Clinical Infectious Diseases

REVIEW ARTICLE

Safety, Efficacy, and Pharmacokinetics of Daily Optimized Doses of Rifampicin for the Treatment of Tuberculosis: A Systematic Review and Bayesian Network Meta-Analysis

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(See the Major Article by Arbiv et al on pages 119–28; Editorial Commentary by Maranchick and Peloquin on pages 143–4.)

Background. Higher than standard doses of rifampicin could improve the treatment outcome of drug-susceptible tuberculosis (TB) without compromising the safety of patients.

Methods. We performed a systematic review of prospective clinical studies including adults with pulmonary and extrapulmonary TB receiving rifampicin doses above 10 mg/kg/day. We extracted the data on overall adverse events (AE), hepatic AE, sputum culture conversion (SCC) at week 8, recurrence, mortality, and pharmacokinetics. We performed a Bayesian network meta-analysis (NMA) using a random-effects model.

Results. In 19 studies, 2033 out of 3654 participants received rifampicin doses higher than 10 mg/kg/day. The NMA showed an increased risk of overall and hepatic AE for the 40 mg/kg/day dose (risk ratio [RR] 4.8, 95% credibility interval [CrI]: 1.1, 25, and 15.00; 95% CrI: 1.1, 58.0, respectively), but no other doses, including 50 mg/kg/day showed such an increase. Increasing doses improved sputum culture conversion at week 8 (RR 1.3, 95% CrI: 1.1, 1.7 for SCC with 35 mg/kg/day).

Conclusions. Optimal doses of rifampicin may be between 25 and 35 mg/kg/day, but should be tailored at the individual or, at least, at the population level.

Keywords. tuberculosis; rifampicin; systematic review; network meta-analysis; clinical trials.

In 2022, an estimated 10 million people fell ill with tuberculosis (TB), and approximately 1.5 million died because of the disease [1]. Most TB cases in 2022 happened in 3 World Health Organization (WHO) regions: Southeast Asia (46%), Africa (23%), and Western Pacific (18%). India alone accounts for 28% of the global TB burden [1].

Rifampicin can kill both rapid-growing and dormant bacilli, which makes it one of the essential first-line anti-tuberculosis drugs [2]. Rifampicin was approved by the Food and Drug Administration (FDA) in 1971 for its use in adults with TB [3]. The current standard 10 mg/kg/day dose was selected balancing efficacy, safety (mainly due to hypersensitivity reactions with high, intermittent doses of rifampicin), and cost at that time [4, 5]. Subsequent preclinical studies suggested that rifampicin exposure could be optimised with doses above 10 mg/kg/day, leading to increased efficacy and shorter treatments [6, 7]. Today, rifampicin is cheap and widely available in most high-burden countries. Both fixed-dose combinations and loose rifampicin capsules are included in the WHO's Essential Medicines List. Rifampicin is used for the treatment of brucellosis, other mycobacteria and methicillin-resistant

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Staphylococcus aureus [8]. Despite several reviews published in recent years, it is yet unclear what the optimal dose range of rifampicin should be, mainly due to a narrative design and the limitations of conventional meta-analysis [9, 10].

The objective of this review was to synthesize the available evidence to determine the optimal range of rifampicin dose in adults with drug-susceptible TB. The primary focus was on safety, complemented with efficacy, and pharmacokinetics. The secondary objective was to describe the population included in recent rifampicin dose clinical trials.

METHODS

We conducted a systematic review and meta-analysis on the safety, efficacy, and pharmacokinetics of rifampicin doses of more than 10 mg/kg/day for adults with tuberculosis following the PRISMA standards (PRISMA checklist with the Supplementary material).

Data Sources and Search Strategy

We searched the PubMed, SCOPUS, and ISI databases for publications without language restrictions. The search term is in the Supplementary Appendix. We included additional studies by backward citation.

Eligibility Criteria

We included studies published from 1 January 2007 to 31 July 2023. A systematic review found an increase in adverse events (AE) in studies before 2007, possibly related to the use of intermittent administration of optimized rifampicin doses [8]. We considered studies including all forms of rifampicin-susceptible TB in adolescents or (≥16 years-old). There were no exclusion criteria regarding participant's comorbidities.

The review focused on prospective studies and clinical trials, excluding retrospective studies, and prospective series reporting <5 participants, with no restriction per treatment arm size. We also excluded book chapters, conference proceedings, and abstracts.

Screening and Data Extraction

Publications were screened by title, abstract, and keywords and then selected by full text review by E. N., A. M., and G. M., and conflicts were resolved by A. A.

E. N., G. M., and A. A. extracted the data, and JE reviewed it. The coprimary safety outcomes were overall grade ≥3 adverse events (AE) and hepatic grade ≥3 AE in both pulmonary and extrapulmonary TB. Efficacy and pharmacokinetics outcomes were early bactericidal activity (EBA) at day 5 and 14 (mean decrease compared to baseline bacterial load in log CFU/mL in sputum), sputum culture conversion (SCC) rate at 8 weeks (considering liquid and solid culture media separately), and recurrence in pulmonary TB; and mortality in TB meningitis (TBM). Pharmacokinetics included maximum concentration (C_{max}), area under the curve between treatment dose and 6 or 24 hours (AUC_{0-6}, AUC_{0-24}, respectively), time to the maximum concentration (T_{max}), and elimination half-life ($t_{1/2}$).

As rifampicin can induce its metabolism over the first weeks of treatment, for those studies with two or more sampling times, we planned a sensitivity analysis excluding the studies in which the only PK samples were taken within the first week of treatment [11].

Data Analysis

The risk of bias for each study was analysed by AA and JE according to Cochrane guidelines, using the "RoB assessment tool" version 2.0 [12]. We grouped treatment arms according to the dose of rifampicin relative to weight using, when provided, the mean dose per kilogram per day (Table 2). We used the Mantel-Haenszel method for binomial variables (eg, incidence of AE or SCC rate) and the method by McGrath et al for continuous variables (eg, PK parameters), which were summarised as Risk Ratio (RR) and Mean Difference (MD), respectively [13].

We performed a Bayesian Network meta-analysis (NMA) using Markov-Chain Monte-Carlo (MCMC) process. The outcomes were estimated using a Random Effects Model and inter-study heterogeneity with Restricted Maximum Likelihood approach. Data handling strategies and assessment of model fit are further discussed in section 3 of the Supplementary Appendix. Inconsistencies were assessed using the node splitting method with a significance threshold of <.05 [14]. Results are presented with 95% credibility intervals (CrI). Data were analysed using R software version 4.3.1, and JAGS 4.3.0 for the MCMC simulations [15].

RESULTS

Figure 1 illustrates the flow diagram of the systematic review. We screened 2811 records, leaving 41 manuscripts for full-text review. From these, 19 were included in the qualitative analysis (Table 1). Most of the excluded publications included children, analysed treatments without rifampicin (including multi-drug resistant TB), or were focused on TB infection.

From the 19 studies included, there were two phase 3 trials, one including pulmonary TB and one TBM [21, 28], and one was a multi-stage trial [34]. Three studies were early phase 2 [16, 17, 22], and the remaining 13 were mid-late phase 2 clinical trials [18–20, 23–27, 29–34].

Overall, the risk of bias was low or moderate (Figure 2 and Supplementary Figure 1), the main concerns being the non-randomized allocation of participants in three studies [17, 19, 22], and open-label design in most studies [16–19, 22–26, 30]. Due to the significant risk of bias in one non-randomized study with historical controls, we included 18 studies in the meta-analysis for the primary safety outcomes (Figure 1) [17].

