Evaluating the Effectiveness and Safety of a Shortened Rifapentine-Moxifloxacin Regimen in Treating Drug-Sensitive Pulmonary Tuberculosis: A Systematic Review

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Abstract

Background:
Prolonged treatment duration remains a key challenge in managing drug-sensitive pulmonary tuberculosis (DS-TB), contributing to poor adherence and treatment failure. Recent evidence suggests that regimens incorporating rifapentine and moxifloxacin (RPT+MOX) may allow for effective 4-month treatment courses.
Methods:
We conducted a systematic review and meta-analysis following PRISMA 2020 guidelines to evaluate the effectiveness and safety of shortened RPT+MOX regimens. PubMed, EMBASE, and Scopus were searched up to May 2025. Eligible studies included randomized trials or observational cohorts comparing shortened RPT+MOX regimens with standard 6-month therapies in patients with DS-TB. Outcomes included culture conversion at 8 weeks, relapse or treatment failure, and serious adverse events. Risk of bias was assessed using the ROBINS-I tool.
Result:
Five studies (three RCTs, two observational) met inclusion criteria. Pooled analysis showed no significant difference in risk for relapse or treatment failure (RR 0.79, 95% CI: 0.37–1.67), culture conversion (RR 1.16, 95% CI: 0.80–1.69), or serious adverse events (RR 0.92, 95% CI: 0.65–1.29) between RPT+MOX and standard regimens. Risk of bias ranged from minimal to moderate. The GRADE assessment supported high certainty of evidence.
Conclusions:
Shortened RPT+MOX regimens demonstrate comparable effectiveness and safety to standard 6-month treatment for DS-TB, supporting their use in appropriate settings. Further studies are warranted to assess long-term outcomes, real-world adherence, and feasibility across diverse populations.

Introduction

Tuberculosis (TB) remains a major global health threat, ranking among the top 10 causes of death worldwide and the leading cause from a single infectious agent.[1] According to the World Health Organization (WHO), an estimated 10.6 million people developed TB in 2022, and approximately 1.3 million died from the disease.[1] The burden is disproportionately high in low- and middle-income countries, where delayed diagnosis, drug resistance, and treatment nonadherence continue to undermine control efforts.[2,3] Despite advances in diagnostics and therapeutics, the global decline in TB incidence remains

insufficient to meet the End TB Strategy targets set for 2030.[4]

The standard treatment for drug-sensitive pulmonary TB involves a 6-month regimen comprising isoniazid, rifampin, pyrazinamide, and ethambutol during an intensive and continuation phase.[1] Although this regimen has a high cure rate under controlled conditions, the prolonged duration often leads to suboptimal adherence, loss to follow-up, and increased risk of treatment failure or relapse.[1] Furthermore, the extended treatment timeline places significant strain on healthcare systems, particularly in high-burden settings. These limitations have spurred global efforts to develop shorter, more tolerable, and equally effective treatment regimens.

Rifapentine, a long-acting rifamycin with a longer half-life and greater potency than rifampicin, has been explored as a key agent in shortened TB regimens. Combined with moxifloxacin, a fluoroquinolone with proven bactericidal activity against *Mycobacterium tuberculosis*, these novel regimens aim to reduce treatment duration to 4 months or less.[5] Large-scale trials, including Study 31/A5349, have shown that a 4-month regimen substituting rifapentine for rifampicin and moxifloxacin for ethambutol can achieve noninferior cure rates compared to the standard 6-month therapy.[6] However, results from real-world cohorts and subpopulations such as people living with HIV or diabetes have shown variable tolerability, adherence, and safety outcomes, underscoring the need for a comprehensive synthesis of available evidence. This systematic review and meta-analysis aims to evaluate the effectiveness and safety of shortened rifapentine–moxifloxacin regimens in the treatment of drug-sensitive pulmonary tuberculosis.

