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Global Prevalence and Burden of Post-Tuberculosis Lung Disease (PTBLD): A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - All authors declare no financial or non-financial conflicts of interest in relation to this protocol or the conduct of the planned systematic review and meta-analysis. No author has received payments, honoraria, travel grants, or any other form of remuneration from commercial entities with a potential interest in the outcomes of this review. The review is not sponsored by, and has no financial relationship with, any pharmaceutical manufacturer, diagnostic company, or government regulatory body. Authors commit to disclosing any emerging conflicts of interest that arise during the conduct of the review by submitting a protocol amendment to INPLASY.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 May 2026 and was last updated on 22 May 2026.

INTRODUCTION

Review question / Objective Primary Review Question:
What is the global prevalence, spectrum, and burden of post-tuberculosis lung disease (PTBLD) among individuals who have completed treatment for pulmonary tuberculosis, and how do these estimates vary by WHO region, income setting, HIV co-infection status, and drug-resistance profile?

PICO Framework:
Element Definition Inclusion Exclusion
P — Population Individuals who have completed treatment for pulmonary TB (bacteriologically confirmed or clinically diagnosed) Adults and children; DS-TB and MDR/XDR-TB; HIV-positive and HIV-negative; any WHO region Active or recurrent TB; extrapulmonary TB only; LTBI without prior active disease
I — Index Condition Post-TB lung disease: any respiratory sequela attributable to prior TB or its treatment, after treatment completion Any standardised spirometric, radiological, symptomatic, or composite PTBLD case definition Pre-existing respiratory disease not attributable to TB; no PTBLD-specific outcome measured
C — Comparator General population, TB-unexposed individuals, or pre-treatment baseline lung function Studies with or without a comparator; prevalence-only studies eligible No specific comparator required; absence of comparator does not exclude a study
O — Outcomes Prevalence of PTBLD; spirometric abnormality; radiological sequelae; quality of life;

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functional capacity; mortality Prevalence proportions, lung function values, QoL scores, functional capacity, mortality rates Studies reporting only microbiological outcomes with no PTBLD-specific data
S — Study Design Observational epidemiological designs Cross-sectional, prospective/retrospective cohort, case-control, registry-based studies Case reports; case series <10 participants; editorials; reviews without primary data.

Rationale Post-tuberculosis lung disease (PTBLD) refers to the spectrum of persistent or progressive structural and functional pulmonary sequelae that occur following microbiologically successful treatment of pulmonary tuberculosis (TB). Despite global advances in TB control, PTBLD remains a substantially under-quantified burden affecting tens of millions of TB survivors worldwide and is increasingly recognised as a major driver of chronic respiratory morbidity, disability, and premature mortality in high-burden settings.
Tuberculosis continues to rank among the leading infectious causes of death globally, with the World Health Organisation (WHO) estimating approximately 10.6 million new cases and 1.3 million deaths in 2022. Because a meaningful proportion of TB survivors develop clinically significant residual lung impairment even after successful bacteriological cure, any comprehensive accounting of TB's global burden must extend beyond treatment success rates to capture post-treatment sequelae. These sequelae encompass a wide and heterogeneous spectrum of pathological processes, including chronic airflow obstruction, bronchiectasis, pulmonary fibrosis, destroyed lung, pleural disease, aspergillosis-related complications, and exercise-limiting respiratory impairment.
Despite the scale of the problem, the evidence base for PTBLD suffers from profound heterogeneity in case definitions, inconsistent measurement instruments, geographic under-representation, and a persistent failure to integrate structural, functional, and symptomatic outcome domains within a unified framework. Existing systematic reviews have often been restricted in geographic scope, limited to spirometric outcomes alone, or have not accounted for variation by HIV co-infection status, drug resistance profile, or TB treatment history. This protocol establishes a rigorous, comprehensive, and reproducible framework for a global systematic review and meta-analysis to address these evidence gaps.

Condition being studied Post-Tuberculosis Lung Disease (PTBLD) is defined as any clinically significant respiratory impairment — structural, functional, or symptomatic — occurring in an individual who has completed a full course of anti-TB therapy and achieved microbiological cure or treatment completion, in the absence of recurrent or active TB disease. This definition aligns with the 2023 Union/WHO Consensus Statement on PTBLD.

