Acta Medical and Health Sciences, 3(3) : 151-162(2025)

Advance Access Publication Date: Feb 2025
DOI : https://doi.org/10.35990/amhs.v3n3.p151-162

REVIEW ARTICLE

Efficacy and safety of short vs. Standard long regimens for multidrug-resistant tuberculosis: a network meta-analysis

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ABSTRACT

Drug-resistant tuberculosis (DR-TB) remains a critical health concern, particularly in high-burden regions like Indonesia. Shorter treatment regimens have been proposed to improve outcomes for multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). This systematic review and Bayesian network meta-analysis aimed to evaluate the efficacy and safety of these shorter regimens. Using PRISMA-NMA guidelines, we systematically searched multiple databases, including PubMed, Cochrane, Scopus, WOAJ, and WOS, for studies published between 2014 to 2024. We included 23 eligible studies comprising a total of 6,343 MDR/RR-TB patients. Results showed that treatment with a 9-12 month regimen, specifically Kanamycin (Km)/Capreomycin (Cm), Moxifloxacin (Mfx)/Levofloxacin (Lfx), Prothionamide (Pto), Clofazimine (Cfz), Pyrazinamide (Z), Ethambutol (E), High-dose Isoniazid (Hh) demonstrated almost twice the probability of favorable outcomes defined as cure or treatment completion, compared to the standard regimens [RR 1.66 (95%CrI 1.34;2.04), P=0.0094]. Additionally, the 6-month regimen Bedaquiline (Bdq), Pretomanid (Pa), Linezolid (Lzd), Moxifloxacin (Mfx) also showed significantly higher favorable outcomes [RR 1.59 (95%CrI 1.29;2.03), P<0.001]. For safety outcomes, regimens containing bedaquiline, such as the 6-month Bdq, Pa, Lzd, Mfx regimen, had a 38% reduction in the risk of adverse events compared to the standard [RR 0.623 (95%CrI 0.280;1.29), P < 0.0001]. This was followed by the 6-month Bdq, Pa, Lzd and the Bdq, Pa, Lzd, Cfz regimen, which also showed lower risks of adverse events. In conclusion, shorter MDR/RR-TB regimens, especially those containing bedaquiline, appear to enhance cure rates while reducing adverse effects, supporting current WHO guidelines for 6-month treatment options

Keyword: Multidrug-resistant tuberculosis (MDR-TB), Rifampicin-resistant tuberculosis (RR-TB), Short-term regimens TB, Standard regimen TB, Tuberculosis (TB)

Received: 2025-01-16, Revised: 2025-02-01 Accepted: 2025-02-16, Published: 2025-02-28.

How to cite :
Simanjuntak, J. G. R., Gandhy, M. A. K. and Sadha , K.(2025) "Efficacy and safety of short vs. Standard long regimens for multidrug-resistant tuberculosis: a network meta-analysis", Acta Medical and Health Sciences, 3(3).p151-162. Doi: https://doi.org/10.35990/amhs.v3n3.p151-162

INTRODUCTION

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* (M. tb) that most frequently affects lungs and can spread through the air. This disease is a leading cause of death a major global health concern. According to data from World Health Organization (WHO), in 2023, an estimated 10.8 million people were affected by tuberculosis worldwide, and 1.25 million people died from this disease. Indonesia has seen an increasing trend in tuberculosis cases from 2020 until 2023 and ranks second globally, after India, with 1.090.000 reported cases in 2023.[1]

According to the 2021 guidelines from the Indonesian Lung Doctors Association (*Perhimpunan Dokter Paru Indonesia*), tuberculosis treatment involves Anti-Tuberculosis Drugs (ATDs), which consist of four first-line medications: Rifampicin (R), Isoniazid (H), Pyrazinamide (Z), and Ethambutol (E) during the initial two-month intensive phase. This is followed by the continuation phase, where Isoniazid (H) and Rifampicin (R) are administered for the next four to seven months. Most tuberculosis patients, can be cured and survived. However, some may experience adverse effects, ranging from mild to severe, such as skin rash, dizziness, reduced urine output, neurological disturbances, QTc prolongation, and liver dysfunction. In addition to physical adverse effects, tuberculosis treatments often face some problems in the community, such as incorrect prescriptions from healthcare providers, poor-quality drugs, and patients prematurely discontinuing treatment.[2]