Material And Methods

This systematic review and meta-analysis adhered to the PRISMA 2020 guidelines and involved a comprehensive literature search conducted on 30 May 2025 across PubMed, EMBASE, and Scopus.[7] The search strategy incorporated both MeSH terms and free-text keywords related to “tuberculosis,” “rifapentine,” “moxifloxacin,” and “shortened regimen,” without restrictions on publication year or language. Additional studies were sourced through manual screening of reference lists from relevant articles and reviews. Eligibility criteria, defined by the PICO framework, included studies involving individuals of any age with drug-sensitive pulmonary tuberculosis, evaluating shortened regimens containing rifapentine and moxifloxacin versus standard 6-month rifapentine-based or non-rifapentine regimens. Primary outcomes were culture conversion and unfavourable treatment outcomes, such as treatment failure, relapse, death, or loss to follow-up. Both randomized controlled trials and observational studies assessing clinical effectiveness or safety were included, while studies on extrapulmonary TB, drug-resistant TB, or latent TB infection were excluded.

Study selection and data extraction were performed independently by two reviewers using predefined criteria and a standardized form, with discrepancies resolved through discussion. Risk of bias in included studies was assessed using the ROBINS-I tool across seven domains, also evaluated independently by two reviewers. Statistical analyses were conducted in RStudio using the ‘meta’ package, employing a random-effects model to account for clinical and methodological heterogeneity. Results were reported as pooled risk ratios (RRs) with 95% confidence intervals, and significance was set at $p < 0.05$. Funnel plots and Begg’s and Egger’s tests were used to evaluate potential publication bias.

Result

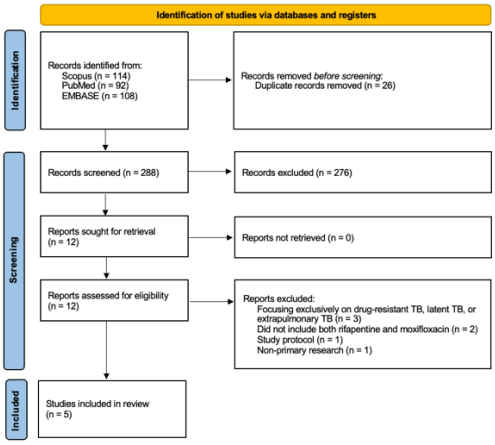

Figure 1. Study Identification and Selection Flowchart (adapted from PRISMA guidelines).

A systematic literature review was conducted across Scopus, PubMed, and EMBASE databases, yielding a total of 314 records. After removing 26 duplicates, 288 unique records were screened based on title and abstract. Of these, 276 were excluded for not meeting inclusion criteria, and 12 full-text reports were retrieved and assessed for eligibility. Ultimately, five studies were included in the review.[6,8–11] Exclusion at the full-text stage was primarily due to a focus on drug-resistant, latent, or extrapulmonary TB (n = 3), lack of inclusion of both rifapentine and moxifloxacin (n = 2), being a study protocol (n = 1), or not constituting primary research (n = 1). This screening and selection process is illustrated in Figure 1.

Recent clinical and observational studies have assessed the viability of shortening TB treatment regimens by combining RPT with Moxi. Notably, Phase 3 randomized controlled trials (RCTs) such as Jindani et al. (2014) and Dorman et al. (2021) demonstrated that a 4-month RPT+Moxi regimen is noninferior to the traditional 6-month standard therapy in adults and adolescents with drug-sensitive TB, though Jindani et al. reported increased unfavourable outcomes with daily dosing.[8,9] Conde et al. (2016) found comparable bactericidal activity between regimens and faster culture conversion with RPT+Moxi.[9] Observational findings from Kurbatova et al. (2025) in diabetic TB patients highlighted the lowest unfavourable outcome rates in those receiving RPT+Moxi (13.8%) versus RPT alone.[11] However, Louie et al. (2024) noted poor regimen adherence, with only 40.9% completing the 4-month course, raising concerns about feasibility in real-world settings.[10]

The RPT+Moxi regimen is prescribed dur to their complementary pharmacokinetic and pharmacodynamic profiles. Rifapentine, a long-acting rifamycin, achieves high intracellular concentrations and prolonged half-life, facilitating intermittent dosing and better macrophage penetration. Moxifloxacin, a fluoroquinolone, exhibits potent bactericidal activity against *Mycobacterium tuberculosis* through DNA gyrase inhibition, with excellent tissue distribution and oral bioavailability. Both agents are extensively metabolized—RPT by hepatic enzymes and Moxi via glucuronidation and sulfation—minimizing pharmacokinetic overlap and enhancing treatment synergy. The enhanced sterilizing activity supports the rationale for regimen shortening; however, variability in adherence, especially under non-trial conditions, underscores the need for further evaluation of tolerability, real-world completion rates, and safety in diverse populations.

