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TRANSFORMING MDR-TB TREATMENT: EVIDENCE FOR SHORTER, SAFER, AND COST-SAVING REGIMENS WITH BPAL

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ABSTRACT

Background: Tuberculosis (TB) remains a major global public health challenge, with multidrug-resistant TB (MDR-TB) contributing substantially to poor outcomes. Conventional regimens span 18–24 months, leading to limited adherence and treatment success. Shorter treatment regimens (STRs), such as the BPaL regimen (bedaquiline, pretomanid, and linezolid), have emerged as promising alternatives. This systematic review assessed the efficacy, safety, and economic impact of 6-month STRs for drug-resistant TB. Methods: A systematic literature review was conducted in accordance with PRISMA 2020 guidelines. PubMed and ScienceDirect were searched for studies published between 2021 and 2025. Eligible studies included clinical trials, cohort studies, and economic evaluations of regimens lasting ≤6 months. Study quality was appraised using the Joanna Briggs Institute (JBI) Critical Appraisal Tools. Results: Five studies met the inclusion criteria. BPaL regimens consistently achieved high treatment success rates (>80%), with faster sputum conversion and lower mortality compared with conventional injectable-based regimens. For example, one study in Thailand reported 82.1% favorable outcomes with BPaL versus 61–65% with standard long regimens. The all-oral BPaL regimen was generally well tolerated, with substantially fewer serious adverse events such as ototoxicity and nephrotoxicity. Economic evaluations demonstrated significant cost savings for both health systems and patients, alongside gains in disability-adjusted life years (DALYs) averted. Conclusion: Six-month, all-oral BPaL regimens are effective, safer, and more cost-efficient than conventional MDR-TB therapies. Despite challenges related to drug availability and the infrastructure needed to monitor adverse events, the evidence strongly supports their accelerated global implementation to improve MDR-TB outcomes.

INTRODUCTION

The major burden of global public health is related to tuberculosis (TB) caused by the bacillus Mycobacterium tuberculosis. The pattern of transmission of this disease is through coughing in expelling bacteria into the air.[1] According to the 2024 Global Tuberculosis Report from the World Health Organization (WHO), there were 8.2 million cases of TB and 1.09 million deaths in 2023. This data shows that TB is again the leading cause of global death from a single infectious agent [2].

Drug-resistant tuberculosis (DR-TB) remains a global health threat, with an estimated 500,000 new cases annually.[3,4] Drug-resistant tuberculosis (DR-TB) remains a significant global health threat, with around 500,000 new cases annually. Beyond its clinical challenges, DR-TB imposes a considerable socioeconomic burden, as treatment costs frequently lead to catastrophic health expenditures and severe financial hardship for patients.[5] Although ambulatory care models have achieved treatment success rates of approximately 70%, loss to follow-up and treatment failure remain common barriers.[6] Furthermore, socioeconomic hardship and stigma substantially reduce treatment retention, with many patients discontinuing therapy due to transport costs, income

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loss, and discrimination.[7] A meta-analysis revealed a global prevalence of multi-drug resistant TB at 11.6%.[8] Despite advances in diagnostics and treatment, only about one-third of cases are detected and treated each year.[4] Novel regimens including bedaquiline , pretomanid , linezolid, and moxifloxacin have shown promise in mitigating the DR-TB threat.[9] However, emerging resistance to these new drugs and the COVID-19 pandemic pose ongoing challenges.[3,9] WHO has classified DR-TB into five categories, with XDR-TB being the most resistant form.[4] Continued investment in DR-TB services and sustained development of new drugs targeting resistant strains are crucial for future efforts against DR-TB.[3,9]

Recent evidence has demonstrated that shorter treatment regimens (STRs) for multidrug-resistant tuberculosis (MDR-TB) are effective and address the limitations of conventional 18–24 month therapies. STRs of 9-12 months have shown superior outcomes compared to longer regimens, including higher treatment success rates, lower mortality, and faster sputum culture conversion.[10,11] In Kyrgyzstan, STR achieved 83% treatment success compared to 50-59% for longer regimens.[11] Similarly, in the Philippines and Nepal, STRs demonstrated high treatment success rates of 77.8% and 79.6%, respectively.[12,13] STRs also resulted in reduced loss to follow-up, although this remains a challenge.[12]

