


# BMJ Open Burden, clinical features and outcomes of post-tuberculosis lung disease in sub-Saharan Africa: a protocol for a systematic review and meta-analysis

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**To cite:** Nuwagira E, Baluku JB, Meya DB, *et al.* Burden, clinical features and outcomes of post-tuberculosis lung disease in sub-Saharan Africa: a protocol for a systematic review and meta-analysis. *BMJ Open* 2022;**12**:e062260. doi:10.1136/bmjopen-2022-062260

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-062260>).

Received 23 February 2022  
Accepted 05 August 2022



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## ABSTRACT

**Introduction** Tuberculosis (TB) is significantly associated with multiple postinfectious, non-communicable diseases after microbiological cure. For example, those with a history of TB disease have a higher risk of developing chronic lung diseases at a younger age. However, the extent and nature of post-TB complications are not well described. Here, we present a protocol for a systematic review and meta-analysis, which aims to synthesise literature on the burden of post-TB lung disease (PTLD) in sub-Saharan Africa, describe phenotypes, long-term outcomes and the health-related quality of life of people with PTLT.

**Methods and analysis** A systematic search will be conducted using PubMed, EMBASE, Web of Science, African Journals Online and the Cochrane Library of Systematic Reviews. Papers published in English and French languages that report the prevalence, clinical features, quality of life and long-term outcomes of people with PTLT in sub-Saharan Africa will be considered. We will assess and critically appraise the methodological quality of all studies using the modified covidence. Qualitative and quantitative (network and meta-analysis) synthesis will be performed and STATA V.16 will be used to estimate the burden of PTLT.

**Ethics and dissemination** Ethical approval is not required for this systematic review and meta-analysis. Our results will be published in peer-reviewed journals.

**PROSPERO registration number** CRD42021274018.

## INTRODUCTION

Pulmonary tuberculosis (TB) is increasingly recognised as an important risk factor for chronic respiratory disease (CRD) with existing literature suggesting that most patients have an obstructive deficit on lung function testing.<sup>1–4</sup> Consequently, TB survivors contribute significantly to the growing global burden of chronic obstructive pulmonary disease (COPD), a major public health problem that receives little attention in low and middle-income country health service delivery systems.<sup>5</sup> By the end of 2020, there

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a study that will describe in detail burden of post-tuberculosis lung disease (PTLD), the associated factors and health-related quality of life of patients with PTLT in sub-Saharan Africa.
- ⇒ This study will raise awareness of the need for post-tuberculosis (TB) care strategies such as pulmonary rehabilitation.
- ⇒ The major limitation of this review is that there was no standard definition and diagnostic criteria for PTLT prior to the post-TB symposium in 2019.
- ⇒ The topic may be generally understudied in sub-Saharan Africa, leading to scanty literature yield and fewer studies included.
- ⇒ The clinical heterogeneity between studies in terms of measuring PTLT and quality of life may compromise the evidence strength of our meta-analyses.

were approximately 155 million TB survivors globally, with the majority of these being average aged men, 45 years (IQR 33–57), an economically productive age group.<sup>5 6</sup> TB survivors have up to three times the risk of mortality compared with the general population, with a prevalence of lung impairment between 18% and 87%.<sup>7</sup>

Since TB may permanently damage host tissues, it transitions from being a treatable infectious disease to non-communicable disease.<sup>8</sup> The lung parenchymal damage from TB leads to a reduction in ventilation and perfusion, which subsequently impairs the survivors' quality of life. Post-tuberculosis lung disease (PTLD) is characterised by abnormal spirometry (airflow obstruction and/or low forced vital capacity) and recurrent symptoms that are often mistakenly treated as recurrent TB infection, with some patients experiencing significant adverse effects from unnecessary TB treatment due to drug toxicity. Furthermore, patients with such

a CRD experience secondary impairments such as peripheral muscle wasting, nutritional deficits and psychosocial dysfunction,<sup>9</sup> which leads to a reduced health-related quality of life and exercise tolerance compared with healthy individuals. Symptoms like chronic cough tend to bring significant social and healthcare-associated stigma. The frequent hospital visits and repeated testing for TB have a negative social, psychological and economic impact on the patients as they spend more time on frequent hospital visits than at work.<sup>6</sup> This is likely to continue the vicious cycle of TB and poverty.<sup>10 11</sup>

In sub-Saharan Africa, the burden of PTLD seems to be steadily increasing, leading to disability among the survivors.<sup>1 12</sup> Despite this burden, there are no designed interventions for treating people affected by TB after treatment completion and microbiological cure. Although this is an important indicator of successful treatment, such an approach does not adequately address the physical, mental and social suffering of TB survivors.<sup>13</sup>