The meta-analysis included pooled estimates from studies evaluating the RPT+MOX regimen versus control for three outcomes. Figure 2 presents the pooled RR for treatment relapse or treatment failure, which was 0.79 (95% CI: 0.37 to 1.67). Figure 3 shows the pooled RR for culture conversion at 8 weeks, which was 1.16 (95% CI: 0.80 to 1.69). Figure 4 displays the pooled RR for

serious adverse events (grade ≥3), which was 0.92 (95% CI: 0.65 to 1.29). The included studies, assessed using the ROBINS-I tool, demonstrated a minimal to moderate risk of bias across most domains (figure 5).

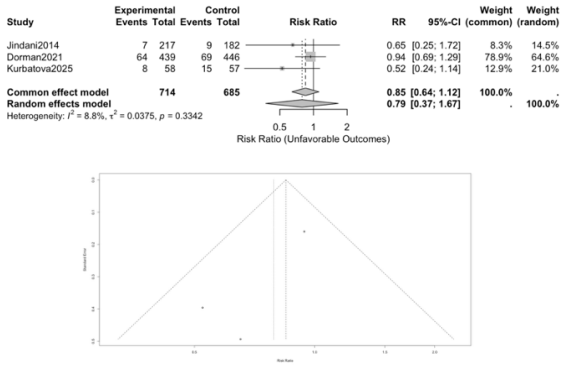

Figure 2. Meta-analysis for treatment relapse or treatment failure.

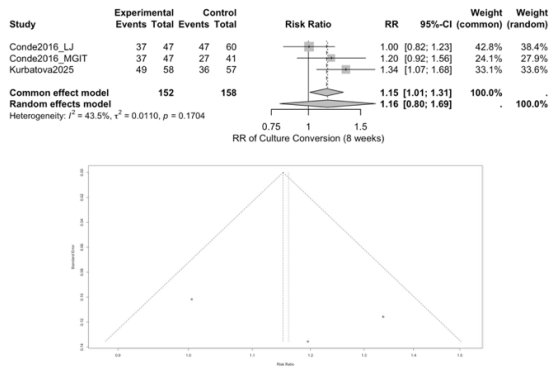

Figure 3. Pooled effect estimate for culture conversion rate in 8 weeks.

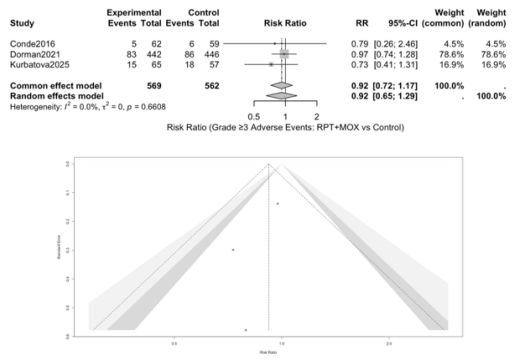

Figure 4. Pooled effect estimate for serious adverse events.

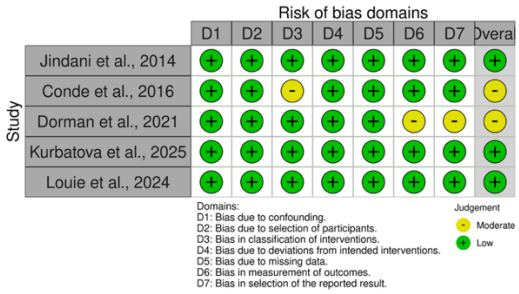

Figure 5. Risk of bias assessment using the ROBINS-I.

Table 1. Demographic characteristics of included studies.

