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Efficacy and safety of shorter multidrug-resistant or rifampicin-resistant tuberculosis regimens: a network meta-analysis

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Abstract

Background Drug-resistant tuberculosis (DR-TB) remains a threat to public health. Shorter regimens have been proposed as potentially valuable treatments for multidrug or rifampicin resistant tuberculosis (MDR/RR-TB). We undertook a systematic review and network meta-analysis to evaluate the efficacy and safety of shorter MDR/RR-TB regimens.

Methods We searched PubMed/MEDLINE, Cochrane Center for Clinical Trials (CENTRAL), Scopus, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, US Food and Drug Administration, and Chinese Clinical Trial Registry for primary articles published from 2013 to July 2023. Favorable (cured and treatment completed) and unfavorable (treatment failure, death, loss to follow-up, and culture conversion) outcomes were assessed as the main efficacy outcomes, while adverse events were assessed as the safety outcomes. The network meta-analysis was performed using R Studio version 4.3.1 and the Netmeta package. The study protocol adhered to the PRISMA-NMA guidelines and was registered in PROSPERO (CRD42023434050).

Result We included 11 eligible studies (4 randomized control trials and 7 cohorts) that enrolled 3,548 patients with MDR/RR-TB. Treatment with a 6-month combination of BdqLzdLfxZTrd/Eto/H had two times more favorable outcomes [RR 2.2 (95% CI 1.22, 4.13), $P=0.0094$], followed by a 9–11 month combination of km/CmMfx/LfxPtoCfzZEHh [RR1.67 (95% CI 1.45, 1.92), $P<0.001$] and a 6-month BdqPaLzdMfx [RR 1.64 (95% CI 1.24, 2.16), $P<0.0005$] compared to the standard longer regimens. Treatment with 6 months of BdqPaLzdMfx [RR 0.33 (95% CI 0.2, 0.55), $P<0.0001$] had a low risk of severe adverse events, followed by 6 months of BdqPaLzd [RR 0.36 (95% CI 0.22, 0.59), $P\leq 0.001$] and BdqPaLzdCfz [RR 0.54 (95% CI 0.37, 0.80), $P<0.0001$] than standard of care.

Conclusion Treatment of patients with RR/MDR-TB using shorter regimens of 6 months BdqLzdLfxZTrd/Eto/H, 9–11 months km/CmMfx/LfxPtoCfzZEHh, and 6 months BdqPaLzdMfx provides significantly higher cure and treatment completion rates compared to the standard longer MDR/RR-TB. However, 6BdqPaLzdMfx, 6BdqPaLzd, and 6BdqPaLzdCfz short regimens are significantly associated with decreased severity of adverse events. The findings are in support of the current WHO-recommended 6-month shorter regimens.

Keywords Rifampicin-resistant tuberculosis (RR-TB), Multidrug-resistant tuberculosis (MDR-TB), Short- term regimens, Systematic review, Network meta-analysis

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Introduction

Drug-resistant tuberculosis (DR-TB) remains a threat to the public's health and hurts individuals, communities, and healthcare facilities. According to recent figures, the burden of DR-TB is estimated to be 410 000 people (95% UI: 370 000–450 000) in cases of multidrug resistance (MDR-TB) or rifampicin-resistant TB (RR-TB) in 2022, out of which 3.3% were new cases [1, 2]. Treatment success rates have increased from 50% in 2012 to 60% in 2019, with 15% of MDR/RR-TB patients still dying from the disease [3].

Treatment of MDR/RR-TB using longer regimens (standard of care) requires a longer course of therapy (>18 months) based on the drug groupings (A, B, and C). All three Group A agents and at least one Group B agent should be used in MDR/RR-TB patients on longer regimens to guarantee that treatment begins with at least four TB agents that are likely to be effective and that at least three agents are used for the duration of treatment after bedaquiline is stopped. It is necessary to include both Group B agents if only one or two Group A agents are utilized. Agents from Group C are added to the regimen if agents from Groups A and B alone are unable to successfully complete the duration of the treatment [4]. However, they pose a greater pill load and have a higher toxicity profile than drug-susceptible TB regimens [5–7]. Moreover, patients may experience serious adverse events and worse treatment outcomes. Currently, approximately 20% of globally estimated MDR/RR-TB patients receive the needed second-line MDR/RR-TB regimens, and outcomes among these patients are poor, with only half reported as being successfully treated or completed [8, 9].

Acknowledging the challenges with the use of longer MDR/RR-TB regimens, the TB scientific community has been searching for improved regimen options, including for extensive drug resistance. Various studies and initiatives have been launched to explore novel regimens, including repurposed and newer medications. Shorter (<12-month) MDR-TB regimens include 6-month and 9-month treatment regimens in patients with MDR/RR-TB in whom resistance to fluoroquinolones (FQs) has been excluded. These may have the advantage of a better therapeutic effect and fewer adverse events [10–12].

Several randomized clinical trials are underway [13–17], and there are a couple of shorter regimen trials and cohort studies conducted worldwide.

First, a 6-month regimen based on bedaquiline, pretomanid, and linezolid (BPaL) in combination with moxifloxacin (BPaLM) and clofazamin (BPaLC) was evaluated in the TB-PRACTECAL randomized clinical trial [18, 19]. The other 6-month regimens based on the BPaL combination with decreased exposure to linezolid (lower dosing or shorter duration) were evaluated in the ZeNix study [20, 21]. Patients received 26 weeks of treatment, with the option of extending it to 39 weeks if they remained culture-positive with clinical evidence of active TB between 16 and 26 weeks. In addition, the NExT trial was performed with a linezolid, bedaquiline, levofloxacin, pyrazinamide, and either ethionamide, high-dose isoniazid (INH), or teridazone regimen [22]. Compared with traditional injectable-containing regimens, an all-oral 6-month MDR/RR-TB regimen was associated with a significantly improved 24-month WHO-defined treatment outcome (predominantly owing to toxicity-related drug substitution). However, drug toxicity occurred frequently in both arms.

The second, a shorter regimen (9–11 months), was noninferior to the longer regimen (22–20 months, following the 2011 WHO guidelines) with respect to the primary efficacy outcome and was similar to longer regimens in terms of safety. However, participants in the short-term regimen group had more adverse events (grade 3 or more) and death [23]. Other 9-month treatments with oral delamanid, linezolid, levofloxacin, and pyrazinamide showed a noninferior outcome and no difference in safety outcome compared to standard care regimens [24].

In the third 12-month regimen, a superiority study was performed to evaluate the benefit of a clofazimine (CFZ)-based regimen on clinical outcomes for MDR/RR-TB patients [25]. It showed a rapid sputum conversion rate and a comparable successful outcome compared with the standard of care.

In addition to randomized controlled trials, cohort studies performed on short-term regimens showed better primary and secondary outcomes than WHO standards of care regimens [26–31]. High scientific evidence is needed to use better regimens beyond programmatic use. Several systematic reviews as well as meta-analyses have documented shorter MDR/RR-TB regimens; however, there have been no network meta-analyses performed to compare multiple MDR/RR-TB shorter regimens simultaneously in a single analysis.

As a result, we conducted this systematic review and network meta-analysis of randomized controlled trials (RCTs) and cohort studies using the frequentist model to provide an up-to-date summary and analysis of previously published studies that have evaluated shorter MDR/RR-TB regimens. We also made instructive comparisons of their relative efficacy and adverse event profiles.

Methods

A systematic review and network meta-analysis was conducted, and the report followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for Network Meta-analysis (PRISMA-NMA) [32]. The protocol was prospectively registered with PROSPERO 2023 (ID: CRD42023434050).

Eligibility criteria

Randomized controlled trials and cohort studies comparing the efficacy and safety of WHO-approved treatment regimens of ≤12 months duration (shorter regimens) vs. WHO-approved treatment regimens of >12 months duration (longer regimens), and participants in all age groups with confirmed MDR/RR-TB were included. Single-arm studies and participants with XDR-TB were excluded from the review. Eligible treatments included in the treatment network were not clustered or merged into the same node.

The PICOS (participant/population, intervention, controls, outcome, and study design) description model was used to set eligibility criteria for the study.

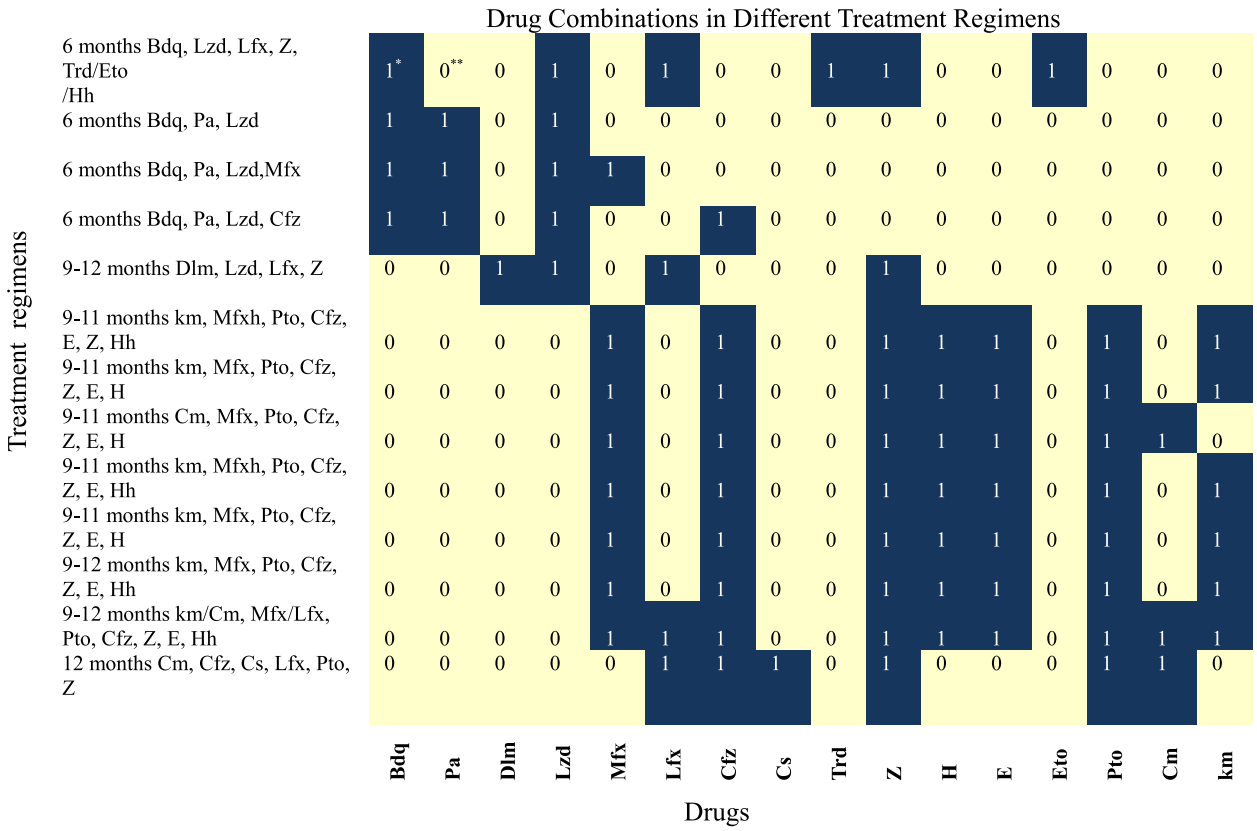
Participant

- Microbiologically confirmed *M. tuberculosis* in sputum and resistance to rifampicin and isoniazid irrespective of fluroquinolones.
- All age groups were included in the analysis.

Interventions

- Any short anti-TB drug (<12-month duration) tested to evaluate the efficacy and safety in patients diagnosed with MDR/RR- TB. The short-term regimens are summarized in Table 1.
- 6 months Bdq, Lzd, Lfx, Z, Trd/Eto/Hh regimen. Bedaquiline:400 mg daily for 2 weeks, followed by 200 mg 3 times per week for 24 weeks, Linezolid:

Table 1 Summary of the short-term regimens used for MDR/RR-TB treatment



Bdq Bedaquiline, *Cfz* Clofazimine, *Cm* Capreomycin, *Cs* Cycloserine, *Dlm* Delamanid, *Eto* Ethionamide, *H* Isoniazid, *Hh* Isoniazid high does, *km* Kanamycin, *Lfx* Levofloxacin, *Lzd* Linezolid, *Mfx* Moxifloxacin, *Mfxh* Moxifloxacin high dose, *Pa* Pretomanid, *Pto* Prothionamide, *Trd* Terizidone, *Z* Pyrazinamid

*Drug included in the regimens; **Drug not included in the regimens

600 mg, Levofloxaciline 750 mg for < 50 kg and 1000 mg for > 50 kg), Pyrazinamide 1000-1,750 mg for 40–50 kg, 1,750–2000 mg for 51–70 kg and 2000- 2,500 mg for 71–90 kg), Terizidone750 mg for 40–70 kg, and 750 − 100 mg for 71–90 kg) or Ethionamide: 15 mg/kg or high dose isoniazid 500 mg for 40–50 kg, 750 mg for 51–70 mg and 750–1000 mg for 71–90 kg).