The 19 studies reported data from 3962 participants. Of these, >50% were from Vietnam, Bangladesh, Indonesia,

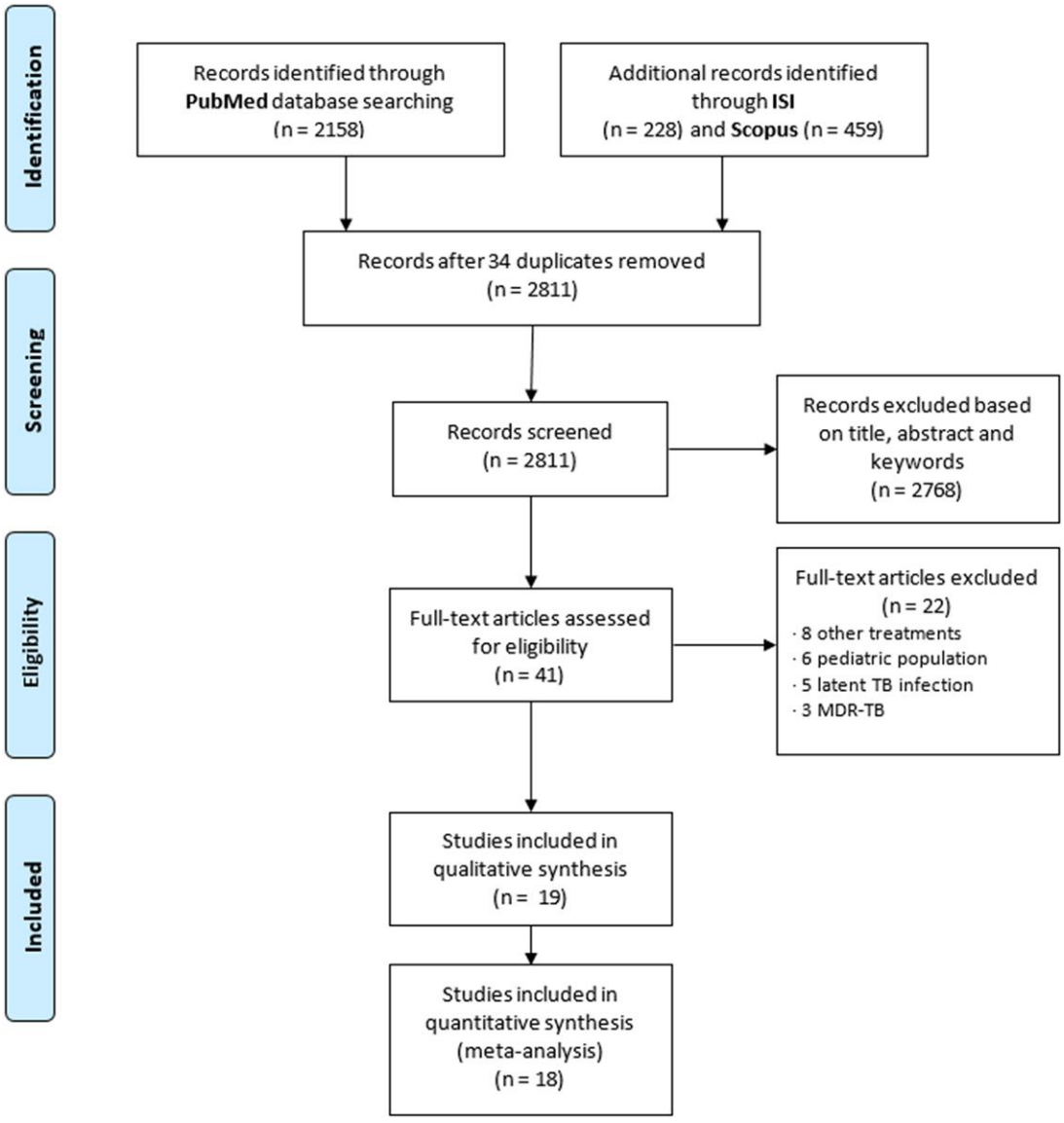

Figure 1. PRISMA flow diagram of the review.

and Uganda. More than two-thirds of the participants were male. The median age was 32.8 years old (95% confidence interval (CI) 30.5; 35.3). The most common comorbidity was HIV coinfection (15.8%), and 12.2% of the pulmonary TB participants had cavitation. Other key comorbidities such as diabetes mellitus were reported in <1% of the participants. The TBM studies included 1074 (27.2%) participants [18, 21, 22, 27, 30, 31, 35]. There were no other forms of extrapulmonary TB included. Additional characteristics of the study populations are shown in Supplementary Table 1 in the Supplementary Appendix.

Table 2 summarizes the treatments and follow-up times from the different studies. Of all participants, 2033 (55.6%) received rifampicin above 10 mg/kg/day; 426 (20.9%) 30 mg/kg/day or higher. The medians for follow-up and intervention duration were 25 (range 2–96) and 8 weeks (range 1–24), respectively. Excluding the standard first-line treatment, 11 different regimens were tested considering only rifampicin, and 29 considering all drug combinations (Table 2 and Supplementary Table 2).

Figure 3 shows the overall network of comparisons. The model was well adjusted, with good density and convergence of data, with PSRF under the 1.05 threshold for all outcomes. Node-splitting, were applicable, did not show relevant data inconsistencies except for the 30 mg/kg/day versus 20 mg/kg/day comparison in all AE and hepatic AE ($P = .008$ and .005, respectively), 30 versus 35 mg/kg/day for hepatic AE ($P = .035$), AUC_{0-24} ($P = .009$). This could be related with pooling arms