PTBLD encompasses a heterogeneous spectrum of pathological processes:
• Obstructive ventilatory defects: post-bronchodilator FEV_1/FVC <0.70 (GOLD criteria) or below the lower limit of normal (LLN) per GLI 2012 reference equations.
• Restrictive ventilatory defects: FVC <LLN with FEV_1/FVC ≥LLN (spirometric surrogate); confirmed by TLC 3 months post-treatment; reduced six-minute walk test (6MWT) distance; impaired quality of life on validated instruments (mMRC, CAT, SGRQ).

PTBLD is distinct from active TB, TB relapse, or latent TB infection, and is increasing in global importance as TB treatment success rates improve and large survivor cohorts accumulate in high-burden settings across sub-Saharan Africa, South and South-East Asia, and Eastern Europe.

METHODS

Search strategy The search strategy follows the Peer Review of Electronic Search Strategies (PRESS) 2015 Guideline Statement and will be developed and finalised in collaboration with a specialist medical librarian. Boolean operators (AND, OR, NOT) combine the following concept blocks, adapted to each database using controlled vocabulary (MeSH for MEDLINE; Emtree for EMBASE) and supplemented by free-text terms.

Concept Blocks and Key Terms:
• Block 1 — TB Population: tuberculosis [MeSH] OR "pulmonary tuberculosis" OR "Mycobacterium tuberculosis" OR "post-TB" OR "TB survivor*" OR "treated tuberculosis" OR "TB treatment completion" OR "cured tuberculosis" OR "anti-tuberculosis therapy"
• Block 2 — PTBLD Condition: "post-tuberculosis lung disease" OR "PTBLD" OR "post-TB sequelae" OR "post-tuberculous" OR "tuberculosis sequelae" OR "residual lung disease" OR "TB-destroyed lung" OR "lung sequelae after tuberculosis" OR "post-infectious lung disease"
• Block 3 — Outcome Terms: spirometry OR "pulmonary function tests" OR FEV_1 OR FVC OR "airflow obstruction" OR COPD OR bronchiectasis OR "pulmonary fibrosis" OR "destroyed lung" OR aspergilloma OR "respiratory impairment" OR

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DLCO OR "6-minute walk" OR "exercise capacity" OR "pleural thickening" OR "pulmonary disability"
• Block 4 — Study Filter (optional): prevalence OR burden OR epidemiology OR cohort OR "cross-sectional" OR "meta-analysis" OR incidence OR "observational study"

Full PubMed/MEDLINE Boolean String (illustrative): (tuberculosis[MeSH] OR "pulmonary tuberculosis"[MeSH] OR "post-TB"[tiab] OR "TB survivor*"[tiab]) AND ("post-tuberculosis lung disease"[tiab] OR "PTBLD"[tiab] OR "tuberculosis sequelae"[tiab] OR "residual lung disease"[tiab]) AND (spirometry[MeSH] OR "pulmonary function tests"[MeSH] OR "FEV1"[tiab] OR bronchiectasis[MeSH] OR "airflow obstruction"[tiab] OR "destroyed lung"[tiab] OR "respiratory impairment"[tiab]).

Participant or population The review will include studies involving individuals of any age (adults and children aged ≥7 years) who have a documented history of bacteriologically confirmed or clinically diagnosed pulmonary tuberculosis and who have received any course of anti-TB therapy. Both drug-sensitive TB (DS-TB) and drug-resistant TB (MDR-TB and XDR-TB) populations will be included. Studies conducted in any WHO region and any World Bank income setting are eligible. HIV-positive, HIV-negative, and HIV-mixed/unreported populations will all be included, with HIV status captured as a subgroup variable. There is no restriction on TB treatment regimen or duration, provided the study reports post-treatment respiratory outcomes.

