absolute FEV_1 and FVC volumes (ml) and FEV_1/FVC ratio (%), and logistic regression models for the presence/absence of Obstructive and Low FVC patterns of spirometric deficits were built. Age, gender and height were included in all models to 'standardise' for these well-known determinants of lung volumes.

- COVARIATES

The selection of participant characteristics to include in the models as covariates was hypothesis driven.

- HIV status and CD4 count were combined into a single variable, in order to allow both parameters to be included within a combined model for HIV infected and uninfected participants.
- Baseline TB microbiology was included as a binary variable, with participants defined as having positive microbiology if they were sputum smear, culture, or GeneXPert positive at diagnosis.
- BMI at TB treatment completion was included as a marker of overall wellbeing, nutritional status, and muscle bulk at the end of treatment. Haemoglobin at treatment completion was included as a marker of general wellbeing, and a potential predictor of breathlessness.
- Ever-smoking was included, but strong co-linearity with cannabis exposure meant that it was not possible to include the latter also. The quality of self-reported individual level biomass exposure obtained within the study was felt to be unreliable and therefore not included.
- A binary variable for urban socioeconomic quintile was included to reflect limited wealth and associated exposures. Food insecurity was present if participants reported difficulty getting food within the past month sometimes or often, and included as a measure of acute poverty.
- Illness duration prior to treatment was included as a binary variable due to the likely limited accuracy and low resolution of this variable. It was thought more likely to determine baseline spirometry, rather than change over time, and was therefore not included in models of the latter.

In order to determine the extent to which the severity of lung pathology at TB treatment completion determines spirometry 1-year later, the following measures of baseline pathology were included in models of 1-year spirometry:

- Spirometry at TB treatment completion: co-linearity between FEV_1, FVC and FEV_1/FVC ratio meant that all three parameters could not be included together in each model, and only the measure related to the parameter being modelled was therefore 'controlled for' (e.g. in a model for FEV_1 at 1-year, the FEV_1 at treatment completion was controlled for)
- CT pathology at TB treatment completion: the parameters of CT PTLD included within the *a priori* definition of disease (≥3 lobes with mod-severe bronchiectasis, ≥1/3 abnormal parenchyma) were included as simple measures of extensive baseline lung pathology

Variables for ongoing respiratory exacerbations over the course of the 1-year period and recurrent TB disease were also included, as potential drivers of ongoing decline.

- MODEL BUILDING APPROACH

The need for an interaction term between HIV and TB was investigated. Linear regression assumptions including the normality of residuals, homoscedasticity of and co-linearity between predictors, and the linearity of relationships between continuous predictor variables and the spirometric outcomes were investigated to ensure that models were appropriate. Primary data for outliers were reviewed, and data points excluded if errors suspected.

All individuals with BOLD valid spirometry data at TB treatment completion were included in the models for spirometry at TB treatment completion (n=330). However, only those who had had completed BOLD standard spirometry at both treatment completion and the 1-year time points, and had been imaged with CT scanning at baseline were including in models for change over time, and spirometry at 1-year (n=290). Participants with missing HIV status (n=2) and SES (n=33) were excluded from analyses.

Logistic regression models constructed for patterns of spirometric deficits included participants with either Obstruction vs. 'normal' spirometry, or Low FVC vs 'normal' spirometry at each time point.

RELATIONSHIPS BETWEEN PTLD AND PATIENT-CENTRED OUTCOMES

Multivariate regression models were built to determine the relationship between post-TB lung damage at TB treatment completion, and ongoing morbidity/mortality in the subsequent 1-year follow up period (Table 11). Exposure and outcome variables have been described above.

Table 11: Variables to be included in multivariate models of patient-centred outcomes

Parameter	Exposure of interest	Outcomes of interest	Potential confounders
Variables	Primary analysis: - Either spirometric OR CT PTLD at TB treatment completion Secondary analysis: - Spirometric PTLD - CT PTLD - Both spirometric and CT PTLD	Quality of life at 1yr Chronic respiratory symptoms at 1 yr Acute respiratory exacerbations over1 yr TB retreatment over 1yr All-cause mortality over 1yr	Age Gender HIV and CD4 count (collapsed variable) Baseline TB microbiology BMI at TB treatment completion Hb at TB treatment completion Ever smoking Socioeconomic status Food instability

Spirometric PTLD: Airway obstruction (FEV1/FVC ratio<LLN and FEV1<LLN) / Low FVC (FEV1/FVC ratio≥0.7 and FVC<LLN) using GLI-2012 reference equations
CT PTLD: Moderate-severe bronchiectasis in ≥3 lobes / parenchymal abnormality of ≥1/3 of the lung tissue, excluding mosaicism

- MODEL BUILDING APPROACH

Models were built in a stepwise process using pre-specified sets of predictors with no reduction strategy. A minimum number of potentially confounding patient and clinical characteristics were first included, followed by inclusion of the PTLD exposure parameter of interest.

The selection of participant characteristics to include in the models as covariates was hypothesis driven, and similar to that listed above. Because these models were aimed at identifying the relationship between PTLD at treatment completion and ongoing outcomes, no information on the duration of illness prior to treatment completion was included.

All outcomes investigated here were binary, and logistic models were therefore used. The need for an interaction term between HIV and TB was investigated within each model, but no other interaction terms were tested.

- MISSING DATA

Baseline socioeconomic status was missing in 33 individuals who failed to complete the 6-month visit and therefore did not have their household data (floor, wall, and ceiling materials) completed. A high proportion of these participants missed this visit because they were unwell / died, and excluding their data was thought likely to bias model results. Data for the housing materials were therefore imputed for these individuals, and SES quintiles calculated. All models were constructed using this imputed data set. Two participants with missing HIV status were excluded from the analysis. No other data were found to be missing.

Only individuals who had both valid spirometry and CT data at TB treatment completion were included in the analysis.

- EXPLORATORY ANALYSES – SPECIFIC IMAGING / SPIROMETRY PARAMETERS

Additional models were constructed to examine the relationship between specific CT and spirometry features of interest, rather than the *a priori* PTLD definition, and patient outcomes controlling for confounders. These models were exploratory, and generated in response to data findings rather than specified in the data analysis plan. The exposures of interest are listed below:

- Bronchiectasis

  Models were constructed including bronchiectasis as an exposure in three different ways: using the number of lobes affected by moderate – severe bronchiectasis as a continuous predictor, using the presence of bronchiectasis affecting ≥3 lobes as a binary predictor, and using the whole lung bronchiectasis severity score as a continuous predictor.
- Destroyed lobes

  The presence of ≥1 destroyed lobe with ≥90% parenchyma non-functioning due to atelectasis, parenchymal banding, or cavities / cystic airspaces was explored as a potential predictor of outcome.

- Potentially inflammatory pathology

  Exploratory models for the relationship between nodules seen on CT at treatment completion, the extent of ground glass and consolidation as a continuous variable, and the presence of ground glass or consolidation covering at least half of a lobe on baseline CT as a binary variable, and the outcomes of TB retreatment and death were constructed.

- Spirometry

  Exploratory models were constructed using Obstruction and Low FVC patterns as distinct exposures of interest. Exploratory models were also constructed to investigate the relationship between FEV_1 and FVC z-scores as continuous predictors of outcome.

- DESCRIPTIVE ANALYSIS OF HEALTH ECONOMIC DATA

Direct and indirect costs incurred by participants over the 1-year follow-up period were described, together with data on dissaving, in order to describe the financial impact of PTB disease beyond the end of TB treatment.

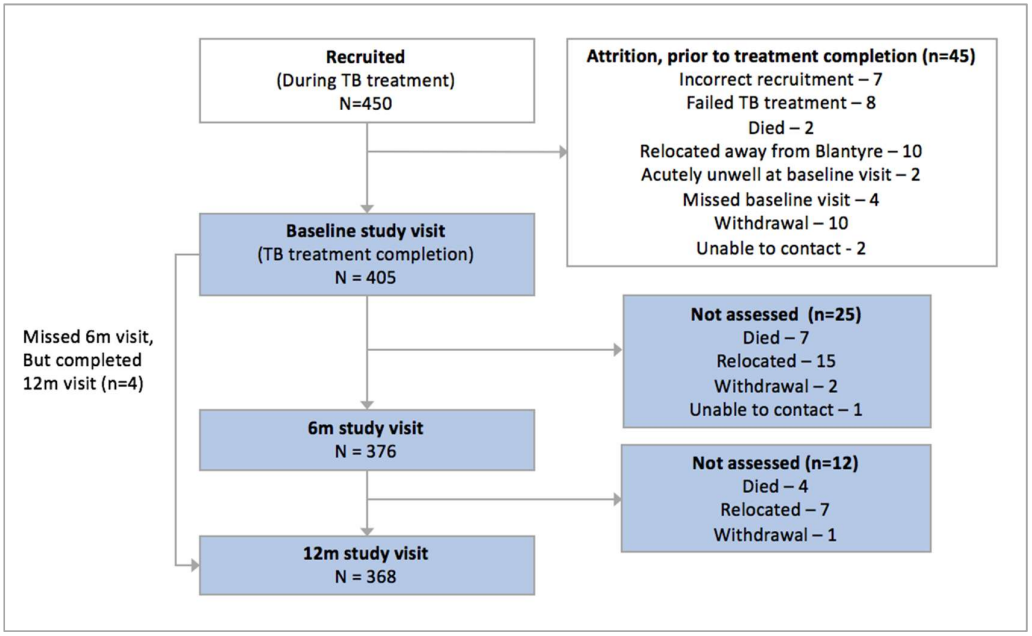
5.3 RESULTS

5.3.1 PARTICIPANTS

Between 10th February 2016 and 27th April 2017, 450 individuals were referred by TB Officers for screening of whom 405 met eligibility criteria by the time of TB treatment completion and were included in the study (Figure 2). The 1-year follow-up of enrolled subjects was completed on 30th April 2018.

A total of 364/405 (89.9%) of participants completed all study visits and contributed outcome data for the full 1-year follow up period. A further 16/405 (3.9%) of participants contributed 6-months data only, including those who completed the first half of the study (n=12), and those who contributed data for the latter half (n=4). 25/405 (6.2%) participants completed the baseline study visit only and did not contribute any further data. Amongst the 37/405 (9.1%) participants lost to follow up over the course of the study, 59.5% (22/37) were alive but relocated away from Blantyre, 29.7% (11/37) died, and 8.1% (3/37) withdrew. Contact was lost with only 1 participant. Limited data were available for the 45 participants initially referred for recruitment, but who did not formally enter the study at TB treatment completion (n=45). No statistically significant differences were observed in median age (35yrs (IQR 28-41) vs. 33yrs (IQR 28-41) years, p=0.865), or gender (67.9% vs. 60.0% male, p=0.284).

Figure 2: Flow diagram for study



5.3.2 PARTICIPANT CHARACTERISTICS

A total of 77.3% (313/405) of participants had had microbiologically confirmed disease at diagnosis. Of these, 68.1% (213/313) were diagnosed based on a positive sputum smear result and 31.9% (100/313) were diagnosed using XPert MTB-RIF testing (Table 12). No smear status was documented for the latter group, and 32.0% (78/244) of these individuals were HIV co-infected.

Of the 91 participants in the cohort who had been started on TB treatment in the absence of microbiological confirmation, 58.2% (54/91) had been documented in the TB register as having radiological evidence of disease on CXR at treatment initiation.

Table 12: Baseline TB diagnostics by HIV status

Microbiological status	Total	HIV negative	HIV positive	p-value
Microbiologically confirmed (n=313)				
- Smear positive, not specified	4 (1.3%)	2 (1.4%)	2 (1.4%)	<0.001***
- Scanty smear positive	28 (9.0%)	13 (9.4%)	15 (8.7%)	
- Smear 1+	39 (12.5%)	21 (15.1%)	18 (10.4%)	
- Smear 2+	53 (16.9%)	30 (21.6%)	23 (13.3%)	
- Smear 3+	89 (28.4%)	52 (37.4%)	37 (21.4%)	
- Xpert MTB-RIF	100 (31.9%)	21 (15.9%)	78 (45.1%)	
No microbiological confirmation (n=91)				
- Radiological diagnosis	54 (58.2%)	10 (50.0%)	43 (60.6%)	0.446
- Clinical diagnosis	38 (41.8%)	10 (50.0%)	28 (39.4%)	

*p<.05, **p<.01, ***p<.001

The characteristics of the 405 participants completing baseline data collection are shown in Table 13, stratified by these baseline microbiology results.

Table 13: Participant characteristics, stratified by baseline TB microbiology

Characteristic	Total (n=405)	Micro –ve (n=92)	Micro +ve (n=313)	p-value
Demographics				
Age (yrs)	35 (28 – 41)	37.5 (32.5 – 43)	34 (28 - 39)	<0.001***
Age group				
- 15-19yrs	17 (4.2%)	1 (1.1%)	16 (5.15)	0.017*
- 20-29yrs	95 (23.5%)	16 (17.4%)	79 (25.2%)	
- 30-39yrs	180 (44.4%)	38 (41.3%)	142 (45.3%)	
- 40-49yrs	86 (21.2%)	28 (30.4%)	58 (18.5%)	
- 50-59yrs	17 (4.2%)	4 (4.4%)	13 (4.2%)	
- 60yrs+	10 (2.5%)	5 (5.4%)	5 (1.6%)	
Sex				
- Male	275 (67.9%)	59 (64.1%)	216 (69.0%)	0.378
- Female	130 (32.1%)	33 (35.9%)	97 (31.0%)	
TB variables from diagnosis				
Self-reported duration of illness prior to treatment initiation (weeks)	8.7 (4.3 – 13.0)	13.0 (4.3 – 26.1)	8.7 (4.3 – 13.0)	0.027*
Location at diagnosis				
- Outpatient	346 (85.4%)	71 (77.2%)	275 (87.9%)	0.011*
- Inpatient	59 (14.6%)	21 (22.8%)	38 (12.1%)	
Steroid use during treatment				
- No	360 (88.9%)	79 (85.9%)	281 (89.8%)	0.559
- Yes	22 (5.4%)	6 (6.5%)	16 (5.1%)	
- Unknown	23 (5.7%)	7 (7.6%)	16 (5.1%)	
HIV variables				
HIV status				
- Negative	159 (39.3%)	20 (21.7%)	139 (44.4%)	<0.001***
- Positive	244 (60.3%)	71 (77.2%)	173 (55.3%)	
- Unknown	2 (0.5%)	1 (1.1%)	1 (0.3%)	
ART use (n=244)				
- No	20 (8.2%)	9 (12.7%)	11 (6.4%)	0.102
- Yes	224 (91.8%)	62 (87.3%)	162 (93.6%)	
Co-trimoxazole use (n=234)				
- No	23 (9.8%)	11 (16.2%)	12 (7.2%)	0.037*
- Yes	211 (90.2%)	57 (83.8%)	154 (92.8%)	
Duration on ART (months) (n=221)	6.6 (5.5 – 24.6)	7.4 (6.1 – 25.6)	6.1 (5.5 – 24.0)	0.068
CD4 if HIV-positive (cells/µL) (n=242)	229 (127 – 397)	206 (130 – 386)	233 (120 – 403)	0.514
Respiratory exposures				
Ever smoking				
- Never	285 (70.4%)	77 (83.7%)	208 (66.5%)	0.001***
- Ever	120 (29.6%)	15 (16.3%)	105 (33.6%)	
Pack years, amongst smokers (n=120)	2.7 (0.7 – 6.0)	3.0 (0.5 – 7.2)	2.6 (0.7 – 6.0)	0.407
Ever smoked cannabis (n=362)				
- Never	308 (85.1%)	77 (92.8%)	231 (82.8%)	0.025*
- Ever	54 (13.3%)	6 (7.2%)	48 (17.2%)	
Cannabis exposure (Joints per day*years smoked) (n=54)	5.5 (2.0 – 15.0)	7.5 (3.0 – 14.0)	5.5 (2.0 – 15.5)	0.730
Main fuel				
- Electricity	21 (5.2%)	8 (8.7%)	13 (4.2%)	0.225
- Charcoal	338 (83.5%)	74 (80.4%)	264 (84.4%)	
- Wood	46 (11.4%)	10 (10.9%)	36 (11.5%)	
Existing diagnoses				
Chronic respiratory disease	9 (2.2%)	2 (2.2%)	7 (2.2%)	1.000
Cardiac disease	1 (0.3%)	1 (1.1%)	0 (0.0%)	0.227
Diabetes	6 (1.5%)	0 (0.0%)	6 (1.9%)	0.344

*p<.05, **p<.01, ***p<.001

- DEMOGRAPHICS

The median age within the cohort was 35yrs (IQR 28-41). The overall proportion of males was 67.9% (275/405), and 4/130 of the female participants were pregnant at the time of TB treatment completion.

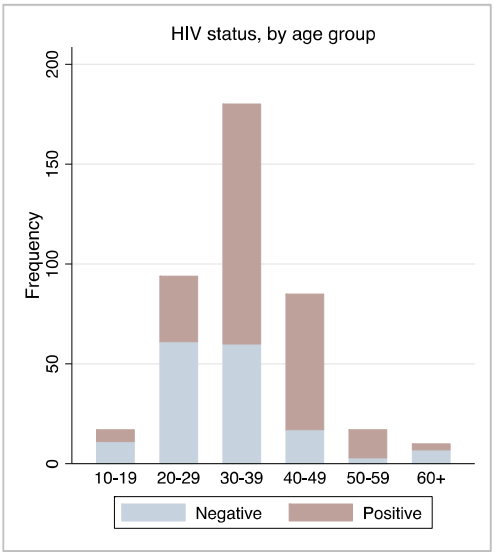
- HISTORY OF TB DISEASE

Participants were unwell with symptoms include cough, weight loss or fever for a median of 8.7 weeks (IQR 4.4 – 13.0 weeks) before TB treatment initiation. Those who were microbiologically negative at diagnosis had a longer illness duration than those with microbiological confirmation of disease (13.0 wks (IQR 4.3-26.1) vs. 8.7 wks (IQR 4.3-13.0), p=0.027). A total of 14.4% of the cohort had been admitted to QECH at the time of TB-diagnosis, including a higher proportion of HIV positives compared to HIV negatives (17.2% (42/244) vs. 10.1% (16/159), p=0.046). Only 5.4% (22/385) of the cohort had clearly documented use of steroids over the course of treatment.

- HISTORY OF HIV DISEASE

HIV-status was verified in 403 study participants, with 2 participants declining testing. A total of 60.3% (244/405) of the cohort confirmed to be HIV-infected at TB treatment completion. The highest HIV-prevalence was seen in the 30-39-year (66.7%, 120/180) and 40-49-year (80.0%, 68/85) age groups (Figure 3).

Figure 3: HIV prevalence by age group, at TB treatment completion (n=403)



Amongst those who were HIV infected, 91.8% (224/244) were receiving ART and 86.5% (211/244) were taking co-trimoxazole. The date of ART treatment initiation was available for 221 participants, amongst whom median time on treatment was 6.6 months (IQR 5.5 – 24.6). That is, of the HIV positive participants within the cohort who were receiving ART, 40.3% (89/221) had started treatment after/together with TB treatment initiation, 25.8% (57/221) had started treatment within the 6-months prior to TB diagnosis, and 33.9% (75/221) had started prior to this. CD4 cell counts were also available for 242/244 HIV-infected participants at TB treatment completion: median cell count was 228 cells/µL (IQR 127-397), and 42% (102/242) of HIV-infected participants had a CD4 count which

remained below 200 cells/µL. The nadir CD4 count, documented within 1-month of HIV diagnosis, was available for only 61 participants with a median of 156 cells/µL (IQR: 79 – 246).

- CIGARETTE SMOKING

29.6% (120/405) of the cohort were ever-smokers, with median exposure of 2.6 pack-years (IQR: 0.7 - 6.0) (Table 4). There was a strong gender gradient with 43.3% (119/275) of men and only 0.8% (1/130) of women reporting ever-smoking. The median number of cigarettes smoked per day was 4.5/day (IQR: 2.0 – 9.0/day), the median duration of smoking was 10yrs (IQR 5 – 16yrs). The median age of starting smoking was 21 years (IQR 18 – 25.5yrs), with no significant trend observed in the prevalence of ever smoking across the age groups. Only 7/120 (5.8%) of ever-smokers confirmed that they were still smoking. The majority of ever-smokers used manufactured rather than hand rolled cigarettes (90%, 108/120) with 5% (6/120) using both.

Ever smoking was more common amongst those with microbiologically confirmed PTB disease (33.6% (105/313) vs. 16.2% (15/92), p=0.001). This relationship persisted even when examined amongst men only. No difference in any measures of smoking exposure (pack-years, duration, cigarettes/day, age of onset) was observed between the two groups. Smoking was more common amongst the HIV-negative participants compared to the HIV positives (35.2% vs. 25.4%, p=0.034). However, this relationship appeared to be confounded by gender - no difference was seen in the prevalence of ever smoking amongst HIV negative compared to positive women (0% vs. 1.2%, p-value 0.473), and whilst the prevalence of smoking remained higher amongst HIV negative compared to positive men (48.7% vs. 38.6%), the p-value for this relationship was no longer significant (p=0.096). A strong socioeconomic gradient was observed in smoking exposure – the prevalence of ever-smoking was 34.6% (70/202) in the poorest 3 quintiles, compared to 22.4% (38/170) in the richest 2 quintiles (p=0.009).

- CANNABIS USE

Data on cannabis use was collected in 362/405 (89.4%) participants– the missing data was a result of the late addition of this variable to the data collection tool, rather than refusal to answer. Like smoking, cannabis use was seen mainly by men with ever use in 21.6% (53/245) of men and 0.9% (1/117) of women. The mean age of starting cannabis use was 19.5 years (IQR: 18-23yrs). The mean duration of use was 5 years (IQR: 2-8 years), and the median number of joints smoked per day was 1 (IQR:1 – 1). Cannabis use was lowest in the poorest socioeconomic quintile (5.3%, 1/19) but no trend was observed in the frequency of reported cannabis use across the other quintiles.

Ever use of cannabis was positively correlated with positive TB microbiology at diagnosis: ever use was seen in 88.9% (48/279) of those with positive microbiology vs. 11.1% (6/83) in those without (p=0.025). More cannabis use was seen amongst HIV-negative participants (25.4%, 35/138) compared to HIV-positive participants (8.6%, 19/222) in univariate analysis (p-value <0.001). Tobacco smoking

and cannabis smoking were strongly correlated: 39.8% (41/103) of ever smokers reported ever use of cannabis compared to 5.0% (13/259) of never smokers (p<0.0001)

- BIOMASS EXPOSURE

The majority of individuals used charcoal (83.5%, 338/405) or wood (11.4%, 46/405) as their main fuel. All participants who said that their main fuel was electricity and 51.9% (210/405) of participants overall used multiple fuels. Although efforts were made to determine the duration and pattern of biomass exposure at an individual level, the quality of the final data collected were poor with conflation of individual and household level exposures which it was not possible to remedy through cleaning. These data were considered to provide inaccurate measures of exposure and are therefore not included here.

- CARDIORESPIRATORY CO-MORBIDITIES

42.7% (173/405) of individuals had a previous respiratory diagnosis, other than TB. The majority of previous respiratory illness episodes were due to infections with (32.8%, 133/405) of participants having had a previous pneumonia, or 7.2% (29/405) an upper/lower respiratory tract infection. Only 9/405 (2.2%) of participants had been given any formal diagnosis of a chronic lung disease by the time of TB treatment completion: 4 had been diagnosed with bronchitis, and 5 with asthma. Only 5/405 (1.2%) of participants were on regular respiratory medications: 1 was using oral salbutamol, 3 inhaled salbutamol, and 3 were on oral theophylines. 1 participant had a history of cardiovascular disease (cardiomegaly), and 1.5% (6/405) of participants had a history of diabetes.

- SOCIOECONOMIC SITUATION

Full data required to calculate the SES quintile were available for 91.9% (372/405) of participants; the remaining participants missed their 6-month home visit and therefore did not have their household wall / floor / roofing materials recorded. When the national wealth quintile score was used, 88.2% of participants for whom full data were available fell in to the wealthiest quintile for Malawi with no participants falling into the poorest group. Data were distributed more widely when the urban quintile tool was used but still relatively few participants were in the poorest (5.9%) quintile with the majority falling in the middle ranges (Table 14).

SES appeared lower in those with microbiologically proven disease compared to those without: 90.9% (20/22) of the poorest quintile had microbiologically proven disease, compared to 66.1% (37/56) of the wealthiest cohort (p= 0.005). Stratification by HIV status reduces the strength of this association, with Chi^2 p-values falling to 0.074 and 0.077 in the separate HIV negative and positive groups.

Table 14: Socioeconomic situation of study participants at TB treatment completion, stratified by baseline microbiology (n=405)

Characteristic	Total (n=405)	Micro –ve (n=92)	Micro +ve (n=313)	p-value
Urban SES quintile (n=372)				
- Poorest	22 (5.9%)	2 (2.4%)	20 (7.0%)	0.005**
- 2nd poorest	85 (22.8%)	14 (16.5%)	71 (24.7%)	
- Middle	95 (25.5%)	15 (17.6%)	80 (27.9%)	
- 2nd most wealthy	114 (30.6%)	35 (41.2%)	79 (27.5%)	
- Most wealthy	56 (15.1%)	19 (22.4%)	37 (12.9%)	
Years formal education	10 (7 – 12)	10 (8 – 12)	10(7 – 12)	0.106
Maximum education level				
- No school	14 (3.5%)	3 (3.3%)	11 (3.5%)	0.383
- Primary	140 (34.6%)	27 (29.4%)	113 (36.1%)	
- Secondary	207 (51.1%)	48 (52.2%)	159 (50.8%)	
- Higher	44 (10.9%)	14 (15.2%)	30 (9.6%)	
Difficulty getting food for household	277 (68.4%)	73 (79.4%)	204 (65.2%)	0.036*
- Never	92 (22.7%)	14 (15.2%)	78 (24.9%)	
- Sometimes	36 (8.9%)	5 (5.4%)	31 (9.9%)	
- Often				

*p<.05, **p<.01, ***p<.001

- EDUCATION

The distribution of the number of years of formal education received was left skewed with a median of 10 years (IQR: 7 – 12 yrs), and 38% (154/405) had either no education or primary school education only. Wealth quintile was positively correlated with educational standards, as would be expected: the majority of participants in the poorest quintile received no/primary education only (77.3%, 17/22) and none went on to higher education, whilst amongst the richest all participants had attended school, with the majority receiving either secondary or higher education (87.5%, 49/56).

- FOOD SECURITY

Within the cohort 14.3% (58/405) of participants reported that adults in the household had skipped meals so that children could eat within the past fortnight, and when asked whether difficulty getting food for the household had been experienced within the past 1-month, 22.7% (92/405) said this was the case sometimes, and 8.9% (36/405) said that this was often the case. Difficulties were concentrated in the lower socioeconomic quintiles, with 49.5% (100/202) of participants in the lowest three SES groups experiencing challenges sometimes/often, compared to 12.4% (21/170) of those in the higher quintiles. Difficulty accessing food was seasonal with the greatest proportion of individuals experiencing difficulty highest amongst the summer months / rainy season.

5.3.3 CLINICAL AND RESPIRATORY PARAMETERS OVER 1-YEAR

In this section of the results, population level data are presented for quality of life and symptom assessments, clinical observations, measures of functional capacity, blood results, spirometry, and the CT and CXR imaging in turn. Data from baseline, 6-month and 12-month visits are presented together for each set of variables. The heterogeneity observed in change over time between individuals is

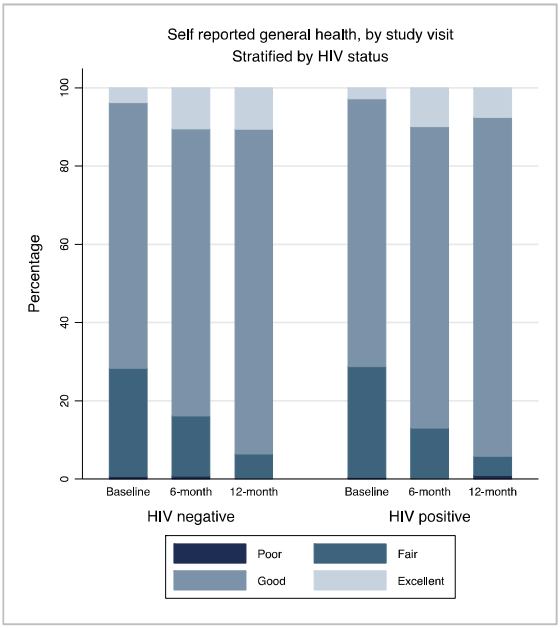
described across multiple parameters, and the relationship between symptom, imaging, and patterns of spirometry at TB treatment completion are then described.

QUALITY OF LIFE DATA

- GENERAL HEALTH

When asked to rank their health on a Likert scale from poor to excellent, 28.4% (115/405) reported ongoing poor / fair health at TB treatment completion. This proportion fell to 6.0% (22/368) at the 1-year follow up point, and trends were similar in both HIV-infected and HIV-negative participants (Figure 4).

Figure 4: Self-reported general health at each study visit, stratified by HIV status (Baseline n=405, 6-months n=376, 12-months n=368)



A similar proportion of individuals (28.2% (114/405)) were still missing work due to poor health at TB treatment completion, but this figure fell to 10.0% (37/368) by 1-year later. There was strong agreement between self-reported health related absence from work, and self-reported general health: combining data from all study visits, all of those with poor health had experienced time off work in the last month in relation to this (100% (4/4)), whilst only 6.5% (3/46) of the group with 'excellent' self-reported health had taken time off work for health reasons in the past 1-month.

- SGRQ RESULTS

Data for all of the SGRQ summary scores were right skewed with the majority of participants having low values. Wide distributions were observed for each summary score at each time point, confirming significant heterogeneity across the cohort (Table 15): at TB treatment completion, the median SGRQ

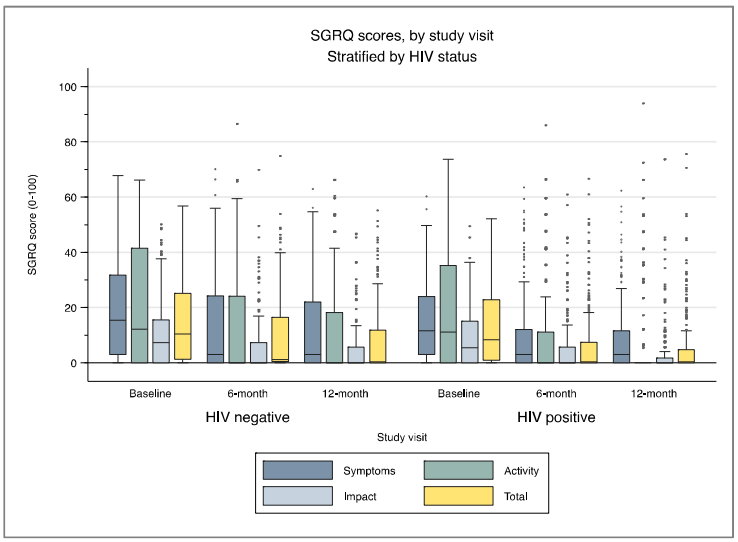
total score was 8.7 (IQR 1.2 – 23.7) but scores ranged from 0 – 53.6/100. Amongst the sub scores, Symptom and Activity scores were higher than Impact scores throughout.

Table 15: Population median (IQR) and [Full range] of the SGRQ summary scores for each study visit

	Baseline (n=403)	6-month (n=376)	1-year (n=368)
Symptom score	11.6 (3.0 – 26.0) [0 – 67.8]	3.0 (0 – 15.4) [0 – 70.0]	3.0 (0 – 15.4) [0 – 63.0]
Activity score	11.2 (0 – 35.5) [0 – 73.7]	0 (0 – 11.9) [0 – 86.5]	0 (0 – 6.2) [0 – 93.9]
Impact score	5.6 (0 – 15.5) [0 – 50.0]	0 (0 – 6.5) [0 – 69.8]	0 (0 – 3.7) [0 – 73.6]
Total score	8.7 (1.2 – 23.7) [0 – 56.7]	0.4 (0 – 10.8) [0 – 74.9]	0.4 (0 – 7.0) [0 – 75.6]

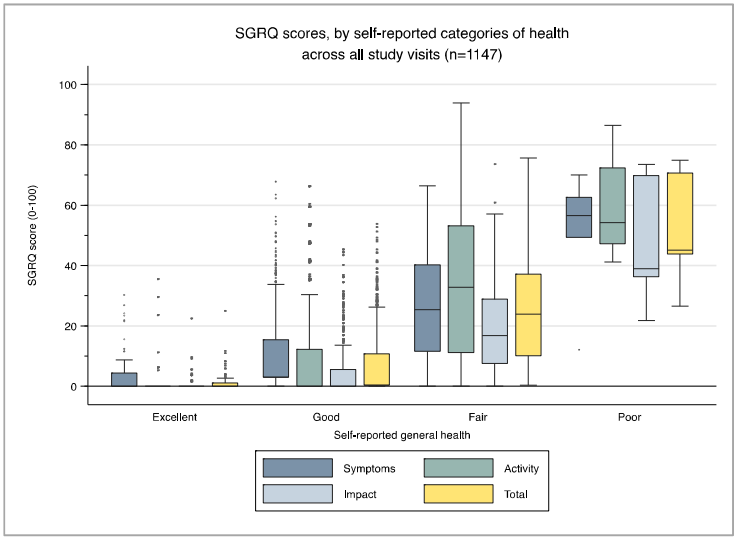
There was a general trend towards improvement – particularly over the first 6 months following treatment completion. By 1-year post TB treatment completion, the median total SGRQ score was 0.40 (IQR: 0 – 7.0), with a total range from 0 – 76 points. There we no statistically significant differences in total SGRQ total scores between HIV infected / negative groups at any of the study visits, and the trend to improvement was similar in both groups (Figure 5).

Figure 5: Box plots of SGRQ total and sub scores (symptom, activity, impact) across the three study visits, stratified by HIV status



A high proportion of individuals scored '0' for both sub and total SGRQ scores at each study visit, raising some concerns about the validity of the SGRQ data. However, when SGRQ scores were stratified by the Likert-score self-reported categories of health, these 'zero' values belong largely to those reporting good or excellent health (Figure 6).

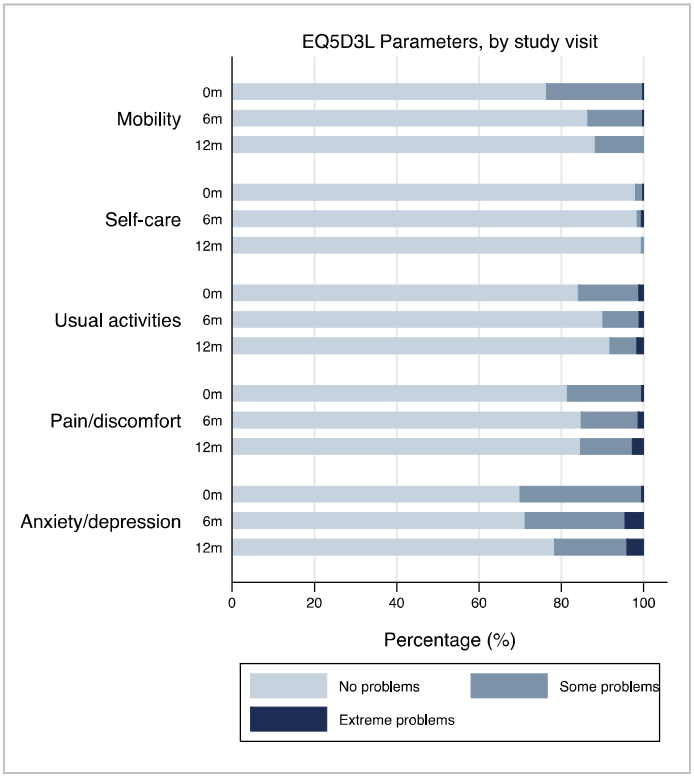
Figure 6: SGRQ Total scores across all study visits (n=1147), stratified by self-reported general health at that time



- EQ5D3L RESULTS

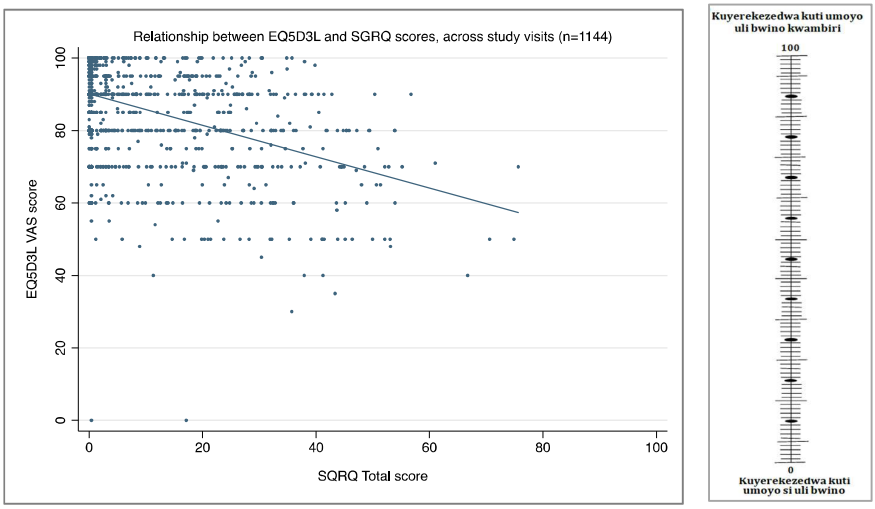
23.6% (95/403) of individuals had challenges in mobility at the baseline visit and 11.7% (43/366) at the 1-year visit using the EQ5D3L questionnaire. Pain, which was not assessed in the SGRQ, was reported by 18.5% (74/400) / 15.3% (56/366) of individuals at baseline / 1-year. In keeping with the SGRQ data the parameter of health least affected was the ability to self-care – very few individuals had any problems with this at any of the study visits. Also, in keeping was a trend to improvement across study visits, with the percentage of participants reporting problems in any of these dimensions decreasing in the first 6-months in particular (Figure 7). The EQ5D3L results from the anxiety/depression score are difficult to interpret: this symptom appears common across all study visits within the dataset, with less resolution over time, but there was some concern from amongst the study team that these concepts – even after translation and previous validation of this tool in the local language, Chichewa – were difficult for study participants to grasp, and as such confidence in the accuracy of this measure is limited.

Figure 7: EQ5D3L results, across serial study visits



A negative correlation was observed between the EQ5D3L Visual Analogue Score (VAS) and the SGRQ total score (Pearson's correlation coefficient: -0.44, p<0.001) (Figure 13). VAS scores were clustered around the 10-unit intervals corresponding to the layout of the VAS scale on the scoring sheet, which highlights these intervals (Figure 8).

Figure 8: Scatter diagram illustrating the relationship between the SGRQ Total score and the EQ5D3L visual analogue score (VAS), with data combined across study visits (n=1144), accompanied by a visual representation of the VAS score on the scoring sheet

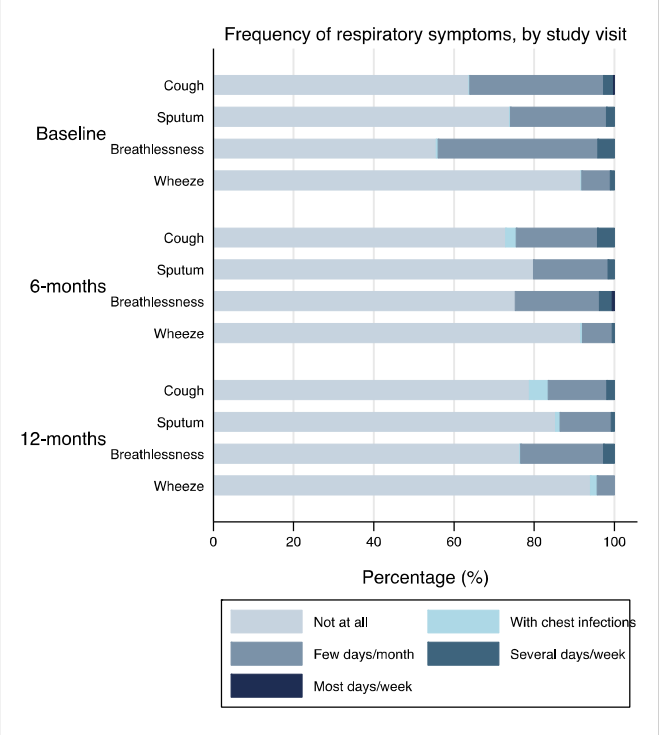


CLINICAL SYMPTOM DATA

At TB treatment completion 60.7% (246/405) of participants continued to experience at least 1 respiratory symptom for at least a few days each month, and 7.7% (31/405) reported symptoms on several or most days each week. Although the burden of monthly and weekly symptoms was slightly lower amongst HIV positives vs. negatives, the difference was not statistically significant (monthly: 58.2 vs. 64.8%, p=0.186 / weekly: 5.7% vs. 10.7%, p=0.068).

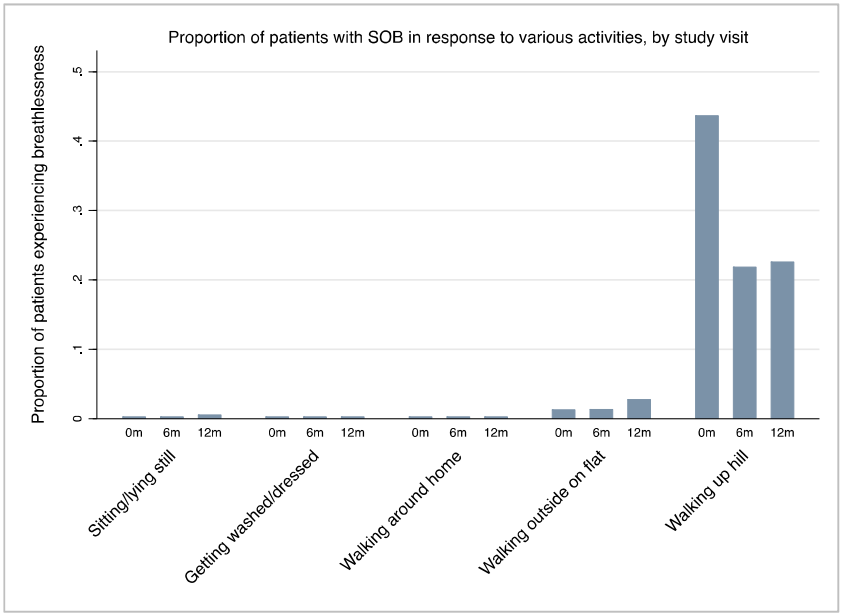
The prevalence of symptoms decreased over time such that 30.7% (113/368) had monthly and 4.1% (15/368) weekly symptoms by the 1-year follow up point. The most common regular symptom was shortness of breath, which was experienced monthly or weekly in 39.8% and 4.2% of participants at baseline, and 23.4% and 2.7% of participants at the 1-year point. Wheeze was the least common symptom throughout. Self-reported sputum production was infrequent, and was experienced monthly by 12.8% (47/368) and weekly by 0.8% (3/368) of the cohort by the 1-year time point (Figure 9).

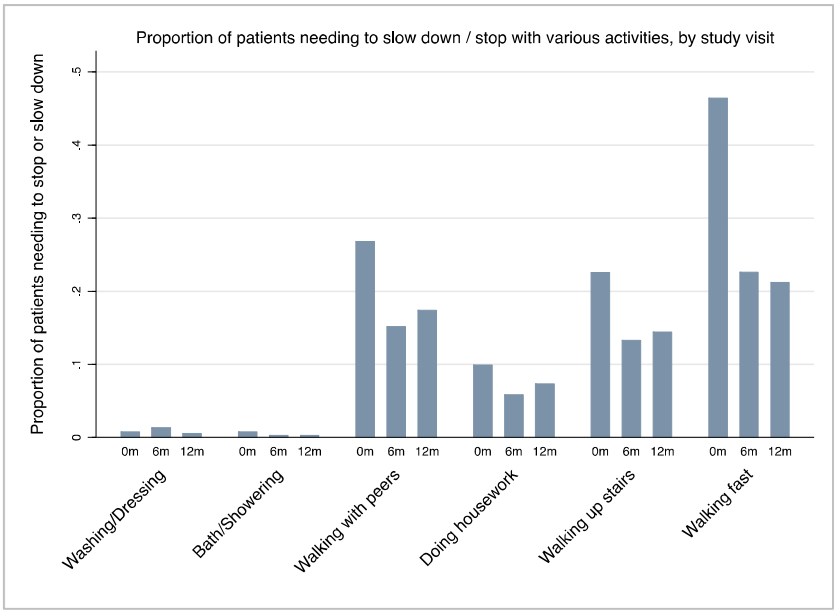
Figure 9: Self-reported frequency of respiratory symptoms, at each study visit



Breathlessness when sitting still, washing, walking inside the house, or performing activities of personal care was rare at all study visits. Few participants were breathless when walking outside on the flat (1.2% (5/403) at baseline / 2.7% (10/368) at 1-year), but a higher proportion of participants needed to walk slower than peers or stop for rest when walking at their own pace at all study visits (26.8% (108/403) at baseline / 17.4% (64/368) at 1-year). Breathlessness when going up hills was reported by 43.7% (176/403) at baseline and 22.6% (83/368) at 1-year (Figure 10).

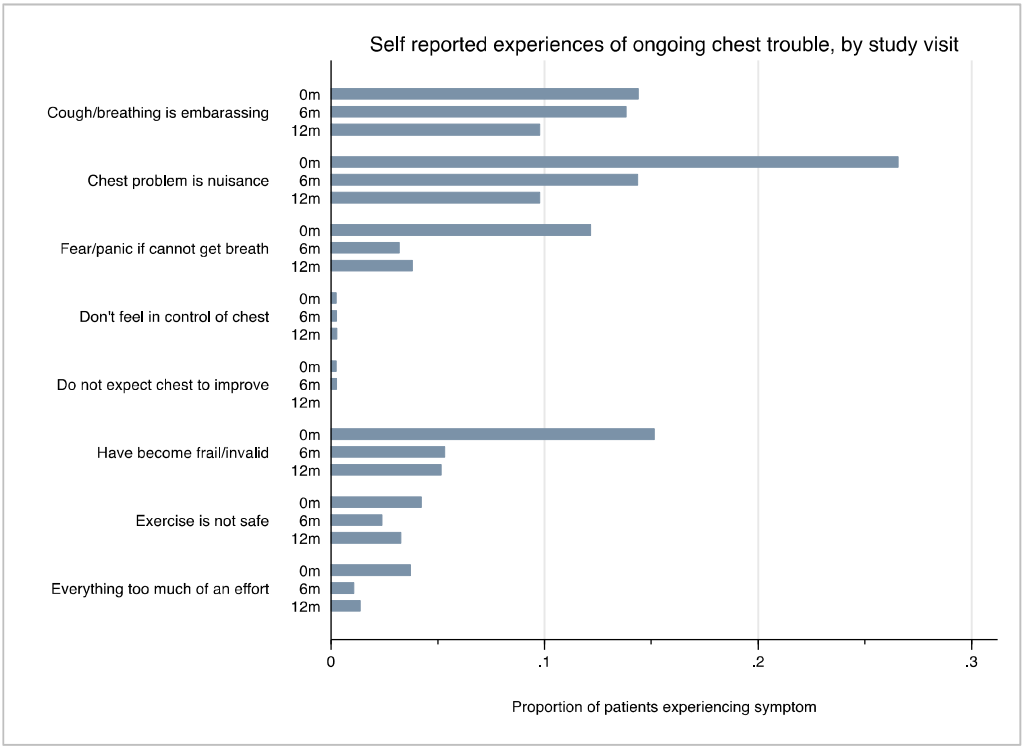
Figure 10: Proportion of participants experiencing breathlessness, or need to stop/slow down with various activities, at each study visit





The psychological impact scores were the lowest out of the three SGRQ subgroup scores. At TB treatment completion 14.4% (58/403) were ashamed of their chest issues and 26.6% (107/403) felt that their chest issues were a nuisance. A trend to improvement was seen over time such that by 1-year, 9.8% (36/368) felt ashamed, and the same number found their chest to be a nuisance by this time point. 15.2% (61/403) felt frail at TB treatment completion, falling to 5.2% (19/368) by 1-year (Figure 11). The majority of individuals retained a sense of hope that things would improve, throughout the study period.

Figure 11: Proportion of participants experiencing psychosocial issues related to ongoing respiratory problems.



At the time of TB treatment completion, 40.0% (162/405) of study participants had chest symptoms that interfered with their work / preventing them from working, and 12.2% (45/368) of participants reported symptoms at the 1-year time point.

Over half of the cohort (50.4% (205/405)) felt that their usual activities were limited at TB treatment completion, but this proportion fell to 19.8% (73/368) by 1-year. Specific challenges raised by participants on open questioning included: difficulty farming (19.4% (78/403 at TB treatment completion / 4.1% (15/368) at 1-year), and difficulty lifting heavy items (18.4% (74/403) at TB treatment completion / 7.1% (26/368) at 1-year).

CLINICAL OBSERVATIONS

- VITAL SIGNS

Heart rate was normally distributed across the population with mean values of 79 beats per minute (SD: 15.4) / 78bpm (SD:14.2) and 77bpm (SD: 13.8) at each of the study visits. The prevalence of tachycardia (heart rate >100 beats per minute) declined over the 1-year period from 8.9% (36/405) at TB treatment completion to 3.5% (13/368) at the 1-year follow up (p=0.002).

Tachypnoea (respiratory rate >20 breaths per minute) was seen in only 21.8% (88/404) of individuals at baseline, but was observed in 28.2% (106/376) at 6-months, and 46.7% (172/368) at the 1-year study visit (p<0.001). Oxygen saturations were normally distributed with mean values at sequential

study visits of 97.8% (SD: 1.6%), 97.8% (SD: 1.5%), and 97.4% (SD: 2.2%). Only 1.5% (6/405) individuals at TB treatment completion and 0.8% (3/368) at the 1-year visit had saturations which were ≤92% at rest.

- BMI AND MUAC

BMI at TB diagnosis had been recorded within routine clinical services for 88.6% (359/405) participants, with a median value of 18.6 kg/m^2 (IQR: 16.7 – 20.3 kg/m^2). BMI was lower in those with microbiologically proven PTB disease, compared to those with negative microbiology (18.4 vs. 19.6 kg/m^2, p=0.016) at this time (Table 16).

BMI at TB treatment completion was measured in the full study cohort, with a median value of 20.5 kg/m^2 (IQR: 19.0-22.3 kg/m^2). At this point, 17.5% (71/405) of participants were underweight with BMI <18.5 kg/m^2, and 6.4% (30/405) were overweight or obese with BMI ≥25.0 kg/m^2. Lower BMI values were seen amongst those reporting difficulties procuring food often compared to those with no difficulties (19.4 kg/m^2 vs. 20.8 kg/m^2, p=0.003). No relationship was observed between baseline microbiology and BMI at TB treatment completion.

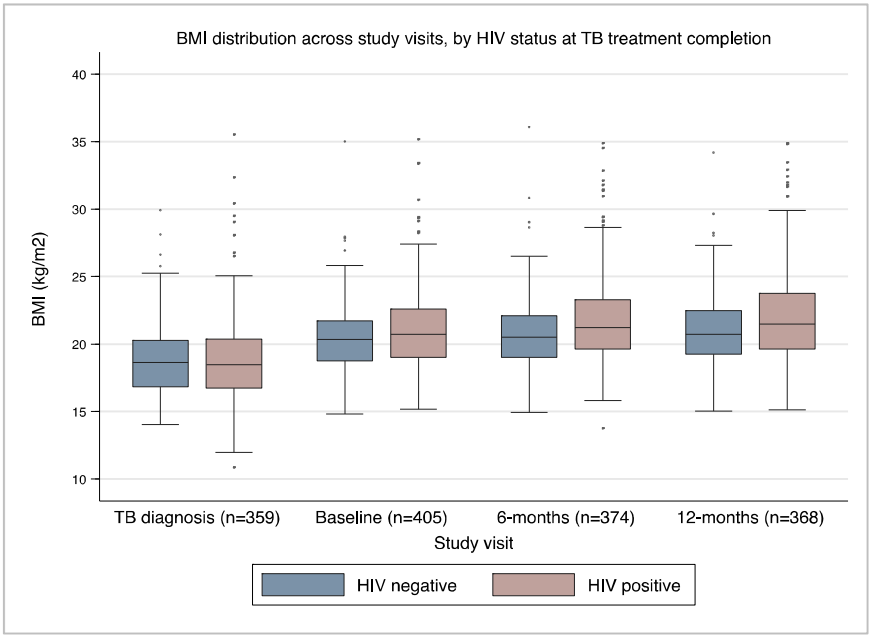
Table 16: BMI and MUAC measurements at TB treatment completion, stratified by baseline microbiology

Characteristic	Total (n=405)	Micro –ve (n=92)	Micro +ve (n=313)	p-value
BMI recorded at TB diagnosis (kg/m^2) (n=359)	18.6 (16.8-20.3)	19.6 (16.7 – 21.4)	18.4 (16.8 – 20.1)	0.016*
BMI (kg/m2)	20.5 (19.0 – 22.3)	20.9 (18.9 – 22.7)	20.4 (19.0 – 22.1)	0.067
BMI categories - Underweight (<18.5 kg/m2) - Normal (18.5 – 24.9 kg/m2) - Overweight (25 – 29.9 kg/m2) - Obese (≥30 kg/m2)	 71 (17.5%) 304 (75.1%) 25 (6.2%) 5 (1.2%)	 16 (17.4%) 63 (68.5%) 12 (13.0%) 1 (1.1%)	 55 (17.6%) 241 (77.0%) 13 (4.2%) 4 (1.3%)	0.026
Mid-upper arm circumference (MUAC) (cm)	24.6 (23.3 – 26.4)	25.1 (23.3 – 27.2)	24.6 (23.3 – 26.3)	0.335

*p<.05, **p<.01, ***p<.001

A general trend to improvement in BMI was observed over the 1-year follow up period, with an average increase of 0.7kg/m^2. No difference in BMI was noted between HIV positive and negative individuals at TB diagnosis but BMI recordings for HIV-positive participants were higher than those for HIV-negative participants at all subsequent study visits (p<0.05 for all visits) (Figure 12). This relationship persisted with stratification for gender (not shown).

Figure 12: BMI measurements at TB diagnosis and at each study visit from TB treatment completion, stratified by HIV status



Median MUAC at TB treatment completion was 24.6cm (IQR: 23.3 – 26.4). A strongly positive linear correlation was observed between MUAC and BMI measurements across study visits, with a Pearson correlation coefficient of 0.79, and a 0.86 kg/m^2 (95% CI: 0.79 - 0.92) increase in BMI for every 1cm increase in MUAC.

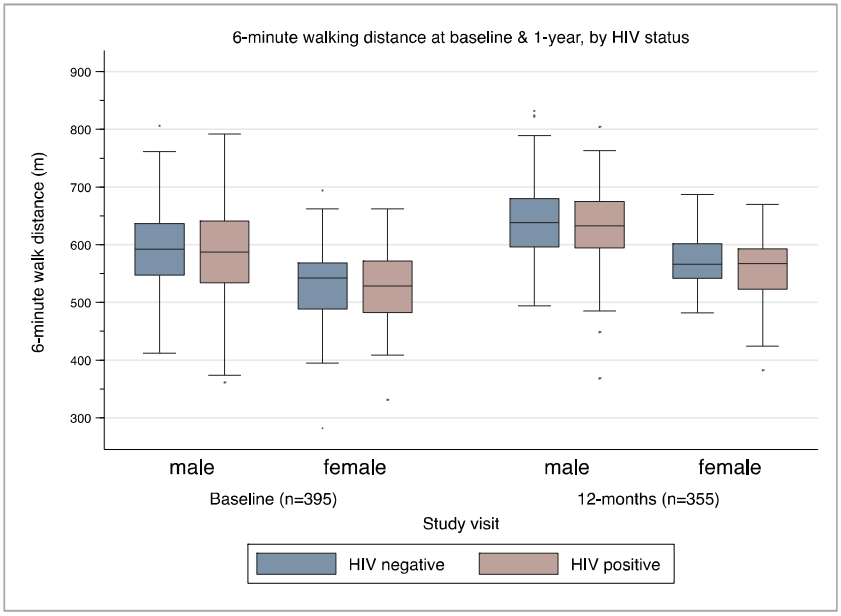
- FOCUSED CLINICAL EXAMINATION

Pitting pedal oedema to the level of the ankles or shins was found in 1.7% (7/405) of participants at TB treatment completion, and 0.8% (3/368) participants with mild oedema of their ankles were observed at the 1-year study visit. Palatal Kaposi's Sarcoma was observed in 2.0% (8/405) participants at TB treatment completion, and 0.3% (1/368) of participants at the 1-year study visit.