The emergence of tuberculosis has increased due to mutations in *Mycobacterium tuberculosis* resulting from previous inappropriate treatments. Multidrug-resistant tuberculosis (MDR-TB) is caused by strains of the *Mycobacterium tuberculosis* complex that are resistant to the first-line tuberculosis drugs, including rifampicin and isoniazid.[3] Globally, MDR-TB cases were estimated to reach 400.000 in 2022, posing a potential health crisis and threat. Indonesia ranks eighth among 27 countries with the highest MDR-TB burden. According to data from Indonesian Ministry of Health (*Kementerian Kesehatan Republik Indonesia*), the estimated number of MDR-TB cases in Indonesia reached 28.000 in 2021, reflecting a 17% increase compared to the previous year.[4]

Treatment for MDR-TB is more complex, requiring a combination of several drugs, is more expensive, less effective, and takes longer time, approximately 18 - 24 months. MDR-TB generally follows guidelines for second-line-Anti-Tuberculosis Drug (ATDs). Initially, the treatment for MDR-TB involved administering anti-TB drugs through intramuscular or intravenous injection. However, this method is no longer recommended due to the specialized expertise requires, which is not available in all settings. In 2018, the WHO recommended several regiments of longer MDR-TB drugs treatments. Group A, the first-line group, includes fluoroquinolones, bedaquiline, and linezolid, which are effective and recommended for treating MDR-TB. The second group, group B, contains clofazimine and either cycloserine or terizidone. Group C drugs can be used when group A and B drugs are ineffective against the bacteria. In 2022, the World Health Organization (WHO) revised its recommendations for the treatment of MDR-TB, introducing new therapeutic options, including the BPaLM regimen (a 9-month all-oral regimen) and longer individualized regimens for patients with MDR-TB ineligible for the 6-month or 9-month regimens. The BPaLM regimen consists of bedaquiline, pretomanid, linezolid (600 mg once daily for 26 weeks), and moxifloxacin. The 9-month all-oral regimen is recommended for patients with MDR-TB who do not have resistance to fluoroquinolones. This regimen includes bedaquiline in combination with a

fluoroquinolone (levofloxacin or moxifloxacin), ethionamide (or linezolid at a dosage of 600 mg daily), ethambutol, high-dose isoniazid, pyrazinamide, and clofazimine during the intensive phase, followed by a continuation phase comprising fluoroquinolones, clofazimine, ethambutol, and pyrazinamide. The final WHO-recommended treatment option is an extended regimen lasting 18 to 20 months, designed for patients who do not meet the eligibility criteria for the shorter regimens.[5]

The use of second-line drugs for treating MDR-TB requires careful consideration of their effectiveness and efficacy. Each drug has its own benefits and potential side effects, which cannot be overlooked. Therefore, we conducted research to assess the differences in efficacy and safety between short regimens and standard long regimens. The novelty of this study lies in its analysis of treatment success using second-line drugs, so that the findings can serve as a reference for healthcare providers managing patients with multidrug-resistant tuberculosis (MDR-TB), thereby contributing to a reduction in MDR-TB incidence in Indonesia.

