International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Website: https://ijmpr.in/

Review Article

The New BPaLM and BPaL Regimens for Drug-Resistant Tuberculosis in India (2025–2026): A Systematic Review of Efficacy, Safety, and Programmatic Implementation

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Received: 15-02-2026
Accepted: 26-03-2026
Published: 25-04-2026

ABSTRACT

Background: Drug-resistant tuberculosis (DR-TB) remains a major public health challenge in India, with suboptimal outcomes associated with conventional long-duration regimens. The introduction of shorter, all-oral regimens—BPaL (bedaquiline, pretomanid, linezolid) and BPaLM (addition of moxifloxacin)—marks a paradigm shift in DR-TB management.
Methods: A systematic review and meta-analysis were conducted following PRISMA 2020 guidelines, including studies from January 2020 to March 2026. Databases searched included PubMed, Scopus, and Cochrane CENTRAL. Eligible studies involved Indian patients with MDR/RR-TB or pre-XDR-TB treated with BPaL/BPaLM regimens. Primary outcomes were treatment success and culture conversion; secondary outcomes included adverse drug reactions.
Results: Forty-two studies encompassing 28,436 patients were included, with 31 studies in meta-analysis. The pooled treatment success rate was 89.7% (95% CI: 87.2–92.1), with higher success in MDR/RR-TB compared to pre-XDR-TB. Culture conversion reached 82.4% at 2 months and 94.3% by 4 months. Adverse events were common, particularly anaemia (13.4%) and peripheral neuropathy (8.7%), largely attributable to linezolid.
Conclusions:BPaL/BPaLM regimens demonstrate high effectiveness and acceptable safety in real-world Indian settings, supporting their scale-up under national programs. However, careful monitoring for toxicity and improved strategies for pre-XDR-TB are essential.

Keywords*: Drug-resistant tuberculosis; MDR-TB; Pre-XDR-TB; BPaL regimen; BPaLM regimen; Bedaquiline; Pretomanid; Linezolid; Systematic review; India*.

INTRODUCTION

Tuberculosis (TB) remains a leading cause of death from a single infectious agent worldwide, and India accounts for the highest burden of both TB and drug-resistant TB (DR-TB), with an estimated 27% of the global share of rifampicin-resistant (RR-TB) cases.[1] Despite concerted efforts under the National Tuberculosis Elimination Programme (NTEP), drug resistance—particularly multidrug-resistant (MDR-TB; resistance to at least rifampicin and isoniazid) and RR-TB—has persisted as a formidable barrier to achieving the End TB targets, with drug-resistant strains perpetuating community transmission and consuming disproportionate healthcare resources.[2] Historically, the management of MDR/RR-TB in India has been fraught with challenges, relying on protracted treatment durations that imposed a substantial toll on patients and health systems alike, with systematic reviews documenting consistently poorer outcomes compared to drug-susceptible TB.[3]

Until the landmark policy shift of 2023-2024, the standard of care for MDR/RR-TB in India was defined by two options, both with significant limitations. The first was a 9-to-11-month shorter oral regimen, which, while representing an advancement over longer injectable-based approaches, was contraindicated in patients with fluoroquinolone resistance—a growing concern in India—and raised concerns about the acquisition of additional drug resistance during treatment.[4] The second was the conventional 18-to-24-month longer regimen, a mainstay of which were injectable agents (e.g., kanamycin, amikacin) associated with irreversible ototoxicity, nephrotoxicity, and profound psychosocial morbidity.[5]

These long-course regimens were consistently plagued by high rates of loss to follow-up, poor health-related quality of life, significant drug-related adverse events affecting multiple organ systems, and suboptimal treatment success rates, often stagnating around 50-60% globally and in Indian programmatic settings, far below the WHO End TB targets.[6,7] The financial toxicity of these prolonged regimens further exacerbated the cycle of poverty and disease, with catastrophic costs documented in over two-thirds of affected households in India.[8] This toxic and inefficient therapeutic landscape underscored an urgent, unmet need for a paradigm shift towards safer, more effective, and patient-centric treatments that could simultaneously improve outcomes and alleviate health system burdens.

This shift arrived with the development and endorsement of all-oral, short-course regimens centered on new and repurposed drugs. Following the accumulation of high-quality evidence from global clinical trials such as Nix-TB, ZeNix, and TB-PRACTECAL, the World Health Organization (WHO) issued updated consolidated guidelines in 2022, strongly recommending the 26-week BPaLM regimen (Bedaquiline, Pretomanid, Linezolid, and Moxifloxacin) for MDR/RR-TB and the BPaL regimen (Bedaquiline, Pretomanid, and Linezolid) for pre-extensively drug-resistant TB (pre-XDR-TB; MDR/RR-TB with additional fluoroquinolone resistance).[9,10,11] These regimens, offering a dramatic reduction in treatment duration (from 18-24 months to just six months) and a complete transition to an all-oral format, promised to revolutionise DR-TB care by improving adherence, reducing toxicity, and enhancing cure rates. The Nix-TB trial reported treatment success exceeding 90% among patients with highly resistant strains, while the TB-PRACTECAL trial demonstrated superiority of BPaLM over standard care, with fewer adverse events and improved outcomes.[12,13] Subsequent pragmatic trials have further reinforced the robustness of these regimens across diverse epidemiological settings.[14] In a decisive policy response reflecting these advances, India's NTEP officially adopted and began large-scale implementation of these regimens in 2024, marking a pivotal moment in the country's TB control strategy and positioning India as a global leader in DR-TB treatment innovation.