Table 1. Summary of Studies Meeting Inclusion Criteria

	Population	Study Type	Rifampicin Dose	N	All AE[a]	Hepatic AE[a]	SCC Week 8/n		Mortality/ n	Rifampicin AUC^{b}_{0-24}
							LJ	MGIT		
Ruslami et al (2007) [16]	≥18 y old with confirmed pulmonary DS-TB	Phase II, double blind, randomised	R 450 mg/day	25	…	3	…	…	…	48.5 (26.7–72.8)[1]
			R 600 mg/day	25	…	1	…	…	…	79.7 (38.7–138.1)[1]
Diacon et al (2007) [17]	Confirmed pulmonary DS-TB	Prospective cohort, historical controls	R 10 mg/kg/day	8	0	…	…	…	…	100 (±21)[2]
			R 20 mg/kg/day	13	1	…	…	…	…	171 (±56)[2]
Ruslami et al (2013) [18][c]	>14 y old with clinically suspected TB meningitis	Phase II, open label, randomised	R 450 mg/day	31	5	5	…	…	20/31	26 (19–35.6)[1]
			R 600 mg/day iv	29	7	6	…	…	10/29	78.7 (71–87.3)[1]
Boeree et al (2015) [19] and te Brake et al (2021) [20]	18–65 y old with confirmed pulmonary DS-TB	Phase II, open label, sequential allocation	R 10 mg/kg/day	8	0	0	…	…	…	26.3 (21.3–40.9)[1]
			R 20 mg/kg/day	15	2	0	…	…	…	113 (77.5–162)[1]
			R 25 mg/kg/day	15	0	0	…	…	…	135 (91.5–228)[1]
			R 30 mg/kg/day	15	1	1	…	…	…	190 (84.7–436)[1]
			R 35 mg/kg/day	15	1	0	…	…	…	235 (166–321)[1]
			R 40 mg/kg/day	15	4	2	…	…	…	257 (173–349)[1]
			R 50 mg/kg/day	17	1	0	…	…	…	370 (231–559)[1]
Heemskerk et al (2016) [21][d]	≥18 y old with clinically suspected TB meningitis	Phase III, double blind, randomised	R 10 mg/kg/day	409	229	28	…	…	114/409	48.2 (18.2–93.8)[1]
			R 20 mg/kg/day	408	240	17	…	…	113/408	82.5 (8.7–161)[1]
Yunivita et al (2016) [22][e]	≥18 y old with clinically suspected TB meningitis	Phase II, open label, randomised	R 750 mg/day	11	…	3	…	…	…	48.5 (26.7–72.8)[1]
			R 900 mg/day	9	…	4	…	…	…	100.1 (46.1–162.3)[1]
			R 600 mg/day iv	10	…	2	…	…	…	100.2 (41.7–167.8)[1]
Jindani et al (2016) [23]	18–65 y old with confirmed pulmonary DS-TB	Phase II, open label, randomised	R 10 mg/kg	100	1	…	17/32	69/92	…	…
			R 15 mg/kg/day	100	2	…	14/27	66/80	…	…
			R 20 mg/kg/day	100	4	…	20/32	76/91	…	…
Aarnoutse et al (2017) [24]	18–65 y old with confirmed pulmonary DS-TB	Phase II, double blind, randomised	R 600 mg/day	50	3	3	36/49	24/49	…	23.9 (9.1–118.5)[1]
			R 900 mg/day	50	1	0	36/48	24/48	…	50.8 (18.9–153.6)[1]
			R 1200 mg/day	50	4	4	39/48	29/48	…	76.1 (43.5–167)[1]
Boeree et al (2017) [25][f]	≥18 y old with confirmed pulmonary DS-TB	Phase IIb-c, open-label, randomised	R 10 mg/kg/day	182	1	2	154/181	75/181	0/150	20.8 (17.3–24.3)[1]
			R 20 mg/kg/day	120	4	3	106/119	55/119	0/102	62.8 (53.5–72.1)[1]
			R 35 mg/kg/day	63	3	5	59/63	36/63	1/54	170 (103–266)[1]
Velásquez et al (2018) [26]	18–60 y old with confirmed pulmonary DS-TB	Phase II, double blind, randomised	R 10 mg/kg/day	60	26	16	46/53	…	…	24.9 (17.6–32.1)[3]
			R 15 mg/kg/day	60	31	14	44/50	…	…	43.1 (30.3–57.5)[3]
			R 20 mg/kg/day	60	23	14	45/52	…	…	55.5 (35.7–73.2)[3]
Dian et al (2018) [27][g]	>14 y old clinically suspected TB meningitis	Phase II, double-blind, randomised	R 450 mg/day	20	3	3	…	…	5/14	39.2 (17.4–66.5)[1]
			R 900 mg/day	20	8	5	…	…	6/13	144.1 (86.2–241.7)[1]
			R 1350 mg/day	20	4	4	…	…	1/15	187.9 (41.6–392.1)[1]
Maug et al (2020) [28][h]	≥15 y old with confirmed pulmonary DS-TB	Phase III, open label, randomised	R 10 mg/kg/day	349	15	7	…	…	11/343	…
			R 20 mg/kg/day	352	9	3	…	…	5/347	…
Atwine et al (2020) [29]	≥15 y old with confirmed pulmonary DS-TB	Phase II, open label, randomised	R 10 mg/kg/day	33	6	3	28/31	24/30	1/33	…
			R 20 mg/kg/day	64	12	4	47/53	50/58	1/64	…
Cresswell et al (2021) [30]	≥18 y old with clinically suspected TB meningitis	Phase II, open label, randomised	R 10 mg/kg/day	21	15	4	…	…	7/21	42.9 (29.2–63)[1]
			R 35 mg/kg/day	20	11	2	…	…	10/20	327 (248–430)[1]
			R 20 mg/kg/day iv[i]	20	10	1	…	…	7/20	249 (202–306)[1]

Table 1. Continued

	Population	Study Type	Rifampicin Dose	N	All AE[a]	Hepatic AE[a]	SCC Week 8/n		Mortality/ n	Rifampicin AUC^{b}_{0-24}
							LJ	MGIT		
Wasserman et al (2021) [31][j]	≥18 y old with clinically suspected TB meningitis	Phase II, open label, randomised	R 10 mg/kg/day	20	6	0	…	…	3/20	42.9 (24.5–75)[1]
			R 35 mg/kg/day	30	14	2	…	…	4/30	(n = 15) 295.2 (198.9–458.8)[1]
			R 20 mg/kg/day iv	…	…	…	…	…	…	(n = 14) 206.5 (154.6–275.8)[1]
Souleymane et al (2023) [32]	All smear positive recurrent pulmonary TB	Phase II, pragmatic, open label, randomised	R 10 mg/kg/day	65	2	0	…	…	…	…
			R 30 mg/kg/day	62	11	4	…	…	…	…
Sekaggya-Wiltshire et al (2023) [33]	≥18 y old, HIV, confirmed pulmonary DS-TB	Phase II, open label, randomised	R 10 mg/kg/day	67	4	3	…	29/67	…	…
			R 35 mg/kg/day	61	6	5	…	35/61	…	…
Paton et al (2023) [34][k]	18–65 y old with confirmed pulmonary DS-TB	Phase II-III, open label, randomized	R 10 mg/kg/day	181	29	6	…	…	…	
			R 20 mg/kg/day	96	15	2	…	…	…	…
			R 35 mg/kg/day	88	17	6	…	…	…	…

Abbreviations: AAS, aspirin; R, rifampicin; H, isoniazid; Z, pyrazinamide; E, ethambutol; L, levofloxacin; Lz, linezolid; M, moxifloxacin; Q, SQ109; iv, intravenous; IQR, interquartilic range.

[a]Adverse events grade 3 or superior, different studies use different classifications for grading adverse events (see text and Supplementary material).

[b]In mg·h/L; 1: mean and range; 2: mean and standard deviation; 3: median and IQR.

[c]Two consecutive randomizations to allocate patients to 6 interventions: R 450 and R 600 iv combined with E, M 400 mg/day, or M at 800 mg/day.

[d]No median R dose is provided for the two arms. According to the dosing scheme provided with the study, control arm has some underdosed weights (down to 7.7 mg/kg), but intervention arm has always >15 mg/kg for all weights. In the intervention arm, R was combined with L at 20 mg/kg/day.

[e]There is also a R 450 mg control arm with 24 patients borrowed from Ruslami et al (2007) [16]. The exposure in the intravenous R arm was similar to that of the R 900 arm.

[f]The R 10 mg/kg was given alone (control arm) or in combination with Q; the R 20 mg/kg was combined either with Q or M.

[g]In these studies, patients were clinically followed until the end of the TB treatment, but ancillary tests were collected only for 8 weeks.

[h]Due to an erroneously made bench aid, the 33–41 kg weight band participants received two thirds of the standard HZE dose.

[i]In this arm, participants received intravenous rifampicin at 20 mg/kg/day for the first two weeks, then switching to 35 mg/kg for the remaining 6 weeks.

[j]Participants were randomized twice. First, for intensified R plus Lz, intensified R plus Lz plus aspirin, or standard of care. Second, for intensified R as 35 mg/kg oral or 20 mg/kg intravenous. Safety and efficacy results were reported according to the randomisation to aspirin, not to the pharmacokinetic randomisation. Therefore, saferty data is reported for the 35 mg/kg arm pooling arms 2 and 3 (with/without aspirin).

[k]Rifampicin dose was 35 mg/kg the first year of the trial but lowered to 20 mg/kg/day the second year.

