Update in tuberculosis treatment: a scoping review of current practices

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Shareable abstract (@ERSpublications)
Shorter, all-oral regimens for DR-TB show superior safety and effectiveness compared with traditional injectable therapies. Regimens incorporating novel drugs are both non-inferior and often superior to standard treatments, with fewer adverse events. https://bit.ly/4fHxZHz

Cite this article as: Lopes SR, Marçal M, Fernandes N, *et al*. Update in tuberculosis treatment: a scoping review of current practices. *Breathe* 2025; 21: 240232 [DOI: 10.1183/20734735.0232-2024].

Received: 30 Sept 2024
Accepted: 2 Dec 2024

Abstract

Background Tuberculosis (TB) remains a significant global health challenge despite ongoing control efforts, particularly in the context of drug-resistant TB (DR-TB), where treatment success rates remain low, underscoring the need for new therapeutic options. This review synthesises current evidence, since the publication of the World Health Organization guidelines in 2022, on the safety and efficacy of existing and new regimens for drug-susceptible TB (DS-TB) and DR-TB in adults and children.

Methods A comprehensive search was performed across three databases for studies published between January 2022 and February 2024, focusing on current and new TB treatment regimens. Additional backward and forward citation searches were conducted to identify relevant literature.

Results 35 studies were included, evaluating the efficacy, safety and economic impact of new oral regimens for DS-TB and DR-TB. Regimens based on bedaquiline or delamanid demonstrated high success rates and good tolerability. The BPaLM (bedaquiline, pretomanid, linezolid and moxifloxacin) regimen was more effective and safer than the standard care, while shorter DR-TB regimens reduced costs and increased success rates. However, shorter regimens for DS-TB were associated with increased drug costs. Though limited, paediatric studies suggest that shorter, safer regimens may benefit children.

Conclusion Evidence supports the adoption of shorter treatment regimens for both DR-TB and DS-TB to improve safety, effectiveness and cost-effectiveness, particularly in resource-limited settings.

Introduction

Tuberculosis (TB) remains a significant global health challenge, with nearly 10 million cases and over 1.4 million deaths annually, according to the World Health Organization (WHO) [1]. It persists as a leading cause of death from infectious diseases, particularly in low- and middle-income countries, despite global efforts to control its spread [1]. The emergence of drug-resistant tuberculosis (DR-TB), including multidrug-resistant (MDR-TB) and extensively drug-resistant TB (XDR-TB), presents substantial challenges to treatment and disease control as these forms of TB demand longer, more expensive and often more toxic regimens compared to drug-sensitive TB (DS-TB) [1, 2].

Recent advances in TB treatment have focused on improving outcomes for both DS-TB and DR-TB by reducing treatment duration, minimising side effects and increasing success rates [1–3]. Developing new drugs, novel treatment regimens and enhanced diagnostic tools has paved the way for more effective TB management [2, 3]. However, the shift towards all-oral regimens has highlighted the importance of understanding and managing adverse effects (AEs) to optimise treatment and improve patient adherence.

Traditionally, the WHO's treatment guidelines for DS-TB have recommended a 6-month regimen, combining isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) (*i.e.* HRZE) during the intensive phase, followed by HR in the continuation phase. Treatment for DR-TB, including MDR-TB and XDR-TB, has typically required complex regimens with combinations of oral drugs and durations of 18–20 months. In contrast, the updated 2022 WHO treatment guidelines, informed by key clinical studies such as the STREAM and Nix-TB trials, have demonstrated the efficacy of shorter, more tolerable and less toxic regimens that incorporate novel drugs like bedaquiline (Bdq), pretomanid (Pa) and delamanid (Dlm) [4, 5]. Additionally, recent studies have shown that a 4-month treatment regimen for DS-TB, including rifapentine (Rp) and moxifloxacin (Mfx), can be as effective as the standard 6-month regimen [6]. These findings have led to new recommendations for shorter, more tolerable regimens for DS-TB and DR-TB in the 2022 WHO guidelines. For MDR-TB patients, a 6-month regimen combining Bdq, Pa, linezolid (Lzd) and BPaLM, is now recommended; while a 4-month regimen of H, R, Mfx and Z is suggested for individuals aged 12 and older with DS-TB [2, 3]. However, their implementation varies widely due to differences in healthcare infrastructure, drug availability, and socioeconomic conditions [2, 3].

This scoping review aims to provide a comprehensive overview of current practices in treating DS-TB and DR-TB in children and adults, focusing on recent updates in treatment strategies. This review includes studies published after 2022 to specifically capture the updates and advances in TB treatment following the latest WHO guidelines. By synthesising the latest evidence, this review will highlight advancements in TB treatment regarding safety, efficacy, and economic impact in the last 2 years while also underscoring the progress made and the ongoing challenges that must be addressed to achieve global TB control and elimination.

Methods

Study design

A scoping review of published peer-reviewed research and grey literature, including reports from health organisations, conference papers and dissertations, was conducted following the methodological framework established by Arksey and O'Malley [7]. The literature search was performed using the PubMed, SCOPUS and Web of Science databases. The review and screening process adhered strictly to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines [8]. Two independent reviewers screened titles and abstracts, resolving discrepancies by consultation with a third reviewer.

Eligibility criteria

Studies were eligible for inclusion if they focused on new TB treatment strategies, including novel drug therapies and treatment regimens. They evaluated the efficacy, economic impact and AEs in adult and paediatric populations. Only studies published after January 2022 were considered. Exclusion criteria included articles that focused solely on diagnostic methods, biomarkers, adherence or epidemiology without discussing treatment; studies addressing TB as a secondary illness or comorbidity; articles centred on TB prevention or other mycobacteria; research examining single drugs (including pharmacokinetics and pharmacodynamics data or experimental drugs); nonprimary studies; and articles not available in English or as full-text.

Search strategy

A comprehensive literature search was conducted from January 2022 to February 2024 across three electronic databases (PubMed, SCOPUS and Web of Science) and three clinical trial registries (Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov and the Tuberculosis Network European Trials Group (TBnet)). The search strategy employed a combination of medical subject headings (MeSH) terms and free-text keywords related to "tuberculosis", "treatment" and "new".

Study selection

After removing duplicates, two teams of two reviewers independently screened the titles and abstracts of all identified records to assess eligibility. Any discrepancies between the reviewers were resolved through consultation with the opposite team. Subsequently, the same teams retrieved and evaluated the full texts of articles for inclusion, using the same resolution method for further disagreements. Additionally, backward and forward citation searches were conducted on all selected studies within the same databases and timeframe. A study was only included in the review when at least two reviewers agreed on its relevance. Review articles were retained for hand-searching their references.

Data extraction and synthesis

The research team developed and piloted a data extraction form to systematically capture relevant information from the included studies. Extracted data included study characteristics (authors, year of publication, study design and country), population details (target population and sample size), TB sensitivity profiles (DS, MDR-TB, XDR-TB) and details of the interventions and outcomes (efficacy, safety and other relevant clinical outcomes). Four reviewers independently extracted the data, with discrepancies resolved through consensus. Identified trends and gaps in the literature were subsequently analysed and discussed.