Recently, we conducted a cross-sectional study on the effect of multidrug-resistant TB on lung function among Ugandan adults, and 23% of the enrolled patients had obstructive lung disease. Poverty was significantly associated with obstructive lung disease.<sup>14</sup> At Mulago National Referral Hospital in Kampala, Uganda, a pulmonary rehabilitation programme that enrolled patients with obstructive lung disease reported that up to 30% of the attendees of the respiratory clinic have a history of pulmonary TB.<sup>15</sup> The true burden of PTLD remains poorly described. There is limited to no data available regarding chronic respiratory impairment in TB survivors and the impact of post-TB sequelae on their lives.<sup>16</sup>

Currently, health systems in Africa do not recognise that TB care extends beyond the initial infection, which leaves majority of the survivors at risk of both clinical and socio-economic consequences even after microbiologic cure of TB. Furthermore, the long-term outcomes and drivers of morbidity and mortality after cure of TB have not been well studied, which leaves a wide knowledge gap in PTLD in resource-limited high-TB burden sub-Saharan Africa.

This article describes the protocol for a systematic review that will determine the burden of PTLD, imaging patterns and quality of life of patients with PTLD. Our main goal is to systematically review all published literature on PTLD from sub-Saharan Africa and determine the burden, risk factors and quality of life of patients with PTLD. Knowledge of the clinical and genetic predictors of PTLD will be used to comprehensively understand and to predict the long-term outcomes of PTLD.

## OBJECTIVES

The main objective of this study is to determine the burden of PTLD, the associated factors and health-related quality of life of patients with PTLD. The specific objectives are to;

1. estimate the incidence of PTLD after TB treatment.
2. Describe the clinical spectrum of PTLD.

3. Describe outcomes, including quality of life, functionality and mortality in individuals with PTLD.

## METHODS AND DESIGN

This systematic review and meta-analysis protocol has been developed following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols and as recommended by the Meta-analyses of Observational Studies in Epidemiology. Our inclusion criteria will be as follows:

1. Population: adults ( $\geq 18$  years) living in sub-Saharan Africa who have completed TB treatment.
2. Interventions: Any interventions whose primary aim is to prevent or treat PTLD.
3. Comparator or control: No specified comparator or control.
4. Outcomes: The outcome of interest will be PTLD which will be defined as chronic respiratory symptoms and eventually CRD such as bronchiectasis, fibrosis or COPD that are attributed to a previously documented episode of pulmonary TB. The definition of PTLD may also include the abnormal pulmonary function tests, persistence of respiratory symptoms or any other respiratory pathology in an individual that completed TB treatment.<sup>7</sup> Other outcomes include; the patients' health-related quality of life, such as the socioeconomic status and the radiological patterns reported.
5. Study design: We will include randomised control trials, cohort studies, case-control studies and case series with at least 10 participants reporting on the prevalence, incidence, clinical features, quality of life and outcomes of patients and are presenting with a spectrum of symptoms classified as post-TB lung disorders.

The following will be excluded from the review: case reports, commentaries, opinion papers, policy papers, reviews and meta-analyses, study protocols, animal studies and conference or symposium proceedings as shown in [figure 1](#).

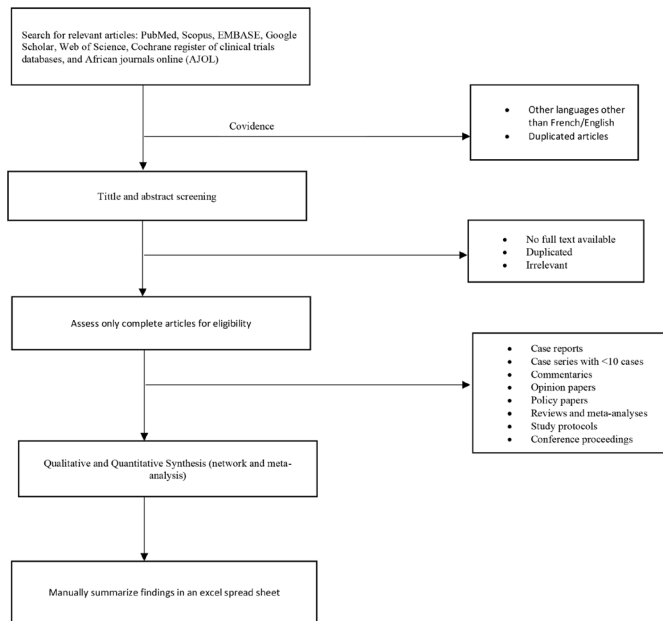
## Patient and public involvement

The public and patients will not be involved in this systematic review and meta-analysis.