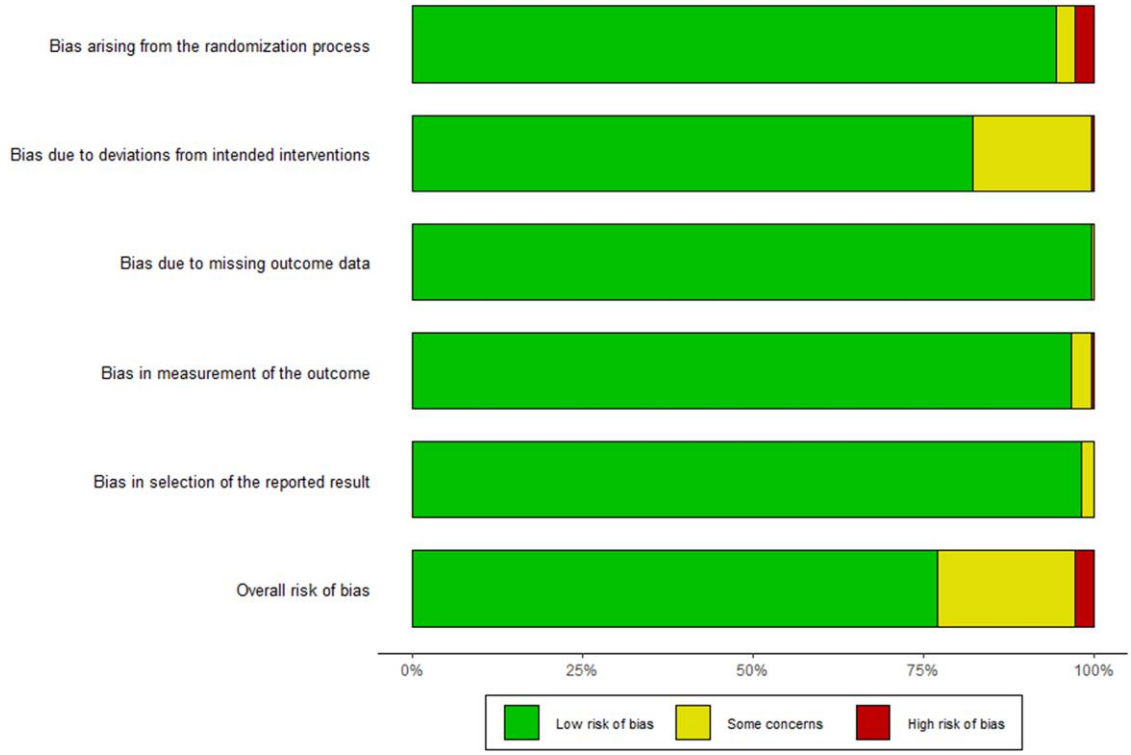

Figure 2. Overall risk of bias*. Footnote: Based on the RoB tool provided by Cochrane [15]. Overall RoB was low, with one study that was not randomized, and concerns about the adjustment of drug doses. In the study by Maug et al [28] a group of participants did not receive adequate doses of the background first-line TB treatment, but authors report separately all participants and then those who were correctly dosed. We only included the latter in the meta-analysis. Abbreviation: RoB, risk of bias.

with the same rifampicin dose (see Supplementary Appendix, Supplementary Tables 3 to 15).

Safety Results

Fifteen studies, including 3265 participants reported data on the incidence of severe AE of any type that were grade 3 or higher [17, 18, 21, 23–29, 31, 33, 34, 36]. No individual study reported an increase in overall adverse events related to rifampicin dose. However, the HIRIF-1 study, reported that tolerability (gastrointestinal symptoms, pruritus, and jaundice) led to treatment stop in 11 out of 17 participants in the 50 mg/kg arm [20].

In the NMA, only the 40 mg/kg (but not the 50 mg/kg) dose showed an increase in the risk of grade ≥3 AE (RR 4.8, 95% CrI 1.1; 25) (Figure 4*A*). The rank plot and the SUCRA (Supplementary Figure 2 and Supplementary Table 3) score that the treatment dose with the highest probability of being the safest (lower risk of severe adverse events) is 25 mg/kg/day (SUCRA 0.99), and the 50 mg/kg dose fell right behind the standard 10 mg/kg (SUCRA 0.59 and 0.62, respectively).

Results were similar regarding grade 3 or higher hepatic AE. Sixteen studies included 3045 participants [16, 18, 21, 22, 24–30]. The 40 mg/kg dose had a higher risk of hepatic grade ≥3 AE (RR 15.00, 95% CrI 1.1; 58.0). However, consistently with the wide credibility intervals, the probability rank and the SUCRA did not show an increasing probability of severe hepatic AE with each increase in rifampicin dose (Figure 4*B*, Supplementary Figure 3, and Supplementary Table 4).

The complete set of safety data is available as a deliverable of the EUSAT consortium. No increase in other AE, including hematologic, cutaneous, or "flu-like" symptoms was detected [8, 37, 38].

Efficacy Results

Four studies report EBA at day 5 (451 participants) [17, 19, 24, 26], and 3 report EBA at day 14 (416 participants) [19, 24, 26]. Increasing doses of rifampicin showed higher EBA (negative MD in sputum bacterial load) at day 5 and 14 compared to standard doses. This difference was significant for 30 mg/kg/day or higher doses (Figures 5*A* and 5*B*). Figure 6 shows the pooled MD in bacterial load Interestingly, the difference in bactericidal activity is smaller at day 14 for doses <30 mg/kg/day.

The pooled SCC rate at 8 weeks was 10% lower in the experimental arms with liquid media. Therefore, we present the results for the two culture methods in parallel. Seven studies reported SCC at 8 weeks: 987 participants in liquid media [23–25, 29, 33], and 838 in solid media [24–26, 29, 39]. The maximum dose evaluated, 35 mg/kg/day, showed a small but significant increase in the SCC at week 8 for liquid media,

Table 2. Follow-up and Treatments

Study	Follow-up	Intervention		Duration	N[a]	Median R Dose in Mg/kg (r, IQR)
Ruslami et al (2007) [16][b]	26 w	R 450 mg		16 w	25	9.5 (mean), 1.7 (SD)
	…	R 600 mg		16 w	25	12.9 (mean), 1.4 (SD)
Diacon et al (2007) [17]	2 w	R 20 mg/kg		5 d	13	…
Ruslami et al (2013) [18][c]	26 w	R 450 mg	E	2 w	12	9.2 (8.5–9.8)
			M 400	2 w	10	
			M 800	2 w	9	
		R 600 mg iv	E	2 w	10	12.7 (11.7–13.8)
			M 400	2 w	9	
			M 800	2 w	10	
Boeree et al (2015) [19]	12 w	R 10 mg/kg		2 w	8	…
te Brake et al (2021) [20]	…	R 20 mg/kg		2 w	15	…
	…	R 25 mg/kg		2 w	15	…
	…	R 30 mg/kg		2 w	15	…
	…	R 35 mg/kg		2 w	15	…
	…	R 40 mg/kg		2 w	15	…
	…	R 50 mg/kg		2 w	17	…
Heemskerk et al (2016) [21][d]	36 w	R 10 mg/kg	…	8 w	409	…
	…	R 15 mg/kg	L 20 mg/kg	8 w	408	…
Yunivita et al (2016) [22][e]	2 w	R 750 mg		2 w	11	16.7 (13.9–18.8) //
	…	R 900 mg		2 w	9	18 (15–22.5)
	…	R 600 mg iv		2 w	10	13.3 (10.0–15.0)
Jindani et al (2016) [23]	16 w	R 10 mg/kg		8 w	100	9.6 (r 7.7–11.8)
	…	R 15 mg/kg		16 w	100	15.0 (r 12.5–18.3)
	…	R 20 mg/kg		16 w	100	18.8 (r 14.4–25.5)
Aarnoutse et al (2017) [24]	12 w	R 600 mg		8 w	50	10.7 (mean, r 8.3–12.0)
	…	R 900 mg		8 w	50	16.7 (mean, r 14.1–17.7)
	…	R 1200 mg		8 w	50	21.4 (mean, r 17.1–23.5)
Boeree et al (2017) [25]	26 w	R 10 mg/kg	…	8 w	123	…
	…	R 35 mg/kg	E	12 w	63	…
	…	R 10 mg/kg	Q	12 w	59	…
	…	R 20 mg/kg	Q	12 w	57	…
	…	…	M	12 w	63	…
Velásquez et al (2018) [26]	12 w	R 10 mg/kg		8 w	60	9.6 (8.7–10.2)
	…	R 15 mg/kg		8 w	60	13.7 (12.4–15.6) //
	…	R 20 mg/kg		8 w	60	18.8 (15.2–20.4)
Dian et al (2018) [27][b]	26 w	R 450 mg		4 w	20	10 (9.5–11.3)
	…	R 900 mg		4 w	20	20 (17.8–23.4)
	…	R 1350 mg		4 w	20	28 (24.7–32.4)
Maug et al (2020) [28][f]	72 w	R 10 mg/kg		24 w	349	…
	…	R 20 mg/kg		24 w	352	…
Atwine et al (2020) [29]	28 w	R 10 mg/kg		8 w	33	…
	…	R 20 mg/kg		8 w	64	…
Cresswell et al (2021) [30]	24 w	R 10 mg/kg		8 w	21	…
	…	R 35 mg/kg		8 w	20	…
	…	R 20 mg/kg iv[g]		8 w	20	…
Wasserman et al (2021) [31][h]	26 w	R 10 mg/kg	…	8 w	20	9 (8–10)
	…	R 35 mg/kg	Lz	8 w	15	34 (33–36)
	…	…	Lz + ASA	8 w	…	…
	…	R 20 mg/kg iv	Lz	8 w	14	22 (22–24)
	…	…	Lz + AS	8 w	…	…
Souleymane et al (2023) [32]	72 w	R 10 mg/kg	…	24 w	65	…
	…	R 30 mg/kg	H 15 mg/kg	24 w	62	…
Sekaggya-Wiltshire et al (2023) [33]	24 w	R 10 mg/kg	…	8 w	67	…
	…	R 30 mg/kg	…	8 w	61	…
Paton et al (2023) [34][i]	96 w	R 10 mg/kg	…	24 w	181	…
	…	R 20 mg/kg	Lz	8–12 w	96	…