Recent studies have shown promising results for shorter treatment regimens in tuberculosis (TB) management. A 9-12 month shorter treatment regimen (STR) for multidrug-resistant TB demonstrated high success rates and low recurrence in Nepal, with 79.6% treatment success and only 2.4% recurrence at 12 months post-treatment.[13] Similarly, in Pakistan, STR exhibited superior antimicrobial activity against MDR-TB compared to longer regimens, resulting in earlier sputum culture conversion and higher cure rates.[10] However, not all shortened regimens are equally effective. While some 4-month regimens may be as effective as the standard 6-month treatment, others have shown inferior results.[14] A clinical trial in China found that a 4-month regimen containing clofazimine had inferior efficacy and higher hepatitis incidence compared to the standard regimen, although it showed promise in the per-protocol population.[15]

Although early data on short-duration regimens show promising results, their efficacy, safety, and long-term success factors still need to be studied more systematically. Therefore, this literature review aims to evaluate the efficacy of MDR-TB treatment regimens with a duration of ≤6 months based on current evidence, while identifying challenges and opportunities for their implementation in various clinical settings.

METHODS

Search Strategy and Selection Criteria

This systematic literature review (SLR) was conducted following PRISMA 2020 guidelines. Literature searches were performed in PubMed, ScienceDirect, and other databases for articles published between 2021 and 2025. The keywords used included: "shorter regimen", "MDR-TB", "XDR-TB", "drug-resistant tuberculosis", " BPaL ", " BPaLM ", "short-course treatment", and "6-month tuberculosis treatment".

Inclusion criteria

a. Clinical studies (RCTs, cohort studies, implementation studies) on drug-resistant TB (MDR-TB, XDR-TB, RR-TB).
b. Regimen duration ≤6 months.
c. Outcomes reporting efficacy, safety, or implementation feasibility.

Exclusion criteria

a. Studies conducted on drug-susceptible TB patients only.
b. Regimens with a duration longer than 6 months.
c. Non-English publications.

Study Selection

Following the removal of duplicates, two independent reviewers screened the titles and abstracts. Full-text articles that met the eligibility criteria were then assessed based on predefined inclusion and exclusion standards. Any disagreements were resolved through discussion and consensus, or with the involvement of a third reviewer when necessary. The study selection process is summarized in Figure 1 (PRISMA Flow Diagram).

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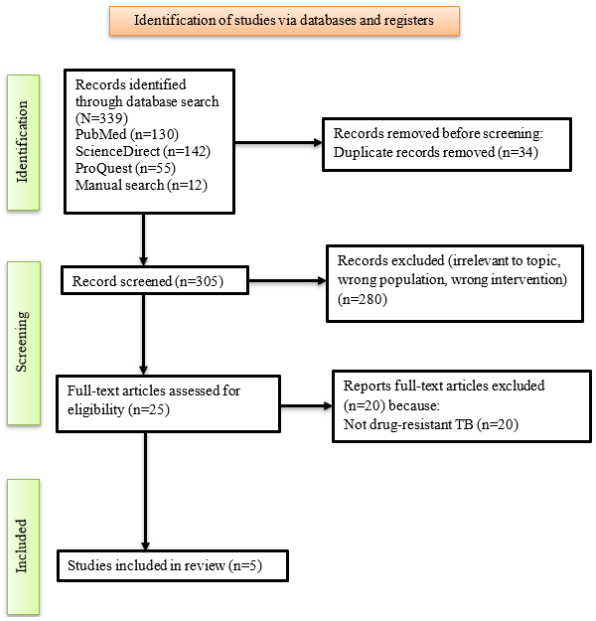
Figure 1. PRISMA 2020 Flow Diagram for Systematic Literature Review



Data Extraction and Quality Assessment

Data were extracted using a standardized form capturing key study details, including authorship, year, location, design, population, treatment regimen, duration, and outcomes. Study quality was assessed using the appropriate JBI Critical Appraisal Tools.

Data Analysis and Synthesis

A narrative synthesis was conducted due to heterogeneity in study designs, outcomes, and settings. Quantitative pooling (meta-analysis) was not performed.

