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Systematic Review

Efficacy & safety of high-dose rifampicin in pulmonary tuberculosis: A systematic review & meta-analysis

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***Background & objectives*: Evidence suggests that higher doses of rifampicin aid in faster culture conversion, but its effects on unfavourable outcomes are unclear. We aimed to synthesise evidence on the efficacy and safety of high-dose rifampicin (>15 mg/kg) containing anti-tuberculosis regimen compared to a regimen with standard dose of rifampicin in adults with pulmonary tuberculosis.**

***Methods*: We searched for studies from MEDLINE, Embase, Web of Science, Google Scholar, and the Cochrane Library without geographical restriction. We included randomised controlled trials that evaluated high-dose rifampicin (>15 mg/kg for 8 wk) with a six-month duration. Our outcomes of interest were sputum conversion at eight wk, mortality, treatment failure at six months, Grade 3 and Grade 4 hepatotoxicity, and adverse events leading to treatment discontinuation. Two authors independently screened titles, abstracts, and full texts and extracted data. We performed a meta-analysis using the RevMan web software as per the Cochrane Handbook for Systematic Reviews of Interventions.**

***Results*: Out of 3950 articles screened, we included nine for meta-analysis. High-dose rifampicin (≥15 mg/kg) showed little benefit compared to the standard dose for sputum conversion at eight wk [(83% *vs*. 78%, Relative risk (RR) 1.05 (95% confidence interval (CI): 1.0-1.09), Number needed to treat (NNT)-24)] and this benefit was higher as the rifampicin dose increased [20-30 mg RR: 1.07 (95% CI 1.02-1.14), NNT-17]; >30 mg RR: 1.12 (95% CI 1.04 -1.20) NNT-9]. However, treatment failure and mortality showed no benefit with high-dose rifampicin. Grade 3 and 4 hepatotoxicity and treatment discontinuation due to toxicity had a dose-response relationship and were significantly higher in the more than 30 mg/kg group [RR: 4.01 (95%CI 1.75-9.19), Number needed to harm -20].**

***Interpretation & conclusions*: High doses of rifampicin (≥15 mg/kg) increased the rate of sputum culture conversion after two months of the intensive phase. There was no difference in mortality and treatment failure between high-dose rifampicin and standard arms. In the subgroup analysis, the 20-30 mg/kg dose exhibited a beneficial effect in sputum conversion with no significant risk of hepatotoxicity and adverse drug reactions (ADR) leading to treatment discontinuation. This dose could be administered with close**

Tuberculosis (TB) is curable but still remains the most common cause of death due to infectious diseases, with an estimated 1.3 million deaths globally in 2022[1]. Since 1994, the first line of TB treatment has been chemotherapy combined with isoniazid (H), rifampicin (R), ethambutol (E), and pyrazinamide (Z). The first three drugs have been part of the World Health Organization (WHO)-recommended TB treatment

monitoring of adverse events and hepatotoxicity. There is an urgent need for adequately powered trials that assess long-term treatment outcomes, including recurrence.

Key words Culture conversion - high-dose rifampicin - pulmonary tuberculosis - rifampicin - safety and efficacy

regimens since the 1980s[2,3]. Rifampicin was added to the already discovered drugs, such as isoniazid and Ethambutol, in the 1970s. Eventually, the introduction of pyrazinamide replacing streptomycin in the 1980s was a major event in designing the short-course chemotherapy of six to eight months of treatment duration[4]. Rifampicin plays an important role in TB treatment regimens, because of its potent bactericidal and sterilising capacity, and also as a potential treatment shortening agent[5].

Contemporarily, the standard of care for pulmonary TB is HRZE for eight wk, followed by HR for the next 24 wk. Longer durations and adverse events that impact drug compliance may lead to unfavourable TB treatment outcomes[6]. Currently, Rifampicin is given at a dose of 10 mg/kg as per the WHO recommendation[7]. Pharmacokinetic studies have shown that conventional dosage (10 mg/kg) of rifampicin is associated with sub-therapeutic concentration, which affects the TB treatment outcomes and contributes to the emergence of multidrug-resistant TB[8,9]. Hence, there is a need for modification of the existing dosage for better treatment outcomes and to achieve early culture conversion. Many trials in recent years have proven that high-dose rifampicin was efficacious and safe, but also cost-effective in the treatment of pulmonary TB[10-14]. Even though high-dose rifampicin is found beneficial, the impact of higher doses on treatment outcomes and long-term recurrence-free survival is unclear.

According to a systematic review and meta-analysis that informed WHO recommendations, higher doses of rifampicin may reduce treatment failure rates, recurrence, and all-cause mortality due to tuberculosis; however, the evidence for these outcomes is unclear or low[15]. Steingart *et al*[16], in their systematic review, concluded that high-dose rifampicin at 900 mg had an increased culture conversion rate. A systematic review done by Onorato *et al*[17] demonstrated that patients on high-dose rifampicin, particularly on more than 20 mg/kg, had a significantly higher proportion of culture conversion. In contrast, they found no differences in treatment failure, adverse events, and mortality. There have been a few new trials evaluating high-dose rifampicin in pulmonary TB, and there is a need to update the current evidence. Hence, we performed this systematic review to synthesise evidence on the efficacy and safety of high-dose rifampicin (>15 mg/kg) containing anti-TB regimen compared to a regimen with standard dose (10 mg/kg) in adults with pulmonary tuberculosis.