MEASURES OF FUNCTIONAL CAPACITY

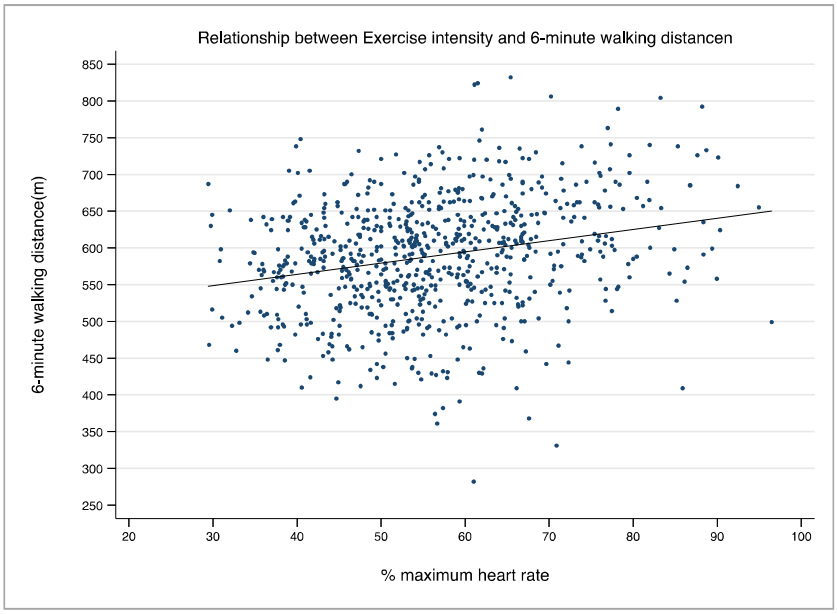
The full six-minute walk test was completed by 97.3% (395/405) and 96.5% (355/368) participants at TB treatment completion and at the 1-year visit, respectively. Data for the distance walked were normally distributed. A mean distance of 568m (SD: 79.7m) and 611.2m (SD: 71.0m) was walked at TB treatment completion and at the 1-year study visit, respectively ($p<0.001$). The mean improvement observed over the 1-year period was 41.3m (SD:62.6m). The proportion of individuals with saturations ≤92% at the end of the walk were 3.8% (15/395) and 2.8% (10/355) at these two time points. Women walked shorter distances than men at both study visits ($p<0.001$ for both). No statistically significant differences in distance were identified by HIV status, after stratifying for gender (Figure 13).

Figure 13: 6-minute walking distance at baseline and 1-year study visits, according to gender and HIV status.



The maximum heart rate reached during the 6MWT was positively correlated with the 6MWD achieved (Spearman's r=0.221, p<0.001) across all study data (Figure 14), confirming that the distance walked increases as cardiovascular effort increased. At TB treatment completion the median % maximum heart rate was 53.6% (IQR 45.1-62.0%), and at the 1-year visit this was 57.0% (IQR 50.0 – 65.1%), in keeping with a higher level of exercise intensity at the 1-year time point.

Figure 14: Correlation between exercise intensity and 6-minute walking distance achieved, across both study visits (1 data point per patient visit, with up to 2 measures per patient)



There was no clear correlation between walking distance and BMI after controlling for gender. However, a strong positive correlation was observed between Haemoglobin and walking distance:

after controlling for gender, a 1-unit increase in haemoglobin was associated with a 6.7m longer walking distance (95% CI: 3.2 – 10.2, p<0.001).

Across both baseline and 1-year study visits, the distance walked was lower in those who had reported the need to stop or slow down when walking on the flat (569m vs. 598m, p<0.001), and those who reported breathlessness walking up hills (570m vs. 601m, p<0.001) compared to those who did not report these limitations. Weak negative correlations were observed between the 6MWD and the various SGRQ summary scores (-0.19 to -0.22, all p<0.001).

5.3.4 BLOOD TESTS

The mean haemoglobin (Hb) within the cohort was 13.7 g/dL (IQR: 12.3 – 15.1), and values were lower in HIV-infected participants (median 13.0 vs. 14.6 g/dL, p<0.001). Platelet and neutrophil levels were higher in the HIV-positive group, but lymphocyte counts were lower (1.8 vs. 1.9 $x10^9$ cells/L). There was no significant difference in the eosinophil counts between the groups (Table 17). Preliminary Aspergillus serology assays found that 2/404 samples were positive using the Bio-Rad assay (cut off 10AU/ml), and 3/404 samples were positive using the Bordier assay at TB treatment completion.

Table 17: Blood results at TB treatment completion

Parameter	HIV negative (n=159)	HIV positive (n=244)	P-value for comparison
Haemoglobin (g/dL)	14.6 (13.3 – 15.6)	13.1 (11.7 – 14.5)	<0.001***
Platelets (10^9/L)	234 (175 – 307)	277 (216 – 338)	<0.001***
White cell count (10^9/L)	4.4 (3.6 – 5.1)	4.0 (3.3 – 5.0)	0.044*
Neutrophil count (10^9/L)	1.8 (1.3 – 2.4)	1.9 (1.4 – 2.6)	0.010*
Lymphocyte count (10^9/L)	1.9 (1.5 – 2.4)	1.8 (1.3 – 2.2)	0.004**
Eosinophil count (10^9/L)	0.1 (0.1 – 0.3)	0.1 (0.1 – 0.3)	0.399

*p<.05, **p<.01, ***p<.001

5.3.5 SPIROMETRY

Spirometry was attempted by 98.8% (399/405) / 96.9% (364/376) / 96.2% (354/368) at each of the three study visits. Post-bronchodilator spirometry data of sufficient quality (2 usable curves with repeatability for both FEV_1 and FVC) were available for 90.1% (365/405) of participants at baseline, 90.7% (341/376) of participants at the 6-month visit, and 91.3% (336/368) of participants completing the 12-month visit. 75.3% (305/405) of the cohort contributed BOLD valid readings at both TB treatment completion, and the 1-year follow up period. Participant characteristics were similar, except for a slightly higher proportion of males amongst those with valid data at both time points (70.5%vs. 60.0%, p=0.051) (Table 18).

Table 18: Comparison of patient characteristics, for those with / without BOLD valid post-bronchodilator FEV_1 and FVC readings at both TB treatment completion and the 1-year time point

	BOLD valid spirometry missing from one time point (n=100)	BOLD valid spirometry complete at TB Rx completion and 1-year (n=305)	p-value
Age (median, IQR)	33 (28 – 38)	35 (29 – 41)	0.094
Male gender (n, %)	60 (60.0%)	215 (70.5%)	0.051
HIV infected (n, %) (n=403)	55 (55.6%)	189 (62.2%)	0.242
Microbiological evidence of PTB at diagnosis (n, %)	76 (76.0%)	237 (77.7%)	0.724
BMI at TB treatment completion (kg/m^2) (median, IQR)	20.8 (19.1 – 22.6)	20.4 (18.9 – 22.2)	0.280
Total abnormal parenchyma (0-600) (median, IQR)	125 (30 – 248)	145 (60 – 233)	0.357
Presence of any moderate-severe bronchiectasis (n, %)	31/85 (36.5%)	139/300 (46.3%)	0.106
SGRQ total score (median, IQR)	12.5 (1.2 – 26.6)	7.9 (1.1 – 22.9)	0.146
Regular monthly respiratory symptoms (n, %)	63 (63.0%)	183 (60.0%)	0.594

The mean z-scores for the FEV_1 readings, FVC readings, and FEV_1/FVC ratios were negative at all study visits, confirming that the volumes measured were lower than the age, gender and height standardised expected values provided by the GLI-2012 black reference ranges at all three study visits (Table 19). The parameter with the lowest z-scores was the FEV_1 volume which was, on average 1.06 standard deviations (SD 0.69) below the expected mean FEV_1 value at the point of TB treatment completion and remained on average 0.88 standard deviations lower (SD:1.19) than expected by the 1-year follow up point. Both the FEV_1 and FVC increased over the course of the study, with a larger mean increase in the FVC compared to the FEV_1 (0.20 (SD:0.55) vs. 0.33 (SD: 0.55) z-scores). Changes in the FEV_1 and FVC z-scores were statistically significant (t test p-values: 0.043 / <0.001), but the change in the FEV_1/FVC ratio was not.

Table 19: Average spirometry readings for each study visit, reported as absolute values and z-scores after standardization with the GLI-2012 Black reference ranges, with average difference measured between baseline and 1-year

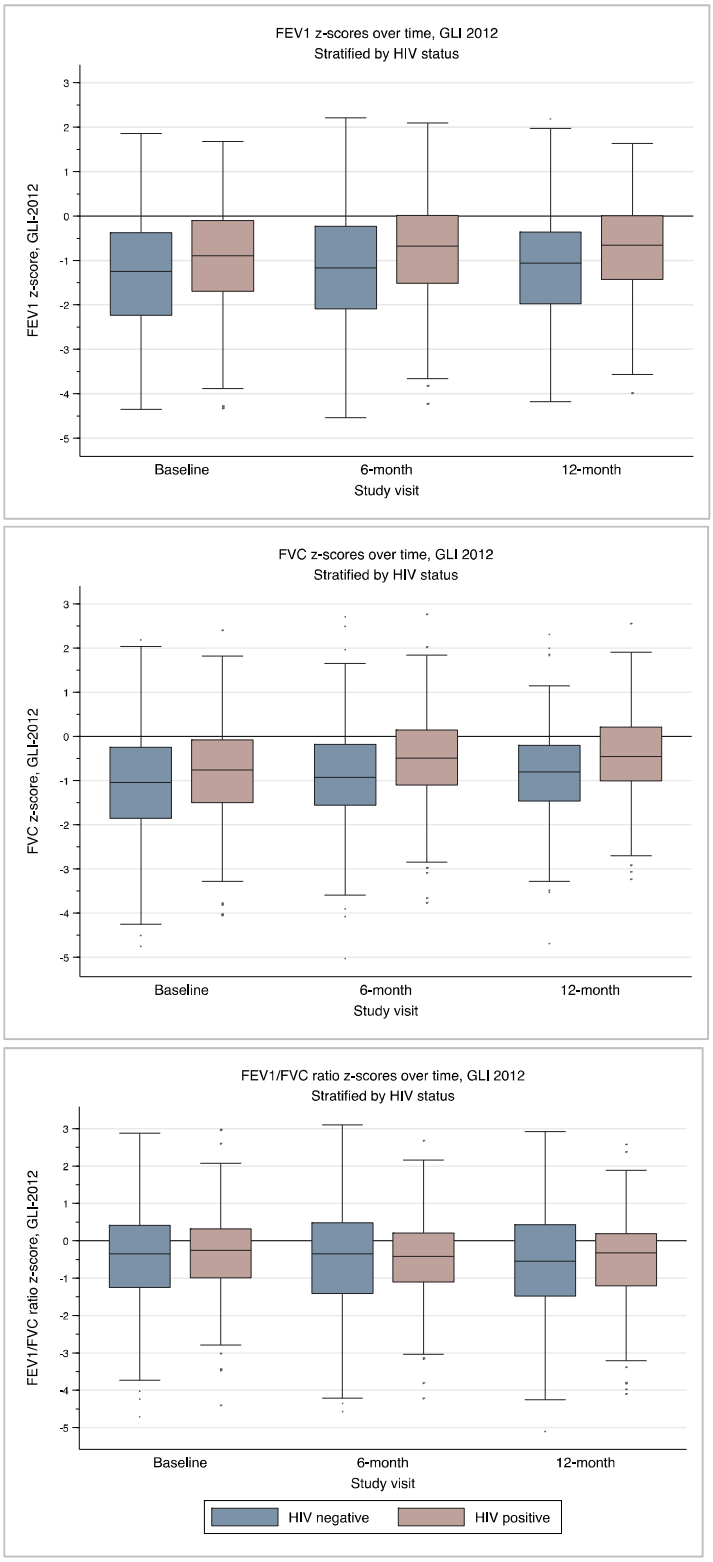
Variable	TB treatment completion (mean, sd) (n=365)		6 months (mean, sd) (n=341)		12 months (mean, sd) (n=336)		Average change, over 1-year follow up (mean, sd) (n=305)		
	Absolute value	Z-score	Absolute value	Z-score	Absolute value	Z-score	Absolute difference	Z-score	p-value for difference in z-scores
FEV_1 (L)	2.57 (0.69)	-1.06 (1.26)	2.63 (0.68)	-0.90 (1.25)	2.63 (0.67)	-0.88 (1.19)	0.07 (0.24)	0.20 (0.55)	0.043*
FVC (L)	3.18 (0.78)	-0.91 (1.23)	3.29 (0.78)	-0.66 (1.19)	3.31 (0.76)	-0.61 (1.09)	0.15 (0.27)	0.33 (0.55)	<0.001***
FEV_1/FVC (%)	80.87(8.92)	-0.38 (1.26)	79.85(9.30)	-0.51 (1.28)	79.54(9.55)	-0.54(1.29)	-1.37 (4.26)	-0.17 (0.66)	0.086

*p<.05, **p<.01, ***p<.001

Population distributions of both the FEV_1 and FVC z-scores were lower in the HIV-negative compared to HIV-infected groups throughout all study visits (mean FEV_1 -1.27 vs -0.94, p= 0.015; mean FVC -1.08

vs -0.80, p= 0.037) (Figure 15). The whiskers of these box plots are very wide for each group at each time point, reflecting the heterogeneity of 'standardised' z-scores between individuals.

Figure 15: Box plots of FEV1, FVC, and FEV1/FVC ratio z-scores, stratified by HIV status, over time



PATTERNS OF SPIROMETRIC DEFICIT

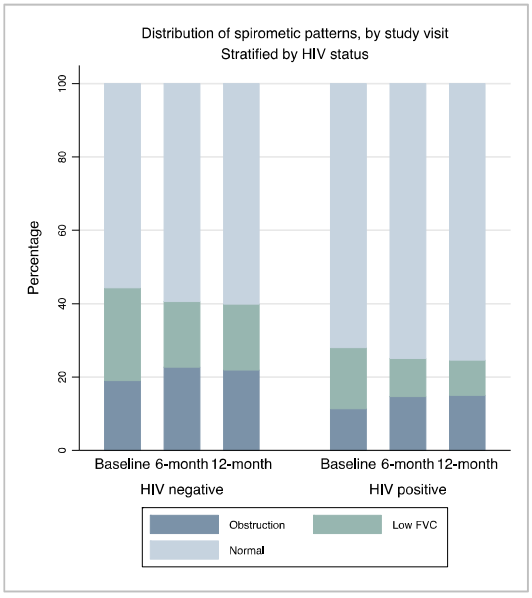
Abnormal spirometry at TB treatment completion was seen in 34.2% (125/365) of participants: 20% (73/365) and 14.2% (52/365) had a low FVC and obstructive pattern, respectively. In keeping with the changes in the distribution of z-scores presented above, the proportion of participants in the low FVC group decreased to 12.8% (43/336) by 1-year, whilst the proportion of participants classified as having airway obstruction rose to 17.9% (60/336) (Table 20).

Table 20: Proportion of participants with abnormal spirometry at each of the study visits, classified using the 5th centile lower limit of normal (LLN) cut offs calculated using the GLI-2012 reference ranges.

Pattern	TB treatment completion(n=365)	6 months (n=341)	12 months (n=336)
Obstruction	52 (14.2%)	61 (17.9%)	60 (17.9%)
Low FVC	73 (20.0%)	45 (13.2%)	43 (12.8%)
Normal	240 (65.8%)	235 (68.9%)	233 (69.4%)

The proportion of participants with abnormal spirometry was higher amongst HIV-negatives compared to HIV-positives at all time points. However, the pattern of change over time with falling numbers in the low-FVC group and rising numbers classified as having obstruction was similar in both groups (Figure 16).

Figure 16: Proportion of participants falling into each category of spirometric deficit, at each study visit, stratified by HIV status



At an individual level, the majority of participants remained in the same category over the course of the study (Table 21). Recovery from an abnormal to normal pattern was more common amongst those originally in the low FVC group (31.7%, 19/60) compared to the obstructed group (16.3%, 7/43) at TB treatment completion. Amongst the 18 individuals found to have 'new' obstruction over the course of the study, only 50% (9/18) had experienced a true decline in their FEV_1 z-score over this period. The

other half had experienced an improvement in both FEV_1 and FVC but with a disproportionate rise in the latter and a corresponding fall in their FEV_1/FVC ratio.

Table 21: Relationship between spirometry pattern at TB treatment completion, and that measured at 1-year, in participants for whom BOLD valid readings were available for both study visits (n=305). Boxes highlighted in grey imply no change in classification over the 1-year follow up period.

Spirometry at TB treatment completion	Spirometry 1-year post treatment completion			
	Obstruction	Low FVC	Normal	TOTAL
Obstruction	36 (83.7%)	0	7 (16.3%)	43 (100%)
Low FVC	3 (5.0%)	38 (63.3%)	19 (31.7%)	60 (100%)
Normal	15 (7.4%)	3 (1.5%)	184 (91.1%)	202 (100%)
TOTAL	54 (17.7%)	41 (13.4%)	210 (68.9%)	305 (100%)

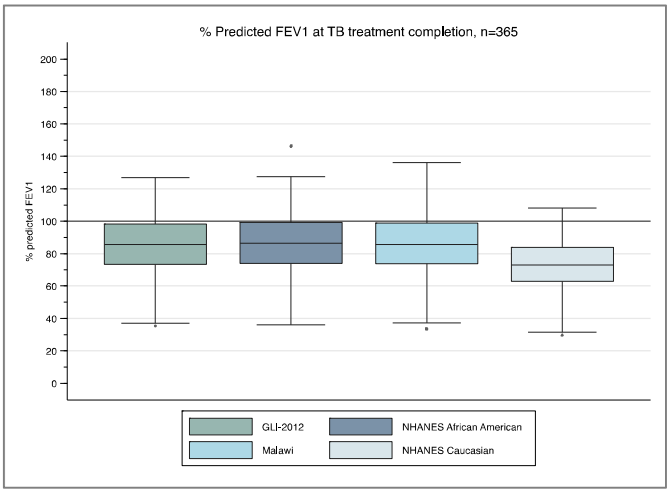
REVERSIBILITY

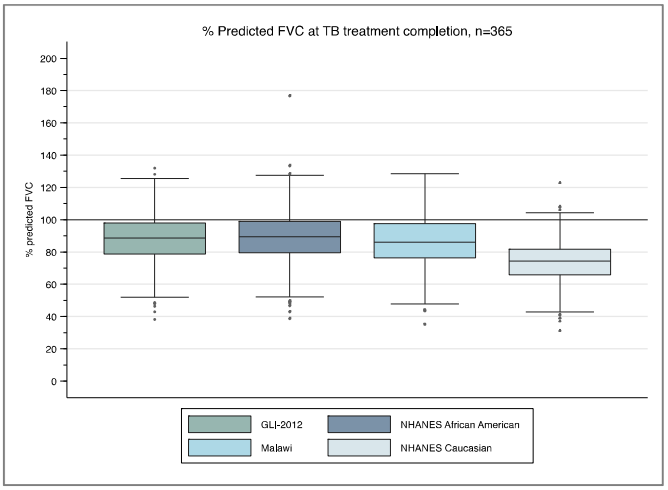
Amongst those with airway obstruction at TB treatment completion (FEV_1/FVC ratio<LLN), the prevalence of reversibility was 5.8% (3/52) at TB treatment completion, 1.6% (1/61) at 6-months, and 8.3% (5/60) at the 1-year follow-up point.

COMPARISON BETWEEN REFERENCE RANGES

The GLI-2012, NHANES III African American, and Malawian reference ranges lead to broadly similar data distributions with similar mean FEV1 values of 85.2 – 86.0% predicted, and FVC values of 86.7 – 89.1% predicted. However, due to larger predicted lung volumes, standardisation using the NHANES III Caucasian ranges produces a lower mean FEV1 of 72.8% predicted and FVC of 73.8% predicted (Figure 17). The difference in the mean % predicted scores derived from the GLI-2012 and NHANES III Caucasian reference ranges is statistically significant for both the FEV1 (mean 85.2% vs. 72.8%, p<0.001) and FVC (mean 88.2% vs.73.8%, p<0.001).

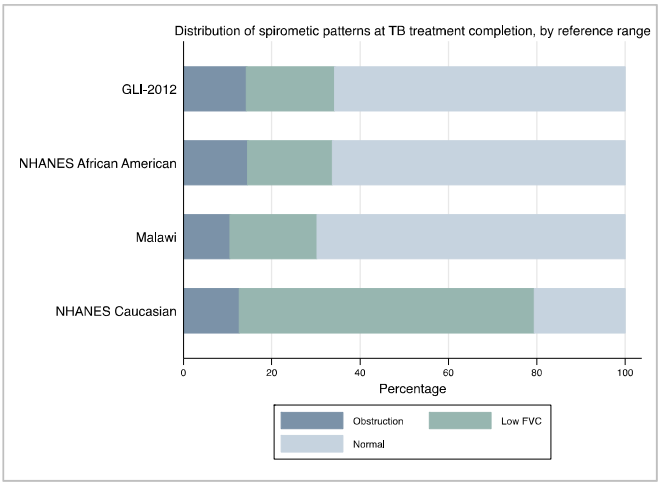
Figure 17: Distribution of % predicted values of FEV_1 and FVC at TB treatment completed, calculated using different reference ranges.





When participants are classified according to their pattern of deficit using LLN cut-off values, the GLI-2012, NHANES African, and Malawi reference ranges produce similar results, but a higher proportion of participants are allocated to the Low FVC group when the NHANES III Caucasian reference range is used (NHANES Caucasian: 66.9%, 244/365 vs. GLI-2012: 20.0% (73/365)) (Figure 18).

Figure 18: Prevalence of spirometric patterns at TB treatment completion, defined using LLN cut offs from different reference ranges



When % predicted cut offs are used to define the severity of FEV_1 impairment, a larger proportion of individuals are classified as having 'severe' airflow obstruction with FEV_1<50% predicted if the NHANES III Caucasian reference range is used. Of note - no participants were classified as having 'Very Severe' airflow obstruction using any of the reference ranges (Table 22).

Table 22: Severity classification amongst the 35 participants with a fixed FEV_1/FVC ratio<0.7 at TB treatment completion

Severity classification	GLI-2012	NHANES III African American	Malawi	NHANES III Caucasian
FEV_1≥80%	10 (28.6%)	10 (28.6%)	9 (25.7%)	5 (14.3%)
50%≤ FEV_1 <80%	19 (54.3%)	19 (54.3%)	19 (54.3%)	17 (48.6%)
30%≤ FEV_1<50%	6 (17.1%)	6 (17.1%)	7 (20.0%)	13 (37.1%)
FEV_1<30%	0	0	0	0

COMPARISON WITH LOCAL BOLD DATA

Age stratified spirometry findings from TB treatment and 1-year time point are shown in Table 23, standardized by NHANES III Caucasian reference ranges, and are compared with data from the 2013-14 urban Blantyre BOLD study.

Table 23: Comparison of the age- stratified prevalence estimates of moderate-severe airway obstruction and spirometric restriction, within this study cohort and the survey weighted prevalence estimates from the 2013-2014 BOLD study in urban Blantyre.

Age group (n at baseline / 1-year)	Mod-severe obstruction FEV/FVC<0.7 and FEV1<80% predicted			Low FVC FEV1/FVC>=0.7 and FVC<80% predicted		
	Post-TB data set TB Rx completion % (SE)	Post-TB data set 1-year f'up % (SE)	BOLD data set % (SE)	Post-TB data set TB Rx completion % (SE)	Post-TB data set 1-year f'up % (SE)	BOLD data set % (SE)
15-19yrs (n=17/13)	11.8% (7.8%)	15.4% (10.0%)	-	82.4% (9.2%)	61.5% (13.5%)	-
20-29yrs (n=83/77)	4.8% (2.4%)	6.5% (2.8%)	2.4% (1.0%)	71.1% (5.0%)	64.9% (5.4%)	32.7% (4.0%)
30-39yrs (n=160/147)	7.5% (2.1%)	8.8% (2.3%)	2.9% (1.5%)	64.4% (3.8%)	55.8% (4.1%)	42.0% (3.8%)
40-49yrs (n=79/75)	11.4% (3.6%)	16.0% (4.2%)	2.3% (0.9%)	62.0% (5.5%)	41.3% (5.7%)	28.3% (4.4%)
50-59yrs (n=17/15)	11.8% (7.8%)	13.3% (8.8%)	9.8% (2.8%)	17.6% (9.2%)	6.7% (6.4%)	39.4% (6.6%)
60+yrs (n=9/9)	11.1% (10.5%)	33.3% (15.7%)	12.0% (4.4%)	33.3% (15.7%)	33.3% (15.7%)	13.8% (6.4%)

The prevalence of obstructive and low FVC patterns was higher at TB treatment completion and 1-year later in the majority of age strata within this post-TB cohort, compared to that seen in the BOLD community sample. The low FVC pattern appears to be more common than obstructive spirometry in most age strata, within both the BOLD community sample, and this cohort of post-TB participants.

5.3.6 CT IMAGING

HRCT imaging findings are presented before CXR findings as this test is the 'gold standard' for the diagnosis of structural pathology and was performed at TB treatment completion only.

CT IMAGING LOCATION

A total of 385 CT scans were completed, including 148 (38.4%) at the Blantyre Adventist Hospital (BAH) in Blantyre, and 237(61.6%) at Kamuzu Central Hospital (KCH) in Lilongwe. Time to CT scanning is shown in Table 24 – over three quarters of the imaging was completed within 2-months of TB treatment completion.

Random review of CT radiation doses administered to participants at both locations showed that exposures were within normal range and below UK safety thresholds.

Table 24: Time to CT imaging, weeks (n=385)

Time from baseline visit to CT imaging	Number (%)
≤4 weeks	186 (48.3%)
4-8 weeks	113 (29.4%)
8-12 weeks	29 (7.5%)
12-16 weeks	33 (8.6%)
>16 weeks	24 (6.2%)

MISSING CT DATA

CT imaging was missed for 20 participants (Table 25). The category of 'Physical comorbidity' includes one elderly participant and another alcohol dependent participant, neither of whom were fit for the return journey to Lilongwe for imaging during the period when the more remote KCH facility was being used. The category of 'Machine error' includes one participant who was scanned but images lost, together with 2 participants who were not scanned as the CT machine was broken at the time they attended for imaging, and they declined / were unable to re-attend on other dates.

Table 25: Reasons for missing CT data (n=20)

Reason for absence of CT scan	Number
Pregnant	3
Unable to travel to imaging facility – comorbidities	2
Unable to travel to imaging facility – participant location	4
Study team unable to contact participant	2
Did not attend, despite booking	1
Booking error – missed bookings	5
Machine error	3
Total	20

There were no significant differences in demographic and clinical characteristics of participants who missed vs completed imaging (Table 26).

Table 26: Comparison of participant characteristics, for those who missed CT imaging

Characteristic	Scan completed (N=385)	Scan missed (n=20)	p-value
Age (median, IQR)	34 (28-40)	36 (28-42)	0.715
Male gender (n,%)	262 (68.0%)	13 (65.0%)	0.776
HIV infected (n, %) (n=403)	235 (61.4%)	9 (45.0%)	0.145
CD4 cell count (g/dL) (median, IQR)	226 (122-392)	375 (182-484)	0.308
Microbiological evidence of PTB at diagnosis (n, %)	299 (77.7%)	14 (70.0%)	0.425
BMI at TB treatment completion (kg/m^2)	20.5 (18.9 - 22.3)	20.9 (19.8 - 23.1)	0.149
FEV1 z-score (median, IQR)	-1.04 (-1.96 - -0.14)	-1.33 (-1.72 - 0.27)	0.780
FVC z-score (median, IQR)	-0.84 (-1.6 - - 0.15)	-1.03 (-1.65 - 0.38)	0.662
FEV1/FVC z-score (median, IQR)	-0.30 (-1.08 – 0.38)	-0.09 (-1.21 - 0.41)	0.808
SGRQ total score (median, IQR)	8.9 (1.2-23.6)	5.9 (1.4 - 26.7)	0.755
Regular monthly respiratory symptoms (n, %)	234 (60.8%)	12 (60.0%)	0.945

CT INTER-READER AGREEMENT

A total of 239/385 (62.1%) of scans were selected for consensus review of at least 1 variable in ≥1 lobe. Levels of inter-reader agreement, and the number of lobes for which there were clean reads (with either identical scores from original readers, or a score confirmed by consensus review) varied widely between variables (Table 27).

Table 27: Inter-reader agreement measures, for variables reported in the original CT scoring system

Pathology	Variable	Measure of inter-reader consistency for whole-lung variable ICC (95% CI) OR Kappa (SE)*	Number of lobes for which clean reads available (RUL/RML/RLL – LUL/Lingula/LLL) n (%) of scans with all lobes having clean reads
Parenchymal variables			
Atelectasis	Whole lung score (0-600)	ICC: 0.81 (0.77-0.84)	R lobes: 308 / 330 / 334 L lobes: 308 / 321 / 332 Clean reads all lobes: 177/385 (46.0%)
Cavities / cystic air spaces	Whole lung score (0-600)	ICC: 0.81 (0.77-0.84)	R: 344 / 378 / 370 L: 349 / 380 / 375 Clean reads all lobes: 301/385 (78.2%)
Normal parenchyma	Whole lung score (0-600)	ICC: 0.80 (0.76 – 0.83)	R:183 / 161 / 172 L: 196 / 208 /186 Clean reads all lobes: 73/385(19.0%)
Mosaicism	Whole lung score (0-600)	ICC: 0.55 (0.48-0.62)	R: 236 / 242/232 L: 234 / 259 / 226 Clean reads all lobes:105/385 (27.3%)
Emphysema	Whole lung score (0-600)	ICC: 0.50 (0.42 – 0.57)	R: 335 / 372/ 364 L: 339 / 375 / 363 Clean reads all lobes:291/385 (75.6%)
Ground glass	Whole lung score (0-600)	ICC: 0.49 (0.41 – 0.57)	R: 353 / 367 / 366 L: 362/366 / 360 Clean reads all lobes: 292/385 (75.8%)
Consolidation	Whole lung score (0-600)	ICC: 0.43 (0.34 – 0.51)	R 311 / 346 / 338 L: 301 / 338 / 342 Clean reads all lobes: 194/385 (50.4%)
Parenchymal banding	Whole lung score (0-600)	ICC: 0.43 (0.35 -0.51)	R: 221/204/232 L: 231 / 244/ 238 Clean reads all lobes: 86/385 (22.3%)
Emphysematous destruction	Whole lung score (0-600)	ICC: 0.27 (0.18 – 0.36)	R: 379 / 380 / 378 L: 374 / 384 / 371 Clean reads all lobes: 346/385 (89.9%)
Airway variables			
Bronchiectasis	Total extent score (0-18)	Weighted kappa : 0.72 (0.05)	R: 296 / 340/ 324 L: 297 / 337 / 321 Clean reads all lobes: 195/385 (50.7%)
	Total severity score (0-18)	Weighted kappa: 0.66 (0.05)	R: 281 / 315 / 299 L: 266 / 307 / 292 Clean reads all lobes: 133/385 (34.6%)
	Lobar bronchiectasis pattern, if mod-severe bronchiectasis seen	N/a	R: 41/78 (52.6%); 7/15 (46.7%); 16/35 (45.7%) L: 42/80 (52.5%); 29/39 (74.4%); 25/39 (64.1%)
Airway plugging	Total severity score (0-18)	Weighted kappa: 0.51 (0.05)	R: 284 / 328 / 302 L: 280 / 313 / 313 Clean reads all lobes: 153/385 (39.7%)
Tree in bud	Total severity score (0-18)	Weighted kappa: 0.45 (0.04)	R: 217 / 247 / 226 L: 219 / 248 / 225 Clean reads all lobes: 67/385 (17.4%)
Bronchial wall thickening	Total severity score (0-18)	Weighted kappa: 0.42 (0.05)	R: 193 / 248 / 228 L: 198 / 226 / 205 Clean reads all lobes: 73/385 (19.0%)
Airway narrowing	Total extent score (0-18)	Weighted kappa: 0.17 (0.03)	R: 378 / 383 / 377 L: 367 / 383 /381 Clean reads all lobes: 349/385 (90.7%)
Other variables			
Cavities	Total extent score (0-18)	Weighted kappa: 0.65 (0.04)	R: 359 / 383 / 372 L: 362 / 380 / 371 Clean reads all lobes: 327/385 (84.9%)
	Mycetoma presence / absence, if cavities seen	Kappa: 0.49 (0.05)	R: 98/100 (98.0%); 16/16 (100%); 32/32 (100%)

			L: 103/105 (98.1%); 25/26 (96.2%); 44/44 (100%)
Nodules	Total pattern score (0-18)	Weighted kappa: 0.65 (0.05)	R: 267 / 320 / 304 L: 274 / 315/ 291 Clean reads all lobes: 115/385 (29.9%)
Pleural pathology	Presence / absence	Kappa: 0.60 (0.05)	368/385 (95.6%)
Lymphadenopathy	Presence / absence	Kappa: 0.17 (0.05)	339/385 (88.1%)

*ICC - intra-class correlation coefficient. Weighted kappa scores calculated using quadratic wgt(w2) function in Stata v13.

- PARENCHYMAL VARIABLES

The greatest level of agreement was seen for atelectasis, cavity / cystic airspace, and normal parenchymal scores at the whole lung level (ICC ≥0.8). Agreement on the amount of mosaicism, emphysema, ground glass change, consolidation, and parenchymal banding was reasonable (ICC 0.43 – 0.55). The variable 'emphysematoid destruction' had a very low ICC of 0.27 (95% CI: 0.18-0.36).

Some systematic differences in the reporting approaches of the two original readers were noted in analysis. For example, reader 1 allocated higher scores for parenchymal banding whilst reader 2 allocated higher scores for consolidation. This likely reflects differences in interpretation, but it is not possible to way in which this differential allocation of scores has happened, and therefore no variables were collapsed or adjusted to compensate for this.

- AIRWAY VARIABLES

Weighted Kappa scores were high for the whole lung airway dilatation severity and extent scores (0.72 and 0.66), and reasonable for airway plugging and tree in bud severity scores (0.45 – 0.51). The number of individual lobes in which absolute agreement was achieved for these variables was, however, low throughout.

The kappa score was only 0.17 for the whole lung airway narrowing score – this variable was therefore not consensus reviewed and was not used in further analyses.

A 'clean' report on the pattern of bronchiectasis was achieved for 55.9% (160/286) of lobes with moderate – severe bronchiectasis. Discrepant reporting of cystic bronchiectasis – the pattern with greatest prognostic significance – was common, but no systematic over / under reporting by either reader was observed.

At least one reader felt that it was not possible to score bronchial wall thickness in at least 1 lobe in 58/385 (15.1%) of scans, and whole lung bronchial wall thickening severity scores were therefore not available for these scans. The majority of participants who had missing data for this variable were HIV negative (54.4%, 31/57). The total amount of abnormal parenchyma seen in these scans was more extensive than that in scans where bronchial wall thickening was fully reported (parenchymal score of 277.5/600 vs. 112.5/600, $p<0.001$), and they were more likely to contain at least one extensively damaged or 'destroyed' lobe (46.5% vs 2.7%, $p<0.001$). This is consistent with the observation that

where there is extensive surrounding parenchymal pathology, it is often not possible to interpret the thickness of the bronchial wall itself.

- OTHER VARIABLES

Levels of agreement for cavity, nodule, and pleural scores were reasonable, with kappa values ranging from 0.49 – 0.65. The level of agreement for the presence / absence of mediastinal lymphadenopathy – which is usually identified using CT imaging with contrast – was extremely low (Kappa 0.17). This variable was not consensus reviewed and was not used in further analysis.

CT RESULTS

There was a high prevalence of residual pathology seen on CT imaging at the point of TB treatment completion: only 13/385 participants (3.4%) had completely normal parenchyma, and only 3.4% (13/385) of the cohort had completely normal airways.

The median abnormal parenchymal score was 137.5/600 (IQR: 55.0 – 235.0) suggesting that on average, participants had the equivalent of 1.4 lobes of abnormal tissue on their imaging. Atelectasis and banding, and mosaicism were the dominant patterns seen. 9.3% (36/385) of the cohort had at least one lobe in which ≥90% of parenchyma was non-functioning and had been replaced by banding, atelectasis, or cavities / cystic airspaces (Table 28).

A total of 44.2% (170/385) of the cohort had moderate to severe airway dilatation, or bronchiectasis, in at least 1 lobe, and 7.5% (29/385) of participants had bronchiectasis affecting ≥3 lobes.

Data from the 'final' dataset are presented here, stratified by HIV status. No data are presented for airway narrowing and lymphadenopathy as these had very poor inter-reader agreement and were therefore felt to be inaccurate measures and not consensus reviewed. Data for emphysematoid destruction are presented – this had low levels of inter-reader agreement, but was consensus reviewed, and continues to contribute to the overall abnormal parenchyma scores, but it must be interpreted with caution.

Table 28: CT imaging final score results, by HIV status (both CT and HIV status available for n=383 individuals)

Pathology	All scans (n=385) Median (IQR) [Full range]	HIV non-reactive (n=148), Median (IQR)	HIV reactive (n=235), Median (IQR)	p-value
Parenchymal pathology scores, whole lung level†				
Atelectasis and banding score (0-600)~	45.0 (17.5 – 85.0) [0.0 – 320.0]	55.0 (35.0 – 105.0) [0.0 – 320.0]	35.0 (15.0 – 70.0) [0.0 – 260.0]	<0.001***
Cavities / cystic air spaces score (0-600)	0.0 (0.0 – 10.0) [0.0 – 280.0]	5.0 (0.0 – 16.3) [0.0 – 280.0]	0.0 (0.0 – 5.0) [0.0 – 165.0]	<0.001***
Mosaicism score (0-600)	32.5 (5.0 – 85.0) [0.0 – 325.0]	40.0 (12.5 – 91.3) [0.0 – 252.5]	27.5 (2.5 – 75.0) [0.0 – 325.0]	0.024*
Emphysema score (0-600)	0.0 (0.0 – 5.0) [0.0 – 430.0]	0.0 (0.0 – 2.5) [0.0 – 385.0]	0.0 (0.0 – 5.0) [0.0 – 430.0]	0.016*
Ground glass score (0-600)	0.0 (0.0- 5.0) [0.0 – 270.0]	0.0 (0.0 – 5.0) [0.0 – 165.0]	0.0 (0.0 – 5.0) [0.0 – 270.0]	0.276

Consolidation score (0-600)	5.0 (0.0 – 12.5) [0.0 – 110.0]	5.0 (0.0 – 12.5) [0.0 – 110.0]	5.0 (0.0 – 12.5) [0.0 – 75.0]	0.128
Emphysematous destruction score (0-600)	0.0 (0.0 – 2.5) [0.0 – 165.0]	0.0 (0.0 – 5.0) [0.0 – 120.0]	0.0 (0.0 – 2.5) [0.0 – 165.0]	0.119
Total normal parenchyma score (0-600)	463.5 (3650 – 545.0) [0.0 – 600.0]	420.0 (353.8 – 518.8) [0.0 – 600.0]	490 .0 (372.5 – 560.0) [25.0 – 600.0]	<0.001***
Total abnormal parenchyma score (0-600)[#]	137.5 (55.0 – 235.0) [0.0 – 600.0]	180.0 (81.3 – 246.3) [0.0 – 600.0]	110.0 (40.0 – 227.5) [0.0 – 575.0]	<0.001***
Total abnormal parenchyma score, excluding mosaicism (0-600)	72.5 (30.0 – 150.0) [0.0 – 600.0]	93.8 (47.5 – 180.0) [0.0 – 600.0]	60.0 (22.5 – 130.0) [0.0 – 540]	<0.001***
Number of 'destroyed' lobes[$]				
0	349 (90.7%)	126 (85.1%)	222 (94.5%)	0.009**
1	27 (7.0%)	15 (10.1%)	11 (4.7%)	
2	6 (1.6%)	4 (2.7%)	2(0.9%)	
3	3 (0.8%)	3 (2.0%)	0 (0%)	
Airway scores, whole lung level				
Bronchiectasis extent score (0-18)	2.5 (0.5 – 4.5) [0.0 – 15.5]	3.0 (2.0 – 5.5) [0.0 – 15.5]	1.5 (0.0 – 4.0) [0.0 – 13.5]	<0.001***
Bronchiectasis severity score (0-18)	2.5 (0.5 – 5.0) [0.0 – 15.5]	3.5 (1.5 – 6.0) [0.0 – 15.5]	2.0 (0.0 – 4.0) [0.0 – 14.5]	<0.001***
Number of lobes with moderate - severe bronchiectasis[^]				
0	215 (55.8%)	65 (43.9%)	149 (63.4%)	0.004**
1	101 (26.2%)	47 (31.8%)	54 (23.0%)	
2	40 (10.4%)	24 (16.2%)	15 (6.4%)	
3	17 (4.4%)	8 (5.4%)	9 (3.8%)	
4	8 (2.1%)	3 (2.0%)	5 (2.1%)	
5	2 (0.5%)	0 (0.0%)	2 (0.9%)	
6	2 (0.5%)	1 (0.7%)	1 (0.4%)	
Any moderate-severe cystic bronchiectasis [^^]				
No	336 (87.3%)	120 (81.1%)	215 (91.5%)	0.003**
Yes	49 (12.7%)	28 (18.9%)	20 (8.5%)	
Bronchial wall thickening severity score (0-18)[@](n=327)	3.0 (1.5 – 5.5) [0.0 – 14.5]	3.0 (1.5 – 5.5) [0.0 – 13.5]	3.0 (1.0 – 6.0) [0.0 – 14.5]	0.388
Tree in bud severity score (0-18)	3.5 (1.5 – 6.0) [0.0 – 17.0]	4.5 (2.5 – 6.5) [0.0 – 14.5]	3.0 (1.0 – 6.0) [0.0 – 17.0]	<0.001***
Airway plugging severity score (0-18)	1.0 (0.0 – 2.0) [0.0 – 12.0]	1.0 (0.5 – 2.5) [0.0 – 9.0]	1.0 (0.0 – 2.0) [0.0 – 12.0]	0.020*
Other variables, whole lung level				
Presence of mycetoma				
No	380 (98.7%)	144 (97.3%)	234 (99.6%)	0.003**
Yes	5 (1.3%)	4 (2.7%)	1 (0.4%)	
Presence of any nodules				
No	64 (16.6%)	30 (20.3%)	33(14.0%)	0.154
Yes	228 (59.2%)	88 (59.5%)	139 (59.2%)	
Unclear	93 (24.2%)	30 (20.3%)	63 (26.8%)	
Presence of miliary nodules				
No	381 (98.9%)	148 (100.0%)	231 (98.3%)	0.111
Yes	4 (1.0%)	0 (0.0%)	4 (1.7%)	
Presence of pleural pathology (effusions or thickening)				
No	354 (92.0%	136 (91.9%)	216 (91.9%)	0.994
Yes	31 (8.1%)	12 (8.1%)	19 (8.1%)	

*p<.05, **p<.01, ***p<.001

†Parenchymal score off 100 is equivalent to one lung lobe. Total possible score across the lung, including all 6 lobes, is 600.

~Atelectasis and banding reported separately, but data presented together due to conflation in reporting

[#]Sum of scores for all parenchymal pathologies, including atelectasis, parenchymal banding, cavities/cystic airspaces, mosaicism, emphysema, ground glass opacification, consolidation, and emphysematoid destruction

[$]Destroyed lobe is one in which ≥90% of parenchyma is occupied by banding, atelectasis, or cavities / cystic airspaces

^Bronchiectasis classified as present if average severity score between two readers, or consensus score, was ≥2, so on average bronchial lumen considered to be 2-3 times adjacent vessel diameter in these lobes

^^Present if moderate to severe bronchiectasis seen in at least 1 lobe, and pattern here deemed to be cystic based on initial agreement between readers or consensus review of scans, or random selection of initial reader reports where disagreement seen but absence of consensus review

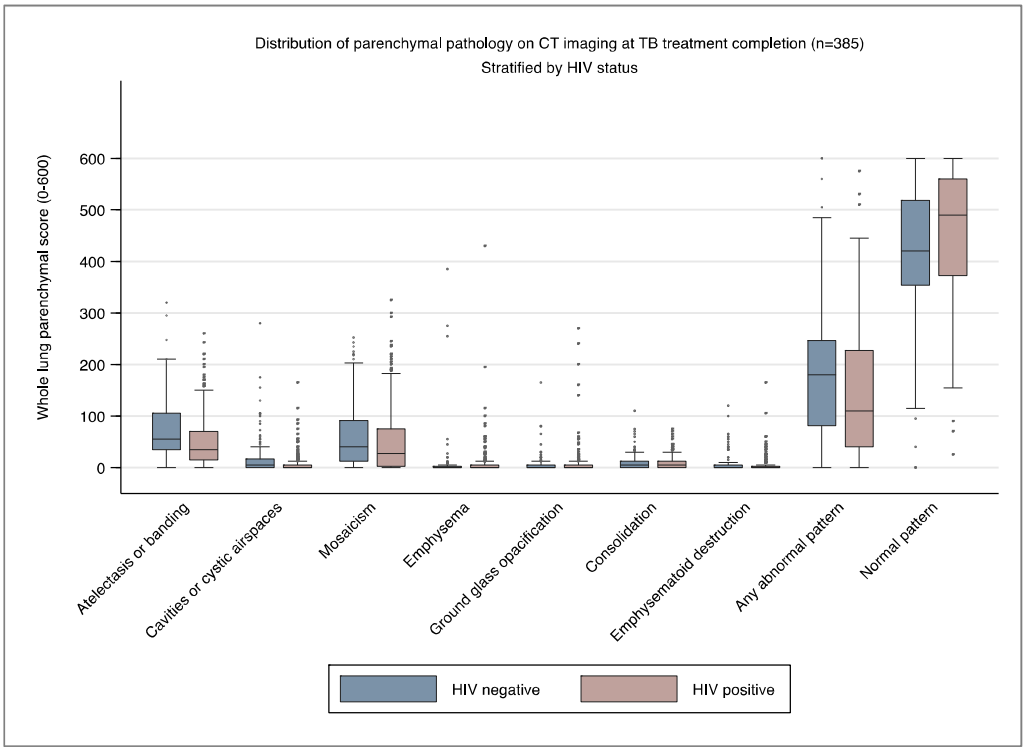
[@]Absent for scans where unable to report wall thickness in at least 1 lobe, therefore likely biased towards milder pathology

- PARENCHYMAL PATHOLOGY

There was a large degree of heterogeneity in the extent of each pattern of pathology, within the cohort: all data were right skewed with most participants having small volumes of pathology, but wide distributions were seen for both HIV infected and uninfected groups, and a subset of individuals were observed to have extensive ongoing abnormality with each pattern (Figure 19). The most extensive pathologies observed in both groups were atelectasis and banding, followed by mosaicism.

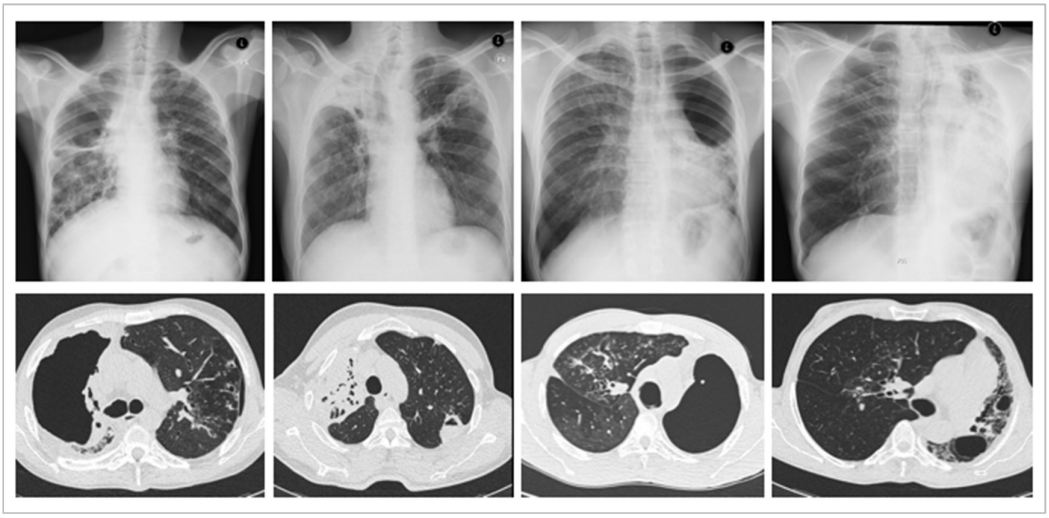
Statistically lower amounts of atelectasis and banding, cavities and cystic airspaces, and mosaicism were noted in HIV infected adults, compared to HIV uninfected adults (median: 55.0 vs. 35.0, p<0.001 / 5.0 vs. 0.0, p<0.001 / 40.0 vs. 27.5, p<0.001). However, this pattern was reversed for emphysema, where the IQR of the extent of pathology was marginally but statistically higher for the HIV-infected group. No differences were seen in the extent of ground glass opacification and consolidation between HIV infected / uninfected groups.

Figure 19: Box plots of the total extent of patterns of parenchymal pathology, stratified by HIV status, seen on CT imaging at TB treatment completion



Focal residual destruction of an individual lung lobe was common (Figure 20), with a higher prevalence in HIV negatives compared to HIV positives (15% (22/148) vs. 5.6% (13/235)). A total of 3/385 (0.8%) of participants, all of whom were HIV negative, completed TB treatment with 3 lobes or the equivalent of a hemithorax being destroyed.

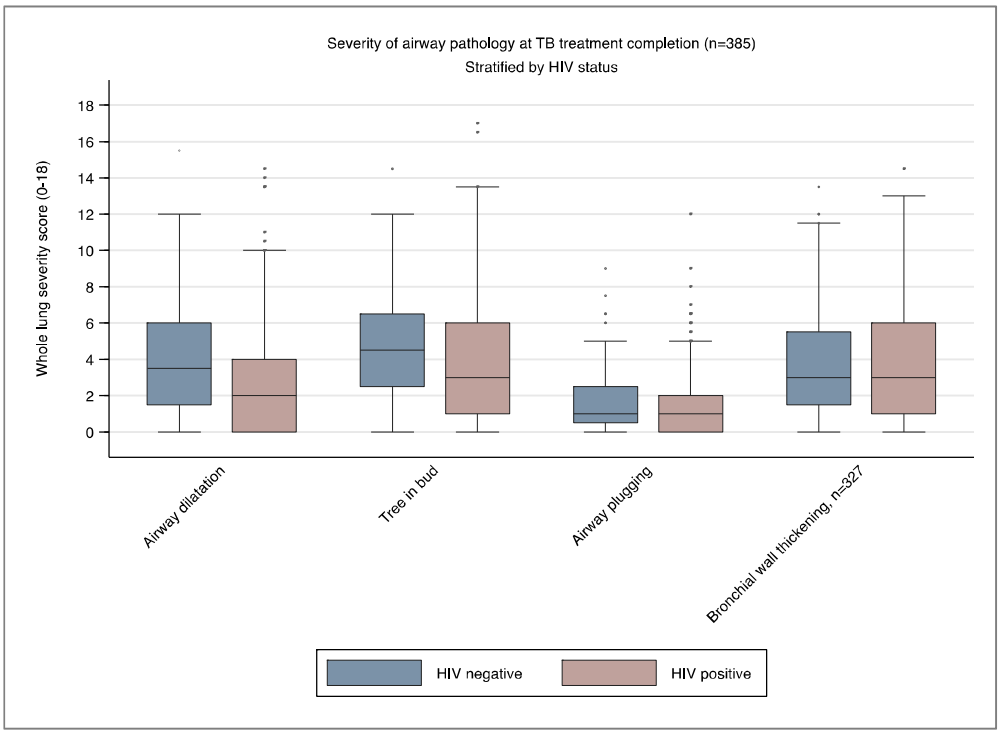
Figure 20: Paired X-rays and CT slices from participants with at least one destroyed lung lobe



- AIRWAYS PATHOLOGY ON CT

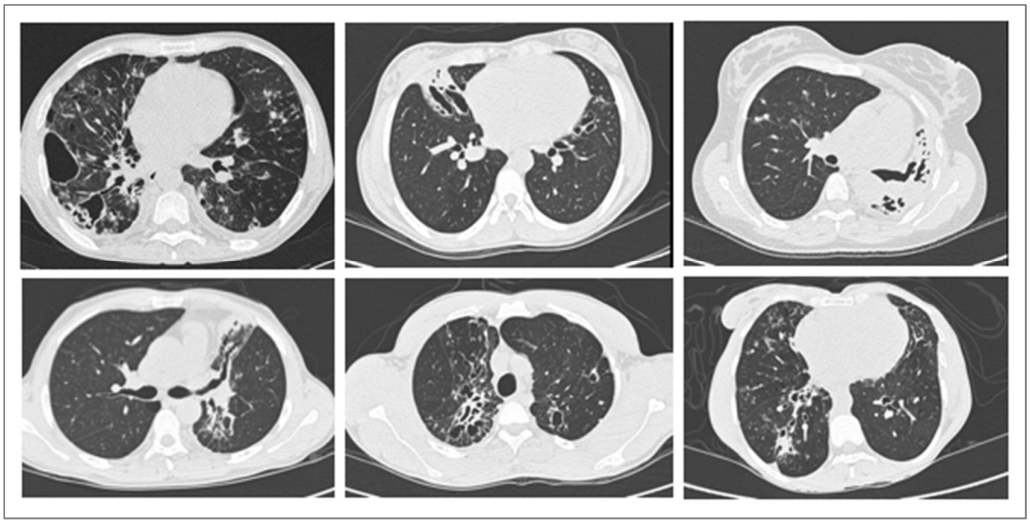
A wide range of severities of airway dilatation, airway plugging, and tree in bud were observed (Figure 21). The median bronchiectasis severity score was higher in HIV negative compared to HIV positive individuals (3.5 vs. 2.0/18, p<0.001), and the proportion of participants with moderate to severe airway dilatation documented in at least 1-lobe was also higher amongst the HIV-negative group (56.1%(83/148) vs. (36.6% (86/235), p=0.004).

Figure 21: Box plots of airway pathology severity scores, seen on CT imaging at TB treatment completion, stratified by HIV status



Amongst the scans in which it was reported, no difference in the bronchial wall thickening severity scores were observed between HIV infected and uninfected groups. However, as noted above the majority of participants who had missing data for this variable were HIV negative, and also had more severe parenchymal pathology, such that these data could be biased. A close relationship was observed between bronchial dilatation and bronchial wall thickening on images (Figure 22).

Figure 22: Axial slices from CT images of participants with bronchiectasis and bronchial wall thickening



Cystic bronchiectasis was seen in 12.7% (49/385) participants at TB treatment completion, and was more common in HIV negative compared to HIV positive individuals, although these data need to be interpreted with some caution, given the limitations of measurement and discrepancies in the reporting of pattern outlined above.

- OTHER PATHOLOGIES

59.2% (228/385) had nodules confirmed by both readers / reported by the consensus scorer at TB treatment completion, but no difference in prevalence was seen between those with and without HIV infection.

A miliary pattern of pathology was seen in 4 individuals. One was restarted on TB treatment during the 1-year follow up interval, with respiratory symptoms and signs consistent with disseminated TB disease and an ongoing positive Xpert MTB test. None of the other three individuals were restarted on treatment – all were followed up for the full 1-year period and remained alive, suggesting that these imaging findings may not infact have been related to active TB disease.

