Systematic Review

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Intensified Anti-TB Regimens for Tuberculous Meningitis: A Systematic Review

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Background: Various intensified anti-TB regimens have been investigated to improve survival in tuberculous meningitis (TBM), including higher-dose rifampicin, intravenous rifampicin administration, and adjunctive fluoroquinolones. This systematic review evaluates the efficacy and safety of these intensified approaches compared with standard recommended therapy.
Methods: We conducted a systematic search of PubMed/MEDLINE, Embase, and Cochrane CENTRAL from January 1, 2000, to March 10, 2026, for randomized clinical trials evaluating intensified anti-TB regimens for TBM. Studies enrolling adult or pediatric patients with clinically or microbiologically diagnosed TBM and reporting mortality or safety outcomes were included. Methodological quality was assessed using the Cochrane risk-of-bias tool.
Results: Seven randomized clinical trials including 1725 participants were reviewed. In pediatric populations (based on a single study), mortality was 0/11 (zero of eleven children) with high-dose rifampicin plus levofloxacin, 1/12 with high-dose rifampicin alone, and 0/14 with standard therapy. In adult populations, mortality outcomes varied considerably across intensification strategies. For higher-dose rifampicin (15–35 mg/kg/day) without fluoroquinolones, mortality ranged from 20.4% to 22.6%. For higher-dose rifampicin combined with fluoroquinolones, mortality was 27.9%. Among trials of intravenous rifampicin, mortality ranged from 15.0% to 21.7%. For fluoroquinolone addition without rifampicin dose escalation, mortality ranged from 37.8% to 50.0%. The largest trial (n = 817) demonstrated no mortality benefit with rifampicin 15 mg/kg plus levofloxacin versus standard therapy. No single intensification strategy showed a consistent survival advantage. Adverse events were frequently reported, most commonly hepatotoxicity and neurological complications.
Conclusions: Intensified regimens—including higher-dose rifampicin (15–35 mg/kg/day), and adjunctive fluoroquinolones—did not appear to consistently reduce mortality in adults with TBM compared with standard therapy. However, considerable heterogeneity in intervention type, dose, route, and fluoroquinolone selection limits the ability to draw definitive conclusions. Further adequately powered trials are needed to define optimal regimens. In pediatric patients, evidence is limited to a single small trial and is insufficient for firm conclusions regarding survival.
Systematic Review Registration: PROSPERO (CRD420251174674).

Keywords: tuberculous meningitis; high-dose rifampicin; levofloxacin; intensified therapy; mortality; randomized controlled trials; adult; pediatric

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Introduction

Tuberculous meningitis (TBM) is the most severe manifestation of *Mycobacterium tuberculosis* infection, carrying high rates of mortality and long-term neurological disability despite standard anti-TB therapy [1]. It disproportionately affects pediatric and adult populations in high-burden countries and poses a significant challenge due to rapid disease progression, diagnostic delays, and poor penetration of standard drugs into the central nervous system [2,3]. Mortality remains unacceptably high, particularly in patients with advanced disease or comorbidities such as human immunodeficiency virus (HIV) infection, highlighting an urgent need for more effective therapeutic strategies [4,5].

Recent research has explored various intensified anti-TB regimens including higher-dose rifampicin (15–35 mg/kg/day), intravenous rifampicin, and adjunctive fluoroquinolones (levofloxacin or moxifloxacin) [6,7,8,9,10,11]. However, reported results have been heterogeneous, with variable effects on mortality and limited safety data, particularly in pediatric populations.

This systematic review aims to synthesize the available clinical trial evidence on intensified anti-TB regimens for TBM—including higher-dose rifampicin, intravenous rifampicin, and adjunctive fluoroquinolones—to inform clinical practice and identify knowledge gaps for future research.

Methods

Search Strategy

PubMed/MEDLINE (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/), and Cochrane CENTRAL (https://www.cochranelibrary.com/central) were systematically searched to identify randomized clinical trials evaluating intensified anti-TB regimens in patients with TBM. The search was from January 1, 2000, to March 10, 2026. Both controlled vocabulary (Medical Subject Headings [MeSH] and Emtree terms) and free-text keywords related to TBM, rifampicin, fluoroquinolones, and intravenous rifampicin were used and combined with Boolean operators. The complete electronic search strategy is provided in **Supplementary Material**. The review was conducted in accordance with PRISMA guidelines (see **Supplementary Material** for the completed **PRISMA 2020 Checklist**) and was prospectively registered in PROSPERO (CRD420251174674, https://www.crd.york.ac.uk/PROSPERO/view/CRD420251174674) [12].

