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# Impact of all-oral bedaquiline-based shorter regimens in the treatment of drug-resistant tuberculosis: a systematic review and meta-analysis

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## ABSTRACT

**Background** Drug-resistant tuberculosis (DR-TB) presents a significant global obstacle to TB control efforts, necessitating improved intervention strategies. The introduction of potent drugs, such as bedaquiline (Bdq), has led to the development of shorter treatment regimens. This systematic review and meta-analysis aimed to examine the impact of these regimens, synthesising data from recent clinical trials and observational studies.

**Methods** We searched multiple databases, including Medline and Scopus, for studies published from 2012 to February 2024. Eligible studies included clinical trials and cohort studies involving adults diagnosed with DR-TB treated with Bdq-based all-oral regimens lasting up to 12 months. Primary outcomes were treatment success rate (TSR) and incidence of serious adverse events (SAEs). We also compared efficacy and safety with longer oral or injectable regimens in control groups. Meta-analyses were conducted to pool event rates and risk ratios (RRs). Subgroup analyses and meta-regression were performed to identify potential sources of heterogeneity.

**Results** Data from 12 studies involving 1902 DR-TB patients across 11 countries were analysed. The pooled TSR was 83% (95% CI 77% to 89%), with mortality, treatment failure and loss to follow-up (LTFU) rates of 5% (3–8), 4% (2–6) and 4% (2–6), respectively. Subgroup analyses showed no significant differences in TSR by DR-TB type or HIV status. The incidence rate of SAE was 19% (13–24), with prolonged corrected QT interval (QTc) in 5% (2–8) of cases. Compared with the control regimens, all-oral Bdq-based shorter regimens significantly improved treatment success (RR 1.22, 1.04–1.43) but reduced mortality (RR 0.73, 0.69–0.99), treatment failure (RR 0.33, 0.32–0.62) and QTc prolongation (RR 0.39, 0.21–0.73).

**Conclusions** All-oral Bdq-based shorter regimens have improved treatment outcomes and significantly advanced DR-TB management. We urge policymakers, clinicians and stakeholders to expand access to and expedite the implementation of these regimens.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Drug-resistant tuberculosis (DR-TB) poses significant challenges in global health, traditionally requiring lengthy treatment regimens of 18 to 24 months with low success rates. Existing literature has predominantly focused on longer oral regimens or those combined with injectables, leaving a gap in understanding the efficacy and safety of all-oral bedaquiline (Bdq)-based shorter regimens lasting up to 12 months.

### WHAT THIS STUDY ADDS

⇒ This study provides a systematic review and meta-analysis of clinical trials and observational studies, demonstrating that all-oral Bdq-based shorter regimens significantly improve treatment success rates and reduce mortality and treatment failure compared with longer oral or injectable regimens. The findings highlight a pooled treatment success rate of 83%, surpassing current global averages, with manageable adverse event profiles.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings advocate for the adoption of all-oral Bdq-based shorter regimens as a viable option for DR-TB management, suggesting that policymakers and healthcare providers should prioritise these treatments to improve patient outcomes and encourage broader access to these effective treatment options.

## INTRODUCTION

Although tuberculosis (TB) is preventable, treatable and curable, in 2023, it returned to being the leading cause of death globally among infectious diseases, surpassing COVID-19.[1 2] As of 2023, approximately 1.25 million TB-related deaths have been recorded globally, including 161 000 among individuals living with HIV.[1] Despite extensive global

efforts to reduce TB-related mortality, drug-resistant TB (DR-TB) remains a significant health concern.[3 4] In 2023, an estimated 400 000 cases of multidrug/rifampicin-resistant tuberculosis (MDR/RR-TB) were reported, but only approximately 2 in 5 of these cases were diagnosed and treated.[1]

The increasing burden of DR-TB over the past decade has severely impacted patients, communities and healthcare systems, leading to suboptimal diagnoses, poor outcomes and escalating costs.[5–8] Historically, treatment for DR-TB has required a long course of multiple drugs taken over 18 to 24 months, resulting in low success rates and a high incidence of adverse events.[8 9] Recent WHO treatment regimens have achieved a global success rate of only 68%, indicating a pressing need for more effective intervention strategies.[1 10] In response to the growing burden of TB, especially in its drug-resistant forms, international initiatives have been launched to enhance prevention, diagnosis and treatment strategies.[11] A vital component of these efforts is the WHO's 'End TB Strategy', which aims to eliminate TB as a public health threat by 2035.[12] This initiative promotes universal access to quality TB care, innovative diagnostic tools and treatment regimens, as well as community engagement, while also addressing social determinants of health.[11 12]

The recent discovery of more potent drugs such as bedaquiline (Bdq), pretomanid (Ptd) and delamanid (Dlm), coupled with repurposed drugs such as linezolid (Lzd) and clofazimine (Cfz) for use against *Mycobacterium TB (MTB*), has led to the development of drug combinations that allow for shorter treatment durations.[11] This shift from longer and more complex regimens to shorter, all-oral treatments has resulted in improvements in successful treatment outcomes for DR-TB patients.[1 13] By integrating these strategies into national health policies, countries can significantly advance their efforts toward controlling and ultimately eliminating TB.[8]

All-oral Bdq-based regimens include Bdq and other background drugs that significantly influence both safety and efficacy profiles, where each companion drug has distinct mechanisms of action and safety profiles that can contribute to variations in treatment outcomes and adverse events (AEs).[8 14] Following the findings of recent clinical trial studies, [13 15 16] the WHO updated its guidelines in 2022 to prioritise a 6-month regimen of Bdq, Lzd, Ptd and moxifloxacin (Mfx) for eligible patients, replacing the previous 9-month or 18-month regimens.[8 17] These updated guidelines signify a pivotal moment in DR-TB management, providing various all-oral, shorter and more patient-focused alternatives.[8 18]

Bdq is a novel oral diarylquinoline anti-TB agent developed for treating DR-TB that inhibits mycobacterial ATP synthase, an enzyme crucial for the survival of *MTB*.[19 20] Multiple cohort studies and clinical trials across various settings and populations have provided evidence of the clinical efficacy and safety of Bdq against DR-TB.[21–28] Although Bdq holds promise as a significant and core anti-TB agent, concerns regarding its effectiveness and safety persist.[1 29] In one clinical trial,[26] increased deaths and prolonged QT intervals were observed in patients receiving Bdq, leading to the recommendation for regular ECG monitoring, particularly during treatment initiation.[8 30] However, recent multicentric, prospective observational cohort studies reported that the risk of prolonged QT interval for Bdq-containing regimens is rare (<3%) compared with other safety events.[31 32] The most clinically relevant adverse events reported were peripheral neuropathy (26.4–28.4%) and electrolyte depletion (19.9–26%).[31 32]