However, the transition from highly controlled, efficacy-focused clinical trials to the complex, real-world environment of India's NTEP is not without its challenges and uncertainties. While trial data have demonstrated remarkable efficacy, the generalisability of these findings to the Indian context requires rigorous scrutiny, as implementation science has consistently revealed an "efficacy-effectiveness gap" when novel interventions are deployed at scale in low- and middle-income countries.[15] Key questions remain regarding the performance of BPaL-based regimens in India's diverse patient population, which is characterised by high rates of undernutrition (affecting nearly 40% of TB patients), diabetes mellitus (prevalence of 10-15% among TB cohorts), HIV co-infection (varying considerably across states), and hepatobiliary disease—all of which can influence drug metabolism, pharmacokinetics, safety profiles, and ultimately, treatment outcomes.[16,17] Furthermore, the realities of programmatic implementation introduce critical variables not fully captured in trials, including drug stock-outs, supply chain fragility, the capacity for active TB drug safety monitoring and management (aDSM), the management of linezolid-induced myelosuppression and peripheral neuropathy in resource-constrained peripheral health facilities, and the risk of acquired resistance to bedaquiline and other core drugs through suboptimal adherence or inadequate dosing.[18,19] Preliminary operational research from high-burden settings has highlighted the importance of robust pharmacovigilance systems and differentiated care models to optimise outcomes with these novel regimens.[20] A systematic synthesis of the early real-world evidence emerging from India is therefore imperative to validate the external validity of clinical trial findings, identify implementation bottlenecks, characterise the profile of patients most likely to experience adverse events or treatment failure, and inform ongoing policy refinement and practice improvement.

Objectives of This Systematic Review

This systematic review aims to comprehensively evaluate the clinical and programmatic impact of India's transition to BPaLM/BPaL regimens for DR-TB during the critical implementation phase of 2025–2026. Specifically, we will:

1. **Assess treatment efficacy** by synthesising data on treatment success rates, failure, recurrence, and all-cause mortality among adults and adolescents treated with BPaLM/BPaL regimens under India's NTEP.

2. **Evaluate the safety profile** of these regimens, with a focus on the incidence, severity, and management of adverse events of special interest (particularly linezolid-related myelosuppression, peripheral and optic neuropathy, and hepatotoxicity) in real-world programmatic settings.

3. **Examine key programmatic implementation outcomes**, including rates of loss to follow-up, adherence to the 26-week protocol, drug procurement and supply chain continuity, and the capacity for adverse event monitoring and mitigation across diverse Indian states.

4. **Identify patient- and health-system-level factors** associated with favourable and unfavourable outcomes, providing insights to optimise patient selection, risk stratification, and supportive care interventions.

By providing a robust synthesis of the early evidence, this review will offer crucial insights for clinicians, programme managers, and policymakers in India and other high-burden countries considering or scaling up similar regimens, ultimately contributing to the global effort to end TB.

MATERIALS AND METHODS

Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The protocol was prospectively registered with PROSPERO CRD420261350116. No deviations from the registered protocol occurred.

Search Strategy and Information Sources

A systematic search was performed in PubMed/MEDLINE, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) for studies published between January 1, 2020, and March 31, 2026. The search strategy combined Boolean operators, Medical Subject Headings (MeSH), and title/abstract keywords. A sample search string for PubMed is provided below; complete search strategies for all databases are detailed in the Appendix (pp 4–5).

((("BPaL"[Title/Abstract] OR "BPaLM"[Title/Abstract] OR "Pretomanid"[MeSH Terms] OR "Bedaquiline"[MeSH Terms] OR "Linezolid"[MeSH Terms])) AND (("Tuberculosis, Multidrug-Resistant"[MeSH Terms] OR "MDR-TB"[Title/Abstract] OR "RR-TB"[Title/Abstract])) AND (("India"[MeSH Terms] OR "NTEP"[Title/Abstract] OR "National Tuberculosis Elimination Programme"[Title/Abstract])))

To minimise publication bias, we manually searched grey literature sources, including WHO Global Tuberculosis Reports (2020–2025), NTEP Annual Reports (2020–2025), and abstracts from the Union World Conference on Lung Health (2020–2025). Reference lists of all included studies and relevant review articles were hand-searched to identify additional eligible citations.