- 12 months Cm, Cfz, Cs, Lfx, Pto, Z regimen. Capreomycin, Clofazimine, Cycloserine, Levofloxacin, Prothionamide, and Pyrazinamide).
- 9–11 months km, Mfx, Pto, Cfz, Z, E, H regimen(4–6 Km Mxf, Pto Cfz, E, Z, H and 5 Mxf, Cfz, EZ) : Dose for < 33 kg, 33–50 kg, > 50 kg, respectively: Moxifloxacin (400 mg, 600 mg, 800 mg); Clofazimine (50 mg, 100 mg, 100 mg); Kanamycin (15 mg per kg); Ethambutol (800 mg, 800 mg, 1200 mg); Pyrazinamide (1000 mg, 1500 mg, 2000 mg); Isoniazid (300 mg, 400 mg, 600 mg); and prothionamid (250 mg, 500 mg, 750 mg).
- 6 months Bdq, Pa, Lzd regimen: Bedaquiline 400 mg daily for 2 weeks, followed by 200 mg three times per week for 22 weeks; Protionamide 200 mg daily for 24 weeks; and linezolid 600 mg daily for 16 weeks, followed by 300 mg daily for 8 weeks.
- 6 months Bdq, Pa, Lzd, Mfx regimen: Bdq, Pa, Lzd plus Moxifloxacin 400 mg daily for 24 weeks.
- 6 months Bdq, Pa, Lzd, Cfz regimen: Bdq, Pa, Lzd plus Clofazimine 100 mg daily (or 50 mg if the patient weighed < 30 kg) for 24 weeks.
- 9–12 months Dlm, Lzd, Lfx, Z regimen: Delamanid 100 mg twice daily, Linezolid 600 mg per day for 2 months and 300 mg per day afterward, Levofloxacin 750–1000 mg per day and Pyrazinamide 1000–2000 mg per day.
- 9–11 months km, Mfxh, Pto, Cfz, E, Z, Hh regimen(4–6 Km, Mfxh, Pto, Cfz, Z, E, Hh and 5 Mfxh, Cfz, E, Z) : Kanamycin, high-dose moxifloxacin, prothionamide, Clofazimine, Pyrazinamide, Ethambutol and high-dose isoniazid.
- 9–11 months Cm, Mfx, Pto, Cfz, Z, E, H regimen(4–6 Cm, Mfx, Pto, Cfz, Z, E, H and 5 Mfx, Pto, Cfz, Z, E) : Capreomycin, Moxifloxacin, prothionamide, Clofazimine, Pyrazinamide, Ethambutol, and Isoniazid.
- 9–11 months km, Mfxh, Pto, Cfz, Z, E, Hh regimen(4–6 Km, Mfxh, Pto, Cfz, Z, E, Hh and 5 Mfxh, Cfz, E, Z) : kanamycin, high-dose moxifloxacin, prothionamide, clofazimine, pyrazinamide, ethambutol and high-dose isoniazid.
- 9–11 months km, Mfx, Pto, Cfz, Z, E, H regimen(4–6 Km, Mfx, Pto, Cfz, Z, E, H and 5 Mfx, Cfz, Z): kanamycin, Moxifloxacin, prothionamide, Clofazimine, Pyrazinamide, Ethambutol and Isoniazid.9–12 months km, Mfx, Pto, Cfz, Z, E, Hh regimen(4–6 Km, Mfx, Pto, Cfz, Z, E, Hh and 5 Mfx, Cfz, Z, E) : kanamycin, Moxifloxacin, prothionamide, Clofazimine, Pyrazinamide, Ethambutol and high-dose isoniazid.
- 9–12 months km/Cm, Mfx/Lfx, Pto, Cfz, Z, E, Hh regimen(4–6 Km/Cm, Mfx/Lfx, Pto, Cfz, Z, E, Hh and 5–6 Mfx/Lfx, Pto, Cfz, Z, E) : Kanamycin/Capreomycin, Moxifloxacin/Levofloxacin, Prothionamide, Clofazimine, Pyrazinamide, Ethambutol and high-dose isoniazid.

Control/Comparator

- Standard of care, thus long MDR/RR-TB regimens given > 18 months duration as stated in the WHO guidelines, and long regimens > 18 months duration with local modification based on the patient characteristics and drug availability. All three Group A agents and at least one Group B agent should be used in MDR/RR-TB patients on longer regimens to guarantee that treatment begins with at least four TB agents that are likely to be effective and that at least three agents are used for the duration of treatment after bedaquiline is stopped. It is necessary to include both Group B agents if only one or two Group A agents are utilized. Agents from Group C are added to the regimen if agents from Groups A and B alone are unable to successfully complete the duration of the treatment [4].

Group A: Levofloxacin or Moxifloxacin, Bedaquiline, and Linezolid.
Group B: Clofazimine, Cycloserine or Terizidone.
Group C: Ethambutol, Delamanid, Pyrazinamide, Imipenem–Cilastatin or.
Meropenem, Amikacin or Streptomycin, Ethionamide or Prothionamide, and P-aminosalicylic acid.

Outcome

The study used the following summary outcomes for analysis:

Primary outcomes

o Favorable outcome (cure, treatment completed, and culture conversion).
o Unfavorable outcomes (treatment failure, death, and loss to follow-up).

Secondary outcome

o Adverse events of the drugs. It was stratified by severity using the National Institute of Allergy and Infectious Diseases, Division of AIDS (DAIDS) system [33] .

The following treatment outcome definitions were adapted from WHO guidelines [34].

Cure: Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment completion: A patient who completed treatment as recommended by the national policy whose outcome does not meet the definition for cure or treatment failure.
Closure of the TB cavity: A sputum culture conversion and corresponding changes in the size of the cavity observed on CT scan images.
Culture conversion: Culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.
Death: Death from any cause during treatment not meeting the criteria for failure.
Favorable outcome/success/: The sum of cured and treatment completed.
Lost to follow-up: A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Treatment failure: Treatment terminated or need for a permanent regimen change of at least two anti-TB drugs because of a lack of conversion by the end of the intensive phase or bacteriological reversion in the continuation phase after conversion to negative, or evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or adverse drug reactions (ADRs).
Serious Adverse Events (SAEs): are defined as any undesirable experience occurring to a patient, whether or not considered related to the treatment. A serious adverse event is any untoward medical occurrence that results in death or is life-threatening (i.e. the patient was at immediate risk of death at the time the reaction was observed), requires hospitalization or prolongation of hospitalization, results in severe/permanent disability and a congenital anomaly/birth defect.
Sever adverse event: is a measure of intensity, thus grade 3 events leading marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible. A severe adverse event is not necessarily serious.

Study design:

– Randomized controlled trials and cohort studies published in the English language.

Information sources

A systematic literature search was performed to identify relevant articles from the online databases PubMed/MEDLINE, Scopus, and the Cochrane Center for Clinical Trials (CENTRAL) for primary articles published from 2013 to July 2023. To search and assess ongoing or unpublished trials, ClinicalTrials.gov, China's clinical trial registry databases, the WHO International Clinical Trials Registry Platform, and the US Food and Drug Administration (FDA) registers were searched. Web search using Google Scholar and gray literature search was not done. The search was performed according to guidance provided in the Cochrane Handbook for Systematic Reviews of Interventions [35].

Electronic searches

The search strategies in PubMed for the text words were ((((((((((((((((((Multidrug- resistance tuberculosis) AND (Rifampicin- resistant tuberculosis)) AND (Short-term regimens)) OR (Bedaquiline)) OR (Linezolid)) OR (Pyrazinamide)) OR (Terizidone)) OR (Ethionamide)) OR (Isoniazid)) OR (Capreomycin)) OR (Clofazimine)) OR (Cycloserine)) OR (Levofloxacin)) OR (Prothionamide)) OR (Moxifloxacin)) OR (Kanamycin)) OR (Delamanid)) OR (Gatifloxacin)) OR (Pretomanid)) OR (Amikacin).

Study selection

Two authors (YA and DGA) independently reviewed the results, and disagreements were resolved through discussion. When clarification was necessary, the trial authors were contacted.

Data extraction and management

The title and abstract were generated by an electronic search and independently screened by two authors (YA and DGA). We designed a data extraction form to collect data from eligible studies. The extracted data were compared, and any inconsistencies were addressed through discussion.

Data items

Variables of interest used to extract data include characteristics of the study (such as countries, settings, number of centers, funding sources, registration status, and drug regimens), characteristics of the study design (such as

randomized or non-randomized), characteristics of participants (such as age, sex, previous TB treatment, lung cavity, AFB, HIV, and diabetes), the number of participants enrolled and included in analyses, characteristics of the interventions (such as short- and long-term regimens, drug dosage, and duration of the regimens) and the results (such as summary statistics, favorable outcome, loss to follow-up, death, treatment failure, culture conversion, TB cavity closure, and adverse events).

Geometry of network

Network geometry used nodes to represent different shorter regimens for MDR-TB treatments and edges to represent the head-to-head comparisons between network nodes. The node size and edge thickness represented the sample sizes of the intervention and the numbers of included trials, respectively.

Assessment of risk of bias

The risk of bias for each trial was independently evaluated by two review authors using the Cochrane Collaboration's tool for assessing the 'Risk of bias' [35] and Cochrane's risk of bias tool for nonrandomized studies (ROBINS-I) [36].

Summary measures

The risk ratio was used to present summary findings from the meta-analysis.

Planned method of analysis

The network meta-analysis was performed using R- studio Version 4.3.1. The network meta-analysis was performed using the frequentist model for each treatment comparison using the Netmeta package.

Assessment of heterogeneity

Heterogeneity among the included trials was assessed by inspecting the forest plots, and the Cochrane Q and I^2 statistic was used to measure heterogeneity among the trials in each analysis. The Chi^2 test with a $P<0.05$ to indicate statistical significance was used. To further determine whether specific study characteristics influence the magnitude of effect sizes found in our network and check for variables that may explain inconsistency, network meta-regression was performed.

Results

The search resulted in a total of 36,522 studies, of which 44 full-text eligible studies were evaluated further, and 11 of them fulfilled the inclusion criteria and were included in the network meta-analysis Fig. 1. Of the 11 studies (4 RCTs and 7 cohort), four were randomized controlled trials [19, 22–24], and seven were cohort studies [25–31].

Characteristics of the included studies

All studies reported only MDR/RR-TB patients and provided information regarding drug susceptibility testing for fluoroquinolones and second-line drugs. Hence, 111 patients in these studies had fluoroquinolone resistance, while 93 were resistant to second-line injectables.

From a total of 3,548 patients, 1,164 (51.8% of those with information) had a history of prior treatment with first-line drugs, 1,651 (65.6% with chest radiography information) had cavitation on a chest radiograph, and 1,924 (67.6% with acid-fast bacilli (AFB) results) were AFB sputum smear positive. Only 398 (61.4% of tested) had HIV co infection, and 61 (17.8% of those with information) had diabetes mellitus. The study design, demographics, and outcome information are summarized in Table 2, and other baseline characteristics are summarized in supplementary document S1.

Methodological quality and risk of bias

Our summary shows that the majority of the studies were either open-label (high risk for bias) or unclearly biased. The rest of the domains had a low risk for bias. The risk of bias assessments are summarized in Figs. 2 and 3.

Favorable outcome

In this analysis, 10 studies, 15 pairwise comparisons and 12 treatment groups were included. The network diagram shows that most of the studies compared the standard treatment with KmMfxPtoCfzZEHh (Fig. 4).

The forest plot show that the risk of developing favorable outcomes was two times higher for RR 2.2 (95% CI 1.22; 4.13, $P=0.0094$) than the standard treatment in patients who were treated with 6BdqLzdLfxZTrd/Eto/H followed by 9–12 km/CmMfx/LfxPtoCfzZEHh (4–6 km/CmMfx/LfxPtoCfzZEHh and 5–6 Mfx/LfxPto CfzZE) RR1.67 (95% CI 1.45; 1.92, $P<0.0001$) as shown in Fig. 5. The overall heterogeneity was not significant ($p=0.749$, $tau^2=0$; tau = 0; $I^2=0\%$) in Fig. 6.