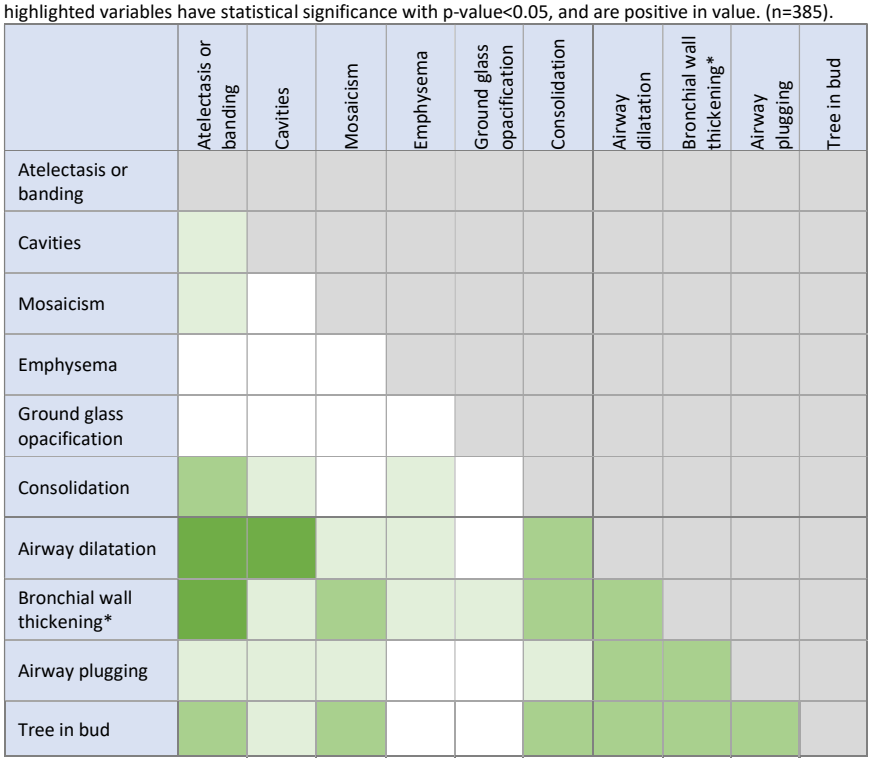
Residual pleural pathology – thickening or effusion – was seen in 8.1% (31/385) of participants only. This was rarer than anticipated, particularly as this pathology was defined as present if either reader reported it as such. No difference was seen by HIV status.

Mycetoma were rare, and their presence agreed on in only 1.3% (5/385) participants. Interestingly, none of these participants had positive or borderline positive immunology on aspergillus serology assays.

RELATIONSHIPS BETWEEN CT VARIABLES

A heat map showing the relationships between key airway and parenchymal pathologies, represented by pairwise Pearson correlation coefficients between variables reported at the whole lung level, is shown below (Figure 23).

Figure 23: Heat map of Pearson correlation coefficients between CT pathologies reported at the whole lung level. All highlighted variables have statistical significance with p-value<0.05, and are positive in value. (n=385).



Parenchymal scores – whole lung total score, 0-600; Airway scores – whole lung severity score, 0-18
*n=327 for bronchial wall thickening correlations

Legend for correlation coefficients, all with p-value<0.005

	≥0.5
	≥0.3 and <0.5
	≥0.1 and <0.3
	<0.1

- RELATIONSHIPS BETWEEN PARENCHYMAL VARIABLES

The extent of atelectasis and banding was highly correlated with other parenchymal pathologies including the extent of consolidation (Pearson's correlation coefficient R:0.427, p<0.001). The extent of cavities or cystic airways was also weakly associated with both the amount of atelectasis and banding (R: 0.299, p<0.001), and consolidation (R: 0.182, p<0.001).

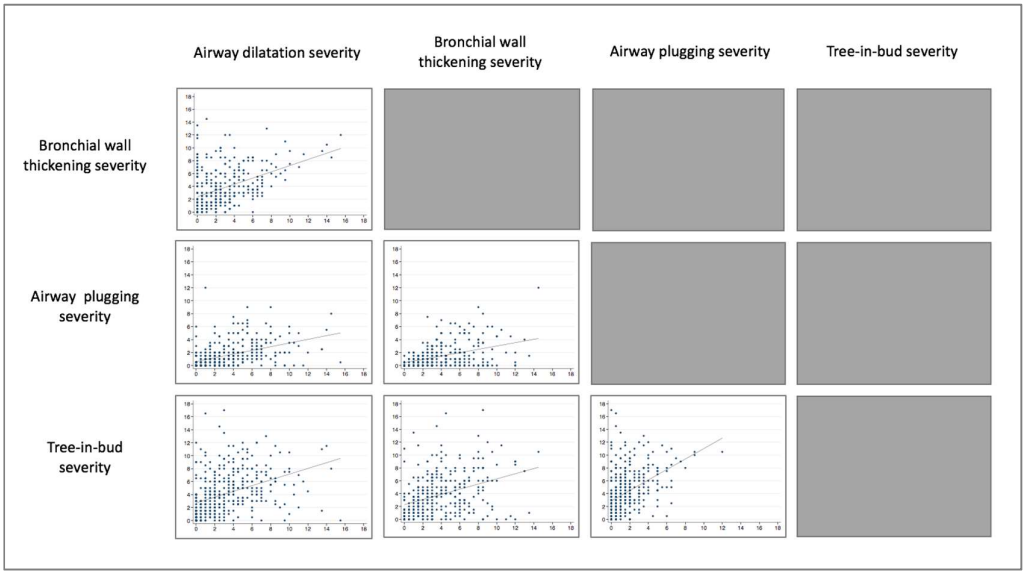
Ground glass opacification and mosaicism were the most independent patterns, with few correlations with other parenchymal parameters. Mosaicism and emphysema – two pathologies which can be associated with airway obstruction on spirometry – did not appear to be correlated with each other, suggesting that they did not tend to occur together.

- RELATIONSHIPS BETWEEN AIRWAY VARIABLES

Bronchiectasis extent and severity scores were very strongly correlated with each other (Pearson's R: 0.929, p<0.001) suggesting that participants with more BP segments affected also had a greater degree of airway dilatation. The severity score only was therefore used in further analyses.

The severity scores for all four patterns of airway pathology (airway dilatation, bronchial wall thickening, airway plugging, and tree-in-bud change) were correlated with each other: Pearson's R values ranged from 0.377 – 0.448, and all were significant at p<0.001 (Figure 24).

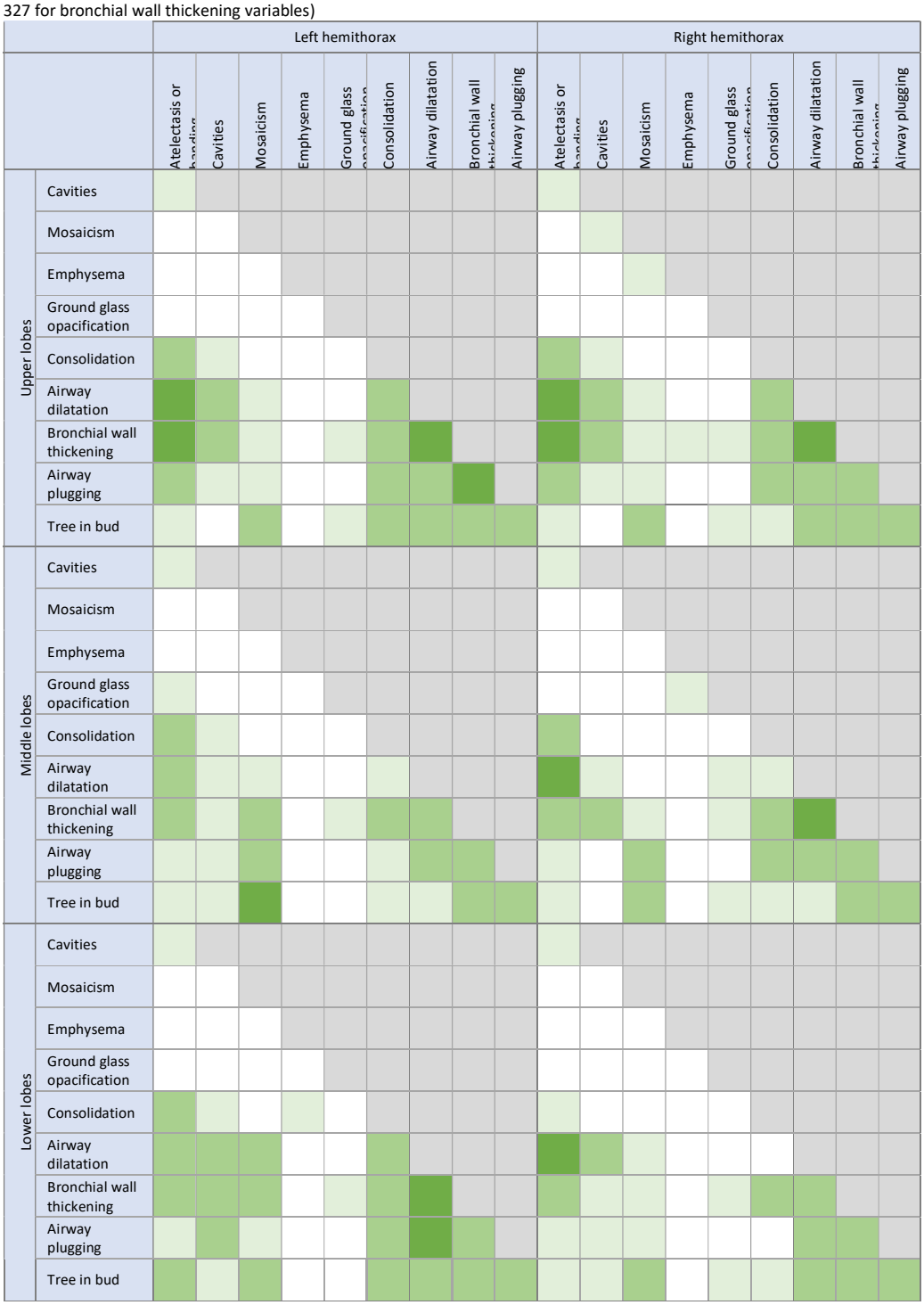
Figure 24: Scatter plots of relationships between whole lung severity scores for airway pathologies (n=385 /n=327 for bronchial wall thickening graphs)



- RELATIONSHIPS BETWEEN PARENCHYMAL AND AIRWAY VARIABLES

The strongest correlations seen between airway and parenchymal variables were observed between the bronchiectasis severity score, and the extent of atelectasis/ banding (Pearson's R: 0.657, p<0.001), and cavities/cystic airspaces (R: 0.504, p<0.001). These relationships remained present when data were examined at a lobar level (Figure 25), suggesting that these patterns occur together in the lung.

Figure 25: Heat map showing associations between airway severity and parenchymal extent scores reported on CT imaging, at the lobar level within scans. All highlighted variables have p-value<0.05, and are positive in value. Legend as above. (n=385 / 327 for bronchial wall thickening variables)



- RELATIONSHIPS WITH NODULES AND PLEURAL PATHOLOGY

The odds of having nodules reported were higher in individuals with more extensive atelectasis and banding (OR 1.01 for a 1-unit increase in parenchymal score, p=0.001), consolidation (OR 1.05, p=0.001), and mosaicism (OR 1.01, p-0.008). A consistently positive relationship was observed between the presence of nodules and the severity scores of all four patterns of airway pathology (OR 1.14 – 1.31, with p-values from <0.001 to 0.026).

Pleural pathology was positively associated with atelectasis/banding (OR 1.01, p<0.001), and cavities and cystic airspaces (OR 1.01, p=0.002). Amongst the airway pathologies was positively correlated with the airway dilatation severity score only (OR 1.11, p=0.035). The odds of having pleural pathology were over 8-fold higher amongst those with mycetoma (OR 8.07, 95% CI: 1.30 - 50.2), but mycetoma were rare within this cohort: amongst the 5 participants with this finding, only 2 were seen to have concurrent pleural thickening. In these two participants, the areas of pleural thickening are extremely near to the location of the mycetoma – whilst this might suggest invasive fungal disease, aspergillus serology was negative in both individuals.

CT SENSITIVITY ANALYSES

- TIME TO SCANNING

No significant differences in participant characteristics including age, gender, HIV status, baseline TB microbiology or BMI at treatment completion were observed between those imaged within 1-month of treatment completion (n=186) vs. those imaged after this time (n=199). Ground glass opacification was more extensive in those who were imaged later with a wider IQR observed (0-5.0 vs. 0-2.5/600, p=0.012) but no other differences in parenchymal or airway parameters were identified

- SCANNING LOCATION

Participant characteristics and imaging features were compared between participants scanned in each of the two CT-imaging locations (Table 29). Those imaged in Blantyre waited longer to be imaged. A slightly higher proportion of participants with microbiologically proven disease was seen amongst those travelling to Lilongwe (81.9% vs. 71.0%, p=0.012), but groups were otherwise similar. Comparisons of imaging results suggests small but statistically larger amount of emphysema observed on the Lilongwe scans, but more extensive ground glass change, and higher bronchial wall thickening and airway plugging scores on the Blantyre scans.

Table 29: Comparison of participant and imaging features between those imaged locally in Blantyre, and those imaged in Lilongwe (n=385)

Characteristic	Blantyre (n=148) Median (IQR) / N (%)	Lilongwe (n=237) Median (IQR) / N (%)	p-value
Participant characteristics			
Age (median, IQR)	36 (28-41)	34 (29-40)	0.488
Male gender (n,%)	96 (64.9%)	166 (70.0%)	0.289
HIV infected (n, %) (n=383)	86 (58.5%)	149 (63.1%)	0.365
Microbiological evidence of PTB at diagnosis (n, %)	105 (71.0%)	194 (81.9%)	0.012*
BMI at TB treatment completion (kg/m^2)	20.5 (18.7 – 22.3)	20.5 (19.0 – 22.2)	0.890
Time to imaging (weeks)	6.5 (4.0-12.7)	3.6 (1.7-5.1)	<0.001***
Imaging features with statistically significant differences between groups			
Emphysema	0 (0-1.3)	0 (0-5.0)	<0.001***
Ground glass opacification	0 (0-5.0)	0 (0-2.5)	0.010*
Bronchial wall thickness severity	3.5 (1.5 – 6.0)	3 (1.0-5.5)	0.022*
Airway plugging severity	1.5 (0.5 – 3.0)	0.5 (0-2.0)	<0.001***

*p<.05, **p<.01, ***p<.001

5.3.7 CXR IMAGING

CXR IMAGING TYPE

403/405 individuals were imaged at TB treatment completion, and 361/368 at 1-year. Amongst the 359 participants imaged at both study visits, 26.2% (94/359) received digital imaging at both time points (Table 30).

Table 30: Imaging type by study visit

Baseline study visit	1-year study visit			Total
	Digital image	Hard image	No imaging	
Digital image	94	145	35	274 (67.7%)
Hard image	120	0	9	129 (31.9%)
No imaging	2	0	0	2 (0.5%)
Total	216 (53.3%)	145 (35.8%)	44 (10.9%)	405 (100.0%)

MISSING CXR DATA

On average, those who did not receive CXR imaging at both time points (n=46) had a higher SGRQ total score (15.9 vs. 8.1, p=0.035) and a non-significantly higher prevalence of monthly symptoms (73.9% vs. 59.1%, p=0.052) compared to those who were imaged at both time points (n=359) (Table 31).

Table 31: Comparison of participant characteristics, for those with / without CXR imaging available at both TB treatment completion and the 1-year time point

	CXR missing from at least 1 time point (n=46)	CXR available for both time points (n=359)	p-value
Age (median, IQR)	34.5 (27.0 – 41.0)	35.0 (29.0 – 40.0)	0.686
Male gender (n, %)	29 (63.0%)	246 (68.5%)	0.454
HIV infected (n, %) (n=403)	25 (55.6%)	219 (61.2%)	0.467
Microbiological evidence of PTB at diagnosis (n, %)	34 (73.9%)	279 (77.7%)	0.562
BMI at TB treatment completion (kg/m^2) (median, IQR)	20.7 (19.4 – 22.3)	20.5 (18.8 – 22.3)	0.475
FEV_1 z-score at TB treatment completion (median, IQR)	-0.92 (-1.69 - -0.10)	-1.07 (-1.96 - -0.13)	0.581
FVC z-score at TB treatment completion (median, IQR)	-0.82 (-1.63 – 0.02)	-0.87 (-1.61 - -0.18)	0.429
SGRQ total score (median, IQR)	15.9 (5.1 – 26.1)	8.1 (0.9 – 23.2)	0.035*
Regular monthly respiratory symptoms (n, %)	34 (73.9%)	212 (59.1%)	0.052

*p<.05, **p<.01, ***p<.001

CXR INTER-READER AGREEMENT

203/403 (50.4%) of the baseline and 218/361 (60.4%) of the 1-year images were selected for consensus review of at least 1 variable in ≥1 zone. Levels of agreement between the two readers are presented below. Data are presented separately for the images collected at baseline and 1-year, and the number of zones / images for which there was a 'clean read' available after consensus review are shown (Table 32). The range of ICC and Kappa values for the variables reported are similar to those observed in the CT data reporting described above.

Table 32: Individual reader and consensus data for the whole-lung variables scored on CXR at TB treatment completion, and the 1-year time point

		Baseline CXR (n=403)		1-year CXR (n=361)	
Pathology	Variable	Inter-reader consistency, whole-lung variable ICC# (95% CI) / Kappa^ (SE)	# Zones for which clean reads available (Right upper/ middle/lower – Left upper/middle/lower) % of scans with all lobes having clean reads	Inter-reader consistency, whole-lung variable ICC# (95% CI) / Kappa^ (SE)	# zones for which clean reads available (Right upper/ middle/lower – Left upper/middle/lower) % of scans with all lobes having clean reads
Parenchymal banding	Whole lung score (0-600)	ICC: 0.40 (0.31-0.48)	R: 384/391/384 L: 380/386/372 Clean reads all lobes: 302 (74.9%)	ICC: 0.38 (029 – 0.47)	R: 340/348/344 L: 338/350/343 Clean reads all lobes: 277(76.7%)
Consolidation / ground glass	Whole lung score (0-600)	ICC: 0.73 (0.68-0.77)	R: 325/328/341 L: 339/332/353 Clean reads all lobes: 183 (45.4%)	ICC: 0.52 (0.44 - 0.59)	R: 309/331/323 L: 313/332/325 Clean reads all lobes: 203 (56.2%)
Cavities / cystic air spaces	Whole lung score (0-600)	ICC: 0.89 (0.87-0.91)	R: 379/393/398 L: 383/390/400 Clean reads all lobes: 340 (84.4%)	ICC: 0.70 (0.74 – 0.75)	R: 317/344/353 L: 331/347/358 Clean reads all lobes: 264 (73.1%)
Atelectasis	Whole lung score (0-600)	ICC: 0.76 (0.71-0.79)	R: 359/395/394 L: 376/396/394 Clean reads all lobes: 315 (78.2%)	ICC: 0.68 (0.62 – 0.73)	R: 319/350/353 L: 318/354/353 Clean reads all lobes: 257 (71.2%)
Normal	Whole lung score (0-600)	ICC: 0.89 (0.87-0.91)	R: 307/317/326 L: 319/320/331 Clean reads all lobes: 154 (38.2%)	ICC: 0.82 (0.79 – 0.85)	R: 290/307/309 L: 289/311/308 Clean reads all lobes: 154 (42.7%)
Ring and tramlines	Total severity score (0-18)	Weighted kappa: 0.61 (0.05)	R: 336/324/339 L: 329/314/362 Clean reads all lobes: 211 (52.4%)	Weighted kappa: 0.59 (0.05)	R: 304/302/318 L: 306/310/338 Clean reads all lobes: 199 (55.1%)
Nodules	Total pattern score (0-18)	Weighted kappa: 0.53 (0.05)	R: 396/400/399 L: 397/394/401 Clean reads all lobes:	Weighted kappa: 0.64 (0.05)	R: 356/353/358 L: 358/359/360 Clean reads all lobes:

			387 (96.0%)		348 (96.4%)
Mycetoma	Presence / absence	N/a*	401/403 (99.8%)	N/a*	361/361 (100.0%)
Pleural pathology	Presence / absence	Kappa: 0.52 (0.05)	355/403 (88.1%)	Kappa: 0.42 (0.05)	309/361 (85.6%)
Lymphadenopathy	Presence / absence	Kappa: 0.25 (0.05)	392/403 (97.3%)	Kappa: 0.01 (0.04)	352/361 (97.5%)
Hyper expansion	Presence / absence	Kappa: 0.07 (0.02)	343/403 (84.9%)	Kappa: 0.15 (0.04)	317/361 (87.8%)

*Not possible to calculate kappa scores here, as pathology too rare. #ICC - intra-class correlation coefficient. ^Weighted kappa scores calculated using quadratic wgt(w2) function in Stata v13.

CXR RESULTS

Results from the final dataset are presented for individuals completing CXR imaging at both baseline and 1-year time points (n=359) in Table 33.

Table 33: CXR imaging results at baseline and 1-year (n=359)

Pathology	Baseline visit, Median (IQR) [Full range]	1-year, Median (IQR) [Full range]	p-value
Parenchymal pathology scores, whole lung level~			
Total abnormal parenchymal scores (0-600)	18 (3 – 55) [0 – 310]	13 (0 – 43) [0 – 425]	0.023*
Cavities / cystic air spaces score (0-600)	0 (0 – 2.5) [0 – 293]	0 (0 – 5) [0 – 215]	0.007**
Atelectasis / banding score (0-600)	0 (0 – 20) [0 – 185]	5 (0-20) [0 – 240]	0.564
Consolidation / ground glass score (0-600)	10 (0 – 25) [0 – 195]	3 (0 – 13) [0 – 195]	<0.001***
Presence of ≥1 'destroyed' zone (n, %)#	10 (2.8%)	16 (4.5%)	0.231
Bronchiectasis, whole lung level			
Ring and tramline severity score (0-18)	1 (0 – 3) [0 – 14]	1 (0 – 3) [0 – 15]	0.260
Number of zones with mod-severe ring and tramline change^ 0 1 2 3 4 5 6	 251 (69.9%) 77 (21.5%) 22 (6.1%) 7 (2.0%) 0 (0.0%) 1 (0.3%) 1 (0.3%)	 258 (71.9%) 73 (20.3%) 15 (4.2%) 8 (2.2%) 2 (0.6%) 3 (0.8%) 0 (0.0%)	0.470
Other scores, whole lung level			
Nodules Absent Present Unclear	 286 (79.7%) 66 (18.4%) 7 (2.0%)	 273 (76.0%) 80 (22.3%) 6 (1.7%)	0.423
Mycetoma Absent Present Unclear	 357 (99.4%) 1 (0.3%) 1 (0.3%)	 358 (99.7%) 1 (0.3%) 0 (0.0%)	0.606
Pleural pathology (effusions or thickening) Absent Present	 352 (87.3%) 51 (12.7%)	 303 (83.9%) 58 (16.1%)	0.178
Hyper-expansion Absent Present	 341 (84.6%) 62 (15.4%)	 317 (87.8%) 44 (12.2%)	0.202

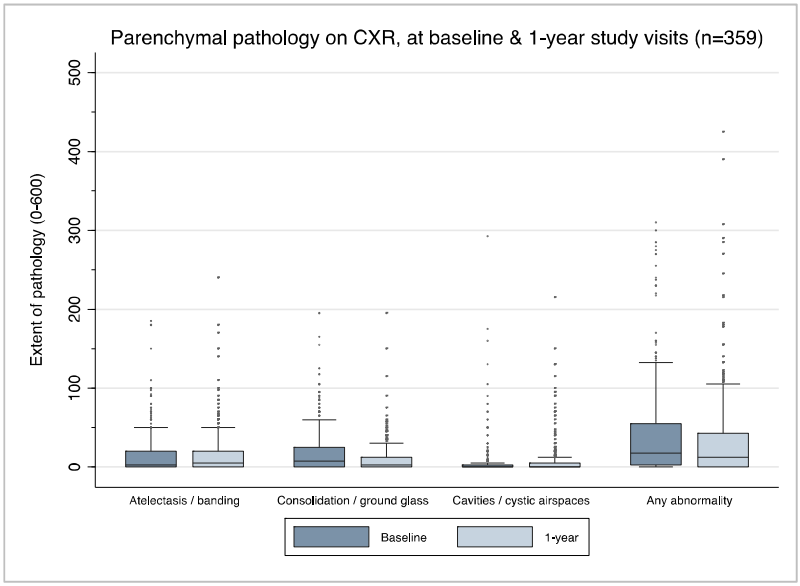
*p<.05, **p<.01, ***p<.001

~Parenchymal score off 100 is equivalent to one lung zone. Total possible score across the lung, including all 6 zones, is 600.
#Destroyed lobe is one in which ≥90% of parenchyma is occupied by banding, atelectasis, or cavities / cystic airspaces
^Present if final ring and tramline score is ≥2 for the zone

- PARENCHYMAL PATHOLOGY

On average, an improvement was seen in the extent of parenchymal pathology reported on CXR over 1-year with a decrease in the median amount of abnormal parenchyma seen (18 points (IQR: 3-55) vs 13 points (IQR: 0-43), p=0.023). Improvement was particularly marked for consolidation and ground glass change: these patterns were relatively sparse on CXR imaging, but were more extensive at TB treatment completion compared to 1-year (10 points (IQR: 0 - 25) vs 3 points (IQR: 0 - 13), p<0.001) (Figure 26).

Figure 26: Population level data for the extent of parenchymal pathologies seen on CXR, at baseline and 1-year (n=359)



CT imaging findings suggested that at TB treatment completion, 9.3% (36/385) of scans had at least 1 lobe essentially 'destroyed' by atelectasis, cavities / cystic airspaces, and banding. Chest x-ray imaging was less sensitive to this finding: only 2.8% of CXR films were found to have at least 1 destroyed lobe at the same time point. At 1-year, 4.5% (16/359) of CXR images were found to have at least 1 destroyed lobe.

- RING AND TRAMLINES

Ring and tramline change was also seen less frequently on CXR than bronchiectasis was seen on CT imaging: 29.5% (119/403) of participants had moderate-severe ring and tramline change in at least one zone on CXR at TB treatment completion, compared to 44.2% (170/385) with moderate to severe bronchiectasis in at least one lobe in on CT imaging. However, correlation between the overall severity scores for ring and tramline on CXR and bronchiectasis on CT imaging was reasonable (Pearson correlation coefficient 0.627, p<0.001).

At the population level, no significant change was observed in average ring and tramline severity scores between baseline and 1-year: median severity scores remained 1 with IQR 0 -3 at both time points. At the end of the 1-year follow up period, 28.0% (101/361) of individuals have moderate-severe ring and tramline pathology seen in at least 1 lobe.

- OTHER PATHOLOGIES

The proportion of participants with non-miliary nodules remained similar from baseline (18.4% (66/403)) to 1-year (22.3% (80/359)).

Mycetoma were seen on CXR for only one individual at the 12-month time point. This participant had not had confirmed mycetoma on CT imaging at baseline.

Pleural pathology was seen in 12.7% (51/403) of baseline and 16.1% (58/361) of repeat CXRs. Both values were higher than that seen on CT imaging at the point of treatment completion, where the prevalence was 8.1% (31/385) only.

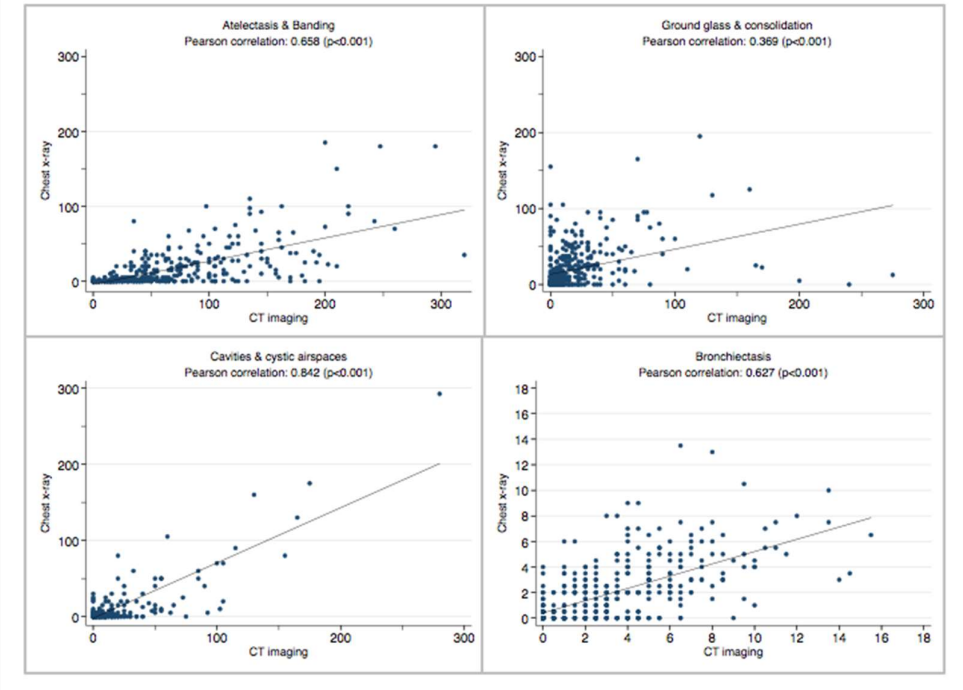
Hyper-expansion was noted in 15.4% (62/403) of baseline CXRs, and 12.2% (44/361) of 1-year CXRs. The difference in prevalence at these time points was not statistically significant. No correlation was identified between the presence of hyper-expansion on CXR at TB treatment completion, and the extent of CT based features of airway disease including mosaicism, emphysema, or bronchiectasis severity (data not shown).

COMPARISON OF CXR AND CT IMAGING RESULTS

The prevalence of pathology was higher on CT imaging: only 3.4% (13/385) individuals had completely normal parenchyma on baseline CT compared to 24.3% (98/403) on baseline CXR. On average, the extent of pathology detected was also greater on CT where the median amount of abnormal pathology was 138 points (IQR: 55-235) including mosaicism / 73 points (IQR: 30-150) excluding mosaicism, compared to just 18 points (IQR: 2.5 – 55) on CXR imaging.

However, the broad patterns and relative severities of pathology seen were similar between modalities. The extent of parenchymal pathologies, and the total ring and tramline / bronchiectasis severity scores were correlated between modalities (Figure 27). Atelectasis and banding were amongst the most widespread pathologies reported using both modalities, and CT and CXR extent scores were strongly correlated for this variable (Pearson's R 0.658, $p<0.001$). Cavities/cystic airspaces much less extensive using both modalities, but readings were also strongly correlated (Pearson's R 0.842, $p<0.001$). The weakest correlation was seen for ground glass change and opacification (Pearson's R 0.369, $p<0.001$), which was reported more extensively on CT imaging. Ring and tramline scores on CXR, and airway dilatation or bronchiectasis severity scores on CT were well correlated, with Pearson's R of 0.627, $p<0.001$.

Figure 27: Correlation between CT imaging and CXR findings, for the extent of parenchymal and airway pathology.



SENSITIVITY ANALYSIS

The patterns of pathology and change over time observed amongst those who received digital imaging at both time points (n=94) were similar to those seen in the broader cohort (Table 34).

Table 34: CXR imaging results at baseline and 1-year for those imaged with digital CXR at both time points (n=94)

Pathology	Baseline visit Median (IQR) [Full range]	1-year Median (IQR) [Full range]	p-value
Parenchymal pathology scores, whole lung level*			
Total abnormal parenchyma (0-600)	16 (0 – 48) [0 – 300]	11 (3 – 43) [0 – 245]	0.899
Cavities / cystic air spaces score (0-600)	0 (0 – 3) [0 – 293]	0 (0-8) [0 – 150]	0.107
Atelectasis / banding score (0-600)	3 (0 – 15) [0 – 150]	5 (0 – 20) [0 – 110]	0.793
Consolidation / ground glass score (0-600)	5 (0 – 23) [0 – 125]	3 (0 – 10) [1 – 75]	0.104
Presence of ≥1 'destroyed' zone (n, %)	3 (3.2%)	4 (4.3%)	0.700
Bronchiectasis, whole lung level			
Ring and tramline severity score (0-18)	2 (0 – 3.5) [0 – 10.5]	1 (0 – 2.5) [0 – 11]	0.289
Number of zones with mod-severe ring and tramline change^ 0 1 2 3 4	 58 (61.7%) 24 (25.5%) 8 (8.5%) 4 (4.3%) 0 (0.0)	 65 (69.2%) 20 (21.3%) 3 (3.2%) 4 (4.3%) 2 (2.1%)	0.284
Other scores, whole lung level			
Nodules Absent	 80 (85.1%)	 77 (81.9%)	0.832

Present Unclear	13 (13.8%) 1 (1.1%)	16 (17.0%) 1 (1.1%)	
Mycetoma Absent Present Unclear	 93 (98.9%) 0 (0.0) 1 (1.11%)	 93 (98.9%) 1 (1.1%) 0 (0.0)	0.398
Pleural pathology (effusions or thickening) Absent Present	 85 (90.4%) 9 (9.6%)	 78 (83.0%) 16 (17.0%)	0.133
Hyper-expansion Absent Present	 83 (88.3%) 11 (11.7%)	 84 (89.4%) 10 (10.6%)	0.817

*Parenchymal score off 100 is equivalent to one lung zone. Total possible score across the lung, including all 6 zones, is 600.
#Destroyed lobe is one in which ≥90% of parenchyma is occupied by banding, atelectasis, or cavities / cystic airspaces
^Present if final ring and tramline score is ≥2 for the zone

5.3.8 INDIVIDUAL LEVEL HETEROGENEITY IN CHANGE OVER TIME, ACROSS PARAMETERS

As shown above, trends to improvement were demonstrated across the majority of the clinical and respiratory parameters measured over the 1-year time period. However, heterogeneity was observed at the individual level across many of these parameters, with subgroups of individuals showing no change, improvement, and deterioration over the 1-year follow up period (Table 35), and variation in the magnitude of change observed within these groups.

Table 35: Individual level heterogeneity observed within key clinical and respiratory parameters, over the 1-year follow up period

Parameter	Proportion of participants with each pattern of change observed over 1-year			Size of change amongst those deteriorating Median (IQR)
	Improvement	No change	Deterioration	
Quality of life and symptoms				
General health, Likert score	31.3% (115/368)	62.2% (229/368)	6.5% (24/368)	N/a
SGRQ total score	68.3% (250/366)	12.0% (44/366)	19.7% (72/366)	6.8 points (3.0 – 19.1)
Presence of monthly respiratory symptoms	Resolution of symptoms – 36.1% (133/368)	No change in symptoms – 56.6% (207/368)	New monthly symptoms – 7.6% (28/368)	N/a
Functional capacity				
6MWD (m)	77.0% (268/348)	0.3% (1/368)	22.7% (79/348)	-34m (-54 - - 10)
Clinical observations				
BMI	70.1% (258/368)	1.4% (5/368)	28.5% (105/368)	-0.6kg/m^2 (0.3 - -1.2)
Spirometry data				
FEV1 z-score	66.2% (202/305)	0	33.8% (103/305)	-0.2 z-scores (-0.1 - -0.5)
FVC z-score	75.1% (229/305)	0	24.9% (76/305)	-0.2 z-scores (-0.1 - -0.4)
CXR data				
Total abnormal parenchyma score	50.4% (181/359)	21.2% (76/359)	28.4% (102/359)	12.5 points (5.0 – 22.5)
Ring and tramline score	37.6% (135/359)	30.4% (109/359)	32.0% (115/359)	1.5 points (0.5 – 2.0)

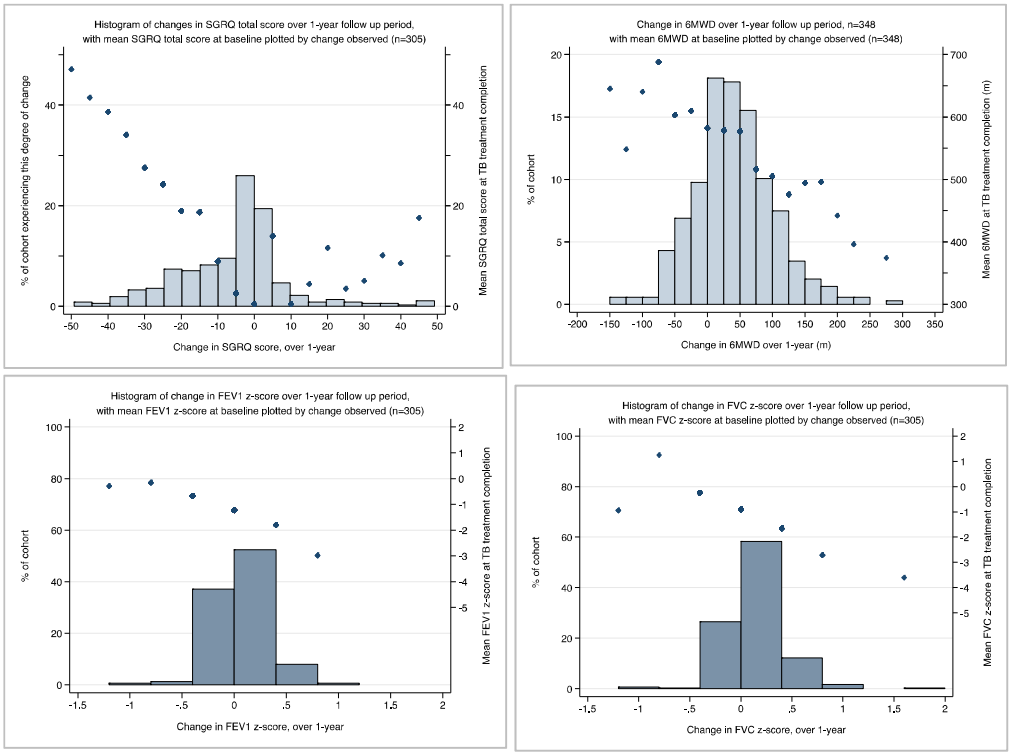
- PARTICIPANTS EXPERIENCING DETERIORATION

Between 19.7 – 33.8% percent of participants experienced any deterioration in at least one of the key clinical and respiratory parameters over the 1-year follow up period. The magnitude of this deterioration was often marked. The overlap between groups experiencing decline in each of these parameters has yet to be explored.

- PARTICIPANTS EXPERIENCING IMPROVEMENT

A 'catch up' phenomenon was observed amongst those experiencing improvement whereby those with the greatest deficit at TB treatment completion showed the largest amount recovery over time. This pattern was seen for multiple parameters including the SGRQ scores, the 6-minute walking distance, and spirometry parameters (Figure 28).

Figure 28: Graph to show the relationship between baseline levels of impairment, and change observed over 1-year period for the SGRQ total score, 6-minute walking distance, FEV_1 and FVC z-scores
Histograms: Magnitude of change observed over the 1-year period
Scatter plot: Mean baseline observation, for the group represented by each bar



Despite this 'catch up' phenomenon, recovery was incomplete: on average, participants with the worst parameters at TB treatment completion still had the worst parameters at 1-year. This pattern was again observed amongst multiple parameters including quality of life scores, 6-minute walking distances and CXR parameters when participants were stratified into quintiles based on their baseline

scores (Figure 29), as well as spirometry parameters when participants were stratified by LLN cut-offs at baseline (Figure 30).

Figure 29: Average scores at each study visit for participants stratified into quintiles by baseline scores for SGRQ total score, 6-minute walking distance, and CXR parameters.

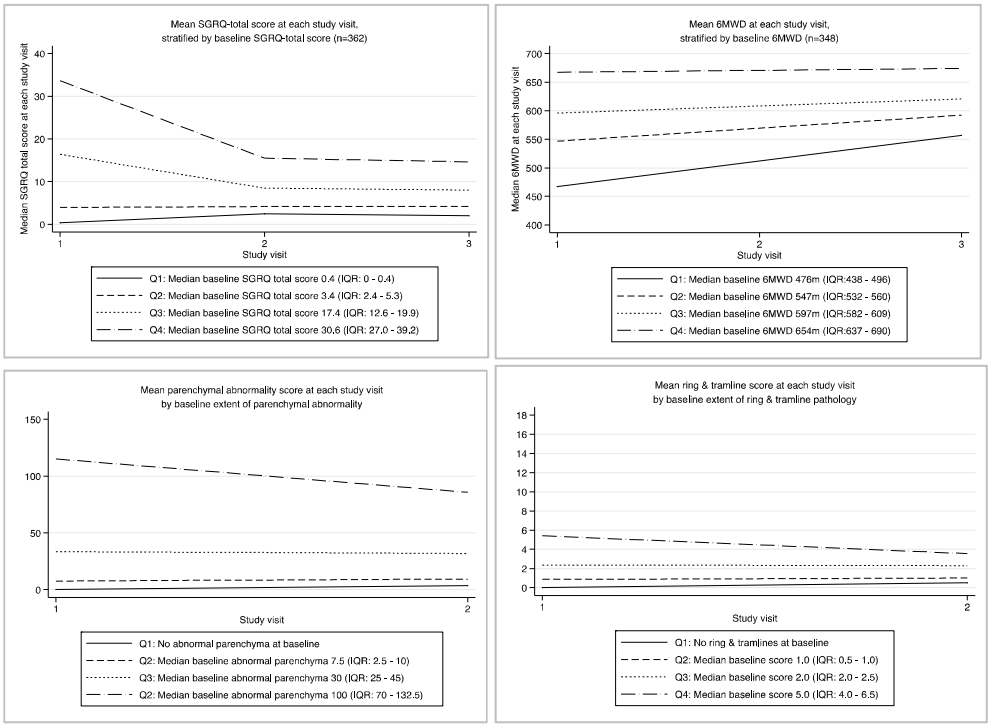
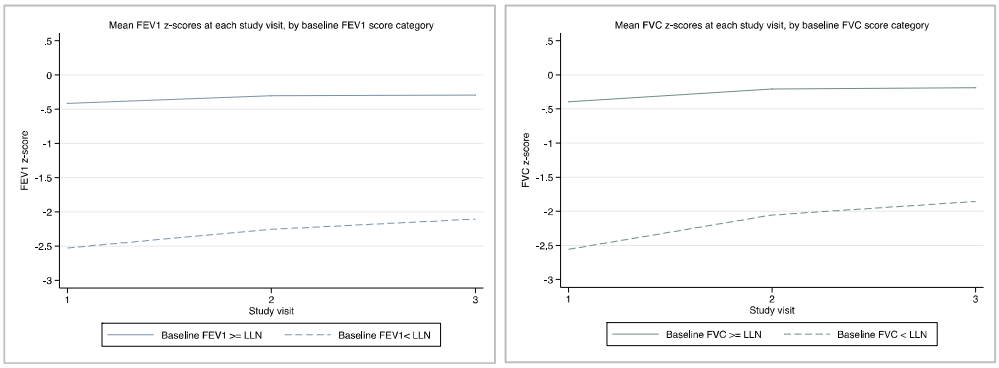


Figure 30: Mean FEV1 and FVC z-scores at each of the three study visits, according to whether volumes measured at TB treatment completion were above or below the lower-limit of normal cut off calculated using the GLI-2012 reference range.



It must be noted that in these exploratory analyses, individuals have been classified as showing improvement or decline if any positive or negative change was observed in repeated measures. In fact, some of the variation observed here may be related to test-retest variability in the measures used, rather than true change in clinical status. Further analyses are required to identify individuals improving or deteriorating by a magnitude greater than the minimal clinically important difference (MCID) for each parameter.

5.3.9 RELATIONSHIP BETWEEN SYMPTOMS, CT IMAGING AND SPIROMETRY AT TB TREATMENT COMPLETION

Comparing participants with any abnormal spirometry (including both obstructive and low-FVC groups) to those with normal spirometry at TB treatment completion, those with abnormal spirometry were more likely to be HIV negative (50.4% vs. 33.2%, p=0.001), to have lower BMI (19.9 vs. 20.6, p=0.002), and to have lower socioeconomic situations (67.6% vs. 48.9%, p=0.001). The majority of patterns of structural pathology seen on CT imaging were more extensive in those with abnormal vs. normal spirometry, except for the extent of ground glass and emphysema where no difference was observed. Summary SGRQ scores were all higher in those with abnormal spirometry (SGRQ total score 18.6 vs. 6.1, p=0.001), and regular breathlessness experienced at least monthly was more common in this group (56.8% vs. 37.9%, p=0.001) (Table 36).

However, when groups with obstruction and low FVC only were compared, few differences were observed. Individuals with obstruction were older (36.5 vs. 32 yrs, p=0.014) and a higher proportion come from the lowest SES quintiles (78.7% vs. 59.4%, p=0.031), but the only statistically significant differences in CT pathology were a larger amount of atelectasis and banding in those in the low FVC group (median score 64/600 vs. 78/600, p=0.026), and a higher extent of bronchial wall thickening in the obstruction group (median score 6.8/18 vs 3.5/18, p<0.001). No differences in the SGRQ scores or the burden of specific symptoms were observed.

Table 36: Characteristics of participants with obstruction, low FVC, or normal spirometry at TB treatment completion, with p-values presented for comparisons between any normal and any abnormal patterns (n=365), and the obstruction and low FVC groups only (n=125)

Parameter	Spirometry pattern, at TB treatment completion			p-value for comparison	
	Obstruction (n=52)	Low FVC (n=73)	Normal (n=240)	Normal vs. abnormal	Obstruction vs. Low FVC
Participant characteristics					
Age	36.5 (18 – 41.5)	32 (26 – 37)	36 (30 – 41.5)	0.028*	0.014*
Male gender	35 (67.3%)	47 (64.4%)	170 (70.8%)	0.305	0.734
Positive HIV status	25 (48.1%)	37 (50.7%)	159 (66.8%)	0.001**	0.774
CD4 count (cells / uL)	242 (171 – 398)	300 (196 – 499)	210 (106 – 376)	0.005**	0.528
Positive baseline TB microbiology	41 (78.9%)	62 (84.9%)	180 (75.0%)	0.108	0.379
BMI (kg/m^2) at TB Rx end	20.5 (18.5 – 22.2)	19.8 (18.6 – 21.0)	20.6 (19.3 – 22.3)	0.002**	0.438
Ever smoker	19 (36.5%)	20 (27.4%)	72 30.0%)	0.813	0.277
Poorest 3 SES quintiles	37 (78.7%)	38 (59.4%)	110 (48.0%)	0.001**	0.031*
Imaging at TB treatment completion					
Total abnormal parenchyma (0-600)	260 (188 – 340)	228 (173 – 295)	90 (40 – 175)	<0.001***	0.227
Atelectasis / banding score (0-600)	64 (35 – 103)	78 (45 – 158)	35 (15 – 63)	<0.001***	0.026*
Cavities / cystic airspaces (0-600)	10 (0 – 20)	8 (0 – 30)	0 (0 – 5)	<0.001***	0.618

Mosaicism score (0-600)	60 (8 – 155)	50 (18 – 118)	23 (5 – 65)	<0.001***	0.738
Emphysema score (0-600)	0 (0 – 10)	0 (0 – 3)	0 (0 – 5)	0.411	0.083
Ground glass score (0-600	0 (0 – 10)	0 (0 – 5)	0 (0 – 5)	0.367	0.823
Consolidation score (0-600)	8 (3 – 25)	8 (3 – 18)	4 (0 – 10)	<0.001***	0.803
Presence of ≥1 destroyed lobe	5 (9.6%)	14 (19.2%)	15 (5.4%)	0.002**	0.142
Bronchiectasis severity score (0-18)	4 (2 – 6)	4.5 (2 – 6.5)	2 (0 – 3.5)	<0.001***	0.842
Bronchial wall thickening severity scores (0-18) (n=306)	6.8 (4.5 – 9.5)	3.5 (1.5 – 6.0)	2.5 (1.0 – 4.5)	<0.001***	<0.001***
Tree in bud severity score (0-18)	5.3 (2.5 – 9.0)	5.0 (2.5 – 7.0)	3.0 (1.0 – 5.5)	<0.001***	0.475
Airway plugging severity score (0-18)	2.0 (0.5 – 4.0)	1.5 (0.5 – 2.5)	0.5 (0 – 2.0)	<0.001***	0.097
Clinical parameters at TB treatment completion					
SGRQ Activity score (0-100)	23.3 (0 – 53.2)	24.1 (0 – 41.4)	5.8 (0 – 30.4)	<0.001***	0.409
SGRQ Symptom (0-100)	19.4 (3.0 – 34.7)	21.8 (3.0 – 28.5)	11.6 (3.0 – 24.0)	<0.001***	0.479
SGRQ Impact score (0-100)	11.2 (1.6 – 26.9)	8.2 (1.6 – 20.8)	5.1 (0 – 11.5)	<0.001***	0.358
SGRQ Total score (0-100)	19.5 (3.0 – 34.2)	18.5 (2.1 – 25.2)	6.1 (0.8 – 19.9)	<0.001***	0.330
Cough ≥ monthly	24 (46.2%)	28 (38.4%)	82 (34.2%)	0.162	0.383
Breathlessness ≥ monthly	30 (57.7%)	41 (56.2%)	91 (37.9%)	0.001**	0.865
Sputum production ≥ monthly	19 (36.5%)	18 (24.7%)	61 (25.4%)	0.392	0.151
6-minute walk distance (m)	554 (489 – 642)	569 (509 – 611)	579 (525 – 627)	0.086	0.973

*p<.05, **p<.01, ***p<.001

5.3.10 PARTICIPANT OUTCOME DATA

Some of the outcomes to be included in the cohort analyses draw on the data already presented, including those relating to persistent symptoms and quality of life scores. However, in this section data on the incidence of ongoing respiratory events, TB retreatment and mortality will be given.

HEALTH SERVICE USE

Three types of health seeking episode were seen during the 1-year follow up of this cohort: planned outpatient appointments (n=264, across 168 individuals), unscheduled outpatient visits (n=173, across 130 individuals), and inpatient admissions (n=11, in 11 individuals).

A total of 437 all-cause outpatient appointments were identified across 254 participants, and 27 all-cause inpatient admissions were observed across 24 individuals (Table 37). Amongst the outpatient visits recorded, 60.4% (264/437) were pre-booked, and 39.6% (173/437) were unscheduled. Of all participants contributing follow up data to the study, 44.2% (168/380) individuals had at least 1 booked outpatient visit within the year, and 34.2% (130/380) had at least 1 unscheduled outpatient visit.

Table 37: Number of unscheduled outpatient visits and Inpatient admissions per person, presented across the whole study population (n=380), as well as separately for those contributing 1-year (n=364) or 6-month (n=16) of follow up data.

Number of events	All participants contributing follow up data (n=380)		Full 1-year follow up (n=364)		6-month follow-up (n=16)	
	Any cause	Respiratory cause	Any cause	Respiratory cause	Any cause	Respiratory cause
Outpatient visits						
0	126 (33.2%)	323 (85.0%)	118 (32.4%)	311 (85.4%)	8 (50.0%)	12 (75.0%)
1	135 (35.5)	47 (12.4%)	129 (35.4%)	43 (11.8%)	6 (37.5%)	4 (25.0%)
2	76 (20.0%)	7 (1.8%)	75 (20.6%)	7 (1.9%)	1 (6.3%)	0
3	27 (7.1%)	3 (0.8%)	27 (7.4%)	3 (0.8%)	0	0
4	12 (3.2%)	0	11 (3.0%)	0	1 (6.3%)	0
5	3 (0.8%)	0	3 (0.8%)	0	0	0
6	1 (0.3%)	0	1 (0.3%)	0	0	0
Inpatient admissions						
0	356 (93.7%)	353 (97.0%)	341 (93.6%)	15 (93.8%)	11 (91.7%)	16 (100%)
1	22 (5.8%)	11 (3.0%)	21 (5.8%)	1 (6.3%)	1 (8.3%)	0
2	1 (0.3%)	0	1 (0.3%)	0	0	0
3	1 (0.3%)	0	1 (0.3%)	0	0	0

- RESPIRATORY EPISODES

16.3% (62/380) of individuals had at least one scheduled or unscheduled health-seeking episode related to respiratory symptoms during follow-up. A higher incidence was seen amongst those contributing 6-month vs. 1-year of follow up data (25.0% (4/16) vs. 15.9% (58/364)), but this difference was not statistically significant.

Of the 62 individuals, the majority (77.4%, 28/62) had one episode, with only 14 individuals experiencing between 2-4 events. The median time to the first respiratory outpatient visit was 152 days (IQR: 116-191 days, n=57), and median time to the first respiratory admission was 225 days (IQR: 188 – 276 days, n=11).

- OUTPATIENT EVENTS

Booked visits were more commonly seen in HIV infected individuals: 66.4% (154/232) of HIV positives had at least one pre-booked outpatient appointment during follow-up, of which the majority were to the ART / HIV clinic (92.0%, 230/250), compared to only 9.6% (14/146) of HIV negatives. Across both groups, only 3.6% (9/264) of scheduled outpatient visits were to the chest clinic.

40.5% (70/173) of the unscheduled outpatient visits were for respiratory reasons and classified as acute respiratory exacerbations. Approximately half were due to increased cough (55.7%, 39/70), and a third related to increased breathlessness (34.3%, 24/70), with other reasons including chest pain, sputum production, and wheeze. These 70 respiratory visits were shared across 58 participants, with the majority (65.5%, 38/58) experiencing one visit only. The majority of unplanned respiratory

outpatient visits were to the primary health centre or public hospital (85.7%, 60/70), with only 2 visits to the local pharmacy or grocer. Antibiotics were prescribed in 80% of unscheduled respiratory visits. The most commonly used antibiotics were amoxicillin (21/56, 55.4%) and co-trimoxazole (14/56, 25.0%), but ciprofloxacin, erythromycin, ceftriaxone or various combinations were also used. More HIV-negative individuals experienced unscheduled outpatient visits compared to HIV-infected participants (40.4% vs. 30.2%, p=0.041).

- ADMISSIONS

40.7% (11/27) of inpatient admissions during follow up were for respiratory reasons including increased breathlessness and increased cough. Six of the respiratory admissions occurred amongst five individuals who were started on TB retreatment during the follow up period.

The majority of respiratory admissions were at public hospitals (90.9%, 10/11), and in 72.7% (8/11) of cases the individual was accompanied by a guardian. Antibiotics were known to have been received in 54.6% (6/11) of cases, and included co-amoxiclav, co-trimoxazole, ceftriaxone, multiple antibiotics or in 2 cases unknown medications. Median admission duration was 20 nights (IQR: 4-59), but this long duration was driven by participants admitted for TB treatment, who at the time of this study were required to receive inpatient treatment with intramuscular streptomycin for the first 2-months of the retreatment regimen. Amongst those admitted but not restarted on TB retreatment, the median duration of admission was 6.5 days (IQR: 3-10 days).

- TB SYMPTOMS AND RETREATMENT

18.9% (71/376) of participants had a positive TB symptom screen at the 6-month visit, and 10.6% (39/368) at the 1-year visit. Current cough was the most common TB symptom identified: this was reported by 18.1% (68/376) of individuals at the 6-month time point, and 9.5% (35/368) at the 1-year visit. Sputum was obtained at 100/110 of the symptom positive study visits, amongst which 4% (4/100) were found to have MTB confirmed disease on culture. Drug sensitivities were not available. Three further individuals had an NTM isolated on a primary culture but repeat samples were negative, suggesting that these were contaminants only. Of the 92 individuals with a positive symptom screen, 11 were started on retreatment during study follow-up. Amongst the 81 symptomatic participants who were not started on TB retreatment, only 1 died over the study duration.

In total, 3.7% (15/405) of study participants started TB retreatment during study follow-up. The median time from TB treatment completion to retreatment was 204 days (total range: 57-318 days, n=13). Overall, evidence with either smear or culture positivity was available for 46.7% (7/15) of individuals started on retreatment (Table 38). A total of 4 individuals were started on retreatment due to persistently positive Xpert MTB results, and the time to diagnosis from the initial TB treatment completion for these individuals were 76 days, 115 days, 180 days, and 259 days. Sputum cultures are

not available for any of these individuals, but all had experienced associated clinical features which could be suggestive of active disease.