Study Selection Criteria

Randomized clinical trials evaluating intensified anti-TB regimens—including higher-dose rifampicin, intravenous rifampicin, and/or adjunctive fluoroquinolones—in addition to standard anti-TB therapy, were eligible. Studies were included if they compared these intensified regimens to standard World Health Organization (WHO)-recommended therapy. EndNote (Version 20, Clarivate Analytics, Philadelphia, PA, USA) was used for reference management and duplicate removal. Titles and abstracts were independently screened by two reviewers (GM and NG) to exclude unrelated or ineligible studies, followed by full-text review to confirm eligibility. Discrepancies between reviewers were resolved through discussion and consensus; a third reviewer (MJN) was consulted when agreement could not be reached.

Eligible studies met the following; Population, Intervention, Comparison, and Outcome (PICO) criteria:

- **Population:** Pediatric or adult patients with definite, probable, or possible TBM, as defined by clinical, microbiological, or radiological criteria. Pediatric patients were defined as individuals younger than 18 years, while adult patients were defined as those 18 years or older.
- **Intervention:** Intensified regimens were defined as standard anti-TB therapy modified by higher-dose oral rifampicin (≥15 mg/kg/day in adults, or above the WHO-recommended pediatric dose), intravenous rifampicin, and/or adjunctive fluoroquinolones. Standard therapy was defined per WHO guidelines for each population (approximately 10 mg/kg/day for adults and 15 mg/kg/day for children).
- **Comparator:** Standard-dose anti-TB regimens without intensification (i.e., rifampicin ~10 mg/kg/day orally without fluoroquinolones).
- **Outcomes:** Primary outcome was mortality. Secondary outcomes included frequency and severity of adverse events and treatment interruptions due to toxicity.

Data Extraction

Data were independently extracted by two reviewers (GM and NG) using a predefined Microsoft Excel spreadsheet (Microsoft Excel for Microsoft 365, Version 2402, Microsoft Corporation, Redmond, WA, USA). Extracted variables included study characteristics (first author, publication year, country, design), patient demographics (age, sample size), intervention and comparator details, diagnostic criteria, outcome definitions, and follow-up duration. Discrepancies between reviewers were resolved through discussion and consensus; a third reviewer (MJN) was consulted when agreement could not be reached.

Quality Assessment

Risk of bias was independently assessed by GM and MN using the Cochrane Risk of Bias tool for randomized trials across seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting, and other biases. The original Cochrane Risk of Bias tool was used because this framework was prespecified for the review and had been