Materials & Methods

Protocol and registration: We conducted a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. We registered our protocol with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42024570926).

Inclusion criteria: We included randomised control trials (RCTs) that fulfilled the PICO criteria. Our inclusion criteria were adults (≥18 yr) with pulmonary TB who were on daily anti-TB regimens with or without comorbid illnesses, either managed as inpatients or outpatients. We included trials where participants received a high-dose of rifampicin (≥15 mg/kg) for eight wk along with other first-line anti-tuberculosis medicines (ethambutol, pyrazinamide, isoniazid) in the intervention group, while the control group received a conventional dose of rifampicin (10 mg/kg). Our outcomes of interest were sputum conversion at eight weeks, mortality rates, Grade 3 or 4 hepatotoxicity, adverse drug reactions (ADR) leading to treatment discontinuation, and treatment failure. We excluded case reviews, ecological studies, case-control, cross-sectional, and other study designs. We included studies published in any language and from any country.

Definition of the outcomes: Our primary outcome was sputum conversion either by microscopy or culture at the end of eight wk. Secondary outcomes were mortality until the last follow up, Grade 3 or 4 hepatotoxicity during treatment, adverse drug reactions leading to treatment discontinuation, and treatment failure at six months.

Sputum conversion: Sputum culture conversion from a positive to negative result at the end of eight weeks of anti-TB treatment, confirmed by at least two consecutive liquid or solid culture methods.

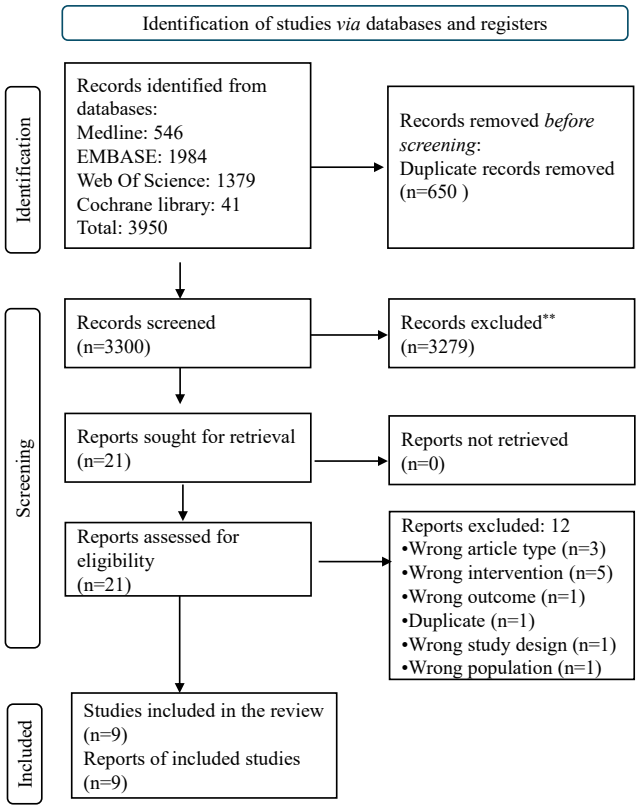

Fig. 1. PRISMA flow diagram.

Treatment failure: Sputum smear or culture positive within the last month of treatment.

Mortality: Death from any cause before the initiation, during the course of treatment, or during follow up.

Grade 3 and Grade 4 hepatotoxicity: An abnormal liver function test graded as 3 or 4 by standard criteria.

ADR leading to treatment discontinuation: Adverse events resulting in discontinuation of study medication at any time during the treatment.

Data source & search strategy: We performed the search between May 19-20, 2024 through OVID in the following databases: MEDLINE, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) in Cochrane Library. We remained restricted to articles published after 1990 as the international guidelines recommended the combination regimen of the current standard of care for drug-susceptible tuberculosis as the first-line regimen from 1990 till 2024[18]. The search strategies (Supplementary Material 1) were developed based on our PICO (participants, intervention, comparator, and outcome). We used search terms such as 'tuberculosis', 'TB', 'pulmonary tuberculosis', PTB, rifampicin, and high-dose rifampicin, and used the MeSH explode option in the OVID database. The search results from the different individual databases were downloaded as an "RIS" file and exported into Rayyan software for removing duplicates before title and abstract screening. We also manually searched the reference list of the selected articles for additional studies missed during the initial electronic search. The bibliographies of all full-text articles and previous systematic reviews were also examined for potential articles.

Data collection:

Study selection: Titles/abstracts provided by the search expert (MKS) were imported into the Rayyan software, and duplicates were excluded. Two independent reviewers (AB/JA) screened the titles and abstracts using the above mentioned PICO criteria and shortlisted potential publications for detailed assessment. Two reviewers (AB/JA) further analysed the shortlisted articles independently and documented specific reasons for exclusion. The discrepancies between the two reviewers were resolved by a third investigator (LR). All decisions made during the selection process were recorded and presented in a PRISMA flow diagram (Fig. 1).