METHODS

This systematic review and network meta-analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions 6.2 and was processed following the PRISMA-NMA framework using MetaInsight 6.2. The databases utilized included PubMed, Scopus, Cochrane, Directory of Open Access Journals (DOAJ), and Web of Science. Data were collected on October 12, 2024, using Boolean operator keywords: ("Bedaquiline" OR "Bedaquiline"[MeSH Terms] OR "Bedaquiline-containing regiment" OR "BPaL" OR "BPaMZ" OR "BPaLM" OR "Delamanid" OR "Delamanid"[MeSH Terms] OR "Second-line drugs" OR "Moxifloxacin" OR "Moxifloxacin"[MeSH Terms] OR "Linezolid" OR "Linezolid"[MeSH Terms] OR "Clofazimine" OR "Clofazimine"[MeSH Terms] OR "Cycloserine" OR "Cycloserine"[MeSH Terms] OR "Terizidone" OR "Terizidone"[MeSH Terms] OR "Ethambutol" OR Ethambutol [MeSH Terms] OR "Pyrazinamide" OR "Pyrazinamide"[MeSH Terms] OR "Imipenem-cilastatin" OR "Imipenem-cilastatin"[MeSH Terms] OR "Meropenem" OR "Meropenem"[MeSH Terms] OR "Amikacin" OR "Amikacin"[MeSH Terms] OR "Streptomycin" OR "Streptomycin"[MeSH Terms] OR "Ethionamide" OR "Ethionamide"[MeSH Terms] OR "Prothionamide" OR "Prothionamide"[MeSH Terms] OR "Pretomanid" OR "Pretomanid"[MeSH Terms] OR "p-aminosalicylic acid" OR "p-aminosalicylic acid"[MeSH Terms]) AND (("MDR-TB" OR "RR-TB" OR "Multidrug-resistant Tuberculosis" OR "Rifampicin-resistant Tuberculosis" OR "Isoniazid-resistant Tuberculosis" OR "Rifampicin and Isoniazid Resistant Tuberculosis") OR ("XDR-TB" OR "Extensively Drug-resistant TB" OR "Second-line Resistance" OR "RR-TB with fluoroquinolone and group A resistant") OR ("pre-XDR TB" OR "pre-Extensively Tuberculosis" OR "RR-TB with fluoroquinolone resistance")) AND (("Efficacy OR "Cure Rate" OR "Sputum Conversion") OR ("Safety" OR "Injury" OR "Toxicity" OR "Hepatotoxic" OR "Liver Injury" OR "QT "Prolongation" OR "Cardiac Injury") OR ("Loss to Follow Up")).

Inclusion criteria were applied according to the PICOS framework (Patient/Problems, Intervention/Exposure, Comparison/Control, Outcome) and included: (1) Population: all ages; (2) Intervention: short-term regimen anti-tuberculosis drugs (see Table 2 on attachments); (3) Comparison: standard long-term regimen anti-tuberculosis drugs; (4) Outcome: favorable cure, treatment completion, adverse event, and treatment unsuccessful.

Exclusion criteria were as follows: (1) incomplete at the time of search; (2) studies without full-text articles; and (3) studies published in languages other than English. Rayyan.ai software was used to screen articles for inclusion and exclusion based on the predefined criteria and to remove duplicates. Figure 1 shows the search strategy flowchart.