Previous systematic reviews and meta-analyses have focused primarily on Bdq-based regimens with longer treatment durations or a combination of shorter and longer regimens, often including injectable options.[29 33–36] While these analyses provide valuable insights into the overall efficacy and safety of Bdq, they do not isolate the unique contributions of all-oral Bdq-based regimens lasting up to 12 months, which are essential given evolving treatment guidelines and the urgent need for patient-friendly options. By concentrating entirely on oral regimens limited to 12 months, this study offers a distinct perspective on treatment outcomes and adverse events, highlighting the potential benefits of shorter regimens for DR-TB management that prior reviews have not thoroughly explored.[29 33–36]

This study aims to evaluate the efficacy and safety of these shorter all-oral Bdq-based regimens for managing DR-TB, synthesising data from recent observational studies and clinical trials. The findings from this systematic review will align with global initiatives that support the WHO's goal of ending the TB epidemic.[12] These outcomes will provide evidence-based insights to aid policymakers, clinicians and researchers in making informed decisions about current DR-TB treatment strategies, ultimately improving patient outcomes.

## METHODS

### Protocol and search strategy

The systematic review and meta-analysis were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement [37] and the Cochrane Handbook of Systematic Reviews and Meta-analysis of Interventions.[38] The study protocol was registered with the Prospective Register of Systematic Reviews (PROSPERO) number CRD42024523086.[39]

A systematic search was conducted in the Medline, APA PsycINFO, Embase, Scopus, EBSCOhost/CINAHL, Cochrane Library, Web of Science, Center for Review and Dissemination (CRD), ScienceDirect and Institute for IEEE Xplore databases. The preliminary search revealed that publications on Bdq-based regimens began in 2012, and the search period, therefore, included relevant studies published between January 2012 and February 2024. The key search terms used included 'drug-resistant tuberculosis', 'bedaquiline', 'oral regimen', 'efficacy', 'safety' and 'treatment outcome'. A manual search

was also conducted on Google and Google Scholar for relevant studies corresponding to the citations listed in the included studies and related systematic reviews. A detailed search strategy for different databases is found in online supplemental Appendix 1.

### Eligibility criteria and study selection

We included English-language full-text journal articles that satisfied the following eligibility criteria: (1) adult individuals (≥18 years) diagnosed with DR-TB according to the WHO criteria[1] (online supplemental Appendix 2); (2) patients treated with all-oral Bdq-based shorter regimens (≤12 months) as interventions; (3) clinical trials and observational studies with or without control groups; (4) treatment outcomes (treatment success, treatment failure, mortality and loss to follow-up) reported according to the WHO guidelines;[2] and (5) safety outcomes (serious adverse events, any type of adverse events, and systemic or organ-based adverse events) reported. No restrictions were placed on sex, setting, TB diagnosis strategy, HIV status or previous TB treatment history. The exclusion criteria included case reports, correspondence, protocols, editorials, reviews, comments and publications lacking efficacy and safety outcomes of interest. Additionally, interim outcome analysis, duplicate publications and patients receiving adjunctive surgery were excluded from the study.

The eligible studies were selected in two steps. Initially, duplicates were eliminated, and then the titles and abstracts of the remaining articles were screened. An extensive review of the full-text articles was subsequently performed to verify the eligibility criteria. Citation management and duplicate removal were performed via the EndNote V.20 (Thomson Reuters, Toronto, ON, Canada). Three reviewers (GiF, TT, FB) independently conducted all screening stages, and any discrepancies were thoroughly discussed and resolved with a fourth member of the research team (WKM).

### Data extraction

Two independent reviewers (GiF, GeF) extracted data from each study via a data extraction checklist. The data extraction template was originally developed, subsequently modified and validated through discussions. Any discrepancies during the data extraction process were discussed and resolved by involving a third reviewer (TRF). The extracted data included (1) study characteristics (author name, study setting, study design, publication year, study period and sample size); (2) patient characteristics (patient age, sex, TB resistance profile and HIV status); (3) TB treatment characteristics (treatment regimens, doses, duration of treatment and follow-up period); and (4) treatment outcomes, including efficacy (culture conversion, treatment success, mortality, treatment failure and loss to follow-up) as well as safety (serious adverse events, any adverse events, and other systemic or organ-based adverse events).

### Risk of bias assessment

The risk of bias evaluation was conducted by two reviewers (GiF, ET) via the Cochrane Risk of Bias V.2.0 (ROB V.2.0) tool for randomised controlled trials (RCTs)[40] and the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool for non-randomised studies (NRS).[41] The ROB V.2.0 tool consists of five domains of bias: randomisation process bias, bias caused by deviations from intended interventions, bias stemming from missing outcome data, missing outcome data bias and selection of reported findings bias. Within each domain, specific questions are designed to gather relevant information for evaluating the potential for bias. The response categories include 'no', 'probably no', 'probably yes', 'yes' and 'no information'. On the basis of the provided responses, judgments can then be made and classified as either 'high risk of bias', 'some concerns' or 'low risk of bias'.[40]

On the other hand, the ROBINS-I tool consists of seven domains, including participant selection bias, classification of intervention bias, bias resulting from deviations from intended interventions, missing outcome data bias, measuring outcome bias and selecting reported results bias. Like ROB V.2.0, the domains in ROBINS-I consist of a series of signalling questions, which allow for categorising bias risk judgments as 'critical', 'serious', 'moderate' or 'low'.[41] The risk of bias plots were generated via the Robvis visualisation tool.[42] Any discrepancies in the risk of bias assessments were resolved through discussions involving other senior authors (TRF, WKM).

### Outcome measurements

The primary efficacy outcome included the treatment success rate (TSR), whereas the safety outcome included the incidence rate of serious adverse events (SAEs). The secondary efficacy outcomes include sputum culture conversion (SCC), treatment failure, loss to follow-up (LTFU) and mortality rates. The secondary safety outcomes include any adverse events (AEs), grade 3 or 4 AEs, and AEs resulting in treatment interruption, dose reduction, or discontinuation. In addition, organ or systemic AEs were also analysed.

A comparison of TSRs based on HIV status and drug resistance profiles was also performed. Furthermore, the efficacy and safety of all-oral Bdq-based shorter regimens (interventions) were compared with those of studies that included controls, which included conventional, longer or injectable regimens. The treatment outcome definitions were in accordance with the WHO guidelines[2] (online supplemental Appendix 3). Treatment success includes the sum of all patients who are cured and whose treatment is completed.[2] Grade 3 or 4 AEs encompass medically significant and life-threatening events, while SAEs include events that lead to death, life-threatening experiences, hospitalisation, permanent disability or congenital anomalies.[8]

### Data synthesis and statistical analyses

We used descriptive analysis and narrative synthesis to summarise the characteristics of the studies and TB treatment strategies. To present the meta-analysis results, we used the pooled event rate with a 95% CI for proportion data and the risk ratio (RR) with a 95% CI for binary data.