Data extraction & Risk of bias assessment: Two independent reviewers (KB/JA) planned to extract the data from the included studies into a data extraction form. We used the Cochrane Risk of Bias (RoB) V.2.0 scale to assess bias in the included articles[19]. JA and AB assessed the articles, and LR played the role of arbitrator in resolving the discrepancies. All the outcomes were binary, and we recorded the number of events and total participants for the outcomes. RoB-2 consists of five domains that assess bias: arising from the randomisation process, due to deviation from intended intervention, due to missing outcome data, measurement of the outcome, and selection of the reported results. Each study was assigned a judgement of high risk of bias, some concerns of bias, and low risk of bias.

Statistical analysis: We performed analyses according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions using RevMan web online software. We calculated pooled risk ratios (RR) using the Mantel-Haenszel method and fixed effect models, as we assumed the effect size would be similar across the studies. We used intention-to-treat or

modified intention-to-treat analysis. We assessed the heterogeneity of treatment effects between trials using the I^2 statistic and visual examination to quantify the statistical heterogeneity. We also performed a subgroup analysis according to the dose of rifampicin (<20, 20-30, and >30 mg/kg). We reported a pooled risk ratio with a 95% Confidence interval (CI), and a $P< 0.05$ was considered significant. We assessed the certainty of the evidence using the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for reviews of interventional studies, and we made judgments separately for all the outcomes using GRADEpro GDT online software[20,21].

Results

Results of the search: We obtained 3909 articles across all databases and screened 3300 after de-duplication. We excluded 3279 and screened 21 full texts. As mentioned above, two review authors screened these full-text articles, and a third author resolved any discrepancies between them. We finally included nine studies for meta-analysis (Fig. 1). We described the reasons for exclusion in supplementary material 2.

Characteristics of the included studies and intervention: The characteristics of the nine included studies are described in table I. All included studies were individual randomised controlled trials, and three were multi-country trials[13,22,23]. The sample size ranged from 65 to 701, with a median of 300 (IQR: 165-194). Three studies used a two-month intensive phase with four drugs followed by four months of continuation phase with two drugs (3HRZE+4HR)[12,23,24]. Two trials administered two months of intensive phase with four drugs, followed by four months of continuation phase with three drugs (2HRZE+4HRE)[14,25]. In one study, participants received five months of HRE during the continuation phase (2HRZE+5HRE)[26]. In the intervention arm, Jindani *et al*[13] administered a four-month regimen (2HRZE/2HR), while Boere *et al*[11] administered 3HRZE followed by 3HR. Both used 2HRZE followed by 4HR in the control arm[11,22]. The trials of Jindani *et al*[13,22] reported a 16-wk exposure to high-dose rifampicin, whereas Boere *et al*[11] reported a 12-wk exposure. All other studies administered high-dose rifampicin for eight wk. The high-dose rifampicin dose had a range of 15 to 35 mg/kg. Five studies included individuals living with HIV (PLHIV)[11,12,23,25,26], while Sanni *et al*[23] and Atwine *et al*[26] exclusively included PLHIV. All of the studies reported outcomes by intention-to-treat analysis, except for Arantouse *et al*[25], which did not specify the type of analysis.

Table I. Key characteristics of included studies

		High dose group							Standard dose group				
Author & yr	Country	N	Regimen	Dose (mg/kg)	Duration of Rif exposure (wk)	N	Age (yr), median (IQR)	Males, n (%)	HIV, n (%)	Regimen	N	Age (yr), median (IQR)	Males, n (%)	HIV, n (%)
Jindani *et al*[13], 2016	Bolivia, Nepal, Uganda	300	2EHRZ/4HR 2EHRZ/4HR	15 20	16	R15: 100 R20: 100	27.5 (16-67) 30 (19-66)	139 (69.5)	0	2HRZE+ 4HR	100	28.5 (18-67)	66 (66)	0
Arantouse *et al*[25], 2017	Tanzania	150	2HRZE+4HRE	16 21	8	R16:50 R21:50	33.0 33.5	46 (92) 45 (90)	5 (10) 6 (12)	2HRZE+4HRE	50	35 (28-41)	44 (88)	4 (12)
Boere *et al*[11], 2017	Tanzania	186	3HRZE+3 HR	35	12	R35:63	33 (23-40)	126 (68.8)	10 (5.5)	2HRZE+4HR	123	34 (26-41)	94 (76)	9 (7)
Velasquez *et al*[12], 2017	Peru	180	2HRZE+4HR	15 20	8	R15:60 R20:60	25 (20-25) 27 (22-37)	75 (60.8)	3 (2.5)	2HRZE+4HR	60	24 (21-37)	39 (65)	2 (3.3)
Atwine *et al*[26], 2019	Uganda	65	2HRZE+5HRE	20	8	32	33.4 (28.0-36.6)	22 (71.0)	32 (100)	2HRZE+5HRE	33	34.1 (29.6-38.1)	22 (71)	33 (100)
Maug *et al*[24], 2020	Bangladesh	701	2HRZE+4HR	20	8	R20:353	45 (28-55)	260 (74)	0	2HRZE+4HR	348	42 (28-55)	251 (72.7)	0
Sanni *et al*[23], 2021	Benin	517	2HRZE+4HR	15	8	R15:259	36.5+/-10.1	146 (56.6)	100	2HRZE+4HR	258	35.9+/-9.7	141 (54.4)	259 (100)
Jindani *et al*[22], 2023	Multi country	672	2HRZE/2HR	23 34	16	R23- 223 R34- 225	29 (22-36) 28 (23-43	151 146	0	2HRZE+4HR	224	29 (23-38)	137	0
Bhavani *et al*[14], 2024	India	323	2HRZE+4HRE	25 35	8	R25:112 R35:106	33.5 35.5	82 75	0	2HRZE+4HRE	105	35.9	76 (69.7)	0