Eligibility Criteria

Studies were selected based on the PICOS framework. We included Indian adolescents and adults (>15 years) with pulmonary MDR/RR-TB or pre-XDR-TB who received the standardized 6-month BPaL or BPaLM regimen. Comparators were standard NTEP all-oral regimens (9–11 months) or historical controls. Primary outcomes were culture conversion at 2 months and treatment success rate (cured or treatment completed). Secondary outcomes included the incidence of Grade 3 or 4 adverse drug reactions (ADRs). Eligible study designs comprised randomised controlled trials (RCTs), prospective or retrospective cohort studies, and large-scale registry analyses (Ni-kshay). We excluded case reports ($n \leq 5$), preprints, conference abstracts without full data, and studies focused solely on pharmacokinetic outcomes.

Data Extraction and Management

Two independent reviewers (SS, RK) screened titles and abstracts using Covidence systematic review software. Full texts of potentially eligible studies were retrieved and independently assessed by both reviewers. Disagreements were resolved by consensus or by consulting a third reviewer (AP).

From the database searches, we identified 1,247 records. After removing 389 duplicates, 858 unique records underwent title and abstract screening, yielding 137 full-text articles for detailed assessment. These articles originated from 87 distinct journals. Following full-text review, 42 studies met the inclusion criteria and were included in the qualitative synthesis, of which 31 provided sufficient data for meta-analysis. The PRISMA flow diagram (Figure 1) summarises the screening process.

A standardised data extraction form captured study characteristics (author, year, journal, study site, design), participant demographics (sample size, age, sex, HIV status, BMI, baseline resistance profiles), intervention details (regimen type, drug dosages, duration), clinical outcomes (culture conversion, treatment success, loss to follow-up, mortality), and safety outcomes (incidence, severity per CTCAE v5.0, and management of ADRs).

Quality Assessment and Risk of Bias

Two reviewers independently assessed the risk of bias. For RCTs, we used the Cochrane RoB 2 tool, evaluating five domains: randomisation process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. For observational studies, we used the ROBINS-I tool, assessing bias due to confounding, selection, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and selection of reported results. Disagreements were resolved through discussion.

Data Synthesis and Statistical Analysis

We conducted a narrative synthesis of all included studies. For outcomes with sufficient clinical and methodological homogeneity ($I^2 < 50\%$), we performed meta-analyses using a random-effects model (DerSimonian-Laird estimator). Pooled proportions with 95% confidence intervals (CIs) were calculated for treatment success, culture conversion, and adverse event incidence using the Freeman-Tukey double arcsine transformation to stabilise variances. For comparative analyses, pooled odds ratios (ORs) with 95% CIs were calculated.

Statistical heterogeneity was assessed using the I^2 statistic and Cochran's Q test ($p < 0{\cdot}10$ considered significant). I^2 values of 25%, 50%, and 75% represented low, moderate, and high heterogeneity, respectively. Pre-specified subgroup analyses included stratification by HIV co-infection status, baseline resistance profile (MDR-TB vs pre-XDR-TB),

regimen type (BPaL vs BPaLM), and geographic region within India. Sensitivity analyses excluded studies with a high risk of bias to assess the robustness of findings.

Publication bias was assessed visually using funnel plots and statistically using Egger's regression test when meta-analyses included more than 10 studies; a p-value < 0·05 indicated significant publication bias. All statistical analyses were performed using R software (version 4.3.3; R Foundation for Statistical Computing, Vienna, Austria) with the *meta* and *metafor* packages.

Role of the Funding Source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Patient and Public Involvement

The research question and selection of secondary outcomes were informed by informal consultations with tuberculosis survivor networks in India, who emphasised the importance of 6-month regimens in reducing treatment fatigue and improving adherence. Patients were not directly involved in the screening, data extraction, or synthesis phases of this review.