Heterogeneity across studies was assessed via Cochran's $\chi^2$ (Q) test, reported as the p value and quantified with the inconsistency index ($I^2$) statistic.[43 44] Significant heterogeneity was indicated by a Q test with p<0.05 and $I^2$>50%.[44 45] A random-effects model was used to estimate a pooled summary when significant heterogeneity was observed among the participants from different studies.[44] On the other hand, when the level of heterogeneity was low, a fixed effects model was used.[44] Subgroup analyses stratified by the length of Bdq therapy, duration of TB treatment and presence of specific anti-TB medications were performed to minimise heterogeneity and explain the variation in effect estimates between the included studies. Meta-regression was also performed using publication year and sample size as predictor variables to identify potential sources of heterogeneity. To quantify the influence of these potential outliers on the estimation of the overall effect size, a sensitivity analysis was performed via the leave-one-out method, which investigated the effect of each single study on the overall effect size estimate.

A funnel plot was employed to check for publication bias when at least 10 studies were included in the meta-analysis.[38] Additionally, Egger's and Begg's tests were used to assess the statistical significance of publication bias.[46 47] A p value <0.05 was considered evidence of statistically significant publication bias. In cases where such bias was identified, the trim-and-fill method was employed to adjust for potential publication bias.[47] All the statistical analyses were performed via STATA V.18.0 (StataCorp LLC, College Station, Texas, USA).

## RESULTS

### Study selection and characteristics

The literature search revealed 3032 articles, with 2984 retrieved from the databases and 48 obtained through a manual search. Following the removal of 971 duplicate records, 2061 records remained for further screening. After screening the titles and abstracts, 1978 articles were excluded, resulting in 83 studies that underwent full-text evaluation. Among these, 71 studies were subsequently excluded based on eligibility criteria. Finally, 12 studies[14–16 48–56] fulfilling the eligibility criteria were included in the meta-analysis: 5 were RCTs,[15 16 49 51 55] 4 were prospective cohort studies[50 52 54 56] and 3 were retrospective cohort studies[14 48 53] (figure 1).

All the studies were conducted in high-burden DR-TB countries across Africa, Asia and Europe. All the included studies were published within the past 4 years (2020–2024). Seven studies enrolled only MDR/RR-TB patients,[14 48 49 51–54] whereas the remaining studies evaluated both MDR/RR-TB patients and pre-XDR-TB patients[15 16 50 55 56] following the WHO's post-2021 definition of XDR-TB[57] (table 1).

The combined studies included data from 1902 patients, of which 1180 (62.0%) were male. The patients' pooled mean age was 36.7±5.2 years. Among the study population, 802 patients (42.2%) were diagnosed with HIV, and 991 (52.1%) had a history of previous TB treatment (table 1). In terms of TB treatment, the duration of Bdq therapy ranged from 6 to 9 months, whereas the overall duration of the TB treatment regimen varied from 6 to 12 months. The follow-up period after the initiation of treatment ranged from 9 to 24 months. All patients with MDR/RR-TB, as reported in nine studies, received fluoroquinolones (FQs), either levofloxacin (Lfx) or Mfx, as part of their treatment regimen. In three studies,[15 16 55] the recently approved Ptd was administered for 6 months, with Lzd doses ranging from 600 mg to 1200 mg daily (online supplemental table S1).

### Risk of bias assessment results

The results of RoB V.2 indicated the risk of bias assessment for the RCTs, with three studies classified as low risk, one study classified as having some concern and one study classified as having a high risk of bias. The ROBINS-I assessment for the NRSs reported a range of bias evaluations from low to serious, with no critical risk observed (online supplemental figure S1). All trials were free of bias concerning missing outcomes, outcome measurements and the selection of reported findings. However, one RCT exhibited a high risk of bias attributed to the randomisation process.[15] On the other hand, all NRS studies demonstrated a low risk of bias regarding the selection of reported findings (online supplemental figure S2).

### Pooled efficacy analyses

Treatment outcomes, including treatment success, treatment failure, death and LTFU, were reported for 1872 participants across 12 studies. The pooled TSR was 83% (95% CI 77% to 89%; figure 2). The overall analysis revealed significant heterogeneity (p<0.01, $I^2$=90.55%). The subgroup analyses revealed a significant improvement in the TSR due to the use of Ptd and the absence of pyrazinamide (Pza). Incorporating Ptd in the regimen yielded a higher TSR (89%, 86–92) than when Ptd was not used (80%, 73–88; p=0.03). Conversely, patients receiving Pza-containing regimens had a lower TSR (78%, 69–86) than did those who did not receive Pza (90%, 87–92; p=0.01) (online supplemental figure S3). A subgroup analysis was also conducted to assess the TSR and its association with factors such as the drug resistance profile[15 16 50 56] and HIV status.[16 51 53 55] However, no significant differences were found between MDR/RR-TB patients and pre-XDR-TB patients (RR 1.02, 0.93–1.11, p=0.75) or between HIV-negative patients and individuals living with HIV (RR 1.08, 0.95–1.22, p=0.23) (online supplemental figure S4).

