

Daily versus thrice-weekly antituberculosis therapy for drug-susceptible pulmonary tuberculosis in adults: A systematic review and exploratory meta-analysis.

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Page | 1

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Abstract

Background:

Historical thrice-weekly antituberculosis regimens reduced the number of supervised treatment encounters, but concerns remain regarding microbiological efficacy, relapse, and acquired resistance compared with daily therapy. This systematic review and exploratory meta-analysis aimed to compare the efficacy, safety, treatment outcomes, relapse, and acquired drug resistance associated with daily versus thrice-weekly antituberculosis therapy in adults with drug-susceptible pulmonary tuberculosis.

Methods:

Comparative randomized and observational studies involving adults with drug-susceptible or presumed drug-susceptible pulmonary tuberculosis were synthesized. Risk ratios (RRs) were calculated for dichotomous outcomes. Randomized evidence was prioritized, while pooled analyses incorporating observational studies were considered exploratory. Risk of bias was assessed using Cochrane RoB 2 for randomized trials and ROBINS-I for observational studies, and certainty of evidence was evaluated using GRADE principles.

Results:

Six unique studies constituted the strict/historical adult-focused evidence set, with two additional observational studies included as supportive sensitivity evidence. Two-month culture conversion was higher with daily than thrice-weekly treatment (85% vs 77%; RR 1.10, 95% CI 1.04–1.17). In the HIV-positive whole-course randomized trial, favourable outcome was 91% versus 77% (RR 1.19, 95% CI 1.05–1.35), with acquired rifampicin resistance occurring only in the intermittent arm. The exploratory pooled favourable-outcome estimate was RR 1.08 (95% CI 0.94–1.24; I²=22.6%). Safety evidence remained sparse and heterogeneous.

Conclusions:

Randomized evidence most consistently favours daily therapy for microbiological conversion and prevention of acquired resistance. Planned thrice-weekly therapy should not be preferred over guideline-concordant daily treatment. Future research should prioritize patient-centred delivery of daily therapy, predictors of toxicity and poor drug exposure, consequences of missed doses, and individual-patient-data analyses to identify clinically vulnerable subgroups.

Keywords: Tuberculosis, Pulmonary; Antitubercular Agents; Drug Therapy; Directly Observed Therapy; Treatment Outcome; Drug Resistance, Microbial; Sputum Conversion; Systematic Review; Meta-Analysis.

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Introduction

Intermittent anti-tuberculosis chemotherapy was developed to make supervised treatment operationally feasible, reduce the number of observed treatment encounters, and exploit the post-antibiotic effects of potent first-line agents. It consequently became embedded in several national DOTS programmes, including India's former RNTCP. India explicitly described its pre-2017 regimen as three times weekly, before replacing it with daily fixed-dose combination treatment [1]. The practical attraction of intermittent treatment, however, is distinct from the biological question of whether reducing the number of effective rifampicin-containing exposures compromises sterilising activity, increases relapse, or facilitates selection of resistance.

This distinction has become increasingly important because “DOTS” is often used colloquially as though it were a dosing schedule. It is not. Directly observed treatment and drug-dosing frequency are separable components of TB care: some historical intermittent regimens were fully supervised, some daily regimens were self-administered, and the modern WHO recommendation combines daily pharmacotherapy with patient-centred supervision and adherence support. WHO currently defines “daily” treatment as seven days per week, regards daily dosing as the best frequency, and does not recommend thrice-weekly dosing for either the intensive or continuation phase of DS-TB treatment. Consequently, comparisons in which daily self-administration is contrasted with thrice-weekly direct observation can underestimate or obscure pharmacological differences because treatment frequency and delivery strategy change simultaneously.

WHO's current standard six-month DS-TB regimen is 2HRZE/4HR, meaning two months of isoniazid, rifampicin, pyrazinamide and ethambutol followed by four months of

isoniazid and rifampicin, administered daily. WHO states that this regimen is appropriate in the absence of documented isoniazid or rifampicin resistance and emphasises susceptibility testing where available [2]. The historical RCT evidence relevant to dosing frequency, however, extends back several decades and includes regimens that are no longer standard, including eight-month regimens with 6HE continuation phases and formulations or supervision models that differ substantially from present practice. [3]

The most comprehensive previous RCT-level synthesis found an important discordance between apparently acceptable treatment completion in some intermittent programmes and less favourable microbiological outcomes. Across 56 RCTs and 110 treatment arms, relapse was 6.8% with thrice-weekly therapy throughout and 2.5% with daily therapy; adjusted analyses also indicated increased failure and acquired resistance with thrice-weekly treatment [4]. A major limitation of that evidence was that most comparisons were between trial arms across different trials, not randomised head-to-head comparisons of identical drugs administered at different frequencies. The present review therefore prioritises original direct-comparison research—RCTs first, comparative cohorts second—and explicitly separates frequency effects from differences in regimen composition, phase, supervision, HIV status and diabetes.

Therefore, the objective of this systematic review and exploratory meta-analysis was to systematically evaluate and compare the efficacy and safety of daily versus thrice-weekly antituberculosis therapy in adults with drug-susceptible or presumed drug-susceptible pulmonary tuberculosis, with particular emphasis on favourable treatment outcomes, microbiological conversion, relapse or recurrence, mortality, adverse events, treatment adherence or loss to follow-up, and acquired drug resistance.

Table1. Prespecified Review Eligibility and Outcome Definitions

Domain	Prespecified review definition
Population	Adults with active pulmonary TB that was drug-susceptible by baseline DST or was treated as first-line drug-susceptible TB without known rifampicin/isoniazid resistance. Historical adult-predominant RCTs with incompletely reported minimum age were retained but downgraded for indirectness.
Intervention	Historical intermittent thrice-weekly therapy: 3 doses/week, either throughout treatment or in a defined phase. Exact regimen notation and dose were extracted when reliably reported. Literal once-weekly active-TB treatment was not considered equivalent, and no such regimen was included. WHO itself frames the relevant PICO as daily versus three times weekly.
Comparator	Daily first-line treatment, generally 7 doses/week where “daily” was explicitly defined. Direct observation versus self-administration was extracted separately because it can confound frequency comparisons. WHO defines daily as seven days/week.
Primary outcomes	Treatment success/cure/favourable bacteriological outcome; sputum smear or culture conversion; bacteriological relapse/recurrence after treatment.

Secondary outcomes	Any and serious adverse events, hepatotoxicity, mortality, adherence, default/LTFU; acquired drug resistance was additionally extracted as a clinically critical microbiological outcome.
Study designs	Original RCTs and comparative prospective or retrospective cohort studies only. Reviews, guidelines, case series and pharmacokinetic-only studies were excluded from the primary evidence set.

Methods

Review Design

This systematic review and exploratory meta-analysis was conducted as a systematic synthesis of comparative evidence evaluating daily versus thrice-weekly antituberculosis treatment in adults with drug-susceptible or presumed drug-susceptible pulmonary tuberculosis. The evidence search was updated through 27 August 2026, with no language restriction applied at the eligibility stage.

Search Strategy and Information Sources

PubMed/MEDLINE and web-accessible publisher and full-text indexes were systematically searched using combinations of controlled vocabulary and free-text terms relating to pulmonary tuberculosis, daily treatment, intermittent treatment, thrice-weekly or three-times-weekly dosing, DOT/DOTS, rifampicin/rifampin, treatment outcomes, relapse, microbiological conversion, randomized trials, and cohort studies. Backward citation searching was additionally undertaken from eligible original studies and from the previous randomized-trial synthesis by Johnston and colleagues. The WHO TB Knowledge Sharing Platform and official Government of India/Ministry of Health and Family Welfare resources were searched separately to establish contemporary and historical policy context.

A representative PubMed search strategy was: (*"pulmonary tuberculosis" OR "pulmonary TB"*) AND (*rifampicin OR rifampin*) AND (*daily OR "7 days" OR "seven times weekly"*) AND (*intermittent OR "thrice weekly" OR "three times weekly" OR DOTS*) AND (*random OR trial OR cohort OR prospective OR retrospective*).

Supplementary searches incorporated the terms *drug susceptible, treatment success, cure, culture conversion, sputum conversion, relapse, recurrence, treatment failure, mortality, default, loss to follow-up, adverse event, hepatotoxicity, and acquired rifampicin resistance*. Reference lists of relevant systematic reviews and eligible primary studies were also examined to identify additional historical comparative studies.

Eligibility criteria.

Included studies had to be original RCTs or cohorts containing a direct comparison between a daily and intermittent treatment schedule and reporting pulmonary-TB outcomes. Eligible participants had active pulmonary

disease and no known MDR/RR-TB at treatment initiation; where older programme studies did not report modern universal DST, the population was classified as "presumed DS" and certainty downgraded. There is exclusion of preventive treatment/latent TB, MDR/RR-TB regimens, paediatric-only studies, non-comparative cohorts, case-control toxicity studies, pharmacokinetic-only comparisons, reviews, modelling studies, and mixed pulmonary/extrapulmonary cohorts without extractable pulmonary results.