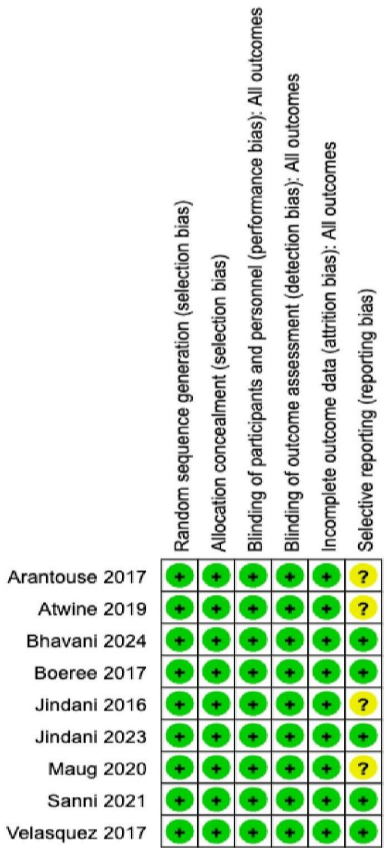

Fig. 2. Risk of bias summary.

Outcome measures: Four studies[11,14,25,26] used both solid cultures using Lowenstein–Jensen (LJ) medium and liquid cultures using Mycobacteria Growth Indicator Tube (MGIT), whereas three[12,13,24] used MGIT. Jindani *et al*[22] used Lowenstein–Jensen and Ogawa culture. Sanni *et al*[23] did not specify the culture method used to evaluate the sputum conversion.

Regarding adverse events reporting, five studies[13,14,22,23,26] used the Division of AIDS (DAIDS) for grading the adverse events[27] while two studies[11,25] referred to Common Terminology Criteria for Adverse Events (CTCAE)[28]. Velasquez *et al*[12] used the Division of Microbiology and Infectious Diseases adult toxicity table by the National Institute of Allergy and Infectious Diseases[29]. Maug *et al*[24] also graded based on the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for human use (ICH) guidelines for good clinical practice[30].

Assessment of risk of bias: Figure 2 illustrates the methodological quality assessment of the included studies. The risk of bias was assessed as low across all domains for five of the nine studies. The other four studies presented an unclear risk of bias in selective reporting, as we were uncertain whether the analyses followed a pre-specified analysis plan. Nevertheless, the overall risk of bias for all the included studies was assessed as low.

Findings:

Sputum conversion: We included nine studies for the meta-analysis of sputum conversion at eight wk. High dose rifampicin group had better sputum culture conversion (83.6%) compared to the control group (77.8%) with a pooled relative risk (RR) of 1.05 (95% CI: 1-1.09; *P*=0.03; moderate certainty of evidence) (Fig. 3A; Table II). We observed a moderate heterogeneity with I^2 of 52 per cent (*P*=0.04). We estimated a number needed to treat (NNT) of 24 for sputum conversion with high-dose rifampicin (Table III). We estimated a comparable pooled RR of 1.07 (95% CI: 1.02-1.14, *P*=0.01; NNT=17) and 1.12 (95% CI: 1.04-1.20, *P*=0.002; NNT=9) for dosages of 20-30 mg/kg and >30 mg/kg of rifampicin, respectively (Supplementary Fig. 1A-C). However, a dosage of less than 20 mg/kg of rifampicin did not show any significant difference (RR0.96; 95% CI: 0.91-1.02, *P*=0.21; NNT=30) (Supplementary Fig. 1A).

Grade 3 and 4 hepatotoxicity: High dose rifampicin group had a higher incidence of grade 3 or 4 hepatoxicity (7.6% *vs.* 6.1%) compared to the standard dose (RR1.17; 95% CI: 0.87-1.57; low certainty of evidence) with no statistically significant difference (*P*=0.3; Fig. 3B). The Number needed to harm (NNH) was 66. We observed a dose-dependent relationship on the hepatotoxicity as the pooled RR was higher as the dose increased from <20 mg/kg (RR0.9; 95% CI: 0.54 -1.55, *P*=0.74; NNH=100) to >30 mg/kg (RR3.11; 95% CI: 1.68-5.75, *P*=0.0003; NNH=15) (Supplementary Fig. 2A-C).