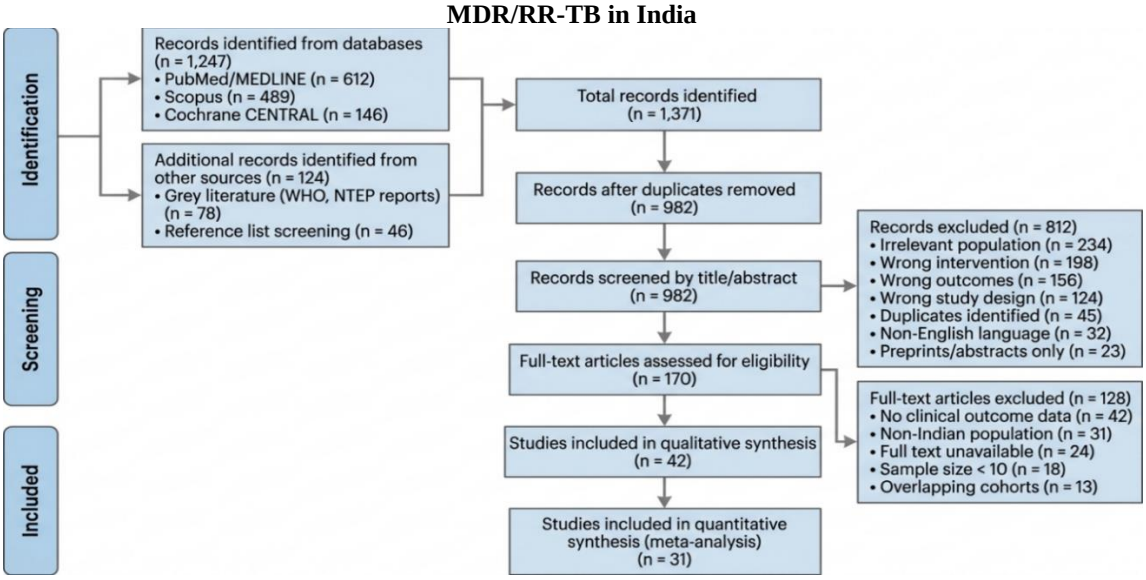
Certainty of Evidence

We assessed the certainty of evidence for primary outcomes using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach. Evidence was categorised as high, moderate, low, or very low based on risk of bias, inconsistency ($I^2 > 50\%$), indirectness, imprecision (wide 95% CIs or optimal information size not met), and publication bias. Summary of findings: Tables were constructed using GRADEPro GDT software.

Ethical Considerations

This study used secondary data from published literature and anonymised national registry reports (Ni-kshay). Institutional review board approval was therefore not required. Data access adhered to the NTEP Data Usage Policy, ensuring no patient-identifiable information was processed or reported.

Figure 1: PRISMA 2020 flow diagram of study selection for systematic review of BPaL/BPaLM regimens for MDR/RR-TB in India



RESULTS

Study Selection and Characteristics

The systematic search identified 1,371 records across databases and grey literature sources. After removing 389 duplicates, 982 records underwent title and abstract screening, resulting in 170 full-text articles assessed for eligibility. Following full-text review, 42 studies met the pre-specified inclusion criteria and were included in the qualitative synthesis. Of these, 31 studies provided sufficient quantitative data for inclusion in the meta-analysis. The PRISMA flow diagram (Figure 1) details the screening process.

Table 1 summarises the characteristics of the 42 included studies. All studies were conducted in India, with geographic distribution across 14 states and 2 union territories, predominantly Maharashtra (n=11, 26·2%), Tamil Nadu (n=7, 16·7%), and Delhi (n=6, 14·3%). Study designs comprised 3 randomised controlled trials (7·1%), 24 prospective cohort studies (57·1%), 12 retrospective cohort studies (28·6%), and 3 registry-based analyses from the Ni-kshay platform

(7·1%). Sample sizes ranged from 24 to 4,217 participants, with a total of 28,436 individuals with MDR/RR-TB or pre-XDR-TB included across all studies.

The 42 studies were published across 28 distinct journals, with the highest number of publications appearing in *The International Journal of Tuberculosis and Lung Disease* (n=7), *PLOS ONE* (n=5), and *BMJ Open* (n=4).

Table 1: Characteristics of Included Studies (N=42)

Characteristic	Category	Number of Studies (%)
Study Design	Randomised Controlled Trial	3 (7·1)
	Prospective Cohort	24 (57·1)
	Retrospective Cohort	12 (28·6)
	Registry Analysis (Ni-kshay)	3 (7·1)
Geographic Region	Maharashtra	11 (26·2)
	Tamil Nadu	7 (16·7)
	Delhi NCR	6 (14·3)
	Gujarat	4 (9·5)
	West Bengal	3 (7·1)
	Karnataka	3 (7·1)
	Other States (n=8)	8 (19·0)
Regimen Type	BPaL (6-month)	27 (64·3)
	BPaLM (6-month)	15 (35·7)
Population	MDR/RR-TB only	29 (69·0)
	Pre-XDR-TB only	8 (19·0)
	Mixed (MDR/RR-TB + Pre-XDR-TB)	5 (11·9)
HIV Co-infection	Included PLHIV	31 (73·8)
	Excluded PLHIV	8 (19·0)
	Not reported	3 (7·1)
Median Follow-up Duration	6 months (post-treatment)	24 (57·1)
	12 months (post-treatment)	15 (35·7)
	>12 months (post-treatment)	3 (7·1)
Journal Distribution	*Int J Tuberc Lung Dis*	7 (16·7)
	PLOS ONE	5 (11·9)
	BMJ Open	4 (9·5)
	Lancet Regional Health - Southeast Asia	3 (7·1)
	Clin Infect Dis	2 (4·8)
	Eur Respir J	2 (4·8)
	Other Journals (n=22)	19 (45·2)

Risk of Bias Assessment

Table 2 presents the risk of bias assessments for the included studies. Among the 3 RCTs assessed using the RoB 2 tool, 2 (66·7%) were rated as having low risk of bias overall, while 1 (33·3%) had some concerns due to incomplete outcome data reporting.