RESULTS

This review consisted of a pool contributing of 5 studies that were published from 2021 to 2025. All the included studies uniformly assessed treatment-shortening (< = 6 months) regimens for drug-resistant tuberculosis (DR-TB), specifically studied in the context of MDR-TB, RR-TB or pre-XDR-TB cases.

Two analyses (Connors and Auer) noted the morbidity benefits and cost savings of BPaL / BPaLM regimens. The SLASH-TB model and TB-PRACTECAL economic evaluations both found that 6-month regimens were cost savings to health systems and patients while 6-month regimens had high rates of success and also for DALYs averted.

In South Africa, a single large cohort study indicated greater >80% success rates and lower mortality in patients initiated on all oral bedaquiline containing regimens with an injectable containing regimen in the historical treatment cohort; the bedaquiline-based arm had a success rate 14% higher than the mortality. This is consistent with shift to lower major toxic oral treatment form more toxic injectable drugs. In Canada, a successful effort to use the BPaL regimen when personalized for pre-XDR TB has been reported, while access and implementation challenges for new TB medicines, including availability of pretomanid, have been documented.

A further policy type article reiterated the need for the accelerated implementation of shorter regimens worldwide, especially in the face of a potential increase in cases of MDR-TB as a result of healthcare disruption due to COVID-19.

Collectively, in a variety of settings and study types, the reviewed body of evidence shows that 6-month regimens with new anti-TB drugs (including bedaquiline , pretomanid , and linezolid), are effective, cost saving and better tolerated than longer or injectable-containing regimens.

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Table 1. Summary of Included Studies (Sorted by Year of Publication)

No	Author (Year)	Country	Study Design	Population	Regimen	Duration (Months)	Outcomes
1	Tiberi *et al*. 2021.[4]	Global	Review/Policy Perspective	MDR-TB	Bedaquiline, delamanid, pretomanid-based regimens (WHO 6-month oral regimens)	6	Highlighted emerging evidence of shorter, more effective regimens; described urgent adoption.
2	Ndjeka *et al*. 2022.[16]	South Africa	Retrospective cohort study	RR-TB patients	All-oral bedaquiline regimen vs. injectable-containing	9-12	Treatment success was 14% higher in bedaquiline group vs injectable group.
3	Connors *et al*. 2023.[17]	Canada	Case report + implementation analysis	Pre-XDR TB	BPaL	6	Successfully treated pre-XDR TB case with challenges in drug access highlighted.
4	Auer *et al*. 2024.[18]	Pakistan, Philippines, South Africa, Ukraine	Economic evaluation	DR-TB patients	BPaL/BPaLM vs. SSOR/SLOR	6	Cost-saving regimens, higher cure rates, DALYs averted in all countries.
5	Sweeney *et al*. 2025.[19]	Belarus, Uzbekistan, South Africa	Economic evaluation (within RCT)	RR-TB patients	BPaL ± moxifloxacin or clofazimine vs. SOC	6	BPaL -based regimens are cost-saving and highly effective compared to standard care.

Table 2. Safety and Tolerability of BPaL-Based Regimens Across Included Studies

Study (Year)	Setting/ Population	Regimen (s)	Key Safety Findings	Mortality	Notable Adserve Events
Tiberi *et al*. 2021.[4]	Global review	Bedaquiline, delamanid, pretomanid-based regimens (WHO 6-month oral regimens)	Shorter regimens more tolerable, fewer adverse effects, improved adherence.	Lower mortality compared to historical regimens.	Emphasized need for toxicity monitoring and infrastructure.
Ndjeka *et al*. 2022.[16]	South Africa, 1,387 RR-TB patients	All-oral bedaquiline regimen vs. injectable-containing	Bedaquiline group had higher treatment success (70% vs 57%); reduced loss to follow-up (6% vs 12%).	17% vs 22.4% mortality, favoring BPaL group.	Lower ototoxicity and nephrotoxicity compared to injectable regimen.
Connors *et al*. 2023.[17]	Canada, pre-XDR-TB single case	BPaL	Successfully completed regimen with no major safety concerns.	None reported.	Mild rash resolved after withdrawal of clofazimine/cycloserine; linezolid dose adjusted for tolerability.
Auer *et al*. 2024.[18]	Multi-country modeling (Pakistan, Philippines, South Africa, Ukraine)	BPaL/BPaLM vs. SSOR/SLOR	Modeled outcomes consistent with clinical trials: improved treatment success and safety.	Lives saved: 411–1,371 annually depending on country.	Reduced hospitalization burden; fewer drug-related adverse events assumed.
Sweeney *et al*. 2025.[19]	TB-PRACTECAL trial sites (Belarus, Uzbekistan, South Africa)	BPaL ± moxifloxacin or clofazimine vs. SOC	All BPaL regimens showed fewer unfavorable outcomes at 72 weeks.	Mortality markedly reduced compared to SOC.	Adverse events were less frequent; hospital stay reduced (1–12 weeks vs. prolonged).