Results

A total of 1988 records were identified through database searches. After deduplication, 1260 unique citations remained (figure 1). Of these, 1096 records were excluded based on title and abstract screening, and 24 could not be retrieved, leaving 140 for further assessment. Among the 140 full-text articles assessed for eligibility, 118 were excluded, resulting in 22 articles being included in our review. Additionally, records were identified through citation searching, with 13 meeting the inclusion criteria. In total, 35 articles were included in the review. Study characteristics are summarised in table 1.

Study characteristics

Among the 35 included studies, 20 focused on the efficacy of DR-TB regimens [9–28] while four examined regimens for DS-TB [29–32]. 17 studies evaluated the AEs and safety of these regimens [10, 12, 15, 16, 22–24, 27, 28, 30, 32–38] and six investigated the socio-economic impact [33, 39–43]. Three studies were conducted exclusively in children [14, 15, 30], eight included both children and adults [10, 16, 18, 19, 23, 26, 33, 37] and the remaining studies focused solely on adults [9, 11–13, 17, 20–22, 24, 25, 27–29, 31, 32, 34–36, 38–43].

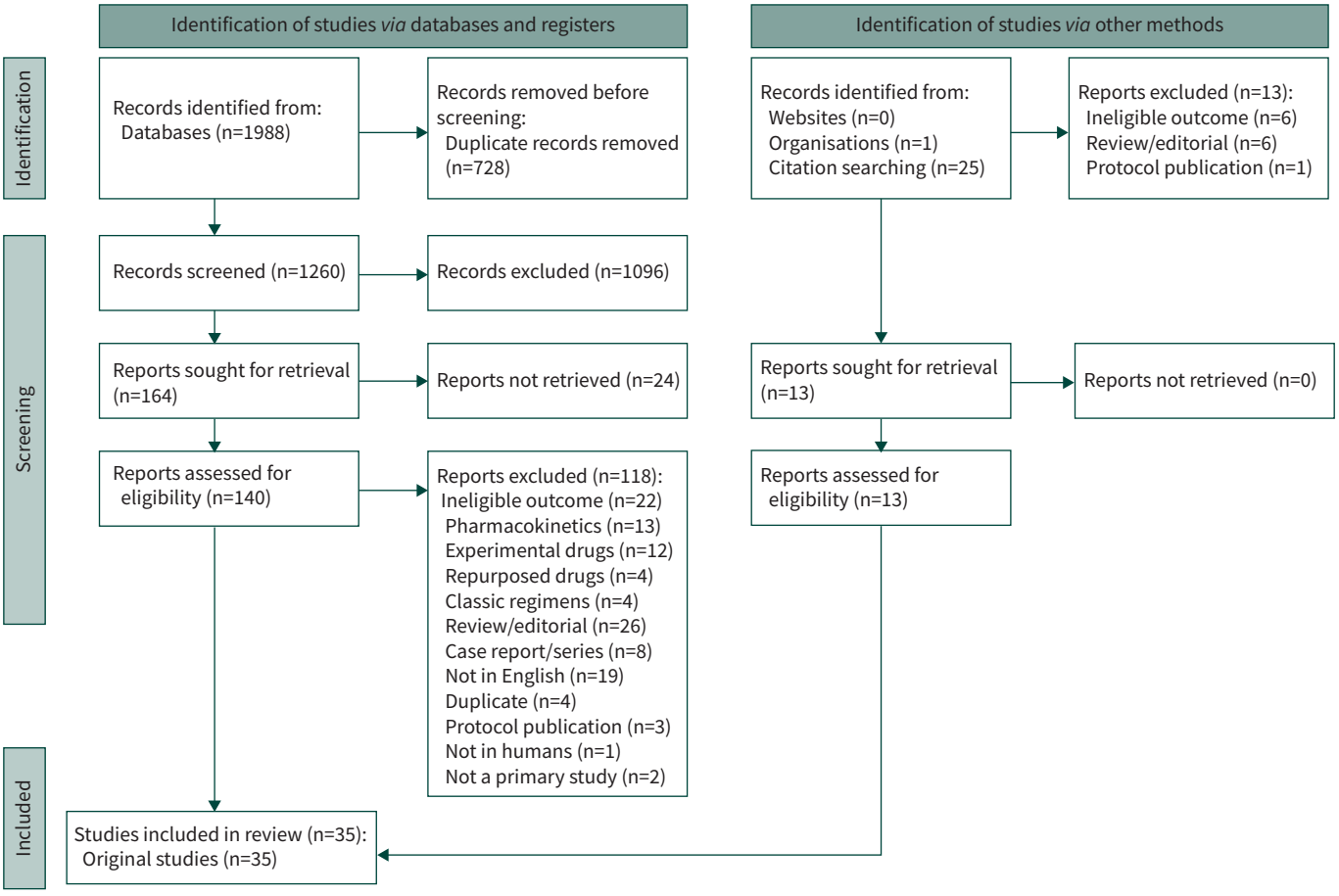

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram of review process.

TABLE 1 Summary of included studies

Author, year	Country	Study design	Population	Age (years)	Female (%)		Sample size			TB sensibility	TB regimens		Outcome	Main findings
					Intervention	Control	Intervention	Control	Total		Intervention	Control		
Belachew 2022 [13]	Ethiopia	Retrospective cohort	Patients with MDR/RR-TB treatment	1–73	38.5				389	MDR, RR	MDR-TB regimens		Unsuccessful treatment outcomes, and associated factors	23% of MDR/RR-TB patients had unsuccessful treatment outcomes; being older was significantly correlated with unsuccessful treatment outcomes
Conradie 2022 [19]	South Africa, Georgia, Moldova, Russia	RCT	Patients with XDR, pre-XDR or RR-TB	⩾14	33				181	MDR, pre-XDR, XDR	BDQ+Pa+LZD 1200 mg or 600 mg, for 26 or 9 weeks		Incidence of treatment favourable outcome at 26 weeks; safety profile	84–93% had a favourable outcome; overall risk–benefit ratio favoured LZD 600 mg for 26 weeks, with lower AEs
Cutfield 2022 [12]	New Zealand	Retrospective cohort	Patients treated for MDR-TB	12–67	60				41	MDR	MDR-TB regimens based on susceptibility testing, comorbidities and AEs		Treatment outcomes when compared to other low-incidence countries	Rates of good outcomes for patients who completed treatment in New Zealand were high but there was a significant number of patients who left New Zealand prior to completion of treatment and their outcomes are unknown (in 54%); MDR-TB treatment, especially prolonged *i.v.* aminoglycoside therapy, has been associated with ototoxicity in 47% and complications of long-term venous *i.v.* access in 27%
Duga 2023 [37]	WHO VigiBase (39 countries)	Retrospective cohort	Children; adults; elderly	0– >65	46.1				7474	MDR, RR			AEs descriptive analysis	From 349 831 reports, only 7474 were validated as an AE; almost 50% were serious AEs; one third required medication withdrawal; >40% of the reports indicated that AEs; appeared 2 months after the commencement of treatment