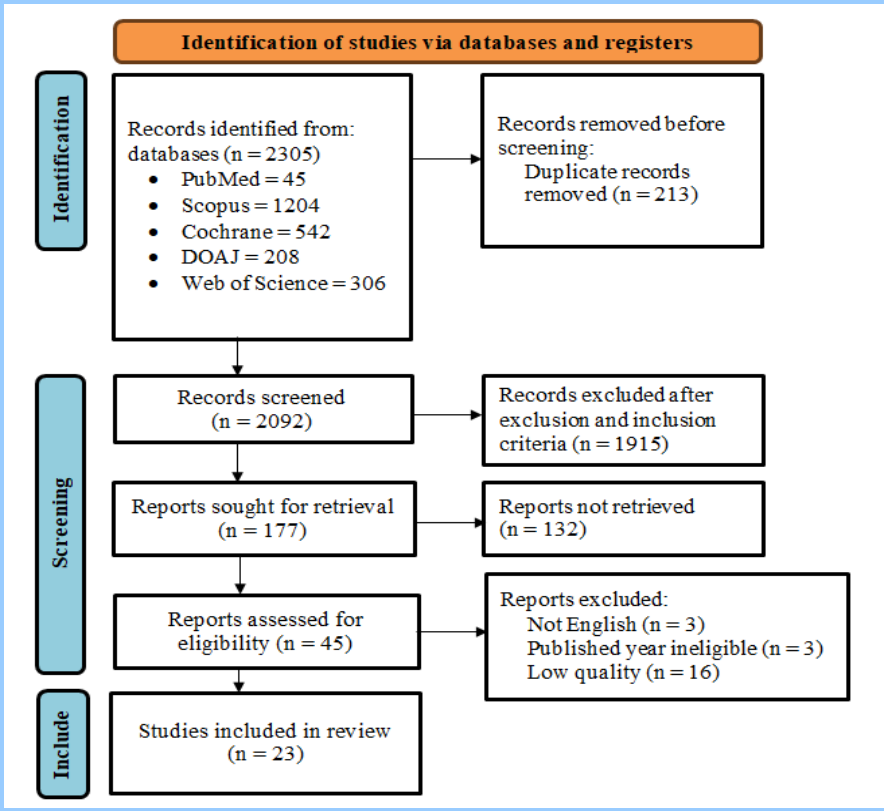

Figure 1. *PRISMA Framework*

Three independent reviewers (JGRS, MAKG, and KS) screened the titles and abstracts of papers according to eligibility criteria. Any disagreements were discussed with the first author to reach a consensus (JGRS). A total of 23 studies were included in this systematic review and network meta-analysis, comprising various study designs: 14 randomized controlled trials, 3 clinical trials, and 6 cohort studies. The results from each study were extracted in tabular form, with columns for the following: (1) title; (2) author and year; (3) country; (4) study design; (5) diagnosis method; (6) population; (7) age; (8) treatment; (9) follow-up; (10) favorable outcome; and (11) unfavorable outcome.

Bias assessment was conducted for all studies. The revised Risk of Bias Tool (RoB 2), consisting of five domains, was used to assess potential bias in the included RCTs. The Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I), with seven domains, was applied to evaluate bias in non-RCTs. Results were documented in a bias domain file (.xlsx) and subsequently published on the ROBVIS website for display. Three reviewers independently assessed study quality, with any disagreements resolved by consensus among reviewers.

RESULTS AND DISCUSSION

Our review successfully gathered 23 studies, comprising 14 randomized controlled trials (RCTs), 3 clinical trials, and 6 cohort studies, which were analyzed both quantitatively (through Bayesian network meta-analysis) and qualitatively. These studies, published from 2014 to 2024, were conducted across various countries. The study population included patients with drug-resistant tuberculosis (DR-TB), specifically those with multi-drug-resistant TB (MDR-TB) or rifampicin-resistant TB (RR-TB), who received either short-term or long-term regimens, as recommended by the WHO for MDR-TB/RR-TB treatment.

Overall, the studies we reviewed reported both favorable and unfavorable outcomes in patients receiving short-term or long-term treatment regimens (the latter serving as the control group). More specifically, favorable outcomes were analyzed by subgroup, including cure rates and treatment completion (completion of treatment without a cure outcome), while unfavorable outcomes were categorized into subgroups comprising adverse events (AEs) and treatment non-adherence. Our study also gathered data on certain concerning adverse events in short-term treatments using various drug regimens, such as QTc prolongation and hepatotoxicity.

In summary, our study indicates that treatment with shorter regimens shows similar or even superior cure rates compared to the long-term standard treatments recommended by the WHO. Additionally, adherence rates were generally higher, with a significantly greater overall favorable outcome in short-term regimens compared to standard treatment. Regarding unfavorable outcomes, short-term treatments performed comparably or even better than standard treatments, with no significant differences observed in adverse events of concern between the two treatment durations.

Quantitative Analysis

Favorable Outcome

This analysis included 22 studies, encompassing 26 pairwise comparisons and 16 treatment groups. The random-effects model revealed no statistically significant heterogeneity within study designs or inconsistency between designs (p = -; τ^2 = NA; τ = NA; I^2 = NA%). Findings from the network ranking analysis and forest plot demonstrated that favorable outcomes were 1.66 times more likely, with a relative risk (RR) of 1.66 (CrI: 1.34–2.04) compared to standard treatment in patients receiving the 9–12 month Mfx/Lfx, Pto, Cfz, Z, E, Hh regimen. The second regimen, with the most favorable outcome was the 6-monthBdq, Pa, Lzd, Mfx regimen, which showed an RR of 1.59 (CrI: 1.29–2.03). Figure 2 presents the forest plot of favorable outcome.