Selection Process

Records identified through the searches were screened against the prespecified eligibility criteria. Two reviewers independently assessed titles and abstracts for potential eligibility, followed by independent full-text assessment of potentially relevant reports. Disagreements regarding eligibility were resolved through discussion and consensus; where consensus could not initially be reached, a third reviewer was consulted. Multiple publications arising from the same underlying study were linked and treated as a single study to avoid double counting. Reasons for exclusion at the full-text stage were documented and incorporated into the PRISMA flow diagram.

Data extraction.

Extracted variables comprised country, setting, study period, design, sample size, age and HIV/diabetes status, microbiological eligibility, susceptibility testing, treatment history, drug composition, phase-specific dosing frequency, numeric dose when reliably reported, duration, observation/self-administration strategy, follow-up duration, definitions and event counts for cure/treatment success, culture or smear conversion, failure, recurrence/relapse, resistance, deaths, defaults/LTFU and adverse events.

Risk of bias.

Randomised studies were appraised conceptually using Cochrane RoB 2 domains: randomisation, deviations from intended intervention, missing outcome data, outcome measurement and selective reporting. Cohort studies were assessed with ROBINS-I domains, with particular attention to confounding by treatment era, indication, HIV/DM status

and treatment supervision, selection, exposure classification, missing data and outcome measurement. Assessments refer to the information available in the retrieved reports; lack of documentation was not interpreted as proof that a safeguard was absent.

Reporting Bias Assessment

Risk of bias due to missing results and selective reporting was considered by comparing reported outcomes with the outcomes and methods described in the available study reports and, where available, trial-related documentation. Particular attention was given to selective omission of efficacy, relapse, resistance, mortality, and safety outcomes. Small-study effects and publication bias were considered at the synthesis level. Formal statistical tests for funnel-plot asymmetry, including Egger's test, were not undertaken because no pooled outcome included the conventionally recommended minimum of approximately 10 studies. Where a funnel plot was presented despite fewer studies, it was interpreted as exploratory and descriptive rather than as a formal assessment of publication bias.

Certainty Assessment

The certainty of the body of evidence for each clinically relevant outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. Certainty was evaluated across the domains of risk of bias, inconsistency, indirectness, imprecision, and other considerations, including potential reporting bias. Randomized evidence initially contributed higher-certainty evidence, whereas observational evidence was interpreted with appropriate consideration of confounding and other design limitations. Certainty was categorized as high, moderate, low, or very low. Particular attention was given to indirectness arising from historical treatment regimens, differences in treatment phase and supervision strategy, heterogeneity of study populations, sparse event counts, wide confidence intervals, and inclusion of observational evidence in exploratory pooled analyses.

Meta-analysis.

Effect estimates were calculated as risk ratios (RR), with daily therapy as the numerator. Thus, for beneficial outcomes such as treatment success or conversion, $RR > 1$ favours daily therapy; for harmful outcomes such as adverse events, death or default, $RR < 1$ favours daily therapy. Study-level log RRs and conventional 95% CIs were calculated from reported events and denominators. Zero-cell analyses used a 0.5 continuity correction.

For outcomes with at least two clinically interpretable comparisons, random-effects models used restricted maximum likelihood (REML) estimation of between-study variance, with modified Hartung-Knapp confidence intervals to reduce overconfidence with few studies. Heterogeneity was summarised using τ^2 and I^2 . Formal funnel-plot/Egger testing was not performed because no pooled endpoint approached the usual threshold of 10 studies.

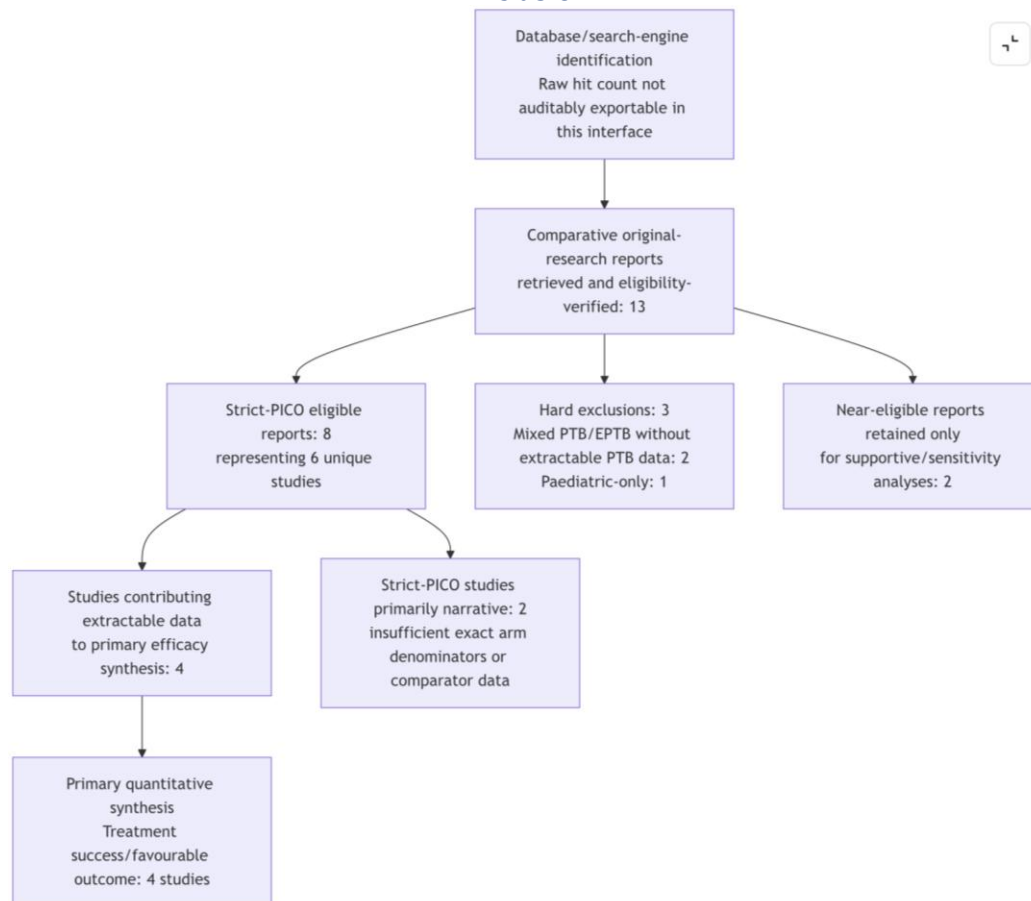
The primary pooled efficacy analysis used studies with extractable treatment-success/favourable outcome data. Secondary pooling of adverse events and default/LTFU was explicitly designated exploratory because event definitions and populations differed and because sparse strict-PICO data required addition of near-eligible observational studies. Microbiological conversion and relapse were not forced into a single pooled estimate when phases, denominators, or follow-up definitions were incompatible.

Subgroups and sensitivity analyses.

Prespecified clinical strata were HIV-positive versus HIV-negative, diabetes versus no specified diabetes, whole-course versus intensive-phase-only versus continuation-phase-only intermittency, RCT versus cohort, and daily DOT/program-supported therapy versus daily self-administration. Sensitivity analyses excluded serious/critical-risk cohorts, studies without clearly adult-only populations, and studies without clear baseline drug-susceptibility documentation. Because most subgroups contained only one or two studies, subgroup findings are presented primarily as stratified estimates rather than unreliable tests for interaction.

Results

Figure No. 1: PRISMA Flow Diagram of Study Identification, Screening, Eligibility, and Inclusion



Six unique studies formed the strict or historical adult-focused PICO evidence set: three randomised programmes/trials and three comparative cohorts; three separate publications reported the long-term Hong Kong

randomised study. Two additional observational studies were retained only as supportive/sensitivity evidence because of age, retreatment, or drug-susceptibility uncertainty.

Table No. 2: Study Characteristics and Regimen Structure

Study	Population/design	Daily regimen	Intermittent regimen	Key outcome information	Applicability
Yu X et al. [6]	Random allocation; sputum-positive PTB; 833 patients with pretreatment drug-sensitive isolates across five regimens.	6-month daily HRZE (HRZE7); exact drug-specific mg/kg not reliably recoverable.	Four 6-month thrice-weekly regimens; cleanest frequency comparison HRZE3 vs daily HRZE; other arms varied S/E/Z composition.	All 833 DS patients had favourable bacteriologic response; relapse ≈1% daily HRZE vs ≈2% thrice-weekly HRZE at 18 months; non-PZA intermittent regimen ≈8% relapse.	Direct historical whole-course evidence; exact arm denominators unavailable and formulations historical.
Harries et al., Malawi, 2001 [7]	Programme cohort; high-HIV-prevalence setting; new smear-positive PTB; 2,671 patients received intermittent regimen.	Contemporary/historical programme comparator; exact denominator not reliably extractable.	2R3H3Z3E3/6HE, oral ambulatory regimen.	Mortality 23% in intermittent cohort; overall mortality reportedly similar in concurrent comparisons, but first-month mortality higher with intermittent treatment.	Serious confounding; HIV status largely ecological/programmatic; regimen composition not frequency-only.
Jindani et al., 2004 [3]	International multicentre RCT; 1,355 newly diagnosed smear-positive PTB patients.	Frequency-matched 8-month arm: 2EHRZ/6HE. Separate standard control: 2EHRZ/4HR.	2(EHRZ)3/6HE: thrice-weekly EHRZ in intensive phase, followed by the same daily HE continuation.	2-month culture negative: 700/828 (85%) daily-IP vs 333/433 (77%) intermittent-IP. Unfavourable outcome: 36/346 (10%) vs 48/351 (14%). Toxicity interruption	High-value intensive-phase frequency contrast; 6HE continuation and 8-month regimen are obsolete.