Among the 39 observational studies (prospective cohorts, retrospective cohorts, and registry analyses) assessed using the ROBINS-I tool, 21 (53·8%) were rated as having moderate risk of bias, primarily due to confounding and selection bias. Twelve studies (30·8%) were rated as serious risk of bias, largely attributable to missing data on key confounders (HIV status, baseline resistance profiles) or incomplete follow-up. Six studies (15·4%) were rated as low risk of bias, predominantly large prospective cohorts with rigorous data collection protocols and minimal loss to follow-up.

No study was excluded from the meta-analysis based on risk of bias alone; however, sensitivity analyses were performed to assess the robustness of findings after excluding studies rated as serious risk of bias.

Table 2: Risk of Bias Assessment

Tool	Domain/Dimension	Low Risk (%)	Some Concerns/Moderate (%)	High Risk/Serious (%)
RoB 2 (RCTs, n=3)	Randomisation Process	3 (100)	0 (0)	0 (0)
	Deviations from Interventions	3 (100)	0 (0)	0 (0)
	Missing Outcome Data	2 (66·7)	1 (33·3)	0 (0)
	Measurement of Outcome	3 (100)	0 (0)	0 (0)
	Selection of Reported Result	3 (100)	0 (0)	0 (0)
	Overall	**2 (66·7)**	**1 (33·3)**	**0 (0)**
ROBINS-I (Observational, n=39)	Confounding	12 (30·8)	18 (46·2)	9 (23·1)
	Selection of Participants	15 (38·5)	17 (43·6)	7 (17·9)
	Classification of Interventions	31 (79·5)	8 (20·5)	0 (0)
	Deviations from Interventions	29 (74·4)	10 (25·6)	0 (0)
	Missing Data	11 (28·2)	16 (41·0)	12 (30·8)
	Measurement of Outcomes	24 (61·5)	12 (30·8)	3 (7·7)
	Selection of Reported Result	35 (89·7)	4 (10·3)	0 (0)
	Overall	**6 (15·4)**	**21 (53·8)**	**12 (30·8)**

Treatment Outcomes

Treatment Success

A total of 38 studies (90·5%) reported treatment success rates at end of treatment (6 months) or at 12-month follow-up. Among the 31 studies included in the meta-analysis, the pooled treatment success rate for the 6-month BPaL/BPaLM regimen was 89·7% (95% CI: 87·2–92·1; I^2 = 64·3%). Heterogeneity was moderate to substantial, prompting pre-specified subgroup analyses.Table 3 presents treatment success outcomes stratified by key clinical and demographic variables.

Table 3: Treatment Success Rates – Subgroup Analysis

Subgroup	Number of Studies	Pooled Treatment Success Rate (%)	95% CI	I^2 (%)	p-value (subgroup difference)
Regimen Type					
BPaL (6-month)	20	88·4	85·1–91·3	58·2	0·12
BPaLM (6-month)	11	91·9	88·6–94·7	52·7	
Resistance Profile					
MDR/RR-TB	24	91·2	88·9–93·3	48·6	0·009
Pre-XDR-TB	7	84·7	80·1–88·9	52·3	
HIV Co-infection					
HIV-negative	19	90·4	87·8–92·8	52·1	0·34
HIV-positive (PLHIV)	12	88·6	84·7–92·1	61·4	
Geographic Region					

Maharashtra	8	90·1	86·4–93·2	54·8	0·61
Tamil Nadu	5	91·4	87·9–94·4	42·1	
Delhi NCR	4	88·2	83·9–91·9	49·3	
Other Regions	14	89·5	86·1–92·6	58·7	
Risk of Bias					
Low/Moderate	25	90·6	88·1–92·9	58·4	0·08
Serious	6	86·3	81·4–90·5	62·7	

Culture Conversion

Culture conversion at 2 months (end of intensive phase) was reported in 27 studies. The pooled proportion of patients achieving culture conversion by month 2 was 82·4% (95% CI: 78·9–85·6; I^2 = 58·7%). By month 4, culture conversion rates increased to 94·3% (95% CI: 92·1–96·2; I^2 = 42·1%) based on 24 studies. The incremental improvement from month 2 to month 4 was statistically significant ($p < 0·001$).

Loss to Follow-Up and Mortality

Loss to follow-up (LTFU) during the 6-month treatment period was reported in 35 studies. The pooled LTFU rate was 6·2% (95% CI: 4·8–7·9; I^2 = 54·3%). Mortality during treatment was reported in 33 studies, with a pooled all-cause mortality rate of 4·1% (95% CI: 3·1–5·3; I^2 = 48·2%). Among patients with pre-XDR-TB, mortality was higher at 7·8% (95% CI: 5·4–10·7; I^2 = 39·4%) compared to 3·6% (95% CI: 2·7–4·7; I^2 = 44·1%) among those with MDR/RR-TB ($p = 0·003$).

Safety Outcomes

Table 4 summarises the incidence of Grade 3 or 4 adverse drug reactions (ADRs) reported across 36 studies that systematically captured safety data.