Mortality: Eight studies reported mortality as an outcome, and the pooled RR was not statistically significantly different between the two arms (RR0.83; 95% CI: 0.55 -1.26, *P*=0.38; NNH=125; low certainty of evidence; Fig. 3C). Similar results were observed even in the subgroup analysis across different doses of rifampicin. High dose rifampicin was not found to be beneficial in reducing the mortality even at the doses of 20-30 mg/kg (RR 0.81; 95% CI: 0.43-1.51, NNH=200) and more than 30 mg/kg (RR 0.72;95% CI: 0.26-1.99, NNT=200; Supplementary Fig. 3A-C).

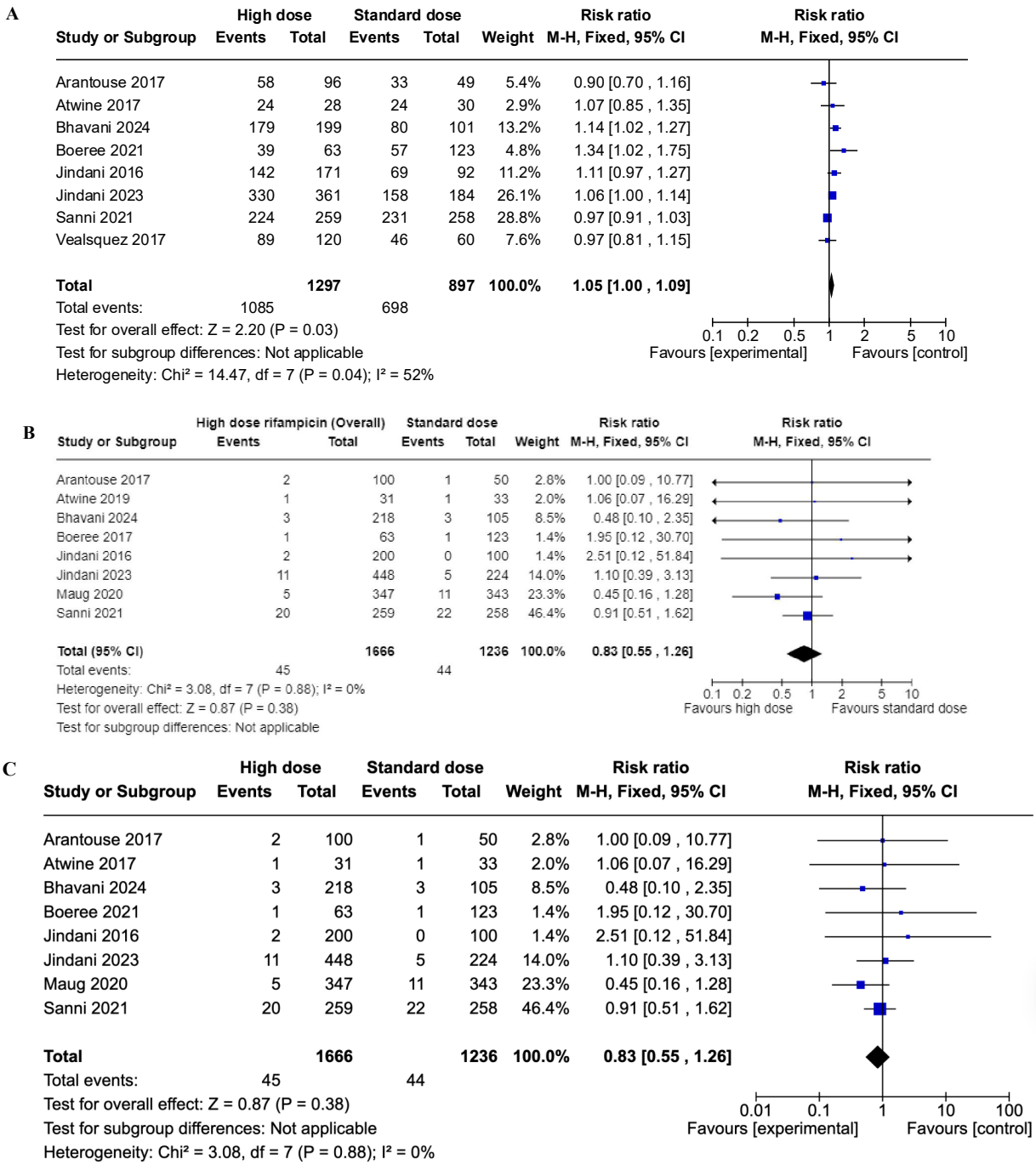

Fig. 3. Forest plot analysis of **(A)** High dose rifampicin *vs.* standard dose: sputum conversion at eight wk. (**B**) High dose rifampicin *vs.* standard dose: grade 3 and 4 hepatotoxicity. (**C**) High dose *vs.* standard dose: mortality.

Treatment failure: Of the 1348 participants in the high dose rifampicin group, 24 (1.78%) had treatment failure, while 25 of the 986 (2.5%) in the standard dose group with no significant difference (RR0.76; 95% CI: 0.46-1.32, *P*=0.35; NNH=142; low certainty of evidence; Fig. 4A). The subgroup analysis of different doses of high dose rifampicin revealed no beneficial effect. (<20 mg/kg, RR 0.7; 95% CI: 0.27- 1.8, NNH=111; 20-30 mg/kg, RR 0.78; 95% CI: 0.40 -1.52, NNH=166 ;>30 mg/kg, RR 0.54; 95% CI: 0.15 -1.95, NNH=91; Supplementary Fig. 4A-C).