Study	Population/design	Daily regimen	Intermittent regimen	Key outcome information	Applicability
				≥7 days: 12 vs 5.	
Gopalan et al., 2018 [8]	Open-label RCT, South India; 331 HIV-positive adults with newly diagnosed culture-positive PTB; daily n=111, intermittent n=110; mITT efficacy 98 vs 98.	2EHRZ7/4HR7; weekdays directly observed, weekends/holidays self-administered.	2EHRZ3/4HR3; thrice weekly throughout treatment.	Favourable: 89/98 (91%) vs 75/98 (77%); recurrence 6 vs 6; deaths 4 vs 5; any ADR 30/111 vs 19/110; acquired rifampicin resistance only in intermittent arm (n=4).	Most relevant modern full-course RCT, but restricted to PLHIV; baseline resistance identified by DST.
Bhatt et al., 2020 [9]	Retrospective cohorts, South India; 191 HIV-negative newly diagnosed sputum-positive adults; daily n=59, intermittent n=132.	Daily self-administered exact mg/dose not reliably extractable.	RNTCP thrice-weekly directly observed short-course regimen.	Success 76.2% vs 70.4%; default 11.9% vs 18.2%; death 6.8% vs 5.3%; failure 5.1% vs 4.6%; relapse 0 vs 1.5%.	Frequency and supervision both differed; treatment choice non-random.
Siane et al., 2020 [10]	Retrospective cohort; adults >18 years with TB-DM, smear-positive at diagnosis, HIV-negative; n=72; daily n=29, intermittent n=43.	2RHZE/4RH; daily continuation using individual tablets.	2RHZE/4R3H3; first 2 months daily in both groups, then thrice-weekly FDC continuation.	Cure 12/29 (41.4%) vs 19/43 (44.2%); LTFU 15/29 (51.7%) vs 23/43 (53.5%); failure 2 vs 1; ADR 1 vs 6.	Continuation-phase-only comparison; very high attrition; TB-DM population.
Mandal et al., 2013 [5] — supportive	Prospective observational study; n=83; intermittent 43, daily 40; Category I and II; mixed-age population.	Daily initial intensive phase; n=40; exact mg/kg conservatively considered not reliably extractable.	RNTCP intermittent initial phase, 3 doses/week.	Conversion among evaluable: 36/38 (94.74%) vs 37/39 (94.87%); default 2/40 vs 4/43; ADR 14/40 vs 11/43.	Not strict PICO because of mixed ages/retreatment; supportive/sensitivity evidence.

Study	Population/design	Daily regimen	Intermittent regimen	Key outcome information	Applicability
Bhangari et al., 2020 [11] — supportive	Retrospective PTB cohort, India; daily n=55, intermittent n=50; age bands began at 16 years; DST criteria not stated.	Daily first-line regimen; exact phase-specific drug doses not specified in retrieved text.	Historical intermittent regimen; exact phase-specific dosing not specified in any retrieved text.	Cure 30/55 vs 31/50; deaths 8/55 vs 12/50; default 1/55 vs 5/50; any ADR 19/55 vs 12/50.	High/critical confounding; age imbalance and uncertain DS definition.

Table No.3: Risk-of-Bias Assessment of Included and Supportive Studies

Study	Tool	Main concerns	Overall judgement
Yu X et al.	RoB 2	Random allocation is explicitly reported, and bacteriological endpoints are objective; accessible reports provide limited information on sequence generation/concealment and complete arm-level attrition.	Some concerns
Jindani et al.	RoB 2	Randomised multicentre design, intention-to-treat analysis and serial microscopy/culture reduce bias; blinding and concealment details are incompletely represented in the accessible abstract.	Some concerns
Gopalan et al.	RoB 2	Concealed randomisation and objective microbiology are strengths. Open-label treatment, modified ITT analysis and early termination after a prespecified interim boundary add some potential bias, although stopping was DSMC-driven.	Some concerns; low for microbiological measurement
Harries et al.	ROBINS-I	Programme/historical comparison, differing regimen composition, high background HIV burden and potential time/health-system confounding.	Serious
Bhatt et al.	ROBINS-I	Patients opted for daily SAT while comparator received intermittent DOT; confounding by patient choice, adherence supervision, and treatment era is unavoidable.	Serious
Siane et al.	ROBINS-I	Retrospective assignment, diabetes-specific population, continuation-phase-only exposure, and >50% LTFU; authors explicitly noted insufficient sample size and inability to ascertain reasons for dropout.	Critical/serious
Mandal et al.	ROBINS-I	Non-random treatment allocation, mixed age, mixture of new and retreatment patients, no clean adult DS subgroup. [9]	Serious; supportive only
Bhangari et al.	ROBINS-I	Retrospective, substantial age imbalance, uncertain susceptibility, unclear allocation, and differing outcome ascertainment. [	Critical/serious; supportive only

Note. RoB 2 = Cochrane Risk of Bias tool, version 2; ROBINS-I = Risk Of Bias In Non-randomized Studies of Interventions; ITT = intention-to-treat; DSMC = Data and Safety Monitoring Committee; SAT = self-administered treatment; DOT = directly observed treatment; LTFU = loss to follow-up; DS = drug-susceptible.

Treatment success or favourable outcome

Four studies supplied sufficiently explicit data for the prespecified exploratory efficacy meta-analysis. Jindani's "favourable" count was calculated as the complement of

reported failure/relapse composite in its frequency-matched 8-month arms: 310/346 daily-intensive-phase versus 303/351 intermittent-intensive-phase. Gopalan reported 89/98 versus 75/98 directly. Bhatt's published percentages

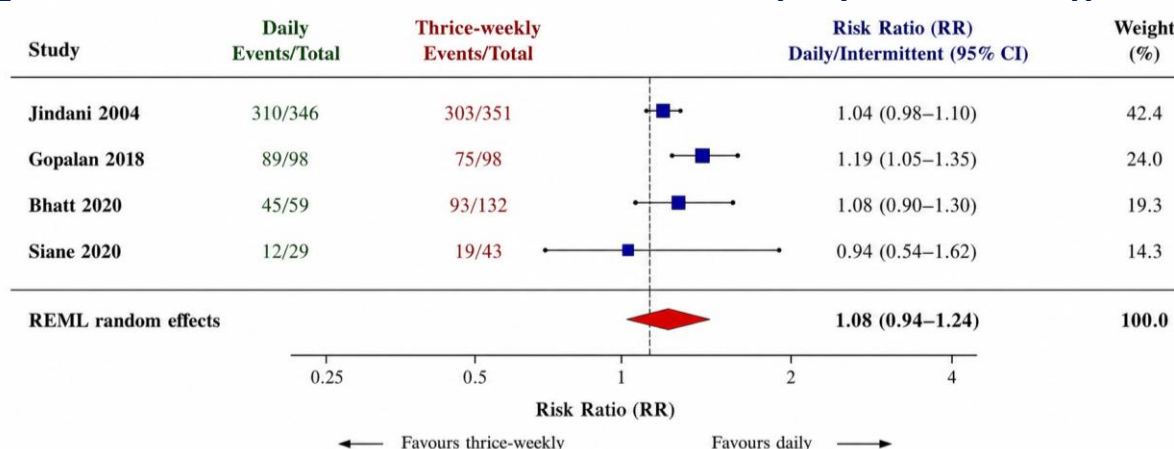
correspond to approximately 45/59 versus 93/132, while Siane reported 12/29 versus 19/43.

Table 4: Favourable Treatment Outcome: Daily Versus Thrice-Weekly Regimens

Study	Daily	Thrice-weekly comparison	RR for favourable outcome, daily/intermittent (95% CI)
Jindani, 2004	310/346	303/351	1.04 (0.98–1.10)
Gopalan, 2018	89/98	75/98	1.19 (1.05–1.35)
Bhatt, 2020	45/59	93/132	1.08 (0.90–1.30)
Siane, 2020	12/29	19/43	0.94 (0.54–1.62)

Note. Values in the Daily and Thrice-weekly columns are favourable outcomes/total participants. RR = risk ratio; CI = confidence interval. An RR > 1 indicates a higher probability of a favourable treatment outcome with daily therapy.