Table 2. Continued

Study	Follow-up	Intervention		Duration	N[a]	Median R Dose in Mg/kg (r, IQR)
	…	R 35 mg/kg	Lz	8–12 w	88	…
	…	…	Cf	8–12 w	78	…

Abbreviations: ASA, aspirin; R, rifampicin; H, isoniazid; Z, pyrazinamide; E, ethambutol; L, levofloxacin; Lz, linezolid; Cf, clofazimine; M, moxifloxacin; Q, SQ109; N, number of participants per arm; mo, months; w, weeks; d, days; or, oral; iv, intravenous; IQR, interquartilic rate; r, range.

[a]Allocation ratio was 1:1 for all studies but Boeree 2017, with 2:1:1:1:1 favoring controls.

[b]In these studies, patients were clinically followed until the end of the TB treatment, but ancillary tests were collected only for 8 weeks.

[c]The study by Ruslami 2013, used two consecutive randomizations to allocate patients to 6 interventions.

[d]In Heemskerk 2016, no median R dose is provided for the two arms. According to the dosing scheme provided with the study, control arm has some underdosed weights (down to 7.7 mg/kg), but intervention arm has always >15 mg/kg for all weights.

[e]There is also a R 450 mg control arm with 24 patients borrowed from Ruslami 2007. The exposure in the intravenous R arm was similar to that of the R 900 arm.

[f]There were few issues regarding dose-weight adjustment. In Yunivita 2016 two arms received almost the same dose. In Velasquez 2018, most participants in the 15 mg/kg arm received slightly lower dose. In Maug 2020, due to an erroneously made bench aid, the 33–41 kg weight band participants received two thirds of the standard HZE dose.

[g]In this arm, participants received intravenous rifampicin at 20 mg/kg/day for the first two weeks, then switching to 35 mg/kg for the remaining 6 weeks.

[h]Participants were randomized twice. First, for intensified R plus Lz, intensified R plus Lz plus aspirin, or standard of care. Second, for intensified R as 35 mg/kg oral or 20 mg/kg intravenous.

[i]Rifampicin dose was 35 mg/kg the first year of the trial but lowered to 20 mg/kg/day the second year. Note that safety and efficacy outcomes are not reported in the publication for the R-Cf arm.

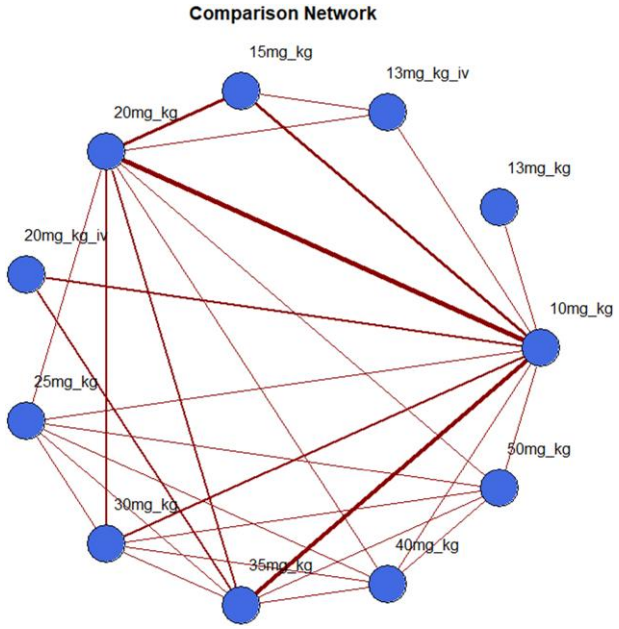

Figure 3. Overall network of comparisons. Footnote: Each blue circle represents a dose of rifampicin in milligrams per kilogram of body weight per day, and each marron line is a direct comparison. The lines are thicker proportionally to the number of comparisons included in the meta-analysis. All doses are oral, except for those finished in i.v., which indicates intravenous administration.

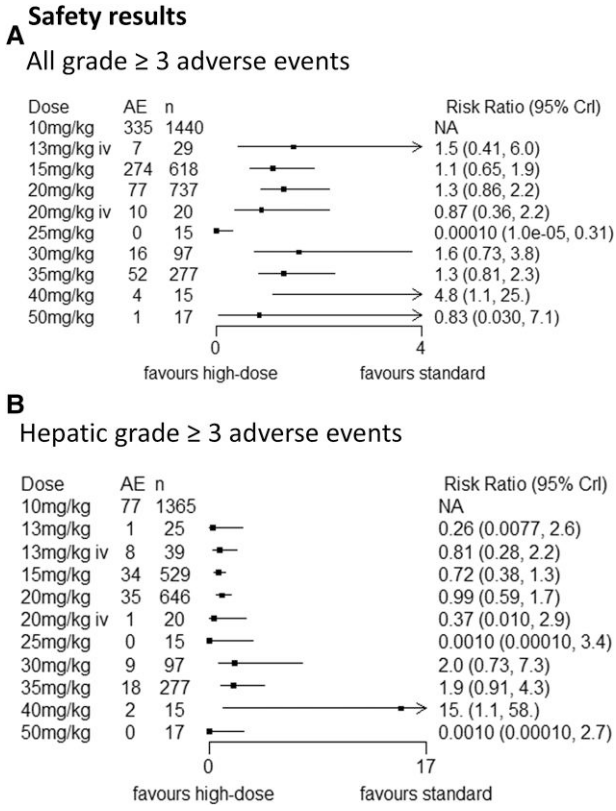

Figure 4. Safety results. Footnote: The studies included in the meta-analysis reported safety outcomes in different ways. Only the rate of participants suffering any AE event grade 3 or higher, and the rate of hepatic AE grade 3 or higher were consistently reported across studies, showing no increased risk of AE for doses between 13 and 35 mg/kg/day, as compared to 10 mg/kg/day. The 40 mg/kg/day dose had a significant increase in the risk of adverse events, although the small sample size may bias the results.

but not for solid media (RR 1.3, 95% CrI 1.1; 1.7 vs 1.1, 95% CrI 0.94; 1.2) (Figures 5*C* and 5*D*). The probability for a higher EBA and negative sputum culture at week 8 increased with the dose, as reflected by the rankogram and the SUCRA. (Supplementary Figures 4–7, and Supplementary Tables 7 and 8).

Four studies including 1215 participants reported 23 events of recurrence after treatment completion [25, 26, 28, 34]. In one study only two confirmed relapses of the same infection occurred in the 10 mg/kg/day arm [26]. In Boeree et al, no recurrent episodes were diagnosed in the 35 mg/kg/day arm and 20 mg/kg/day + moxifloxacin, in contrast to nine recurrences in the remaining arms [25].