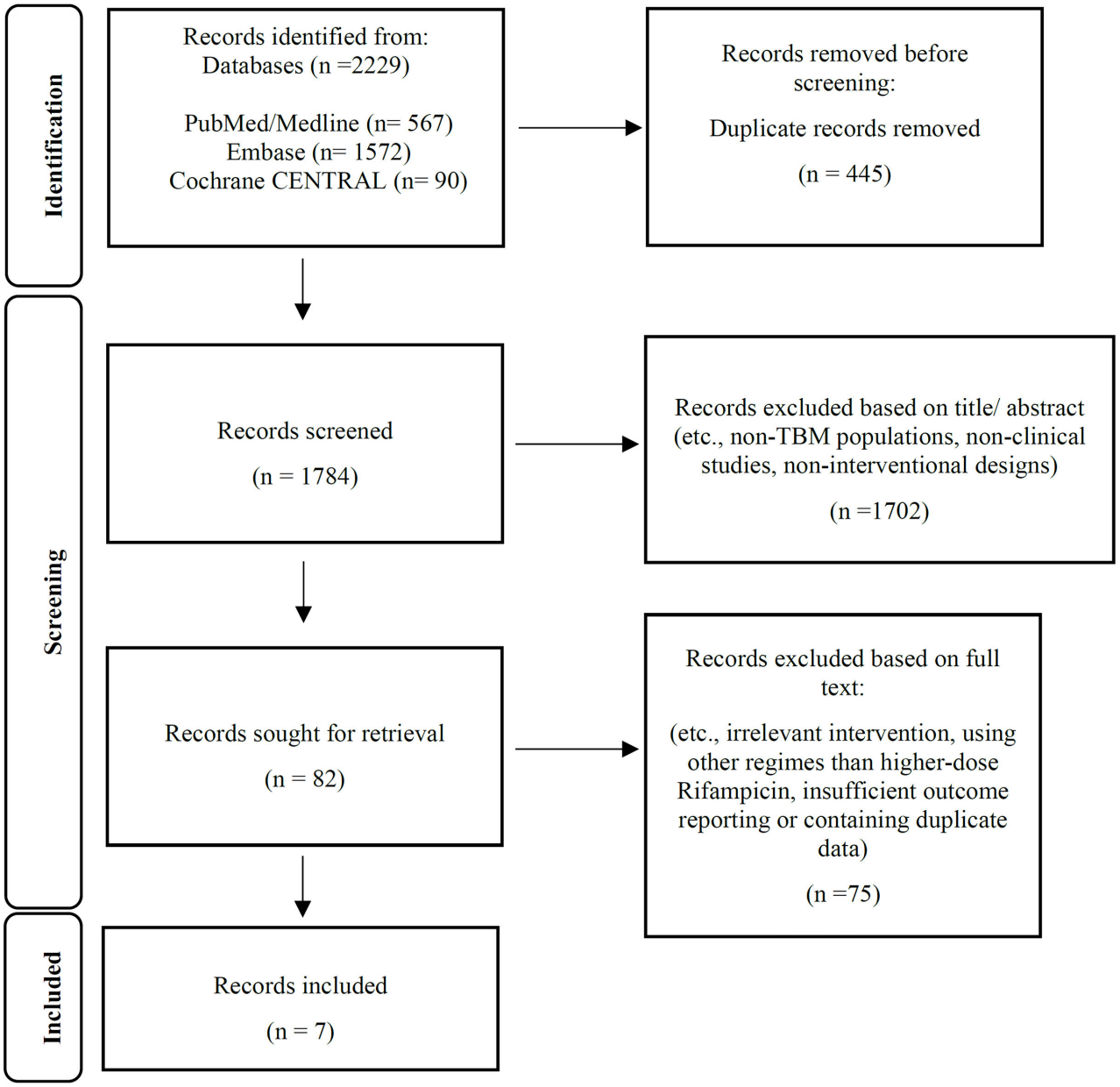


Fig. 1. Flowchart of study selection.

applied consistently across all included trials. Each domain was rated as low, high, or unclear risk of bias. Overall study quality was interpreted based on the cumulative risk across domains. Discrepancies between reviewers were resolved through discussion and consensus; a third reviewer (MH) was consulted when agreement could not be reached.

Results

Of 2229 records identified, 445 duplicates were removed, leaving 1784 for screening. After excluding 1702 irrelevant records, 82 full-text articles were assessed, of which 75 were excluded. Ultimately, seven randomized trials met the inclusion criteria, assessing the efficacy of intensified anti-TB therapy—including higher-dose rifampicin, intravenous rifampicin, and/or adjunctive fluoroquinolones—in both pediatric and adult patients with clinically suspected or confirmed TBM (Fig. 1) [13,14,15,16,17,18,19].

Study Characteristics

Seven randomized trials of intensified anti-TB therapy for suspected or confirmed TBM were included (Table 1, Ref. [13,14,15,16,17,18,19]). Studies were conducted in high TB-burden countries: India, Vietnam, Uganda, and Indonesia. Study designs included double-blind, assessor-blinded, and open-label trials. Total participants across all arms was 1725; with median age from 6 years (pediatric co-

hort) to 35 years (adults). Most participants had MRC grade II–III disease; 422 were HIV-positive. Diagnostic confirmation used clinical, neuroimaging, cerebrospinal fluid (CSF), and molecular testing.