Figure No. 2: Forest Plot of Favourable Treatment Outcome (Daily vs Thrice weekly)



REML: restricted maximum likelihood; CI: confidence interval; RR: risk ratio; I^2 : 22.6%; τ^2 : 0.0027

Overall effect: $Z = 1.29$, $p = 0.20$

Microbiological conversion

The strongest conversion evidence came from Jindani et al. At two months, 700/828 (85%) participants assigned a daily EHRZ intensive phase were culture-negative compared with 333/433 (77%) assigned EHRZ three times weekly, giving RR 1.10 (95% CI 1.04–1.17). [5] This is a clinically important hard microbiological endpoint and supports greater early bactericidal/sterilising effectiveness with daily exposure.

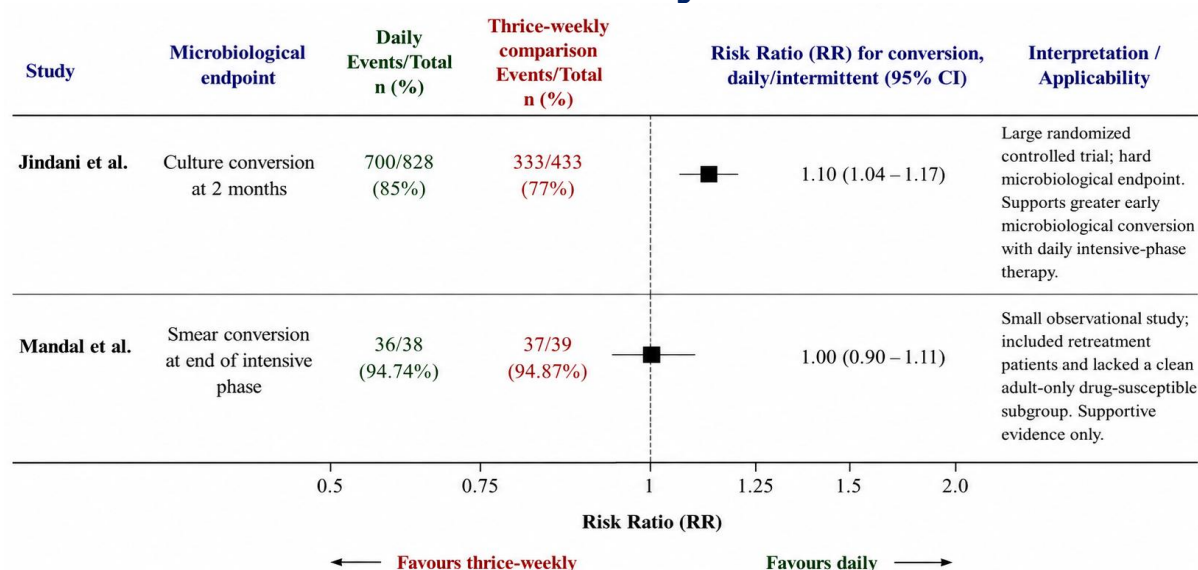
Mandal et al. found virtually identical end-intensive-phase smear conversion among those remaining evaluable—36/38 (94.74%) daily and 37/39 (94.87%) intermittent, RR 1.00 (95% CI 0.90–1.11)—but the study was observational, small, contained retreatment patients, and did not provide a clean adult-only DS subgroup. [6] Because Jindani measured culture at two months in a large RCT whereas Mandal measured smear after different Category I/II intensive-phase durations among survivors, pooling these endpoints would obscure rather than clarify the evidence.

Table 5: Microbiological Conversion with Daily Versus Thrice-Weekly Regimens

Study	Microbiological endpoint	Daily	Thrice-weekly comparison	RR for conversion, daily/intermittent (95% CI)	Interpretation/applicability
Jindani et al.	Culture conversion at 2 months	700/828 (85%)	333/433 (77%)	1.10 (1.04–1.17)	Large randomized controlled trial; hard microbiological endpoint. Supports greater early microbiological conversion with daily intensive-phase therapy.
Mandal et al.	Smear conversion at end of intensive phase	36/38 (94.74%)	37/39 (94.87%)	1.00 (0.90–1.11)	Small observational study; included retreatment patients and lacked a clean adult-only drug-susceptible subgroup. Supportive evidence only.

Note. Values in the Daily and Thrice-weekly columns are participants achieving microbiological conversion/total evaluated, with percentages in parentheses. RR = risk ratio; CI = confidence interval. An RR > 1 indicates greater microbiological conversion with daily therapy.

Figure No. 3: Forest Plot of Microbiological Conversion with Daily versus Thrice-Weekly Antitubercular Regimens



Relapse, recurrence and acquired resistance

The historical Hong Kong randomised trial provides the cleanest direct whole-course relapse comparison among drug-susceptible patients. All 833 pretreatment-DS participants had favourable bacteriological responses during chemotherapy; at 18 months after treatment, relapse was approximately 1% after daily HRZE and 2% after thrice-weekly HRZE. [1,2] The small absolute difference and

unavailable exact per-arm denominator in the retrieved report prevent a reliable RR calculation. The five-year follow-up continued to demonstrate generally low relapse among pyrazinamide-containing regimens, whereas the intermittent regimen omitting pyrazinamide performed substantially worse, demonstrating why regimen composition cannot be ignored when attributing outcomes purely to frequency. [3]

Gopalan found recurrence in 6/98 patients in both the fully daily and fully intermittent efficacy populations—RR 1.00 (95% CI 0.33–2.99)—but this occurred after a significant excess of failures had already accumulated in the intermittent arm. [7] Bhatt observed no relapse among 59 daily-SAT patients versus two relapses among 132 intermittent-DOT patients, but the estimate is extremely imprecise and susceptible to differential follow-up. [8] These sparse direct relapse data do not justify a precise pooled estimate.

Acquired resistance strengthens the argument against intermittent dosing. In Gopalan, all four cases of acquired rifampicin resistance occurred in the intermittent arm, and the trial was stopped after the daily-versus-intermittent efficacy boundary was crossed. [7] This finding is biologically and clinically concordant with the broader RCT evidence synthesis, in which thrice-weekly therapy throughout was associated with adjusted incidence-rate ratios of 2.2 for relapse, 3.7 for failure and 10.0 for acquired drug resistance compared with daily therapy. WHO similarly cites lower acquired-resistance risk with daily dosing when explaining its present recommendation.

Adverse events and hepatotoxicity

Gopalan supplies the most reliable direct safety comparison. Any treatment-emergent adverse drug reaction was recorded in 30/111 (27%) daily versus 19/110 (17%) intermittent, RR 1.56 (95% CI 0.94–2.61). Grade 3–4 gastrointestinal/hepatic reactions were 11 versus 2, and jaundice occurred in 11 daily versus two intermittent participants. When both regimens containing a daily intensive phase were combined, hepatotoxicity occurred in 19/221 (9%) versus 2/110 (2%) receiving intermittent intensive-phase therapy. No drug-induced deaths were reported. [7]

The smaller observational studies were inconsistent. Siane recorded adverse effects in only 1/29 daily versus 6/43 intermittent patients, although more than half of the cohort was lost to follow-up and the investigators explicitly could not determine whether some losses were toxicity-related. [9] Mandal reported any adverse reaction in 14/40 (35%) daily versus 11/43 (25.6%) intermittent participants; Bhangari reported 19/55 versus 12/50. [6,10]

An exploratory random-effects sensitivity meta-analysis of these four safety datasets gave RR 1.41 (95% CI 0.82–2.42; I^2 0%) for any adverse event with daily versus intermittent treatment. The apparently low statistical heterogeneity should not be mistaken for clinical homogeneity: populations, surveillance intensity, treatment phase, and study quality differed substantially.