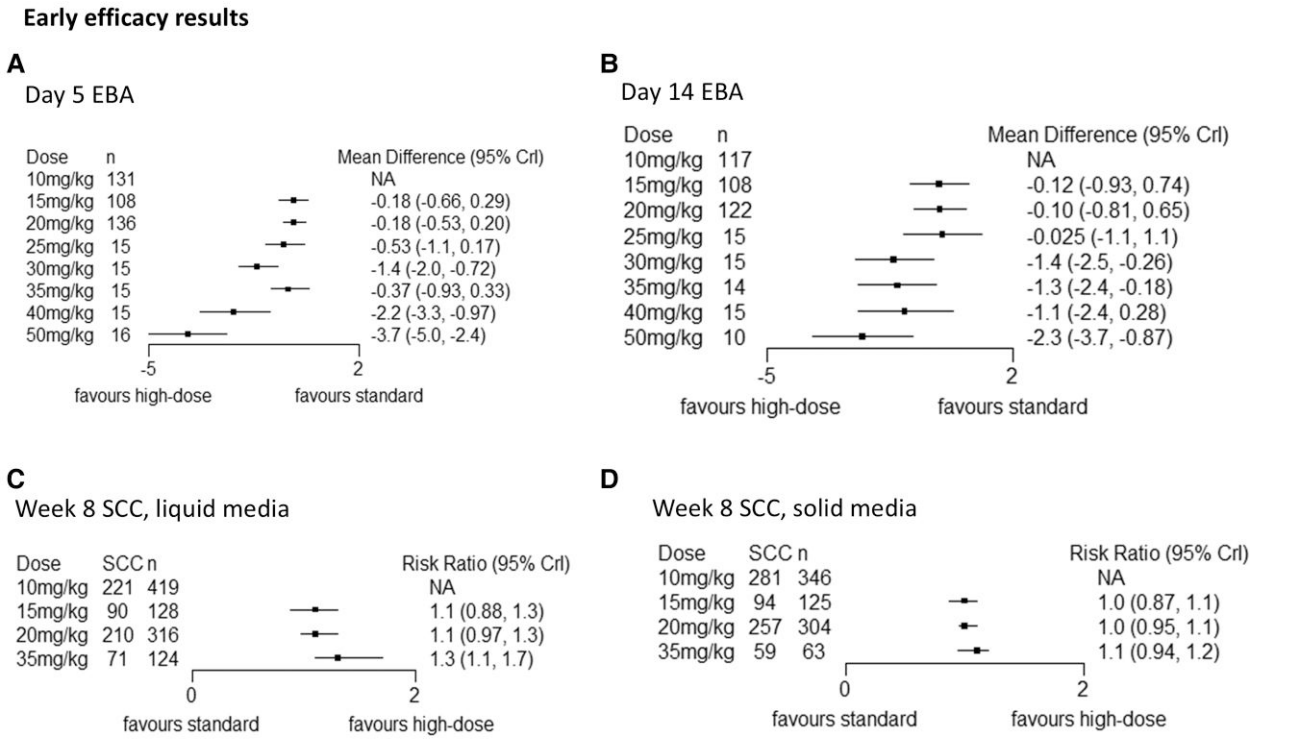

Figure 5. Microbiological efficacy results. Footnote: Panels 5*A* and 5*B* show the results for EBA at 5 and 14 d, respectively. All rifampicin doses have point estimates that are negative as compared to the standard 10 mg/kg/day, reflecting an increased bactericidal activity. The results in SCC in solid and liquid media (paneks 5*C* and 5*D*) are similar, showing a small but significant increase in the probability of obtaining a negative sputum culture by week 8 with 35 mg/kg/day. Abbreviations: EBA, early bactericidal activity; LJ, Löwenstein-Jensen; MGIT, mycobacterial growth indicator tube; SCC, sputum culture conversion.

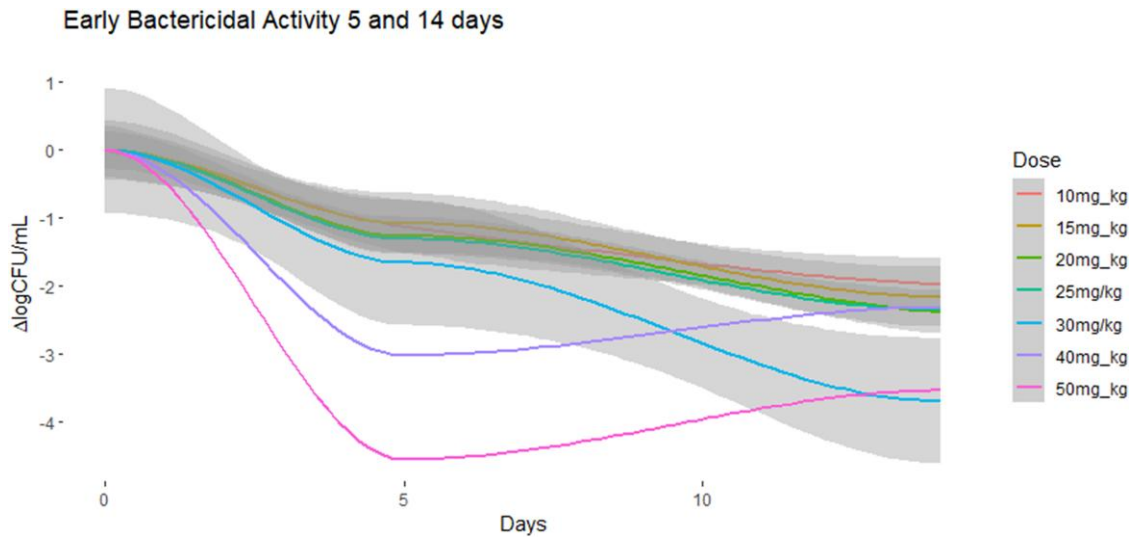

Figure 6. Pooled mean difference logCFU/m Lat baseline, 5 and 14 d, according to rifampicin dose range. Footnote: Point values are expressed as the MD in the mean bacterial load in the sputum of participants treated with increased doses of rifampicin as compared to baseline. Bacterial load was measured with log CFU/mL in solid media. There were no differences between the experimental and the control arms in baseline bacterial load in sputum. At day 5, doses of rifampicin higher than the standard ones have a higher decrease in bacterial load. At day 14, doses up to 25 mg/kg/day seem to loose some of this advantage over the standard doses, but doses of 30 to 35 mg/kg/day could maintain a higher decline in the bacterial load. Abbreviation: CFU, colony forming units; MD, mean difference.

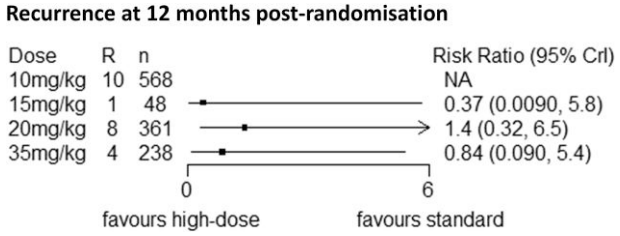

Figure 7. Relapse in pulmonary TB. Footnote: Only four studies reported relapse rates after treatment completion at 12- and 18-months post-randomisation, hence data of all relapses at 12 m was included for the meta-analysis. The network meta-analysis incudes data from 1215 participants, of which one third come from a single study with only one comparison (rifampicin 10 vs 20 mg/kg/day). Since this study did not use molecular tests to differentiate recurrence of the infection by the original strain from reinfection from a new strain, we pooled all the reported relapses. Even considering together reinfections and recurrences, there were only 23 events. This may explain the wide credibility intervals and the apparent worse outcome for the 20 mg/kg/day when the tendency for 15 and 35 mg/kg/day dose is to a lower risk of relapse.