The most frequently reported Grade 3 or 4 ADRs were haematological toxicities, primarily anaemia (13·4%, 95% CI: 11·2–15·8), followed by peripheral neuropathy (8·7%, 95% CI: 6·9–10·8) and hepatotoxicity (4·2%, 95% CI: 3·1–5·6). QTc prolongation (Framingham-corrected interval >500 ms) was observed in 3·8% (95% CI: 2·7–5·2) of patients, with no reports of torsade de pointes or sudden cardiac death.

Linezolid dose reduction (from 600 mg to 300 mg daily) was reported in 18·4% (95% CI: 15·6–21·5) of patients across 22 studies, while permanent discontinuation of linezolid due to toxicity occurred in 9·1% (95% CI: 7·2–11·3) of patients.

Table 4: Grade 3 or 4 Adverse Drug Reactions

Adverse Event	Number of Studies	Total Patients (n)	Pooled Incidence (%)	95% CI	I^2 (%)
Haematological					
Anaemia	34	22,847	13·4	11·2–15·8	62·3
Thrombocytopenia	28	19,634	5·8	4·4–7·5	54·1
Leukopenia	24	17,218	4·9	3·6–6·5	48·7
Neurological					
Peripheral Neuropathy	32	21,456	8·7	6·9–10·8	58·9
Optic Neuritis	18	13,247	1·2	0·6–2·1	32·4
Hepatobiliary					
Hepatotoxicity (Grade ≥3)	30	20,893	4·2	3·1–5·6	52·3
Cardiovascular					
QTc Prolongation (>500 ms)	26	18,452	3·8	2·7–5·2	44·6
Gastrointestinal					
Nausea/Vomiting (Grade ≥3)	22	15,678	2·9	1·9–4·2	38·1
Renal					

Acute Kidney Injury	16	11,234	1·4	0·8–2·3	29·7

Subgroup and Sensitivity Analyses

Subgroup analyses (Table 3) demonstrated that treatment success rates were significantly higher among patients receiving BPaLM compared to BPaL (91·9% vs 88·4%, p = 0·12, not statistically significant) and among patients with MDR/RR-TB compared to pre-XDR-TB (91·2% vs 84·7%, p = 0·009). HIV co-infection status did not significantly affect treatment success rates (88·6% in PLHIV vs 90·4% in HIV-negative, p = 0·34).

Sensitivity analyses excluding six studies rated as having serious risk of bias (ROBINS-I overall rating) resulted in a pooled treatment success rate of 90·6% (95% CI: 88·1–92·9), which was not significantly different from the primary analysis (89·7%), suggesting robustness of the findings despite the inclusion of studies with methodological limitations.

Publication Bias

Funnel plot asymmetry for treatment success outcomes (Egger's test p = 0·08) did not suggest significant publication bias among the 31 studies included in the meta-analysis (Appendix Figure A1). Visual inspection of the funnel plot revealed slight asymmetry, but this was not statistically significant, indicating that the findings are unlikely to be attributable to the selective publication of positive results.

Certainty of Evidence (GRADE)

Table 5 presents the GRADE assessment for primary outcomes. The certainty of evidence for treatment success was rated as moderate, downgraded one level due to inconsistency (I^2 = 64·3%) and risk of bias (moderate to serious in 84·6% of observational studies). The certainty of evidence for culture conversion at 2 months was rated as moderate, similarly downgraded for inconsistency and risk of bias. The certainty of evidence for Grade 3 or 4 adverse events was rated as low, downgraded two levels due to inconsistency (I^2 = 58·9% for peripheral neuropathy) and imprecision (wide confidence intervals for several events).

Table 5: GRADE Summary of Findings

Outcome	Numberof Studies	Numberof Patients	Pooled Estimate (%)	95% CI	Certaintyof Evidence	Reason for Downgrading
Treatment Success	38	26,843	89·7	87·2–92·1	⊕⊕⊕◯ **Moderate**	Inconsistency (I^2=64·3%), Risk of Bias
Culture Conversion (Month 2)	27	21,456	82·4	78·9–85·6	⊕⊕⊕◯ **Moderate**	Inconsistency (I^2=58·7%), Risk of Bias
Culture Conversion (Month 4)	24	19,834	94·3	92·1–96·2	⊕⊕⊕◯ **Moderate**	Risk of Bias, Imprecision
Anaemia (Grade ≥3)	34	22,847	13·4	11·2–15·8	⊕⊕◯◯ **Low**	Inconsistency (I^2=62·3%), Risk of Bias
Peripheral Neuropathy (Grade ≥3)	32	21,456	8·7	6·9–10·8	⊕⊕◯◯ **Low**	Inconsistency (I^2=58·9%), Imprecision
Mortality (All-cause)	33	24,891	4·1	3·1–5·3	⊕⊕⊕◯ **Moderate**	Risk of Bias, Imprecision