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TABLE 1 Continued

Author, year	Country	Study design	Population	Age (years)	Female (%)		Sample size			TB sensibility	TB regimens		Outcome	Main findings
					Intervention	Control	Intervention	Control	Total		Intervention	Control		
Esmail 2022 [24]	South Africa	RCT	Newly diagnosed MDR/RR-TB, with susceptibility to FQ and aminoglycosides	⩾18	31	36	49	44	93	MDR, RR	All oral 6 months of BDQ+LZD+LFX+TRZ/ETO/high dose H	18 to 20 months of KN+MFX+Z+TRZ/ETO/high dose H or 9 to 11 months of KN +MFX/LFX+CFZ+Z+E +TRZ/ETO/high dose H	Favourable outcome (cure or treatment completed); >12-month relapse-free cure; FU of 24 months after the initiation of treatment, AEs	An all-oral 6-month regimen when compared with >9-month injectable-containing regimen, was associated with significantly improved favourable outcomes; >12-month relapse-free cure were similar between the regimens; toxicity with the all-oral regimen remained considerable (24.2%)
Farrukh 2024 [9]	Armenia, Georgia, Haiti, Indonesia, Kazakhstan, Lesotho, Pakistan, Peru	Retrospective cohort	Pregnant women	15–49	100				43	MDR, RR	BDQ or DLM based treatment regimens		Treatment: cure or treatment completion; Pregnancy: live birth, elective termination of pregnancy or spontaneous abortion; FU at least until the end of MDR/RR-TB treatment, and pregnancies were followed until their outcome was known	98% of all mothers had successful treatment outcomes; at least 81% of continued pregnancies resulted in live births with 68% normal birthweight neonates
Ge 2023 [29]	China	Retrospective cohort	Patients with bacteriologically confirmed recurrent DS pulmonary TB	18–65	22.5	21.2			381	DS	Modified regimen: 4 months H-Rt-E-Z-S (Lfx) + 4 months H-Rt-E	Standard regimen: 2 months H-R-E-Z-S + 6 months H-R-E or 3 months H-R-E-Z + 6 months H-R-E	Successful treatment rate; recurrence rate; FU period from 2009 to 2014 to 31 December 2020	Modified retreatment regimen had more favourable treatment effects: higher treatment success rate (84% *versus* 74.5%) and lower recurrence rate (1.5% *versus* 7.9%)

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TABLE 1 Continued

Author, year	Country	Study design	Population	Age (years)	Female (%)		Sample size			TB sensibility	TB regimens		Outcome	Main findings
					Intervention	Control	Intervention	Control	Total		Intervention	Control		
Guglielmetti 2024 [28]	Georgia, India, Kazakhstan, Lesotho, Pakistan, Peru, South Africa	Phase 3, RCT, non-inferiority	Patients with FQ susceptible TB	⩾18	37.9	40.3	120–128	130	754	RR-TB	9-month oral regimens: 9BLMZ 9BCLLfxZ 9BDLLfxZ 9DCLLfxZ 9DCMZ	Standard regimens	Outcomes at week 73 post randomisation: 1) 2 consecutive, negative cultures or 2) favourable bacteriological, radiological, and clinical evolution; safety outcomes were grade 3 or higher AEs, serious AEs, death	The endTB trial increases treatment options for RR-TB with three shortened, all-oral regimens (BLMZ, BCLLfxZ, BDLLfxZ) that were non-inferior to a current well-performing standard of care
Hewison 2022 [38]	Multicountry#	Prospective cohort	Patients who started regimen through endTB project	9–88	35.5				2296	MDR, RR	BDQ and/or DLM containing regimens		AEs incidence, severity, causality assessment and contributing factors	Most common AEs: peripheral neuropathy (26.4%), electrolyte depletion (26.0%), and hearing loss (13.2%); patients receiving injectables and linezolid were most likely to experience events during exposure
Jindani 2023 [32]	Africa, South Asia and South America	Phase 3, RCT, non-inferiority	Patients who had undergone no more than 1 week of treatment	⩾18	SR1: 41 SR2: 49	54	192–195	191	578	DS	Study regimen 1: 4 months of R at a daily dose of 1200 mg and H, with E and Z for 2 months; Study regimen 2: 4 months of R at a daily dose of 1800 mg and H, with E and Z for 2 months	Standard 6-months treatment with daily R (10 mg·kg^{-1}) and H, with E and Z for the first 2 months	Efficacy and safety of a higher dose of R; FU of 18 months from the randomisation	4-month regimens including high-dose R did not have dose-limiting toxicities or AEs but did not meet non-inferiority criteria
Kalawadia 2024 [14]	India	Retrospective cohort	Children	6–17	78.3				60	DR	DLM-based regimens		Bacteriological conversion rate after 6 months	Sputum bacteriological conversion rate was almost 79.3% at the end of 6 months
Khan 2022 [20]	Multicountry#	Prospective cohort	Patients with positive baseline culture	12–82	33		623	497	1120	MDR, RR	All oral regimens containing BDQ and/or DLM	Injectable-containing regimen at baseline, with BDQ and/or DLM	Effectiveness (by sputum culture conversion in the first 6 months)	No significant difference between those who received an injectable and those who did not, regarding culture conversion within 6 months (85.5% *versus* 83.8%)

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TABLE 1 Continued

Author, year	Country	Study design	Population	Age (years)	Female (%)		Sample size			TB sensibility	TB regimens		Outcome	Main findings
					Intervention	Control	Intervention	Control	Total		Intervention	Control		
Kohler 2022 [39]	Uzbekistan	Economic modelling	Patients treated for TB							DS and DR	DS-TB 6- and 4-month regimens; DR-TB 20-, 9- and 6-month regimens		Purchase and import costs	4-month regimen in DS-TB increased the purchase and import cost (*versus* 6-month); purchasing and importing the DR-TB 6-month regimen cost more than the 9-month regimen, but less than the 20-month regimen
Kohler 2023 [40]	Uzbekistan	Economic modelling								DS and MDR			Costs and import costs of TB drug regimens	A new and shorter DS-TB regimen may increase the costs and for MDR-TB may decrease the costs for drug purchase and import
Kushemererwa 2023 [35]	Uganda	Retrospective cohort	Patients with adequate pharmacovigilance data documented	⩾18	27				178	MDR			AEs	Majority of patients (67.4%) experience at least one AE during treatment, of which 18.3%, 14.6%, 13.5% and 11.4% affected the endocrine/metabolic, optic, musculoskeletal body and GI systems, respectively
Laniado-Laborín 2022 [22]	Mexico (Tijuana)	Retrospective cohort	DR-TB patients		34.6				26	MDR, RR	BDQ+LFX+LZD+CFZ for 18 months		Smear microscopy conversion time; AEs	Smear microscopy conversion time was 7 weeks, and culture conversion time was 6 weeks; AEs were reported in 71.3% of the patients, GI were the most frequent; 19.2% required a temporary suspension due to QT prolongation