Table 38: The basis of diagnosis of recurrent TB disease, according to the system within which diagnosed (n=15)

Basis of TB diagnosis	Malawi NTP (n=11)	Research study (n=4)	Total (n=15)
Smear positive	4	0	4 (26.7%)
Smear positive / Culture negative	0	1	1 (6.7%)
Spear negative / Culture positive	0	2	2 (13.3%)
Xpert positive	3	1	4 (26.7%)
Radiological diagnosis	3	0	3 (20.0%)
Unknown	1	0	1 (6.7%)

Mortality amongst those starting retreatment was high: one third died during the course of follow-up (5/15), but only two had completed their 8-month TB retreatment regimens by the time of the final study visit and so final outcomes for the majority of cases are unknown.

- MORTALITY

11 participants died during the 1-year follow up period: 7 passed away within the first 6-months of follow up, and 4 thereafter. Amongst those who died, 5/11 (45.5%) had been started on TB retreatment (Table 39).

Table 39: Adverse outcomes (death and TB retreatment) during the 1-year follow up period (n=405)

TB retreatment	Death	
	No	Yes
No	384 (94.8%)	6 (1.5%)
Yes	10 (2.5%)	5 (1.2%)

5.3.11 FACTORS ASSOCIATED WITH ABNORMAL SPIROMETRY

Exploratory analyses of the factors predicting spirometry results at TB treatment completion and 1-year, and those predicting change over time, are shown below. These include linear models for individual spirometry parameters (absolute FEV_1, absolute FVC, and FEV_1/FVC ratio), and logistic models for patterns of deficit (obstruction vs. normal spirometry, low FVC vs. normal spirometry) at the various time points.

A reduced set of models are presented for each spirometry measure, across each of the three time points, in the main text. Detailed tables with models grouped by the time point of interest (spirometry at TB treatment completion, change over time, spirometry at 1-year) rather than by parameter are given in Appendix 5.

MODEL CONSTRUCTION

During construction of the linear models for factors predicting the change in spirometry measurements over time, 4 outliers were identified. Manual review of spirometry traces for these individuals showed that although both baseline and 1-year traces had been independently quality controlled and felt to include usable data, when these readings were compared, they appeared inconsistent, suggesting that either the baseline or 1-year readings were incorrect. These 4 data points were therefore excluded from all models.

The additional inclusion of a quadratic 'height^2' variable was considered across the models but was found to have limited effect on the variable co-efficients whilst improving R^2 values only very slightly, and as such was not incorporated in final models. In addition, an inconsistent signal of interaction between HIV and TB was identified across the models, but as this was seen in a minority of models only was not included in final models either.

LINEAR REGRESSION: ABSOLUTE FEV_1 AT TREATMENT COMPLETION AND 1-YEAR, AND CHANGE OVER TIME

Table 40: Linear regression models for absolute FEV_1 volume at TB treatment completion (n=330), change in volume over 1-year follow-up (n=290), and absolute volume at 1-year (n=290)

	TB treatment completion (n=330)	Change over 1 year (n=290)		1-year post TB treatment completion (n=290)			
	Multivariate model R^2 0.455	Participant characteristics R^2: 0.114	Full multivariate model R^2:0.232	Basic multivariate model R^2: 0.513	+ Baseline spirometry R^2: 0.924	+ Baseline imaging R2: 0.580	Full multivariate model R^2: 0.926
Age (yrs)	-12.6 (-18.6 – -6.7)***	-4.1 (-6.6 – -1.7)**	-5.6 (-8.0 – -3.2)***	-15.5 (-21.4 – -9.6)***	-5.7 (-8.1 – -3.3)***	-14.4 (-19.9 – -8.8)***	-5.6 (-8.0 – -3.2)***
Male gender	401.1 (231.2 – 571.0)***	72.1 (-3.1 – 144.0)	131.2 (60.2 – 202.2)***	468.2 (196.2 – 640.3)***	125.4 (55.1 – 195.7)**	506.9 (345.9 – 667.9)***	130.8 (59.5 – 202.0)***
Height (m)	37.9 (28.8 – 47.0)***	1.4 (-2.5 – 5.3)	6.1 (2.0 – 10.2)**	39.2 (29.9 – 48.4)***	6.4 (2.4 – 10.4)**	38.7 (30.0 – 47.3)***	6.1 (2.0 – 10.2)**
HIV positive at TBRx end - CD4≥200 cells/uL - CD4<200 cells/uL	47.8 (-85.0 – 180.6) 189.9 (40.4 – 339.4)*	103.1 (47.2 – 159.0)** 68.6 (5.8 – 131.5)*	105.9 (52.7 – 159.1)*** 86.4 (25.4 – 147.4)**	127.1 (-7.0 – 261.3) 243.7 (93.1 – 394.3)**	107.1 (54.0 – 160.1)** 92.5 (32.4– 152.6)**	141.6 (15.8 – 267.3)* 212.2 (71.5 – 353.0)**	105.3 (51.8 – 158.8)*** 86.0 (24.0 – 147.2)**
Positive baseline TB microbiology	22.1 (-117.2 – 161.5)	-42.9 (-101.2 – 15.4)	-33.4 (-88.2 – 21.5)	-12.7 (-152.0 – 126.6)	-38.6 (-93.7 – 16.6)	-12.2 (-142.1 – 117.7)	-33.6 (-88.7 – 21.4)
BMI at TB treatment completion (kg/m^2)	38.6 (18.3 – 58.8)***	-4.2 (-13.2 – 4.8)	0.21 (-8.5 – 8.9)	33.9 (12.4 – 55.3)**	0.9 (-7.7 – 9.6)	18.6 (-1.9 – 39.1)	0.2 (-8.5 – 8.9)
Illness duration ≥1-month prior to TB treatment	-116.1 (-231/8 – 0.3)*			-123.8 (-241.3 – -6.20)*	-9.4 (-56.3 – 37.5)	-80.8 (-191.3 – 29.6)	-5.6 (-52.5 – 41.3)
Ever smoking	-87.3 (-226.6 – 52.1)	24.7 (-33.4 – 82.7)	10.5 (44.6 – 65.6)	-64.5 (-203.2 – 74.1)	12.7 (-42.3– 67.8)	-35.6 (-202.6 – 40.1)	10.5 (-44.7 – 65.7)
Poorest 3x SES quintiles	-99.2 (-226.4 – 28.0)	16.4 (-37.7 – 70.5)	-2.3 (-53.8 – 49.2)	-103.2 (-232.8 – 26.4)	1.2 (-50.4 – 52.7)	-81.2 (-202.6 – 40.1)	-2.8 (-54.6 – 49.0)
Intermittent food insecurity	-10.3 (-139.8 – 119.2)	17.3 (-37.4 – 72.0)	16.9 (-34.6 – 68.4)	11.3 (-119.5 – 142.0)	16.2 (-35.6– 67.9)	24.4 (-97.7 – 146.5)	17.2 (-34.4 – 68.8)
FEV_1 (ml) at TBRx completion			-0.14 (-0.18 – -0.09)***		0.87 (0.82 – 0.91)***		0.86 (0.82 – 0.91)***
≥1/3 abnormal parenchyma			12.2 (-58.0 – 82.5)			-406.0 (-563.3 – -248.8)***	12.5 (-57.9 – 82.9)
≥3 lobes with mod-severe bronchiectasis			-42.3 (-131.0 – 46.3)			-243.1 (-452.0 – -34.3)*	-41.7 (-130.6 – 47.3)
Any OPD / IP respiratory visits			-41.1 (-109.2 – 27.0)				-40.8 (-109.1 – 27.5)
TB retreatment			-165.4 (-366.0 – 35.2)				-165.1 (-366.1 – 35.9)

*p<.05, **p<.01, ***p<.001

LINEAR REGRESSION: ABSOLUTE FVC AT TREATMENT COMPLETION AND 1-YEAR, AND CHANGE OVER TIME

Table 41: Linear regression models for absolute FVC volume at TB treatment completion (n=330), change in volume over 1-year follow-up (n=290), and absolute volume at 1-year (n=290)

	TB treatment completion (n=330)	Change over 1 year (n=290)		1-year post TB treatment completion (n=290)			
	Multivariate model R^2 0.505	Participant characteristics R^2: 0.139	Full multivariate model R^2:0.291	Basic multivariate model R^2: 0.576	+ Baseline spirometry R^2: 0.929	+ Baseline imaging R^2:0.628	Full multivariate model R^2: 0.932
Age (yrs)	-5.3 (-11.7 – 1.2)	-3.0 (-5.8 – -0.3)*	-3.4 (-6.0 - -0.8)**	-7.2 (-13.4 – -0.9)*	-3.7 (-6.3 – -1.1)**	-6.0 (-11.9 – -0.12)*	-3.4 (-6.0 – -0.9)**
Male gender	480.9 (296.2 – 665.6)***	98.5 (18.5 – 178.5)*	174.2 (97.3 – 251.1)***	526.3 (344.4 – 708.2)***	165.7 (88.8 – 242.7)***	567.5 (395.7 – 739.2)***	175.5 (98.3 – 252.7)***
Height (cm)	47.2 (37.3 – 57.2)***	1.3 (-3.0 – 5.6)	8.2 (3.6 – 12.8)**	50.4 (40.6 – 60.2)***	8.8 (4.2– 13.4)***	49.7 (40.5 – 58.9)***	8.1 (3.5 – 12.8)**
HIV positive at TBRx end - CD4≥200 cells/uL - CD4<200 cells/uL	 26.5 (-117.8 – 170.8) 170.5 (8.0 – 333.0)*	 126.3 (64.1 – 188.6)*** 102.9 (32.9 – 172.9)**	 123.2 (65.5 – 180.9)*** 115.7 (49.6 – 181.8)**	 117.4 (-24.5 – 259.2) 272.1 (112.9 – 431.4)**	 126.8 (68.7 – 184.9)*** 130.5 (64.8 – 196.1)***	 136.0 (1.84 – 270.1)* 241.1 (91.0 – 391.2)**	 124.5 (66.5 – 182.6)*** 116.6 (50.3 – 182.8)**
Positive baseline TB microbiology	17.0 (-134..5 – 168.5)	-9.5 (-74.3 – 55.4)	4.1 (-55.5 – 63.7)	28.7 (-118.6 – 176.1)	-2.9 (-63.3 – 57.5)	30.0 (-108.6 – 168.5)	4.7 (-55.1 – 64.4)
BMI at TB treatment completion (kg/m^2)	51.5 (29..5 – 73.5)***	-12.3 (-22.3 – -2.4)*	-5.2 (-14.7 – 4.4)	38.5 (15.8 – 61.1)**	-4.4 (-14.0 – 5.1)	23.0 (1.17 – 44.9)*	-5.1 (-14.7 – 4.4)
Illness duration ≥1-month prior to TB treatment	-72.6 (-198.5 – 53.2)			-70.0 (-194.3 – 54.3)	6.6 (-44.5 – 57.7)	-26.0 (-143.8 – 91.8)	12.7 (-38.0 – 63.4)
Ever smoking	-23.1 (-174.6 – 128.4)	24.9 (-39.7 – 89.5)	14.0 (-45.7 – 73.8)	2.7 (-143.9 – 149.4)	21.3 (-38.8 – 81.4)	28.0 (-110.6 – 166.6)	13.9 (-45.9 – 73.7)
Poorest 3x SES quintiles	-12.9 (-151.2 – 125.4)	16.8 (-43.4 – 77.0)	3.0 (-52.7 – 58.7)	-15.7 (-152.8 – 121.3)	13.4 (-42.8 – 69.6)	2.9 (-126.5 – 132.4)	4.1 (-51.8 – 60.1)
Intermittent food insecurity	36.8 (-104.0 – 177.6)	25.7 (-35.2 – 86.6)	35.6 (-20.3 – 91.6)	80.5 (-57.7 – 218.8)	33.3 (-23.5 – 90.0)	95.5 (-34.7 – 255.8)	35.0 (-21.1 – 91.1)
FVC (ml) at TB treatment completion			-0.16 (-0.21 – -0.11)***		0.85 (0.80 – 0.89)***		0.84 (0.79 – 0.89)***
≥1/3 abnormal parenchyma			40.6 (-35.0 – 116.1)			-368.0 (-535.7 – -200.2)***	39.7 (-36.1 – 115.4)
≥3 lobes with mod-severe bronchiectasis			-92.8 (-189.0 – 3.4)			-309.1 (-531.9 - -86.3)**	-94.4 (-191.0 – 2.1)
Any OPD / IP respiratory visits			-79.9 (-153.8 – -6.0)*				-80.6 (-154.7 – -6.5)*
TB retreatment			-114.4 (-332.0 – 103.2)				-114.8 (-332.8 – 103.1)

*p<.05, **p<.01, ***p<.001

LINEAR REGRESSION: FEV_1/FVC RATIO AT TREATMENT COMPLETION AND 1-YEAR

Table 42: Linear regression models for FEV_1/FVC ratio (%) at TB treatment completion (n=330) and 1-year later (n=290)

	TB treatment completion (n=330)	1-year post TB treatment completion (n=290)			
	Multivariate Model $R^2$0.165	Basic multivariate model R^2: 0.204	+ Baseline spirometry R^2: 0.841	+ Baseline imaging R^2:0.216	Full multivariate model R^2: 0.843
Age (yrs)	-0.3 (-0.4 – -0.2)***	-0.3 (-0.4 – -0.2)***	-0.1 (-0.1 – -0.0)**	-0.3 (-0.4 – -0.2)***	-0.1 (-0.1 – -0.0)***
Male gender	-0.1 (-2.9 – 2.7)	1.2 (-1.9 – 4.2)	0.1 (-1.3 – 1.4)	1.3 (-1.7 – 4.4)	-0.0 (-1.4 – 1.4)
Height (m)	-0.0 (-0.2 – 0.1)	-0.0 (-0.2 – 0.1)	0.0 (-0.1 – 0.1)	-0.0 (-0.2 – 0.12)	-0.0 (-0.1 – 0.1)
HIV positive at TB treatment completion - CD4≥200 cells/uL - CD4<200 cells/uL	 1.2 (-1.0 – 3.3) 2.1 (-0.4 – 4.5)	 1.3 (-1.1 – 3.6) 1.4 (1.3 – 4.0)	 0.2 (-0.9 – 1.2) 0.0 (-1.2 – 1.2)	 1.3 (-1.1 – 3.6) 1.2 (-1.5 – 3.8)	 -0.1 (-0.9 – 1.2) -0.2 (-1.1 – 1.4)
Positive baseline TB microbiology	0.1 (-2.1 – 2.4)	-1.3 (-3.8 – 1.1)	-1.1 (-2.2 – -0.0)*	-1.3 (-3.8 – 1.1)	-1.2 (-2.3 – -0.0)*
BMI at TB treatment completion (kg/m^2)	-0.0 (-0.4 – 0.3)	0.2 (-0.2 – 0.5)	0.2 (0.0 – 0.4)*	0.1 (-0.2 – 0.5)	0.2 (0.0 – 0.4)*
Illness duration ≥1-month prior to TB treatment	-2.1 (-4.0 – -0.2)*	-2.1 (-4.2 – -0.1)*	-0.3 (-1.2 – 0.7)	-1.9 (-4.0 – 0.2)	-0.3 (-1.2 – 0.7)
Ever smoking	-1.5 (-3.8 – 0.8)	-1.2 (-3.7 – 1.3)	0.1 (-1.0 – 1.2)	-1.0 (-3.4 – 1.5)	0.2 (-0.9 – 1.3)
Poorest 3x SES quintiles	-2.8 (-4.9 – -0.7)**	-3.0 (-5.3 – -0.7)*	-0.3 (-1.4 – 0.7)	-2.8 (-5.1 – -0.5)*	-0.2 (-1.3 – 0.8)
Intermittent food insecurity	-1.1 (-3.2 – 1.0)	-1.4 (-3.7 – 0.9)	-0.2 (-1.2 – 0.9)	-1.4 (-3.7 – 0.9)	-0.2 (-1.2 – 0.9)
FEV_1/FVC ratio (%) at treatment completion			0.91 (0.86 – 0.96)***		0.91 (0.86 – 0.97)***
≥1/3 abnormal parenchyma				-3.0 (-6.0 – -0.0)	-0.3 (-1.7 – 1.1)
≥3 lobes with mod-severe bronchiectasis				-0.2 (-4.1 – 3.8)	0.9 (-0.8 – 2.7)
Any OPD / IP respiratory visits					0.6 (-0.8 – 2.0)
TB retreatment					-2.7 (-6.8 – 1.4)

*p<.05, **p<.01, ***p<.001

LOGISTIC REGRESSION: OBSTRUCTION VS. NORMAL SPIROMETRY AT TREATMENT COMPLETION AND 1-YEAR

Table 43: Logistic regression models for airway obstruction (FEV_1/FVC <LLN) vs. normal spirometry at TB treatment completion (n=267) and 1-year later (n=250)

	TB treatment completion (n=267)	1-year post TB treatment completion (n=250)	
Age (yrs)	1.01 (0.98 – 1.05)	1.02 (0.98 – 1.05)	1.02 (0.98 – 1.08)
Gender			
- Female	1.0	1.0	1.0
- Male	0.84 (0.30 – 2.38)	0.84 (0.30 – 2.31)	1.35 (0.31 – 5.96)
Height (cm)	1.01 (0.95 – 1.07)	0.99 (0.93 – 1.04)	0.95 (0.87 – 1.03)
HIV status			
- Negative	1.0	1.0	1.0
- Positive, CD4>=200 cells/uL	0.50 (0.22 – 1.10)	0.53 (0.24 – 1.18)	0.9 (0.32 – 3.50)
- Positive, CD4<200 cells/uL	0.30 (0.11 – 0.80)*	0.58 (0.93 – 1.04)	1.5 (0.38 – 5.71)
Baseline TB microbiology			
- Negative	1.0	1.0	1.0
- Positive	0.72 (0.29 – 1.78)	1.44 (0.57 – 3.64)	3.36 (0.83 – 13.56)
BMI at TB treatment completion (kg/m^2)	0.91 (0.79 – 1.05)	0.91 (0.78 – 1.05)	1.00 (0.81 – 1.24)
Illness duration prior to TB treatment			
- <1-month	1.0	1.0	1.0
- ≥1-month	1.79 (0.86 – 3.74)	1.60 (0.78 – 3.26)	1.54 (0.54 – 4.39)
Ever smoking			
- Never	1.0	1.0	1.0
- Ever	1.03 (0.45 – 2.36)	1.30 (0.59 – 2.89)	1.63 (0.52 – 5.10)
Urban SES quintile			
- Least poor quintiles x2	1.0	1.0	1.0
- Poorest quintiles x3	3.08 (1.31 – 7.23)*	1.79 (0.80 – 3.98)	0.74 (0.23 – 2.36)
Food insecurity			
- Never	1.0	1.0	1.0
- Sometimes / often	1.91 (0.91 – 4.01)	1.95 (0.95 – 4.03)	1.59 (0.53 – 4.70)
Baseline spirometry pattern			
- Normal			1.0
- Obstruction			117.91 (31.26 – 444.73)***
- Low FVC			2.92 (0.64 – 13.40)
Parenchyma, except mosaicism			
- <1/3 abnormal			1.0
- ≥1/3 abnormal			1.38 (0.36 – 5.26)
Mod-severe bronchiectasis			
- <3 lobes			1.0
- ≥3 lobes			2.58 (0.41 – 16.20)
Any OPD / IP respiratory visits			
- No			1.0
- Yes			0.33 (0.07 – 1.67)

*p<.05, **p<.01, ***p<.001

LOGISTIC REGRESSION: LOW FVC VS. NORMAL SPIROMETRY AT TREATMENT COMPLETION AND 1-YEAR

Table 44: Logistic regression models for low FVC pattern (FEV_1/FVC ≥LLN and FVC<LLN) vs. normal spirometry at TB treatment completion (n=283) and 1-year later (n=242)

	TB treatment completion (n=283)	1-year post TB treatment completion (n=242)	
Age (yrs)	0.96 (0.92 – 0.99)*	0.96 (0.91 – 1.01)	1.00 (0.93 – 1.08)
Gender - Female - Male	 1,0 0.99 (0.41 – 2.37)	 1.0 0.41 (0.14 – 1.20)	 0.06 (0.01 – 0.50)*
Height (cm)	0.99 (0.94 – 1.04)	1.02 (0.95 – 1.08)	1.12 (0.98 – 1.28)
HIV status - Negative - Positive, CD4>=200 cells/uL - Positive, CD4<200 cells/uL	 1.0 0.82 (0.44 – 1.75) 0.42 (0.17 – 1.07)	 1.0 0.61 (0.27 – 1.41) 0.34 (0.10 – 1.16)	 1.0 0.16 (0.04 – 0.70)* 0.21 (0.03 – 1.59)
Baseline TB microbiology - Negative - Positive	 1.0 1.11 (0.50 – 2.46)	 1.0 1.30 (0.50 – 3.39)	 1.0 1.82 (0.35 – 9.46)
BMI at TB treatment completion (kg/m^2)	0.89 (0.79 – 1.01)	0.87 (0.75 – 1.02)	0.96 (0.77 – 1.20)
Illness duration prior to TB treatment - <1-month - ≥1-month	 1.0 1.28 (0.68 – 2.39)	 1.0 1.40 (0.64 – 3.08)	 1.0 0.43 (0.11 – 1.67)
Ever smoking - Never - Ever	 1.0 0.86 (0.40– 1.86)	 1.0 1.04 (0.40 – 2.70)	 1.0 1.25 (0.24 – 6.45)
Urban SES quintile - Least poor quintiles x2 - Poorest quintiles x3	 1.0 1.31 (0.65 – 2.63)	 1.0 1.19 (0.51 – 2.78)	 1.0 0. 67 (0.14 – 3.09)
Food insecurity - Never - Sometimes / often	 1.0 1.65 (0.83 – 3.26)	 1.0 2.03 (0.88 – 4.65)	 1.0 1.48 (0.35 – 6.30)
Baseline spirometry pattern - Normal - Obstruction - Low FVC			 1.0 Empty^ 216.98 (37.87 – 1243.21)***
Parenchyma, except mosaicism - <1/3 abnormal - ≥1/3 abnormal			 1.0 1.53 (0.31 – 7.62)
Mod-severe bronchiectasis - <3 lobes - ≥3 lobes			 1.0 15.37 (1.19 –199.01)*
Any OPD / IP respiratory visits - No - Yes			 1.0 0.94 (0.16 – 5.39)
TB retreatment - No - Yes			 1.0 1.31 (0.00 – 512.60)

*p<.05, **p<.01, ***p<.0001

MODEL FINDINGS

- ### HIV AND TB MICROBIOLOGY AT BASELINE

HIV-infected participants had preserved spirometry at TB treatment completion and 1-year later, compared to HIV negatives: controlling for other participant characteristics, the absolute FEV_1 volume in HIV positives with CD4 counts <200cells/uL was was 190ml (95% CI: 40 - 339ml) larger at baseline and 244 ml (95% CI: 93 - 394ml) larger at 1-year compared to HIV negative adults, and absolute FVC volume was 171ml (95% CI: 8 - 333ml) larger at baseline and 272ml (95% CI: 113 - 431ml) larger at 1-year. Because the magnitude of the associations with absolute FEV_1 and FVC volumes are broadly similar HIV status was not independently associated with the FEV_1/FVC ratio. HIV status was not associated with airway obstruction or low FVC patterns of deficit in the logistic models.

HIV-infected participants also showed a greater recovery in their lung volumes over the follow-up period. This pattern was consistent across both CD4 groups: on average, controlling for other participant characteristics, the increment in FEV1 was 69-103ml larger and in FVC was 103-126ml larger in HIV positives compared to negatives.

In the majority of models, baseline TB microbiology was not a significant predictor of spirometry outcomes in either univariate or multivariate analyses controlling for HIV.

- ### BMI

Participants with higher BMI values at TB treatment completion had better lung volumes at both this time point and 1-year later: controlling for characteristics including food security, SES and HIV, a 1.0kg/m^2 higher BMI at treatment completion was associated with FEV_1 volumes which were 39ml / 34ml higher at baseline and 1-year, and FVC volumes which were 52ml / 39ml higher.

- ### SOCIOECONOMIC STATUS AND DELAYS TO TREATMENT

Neither socioeconomic quintile nor food insecurity were independently associated with absolute FEV_1 or FVC volumes at baseline or 1-year in multivariate models. However, low SES was an independent predictor of the FEV_1/FVC ratio: on average participants from lower socioeconomic quintiles had ratios which were 2.8% lower (95% CI: 0.7-4.9% lower) at TB treatment completion, and 3.0% lower (95% CI: 0.7-5.3% lower) 1-year later. That is, whilst the individual negative relationships between SES and individual FEV_1 or FVC measures were not statistically significant, the differential association with the FEV_1 and FVC parameters was sufficient to alter the ratio and act as a risk factor for increasing airway obstruction.

Illness duration prior to treatment was negatively correlated with both the FEV_1 and FEV_1/FVC ratio: on average, and controlling for other participant characteristics, those who had been unwell for ≥1-

month had FEV_1 volumes which were 116ml lower (95% CI: 0.3 – 239ml) at baseline and 124ml lower (95% CI: 6 – 241ml) at 1-year, and FEV_1/FVC ratios which were 2.1% (95% CI: 0.1 – 4.2%) lower at both time points, compared to those with <1-month to treatment. The relationship between illness duration and FVC was not statistically significant at either time point.

- SMOKING

Ever smoking was not correlated with lung function measures at either TB treatment completion, or 1-year later in multivariate analyses. It was also not correlated with change in lung function over time.

- BASELINE PATHOLOGY AS A PREDICTOR OF SPIROMETRY AT 1-YEAR

Spirometry at TB treatment completion was the strongest predictor of spirometry at 1-year – this pattern was seen in both linear models of absolute FEV_1 and FVC volumes, and logistic models for patterns of deficit. Controlling for participant characteristics, a 100ml larger baseline FEV_1 volume was associated with an 87ml larger (95% CI: 82-91ml) FEV_1 at 1-year, and a 100ml larger baseline FVC volume was associated with an 85ml larger (95% 80-89ml) FVC at 1yr. In the linear models for both FEV_1 and FVC at 1-year, the addition of baseline spirometry to predictive models including participant characteristics increased the model R^2 values from 0.51 to 0.92 for FEV_1, and 0.58 to 0.93 for FVC, suggesting that spirometry at TB treatment completion explains much of the heterogeneity in the volumes at 1-year.

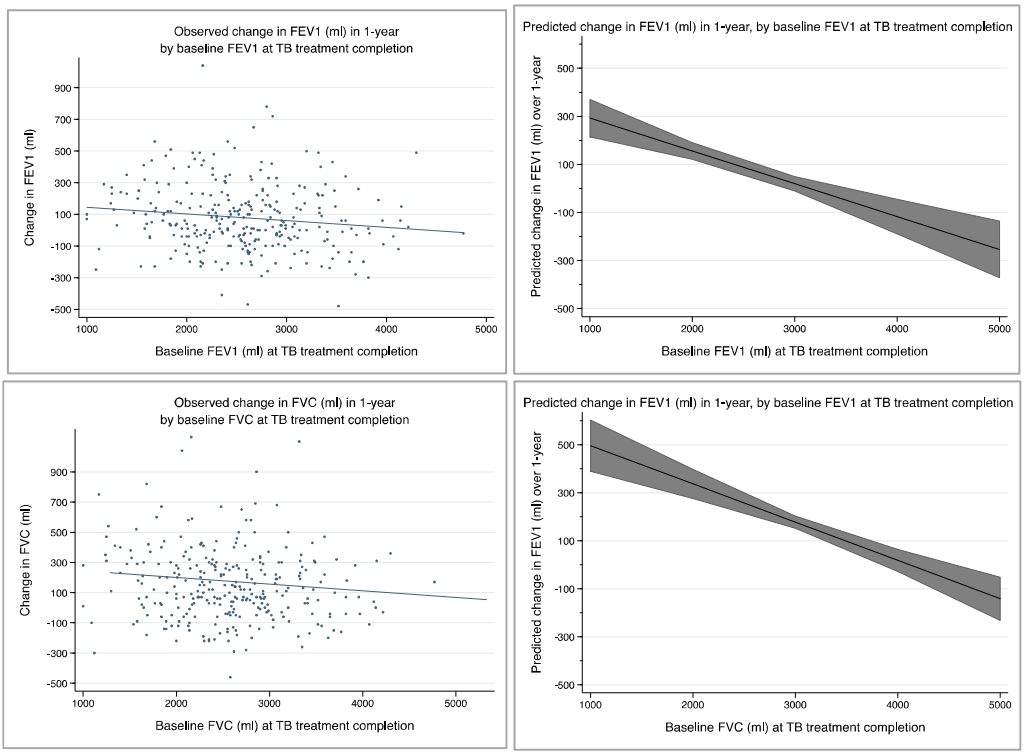
The extent of structural damage on CT at TB treatment completion was an alternative predictor of spirometry at 1-year: controlling for participant characteristics, the presence of parenchymal pathology affecting ≥1/3 of the lung at TB treatment completion was associated with FEV_1 and FVC volumes which were on average 406ml (95% CI: 249 – 563ml) and 368ml (95% CI: 200 – 536ml) lower at 1-year, and the presence of bronchiectasis affecting ≥3-lobes at TB treatment completion was associated with FEV_1 and FVC volumes which were on average 243ml (95% CI: 34 – 452ml)and 309ml (95% CI: 86 – 532ml) lower at 1-year.

If both measures of baseline spirometry and baseline CT pathology were included together in models for 1-year spirometry outcomes, the relationships between imaging and outcome were no longer significant. This suggests that the effect of baseline imaging on 1-year spirometry is mediated through its effect on baseline spirometry. The same is true for BMI, SES and illness duration whose relationship with spirometry at 1-year becomes no longer statistically significant when baseline spirometry is controlled for, suggesting that their association with 1-year lung function is mediated by their impact on spirometry at TB treatment completion.

- BASELINE LUNG FUNCTION AND IMAGING AS PREDICTORS OF CHANGE OVER TIME

The R^2 values for the models describing change in FEV_1 and FVC over time were very poor, ranging from 0.114 – 0.291. The ability of these models to predict the trajectory of change over this 1-year interval is limited, in comparison to the predictive capacity of the models constructed for static spirometry findings at TB treatment completion or 1-year. However, within these models spirometry at TB treatment completion emerged as a strong predictor of change over time. The 'catch up' phenomenon described in univariate analysis of the primary data above was observed again within multivariate models: on average those with 100ml lower baseline FEV1 volumes had an increase in FEV_1 volume which was 14ml (95% CI: 9 – 18ml) larger over 1-year, and those with 100ml lower baseline FVC volumes had an average increase which was 16ml (95% CI: 11-21ml) larger (Figure 31).

Figure 31: Observed and predicted values for change in FEV_1 and FVC (ml) over the 1-year follow up period, plotted by baseline spirometry measures at TB treatment completion. Predicted values derived from models controlling for participant characteristics and baseline imaging / lung function, with 95% Confidence intervals.



The same pattern of greater recovery amongst those with the more extensive parenchymal pathology at TB treatment completion was seen with imaging: in models controlling for participant characteristics, those with ≥1/3 abnormal parenchyma at TB treatment completion had a larger increase in FEV1 (72ml, 95% CI: 2 – 142ml) and FVC (110ml, 95% CI: 31 – 188ml) over the follow up period, compared to those without such marked damage at baseline. Again, when both spirometry and imaging at treatment completion were included together and 'controlled for' in models of change

over time, the relationship between imaging and change ceased to be statistically significant. No association between extensive bronchiectasis (moderate to severe pathology affecting ≥3 lobes) and change in either FEV_1 or FVC were seen in any of the models, including those in which bronchiectasis was the only imaging parameter of interest (not shown).

- IMPORTANCE OF ONGOING RESPIRATORY INFECTIONS

Controlling for participant characteristics +/- baseline lung pathology, the presence of ≥1 respiratory exacerbation and restarting TB treatment were negatively correlated with change in both FEV_1 and FVC over time and their final values at 1-year. However, this relationship was statistically significant for FVC only: controlling for participant characteristics and spirometry / imaging at TB treatment completion, individuals experiencing ≥1 respiratory exacerbation had an 80ml greater loss in FVC (95% CI: 6 – 154ml) and final FVC volumes which were on average 81ml smaller (95% CI: 6.5 – 155ml) at 1-year, compared to those without any exacerbations. However, the wide confidence intervals around these estimates must be noted.

5.3.12 RELATIONSHIP BETWEEN PTLD AND OUTCOMES

In this section the relationship between PTLD defined using the *a-priori* criteria outlined above, and adverse patient outcomes are described, using multivariate models controlling for participant characteristics.

Findings of exploratory analysis investigating the relationship between specific imaging / spirometry parameters at TB treatment completion and outcomes are also presented.

MODEL CONSTRUCTION

- A PRIORI PTLD

The prevalence of PTLD defined by spirometry criteria at TB treatment completion was 29.6% (108/365), including 73 individuals with Low FVC (FEV1/FVC ratio≥0.7 and FVC<LLN) and 35 individuals with moderate airway obstruction (FEV1/FVC ratio<LLN and FEV1<LLN).

The prevalence of CT based PTLD was 19.0% (73/385), including 29 individuals with moderate-severe bronchiectasis in ≥3 lobes, and 64 individuals with parenchymal abnormality of ≥1/3 of the lung tissue, excluding mosaicism, with an overlap between features seen in 20 individuals.

A total of 142 individuals had either CT or spirometry defined PTLD giving a prevalence of 35.1%, whilst 39/405 individuals had both CT and spirometry based PTLD giving a prevalence of 9.6% (Table 45).

Table 45: Relationship between the *a priori* PTLD groups defined by CT and spirometry findings

CT defined PTLD	Spirometry defined PTLD			TOTAL
	Absent	Present	Missing	
Absent	219	64	29	312
Present	27	39	7	73
Missing	11	5	4	20
TOTAL	257	108	40	405

Spirometry defined PTLD: Airway obstruction (FEV1/FVC ratio<LLN and FEV1<LLN), OR Low FVC (FEV1/FVC ratio≥0.7 and FVC<LLN)
CT defined PTLD: Moderate-severe bronchiectasis in ≥3 lobes, OR Parenchymal abnormality of ≥1/3 of the lung tissue
Dark green: Both CT and spirometry defined PTLD; Light green: Either CT or spirometry defined PTLD

- A TOTAL OF 349/405 STUDY PARTICIPANTS HAD BOTH VALID CT DATA AND VALID SPIROMETRY DATA AVAILABLE FROM TB TREATMENT COMPLETION. HIV-STATUS WAS MISSING FOR 2 OF THESE PATIENTS, SUCH THAT DATA FROM 347 PARTICIPANTS WAS AVAILABLE FOR INCLUSION IN THE MODELS OF PARTICIPANT OUTCOMES CONSTRUCTED HERE. OUTCOME EVENTS

The most common outcomes observed were the presence of impaired quality of life (37.2%, 137/368) and regular respiratory symptoms (30.7%, 113/368) at 1-year. Amongst those contributing either 1-year (n=364) or 6-months (n=16) of follow-up data, 16.3% (62/380) had ≥1 respiratory exacerbation and 3.9% (15/380) were restarted on TB treatment – these numbers were too low to perform a person-time analysis. 2.7% (11/404) of the cohort died during follow up (Table 46).

Table 46: Prevalence of adverse outcomes and description of data included in models

Outcome variable	Definition	Prevalence in total study population* N(%)	Outcome data included in logistic models^ N (%)
Quality of life	Prevalence of impaired quality of life (SGRQ total score >6), 1-year post TB treatment completion	137/368 (37.2%)	85/325
Chronic respiratory symptoms	Prevalence of self-reported cough OR sputum production OR breathlessness OR wheeze occurring at least monthly (several days/ week, or most days/week), 1-year post TB treatment completion.	113/368 (30.7%)	102/325
Acute respiratory exacerbation	Presence of ≥1 unscheduled visit to a health care provider (outpatient or inpatient) due to a respiratory complaint (cough, breathlessness, wheeze, sputum production) within the 1-year period	62/380 (16.3%)	56/335
TB retreatment	Initiation of TB retreatment within 1-year from TB treatment completion – including those with and without microbiological evidence of disease recurrence.	15/380 (3.9%)	13/347
Mortality	All-cause mortality within 1-year from TB treatment completion	11/404 (2.7%)	8/347

^Denominators for parameters measured at 1-year (Quality of life & Chronic respiratory symptoms) include participants completing the 1-year study visit (n=368);Denominator for parameters measured over time (Acute respiratory exacerbations & TB retreatment) include both those completing full 1-year follow-up (n=364) and those contributing 6-months of follow-up data (n=16); Denominator for mortality includes the full cohort, except 1-participant who was lost to follow up and whose vital status was not ascertained (n=404)

^Final models include only those with valid CT data, spirometry data, and HIV-status at TB treatment completion (maximum n=347), as well as those meeting conditions in previous column.

MODEL FINDINGS

Results for the multivariate models constructed to explore the relationship between PTLD and these outcomes, controlling for participant characteristics, are presented in Tables 47 – 51. Table 52 is a summary table that lists the correlation coefficients of the PTLD parameters included in the multivariate models constructed for each of the outcomes for comparison, together with specific imaging / spirometry variables included as predictors of outcome in exploratory models.

- PARTICIPANT CHARACTERISTICS PREDICTING ADVERSE OUTCOMES

HIV infection was associated with decreased odds of adverse respiratory outcomes at 1-year, regardless of CD4 count: controlling for other participant characteristics, HIV positive individuals were less likely to have an elevated SGRQ-total score at 1-year (CD4≥200: OR 0.28 (95% CI 0.15-0.55) / CD4<200: OR 0.36 (95% CI: 0.17-0.75)), less likely to have chronic respiratory symptoms at 1-year (CD4≥200: OR 0.31 (95% CI 0.17-0.58) / CD4<200: OR 0.36 (95% CI: 0.18-0.73)), and less likely to have experienced an acute respiratory episode by 1-year (CD4≥200: OR 0.40 (95% CI 0.19-0.82) / CD4<200: OR 0.29 (95% CI: 0.12-0.70)), compared to HIV negatives. No association was demonstrated between

HIV status and TB retreatment. Although HIV infection with CD4 count<200 cells/uL was associated with increased odds of death in the year following treatment completion in univariate analysis, this was not significant in multivariate models.

Higher levels of haemoglobin at TB treatment completion were associated with reduced odds of having an elevated SGRQ-total score (OR 0.79, 95% CI: 0.67-0.94) or chronic respiratory symptoms at 1-year (OR 0.82, 95% CI:0.70 – 0.97), as well as decreased odds of all-cause mortality over this year (OR 0.63, 95% CI 0.41 – 0.97).

No other participant characteristics were identified as clear predictors of adverse outcomes across the models, including demographic factors, socioeconomic status, and ever-smoking.

- PTLD AND PERSISTENT RESPIRATORY SYMPTOMS

Controlling for participant characteristics, the presence of respiratory symptoms occurring on a weekly or monthly basis 1-year after TB treatment completion was the outcome most widely associated with different measures of post-TB lung damage. In the primary analysis, the odds of persistent symptoms were 1.74 times higher in those who had had either spirometry or CT defined PTLD (95% CI:1.03 – 2.95) at treatment completion. In the secondary analysis, the odds of persistent symptoms were 3.65 times higher (95% CI: 1.62 – 8.22) in who met the criteria for both CT and spirometry defined PTLD at treatment completion.

In the exploratory analysis, moderate to severe bronchiectasis in ≥3 lobes was independently associated with ongoing symptoms at 1-year (OR 2.88, 95% CI: 1.16 – 7.10). The presence of moderate obstruction on spirometry at treatment completion was predictive of ongoing symptoms (OR 2.53, 95% CI: 1.15 – 5.59), and higher FEV_1 z-scores and FEV_1/FVC ratios at TB treatment completion were associated with decreased odds of persistent symptoms. Although FVC z-scores were associated with a reduction in symptoms, the OR for this relationship was not statistically significant.

- PTLD AND IMPAIRED QUALITY OF LIFE

In primary analysis, controlling for participant characteristics, the relationship between PTLD defined by either CT or spirometry criteria, and the presence of an increased SGRQ score at 1-year was not statistically significant (OR 1.54, 95% CI: 0.99 – 2.69). However, on secondary analysis, the odds of having a reduced quality of life at 1-year were 3.57 times higher in those who had had both extensive CT and spirometry abnormalities at TB treatment completion (95% CI: 1.55 – 8.25).

In the exploratory analysis conducted for this outcome, the imaging parameter which best predicted an impaired quality of life at 1-year was the presence of extensive parenchymal pathology of ≥1/3 parenchyma (OR2.19, 95% CI: 1.11 – 4.31) at treatment completion. Spirometry classified according

to the pattern of deficit was not independently associated with the outcome, but higher FEV_1 z-scores, FVC z-scores and FEV_1/FVC ratios were all protective against impaired quality of life.

- PTLD AND ACUTE RESPIRATORY EVENTS / TB RETREATMENT / ALL-CAUSE MORTALITY

Controlling for participant characteristics, no associations were observed between any measures of PTLD at TB treatment completion, and the occurrence of an acute respiratory event (n=56) or all-cause mortality (n=8) within the 1-year follow up period for the participants with full data who were included in the models (n=335/n=347). This was the case for both the broad PTLD groups specified *a-priori,* and parameters included in the exploratory analyses.

None of the *a-priori* PTLD definitions were associated with the initiation of TB retreatment during follow up, but an increase in FEV_1 z-score at treatment completion was associated with a reduction in the odds of TB retreatment during follow up of 43% (OR: 0.57, 95% CI: 0.34-0.96).

The potentially inflammatory pathologies (ground glass change, consolidation, nodules) were not associated with either TB retreatment or death during follow up. The presence of a destroyed lung lobe was not correlated with any of the outcomes measured.

PRESENCE OF REDUCED QUALITY OF LIFE AT 1-YEAR

Table 47: Logistic regression models for elevated (>6) vs. normal (≤6) SGRQ total score, at 1-year post TB treatment completion. OR (95% CI) presented. (n=325)

	Univariate analysis	Participant characteristics	+ Spiro PTLD	+ CT PTLD	+ Either PTLD^	+ Both PTLD$ (n=238)
Age (yrs)	1.01 (0.99 – 1.04)	1.01 (0.99 – 1.04)	1.02 (0.99 – 1.04)	1.01 (0.99 – 1.04)	1.01 (0.99 – 1.04)	1.01 (0.97 – 1.04)
Gender						
- Female	1.0	1.0	1.0	1.0	1.0	1.0
- Male	0.75 (0.45 – 1.28)	0.93 (0.44 – 1.97)	0.96 (0.45 – 2.04)	0.89 (0.42 – 1.90)	0.94 (0.44 – 2.00)	0.87 (0.35 – 2.14)
HIV status						
- Negative	1.0	1.0	1.0	1.0	1.0	1.0
- Positive, CD4≥200 cells/uL	0.42 (0.24 – 0.76)**	0.28 (0.15 – 0.55)***	0.30 (0.15 – 0.58)***	0.28 (0.14 – 0.54)***	0.29 (0.15 – 0.57)***	0.27 (0.12 – 0.60)**
- Positive, CD4<200 cells/uL	0.62 (0.33 – 1.15)	0.36 (0.17 – 0.75)**	0.39 (0.19 – 0.83)*	0.37 (0.18 – 0.78)**	0.40 (0.19 – 0.84)*	0.32 (0.14 – 0.715)**
Baseline TB microbiology						
- Negative	1.0	1.0	1.0	1.0	1.0	1.0
- Positive	0.88 (0.49 – 1.58)	0.77 (0.40 – 1.47)	0.78 (0.41 – 1.50)	0.78 (0.41 – 1.51)	0.77 (0.40 – 1.47)	0.61 (0.28 – 1.30)
BMI at TB treatment end (kg/m^2)	0.99 (0.91 – 1.09)	1.02 (0.93 – 1.13)	1.04 (0.94 – 1.14)	1.04 (0.95 – 1.15)	1.04 (0.94 – 1.14)	1.07 (0.95- 1.21)
Hb at TB treatment end(g/dL)	0.86 (0.75 – 0.97)*	0.79 (0.67 – 0.94)**	0.80 (0.66 – 0.94)**	0.79 (0.66 – 0.94)*	0.79 (0.66 – 0.94)**	0.80 (0.65 – 0.97)*
Ever smoking						
- Never	1.0	1.0	1.0	1.0	1.0	1.0
- Ever	1.11 (0.65 – 1.89)	1.22 (0.64 – 2.33)	1.27 (0.66 – 2.44)	1.18 (0.61 – 2.27)	1.24 (0.65 – 2.37)	1.50 (0.68 – 3.29)
Urban SES quintile						
- Least poor quintiles x2	1.0	1.0	1.0	1.0	1.0	1.0
- Poorest quintiles x3	1.10 (0.66 – 1.81)	1.01 (0.56 – 182)	0.96 (0.53 – 1.74)	0.97 (0.53 – 1.76)	0.96 (0.53 – 1.74)	0.78 (0.37 – 1.61)
Food insecurity						
- Never	1.0	1.0	1.0	1.0	1.0	1.0
- Sometimes / often	1.15 (0.68 – 1.93)	1.16 (0.63 – 2.11)	1.09 (0.60 – 2.01)	1.13 (0.61 – 2.08)	1.11 (0.61 – 2.04)	1.39 (0.65 – 2.96)
Spirometric PTLD#						
- No	1.0		1.0			
- Yes	1.78 (1.06 – 3.01)*		1.76 (0.99 – 3.13)			
CT PTLD#						
- No	1.0			1.0		
- Yes	1.85 (1.03 – 3.34)*			2.07 (1.09 – 3.96)*		
Either spiro or CT PTLD^						
- No	1.0				1.0	
- Yes	1.57 (0.95 – 2.60)				1.54 (0.88 – 2.69)	
Both spiro and CT PTLD$						
- No	1.0					1.0
- Yes	3.03 (1.46 – 6.31)**					3.57 (1.55 – 8.25)**

*p<.05, **p<.01, ***p<.001

#Spirometric PTLD: Airway obstruction (FEV1/FVC ratio<LLN and FEV1<LLN) / Low FVC (FEV1/FVC ratio≥0.7 and FVC<LLN) using GLI-2012 reference equations; CT PTLD: Moderate-severe bronchiectasis in ≥3 lobes / parenchymal abnormality of ≥1/3 of the lung tissue, excluding mosaicism

^Participants with either Spirometric and CT PTLD (n=121) at baseline compared to those with neither (n=198) at baseline

$Participants with both Spirometric and CT PTLD (n=36) at baseline compared to those with neither (n=198) at baseline

PRESENCE OF CHRONIC RESPIRATORY SYMPTOMS AT 1-YEAR

Table 48: Logistic regression models for chronic respiratory symptoms at 1-year, OR (95% CI) presented. (n=325).
Chronic respiratory symptoms defined as the presence of self-reported cough OR sputum production OR breathlessness OR wheeze occurring at least monthly (several days/ week, or most days/week)

	Univariate analysis	Participant characteristics	+ Spiro PTLD	+ CT PTLD	+ Either PTLD^	+ Both PTLD$ (n=238)
Age (yrs)	0.99 (0.97 – 1.02)	1.00 (0.97 – 1.02)	1.00 (0.97 – 1.02)	0.99 (0.97- 1.02)	0.99 (0.97 – 1.02)	0.97 (0.94 – 1.01)
Gender						
- Female	1.0	1.0	1.0	1.0	1.0	1.0
- Male	0.61 (0.37 – 1.00)	0.85 (0.42 – 1.71)	0.87 (0.43 – 1.77)	0.82 (0.40 – 1.66)	0.86 (0.42 – 1.73)	0.92 (0.40 – 2.16)
HIV status						
- Negative	1.0	1.0	1.0	1.0	1.0	1.0
- Positive, CD4>=200 cells/uL	0.46 (0.26 – 0.79)**	0.31 (0.17 – 0.58)***	0.33 (0.17 – 0.61)***	0.30 (0.16 – 0.56)***	0.32 (0.17 – 0.59)***	0.37 (0.17 – 0.78)**
- Positive, CD4<200 cells/uL	0.53 (0.29 – 0.98)*	0.36 (0.18 – 0.73)**	0.40 (0.20 – 0.82)*	0.37 (0.18 – 0.76)**	0.40 (0.20 – 0.83)*	0.41 (0.18 – 0.92)*
Baseline TB microbiology						
- Negative	1.0	1.0	1.0	1.0	1.0	1.0
- Positive	0.80 (0.46 – 1.40)	0.66 (0.36 – 1.22)	0.67 (0.36 – 1.24)	0.67 (0.36 – 1.25)	0.66 (0.36 – 1.22)	0.52 (0.25 – 1.08)
BMI at TB Rx end (kg/m^2)	1.01 (0.93 – 1.10)	1.04 (0.95 – 1.14)	1.07 (0.97 – 1.17)	1.07 (0.97 – 1.17)	1.07 (0.97 – 1.17)	1.06 (0.94 – 1.19)
Haemoglobin at TBRx end (g/dL)	0.88 (0.78 – 1.00)	0.82 (0.70 – 0.97)*	0.82 (0.70 – 0.97)*	0.82 (0.69 – 0.97)*	0.82 (0.69 – 0.97)	0.85 (0.70 – 1.02)
Ever smoking						
- Never	1.0	1.0	1.0	1.0	1.0	1.0
- Ever	0.83 (0.49 – 1.39)	0.93 (0.50 – 1.73)	0.98 (0.52 – 1.84)	0.89 (0.47 – 1.66)	0.94 (0.50 – 1.75)	1.20 (0.57 – 2.54)
Urban SES quintile						
- Least poor quintiles x2	1.0	1.0	1.0	1.0	1.0	1.0
- Poorest quintiles x3	1.25 (0.78 – 2.02)	1.39 (0.80 – 2.42)	1.32 (0.75 – 2.31)	1.3 (0.77– 2.37)	1.32 (0.75 – 2.30)	1.18 (0.60 – 2.32)
Food insecurity						
- Never	1.0	1.0	1.0	1.0	1.0	1.0
- Sometimes / often	1.08 (0.66 – 1.76)	1.00 (0.57 – 1.77)	0.93 (0.52 – 1.66)	0.98 (0.55 – 1.75)	0.96 (0.54 – 1.70)	1.01 (0.49 – 2.06)
Spirometric PTLD#						
- No	1.0		1.0			
- Yes	2.19 (1.33 – 3.61)**		2.11 (1.22– 3.65)*			
CT PTLD#						
- No	1.0			1.0		
- Yes	1.72 (0.97 – 3.04)			2.03 (1.09 – 3.80)*		
Spiro or CT PTLD^						
- No	1.0				1.0	
- Yes	1.75 (1.09 – 2.83)*				1.74 (1.03 – 2.95)	
Spiro and CT PTLD$						
- No	1.0					1.0
- Yes	3.43 (1.66 – 7.09)**					3.65 (1.62 – 8.22)**

*p<.05, **p<.01, ***p<.001

#Spirometric PTLD: Airway obstruction (FEV1/FVC ratio<LLN and FEV1<LLN) / Low FVC (FEV1/FVC ratio≥0.7 and FVC<LLN) using GLI-2012 reference equations

#CT PTLD: Moderate-severe bronchiectasis in ≥3 lobes / parenchymal abnormality of ≥1/3 of the lung tissue, excluding mosaicism

^Participants with either Spirometric and CT PTLD (n=121) at baseline compared to those with neither (n=198) at baseline

$Participants with both Spirometric and CT PTLD (n=36) at baseline compared to those with neither (n=198) at baseline

≥1 ACUTE RESPIRATORY EPISODE OVER 1-YEAR

Table 49: Logistic regression models for the presence / absence of ≥1 acute respiratory episode in the 1-year follow period amongst those contributing 6-12m follow up person time (n=335). OR (95% CI) presented.

	Univariate analysis	Participant characteristics	+ Spiro PTLD	+ CT PTLD	+ Either PTLD^	+ Both PTLD[$] (n=247)
Age (yrs)	1.01 (0.99 – 1.04)	1.02 (0.99 – 1.05)	1.03 (1.00 – 1.06)	1.02 (0.99 – 1.05)	1.02 (0.99 – 1.05)	1.01 (0.97- 1.05)
Gender						
- Female	1.0	1.0	1.0	1.0	1.0	1.0
- Male	0.78 (0.42 – 1.42)	1.13 (0.49 – 2.58)	1.16 (0.50 – 2.68)	1.10 (0.48 – 2.53)	1.14 (0.49 – 2.64)	1.72 (0.61 – 4.81)
HIV status						
- Negative	1.0	1.0	1.0	1.0	1.0	1.0
- Positive, CD4>=200 cells/uL	0.51 (0.26 – 1.00)*	0.40 (0.19 – 0.82)*	0.41 (0.20 – 0.86)	0.39 (0.19 – 0.81)*	0.41 (0.20 – 0.85)*	0.50 (0.20 – 1.26)
- Positive, CD4<200 cells/uL	0.50 (0.23 – 1.06)	0.29 (0.12 – 0.70)**	0.32 (0.13 – 0.77)	0.30 (0.12 – 0.71)**	0.33 (0.13 – 0.80)*	0.37 (0.14 – 1.02)
Baseline TB microbiology						
- Negative	1.0	1.0	1.0	1.0	1.0	1.0
- Positive	1.05 (0.52 – 2.11)	1.17 (0.55 – 2.51)	1.20 (0.56 – 2.56)	1.19 (0.56 – 2.54)	1.17 (0.55 – 2.50)	1.03 (0.43 – 2.49)
BMI at TB treatment end (kg/m^2)	0.98 (0.89 – 1.09)	0.99 (0.89 – 1.11)	1.01 (0.90 – 1.13)	1.01 (0.90 – 1.13)	1.01 (0.91 – 1.13)	0.99 (0.86 -1.15)
Hb at TB treatment end (g/dL)	0.90 (0.78 – 1.04)	0.84 (0.70 – 1.01)	0.84 (0.70 – 1.01)	0.83 (0.69 – 1.00)	0.83 (0.69 – 1.00)	0.79 (0.63 – 0.98)
Ever smoking						
- Never	1.0	1.0	1.0	1.0	1.0	1.0
- Ever	0.61 (0.31 – 1.22)	0.58 (0.26 – 1.26)	0.59 (0.27 – 1.31)	0.56 (0.25 – 1.24)	0.58 (0.26 – 1.28)	0.60 (0.23 – 1.56)
Urban SES quintile						
- Least poor quintiles x2	1.0	1.0	1.0	1.0	1.0	1.0
- Poorest quintiles x3	0.77 (0.43 – 1.36)	0.73 (0.38 – 1.43)	0.69 (0.35 – 1.36)	0.72 (0.37 – 1.41)	0.69 (0.35 – 1.35)	0.76 (0.33 – 1.73)
Food insecurity						
- Never	1.0	1.0	1.0	1.0	1.0	1.0
- Sometimes / often	0.92 (0.50 – 1.69)	1.00 (0.49 – 2.02)	0.94 (0.46 – 1.92)	0.98 (0.48 – 2.00)	0.94 (0.46 – 1.91)	0.65 (0.25 – 1.71)
Spirometric PTLD[#]						
- No	1.0		1.0			
- Yes	1.76 (0.97 – 3.20)		1.73 (0.90 – 3.34)			
CT PTLD[#]						
- No	1.0			1.0		
- Yes	1.38 (0.69 – 2.77)			1.53 (0.72 – 3.24)		
Either spiro or CT PTLD^						
- No	1.0				1.0	
- Yes	1.75 (0.98 – 3.12)				1.74 (0.92 – 3.31)	
Both spiro and CT PTLD[$]						
- No	1.0					1.0
- Yes	1.79 (0.75 – 4.31)					1.96 (0.74 – 5.18)

*p<.05, **p<.01, ***p<.001

[#]Spirometric PTLD: Airway obstruction (FEV1/FVC ratio<LLN and FEV1<LLN) / Low FVC (FEV1/FVC ratio≥0.7 and FVC<LLN) using GLI-2012 reference equations

[#]CT PTLD: Moderate-severe bronchiectasis in ≥3 lobes / parenchymal abnormality of ≥1/3 of the lung tissue, excluding mosaicism

^Participants with either Spirometric and CT PTLD (n=121) at baseline compared to those with neither (n=198) at baseline [$]Participants with both Spirometric and CT PTLD (n=36) at baseline compared to those with neither (n=198) at baseline

INITIATION OF TB RETREATMENT DURING 1-YEAR

Table 50: Logistic regression models for TB retreatment (n=13) within the year follow-up (n=347). OR (95% CI) presented.