Lost to follow-up

In this analysis, 6 studies, 13 pairwise comparisons and 9 treatment groups were included. The network diagram shows that most of the studies compared the standard treatment with 9–12 km/CmMfx/LfxPtoCfzZEHh (4–6 km/CmMfx/LfxPtoCfzZEHh and 5–6 Mfx/LfxPto CfzZE), Fig. 7.

The net rank result and forest plot show that the risk of loss to follow-up was 80% lower, RR 0.20 (95% CI 0.1; 0.38, $P=0.0002$), than the standard treatment in patients who were treated with 6BdqPaLzdMfx and 6BdqPaLzd Cfz followed by 12DlmLzdLfxZ, RR 0.30 (95% CI 0.03; 2.58, $P=0.0003$). The overall heterogeneity was not significant (P = -; tau2 = NA; tau = NA; I2 = NA) in Fig. 8.

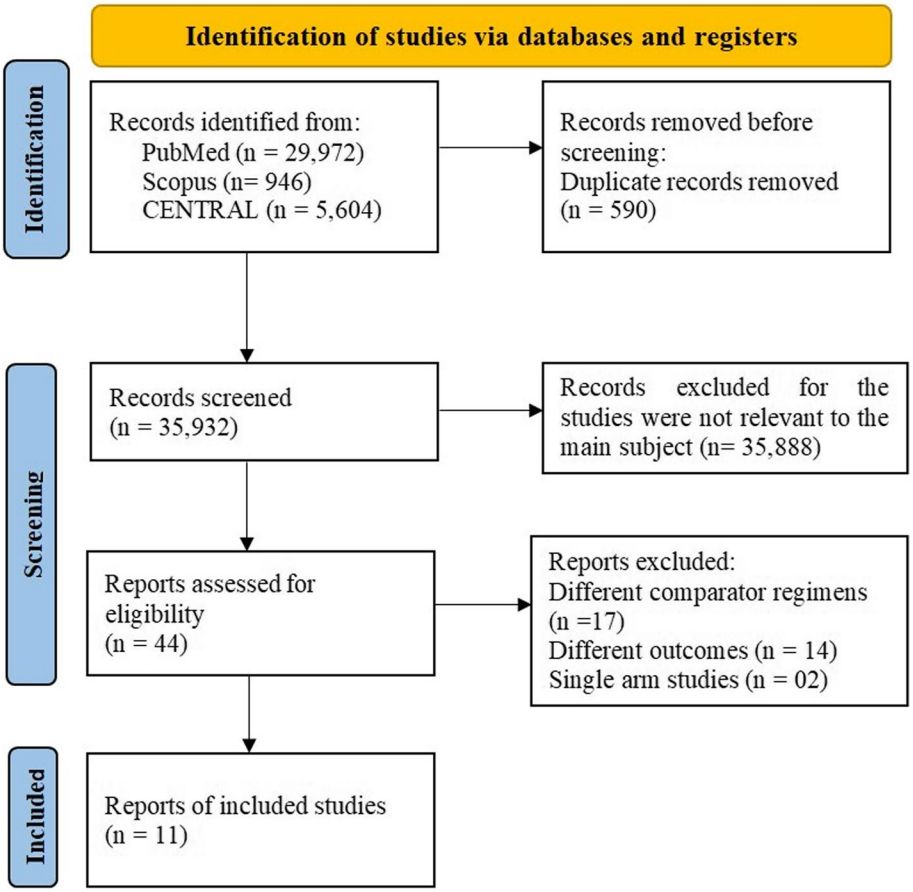


Fig. 1 PRISMA-NMA flow chart of study selection for inclusion in the systematic review and network meta-analysis

Treatment failure

In this analysis, 7 studies, 7 pairwise comparisons, and 8 treatment groups were included. The forest plot shows that there is no statistically significant difference in the risk of developing treatment failure between the shorter regimens and longer standard treatment. However, there is a clinically significant reduction in the risk of treatment failure among patients who were treated with a combination of 9-11KmMfxhPtoCfzZEHh (4–6 KmMfxhPtoCfzZEHh and 5MfxhCfzEZ) and 12DlmLzdLfxZ, Fig. 9. The tests of heterogeneity (within designs) and inconsistency (between designs) show that there is no heterogeneity or inconsistency.

Cultural conversion

In this analysis, 8 studies and 11 treatment groups were included. The test random effect model for heterogeneity (within designs) and inconsistency (between designs) were not statistically significant. The net rank and forest plot show that the risk of culture conversion 2 months after the start of the regimens was 34% higher RR 1.34 (95% CI 1.05; 1.71, $P=0.01$) than the standard treatment in patients who were treated with 9–12 km/CmMfx/LfxPtoCfzZEHh (4–6 km/CmMfx/LfxPtoCfzZEHh and 5–6 Mfx/LfxPto CfzZE) followed by CmMfxPtoCfzZEH (4-6CmMfxPtoCfzZEH and 5MfxPtoCfzZE) RR 1.34 (95% CI 1.10; 1.62, $P=0.0029$), as shown in Fig. 10. The overall heterogeneity was not significant ($tau^2=NA$; $tau=NA$; $I^2=NA$ %).

Cavity closure

One study [25] showed that the cavity closure rate in the short-term regimen was 37.5% (18/48) by the end of treatment, which was better than that of the standard-of-care regimen (24.1%, 14/58; $P=0.06$).

Adverse events

The included studies [23, 25, 28] reported hypokalemia as an adverse event, and it was more common among patients who were treated with 12CmCfzCsLfxPtoZ (6CmCfzCsLfxPtoZ and 6CfzCsLfxPtoZ) (2/67, 3%) and 9-11KmMfxPtoCfzZEH (4–6 KmMfxPtoCfzZEH and.

5MfxCfzZ) (3/282, 1.1%) and 9–11 KmMfxhPtoCfzZEHh (4–6 KmMfxhPtoCfzZEHh and.

5MfxhCfzEZ) (1/140, 0.7%). Furthermore, anemia was also common among patients who were treated

Table 2 Summary characteristics of studies included in the systematic review and network meta-analysis

Authors/ year	Setting/ country registration number	Study design, Sample size and Arm	Age in year Median (IQR)		Sex		Intervention regimen		Comparator regimen		Outcome (primary; secondary)	
			Intervention group	Comparator group	Male	Female	Intensive	Continuation			Intervention groups	Comparator groups
Du, Y.,2020 [25]	China Chi CTR 1,800,020,391	Cohort,135	37.9 19–63	39 19–61	89	64	6Cm, Cfz, Cs, Lfx, Pto, Z	6Cfz, Cs, Lfx, Pto, Z	6Cm, E,Cs, Lfx, Pto, Z	12E, Cs, Lfx, Pto, Z	Favorable outcome: 46/67	44/68
											Death: 2/67	1/68
											LTF: 12/67	13/68
											TF: 7/67	10/68
											Culture conversion: 46/67	38/68
											Cavity closure: 18/48	14/58
											AE: 35/67	32/68
Esmail,2022 [22]	South Africa NCT02454205	RCT,93 (1:1)	36 (29–46.5)	37 (31–43)	65	31	6Bdq, Lzd, Lfx, Z,Trd/Eto/Hh		SOC with local modification		Favorable outcome: 25/49	10/44
											Death: 4/49	4/44
											LTF: 5/49	1/44
											TF: 3/49	5/44
											Culture conversion :37/43	29/41
											AE: 76/56	79/55
Hassane-Harouna, S.,2020 [26]	Guinean	Cohort,271	26 (21–39)	30 (24–38)	195	76	4–6 km, Mfxh, Pto, Cfz, Z,E, Hh	5Mfxh, Cfz, E,Z	6Km, Lfx, Cs, Pto, Z	18Lfx, Pto, Cs, Z	Favorable outcome: 145/196	44/75
											Death: 30/196	11/75
											LTF: 16/196	15/75
											TF: 5/196	5/75
Mleoh, L.,2023 [28]	Tanzania	Cohort,382	NA	NA	NA	NA	4–6 km, Mfxh, Pto, Cfz, Z,E, Hh	5Mfxh, Cfz, E,Z	SOC		Favorable Outcome: NA Death : LTF: TF:	
											AE: 53/140	35/90
Mok, J.,2018 [24]	South Korea NCT02619994	RCT,168 (1:1)	49 (39–57)	46 (34–60)	116	52	6Dlm, Lzd, Lfx, Z	3Dlm, Lzd, Lfx, Z	SOC		Favorable outcome: 54/72	60/85
											Death: 2/72	2/85
											LTF: 1/72	4/85
											TF: 5/72	11/85
											Sever AE: 29/79	26/89
											Serious AE : 20/79	19/89
Myemb, D.T,2020 [29]	Tanzania	Cohort,300	NA	NA	NA	NA	4–6 km, Mfx, Pto, Cfz, Z,E, H	5Mfx, Cfz, PZA	8Km/Cm, Cs, Lfx, Eto, PZA,+_E	12Cs, Eto, PZA, Lfx,+_E	Favorable Outcome: 53/62	97/109
											Death: 8/60	9/125
											LTF: TF: NA AE	NA

Table 2 (continued)

Authors/ year	Setting/ country registration number	Study design, Sample size and Arm	Age in year Median (IQR)		Sex		Intervention regimen		Comparator regimen	Outcome (primary; secondary)	
			Intervention group	Comparator group	Male	Female	Intensive	Continuation		Intervention groups	Comparator groups
Nunn, A.J., 2019 [23]	Multi country (Ethiopia, Mongolia, South Africa, Vitenam) NCT02409290	RCT,383,(2:1)	NA	NA	234	149	4-6Km, Mxf, Pto Cfz, E,Z, H	5Km, MxfP-toCfzEZH	SOC with local modification	Favorable Outcome: 193/245	99/124
										Death: 8/282	3/142
										LTF: 1/245	3/124
										TF: NA	NA
										Culture conversion: 145/253	72/130
										AE: 136/282	64/142
Nyang'wa, 2022 [19]	South Africa, Belarus, Uzbekistan), NCT02589782	RCT,252, 4(1:1:1:1)	35 (17–71) 32 (15–67) 35 (15–72)	37 (18–71)	141	111	6Bdq Pa, Lzd 6BdqPa, Lzd, Mfx 6Bdq Pa, Lzd, Cfz		SOC with modification	Favorable Outcome[a] (46/70, 55/72 and 52/72)	34/73
										Death: [a](0/70, 0/72 and 1/72)	2/73
										LTF: [a](8/70 ,5/72 and 6/72)	28/73
										TF: (0/70, 0/72 and 1/72)	0/73
										Culture conversion [a](73/90 ,85/96 and 84/97)	78/99
										AE: [a](15/70, 14/72 and 23/72)	43/73
P.du, Cross, 2017 [27]	Uzbekistan	Cohort,298	31.0 (24.0; 50.8)	29.4(23.9; 42.8)	178	162	4–6 Cm, Mfx, Pto, Cfz, Z,E, H	5MfxPtoCfzZE	SOC	Favorable outcome: 74/110 Culture conversion: 61/88	158/231 109/210
Wahid, A., 2022 [30]	Pakistan	Cohort	NA	NA	345	356	4–6 km, Mfx, Pto, Cfz, Z,E, Hh	5Mfx, Cfz, Z,E	SOC	Favorable outcome: 262/313	284/388
										Death: 31/313	37/388
										LTF: 16/313	27/388
										TF: 4/313	6/388
										Culture Conversion: 272/313	331/388

Table 2 (continued)

Authors/ year	Setting/ country registration number	Study design, Sample size and Arm	Age in year Median (IQR)		Sex		Intervention regimen		Comparator regimen		Outcome (primary; secondary)	
			Intervention group	Comparator group	Male	Female	Intensive	Continuation			Intervention groups	Comparator groups
Zhdanova, E., 2021 [31]	Kyrgyzstan	Cohort	NA	NA	241	165	4–6 km/Cm, Mfx/Lfx, Pto, Cfz, Z,E, Hh	5–6 Mfx/Lfx, Pto, Cfz, Z,E	8Cm/km, Lfx/ Mfx, Pto, Cs, PZA, PAS	12Lfx/Mfx, Pto, Cs, PZA, PAS	Favorable outcome: 110/132	137/274
											Death: 0/132	36/274
											LTF: 18/132	93/274
											TF: 4/132	8/274
											Culture conversion: 62/132	96/274

Bdq Bedaquiline, *Cfz* Clofazimine, *CI* Confidence interval, *Cm* Capreomycin, *Cs* Cycloserine, *Dlm* Delamanid, *Eto* Ethionamide, *H* Isoniazid, *Hh* Isoniazid high does, *km* Kanamycin, *Lfx* Levofloxacin, *Lzd* Linezolid, *LTF* Lost to follow up, *Mfx* Moxifloxacin, *Mfxh* Moxifloxacin high dose, *Pa* Pretomanid, *Pto* Prothionamide, *RCTs* Randomized control trials, *SOC* Standard of Care, *STR* Short treatment regimen, *TF* Treatment failure, *Trd* Terizidone, *Z* Pyrazinamide