ADR leading to discontinuation of treatment: The incidence of ADR leading to treatment discontinuation

Table II. Efficacy and safety of high dose rifampicin (overall) *vs*. standard dose

Outcome	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			NNT/ NNH	Difference*	Certainty of evidence
			Standard dose	High dose rifampicin (overall)	Difference*			
Sputum conversion at 8 weeks	2594 (8 RCTs)	RR=1.05 (1.00 to 1.09)	78 per 100	82 per 100 (84 to 91)	4 more per 100 (from 0 fewer to 7 more)	24	4.2% more (0 fewer to 7.5 more)	⊕⊕⊕◯ Moderate
Grade 3 & Grade 4 toxicity	2577 (8 RCTs)	RR=1.17 (0.87 to 1.57)	6 per 100	7 per 100 (5 to 10)	1 more per 100 (from 1 fewer to 3 more)	66	1.0% more (0.8 fewer to 3.5 more)	⊕⊕◯◯ Low
Mortality	2902 (8 RCTs)	RR=0.83 (0.55 to 1.26)	4 per 100	3 per 100 (2 to 4)	1 fewer per 100 (from 2 fewer to 1 more)	125	0.6% fewer (1.6 fewer to 0.9 more)	⊕⊕◯◯ Low
Treatment failure	2334 (6 RCTs)	RR=0.78 (0.46 to 1.32)	3 per 100	2 per 100 (0 to 1)	1 fewer per 100 (from 1 fewer to 1 fewer)	142	0.1% fewer (0.3 fewer to 0.2 more)	⊕⊕◯◯ Low
Treatment discontinuation	1612 (6 RCTs)	RR=2.01 (1.90 to 3.40)	3 per 100	5 per 100 (5 to 9)	3 more per 100 (from 2 more to 6 more)	33	2.7% more (2.4 more to 6.3 more)	⊕⊕⊕⊕ High

CI, confidence interval; RR, risk ratio; NNT, number needed to treat; NNH, number needed to harm; RCT, randomised controlled trials

was higher among the participants who received high-dose rifampicin (5.5% *vs*. 2.6%) and the pooled RR was significantly greater (RR: 2.01; 95% CI:1.19-3.4, *P*=0.009; NNH=33; high certainty of evidence; Fig. 4B). The pooled risk RR increased for treatment discontinuation as the dose of the rifampicin increased (<20 mg/kg, RR 1.35; 95% CI: 0.59-3.09, NNH=53; 20-30 mg/kg, RR 1.48; 95%CI: 0.78-2.81, NNH=71; >30mg/kg, RR 4.01; 95% CI: 1.75-9.19, NNH=20). We also observed a similar phenomenon in grade 3 and 4 hepatotoxicity (Supplementary Fig. 5 A-C).

Publication bias: We did not detect publication bias for all the outcomes, and funnel plots are shown in supplementary figure 6 A-E.

Discussion

Early sputum conversion is a valuable tool widely used as a surrogate marker for treatment response and those who are at risk for relapse in pulmonary TB. Rifamycins are crucial drugs in the anti-TB regimen, which sterilise the lesions and aid in recurrence-free cure. Although most of our included studies did not assess relapse or recurrence after treatment, the ability of high-dose rifampicin to achieve early sputum conversion and eliminate the persistent bacteria that cause relapse could potentially lead to recurrence-free survival[31-33]. Early bacterial clearance is also of public health importance as this could potentially reduce disease transmission in the community. Of the nine included studies, five showed a significant sputum conversion rate with high-dose rifampicin[11,13,14,22,26,27]. These five studies used rifampicin doses ranging from 20 to 35 mg/kg. We also observed that the studies, which used lower doses of rifampicin (15 to 21 mg/kg) did not show significant benefit with sputum conversion individually as well as in the meta-analysis (RR 0.96; 95% CI:0.91-1.02)[12,23,25]. Pharmacokinetic studies have shown that patients treated with higher doses of rifampicin achieve adequate serum drug

Table III. Sub-group analysis of different doses of high dose rif

Outcome	High dose rifampicin (<20 mg/kg)			High dose rifampicin (20-30 mg/kg)			High dose rifampicin (>30 mg/kg)		
	Participants (studies)	Relative effect (95% CI)	NNT/ NNH	Participants (studies)	Relative effect (95% CI)	NNT/ NNH	Participants (studies)	Relative risk (95% CI)	NNT/ NNH
Sputum conversion at 8 wk	916 (4 RCTs)	RR=0.96 (0.91 to 1.02)	30	1027 (6 RCTs)	RR=1.07 (1.02 to 1.14)	17	747 (3 RCTs)	RR=1.12 (1.04 to 1.20)	9
Grade 3 & Grade 4 toxicity	420 (3 RCTs)	RR=0.91 (0.54 to 1.55)	100	1850 (7 RCTs)	RR=0.96 (0.69 to 1.34)	500	846 (3 RCTs)	RR=3.11 (1.68 to 5.75)	15
Mortality	817 (3 RCTs)	RR=0.95 (0.55 to 1.66)	500	1718 (6 RCTs)	RR=0.81 (0.43 to 1.51)	200	846 (3 RCTs)	RR=0.72 (0.26 to 1.99)	200
Treatment failure	637 (2 RCTs)	RR=0.70 (0.27 to 1.81)	111	1465 (5 RCTs)	RR=0.78 (0.40 to 1.52)	166	584 (2 RCTs)	RR=0.54 (0.15 to 1.95)	91
Treatment discontinuation	320 (2 RCTs)	RR=1.35 (0.59 to 3.09)	53	974 (5 RCTs)	RR=1.48 (0.78 to 2.81)	71	770 (3 RCTs)	RR=4.01 (1.75 to 9.19)	20