## Search strategy

With help of an experienced medical librarian, we shall search for relevant references from January 2000 to December 2021 in the EMBASE, PubMed/MEDLINE, Web of Science, Cochrane register of clinical trials databases, and African Journals Online (AJOL) using the search terms below. Studies will be restricted to the English and French languages. The following Medical Subject Headings (MeSH) terms will be used; 'sub Saharan Africa', OR each of the individual 48 countries of sub-Saharan Africa, 'incidence', 'prevalence', 'post-TB lung disease', 'post-TB sequelae', 'post-TB airway disease', 'post-TB COPD', 'post-TB pulmonary disease'.

The search terms will be translated to French language and a similar search strategy used. A combination of



**Figure 1** Showing how studies will be generated, assessed and selected for use in the systematic review and meta-analysis.

free text and controlled vocabulary terms will be used as appropriate and translated for use in each database. The citations will be downloaded and managed in Covidence. The MeSH terms will be combined using Boolean logical operators (OR, AND, NOT). We will also conduct a manual search of the references included in the selected articles and analyse these using the Rayyan web software. Selected articles will be reviewed independently by investigators with experience in systematic reviews.

With help from an experienced librarian (LLP), a full search strategy will be developed and run (see online supplemental file 1), not later than 1 August 2022. Titles and abstracts of all identified studies will be reviewed by two investigators (EN, JBB) and studies deemed not relevant based on the review of the title and abstract will be excluded.

In case of any disagreements, the third reviewer (PSL) will be asked to resolve them. Second, the full-text versions of the articles selected in the first stage will be checked against the eligibility criteria. In addition, we shall search for grey literature on Google Scholar and additional publications in the reference lists of eligible studies.

### Quality assessment

Because of methodological differences, the quality of the included research articles will be assessed using the modified version of the Newcastle-Ottawa Quality Assessment Scale. This tool is reliable and valid to assess cohort and case-control studies and was endorsed by the Cochrane collaboration to assess the quality of observational studies.<sup>17</sup>

A score between 1 and 3 will be defined as low quality, scores between 4 and 6 will be defined as moderate

quality, whereas a score between 7 and 9 will be defined as high quality. A third author will be involved to resolve disagreement in case the two primary authors do not agree.

### Data extraction and management

Data from all the selected studies will be thoroughly reviewed by the two main investigators. Study methods and characteristics, design, inclusion/exclusion criteria, loss to follow-ups and withdrawals or dropouts will also be assessed. Depending on the methodology used, we will extract data on the participants' characteristics, disease course and interventions if any. Some of the variables that will be extracted include age, sex, TB category (drug susceptible or multidrug resistant), treatment received, comorbidities such as HIV and diabetes mellitus, mode of diagnosis of PTLD, functional status, quality of life measurements and tools used to measure both the functional status and quality of life. We will also describe the controls in detail, for case-control studies and report long-term outcomes as those reported after at least 2 years (24 months) of follow-up.

### Data synthesis and analysis

We are interested in the burden of PTLD reported as incidence or prevalence, the steps made in simplifying the diagnosis and treatment options for patients with PTLD in sub-Saharan Africa. We will use Microsoft Excel V.16.57 and STATA V.16 software (Stata Corp, College Station, Texas) for analysis. We will perform, qualitative, quantitative (network and meta-analysis) synthesis and critical interpretive synthesis to assess the content and utility of the selected studies. A random or fixed-effect model meta-analysis will be performed using metaprop command for analysis of proportions in STATA. A forest plot will be used to present the results of the meta-analysis. A sensitivity analysis will also be done to examine the influence of HIV coinfection, gender, cigarette smoking, TB drug resistance and regions of Africa (East, West, Southern and North Africa).

Heterogeneity of studies will be assessed using Cochrane's  $Q$  and  $I^2$  statistic,<sup>18</sup> and  $p$  value will be used to report heterogeneity between studies. Heterogeneity will be considered as low ( $I^2=0\%–25\%$ ), moderate ( $I^2=26\%–50\%$ ) or high ( $I^2>50\%$ ). Depending on the heterogeneity of the data, random-effect (for  $I^2\geq 50\%$ ) or fixed-effect (for  $I^2<50\%$ ) models will be used to determine the pooled prevalence of PTLD. The Mann-Kendall trend test will then be used to evaluate the trend in the prevalence of PTLD over the study period.