[a] (6BdqPaLzd, 6BdqPaLzdMfx, and 6BdqPaLzdCfz)

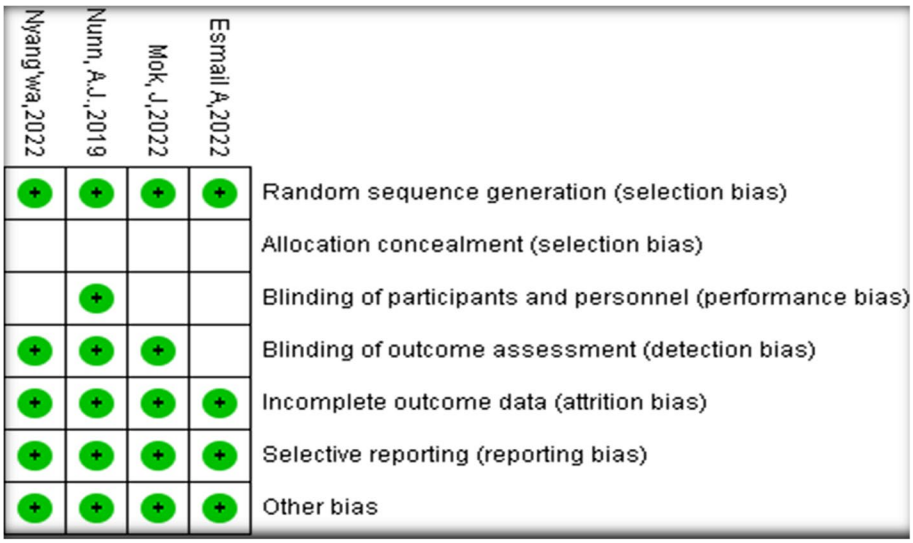


Fig. 2 Risk of bias summary: review authors' judgments about each risk of bias item for each included study using the Cochrane Collaboration's tool for assessing the 'Risk of bias'

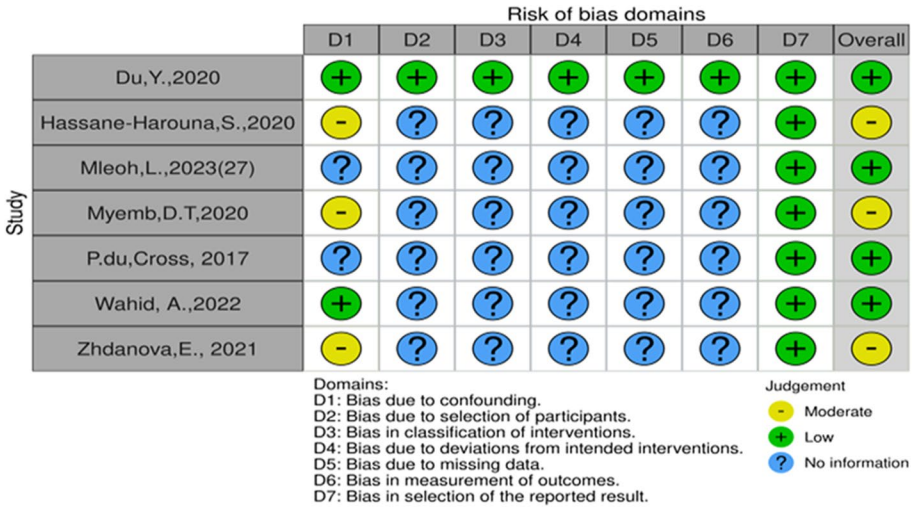


Fig. 3 Risk of bias summary: review authors' judgments about each risk of bias item for each included study using ROBIN's tool

with BdqLzdLfxZTrd/Eto/Hh (10/49, 20.4%), BdqPaLzdMfx (2/72, 3%) and BdqPaLzd (1/69, 1%) [19, 22]. In addition, these two studies reported adverse event-related drug discontinuation or modification, and it was more common among patients who had been treated with 6BdqLzdLfxZTrd/Eto/Hh [22] (17/49, 34.6%), of whom linezolid was identified as a culprit drug in 11/17 (64.7%) participants with adverse events where the drug was stopped; the majority of linezolid events (10/11, 90.9%) were related to anemia, and participants who used 9-11KmMfxPtoCfzZEH (4-6KmMfxPtoCfzZEH and 5MfxCfzZ) [23] treatment was modified in response to prolongation of the QT or QTcF (32/282, 11.3%), the moxifloxacin dose was reduced in 21 participants, and moxifloxacin was switched to levofloxacin in 12 participants, of whom 3 also discontinued clofazimine and 1 continued clofazimine at half the dose.

Severe adverse events

In this analysis, 3 studies and 6 treatment groups were included. The network diagram shows that most of the studies compared the standard treatment with 9–11 KmMfxPtoCfzZEH (4-6KmMfxPtoCfzZEH and 5MfxCfzZ), Fig. 11.

The test random effect model for heterogeneity (within designs) and inconsistency (between designs) were

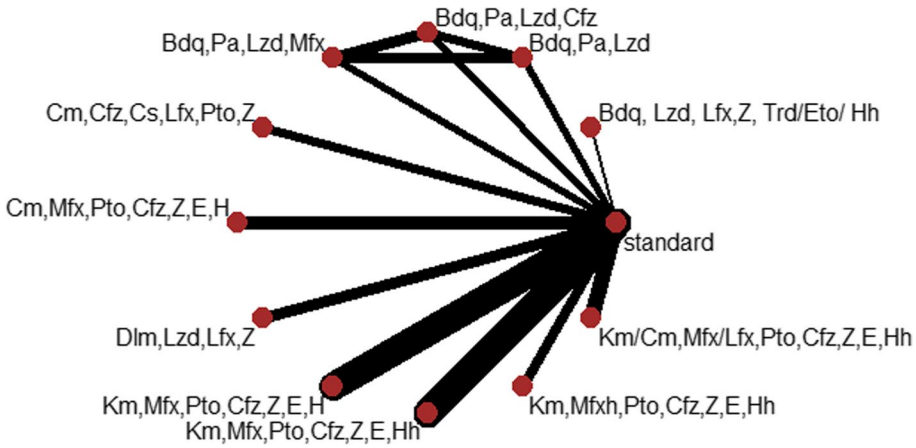


Fig. 4 Network diagram for a favorable outcome among MDR-TB patients treated with short regimens

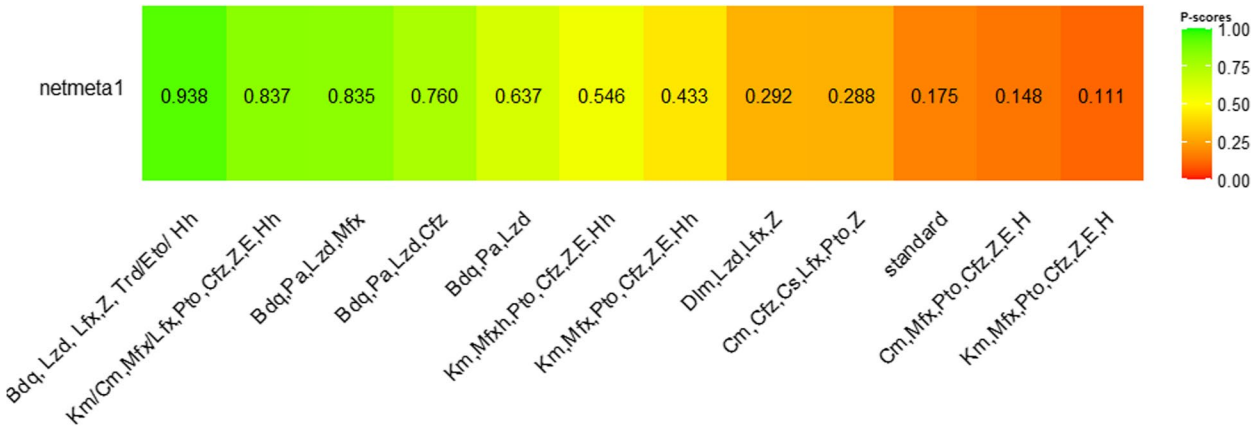


Fig. 5 Forest plot for favorable outcomes among MDR-TB patients treated with shorter regimens

not statically significant (p= -; tau^2 = NA; tau = NA; I^2 = NA %). The net rank result and forest plot show that the risk of severe adverse events was 67% lower RR 0.33 (95% CI 0.2; 0.55, $P < 0.0001$) than the standard treatment in patients who were treated with 6BdqPaLzd-Mfx followed by 6BdqPaLzd RR 0.36 (95% CI 0.22; 0.59, $P = 0.001$). In contrast, the risk of developing severe adverse events was significantly higher in patients who were treated with 6BdqLzdLfxZTrd/Eto/Hh (RR 1.43, 95% CI 1.09; 1.9, $P = 0.0090$) Fig. 12.

Renal adverse events

In this analysis, 4 studies, 9 pairwise comparisons and 7 treatment groups were included. The test random effect model for heterogeneity (within designs) and inconsistency (between designs) were not statistically significant (p= -; tau^2 = NA; tau = NA; I^2 = NA%). The net rank result and forest plot show that the risk of renal disorder was 93% lower RR 0.07 (95% CI 0.003; 1.16, $P = 0.06$) than the standard treatment in patients who were treated with 6BdqPaLzdCfz followed by 6BdqPaLzdMfx RR 0.2 (95% CI 0.04; 1.14, $P = 0.06$) Fig. 13.

Hepatic adverse events

In this analysis, 3 studies, 9 pairwise comparisons, and 6 treatment groups were included. The test random effect model for heterogeneity (within designs) and inconsistency (between designs) were not statically significant ($p = 0.278$; tau^2 = 0,022; tau = 0.47; I^2 = 14.9%). The net rank result and forest plot show that the risk of hepatic adverse events was 79% lower RR 0.21 (95% CI 0.05; 0.92, $P = 0.036$) than the standard treatment in patients who were treated with 6BdqPaLzd, Fig. 14.

Cardiac conduction (QTc prolongation) adverse events

In this analysis, 3 studies, 9 pairwise comparisons, and 6 treatment groups were included. The test for random

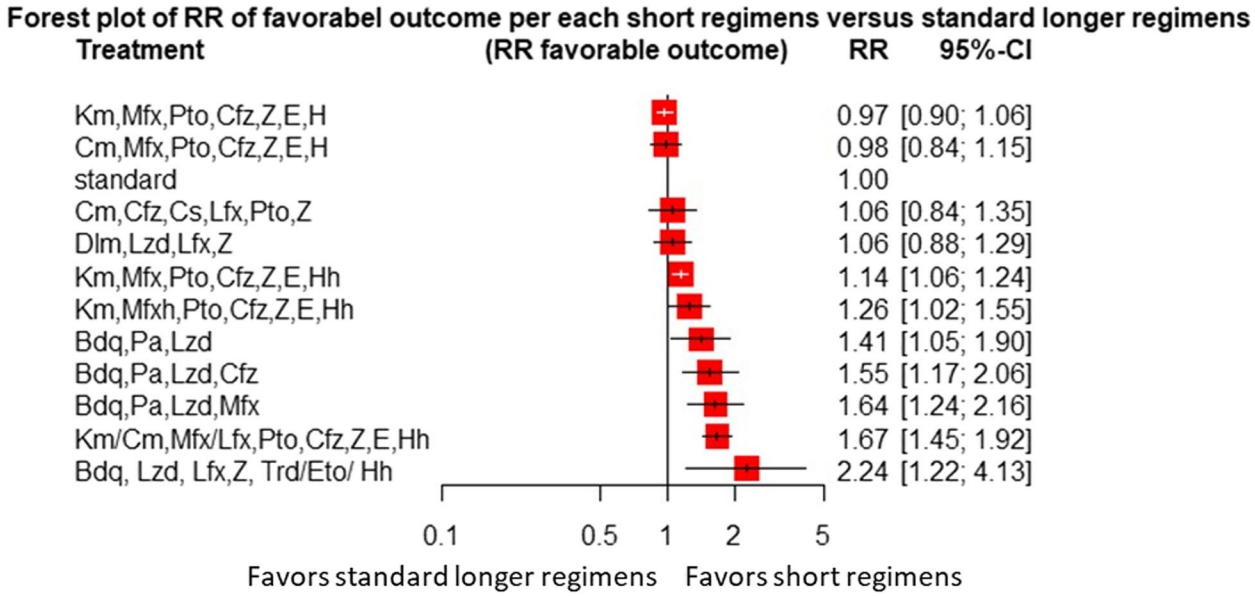


Fig. 6 Net rank plot for a favorable outcome among MDR-TB patients treated with short regimens