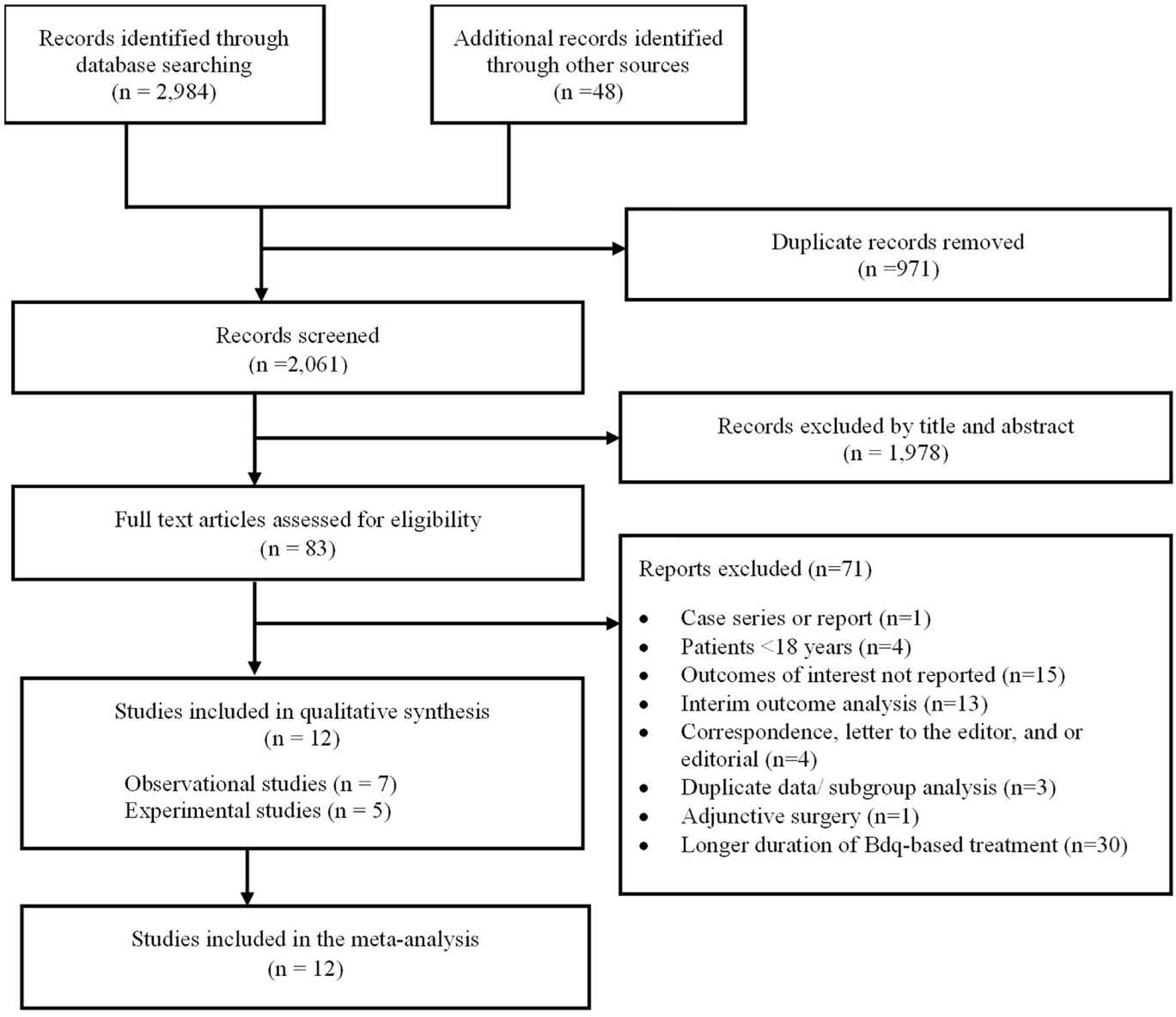


**Figure 1** The article selection process. Bdq, bedaquiline.

The overall TFR was 4% (95% CI 2% to 6%, $I^2$=80.82%; figure 2). The subgroup analyses revealed no significant differences in TFR (online supplemental figure S5). The overall mortality rate, pooled from all studies, was 5% (95% CI 3% to 8%, $I^2$=95.11%; figure 3). The subgroup analyses revealed higher mortality rates in the 6 month Bdq treatment group than in the 9 month Bdq treatment group (p=0.02), as well as in the groups that did not use Ptd than in those that did (p=0.02) (online supplemental figure S6). The pooled LTFU rate was 4% (95% CI 2% to 6%, $I^2$=82.37%; figure 2). The subgroup analyses revealed lower rates of LTFU in patients receiving 6–9 months of TB treatment (p<0.01). Moreover, the absence of Ptd and the use of Pza in the regimen were associated with higher LTFU rates than were the respective control groups (p<0.01) (online supplemental figure S7).

A total of 688 participants from seven studies[16 48–51 54 56] reported an SCC rate of 85% (95% CI 79% to 91%) at 2 months. Three studies including 140 patients[15 48 52] reported an SCC rate of 95% (89–100) at 4 months. Additionally, five studies comprising 358 patients[14 15 48–52] reported an SCC rate of 96% (94–98) at 6 months (online supplemental figure S8). The subgroup analyses revealed higher SCC rates at 2 months in the 6-month Bdq treatment group than in the 9-month Bdq treatment group (p=0.03), as well as in the groups that did use Pza than in those that did not (p=0.01). However, no significant differences were found between SCCs at 4 and 6 months in subgroup analysis (online supplemental figure S9).

### Comparative efficacy analyses

Five studies[49–51 53 55] provided data on treatment outcomes and compared the intervention, all-oral Bdq-based shorter regimens (n=1127 patients), with the control, including longer oral or injectable-based regimens (n=1109 patients). Compared with the control, the intervention significantly improved treatment success (RR 1.22, 95% CI 1.04 to 1.43, p=0.01; online supplemental

**Table 1** Study characteristics

| Author (year) | Study design | Study setting | Study (recruitment) period | Study participants/ resistance profile* | External control group† | Sample size | Age, year (mean (ranges)) | Sex, male, % (n) | HIV positive, % (n) | On ART, %(n) | Previous TB history, % (n) | Baseline culture positive, % (n) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Avaliani *et al* (2021)[48] | RCS | Georgia | March to August 2019 | MDR/RR-TB | No | 25 | 48 (18–77) | 68.0 (17) | 8.0 (2) | NR | NR | 64.0 (16) |
| Conradie *et al* (2020)[15] | RCT | South Africa | April 16 to November 2017 | MDR/pre-XDR-TB | No | 109 | 35 (17–60) | 52.3 (57) | 51.4 (56) | 100 (56) | 17.4 (19) | 85.3 (93) |
| Conradie *et al* (2022)[16] | RCT | Multicenter‡ | November 2017 to December 2019 | MDR/pre-XDR-TB | No | 181 | 36 (30–44) | 67.4 (122) | 19.9 (36) | NR | 100 (181) | 79.0 (143) |
| Esmail *et al* (2022)[49] | RCT | South Africa | November 2015 to October 2019 | MDR/RR-TB | Yes | 49 | 37 (31–43) | 69.4 (34) | 55.1 (27) | NR | 38.8 (19) | 87.8 (43) |
| Fu *et al* (2023)[50] | PCS | China | May 2020 to December 2020 | MDR/pre-XDR-TB | Yes | 58 | 35 (29–52) | 72.4 (42) | Excluded | NA | 69.5 (41) | 94.8 (55) |
| Goodall *et al* (2022)[51] | RCT | Multicenter§ | March 2016 to January 2020 | MDR/RR-TB | Yes | 196 | 33 (26–42) | 63.3 (124) | 13.8 (27) | 100 (27) | 79.6 (156) | 100 (196) |
| Govender *et al* (2022)[52] | PCS | South Africa | July 2019 to July 2020 | MDR/RR-TB | No | 57 | 36 (26–46) | 68.4 (39) | 73.7 (42) | 64.3 (27) | 42.1 (24) | 54.4 (31) |
| Ndjeka *et al* (2022)[53] | RCS | South Africa | January to December 2017 | MDR/RR-TB | Yes | 688 | 42 (33–51) | 61.5 (423) | 71.7 (493) | 97.0 (47) | 39.8 (274) | 72.8 (342) |
| Nguyen *et al* (2022)[54] | PCS | Vietnam | July 2020 to February 2021 | MDR/RR-TB | No | 106 | 41 (29–57) | 70.8 (75) | 0.9 (1) | 100 (1) | 37.7 (40) | 66.0 (70) |
| Nyang'wa *et al* (2024)[55] | RCT | Multicenter¶ | January 2017 to March 2021 | MDR/pre-XDR-TB | Yes | 151 | 35 (17–71) | 56.3 (85) | 25.2 (38) | NR | 11.9 (18) | 85.4 (129) |
| Padmapriyadarsini *et al* (2023)[56] | PCS | India | April 2019 to January 2021 | MDR/pre-XDR-TB | No | 165 | 27 (18–56) | 55.8 (92) | Excluded | NA | 100(165) | 98.2 (162) |
| Tack *et al* (2021)[14] | RCS | South Africa | July 2018 to April 2019 | MDR/RR-TB | No | 117 | 35 (27–44) | 59.8 (70) | 68.4 (80) | 77.5 (62) | 46.2 (54) | 57.3 (67) |