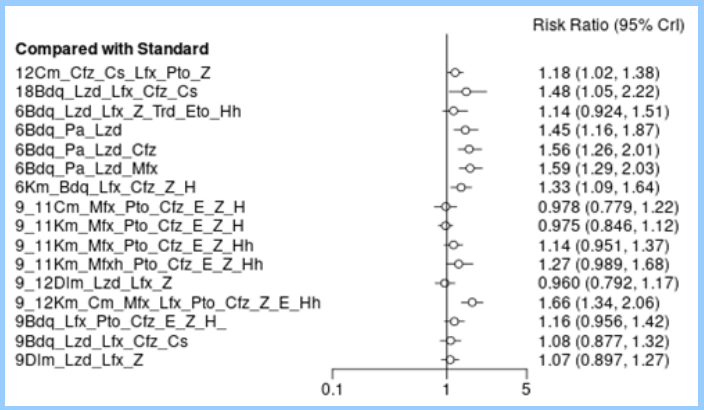

Figure 2. Forest Plot of Favorable Outcome

Cure Rate

This analysis incorporated 14 studies, comprising 16 pairwise comparisons and 13 treatment groups. The random-effects model assessment indicated that heterogeneity within study designs and inconsistency across designs were not statistically significant (p = -; τ^2 = NA; τ = NA; I^2 = NA%). Findings from the network ranking analysis and forest plot demonstrated that the cure rate was 1.49 times higher, with a relative risk (RR) of 1.49 (CrI: 0.803–2.82), compared to standard treatment in patients receiving the 18 Bdq, Lzd, Lfx, Cfz, Cs regimen. The regimen with the second-highest cure rate was the 6-month Bdq, Lzd, Lfx, Z, Trd/Eto/Hh regimen, which exhibited an RR of 1.43 (CrI: 0.715–3.01). Figure 3 presents the forest plot of cure rate.

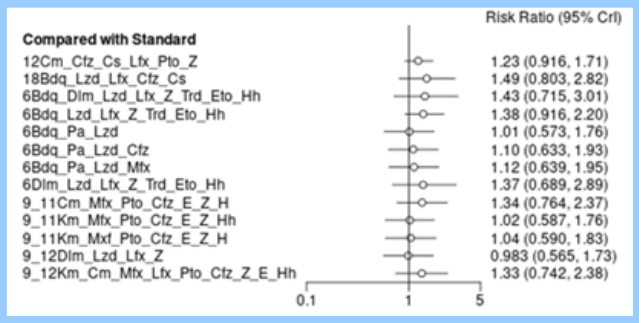

Figure 3. Forest Plot of Cure Rate

Treatment Complete

Overall, treatment completion without culture conversion (treatment completion) is one component of favorable outcomes. Several studies documenting treatment completion indicate that the rate of treatment completion without culture conversion was lower in the short-term treatment group compared to the long-term group. The network plot, rank plot, and forest plot can be found in the supplementary file.

Adverse Event

This analysis included 17 studies, encompassing 29 pairwise comparisons and 15 treatment groups. The evaluation using the random-effects model indicated that heterogeneity within study designs and inconsistency across designs were not statistically significant (p = -; τ^2 = NA; τ = NA; I^2 = NA%). Results from the network ranking analysis and forest plot demonstrated that the likelihood of experiencing adverse events was reduced by 38%, with a relative risk (RR) of 0.623 (CrI: 0.280–1.29), compared to standard treatment in patients receiving the 6-month Bdq, Pa, Lzd, Mfx regimen. The regimen with second-lowest probability of adverse events was the 6-month Bdq, Pa, Lzd regimen, which exhibited an RR of 0.627 (CrI: 0.286–1.32). Figure 4 presents the forest plot of adverse event.

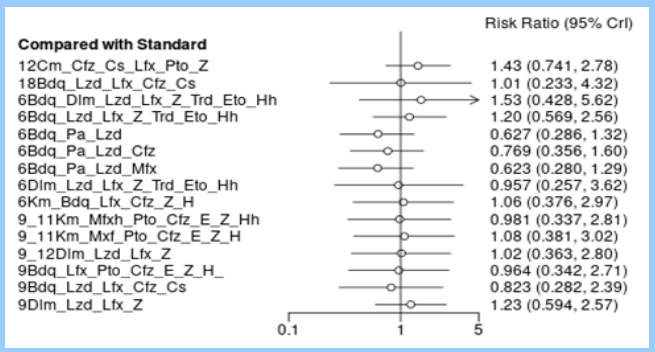

Figure 4. Forest Plot of Adverse Event

Cardiac Conduction (QTc Prolongation)

This analysis encompassed 13 studies, incorporating 20 pairwise comparisons and 15 treatment groups. The assessment using the random-effects model revealed no statistically significant heterogeneity within study designs or inconsistency across designs (p = -; τ^2 = NA; τ = NA; I^2 = NA%). Findings from the network ranking analysis and forest plot indicated that the likelihood of QTc interval prolongation was reduced by 38%, with a relative risk (RR) of 0.623 (CrI: 0.280–1.29), compared to standard treatment in patients receiving the 6-month Bdq, Pa, Lzd, Mfx regimen. The second most favorable regimen in terms of QTc safety was the 6-month Bdq, Pa, Lzd regimen, which demonstrated an RR of 0.627 (CrI: 0.286–1.32). Figure 5 presents the forest plot of cardiac conduction (QTc prolongation).