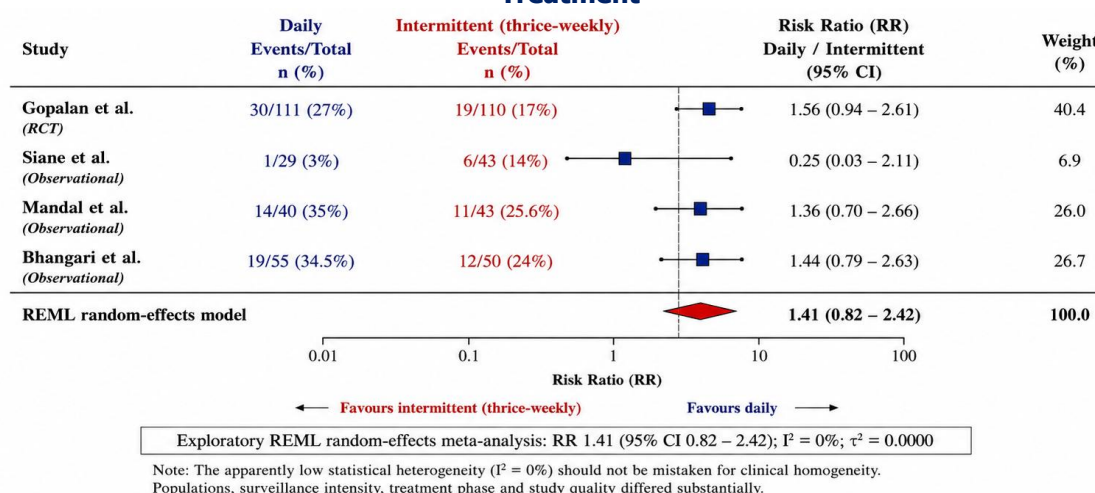
Table 6: Adverse Events With Daily Versus Thrice-Weekly Antitubercular Regimens

Study	Design	Safety outcome	Daily	Thrice-weekly	RR, daily/intermittent (95% CI)	Interpretation/applicability
Gopalan et al.	Randomized clinical trial	Any treatment-emergent ADR	30/111 (27.0%)	19/110 (17.3%)	1.56 (0.94–2.61)	Most reliable direct safety comparison. Grade 3–4 gastrointestinal/hepatic reactions: 11 vs 2; jaundice: 11 vs 2. No drug-induced deaths.
Siane et al.	Retrospective observational study	Any adverse effect	1/29 (3.4%)	6/43 (14.0%)	Not stated	>50% LTFU; investigators could not determine whether some losses were toxicity-related. High risk of incomplete safety ascertainment.
Mandal et al.	Observational comparative study	Any adverse reaction	14/40 (35.0%)	11/43 (25.6%)	Not stated	Small non-randomized study; safety surveillance and population differed from the randomized evidence.
Bhangari et al.	Retrospective comparative study	Any adverse reaction	19/55 (34.5%)	12/50 (24.0%)	Not stated	Retrospective evidence with potential differences in ascertainment and baseline characteristics.
Exploratory REML	Sensitivity meta-analysis	Any adverse event	—	—	1.41 (0.82–2.42)	I^2 = 0%. Statistical homogeneity should not be interpreted as clinical homogeneity because populations,

Study	Design	Safety outcome	Daily	Thrice-weekly	RR, daily/intermittent (95% CI)	Interpretation/applicability
random effects						surveillance intensity, treatment phase, and study quality differed substantially.

Note. Values are participants experiencing an adverse event/total participants, with percentages in parentheses where reported. ADR = adverse drug reaction; RR = risk ratio; CI = confidence interval; LTFU = loss to follow-up; REML = restricted maximum likelihood. An RR > 1 indicates a higher risk of adverse events with daily therapy. The pooled estimate is exploratory because of substantial clinical and methodological heterogeneity.

Figure No. 4: Forest Plot of Adverse Events with Daily versus Intermittent Antitubercular Treatment



Hepatotoxicity – direct comparison from Gopalan et al. 2018

Safety outcome	Daily (n/N, %)	Intermittent (thrice-weekly) (n/N, %)	Risk Ratio (RR) (95% CI)
Grade 3–4 gastrointestinal/hepatic reactions	11/111 (9.9%)	2/110 (1.8%)	5.50 (1.27 – 23.79)
Jaundice	11/111 (9.9%)	2/110 (1.8%)	5.50 (1.27 – 23.79)
Hepatotoxicity – combined daily intensive-phase regimens	19/221 (8.6%)	2/110 (1.8%)	4.74 (1.12 – 20.15)
Drug-induced deaths	0/221 (0%)	0/110 (0%)	—

RCT: randomized controlled trial; RR: risk ratio; CI: confidence interval; REML: restricted maximum likelihood.

Mortality, adherence, default and loss to follow-up

Mortality differences were too sparse and confounded for a robust pooled conclusion. In Gopalan, deaths during therapy numbered **4/111 daily versus 5/110 intermittent**. [7] Bhatt reported death in **6.8% of daily versus 5.3% of intermittent** patients. [8] In Malawi's high-HIV-prevalence programme, mortality among 2,671 patients placed on the evaluated intermittent regimen was 23%; concurrent overall comparisons were reportedly similar, although a higher early death rate in the first month was

noted with the intermittent regimen. [4] Because these studies span radically different HIV epidemiology, antiretroviral eras, and regimen composition, the absence of a pooled mortality difference should not be interpreted as proof of equivalence.

Adherence outcomes likewise depended strongly on how treatment was delivered. Bhatt found default in **7/59 (11.9%) daily SAT versus 24/132 (18.2%) intermittent DOT**, despite the expectation that direct observation might favour adherence. [8] Siane found extremely high and nearly equal LTFU—**15/29 (51.7%) daily and 23/43 (53.5%) intermittent**—limiting all efficacy comparisons.

[9] Mandal and Bhangari, retained only as sensitivity evidence, also numerically favoured daily therapy for default. [6,10]

An exploratory synthesis including these observational data gave RR 0.79 (95% CI 0.41–1.55; I² 1.7%) for

default/LTFU with daily versus intermittent treatment. The estimate is highly imprecise and does not support the premise that thrice-weekly DOT inherently improves retention.

Table 7: Mortality and Adherence Outcomes with Daily Versus Intermittent Antitubercular Treatment

A. Mortality outcomes

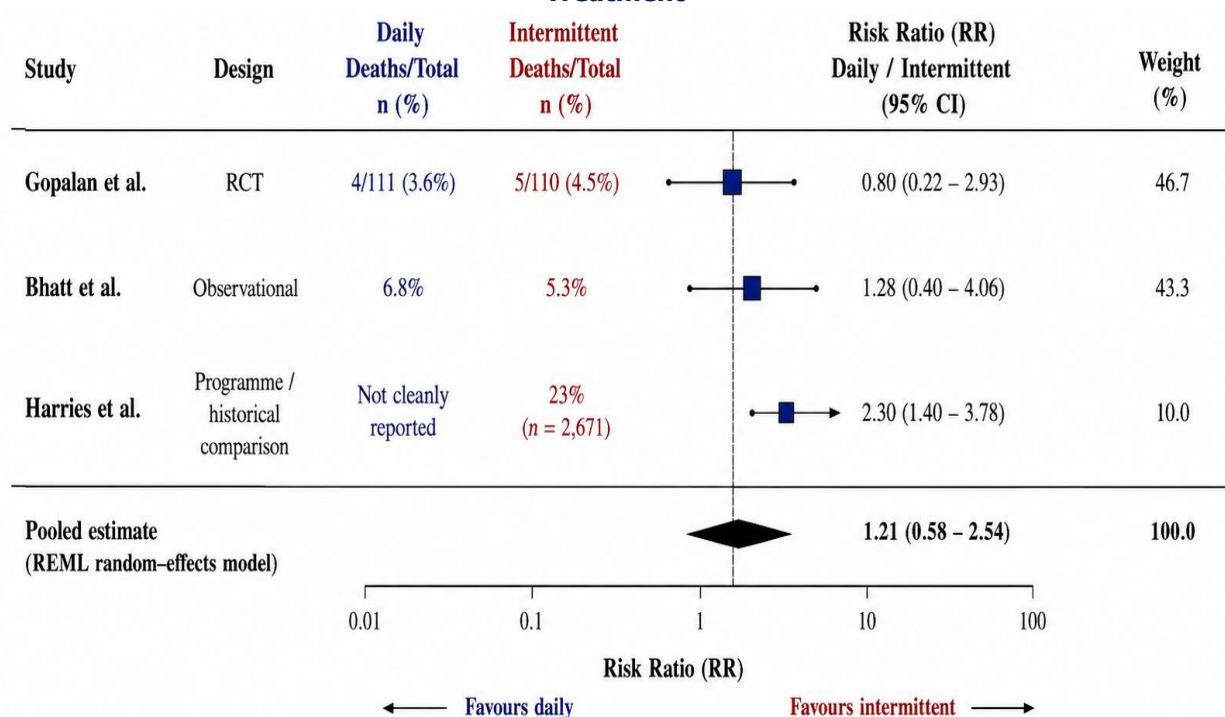
Study	Design	Daily	Intermittent	Interpretation/applicability
Gopalan et al.	RCT	4/111 (3.6%)	5/110 (4.5%)	Sparse deaths; direct randomized comparison.
Bhatt et al.	Observational	6.8%	5.3%	Small absolute difference; susceptible to confounding.
Harries et al.	Programme/historical comparison	Not cleanly reported	23% (intermittent cohort; n = 2,671)	High-HIV-prevalence Malawi programme; concurrent overall comparisons reportedly similar, but a higher early first-month death rate was noted with intermittent treatment. Major HIV-era, health-system and regimen confounding.