*According to the WHO post-2021 definition of XDR-TB.
†Standard of care, longer or injectable-based regimen.
‡South Africa, Georgia, Moldova and Russia.
§Ethiopia, Georgia, India, Moldova, Mongolia, South Africa and Uganda.
¶Belarus, South Africa and Uzbekistan.
ART, antiretroviral therapy; MDR/RR-TB, multidrug/rifampicin-resistant tuberculosis; NA, not applicable; NR, not reported; PCS, prospective cohort study; Pre-XDR-TB, pre-extensively drug-resistant tuberculosis; RCS, retrospective cohort study; RCT, randomised clinical trial; TB, tuberculosis.

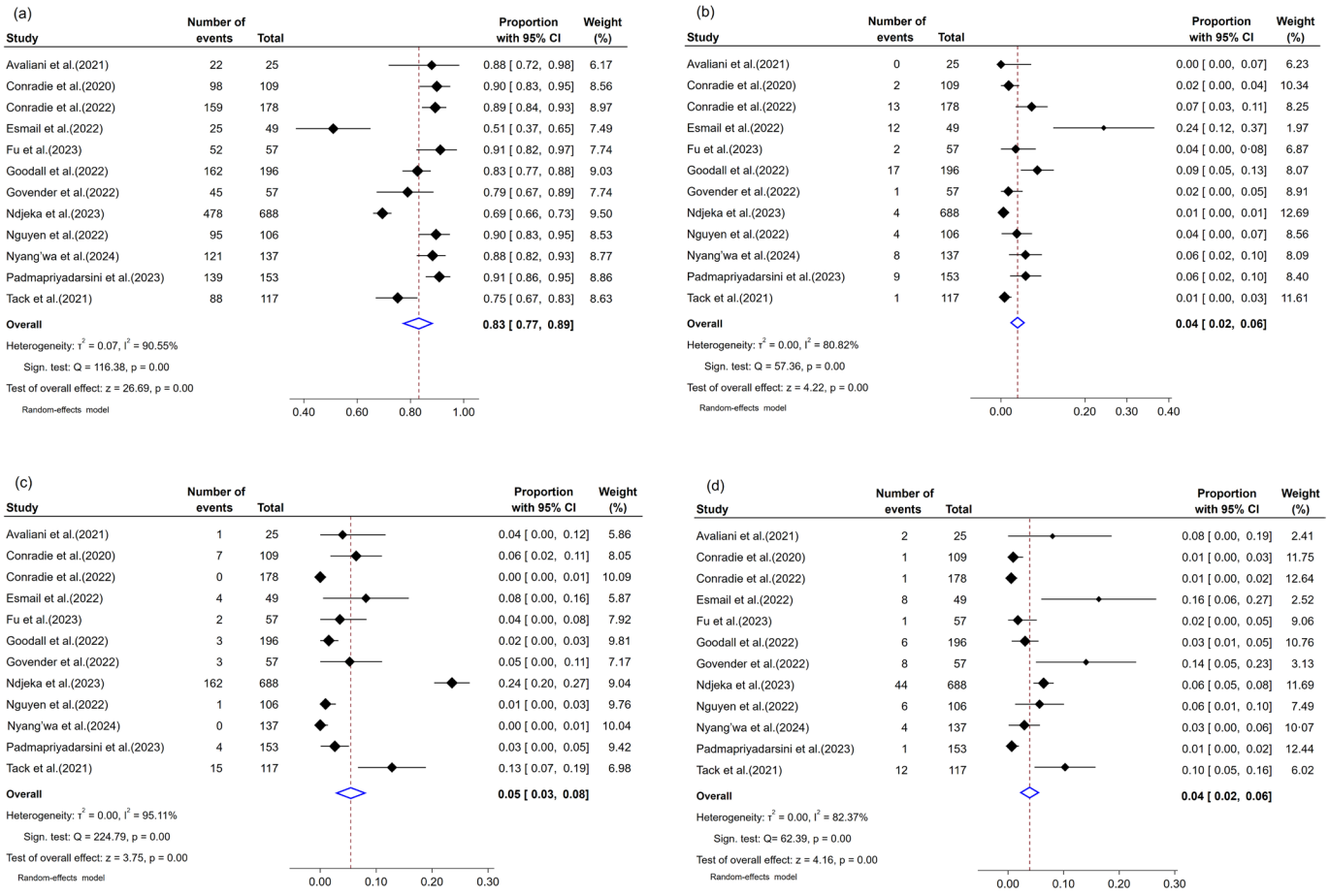


**Figure 2** Forest plot of (a) the TSR, (b) TFR, (c) mortality rate and (d) LTFU rate for DR-TB patients treated with all-oral Bdq-based shorter regimens. Bdq: bedaquiline; CI: confidence interval; DR-TB: drug-resistant tuberculosis; TSR: treatment success rate; TFR: treatment failure rate.