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Table 3. Economic and Cost-Effectiveness Outcomes of BPaL-Based Regimens

Study (Year)	Setting	Comparison	Key Economic Outcomes
Tiberi *et al*. 2021.[4]	Global review	Standard regimens vs. WHO 6-month	Highlighted the need for cost-efficient rollout of BPaL regimens; argued that shorter, safer regimens lower economic burden on health systems.
Ndjeka *et al*. 2022.[16]	South Africa	Bedaquiline regimen vs. injectable regimen	Although not a formal cost study, improved survival and reduced hospitalizations imply indirect cost savings; reduction in ototoxicity/nephrotoxicity lowers long-term care costs.
Connors *et al*. 2023.[17]	Canada	First BPaL case	Not an economic evaluation, but highlighted implementation costs (drug procurement delays, monitoring infrastructure). Suggested overall long-term savings if widely adopted.
Auer *et al*. 2024.[18]	Pakistan, Philippines, South Africa, Ukraine	BPaL/BPaLM vs. SSOR/SLOR	Cost savings per patient: USD 478–2,636; lives saved annually: 411–1,371; DALYs averted: 20,179–33,384. Significant budget impact reduction projected over 5–10 years.
Sweeney *et al*. 2025.[20]	TB-PRACTECAL sites (Belarus, Uzbekistan, South Africa)	BPaL-based vs. SOC	Provider savings: mean USD 14,868 per patient; patient-incurred cost savings: USD 172. BPaL averted 1.28 DALYs/person; consistently cost-saving in sensitivity analyses.

DISCUSSION

Effectiveness

All studies show that the short regimen is 6 months based on BPaL or BPaLM give level more success tall compared to standard regimen previously , well in MDR-TB, pre-XDR TB, and RR-TB.

Recent studies have demonstrated that a 6-month BPaL regimen, with or without moxifloxacin (BPaLM), is highly effective in treating drug-resistant tuberculosis (DR-TB). This treatment has demonstrated higher success rates compared to standard regimens, particularly for multidrug-resistant tuberculosis (MDR-TB), pre-extensively drug-resistant tuberculosis (pre-XDR-TB), and rifampicin-resistant tuberculosis (RR-TB).[21,22] BPaL regimens enhance treatment outcomes, streamline care, and may unify the management of drug-sensitive and drug-resistant TB. They are also cost-effective, providing substantial economic benefits for health systems.[20,22] However, careful monitoring of side effects, especially those associated with linezolid, is necessary during treatment.[21] Linezolid is associated with clinically significant, dose- and duration-dependent toxicities that may limit its long-term use in clinical practice. The most frequent adverse events include hematologic toxicities, particularly anemia (up to 38%) and thrombocytopenia (11–42%). In addition, peripheral neuropathy (up to 47%) and optic neuropathy (6–13%) are commonly observed with prolonged exposure. Although rare, severe complications such as lactic acidosis, pancreatitis, and rhabdomyolysis have also been documented, underscoring the need for careful monitoring during therapy.[23]

Safety and Tolerability

Bedaquiline, pretomanid, and linezolid in combination have been shown to be safer and more acceptable to patients than injection-based regimens. A recent study showed that a new regimen containing bedaquiline, pretomanid, and linezolid (BPaL) is safer and more effective for the treatment of drug-resistant tuberculosis, offering a favorable alternative to conventional regimens. The BPaL combination showed better outcomes and faster culture conversion than the bedaquiline-linezolid-based regimen.[24] The BPaL regimen with linezolid 600 mg every day relatively tolerated with well , for now higher dose high (1200 mg) increase risk effect side.[25] Ongoing research in progress evaluate optimal dose and duration of linezolid in BPaL regimen For maximize effectiveness at a time minimize toxicity.[26] Full oral BPaL regimen with duration more short This show hope in increase compliance treatment and results For patient resistant tuberculosis to drug compared to with a regimen based on longer injection.