B. Default / loss-to-follow-up outcomes

Study	Outcome	Daily	Intermittent	Interpretation/applicability
Bhatt et al.	Default	7/59 (11.9%)	24/132 (18.2%)	Daily SAT versus intermittent DOT; numerically favoured daily treatment despite direct observation in the intermittent arm.
Siane et al.	LTFU	15/29 (51.7%)	23/43 (53.5%)	Extremely high and nearly equal attrition; severely limits efficacy comparisons.
Mandal et al.	Default	Numerically lower	Numerically higher	Supportive/sensitivity evidence only; numerically favoured daily therapy.
Bhangari et al.	Default	Numerically lower	Numerically higher	Supportive/sensitivity evidence only; numerically favoured daily therapy.
Exploratory random-effects synthesis	Default/LTFU	—	—	RR = 0.79 (95% CI [0.41, 1.55]); I ² = 1.7%. Highly imprecise and does not establish superior retention with thrice-weekly DOT.

Note. RCT = randomized controlled trial; SAT = self-administered treatment; DOT = directly observed treatment; LTFU = loss to follow-up; RR = risk ratio; CI = confidence interval. For default/LTFU, an RR < 1 favours daily therapy. The pooled default/LTFU estimate is exploratory and should be interpreted cautiously because of imprecision and differences in study design and treatment delivery.

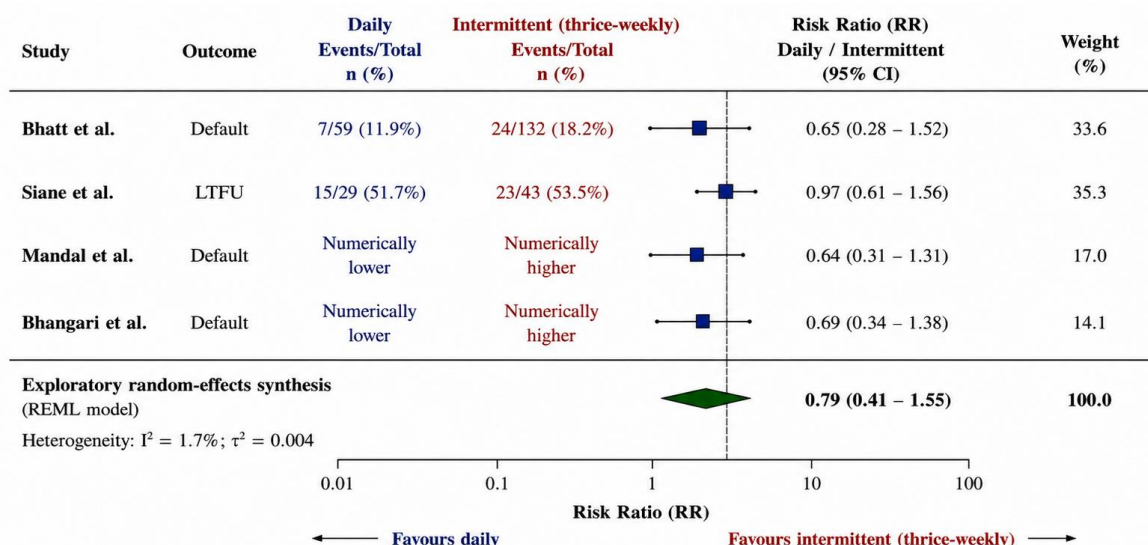
Figure No. 5: Forest Plot of Mortality with Daily versus Intermittent Antitubercular Treatment



NOTE: Mortality data are sparse and highly heterogeneous. These studies differ markedly in HIV prevalence, antiretroviral era, health-system context, regimen composition and reporting. Absence of a pooled mortality difference should not be interpreted as evidence of equivalence.

RCT: randomized controlled trial; RR: risk ratio; CI: confidence interval; REML: restricted maximum likelihood.

Figure No. 6: Forest Plot of Default/Loss-to-Follow-up with Daily versus Intermittent Antitubercular Treatment



NOTE: Exploratory synthesis includes observational data with substantial clinical and methodological heterogeneity. The pooled estimate is highly imprecise and does not support the premise that thrice-weekly DOT inherently improves retention compared with daily treatment.

RR: risk ratio; CI: confidence interval; REML: restricted maximum likelihood; I^2 : inconsistency statistic.

Subgroup findings

The most credible treatment-effect modification signal concerns HIV. In the HIV-positive RCT, fully daily therapy produced a 14-percentage-point absolute improvement in favourable outcome over fully thrice-weekly therapy and eliminated the acquired-rifampicin-resistance events seen in the intermittent arm. [7] This is consistent with the pharmacological concern that intermittent rifamycin exposure is particularly hazardous when bacterial burden, immunosuppression, malabsorption or baseline INH resistance reduce regimen robustness.

Among HIV-negative adults, Bhatt's observational study found no statistically clear difference in overall programme outcome, although point estimates favoured daily therapy for treatment success and default. [8] Its interpretation is limited because daily therapy was self-administered whereas intermittent treatment was directly observed.

Among patients with diabetes, Siane found no convincing difference between daily and thrice-weekly continuation therapy, but treatment success was only 41–44% because approximately half were lost to follow-up, and the study was substantially underpowered. [9] This cannot establish equivalence in TB-DM.

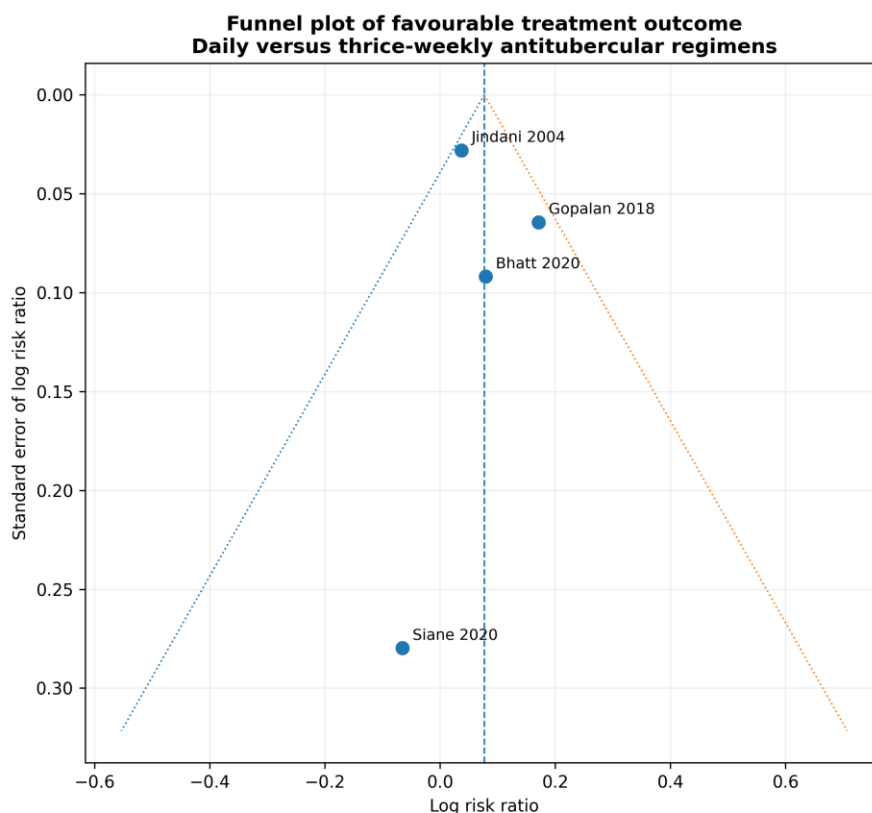
The effect also appears related to which phase is intermittent. Jindani showed significantly poorer two-month culture conversion when the intensive phase alone was thrice weekly. [5] Siane's continuation-only comparison showed no difference but was low quality and severely attrited. [9] Gopalan, in which the entire six-month course was thrice weekly, demonstrated the clearest clinically important inferiority. [7] This pattern is compatible with WHO's decision not to recommend thrice-weekly dosing in either phase.