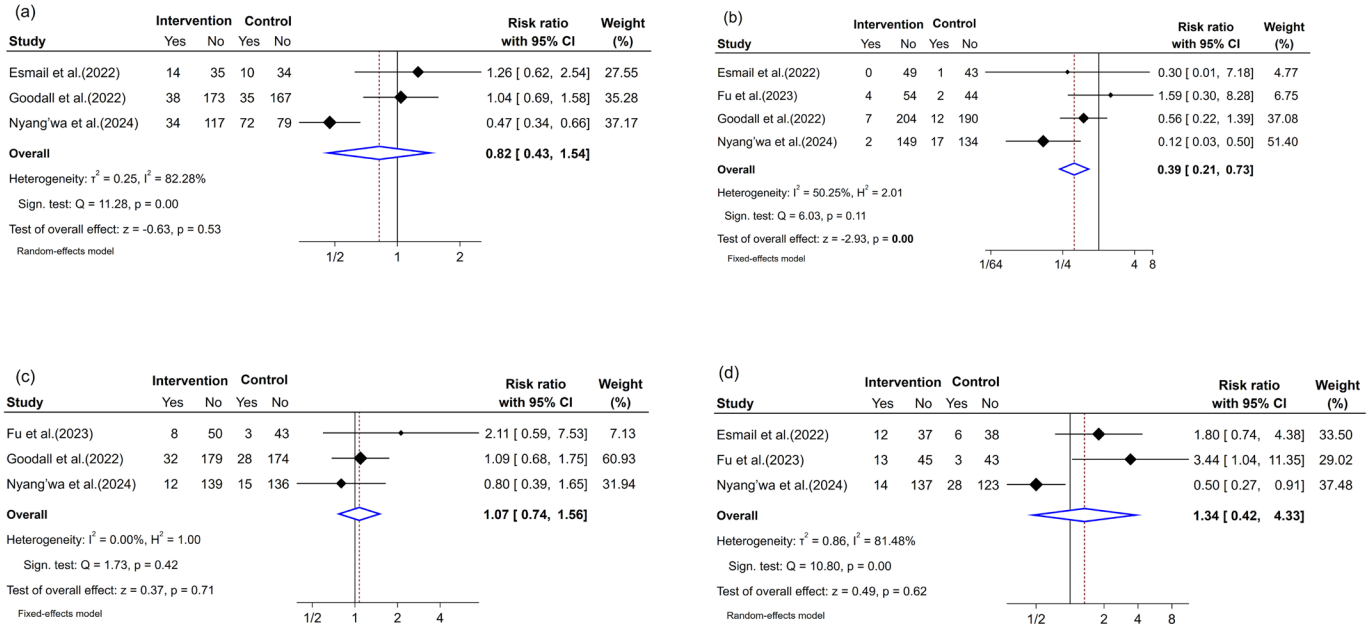


**Figure 3** Forest plot comparing the incidences of (a) SAE, (b) cardiovascular disorders (QTc prolongation), (c) liver disease, and (d) peripheral neuropathy between all-oral Bdq-based shorter regimens and the control regimens. Bdq: bedaquiline; CI: confidence interval; SAE: serious adverse events.

figure S10). The findings also revealed that the intervention significantly reduced treatment failure (RR 0.33, 0.32–0.62; p<0.01) and mortality (RR 0.73, 0.69–0.99; p=0.03). However, there was no notable significant difference in LTFU between the treatment regimens (RR 1.30, 0.51–3.26; p=0.58) (online supplemental figure S10). A significant difference in the SCC was observed at 2 months (RR 1.18, 1.01–1.37) (online supplemental figure S11).

### Pooled safety analyses

With respect to safety, three studies with a total of 284 participants[48 54 55] reported a median time to SAE incidence of 91.3 days (77.0–98.5). All studies, except for the one by Ndjeka *et al*,[53] which involved 1173 participants, reported the incidence rate of SAE to be 19% (95% CI 13% to 24%; $I^2$=82.37%) (online supplemental figure S12). The subgroup analyses revealed no significant differences among the different factors in terms of SAE (p>0.05) (online supplemental figure S13). AEs of any type were reported in 85% (79–90) of the patients, whereas 38% (20–56) experienced grade 3 or 4 AEs. A total of 26% (19–53) of the patients reported interrupting, discontinuing or reducing the dose of Bdq-based treatment (table 2). The most notable organ-specific or system-specific events included peripheral neuropathy (21%), haematological disorders (17%) and liver disease (15%). A prolonged QTc interval was observed in 81 out of the 1122 patients (5%, 2–8) (table 2, (online supplemental figure S14-S32).

### Comparative safety analyses

Four comparative studies[49 51 55] involving 411 patients in the intervention group and 397 patients in the control group reported SAE incidence rates. The findings revealed no statistically significant difference in SAEs between these two regimens (RR 0.82, 95% CI 0.43 to 1.54; p=0.53) (figure 3). However, the intervention regimens significantly reduced the incidence of cardiovascular disorders (specifically QTc prolongation) compared with the control regimens (RR 0.39, 0.21–0.73, p<0.001) (figure 3). Nevertheless, no statistically significant differences were observed between the regimens regarding other AEs (figure 3, online supplemental figure S33–S37).

### Meta-regression, publication bias and sensitivity analyses

In the meta-regression analysis, the sample size and year of publication had no significant effect on the TSR, TFR, LTFU rate or incidence of SAEs. However, the sample size had a significant effect on the mortality rate (β=0.0003; p<0.01).

There was no significant publication bias for the TSR or SAE (online supplemental figure S38 and S39). However, there was a general asymmetry in the funnel plot, and statistical tests, including Begg's test and Egger's test (p<0.05), revealed significant publication bias for the TFR, mortality rate and LTFU rate (online supplemental figure S40–S42). To address this bias, the trim and fill linear estimator adjusted the LTFU rate to 2.6% (0.7–4.4) by imputing the estimated four studies. However, the trim and fill linear estimator could not adjust for publication bias for the TFR and mortality rate.

The sensitivity analyses, which involved omitting individual studies one at a time, indicated the robustness of the findings for the TSR, TFR, LTFU rate and SAE incidence rate (online supplemental figure S43–S46). A study conducted by Ndjeka *et al*[53] reported higher mortality rates (24%), which may introduce bias and lead to an overestimation of the overall mortality effect, particularly when comparing the 6-month regimen with the 9-month regimen in the subgroup analysis (online supplemental figure S47). In a sensitivity analysis where the study by Ndjeka *et al*[53] was omitted, the mortality rate changed from 5% (3–8) to 2% (1–4).