Intervention This is an epidemiological systematic review of observational studies; no therapeutic intervention is under evaluation. The "index condition" — in PICO terminology — is prior pulmonary tuberculosis and its treatment (anti-TB therapy of any duration or regimen), with PTBLD as the resulting post-treatment sequela of interest. Exposure to pulmonary TB and its treatment is the relevant antecedent; the post-treatment lung disease burden constitutes the primary outcome rather than an intervention response. Studies with and without an active comparator group are both eligible.

Comparator No specific comparator is required for eligibility. Studies reporting PTBLD prevalence without a comparison group will be included for meta-analytic pooling. Where available, comparators may include: (i) the general population without a history of TB; (ii) TB-unexposed individuals matched for age, sex, and smoking status; or (iii) pre-treatment (baseline) lung function values within the same study population. The presence or absence of a comparator will be recorded at data extraction and explored as a source of heterogeneity in subgroup analysis.

Study designs to be included Observational epidemiological study designs will be included:• Cross-sectional surveys• Prospective cohort studies• Retrospective cohort studies• Case-control studies (where PTBLD outcomes are reported)• Registry-based studies with primary data on lung outcomes• Government or NGO programme reports containing primary outcome dataExcluded designs: randomised controlled trials (not applicable to this prevalence question), case reports, case series with fewer than 10 participants, review articles, editorials, letters, and commentaries without extractable primary data.

Eligibility criteria Inclusion Criteria:
• Study design: cross-sectional, cohort (prospective or retrospective), case-control, or registry-based
• Population: individuals with documented history of pulmonary TB (bacteriologically confirmed or clinically diagnosed) who have received anti-TB treatment
• Outcome: any standardised measure of PTBLD — spirometric (FEV_1, FVC, FEV_1/FVC), radiological (HRCT, CXR), symptomatic (mMRC, CAT, SGRQ), or composite
• Minimum sample size: ≥10 participants with PTBLD outcome data
• Language: English, French, Spanish, Portuguese (studies in other languages will be translated where resources permit)
• Publication type: peer-reviewed journal articles; government or NGO reports with primary data
• Publication period: database inception to date of final search (no date restriction)

Exclusion Criteria:
• Active, relapsing, or recurrent TB (treatment not completed)
• Extrapulmonary TB only — no pulmonary component
• Latent TB infection (LTBI) without history of active disease
• Case reports or case series with fewer than 10 participants
• Review articles, editorials, letters, or commentaries without extractable primary data
• No PTBLD-specific outcome measure reported
• Animal studies, in vitro studies, or experimental models
• Studies in which PTBLD data cannot be disaggregated from other respiratory diagnoses.

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Information sources Bibliographic Databases:
• MEDLINE / PubMed (NLM / NIH) — core biomedical literature; MeSH controlled vocabulary
• EMBASE via Ovid (Elsevier) — European and pharmacological coverage; Emtree thesaurus; conference abstracts
• Cochrane Central Register of Controlled Trials (CENTRAL) — curated trials registry
• CINAHL (EBSCOhost) — nursing, allied health, and community respiratory outcomes
• Scopus (Elsevier) — multidisciplinary; strong Asian and Latin American coverage
• Web of Science (Clarivate Analytics) — citation tracking; Science Citation Index Expanded
• African Journals Online (AJOL) — sub-Saharan Africa publications not indexed elsewhere.

Main outcome(s) Primary Outcome:
• Prevalence of PTBLD — any standardised spirometric, radiological, symptomatic, or composite case definition; reported as a proportion with 95% confidence interval; pooled using Freeman-Tukey double arcsine transformation under a random-effects model.

Secondary Main Outcomes:
• Obstructive ventilatory defect: post-bronchodilator FEV_1/FVC <0.70 (GOLD) or <LLN (GLI 2012); prevalence proportion; timing: at ≥1 month post-treatment completion.
• Restrictive ventilatory defect: FVC <LLN with FEV_1/FVC ≥LLN; spirometric surrogate; timing: at any post-treatment follow-up.
• Radiological sequelae: prevalence of bronchiectasis (HRCT-defined), pulmonary fibrosis, destroyed lung, pleural thickening, aspergilloma; timing: any post-treatment imaging.
• Quality of life and functional impairment: SGRQ total score ≥25; CAT ≥10; mMRC ≥Grade 2; 6MWT ≤400 m; effect measure: mean difference or standardised mean difference (SMD) where appropriate.
• Respiratory-related mortality: hazard ratio, risk ratio, or mortality rate in PTBLD versus TB-unexposed; timing: any follow-up period.