	Univariate analysis	Participant characteristics	+ Spiro PTLD	+ CT PTLD	+ Either PTLD	+ Both PTLD (n=256)
Age (yrs)	1.00 (0.95 – 1.06)	0.98 (0.92 – 1.05)	0.99 (0.92 – 1.05)	0.98 (0.92 – 1.05)	0.98 (0.91 – 1.05)	0.96 (0.87 – 1.06)
Gender						
- Female	1.0	1.0	1.0	1.0	1.0	1.0
- Male	1.53 (0.41 – 5.67)	3.40 (0.58 – 19.71)	3.73 (0.62 – 22.43)	3.44 (0.58 – 20.54)	3.75 (0.61 – 22.97)	18.77 (1.36 – 259.01)*
HIV status						
- Negative	1.0	1.0	1.0	1.0	1.0	1.0
- Positive, CD4>=200 cells/uL	0.64 (0.15 – 2.74)	0.64 (0.13 – 3.08)	0.69 (0.14 – 3.33)	0.62 (0.13 – 2.99)	0.69 (0.14 – 3.32)	0.25 (0.03 – 2.12)
- Positive, CD4<200 cells/uL	1.49 (0.42 – 5.30)	0.95 (0.20 – 4.58)	1.09 (0.22 – 5.43)	0.96 (0.20 – 4.63)	1.14 (0.22 – 5.84)	0.24 (0.03 – 2.13)
Baseline TB microbiology						
- Negative	1.0	1.0	1.0	1.0	1.0	1.0
- Positive	1.57 (0.34 – 7.22)	1.99 (0.38 – 10.46)	2.07 (0.40 – 10.78)	1.99 (0.38 – 10.34)	2.02 (0.39 – 10.48)	4.85 (0.42 – 55.68)
BMI at TB treatment completion (kg/m^2)	0.77 (0.59 – 1.00)	0.84 (0.63 – 1.10)	0.86 (0.65 – 1.14)	0.86 (0.65 – 1.13)	0.86 (0.65 – 1.14)	0.75 (0.50 – 1.12)
Haemoglobin at TB treatment completion (g/dL)	0.75 (0.58 – 0.96)	0.68 (0.50 – 0.92)	0.67 (0.49 – 0.92)	0.66 (0.48 – 0.91)*	0.67 (0.48 – 0.92)	0.54 (0.34 – 0.86)**
Ever smoking						
- Never	1.0	1.0	1.0	1.0	1.0	1.0
- Ever	1.04 (0.31 – 3.46)	0.85 (0.22 – 3.34)	0.88 (0.22 – 3.47)	0.83 (0.21 – 3.31)	0.86 (0.22 – 3.39)	0.26 (0.04 – 1.80)
Urban SES quintile						
- Least poor quintiles x2	1.0	1.0	1.0	1.0	1.0	1.0
- Poorest quintiles x3	1.11 (0.34 – 3.56)	1.20 (0.30 – 4.80)	1.14 (0.29 – 4.55)	1.16 (0.29 – 3.31)	1.14 (0.28 – 4.54)	0.74 (0.12 – 4.69)
Food insecurity						
- Never	1.0	1.0	1.0	1.0	1.0	1.0
- Sometimes / often	0.91 (0.27 – 3.00)	0.75 (0.17 – 3.18)	0.66 (0.15 – 2.91)	0.71 (0.16 – 3.06)	0.66 (0.15 – 2.92)	1.61 (0.24 – 10.74)
Spirometric PTLD[#]						
- No	1.0		1.0			
- Yes	2.09 (0.69 – 6.39)		2.08 (0.58 – 7.40)			
CT PTLD[#]						
- No	1.0			1.0		
- Yes	1.95 (0.58 – 6.54)			1.78 (0.48 – 6.60)		
Either spiro or CT PTLD^						
- No	1.0				1.0	
- Yes	2.00 (0.66 – 6.09)				2.09 (0.59 – 7.34)	
Both spiro and CT PTLD[$]						
- No	1.0					1.0
- Yes	2.93 (0.70 – 12.25)					1.84 (0.36 – 9.50)

*p<.05, **p<.01, ***p<.001

[#]Spirometric PTLD: Airway obstruction (FEV1/FVC ratio<LLN and FEV1<LLN) / Low FVC (FEV1/FVC ratio≥0.7 and FVC<LLN) using GLI-2012 reference equations

[#]CT PTLD: Moderate-severe bronchiectasis in ≥3 lobes / parenchymal abnormality of ≥1/3 of the lung tissue, excluding mosaicism

^ Participants with either Spirometric and CT PTLD (n=121) at baseline compared to those with neither (n=198) at baseline

[$]Participants with both Spirometric and CT PTLD (n=36) at baseline compared to those with neither (n=198) at baseline

ALL-CAUSE MORTALITY DURING 1-YEAR

Table 51: Logistic regression models for death (n=8) within the year follow-up (n=347), OR (95% CI) presented.

	Univariate analysis	Participant characteristics	+ Spiro PTLD	+ CT PTLD	+ Either PTLD	+ Both PTLD (n=256)
Age (yrs)	1.04 (0.99 – 1.11)	1.02 (0.94 – 1.11)	1.02 (0.94 – 1.11)	1.02 (0.94 – 1.11)	1.02 (0.94 – 1.11)	1.05
Gender - Female - Male	1.0 1.36 (0.27 – 6.87)	1.0 1.26 (0.13 – 12.64)	1.0 1.24 (0.12 – 12.58)	1.0 1.28 (0.13 – 12.55)	1.0 1.21 (0.12 – 12.05)	1.0 0.64 (0.05- 8.51)
HIV status - Negative - Positive, CD4>=200 cells/uL - Positive, CD4<200 cells/uL	1.0 1.08 (0.07 – 17.49) 9.32 (1.10 – 78.76)*	1.0 0.75 (0.04 – 13.29) 3.73 (0.34 – 41.05)	1.0 0.74 (0.04 – 13.19) 3.64 (0.32 – 41.17)	1.0 0.82 (0.05 – 14.80) 3.88 (0.34 – 43.88)	1.0 0.72 (0.04 – 12.74) 3.36 (0.30 – 38.08)	1.0 0.54 (0.03 – 10.46) 1.99 (0.16 – 25.00)
Baseline TB microbiology - Negative - Positive	1.0 0.27 (0.07 – 1.10)	1.0 0.37 (0.07 – 1.91)	1.0 0.37 (0.07 – 1.91)	1.0 0.38 (0.07 – 2.04)	1.0 0.38 (0.07 – 1.99)	1.0 0.61 (0.09 – 4.11)
BMI at TB treatment completion (kg/m^2)	0.69 (0.49 – 0.98)*	0.73 (0.49 – 1.07)	0.72 (0.49 – 1.08)	0.71 (0.47 – 1.07)	0.72 (0.48 – 1.07)	0.56 (0.32 – 0.97)
Haemoglobin at TB treatment completion (g/dL)	0.57 (0.41 – 0.80)**	0.63 (0.41 – 0.97)*	0.63 (0.41 – 0.97)	0.64 (0.41 – 0.98)*	0.63 (0.41 – 0.98)	0.71 (0.41 – 1.23)
Ever smoking - Never - Ever	1.0 0.77 (0.15 – 3.90)	1.0 1.00 (0.14 – 6.91)	1.0 0.99 (0.14 – 6.90)	1.0 0.94 (0.13 – 6.59)	1.0 0.96 (0.14 – 6.73)	1.0 0.39 (0.03 – 4.74)
Urban SES quintile - Least poor quintiles x2 - Poorest quintiles x3	1.0 0.61 (0.13 – 2.77)	1.0 0.86 (0.15 – 4.95)	1.0 0.89 (0.14 – 5.61)	1.0 0.96 (0.15 – 5.95)	1.0 0.98 (0.15 – 6.29)	1.0 0.53 (0.06 – 4.81)
Food insecurity - Never - Sometimes / often	n/a no deaths amongst those missing meals					
Spirometric PTLD[#] - No - Yes	1.0 0.79 (0.16 – 3.96)		1.0 0.88 (0.12 – 6.43)			
CT PTLD[#] - No - Yes	1.0 0.60 (0.07 – 4.98)			1.0 0.49 (0.05 – 5.14)		
Either spiro or CT PTLD^ - No - Yes	1.0 0.55 (0.11 – 2.76)				1.0 0.63 (0.09 – 4.33)	
Both spiro and CT PTLD[$] - No - Yes	1.0 0.93 (0.11 – 7.91)					1.0 0.46 (0.04 – 5.58)

*p<.05, **p<.01, ***p<.001

[#]Spirometric PTLD: Airway obstruction (FEV1/FVC ratio<LLN and FEV1<LLN) / Low FVC (FEV1/FVC ratio≥0.7 and FVC<LLN) using GLI-2012 reference equations

[#]CT PTLD: Moderate-severe bronchiectasis in ≥3 lobes / parenchymal abnormality of ≥1/3 of the lung tissue, excluding mosaicism

^Participants with either Spirometric and CT PTLD (n=121) at baseline compared to those with neither (n=198) at baseline

[$]Participants with both Spirometric and CT PTLD (n=36) at baseline compared to those with neither (n=198) at baseline

SUMMARY TABLE FOR ALL MODELS: PTLD CORRELATION COEFFICIENTS ONLY

Table 52: Correlation coefficients from multivariate models for each outcome, including ORs for PTLD parameters controlling for participant characteristics

Category of exposure	PTLD measure	SGRQ ≥6[#] (n=85/325)	Chronic respiratory symptoms[#] (n=102/325)	≥1 acute respiratory event in 1-year^ (n=56/335)	TB retreatment[§] (n=13/347)	Death[§] (n=8/347)
Composite PTLD exposures, at TB treatment completion *Primary analysis	Spiro PTLD	1.76 (0.99 – 3.13)	2.11 (1.22 – 3.65)**	1.73 (0.90 – 3.34)	2.08 (0.58 – 7.40)	0.88 (0.12 – 6.43)
	CT PTLD	2.07 (1.09 – 3.96)*	2.03 (1.09 – 3.80)*	1.53 (0.72 – 3.24)	1.78 (0.48 – 6.60)	0.49 (0.05 – 5.14)
	Either Spiro OR CT PTLD	1.54 (0.99 – 2.69)	1.74 (1.03 – 2.95)*	1.74 (0.92-3.31)	2.09 (0.59 – 7.34)	0.63 (0.09 – 4.33)
	Both Spiro and CT PTLD	3.57 (1.55 – 8.25)** n=238	3.65 (1.62 – 8.22)** n=238	1.96 (0.74 – 5.18) n=247	1.84 (0.36 – 9.50) n=256	0.46 (0.04 – 5.58) n=256
Imaging parameters, at TB treatment completion	Total extent of abnormal parenchyma (0-600)	1.00 (1.00 – 1.00)	1.00 (1.00 -1.00)	1.00 (1.00 -1.00)	1.00 (1.00 -1.00)	0.98 (0.99 – 1.00)
	>1/3 Abnormal parenchyma	2.19 (1.11 – 4.31)*	1.82 (0.94 – 3.54)	1.46 (0.66 – 3.25)	2.21 (0.59 – 8.30)	0.61 (0.06 – 6.49)
	Number of lobes containing moderate–severe bronchiectasis (0-6)	1.21 (0.96 – 1.53)	1.19 (0.94 – 1.49)	1.06 (0.80 – 1.39)	1.40 (0.91 – 2.14)	0.80 (0.36 – 1.77)
	Mod-severe bronchiectasis in ≥3 lobes	2.37 (0.94 – 6.00)	2.88 (1.16 – 7.10)*	1.65 (0.58 – 4.72)	3.49 (0.75 – 16.18)	1.40 (0.11 – 18.66)
	Whole lung bronchiectasis severity score (0-18)	1.07 (0.98 – 1.17)	1.04 (0.95 – 1.13)	0.97 (0.87 – 1.08)	1.09 (0.92 – 1.28)	0.92 (0.70 – 1.20)
	≥1 destroyed lobe	0.63 (0.24 – 1.64)	0.62 (0.25 – 1.55)	0.58 (0.18 – 1.81)	1.88 (0.36 – 9.78)	No deaths amongst those with >=1 lobe destroyed
	Total extent of ground glass and consolidation (0-600)				1.00 (0.99 – 1.02)	0.99 (0.97 – 1.02)
	Ground glass and consolidation affecting ≥half a lobe				2.23 (0.50 – 9.89)	0.48 (0.04 – 5.87)
	Nodules confirmed by 2 original readers / consensus reader				4.45 (0.89 – 22.2)	0.62 (0.12 – 3.20)
Spirometric parameters, at TB treatment completion	Moderate obstruction	1.82 (0.80 – 4.11)	2.53 (1.15 – 5.59)*	1.31 (0.50 – 3.41)	1.61 (0.30 – 8.60)	1.00 (0.09 – 11.48)
	Low FVC	1.43 (0.75 – 2.73)	1.49 (0.80 – 2.75)	1.69 (0.82 – 3.47)	1.79 (0.46 – 6.99)	0.84 (0.08 – 9.38)
	FEV1 z-score	0.68 (0.54 – 0.86)**	0.73 (0.58 – 0.90)**	0.79 (0.61 – 1.02)	0.57 (0.34 – 0.96)*	0.88 (0.42 – 1.85)
	FVC z-score	0.76 (0.61 – 0.96)*	0.83 (0.67 – 1.03)	0.83 (0.63 – 1.07)	0.66 (0.41 – 1.08)	1.13 (0.54 – 2.39)
	FEV1/FVC ratio	0.96 (0.93 – 0.99)**	0.96 (0.93 – 0.99)**	0.98 (0.95 – 1.02)	0.97 (0.91 – 1.03)	0.97 (0.89 – 1.05)

*p<.05, **p<.01, ***p<.001

[#]Participants with CT and valid spirometry at baseline, who completed 1-year study visit, with symptom and QoL data available (n=325)

^Participants with CT and valid spirometry at baseline, who contributing any duration of follow up data – 6m or 12m (n=335)

[§]Participants with CT and valid spirometry at baseline (n=347)

5.3.13 HEALTH ECONOMIC DATA

This chapter has thus far focused on the burden of clinical and respiratory morbidity following PTB disease. In this section data on the economic impact of PTB disease will be reviewed.

ECONOMIC SITUATION AT TB TREATMENT COMPLETION

Table 53: Socioeconomic situation of study participants at TB treatment completion, stratified by baseline microbiology (n=405)

Characteristic	Total (n=405)	Micro –ve (n=92)	Micro +ve (n=313)	p-value
Occupation				
- Unemployed	148 (36.5%)	33 (35.9%)	115 (36.7%)	0.695
- Student	33 (8.2%)	5 (5.4%)	28 (9.0%)	
- Self employed / business person	109 (26.9%)	28 (30.4%)	81 (25.9%)	
- Employed – Gov / NGO / private	109 (26.9%)	24 (26.1%)	85 (27.2%)	
- Other	6 (1.5%)	2 (2.2%)	4 (1.3%)	
Monthly individual income (USD)* (n=402)	41.32 (11.02 – 96.42)	55.20 (16.53 – 110.19)	41.32 (11.02 – 96.42)	0.337
Monthly household income (USD)*(n=285)	85.40 (44.08 – 192.84)	104.68 (42.70 – 192.84)	82.64 (44.08 – 192.84)	0.856
Dissaving incurred during treatment				
- No	107 (26.4%)	27 (29.4%)	80 (25.6%)	0.469
- Yes	298 (73.6%)	65 (70.7%)	233 (74.4%)	
Amount of dissaving incurred ($ USD)* (n=283)	59.23 (20.66 – 137.74)	68.87 (39.60 – 137.74)	53.03 (19.29 – 137.74)	0.032*

*p<.05, **p<.01, ***p<.001

- INCOME AND OCCUPATION

Median monthly individual income across the cohort was the equivalent of $41.32 per week (IQR: $11.02 – 96.42) at TB treatment completion, and just over half (54.6% (221/405)) the participants were the highest earner in their household. Only 285 individuals were able to report their household income at the point of TB treatment completion – reporting was gender biased with 75.6% of men (208/275) and only 59.2% (77/130) aware of this figure. Where current household income was given, the median figure was $85.40 per month (IQR: $44.08 – 192.84) (Table 53).

Over one third of participants were unemployed (36.5% (148/405)) at the point of TB treatment completion. Of note, even participants who were reported as unemployed within our study reported some income – this was mainly derived from intermittent piecework or money given to them from family or community members. The median income amongst the unemployed at treatment completion was $11.02 per month (IQR: 0 – 38.57).

- DISSAVING

Almost three quarters of the cohort (73.6% (298/405)) had experienced some dissaving between the onset of TB illness to the point of TB Treatment completion, with a median value of $59.23 (20.66 – 137.74). This money had been obtained from the use of household savings in 44.7% (181/405),

borrowing money in 43.7% (177/405), and selling household property to cover illness related costs in 32.6% (132/405). Household items, mobile phones, and means of transport were the most common items sold. The median amount of dissaving across the whole cohort was $27.55 (IQR: $0 – 97.38). There was a strong socioeconomic gradient to this dissaving: amongst the poorest quintile 90.2% (20/22) experienced dissaving with a median amount of $33.06 (IQR: $13.77 – 99.17), compared to the richest quintile where dissaving was experienced by 50% only but at a higher amount of $165.29 ($93.66 – 419.42). An indication of the impact of dissaving on family wellbeing is that 17.0% (69/405) reported that at least one child in the family had had either dropped out of school or had their schooling interrupted over the last year due to the participant's illness. The gender distribution amongst the first child pulled out was approximately equal (46.4% female / 53.6% male), and the mean age was 12.9yrs (SD 4.6yrs).

COSTS INCURRED DURING 1-YEAR FOLLOW-UP

- DIRECT COSTS

The majority of both outpatient visits (95.0%, 415/437) and inpatient admissions (88.9%, 24/27) occurred within the public sector, where care is free at the point of delivery. Nevertheless, direct costs were incurred by participants in 63.3%, 68.8%, and 100% of the planned outpatient, unscheduled outpatient, and inpatient events respectively (Table 54).

Table 54: Median direct costs incurred (US $) for each type of study visit*

Cost description	Planned OPD visits (n=264)		Unscheduled OPD visits (n=173)		Inpatient admissions (n=27)	
	Incurred (n, %)	Amount, if cost incurred ($USD) (median, IQR)	Incurred (n, %)	Amount, if cost incurred ($USD) (median, IQR)	Incurred (n, %)	Amount, if cost incurred ($USD) (median, IQR)
Clinic fees	2 (0.8%)	0.34 (0.28 – 0.41)	13 (7.5%)	0.69 (0.34 – 2.75)	3 (11.1%)	9.64 (6.89 -43.33)
Medication	3 (1.1%)	2.07 (0.62 – 4.41)	18 (10.4%)	2.41 (1.03 – 2.89)	2 (7.4%)	41.32 (27.55 – 55.10)
Travel	141 (53.4%)	0.83 (0.69 – 1.10)	103 (59.5%)	0.96 (0.69 – 1.65)	26 (96.3%)	7.85 6.89 – 11.71
Accommodation	0	n/a	0	n/a	2 (7.4%)	35.47 (8.95 – 61.98)
Food	40 (15.2%)	0.38 (0.28 – 0.69)	54 (31.2%)	0.65 (0.34 – 0.69)	27 (100%)	9.23 (5.23 – 15.15)
Airtime	82 (31.1%)	0.21 (0.14 – 0.28)	57 (33.0%)	0.28 (0.14 – 0.28)	23 (85.2%)	1.03 (0.55 – 1.79)
Any direct costs	167 (63.3%)	0.96 (0.55 – 1.38)	119 (68.8%)	1.38 (0.83 – 2.75)	27 (100%)	19.56 (13.57 – 55.79)

*Costs reported in Malawi Kwacha and converted into US Dollars using the exchange rate from the study mid point (March 2017, $1 USD: 726MK)

Costs per visit were on average limited for outpatient visits: when these were incurred, median values were between $0.96 – $1.38 USD. Inpatient admissions were much more expensive with median cost $19.56 (IQR: $13.57 – 55.79). Median expenses were $17.22 (IQR: 12.67 – 19.97) in non-retreatment

admissions, and $54.55 (IQR: 33.75 – 72.73) in retreatment related stays. If direct health care costs incurred over the 1-year period were calculated at an individual level, rather than on a per-visit basis, on average individuals who contributed a full year of follow-up data (n=364) had costs of $0.21 (IQR: 0 - $1.72) over the course of follow-up.

- INDIRECT COSTS

The median amount of time taken for any outpatient appointment was 3 hours (IQR: 2-4hrs). Participants were asked whether they had lost any income time – that is, time when they would have been working – as a result of the visit, and the answer was positive for just 56.4% (149/264) outpatient episodes. Where any income time was lost, the amount of time lost was minimal (median 1 hour (IQR: 0 – 1 hrs) (Table 55).

Table 55: Indirect costs incurred by participants and guardians at each type of health seeking episode, with average amount spent when cost was incurred

Variable	Planned OPD visit (n=264)	Unscheduled OPD visits (n=173)	Inpatient admissions (n=27)
Time taken for visit (median, IQR)	3 hours (2-3)	3 hours (2-4)	4 nights (2-19)
Any loss of income time reported (n, %)	149 (56.4%)	83 (48.0%)	8 (29.6%)
Self-reported income hours lost, if yes	1 hour (1-2)	2 hours (1-2)	74.5 hours (28-664)
Attendance by guardian	4 (1.5%)	32 (18.5%)	24 (88.9%)
Reported loss of income time by guardian (n, %)	0 (0%)	2 (6.3%)	1 (4.1%)
Reported income hours lost by guardian, if yes	0 hours	2 hours (2-2)	4 hours (4-4)

Although the average duration of admissions experienced during follow up was 4 nights (IQR: 2-19 nights), under a third of participants reported missing income time during the admission period. This difference may be related to gender: 63% (276/437) outpatient episodes were amongst men, but 67% (18/27) of admissions were seen in women, and women were less likely to report loss of income time compared to men (11% vs. 67%). The male dominance of outpatient visits may explain the higher prevalence of income time lost here.

Our data show that a guardian accompanied the unwell participant for only 4/264 planned and 32/173 unscheduled outpatient visits, and that loss of income time for guardians was rare and limited during these episodes. Although a higher proportion of admissions were accompanied by a guardian (24/27), again only 1 reported a loss of income during this time.

Per person, amongst participants contributing full follow up data within this study (n=364), income time was lost in relation to ongoing health seeking by 44.2% (161/364), and the median amount of time lost for each of these individuals was 2 hours (IQR: 1 – 3). Income time was lost by guardians to 3/364 of these individuals, and the median amount of time lost by guardians in these cases was 2 hours (IQR 2- 4).

FINANCIAL IMPACT OF TB DISEASE

- INCOME AND EMPLOYMENT

A general decline was observed across all income and employment variables from the period prior to TB related illness to the point of TB treatment completion, with a gradual but incomplete recovery over the subsequent year (Table 56).

Table 56: Self-reported occupation and income prior to TB related illness, after treatment, and 1-year after this

Variable	Prior to PTB disease (n=405)~	TB treatment completion (n=405)#	1-year post treatment completion (n=368)#	p-value
Occupation (n, %) - Unemployed - Student - Self-employed - Employed – Gov / NGO / Private - Other	 76 (18.8%) 35 (8.6%) 133 (32.8%) 154 (38.0%) 7 (1.7%)	 148 (36.5%) 33 (8.2%) 109 (26.9%) 109 (26.9%) 6 (1.5%)	 110 (29.9%) 24 (6.5%) 95 (25.8%) 117 (31.8%) 22 (6.0%)	<0.001***
Monthly individual income (USD)^	55.10 (20.39 – 132.23)	41.32 (11.02- 96.42)	43.53 (0.0 – 104.68)	0.002**
Monthly household income (USD)^§	126.72 (66.12 – 231.41) n=283	85.40 (44.08 – 192.84) n=285	93.66 (49.59 – 154.27) n=267	<0.001***
Individual as primary earner in household (n, %)	231 (57.0%)	221 (54.6%)	223 (60.6%)	0.237

*p<.05, **p<.01, ***p<.001
~Data collected at baseline study visit at TB treatment completion, with participants asked to recall situation prior to illness
#Data collected contemporaneously at study visits at TB treatment completion / 1-year later
^Income data collected in Malawi Kwacha, but standardized using exchange rate at study midpoint ($1 USD: 726MK, March 2017)
§Household income data available for 76.7% (633/825) of data points collected amongst men, and 51.8% (202/390) of data points collected amongst women, due to limited participant recall

The proportion of individuals who were unemployed increased from 18.8% prior to illness to 36.5% at the point of TB treatment completion. Although both the number and proportion of individuals who were unemployed did subsequently decline in the 1-year period following TB treatment, still almost 1/3rd of participants remained unemployed at the end of follow-up. Many individuals categorized as 'unemployed' were however working in the informal sector with some income from piece work, or from money provided to them by friends and family, but the median individual income in individuals reporting unemployment at any of the data collection time points was $0 (IQR $0 - 38.02) per month.

Self-reported individual and household incomes followed the same pattern: median individual earnings fell from $55.10 pre illness to $41.32 at treatment completion and rose to $43.53 one year later; median household income fell from $126.72 prior to the start of the TB illness episode to $85.40 at TB treatment completion, before recovering to $93.66 one year later. For both individual and household income, recovery was incomplete and even at 1-year earnings were not back to baseline. The proportion of participants who were the primary earner in the household remained broadly similar across this period.

- DISSAVING

In the year prior to TB treatment completion, almost ¾ of the cohort had experienced some dissaving (72.6%, 298/405). Amongst these participants, dissaving generated a median of $59 (IQR: $21 – 138) (Table 57), which on average equated to 66% (IQR: 30 – 172%) of the monthly income for the household at TB treatment completion for this group, amongst those for whom household income was known (n=221). The proportion of individuals experiencing dissaving due to illness was lower in the year following TB treatment (50.5%, 186/368). Amongst these individuals, the median total amount generated was $41 (IQR: $21 – 94), or 72% (IQR: 27 – 161%) of the monthly household income at TB treatment completion amongst those for whom household income was known (n=143).

The most common form of dissaving in the year prior to TB treatment completion was the use of savings in 44.7% (181/405) of participants. The proportion of individuals still able or choosing to use this method of dissaving in the year after treatment completion fell to 4.6% (17/368). In contrast, borrowing money was common throughout the 2-year period, with no significant change in the proportion of individuals using this approach in the first and second year (43.7% vs. 39.7%, p=0.257). Friends and family were common sources of funds, but the black market was also frequently used: 10.7% of those borrowing money prior to TB treatment completion and 17.1% of those borrowing money thereafter used this source. 32.6% of individuals sold assets to generate funds in the year prior to TB treatment completion and 23.6% of participants in the subsequent year. Household goods and phones were the most common items sold, but the sale of potentially income generating assets including land, livestock, and means of transport were also observed.

Dissaving was more common in poorer wealth quintiles: it was seen in 90.9% (20/22) of the poorest vs. 50.0% (28/56) of the least poor quintile in the year prior to treatment completion, and 59.1% (13/22) of the poorest vs. 21.8% (12/56) of the least poor quintile in the year following treatment completion. Use of savings was the most common form of dissaving in the highest socioeconomic quintile, and was still being used by 9.1% in the year following TB treatment completion, whilst no individuals in the poorest two quartiles used savings to release funds by this second year. The average absolute amounts of money released by dissaving were similar between quintiles, ranging from $33.75 – 50.96, with no clear gradient observed. However, when standardized by monthly household income reported at TB treatment completion, the poorest households are seen to experience a proportionately larger amount of dissaving (85.9% vs. 29.5% of monthly household income in the poorest vs. least poor quintiles).

Table 57: Dissaving incurred over the 1-year PTB disease and treatment period (n=405), and the subsequent 1-year of recovery (n=368), with values presented averaged across the whole cohort, and averaged amongst those who incurred dissaving.

	Variable	1-year preceding TB treatment completion (n=405)	1-year following TB treatment completion (n=368)	P-value
Overall dissaving	Any dissaving incurred (n,%)	298 (72.6%)	186 (50.5%)	<0.001***
	Dissaving incurred, across full cohort (USD) (Median, IQR)	$27.55 (0 – 97.38)	$3.44 (0 – 41.32)	<0.001***
	Dissaving incurred, amongst those incurring dissaving only (Median, IQR)	$59.23 (20.66-137.74) n=283	$41.32 (20.66 – 93.66) n=183	0.040*
Use of savings	Any use of savings (n, %)	181 (44.7%)	17 (4.6%)	<0.001***
	Amount used, across cohort (USD) (Median, IQR)	$0 (0-45.04)	$0 (0-0)	<0.001***
	Amount used, amongst those using savings (USD) (Median, IQR)	$68.87 (27.55 – 137.74) n=169	$118.46 (34.44 – 210.06) n=16	0.209
Borrowing of money	Any borrowing of money (n, %)	177 (43.70%)	146 (39.67%)	0.257
	Amount borrowed, across cohort (USD) (Median, IQR)	$0 (0-14.46)	$ 0 (0-20.66)	0.832
	Amount borrowed, amongst those borrowing money (USD) (Median, IQR)	$20.66 (9.64 – 41.32) n=172	$26.86 (13.77 – 51.65) n=144	0.010*
	From family (n,%)	52/177 (29.4%)	65/146 (44.5%)	0.005**
	From friends (n,%)	111/177 (62.7%)	113/146 (77.4%)	0.004**
	From black market (n,%)	19/177 (10.7%)	25/146 (17.1%)	0.096
	From co-operative (n,%)	12/177 (6.8%)	6/146 (4.1%)	0.298
	From employer (n,%)	12/177 (6.8%)	2 (1.4%)	0.017*
	From bank (n,%)	3/177 (1.7%)	0/146	0.114
	From other source (n,%)	1/177 (0.6%)	0	0.370
Selling of assets	Any assets sold (n,%)	132 (32.6%)	87 (23.6%)	0.006**
	Amount generated, across cohort (USD) (Median, IQR)	$0 (0-10.67)	$0 (0-0)	0.018*
	Amount generated amongst those who sold assets (USD) (Median, IQR)	$27.55 (11.02 – 61.98) n=131	$46.49 (13.77 – 89.53) n=86	0.059
	Sale of household item (n,%)	104/132 (78.8%)	65/87 (74.7%)	0.482
	Sale of mobile phone (n,%)	27/132 (20.5%)	19/87 (21.8%)	0.806
	Sale of means of transport (n,%)	10/132 (7.6%)	10/87 (11.5%)	0.325
	Sale of land (n,%)	5/132 (3.8%)	0	0.066
	Sale of livestock (n,%)	5/132 (3.8%)	10/87 (11.5%)	0.027*
	Sale of farm produce (n,%)	3/132 (2.3%)	1/87 (1.2%)	0.544
School dropout	Any children in household dropped out / interrupted schooling to assist family (n,%)	69 (17.0%)	35 (9.5%)	0.002**

*p<.05, **p<.01, ***p<.001

- INTERRUPTION OF EDUCATION

A high proportion of individuals needed to pull children out of school / interrupt their education to assist the household due to their illness in the year following TB treatment completion. This was reported by 17% (69/405) of study participants during the period of TB illness and treatment but continued to be reported by 9.5% (35/368) of participants in the year after treatment completion.

5.4 DISCUSSION

The key findings from this prospective study of residual lung damage amongst HIV-positive and negative individuals completing treatment for PTB in urban Blantyre include a substantial burden of persistent lung pathology following PTB treatment in both groups, with marked variation in the pattern and severity of damage, and a lower burden but similar pattern of disease amongst HIV-infected adults. A general trend to recovery was observed across multiple clinical and respiratory parameters, but this recovery was incomplete such that pathology persists at 1-year, and heterogeneity in the direction and magnitude of change was observed between individuals. The presence of residual lung damage at TB treatment completion was found to be positively correlated with impaired quality of life and ongoing chronic respiratory symptoms 1-year later. There are no dedicated health services available to address these problems in Malawi. Lastly, these data demonstrate that even at TB treatment completion, adults remain physically and economically vulnerable, and continue to experience health-related costs and dissaving..

- ### A HIGH BURDEN OF RESIDUAL LUNG PATHOLOGY IS SEEN AT TB TREATMENT COMPLETION

This study found a high burden of residual lung pathology at TB treatment completion across multiple respiratory parameters.

CHRONIC RESPIRATORY SYMPTOMS AT TB TREATMENT COMPLETION

At TB treatment completion 60.7% (246/405) of participants experienced ≥1 respiratory symptom for at least a few days each month, and 7.7% (31/405) had symptoms on several/most days each week. Although the 3-month SGRQ questionnaire used to collect these data asked about symptoms over the preceding 3-months, such that these data may reflect the symptom burden within the latter portion of the TB treatment period, the presence of symptoms was correlated with the presence of abnormal spirometry at treatment completion, suggesting that what was reported is consistent with true residual pathology.

The most common regular symptom was shortness of breath, which was experienced regularly on a monthly basis by 39.8% and on a weekly basis by 4.2% of participants at treatment completion. 26.8% (108/403) needed to walk slower than peers or stop for rest when walking at their own pace, which may be equivalent to MRC III dyspnoea score. This finding is consistent with previous studies which have found a high burden of breathlessness amongst post-TB cohorts, with increased breathlessness seen in those with more extensive imaging pathology or spirometric deficits.[107 110]

Cough and sputum were the next most common symptoms after breathlessness, experienced on a regular monthly basis in 36.0% (146/405) / 25.9% (105/405) of individuals and a weekly basis in 2.7%

(11/405) / 2.0% (8/405) of individuals. This may have implications for stigma within this population: previous work from this setting has suggested that cough, HIV and TB disease are often conflated in public opinion in Malawi and all are classed as severe illnesses,[43] with joint public health screening activities emphasizing cough as a 'sign' of underlying HIV and TB disease compounding this belief. Both HIV and TB remain highly stigmatizing in many sSA settings, and this may explain the high proportion of individuals who felt ashamed of their cough/breathing at treatment completion (14.4% (58/403)). No studies of patient experiences of stigma following TB disease or stigma experienced in relation to ongoing symptoms were identified in the literature, but further qualitative work is required to explore this phenomenon.

A low prevalence of wheeze was seen at each study visit. Although a correlation with airway obstruction was demonstrated, the concept of 'wheeze' was noted to be difficult to explain to study participants, and the caution must be used when interpreting data for this construct. However, if true, this would suggest that this is a poor 'screening' test for airway obstruction being present in only 13% of those with this spirometric deficit.

Difficulties farming were raised by 19.4% (78/403) and challenges with lifting heavy items by 18.4% (74/403) of individuals at TB treatment completion. It is likely that this level of impairment is related to general physical deconditioning as well as respiratory impairment, but it is of concern in this setting. Although Blantyre is an urban environment, a large proportion of the population here are involved in manual work, either for running the household, income generation, or the farming of subsistence crops. In addition, it is a hilly city, with poor infrastructure and limited public transport access deep into settlement areas. As such, the potential for a given level of respiratory pathology, reduced general health, or symptom such as breathlessness to significantly effect participants' lives is significant.

QUALITY OF LIFE AT TB TREATMENT COMPLETION

Median SGRQ total scores were 8.7 with a wide IQR (1.2- 23.7). No normative data were available from this setting for comparison, but existing data from COPD cohorts in resource rich settings suggest that a score >6 is abnormal, and over half of the cohort had a score above this level at this time point (54.8%, 221/403).[156] These data are supported by a previous study of SGRQ scores amongst a US based cohort of post-TB patients which demonstrated a negative correlation between spirometric indices and quality of life scores. [120]The symptom and activity sub scores were highest throughout, suggesting that these parameters were of greatest concern to participants. Although the impact score was the lowest, still 14.4% (58/403) felt ashamed of their cough/breathing, over a quarter felt that their chest problem was a nuisance (26.6%, 107/403), and 15.1% (61/403) felt that they had become frail or an invalid. Clearly then, PTB disease and its respiratory sequelae are important for patients' quality of life at TB treatment completion.

This was the first study to use the SGRQ within a post-TB population in the African setting. Good correlations observed between SGRQ scores and other measures of quality of life within this cohort (EQ5D3L VAS score and Likert self-reported health scores) are reassuring and suggest that this is likely a valid measure. However, a few areas of concern with its use were identified: a high proportion of the cohort had total / sub-scores of 0 at each study visit, which is relatively unusual – previous studies based in European settings have suggested that even amongst 'well' individuals, median SGRQ scores are usually higher than 0,[231] with the mean total score in healthy individuals with no history of respiratory disease quoted at 6 (IQR: 5-7) in the original SGRQ manual.[156] These studies have often included individuals who are older than those in this cohort, which may explain some of the difference. However, there may also some cultural differences in the way the questions are interpreted/ answered between cultures, with previous North American studies showing differences in questionnaire responses between white US born, foreign-born, and non-white participants in the same setting, which may reflect some cultural bias.[120] In addition, during the conduct of this study some of the questions included within the SGRQ – particularly those relating to sports and the use of stairs – were observed to be confusing for study participants and perhaps inappropriate for a poor Malawian setting. Locally relevant activities such as farming and manual work were not addressed at all, and symptoms such as 'chest pain' which are commonly reported manifestations of respiratory pathology within the Malawian setting were not enquired about. Whilst the SGRQ is likely a valid measure of quality of life in this context, if it is continued to be used here, some adjustments in either the questions included, or the weighting algorithm used to calculate scores may be required. Simpler alternatives such as a simple general health Likert score or the MRC dyspnoea may provide viable alternatives.

SPIROMETRY FINDINGS AT TB TREATMENT COMPLETION

When standardized using the GLI-2012 African American reference ranges, z-scores for all measured respiratory parameters were negative at TB treatment completion (FEV_1 -1.06 (SD: 1.26), FVC -0.91 (SD: 1.23), FEV_1/FVC ratio -0.38 (SD: 1.26), suggesting that on average, all of these parameters were lower than expected given the age, height and gender of study participants. 34.2% of participants were classified as having abnormal spirometry at treatment completion – low FVC pattern was the dominant pattern seen in 20% of the cohort, with 14.2% observed to have an obstructive pattern. The broad similarity in data distributions between reference ranges confirms that these negative values are unlikely to be a function of reference range alone, and in fact underestimates the degree of abnormality which would likely have been seen had the NHANES III Caucasian reference ranges been used. Comparison with age stratified data from the community based BOLD study completed in urban Blantyre in 2013-14 shows that the prevalence of both of these patterns of abnormality in the post-TB group is likely higher than that seen in the general population.

These are the first data from a post-TB population in the sSA region, outside of South Africa, but support finding from previous studies which have suggested that PTB disease is associated with increased odds of both airway obstruction and spirometric restriction, with more recent BOLD data suggesting that those with a self-reported history of PTB disease have lower FEV_1/FVC ratios and FVC values.[13-15 104]

The high burden of spirometric deficits within this generally young and active group is likely to have long-term implications for respiratory and non-respiratory morbidity, and mortality. Exploratory analyses completed within this post-TB cohort show that higher FEV_1, FVC and FEV_1/FVC ratio z-scores at TB treatment completion are protective against ongoing symptoms and impaired quality of life at 1-year. However, previous studies of broader populations from resource rich settings have shown associations between reduced FEV_1, FVC and FEV_1/FVC ratios and adverse long-term outcomes including increased dyspnoea[232], but also increased health care use / respiratory exacerbations, and mortality.[134 135 137-139] Detrimental associations between impaired lung function and non-respiratory outcomes including cardiac and metabolic disorders, evidence of increased systemic inflammation, and a higher incidence of premature death have also been demonstrated.[233] It is plausible that reduced 'peak' lung function in early adulthood occurring as a result of PTB disease in resource poor settings such as Malawi could give rise to similar adverse outcomes in this setting over time, and further investigation of these outcomes in the post-TB population are required.

CT IMAGING FINDINGS AT TB TREATMENT COMPLETION

This high burden of spirometry deficits was matched by a significant burden of structural abnormality on HRCT imaging. Only 1.3% (5/385) of participants imaged with CT had both completely normal lung tissue and completely normal airways at TB treatment completion. The median extent of abnormal parenchyma seen was the equivalent of almost 1.4 lobes, 44.2% of individuals had moderate to severe bronchiectasis (airway dilatation ≥2 times diameter of adjacent vessel) in at least one lobe, and 9.3% of individuals were left with at least one non-functioning lobe (≥90% of tissue occupied by atelectasis and banding, or cavities and cystic airspaces).

The high prevalence of bronchiectasis seen here is consistent with estimates from previous studies in the Americas / Taiwan where bronchiectasis was reported in 35 - 86% of post-TB cases,[179 202-205] and is of some concern. Data from cohorts of bronchiectasis patients in resource rich settings suggest that extensive disease is associated with adverse outcomes over 6m-14 year follow up periods including accelerated FEV1 decline, recurrent exacerbations, hospital admissions, and all-cause mortality.[135 150 152-155] Thus far, within this cohort study, the presence of moderate-severe bronchiectasis in ≥3 lobes has been shown to be associated with the presence of chronic respiratory symptoms at 1-year as might be expected, but no other outcomes. Further follow up of post-TB study participants with this pathology is required.

Of note, at both the whole lung and lobar level in this cohort, severe airway dilatation was associated with more extensive atelectasis / banding, cavities / cystic airspaces, and consolidation. This suggests that bronchiectasis is generally not an isolated phenomenon in the post-TB context – rather, it is associated with a broader pattern of lung damage and destruction as described above, and may in part be 'traction' bronchiectasis, secondary to the architectural destruction. It may be the case that it is the combined effect of this destruction and distortion, rather than factors related to bronchiectasis alone, that drives outcomes in this patient group. In addition, post-TB bronchiectasis appears to be fairly focal with the majority of people with bronchiectasis experiencing this in 1-2 lung lobes only (82.9%, 141/170). Studies of outcomes amongst Western cohorts have often used the presence of bronchiectasis affecting ≥3 lobes as an imaging marker of disease severity – although the same approach was used in the analyses presented here,[135 154] further exploration of the extent of disease which is clinically important in this context may be warranted. No data on the distribution and nature of bronchiectasis are available from previous CT-based studies for comparison.

A second finding of interest within the imaging data was the high burden of potential signs of ongoing inflammatory pathology at TB treatment completion: all individuals included within this study had received 6-months of treatment and deemed to have 'treatment success', but residual consolidation was seen in 69.4%(267/385) of the cohort, ground glass opacification in 36.6% (141/385), and nodules confirmed by both readers in 228/365 (59.2%). Serial CXR imaging showed that the majority of individuals experienced a decline in the extent of consolidation and ground glass over the course of the year (54.0%, 194/359), confirming that many of these abnormalities were inflammatory and reversible in nature. As described in the introduction, PET-CT studies in Cape Town have previously demonstrated ongoing increased metabolic activity in focal lesions in 72% of a cohort of HIV-negative adults completing TB treatment,[102] but that it was unclear whether these lesions represented persistent live mycobacterial presence or an indolent host immune response perhaps to dead organisms. The lack of association observed between any of these patterns of inflammation and either TB retreatment or death within the 1-year follow up within data from this cohort suggests that the latter may be more likely, but further follow up is required to confirm this, and exploration of the reason for such a prolonged persistent host immune response amongst a subgroup of those completing TB treatment is required.

In addition to the large total volumes of pathology across the whole lung, clustering of pathology within a single extensively damaged lobe was a pattern commonly seen, and 9.4% (36/385) of the cohort had at least one lobe with ≥90% of tissue non-functional due to atelectasis / banding or cavities / cystic airspaces. No other CT studies reporting the prevalence of this pathology at the point of TB treatment completion[191] have been identified – the absence of a definition for this pattern of pathology from the widely used Fleischner guidelines for CT reporting may explain reluctance to report this feature, and a consensus definition may be required for further work. Of note, previous studies of patients with extensive TB-destroyed lung identified some years after TB treatment have documented

a high burden of pulmonary hypertension, infection, respiratory failure and mortality.[109 119 234] The outcome data presented here do not support this – within the 1-year of follow up, the presence of at least 1 destroyed lobe was not associated with any of the adverse outcomes measured. This may be a result of the limited follow up duration within this study, but confidence intervals for the odds ratios estimated within all of the models constructed were very wide, and it may be that focal lung damage of this nature is a benign finding. Further follow up data and perhaps some comparison between those with collapsed vs. destroyed lobes may be warranted to better understand this.

The prevalence and extent of mosaicism observed within this study was a surprising finding: the median extent of pathology was 32.5 points, but the IQR was 5 – 85, and the full range of scores spanned 0 – 325 points with the upper level representing the equivalent of over three lobes of decreased attenuation tissue. Mosaicism is defined in the Fleischner guidelines as 'a patchwork of regions of differing attenuation' but it is important to note that a degree of parenchymal heterogeneity can be seen in normal individuals, with up to 20% showing mild mosaicism on inspiratory scans. No absolute cut-offs for a 'normal' amount of mosaicism has been defined. It is also important to note that this is often an extremely subtle feature - although the ICC values for this variable were reasonable between readers (0.55 (95% CI: 0.48-0.62)) verbal feedback described reporting of this feature to be subjective and challenging, such that results must be interpreted with caution. Nevertheless, these data fit with findings from the only previous CT study to report this feature which identified mosaicism amongst 70% of patients completing TB treatment (n=20) in Canada in 1998.[179]

As described in Chapter 3, high amounts of lung attenuation can be caused by obstruction of the small airways, with gas trapping distal to the point of obstruction +/- shunting and decreased perfusion through vessels in these areas, or may reflect pulmonary hypertension with regional differences in lung perfusion and hence a 'patchy' density seen on imaging.[192] The pulmonary artery diameter was not routinely measured by radiologists in this data set, but clinical features of cor-pulmonale with pedal oedema were seen in 1.5% (6/385) of imaged patients only, suggesting that few are likely to have had extremely high right sided pressures. In addition, the amount of mosaicism seen was positively correlated with the severity of airway pathology at both a whole lung and lobar level on analysis, perhaps pointing to an airways cause of disease. One context in which both large airway pathology (bronchiectasis) and small airway damage (mosaicism) have been seen together in low resource sSA settings is in adolescents with vertically acquired HIV, where an 'obliterative bronchiolitis' picture has been observed.[27] However, there is no evidence to support a HIV-mediated cause of mosaicism in this cohort, as the extent of low attenuation tissue actually higher in the HIV-negative group (40.0 vs. 27.5 points, p=0.024). Nevertheless, it is possible that mosaicism – which was far more commonly reported and more extensive than emphysema – is the pathology underlying airway obstruction within this cohort. Further investigation of this finding with echocardiography and

perhaps expiratory CT imaging which is more sensitive / specific for pathological mosaicism may be warranted.

Finally, it is worth noting that only 1.3% (5/385) of participants had mycetoma seen. Together with the very low prevalence of positive aspergillus serology (<1%, 3-4/404) at this time point, these data suggests a low burden of *Aspergillus fumigatus* disease in this population at TB treatment completion. Further follow up is required to determine whether this changes over time, and given the absence of positive *A. fumigatus* serology amongst several patients with imaging suggestive of fungal disease, investigation of the burden of other Aspergillus species may be worthwhile.

- ## HIV-INFECTED INDIVIDUALS HAVE A LOWER BURDEN OF DISEASE, BUT PATTERNS OF PATHOLOGY ARE SIMILAR

This is the first large study in the sSA region to present disaggregated data on the prevalence and pattern of post-TB Lung damage according to HIV status.

HIV-positive status at TB treatment completion was associated with less extensive pathology at TB treatment completion. In univariate analysis of spirometry data, mean z-scores for both FEV_1 and FVC were lower amongst HIV-uninfected compared to HIV-infected individuals (FEV_1 -1.27 vs -0.94, p= 0.015; FVC -1.08 vs -0.80, p= 0.037) at TB treatment completion. The same pattern was seen in multivariate models for factors predicting abnormal spirometry where controlling for other participant characteristics HIV-infected adults with CD4 counts <200cells/uL had FEV_1 and FVC volumes which were statistically larger than HIV-negative individuals by 189.9mls (40.4 – 339.4) and 170.5mls (8.0 – 333.0) at TB treatment completion. On CT imaging HIV negative individuals had more extensive parenchymal abnormality (total abnormal parenchyma score 180/600 (IQR: 81-246) vs. 110/600 (IQR: 40 – 228), p<0.001) and statistically more severe airway dilatation, tree in bud, and airway plugging.

Much has been published about the suppressed immune response in the context of HIV infection 'protecting' against lung destruction and cavitation in response to active TB disease.[83] The data from this study support this notion, and suggest that this protective effect during active disease translates into less extensive respiratory pathology at TB treatment completion. However, whilst the extent of pathology is on average reduced in HIV-infected individuals, the patterns of damage seen appear broadly similar, and abnormalities are still present with extensive pathology observed amongst some HIV-infected individuals. In addition, given ongoing moves to 'test and treat' approaches to ART initiation, it may be that we see convergence between the pathology seen in HIV positives and negatives. This is not a group that can be discounted, as it has been in the literature on post-TB lung damage to date. Instead, further investigation of the effect of ART duration and IRIS during TB treatment are required to better understand the relationship between HIV and post-TB lung damage.

Despite the protective effect of HIV co-infection against 'objective' respiratory damage on spirometry and imaging, it is of interest that no difference in SGRQ scores or 6-minute walking distance were observed between HIV positive and negative groups at TB treatment completion. Although both of these tests are designed to be respiratory assessments, they are not specific and are also affected by general physical health and conditioning – it may be that the less severe respiratory pathology seen amongst HIV-positives is 'cancelled out' by a generally increased level of physical morbidity in this group amongst whom the median CD4 count was 229 cells/uL (95% CI: 127 – 397), such that scores appear similar.

Interestingly, controlling for HIV status, baseline TB microbiology was not consistently associated with any of the spirometry parameters measured at TB treatment completion. This suggest that the respiratory pathology seen in participants with / without positive TB microbiology at diagnosis are similar and supports the hypothesis that a high proportion of those with microbiologically negative PTB diagnosis did in fact have TB disease, and were likely exposed to the same respiratory insult as the rest of the study population.

- ## PATTERNS OF PATHOLOGY AT TB TREATMENT COMPLETION ARE HETEROGENEOUS

Although a high average burden of respiratory pathology was observed within this cohort, the wide degree of heterogeneity seen between individuals was marked. This was evident across all continuous respiratory parameters measured, including spirometry, imaging, clinical observations such as BMI, quality of life and 6-minute walk distance, and is reflected in the long tails seen on the population distributions plotted above.

The wide distributions seen across respiratory parameters illustrates how diverse the respiratory response to TB as a respiratory insult can be, and is a call for more work into the host, mycobacterial, and environmental factors driving the nature and duration of the host immune response in PTB disease.[89] It is only through understanding this that we may be able to identify modifiable factors which could help us shift patients from more extreme to milder patterns of lung damage in response to TB disease.

Importantly, these findings also support the hypothesis that although some degree of residual post-TB pathology is widespread there are a minority of patients who are left with extensive pathology: only 29.6% (108/365) of participants met the *a-priori* criteria for PTLD with either extensive CT or spirometry abnormalities, and 9.6% (39/405) had severe abnormalities of both imaging and spirometry. These are perhaps one group of patients in whom we should be concerned about adverse outcomes.

- ## RECOVERY IS SEEN, BUT THIS IS INCOMPLETE AND HETEROGENEOUS

A consistent trend to recovery was seen at a population level in the 1-year period following TB treatment completion. Spirometry data show that the average FEV_1 rose from -1.06 to -0.88 z-scores at 1-year, and average FVC rose from -0.91 to -0.61 z-scores at 1-year. CXR data show an average reduction in the total extent of abnormal parenchyma, which fell from a median score of 18 (IQR:3-55) at treatment completion to 13 (IQR: 0-43) 1-year later (p=0.023). Six-minute walk distances increased by 41.3m on average, which is greater than the proposed minimum clinically important distance of 30m.[161] The same pattern was also seen in clinical parameters such as BMI, and quality of life scores, with the biggest improvements seen within the first 6-months after treatment completion.

In the literature review at the start of this thesis, the paucity of longitudinal data on the evolution of post-TB lung damage was highlighted, and only two previous modelling studies of change in spirometry over time were identified. Both of these studies suggested an initial population level decline with nadir lung function at 12-18 months post treatment completion[112 235]. This pattern is different to what has been observed here, where average lung function at a population level has improved over time. This difference can be explained by our use of real longitudinal data in comparison to modelling based on cross sectional data but may also be related to the way in which spirometry outcomes were measured. As noted in the results above, we observed an increase in the proportion of participants defined as having obstruction over the course of the study which rose from 14.2% (52/365) at TB treatment completion, to 17.9% (60/336) at the 1-year time point. In fact, this was driven in part by a disproportionate increase in both FEV_1 and FVC, rather than any true deterioration in lung volumes. This finding supports the use of absolute volumes or z-scores when interpreting changes over in time in spirometry, rather than patterns of deficit alone.

However, just as significant heterogeneity was observed in the extent and pattern of pathology at TB treatment completion, so marked variation in the direction and rate of change in pathology over time was seen. A 'catch up' phenomenon was observed across multiple parameters, whereby those with the most extensive / severe pathology at TB treatment completion experienced the biggest improvement over the 1-year follow up period. This pattern was consistently seen in descriptive analyses of quality of life, walking distance, BMI, imaging, and spirometry data. It was also observed in the multivariate models of spirometry outcomes where, controlling for participant characteristics, individuals with the most impaired FEV_1 and FVC values at TB treatment completion experienced larger improvement in FEV_1 and FVC in the following year. It is possible that this simply reflects 'regression to the mean' alone. However, given the magnitude of change observed it could be a reassuring sign that there is an ongoing period of recovery which takes place following the completion of TB treatment, with those who were the most unwell showing the greatest capacity for improvement.

This ‘catch up’ pattern was however incomplete, such that participants with the most extensive deficits at TB treatment completion still had the most extensive deficits 1-year later. Again, this was seen consistently across parameters in descriptive analyses. It was also observed in the multivariate models of spirometry outcomes at 1-year: poor baseline FEV_1 and FVC volumes at TB treatment completion were associated with poor FEV_1 and FVC volumes at 1-year, a reduced ratio at baseline was a predictor of a reduced ratio at 1-year, and those classified as having an obstructive or low FVC pattern at baseline had markedly increased odds of being classified in the same group at the end of follow-up.

Also of note is that whilst the majority of individuals did experience some recovery over the 1-year follow up, a sub-group of participants experienced deterioration over this period: depending on the parameter used to measure respiratory pathology or general health, between 19.7 – 41.5% of the cohort experience some deterioration over the 1-year follow up period. Whilst further analyses are required to determine the proportion of patients experiencing declines that are greater than the MCID for each parameter, this does suggest a subgroup of individuals who are at risk of ongoing deterioration instead of recovery.

The implications of these findings are twofold. Firstly, despite the trend to improvement at a population level, a significant burden of pathology and impairment remains at 1-year. At this time point, 30.7% (113/368) of individuals continued to report regular respiratory symptoms on a monthly basis, and 4.1% (15/368) had weekly symptoms. Almost 1 in 5 participants (19.8% (73/368)) experienced ongoing limitations in their usual activities, whilst 12.2% felt that their chest symptoms were continuing to interfere with their work. Deficits in spirometry persisted: mean FEV_1, FVC and FEV_1/FVC ratio z-score values remained negative at -0.88 (SD: 1.19), -0.61 (SD: 1.09) and -0.54 (1.29), and 12.8% (43/336) of the cohort were defined as having a low FVC deficit whilst 17.9% (60/336) were defined as having obstruction. Despite some recovery in the year following TB treatment completion, evidence of respiratory pathology and its sequelae persisted.