Table 8: Certainty of Evidence Assessment for Daily Versus Thrice-Weekly Antitubercular Treatment

Outcome	Evidence base	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect estimate/evidence summary	Certainty	Rationale
Favourable treatment outcome	4 studies (RCT + observational)	Serious	Not serious	Serious	Serious	None identified	RR 1.08 (95% CI 0.94–1.24); $I^2 = 22.6\%$	Low	Pooled estimate is imprecise and crosses the null. Evidence is weakened by inclusion of observational studies and clinically heterogeneous regimen structures.
Microbiological conversion	2 studies (1 RCT + 1 observational)	Serious	Serious	Not serious	Serious	None identified	Jindani: RR 1.10 (95% CI 1.04–1.17); Mandal: RR 1.00 (95% CI 0.90–1.11); not pooled	Low	Large RCT supports better 2-month culture conversion with daily therapy, but the second study measured smear conversion in a different population and treatment context.
Any adverse event	4 studies (RCT + observational)	Serious	Serious	Not serious	Serious	None identified	Exploratory RR 1.41 (95% CI 0.82–2.42); $I^2 = 0\%$	Very low	Wide confidence interval and substantial clinical/methodological heterogeneity despite low statistical heterogeneity; adverse-event surveillance differed across studies.
Hepatotoxicity / severe hepatic events	Primarily 1 RCT	Not serious	Serious	Not serious	Very serious	None identified	Hepatotoxicity 19/221 vs 2/110; severe GI/hepatic reactions	Low	Direct randomized evidence suggests more hepatic toxicity with regimens

Outcome	Evidence base	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect estimate/evidence summary	Certainty	Rationale
							11/111 vs 2/110		containing a daily intensive phase, but estimates are based on few events and limited comparative data.
Mortality	3 heterogeneous comparative datasets	Serious	Very serious	Serious	Very serious	None identified	No pooled estimate; deaths sparse and comparisons strongly confounded	Very low	Differences in HIV prevalence, ART era, programme context and regimen composition make a pooled mortality conclusion unreliable.
Default/loss to follow-up	4 studies, predominantly observational	Very serious	Serious	Not serious	Very serious	None identified	Exploratory RR 0.79 (95% CI 0.41–1.55); $I^2 = 1.7\%$	Very low	Estimate is highly imprecise; adherence is strongly confounded by treatment delivery (SAT vs DOT), attrition, and study design.
Acquired drug resistance	Limited direct comparative evidence	Serious	Serious	Not serious	Very serious	None identified	Events uncommon; signal favours daily therapy in the strongest randomized evidence	Low	Clinically critical outcome, but the number of resistance events is small and compatible data across studies are limited.

Note. Certainty was assessed across the domains of risk of bias, inconsistency, indirectness, imprecision, and other considerations. RCT = randomized controlled trial; RR = risk ratio; CI = confidence interval; GI = gastrointestinal; HIV = human immunodeficiency virus; ART = antiretroviral therapy; SAT = self-administered treatment; DOT = directly observed treatment. Certainty categories are reported as low or very low in accordance with the assessment presented in the review.



Exploratory only: 4 studies. Funnel-plot asymmetry and publication bias cannot be reliably assessed with <10 studies.

Figure No. 7. Funnel plot of favourable treatment outcomes comparing daily versus thrice-weekly antitubercular regimens.

The funnel plot displays the log risk ratio against its standard error for the four studies contributing to the exploratory synthesis of favourable treatment outcomes. The vertical dashed line represents the pooled random-effects effect estimate, while the diagonal lines delineate the approximate 95% pseudo-confidence limits. The larger studies (Jindani 2004, Gopalan 2018, and Bhatt 2020) cluster relatively close to the pooled estimate, whereas the smaller Siane 2020 study lies further from the centre with substantially greater standard error. Although some visual asymmetry is apparent, the very small number of studies ($n = 4$) precludes meaningful assessment of funnel-plot asymmetry, small-study effects, or publication bias. Accordingly, the funnel plot should be regarded as exploratory and descriptive rather than as evidence for or against publication bias.

Discussion

This systematic synthesis yields a clinically important distinction: programme-level “treatment success” can appear similar even when hard microbiological outcomes favour daily therapy. The pooled favourable-outcome RR of 1.08 did not reach conventional statistical significance, but this result is generated from heterogeneous studies in which treatment success is heavily influenced by LTFU, supervision, duration and outcome definition. It therefore cannot be used as evidence that thrice-weekly therapy is non-inferior. In contrast, the large, randomised evidence for early culture conversion, the contemporary whole-course HIV RCT, acquired rifampicin resistance data, and the broader RCT relapse evidence all move in the same direction—towards greater microbiological robustness with daily dosing 3.

The Gopalan RCT is particularly influential because it isolates the question more closely than most historical comparisons. The fully daily and fully intermittent arms used the same drug classes and six-month structure—2EHRZ₇/4HR₇ versus 2EHRZ₃/4HR₃—and treatment allocation was concealed and stratified. Its 91% versus 77% favourable response and confinement of acquired rifampicin resistance to intermittent therapy provide direct evidence that three doses weekly can be biologically insufficient in a vulnerable host despite ART. The trial's HIV-positive population limits generalisability to immunocompetent adults but increases, rather than diminishes, its policy importance for high-risk groups [8].

The Jindani trial adds a complementary finding: reducing only the intensive-phase frequency from daily to three times weekly impaired early culture conversion from 85% to 77%, even when the continuation regimen was the same. This suggests that intermittent exposure can matter before any difference in subsequent adherence or continuation treatment arises. Its eight-month HE continuation regimen is no longer a preferred standard, so its long-term outcome estimate is indirect for modern 2HRZE/4HR; the two-month culture comparison, however, remains highly relevant mechanistically [3].

The Yu X et al. trial is sometimes invoked as evidence that thrice-weekly treatment “works,” and that interpretation is partly correct: well-constructed, fully supervised intermittent regimens containing rifampicin and pyrazinamide achieved excellent outcomes under trial conditions. But “effective” is not synonymous with “equivalent to daily”. The HRZE₃ regimen had roughly 2% relapse versus 1% with daily HRZE, and the trial was not designed or powered as a modern non-inferiority comparison of dosing frequency. Moreover, when one intermittent regimen lacked pyrazinamide, relapse rose markedly, illustrating the narrow margin within which intermittent therapy can remain robust [6].

The prior RCT-wide synthesis is therefore highly informative despite being indirect. Its pooled relapse estimates—6.8% thrice weekly versus 2.5% daily—and adjusted increases in failure, relapse and acquired drug resistance helped resolve uncertainty that the comparatively few head-to-head trials could not resolve alone 4. WHO's current guidance reflects this total evidence base: daily treatment is recommended as the optimal frequency, and thrice-weekly treatment is not recommended in either phase [2].

Safety requires a balanced interpretation.

More frequent dosing increases cumulative drug exposures and may increase some toxicities. Gopalan's excess of hepatotoxic events with daily intensive-phase therapy is credible because adverse events were systematically recorded and the comparison was randomised. Nevertheless, serious toxicity remained manageable, no drug-related deaths occurred, and the efficacy/resistance benefit was substantial. Consequently, the rational response to treatment toxicity is careful assessment, temporary interruption where indicated, identification of the causative agent, dose/regimen modification according to guidelines, and monitoring—not routine substitution of an inferior intermittent schedule.

Conversely, the observational adverse-event signal is inconsistent. Siane found more recorded symptoms with thrice-weekly continuation therapy, whereas Mandal and Bhangari found more with daily therapy. These inconsistencies probably reflect differences in active versus passive toxicity surveillance, treatment phase, diabetes/HIV, loss to follow-up, and small samples, as much as true pharmacological differences. The GRADE certainty for overall adverse events is therefore low.

Adherence is not an argument for intermittent pharmacology by itself. The premise of historical intermittent DOTS was that fewer supervised encounters might facilitate treatment delivery. Yet a missed dose in a thrice-weekly regimen removes a much larger fraction of effective weekly treatment than a single missed dose during daily therapy; WHO explicitly cites this vulnerability when explaining its preference for daily dosing 2. Moreover, Bhatt's daily self-administered cohort had numerically fewer defaults than the intermittent directly observed cohort despite the latter's supervision. The correct policy inference is to improve patient-centred adherence support around a microbiologically robust daily regimen rather than lower drug exposure to accommodate the supervision model.

The distinction between DOT and dosing frequency also explains some apparent contradictions in the literature. Bhatt's comparison altered both variables simultaneously: daily patients self-administered drugs, while intermittent patients received DOT. A finding of similar outcomes in such a study could mean that the pharmacological advantage of daily therapy offsets poorer supervision, that motivated patients selected daily therapy, or both. It cannot establish that the pharmacological schedules are equivalent. Future observational comparisons should separate frequency, formulation, supervision modality, and treatment support analytically.

The current policy context is consequently coherent with the evidence. WHO recommends daily 2HRZE/4HR for eligible DS-TB and explicitly does not recommend thrice-weekly therapy in either phase. India's Ministry of Health announced its national switch in November 2017 from the previous three-times-weekly regimen to daily FDCs, including adherence-support mechanisms. This means that, for routine adult DS pulmonary TB in India in 2026, the historical thrice-weekly regimen is a comparator of historical and research interest, not an alternative standard regimen 1,2.

Implications for practice.

For adults with rifampicin- and isoniazid-susceptible pulmonary TB who are receiving a conventional six-month first-line regimen, the evidence favours administering the regimen daily rather than three times per week. This conclusion is strongest for patients with HIV and for preventing microbiological failure/acquired resistance, but there is no convincing evidence base supporting routine thrice-weekly treatment in HIV-negative adults either. WHO's recommendation encompasses the broader DS-TB population.

"Daily DOTS" should not necessarily be interpreted as requiring seven clinic-based directly observed encounters every week. The pharmacological requirement is daily dosing; supervision and adherence support should be designed around patient circumstances. WHO explicitly separates treatment frequency from the requirement that national programmes provide supervision and support for treatment completion.

Policy implications.