Additional outcome(s) • Global absolute burden estimate of PTBLD: estimated number of PTBLD cases worldwide, derived by applying pooled regional prevalence estimates to WHO TB notification and treatment success cohort data (burden estimation framework).
• Diffusing capacity (DLCO): DLCO 3 months post-treatment.
• Determinants and risk factors: pooled odds ratios or risk ratios for MDR-TB, HIV co-infection, retreatment history, smoking, household air pollution exposure, and treatment duration as predictors of PTBLD.

Data management All citation records retrieved from database searches will be imported into a systematic review management platform (Rayyan). Duplicate records will be identified and removed using automated deduplication algorithms, with manual verification of any uncertain pairs.

Title and abstract screening, and full-text eligibility assessment, will each be conducted independently by two reviewers using the pre-specified eligibility criteria. Disagreements at each stage will be resolved first by consensus discussion, and if unresolved, by adjudication from a third senior reviewer. All screening decisions, including reasons for exclusion at full-text stage, will be documented and reported in a PRISMA 2020 flow diagram.

Data extraction will be performed using a standardised, pre-piloted data extraction form developed in Microsoft Excel or REDCap. Variables to be extracted include: study identification (author, year, country, design), population characteristics (sample size, age, sex, HIV status, TB drug-sensitivity, treatment history), case definition used for PTBLD (classified as DEF-A through DEF-E per the operational framework), outcome data (prevalence, lung function values, QoL scores, mortality), and risk of bias indicators. A 10% random sample of extractions will be verified by a second reviewer to ensure accuracy.

Quality assessment / Risk of bias analysis Risk of bias (RoB) will be assessed independently by two reviewers for every included study using validated, design-specific instruments:
• Cross-sectional studies: Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Prevalence Studies (9-item tool); scores ≧7/9 indicate low risk of bias.
• Cohort studies: Newcastle-Ottawa Scale (NOS) for cohort studies (maximum 9 stars); NOS ≧7 considered low risk.
• Case-control studies: Newcastle-Ottawa Scale for case-control studies (maximum 9 stars).

Key domains assessed will include: representativeness of the sample; validity and standardisation of PTBLD case definition and measurement instrument; completeness of follow-up (for cohort designs); adequacy of confounder adjustment; and appropriateness of statistical analysis. Inter-rater reliability of RoB assessments will be quantified using Cohen's kappa coefficient; disagreements will be resolved by discussion or third-reviewer adjudication.

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Overall methodological quality will be visually summarised in traffic-light plots. Studies will not be excluded solely on the basis of quality; rather, quality scores will be incorporated as a categorical variable in sensitivity and subgroup analyses to explore its influence on pooled prevalence estimates.

Strategy of data synthesis Pooling of Prevalence Estimates:
Prevalence data will be transformed using the Freeman-Tukey double arcsine transformation prior to pooling to stabilise variance for proportions approaching 0 or 1. A random-effects model (DerSimonian-Laird method for primary analysis; Restricted Maximum-Likelihood [REML] as sensitivity) will be applied, given the anticipated substantial between-study heterogeneity attributable to differences in case definitions, populations, and settings. Pooled prevalence estimates and 95% confidence intervals will be back-transformed to the original proportion scale for presentation.

Heterogeneity Assessment:
• Cochran's Q test ($p < 0.10$ considered statistically significant for heterogeneity)
• I^2 statistic: 75% high heterogeneity
• Tau^2 (between-study variance) estimated by DL and REML
• 95% prediction intervals reported alongside CIs to characterise uncertainty in individual future study estimates

Meta-Regression:
Random-effects meta-regression (REML) will model continuous moderators of heterogeneity, including: year of publication, mean patient age, proportion HIV-positive, proportion MDR-TB, country TB incidence rate, and overall study quality score. The Knapp-Hartung modification will be applied to adjust for uncertainty in tau^2 in small samples.