## DISCUSSION

We analysed data from 12 studies involving 1902 DR-TB patients across 11 countries. Our findings indicated that shorter Bdq-based oral regimens yielded a high TSR of 83%. The pooled rates for treatment failure, mortality and LTFU were relatively low, at 4%, 5% and 4%, respectively. We observed no significant differences in the TSR between MDR/RR-TB patients and pre-XDR-TB patients or between HIV-negative patients and individuals living with HIV. These findings support prior meta-analyses that have demonstrated the effectiveness of Bdq-containing regimens as the standard of care.[34 36] For example, a study by Rehman *et al*, which included 41 studies and 10 402 patients, reported an average pooled TSR of approximately 79%.[34]

However, it is important to consider that our study reported a higher TSR than a meta-analysis of the 9-month to 12-month WHO-recommended all-oral regimen, demonstrating treatment success in 73% of cases.[58] Furthermore, the WHO report also indicated an overall lower TSR of 68% in 2023.[1] This discrepancy might be attributed to the fact that our present study included studies involving shorter all-oral regimens and more effective medications (Bdq, Cfz, Ptd and Lzd), unlike previous studies that included longer all-oral regimens or a mix of oral and injectable drugs. Treatment adherence is also a core component of rapid and effective TB treatment,[59] and shorter oral treatment regimens increase adherence, thus significantly increasing the likelihood of treatment success.

We also compared the treatment outcomes of the Bdq-based regimens with those of the control group, including longer oral, injectable-based or mixed regimens. Our findings revealed that all-oral Bdq-based shorter regimens significantly improved SCC and treatment success while reducing mortality and treatment failure. However, we did not find a significant difference in the number of LTFUs. These findings were consistent with previous meta-analyses of standard Bdq-containing

**Table 2** Details of the adverse event results of the included studies

| Outcomes | Number of studies | Number of patients included | Estimates | | | Heterogeneity | |
|---|---|---|---|---|---|---|---|
| | | | Incidence rate | 95%CI | P value | $I^2$ (%) | P value |
| Any type of AEs | 10 | 1066 | 85% | 79 to 90 | <0.001 | 97.46 | <0.001 |
| Grade 3 or 4 AEs | 5 | 667 | 38% | 20 to 56 | <0.001 | 96.50 | <0.001 |
| Treatment interruption, dose reduction or discontinuation | 10 | 1174 | 26% | 19 to 53 | <0.001 | 98.36 | <0.001 |
| Peripheral neuropathy | 10 | 1020 | 21% | 9 to 33 | <0.001 | 98.43 | <0.001 |
| Haematological disorders (anaemia, thrombocytopenia, neutropenia, myelosuppression) | 10 | 1206 | 17% | 11 to 22 | <0.001 | 97.52 | <0.001 |
| Liver disease (hepatotoxicity, liver enzyme elevation) | 10 | 1182 | 15% | 9 to 22 | <0.001 | 92.12 | <0.001 |
| Dermatological disorders | 8 | 946 | 14% | 7 to 20 | <0.001 | 97.74 | <0.001 |
| Electrolyte abnormalities | 2 | 289 | 9% | 0 to 17 | 0.04 | 85.98 | 0.01 |
| Musculoskeletal disorder (arthralgia, myalgia) | 7 | 625 | 7% | 3 to 11 | <0.001 | 83.87 | <0.001 |
| Cardiovascular disorders (QTc prolongation) | 10 | 1122 | 5% | 2 to 8 | <0.001 | 85.52 | <0.001 |
| Pancreatic enzyme elevation | 3 | 497 | 5% | 0 to 11 | 0.06 | 92.36 | <0.001 |
| Gastro-intestinal tract disorders (diarrhoea, vomiting, nausea, abdominal pain) | 10 | 1174 | 4% | 2 to 6 | <0.001 | 87.00 | <0.001 |
| Renal disorders (increased creatinine levels) | 5 | 717 | 4% | 1 to 6 | 0.02 | 85.77 | <0.001 |
| Respiratory disorders | 7 | 923 | 3% | 1 to 6 | <0.001 | 78.22 | <0.001 |
| Neurological (central nervous system) disorders | 8 | 984 | 3% | 1 to 5 | 0.01 | 87.75 | <0.001 |
| Infections and infestations | 3 | 507 | 3% | 2 to 5 | <0.001 | 25.82 | 0.26 |
| Ear disorder (ototoxicity, hearing loss) | 4 | 498 | 2% | 1 to 3 | <0.001 | 0.00 | 0.69 |
| Psychiatric disorders | 7 | 806 | 3% | 1.5 | 0.01 | 77.48 | <0.001 |
| Eye disorders (optic neuropathy, blurred vision) | 7 | 884 | 2% | 0 to 3 | 0.01 | 60.40 | 0.02 |

AEs, adverse events; QTc, corrected QT interval.

regimens.[29 33] For example, a meta-analysis conducted by Wang *et al* involving 21 836 patients reported a higher SCC rate (RR 1.27, 1.17–1.39) and reduced mortality (RR 0.53, 0.45–0.62) in the Bdq-based regimen group than in the control group.[33] Another meta-analysis including 23 358 individuals revealed that the use of Bdq-based

regimens resulted in increased cure rates, decreased failure rates, reduced all-cause death and no difference in the LTFU rate compared with non-Bdq-containing regimens.[29] This finding supports the use of Bdq in shorter regimens, particularly since the control regimens tend to be lengthy and associated with a greater proportion of poor outcomes.[7 60]

The higher rate of successful treatment and lower mortality rate observed with Bdq can be attributed to its unique mechanism of action, which inhibits mycobacterial cellular energy via ATP synthesis by MTB.[19 20] This is achieved by obstructing the ion-binding sites in the c-subunit of the F0 domain of ATP synthase, disrupting energy metabolism pathways.[19 20 61] With this mechanism, Bdq effectively combats all forms of MTB, including dormant, active, non-replicating, replicating, and extracellular and intracellular bacteria.[62] Moreover, the high plasma protein binding (>99.9%), long elimination half-life (~5.5 months) and broad tissue distribution of Bdq further increase its efficacy and minimise the likelihood of developing resistance.[19 63]

In terms of safety, even though most of the patients (85%) experienced any type of AE, similar to previous studies,[9 64 65] most of these AEs were mild (grades 1–2) and did not lead to treatment discontinuation. However, a significant proportion of individuals (19%) experienced SAEs during treatment. These findings suggest that the safety profile of these regimens still raises concerns, highlighting the importance of careful monitoring and evaluation of patients for SAEs during Bdq-based treatment.

One concerning AE of Bdq is a prolonged QTc interval, which was observed in 5% of the patients in our study. This condition can cause irregular heart rhythms and increase the risk of sudden cardiac death, especially when coupled with other medications and in patients with heart problems. This incidence rate was lower than that reported in a previous meta-analysis by Rehman *et al* (10.2%),[34] possibly because of the shorter duration of concomitant anti-TB drugs that prolong the QT interval. However, similar to other AEs, QT prolongation gradually decreased after treatment discontinuation.[9 66] Therefore, caution should be exercised when using Bdq in patients with or at risk of QT prolongation, and frequent ECG monitoring is recommended.