National programmes should not revert to intermittent treatment solely to reduce service-contact burden. Programme efficiencies should instead come from fixed-dose combinations, decentralised dispensing, digital or community adherence support, differentiated care and reliable drug supply while preserving daily drug exposure. India's 2017 change specifically combined daily FDCs with information-technology-enabled adherence support, illustrating that adherence infrastructure can change without reducing pharmacological intensity.

Research gaps.

A new RCT deliberately testing fully thrice-weekly against daily conventional treatment would be difficult to justify now that WHO advises against thrice-weekly DS-TB therapy. More valuable research questions include comparative effectiveness of patient-centred delivery

models for daily therapy; predictors and prevention of hepatotoxicity under daily first-line treatment; individual-patient-data analyses of intermittent historical trials by HIV, cavitation, baseline bacillary burden, acetylator status and initial INH resistance; post-programme-switch cohort analyses that control for diagnostic and support improvements; and pharmacological studies clarifying how missed daily doses, rather than planned intermittency, influence sterilising exposure.

An individual-patient-data meta-analysis of the historical trials could be particularly useful. Trial-arm meta-regression has already shown an excess of relapse, failure and acquired resistance with thrice-weekly therapy, but individual data could determine whether this excess concentrates among patients with cavitation, delayed conversion, HIV, low drug exposure or unsuspected baseline monoresistance.

Conclusion

Daily antitubercular therapy provides the more robust microbiological strategy for drug-susceptible pulmonary TB, with stronger evidence for early culture conversion, favourable treatment outcomes, and prevention of acquired drug resistance. Although historical thrice-weekly DOTS regimens achieved high cure rates, the available evidence does not establish their non-inferiority to contemporary daily therapy. The pooled treatment-success estimate was imprecise and should not be interpreted as equivalence, while the most clinically relevant microbiological outcomes consistently favoured daily exposure. Any potential increase in toxicity with daily treatment appears insufficient to outweigh its efficacy and resistance-prevention advantages. Therefore, guideline-concordant daily therapy should remain the standard of care, and planned thrice-weekly DOTS should not be preferred for adults with drug-susceptible pulmonary tuberculosis.

Limitations

This review has several limitations. The number of trials directly comparing otherwise similar daily and thrice-weekly regimens was small, and substantial heterogeneity existed in treatment duration, drug combinations, and the phase in which intermittent therapy was administered. Historical studies also used variable definitions of drug-susceptible tuberculosis and often lacked contemporary baseline drug-susceptibility testing. Observational studies were susceptible to confounding by treatment era, treatment selection, and differences between directly observed and self-administered therapy. Outcome definitions and adverse-event ascertainment were inconsistent, with substantial loss to follow-up in some studies. Consequently,

pooled estimates should be regarded as exploratory rather than evidence of non-inferiority or equivalence.

Recommendations

Based on the available direct randomized evidence, supportive observational data, microbiological outcomes, acquired drug-resistance findings, and current international guidance, daily antituberculosis therapy should remain the preferred dosing strategy for adults with drug-susceptible pulmonary tuberculosis, and planned thrice-weekly treatment should not be used as a routine alternative to daily therapy.

The principal rationale for this recommendation is microbiological rather than merely programmatic. Although the pooled estimate for favourable treatment outcome was imprecise and did not demonstrate a statistically significant overall difference, this finding should not be interpreted as evidence of equivalence or non-inferiority. More specific microbiological outcomes provide a more consistent signal in favour of daily exposure, including superior early culture conversion in randomized evidence and fewer clinically important failures and acquired rifampicin-resistance events in the most directly applicable whole-course randomized comparison.

Accordingly, the following clinical and programmatic recommendations are proposed:

1. **Daily dosing should be maintained throughout both the intensive and continuation phases of conventional first-line treatment for drug-susceptible pulmonary tuberculosis unless an alternative evidence-based regimen is specifically indicated.**
2. **Planned thrice-weekly dosing should not be reintroduced as a strategy to reduce treatment burden, health-system workload, or the number of supervised treatment encounters.** The logistical advantages of fewer treatment contacts do not adequately compensate for the potential increase in microbiological failure, relapse, and selection of acquired drug resistance.
3. **Dosing frequency should be separated conceptually from treatment supervision.** Daily pharmacotherapy does not require daily facility-based directly observed treatment. Where treatment burden is problematic, programmes should preserve daily drug exposure while improving patient-centred adherence through decentralized dispensing, community-based support, digital adherence technologies, treatment

supporters, and other locally appropriate mechanisms.

4. **Particular caution against intermittent treatment is warranted in patients at increased risk of poor microbiological outcomes**, including people living with HIV, patients with high bacillary burden or cavitary disease, those with delayed microbiological conversion, suspected malabsorption, poor adherence, or baseline drug resistance. However, the present review does not provide sufficiently robust subgroup data to quantify differential treatment effects for all of these populations, and these recommendations should therefore be interpreted alongside contemporary TB guidelines.
5. **Drug toxicity should be actively monitored rather than managed by routinely reducing treatment frequency.** The randomized evidence suggests that daily exposure may increase some hepatic adverse events, particularly in vulnerable populations. Appropriate clinical and biochemical monitoring, temporary treatment interruption when indicated, identification of the responsible drug, and guideline-directed rechallenge or regimen modification are preferable to planned intermittent dosing.
6. **Baseline molecular or phenotypic drug-susceptibility testing should be obtained whenever feasible.** The potential for intermittent drug exposure to facilitate acquired resistance makes early recognition of pre-existing rifampicin or isoniazid resistance particularly important.
7. **Treatment programmes should monitor microbiological outcomes in addition to conventional programme-level treatment success.** Culture or smear conversion, treatment failure, recurrence, and acquired drug resistance may provide more clinically informative indicators of regimen robustness than composite treatment-success measures that are strongly influenced by loss to follow-up and treatment-delivery factors.
8. **Future research should focus on optimizing the delivery of daily therapy rather than re-establishing the efficacy of planned thrice-weekly treatment.** Priorities should include identifying predictors of toxicity and poor drug exposure, determining the consequences of missed doses during daily therapy, evaluating patient-centred and digital adherence strategies, and

examining outcomes in clinically vulnerable subgroups.

9. **Individual-patient-data meta-analysis of historical randomized trials should be prioritized.** Such analyses could determine whether the adverse effects of intermittent dosing are concentrated among patients with HIV infection, cavitary disease, high baseline bacillary burden, delayed culture conversion, low antituberculosis-drug exposure, rapid acetylator phenotype, or unsuspected baseline isoniazid resistance.

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Conflict of Interest

The authors declare that they have no competing interests or conflicts of interest relevant to the content of this manuscript.

Ethics Approval and Consent to Participate

Ethics committee approval and individual informed consent were not required because this systematic review synthesised data from previously published studies and did not involve the recruitment of new human participants or access to identifiable individual-level participant information.

Data Availability Statement

All data used in this systematic review were derived from published studies and publicly available sources cited in the manuscript. The study-level data used for quantitative synthesis should be provided in the manuscript and/or supplementary materials. The completed data-extraction dataset and statistical analysis files may additionally be made available as supplementary material or through a suitable open repository.

Protocol and Registration

The protocol for this systematic review was not prospectively registered.

Abbreviations

ADR	—	Adverse	drug	reaction
ART	—	Antiretroviral		therapy
CI	—	Confidence		interval
DM	—	Diabetes		mellitus
DOT	—	Directly	observed	treatment
DOTS	—	Directly	observed	treatment, short-course
DS-TB	—	Drug-susceptible		tuberculosis
DST	—	Drug-susceptibility		testing
FDC	—	Fixed-dose		combination
GRADE	—	Grading of Recommendations	Assessment,	
Development		and	Evaluation	
HIV	—	Human	immunodeficiency	virus
INH	—			Isoniazid
ITT	—			Intention-to-treat
LTFU	—	Loss	to	follow-up
mITT	—	Modified		intention-to-treat
MDR-TB	—	Multidrug-resistant		tuberculosis
PRISMA	—	Preferred Reporting Items for Systematic		
Reviews		and	Meta-Analyses	
PTB	—	Pulmonary		tuberculosis
RCT	—	Randomized	controlled	trial
REML	—	Restricted	maximum	likelihood
RIF	—			Rifampicin
ROBINS-I	—	Risk Of Bias In Non-randomized Studies of		
Interventions				
RoB 2	—	Cochrane Risk of Bias tool, version 2		
RR	—		Risk	ratio
RR-TB	—	Rifampicin-resistant		tuberculosis
SAT	—	Self-administered		treatment
TB	—			Tuberculosis
WHO	—	World Health Organization		

Authorship contribution

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Snehasini Dash: Investigation, Data curation, Validation, Writing – review & editing.

Pratyush Mishra: Methodology, Investigation, Validation, Data curation, Risk-of-bias assessment, Writing – review & editing.

Srikanta Panigrahy: Investigation, Data curation, Validation, Writing – review & editing.

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