concentrations, which is vital for early bacterial clearance, and the therapeutic concentration in those who receive less than 20 mg probably did not result in sputum culture conversion[12,34]. We found high-dose rifampicin efficacious, leading to a higher sputum conversion rate at eight wk. Our findings corroborate with a systematic review done by Onorato *et al*[17], which showed an increased sputum conversion rate (83.7% *vs*. 80.6%) among the participants in the high-dose rifampicin arm (RR 1.06) from five included studies[17]. The authors reported that the sputum conversion was better in participants receiving less than 20 mg/kg[17]. However, we estimated a significant benefit in the higher doses above 30 mg/kg (RR 1.12; 95% CI: 1.04 - 1.2), followed by the 20-30 mg/kg group (RR 1.07; 95% CI: 1.02-1.14).

Though high-dose rifampicin had a significant efficacy in increasing sputum conversion rate, it was not effective in reducing the treatment failure (RR 0.78; 95% CI: 0.46 -1.32). While six studies contributed to this outcome, only one study, which used 20 mg/kg of rifampicin, showed significant benefit with high-dose rifampicin (RR 1.48; 95 CI: 0.61 to 3.58)[24]. One of the major concerns regarding increasing the dose of rifampicin and rolling it out in the TB programme is that rifampicin causes drug-induced liver injury (DILI). Our analyses suggest that there was a dose-dependent relationship for the hepatotoxicity grades 3 and 4 and adverse drug reactions resulting in the discontinuation of the treatment. It should be noted that the hepatotoxicity was not very significant in the group receiving less than 20 mg/kg or 20 to 30 mg/kg. In addition, we also observed that the pooled RR was not significant even in these doses for ADR leading to treatment discontinuation. Onorato *et al*[17] did not observe a dose-dependent relationship[17]. However, the authors reported significant hepatoxicity even in the arm that received a low dose (<20 mg/kg) of rifampicin (RR 1.19; 95% CI: 0.59 to 2.39). While Onorato *et al*[17] included four studies contributing to the assessment of hepatoxicity in <20 mg/kg arm, we included only three trials with 817 participants. A systematic review[16], which informed the WHO recommendation, showed that higher doses of rifampicin up to 20 mg/kg may not increase incidences of DILI, thrombocytopenia, or hypersensitivity syndromes, and the evidence on the safety of doses at 30 mg/kg and 35 mg/kg is uncertain[16].

We observed no mortality benefit with high-dose rifampicin (RR 0.83; 95% CI: 0.55- 1.26) between the two arms (2.6% *vs*. 3.5%). A previous systematic review also showed no difference between the two arms in reducing mortality in pulmonary TB[17]. However, high-dose rifampicin has been beneficial in reducing mortality in TB meningitis (TBM), as shown in several trials[35,36]. Haigh and colleagues' systematic review which informed the WHO guidelines included trials on pulmonary TB and TBM and concluded that high dose rifampicin at a dose of 15 mg/kg (RR0.80;