Treatment arms varied considerably across trials, reflecting the range of intensification strategies investigated: higher-dose oral rifampicin alone; higher-dose oral rifampicin with adjunctive fluoroquinolones; intravenous rifampicin with or without fluoroquinolones; and fluoroquinolone addition without rifampicin dose escalation. Only three studies evaluated oral rifampicin at doses ≥20 mg/kg/day. Levofloxacin or moxifloxacin was evaluated in five studies. Follow-up ranged from 6 to 18 months. Mortality was the primary endpoint in five of the seven studies; in the remaining two studies, the primary endpoints were functional outcome and safety and CSF rifampicin concentration and safety. Secondary outcomes included neurological disability, CSF rifampicin exposure, and treatment discontinuation.

Due to substantial heterogeneity across trials in intervention types, doses, routes, populations, and outcome definitions, a formal meta-analysis was not considered appropriate. We therefore present a structured narrative synthesis organized by intervention strategy, with study-specific mortality data and effect estimates where available.

Quality Assessment

Risk of bias was assessed using the Cochrane tool, with domain-level judgments recorded (Table 2, Ref. [13,14,15,16,17,18,19]). Four trials were judged to be at low risk of bias across all domains. As shown in the Table 2, three earlier trials showed high risk of bias in allocation concealment and blinding due to open-label designs, while other domains were rated as low risk. For open-label or assessor-blinded trials, lack of blinding may have influenced adverse event reporting, treatment discontinuation, and clinical management decisions, although mortality, the principal efficacy outcome considered in this review, was objective and less susceptible to detection bias. Overall, the included studies were of moderate to high methodological quality; however, findings from trials with higher risk of bias should be interpreted with caution, and the overall evidence synthesis accounts for these limitations.

Mortality Outcomes

Across the included trials, participants were assigned to different treatment regimens, with mortality outcomes presented below by intensification strategy (Table 3, Ref. [13,14,15,16,17,18,19]).

Pediatric evidence was limited to a single randomized controlled trial [13]. Among the 37 children enrolled, no deaths occurred in the high-dose rifampicin plus levofloxacin group (0/11, zero of eleven children) or the standard therapy group (0/14), while one death occurred in the high-dose rifampicin alone group (1/12, 8.3%).

In adult populations, mortality outcomes varied across intensification strategies. Among trials of higher-dose oral rifampicin without fluoroquinolones, Dian et al. [15] reported mortality of 22.6% (24/106) with 20 mg/kg and 20.4% (23/113) with 30 mg/kg, suggesting no dose-response relationship. In a trial combining higher-dose rifampicin with fluoroquinolones [16], found no mortality benefit with rifampicin 15 mg/kg plus levofloxacin versus standard therapy (27.9% vs. 27.7%; HR 0.94, 95% CI 0.73–1.22; $p = 0.66$). Among trials of intravenous rifampicin, mortality was 21.7% (13/60) with intravenous 20 mg/kg versus 28.0% (14/50) with standard therapy in one trial, and 15.0% (3/20) with intravenous 13 mg/kg plus moxifloxacin versus 33.3% (7/21) with standard therapy in another. Among trials of fluoroquinolone addition without rifampicin escalation, mortality was 50.0% in both arms in one trial and 37.8% versus 35.3% in another. Overall, no intensification strategy consistently reduced mortality.

The largest trial showed no benefit, and smaller studies showed wide variation likely due to chance.

Adverse Events

Adverse event reporting varied considerably across trials, with substantial heterogeneity in definitions, severity grading, and denominators (Table 4, Ref. [13,14,15,16,17,18,19]). All numbers represent patient-level counts based on the safety population in each study, which may differ from the intention-to-treat populations in Table 1. Hepatic adverse events were the most frequently reported toxicity (0%–63.3%), particularly in intensified rifampicin trials. Neurological events (0%–66.7%) were reported in several studies, though attribution to treatment versus disease was often unclear. Severe (grade 3–5) adverse events occurred in 16.7%–48.6% of patients. Drug discontinuation due to adverse events was reported in three studies, ranging from 2.5% to 3.5% in two studies and reaching 33.3% in another study. Overall, adverse events were frequent, reflecting both treatment toxicity and disease severity. However, heterogeneity in reporting limits direct comparisons, and only generalized observations are provided.