Our safety comparison revealed no significant differences in the incidence rates of SAEs, haematological disorders, gastrointestinal disorders, peripheral neuropathy or liver disease between the two treatment regimens. However, the intervention significantly reduced QTc prolongation relative to the control regimens (RR 0.39, 0.21–0.73). This finding contrasts with previous meta-analyses that reported increased incidences of cardiotoxicity in Bdq-containing regimens (RCT: RR 4.54, 1.74–11.87; NRS: RR 6.00, 1.32–27.19).[29] This difference may be attributed to the diverse nature of the control regimens, some of which include Bdq as an all-oral longer regimen or in combination with injectable drugs. Additionally, our study used many concomitant anti-TB drugs, such as Dlm, Cfz and FQs, which can prolong the QT interval for shorter durations than in previous studies where these drugs were used for more extended periods.

While our analysis focused primarily on the efficacy and safety of all-oral Bdq-based regimens, it is essential to acknowledge the pivotal role of companion drugs included in these treatment protocols. The interplay between Bdq and other agents, such as Lzd, Ptd, Dlm, FQs, Cfz, Pooled efficacy analyses (Pza) and others, can significantly influence the overall safety profile. Each drug carries its own risk of adverse events, complicating the interpretation of the results. For example, Lzd is associated with peripheral neuropathy and myelosuppression.[15 16 67] Therefore, the heterogeneous nature of these regimens necessitates careful consideration when interpreting safety outcomes, as differences in regimen composition can lead to variability in both efficacy and adverse effects across studies.[8]

In our subgroup analysis, the inclusion of Ptd, a novel oral bicyclic nitroimidazooxazole, was associated with an improved TSR and lower mortality in patients with DR-TB. Recent clinical findings have highlighted the efficacy of Ptd-based regimens, particularly in patients with DR-TB, which has led to significant improvements in clinical outcomes with shorter treatment durations.[13 15 16] Ptd exerts its effects through both bactericidal and sterilising mechanisms.[68–70] Thus, the role of Ptd as a companion drug in Bdq-based regimens enhances treatment efficacy and underscores the importance of integrating novel therapies into DR-TB management strategies.

Our study revealed that Bdq-based regimens play a significant role in saving lives and ensuring safety in the management of TB. However, the development of Bdq resistance poses a significant threat to the effectiveness of novel DR-TB treatment strategies, with an increasing number of cases reporting acquired Bdq resistance in recent years. Notably, up to 6% of Bdq-naive patients exhibit resistance to Bdq.[71 72] A meta-analysis of 13 studies revealed phenotypic acquired Bdq resistance rates of 2.2% and genotypic acquired resistance rates of 4.4%.[73] Additionally, a pooled prevalence of baseline Bdq resistance of 2.4% and treatment-emergent resistance of 2.1% was reported in another meta-analysis comprising 14 studies.[74] The mechanisms of Bdq resistance include mutations within the Rv0678, atpE and pepQ genes.[75 76]

Furthermore, certain Bdq-resistant mutants also exhibit cross-resistance to Cfz.[76 77] This phenotypic cross-resistance was observed at rates of 1% in pre-XDR-TB/XDR-TB populations and 0.4% in MDR-TB populations.[78] The accumulation of these emerging mutations, which are not yet fully characterised, significantly complicates the management of resistant strains.[79] Understanding both target-based and non-target-based resistance mechanisms is needed to reduce resistance development. Timely and comprehensive drug resistance monitoring for novel DR-TB therapies involving Bdq is imperative. Therefore, it is crucial to prioritise routine

drug susceptibility testing alongside the scale-up of new drugs for the effective management of DR-TB.

This study has several limitations. Primarily, there was significant heterogeneity among the studies regarding treatment regimens, treatment duration, study designs and efficacy analysis. Despite conducting subgroup analyses to identify potential sources of heterogeneity, it is important to acknowledge that residual heterogeneity may still exist and could influence the overall findings. Factors such as comorbidities, socioeconomic status and concomitant medications may also affect treatment outcomes and safety profiles.

Additionally, the reporting of treatment and safety outcomes varied across studies, with some reported immediately after treatment completion and others after several months of follow-up. This inconsistency in reporting could impact the pooled effect and the reliability of the outcome data. Variations in accompanying background drugs could further affect treatment outcomes and safety, complicating the determination of the specific role of individual drugs, including Bdq, within the treatment regimen. Furthermore, we did not evaluate the specific contributions of each companion drug within the regimens.

Another limitation of this study is the inability of the trim and fill linear estimator to effectively adjust for publication bias regarding the TFR and mortality rates. This limitation raises concerns about the potential overestimation or underestimation of these outcomes, as unpublished studies with negative or inconclusive results may skew our understanding. Consequently, the observed outcomes may not fully reflect the true efficacy and safety of Bdq-based regimens, highlighting the need for more comprehensive reporting in future research.

Some studies also had limited data on long-term outcomes and relapse rates, indicating a need for further research with extended follow-up periods. Unfortunately, owing to the scarcity of available data, it was not possible to evaluate the safety of treatment regimens separately in pre-XDR-TB and MDR/RR-TB patients. Finally, the study scope was restricted to English-language articles, potentially excluding relevant publications in other languages.

## CONCLUSIONS

Our systematic review and meta-analysis provide compelling evidence that all-oral Bdq-based shorter regimens significantly improve treatment outcomes for DR-TB. These regimens have demonstrated higher SCCs and TSRs, along with a notable reduction in treatment failure, mortality and cardiotoxicity. This work contributes to the literature by synthesising recent clinical trials and observational data, thus clarifying the efficacy and safety profiles of these regimens.

While our findings affirm the effectiveness of all-oral shorter regimens, it is crucial to emphasise the importance of long-term follow-up for patients undergoing these treatments. Monitoring instances of relapse will provide valuable insights into the durability of treatment outcomes and address concerns raised by clinicians regarding potential recurrence. Further research is needed to assess long-term outcomes, cost-effectiveness and potential barriers to their widespread implementation. Additionally, our analysis underscores the importance of vigilant monitoring for SAEs, as a significant proportion of individuals experienced these events during treatment.

Given the significant clinical and public health implications of these findings, we urge policymakers, clinicians and stakeholders in TB control programmes to expand access to and accelerate the implementation of all-oral Bdq-based regimens. However, it is equally vital to establish robust monitoring frameworks to address safety concerns and ensure optimal patient outcomes.

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