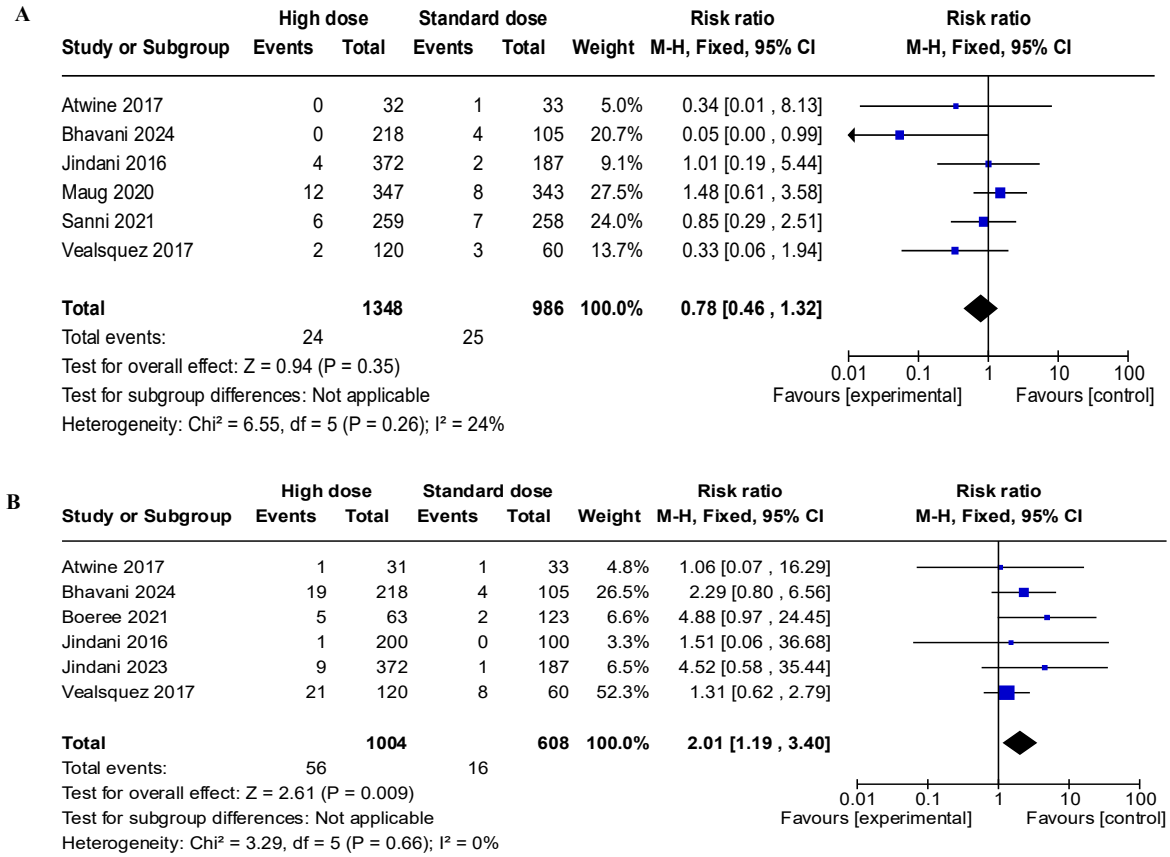

Fig. 4. Forest plot analysis of **(A)** High dose rifampicin *vs*. standard dose: Treatment failure. (**B**) High dose rifampicin *vs*. standard dose: ADR leading to discontinuation of the treatment.

95% CI: 0.47 - 1.37), or 20/mg (RR 0.93; 95% CI: 0.47 -1.81) probably reduces all-cause mortality slightly[16]. These findings are similar to ours, although we included clinical trials conducted only among patients with pulmonary TB. A model-based study suggested that a high dose of rifampicin exposure substantially reduced death among 144 patients with TBM[37]. Our findings substantiate the evidence currently available in the literature that the role of high-dose rifampicin in reducing mortality in pulmonary TB is still unclear.

Heterogeneity was limited in our analyses. Meta-analysis of two outcomes (sputum conversion and hepatotoxicity) had moderate heterogeneity, while all other analyses showed no or low heterogeneity. The possible reason for the heterogeneity in sputum conversion could be variation among the study population. Five studies included PLHIV, of which two included exclusively the PLHIV population. One of these two studies did not show a beneficial effect, as HIV infection is known to be associated with longer duration of sputum conversion compared to HIV negative individuals[38,39]. In addition, only three studies used the MGIT culture method, while four used the solid culture method. The sensitivity of MGIT is significantly higher than that of LJ culture, which could be one reason for the heterogeneity between the studies[40]. Regarding hepatotoxicity, the studies in our review used various criteria for grading the assessments. However, the variations between these criteria were minor, and most studies used DAIDS grading. Most of the studies used a flat dose of rifampicin irrespective of the patient's weight. We calculated the dose for each study using the median weight of the participants. However, Kannabiran *et al*[14] used a weight-based high-dose rifampicin. This could have resulted in the heterogeneity between the studies. It is also important to note that five of the included studies were conducted among participants from African countries. The tolerability of rifampicin could also vary between different ethnic groups[41].

This systematic review has several strengths, with well-defined PICO and a large number of participants

contributing to the meta-analysis for the primary (2594 participants) and secondary outcomes. The outcomes were based on objective assessments with low possibilities for bias. The majority of the included studies were methodologically robust, well-conducted trials and had a low risk of bias in RoB-2. The primary author was not involved in assessing methodological quality, as one of her studies was included in this review. We also had a few limitations. Of the nine included studies, only six reported treatment failure and ADR leading to discontinuation of the treatment. Five studies with a very small number of PLHIV were included in our meta-analysis. Hence, the applicability of these findings to the PLHIV is uncertain.

Overall, high doses of rifampicin (>15 mg/kg) increased the rate of sputum culture conversion after two months of the intensive phase. In the subgroup analysis, the 20-30 mg/kg dose showed a beneficial effect in sputum conversion with no significant risk of hepatotoxicity and ADR leading to treatment discontinuation. High-dose rifampicin of >30 mg/kg was found to have a considerable incidence of grade 3 and 4 hepatotoxicity and an increased incidence of ADR, leading to treatment discontinuation events with a dose-dependent relationship. There was no difference in mortality and treatment failure between high-dose rifampicin and standard arms. In conclusion, a 20-30 mg/kg dose of rifampicin may benefit the patients by providing faster sputum conversion and relapse-free survival, and this could be administered with close monitoring of adverse events and hepatotoxicity. Future trials should focus on evaluating recurrence and relapse after the completion of the treatment.

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