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TABLE 1 Continued

Author, year	Country	Study design	Population	Age (years)	Female (%)		Sample size			TB sensibility	TB regimens		Outcome	Main findings
					Intervention	Control	Intervention	Control	Total		Intervention	Control		
Li 2023 [34]	China	Retrospective cohort	MDR-TB patients	⩾18	38.5	33.3	52	33	85	MDR, RR	BDQ based treatment regimens	BDQ	Effects of BDQ + FQ ± CFZ on the QT interval	BDQ combined with other anti-TB drugs affecting QT interval significantly increased the incidence of grade 3 or 4 QT prolongation; however, no serious ventricular arrhythmia and permanent drug withdrawal occurred
Lopez-Varela 2022 [15]	South Africa	Prospective cohort	Children who had been on treatment for ⩾2 weeks	⩽15	50				174	MDR, RR	Backbone of E, Z, a FQ, TRZ, ETO, and/or high dose H, with a second-line injectable drug		Treatment outcomes; AEs; FU period from November 2011 to October 2015 until the end of treatment	Treatment success remained very high; 91.5% had a favourable outcome at the end of treatment; 8.5% of children treated with injectables developed hearing loss
Mikiashvili 2024 [10]	Georgia	Retrospective cohort	Patients with ⩾6 months of post-treatment FU	⩾16	25				106	MDR, RR	Combined BDQ–DLM regimens		Efficacy; AEs; FU from treatment initiation (November 2017 to December 2020) through 6 months post-treatment (December 2022)	BDQ–DLM use for >24 weeks was well tolerated; poor outcomes were more common among patients with prior exposure to new/companion TB drugs
Mohr-Holland 2022 [21]	South Africa	Retrospective cohort	Patients started treatment during the study period	0– >40	48				2008	MDR, RR	BDQ+LZD+DLM regimens		Factors associated with 6-month mortality	An overall reduction in mortality in patients treated with LZD+BDQ +DLM was observed; however, in adjusted analysis, such reduction was nonsignificant
Mpoh 2023 [36]	Cameroon	Retrospective cohort	Adult patients hospitalised with pulmonary and extrapulmonary TB	18–75	37.3				107	MDR	Standardised short treatment regimen with aminoglycosides: 4–6 months MFX-PTO-H high dose-CFZ-E-Z-AM or KM + 5 months MFX-CFZ-E-Z		Safety profile; severity of AEs; FU from January 2017 to December 2019	89.7% experienced at least one AE, mostly of mild or moderate severity; hearing loss was the most frequent AE and led mostly to aminoglycosides dose reduction (96.7%); GI events were commonly observed; 28% changed the drug or its doses during FU

Continued

TABLE 1 Continued

Author, year	Country	Study design	Population	Age (years)	Female (%)		Sample size			TB sensibility	TB regimens		Outcome	Main findings
					Intervention	Control	Intervention	Control	Total		Intervention	Control		
Mulder 2022 [41]	Indonesia, Kyrgyzstan, Nigeria	Prospective cohort	Patients with laboratory confirmed XDR-TB							XDR	BPaL regimen	Conventional treatment regimen (at least 20 months of BDQ and LZD with four to six additional anti-TB drugs)	Per-patient treatment costs and the 5-year budgetary impact	The cost per patient completing treatment with BPaL was 57%, 78% and 68% lower than the conventional regimens in Indonesia, Kyrgyzstan and Nigeria, respectively; adoption of the BPaL over 5 years would result in a 5-year average national TB budget reduction of 17% in XDR-TB treatment-related expenditure in Indonesia, 15% in Kyrgyzstan and 32% in Nigeria; BPaL can be highly cost-saving compared with conventional regimens
Muniyandi 2022 [43]	India	Economic modelling	Adults with pulmonary TB						100 000	DS	MFX based shorter 4-month treatment regimen (2 months of MFX, H, R, Z and E plus 2 months of MFX, H and R)	6-month regimen (2 months HRZE + 4 months HRE)	QALYs gained, LYs gained	A shorter 4-month TB regimen was cost-saving to patients and the health system in India, with USD 4.62 per LY and USD 5.29 per QALY
Muniyandi 2023 [42]	India	Economic modelling	Adults with pulmonary TB						1000	Pre-XDR	Shorter BEAT-TB India regimen (6–9 months BDQ, DLM, CFZ, LZD)	Longer pre-XDR-TB treatment (18–20 months of LFX, LZD, CFZ, CS, BDQ)	Economic impacts; QALYs gained for both the treatment regimens	BEAT-TB India regimen yielded higher undiscounted LYs and more QALYs gained and was found to be cost-saving when compared to the 18-month regimen
Nyang'wa 2022 [16]	Uzbeskistan, South Africa, Belarus	Phase 2/3 RCT, non-inferiority	Pulmonary TB, with RR	⩾15	BPaLM 43.7 BPaLC 33.3 BPaL 47.2	36.8	BPaLM 151 BPaLC 126 BPaL 123	152	552	RR	Stage 1: 1:1:1:1 Regimens: 1) 24-week oral BDQ, Pa, and LZD (BPaL); 2) BPaL + CFZ (BPaLC); 3) BPaL + MFX (BPaLM); Stage 2: 1:1, BPaLM	Standard care	Stage 1: evaluate the safety and efficacy at 8 weeks after randomisation; Stage 2: composite endpoint of unfavourable outcomes; FU for 72 weeks after randomisation	The BPaLM, BPaLC, and BPaL groups had fewer serious AEs and AEs of at least grade 3 than the standard care group; the 24-week, all-oral BPaLM regimen is safe and efficacious for the treatment of pulmonary RR-TB

Continued

TABLE 1 Continued

Author, year	Country	Study design	Population	Age (years)	Female (%)		Sample size			TB sensibility	TB regimens		Outcome	Main findings
					Intervention	Control	Intervention	Control	Total		Intervention	Control		
Nyang'wa 2024 [23]	Uzbeskistan, South Africa, Belarus	Phase 2B-3 RCT, non-inferiority	Pulmonary TB, with RR	⩾15	BPaLM 44 BPaLC 34 BPaL 49	38	BPaLM 151 BPaLC 126 BPaL 123	152	552	RR	Stage 1: 1:1:1:1 Regimens: 1) 24-week oral BDQ, Pa, and LZD (BPaL); 2) BPaL + CFZ (BPaLC); 3) BPaL + MFX (BPaLM); Stage 2: 1:1, BPaLM	Standard care	Stage 1: safety and efficacy at 8 weeks after randomisation; Stage 2: composite endpoint of unfavourable outcomes; AEs; FU for 72 weeks after randomisation	A 24-week BPaLM, BPaLC and BPaL were non inferior to standard care, with fewer serious AEs and AEs of at least grade 3
Padmapriyadarsini 2023 [27]	India	Prospective cohort	Adults with pulmonary TB	18–56	54.2				165	MDR	BDQ+DLM+LZD+CFZ for 24 weeks		Favourable outcome (2 consecutive negative cultures, 4 weeks apart); unfavourable outcome (bacteriologic or clinical failure); safety analysis; FU from treatment initiation (April 2019 to January 2021) through 6 months post-treatment	Favourable outcome was observed in 91%; cardiotoxicity was minimal, and myelosuppression, while common, was detected early and treated successfully
Paton 2023 [31]	Indonesia, Philippines, Thailand, Uganda, India	Phase 2–3 RCT, non-inferiority	Patients with positive NAAT for TB without RR	18–65	R+LZD: 39 High dose of R+CFZ: 38 RT+LZD: 40 BDQ+LZD: 39	34	42–189	181	674	DS	4 strategy groups (8 weeks): R+LZD High dose of R+CFZ RT+LZD BDQ+LZD All four in combination with H, Z and E	R+H for 24 weeks with Z+E in the first 8 weeks	Composite of death, ongoing treatment or active disease at week 96; FU for 96 weeks after randomisation	A primary-outcome event occurred in 3.9% in the standard-treatment group, as compared with 11.4% in the strategy group with an initial R–LZD regimen and 5.8% in the strategy group with an initial BDQ–LZD regimen; so, a strategy involving initial treatment with an 8-week BDQ–LZD regimen was non-inferior to standard treatment for TB with respect to clinical outcomes