Secondly, these findings suggest that further work is required to understand which individuals are at greatest risk of long-term respiratory abnormalities. This group is likely to include those with the most severe pathology at TB treatment completion as despite recovery and ‘catch up’ these individuals are likely to continue to have severe long-term damage, but also the subgroup of participants who experience deterioration over time, regardless of their starting point. Future studies using individual level, multi-level analyses, may be useful to understand the characteristics and determinants of these groups, as they are likely to be the focus for any interventions aiming to improve long-term outcomes.

- ## POST-TB LUNG DAMAGE IS ASSOCIATED WITH CHRONIC RESPIRATORY SYMPTOMS AND REDUCED QUALITY OF LIFE AT 1-YEAR

The multivariate models constructed here demonstrate that the presence of residual lung damage at TB treatment completion, whether it is measured using spirometry or on imaging, is an important predictor of both a lower quality of life and the presence of chronic respiratory symptoms at 1-year following treatment completion. The increase in odds of each of these outcomes is over three-fold higher amongst those with both extensive lung pathology on imaging (moderate to severe bronchiectasis in ≥3 lobes, or the equivalent of ≥1/3rd abnormal parenchyma), and abnormal spirometry (reduced FVC or moderate airway obstruction), compared to those with neither of these features. In exploratory analysis both individual spirometry parameters and markers of structural pathology have also been shown to be determinants of ongoing symptom burden and quality of life. These data clearly show that having residual post-TB lung pathology is meaningful for participants' experience of life following PTB disease.

However, within this cohort study no association between imaging or spirometry defined PTLD and 'harder' outcomes such as having an acute respiratory event, the initiation of TB retreatment, or all-cause mortality was found, regardless of how PTLD was quantified. It may indeed be the case that these associations do not exist – that is, the severity and pattern of lung pathology sustained during PTB disease and treatment may not be a key predictor of these adverse outcomes. This would run counter to studies conducted in comparable chronic respiratory diseases in resource rich settings in which severe damage is associated with ongoing morbidity and mortality, but may well be the case in a context where there are so many other potentially more significant influences on health – including HIV disease, poverty, environmental exposures and non-respiratory diseases – compared to chronic lung damage. However, it is equally possible that these associations are there, but that out study was underpowered to detect them. The follow-up duration used in this study was limited, and the number of events detected for these outcomes were low. Studies investigating patient outcomes associated with conditions such as bronchiectasis in resource rich settings have shown differences in important outcomes such as hospitalisation and mortality but have required 2-14 years of follow-up to identify these relationships. Further follow up of this cohort is required, in order to determine this.

Whilst we have found no evidence to suggest that acute respiratory events are predicted by the extent of post-TB lung damage seen at TB treatment completion, these data do suggest that acute respiratory events may drive deterioration in spirometry over time. Controlling for participant characteristics and the severity of lung pathology at baseline, the presence of ≥1 respiratory exacerbation in the 1-year of study follow up was associated with a greater loss in FVC over the 1-year period, and smaller FVC volumes at the end of this period by 81ml (95% CI: 6.5 – 155ml). However, this finding was only observed with relation to the FVC, and confidence intervals for the magnitude of change in volume

are wide. Further follow up may help to better define a causal relationship between ongoing infective exacerbations and lung function deterioration.

Another factor which may have limited the ability to detect relationships between post-TB lung damage and outcomes may be the use of simplistic definitions of PLTD, which failed to capture the actual pathology or 'phenotype' of damage that individuals are exposed to following TB disease. In this thesis, attempts were made to determine whether distinct patterns of symptoms and structural pathology were seen in those with airway obstruction or low FVC spirometry patterns at TB treatment completion. In fact, whilst both groups were more breathless, had higher SGRQ scores, and had more extensive imaging pathology than those with normal spirometry, few differences were observed between groups. This analysis suggests that patterns of spirometry deficit are a poor way of defining phenotypes of post-TB lung damage, as the overlap between groups is large. More complex analyses using machine learning techniques or principal components analyses will be required to identify phenotypes empirically, from the data itself, if clusters of patients are to be identified. Relationships between these phenotypes and outcomes must then be investigated.

- ## THERE IS AN UNMET NEED FOR HEALTH CARE POST TB

These data demonstrate both delays to TB diagnosis and treatment, as well as limited access to ongoing health services after treatment completion.

DELAYS TO DIAGOSIS

Delays to diagnosis and treatment are a well-known challenge in the TB treatment cascade – these are particularly marked amongst those who are smear negative, and frequently reflect health system delays and diagnostic challenges.[62] However, the novel finding from this study is that a longer duration of illness prior to treatment was associated with worse lung function by the time of treatment completion: on average the 60% of participants (243/405) who had been unwell for ≥1-month by the time of treatment initiation had FEV_1 volumes which were over 100ml lower at TB treatment completion and at 1-year, and more obstructive FEV_1/FVC ratios at both time points, compared to those with more rapid treatment. This is perhaps unsurprising as delays likely allow more time for lung damage to progress before mycobacterial killing occurs and implies that earlier treatment of PTB disease may reduce the severity of residual damage.

To date, active case finding / TB screening programs aimed at early diagnosis and treatment have been focused largely on the public health impacts of reduced transmission and decreasing mortality.[222] However, these interventions may also have the potential to reduce residual post-TB lung pathology amongst survivors and including measures of post-TB lung pathology within impact studies and cost-benefit analyses for these interventions may be warranted.

ONGOING ACCESS TO HEALTH SERVICES

During the course of PTB treatment individuals in Malawi are required to visit health centres on a monthly basis to obtain TB medications, but at the point of TB treatment completion patients are discharged from TB services with no routine respiratory follow-up in place. Findings from this study show that after discharge, 16% of this cohort had at least one unscheduled health service consultation for a respiratory symptom during the following year, and respiratory complaints made up approximately 40% of unscheduled outpatient and inpatient visits completed by the cohort during the year. In addition, despite the high burden of respiratory symptoms described above, only 2.2% of the cohort had a diagnosis of a chronic respiratory condition other than TB by the point of TB treatment completion. These findings suggest an unmet need for respiratory diagnosis and perhaps ongoing management in this cohort.

When thinking about management of chronic disease in a setting such as Malawi, the relative cost and benefit to both the health service and the individual patient must be considered. Provision of ongoing respiratory input to HIV-infected individuals may be easier to institute, given that 66.4% of individuals within this cohort continued to have planned access to health services in the year following TB treatment completion, largely within existing ART services. However, models of integrated care for HIV and non-communicable diseases (NCDs) have previously been piloted within Malawi, and whilst found to be feasible, constraints around increasing clinic workloads and integration of new services within a vertical / dedicated HIV service were marked.[236] Provision of ongoing care for HIV-negative individuals may be more complex – only 9.6% were booked for scheduled follow up, and few of these appointments were with medical / respiratory services, suggesting limited opportunities to integrate follow up within existing appointments for this patient group.

The provision of routine ongoing follow up for either group is, therefore, likely to be complex and costly for both patients and health services. A proven association between post-TB lung damage and 'hard' adverse outcomes such as recurrent infections, lung function decline, and mortality, may be required to justify this investment, and careful thought should be given to a package of interventions which might alter these outcomes. Screening approaches to identify those at highest risk of adverse outcomes, who would benefit the most from ongoing medical input, must also be developed.

MANAGEMENT OF RESPIRATORY EXACERBATIONS

Antibiotics were prescribed for 80% of respiratory-related outpatient visits identified in this study, and whilst the majority of these were appropriate for respiratory infections, a diverse range of drugs were used, durations of use varied, and it is unclear whether or not they were actually needed. Even in resource rich settings the development of clear management guidelines for infective exacerbations in conditions such as bronchiectasis have been hampered by the paucity of data on exacerbation definitions, aetiology, and antibiotic efficacy.[92] Further work to understand the nature of

exacerbations experienced by this cohort, the decision making processes currently used for antibiotic prescription in different health services, and the microbiology of recurrent infections in this setting may help to guide the management of exacerbations in those who have recently completed PTB treatment in this context.

Potential challenges in screening for recurrent PTB disease amongst this cohort have also been highlighted by these data. Many TB case finding programmes use symptom questionnaires as the first line of screening for active TB disease, however 23% of this cohort were found to have a positive WHO TB symptom screen at some point during the 1-year follow up, and this was frequently the result of ongoing cough. Only 1/81 symptomatic patients not started on TB retreatment died during follow up, suggesting that few of these individuals had active TB disease, and perhaps these ongoing symptoms were related to post-TB lung damage. The specificity of the TB symptom screen for PTB disease in this group may therefore be somewhat reduced. Use of the XPert MTB/RIF assay for screening within this population is also complex. The duration for which GXP stays positive in response to the presence of non-viable mycobacteria after an initial episode of disease remains unclear, but the estimated false positive rate at 6-months following treatment completion is 9%.[237] Clear guidelines for the use and interpretation of PCR testing amongst a post-TB population may be required to minimize false positive results related to such practices. Finally, this cohort has a high burden of underlying lung pathology visible on CXR, and the use of CXR screening for identification of those with disease is likely to be challenging. Given the complexity surrounding the use of symptom, molecular, and imaging screening in this post-TB group, guidelines for TB screening specifically in this population may be of some value.

- ## POST-TB LUNG DAMAGE IS EXPERIENCED ON A BACKGROUND OF PHYSICAL AND ECONOMIC VULNERABILITY

Adults within this cohort had a high burden of concurrent respiratory exposures and had ongoing markers of poor health even at TB treatment completion. Not only had they experienced a significant economic insult during PTB disease and treatment, but economic recovery during the 1-year follow up period was limited with ongoing costs and dissaving incurred. This is a worrying background against which post-TB lung damage is experienced.

CONCURRENT RESPIRATORY EXPOSURES

The total prevalence of ever-smoking within this cohort was 29.6%, compared to an ever-smoking prevalence of 10.4% seen within the population based BOLD survey data presented in Chapter 4. This difference may be explained by confounding by factors such as male gender, which is associated with both PTB disease and smoking: in keeping with global estimates the ratio of men to women was 2.11 within this study, and the prevalence of smoking amongst men was 43.3% (119/275) within this cohort, compared to 0.8% (1/130) amongst women. However, as discussed in Chapter 1, it is also

possible that the high prevalence of ever-smoking is related to its role as a risk factor for PTB disease itself.[16] Although common, ever-smoking was not a significant predictor of spirometry at TB treatment completion or at 1-year, or the rate of change over time in multivariate analyses, perhaps in relation to the current low level of pack-year exposure observed within the cohort. Although this suggests that spirometry outcomes are likely similar for ever and non-smokers, this finding must be interpreted with caution – there are strong epidemiological and clinical data that increasing exposure to tobacco smoke is associated with COPD and increasing rates of lung function loss, and data on longer term outcomes amongst smokers is therefore required.

An additional concern is the high prevalence of cannabis use in the cohort, with over 1/5th of men reporting exposure (21.6% ever-use, 53/245). The risk posed by this remains unclear – chronic marijuana use has been associated with chronic bronchitis, bullous airways disease, and increasing FVC measurements in previous studies, but not with COPD or lung cancer.[238] The strong correlation between smoking and cannabis use within this cohort limited our ability to explore their differential effects of these exposures, but it is possible that this was an unmeasured driver of spirometry outcomes within this setting, and one whose widespread use may be relevant for the general health of this population.

Lastly, the prevalence of biomass exposure is likely high within this cohort. Despite being in an urban setting, charcoal was the dominant fuel used for cooking / heating water by the majority of individuals recruited (83.5%, 338/405). Challenges in data collection meant that we have limited information on self-reported duration / severity of exposure, but previous data from urban Blantyre have suggested that average exposure to CO and $PM_{2.5}$ in this setting exceeds the WHO Air Quality Guidelines,[20] such that this is likely a further exposure of concern.

ONGOING MARKERS OF POOR HEALTH

Although recruitment for this study took place after a 6-month period of TB treatment, the general health of the cohort was noted to be poor. As expected, 60.3% (244/405) were HIV infected, and although the majority were receiving ART treatment by treatment completion median CD4 count across the cohort remained just 229 (IQR: 127 – 397) at the point of TB treatment completion. This is likely a function of the low nadir counts experienced prior to ART initiation, the expected long time-lag to CD4 increment,[239] and the additional hit experienced from TB disease itself. It suggests that at TB treatment completion and when on ART, HIV positive individuals remain vulnerable with often profound immunocompromise.

The high proportion of patients with a markedly low BMI at this point is also striking - 17.5% (71/405) of patients were underweight with BMI<18.5kg/m^2, compared with a population prevalence of 7.9% within the general population included in the BOLD urban Blantyre study.[34] This measure likely reflects many insults including malnutrition, and suggests ongoing vulnerability within the group. In addition,

BMI was positively correlated with both FEV_1 and FVC at TB treatment completion. This effect was independent of both SES and acute food insecurity, suggesting that it is not simply a proxy for wealth / poverty. It was also independent of HIV / the degree of immunosuppression and therefore not simply a reflection of HIV-related co-morbidity. The nature of the relationship between BMI and spirometry at these time points is unclear: this may be a causal relationship whereby patients with reduced BMI at TB treatment completion have reduced respiratory muscle bulk/strength and hence impaired spirometry, there may be confounding by PTB disease severity whereby advanced disease is independently associated with both BMI and lung destruction, or there may be reverse causation whereby a reduced BMI is a result of increased respiratory metabolism experienced by patients with advanced lung damage. Further understanding of factors determining BMI in this cohort, and the relationship between BMI and lung function with further measurement of respiratory muscle function and true lung volumes may help us to understand this relationship and understand whether interventions to improve this modifiable variable may impact the extent of respiratory impairment and patient outcomes following PTB disease.

Given these findings the normal haemoglobin levels observed in the cohort at treatment completion were somewhat surprising. This may reflect a selection bias – anaemia is usually common amongst patients with active TB disease, particularly in the context of HIV co-infection, but is associated with increased mortality during treatment,[240] and the relatively preserved levels amongst this population may reflect a survival bias.[241]

ECONOMIC VULNERABILITY

TB disease has marked economic consequences for adults in this setting. By the point of TB treatment completion, the proportion of unemployed participants had increased to over 1/3, individual and household incomes had declined, and almost ¾ of patients had experienced dissaving with borrowing of money, selling of household items, or using up of savings to meet health care costs over the course of TB disease. Although dissaving was more common amongst poorer individuals, 50% (28/56) of those in the highest SES quintile also experienced dissaving over this period, highlighting the magnitude of TB related costs even when services are ostensibly provided 'free of charge' by the state, and the fact that even relatively wealthy individuals in settings such as Blantyre have limited financial reserve. These data are in keeping with previous literature describing high patient costs during TB illness, with approximately 60% of costs related to loss of income, and 40% related to direct and indirect medical costs.[129]

However, a novel finding from this study is that the financial impact of PTB disease persists, even after TB treatment completion. Incomplete recovery of income and employment was clearly seen: 1-year post treatment completion a higher proportion of individuals remain unemployed compared to pre-disease (29.9% vs. 18.8%), and median participant incomes had not returned to their pre-disease levels

(median income $43.53 at 1-year vs. $55.10 pre-disease). The proportion of study participants who were the main earner within their household remained the same throughout the study period, perhaps reflecting an inability of earning to be transferred to another household member, and accounting for the lack of recovery in household income. Dissaving was also ongoing: in the year following TB treatment completion, half of the cohort experienced dissaving releasing a median of $41.32 (IQR: $20.66 – 93.66) through borrowing money, ongoing sales of household assets, and the use of savings. Perhaps most concerningly, whilst during TB illness and treatment 17% (39/405) of study participants pulled children out of school / interrupted their education to assist the household as a result of their illness, this remained the case for 9.5% (35/368) of study participants in the year following treatment completion. Self-reported direct and indirect costs related to health seeking were in fact low across the cohort, with the exception of participants started on TB retreatment, but it is likely that our data underestimated the 'cost' of time lost for informal or household work.

These are the first data to show an ongoing economic impact of TB disease, following TB treatment completion. The incomplete recovery in income and employment observed here may be a result of difficulty regaining employment once lost in a setting such as Malawi due to high local unemployment rates, and the stigmatizing nature of TB disease / HIV disease. The sale of income generating household assets during the illness period, which within this cohort included means of transport, land, and livestock, may limit capacity to earn. Lastly, the physiological data presented above clearly shows that significant morbidity persists at TB treatment completion, with limited BMIs, ongoing advanced immunosuppression, a high symptom burden, and residual respiratory pathology. The extent to which these parameters impair patients' ability to return to work after treatment completion is unclear. Further exploration of these factors is required if we are to optimize the recovery of these largely young, economically active patients and their households following PTB disease treatment in order to meet the WHO End TB strategy objective of mitigating the financial cost of TB disease. Some focus on the physical and economic rehabilitation of TB patients following treatment completion may be required to achieve this end.

Finally, data from this study show that poverty at TB treatment completion is an independent predictor of airway obstruction at this time point: controlling for other characteristics, those in the lowest 3 urban wealth quintiles had FEV_1/FVC ratios which were on average 2.8% (95% CI: 0.7 – 4.9%) lower than those in the highest quintiles within this cohort. The mechanism underlying this association is unclear. It may be that the association between poverty and airway obstruction seen in this cohort is completely independent of TB disease: analysis of data from general community populations in 12 BOLD study sites showed a positive correlation between increasing wealth and the FEV_1/FVC ratio both within and between sites, independent of age, sex and smoking,[38] and local BOLD study data from urban Malawi have demonstrated a positive correlation between the lack of a private water supply – used as an SES proxy – and an obstructive FEV_1/FVC ratio which is independent of previous TB disease. However, it may also be the case that SES at TB treatment completion is in part a product of the

financial effect of TB disease, such that those who experience the greatest financial hit during disease also sustain more significant lung damage. Whatever the mechanism, and whether this finding is related to or independent of the severity of PTB disease experienced, it is of concern: tuberculosis is in itself is a disease of poverty and social exclusion,[45] and the finding that even amongst those who have PTB disease and within a relatively poor population, it is those who are particularly poor who are at increased risk of airway obstruction, is worrying and further supports the need to address the socioeconomic determinants of poor health within this group.

• STUDY STRENGTHS

This is the first large prospective study of post-TB lung damage in the sSA setting to date. Within this study residual post-TB pathology was measured along multiple respiratory parameters including symptoms, quality of life scores, and spirometry and imaging, to provide a comprehensive description of residual disease. The availability of CT imaging is limited in many resource poor settings, and its inclusion within this study is therefore of particular value.

Questionnaire data were collected electronically, with few missing or incorrect entries. Rigorous methods of quality control were employed for spirometry, CXR, and CT data, with dual reporting and consensus review for each. High quality valid spirometry data were available for >90% of participants at each study visit. CT imaging was available for 95% of participants, and the reporting tool used for interpretation used clearly defined Fleischner terms where possible.

This study included the collection of prospective data, such that it is possible to track change over time. Although it was completed within an urban setting with a highly mobile population, loss to follow up was under 10%. Both HIV positive and negative adults were included, and disaggregated data are presented for each group. The unselected pragmatic recruitment approach taken means that findings can be generalized to a wide spectrum of adults completing PTB in settings such as Malawi.

A strong emphasis was placed on communicating study results back to participants – each individual was seen by a respiratory physician at the end of the 1-year follow up, and written copies of all test reports were given to participants and their implications explained. Collective feedback meetings were also held at the end of the study to communicate research findings to participants.

Multiple patient outcomes were measured within this study, such that the relationship between post-TB lung damage and many relevant outcomes can be assessed from this single cohort. Lastly, the cohort that was established as part of this study is ongoing, and offers unique opportunities to obtain further longitudinal data on patient outcomes and progression of respiratory pathology.

• STUDY LIMITATIONS

Firstly, whilst our aim was to recruit a representative sample of those completing PTB treatment in urban Blantyre, relatively few individuals within the cohort were drawn from the lowest urban wealth quintile. This may reflect a selection bias – the fact that patients were asked to pay for transport to the central tertiary hospital themselves for recruitment, before being reimbursed, may have made it challenging for the poorest individuals to attend. However, as study participants were recruited from the point of TB treatment completion rather than diagnosis, this finding may reflect higher mortality rates amongst those with lower SES such that they are genuinely under-represented by the point of treatment completion.

Secondly, this study does not include any measure of pre-TB lung damage. As such, it is not possible to know whether the pathology identified at TB treatment completion is the result of PTB disease only or related to previous respiratory disease. Whilst the ability to determine causality is certainly limited within this study, the intention of this study was to take a pragmatic approach to describing the burden of lung damage seen in this population at the point of treatment completion, and the outcomes related to this. This is the information of greatest use for health service planning, regardless of cause.

As noted above, the follow-up duration of this study was constrained to 1-year by the duration of this PhD, which was likely too short. This resulted in models being underpowered to detect a relationship between residual lung damage and key long-term outcomes, including acute exacerbations, TB retreatment, and mortality, and also meant that the outcome measures used in the multivariate models constructed were altered from those specified in the original protocol. All revised definitions were however established before the revised models were constructed, thus limiting bias. Further analyses of exacerbation rates using person-time approaches are required, and must incorporate the longer-term data on patient outcomes which will be available from ongoing follow up of the cohort in the coming 2-3 years. No control group was included within this study. The aim of this study was to perform an internal comparison of patient outcomes amongst those with and without severe residual lung damage after PTB treatment completion, and a non-TB control group was not required to this end. However, the availability of community symptom and spirometry data from the BOLD study completed very recently in urban Blantyre has allowed for comparison with background rates of pathology.

Challenges were experienced in the various measures of post-TB lung damage used in this study. Firstly, no pre-existing validated definitions or severity scores for PTLD were identified on literature review, and an *a priori* definition was used in cohort analyses. This definition was not validated and may have limited the power of our analyses. Further exploratory approaches may be required to refine this definition. Measurement of lung function in this study was limited to spirometry, with no lung

volumes recorded, and as a result the true pathology underlying the low-FVC pattern in particular is difficult to determine.

Lastly, several challenges were faced with CT and CXR imaging. Logistical challenges meant that different CT scanners and CXR modalities were used through the course of the study, and whilst sensitivity analyses suggest that the impact of this was likely minimal, this may have influenced findings. No validated reporting tool was available for post-TB lung damage, and one was designed for use in this study – this included several assumptions, including equal weighting of all CT lobes and CXR zones, which may have influenced our results. Manual reading of CT and CXR data resulted in high levels of inter-reader variability, with pragmatic decisions made for consensus review and generation of 'final' scores – machine reading to provide 'objective' measures of pathology may provide a more valid approach.

Across all parameters, interpretations of patterns of change over time were based on 2-3 time points for each individual only. The observed trends to improvement observed may be a result of regression to the mean, expected test-retest variation, or participant learning on repeated testing, but the presence of a subgroup of individuals who deteriorated over time is perhaps reassuring against this. Longitudinal data with multiple ongoing measurements is required to determine if these patterns persist, and further analyses using MCID values to classify changes seen over time may help to determine the clinical relevance of observed patterns.

Although this study was intended to be observational, it is likely that participants received a higher level of support and care than would have been received within routine services, as a result of regular 6-monthly contact with the study team. Efforts were made to signpost individuals to routine services, rather than providing treatment through the study itself, but the fact that individuals received regular testing and review will likely have improved their outcomes.

Finally, this thesis includes multiple exploratory analyses, with no corrections used for multiple comparisons. It is possible that some of the relationships identified are the result of chance alone. Several of the models constructed are vulnerable to over-fitting, with more than 1 variable included per 10 outcome 'events', such that the parameter estimates are vulnerable to bias.[242] This is a single site study, and duplication of this study in diverse sSA settings, with larger total populations and more outcome events would help to reinforce findings and increase confidence in results.

5.5 CONCLUSION

To my knowledge, this study is the first to comprehensively describe the residual lung damage that persists following PTB disease along multiple parameters, together with associated outcomes, in HIV positive and negative adults in sSA.

We found a considerable burden of residual lung damage at TB treatment completion: 60.7% of individuals continued to experience regular respiratory symptoms on a weekly or monthly basis, 34% of participants were left with abnormal patterns of spirometry, and the majority had abnormal imaging with a median of 1.4 lobes of abnormal parenchyma, and moderate-severe bronchiectasis seen in 44%. A trend to recovery was observed over the 1-year follow up period across multiple parameters, but this was on average incomplete, such that the burden of pathology remained high at 1-year following TB treatment completion.

We found that whilst HIV-infection is protective against post-TB lung damage, the burden of pathology amongst people living with HIV is substantial and cannot be ignored – 58% of HIV infected adults had ongoing monthly respiratory symptoms at treatment completion, 28% had abnormal spirometry, and the median amount of abnormal parenchyma in this group was still 1.1 lobes-worth. Whilst severity of disease was reduced in this group, patterns of post-TB pathology remain similar to those those without HIV. This is further reason to prioritise the investigation of post-TB lung damage in sSA, where the burden of HIV-TB co-infection remains high.

Severe post-TB lung damage at TB treatment completion was associated with adverse outcomes 1-year later: the odds of both regular monthly respiratory symptoms and an impaired quality of life at 1-year were three-fold higher amongst those with both extensive structural damage and abnormal airway physiology at treatment completion. However, despite this finding, and the high burden of pathology observed within the cohort, only 2.2% of participants had been recognized as having a chronic lung disease requiring further medical input by the point of TB treatment completion. This is particularly concerning given the high rates of concurrent respiratory exposures seen in this cohort – 1/3 were ever smokers, over 1/5 of men reported previous cannabis use, and 84% used biomass fuels for cooking or heating water – further compounding their risk of adverse respiratory events. There is clearly an unmet need for respiratory services for this patient group, in this setting.

Perhaps as might be expected, rates of ongoing health service use were high with 16% of participants having at least 1 unscheduled health service visit for deteriorating respiratory symptoms in the 1-year follow up period. However, no relationship was found between the extent of post-TB lung damage and the incidence of an exacerbation, perhaps due to limited study follow up and power. Ongoing longitudinal follow up is required to better determine the relationship between residual post-TB lung damage and the rate of respiratory exacerbations.

Finally, this study has found that adults treated for PTB in this suffer a large economic hit from TB disease, and continue to experience dissaving with a limited recovery in employment and income even after treatment completion. Perhaps as a result 9.5% of the cohort took children out of school to help in the home during in the 1-year follow up period. This is clearly of concern for the long-term wellbeing of the household, and means that participants may be particularly vulnerable to the impact of physical morbidity experienced following PTB disease.

6 CONCLUSION

This thesis has focused on post-TB lung damage – the residual lung pathology that persists after successful treatment for pulmonary TB disease. There are two global health agendas which make this a timely contribution: firstly, the increasing recognition of NCDs including chronic lung disease as an important cause of morbidity and mortality in resource poor settings,[243] and secondly, the recognition that integrated, patient centred approaches are needed for TB care if we are to mitigate the long-term impact of disease on patients and their households. These agendas have been enshrined in the 2017 Sustainable Development Goals, and the 2015 End TB strategy.[64 244] This PhD sits very much at the intersection between these agendas. Perhaps the key message of this work is that given the high burden of TB sequelae such as post-TB lung damage, the NCD and TB agendas should be thought of as very much interlinked. In tuberculosis, as well as many other diseases relevant to LMICs, the boundaries between 'infectious' and 'non-infectious' disease are increasingly blurred and approaches to clinical care, research, and policy would likely benefit from being re-designed to reflect this.

• POST-TB LUNG DAMAGE IS COMMON AND IMPORTANT

In the literature and systematic reviews completed during this PhD we found few studies of post-TB lung damage in the sSA context, and HIV positive individuals specifically. This maybe explained by a focus on improving diagnosis and reducing mortality in these groups to date – it is indeed true that TB case fatality rates remain unacceptably high in many LMICs. However, TB related mortality is gradually falling, and global treatment success rates are currently 83%, such that the long term well being of survivors also needs to be prioritized.

The cohort study presented in Chapter 5 of this PhD was a prospective study of post-TB sequelae in sSA which focused specifically on the long-term wellbeing of TB survivors. This study showed that the respiratory and economic wellbeing of many individuals remains limited long after successful completion of PTB treatment. A considerable burden of residual lung pathology was seen amongst HIV positive and negative groups at PTB treatment completion, with ongoing respiratory symptoms in 60%, abnormal spirometry in 34%, bronchiectasis in 44% and at least 1 destroyed lobe in 10% of adults, and extensive pathology at treatment completion was associated with increased odds of poor quality of life and ongoing symptoms even 1-year later. Incomplete recovery of income and employment was widespread, and ongoing dissaving in relation to poor health continued in half the cohort in the year after treatment completion. Although current TB services discharge patients as 'cured' at the end of standard short-course treatment, with no ongoing follow-up, the findings of this study suggest that for many, physical impairment and economic vulnerability persist.

• IMPLICATIONS FOR FUTURE RESEARCH

The high burden of post-TB lung damage reported in this cohort study is of concern. Further work is required to understand how it might be prevented, and once present, how it might be managed. However, if this research field is to grow in a collaborative and cohesive way, consensus is first required in the terminology used to describe post-TB lung pathology, and standardized measures of disease severity and patient outcomes must be agreed. In the absence of clear definitions, researchers working in this field will find it difficult to compare findings across sites in order to generate cohesive guidelines for further research or clinical management. Data from the cohort study presented here may provide some basis for these definitions, but this needs to be a joint effort drawing together all those with an interest in this area. Once terminology has been agreed, I would suggest that there are several areas of research which should be prioritised: understanding the heterogeneity of post-TB lung pathology, measuring associated physical and economic outcomes over a longer follow up duration, and designing interventions to improve these outcomes.

Much heterogeneity has been observed in the patterns of residual pathology amongst those completing treatment for PTB disease, and the evolution of this pathology over time. This wide spectrum is likely a product of host, pathogen, and environmental exposures, and it is only by understanding these factors that we we will be able to design upstream interventions to minimize severe forms of TB related lung damage, and reduce rates of decline in lung function over time. Further analysis of cohort data from this PhD may be of some use here: data driven phenotyping of patterns of post-TB damage may allow us to define categories of participants amongst whom exposures can be compared, and individual level analyses using mixed effects models may allow us to understand the reasons for the diverse trajectories of improvement / decline seen between individuals.

Data from CLD cohorts in resource rich settings suggest that pathology of the nature seen in this context is likely to be associated with adverse outcomes including respiratory exacerbations and mortality. However, the cohort study presented here was likely underpowered to detect these associations. Prolonged follow-up of post-TB patients with outcomes measured over at least 2-5 years will be required in order for us to ascertain the range of physical and economic outcomes which post-TB lung damage is associated with in settings such as Malawi.

If an association with 'hard' adverse outcomes such as exacerbations and mortality is seen, intervention studies will be needed to determine whether these outcomes can be significantly improved. Individuals at high risk of adverse outcomes will need to be defined, and screening tools which can be used to identify these individuals in resource poor settings developed. Potential interventions to improve outcomes may include patient education, chest physiotherapy, appropriate antibiotic use during infective exacerbations, and appropriate TB screening approaches in the event of worsening symptoms. Strong links between TB and medical services will be required to deliver

these. These interventions could perhaps be trialled as a 'package of care' in high risk groups in different locations.

Finally, in addition to studies focused specifically on post-TB lung damage, I would also argue that studies targeted at improving TB health systems, diagnostics and treatment regimens should broaden their focus from microbiological and mortality outcomes, to include measurement of morbidity aswell. Long-term quality of life amongst survivors of TB disease is important, and the impact of novel interventions along the TB treatment cascade in improving this may be significant and should be 'costed' into their assessment.

• IMPLICATIONS FOR CLINICAL PRACTICE AND PUBLIC HEALTH POLICY

At present, the major message for communication to health care providers in sSA is increased awareness of post-TB lung damage. Whilst most individuals completing TB treatment are well with only minor respiratory deficits at TB treatment completion, there are a subset with severe residual lung pathology. For this group, the end of TB treatment is not the end of their illness, and ongoing support may be required. TB officers should be advised to encourage patients who have marked breathlessness and cough at TB treatment completion to present early to health care providers for review, in the event of a deterioration of their symptoms, and general advice on avoiding smoking and cannabis use should be provided. Where patients do present with chronic or worsening respiratory symptoms after a previous episode of PTB, post-TB lung damage should be considered within the differential diagnosis. Caution in the isolated use of the XPert MTB/Rif test for diagnosis of TB disease recurrence soon after TB treatment completion should be encouraged.

It is perhaps too early to advocate for changes in health systems to support individuals with post-TB lung damage – we do not yet know whether these individuals are truly at risk of 'hard' adverse outcomes such as exacerbations and mortality, and we do not yet know whether available interventions would mitigate these outcomes. Ongoing clinical follow-up of these individuals is likely to be costly for both patients and providers, and cost-benefit for all parties must be considered carefully once outcome and intervention data are available.

• SUMMARY

This thesis marks the start of an area of research, rather than its completion. Clearly there is much to be done before we will be able to make clinical and public health recommendations for the management of post-TB lung damage in LMICs. However, the high burden of disease identified within this thesis requires that this work be actively pursued. It is hoped that in time, this will contribute to both mitigating the impact of non-communicable lung diseases, and providing integrated care for vulnerable PTB patients in resource poor settings such that they are able to live healthy and productive lives in the long-term.

7 APPENDICES

7.1 APPENDIX 1: CT IMAGING PROTOCOL

Low dose high resolution CT imaging was performed as per the protocol below. CT data (scout images, axial images, dose data) were saved to disk immediately after the imaging, with one disc per patient. Each disc was labelled with the patient initials, study ID, and date. Due to limited storage capacity at the scan sites, all raw data were deleted from the scanners following completion of the session. Images were anonymised and saved as DICOM files onto an external hard drive and the institutional server. Hard copies of imaging CDs were stored in a secure location within the research institution.

Figure 1: CT chest imaging protocol

Topogram

mA	kV	Scan time	Slice	Topogram length	Tube position	Direction	API	Kernel	Window	Tilt
50	120	5.3 sec	1.0 mm	512 mm	Top	Cranio-caudal (Supine)	Inspiration	T20s Standard	Topogram body	0.0°

Scan

Eff mAs	kV	Scan time	Delay	Slice	CTDL Vol	Pitch	Acquisition	Care dose
50 may depend on patient size	120 may depend on patient size.	12.05	5 sec	Volume HRCT 1mm x 1mm intervals	3.90 mGy	1.15	Spiral scan	Care Dose 4D

Processing

Recon	Image order	Recon increment	Kernel	Window	FOV	Centre X	Centre Y	3D
Axial	Cranial-caudal	1.0mm	B60f	Lung window	380	0 mm	0 mm	VRT & MIP as needed

7.2 APPENDIX 2: SPIROMETRY QUALITY CONTROL

All pre- and post- spirometry attempts recorded for each patient were reviewed by 2 readers (JM & LZ) independently, and graded for errors according to the CDC National Institute for Occupational Safety & Health (NIOSH) guidelines, and the BOLD study quality control procedures (Table 1).[229 230] Tests were reviewed in chronological order in batches of 100 through the duration of the study, with feedback provided to technicians as required.

Table 1: Grading criteria for individual spirometry trials, with source of guidelines listed

Reason for rejection of spirometry curve	Abbreviation for error	Definition of error	Reference/ source
High PEFT	p (PEFT)	PEFT ≥150msecs	BOLD QC requirements, which relaxed the ndd cut off of 120ms
High BEV	b (BEV)	BEV ≥150ml AND BEV ≥5% of FVC	ATS criteria, NIOSH, BOLD QC requirements state that for a curve to be included BEV must be <5% or <150ml, whichever is greater.
Non-maximal effort	e (effort)	Marked lack of peak, indicating weak blast OR Markedly reduced peak compared to other curves, indicating poor filling of lungs at start of test	BOLD QC requirements ATS criteria NIOSH guidelines
Early termination of expiration	t (termination)	Insufficient expiratory phase on volume-time curve – duration of expiration for < 6 secs OR failure to reach plateau of ≥1 sec OR Sharp early drop to 0 on flow-volume curve	BOLD QC requirements ATS criteria NIOSH guidelines
Extra breath	x (extra)	Visible extra breath on flow-volume and or the volume-time curves	BOLD QC requirements NIOSH guidelines
Glottis closure that influences measurement	g (glottis)	Abrupt flat line on volume-time curve, with sharp drop to 0 on flow-volume curve	BOLD QC requirements ATS criteria NIOSH guidelines
Leak	l (leak)	Descent of volume-time curve, after peak is reached, with 'back-track' of flow-volume curve at the end of expiration	BOLD QC requirements ATS criteria NIOSH guidelines
Obstructed mouthpiece	o (obstruction)	Artefact in the flow-volume and volume-time curves, felt to be significant enough to affect measurement	BOLD QC requirements ATS criteria NIOSH guidelines
Cough that affects measurement	c (cough)	Cough within 1st second which is likely to alter FEV_1, or a later cough which causes early termination.	BOLD QC requirements ATS criteria NIOSH guidelines
Zero flow error	z (zero)	Continuous rise of volume-time curve, with no plateau, and long tail on flow-volume curve, which is felt related to error rather than obstructive impairment	BOLD QC requirements NIOSH guidelines

PEFT: Peak expiratory flow time; BEV: Back extrapolated volume
BOLD: Burden of Obstructive Lung Disease Study; ATS: American Thoracic Society; NIOSH: National Institute for Occupational Safety & Health, Centres for Disease Control & Prevention; QC: Quality Control.

Curves where both readers had identified errors were excluded from analysis. In the event of discrepancy between readers, grading was resolved by consensus discussion.

7.2.1 MANUAL REVIEW

Despite the scoring process above, the selected curves for several patients were noted to have prolonged forced expiratory times (FET), possibly related to zero-flow errors with inaccurate zeroing of the spirometer prior to testing. In order to ensure that curves with zero flow errors were not included in the analysis, the 5% of spirometry readings with the longest FET times on the 'best test' at any one study visit were manually reviewed. Traces obtained for the patient at this study visit were compared with those obtained from the patient at previous / later study visits to identify

abnormalities. Spirometry tests felt to have zero flow errors, as evidenced by a linear trend on the volume-time curve, an inconsistent high FVC, and the long FET, were re-classified as not-valid and were not used.

In addition, spirometry readings with the 1% highest and lowest post-bronchodilator maximal FEV1 and FVC values were manually reviewed, and readings compared across study visits to ensure consistency and accuracy. Curves which were clearly inconsistent with other data for a given patient and in whom there was suspicion of an error in study ID or test performance, were classified as not-valid and were not used.

7.2.2 DATA EXTRACTION FROM USABLE TRACES

The following data were extracted separately for pre- and post-bronchodilator spirometry attempts from usable curves only: maximum and next-best FEV_1 maximum and next-best FVC values, FEV_1/FVC ratio. Neither PEF or MEF_{25-75} readings were recorded: PEF is effort dependent, and variation in an individual over course of a day can be up to 20%; Mid expiratory flows are highly dependent on posture and positioning, and because flow measurements are taken at a fixed % but different absolute volumes of the FVC, there is limited ability to compare values between people or over time if the FVC changes.

Repeatability was assessed for usable pre- and post-bronchodilator spirometry attempts for each participant at each study visit by calculating the difference between the maximum and next-best FEV_1 and FVC values. BOLD quality control guidelines require a maximum difference of ≤200ml between the best and next best measurements in order to deem the data valid, whilst the ATS criteria are stricter and require a difference of ≤150ml. For this analysis, data meeting the more relaxed BOLD quality control guidelines were included. Only those spirometry recordings where both post-bronchodilator FEV and FVC readings were repeatable by BOLD standards were used in the analysis.

This means that data was used for a given patient at a given study visit only if 2 usable curves with no errors were available, and if the differences between both the best/next-best FEV_1 and FVC readings across these curves were <200ml. Patients with either no usable post-bronchodilator curves, or with usable curves which did not meet these repeatability criteria, were defined as having ‘missing’ data for this test.

7.3 APPENDIX 3: CT METHODOLOGY DEVELOPMENT

7.3.1 CT SCORING SYSTEM

The CT scoring system used is described in Table 2. Notes generated by the scoring radiologists during the interim / final data reviews are included, and were used to guide data analysis and interpretation.

Table 2: Final CT scoring system used for data analysis, including notes of clarification / concern generated during the course of the study, which may influence how data are interpreted, or inform the design of future studies

Initial name of variable	Initial definition	Scoring options	Notes Generated after r/v of 20 images	Notes – generated during & after review of full dataset
PARENCHYMAL VARIABLES Scored at lobar level. Mutually exclusive variables, summing to 100% for each lobe.				
Parenchymal bands	Linear opacity 1-3mm thick, up to 5cm long. Usually extends to visceral pleura. May be accompanied by anatomical distortion	% of lobe (to nearest 5%)	Interlobular septal thickening to be scored as parenchymal bands if few, and likely resolving inflammation. If extensive or likely related to fluid or other cause, to document in free text.	
Atelectasis	Reduced volume accompanied by increased lucency in the unaffected part of the lung. May be accompanied by displacement of fissures, bronchi, vessels.	% of lobe (to nearest 5%)	To be estimated as the proportion of the normal lobe which has been lost. Eg. One collapsed lung segment in the upper lobe would be 35% atelectasis in the lobe.	Where lobes are completely collapsed, the collapsed parenchymal tissue remains and occupies space. The approach to scoring this collapsed tissue was not discussed in the initial scoring system. Completely collapsed lobes were variably scored as having either 100% atelectasis, or a high % of atelectasis + a limited % of consolidation.
Consolidation	Homogeneous increase in lung parenchymal attenuation which obscures the margins of vessels and airway walls. An air bronchogram may be present.	% of lobe (to nearest 5%)	Thickened wall of a cavitated area and surrounding consolidation to be included in consolidation % score. Classical TB rosettes to be included under consolidation, rather than as tree in bud or nodules	No category of 'other' was included in the % parenchymal score either. Where indeterminate interstitial change was seen, this was classified under consolidation. As such, % consolidation is a broad category that included any type of opacity which did not meet criteria for GGO, nodules, or parenchymal banding, so covers both large areas of dense opacity, as well as areas with indeterminate interstitial change.
Ground glass opacification	Hazy increased lung opacity with preservation of bronchial and vascular margins	% of lobe (to nearest 5%)		
Mosaicism	Areas of reduced lung parenchymal attenuation. Component of the mosaic attenuation	% of lobe with darker areas (to nearest 5%)	In absence of any other signs of airways disease, and in presence of pulsation /	

	pattern, where a patchwork of differing lung attenuation is seen.		breathing artefact, changes should not be scored as mosaicism. Unless unequivocally visible, do not score	
Emphysema	Focal areas or regions of low attenuation usually without visible walls	% of lobe (to nearest 5%)	Appearances consistent with 'classical emphysema'	
Emphysematoid destruction	Focal area of destruction / emphysematous change associated with features of healing TB, suggesting destruction of small airways.	% of lobe (to nearest 5%)	Clear association of emphysematous change (areas of decreased lung attenuation) with signs of TB healing.	
Cavities / cystic airspaces	Gas filled space, seen as a lucency or low-attenuation area within a pulmonary consolidation, a mass, or a nodule. Consolidation may have resolved leaving a thin wall only.	% of lobe (to nearest 5%)	Parenchyma destroyed by cystic airspaces connected to a dilated bronchus will be scored as a cavity, in this section of the scoring tool	Combining 'absent' parenchyma due to either cystic bronchiectasis or true cavitation within this % parenchymal category was a pragmatic decision, and reflects the reality that these pathologies can be very hard to differentiate on imaging, particularly where a cavity has ruptured through into an airway However, this approach means that the scoring system cannot differentiate between these two pathologies, even when the difference was relatively clear. This means that it is not possible to differentiate between negative outcomes associated with the % of tissue destroyed by cystic bronchiectasis, and the % destroyed by cavitation. Finally, it means that this category is likely mislabelled and should be referred to as 'absent' parenchyma, rather than parenchyma destroyed by cavities.
Normal	Normal parenchyma, not affected by any of the pathological processes above	% of lobe (to nearest 5%)		Areas of parenchyma with normal airspaces but interspersed discrete nodules or tree in bud were classified as 'normal' here.
BRONCHIECTASIS VARIABLES Scored at lobar level. Extent assessed first, with Pattern and Severity scored only if bronchiectasis seen.				
Bronchiectasis Airway lumen diameter greater than accompanying pulmonary	Extent	0: Absent 1: ≤1 BP segment 2: 2 BP segments 3: ≥ 3 BP segments		The scoring system did not allow for differentiation of which airways were dilated – this category therefore includes dilatation of both small peripheral airways and the large central airways.

artery outer diameter, OR Airways visible in the lung periphery, OR Lack of normal tapering	Pattern (Scored only if bronchiectasis seen and 'extent' score >0)	1: Cystic (Ballooned' outline, with diameter increasing towards periphery) 2: Cylindrical (Regular and straight outline, with abrupt termination) 3: Varicose (Irregular bronchial outline, with bulbous termination)	Score as cystic bronchiectasis only if appearance typical of this, with a dilated airway connected to an area of destroyed parenchyma. Otherwise should be scored as a slightly dilated bronchus related to a cavity.	If bronchiectasis was present, only 1 pattern could be selected to describe this. In reality, multiple patterns of airway dilatation were often visible in each lobe. In choosing which pattern to document, the reader could choose either the dominant pattern, or the pattern considered to be most important. The approach to this was not specified in the SOP and so may have varied between readers / scans.
	Severity Maximum degree of airway dilatation, to be measured by comparing diameter of airway lumen to diameter of adjacent vessel. (Scored only if bronchiectasis seen and 'extent' score >0)	1: Trivial (bronchial lumen is <twice adjacent vessel diameter) 2: Bronchial lumen is 2-3 times adjacent vessel diameter 3: Bronchial lumen is >3 times adjacent vessel diameter	Overall 'gestalt' impression of severity of dilatation, including both large and small airways	Scores ≥2 were taken to denote moderate-severe airway dilatation.
AIRWAY VARIABLES Scored at lobar level. All variables independent of each other.				
Bronchial wall thickening	Thickening of bronchial walls	0: Absent 1: Mild 2: Moderate 3: Severe Missing: Unable to assess	Score as unable to assess if not measurable due to adjacent collapse / consolidation.	
Mucous plugging	Mucous seen in proximal large airways	0: Absent 1: Mild 2: Moderate 3: Severe		In fact, this category includes obstruction of the airway by any opacity – it is not possible to differentiate the obstructing material, and in the context of post-TB change, this may be TB related granuloma rather than mucous. This category is likely mislabelled and should be referred to as 'airway plugging'.
Tree in bud	Centrilobular branching pattern, resembling a budding tree. Most pronounced at the periphery.	0: Absent 1: Mild 2: Moderate 3: Severe		The scoring system includes what others have referred to as 'micronodules' as tree in bud change, on the grounds that the pathology underlying this is likely to be the same (inflammatory changes in the Centrilobular peripheral small airways)
CAVITY VARIABLES Scored at lobar level. Independent of parenchymal scores. Extent scored first, with size and severity scored only if cavities seen				

Cavity Gas filled space, seen as a lucency or low-attenuation area within a pulmonary consolidation, a mass, or a nodule. Consolidation may have resolved leaving a thin wall only. Mycetoma	Extent	0: Absent 1: 1-2 cavities 2: 3-5 cavities 3: >5cavities	Any markedly dilated airway leading to a cavity will be scored as bronchiectasis, rather than a cavity The category of cavity will include -Cavities which are 'closed' and unrelated to airspaces -Cavities which are 'open' and related to airspaces but where the airway is not clearly dilated / bronchiectatic	Cavities were scored in 2 ways for each lobe, within any given scan: - % parenchyma affected by cavities - Extent of cavities seen (absent / 1-2 / 3-5 / >5 cavities) These variables were not 'linked' within the database during initial scoring, which generated mismatches requiring review in the by the consensus reading process.
	Maximum size	Maximum diameter (mm)		
	Mycetoma Discrete mass of hyphae, within a cavity. May have air crescent sign. May have sponge like pattern with areas of calcification.	0: Absent 1: Present	If uncertain whether this is lung necrosis or aspergilloma, score as the latter.	
OTHER LOBAR VARIABLES Scores at lobar level				
Nodules	Rounded opacities, well or poorly-defined, >5mm, measuring up to 3cm in diameter	0: Absent 1: <5 nodules 2: ≥5 nodules 3: Miliary	If multiple 3-5mm nodules are seen only, to document in free text. Should be documented as an alternative, non-TB diagnosis.	Where multiple dense opacities were seen, likely related to TB rosettes, these were variably scored as consolidation in the % parenchymal score section, or nodules in the categorical variables, or as both. The extent to which this was done differently by readers is not possible to identify.
WHOLE LUNG VARIABLES Scored at level of hemithorax / whole lung				
Pleural effusion	Accumulation of fluid within pleural space	0: Absent 1: Present		
Pleural thickening	Pleural thickening of ≥10mm	0: Absent 1: Present		
Lymph nodes	Mediastinal / hilar lymph nodes ≥10mm diameter	0: Absent 1: Present		
DOMINANT PATHOLOGY Impression of reporting radiologist, after review of individual variables above				
Compatible with resolving PTB – No other pathology				These categories presume that residual consolidative / nodular change was resolving rather than active disease, but in practice it is of course difficult to tell. Terminology should be changed to denote that pathology is consistent with 'recent' PTB instead of resolving PTB.
Compatible with resolving PTB, plus other diagnosis				
Resolving PTB or other diagnosis equally likely				
Not compatible with resolving PTB, other diagnosis likely				

7.3.2 CT CONSENSUS REVIEW

Given the large number of variables measured in this study, a pragmatic approach was taken to the selection of variables for consensus review: imaging patterns that were rarely seen and felt unlikely to have a statistically significant impact on patient outcome (Eg. pleural pathology, airway narrowing), and those which are known to be poorly identified using non-contrast HRCT, and had very poor inter-reader agreement in the original data set (Eg. lymphadenopathy) were not consensus reviewed.

Consensus review was completed for the scans with the most discrepant scores for the remaining variables (Table 3). For continuous variables, the most discrepant ~5% of scans for each variable were selected for review: assuming that the difference in scores between readers had a normal distribution, this rule identified scans with differences >2 standard deviations away from the mean difference. Using this rule, whilst the number of scans re-read for each variable was similar, the magnitude of discrepancy tolerated varied widely, according to the spread of differences in reports between original readers. For example, only scans reported with differences of ≥160 points between readers for mosaicism were re-read, whilst those with differences ≥25 points in emphysema scores were re-read. This is, however, in keeping with usual practice in radiology scoring methodology.

Table 3: Methods used to select scans for consensus review of the CT variables, with both the number of scans reviewed and the approach underlying this decision given

Variable group	Variable reported (Range of scores available for this variable at the whole lung level)	Threshold difference in scores between readers, at which review performed	Number of scans for r/v	Method of selecting scans and lobes for consensus review
Parenchymal variables	Atelectasis (integer, 0-600)	≥60 points	20	Lobar % scores for each parenchymal variable were summed across the 6 lobes for each reader, so that a minimum score of 0 was allocated if the variable was not seen anywhere in the lung, and a maximum score of 600 was given if all the lung parenchyma was affected by this pathology. The difference between the total lung scores generated by each reader was calculated for each scan, for each parenchymal variable. These differences were plotted on a histogram, and the most discrepant 5% of scans were identified for each variable. If a scan was identified as highly discrepant for a given parenchymal variable, this variable was reviewed by the consensus reader in all the lobes where there had been any disagreement in the % score between readers. Because parenchymal scores for different variables were mutually and additive to 100% within each lobe, reallocation of scores for one variable within a lobe invariably meant that all parenchymal variables for this lobe required rescoring. Of note - where % cavities were scored as >0% by the consensus reader, the other categorical cavity
	Parenchymal banding (integer, 0-600)	≥75 points	22	
	Consolidation (integer, 0-600)	≥40 points	18	
	Ground glass opacification (integer, 0-600)	≥60 points	22	
	Mosaicism (integer, 0-600)	≥160 points	22	
	Emphysema (integer, 0-600)	≥25 points	18	
	Emphysematoid destruction (integer, 0-600)	≥15 points	18	
	Cavities (integer, 0-600)	≥25 points	23	
	Normal lung (integer, 0-600)	≥170 points	21	

				variables for the lobe in question were also reviewed and rescored (cavity extent, maximum size, mycetoma) to ensure consistency.
	TOTAL	110 scans		Total number of lobes rescored across pathologies: RUL 96 (24.9%), RML 71 (18.4%), RLL 82 (21.2%), LUL 104 (27.0%), LML 93 (24.2%), LLL 89 (23.1%).
Bronchiectasis	Whole lung bronchiectasis extent score (integer, 0-18)	≥6 points	20	For bronchiectasis extent and severity scores, the lobar scores were summed across all 6 lobes to give a minimum score of 0 (variable not seen) and a maximum score of 18 (maximum severity / extent reported in all lobes) for each reader, for each scan. Differences in the total lung extent / severity scores between readers were calculated, and the 5% of scans with the biggest differences were selected for review. For these scans, all lobes with any disagreement in severity or extent scores between readers were reviewed by the consensus scorer.
	Whole lung bronchiectasis severity score (integer, 0-18)	≥6 points	25	
	Whole lung presence / absence of bronchiectasis (binary)	N/a	79	Any scans with overall disagreement about the presence / absence of any bronchiectasis in the lung between readers were reviewed.
	Number of lobes affected (integer, 0-6)	≥3 lobes	30	Because the overall presence / absence of bronchiectasis and the number of lobes affected by moderate pathology was thought to be of clinical relevance, the total number of lobes with a severity score ≥2 was summed for each scan, giving a total lung score of range 0 (No lobes affected by moderate-severe bronchiecatasis) to 6 (All lobes affected). The 5% of scans with the biggest discrepancy in the number of affected lobes between readers were identified, and lobes in which there was disagreement within these scans reviewed. Of note - for all reviewed lobes, where bronchiectasis was reported as 'present' by the consensus scorer, details about the severity / extent / pattern of bronchiectasis were also reviewed by the consensus scorer.
	Whole lung bronchiectasis pattern score (integer, 0-18)	≥6 points	20	The pattern of bronchiectasis is a nominal rather than ordinal variable – whilst there can be a progression of pathology from tubular to varicose to cystic damage as severity of disease worsens, this is not always the case and cannot be assumed. Having said that, for the purpose of identifying discrepant scans this simplification was felt to be acceptable. The variable was treated as ordinal within each lobe, and a whole lung pattern score was generated for each scan by summing these scores across lobes. The 5% of scans which were most discrepant for this score were consensus reviewed.
	TOTAL	105 scans		
Cavities / cystic airspaces	Whole lung presence / absence of cavities or cystic airspaces	N/a	58	The approach to selection of scans for review of cavity and mycetoma variables was similar to that described above for the whole lung presence/absence, and overall extent scores for bronchiectasis. For all reviewed lobes - where cavities were reported as present by consensus reader, details about maximum size / presence of mycetoma were also consensus reviewed.
	Whole lung cavity /cystic airspace extent score (integer, 0-18)	≥4 points	23	
	Whole lung presence / absence of mycetoma (binary)	N/a	10	

	Maximum cavity size (size in mm)	≥22mm	20	The initial plan had been to take one reader's score for cavity size only, with no consensus review. However, given the issue identified with cavity / cystic bronchiectasis scoring, it was felt that large discrepancies in cavity size could be used to identify scans with differential classification of cystic bronchiectasis and cavities between readers. The 5% of scans most discrepant for the maximum cavity size were therefore also consensus reviewed.
	Parenchymal change allocated to cavities/cystic airspaces, but no cavities seen, in at least 1 lobe	≥10% parenchyma in lobe	7	Cavities were scored in 2 ways for each lobe, within any given scan: % parenchyma affected by cavities/cystic airspaces Extent of cavities seen (absent / 1-2 / 3-5 / >5 cavities) Mismatches were seen between the reports given by a single reader for a single lobe using these two approaches as they were not 'linked' within the database during initial scoring. Both the parenchymal % scores and cavity variables were therefore consensus reviewed for lobes in which cavities > 10mm were reported, but no % parenchyma was allocated to cavities, and lobes in which >10% parenchyma was allocated to cavities but no cavities were reported in any lobe.
	Cavity seen, but no % parenchyma allocated, in at least 1 lobe	≥10mm cavity seen in lobe	26	
	TOTAL	100 scans		
Nodules	Whole lung nodule extent score (integer, 0-18)	≥5	22	Approach as above, for bronchiectasis extent score
	TOTAL	22 scans		
Other airway variables	Whole lung tree in bud severity score (integer, 0-18)	≥9	20	Approach as above for bronchiectasis severity score
	Whole lung airway plugging severity score (integer, 0-18)	≥5	18	
	Whole lung bronchial wall thickening severity score (integer, 0-18)	≥8	22	There were a number of scans where it was deemed 'not possible' to report the severity of bronchial wall thickening, due to surrounding pathology, in at least one lobe. For the purpose of identifying scans for consensus review of this variable, values were generated for these 'missing' lobes by taking the average score across all of the other scored lobes. This assumes relative uniformity of the degree of bronchial wall thickening across the lung, including the area where other pathology was dominant and direct scoring not possible. Total lung scores were then calculated using these imputed values, and the 5% of scans with the most discrepant values for this variable reviewed by the consensus reader.
	TOTAL	54 scans		
ALL VARIABLES	TOTAL SCANS FOR REVIEW	239 scans, requiring review of at least 1 lobe		

7.3.3 GENERATION OF FINAL DATA SET FROM ORIGINAL & CONSENSUS READS

The approach used to generate a final dataset, from the 2 original independent reads, and the data produced by consensus review of discrepant variables for the 239 scans identified above, is outlined below:

- Where agreement seen between original readers

Where there was agreement between original readers for a given variable in a given lobe, the agreed-on score was used as the final result.