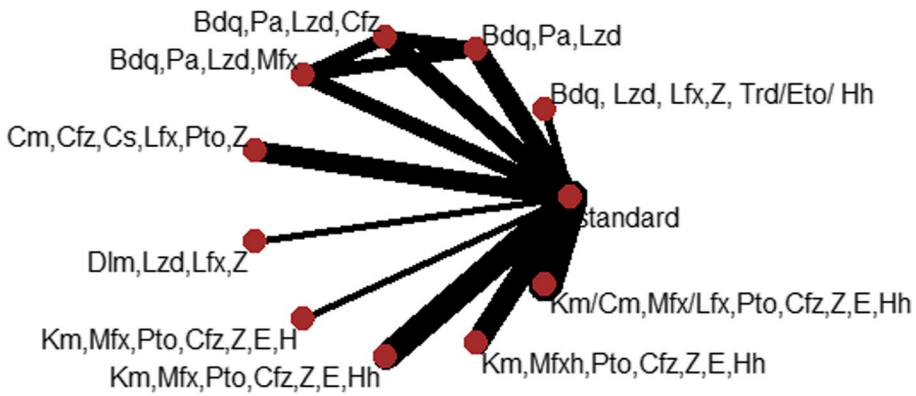


Fig. 7 Network diagram for loss to follow-up among MDR-TB patients treated with short regimens

effect model for heterogeneity (within designs) and inconsistency (between designs) were not statistically significant. The net rank result and forest plot show that the risk of QTc prolongation was 99.5% lower RR 0.05 (95% CI 0.003; 0.92, $P=0.036$) than the standard treatment in patients who were treated with 6BdqPaLzd followed by 6BdqPaLzdMfx RR 0.14 (95% CI 0.03; 0.78, $P=0.024$). However, some patients who were treated with 9-11KmMfxPtoCfzZEH (4-6KmMfxPtoCfzZEH and 5MfxCfzZ) and 12DlmLzdLfxZ experienced QTc prolongation Fig. 15.

Gastrointestinal adverse events

In this analysis, 3 studies, 3 pairwise comparisons and 4 treatment groups were included. The test random effect model for heterogeneity (within designs) and inconsistency (between designs) were not statically significant. The net rank result and forest plot show that the risk of gastrointestinal disorder was 65% lower RR 0.35 (95% CI 0.14; 0.90, $P=0.029$) than the standard treatment in patients who were treated with 9-11KmMfxPtoCfzZEH (4-6KmMfxPtoCfzZEH and 5MfxCfzZ), Fig. 16.

Ear and labyrinth adverse events

In this analysis, 4 studies, 4 pairwise comparisons and 5 treatment groups were included. The test random effect model for heterogeneity (within designs) and inconsistency (between designs) were not statistically significant. The net rank result and forest plot show that the risk of gastrointestinal disorder was 99.5%

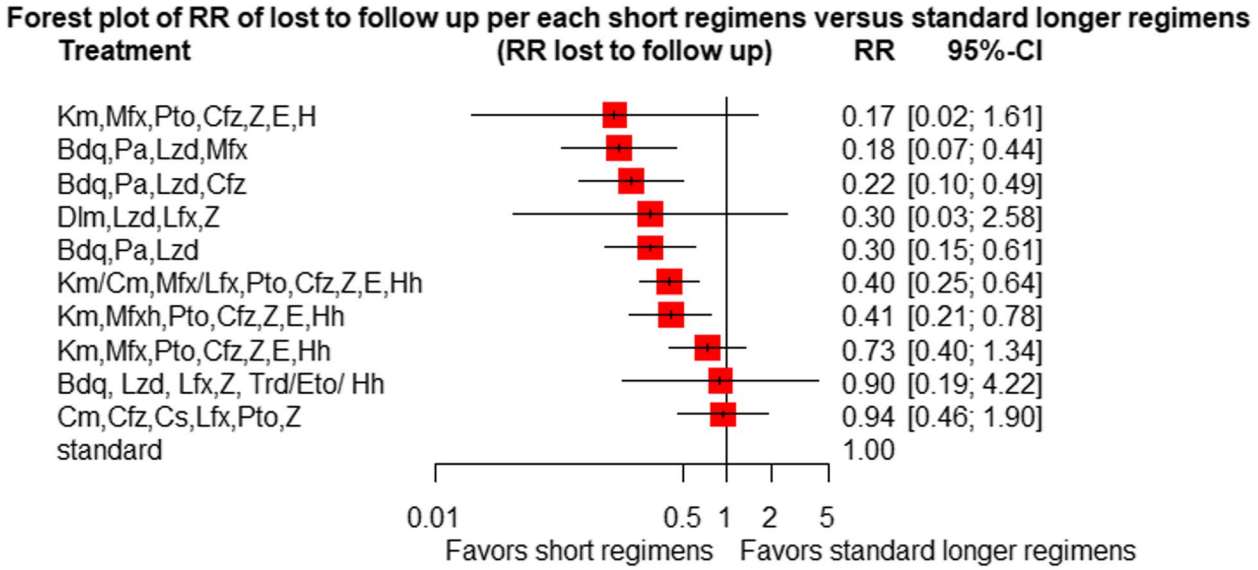


Fig. 8 Forest plot for loss to follow-up among MDR-TB patients treated with short regimens

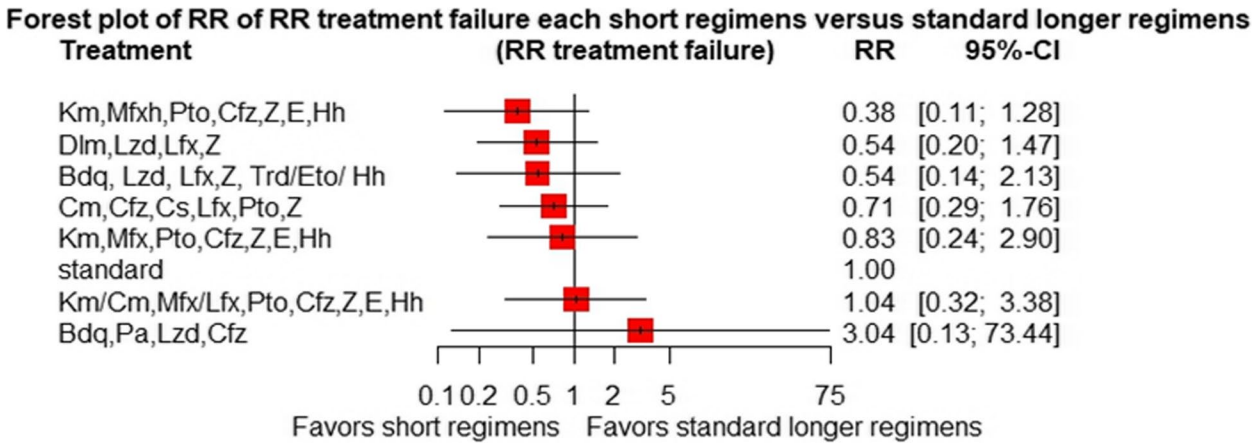


Fig. 9 Forest plot for treatment failure among MDR-TB patients treated with short regimens

lower RR 0.05 (95% CI 0.01; 0.34, $P=0.0024$) than the standard treatment in patients who were treated with 6BdqLzdLfxZTrd/Eto/Hh followed by 12DlmLzdLfxZ RR 0.12 (95% CI 0.02; 0.90). In contrast, adverse events related to the ear and labyrinth was high in patients treated with 9-11KmMfxPtoCfzZEH (4-6KmMfxPto CfzZEH and 5MfxCfzZ) Fig. 17.

Peripheral neuropathy

In this analysis, 3 studies, 8 pairwise comparisons and 6 treatment groups were included. The test random effect model for heterogeneity (within designs) and inconsistency (between designs) were not statically significant. The net rank result and forest plot show that the risk of peripheral neuropathy was 57% lower RR 0.43 (95% CI 0.21; 0.84, $P=0.014$) than the standard treatment in patients who were treated with 6BdqPaLzdCfz followed by 6BdqPaLzdMfx RR 0.50 (95% CI 0.27; 0.91), Fig. 18.

Serious adverse events

Four studies, 3 pairwise comparisons, and 4 treatment groups were included in this analysis.

The tests of heterogeneity (within designs) and inconsistency (between designs) were not statistically significant (tau^2 = NA; tau = NA; I^2 = NA%, P= -).

The net rank and forest plot showed no statistically significant difference from standard-of-care regimens. However,

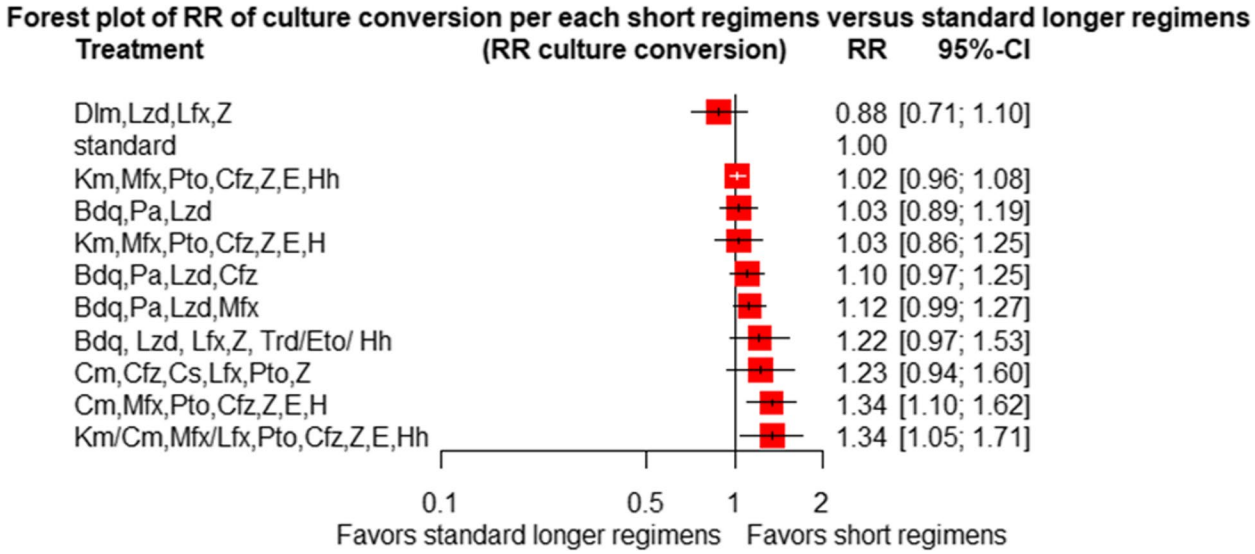


Fig. 10 Forest plot for culture conversion among MDR-TB patients treated with short regimens after 2 months

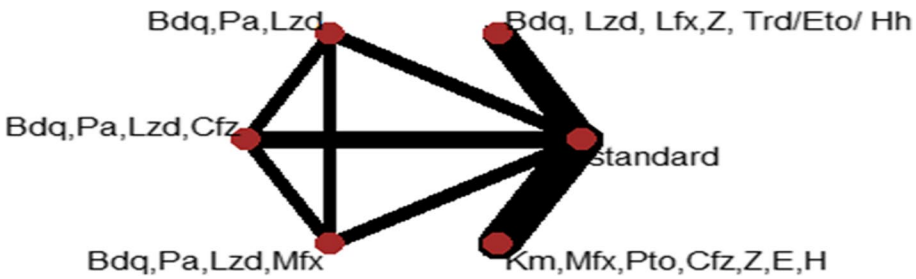


Fig. 11 Network diagram for severe adverse events among MDR-TB patients treated with short regimens