We will perform a meta-regression to assess the impact of study characteristics on heterogeneity and also to correct the meta-analytical estimates for biases. Sensitivity analysis will be conducted by gender, and HIV status. We will consider a  $p$  value of  $<0.05$  to be statistically significant.



## ETHICS AND DISSEMINATION

For this protocol and systematic review, we do not require ethical approval. Our results will be presented in conferences and published in open access peer-reviewed journals following the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines.

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**Contributors** EN and PSL conceptualised and wrote the initial draft of this protocol. JBB and LLP led the search strategy. SM, DBM, FB and MS reviewed and edited the manuscript. EN and PSL are responsible for the overall content as guarantors. EN is the corresponding author and submitted the protocol for publication.

**Funding** This work is funded by the Multi-morbidity Research Capacity Initiative (MURCI) fellowship grant at Mbarara University of Science and Technology, a research training fellowship sponsored by the US National Institutes of Health (NIH) under grant number D43TWO11632.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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## REFERENCES

- Nightingale R, Chinoko B, Lesosky M, *et al*. Respiratory symptoms and lung function in patients treated for pulmonary tuberculosis in Malawi: a prospective cohort study. *Thorax* 2021. doi:10.1136/thoraxjnl-2021-217190. [Epub ahead of print: 22 Dec 2021].
- Menezes AMB, Hallal PC, Perez-Padilla R, *et al*. Tuberculosis and airflow obstruction: evidence from the PLATINO study in Latin America. *Eur Respir J* 2007;30:1180–5.
- Byrne AL, Marais BJ, Mitnick CD, *et al*. Tuberculosis and chronic respiratory disease: a systematic review. *Int J Infect Dis* 2015;32:138–46.
- Amaral AFS, Coton S, Kato B, *et al*. Tuberculosis associates with both airflow obstruction and low lung function: BOLD results. *Eur Respir J* 2015;46:1104–12.
- Quaderi SA, Hurst JR. The unmet global burden of COPD. *Glob Health Epidemiol Genom* 2018;3:e4.
- Dodd PJ, Yuen CM, Jayasooriya SM, *et al*. Quantifying the global number of tuberculosis survivors: a modelling study. *Lancet Infect Dis* 2021;21:984–92.
- Allwood BW, van der Zalm MM, Amaral AFS, *et al*. Post-tuberculosis lung health: perspectives from the first International Symposium. *Int J Tuberc Lung Dis* 2020;24:820–8.
- Romanowski K, Baumann B, Basham CA, *et al*. Long-Term all-cause mortality in people treated for tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2019;19:1129–37.
- Nici L, Donner C, Wouters E, *et al*. American thoracic Society/ European respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006;173:1390–413.
- Barter DM, Agboola SO, Murray MB, *et al*. Tuberculosis and poverty: the contribution of patient costs in sub-Saharan Africa—a systematic review. *BMC Public Health* 2012;12:980.
- Janssens J-P, Rieder HL. An ecological analysis of incidence of tuberculosis and per capita gross domestic product. *Eur Respir J* 2008;32:1415–6.
- Mpagama SG, Msaji KS, Kaswaga O, *et al*. The burden and determinants of post-TB lung disease. *Int J Tuberc Lung Dis* 2021;25:846–53.
- Aggarwal AN. Quality of life with tuberculosis. *J Clin Tuberc Other Mycobact Dis* 2019;17:100121.
- Nuwagira E, Stadelman A, Baluku JB, *et al*. Obstructive lung disease and quality of life after cure of multi-drug-resistant tuberculosis in Uganda: a cross-sectional study. *Trop Med Health* 2020;48:1–7.
- Jones R, Kirenga BJ, Katagira W, *et al*. A pre-post intervention study of pulmonary rehabilitation for adults with post-tuberculosis lung disease in Uganda. *Int J Chron Obstruct Pulmon Dis* 2017;12:3533–9.
- Dodd PJ, Yuen CM, Jayasooriya SM, *et al*. Quantifying the global number of tuberculosis survivors: a modelling study. *Lancet Infect Dis* 2021;21:984–92.
- Higgins JP, Thomas J, Chandler J, *et al*. *Cochrane Handbook for systematic reviews of interventions*. John Wiley & Sons, 2019.
- Thompson SG, Higgins JPT. How should meta-regression analyses be undertaken and interpreted? *Stat Med* 2002;21:1559–73.