Recent studies have demonstrated that the BPaL regimen (bedaquiline, pretomanid, and linezolid) achieves higher treatment success rates compared to

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conventional MDR-TB regimens. In Thailand (2023), 82.1% of patients treated with BPaL achieved favorable outcomes, including rapid sputum conversion within 8 weeks, although 22.2% experienced peripheral neuropathy and 7.1% developed optic neuritis, whereas conventional injection-based regimens in similar populations typically report success rates of 50–60% with higher rates of serious adverse events.[27] In Nigeria (2025), approximately 90–95% of patients receiving BPaL or BPaLM regimens successfully completed treatment, with serious adverse events reported in roughly 10% of patients, including 3.5% who died during therapy, whereas traditional regimens often show lower cure rates, higher mortality, and adverse events in up to 20% of cases.[28] Studies from Pakistan (2024) further confirmed high treatment success with minimal side effects, highlighting the regimen's potential to improve outcomes, reduce treatment duration, and enhance adherence.[29] Collectively, these findings indicate that BPaL regimens not only shorten therapy but also provide superior efficacy relative to longer, injection-based conventional regimens.

Efficiency Cost

Economic studies have shown that implementing shorter TB treatment regimens generates significant cost savings for both health systems and patients. India's BEAT-TB regimen for pre-XDR-TB discovered more economical costs and more effective compared to with regimen standard 18 months, resulting in the years customized life with higher quality (QALY) high and higher costs low.[30] Likewise, introduction regimen BPaL/BPaLM for resistant TB to drug show savings substantial costs and results better health well in many countries.[18] Health-economic evaluations have demonstrated that, for drug-sensitive TB, a 4-month moxifloxacin-based regimen is more cost-effective than the standard 6-month regimen in India.[31] Systematic economic reviews confirm that shorter regimens and agents such as bedaquiline are cost-effective, particularly in low and middle income countries.[32] These findings consistently support the economic benefits of implementing shorter TB treatments for both health systems and patients.

Challenge Implementation

The limited availability of novel anti-TB agents, the emergence of linezolid resistance, and the need for adequate infrastructure to monitor adverse effects remain major challenges in the management of drug-resistant TB. The implementation of newer regimens, particularly the BPaL regimen (bedaquiline, pretomanid, and linezolid), has demonstrated high effectiveness but is constrained by barriers such as timely access to drug susceptibility testing, wider availability of new medicines, and the requirement for specialized expertise in managing complex cases.[17] Although BPaL has transformed treatment for rifampicin-intolerant and drug-resistant TB by reducing treatment duration and improving clinical outcomes, careful monitoring and individualized linezolid dosing remain essential to ensure both safety and therapeutic success.[33] The continued development of new antibiotics is urgent in light of rising antimicrobial resistance and the growing threat of opportunistic pathogens in vulnerable populations. Small molecule antibiotics play a vital role in low- and middle-income countries, where access to advanced medical infrastructure is often limited. However, ongoing antibiotic discovery faces scientific and market-related challenges, requiring continued investment and innovative approaches.[34]

CONCLUSION

Current evidence robustly supports the efficacy, safety, and cost-effectiveness of shorter all-oral regimens—particularly the 6-month BPaL regimen—for the treatment of drug-resistant tuberculosis. These regimens consistently demonstrate higher treatment success rates, lower mortality, and significant cost savings for both health systems and patients. However, implementation challenges persist, including limited access to novel drugs, infrastructure gaps for monitoring adverse events, and rising antimicrobial resistance, particularly to linezolid. Recent studies indicate that shorter regimens such as BPaL reduce treatment duration and improve patient outcomes. However, challenges including linezolid-related adverse events, limited drug availability, and the need for infrastructure and clinical expertise highlight the importance of careful implementation to ensure safe and equitable adoption worldwide.

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