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TABLE 1 Continued

Author, year	Country	Study design	Population	Age (years)	Female (%)		Sample size			TB sensibility	TB regimens		Outcome	Main findings
					Intervention	Control	Intervention	Control	Total		Intervention	Control		
Rosu 2023 [33]	Ethiopia, India, Moldova, Uganda	Phase 3 RCT, non-inferiority	Patients without FQ or aminoglycoside resistance	⩾15	Ethiopia: 51 India: 44 Moldova: 24 Uganda: 41	Oral regimen: 7–32 6 month regimen: 11–19	21	21–25	300	RR	3 strategy groups: 9-month injectable containing regimen; 9-month all-oral regimen with BDQ; 6-month regimen with BDQ and an injectable for the first 2 months	20-month injectable-containing regimen	Cost-utility (by QALYs) and cost-effectiveness	The oral BDQ-containing regimen is unlikely to be cost-effective in many low- and middle-income countries; the 6-month regimen offers a cost-effective alternative if the use of injectables for the first 2 months is acceptable
Solans 2023 [17]	South Africa	Phase 3 single-arm control trial	Adults enrolled in the Nix-TB trial	17–60	49				93	MDR or XDR-TB	26 weeks of oral regimen with BDQ + Pa + high dose LZD		Relationship between the pharmacokinetics of each drug, patient and disease characteristics, and efficacy endpoints; FU from treatment initiation through 6 months post-treatment	At 6 months after the end of treatment, 91% of patients had a favourable outcome; higher body mass index was associated with a lower incidence of unfavourable treatment outcomes; participants with higher baseline disease burden had a significantly delayed time to culture conversion and bacterial clearance
Trevisi 2023 [18]	Armenia, Georgia, India, Kazakhstan, Kyrgyzstan, Lesotho, Myanmar, Pakistan, Peru, South Africa	Target trial	Patients with no prior exposure or evidence of resistance to BDQ	10–78	36.2				1468	RR/ MDR-TB	Three different durations of BDQ treatment (6 months, 7–11 months, and ⩾12 months)		Probability of successful treatment; FU from week 24 of BDQ to the end of treatment	Extending the use of BDQ beyond 6 months did not significantly increase the probability of successful treatment for MDR-TB patients receiving longer, individualised regimens

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TABLE 1 Continued

Author, year	Country	Study design	Population	Age (years)	Female (%)		Sample size			TB sensibility	TB regimens		Outcome	Main findings
					Intervention	Control	Intervention	Control	Total		Intervention	Control		
Turkova 2022 [30]	Uganda, Zambia, South Africa, India	RCT, non-inferiority	Children with symptomatic non-severe and respiratory sample smear-negative TB	<16	48	49	558	563	1121	DS	16-weeks regimen: (8 weeks of HRZ ± E, followed by 8 weeks of HR)	24-weeks regimen (8 weeks of HRZ ± E, followed by 16 weeks of HR)	Unfavourable outcome; AEs; health cost and QALYs; FU for 72 weeks after randomisation	Unfavourable outcomes happened in 3% in both groups; AEs were reported in 12% in both groups; children treated for 16 weeks had similar health outcomes with reduced healthcare costs; QALYs were improved by 0.003 per child
Zainabadi 2023 [11]	Haiti	Prospective cohort	Patients with pulmonary TB	⩾18	DS: 38.7 DR: 43.5		DS: 31 DR: 23		54	RR, DS	DS-TB: 6 months regimen with 2 months HRZE + 4 months HR; RR-TB: 20 months regimen with LFX, CFZ, Z, BDQ (first 22 weeks) and LZD (first 12 months)		Early bactericidal activity; clinical signs and symptoms during the first 2 months of therapy; FU for the duration of their directly observed therapy	Subjects with DR-TB receiving an all oral BDQ-based second-line treatment regimen displayed a similar microbiological response to therapy as subjects with DS-TB receiving a first-line treatment regimen

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https://doi.org/10.1183/20734735.0232-2024

TABLE 1 Continued

Author, year	Country	Study design	Population	Age (years)	Female (%)		Sample size			TB sensibility	TB regimens		Outcome	Main findings
					Intervention	Control	Intervention	Control	Total		Intervention	Control		
Mok 2022 [25]	South Korea	Phase 2–3 RCT, non-inferiority	Patients with pulmonary TB without FQ resistance	19–85	32.9	29.2	79	89	168	MDR-TB	Shorter-regimen: 9–12 months with DLM, LZD, LFX and Z	20–24-months regimen, according to the 2014 WHO guidelines	Treatment outcomes at 24 months	Treatment success rate after 24 months of treatment was higher in the shorter-regimen group (75%) than in control group (70.6%), predefined non-inferiority margin of −10%
Goodall 2022 [26]	Ethiopia, Georgia, India, Moldova, Mongolia, South Africa, Uganda	Phase 3 RCT, non-inferiority	Pulmonary TB, with RR resistance	⩾15	Oral regimen: 37 6 months regimen: 40	39	Long regimen: 26 Oral regimen: 196 6 months regimen: 134	187	517	RR/ MDR-TB	Three strategy groups: Long regimen: 20-month regimen recommended by WHO from 2011 to 2018; 9-month oral regimen: BDQ, LFX, CFZ, E, Z + high-dose H and PTO given for the first 16 weeks; 6-month regimen: BDQ, CFZ, Z and LFX + KN and high-dose H for the first 8 weeks	9-month regimen: higher dose MFX, CFZ, E, Z + KN, high-dose H and PTO given for the first 16 weeks	Treatment outcomes at 76 weeks; FU from randomisation to 132 weeks	Both BDQ-containing regimens, a 9-month oral regimen and a 6-month regimen with 8 weeks of second-line injectable, had superior efficacy compared with a 9-month injectable-containing regimen, with fewer cases of hearing loss

AEs: adverse events; AM: amikacin; BDQ: bedaquiline; BCLLfxZ: bedaquiline + clofazimine + linezolid + levofloxacin + pyrazinamide; BDLLfxZ: bedaquiline + delamanid + linezolid + levofloxacin + pyrazinamide; BLMZ: bedaquiline + linezolid + moxifloxacin + pyrazinamide; BPaL: bedaquiline + pretomanid + linezolid; BPaLC: bedaquiline + pretomanid + linezolid + clofazimine; BPaLM: bedaquiline + pretomanid + linezolid + moxifloxacin; CFZ: clofazimine; CS: cicloserine; DLM: delamanid; DCLLfxZ: delamanid + clofazimine + linezolid + levofloxacin + pyrazinamide; DCMZ: delamanid + clofazimine + moxifloxacin + pyrazinamide; DS: drug susceptible; DR: drug resistant; E: ethambutol; ETO: ethionamid; FQ: fluoroquinolone; FU: follow-up; GI: gastrointestinal; H: isoniazid; KN: kanamycin; Lfx: levofloxacin; LYs: life-years; LZD: linezolid; MDR: multidrug-resistant; MFX: moxifloxacin; NAAT: nucleic acid amplification test; Pa: pretomanid; PTO: prothionamide; QALY: quality-adjusted life-years; R: rifampicin; RCT: randomised controlled trial; RR: rifampicin-resistant; RT: rifapentin; S: streptomycin; TRZ: terizidone; TB: tuberculosis; USD: US dollar; WHO: World Health Organization; XDR: extensively drug-resistant; Z: pyrazinamide. #: Armenia, Bangladesh, Belarus, Ethiopia, Georgia, Haiti, Indonesia, Kazakhstan, Kenya, Kyrgyzstan, Lesotho, Myanmar, North Korea, Pakistan, Peru, South Africa, Vietnam.

https://doi.org/10.1183/20734735.0232-2024

Regarding study design, 12 were retrospective studies [9, 10, 12–14, 21, 29, 34–37, 40], six were prospective observational studies [11, 15, 20, 22, 27, 38], four discussed socioeconomic aspects [39, 41–43] and one was a hypothetical target trial [18]. 12 randomised controlled trials were also included [16, 17, 19, 23–26, 28, 30–33].