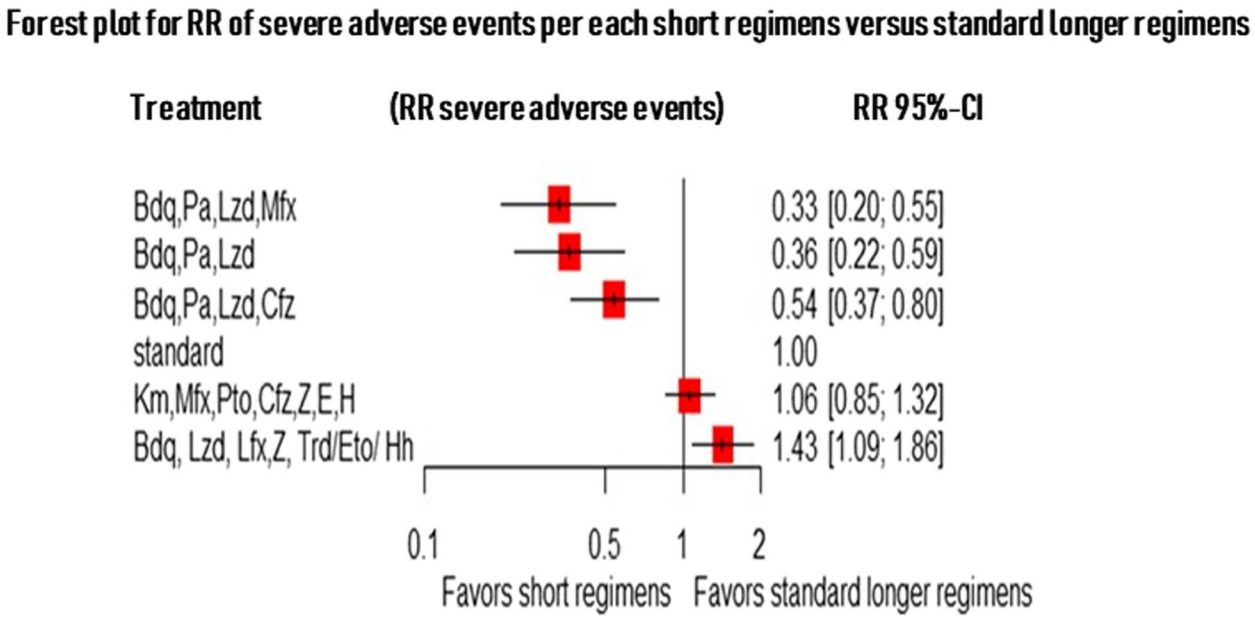


Fig. 12 Forest plot for severe adverse events among MDR-TB patients treated with short regimens

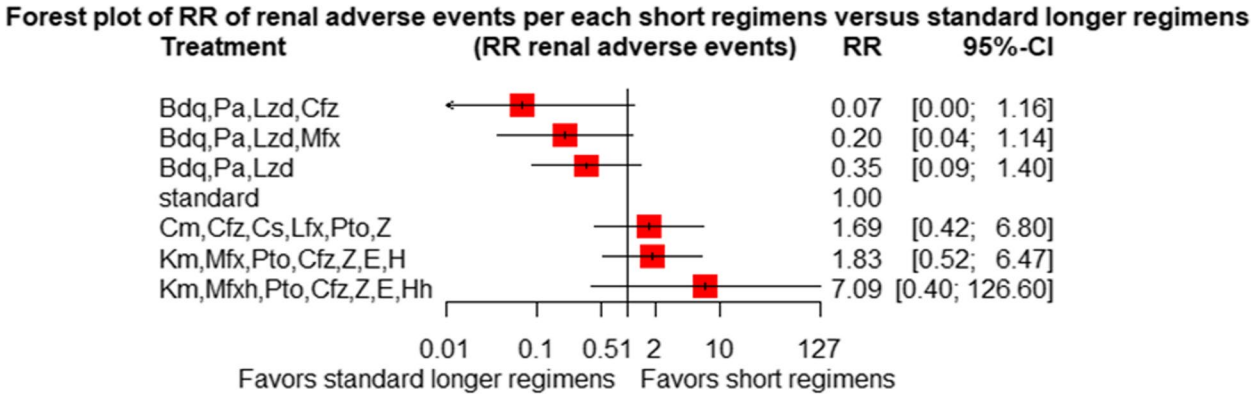


Fig. 13 Forest plot for renal adverse events among MDR-TB patients treated with short regimens

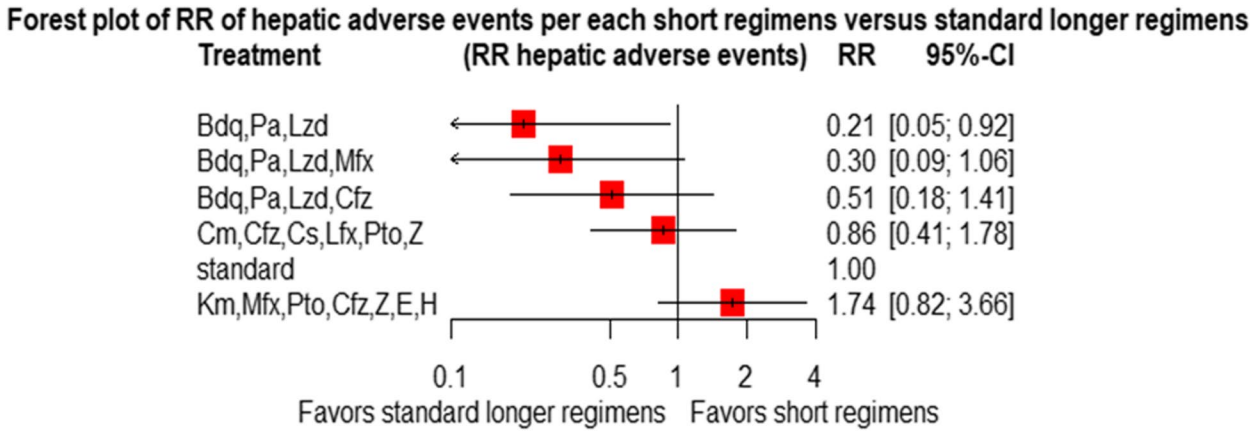


Fig. 14 Forest plot for hepatic adverse events among MDR-TB patients treated with short regimens

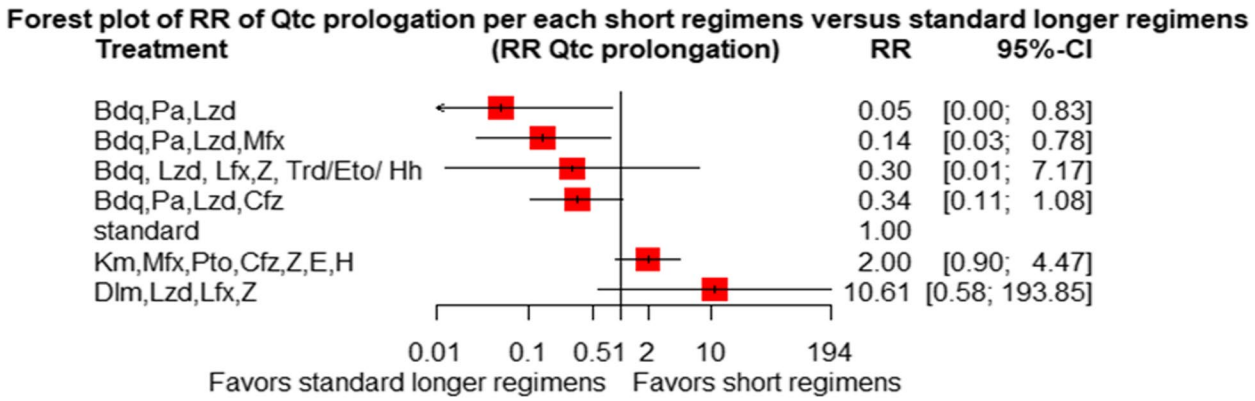


Fig. 15 Forest plot for cardiac conduction (QTc prolongation) adverse events among MDR-TB patients treated with short regimens

there was a clinically significant reduction in serious adverse events among patients treated with 9-11KmMfxPtoCfzZEH (4-6KmMfxPtoCfzZEH and 5MfxCfzZ) regimens than others, Fig. 19.

Death

Nine studies [19, 22–26, 29–31] reported a total of 223 deaths as an unfavorable outcome, and the most common causes of death were tuberculosis-related (184;

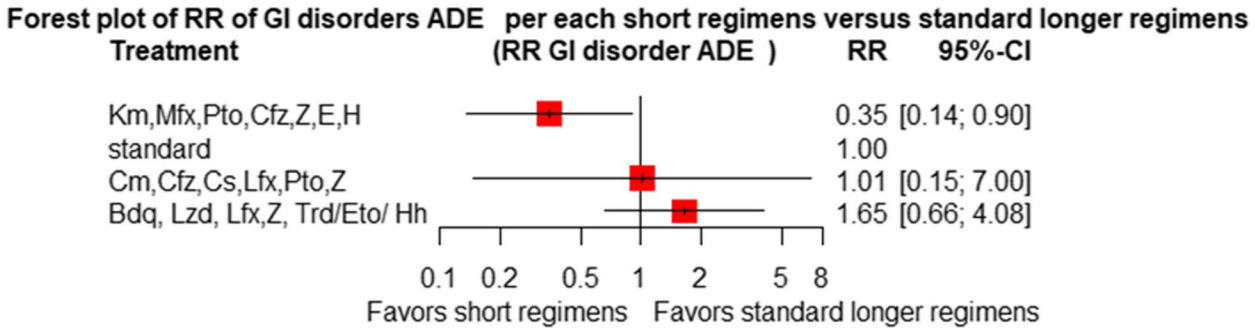


Fig. 16 Forest plot for gastrointestinal adverse events among MDR-TB patients treated with short regimens

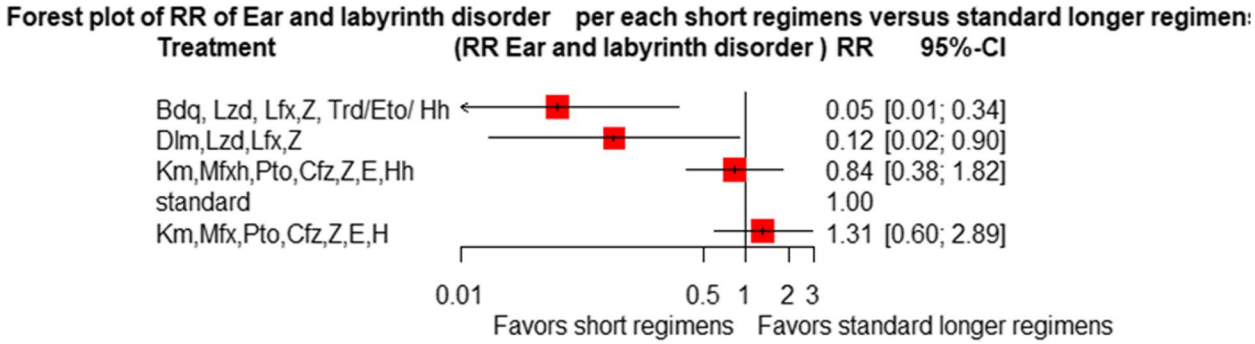


Fig. 17 Forest plot for ear and labyrinth adverse events among MDR-TB patients treated with short regimens

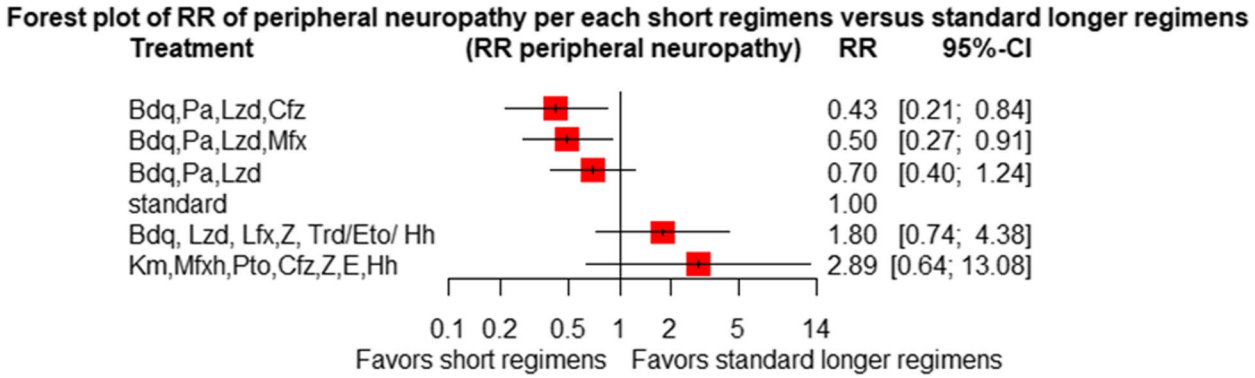


Fig. 18 Forest plot for peripheral neuropathy adverse events among MDR-TB patients treated with short regimens

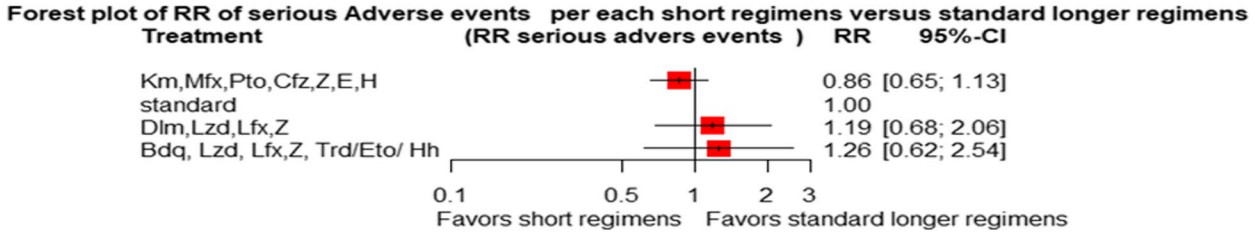


Fig. 19 Forest plot for serious adverse events among MDR-TB patients treated with short regimens

82.5%), HIV-related (9; 4%), hepatitis B-related acute liver failure (1; 0.4%), sepsis (1; 0.4%), heart failure (1; 0.4%), suicide (2; 0.9%), bacterial peritonitis (1; 0.4%), cryptococcal meningitis (1; 0.4%), and other uncertain conditions (23; 10%).