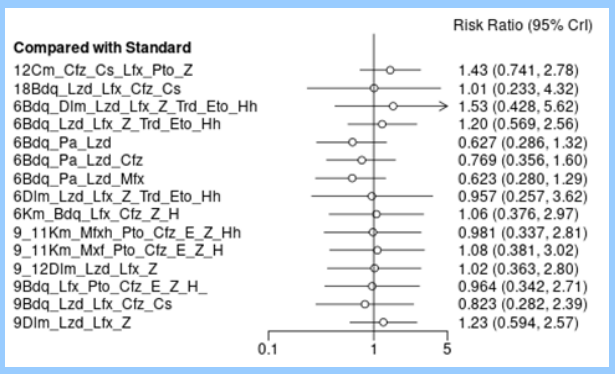

Figure 5. Forest Plot of Cardiac Conduction (QTc Prolongation)

Hepatotoxicity

This analysis included 10 studies, comprising 20 pairwise comparisons and 10 treatment groups. The evaluation using the random-effects model indicated that heterogeneity within study designs and inconsistency across designs were not statistically significant (p = -; τ^2 = NA; τ = NA; I^2 = NA%). Results from the network ranking analysis and forest plot demonstrated that the likelihood of hepatotoxic events was reduced by 80%, with a relative risk (RR) of 0.219 (CrI: 0.0530–0.789), compared to standard treatment in patients receiving the 6-month Bdq, Pa, Lzd regimen. The second most favorable regimen in terms of hepatotoxicity risk was the 9-month Dlm, Lzd, Lfx, Z regimen, which exhibited an RR of 0.260 (CrI: 0.0316–1.70). Figure 6 presents the forest plot of hepatotoxicity.

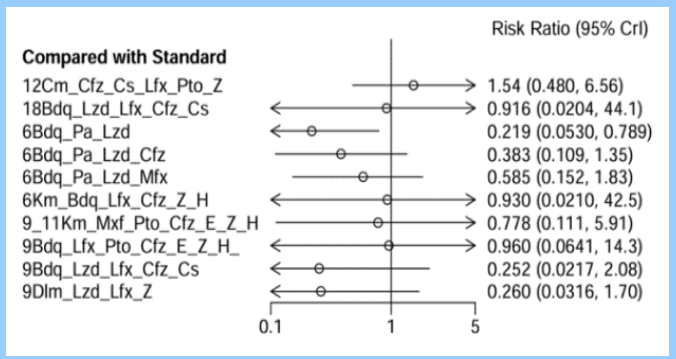

Figure 6. Forest Plot of Hepatotoxicity

Treatment Unsuccessful Treatment Outcomes (Treatment Failure)

Overall, our study suggests that non-adherence rates were lower in the short-term treatment group compared to the long-term treatment group, with a reduction range of 10-70%. The network plot, rank plot, and forest plot of treatment failure can be found in the supplementary file.

Loss to Follow-up

The network plot, rank plot, and forest plot of loss to follow-up can be found in the supplementary file.

Qualitative Analysis

Tuberculosis (TB) remains one of the leading infectious respiratory diseases with high mortality rates. High rates of treatment failure and TB relapse pose major challenges. A key contributor to these issues is the increasing number of drug-resistant TB cases, especially resistance to standard TB treatments. This rise in drug-resistant TB has limited available treatment options. Multidrug-resistant TB (MDR-TB) presents a significant challenge, as it is resistant to both first-line and several second-line treatments. According to WHO data, there were approximately 450,000 cases of MDR-TB in 2021, with 18% of these occurring in patients who had previously undergone TB therapy.[6]