The majority of the studies (n=20; 55.6%) included data from a single country, mainly from the Asian [11, 14, 25, 27, 29, 34, 42, 43] or African continents [13, 15, 17, 21, 24, 35, 36]. The remaining studies included data from multiple countries [9, 16, 18–20, 23, 26, 28, 30–33, 37, 38, 41].

Drug-sensitive tuberculosis treatment

Few studies have focused on updates in treatment regimens for DS-TB [29, 31, 32]. One study examined retreatment of DS-TB with a modified regimen comprising a 4-month intensive phase with isoniazid (H), rifapentine (Rp), ethambutol (E), pyrazinamide (Z) and streptomycin/levofloxacin (S/Lfx), followed by a 4-month continuation phase with H, Rp and E. All the patients with successful treatment were followed up for at least 56 months. This approach resulted in a higher treatment success rate (84% *versus* 74.5%) and a lower recurrence rate (1.5% *versus* 6.9%) [29]. Other strategies included new treatment approaches related to duration and repurposing of DR-TB drugs, such as an initial 8-week bedaquiline (Bdq) and linezolid (Lzd) regimen, which was found to be non-inferior to the standard DS-TB treatment in terms of efficacy and safety [31]. Another study assessed the impact of increasing the rifampicin (R) dose, concluding that higher dosages, administered for a shorter period (4 months *versus* 6 months in the control regimen), did not meet the non-inferiority criteria compared to the standard regimen [32].

Drug-resistant tuberculosis treatment

Recent approaches to treating MDR-TB have increasingly emphasised fully oral regimens that replace traditional injectable-based therapies, driven by the need to improve both efficacy and safety while reducing AEs. Key studies have evaluated the efficacy of new oral regimens, such as BPaL, BPaLM and BPaLC, which include combinations of bedaquiline (Bdq), pretomanid (Pa), linezolid (Lzd), moxifloxacin (Mfx) and clofazimine (Cfz), compared to traditional regimens. Additional comparisons have been made between oral and injectable regimens and shorter treatment courses to optimise outcomes and minimise long-term complications.

Oral versus *injectable regimens*

Several studies have supported the preference for oral over injectable regimens. The NExT Study [24] and the study by Khan *et al*. [20] demonstrated improved outcomes and reduced toxicity with a 6-month all-oral regimen compared with a standard-of-care 9-month WHO-approved injectable-based regimen. The STREAM Stage 2 trial confirmed that shorter bedaquiline-containing regimens were more effective and had fewer AEs than injectable alternatives [26]. Additionally, the MDR-END trial showed that a 9-month all-oral regimen was non-inferior to the traditional 20–24-month course, with higher success rates [25].

Efficacy of short-course and bedaquiline-delamanid regimens

Short-course regimens have been explored for their efficacy and safety. An observational study by Laniado-Laborín *et al*. [22] demonstrated that a four-drug all-oral regimen consisting of bedaquiline, levofloxacin, linezolid and clofazimine achieved culture conversion within 2 months, suggesting the potential for reducing treatment duration. Zainabadi *et al*. [11] found that the early bactericidal activity of both first- and second-line regimens was similar during the first 2 months of therapy. Trevisi *et al*. [18] evaluated extending bedaquiline use beyond 6 months, concluding it did not significantly increase successful treatment outcomes. Additional studies highlighted that prior exposure to new TB drugs was associated with poorer outcomes [10].

Evaluation of BPaL, BPaLM and BPaLC regimens

The BPaLM, BPaLC and BPaL regimens showed superiority over standard care, with higher culture conversion rates, lower costs and fewer AEs of grade 3 or higher [16, 23]. Conradie *et al*. [19] found that a 600 mg dose of linezolid over 26 weeks had the most favourable risk–benefit profile, minimising modifications due to AEs. Similarly, the Nix-TB trial supported the potential for safer and lower doses [17].

New all-oral 9-month treatment regimens

The endTB clinical trial [28] assessed five 9-month, all-oral regimens for treating MDR-TB without fluoroquinolone resistance, which included combinations of medications such as bedaquiline, levofloxacin or moxifloxacin, linezolid, clofazimine, delamanid and pyrazinamide. Three regimens were found to be safe and non-inferior in efficacy when compared to the WHO-recommended longer all-oral bedaquiline-containing regimens (⩾18 months).

Safety of all-oral drug regimens

Several studies examined the safety of all-oral regimens. Combining bedaquiline with other TB drugs increased the incidence of grade 3 or 4 corrected QT interval (QTc) prolongation, although no cases of severe arrhythmia or permanent drug withdrawal were reported [34]. Overall, AEs were more common with linezolid and injectable drugs than with bedaquiline and delamanid [12, 38]. Moreover, AEs frequently led to treatment discontinuation, emphasising the need for continuous monitoring [37].

Treatment in the paediatric population

Most paediatric studies focused on DR-TB [10, 14–16, 18, 19, 26, 30], with only three exclusively involving children [14, 15, 30]. The SHINE trial addressed DS-TB treatment in children, showing non-inferiority of a 4-month regimen compared to the standard 6-month regimen [30]. Other studies found high culture conversion rates in paediatric DR-TB patients, compared with DLM-based therapy, but evidence remains limited [14].

Economic impact of tuberculosis treatment

Limited research exists on the economic impact of new DS-TB regimens. However, studies suggest a cost-saving potential for patients and healthcare systems with shorter DS-TB regimens [43]. In contrast, shorter or all-oral MDR-TB regimens could reduce drug procurement costs [39, 40]. Shorter regimens were more cost-effective than longer ones, with BPaL and other shorter regimens reducing costs by 15–32% [41, 42]. Further economic studies are needed to confirm these findings in diverse settings.

Discussion

In this article, we reviewed recent updates in TB treatment, focusing on new drug regimens for both DS-TB and DR-TB, with most studies primarily addressing DR-TB in adult populations. Our findings suggest that all-oral, shorter regimens for DR-TB offer superior safety and effectiveness compared to the standard of care [16, 23]. Specifically, these regimens were associated with fewer AEs, such as hearing loss, than injectable regimens [12, 26, 38]. However, poor outcomes were more commonly observed in patients with prior exposure to new or companion TB drugs and those with acquired drug resistance [10]. These findings support the current WHO recommendations, emphasising the need for national health systems to adapt to procuring and ensuring the availability of these drug regimens [2, 3, 9].