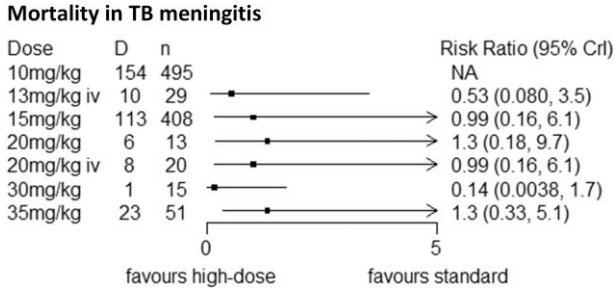

Figure 8. Mortality in TB meningitis. Footnote: Mortality was not improved by increasing the dose of rifampicin. With 980 participants included, the meta-analysis did not show significant differences in the RR of oral or intravenous rifampicin doses, probably because TB meningitis is a complex disease where inflammation and tissue remodelling contribute to the high mortality and sequelae.

In the NMA, no rifampicin dose did significantly decrease the risk of relapse (Figure 7). Consistently, the rankogram and SUCRA did not suggest a lower probability of relapse with increasing doses of rifampicin. (Supplementary Figure 8 and Supplementary Table 9).

Five studies reported 315 (30.5%) deaths among1031 participants [18, 21, 27, 30, 40]. There were 315 (30.5%) deaths. Ruslami et al showed that optimized rifampicin doses were an independent factor for survival [18], but other studies failed to show a survival advantage [21, 40].

In the NMA, no rifampicin dose showed a significant decrease in the RR for mortality (Figure 8). Intravenous doses of 13 mg/kg and 20 mg/kg had the highest 2nd and 3rd SUCRA scores (Supplementary Figure 9 and Supplementary Table 10).

Pharmacokinetics

Twelve studies reported pharmacokinetic data from 1007 participants. Increasing doses of rifampicin led to a more than proportional increase in both C_{max} and AUC_{0-24} (Figures 9*A* and 9*B*) [17–19, 22, 25, 27, 30, 31, 35, 41–43]. The T_{max} and $t_{1/2}$ were slightly affected by rifampicin dose in the NMA (Figures 9*C* and 9*D*, and Supplementary Figures 10–13, Supplementary Tables 11–14) [16–18, 22, 25, 27, 30, 31, 35, 42, 43] Excluding the data from the first week showed modest decrease in the pooled MD between standard and optimized doses of rifampicin (Supplementary Appendix). Figure 10 shows a complete 24 hours PK curve pooling data from 5 studies [16, 19, 24, 31, 44].

DISCUSSION

The results of this NMA suggest that optimized rifampicin dosing, particularly in the range 25–35 mg/kg/day may offer the best balance between safety and enhanced bactericidal and sterilizing activity for young people with pulmonary TB with or without HIV. This dose range is also safe for TBM, but we found no benefit in mortality. There is not enough data for advanced disease (only 12% of the participants had cavities), advanced age, comorbidities (eg, diabetes, immune suppression), and other forms of extrapulmonary TB, the groups with poorer TB treatment outcomes. The number of countries where TB clinical trials are implemented further limits the generalizability of the evidence, compared to the countries with a moderate to high TB burden (Supplementary Figure 14) [45].

We interpret with caution the finding of a significant increase in the RR for grade ≥3 AE in the 40 mg/kg/day, but not with 50 mg/kg/day, given the small numbers of participants included. Considering this NMA and the tolerance data from the original publication, it is reasonable to establish the 40 mg/kg/day as the maximum tolerated dose for rifampicin [20]. Of note, one study in this review stands out as having a large number of hepatic AE in all arms [26]. In contrast, a study from India, published after completing this systematic review, found a significant increase in the incidence of grade ≥3 hepatic adverse events in the 35 mg/kg but not in the 25 mg/kg/day arm; both arms had increased SCC rates [46]. We performed a post hoc sensitivity analysis including the results from Kannabiran et al, with similar results for the overall AE, and SCC at week 8 in liquid media, but with a small increase in the RR of hepatic adverse events for 35 mg/kg/day (Supplementary Figure 15). This highlights the importance of defining the dose that reaches exposure targets, at least at the population level, to find the optimal balance between safety and efficacy [47].

The known association between EBA and rifampicin dose had an inconsistent association with other efficacy outcomes in individual trials. In the NMA, this translated in a modest effect in SCC at week 8, better captured in liquid than in solid media. Two recent conventional meta-analyses, pooling data from

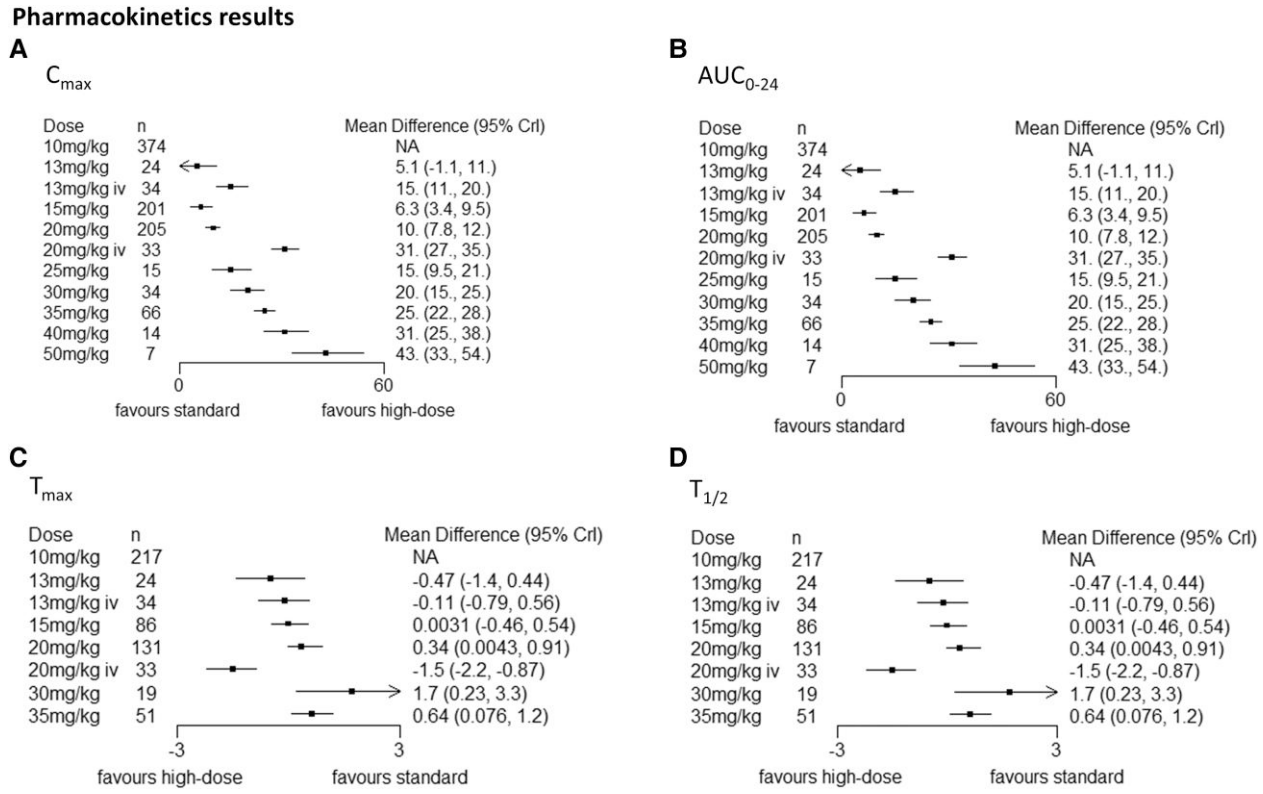

Figure 9. Pharmacokinetics results. Footnote: The figure shows that increasing the dose of rifampicin leads to an orderly increase in C_{max} (panel 9*A*), leading to a significantly higher exposure (AUC_{0-24}, panel 9*B*). A slight increase in T_{max} and $t_{1/2}$, suggests that the mechanisms of absorption and elimination are relatively capable to manage the increased amount of rifampicin in the bloodstream (panels 9*C* and 9*D*).

solid media cultures, had conflicting results regarding SCC at week 8 [10, 48]. This could be related to differences in techniques for pooling data and estimating the variance with relatively small effect sizes.

