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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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 PTLD.

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 PTLD 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 PTLD.

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

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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 PTLD 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 PTLD 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 PTLD and quality of life may compromise the evidence strength of our meta-analyses.

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. 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. By the end of 2020, there 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. 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%. Since TB may permanently damage host tissues, it transitions from being a treatable infectious disease to non-communicable disease. 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 peripher-
al muscle wasting, nutritional deficits and psychosocial
dysfunction,9 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.6 This is likely to continue the
vicious cycle of TB and poverty.10 11

In sub-Saharan Africa, the burden of PTLD seems to be
steadily increasing, leading to disability among the survi-

vors.1 12 Despite this burden, there are no designed inter-
ventions 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.13

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 associ-
ated with obstructive lung disease.14 At Mulago National
Referral Hospital in Kampala, Uganda, a pulmonary reha-

bilitation programme that enrolled patients with obstruc-
tive lung disease reported that up to 30% of the attendees
of the respiratory clinic have a history of pulmonary TB.15

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.16

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 liter-

ature 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, function-
ality 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 (≥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 document-
ed 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.7 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 tri-
aux, cohort studies, case–control studies and case series
with at least 10 participants reporting on the preva-

lence, incidence, clinical features, quality of life and
outcomes of patients and are presenting with a spec-
trum 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 system-
atic 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
The search terms will be translated to French language
and a similar search strategy used. A combination of

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.17

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 Cochran’s Q and I² statistic,18 and p value will be used to report heterogeneity between studies. Heterogeneity will be considered as low (I²=0%–25%), moderate (I²=26%–50%) or high (I²=50%). Depending on the heterogeneity of the data, random-effect (for I²<50%) or fixed-effect (for I²≥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.

REFERENCES