TB-related death

In this analysis, 8 studies, 10 pairwise comparisons, and 9 treatment groups were included. The network diagram shows that most of the studies compared the standard treatment with 9-11KmMfxPtoCfzZEHh (4-6KmMfxPtoCfzZEHh and 5MfxCfzZE) Fig. 20.

The tests of heterogeneity (within designs) and inconsistency (between designs) were not statistically significant (tau^2 = 0; tau = 0; I^2 = 0%, $P = 0.69$). The net rank result and forest plot show that the risk of death was lower by 97% RR 0.028 (95% CI 0.002; 0.46, $P = 0.012$) in patients who were treated with 9–12 km/CmMfx/LfxPtoCfzZEHh (4–6 km/CmMfx/LfxPtoCfzZEHh and 5–6 Mfx/LfxPtoCfzZE) compared to the other treatments, Figs. 21 and 22.

Discussions

In this systematic review and network meta-analysis, we sought to evaluate the efficacy and safety of shorter regimens against the standard of care among RR/MDR-TB patients in terms of favorable and unfavorable outcomes and adverse events. We did not limit our inclusions to

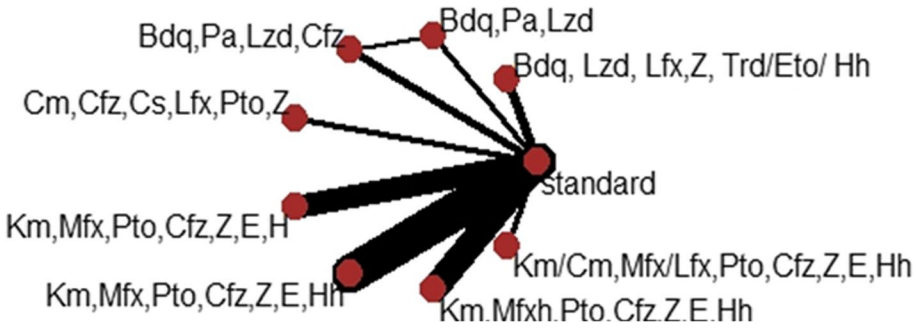


Fig. 20 Network diagram for TB-related death among MDR-TB patients treated with short regimens

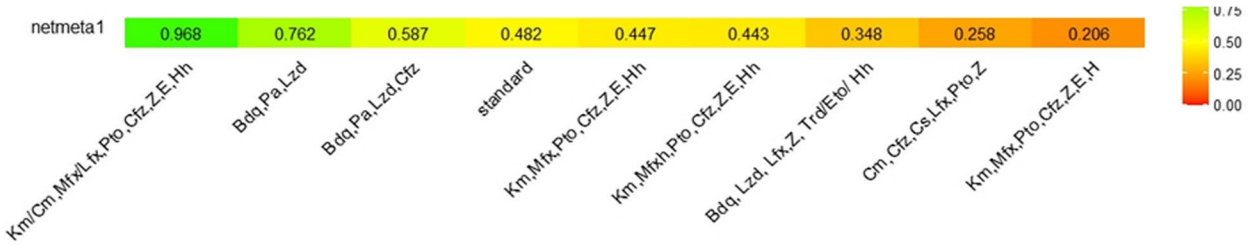


Fig. 21 Net rank plot for TB-related death among MDR-TB patients treated with short regimens

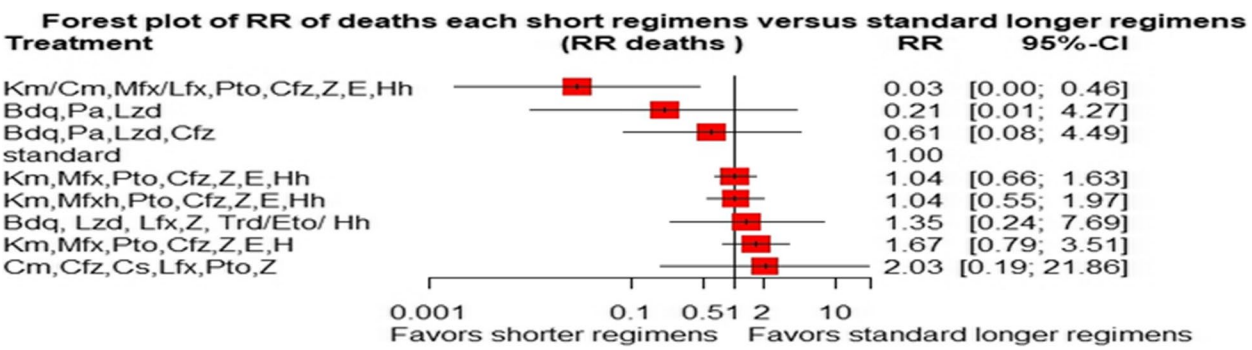


Fig. 22 Forest plot for TB-related death among MDR-TB patients treated with short regimens

RCTs and incorporated cohort studies, as we deemed that, in this analysis, the inclusion of real-world evidence from nonrandomized studies has the potential to add validity to certain findings, provide additional information regarding low-to-moderate incidence adverse events, and improve the density of the network [37].

In this study, the favorable outcome of RR/MDR-TB patients who had taken 6BdqLzdLfxZ Trd/Eto/H was higher, followed by 9–12 km/CmMfx/LfxPtoCfzZEHh and 6BdqPaLzd Mfx. A previous meta-analysis showed that bedaquiline-based shorter regimens have better outcomes [38]. In contrast, other systematic reviews showed that 9–12 KmGfxPtoCfzZEHh short regimens have better outcomes [10].

To enhance the potential benefit of MDR-TB treatment regimens and achieve the anticipated efficacy level, culture conversion needs to be higher [39, 40]. In this study, culture conversion at 2 months after the start was higher among patients who had taken 9–12 km/CmMfx/LfxPtoCfzZEHh and 9–11 CmMfxPtoCfzZEH followed by 12CmCfzCs LfxPtoZ. This result shows that even though the culture conversion was higher than the standard of care regimens, less than 50% and short-term regimens have similar findings. This can be explained by the grades of bacilli in sputum smears, baseline lung cavitation and time of culture test.

This study showed that the risk of deaths related to MDR-TB was lower by 97% in patients who were treated with 9–12 km/CmMfx/LfxPtoCfzZEHh. A previous systematic review showed that patients treated with short regimens had a lower death rate (6%) than those treated with longer regimens (15%) [41].

The network meta-analysis showed that the risk of severe adverse events was 67% and 64% lower than that of standard treatment in patients who were treated with 6BdqPaLzdMfx and 6BdqPaLzd. A previous systematic review and meta-analysis on bedaquiline -based regimens showed an increased risk of severe adverse events (RR 1.42) [42]. The difference can be adverse events associated with background regimens and shorter duration in the TB practical trial. Meanwhile, the systematic review performed in this study showed that the risk of serious adverse events was common in patients who were treated with 12DlmLzdLfxZ (20/72, 25.3%) and 6BdqLzdLfxZTrd/Eto/Hh (14/56, 25%). This resulted from serious adverse events related to linezolid, where drug in 11/17 (64.7%) participants with adverse events where the drug was stopped; the majority of linezolid events (10/11; 90.9%) were related to anemia. A previous systematic review showed that linezolid-related linezolid discontinuation was experienced by 35% of patients, of whom had peripheral neuropathy (31%) and anemia (25%) [43]. However, a systematic review and meta-analysis on delamanid-based regimens showed no serious adverse events [44]. Furthermore, the study showed adverse events associated with drug discontinuation in patients treated with the 9-11KmMfxPtoCfzZEH regimen. This was related to moxifloxacin-related QTc prolongation (32/282, 11.3%), leading to dose reduction and replacement with levofloxacin.

The shorter regimens demonstrated high patient adherence, particularly the BPaL regimens with a short duration and few adverse events [45]. The shorter regimens are widely accepted and feasible among TB stakeholders [46]. Furthermore, cost-effectiveness analyses conducted in India, Georgia, the Philippines, and South Africa revealed cost savings of $112–$1,173 per person [47]. Short-term regimens for the treatment of MDR/RR-TB can be made more practical with the availability and procurement of novel drugs, as well as rigorous clinical outcome monitoring.

This network meta-analysis has several strengths. As no trials currently compare the safety and efficacy of the various short-term regimens directly or indirectly, this network meta-analysis tackles an important evidence gap by comparing the available treatment regimens using valid meta-analysis methods, providing valuable information to clinicians and policy makers. We followed international guidelines on the conduct and reporting of systematic reviews and network meta-analyses, including the Cochrane Handbook and PRISMA-NMA statements. However, the study has some limitations. Foremost, the included studies might have several types of biases, such as randomization processes and deviations from the intended intervention. Furthermore, the included studies had different treatment durations. Thus, the variability of the time period after drug use in the different studies creates a limitation in the availability of similar data in terms of comparing the outcomes of the treatment regimens. The majority of the included studies were conducted in adult patients. Therefore, the results of this study might not be representative of children with MDR/RR-TB.

Conclusion

To our knowledge, this is the first network meta-analysis that compared short-term regimens in terms of efficacy and safety. From this review, it can be concluded that 6 months BdqLzdLfxZTrd/Eto/H, 9–12 months km/CmMfx/LfxPtoCfzZEHh and 6 months BdqPaLzdMfx have a significant impact on increasing favorable outcomes in MDR/RR-TB treatment. The 9–12 month km/CmMfx/LfxPtoCfzZEHh regimen reduces the risk of death. In addition to this 6-month BdqPaLzdMfx regimen, 6-month BdqPaLzd and 6-month BdqPaLzdCfz regimens decrease severe adverse events. However, the 6-month BdqLzdLfxZTrd/Eto/H regimen was

significantly associated with adverse events with drug discontinuation. Furthermore, adverse events related to renal, hepatic, and QTc prolongation and peripheral neuropathy were less common at 6 months BdqPaLzd-Mfx, 6 months BdqPaLzd, and 6 months BdqPaLzdCfz. This result supports the WHO's 2021 recommendation to use bedaquiline-based shorter regimens for MDR/RR-TB. However, doctors should carefully weigh the benefits and drawbacks of using different short regimens according to the specific needs of individual patients, the availability of regimens, and the cost of the drug.

Abbreviations

ADR	Adverse drug reactions
AE	Adverse event
Bdq	Bedaquiline
CENTRAL	Cochrane Central Register of Controlled Trials
Cfz	Clofazimine
CI	Confidence interval
Cm	Capreomycin
Cs	Cycloserine
CT- Scan	Computed Tomography Scan
DAIDS	Division of AIDS
Dlm	Delamanid
Eto	Ethionamide
FDA	Food and Drug Administration
H	Isoniazid
Hh	Isoniazid high does
HIV	Human immunodeficiency virus
km	Kanamycin
Lfx	Levofloxacin
Lzd	Linezolid
MDR	Multidrug Resistance
Mfx	Moxifloxacin
Mfxh	Moxifloxacin high dose
NIAID	National Institute of Allergy and Infectious Diseases
NMA	Network meta-analysis
Pa	Pretomanid
PICO	Population, Intervention, Comparison, and Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Pto	Prothionamide
RCTs	Randomized control trials
RoB 2	Cochrane risk of bias tool for randomized trials
ROBINS-I	Risk Of Bias In Non-randomized Studies of Interventions
RR	Rifampicin Resistance
SAE	Serious adverse event
SOC	Standard of Care
STR	Short treatment regimen
TB	Tuberculosis
Trd	Terizidone
WHO	World Health Organization
Z	Pyrazinamide

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
YA developed the protocol. YA, STG, DTD, DG, and DGA reviewed the reference list and extracted data. YA and DGA conducted the analyses and evaluated the risk of bias. TH, DTD, MY, DG, and TM were responsible for the quality assessment and review of the study. YA developed the draft manuscript, and DGA and TM critically reviewed it. All authors reviewed and edited the manuscript.