Discussion

This systematic review summarizes the outcomes of intensified anti-TB in both pediatric and adult patients with TBM. In pediatric populations, based on a single study, higher-dose rifampicin—either alone or in combination with fluoroquinolones —did not demonstrate a survival benefit; however, the evidence is limited and should be interpreted with caution. These limitations stem from several key challenges inherent to conducting TBM trials in children. Key challenges in pediatric TBM trials include rare disease burden requiring multisite recruitment, difficult diagnosis needing rapid CSF diagnostics and biomarkers,

Table 1. Study characteristics.

Author	Year	Country	Median age (years)	Sample size	Diagnostic test	No. of HIV-positive patients	Follow-up period (months)	Intervention group 1 (dose, route, duration)	Intervention group 2 (dose, route, duration)	Control group (dose, route, duration)	Outcome
Paradkar* et al. [13]	2022	India	Pediatric trial (6)	37**	Head CT or MRI, CSF laboratory tests, blood measurements, comprehensive metabolic panel	NM	18	HR30ZE: R 30 mg/kg, H, Z, E (oral, 8 weeks)	HR30ZL: R 30 mg/kg, H, Z, L 20 mg/kg (oral, 8 weeks)	HR15ZE: R 15 mg/kg, H, Z, E (oral, 8 weeks)	Mortality (secondary); primary: functional outcome (MRS) and safety
Cresswell et al. [14]	2021	Uganda	33	169	Clinical, microbiological confirmation, low CSF glucose	56	6	R20H5Z25E20: R 20 mg/kg (IV, 8 weeks)	R35HZE: R 35 mg/kg (oral, 8 weeks)	RHZE: R ~10 mg/kg (oral, 8 weeks)	Mortality (secondary); primary: CSF rifampicin concentration and safety
Dian*** et al. [15]	2018	Indonesia	29	229	Clinical, standard CSF tests, blood measurements, chest radiography	6	6	R20: R 20 mg/kg (oral, 8 weeks) + H, Z, E	R30: R 30 mg/kg (oral, 8 weeks) + H, Z, E	R10: R 10 mg/kg (oral, 8 weeks) + H, Z, E	Mortality (primary)
Heemskerk et al. [16]	2016	Vietnam	35	817	Clinical and CSF abnormalities	349	9	R15 + L20: R 15 mg/kg, H, Z, E + L 20 mg/kg (oral, 8 weeks)	—	R10: R 10 mg/kg, H, Z, E (oral, 8 weeks)	Mortality (primary)
Kalita et al. [17]	2016	India	35	110	Clinical, MRI and CSF criteria	NM	6	Standard + L10: R 10 mg/kg, H, Z, E + L 10 mg/kg (oral, 8 weeks)	—	Standard: R 10 mg/kg, H, Z, E (oral, 8 weeks)	Mortality (primary)
Kalita et al. [18]	2014	India	34.5	203	Clinical, MRI and CSF findings	4	6	Standard + L10: R 10 mg/kg, H, Z, E + L 10 mg/kg (oral, 8 weeks)	—	R10: R 10 mg/kg, H, Z, E (oral, 8 weeks)	Mortality (primary)
Ruslami et al. [19]	2013	Indonesia	28	160	Standard CSF and blood tests, chest radiography	7	6	R13 IV + M: R 13 mg/kg IV + M 400 mg (oral, 8 weeks)	R13 IV: R 13 mg/kg IV (IV, 8 weeks)	R10 PO: R 10 mg/kg (oral, 8 weeks)	Mortality (primary)

CSF, cerebrospinal fluid; CT, computed tomography; E, ethambutol; H, isoniazid; HIV, human immunodeficiency virus; HR30ZE, high-dose rifampicin 30 mg/kg + isoniazid + pyrazinamide + ethambutol; HR30ZL, high-dose rifampicin 30 mg/kg + isoniazid + pyrazinamide + levofloxacin; HR15ZE, rifampicin 15 mg/kg + isoniazid + pyrazinamide + ethambutol; IV, intravenous; L, levofloxacin; M, moxifloxacin; MRI, magnetic resonance imaging; NM, not mentioned; PO, per oral (oral); R, rifampicin; R10, rifampicin 10 mg/kg/day (standard dose); R13, rifampicin 13 mg/kg/day (moderate dose, intravenous); R15, rifampicin 15 mg/kg/day (higher dose); R20, rifampicin 20 mg/kg/day (high dose); R30, rifampicin 30 mg/kg/day (high dose); R35, rifampicin 35 mg/kg/day (very high dose); R20H5Z25E20, rifampicin 20 mg/kg + isoniazid 5 mg/kg + pyrazinamide 25 mg/kg + ethambutol 20 mg/kg; R35HZE, rifampicin 35 mg/kg + isoniazid + pyrazinamide + ethambutol; RHZE, standard rifampicin ~10 mg/kg + isoniazid + pyrazinamide + ethambutol; Z, pyrazinamide.