One approach to addressing drug-resistant TB has been to increase both the dosage and variety of drugs in treatment regimens. However, such therapies pose a heightened risk of side effects and toxicity due to the higher doses and prolonged treatment duration. Therefore, there is a pressing need for a new therapy that is comparably effective (non-inferior) to existing anti-tuberculosis drugs but offers a shorter and safer treatment duration for patients with MDR-TB.[7]

One promising option for tackling MDR-TB is the use of bedaquiline (BDQ). BDQ, a drug from the diarylquinoline family discovered in 2004, was developed over seven years as a potent solution to the growing challenge of MDR-TB cases that have few effective treatment options. It became the first drug specifically developed for TB in over 40 years, approved by the U.S. Food and Drug Administration (FDA) after the approval of rifampicin in 1974. BDQ has demonstrated its effectiveness in MDR-TB treatment due to its low Minimum Inhibitory Concentration (MIC), shorter treatment duration (approximately six months), minimal side effects, and efficacy comparable to first- and second-line treatments. Given the critical need for effective MDR-TB therapies, the FDA accelerated and extended research on BDQ starting in 2012 through a seven-year program covering phases 1, 2, and 3, all of which yielded promising results. The WHO subsequently issued guidelines in 2016 recommending BDQ as a specific treatment for MDR-TB, categorizing it as a group A drug, thus making it a primary treatment option. Ongoing research, including studies on the Optimal Background Regimen (OBR), continues to investigate ways to optimize BDQ use beyond 2023 and beyond.[8] A study by Putra et al. (2023) in Indonesia demonstrated the initial success of a short-term regimen containing bedaquiline, achieving a sputum culture conversion rate of 97% by the end of the treatment period in patients with rifampicin-resistant (RR-TB) and multidrug-resistant tuberculosis (MDR-TB).[9]

In addition to BDQ, other novel drugs like delamanid and shorter-duration regimens are expanding treatment options for MDR-TB. Delamanid, approved for use in combination with other TB medications, also holds promise due to its safety and efficacy. It targets the synthesis of mycolic acid, which is essential to the TB bacterium's cell wall, thus weakening the bacteria and enhancing treatment outcomes. Delamanid has been recommended as an add-on treatment for MDR-TB and is often used in conjunction

with BDQ and other drugs in clinical trials to test efficacy and tolerability in different combinations. Furthermore, short-course regimens, such as those involving combinations of BDQ, linezolid (LZD), clofazimine (CFZ), and levofloxacin (LFX), aim to improve patient adherence and reduce adverse effects associated with extended treatment durations.[10]

Shorter regimens, typically ranging from 6 to 9 months, offer significant advantages in terms of patient compliance and safety, with studies showing comparable or improved outcomes compared to conventional long-term therapies. Ongoing clinical trials are focused on refining these short-term regimens, often combining BDQ and delamanid with other agents, to enhance their effectiveness and minimize adverse effects, including hepatotoxicity and QT interval prolongation. As research progresses, these advancements are poised to improve treatment outcomes for MDR-TB and extensively drug-resistant TB (XDR-TB) patients, offering a hopeful future for those affected by drug-resistant TB.[11]

Our Bayesian network meta-analysis study overall demonstrates that short-term treatment offers significantly better probabilities of cure and favorable outcomes compared to standard long-term treatment. Several concerns associated with short-term treatment, such as adverse events and serious occurrences like QT interval prolongation and hepatotoxicity, are addressed by our study, which shows no significant differences. In fact, short-term treatment tends to have a better safety profile compared to standard long-term treatment, particularly in terms of reduced incidence of adverse events, hepatotoxicity, and QTc prolongation. Furthermore, the shorter duration of treatment offers a higher probability of adherence compared to long-term treatment.

CONCLUSION

In conclusion, the regimen in our study with the highest probability of favorable outcomes was 12-month km/cm, Mfx/Lfx, Pto, Cfz, Z, E, Hh, with nearly twice the effectiveness of the standard regimen. The regimen with the best safety profile was 6-month Bdq, Pa, Lzd, Mfx, showing a 38% lower risk of adverse events compared to standard treatment. Overall, short-term regimens, particularly those containing bedaquiline, demonstrated the most consistent results, achieving both favorable treatment outcomes and a strong safety profile.

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Attachments are provided in the supplementary file.
https://drive.google.com/file/d/1NP73ZtM0fvuNKZPXMxdfkae9b6rJmLVP/view?usp=sharing

ATTACHMENTS