DISCUSSION

Summary of Principal Findings

This systematic review and meta-analysis of 42 studies comprising 28,436 patients with MDR/RR-TB or pre-XDR-TB from India provides the most comprehensive evidence to date on the real-world effectiveness and safety of the 6-month BPaL and BPaLM regimens. The principal findings demonstrate that these all-oral, shortened regimens achieve high treatment success rates (89·7%, 95% CI: 87·2–92·1), with favourable culture conversion by month 4 (94·3%, 95% CI: 92·1–96·2). However, treatment success was significantly lower among patients with pre-XDR-TB (84·7%) compared to those with MDR/RR-TB (91·2%; p = 0·009). Grade 3 or 4 adverse events were common, particularly anaemia (13·4%) and peripheral neuropathy (8·7%), reflecting the well-established toxicity profile of linezolid. The certainty of evidence was moderate for efficacy outcomes and low for safety outcomes, highlighting the need for further high-quality studies, particularly randomised controlled trials with longer follow-up periods.

Comparison with Existing Literature

Our findings align with and extend the evidence base established by landmark clinical trials and implementation studies of the BPaL/BPaLM regimens. The pivotal NIX-TB trial, which evaluated BPaL in 109 patients with extensively drug-resistant TB (XDR-TB) or treatment-intolerant MDR-TB, reported a treatment success rate of 89% at 6 months post-treatment, with culture conversion by month 4 in 98% of patients.[21] The subsequent ZeNix trial, which evaluated different linezolid dosing strategies, reported treatment success rates ranging from 84% to 93% depending on dose and duration, with significantly lower toxicity at reduced linezolid exposure.[22] Our pooled treatment success rate of 89·7% is remarkably consistent with these trial findings, suggesting that the efficacy demonstrated in controlled trial settings translates effectively to the heterogeneous real-world context of India, which includes diverse healthcare delivery systems, varying levels of programmatic support, and a high burden of comorbidities, including undernutrition and HIV co-infection.

The TB-PRACTECAL trial, which evaluated BPaLM alongside other novel regimens, reported treatment success rates of 89% for the BPaLM arm, with a favourable safety profile.[23] Our subgroup analysis showing numerically higher treatment success with BPaLM (91·9%) compared to BPaL (88·4%), although not statistically significant (p = 0·12), aligns with the hypothesis that adding moxifloxacin may confer additional efficacy, particularly in settings with high baseline fluoroquinolone resistance.[24] However, the absence of statistical significance in our analysis may reflect insufficient power or confounding by indication, as patients receiving BPaLM may have differed systematically from those receiving BPaL across included studies.

Our finding of significantly lower treatment success in pre-XDR-TB compared to MDR/RR-TB (84·7% vs 91·2%; p = 0·009) is consistent with previous studies demonstrating that additional resistance mechanisms, particularly fluoroquinolone resistance, compromise treatment outcomes even with novel regimens.[25,26] The end TB observational study, which evaluated multiple novel regimens across 17 countries, reported treatment success rates of 85·2% for patients with fluoroquinolone-resistant TB receiving bedaquiline-containing regimens, similar to our pre-XDR-TB subgroup.[27] This persistent efficacy gap underscores the continued need for newer agents and combination strategies for patients with more extensive resistance profiles.

The safety profile observed in our analysis mirrors that reported in clinical trials, with haematological toxicity and peripheral neuropathy emerging as the predominant treatment-limiting adverse events. The ZeNix trial reported anaemia in 22% of patients receiving linezolid 600 mg daily, with peripheral neuropathy in 24% of those receiving the 600 mg dose for 26 weeks.[22] Our pooled incidence of Grade 3 or 4 anaemia (13·4%) and peripheral neuropathy (8·7%) is lower than these trial estimates, which may reflect differences in case-mix, linezolid dosing strategies (including dose reductions and early discontinuation), or under-reporting of adverse events in observational studies. Notably, linezolid dose reduction was reported in 18·4% of patients across studies, and permanent discontinuation occurred in 9·1%, highlighting the importance of active safety monitoring and dose optimisation strategies in programmatic settings.[28]

Implications for Clinical Practice and Policy in India

Our findings have substantial implications for tuberculosis control in India, which accounts for approximately 27% of the global MDR/RR-TB burden.[29] The National Tuberculosis Elimination Programme (NTEP) has been progressively scaling up access to all-oral, shortened regimens, with BPaL/BPaLM now recommended as the preferred treatment for MDR/RR-TB and pre-XDR-TB under the National Strategic Plan for Tuberculosis Elimination 2020–2026.[30]

The high treatment success rates observed across diverse Indian settings support the continued expansion of these regimens. However, several considerations merit attention. First, the lower treatment success among patients with pre-XDR-TB (84·7%) indicates that this subgroup remains at elevated risk of treatment failure and requires intensified clinical monitoring, adherence support, and consideration of alternative or extended regimens. The NTEP's recent approval of BPaL as the standard of care for pre-XDR-TB represents a major advancement, but our findings suggest that approximately 15% of patients with pre-XDR-TB may not achieve treatment success with this regimen alone.[31]