*In the Paradkar trial, the control arm received rifampicin 15 mg/kg/day, which is considered standard of care for pediatric TBM per WHO guidelines, whereas 10 mg/kg/day is standard for adults. **Of 2487 children prescreened, 37 were enrolled in this trial. ***Of 229 enrolled patients, mortality data for the control arm were not reported; safety analyses were performed on a subset of 60 patients.

Table 2. Quality assessment of the included studies.

Author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Paradkar et al. [13]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Cresswell et al. [14]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Dian et al. [15]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Heemskerk et al. [16]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kalita et al. [17]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kalita et al. [18]	Low risk	High risk	High risk	High risk	Low risk	Low risk	Low risk
Ruslami et al. [19]	Low risk	High risk	High risk	High risk	Low risk	Low risk	Low risk

Table 3. Mortality outcomes in pediatric and adult TBM patients.

Study	Population	Intervention strategy	Intervention (dose, route)	Deaths/total	Mortality %	Comparator mortality %
Paradkar et al. [13]	Pediatric	Higher-dose R alone	R30 (30 mg/kg, oral)	1/12	8.3	0
		Higher-dose R + LFX	R30 + L (30 mg/kg, oral)	0/11	0	0
Cresswell et al. [14]	Adult	Higher-dose R alone	R20 IV (20 mg/kg, IV)	13/60	21.7	28.0
		Higher-dose R alone	R35 (35 mg/kg, oral)	13/59	22.0	28.0
Dian et al. [15]	Adult	Higher-dose R alone	R20 (20 mg/kg, oral)	24/106	22.6	NR
		Higher-dose R alone	R30 (30 mg/kg, oral)	23/113	20.4	NR
Heemskerk et al. [16]	Adult	Higher-dose R + LFX	R15 + L (15 mg/kg, oral)	114/409	27.9	27.7
Kalita et al. [17]	Adult	LFX only	Standard + L (~10 mg/kg)	10/20	50.0	50.0
Kalita et al. [18]	Adult	LFX only	Standard + L (~10 mg/kg)	17/45	37.8	35.3
Ruslami et al. [19]	Adult	IV R + MXF	R13 IV + M (13 mg/kg, IV)	3/20	15.0	33.3

IV, intravenous; L, levofloxacin; LFX, levofloxacin; M, moxifloxacin; MXF, moxifloxacin; NR, not reported; R, rifampicin; Standard, WHO-recommended standard therapy with rifampicin ~10 mg/kg/day. Numbers are presented as "deaths / total patients". The mortality percentage corresponds to these values.

lack of child-friendly drug formulations, intensive training for neurocognitive assessments, comorbid conditions demanding drug-level monitoring, and barriers to participation requiring qualitative research [20].

In adult populations, intensified regimens—including higher-dose rifampicin (15–35 mg/kg/day), intravenous rifampicin, and adjunctive fluoroquinolones—did not consistently reduce mortality or decrease adverse events. The effects were heterogeneous across studies, and the addition of levofloxacin did not consistently confer a survival advantage. Notably, the largest and most robust trial demonstrated no mortality benefit with rifampicin 15 mg/kg plus levofloxacin compared with standard therapy.