- Where consensus read available

Where there was discrepancy between original readers, but a consensus read was available for a given variable within a given lobe, this consensus read was used as the final data point for this lobe. It was noted that some variables (eg. emphysema, emphysematoid destruction) were systematically scored higher by the consensus reader. It is accepted that using these reads, available for a subset of the scans only, as the 'correct' score will have biased the data for these scans towards the consensus' scorers approach, but this is accepted as a limitation of the method.

- Where neither consensus nor agreement between readers

As described above, it was not possible to consensus score all scans for all variables – only the most discrepant scans for a subset of variables were re-read. For variables where discrepancy was seen but no consensus review had been completed, several potential options for deriving a single combined data point from the divergent original reads were considered, with different approaches used for different variables (Table 4). A pragmatic decision was made not to consider complex imputation frameworks / multilevel models, which are time and labour intensive to develop.

Table 4: Approaches to generating 'final scores' for variables where no consensus read, and disagreement between original readers

Approach	Details	Pros	Cons	Variables this approach used for
Single reader	Use of data from one reader only, for full analysis	Can be used for sensitivity analysis, to check relationships identified using 'combined' output – are these findings robust, across readers.	Biases towards the approach of a single reader	Nil
Average of scores between readers	Numerical average of scores generated by original readers	Includes data from both readers in unbiased way. Appropriate for continuous / ordinal variables only.	Not suitable for nominal variables, where categories cannot be treated as sequential / incremental.	% parenchymal pathology Airway and cavity severity / extent scores Maximum cavity size

			Where categorical variables are treated as numerical, there is an assumption that levels are equidistant apart (ie. gap from level 1 to 2 is the same as distance from level 2 to 3)	
Random selection of original reads	Randomly select the reports given by one or other reader.	Can be used for all variables – including nominal. Makes no assumptions about 'distance' between categories for categorical variables Can be validated by repetition.	Only makes use of half of data. Difficult to assess the impact of any single reader's approach, on results.	Bronchiectasis pattern
Reader agreement required	Pathology counted as present only when identified by both readers Where disagreement, pathology classes as uncertain OR absent	Provides 'conservative' estimates of the presence of any pathology	Likely to bias against more complex scans, where disagreement between readers likely larger.	Nodule pattern Mycetoma
Either reader can identify	Pathology counted as present if either reader identifies this	Provides more lenient estimate of the presence of a given pathology – appropriate where under-reporting likely	Gives lenient estimate of pathology, so may include borderline cases	Pleural pathology

Discrete variables which were felt to be ordinal (ie. increasing in severity / extent, with each category) were treated as numerical: the final score was the average of the scores from the original readers. These variables include parenchymal % scores, bronchiectasis severity & extent scores, tree in bud / mucus plugging / bronchial wall thickening severity scores, cavity extent & maximum cavity size scores.

Discrete scores which were non-ordinal and could not be thought of as numeric could not be averaged in this way. This included bronchiectasis pattern, nodule pattern, and binary presence/absence scores where variable categories likely reflect distinct pathology, and progression between them cannot be assumed. Specific approaches were needed for these variables. Specific approaches taken for certain variables are described together with the study findings, below:

- Bronchiectasis pattern

For lobes in which there was disagreement in bronchiectasis pattern and no consensus review was available, a random selection of one of the the patterns reported by the original readers was used. This approach assumes that both original readers were equally likely to be the 'correct' interpretation of the image.

In lobes deemed to contain moderate to severe bronchiectasis, random selection of pattern was required for the following number of scans: RUL n=37/78 scans, RML n=8/15, RLL n=19/35, LUL

n=38/80, LML n=10/39, LLL n=14/39. We must acknowledge that there is some uncertainty about the bronchiectasis patterns in these lobes/scans.

- Bronchial wall thickness score

As described above, the whole-lung bronchial wall thickness score was missing for 15% of scans (58/385). These were a biased sample of scans in which more severe pathology is seen, and imputation was therefore not used here. Instead, bronchial wall thickening data was simply acknowledged as missing for these ore complex scans, and no 'final' score was generated for these.

- Nodules

The total number of lobes in which mismatched original reads for the nodule pattern were seen, and no consensus reads were available was high: RUL n=118, RML n=65, RLL n=81, LUL n=111, LML n=70, LLL n=94. All lobes where miliary pathology was reported had either been consensus read, or had agreement between original readers.

Mismatches between the number of nodules seen were considered less important than differences in the overall presence / absence of nodules. A collapsed variable was therefore created here, with nodules described as present in a lobe if either the consensus scorer or both original readers reported <5/≥5/miliary nodules, and absent if either the consensus reader or both original readers reported this as absent. Data were reported as 'unclear' where there was no consensus review, and one reader had reported nodules as absent / the other had reported as present. One possible cause for this, based on discussion with readers and review of the data, is differential classification of lesions as consolidation rather than nodules in some cases.

- Mycetoma

Mycetoma were a rare finding within the dataset, and were generally small / difficult to identify. A conservative estimate of prevalence was therefore obtained with the pathology only said to be present if either the consensus or both original readers reported it as such. The pathology was scored as absent when there was disagreement.

- Pleural pathology

For pragmatic reasons, no consensus reads were completed for pleural pathology. Pleural effusion or thickening is relatively easy to detect on imaging. Review of discrepant scans suggested that this in cases where discrepant scores were seen, pathology was usually clearly visible on review, suggesting likely underscoring. Pleural effusion and thickening on the right and left sides were collapsed down into a single variable, and pathology was therefore scored as present if either reader scored it as such.

- Lymphadenopathy

Lymphadenopathy was reported with a high level of inconsistency between readers, and in fact reporting on non-contrast HRCT imaging is known to be unreliable. It was therefore decided that no attempt would be made to generate a single 'final' score for these patterns, and data from the original readers are shown here only (Table 5).

Table 5: Reporting of lymphadenopathy by the two original CT image readers, using non-contrast HRCT imaging

Reader 1	Reader 2		
	Absent	Present	Total
Absent	332 (86.2%)	16 (4.2%)	348
Present	30 (7.8%)	7 (0.2%)	37
Total	362	23	385

- Cavities

Cavities were reported in two sections of the reporting tool, which were unlinked – the amount of parenchymal in each lobe affected by cavities / cystic airspaces, as well as a binary yes/no score for the presence / absence of cavities and a measurement made by 1 reader for the size of the largest cavity seen. On review of the data, it was felt that the parenchymal score was likely the more accurate description of the amount of tissue lost in relation to cavities / cystic airspaces – these features being difficult to differentiate – and this value was therefore used in the analysis.

7.3.4 GENERATION OF NEW CT VARIABLES FOR ANALYSIS

- Whole lung presence/absence & lobar counts

Binary presence / absence scores were generated for the airway variables, in order to count the number of lobes affected by these pathologies. In the scoring system used here, the severity of bronchiectasis, bronchial wall thickening, tree in bud, mucus plugging, and airway narrowing were scored in each lobe on a 4-point scale: absent (0), trivial or mild (1), moderate (2) or severe (3). Once scores had been averaged between readers, the possible 'final' scores ranged from 0-4 with intervals of 0.5. A cut off value of 2.0 was chosen to define the presence / absence of pathology: a pattern was deemed to be absent if the average final score was <2, and present in a lobe only if the final score was ≥2. In practical terms, in the absence of a consensus score, this means that only lobes where both original readers scored moderate pathology (score of 2) OR where one scored it as trivial (score of 1) and the other scored as severe (score of 3) were counted as having this pathology present. Lobes where one scored pathology as absent (score of 0) and the other as severe (score of 3) would average to 1.5 which is below the required threshold. Whole lung presence/ absence scores, and counts of the total number of lobes affected by each of these pathologies, were generated from these lobar presence / absence scores.

- Extensively damaged or 'Destroyed' lobes

During reporting it was noted that a high proportion of patients have a focal concentration of residual parenchymal pathology within the lung, with complete 'destruction' of one lobe but relatively normal parenchyma seen elsewhere. Such focused pathology may act as a source of infection and clinical complications, but may not be captured by the whole lung pathology scores being used here.

In order to capture this pattern of damage, a composite variable was generated at a lobar level:

- The amount of atelectasis, parenchymal banding and lung tissue destroyed by cavities/cystic airspaces was summed at a lobar level. These pathologies were chosen as they reflect lung tissue which is non aerated and non-functioning, and were thought to describe the patterns of damage most commonly seen in destroyed lungs most accurately.
- Lobes were classified as destroyed if ≥90% of parenchyma was occupied by these pathologies. A cut off of 90% was selected instead of 100% as even when lobes are almost completely destroyed, often a small amount of normal / consolidated tissue remains.

- Atelectasis & parenchymal banding

Some conflation between atelectasis and banding was noted within the data. These pathologies are similar in aetiology and appearance – both are seen as densities on imaging with volume loss +/- anatomical distortion resulting from compressed lung parenchyma. The key difference tends to be in volume and shape, with atelectasis tending to be larger in size, and banding often linear in appearance. For the purposes of analysis, these variables have been joined, and the amount of tissue affected by atelectasis and banding will be reported together.

- % Abnormal parenchyma

The amount of abnormal lung tissue seen in each scan was summed, to generate a combined variable for the total % of abnormal lung tissue in each scan. A second version of this variable was created, including all patterns of pathology except mosaicism – this pattern reflects gas trapping within the lung tissue, rather than pathology of the tissue itself, and is therefore somewhat distinct.

7.4 APPENDIX 4: CXR METHODOLOGY DEVELOPMENT

7.4.1 CXR SCORING SYSTEM

As above, the CXR scoring system is described below together with notes generated by the scoring radiologists during reporting and data reviews (Table 6).

Table 6: CXR scoring variables & definitions – including notes generated during scoring process

Initial name of variable	Initial definition	Scoring options	Notes
PARENCHYMAL VARIABLES Scored at lobar level. Mutually exclusive variables, summing to 100% for each lobe.			
Parenchymal bands	Linear opacity 1-3mm thick, up to 5cm long. Usually extends to visceral pleura. May be accompanied by anatomical distortion.	% of lobe (to nearest 5%)	Bronchial wall thickening should be considered for linear changes seen centrally and extending out to the peripheries, anatomically following airways.
Consolidation / ground glass	Consolidation: Homogeneous increase in lung parenchymal attenuation which obscures the margins of vessels and airway walls. An air bronchogram may be present. OR Ground glass appearance: hazy increase in opacification with preservation of bronchial and vascular margins	% of lobe (to nearest 5%)	Initially a category for consolidation only was included. However, less dense areas of opacification were also recognized during scoring and difficult to clearly differentiate, and as such were included here. For these less dense areas the % of lung opacification was estimated and scored within this section.
Cavities / cystic airspaces	Gas filled space, seen as a lucency or low-attenuation area within a pulmonary consolidation, a mass, or a nodule. Consolidation may have resolved leaving a thin wall only.	% of lobe (to nearest 5%)	Large areas of destroyed lung tissue to be scored as cavitation – list 100% if full lobe destroyed and absent.
Atelectasis	Reduced volume accompanied by decreased opacity in the unaffected part of the lung. Signs of volume loss should be seen, and may include: displaced hila / fissures / bronchi, narrowed rib spacing, tortuous trachea, hyper-expansion and linear vessels extending through other lung zones	% of lobe (to nearest 5%)	Where a whole lobe is collapsed, this lobe should be considered as 1 zone of the lung field. The remaining uncollapsed lung field on this side should be divided into 2 zones for scoring. Compression of the lung by an external feature (e.g. pleural effusion), should not be scored as atelectasis. The visible parenchyma should instead be scored independently, adding up to 100%.
CAVITY VARIABLES Reported at a lobar level			
Cavity	Gas filled space, seen as a lucency or low-attenuation area within a pulmonary consolidation, a mass, or a nodule. Consolidation may have resolved leaving a thin wall only.	0 = Absent 1 = 1-2 cavities 2 = 3-5 cavities 3 = >5cavities	
		Maximum diameter of largest cavity, in mm	Not possible to record for hard images, where no scale was available.
Mycetoma	Discrete mass of hyphae, within a cavity. May have air crescent sign.	0 = Absent 1 = Present	
OTHER LOBAR VARIABLES			
Nodules	Rounded opacities, well or poorly-defined, ≥5mm, measuring up to 3cm in diameter.	0 = Absent 1 = <5 2 = ≥5 3 = Miliary	Defined opacities to be called nodules. Confluent / poorly defined opacities to be called consolidation.
Ring & tramline markings	Prominent ring-shaped opacities representing thickened airways seen	0 = Absent 1 = Mild 2 = Moderate	If an area of lung is collapsed / opaque and it is not possible to judge airway thickening, score as absent.

	end-on, or parallel lines if seen longitudinal.	3 = Severe (whole zone)	
WHOLE LUNG VARIABLES			
Hyper-expansion	Large lung fields with flattened hemidiaphragms.	0 = Absent 1 = Present	
Pleural thickening	Visible pleural thickening ≥10mm with any distribution over visceral / parietal surfaces.	0 = Absent 1 = Present	Measure depth from the inside of the inner edge of the adjacent rib to the edge of the pleura. Loss of the CP angle can be attributed to thickening if the appearance is not typical for ongoing fluid (no clear meniscus) and the rest of the image is consistent with chronic damage.
Pleural effusion	Accumulation of fluid within the pleural space, identified by blunted costophrenic angle +/- visible meniscus.	0 = Absent 1 = Present	
Lymph nodes	Prominent mediastinal or hilar lymph nodes.	0 = Absent 1 = Present	
Dominant pathology			
Compatible with resolving PTB – No other pathology		As per the impression of the reader	
Compatible with resolving PTB, plus other diagnosis			
Resolving PTB or other diagnosis equally likely			
Not compatible with resolving PTB, other diagnosis likely			

7.4.2 SELECTION OF IMAGES FOR CXR CONSENSUS REVIEW

The approach to identifying the most discrepant images / variables for consensus review is shown in Table 7 below. As for CT imaging, a pragmatic approach was required to limit the number of images requiring review.

- Cavity size

  During the process of scoring it became clear that specifying the number of cavities on CXR is complex and inaccurate. Because a high proportion of images were taken on hard film it was also not possible to specify the diameter of cavities on all images. The presence / absence of cavities was therefore derived from the % cavity parenchymal score, and data on the number / size of lesions was not used and not consensus reviewed.

- Ring & tramlines

  The level of discrepancy at which consensus review of zonal ring and tramline scores was conducted was pre-set at a difference of ≥2 points between readers (the worse severity recorded was Absent vs. Moderate, Mild vs. Severe, or Absent vs. Severe). Discrepancies smaller than this were felt likely to be clinically meaningless.

- Hyperexpansion

  Review of a subset of CXRs which were discrepant for this variable showed very clearly that this variable was much more consistently reported by the more experienced reader (EJ – the trained radiologist). For pragmatic reasons, rather than performing formal discrepancy review of all CXRs where there was disagreement for this variable, readings entered by EJ only were used only here.

- Lymphadenopathy

  This was rarely reported, and where it was, there was high discrepancy. As for non-contrast CT imaging, the reporting of lymphadenopathy on CXR in this population was felt to be highly unreliable, and unlikely to influence the study outcomes. For pragmatic reasons no consensus was performed for this variable, and data were not used.

Table 7: Methods used to select scans for consensus review of the CXR variables, with both the number of scans reviewed and the approach underlying this decision given for baseline and 1-year visit

Variable group	Variable (type, potential scores)	Baseline visit (n=403)			1-year visit (n=361)			Identification of scans / lobes for discrepancy review
		Cut-off difference for r/v	Method of deciding cut off	Scans for r/v	Cut-off difference for r/v	Method of deciding cut off	Scans for r/v	
Parenchymal variables	Atelectasis (integer, 0-600)	≥40 points	5% cut off	26	≥40 points	5% cut off	24	As for CT imaging
	Parenchymal banding (integer, 0-600)	≥15	Cut off adjusted from 10 to 15	5	≥15	Cut off adjusted from 10 to 15	7	
	Consolidation / ground glass (integer, 0-600)	≥55	5% cut off	23	≥35	5% cut off	22	
	Cavities / cystic airspaces (integer, 0-600)	≥25	Cut off adjusted from 20 to 25	20	≥35	5% cut off	18	
	Normal lung (integer, 0-600)	≥60	5% cut off	25	≥60	5% cut off	19	
	TOTAL	61 X-rays			63 X-rays			
Ring & Tramline (R&T)	Whole lung maximal severity of R&T (0-3)	≥2 points	Cut off 2 points empirically chosen	59	≥2 points	Cut off 2 points empirically chosen	56	Variable denoting the maximal severity of ring & tramline pathology identified across lung generated (range 0-3), and the differences between readers calculated. X-rays where the maximum severity reported between readers differed between 'Absent' and 'Mild' were assumed to be 'Absent', and no consensus review was performed. However, all X-rays with a 2 point difference in the maximum severity between readers were reviewed.
	Whole lung R&T severity score (integer, 0-18)	≥6	Cut off adjusted from 5 to 6	13	≥5	5% cut off	21	Lobar scores for ring & tramline severity were summed across 6 lobes, giving a minimum score of 0 (variable not seen), and a maximum score of 18 (maximum severity / extent in each lobe). The 5% most discrepant X-rays for the total severity score, across lung, were identified, and zones with discrepancy of for R&T severity within these x-rays were reviewed.
	TOTAL	67 X-rays			66 X-rays			

Nodules	Whole lung presence / absence of nodules	N/a	N/a	84	N/a	N/a	84	A variable denoting the presence or absence of nodules anywhere in the lung was generated, and compared between reader. Xrays discrepant for this variable were reviewed. Zones with discrepancy for presence / absence to be reviewed.
	Whole lung nodule extent score (integer, 0-18)	≥3	Cut off adjusted from 2 to 3	15	≥3	Cut off adjusted from 2 to 3	13	As for whole lung R&T severity score
	Whole lung maximal nodule score (0-3)	N/a	N/a	91	N/a	N/a	102	As for whole lung R&T maximum nodule score
	TOTAL	98 X-rays			103 X-rays			
Cavities	Whole lung presence / absence of cavities	N/a	N/a	70	N/a	N/a	84	A variable denoting the presence or absence of cavities and mycetoma, anywhere in the lung was generated, and compared between readers. X-rays discrepant for presence / absence of cavities or mycetoma were reviewed.
	Whole lung presence / absence of mycetoma (binary)	N/a	N/a	2	N/a	N/a	2	
	Mismatch between parenchymal % and categorical cavity sections	N/a	N/a	14	N/a	N/a	N/a	Both the % parenchymal score, and the categorical cavity score were compared – zones in which mismatch between these variables were seen (one reporting the presence of cavities and the other reporting absence or 0%) were reviewed. Required for baseline visit only.
	TOTAL	75 X-rays			85 X-rays			
Whole lung variables	Presence / absence of any pleural pathology	N/a	N/a	49	N/a	N/a	52	X-rays discrepant for presence / absence of any pleural pathology (either pleural thickening or effusions) were reviewed.
	TOTAL	49 X-rays			52 X-rays			
ALL VARIABLES	TOTAL XRAYS FOR REVIEW	203 X-rays requiring review of at least 1 zone			218 X-rays requiring review of at least 1 zone			

7.5 APPENDIX 5: *A PRIORI* PTLD CASE DEFINITION

In order to determine the relationship between post-TB lung damage (PTLD) as an 'exposure' at TB treatment completion, and ongoing morbidity over the duration of the 1-year cohort follow-up, a PTLD case definition was required. As no validated definitions, measurement systems, or severity scores for PTLD were identified in the literature review, a new *a priori* definition was generated here through consensus discussion with the team of respiratory / TB physicians[2].

Although the pattern, extent and severity of lung pathology seen in a post-TB cohort is likely to be high, for reasons of study power and in keeping with the study hypothesis it was decided that this *a priori* PTLD definition should be binary and aim to simply differentiate between those with marked lung damage likely to be clinically relevant and those with milder/absent damage which may be less meaningful.

7.5.1 PARAMETERS FOR INCLUSION IN PTLD DEFINITION

As noted in the literature review, established prognostic scores used in other chronic respiratory conditions including bronchiectasis, COPD, and pneumonia include multiple measures of respiratory pathology to capture disease severity. Spirometry is widely used across scores, with imaging parameters included in bronchiectasis prognostic scores, and the decision was taken to include both of these as objective measures of damage in the *a priori* PTLD definition.

The following parameters were not included, for the reasons given:

- Clinical parameters such as BMI and 6-minute walk distance – vulnerable to confounding by common comorbidities in our study cohort, including HIV co-infection.
- Symptoms such as MRC-dyspnoea – vulnerable to confounding by co-morbidities, and may reflect the consequence of respiratory damage rather than the nature of the damage itself.
- Respiratory microbiology – not available within this study.
- History of previous exacerbations – confounded by the recent episode of PTB experienced by every member of this cohort, and likely subject to significant recall bias
- Hypoxia – potentially a sign of severe lung pathology, but marked hypoxia in the absence of the imaging or spirometric abnormalities already included within the definition felt to be unlikely.

[2] Professor E Jane Carter – Respiratory physician, past President of The Union; Dr Jeremiah Chakaya – Respiratory physician, current President of The Union; Professor Bertie Squire – Infectious Diseases physician, past President of The Union; Dr Peter Macpherson – Intermediate Wellcome Fellow & Senior Lecturer in Public Health; Dr Jamilah Meghji – study PI

SPIROMETRY PARAMETERS

Both airway obstruction and spirometric restriction have been shown to be associated with previous TB disease, but the extent to which they are associated with adverse patient outcomes in PTLD is unclear. Both of these abnormal patterns were therefore included in the binary PTLD definition (Table 8).

Of note – because evidence for adverse outcomes in relation to airway obstruction are stronger if the FEV_1 is reduced in addition to the FEV_1/FVC ratio,[147] only those with both an obstructive ratio and a reduced FEV_1 were included in the PTLD group.

Table 8: Spirometric PTLD criteria

Category	FEV1/FVC ratio	FEV1	FVC
Obstruction	<LLN	<LLN	n/a
Low FVC	≥LLN	n/a	<LLN

*LLN: Lower limit of normal, as classified using GLI 2012 reference ranges

IMAGING PARAMETERS

As TB has been shown in previous studies to result in both parenchymal and airway pathology, and there is no clear literature on the relationship between these parameters / the relative importance of each in determining patient outcomes, both were included in the *a priori* definition (Table 9).

- AIRWAYS PATHOLOGY

Bronchiectasis affecting ≥3 lobes on CT imaging was used as a marker of severity in both the BSI and FACED scores.[134 135] Whilst these scores were developed and validated in cohorts who are profoundly different to the PTB patient population in urban Blantyre, Malawi, it is biologically plausible that similar CT features remain poorly prognostic across settings / populations, and this cut off has therefore been used to define severe airway disease in PTLD here. Because of the consensus approach used in reading the CT imaging, only lobes containing moderate – severe bronchiectasis were included.

For simplicity, more complex aspects of airway pathology including the type of bronchiectasis (cystic, varicose, or tubular) and the degree of bronchial wall thickening were not included within this core definition, but were still measured on CT reporting such that their relationship with outcomes can explored in the future if required.

- PARENCHYMAL PATHOLOGY

The extent of parenchymal pathology was not included in any of the most widely used prognostic scores described above. However, parenchymal damage was a dominant feature in the descriptions of PTLD identified in our systematic review, and has been shown to have prognostic implications in other studies. In their prospective cohort study of 169 COPD patients, Boutou et al. developed a clinical algorithm for prognostic scoring which included both pulmonary function and imaging parameters,[245] They found that the average HRCT emphysema score (ES: the average % of each lobe affected by emphysema) and the functional residual capacity (FRC) were the strongest predictors of mortality, and developed a clinical prognostic tool whereby patients with ES<30% were classified as low risk, those with ES≥65% were classified as high risk, and those with ES scores between these values were classified as low or high risk depending on their FRC volumes. In their prospective study of 215 patients with Scleroderma related interstitial lung disease, Goh et al. showed that the % extent of disease on HRCT and the % FVC were associated with patient outcome, and a developed a similar prognostic tool where those with <10-20% disease on HRCT were defined as having limited ILD, those with >20-30% disease on HRCT defined as having extensive ILD, and those in between defined according to their % FVC value.[246]

Although these studies relate to ILD and COPD, it is plausible that parenchymal pathology covering a similar proportion of the lung parenchyma is significant in the case of PTLD, and the decision was taken to include a variable denoting the extent of abnormal parenchyma in our PTLD prognostic score. Because the relative importance of each pattern of parenchymal pathology is not known, the decision was taken to use a cumulative variable including all patterns of parenchymal pathology. The extent of mosaicism, which reflects gas trapping rather than parenchymal damage, was not be included in this definition. A cut off for the extent of parenchymal damage of 30% was chosen, to reflect the findings of the papers described above.

Table 9: Structural PTLD criteria

Category	Definition
Airway pathology	Moderate to severe bronchiectasis affecting ≥3 lobes on CT imaging
Parenchymal pathology	≥30% abnormal parenchyma, with any pattern excluding mosaicism

COMBINED SPIROMETRY & IMAGING PTLD DEFINITION

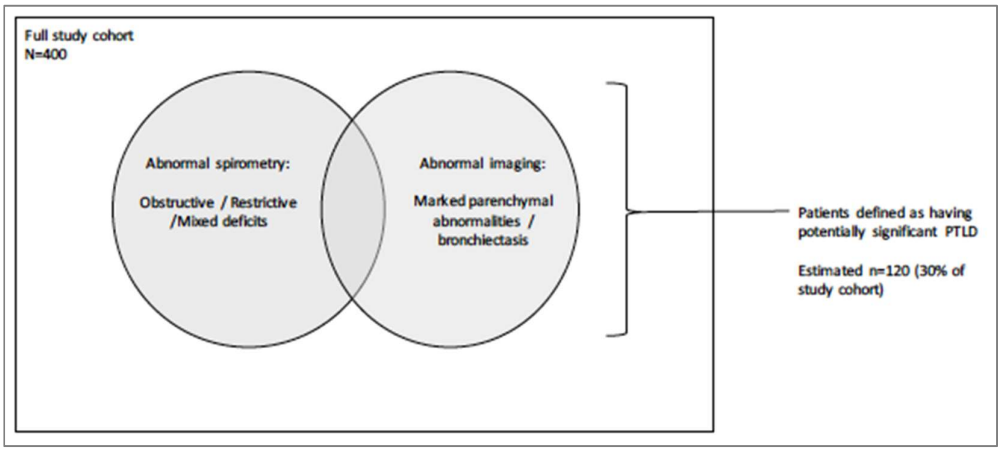
The final *a priori* definition of PTLD is a binary, composite definition, including both spirometry and imaging findings (Table 10). Incomplete overlap between these features is expected (Figure 2), such that participants can be defined as having PTLD with either abnormal spirometry or imaging, or – perhaps in the most severe cases – abnormalities detected using both of these modalities.

Table 10: Composite *a priori* definition of PTLD

Criteria	PTLD present
Abnormal spirometry OR	Airway obstruction with FEV1/FVC ratio<LLN & FEV1<LLN OR Low FVC with FEV1/FVC ratio≥0.7 & FVC<LLN
Abnormal CT Imaging	Moderate-severe bronchiectasis in ≥3 lobes OR Parenchymal abnormality of ≥1/3 of the lung tissue

LLN: Lower limit of normal, as classified using GLI 2012 reference ranges

Figure 2: Schematic of *a priori* PTLD definition



7.6 APPENDIX 6: FACTORS PREDICTING SPIROMETRY

FEV_1, FVC, AND FEV_1/FVC RATIO AT TB TREATMENT COMPLETION

Table 11: Factors associated with the absolute FEV_1 and FVC volume (ml), and the FEV_1/FVC ratio (%) at TB treatment completion. ß coefficients (95% CI) presented. Complete case analysis (n=330)

Variable	FEV_1 (L) (n=330)			FVC (L) (n=330)			FEV_1/FVC percentage#(n=330)		
	Univariate associations	'Standardised" univariate^	Multivariate model R^2 0.455	Univariate associations	'Standardised" univariate^	Multivariate model R^2 0.505	Univariate associations	'Standardised" univariate^	Multivariate Model $R^2$0.165
Age (yrs)	-4.6 (-11.8 – 2.6)		-12.6 (-18.6 – -6.7)***	4.9 (-3.3- 13.1)		-5.3 (-11.7 – 1.2)	-0.3 (-0.4 – -0.2)***		-0.3 (-0.4 – -0.2)***
Male gender	690.6 (552.9 – 828.3) ***		401.1 (231.2 – 571.0)***	911.0 (761.8 – 1060.1)***		480.9 (296.2 – 665.6)***	-1.9 (-3.9 – 0.2)		-0.1 (-2.9 – 2.7)
Height (cm)	50.3 (43.1 – 57.7)***		37.9 (28.8 – 47.0)***	62.9 (55.0 – 70.8)***		47.2 (37.3 – 57.2)***	-0.0 (-0.2 – 0.1)		-0.0 (-0.2 – 0.1)
HIV status (vs negative) - Positive, CD4≥200 cells/uL - Positive, CD4<200 cells/uL	-63.5 (-232.5 – 105.5) 113.3 (-73.7 – 300.2)	73.2 (-60.9 – 207.3) 230.1 (78.4 – 381.9)**	47.8 (-85.0 – 180.6) 189.9 (40.4 – 339.4)*	-76.4 (-269.2 – 116.4) 133.7 (-79.5 – 347.0)	59.8 (-85.2 – 204.9) 191.6 (27.3 – 355.8)*	26.5 (-117.8 – 170.8) 170.5 (8.0 – 333.0)*	0.4 (-1.9 – 2.6) 0.5 (-2.0 – 3.0)	1.2 (-1.0 – 3.4) 2.8 (0.3 – 5.3)*	1.2 (-1.0 – 3.3) 2.1 (-0.4 – 4.5)
Positive baseline TB microbiology	21.5 (-154.0 – 197.1)	-49.8 (-188.6 – 88.9)	22.1 (-117.2 – 161.5)	38.9 (-151.4 – 239.3)	-15.7 (-165.2 – 133.7)	17.0 (-134..5 – 168.5)	-0.4 (-2.7 – 2.0)	-1.2 (-3.5 – 1.0)	0.1 (-2.1 – 2.4)
BMI at TB treatment completion (kg/m²)	21.7 (-3.7 – 47.1)	43.5 (23.5 – 63.6)***	38.6 (18.3 – 58.8)***	28.8 (-0.12 – 57.2)	51.9 (30.5 – 73.4)***	51.5 (29..5 – 73.5)***	0.0 (-0.3 – 0.4)	0.1 (-0.2 – 0.5)	-0.0 (-0.4 – 0.3)
Illness duration ≥1-month prior to TB treatment	-148.6 (-29.97 – 2.5)	-119.5 (-237.9 – -1.0)*	-116.1 (-231/8 – 0.3)*	-113.3 (-286.2 – 59.7)	-84.4 (-212.3 – 43.6)	-72.6 (-198.5 – 53.2)	-2.1 (-4.0 – -0.1)*	-1.9 (-3.8 – 0.0)	-2.1 (-4.0 – -0.2)*
Ever smoking	198.3 (38.5 – 358.1)*	-128.32 (-265.8 – 9.3)	-87.3 (-226.6 – 52.1)	382.0 (202.7 – 561.2)***	-45.4 (-195.7 – 104.9)	-23.1 (-174.6 – 128.4)	-3.2 (-5.3 – -1.1)**	-2.7 (-4.9 – -0.4)*	-1.5 (-3.8 – 0.8)
Poorest 3x SES quintiles	-246.9 (-391.7 – -102.2)**	-139.9 (-278.8 – -1.0)*	-99.2 (-226.4 – 28.0)	-162.1 (-329.2 – 5.04)	-58.8 (-184.4 – 66.9)	-12.9 (-151.2 – 125.4)	-3.6 (-5.5 – -1.7)***	-3.4 (-5.2 – -1.5)***	-2.8 (-4.9 – -0.7)**
Intermittent food insecurity	-254.7 (-406.5 – -102.9)**	-155.7 (-271.3 – 40.0)**	-10.3 (-139.8 – 119.2)	-211.7 (-386.3 - -37.1)*	-29.9 (-161.8 – 102.0)	36.8 (-104.0 – 177.6)	-2.5 (-4.5 – -0.4)*	-2.5 (-4.5 – -0.5)*	-1.1 (-3.2 – 1.0)

*p<.05, **p<.01, ***p<.001; #The FEV_1/FVC ratio given as a % rather than a proportion here (eg. 80% rather than 0.8) for ease of interpretation of ß coefficients; ^Standardised univariate: associations between each predictor and outcome, controlling / standardizing for age, gender & height

Table 12: Factors associated with Airway Obstruction or Low FVC at TB treatment completion. OR (95% CI) presented.

Variable	Airway obstruction, compared to normal (n=267)		Low FVC, compared to normal (n=283)	
	Univariate associations	Multivariate model	Univariate associations	Multivariate model
Age (yrs)	1.01 (0.98 – 1.04)	1.01 (0.98 – 1.05)	0.95 (0.92 – 0.98)**	0.96 (0.92 – 0.99)*
Gender - Female - Male	 1.0 1.03 (0.52 – 2.05)	 1.0 0.84 (0.30 – 2.38)	 1.0 0.67 (0.37 – 1.19)	 1,0 0.99 (0.41 – 2.37)
Height (cm)	0.99 (0.95 – 1.03)	1.01 (0.95 – 1.07)	0.98 (0.95 – 1.02)	0.99 (0.94 – 1.04)
HIV status - Negative - Positive, CD4>=200 cells/uL - Positive, CD4<200 cells/uL	 1.0 0.59 (0.29 – 1.20) 0.30 (0.12 – 0.74)**	 1.0 0.50 (0.22 – 1.10) 0.30 (0.11 – 0.80)*	 1.0 0.74 (0.40 – 1.37) 0.27 (0.12 – 0.64)**	 1.0 0.82 (0.44 – 1.75) 0.42 (0.17 – 1.07)
Baseline TB microbiology - Negative - Positive	 1.0 1.37 (0.62 – 3.02)	 1.0 0.72 (0.29 – 1.78)	 1.0 1.54 (0.75 – 3.16)	 1.0 1.11 (0.50 – 2.46)
BMI at TB treatment completion (kg/m^2)	0.86 (0.75 – 0.98)*	0.91 (0.79 – 1.05)	0.86 (0.76 – 0.97)*	0.89 (0.79 – 1.01)
Illness duration prior to TB treatment - <1-month - ≥1-month	 1.0 1.68 (0.84 – 3.36)	 1.0 1.79 (0.86 – 3.74)	 1.0 1.20 (0.67 – 2.15)	 1.0 1.28 (0.68 – 2.39)
Ever smoking - Never - Ever	 1.0 1.55 (0.80 – 2.98)	 1.0 1.03 (0.45 – 2.36)	 1.0 0.78 (0.41 – 1.49)	 1.0 0.86 (0.40– 1.86)
Urban SES quintile - Least poor quintiles x2 - Poorest quintiles x3	 1.0 3.91 (1.85 – 8.25)***	 1.0 3.08 (1.31 – 7.23)*	 1.0 1.61 (0.91 – 2.84)	 1.0 1.31 (0.65 – 2.63)
Food insecurity - Never - Sometimes / often	 1.0 2.66 (1.40 – 5.06)**	 1.0 1.91 (0.91 – 4.01)	 1.0 1.91 (1.07 – 3.41)*	 1.0 1.65 (0.83 – 3.26)

*p<.05, **p<.01, ***p<.001

Obstruction - FEV_1/FVC ratio <LLN, using GLI-2012 reference range; Low FVC - FEV_1/FVC ratio ≥LLN & FVC<LLN, using GLI-2012 reference range

CHANGE IN FEV_1 OVER 1-YEAR FOLLOW UP

Table 13: Factors associated with change in absolute FEV_1 volumes (ml) over 1-year (n=290)

	Univariate associations	Participant characteristics R^2: 0.114	+ Baseline spirometry R^2:0.213	+ Baseline imaging R2: 0.127	+Respiratory events R^2 :0.126	Full multivariate model R^2:0.232
Age (yrs)	-2.6 (-4.9 – -0.2)*	-4.1 (-6.6 – -1.7)**	-5.7 (-8.1 – -3.3)***	-4.3 (-6.8 – -1.8)**	-4.1 (-6.6 – -1.7)**	-5.6 (-8.0 – -3.2)***
Male gender	72.4 (19.7 – 125.1)*	72.1 (-3.1 – 144.0)	125.9 (55.7 – 196.0)***	69.6 (-2.2 – 141.3)	72.8 (-1.2 – 144.4)*	131.2 (60.2 – 202.2)***
Height (cm)	3.5 (0.5 – 6.6)*	1.4 (-2.5 – 5.3)	6.4 (2.3 – 10.4)**	1.3 (-2.5 – 5.2)	1.2 (-2.7 – 5.1)	6.1 (2.0 – 10.2)**
HIV positive at TB treatment completion - CD4≥200 cells/uL - CD4<200 cells/uL	 86.1 (30.1 – 142.2)** 40.6 (-21.2 – 102.3)	 103.1 (47.2 – 159.0)** 68.6 (5.8 – 131.5)*	 108.0 (55.2 – 160.8)*** 93.2 (33.3 – 153.1)**	 104.5 (48.6 – 160.5)** 73.0 (10.2 – 135.8)*	 99.9 (43.8 – 156.0)** 64.7 (-0.4 – 128.9)	 105.9 (52.7 – 159.1)*** 86.4 (25.4 – 147.4)**
Positive baseline TB microbiology	-26.8 (-84.8 – 31.1)	-42.9 (-101.2 – 15.4)	-38.2 (-93.2 – 16.8)	-42.3 (-100.3 – 15.8)	-39.5 (-97.7 – 18.7)	-33.4 (-88.2 – 21.5)
BMI at TB treatment completion (kg/m^2)	-7.5(-16.2 – 1.2)	-4.2 (-13.2 – 4.8)	0.9 (-7.7 – 9.6)	-2.5 (-11.6 – 6.7)	-4.7 (-13.6 – 4.3)	0.21 (-8.5 – 8.9)
Ever smoking	46.6 (-6.2 – 99.4)	24.7 (-33.4 – 82.7)	12.7 (-42.2 – 67.6)	18.8 (-39.3 – 76.9)	25.3 (-32.7 – 83.4)	10.5 (44.6 – 65.6)
Poorest 3x SES quintiles	20.8 (-28.2 – 69.8)	16.4 (-37.7 – 70.5)	2.2 (-49.1 – 53.4)	12.1 (-42.0 – 66.2)	15.3 (-38.9 – 69.5)	-2.3 (-53.8 – 49.2)
Intermittent food insecurity	21.6 (-29.7 – 72.9)	17.3 (-37.4 – 72.0)	15.7 (-35.9 – 67.3)	16.7 (-37.8 – 71.3)	17.6 (-36.9 – 72.1)	16.9 (-34.6 – 68.4)
FEV_1 at TBRx completion (ml)	-0.04 (-0.08 – -0.01)*		-0.13 (-0.18 – -0.09)***			-0.14 (-0.18 – -0.09)***
≥1/3 abnormal parenchyma, except mosaicism	83.0 (17.8 – 148.1)*			72.1 (2.0 – 142.3)*		12.2 (-58.0 – 82.5)
≥3 lobes with mod-severe bronchiectasis	43.0 (-45.7 – 131.6)			-13.4 (-106.5 – 79.7)		-42.3 (-131.0 – 46.3)
Any OPD / IP respiratory visits	-81.0(-149.1 – -12.8)*				-24.8 (-96.9 – 47.3)	-41.1 (-109.2 – 27.0)
TB retreatment	-165.8 (-374.6 – 43.1)				-172.4 (-384.3 – 39.6)	-165.4 (-366.0 – 35.2)

*p<.05, **p<.01, ***p<.001

CHANGE IN FVC OVER 1-YEAR FOLLOW UP

Table 14: Factors associated with change in absolute FVC volumes (ml) over 1-year (n=290)

	Univariate associations	Participant characteristics R^2: 0.139	+ Baseline spirometry R^2:0.261	+ Baseline imaging R^2: 0.163	+Respiratory events R^2 :0.152	Full multivariate model R^2:0.291
Age (yrs)	-1.3 (-4.0 – 1.3)	-3.0 (-5.8 – -0.3)*	-3.7 (-6.2 – 1.2)**	-3.2 (-5.9 – -0.5)*	-2.8 (-5.6 – -0.0)*	-3.4 (-6.0 - -0.8)**
Male gender	111.1 (52.1 – 170.0)***	98.5 (18.5 – 178.5)*	165.3 (88.5 – 242.0)***	96.8 (17.4 – 176.2)*	100.4 (20.7 – 180.1)*	174.2 (97.3 – 251.1)***
Height (cm)	4.5 (1.1 – 8.0)*	1.3 (-3.0 – 5.6)	8.8 (4.3 – 13.4)***	1.1 (-3.2 – 5.3)	0.8 (-3.5 – 5.2)	8.2 (3.6 – 12.8)**
HIV positive at TB treatment completion - CD4≥200 cells/uL - CD4<200 cells/uL	 101.3 (38.2 – 164.5)** 73.3 (3.7 – 142.9)*	 126.3 (64.1 – 188.6)*** 102.9 (32.9 – 172.9)**	 126.1 (68.3 – 183.9)*** 129.9 (64.5 – 195.3)***	 130.5 (68.6 – 192.4)*** 108.4 (39.0 – 177.9)**	 119.7 (57.3 – 182.2)*** 91.6 (20.1 – 163.1) *	 123.2 (65.5 – 180.9)*** 115.7 (49.6 – 181.8)**
Positive baseline TB microbiology	5.6 (-59.9 – 71.2)	-9.5 (-74.3 – 55.4)	-3.1 (-63.4 – 57.1)	-8.3 (-72.5 – 55.9)	-4.6(-69.3 – 60.2)	4.1 (-55.5 – 63.7)
BMI at TB treatment completion (kg/m^2)	-15.8 (-25.6 – -6.0)**	-12.3 (-22.3 – -2.4)*	-4.4 (-14.0– 5.1)	-10.4 (-20.6 – -0.3)*	-12.7 (-22.6 – -2.7)*	-5.2 (-14.7 – 4.4)
Ever smoking	67.4 (8.0 – 126.8)*	24.9 (-39.7 – 89.5)	21.3 (-38.6 – 81.3)	15.6 (-48.7 – 79.9)	22.9 (-41.7 – 87.5)	14.0 (-45.7 – 73.8)
Poorest 3x SES quintiles	41.1 (-14.2 – 96.3)	16.8 (-43.4 – 77.0)	12.8 (-43.0 – 68.7)	9.6 (-50.2 – 69.4)	12.6 (-47.7 – 72.9)	3.0 (-52.7 – 58.7)
Intermittent food insecurity	37.9 (-19.9 – 95.8)	25.7 (-35.2 – 86.6)	33.6 (-22.9 – 90.2)	26.2 (-34.2 – 86.5)	24.9 (-35.8 – 85.6)	35.6 (-20.3 – 91.6)
FVC at TBRx completion (ml)	-0.04 (-0.08 – -0.00)*		-0.15 (-0.20 – -0.11)***			-0.16 (-0.21 – -0.11)***
≥1/3 abnormal parenchyma, except mosaicism	127.2 (54.3 – 200.1)**			109.8 (32.2 – 187. 5)**		40.6 (-35.0 – 116.1)
≥3 lobes with mod-severe bronchiectasis	39.6 (-60.6 – 139.8)			-56.3 (-159.3 – 46.8)		-92.8 (-189.0 – 3.4)
Any OPD / IP respiratory visits	-115.6 (-192.2 – 39.0)**				-61.5 (-141.7 – 18.7)	-79.9 (-153.8 – -6.0)*
TB retreatment	-120.3 (-356.9 – 116.2)				-109.5 (-345.4 – 126.3)	-114.4 (-332.0 – 103.2)

*p<.05, **p<.01, ***p<.001

FEV_1 AT 1-YEAR

Table 15: Factors associated with absolute volumes of FEV_1 (ml) 1-year after TB treatment completion (n=290)

	Univariate associations	'Standardised' univariate	Basic multivariate model R^2: 0.513	+ Baseline spirometry R^2: 0.924	+ Baseline imaging R2: 0.580	+Respiratory events R^2 :0.517	Full multivariate model R^2: 0.926
Age (yrs)	-6.5 (-14.1 – 1.05)		-15.5 (-21.4 – -9.6)***	-5.7 (-8.1 – -3.3)***	-14.4 (-19.9 – -8.8)***	-15.0 (-21.0 – -9.0)	-5.6 (-8.0 – -3.2)***
Male gender	772.1 (625.5–918.7)***		468.2 (196.2 – 640.3)***	125.4 (55.1 – 195.7)**	506.9 (345.9 – 667.9)***	473.3 (301.7 – 645.0)***	130.8 (59.5 – 202.0)***
Height (cm)	53.5 (45.8 – 61.2)***		39.2 (29.9 – 48.4)***	6.4 (2.4 – 10.4)**	38.7 (30.0 – 47.3)***	38.1 (28.7 – 47.4)***	6.1 (2.0 – 10.2)**
HIV positive at TBRx end - CD4≥200 cells/uL - CD4<200 cells/uL	 28.6 (-153.6 – 210.7) 175.3 (-25.4 – 376.0)	 154.4 (19.1 – 289.7)* 282.4 (129.6 – 435.1)***	 127.1 (-7.0 – 261.3) 243.7 (93.1 – 394.3)**	 107.1 (54.0 – 160.1)** 92.5 (32.4– 152.6)**	 141.6 (15.8 – 267.3)* 212.2 (71.5 – 353.0)**	 113.4 (-21.3 – 248.1) 218.1 (64.2 – 372.0)**	 105.3 (51.8 – 158.8)*** 86.0 (24.0 – 147.2)**
Positive baseline TB microbiology	26.9 (-159.8 – 213.7)	-77.0 (-217.3 – 63.4)	-12.7 (-152.0 – 126.6)	-38.6 (-93.7 – 16.6)	-12.2 (-142.1 – 117.7)	-2.6 (-141.9 – 136.7)	-33.6 (-88.7 – 21.4)
BMI at TB treatment completion (kg/m^2)	16.3 (-12.1 – 44.6)	40.4 (19.0 – 61.7)***	33.9 (12.4 – 55.3)**	0.9 (-7.7 – 9.6)	18.6 (-1.9 – 39.1)	33.4 (12.0 – 54.8)**	0.2 (-8.5 – 8.9)
Illness duration ≥1-month prior to treatment	-177.6 (-339.7 – -15.4)*	-138.2 (-259.2 – -17.1)*	-123.8 (-241.3 – -6.20)*	-9.4 (-56.3 – 37.5)	-80.8 (-191.3 – 29.6)	-117.4 (-234.8 – 0.01)	-5.6 (-52.5 – 41.3)
Ever smoking	255.8 (87.8 – 423.9)**	-109.8 (-249.7 – 30.2)	-64.5 (-203.2 – 74.1)	12.7 (-42.3– 67.8)	-35.6 (-202.6 – 40.1)	-70.6 (-209.4 – 68.2)	10.5 (-44.7 – 65.7)
Poorest 3x SES quintiles	-214.4 (-370.3 – -58.5)**	-155.0 (-273.0 – -36.95)*	-103.2 (-232.8 – 26.4)	1.2 (-50.4 – 52.7)	-81.2 (-202.6 – 40.1)	-112.7 (-242.6 – 17.3)	-2.8 (-54.6 – 49.0)
Intermittent food insecurity	-200.4 (-364.0 – -36.8)*	-76.3 (-200.3 – 47.7)	11.3 (-119.5 – 142.0)	16.2 (-35.6– 67.9)	24.4 (-97.7 – 146.5)	8.5 (-121.9 – 139.0)	17.2 (-34.4 – 68.8)
FEV_1 (ml) at TBRx completion	0.96 (0.92 – 0.99)***	0.88 (0.83 – 0.92)***		0.87 (0.82 – 0.91)***			0.86 (0.82 – 0.91)***
FVC (ml) at TBRx completion	0.76 (0.71 – 0.81)***	0.68 (0.62 – 0.75)***					
FEV_1/FVC ratio (%) at TBRx completion	28.9 (20.8 – 36.9)***	30.2 (24.3 – 36.1)***					
≥1/3 abnormal parenchyma, except mosaicism	-407.4 (-613.9 – -201.0)***	-549.2 (-695.4 – -402.9)***			-406.0 (-563.3 – -248.8)***		12.5 (-57.9 – 82.9)
≥3 lobes with mod-severe bronchiectasis	-492.4 (-772.4 – -212.5)**	-497.7 (-703.7 – -291.7)**			-243.1 (-452.0 – -34.3)*		-41.7 (-130.6 – 47.3)
Any OPD / IP respiratory visits	-357.1 (-574.7 – -139.5)**	-189.8 (-355.2 – -24.3)*				-139.1 (-311.6 – 33.3)	-40.8 (-109.1 – 27.5)
TB retreatment	-260.7 (-934.9 – 413.6)	-361.0 (-863.7 – 141.7)				-131.5 (-638.4 – 375.4)	-165.1 (-366.1 – 35.9)

*p<.05, **p<.01, ***p<.001

FVC AT 1-YEAR

Table 16: Factors associated with absolute volumes of FVC (ml) 1-year after TB treatment completion (n=290)

	Univariate associations	'Standardised' univariate	Basic multivariate model R^2: 0.576	+ Baseline spirometry R^2: 0.929	+ Baseline imaging R^2:0.628	+Respiratory events R^2: 0.583	Full multivariate model R^2: 0.932
Age (yrs)	3.9 (-4.7 – 12.5)		-7.2 (-13.4 – -0.9)*	-3.7 (-6.3 – -1.1)**	-6.0 (-11.9 – -0.12)*	-6.5 (-12.8 – -0.19)*	-3.4 (-6.0 – -0.9)**
Male gender	1014.6 (859.4 – 1169.7)***		526.3 (344.4 – 708.2)***	165.7 (88.8 – 242.7)***	567.5 (395.7 – 739.2)***	532.7 (351.6 – 713.8)***	175.5 (98.3 – 252.7)***
Height (cm)	67.7 (59.7 – 75.7)***		50.4 (40.6 – 60.2)***	8.8 (4.2– 13.4)***	49.7 (40.5 – 58.9)***	49.1 (39.2 – 58.9)***	8.1 (3.5 – 12.8)**
HIV positive at TBRx end - CD4≥200 cells/uL - CD4<200 cells/uL	 22.4 (-183.5 – 228.2) 240.7 (13.9 – 467.5)*	 143.6 (2.3 – 284.9)* 282.6 (123.1 – 442.0)**	 117.4 (-24.5 – 259.2) 272.1 (112.9 – 431.4)**	 126.8 (68.7 – 184.9)*** 130.5 (64.8 – 196.1)***	 136.0 (1.84 – 270.1)* 241.1 (91.0 – 391.2)**	 100.2 (-41.9 – 242.3) 240.0 (77.7 – 402.4)**	 124.5 (66.5 – 182.6)*** 116.6 (50.3 – 182.8)**
Positive baseline TB microbiology	96.2 (-115.3 – 307.6)	1.7 (-144.9 – 148.3)	28.7 (-118.6 – 176.1)	-2.9 (-63.3 – 57.5)	30.0 (-108.6 – 168.5)	41.2 (-105.8 – 188.1)	4.7 (-55.1 – 64.4)
BMI at TB treatment completion (kg/m^2)	16.7 (-15.4 – 48.9)	39.3 (17.0 – 61.6)**	38.5 (15.8 – 61.1)**	-4.4 (-14.0 – 5.1)	23.0 (1.17 – 44.9)*	38.0 (15.4 – 60.6)**	-5.1 (-14.7 – 4.4)
Illness duration ≥1-month prior to treatment	-136.7 (-321.4 – 47.9)	-92.2 (-219.0 – 34.6)	-70.0 (-194.3 – 54.3)	6.6 (-44.5 – 57.7)	-26.0 (-143.8 – 91.8)	-62.1 (-186.0 – 61.8)	12.7 (-38.0 – 63.4)
Ever smoking	456.9 (270.8 – 643.0)***	-5.9 (-152.3 – 140.5)	2.7 (-143.9 – 149.4)	21.3 (-38.8 – 81.4)	28.0 (-110.6 – 166.6)	-5.0 (-151.4 – 141.5)	13.9 (-45.9 – 73.7)
Poorest 3x SES quintiles	-95.5 (-274.1 – 83.2)	-33.6 (-158.0 – 90.8)	-15.7 (-152.8 – 121.3)	13.4 (-42.8 – 69.6)	2.9 (-126.5 – 132.4)	-27.7 (-164.7 – 109.4)	4.1 (-51.8 – 60.1)
Intermittent food insecurity	-114.8 (-301.7 – 72.0)	35.1 (-94.4 – 164.6)	80.5 (-57.7 – 218.8)	33.3 (-23.5 – 90.0)	95.5 (-34.7 – 255.8)	77.1 (-60.6 – 214.7)	35.0 (-21.1 – 91.1)
FEV_1 (ml) at TBRx completion	0.99 (0.93 – 1.06)***	0.79 (0.72 – 0.86)***					
FVC (ml) at TBRx completion	0.96 (0.92 – 0.99)***	0.85 (0.80 – 0.89)***		0.85 (0.80 – 0.89)***			0.84 (0.79 – 0.89)***
FEV_1/FVC ratio (%) at TBRx completion	-0.89 (-10.77 – 8.99)	1.61 (-5.51 – 8.73)					
≥1/3 abnormal parenchyma, except mosaicism	-309.2 (-546.7 – -71.8)*	-497.1 (-653.1 – -341.1)***			-368.0 (-535.7 – -200.2)***		39.7 (-36.1 – 115.4)
≥3 lobes with mod-severe bronchiectasis	-517.1 (-835.4 – -198.8)**	-531.1 (-745.3 – -316.8)***			-309.1 (-531.9 - -86.3)**		-94.4 (-191.0 – 2.1)
Any OPD / IP respiratory visits	434.2 (-680.2 – -188.2)*	-243.7 (-415.2 – 72.1)**				-174.1 (-356.0 – 7.87)	-80.6 (-154.7 – -6.5)*
TB retreatment	-306.9 (-1071.2 – 457.4)	-356.1 (-880.1 – 167.9)				-150.1 (-684.8 – 384.7)	-114.8 (-332.8 – 103.1)

*p<.05, **p<.01, ***p<.001

FEV_1/FVC RATIO AT 1-YEAR

Table 17: Factors associated with the absolute FEV_1/FVC ratio (%), 1-year after TB treatment completion (n=290)