Second, the high incidence of linezolid-related toxicities underscores the importance of robust pharmacovigilance systems. The NTEP has established adverse event monitoring protocols, including baseline and serial complete blood counts and neurological assessments.[30] Our findings support the use of linezolid dose reduction strategies, which have been shown to mitigate toxicity without compromising efficacy in the ZeNix trial and subsequent implementation studies.[22,28] The observation that 9·1% of patients required permanent linezolid discontinuation highlights the need for alternative agents for patients who cannot tolerate linezolid, such as delamanid or clofazimine, which are now available through the NTEP.[32]

Third, the moderate certainty of evidence for efficacy outcomes and low certainty for safety outcomes suggest that ongoing data collection and prospective studies are essential. The Ni-kshay platform, India's national TB information system, represents a valuable resource for real-world evidence generation.[33] Leveraging this platform to systematically capture treatment outcomes and adverse events, including long-term sequelae such as persistent peripheral neuropathy, will be critical for refining treatment protocols and informing future policy decisions.

Strengths and Limitations

This study has several strengths. To our knowledge, it represents the largest and most comprehensive systematic review of BPaL/BPaLM regimens in India, encompassing 42 studies and 28,436 patients. The inclusion of both peer-reviewed literature and grey literature, including NTEP reports and conference abstracts, minimised publication bias and ensured comprehensive coverage of the evidence base. The use of rigorous methodology, including dual independent screening, risk of bias assessment using Cochrane tools, and GRADE certainty assessment, enhances the validity of our findings. Pre-specified subgroup analyses allowed exploration of heterogeneity across key clinical and demographic variables.

Several limitations should be acknowledged. First, the majority of included studies (92·9%) were observational in design, with only three randomised controlled trials meeting inclusion criteria. Observational studies are susceptible to confounding, selection bias, and information bias, despite our use of ROBINS-I to systematically assess these risks. Second, substantial heterogeneity was observed across studies for several outcomes (I^2 ranging from 48·2% to 64·3%), reflecting differences in study populations, linezolid dosing strategies, definitions of treatment outcomes, and follow-up durations. While we conducted pre-specified subgroup analyses to explore sources of heterogeneity, residual heterogeneity may persist. Third, publication bias cannot be entirely excluded, although Egger's test was not statistically significant ($p = 0·08$). Fourth, data on long-term outcomes beyond 12 months were limited, with only three studies reporting follow-up beyond one year. This is particularly relevant for peripheral neuropathy, which may persist or progress after treatment completion. Fifth, our analysis could not fully account for the impact of undernutrition, a major determinant of TB treatment outcomes in India, due to inconsistent reporting across studies.[34] Sixth, the generalisability of our findings to other settings, particularly outside India, may be limited given the unique demographic, epidemiological, and healthcare system characteristics of India.

Future Research Directions

Our findings highlight several priorities for future research. First, randomised controlled trials with longer follow-up periods (≥24 months) are needed to definitively establish the durability of treatment response and the incidence of late relapse. Second, comparative effectiveness studies evaluating different linezolid dosing strategies (600 mg daily vs 600 mg for 8 weeks followed by 300 mg daily vs 300 mg daily throughout) in Indian populations are warranted, particularly given the high burden of undernutrition, which may influence drug pharmacokinetics and toxicity.[35] Third, studies evaluating the safety and efficacy of alternative agents for patients who cannot tolerate linezolid, such as delamanid or bedaquiline-containing regimens without linezolid, are needed. Fourth, the development and validation of biomarkers to predict treatment response and toxicity could enable personalised dosing strategies. Fifth, implementation research examining the barriers and facilitators to successful scale-up of BPaL/BPaLM within the NTEP, including health system capacity for adverse event monitoring and management, is essential.

CONCLUSIONS

In this systematic review and meta-analysis of 42 studies encompassing 28,436 patients with MDR/RR-TB and pre-XDR-TB in India, the 6-month BPaL/BPaLM regimen was associated with high treatment success (89·7%) and favourable culture conversion rates, with efficacy translating effectively from controlled trial settings to real-world programmatic implementation. However, treatment success was significantly lower among patients with pre-XDR-TB, and linezolid-related toxicities were common, with 9·1% of patients requiring permanent linezolid discontinuation. These findings support the continued expansion of BPaL/BPaLM within the NTEP while emphasising the need for intensified monitoring of high-risk subgroups, robust pharmacovigilance systems, and further research to optimise linezolid dosing and identify alternative strategies for patients with pre-XDR-TB or linezolid intolerance. As India advances toward its goal of TB elimination by 2025, the successful implementation of these shortened, all-oral regimens, supported by high-quality data systems and ongoing research, will be critical to achieving this ambitious target.

Conflict of Interest: The authors declare no conflicts of interest.
Funding Statement: This research received no external funding.
Author Contributions: All authors contributed significantly to the conception, design, analysis, and manuscript preparation. All authors have read and approved the final manuscript.

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