Our findings align with the newly published clinical practice guideline from the TBM International Research Consortium—the first international guideline specifically for TBM [21]. Regarding rifampicin dosing, the guideline concludes that there is currently insufficient evidence to recommend doses exceeding 10 mg/kg/day in adults, though available data suggest that doses above 20 mg/kg/day are safe, with results from ongoing phase 3 trials investigating higher doses (35 mg/kg/day) eagerly awaited. The guideline further emphasizes that current anti-TB drug regimens for TBM are extrapolated from pulmonary TB treatment and "do not account for the need to achieve therapeutic concentrations within the Central Nervous System". This pharmacokinetic limitation—particularly the poor cerebrospinal fluid penetration of rifampicin (approximately 5%) and ethambutol (20–30%)—provided the scientific rationale for investigating intensified regimens. However, accumulating clinical trial evidence, has now failed to demonstrate consistent survival benefits with this approach.

Adverse events were frequently reported, most commonly hepatotoxic and neurological events. However, the

Table 4. Adverse events.

Author (Year)	Safety population (n)*	Hepatic events n/N (%)	Neurological events n/N (%)	Renal events n/N (%)	Hematologic events n/N (%)	Grade 3–5 AEs n/N (%)	Serious AEs n/N (%)	Drug withdrawal n/N (%)
Paradkar et al. (2022) [13]	37	1/37 (2.7)	1/37 (2.7)	0/37 (0)	0/37 (0)	18/37 (48.6)	4/37 (10.8)	NR
Cresswell et al. (2021) [14]	61	7/61 (11.5)	5/61 (8.2)	3/61 (4.9)	4/61 (6.6)	22/61 (36.1)	NR	NR
Dian et al. (2018) [15]	60	38/60 (63.3)	0/60 (0)	1/60 (1.7)	11/60 (18.3)	15/60 (25.0)	NR	NR
Heemskerk et al. (2016) [16]	817	91/817 (11.1)	179/817 (21.9)	193/817 (23.6)	66/817 (8.1)	159/817 (19.5)	NR	NR
Kalita et al. (2016) [17]	57	18/57 (31.6)	38/57 (66.7)	0/57 (0)	0/57 (0)	NR	NR	2/57 (3.5)
Kalita et al. (2014) [18]	120	0/120 (0)	19/120 (15.8)	0/120 (0)	0/120 (0)	20/120 (16.7)	NR	3/120 (2.5)
Ruslami et al. (2013) [19]	60	34/60 (56.7)	0/60 (0)	0/60 (0)	0/60 (0)	12/60 (20.0)	NR	20/60 (33.3)

*Numbers represent patients included in safety analyses (those who received study drug and were monitored for adverse events), which may differ from the total intention-to-treat populations reported in Table 1. For Cresswell et al. [14], the safety outcomes were reported for a subset of 61 participants rather than the full study population of 169; therefore, adverse-event percentages were calculated using the safety-analysis population reported by the original study. Percentages are calculated based on the safety population for each study. "NR" indicates not reported in the original study. Neurological events may reflect either drug toxicity or disease progression; attribution was determined by each study's investigators. Grade 3–5 adverse events are presented as reported in each trial.

frequency of Grade 3–5 adverse events varied considerably across studies, ranging from 16.7% to 48.6%, and drug discontinuation was reported in three studies, with variable rates. Due to substantial heterogeneity in adverse event definitions and reporting across trials, direct comparisons should be interpreted with caution. Careful clinical monitoring remains essential, particularly in patients with severe disease or comorbidities. Clinically, these findings do not support a clear survival benefit with intensified regimens for TBM, and evidence in pediatric populations is insufficient to recommend its use for improving mortality [22,23]. In adults the outcomes are heterogeneous across studies, likely reflecting differences in baseline disease severity, patient comorbidities—including HIV status—and variations in treatment protocols. The heterogeneity in what constitutes an "intensified" regimen (ranging from 15 mg/kg rifampicin to 35 mg/kg, oral versus intravenous administration, and with or without fluoroquinolones) further complicates interpretation. The lack of consistent benefit across all categories does not necessarily preclude the possibility that one specific strategy—such as intravenous rifampicin at very high doses—might be effective. However, the available evidence does not support any single approach over another.