Study (Author, Year)	Country/Region	Design	Population (Age, N)	Dosing regiments and outcomes
Jindani et al., 2014	South Africa, Zimbabwe, Botswana, Zambia	Phase 3 RCT (open-label)	Adults ≥18 yrs, N=827 (28% HIV+)	• 6-mo weekly RPT+Moxi = noninferior to standard • 4-mo daily RPT+Moxi = higher unfavourable outcomes (26.9% vs 14.4%)
Conde et al., 2016	Brazil	Phase 2 RCT	Adults ≥18 yrs, N=121	• Similar 8-wk bactericidal activity to control • Faster culture conversion with RPT+Moxi (p=0.03)
Dorman et al., 2021	13 countries (incl. US, Vietnam, Zambia)	Phase 3 RCT (open-label)	Adolescents/Adults, N=2,516 randomized	• 4-mo RPT+Moxi = noninferior to 6-mo standard (15.5% vs 14.6%)
Kurbatova et al., 2025	12-country multicentre	Observational (subgroup)	TB patients ≥12 yrs with diabetes, N=166	• Lowest unfavourable outcomes in RPT+Moxi (13.8%) • RPT-only: 29.4% unfavourable
Louie et al., 2024	USA (San Francisco)	Retrospective cohort	Persons ≥14 yrs, N=22	• Only 40.9% completed 4-mo RPT+Moxi regimen

Discussion

This systematic review and meta-analysis evaluated the effectiveness and safety of a shortened rifapentine-moxifloxacin regimen for treating drug-sensitive pulmonary tuberculosis (DS-TB). The pooled estimates showed that the shortened regimen had comparable treatment success, culture conversion rates, and serious adverse event profiles when compared to the standard 6-month therapy. These findings align with recent pivotal trials, such as the Study 31/A5349, which also found non-inferiority of the 4-month RPT+MOX regimen.[6] However, some variation in relapse and conversion rates across studies indicates that the regimen's performance may be context-dependent, particularly in high-burden settings or among patients with cavitary disease or delayed baseline sputum clearance.

Compared to earlier attempts at treatment shortening, such as

fluoroquinolone-based 4-month regimens using gatifloxacin or levofloxacin, the rifapentine-moxifloxacin combination appears to offer improved outcomes.[12] The superior pharmacokinetic properties of rifapentine, including its prolonged half-life and sustained plasma levels, along with the high tissue penetration and early bactericidal activity of moxifloxacin, likely contribute to its effectiveness.[13,14] Unlike previous regimens that were limited by subtherapeutic exposures or early relapse, this combination benefits from more favourable ADME characteristics. These properties enhance drug bioavailability and target site distribution, which are critical for sterilizing persistent bacilli and preventing relapse, particularly in the shortened duration context.[14]

In addition to clinical outcomes, the practical implementation of shortened RPT+MOX regimens warrants careful consideration. Operational challenges such as drug availability, cost, and infrastructure to monitor adverse events may limit widespread adoption, particularly in resource-limited settings.[15–17] Rifapentine remains significantly more expensive and less accessible than rifampicin in many high-burden countries, and programmatic adaptation may require substantial policy and logistical adjustments.[18–20] Furthermore, the higher pill burden and potential for drug–drug interactions, especially in populations co-infected with HIV or taking antidiabetic medications, must be addressed through tailored dosing strategies and patient education. While pharmacokinetic data support the regimen's sterilizing potential, real-world implementation will depend on careful integration into national TB control programs, ensuring not only efficacy but also feasibility, affordability, and equity in access.[21–23]

Nonetheless, the analysis highlights important limitations. Although risk of bias was generally low to moderate based on ROBINS-I, heterogeneity was present in the culture conversion outcome (I^2 = 43.5%), potentially reflecting variability in study design, patient populations, or microbiological endpoints. Some included studies used different dosing intervals (e.g., intermittent vs. daily rifapentine), which may influence treatment dynamics. Additionally, the meta-analysis relied on study-level data without access to individual patient data, limiting subgroup analyses (e.g., by HIV status, BMI, or cavitary disease).[24] Potential publication bias and regional underrepresentation (e.g., few studies from sub-Saharan Africa) further constrain generalizability.

Conclusion

This meta-analysis supports the use of a shortened rifapentine-moxifloxacin regimen as an effective and safe alternative to standard therapy for DS-TB. Compared to previous shortened regimens, this combination appears more robust, potentially due to enhanced pharmacological profiles. These findings support ongoing global efforts to simplify TB treatment while maintaining efficacy, though future research should aim to validate these results in broader populations and investigate long-term relapse rates, resistance development, and cost-effectiveness.

Acknowledgment
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