Publication Bias:
Funnel plot asymmetry will be visually inspected (minimum 10 studies per analysis). Egger's weighted regression test ($p < 0.10$ as threshold) will formally test for small-study effects. If significant asymmetry is detected, trim-and-fill analysis will be applied. Sensitivity analyses excluding grey literature and preprints will be conducted.

Global Burden Estimation Framework:
Beyond pooled prevalence, an absolute burden estimation framework will be applied: Estimated PTBLD cases (year Y) = Σ [Country TB treatment success cohort (year Y-1)] × [Pooled PTBLD prevalence, region-specific], using WHO Global TB Report notification and treatment success data with regional prevalence estimates from this meta-analysis, with lower and upper bounds from 95% prediction intervals as sensitivity bounds.

Subgroup analysis The following subgroup analyses are pre-specified and will be conducted when a minimum of three studies per subgroup are available:
• WHO region: AFRO, SEARO, AMRO, WPRO, EMRO, EURO — to assess geographic variation in PTBLD burden.
• World Bank income group: Low-income (LIC), Lower-middle-income (LMIC), Upper-middle-income (UMIC), High-income (HIC) — to quantify inequity in PTBLD prevalence.
• HIV status: HIV-positive vs HIV-negative vs mixed/unreported — to evaluate the independent contribution of HIV co-infection to PTBLD risk.
• TB drug sensitivity: DS-TB vs MDR-TB vs XDR-TB vs mixed — to explore the dose-response relationship between treatment complexity and PTBLD severity.
• PTBLD case definition category: DEF-A (spirometric) vs DEF-B (radiological) vs DEF-C (symptomatic/functional) vs DEF-D (composite) vs DEF-E (other) — to quantify case definition-driven variation.
• Spirometric standard applied: GOLD fixed-ratio FEV_1/FVC 12 months post-treatment — to examine temporal trends in PTBLD evolution.

Sensitivity analysis The following sensitivity analyses are pre-specified to evaluate the robustness of pooled estimates and explore the influence of key methodological decisions:
• Post-bronchodilator spirometry only: restricting the pool to studies that measured FEV_1 and FVC after bronchodilator administration, to avoid overestimation of obstructive defects through reversible bronchospasm.
• Low risk-of-bias studies only: excluding studies with JBI score <7/9 or NOS <7/9 to assess whether pooled estimates are driven by methodologically weaker evidence.
• Exclusion of studies with missing confounder adjustment: restricting to studies that adjusted for at least age, sex, and smoking status in multivariate analyses (where applicable).
• Grey literature and preprints: analyses run both including and excluding preprints and grey literature reports to assess their influence on pooled estimates.
• Leave-one-out (one-study-removed) influence analysis: each study removed in turn to identify influential individual studies disproportionately driving pooled estimates.

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• Alternative statistical model: comparing DerSimonian-Laird random-effects results with REML-based estimates, and with fixed-effects results as a reference when heterogeneity is low (I^2 <25%).
• Burden estimation sensitivity: applying the lower and upper bounds of the 95% prediction interval of pooled regional prevalence estimates to the WHO TB notification cohort data to generate plausible PTBLD burden ranges.

Language restriction No strict language restriction will be imposed on the database searches. Studies published in English, French, Spanish, and Portuguese will be assessed for eligibility and included where all eligibility criteria.

Country(ies) involved Nigeria, United Kingdom, update upon author team finalisation.

Keywords post-tuberculosis lung disease; PTBLD; tuberculosis sequelae; pulmonary tuberculosis; systematic review; meta-analysis; spirometry; lung function; bronchiectasis; pulmonary fibrosis; global burden; prevalence.

Dissemination plans The findings of this systematic review and meta-analysis will be submitted for publication in a high-impact, peer-reviewed international respiratory or infectious disease journal.

Contributions of each author

Author 1 - Abimbola Akinyosoye - Conceived the study, wrote the first draft, revised and checked the final draft for important intellectual content.
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