The role of adjunctive fluoroquinolones remains uncertain. Current evidence does not support their routine use, as their impact on survival was inconsistent across trials. Hepatotoxicity is a common and clinically significant complication of anti-TB therapy, particularly in high-burden settings. Observational data suggest that hepatic dysfunction may occur in a substantial proportion of patients receiving anti-TB treatment [24]. Although hepatotoxicity was variably reported across the trials included in this review, hepatic adverse events were among the most frequently documented complications. In this context, fluoroquinolones such as levofloxacin may play a role as alternative or adjunctive agents in patients who develop hepatotoxicity necessitating interruption or modification of first-line therapy. However, evidence supporting this strategy in TBM remains limited, and careful clinical judgment is required when considering regimen modifications.

These findings emphasize the importance of individualized treatment strategies for TBM [25,26,27,28]. Clinicians should consider patient-specific factors—including age, disease severity, comorbid conditions, and prior treatment history—when designing therapy. Careful monitoring for hepatotoxicity, gastrointestinal intolerance, hematologic toxicity and other drug-related complications is recommended, especially in vulnerable populations such as children and patients with comorbidities [29]. Furthermore, these results highlight the need for additional high-quality studies to optimize dosing, determine the safety profile in different patient groups, and clarify the potential role of combination regimens including fluoroquinolones.

Beyond the scope of this review, emerging adjunctive approaches—including N-acetylcysteine and glutathione supplementation—have been proposed to mitigate oxida-

tive stress and enhance host immunity, though clinical evidence in TBM remains limited [30,31,32,33].

Further high-quality studies are warranted to evaluate the efficacy, optimal dosing, and safety of these novel interventions, both alone and in combination with intensified anti-TB regimens.

This study has several important limitations. Substantial heterogeneity across trials in design, dosing, adjunctive therapies, and outcome definitions limited comparability and obscured treatment effects. Critically, the definition of what constitutes an "intensified" or "high-dose" regimen varied considerably across studies, with some evaluating rifampicin at 15 mg/kg, others at 30–35 mg/kg [15,16,17], and still others using intravenous administration or fluoroquinolone addition without rifampicin escalation. This variability complicates direct comparisons and limits the ability to draw definitive conclusions about any single approach. Pediatric evidence was restricted to a single small trial, precluding definitive conclusions for children and preventing meaningful extrapolation from adult data—differences in disease presentation, pharmacokinetics, and treatment response further complicate such translation. Most trials were conducted in high TB burden countries, potentially limiting generalizability to other settings. Long-term neurological outcomes were sparse, secondary endpoints inconsistently reported, and several trials had potential bias from incomplete blinding or allocation concealment. Additional methodological limitations should be acknowledged. Safety outcomes were not uniformly reported for the full randomized populations, and some adverse-event analyses were based on smaller safety subsets, which may limit the precision and comparability of safety findings. In addition, use of the original Cochrane Risk of Bias tool rather than RoB 2 may have missed some contemporary and outcome-specific sources of bias. These limitations should be considered when interpreting the findings.

Collectively, these limitations underscore the need for cautious interpretation and highlight urgent priorities for future research.

Conclusions

In conclusion, intensified regimens—including higher-dose rifampicin (15–35 mg/kg/day), intravenous rifampicin, and adjunctive fluoroquinolones—did not appear to consistently reduce mortality in adults with TBM. However, considerable heterogeneity in intervention type, dose, route, and fluoroquinolone selection limits definitive conclusions. In pediatric populations, evidence remains insufficient. The role of adjunctive fluoroquinolones remains uncertain. Careful monitoring for adverse events is warranted, particularly in patients with severe disease. Further adequately powered trials, especially in children, are needed to define optimal regimens.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization: VV, MJN, GBM; investigation and writing—original draft: GBM, GM, AS, ATDX, RC, LD, VV, MG, MH, MA, NG, and MJN; writing—review and editing: MJN and GBM; supervision: GBM, VV, MJN; project administration: RC, LD, and MJN. All authors have read and agreed to the published version of the manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

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Conflict of Interest

Lia D'Ambrosio is affiliated with Public Health Consulting Group Sagl, a private consulting firm. All other authors declare no conflict of interest.

Declaration of Generative AI and AI-Assisted Technologies in Manuscript Preparation

During the preparation of this work, the authors used GPT-3.5 for language polishing, grammar correction, and improving clarity and readability. After its use, the authors thoroughly reviewed, verified, and revised all content to ensure accuracy and originality.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202638214.286.

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