	Univariate associations	'Controlled' univariate	Basic multivariate model R^2: 0.204	+ Baseline spirometry R^2: 0.841	+ Baseline imaging R^2:0.216	+Respiratory events R^2: 0.204	Full multivariate model R^2: 0.843
Age (yrs)	-0.3 (-0.4 – 0.2)***		-0.3 (-0.4 – -0.2)***	-0.1 (-0.1 – -0.0)**	-0.3 (-0.4 – -0.2)***	-0.3 (-0.4 – -0.2)***	-0.1 (-0.1 – -0.0)***
Male gender	-1.5 (-3.9 – 0.9)		1.2 (-1.9 – 4.2)	0.1 (-1.3 – 1.4)	1.3 (-1.7 – 4.4)	1.2 (-1.9 – 4.2)	-0.0 (-1.4 – 1.4)
Height (cm)	-0.0 (-0.2 – 0.1)		-0.0 (-0.2 – 0.1)	0.0 (-0.1 – 0.1)	-0.0 (-0.2 – 0.12)	-0.0 (-0.2 – 0.1)	-0.0 (-0.1 – 0.1)
HIV positive at TBRx end - CD4≥200 cells/uL - CD4<200 cells/uL	 0.6 (-2.0 – 3.1) -0.2 (-3.0 – 2.6)	 1.5 (-0.9 – 3.9) 2.3 (-0.4 – 5.0)	 1.3 (-1.1 – 3.6) 1.4 (1.3 – 4.0)	 0.2 (-0.9 – 1.2) 0.0 (-1.2 – 1.2)	 1.3 (-1.1 – 3.6) 1.2 (-1.5 – 3.8)	 1.2 (-1.2 – 3.6) 1.3 (-1.5 – 4.0)	 -0.1 (-0.9 – 1.2) -0.2 (-1.1 – 1.4)
Positive baseline TB microbiology	-1.7 (-4.3 – 0.9)	-2.6 (-5.1 – 0.2)*	-1.3 (-3.8 – 1.1)	-1.1 (-2.2 – -0.0)*	-1.3 (-3.8 – 1.1)	-1.3 (-3.8 – 1.2)	-1.2 (-2.3 – -0.0)*
BMI at TB treatment completion (kg/m^2)	0.2 (-0.2 – 0.5)	0.4 (0.0 – 0.7)	0.2 (-0.2 – 0.5)	0.2 (0.0 – 0.4)*	0.1 (-0.2 – 0.5)	0.2 (-0.2 – 0.5)	0.2 (0.0 – 0.4)*
Illness duration ≥1-month prior to treatment	-2.2 (-4.4 – 0.1)	-2.1 (-4.2 – -0.1)	-2.1 (-4.2 – -0.1)*	-0.3 (-1.2 – 0.7)	-1.9 (-4.0 – 0.2)	-2.1 (-4.2 – -0.0)*	-0.3 (-1.2 – 0.7)
Ever smoking	-2.9 (-5.2 – -0.5)*	-2.5 (-4.9 – -0.0)*	-1.2 (-3.7 – 1.3)	0.1 (-1.0 – 1.2)	-1.0 (-3.4 – 1.5)	-1.2 (-3.7 – 1.3)	0.2 (-0.9 – 1.3)
Poorest 3x SES quintiles	-4.4 (-6.5 – -2.3)***	-4.1 (-6.1 – -2.0)***	-3.0 (-5.3 – -0.7)*	-0.3 (-1.4 – 0.7)	-2.8 (-5.1 – -0.5)*	-3.1 (-5.4 – -0.7)*	-0.2 (-1.3 – 0.8)
Intermittent food insecurity	-3.2 (-5.5 – -1.0)**	-3.1 (-5.2 – -0.9)**	-1.4 (-3.7 – 0.9)	-0.2 (-1.2 – 0.9)	-1.4 (-3.7 – 0.9)	-1.4 (-3.8 – 0.9)	-0.2 (-1.2 – 0.9)
FEV_1 (ml) at TBRx completion	0.01 (0.00 – 0.01)***	-0.01 (-0.01 – -0.01)***					
FVC (ml) at TBRx completion	-0.00 (-0.00 – 0.00)	0.00 (-0.00 – 0.00)					
FEV_1/FVC ratio (%) at TBRx completion	0.95 (0.90 – 1.00)***	0.92 (0.87 – 0.98) ***		0.91 (0.86 – 0.96)***			0.91 (0.86 – 0.97)***
≥1/3 abnormal parenchyma, except mosaicism	-4.7 (-7.6 – -1.8)**	-4.4 (-7.1 – -1.6)**			-3.0 (-6.0 – -0.0)		-0.3 (-1.7 – 1.1)
≥3 lobes with mod-severe bronchiectasis	-2.7 (-6.7 – 1.2)	-2.5 (-6.2 – 1.2)			-0.2 (-4.1 – 3.8)		0.9 (-0.8 – 2.7)
Any OPD / IP respiratory visits	-1.0 (-4.0 – 2.1)	-0.5 (-3.4 – 2.4)				-0.5 (-3.6 – 2.6)	0.6 (-0.8 – 2.0)
TB retreatment	-0.7 (-10.§ – 8.6)	-2.7 (-11.5 – 6.1)				-0.3 (-9.3 – 8.8)	-2.7 (-6.8 – 1.4)

*p<.05, **p<.01, ***p<.001

PATTERNS OF DEFICIT AT 1-YEAR

Table 18: Factors associated with Airway Obstruction (n=48) or Low FVC (n=40) at 1-year post TB treatment completion, compared to normal spirometry (n=202). OR (95% CI) presented
Obstruction - FEV_1/FVC ratio <LLN, using GLI-2012 reference range; Low FVC - FEV_1/FVC ratio ≥LLN & FVC<LLN, using GLI-2012 reference range

Variable	Airway obstruction, compared to normal (n=250)			Low FVC, compared to normal (n=242)		
	Univariate associations	Basic multivariate model	Full multivariate model	Univariate associations	Basic multivariate model	Full multivariate model
Age (yrs)	1.01 (0.98 - 1.04)	1.02 (0.98 – 1.05)	1.02 (0.98 – 1.08)	0.94 (0.90 – 0.98)**	0.96 (0.91 – 1.01)	1.00 (0.93 – 1.08)
Gender						
- Female	1.0	1.0	1.0	1.0	1.0	0.06 (0.01 – 0.50)*
- Male	1.03 (0.51 – 2.09)	0.84 (0.30 – 2.31)	1.35 (0.31 – 5.96)	0.47 (0.23 – 0.94)*	0.41 (0.14 – 1.20)	
Height (cm)	0.98 (0.95 – 1.02)	0.99 (0.93 – 1.04)	0.95 (0.87 – 1.03)	0.99 (0.94 – 1.03)	1.02 (0.95 – 1.08)	1.12 (0.98 – 1.28)
HIV status						
- Negative	1.0	1.0	1.0	1.0	1.0	1.0
- Positive, CD4>=200 cells/uL	0.56 (0.27 – 1.17)	0.53 (0.24 – 1.18)	0.9 (0.32 – 3.50)	0.52 (0.25 – 1.10)	0.61 (0.27 – 1.41)	0.16 (0.04 – 0.70)*
- Positive, CD4<200 cells/uL	0.53 (0.24 – 1.19)	0.58 (0.93 – 1.04)	1.5 (0.38 – 5.71)	0.19 (0.06 – 0.60) **	0.34 (0.10 – 1.16)	0.21 (0.03 – 1.59)
Baseline TB microbiology						
- Negative	1.0	1.0	1.0	1.0	1.0	1.0
- Positive	2.08 (0.88 – 4.93)	1.44 (0.57 – 3.64)	3.36 (0.83 – 13.56)	1.68 (0.70 – 4.02)	1.30 (0.50 – 3.39)	1.82 (0.35 – 9.46)
BMI at TB treatment completion (kg/m^2)	0.86 (0.75 – 0.99)	0.91 (0.78 – 1.05)	1.00 (0.81 – 1.24)	0.83 (0.71 – 0.97)*	0.87 (0.75 – 1.02)	0.96 (0.77 – 1.20)
Illness duration prior to TB treatment						
- <1-month	1.0	1.0	1.0	1.0	1.0	1.0
- ≥1-month	1.59 (0.80 – 3.15)	1.60 (0.78 – 3.26)	1.54 (0.54 – 4.39)	1.53 (0.74 – 3.18)	1.40 (0.64 – 3.08)	0.43 (0.11 – 1.67)
Ever smoking						
- Never	1.0	1.0	1.0	1.0	1.0	1.0
- Ever	1.55 (0.81 – 2.98)	1.30 (0.59 – 2.89)	1.63 (0.52 – 5.10)	0.79 (0.36 – 1.71)	1.04 (0.40 – 2.70)	1.25 (0.24 – 6.45)
Urban SES quintile						
- Least poor quintiles x2	1.0	1.0	1.0	1.0	1.0	1.0
- Poorest quintiles x3	2.86 (1.43 – 5.72)**	1.79 (0.80 – 3.98)	0.74 (0.23 – 2.36)	1.44 (0.72 – 2.85)	1.19 (0.51 – 2.78)	0. 67 (0.14 – 3.09)
Food insecurity						
- Never	1.0	1.0	1.0	1.0	1.0	1.0
- Sometimes / often	2.70 (1.42 – 5.13)*	1.95 (0.95 – 4.03)	1.59 (0.53 – 4.70)	2.03 (1.02 – 4.06)*	2.03 (0.88 – 4.65)	1.48 (0.35 – 6.30)
Baseline spirometry pattern						
- Normal	1.0		1.0	1.0		1.0
- Obstruction	78.26 (28.29 – 215.92)***		117.91 (31.26 – 444.73)***	Empty^		Empty^
- Low FVC	2.68 (0.68 – 10.51)		2.92 (0.64 – 13.40)	121.28 (33.97 – 432.96)***		216.98 (37.87 – 1243.21)***
Parenchyma, except mosaicism						
- <1/3 abnormal	1.0		1.0	1.0		1.0
- ≥1/3 abnormal	4.4 (2.0 – 9.5)***		1.38 (0.36 – 5.26)	5.19 (2.32 – 11.58)***		1.53 (0.31 – 7.62)
Mod-severe bronchiectasis						
- <3 lobes	1.0		1.0	1.0		1.0
- ≥3 lobes	4.9 (1.7 – 13.7)**		2.58 (0.41 – 16.20)	6.06 (2.12 – 17.31)**		15.37 (1.19 –199.01)*
Any OPD / IP respiratory visits						
- No	1.0		1.0	1.0		1.0
- Yes	0.9 (0.3 – 2.2)		0.33 (0.07 – 1.67)	1.49 (0.63 – 3.56)		0.94 (0.16 – 5.39)
TB retreatment						
- No	Empty#		Empty	1.0		1.0
- Yes				1.70 (0.17 – 16.78)		1.31 (0.00 – 512.60)

*p<.05, **p<.01, ***p<.001; #No patients with airway obstruction at 1-year had received TB retreatment; ^No patients in the low-FVC group at 1-year had been classed as obstructed at baseline

8 REFERENCES

1. The World Bank. Malawi Overview 2018 [Available from: http://www.worldbank.org/en/country/malawi/overview, accessed 22nd May 2018].

2. Malawi National Statistics Office. Malawi Demographic & Health Survey, 2015-16. Zomba, Malawi, 2017.

3. United Nations Department of Economic and Social Affairs. World Population Prospects: the 2017 Revision 2017 [Available from: https://esa.un.org/unpd/wpp/Graphs/DemographicProfiles/, accessed 22nd May 2018].

4. Rasmussen PE. African Economic Outlook: Malawi: African Development Bank Group, 2018.

5. World Health Organisation. TB Country profile: Malawi. Geneva, Switzerland, 2016.

6. Abouyannis M, Dacombe R, Dambe I, et al. Drug resistance of Mycobacterium tuberculosis in Malawi: a cross-sectional survey. *Bulletin of the World Health Organization* 2014;92(11):798-806.

7. UNAIDS. Country factsheet: Malawi 2017 [Available from: http://www.unaids.org/en/regionscountries/countries/malawi, accessed 22nd May 2018].

8. Choko AT, MacPherson P, Webb EL, et al. Uptake, Accuracy, Safety, and Linkage into Care over Two Years of Promoting Annual Self-Testing for HIV in Blantyre, Malawi: A Community-Based Prospective Study. *PLoS Med* 2015;12(9):e1001873.

9. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;385(9963):117-71.

10. GBD 2016 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet* 2017;390:1260-344.

11. Bennett JE, Stevens GA, Mathers CD, et al. NCD Countdown 2030: worldwide trends in non-communicable disease mortality and progress towards Sustainable Development Goal target 3.4. *The Lancet* 2018;392(10152):1072-88.

12. World Health Organisation. Global Tuberculosis Report 2017. Geneva, Switzerland, 2017.

13. Allwood BW, Myer L, Bateman ED. A systematic review of the association between pulmonary tuberculosis and the development of chronic airflow obstruction in adults. *Respiration* 2013;86(1):76-85.

14. Byrne AL, Marais BJ, Mitnick CD, et al. Tuberculosis and chronic respiratory disease: a systematic review. *Int J Infect Dis* 2015;32:138-46.

15. Ehrlich RI, Adams S, Baatjies R, et al. Chronic airflow obstruction and respiratory symptoms following tuberculosis: a review of South African studies. *Int J Tuberc Lung Dis* 2011;15(7):886-91.

16. van Zyl Smit RN, Pai M, Yew WW, et al. Global lung health: the colliding epidemics of tuberculosis, tobacco smoking, HIV and COPD. *Eur Respir J* 2010;35(1):27-33.

17. Stocks J, Hislop A, Sonnappa S. Early lung development: lifelong effect on respiratory health and disease. *Lancet Respir Med* 2013;1(9):728-42.

18. Burney PG, Hooper R. Forced vital capacity, airway obstruction and survival in a general population sample from the USA. *Thorax* 2011;66(1):49-54.

19. Agusti A. The disease model: implications for clinical practice. *Eur Respir J* 2018;51(4)

20. Jary HR, Aston S, Ho A, et al. Household air pollution, chronic respiratory disease and pneumonia in Malawian adults: A case-control study. *Wellcome Open Res* 2017;2:103.

21. Nturibi EM, Kolawole AA, McCurdy SA. Smoking prevalence and tobacco control measures in Kenya, Uganda, the Gambia and Liberia: a review. *Int J Tuberc Lung Dis* 2009;13(2):165 - 70.

22. Wisdom JP, Juma P, Mwagomba B, et al. Influence of the WHO framework convention on tobacco control on tobacco legislation and policies in sub-Saharan Africa. *BMC Public Health* 2018;18(Suppl 1):954.

23. World Health Organisation. WHO report on the global tobacco epidemic, 2017. Geneva, Switzerland, 2017.

24. Rylance J, Meghji J, Miller RF, et al. Global Considerations in Human Immunodeficiency Virus-Associated Respiratory Disease. *Semin Respir Crit Care Med* 2016;37(2):166-80.

25. Drummond MB, Kirk GD. HIV-associated obstructive lung diseases: insights and implications for the clinician. *Lancet Respir Med* 2014;2(7):583-92.

26. Fitzpatrick M, Crothers K, Morris A. Future directions: lung aging, inflammation, and human immunodeficiency virus. *Clinics in chest medicine* 2013;34(2):325-31.

27. Ferrand RA, Desai SR, Hopkins C, et al. Chronic lung disease in adolescents with delayed diagnosis of vertically acquired HIV infection. *Clin Infect Dis* 2012;55(1):145-52.

28. Buist AS, Vollmer W, Sullivan S, et al. The Burden of Obstructive Lung Disease Initiative (BOLD): Rationale and Design. *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2005;2(2):277-83.

29. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (The BOLD Study): a population-based prevalence study. *The Lancet* 2007;370(9589):741-50.

30. El Rhazi K, Nejjari C, BenJelloun MC, et al. Prevalence of chronic obstructive pulmonary disease in Fez, Morocco: results from the BOLD study. *Int J Tuberc Lung Dis* 2016;20(1):136-41.

31. Daldoul H, Denguezli M, Jithoo A, et al. Prevalence of COPD and tobacco smoking in Tunisia--results from the BOLD study. *International journal of environmental research and public health* 2013;10(12):7257-71.

32. Obaseki DO, Erhabor GE, Gnatiuc L, et al. Chronic Airflow Obstruction in a Black African Population: Results of BOLD Study, Ile-Ife, Nigeria. *COPD* 2015:1-8.

33. Nightingale R, Lesosky M, Flitz G, et al. Non-Communicable Respiratory Disease and Air Pollution Exposure in Malawi (CAPS): A Cross-Sectional Study. *Am J Respir Crit Care Med* 2018

34. Meghji J, Nadeau G, Davis KJ, et al. Non-communicable Lung Disease in Sub Saharan Africa: a Community-based Cross-sectional Study of Adults in Urban Malawi. *Am J Respir Crit Care Med* 2016;194(1):67-76.

35. Obaseki DO, Erhabor GE, Awopeju OF, et al. Reduced Forced Vital Capacity in an African Population. Prevalence and Risk Factors. *Ann Am Thorac Soc* 2017;14(5):714-21.

36. Rylance S, Mortimer K. Galloping Hooves in Africa: Horse, Zebra, or Wildebeest? *Ann Am Thorac Soc* 2017;14(5):624-25.

37. Lamprecht B, McBurnie MA, Vollmer WM, et al. COPD in never smokers: results from the population-based burden of obstructive lung disease study. *Chest* 2011;139(4):752-63.

38. Townend J, Minelli C, Mortimer K, et al. The association between chronic airflow obstruction and poverty in 12 sites of the multinational BOLD study. *Eur Respir J* 2017;49(6)

39. Banda HT, Thomson R, Mortimer K, et al. Community prevalence of chronic respiratory symptoms in rural Malawi: Implications for policy. *PLoS One* 2017;12(12):e0188437.

40. Malawi Ministry of Health. Malawi Tuberculosis Prevalence Survey (2013 - 2014): Malawi National TB Control Programme, 2016.

41. Horton KC, MacPherson P, Houben RM, et al. Sex Differences in Tuberculosis Burden and Notifications in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. *PLoS Med* 2016;13(9):e1002119.

42. Chikovore J, Hart G, Kumwenda M, et al. 'For a mere cough, men must just chew Conjex, gain strength, and continue working': the provider construction and tuberculosis care-seeking implications in Blantyre, Malawi. *Global health action* 2015;8:26292.

43. Chikovore J, Hart G, Kumwenda M, et al. TB and HIV stigma compounded by threatened masculinity: implications for TB health-care seeking in Malawi. *Int J Tuberc Lung Dis* 2017;21(11):26-33.

44. Houben RM, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. *PLoS Med* 2016;13(10):e1002152.

45. Hargreaves JR, Boccia D, Evans CA, et al. The social determinants of tuberculosis: from evidence to action. *American journal of public health* 2011;101(4):654-62.

46. Ortblad KF, Salomon JA, Bärnighausen T, et al. Stopping tuberculosis: a biosocial model for sustainable development. *The Lancet* 2015;386(10010):2354-62.

47. World Health Organisation. TB: A global emergency. Geneva, Switzerland, 1993.

48. Pai M, Schito M. Tuberculosis diagnostics in 2015: landscape, priorities, needs, and prospects. *J Infect Dis* 2015;211 Suppl 2:S21-8.

49. Dowdy DW, Basu S, Andrews JR. Is passive diagnosis enough? The impact of subclinical disease on diagnostic strategies for tuberculosis. *Am J Respir Crit Care Med* 2013;187(5):543-51.

50. Tiemersma EW, van der Werf MJ, Borgdorff MW, et al. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. *PLoS One* 2011;6(4):e17601.

51. Vynnycky E, Fine PEM. The natural history of tuberculosis : the implications of age-dependent risks of disease and the role of reinfection. *Epidemiol Infect* 1997;119:183-201.

52. Getahun H, Campion EW, Matteelli A, et al. Latent Mycobacterium tuberculosis Infection. *N Engl J Med* 2015;372(22):2127-35.

53. Petruccioli E, Scriba TJ, Petrone L, et al. Correlates of tuberculosis risk: predictive biomarkers for progression to active tuberculosis. *Eur Respir J* 2016;48(6):1751-63.

54. Cruciani M, Scarparo C, Malena M, et al. Meta-Analysis of BACTEC MGIT 960 and BACTEC 460 TB, with or without Solid Media, for Detection of Mycobacteria. *J Clin Microbiol* 2004;42(5):2321-25.

55. World Health Organisation. Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Geneva, Switzerland, 2013.

56. Wood R, Racow K, Bekker LG, et al. Lipoarabinomannan in urine during tuberculosis treatment: association with host and pathogen factors and mycobacteriuria. *BMC Infect Dis* 2012;12:47.

57. Gupta-Wright A, Corbett EL, van Oosterhout JJ, et al. Rapid urine-based screening for tuberculosis in HIV-positive patients admitted to hospital in Africa (STAMP): a pragmatic, multicentre, parallel-group, double-blind, randomised controlled trial. *The Lancet* 2018;392(10144):292-301.

58. Theron G, Peter J, Dowdy D, et al. Do high rates of empirical treatment undermine the potential effect of new diagnostic tests for tuberculosis in high-burden settings? *Lancet Infect Dis* 2014;14(6):527-32.

59. Walusimbi S, Bwanga F, de Costa A, et al. Meta-analysis to compare the accuracy of GeneXpert, MODS and the WHO 2007 algorithm for diagnosis of smear-negative pulmonary tuberculosis. *BMC Infect Dis* 2013;13:507.

60. Hargreaves NJ, Kadzakumanja O, Whitty CJM, et al. 'Smear-negative' pulmonary tuberculosis in a DOTS programme: poor outcomes in an area of high HIV seroprevalence. *Int J Tuberc Lung Dis* 2001;5(9):847 - 54.

61. Gupta RK, Lucas SB, Fielding KL, et al. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. *AIDS* 2015;29(15):1987-2002.

62. Storla DG, Yimer S, Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. *BMC Public Health* 2008;8:15.

63. Yuen CM, Amanullah F, Dharmadhikari A, et al. Turning off the tap: stopping tuberculosis transmission through active case-finding and prompt effective treatment. *The Lancet* 2015;386(10010):2334-43.

64. World Health Organisation. The End TB Strategy. Geneva, Switzerland, 2015.

65. Murray JF, Schraufnagel DE, Hopewell PC. Treatment of Tuberculosis. A Historical Perspective. *Ann Am Thorac Soc* 2015;12(12):1749-59.

66. Horsburgh CR, Jr., Barry CE, 3rd, Lange C. Treatment of Tuberculosis. *N Engl J Med* 2015;373(22):2149-60.

67. Nunn AJ, Rusen ID, van Deun A, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. *Trials* 2014;15(353)

68. World Health Organisation. WHO treatment guidelines for drug-resistant tuberculosis: 2016 update. Geneva, Switzerland, 2016.

69. World Health Organisation. Definitions and reporting framework for tuberculosis – 2013 revision. Geneva, Switzerland, 2013.

70. Lange C, van Leth F, Mitnick CD, et al. Time to revise WHO-recommended definitions of MDR-TB treatment outcomes. *Lancet Respir Med* 2018;6(4):246-48.

71. Marx FM, Dunbar R, Enarson DA, et al. The temporal dynamics of relapse and reinfection tuberculosis after successful treatment: a retrospective cohort study. *Clin Infect Dis* 2014;58(12):1676-83.

72. Major Infectious Diseases Control Priorities, 3rd edition. Washington, DC: The World Bank 2017.

73. Wangari IM, Trauer J, Stone L. Modelling heterogeneity in host susceptibility to tuberculosis and its effect on public health interventions. *PLoS One* 2018;13(11):e0206603.

74. Andrews JR, Noubary F, Walensky RP, et al. Risk of progression to active tuberculosis following reinfection with Mycobacterium tuberculosis. *Clin Infect Dis* 2012;54(6):784-91.

75. Netea MG, Joosten LAB. Trained Immunity and Local Innate Immune Memory in the Lung. *Cell* 2018;175(6):1463-65.

76. Yao Y, Jeyanathan M, Haddadi S, et al. Induction of Autonomous Memory Alveolar Macrophages Requires T Cell Help and Is Critical to Trained Immunity. *Cell* 2018;175(6):1634-50 e17.

77. Lerm M, Netea MG. Trained immunity: a new avenue for tuberculosis vaccine development. *J Intern Med* 2016;279(4):337-46.

78. Dierberg KL, Chaisson RE. Human immunodeficiency virus-associated tuberculosis: update on prevention and treatment. *Clinics in chest medicine* 2013;34(2):217-28.

79. Sonnenberg P, Glynn JR, Fielding K, et al. How Soon after Infection with HIV Does the Risk of Tuberculosis Start to Increase? A Retrospective Cohort Study in South African Gold Miners. *J Infect Dis* 2005;191:150-58.

80. Kaplan JE, Benson C, Holmes KK, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports* 2009;58(Rr-4):1-207.

81. Chaisson RE, Schecter GF, Theuer CP, et al. Tuberculosis in patients with the acquired immunodeficiency syndrome. Clinical features, response to therapy, and survival. *The American review of respiratory disease* 1987;136(3):570-4.

82. Chamie G, Luetkemeyer A, Walusimbi-Nanteza M, et al. Significant variation in presentation of pulmonary tuberculosis across a high resolution of CD4 strata. *Int J Tuberc Lung Dis* 2010;14(10):1295 - 302.

83. Lawn SD, Evans AJ, Sedgwick PM, et al. Pulmonary tuberculosis: radiological features in west Africans coinfected with HIV. *Brit J Radiol* 1999;72(856):339-44.

84. Lawn SD, Mwaba P, Bates M, et al. Advances in tuberculosis diagnostics: the Xpert MTB/RIF assay and future prospects for a point-of-care test. *Lancet Infect Dis* 2013;13(4):349-61.

85. Lawn SD, Torok ME, Wood R. Optimum time to start antiretroviral therapy during HIV-associated opportunistic infections. *Curr Opin Infect Dis* 2011;24(1):34-42.

86. World Health Organisation. Latent tuberculosis infection: Updated and consolidated guidelines for programmatic management. Geneva, Switzerland, 2018.

87. Russell DG, Cardona PJ, Kim MJ, et al. Foamy macrophages and the progression of the human tuberculosis granuloma. *Nat Immunol* 2009;10(9):943-8.

88. Jambo KC, Banda DH, Afran L, et al. Asymptomatic HIV-infected individuals on antiretroviral therapy exhibit impaired lung CD4(+) T-cell responses to mycobacteria. *Am J Respir Crit Care Med* 2014;190(8):938-47.

89. Ravimohan S, Kornfeld H, Weissman D, et al. Tuberculosis and lung damage: from epidemiology to pathophysiology. *Eur Respir Rev* 2018;27(147)

90. Elkington PT, Ugarte-Gil CA, Friedland JS. Matrix metalloproteinases in tuberculosis. *Eur Respir J* 2011;38(2):456-64.

91. Chalmers JD, Chotirmall SH. Bronchiectasis: new therapies and new perspectives. *Lancet Respir Med* 2018

92. Aliberti S, Masefield S, Polverino E, et al. Research priorities in bronchiectasis: a consensus statement from the EMBARC Clinical Research Collaboration. *Eur Respir J* 2016;48(3):632-47.

93. Coscolla M, Gagneux S. Does M. tuberculosis genomic diversity explain disease diversity? *Drug Discov Today Dis Mech* 2010;7(1):e43-e59.

94. Martin CJ, Carey AF, Fortune SM. A bug's life in the granuloma. *Semin Immunopathol* 2016;38(2):213-20.

95. Lieberman TD, Wilson D, Misra R, et al. Genomic diversity in autopsy samples reveals within-host dissemination of HIV-associated Mycobacterium tuberculosis. *Nat Med* 2016;22(12):1470-74.

96. Corbett EL, Churchyard GJ, Clayton T, et al. Risk Factors for Pulmonary Mycobacterial Disease in South African Gold Miners: A case control study. *Am J Respir Crit Care Med* 1999;159:94 -99.

97. Charalambous S, Churchyard GJ, Murray J, et al. Persistent radiological changes following miliary tuberculosis in miners exposed to silica dust. *Int J Tuberc Lung Dis* 2001;5(11):1044 - 50.

98. Gajalakshmi V, Peto R, Kanaka TS, et al. Smoking and mortality from tuberculosis and other diseases in India: retrospective study of 43000 adult male deaths and 35000 controls. *Lancet* 2003;362(9383):507-15.

99. Chan ED, Kinney WH, Honda JR, et al. Tobacco exposure and susceptibility to tuberculosis: is there a smoking gun? *Tuberculosis (Edinb)* 2014;94(6):544-50.

100. Hong BY, Maulen NP, Adami AJ, et al. Microbiome Changes during Tuberculosis and Antituberculous Therapy. *Clin Microbiol Rev* 2016;29(4):915-26.

101. Walker NF, Wilkinson KA, Meintjes G, et al. Matrix Degradation in Human Immunodeficiency Virus Type 1-Associated Tuberculosis and Tuberculosis Immune Reconstitution Inflammatory Syndrome: A Prospective Observational Study. *Clin Infect Dis* 2017;65(1):121-32.

102. Malherbe ST, Shenai S, Ronacher K, et al. Persisting positron emission tomography lesion activity and Mycobacterium tuberculosis mRNA after tuberculosis cure. *Nat Med* 2016;22(10):1094-100.

103. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet* 2007;370(9589):741-50.

104. Amaral AF, Coton S, Kato B, et al. Tuberculosis associates with both airflow obstruction and low lung function: BOLD results. *Eur Respir J* 2015;46(4):1104-12.

105. Sin DD, Anthonisen NR, Soriano JB, et al. Mortality in COPD: Role of comorbidities. *Eur Respir J* 2006;28(6):1245-57.

106. Burney P, Jithoo A, Kato B, et al. Chronic obstructive pulmonary disease mortality and prevalence: the associations with smoking and poverty--a BOLD analysis. *Thorax* 2014;69(5):465-73.

107. Baez-Saldana R, Lopez-Areaga Y, Bizarron-Muro A, et al. A novel scoring system to measure radiographic abnormalities and related spirometric values in cured pulmonary tuberculosis. *PLoS One* 2013;8(11)

108. Lai YF, Su MC, Weng HH, et al. Sonographic septation: a predictor of sequelae of tuberculous pleurisy after treatment. *Thorax* 2009;64(9):806-9.

109. Rhee CK, Yoo KH, Lee JH, et al. Clinical characteristics of patients with tuberculosis-destroyed lung. *Int J Tuberc Lung Dis* 2013;17(1):67-75.

110. Panda A, Bhalla AS, Sharma R, et al. Correlation of chest computed tomography findings with dyspnea and lung functions in post-tubercular sequelae. *Lung India* 2016;33(6):592-99.

111. Lee KY, Shin C, Lee JB, et al. Spontaneously healed asymptomatic pulmonary tuberculosis: prevalence of airflow obstruction, and correlation between high-resolution CT findings and pulmonary function tests. *Journal of computer assisted tomography* 2012;36(5):528-33.

112. Hnidzo E SH, Churchyard G. Chronic pulmonary function impairment caused by initial and recurrent pulmonary tuberculosis following treatment. *Thorax* 2000;55:32-38.

113. Mbatchou Ngahane BH, Nouyep J, Nganda Motto M, et al. Post-tuberculous lung function impairment in a tuberculosis reference clinic in Cameroon. *Respir Med* 2016;114:67-71.

114. Angthong W, Angthong C, Varavithya V. Pretreatment and posttreatment radiography in patients with pulmonary tuberculosis with and without human immunodeficiency virus infection. *Jpn J Radiol* 2011;29(8):554-62.

115. Corlan E, Marica C, Macavei C, et al. Immunotherapy with Mycobacterium vaccae in the treatment of tuberculosisis Romania. 2. Chronic or relapsed disease. *Respir Med* 1997;91(1):21-29.

116. Iwashyna TJ. Trajectories of Recovery and Dysfunction after Acute Illness, with Implications for Clinical Trial Design. *Am J Respir Crit Care Med* 2012;186(4):301-2.

117. Godoy MD, Mello FC, Lopes AJ, et al. The functional assessment of patients with pulmonary multidrug-resistant tuberculosis. *Resp Care* 2012;57(11):1949-54.

118. Banu Rekha VV, Ramachandran R, Kuppu Rao KV, et al. Assessment of long term status of sputum positive pulmonary TB patients successfully treated with short course chemotherapy. *Indian J Tuberc* 2009;56(3):132-40.

119. Ryu YJ, Lee JH, Chun EM, et al. Clinical outcomes and prognostic factors in patients with tuberculous destroyed lung. *Int J Tuberc Lung Dis* 2011;15(2):246-50.

120. Pasipanodya JG, Miller TL, Vecino M, et al. Using the St. George respiratory questionnaire to ascertain health quality in persons with treated pulmonary tuberculosis. *Chest* 2007;132(5):1591-8.

121. Fox GJ, Nguyen VN, Dinh NS, et al. Post-treatment Mortality Among Patients With Tuberculosis: A Prospective Cohort Study of 10 964 Patients in Vietnam. *Clin Infect Dis* 2018

122. Harries AD, Ade S, Burney P, et al. Successfully treated but not fit for purpose: paying attention to chronic lung impairment after TB treatment. *Int J Tuberc Lung Dis* 2016;20(8):1010-4.

123. Miller TL, Wilson FA, Pang JW, et al. Mortality hazard and survival after tuberculosis treatment. *American journal of public health* 2015;105(5):930-7.

124. Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and after tuberculosis treatment. *Int J Tuberc Lung Dis* 2011;15(7):871-85.

125. Ayles H, Muyoyeta M, Du Toit E, et al. Effect of household and community interventions on the burden of tuberculosis in southern Africa: the ZAMSTAR community-randomised trial. *Lancet* 2013;382(9899):1183-94.

126. Marx FM, Floyd S, Ayles H, et al. High burden of prevalent tuberculosis among previously treated people in Southern Africa suggests potential for targeted control interventions. *Eur Respir J* 2016;48(4):1224-27.

127. Metcalfe JZ, Mason P, Mungofa S, et al. Empiric tuberculosis treatment in retreatment patients in high HIV/tuberculosis-burden settings. *Lancet Infect Dis* 2014;14(9):794-95.

128. Marx FM, Yaesoubi R, Menzies NA, et al. Tuberculosis control interventions targeted to previously treated people in a high-incidence setting: a modelling study. *Lancet Glob Health* 2018;6(4):e426-e35.

129. Tanimura T, Jaramillo E, Weil D, et al. Financial burden for tuberculosis patients in low- and middle-income countries: a systematic review. *Eur Respir J* 2014;43(6):1763-75.

130. Wingfield T, Boccia D, Tovar M, et al. Defining catastrophic costs and comparing their importance for adverse tuberculosis outcome with multi-drug resistance: a prospective cohort study, Peru. *PLoS Med* 2014;11(7):e1001675.

131. Gospodarevskaya E, Tulloch O, Bunga C, et al. Patient costs during tuberculosis treatment in Bangladesh and Tanzania: the potential of shorter regimens. *Int J Tuberc Lung Dis* 2014;18(7):810-7.

132. Oxlade O, Piatek A, Vincent C, et al. Modeling the impact of tuberculosis interventions on epidemiologic outcomes and health system costs. *BMC Public Health* 2015;15:141.

133. Ukwaja KN, Modebe O, Igwenyi C, et al. The economic burden of tuberculosis care for patients and households in Africa: a systematic review. *Int J Tuberc Lung Dis* 2012;16(6):733-9.

134. Martinez-Garcia MA, Soler-Cataluna JJ, Perpina-Tordera M, et al. Factors associated with lung function decline in adult patients with stable non-cystic fibrosis bronchiectasis. *Chest* 2007;132(5):1565-72.

135. Chalmers JD, Goeminne P, Aliberti S, et al. The bronchiectasis severity index: An international derivation and validation study. *Am J Respir Crit Care Med* 2014;189(5):576-85.

136. Almagro P, Soriano JB, Cabrera FJ, et al. Short- and medium-term prognosis in patients hospitalized for COPD exacerbation: the CODEX index. *Chest* 2014;145(5):972-80.

137. Celli BR, Cote C, Marin JM, et al. The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2004;350:1005 -12.

138. Jones RC, Donaldson GC, Chavannes NH, et al. Derivation and validation of a composite index of severity in chronic obstructive pulmonary disease: the DOSE Index. *Am J Respir Crit Care Med* 2009;180(12):1189-95.

139. Puhan MA, Garcia-Aymerich J, Frey M, et al. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. *Lancet* 2009;374:704 - 11.

140. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003;58:377 - 82.

141. Fine MJ, Auble TE, Yealy DM, et al. Prediction rule to identify low-risk patients with community acquired pneumonia. *N Engl J Med* 1997;336:243-50.

142. Han MK, Agusti A, Calverley PM, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. *Am J Respir Crit Care Med* 2010;182(5):598-604.

143. Chalmers JD, Aliberti S, Filonenko A, et al. Characterization of the "Frequent Exacerbator Phenotype" in Bronchiectasis. *Am J Respir Crit Care Med* 2018;197(11):1410-20.

144. Hankinson J, Odencrantz JR, Fedan KB. Spirometric Reference Values from a Sample of the General U.S. Population. *Am J Respir Crit Care Med* 1999(169):179-87.

145. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40(6):1324-43.

146. Braun L. Race, ethnicity and lung function: A brief history. *Can J Resp Therapy* 2015

147. Quanjer PH, Stanojevic S, Stocks J, et al. GLI-2012 All-Age Multi-Ethnic Reference Values for Spirometry [Available from: https://www.ers-education.org/lrmedia/2012/pdf/266696.pdf, accessed 28th August 2018].

148. Quanjer PH, Enright P, Miller MR, et al. The need to change the method for defining mild airway obstruction. *Eur Respir J* 2010;37(3):720 - 22.

149. Reiff DB, Wells AU, Carr DH, et al. CT findings in Bronchiectasis: Limited value in distinguishing between idiopathic, and specific types. *Am J Roentgenology* 1995;165

150. Bedi P, Chalmers JD, Goeminne PC, et al. The BRICS (Bronchiectasis Radiologically Indexed CT Score)- a multi-center study score for use in idiopathic and post infective bronchiectasis. *Chest* 2018;153(5):1177 - 86.

151. Sheehan RE, Wells AU, Copley SJ, et al. A comparison of serial computed tomography and functional change in bronchiectasis. *Eur Respir J* 2002;20(3):581-87.

152. Onen ZP, Gulbay BE, Sen E, et al. Analysis of the factors related to mortality in patients with bronchiectasis. *Respir Med* 2007;101(7):1390-7.

153. Loebinger MR, Wells AU, Hansell DM, et al. Mortality in bronchiectasis: a long-term study assessing the factors influencing survival. *Eur Respir J* 2009;34(4):843-9.

154. Martinez-Garcia MA, de Gracia J, Vendrell Relat M, et al. Multidimensional approach to non-cystic fibrosis bronchiectasis: the FACED score. *Eur Respir J* 2014;43(5):1357-67.

155. Goeminne PC, Nawrot TS, Ruttens D, et al. Mortality in non-cystic fibrosis bronchiectasis: a prospective cohort analysis. *Respir Med* 2014;108(2):287-96.

156. Jones PW, Forde Y. St George's Respiratory Questionnaire Manual: St George's, University of London, 2009.

157. Pasipanodya JG, McNabb SJ, Hilsenrath P, et al. Pulmonary impairment after tuberculosis and its contribution to TB burden. *BMC Public Health* 2010;10:259.

158. Maheswaran H, Petrou S, MacPherson P, et al. Economic Costs and Health-Related Quality of Life Outcomes of HIV Treatment After Self- and Facility-Based HIV Testing in a Cluster Randomized Trial. *J Acquir Immune Defic Syndr* 2017;75:280 - 89.

159. Chokotho L, Mkandawire N, Conway D, et al. Validation and reliability of the Chichewa translation of the EQ-5D quality of life questionnaire in adults with orthopaedic injuries in Malawi. *Malawi Medical Journal* 2017;29(2):84.

160. Singh SJ, Puhan MA, Andrianopoulos V, et al. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. *Eur Respir J* 2014;44(6):1447-78.

161. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J* 2014;44(6):1428-46.

162. Martinez-Garcia MA, Maiz-Carro L. The challenge of defining exacerbation in bronchiectasis. *Eur Respir J* 2017;49(6)

163. Pasteur MC, Bilton D, Hill AT, et al. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010;65 Suppl 1:i1-58.

164. Hill AT, Haworth CS, Aliberti S, et al. Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. *Eur Respir J* 2017;49(6)

165. Wedzicha JA, Seemungal TAR. COPD exacerbations: defining their cause and prevention. *The Lancet* 2007;370(9589):786-96.

166. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Wisconsen, USA: GOLD, 2017.

167. Stop TB Partnership. Tool to estimate patient's costs, 2018.

168. Madan J, Lonnroth K, Laokri S, et al. What can dissaving tell us about catastrophic costs? Linear and logistic regression analysis of the relationship between patient costs and financial coping strategies adopted by tuberculosis patients in Bangladesh, Tanzania and Bangalore, India. *BMC Health Serv Res* 2015;15:476.

169. Meghji J, Simpson H, Squire SB, et al. A Systematic Review of the Prevalence and Pattern of Imaging Defined Post-TB Lung Disease. *PLoS One* 2016;11(8):e0161176.

170. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottowa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis [Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp, accessed 24th November 2015].

171. de Valliere S, Barker RD. Residual lung damage after completion of treatment for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2004;8(6):767-71.

172. Wyser C, Walzl G, Smedema JP, et al. Corticosteroids in the treatment of tuberculous pleurisy. A double-blind, placebo-controlled, randomized study. *Chest* 1996;110(2):333-8.

173. Wang CH, Lin HC, Lin SM, et al. MMP-1(-1607G) polymorphism as a risk factor for fi brosis after pulmonary tuberculosis in Taiwan. *Int J Tuberc Lung Dis* 2010;14(5):627-34.

174. Hamilton CD, Stout JE, Goodman PC, et al. The value of end-of-treatment chest radiograph in predicting pulmonary tuberculosis relapse. *Int J Tuberc Lung Dis* 2008;12(9):1059-64.

175. Madras Tuberculosis Chemotherapy Centre. Controlled comparison of oral twice-weekly and oral daily isoniazid plus PAS in newly diagnosed pulmonary tuberculosis. *BMJ* 1973;2:7-11.

176. Kenangalem E, Waramori G, Pontororing GJ, et al. Tuberculosis outcomes in Papua, Indonesia: the relationship with different body mass index characteristics between papuan and non-Papuan ethnic groups. *PLoS One* 2013;8(9):e76077.

177. Galarza I, Canete C, Granados A, et al. Randomised trial of corticosteroids in the treatment of tuberculous pleurisy. *Thorax* 1995;50(12):1305-7.

178. Singla N, Singla R, Fernandes S, et al. Post treatment sequelae of multi-drug resistant tuberculosis patients. *Indian J Tuberc* 2009;56(4):206-12.

179. Long R, Maycher B, Dhar A, et al. Pulmonary tuberculosis treated with directly observed therapy: serial changes in lung structure and function. *Chest* 1998;113(4):933-43.

180. Kunter E, Ilvan A, Kilic E, et al. The effect of pleural fluid content on the development of pleural thickness. *Int J Tuberc Lung Dis* 2002;6(6):516-22.

181. Uskul B, Turker H, Ulman C, et al. The relation of the pleural thickening in tuberculosis pleurisy with the activity of adenosine deaminase. *Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace / Fondazione clinica del lavoro, IRCCS [and] Istituto di clinica tisiologica e malattie apparato respiratorio, Universita di Napoli, Secondo ateneo* 2005;63(2):101-7.

182. Wong CF, Leung SK, Yew WW. Percentage reduction of pleural effusion as a simple predictor of pleural scarring in tuberculous pleuritis. *Respirology (Carlton, Vic)* 2005;10(4):515-9.

183. Barbas CS, Cukier A, de Varvalho CR, et al. The relationship between pleural fluid findings and the development of pleural thickening in patients with pleural tuberculosis. *Chest* 1991;100(5):1264-7.

184. de Pablo A, Villena V, Echave-Sustaeta J, et al. Are pleural fluid parameters related to the development of residual pleural thickening in tuberculosis? *Chest* 1997;112(5):1293-7.

185. Frye MD, Pozsik CJ, Sahn SA. Tuberculous pleurisy is more common in AIDS than in non-AIDS patients with tuberculosis. *Chest* 1997;112(2):393-7.

186. Seiscento M, Vargas FS, Antonangelo L, et al. Transforming growth factor beta-1 as a predictor of fibrosis in tuberculous pleurisy. *Respirology (Carlton, Vic)* 2007;12(5):660-3.

187. de la Mora IL, Martinez-Oceguera D, Laniado-Laborin R. Chronic airway obstruction after successful treatment of tuberculosis and its impact on quality of life. *Int J Tuberc Lung Dis* 2015;19(7):808-10.

188. Banu Rekha VV, Ramaschandran R, Kuppu Rao KV, et al. Assessment of Long-term status of sputum positive pulmonary TB patients successfully treated with short course chemotherapy. *Indian J Tuberc* 2009;56:132-40.

189. Lonni S, Chalmers JD, Goeminne PC, et al. Etiology of Non-Cystic Fibrosis Bronchiectasis in Adults and Its Correlation to Disease Severity. *Ann Am Thorac Soc* 2015;12(12):1764-70.

190. Masekela R, Anderson R, Moodley T, et al. HIV-related bronchiectasis in children: an emerging spectre in high tuberculosis burden areas. *Int J Tuberc Lung Dis* 2012;16(1):114-9.

191. Hansell DM, Bankier AA, MacMahon H, et al. Fleischner Society: Glossary of Terms for Thoracic Imaging. *Radiology* 2008;246:697 - 722.

192. Kligerman SJ, Henry T, Lin CT, et al. Mosaic Attenuation: Etiology, Methods of Differentiation, and Pitfalls. *Radiographics : a review publication of the Radiological Society of North America, Inc* 2015;35

193. Alene KA, Clements ACA, McBryde ES, et al. Sequelae of multidrug-resistant tuberculosis: protocol for a systematic review and meta-analysis. *BMJ Open* 2018;8(2):e019593.

194. Yu CT, Wang CH, Huang TJ, et al. Relation of bronchoalveolar lavage T lymphocyte subpopulations to rate of regression of active pulmonary tuberculosis. *Thorax* 1995;50(8):869-74.

195. Al-Hajjaj MS, Joharjy IA. Predictors of radiological sequelae of pulmonary tuberculosis. *Acta Radiol* 2000;41(6):533-37.

196. Buyukoglan H, Gulmez I, Kelestimur F, et al. Leptin levels in various manifestations of pulmonary tuberculosis. *Mediators of Inflammation* 2007;2007:1-6.

197. Swaminathan S, Padmapriyadarsini C, Ponnuraja C, et al. Miliary tuberculosis in human immunodeficiency virus infected patients not on antiretroviral therapy: Clinical profile and response to short-course chemotherapy. *J Postgrad Med* 2007;53(4):228-31.

198. Small PM, Hopewell PC, Schecter GF, et al. Evolution of chest radiographs in treated patients with pulmonary tuberculosis and HIV infection. *J Thorac Imag* 1994;9(2):74-7.

199. Menon B, Nima G, Dogra V, et al. Evaluation of the radiological sequelae after treatment completion in new cases of pulmonary, pleural, and mediastinal tuberculosis. *Lung India* 2015;32(3):241-45.

200. Kallan BM, Kishan J. Clinicoradiological Status of Patients of Pulmonary Tuberculosis after Adequate Treatment. *Indian J Med Sci* 1988;42(1):4-8.

201. Lisha PV, James PT, Ravindran C. Morbidity and mortality at five years after initiating Category I treatment among patients with new sputum smear positive pulmonary tuberculosis. *Indian J Tuberc* 2012;59(2):83-91.

202. Poey C, Verhaegen F, Giron J, et al. High resolution chest CT in tuberculosis: evolutive patterns and signs of activity. *Journal of computer assisted tomography* 1997;21(4):601-7.

203. Bombarda S, Figueiredo CM, Seiscento M, et al. Pulmonary tuberculosis: tomographic evaluation in the active and post-treatment phases. *Sao Paulo medical journal = Revista paulista de medicina* 2003;121(5):198-202.

204. Lee JJ, Chong PY, Lin CB, et al. High resolution chest CT in patients with pulmonary tuberculosis: characteristic findings before and after antituberculous therapy. *European journal of radiology* 2008;67(1):100-4.

205. Capone RB, Capone D, Mafort T, et al. Tomographic Aspects of Advanced Active Pulmonary Tuberculosis and Evaluation of Sequelae following Treatment. *Pulm Med* 2017;2017:9876768.

206. Ralph AP, Ardian M, Wiguna A, et al. A simple, valid, numerical score for grading chest x-ray severity in adult smear-positive pulmonary tuberculosis. *Thorax* 2010;65(10):863-9.

207. Chen YC, Chin CH, Liu SF, et al. Prognostic values of serum IP-10 and IL-17 in patients with pulmonary tuberculosis. *Dis Markers* 2011;31(2):101-10.

208. How SH, Kuan YC, Ng TH, et al. Monitoring treatment response in sputum smear positive pulmonary tuberculosis patients: comparison of weight gain, sputum conversion and chest radiograph. *The Malaysian journal of pathology* 2014;36(2):91-6.

209. National Tuberculosis Association of the USA. Diagnostic standards and classification of tuberculosis. 11th ed. New York1961.

210. Godoy MD, Mello FC, Lopes AJ, et al. The functional assessment of patients with pulmonary multidrug-resistant tuberculosis. *Respir Care* 2012;57(11):1949-54.

211. Willcox PA, Ferguson AD. Chronic obstructive airways disease following treated pulmonary tuberculosis. *Respir Med* 1989;83(3):195-8.

212. Ramos LM, Sulmonett N, Ferreira CS, et al. Functional profile of patients with tuberculosis sequelae in a university hospital. *J Bras Pneumol* 2006;32(1):43-7.

213. Baez-Saldana R, Lopez-Areaga Y, Bizarron-Muro A, et al. A novel scoring system to measure radiographic abnormalities and related spirometric values in cured pulmonary tuberculosis. *PloS one* 2013;8(11):e78926.

214. Barker DJP, Godfrey KM, Fall C, et al. Relation of birthweight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. *BMJ* 1991;303:671 - 75.

215. Shaheen SO, Barker DJ, Holgate ST. Do lower respiratory tract infections in early childhood cause chronic obstructive pulmonary disease? *Am J Respir Crit Care Med* 1995;151(5):1649-51; discussion 51-2.

216. Crothers K. Chronic obstructive pulmonary disease in patients who have HIV infection. *Clinics in chest medicine* 2007;28(3):575-87.

217. Drummond MB, Huang L, Diaz PT, et al. Factors associated with abnormal spirometry among HIV-infected individuals. *AIDS* 2015;29(13):1691-700.

218. Kunisaki KM, Niewoehner DE, Collins G, et al. Pulmonary effects of immediate versus deferred antiretroviral therapy in HIV-positive individuals: a nested substudy within the multicentre, international, randomised, controlled Strategic Timing of Antiretroviral Treatment (START) trial. *Lancet Respir Med* 2016;4(12):980-89.

219. Prescott E, Vestbo J. Socioeconomic status and chronic obstructive pulmonary disease. *Thorax* 1999;54:737-41.

220. Corbett EL, MacPherson P. Tuberculosis screening in high human immunodeficiency virus prevalence settings: turning promise into reality. *Int J Tuberc Lung Dis* 2013;17(9):1125-38.

221. Wood R, Middelkoop K, Myer L, et al. Undiagnosed tuberculosis in a community with high HIV prevalence: implications for tuberculosis control. *Am J Respir Crit Care Med* 2007;175(1):87-93.

222. Corbett EL, Bandason T, Duong T, et al. Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of

infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial. *Lancet* 2010;376(9748):1244-53.

223. Munyati SS, Dhoba T, Mungofa S, et al. Chronic Cough in Primary Health Care Attendees, Harare, Zimbabwe: Diagnosis and Impact of HIV Infection. *Clin Infect Dis* 2005

224. Claassens MM, van Schalkwyk C, Floyd S, et al. Symptom screening rules to identify active pulmonary tuberculosis: Findings from the Zambian South African Tuberculosis and HIV/AIDS Reduction (ZAMSTAR) trial prevalence surveys. *PLoS One* 2017;12(3):e0172881.

225. Lederer DJ, Bell SC, Branson RD, et al. Control of Confounding and Reporting of Results in Causal Inference Studies. Guidance for Authors from Editors of Respiratory, Sleep, and Critical Care Journals. *Ann Am Thorac Soc* 2019;16(1):22-28.

226. EuroQol Group. EQ-5D-3L authorisation. In: Meghji J, ed., 2015.

227. American Thoracic Society. ATS Statement: Guidelines for the Six-Minute Walk Test. *Am J Respir Crit Care Med* 2002;166:111-17.

228. Cooper BG. An update on contraindications for lung function testing. *Thorax* 2011;66(8):714-23.

229. National Institute for Occupational Safety & Health. Spirometry quality assurance: Common errors and their impact on test results. Atlanta, USA: Department for Health & Human Services, Centres for Disease Control & Prevention, 2012.

230. Burden of Obstructive Lung Disease Study. Spirometry quality control guidelines, 2009.

231. Ferrer M, Villasante C, Alonso J, et al. Interpretation of quality of life scores from the St George's Respiratory Questionnaire. *Eur Respir J* 2002;19(3):405-13.

232. Gronseth R, Vollmer WM, Hardie JA, et al. Predictors of dyspnoea prevalence: results from the BOLD study. *Eur Respir J* 2014;43(6):1610-20.

233. Agustí A, Noell G, Brugada J, et al. Lung function in early adulthood and health in later life: a transgenerational cohort analysis. *The Lancet Respiratory Medicine* 2017;5(12):935-45.

234. Jo YS, Park JH, Lee JK, et al. Risk factors for pulmonary arterial hypertension in patients with tuberculosis-destroyed lungs and their clinical characteristics compared with patients with chronic obstructive pulmonary disease. *International journal of chronic obstructive pulmonary disease* 2017;12:2433-43.

235. Chung KP, Chen JY, Lee CH, et al. Trends and predictors of changes in pulmonary function after treatment for pulmonary tuberculosis. *Clinics (Sao Paulo, Brazil)* 2011;66(4):549-56.

236. Pfaff C, Singano V, Akello H, et al. Early experiences integrating hypertension and diabetes screening and treatment in a human immunodeficiency virus clinic in Malawi. *International health* 2018

237. Steingart KR, Schiller I, Dendukuri N. In reply to 'False-positive Xpert(R) MTB/RIF assays in previously treated patients'. *Int J Tuberc Lung Dis* 2015;19(3):366-7.

238. Ribeiro L, Ind PW. Marijuana and the lung: hysteria or cause for concern? *Breathe (Sheff)* 2018;14(3):196-205.

239. Hughes RA, May MT, Tilling K, et al. Long-term trends in CD4 cell counts, CD8 cell counts, and the CD4: CD8 ratio: ART Cohort Collaboration (ART-CC) Study. *AIDS* 2018

240. Kerkhoff AD, Wood R, Cobelens FG, et al. The predictive value of current haemoglobin levels for incident tuberculosis and/or mortality during long-term antiretroviral therapy in South Africa: a cohort study. *BMC Med* 2015;13:70.

241. Marcy O, Laureillard D, Madec Y, et al. Causes and determinants of mortality in HIV-infected adults with tuberculosis: an analysis from the CAMELIA ANRS 1295-CIPRA KH001 randomized trial. *Clin Infect Dis* 2014;59(3):435-45.

242. Peduzzi P, Concato J, Kemper E, et al. A Simulation Study of the Number of Events per Variable in Logistic Regression Analysis. *J Clin Epidemiol* 1996;49:1373-79.

243. Horton R. Non-communicable diseases: 2015 to 2025. *The Lancet* 2013;381(9866):509-10.

244. United Nations. Transforming our world: The 2030 agenda for sustainable development. Geneva, Switzerland: United Nations, 2015.

245. Boutou AK, Nair A, Douraghi-Zadeh D, et al. A combined pulmonary function and emphysema score prognostic index for staging in Chronic Obstructive Pulmonary Disease. *PLoS One* 2014;9(10):e111109.

246. Goh NS, Desai SR, Veeraraghavan S, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med* 2008;177(11):1248-54.