Clinical trials have typically included people with a relatively low baseline risk of relapse, which explains the low number of events. There is a need of operational research with more representative samples, and clinical trials using biomarkers to enrich their enrolment with high-risk of relapse population [49].

A large trial, using a moderate increase in the rifampicin dose (15 mg/kg/day) plus levofloxacin, probably drove the results on mortality in TBM [21]. Interestingly, the SUCRA results from this NMA and a recent model-based meta-analysis suggest that intravenous rifampicin had higher probability of a lower mortality than the same oral dose [50]. Intravenous administration of rifampicin may ensure drug exposure in severe illness [51]. Considering our NMA, only doses above oral 30 mg/kg/day or intravenous 20 mg/kg/day have a lower boundary of the credibility interval above the exposure targets suggested by another individual-level meta-analysis (AUC_{0-24} 116 mg·/L; C_{max} 22 mg/L) [18, 35].

A higher exposure with intravenous rifampicin is well known, and may have implications for clinical practice and clinical trial design. Despite this, the recommendation of a 1:1 dosing between oral and intravenous rifampicin persists in the package insert and relevant guidelines [52, 53]. Of note, the LASER-TBM study considered this difference and pooled together efficacy data from the 20 mg/kg/day intravenous with 35 mg/kg/day oral rifampicin groups, based on the PK sub-study [31]. However, improving mortality in TBM probably requires regimen optimisation plus high-quality support care and adequate immune modulation [54].

This is, to our knowledge, the first comprehensive NMA focused on rifampicin doses in TB. A previous NMA suggested an advantage of adding moxifloxacin to the standard first line treatment [55]. Another NMA focused on whole regimens and found the best balance of efficacy and safety with high-dose rifapentin [56]. Only 4 out of its 15 trials overlap with our review; the highest rifampicin dose in the efficacy network was 20 mg/kg/day.

Limitations

The rigmarole of different reporting criteria and heterogeneous designs limit evidence synthesis. Many studies included in this review were phase 2 trials with less than 16 weeks of follow-up; different trials reported TBM mortality at different times.

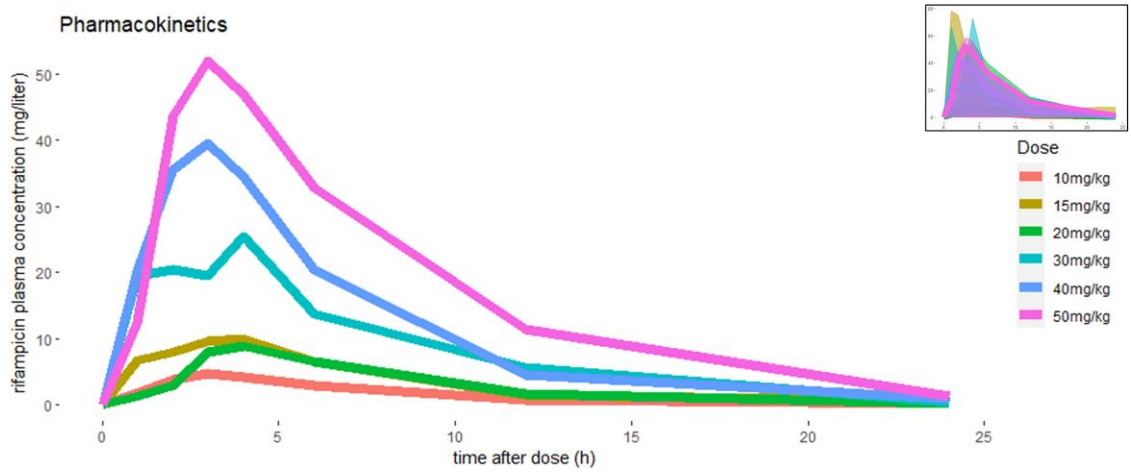

Figure 10. Pooled single-dose PK curves in steady state. Footnote: Six studies reported complete 24 h pharmacokinetic curves for a total of 600 participants. In the figure, the solid lines indicate the mean concentration of rifampicin after a single oral dose for doses of 10 (287 participants, red), 15 (164 participants, yellow), 20 (61 participants, green), and 30 (72 participants, turqoise), 40 (8 participants, blue), and 50 (8 participants, purple) mg/kg/day. The shadowed areas in the figure insert show the pooled confidence intervals. This figure illustrates the exponential increase in rifampicin exposure at the expense of the C_{max}, and the $AUC_{0–24}$. The decline in rifampicin concentration is faster with higher blood concentrations, thus explaining the slight differences in the median half-life ($t_{1/2}$). The wide confidence intervals, that are more than twice the value of the mean rifampicin concentration reflect the great interindividual variability of rifampicin pharmacokinetics, suggesting that optimising the exposure to rifampicin to improve clinical outcomes may require personalized dosing guided by PK testing. $AUC_{0–24}$ area under the curve between baseline and 24 h; C_{max} maximum concentration; PK pharmacokinetics; $t_{1/2}$ median half-life.

However, previous studies suggest that AE and mortality tend to happen early after treatment onset [57–59]. More importantly, we pooled the results regarding only to rifampicin dose. Six out of 19 studies used arms with other modifications to the standard first line treatment. Comparing full regimens instead of rifampicin doses would atomize the network with smaller nodes, decreasing the precision of the effect estimates [56]. Pooling pulmonary TB and TBM studies for safety outcomes is another factor of heterogeneity. The higher severity of TBM could overestimate the effect of rifampicin on severe AE. Despite this, the NMA did not show differences in safety with doses up to 35 mg/kg compared with the standard dose. Finally, routine care is generally not as supportive as clinical trials. People affected by TB and the clinical teams may be less engaged with each other than in clinical trials, and tolerability may have a larger weight in jeopardizing adherence. Some sites in Europe have already implemented optimized rifampicin doses in their daily practice [60]. The challenge is to translate this to settings with limited resources. We need implementation studies and standardized tools to collect real-world tolerability data, and advocate improving rifampicin presentation to reduce pill burden.

Future Perspectives

Several ongoing trials with optimized doses of rifampicin will add to this evidence (NCT02581527, NCT04694586, EudraCT 2021-0016-22). However, as people with low comorbidity and without advanced disease have a lower risk of poor outcomes at any disease stage, some rifampicin dosing trials may have missed their target population. The preliminary results of this review informed the design of the ongoing RIAlta trial (NCT04768231), conducted by the EUSAT-RCS consortium. In line with Study 31, this trial focuses on safety of rifampicin in people with a higher risk of treatment failure at baseline (eg, advanced age, or diabetes).

CONCLUSIONS

The optimal dose of rifampicin for drug-susceptible tuberculosis probably lies between 25 and 35 mg/kg/day. Within this range, targeted studies at the individual or at least the population level should provide the best balance between safety and efficacy.

We need clinical trials and programmatic studies focusing on people at risk of treatment failure or relapse, further regimen optimisation for these populations, and treatment shortening in all forms of TB.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. C. M-E., H. B., R. D., and A. A. designed the review and its objectives. E. N., A. M., G. M., and A. A. designed the review terms and adapted them to the different databases. E. N., A. M., and G. M.

performed the systematic screening and full-text review. A. A. and J. E-P. double-checked the final selection of studies. E. N., A. M., G. M., and J. E-P. extracted the data. J. E-P performed the statistical analysis. A. A. and J. E-P. drafted the first versions of the protocol and M. T., T. T., S. G., J-W. C. A., M. G. G. S., A. S-M., and R. D. provided feedback and implemented subsequent versions of the manuscript. C.M-E., J-W. C. A., R. D., and A. S-M. had the final decision for submitting the manuscript.

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