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Frequency and Clinical Outcomes of Mycobacterium tuberculosis Heteroresistance in Individuals with Cavitary Pulmonary Tuberculosis: A Scoping Review Protocol

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ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 September 2026 and was last updated on 16 September 2026.

INTRODUCTION

Review question / Objective 1. What published evidence exists regarding the frequency and characteristics of Mycobacterium tuberculosis (MTB) heteroresistance among individuals with cavitary pulmonary
tuberculosis?
2. What published evidence exists regarding the association between MTB heteroresistance and clinical outcomes among individuals with cavitary pulmonary tuberculosis?

Background Mycobacterium tuberculosis (MTB) remains one of the leading infectious causes of morbidity and mortality worldwide. Despite advances in diagnostics and therapeutics, treatment failure and emergence of drug resistance continue to threaten MTB control. Drug-resistant MTB has been traditionally viewed as selection of resistant bacterial populations following antibiotic exposure. However, newer evidence suggests that clonal heteroresistance contributes to drug-resistant MTB. Clonal heteroresistance describes the co-existence of drug-sensitive and drug-resistant isolates in a single clinical sample and is considered an intermediate phase towards complete drug resistance. Factors that contribute to heteroresistance include mixed infections which can arise from simultaneous exposure, sequential reinfection and reinfection after partial treatment. Detection and treatment of mixed infections are difficult given that cultures may preferentially grow one strain and sputum may sample only one lesion leading to treatment of the dominantly represented isolate which leads to non-treatment of minority resistant clones and contributes to further antibiotic resistance after treatment. Technologies such as whole-genome sequencing (WGS) and deep sequencing have made detection of heterogeneous samples increasingly possible. Cavitary pulmonary TB creates a unique environment that likely predisposes to heteroresistance development. This is because cavities tend to have high bacterial burden, poor antibiotic penetration, hypoxic and necrotic

microenvironments in addition to spatially distinct bacterial populations.

Rationale Despite this strong rationale linking cavitary disease to heteroresistance, the prevalence of heteroresistance in patients with cavitary MTB has not been comprehensively reviewed. Furthermore, the clinical implications of heteroresistance in this population, including treatment and microbiologic outcomes remain unclear.

METHODS

Strategy of data synthesis Electronic databases included will be MEDLINE, Embase, and Cochrane CENTRAL. A preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews and JBI Evidence Synthesis was conducted and no current or underway systematic reviews or scoping reviews on the topic were identified. Additional sources will include citation searching of included studies.

Search terms:
Tuberculosis
Mycobaterium tuberculosis
MTB
MTBC
Pulmonary tuberculosis
Mixed infection
Heterogeneous infection
Heteroresistance
Hetero-resistance
Clonal heteroresistance
Heterogeneity
Microevolution
Cavitary disease
Cavity
Cavitary
Cavitary disease
Cavitation
Pulmonary cavity.

Eligibility criteria Population - Human participants with microbiologically confirmed pulmonary MTB infection and radiographic evidence of cavitary pulmonary disease.
Age limits of participants - Pediatric and adult populations are eligible
Interventions - No intervention required
Exposure of Interest - Studies evaluating MTB heteroresistance or mixed infections within the same patient detected using phenotypic drug susceptibility testing, line probe assays, whole-genome sequencing, targeted sequencing, deep sequencing, or other validated molecular methods.
Comparators - No comparator required. Studies comparing cavitary versus non-cavitary disease, will be included when available
Outcomes/Endpoints - Studies reporting mixed infection in cavitary disease prevalence. Studies reporting heteroresistance in cavitary disease prevalence. Clinical outcomes including TB-related mortality, all-cause mortality, symptom persistence, symptom resolution, radiographic cavitation improvement, treatment failure, cure, antibiotic resistance
Study Designs - Original peer-reviewed research, including observational studies (cross-sectional, cohort, case-control), prospective and retrospective studies, and clinical trials
Publication Status - Published peer-reviewed studies and pre-prints available in full text.
Settings - Any clinical setting, including hospitals, outpatient clinics, tuberculosis treatment centers, and public health programs.
Countries - No geographic restrictions.
Dates - No restriction on publication date
Languages - English-language publications.

Source of evidence screening and selection A literature search will be conducted with by all three authors. The search strategy will combine vocabulary related to 4 concepts. Two reviewers will independently screen titles and abstracts using a developed title/abstract screening guide. Potentially eligible studies will undergo full-text review. Disagreements will be resolved through discussion or consultation with a third reviewer. Study selection will be documented using a PRISMA flow diagram.

Data management Search results will be exported into Covidence where results will be deduplicated. Covidence will be used for screening, data extraction, reporting and study management.

Reporting results / Analysis of the evidence Analysis of the data will be performed in R studio.

Presentation of the results Upon completion of the analysis, results will be published in a peer-reviewed journal.

Language restriction English.

Country(ies) involved United States of America.
Keywords Mycobacterium tuberculosis; pulmonary tuberculosis; cavitary disease; heteroresistance; mixed-infection.

Contributions of each author

Author 1 - Gitanjali Bhushan - Scoping review protocol development, title/abstract guide development, active screener, data extraction, manuscript writer and reviewer, project management.
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Author 2 - Andy Hickner - Developed the MEDLINE search strategy, contributed to refinement of the scoping review protocol, managed the Covidence platform and citation organization, assisted with retrieval and management of references, and contributed to drafting and revision of the manuscript.
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