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Declarations

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Not applicable.

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Competing interests
The authors declare no competing interests.

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References

1. Global tuberculosis report 2023.World Health Organization. 2023.https://www.who.int/publications-detail-redirect/9789240083851. Cited 2023 Nov 13.
2. Migliori GB, Tiberi S. WHO drug-resistant TB guidelines 2022: what is new? Int J Tuberc Lung Dis. 2022;26(7):590–1.
3. Organization WH. WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-susceptible tuberculosis treatment. In: WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-susceptible tuberculosis treatment. 2022.
4. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization. 2019. In. https://www.ncbi.nlm.nih.gov/books/NBK539518/table/ch1.tab2/.
5. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. Evans C, editor. PLoS Med. 2012;9(8):e1001300.
6. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis – 2011 update. 2011;(WHO/HTM/TB/2011.6). Available from: https://apps.who.int/iris/handle/10665/44597. Cited 2023 Jul 16.
7. World Health Organization. Global Tuberculosis Report 2016. Geneva: World Health, Organization. 2016. - Google Search. https://www.google.com/search?client=firefox-b-d&q=World+Health+Organization.+Global+Tuberculosis+Report+2016.+Geneva%3A+World+Health+Organization%2C+2016. Cited 2023 Jul 16.
8. Bloss E, Kuksa L, Holtz TH, Riekstina V, Skripconoka V, Kammerer S, et al. Adverse events related to multidrug-resistant tuberculosis treatment, Latvia, 2000–2004. Int J Tuberc Lung Dis off J Int Union Tuberc Lung Dis. 2010;14(3):275–81.

9. Nathanson E, Gupta R, Huamani P, Leimane V, Pasechnikov AD, Tupasi TE, et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. Int J Tuberc Lung Dis off J Int Union Tuberc Lung Dis. 2004;8(11):1382–4.
10. Mahardani PN, Wati DK, Siloam A, Savitri NPA, Manggala AK. Effectiveness and safety of short-term regimen for Multidrug-resistant tuberculosis treatment: a systematic review of ohort studies. Oman Med J. 2022;37(1):e337–337.
11. Von Groote-Bidlingmaier F, Patientia R, Sanchez E, Balanag V, Ticona E, Segura P, et al. Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. Lancet Respir Med. 2019;7(3):249–59.
12. NCT03086486. Safety and Efficacy of Various Doses and Treatment Durations of Linezolid Plus Bedaquiline and Pretomanid in Participants With Pulmonary TB, XDR-TB, Pre- XDR-TB or Non-responsive/Intolerant MDR-TB (ZeNix). 2017. https://clinicaltrials.gov/show/NCT03086486. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01562771/full.
13. Lee M, Mok J, Kim DK, Shim TS, Koh WJ, Jeon D, et al. Delamanid, linezolid, levofloxacin, and pyrazinamide for the treatment of patients with fluoroquinolone-sensitive multidrug-resistant tuberculosis (treatment shortening of MDR-TB using existing and New drugs, MDR-END): study protocol for a phase II/III, multicenter, randomized, open-label clinical trial. Trials. 2019;20(1):57.
14. Guglielmetti L, Ardizzoni E, Atger M, Baudin E, Berikova E, Bonnet M, et al. Evaluating newly approved drugs for multidrug-resistant tuberculosis (endTB): study protocol for an adaptive, multi-country randomized controlled trial. Trials. 2021;22(1). Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02321533/full.
15. Bouton TC, Phillips PPJ, Mitnick CD, Peloquin CA, Eisenach K, Patientia RF, et al. An optimized background regimen design to evaluate the contribution of levofloxacin to multidrug-resistant tuberculosis treatment regimens: study protocol for a randomized controlled trial. Trials. 2017;18(1):563.
16. Weng T, Sun F, Li Y, Chen J, Chen X, Li R, et al. Refining MDR-TB treatment regimens for ultra short therapy (TB-TRUST): study protocol for a randomized controlled trial. BMC Infect Dis. 2021;21(1):183.
17. Rossato Silva D, Carvalho De Queiroz Mello F, Battista Migliori G. Shortened tuberculosis treatment regimens: what is new? J Bras Pneumol. 2020;46(2):e20200009–20200009.
18. Berry C, du Cros P, Fielding K, Gajewski S, Kazounis E, McHugh T, et al. TB-PRACTECAL: study protocol for a randomised, controlled, open-label, phase II-III trial to evaluate the safety and efficacy of regimens containing bedaquiline and pretomanid for the treatment of adult patients with pulmonary multidrug-resistant tuberculosis. Trials. 2022;23(1):484.
19. Nyang'wa BT, Berry C, Kazounis E, Motta I, Parpieva N, Tigay Z, et al. A 24-Week, all-oral regimen for Rifampin-resistant tuberculosis. N Engl J Med. 2022;387(25):2331–43.
20. Conradie F, Everitt D, Olugbosi M, Wills G, Fabiane S, Timm J et al. High rate of successful outcomes treating highly resistant TB in the ZeNix study of pretomanid, bedaquiline and alternative doses and durations of linezolid. J Int AIDS Soc. 2021;24(SUPPL 4). https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02348434/full.
21. Conradie F, Bagdasaryan TR, Borisov S, Howell P, Mikiashvili L, Ngubane N, et al. Bedaquiline–Pretomanid–Linezolid regimens for drug-resistant tuberculosis. N Engl J Med. 2022;387(9):810–23.
22. Esmail A, Oelofse S, Lombard C, Perumal R, Mbuthini L, Goolam Mahomed A, et al. An all-oral 6-month regimen for multidrug-resistant tuberculosis: a multicenter, randomized controlled clinical trial (the NExT Study). Am J Respir Crit Care Med. 2022;205(10):1214–27.
23. Nunn AJ, Phillips PPJ, Meredith SK, Chiang CY, Conradie F, Dalai D, et al. A trial of a shorter regimen for Rifampin-resistant tuberculosis. N Engl J Med. 2019;380(13):1201–13.
24. Mok J, Lee M, Kim DK, Kim JS, Jhun BW, Jo KW, et al. 9 months of delamanid, linezolid, levofloxacin, and pyrazinamide versus conventional therapy for treatment of fluoroquinolone-sensitive multidrug-resistant tuberculosis (MDR-END): a multicentre, randomised, open-label phase 2/3 non-inferiority trial in South Korea. Lancet. 2022;400(10362):1522–30.
25. Du Y, Qiu C, Chen X, Wang J, Jing W, Pan H, et al. Treatment outcome of a shorter regimen containing clofazimine for multidrug-resistant tuberculosis: a randomized control trial in China. Clin Infect Dis. 2020;71(4):1047–54.
26. Hassane-Harouna S, Cherif GF, Ortuno-Gutierrez N, Cisse D, Camara LM, Diallo BD, et al. Better programmatic outcome with the shorter regimen for the treatment of multidrug-resistant tuberculosis (MDR-TB) in Guinea: a retrospective cohort study. Ehtesham HS, editor. PLOS ONE. 2020;15(8):e0237355.
27. Du Cros P, Khamraev A, Lister D, Ronnachit A, Berry C, Greig J, Parpieva N, Tillyashaykhov M, Cooke G, Dietrich S, Pylypenko T, Tigay Z, Achar J. (n.d.). Comparing shorter with conventional MDR-TB treatment in Uzbekistan: 2-month culture-conversion rates and treatment outcomes. https://d1hiluowqo0t4b.cloudfront.net/posters/docs/f1000research-164246.pdf [Accessed 7 Oct 2023].
28. Mleoh L, Mziray SR, Tsere D, Koppelaar I, Mulder C, Lyakurwa D. Shorter regimens improved treatment outcomes of multidrug-resistant tuberculosis patients in Tanzania in 2018 cohort. Trop Med Int Health. 2023;28(5):357–66.
29. Myemba DT, Bwire GM, Sambayi G, Maganda BA, Njiro BJ, Ndumwa HP, et al. Clinical characteristics and treatment outcomes of patients with MDR Tuberculosis in Dar Es Salaam region, Tanzania. JAC-Antimicrob Resist. 2020;2(4):dlaa108.
30. Wahid A, Ghafoor A, Khan AW, Al-Worafi YM, Latif A, Shahwani NA, et al. Comparative effectiveness of individualized longer and standardized shorter regimens in the treatment of multidrug resistant tuberculosis in a high burden country. Front Pharmacol. 2022;13:973713.
31. Zhdanova E, Goncharova O, Davtyan H, Alaverdyan S, Sargsyan A, Harries AD, et al. 9–12 months short treatment for patients with MDR-TB increases treatment success in Kyrgyzstan. J Infect Dev Ctries. 2021;15(091):S66–74.
32. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777–84.
33. Division of Acquired Immunodeficiency Syndrome, National Institute of Allergy and Infectious Diseases National Institutes of Health, US Department of Health and Human Services. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events. Vol. corrected version 2.1. 2017. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.
34. World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision: updated December 2014 and January 2020. Définitions et cadre de notification pour la tuberculose – révision 2013. Geneva: World Health Organization; 2013. Available from: https://iris.who.int/handle/10665/79199. Cited 5 Jul 2024.
35. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. editors. Cochrane Handbook for Systematic Reviews of Interventions. 1st ed. Wiley; 2019. https://onlinelibrary.wiley.com/doi/book/10.1002/9781119536604. Cited 2023 Jul 27.
36. Sterne JAC, Hernán MA, McAleenan A, Reeves BC, Higgins JPT. Chapter 25: Assessing risk of bias in a non-randomized study. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. www.training.cochrane.org/handbook
37. Efthimiou O, Mavridis D, Debray TPA, Samara M, Belger M, Siontis GCM, et al. Combining randomized and non-randomized evidence in network meta-analysis. Stat Med. 2017;36(8):1210–26.
38. Hatami H, Sotgiu G, Bostanghadiri N, Abadi SS, Mesgarpour B, Goudarzi H, et al. Bedaquiline-containing regimens and multidrug-resistant tuberculosis: a systematic review and meta-analysis. J Bras Pneumol. 2022;48:e20210384.
39. Lv L, Li T, Xu K, Shi P, He B, Kong W, et al. Sputum bacteriology conversion and treatment outcome of patients with multidrug-resistant tuberculosis. Infect Drug Resist. 2018;11:147–54.
40. Basit A, Ahmad N, Khan AH, Javaid A, Syed Sulaiman SA, Afridi AK, et al. Predictors of two months culture conversion in multidrug-resistant tuberculosis: findings from a retrospective cohort study. PLoS ONE. 2014;9(4):e93206.
41. Ahmad Khan F, Salim MAH, Du Cros P, Casas EC, Khamraev A, Sikhondze W, et al. Effectiveness and safety of standardised shorter regimens for

multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses. Eur Respir J. 2017;50(1):1700061.
42. Tong E, Wu Q, Chen Y, Liu Z, Zhang M, Zhu Y, et al. The efficacy and safety of Bedaquiline in the treatment of pulmonary tuberculosis patients: a systematic review and Meta-analysis. Antibiotics. 2023;12(9):1389.
43. Zhang X, Falagas ME, Vardakas KZ, Wang R, Qin R, Wang J, et al. Systematic review and meta-analysis of the efficacy and safety of therapy with linezolid containing regimens in the treatment of multidrug-resistant and extensively drug-resistant tuberculosis. J Thorac Dis. 2015;7(4):603–15.
44. Nasiri MJ, Zangiabadian M, Arabpour E, Amini S, Khalili F, Centis R, et al. Delamanid-containing regimens and multidrug-resistant tuberculosis: a systematic review and meta-analysis. Int J Infect Dis. 2022;124:S90–103.
45. Labuda SM, Seaworth B, Dasgupta S, Goswami ND. Bedaquiline, pretomanid, and linezolid with or without moxifloxacin for tuberculosis. Lancet Respir Med. 2024;12(2):e5–6.
46. Van De Berg SEJ, Pelzer PT, Van Der Land AJ, Abdrakhmanova E, Ozi AM, Arias M, et al. Acceptability, feasibility, and likelihood of stakeholders implementing the novel BPaL regimen to treat extensively drug-resistant tuberculosis patients. BMC Public Health. 2021;21(1):1404.
47. Sweeney S, Berry C, Kazounis E, Motta I, Vassall A, Dodd M, et al. Cost-effectiveness of short, oral treatment regimens for rifampicin resistant tuberculosis. Muniyandi M, editor. PLOS Glob Public Health. 2022;2(12):e0001337.

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