The 2022 WHO recommendations also highlighted limited evidence regarding the extension of bedaquiline beyond 6 months [2]. Trevisi *et al*. [18] provided new insights, showing that extending bedaquiline did not significantly increase the probability of successful treatment, particularly in patients receiving individualised regimens with drugs such as linezolid, delamanid and clofazimine.

The BEAT-TB trial and end-TB trial provided further information about oral regimens for 6 or 9 months, respectively. Besides demonstrating positive effectiveness and safety findings, its relevance is increased by the additional evidence it provided in children, adolescents, pregnant women and nursing mothers, which sets it apart from the BPaLM studies [28, 44].

According to the WHO update from June 2024, these new, shorter regimens must be incorporated into clinical practice as they offer feasible and more approachable substitutes for the lengthier regimens [44]. These new protocols require a national and international health system adjustment, particularly in nations with low resources. Additional research is needed to assess the implementation of these regimens and their economic impact. Countries' drug formularies can be significantly simplified while maintaining a variety of treatment alternatives. Access to quick and accurate resistance testing is crucial for identifying the onset of resistance and optimising patient selection for these regimens.

Our review assessed several studies focusing on AEs, particularly their role in evaluating DR-TB treatment outcomes. In some studies, AEs were the primary or sole outcome [34–38], underscoring their relevance in clinical practice. The most frequently reported AEs in bedaquiline–delamanid-based regimens included gastrointestinal symptoms, liver disorders, arthralgia, QTc interval prolongation and peripheral neuropathy [22, 37, 38]. Notably, combining bedaquiline with other TB drugs significantly increased the incidence of grade 3 or 4 QTc prolongation, although it did not appear to be directly associated with severe ventricular arrhythmias [34]. Over 40% of the records indicated that AEs appeared within 2 months of initiating treatment, highlighting the need for continuous monitoring throughout the treatment duration [37]. However, the variation in follow-up periods among studies could influence the reported frequency of AEs, and the predominance of retrospective study designs [34–37] introduces potential selection bias.

Few studies have focused on DS-TB treatment in the last 2 years [29, 31, 32]. Most strategies aimed to reduce treatment duration [31], repurpose drugs used in DR-TB [31], or increase core drug dosages [32]. The TRUNCATE-TB trial [31] was the only study showing non-inferiority in efficacy and safety with an initial 8-week bedaquiline–linezolid-containing regimen. However, the trial had a small sample size and no evidence suggested that the strategy promoted drug resistance.

Regarding the paediatric population, only one clinical trial was conducted on children with DS-TB, demonstrating that a 4-month regimen was non-inferior to the traditional 6-month regimen [30]. The remaining studies included children with DR-TB, but most participants were adults, and no subgroup analyses were performed to assess efficacy or safety specifically in children. Many of the treatment recommendations for children with DR-TB are extrapolated from adult efficacy data and based on pharmacokinetic studies [45]. Since this review excluded pharmacokinetic studies, some relevant information may have been overlooked. The scarcity of evidence in paediatric DR-TB treatment can be partly attributed to the significant number of children lacking microbiological confirmation of the disease, often leading to their exclusion from studies of new, shorter all-oral regimens. This further reduces trial sizes and impacts the overall quality of evidence.

To our knowledge, few review articles have addressed the economic impact of recent TB drug regimens. Prior reviews, such as the systematic review by Laurence *et al*. [46], focused on the financial burden of TB treatment, primarily concerning DS-TB. Still, these studies predate the introduction of new, shorter all-oral regimens and the 2022 WHO recommendations update. Our review found that shorter regimens for DR-TB were generally more cost-effective than longer ones [33, 41, 42]. However, this cost reduction was not observed in the 4-month regimen for DS-TB due to the higher number of pills and the increased cost of Rp, which raised procurement costs [39, 40]. All studies were conducted in Asian and African countries, limiting the applicability of these findings to Western and European contexts. Thus, further research is needed to assess the economic impact of these regimens in diverse regions.

Limitations

This review has some limitations. Many of the included studies were retrospective or observational, which introduces potential biases such as selection bias and incomplete data reporting. This is especially relevant for studies focused on AEs, where the retrospective nature may hinder an accurate assessment of drug-related toxicities. Additionally, the heterogeneity in study designs, populations, and treatment regimens complicates direct comparisons across studies, potentially affecting the generalisability of the findings.

Most of the studies were conducted in low- and middle-income countries with high TB incidence, which may limit the applicability of the results to settings with lower TB prevalence, such as Western and European countries. Furthermore, the limited number of studies on paediatric DR-TB and DS-TB treatments constrains the ability to draw robust conclusions about the efficacy and safety of these regimens in children. Paediatric treatment guidelines are frequently extrapolated from adult data, which may not adequately represent younger populations. Moreover, most studies did not perform subgroup analyses to assess outcomes specifically in children, reducing the depth of paediatric-specific insights.

Conclusion

The findings of this review highlight a significant shift towards shorter, all-oral regimens, particularly for DR-TB, which demonstrate improved safety and efficacy compared to traditional injectable therapies. Several studies showed that regimens incorporating novel drugs, such as bedaquiline, pretomanid and linezolid, are not only non-inferior but often superior to standard treatments, with fewer AEs and shorter treatment durations. Similar outcomes were also shown with a broader pool of eligible participants in the BEAT-TB trial and endTB trial for the 6- and 9-month regimens, respectively.

Economic analyses suggest that adopting these newer regimens is cost-effective, particularly in low- and middle-income countries where the burden of TB is highest.

While there is promising evidence supporting these novel regimens for DR-TB, fewer studies have focused on DS-TB. Nonetheless, efforts to repurpose DR-TB drugs and reduce the duration of DS-TB treatment suggest a positive trend toward improving therapeutic options for this population. In the paediatric population, the review reveals a scarcity of studies explicitly addressing DR-TB, with most research based on data extrapolated from adults. However, available evidence also indicates the potential benefits of shorter and safer regimens for children.

The emergence of bedaquiline resistance is a growing concern that may impact the effectiveness of newer DR-TB regimens in the near future [47], especially as bedaquiline is integral to many of the all-oral, shorter regimens. Resistance to bedaquiline could potentially reduce the options available for treating DR-TB, especially for patients who have already been exposed to multiple drugs or have complex resistance profiles. The potential use of bedaquiline for DS-TB to shorten treatment duration might further accelerate resistance development if not carefully monitored. Continuous monitoring of resistance patterns and exploring new therapeutic options remain essential to sustain progress in TB management.

Overall, this scoping review underscores the importance of adopting shorter, safer and more effective treatment regimens for both DS-TB and DR-TB. Implementing these regimens would improve patient outcomes and potentially reduce the economic burden of TB. Furthermore, the review emphasises the need for global health systems to integrate these advancements into routine practice.

Although our review did not include all recent developments, several articles encountered during our research discussed novel pharmacological compounds and emerging technologies specifically designed for TB treatment. This suggests that the field is evolving beyond conventional protocols, with promising discoveries on the horizon that warrant further exploration in future reviews.

Key points

- Shorter, all-oral regimens for DR-TB show superior safety and effectiveness compared to traditional injectable therapies.
- Regimens incorporating novel drugs like bedaquiline, pretomanid and linezolid are both non-inferior and often superior to standard treatments, with fewer adverse events.
- Economic analyses indicate that adopting newer, shorter regimens is cost-effective, especially in low- and middle-income countries.
- There is a critical need for more studies on DS-TB and paediatric DR-TB to optimise treatment strategies further and improve patient outcomes.

Self-evaluation questions

1. What are the main advantages of shorter, all-oral regimens for DR-TB over traditional injectable therapies?
2. Which novel drugs were identified in the review as contributing to the improved safety and efficacy of the TB treatment regimen?
3. What limitations were highlighted regarding the current evidence for TB treatment in paediatric populations?
4. Why is there a need for more studies on DS-TB?

Conflict of interest: P. Barbosa and M. Vieira report contracts from the Institute of Public Health of the University of Porto and the School of Medicine and Biomedical Sciences (ICBAS), all outside the submitted work. J.P. Ramos reports grants or contracts from the Institute of Public Health of the University of Porto, Institute of Biomedical Sciences Abel Salazar, University of Porto Faculty of Psychology and Education Sciences, all outside the submitted work. R. Duarte reports grants or contracts from School of Medicine and Biomedical Sciences (ICBAS), and INSA, all outside the submitted work. All other authors have nothing to disclose.

References

1 World Health Organization. Global tuberculosis report 2023. Date last accessed: 29 September 2024. Date last updated: 7 November 2023. https://reliefweb.int/report/world/global-tuberculosis-report-2023
2 World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: Treatment – Drug-resistant tuberculosis treatment. Geneva, World Health Organization, 2022. https://iris.who.int/bitstream/handle/10665/365308/9789240063129-eng.pdf
3 World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: Treatment – Drug-susceptible tuberculosis treatment. Geneva, World Health Organization, 2022. https://iris.who.int/bitstream/handle/10665/353829/9789240048126-eng.pdf
4 Nunn AJ, Phillips PPJ, Meredith SK, *et al.* A trial of a shorter regimen for rifampin-resistant tuberculosis. *N Engl J Med* 2019; 380: 1201–1213.
5 Conradie F, Diacon AH, Ngubane N, *et al.* Treatment of highly drug-resistant pulmonary tuberculosis. *N Engl J Med* 2020; 382: 893–902.
6 Dorman SE, Nahid P, Kurbatova EV, *et al.* Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. *N Engl J Med* 2021; 384: 1705–1718.
7 Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol* 2005; 8: 19–32.

8 Tricco AC, Lillie E, Zarin W, *et al*. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med* 2018; 169: 467–473.
9 Farrukh IL, Lachenal N, Adenov MM, *et al.* Pregnancy and birth outcomes in patients with multidrug-resistant tuberculosis treated with regimens that include new and repurposed drugs. *Clin Infect Dis* 2024; 78: 144–148.
10 Mikiashvili L, Kempker RR, Chakhaia TS, *et al.* Impact of prior tuberculosis treatment with new/companion drugs on clinical outcomes in patients receiving concomitant bedaquiline and delamanid for multidrug- and rifampicin-resistant tuberculosis. *Clin Infect Dis* 2024; 78: 1043–1052.
11 Zainabadi K, Vilbrun SC, Mathurin LD, *et al.* A bedaquiline, pyrazinamide, levofloxacin, linezolid, and clofazimine second-line regimen for tuberculosis displays similar early bactericidal activity as the standard rifampin-based first-line regimen. *J Infect Dis* 2023; 230: e447–e456.
12 Cutfield T, Mowlem L, Paynter J, *et al.* Treatment and outcomes of multidrug-resistant tuberculosis in Auckland, 1995–2018. *Intern Med J* 2022; 52: 1381–1386.
13 Belachew T, Yaheya S, Tilahun N, *et al.* Multidrug-resistant tuberculosis treatment outcome and associated factors at the University of Gondar Comprehensive Specialized Hospital: a ten-year retrospective study. *Infect Drug Resist* 2022; 15: 2891–2899.
14 Kalawadia D, Gandhi D, Dirkhipa TY, *et al.* Effect of delamanid on interim outcomes of bacteriological conversion amongst pediatric drug resistant tuberculosis cases in India. *Lung India* 2024; 41: 35–39.
15 Lopez-Varela E, Garcia-Prats AJ, Seddon JA, *et al.* Treatment outcomes and safety in children with rifampicin-resistant TB. *Int J Tuberc Lung Dis* 2022; 26: 133–141.
16 Nyang'wa BT, Berry C, Kazounis E, *et al.* A 24-week, all-oral regimen for rifampin-resistant tuberculosis. *N Engl J Med* 2022; 387: 2331–2343.
17 Solans BP, Imperial MZ, Olugbosi M, *et al.* Analysis of dynamic efficacy endpoints of the Nix-TB trial. *Clin Infect Dis* 2023; 76: 1903–1910.
18 Trevisi L, Hernán MA, Mitnick CD, *et al.* Effectiveness of bedaquiline use beyond six months in patients with multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2023; 207: 1525–1532.
19 Conradie F, Bagdasaryan TR, Borisov S, *et al.* Bedaquiline–pretomanid–linezolid regimens for drug-resistant tuberculosis. *N Engl J Med* 2022; 387: 810–823.
20 Khan PY, Franke MF, Hewison C, *et al.* All-oral longer regimens are effective for the management of multidrug-resistant tuberculosis in high-burden settings. *Eur Respir J* 2022; 59: 2004345.
21 Mohr-Holland E, Daniels J, Reuter A, *et al.* Early mortality during rifampicin-resistant TB treatment. *Int J Tuberc Lung Dis* 2022; 26: 150–157.
22 Laniado-Laborín R, Castro-Mazon G, Salcido-Gastelum J. Efficacy and safety of a new short regimen for treatment of tuberculosis resistant to rifampicin. A pilot study. *Neumol Cir Torax (Mexico)* 2022; 81: 1087.
23 Nyang'wa BT, Berry C, Kazounis E, *et al.* Short oral regimens for pulmonary rifampicin-resistant tuberculosis (TB-PRACTECAL): an open-label, randomised, controlled, phase 2B-3, multi-arm, multicentre, non-inferiority trial. *Lancet Respir Med* 2024; 12: 117–128.
24 Esmail A, Oelofse S, Lombard C, *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: 1214–1227.
25 Mok J, Lee M, Kim DK, *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: 1522–1530.
26 Goodall RL, Meredith SK, Nunn AJ, *et al.* Evaluation of two short standardised regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): an open-label, multicentre, randomised, non-inferiority trial. *Lancet* 2022; 400: 1858–1868.
27 Padmapriyadarsini C, Vohra V, Bhatnagar A, *et al.* Bedaquiline, delamanid, linezolid, and clofazimine for treatment of pre-extensively drug-resistant tuberculosis. *Clin Infect Dis* 2023; 76: 1483–1491.
28 Guglielmetti L, Khan U, Velásquez GE, *et al.* Nine-month, all-oral regimens for rifampin-resistant tuberculosis. *medRxiv* 2024; preprint [https://doi.org/10.1101/2024.01.29.24301679].
29 Ge Q, Ma Y, Zhang L, *et al.* Effect of a modified regimen on drug-sensitive retreated pulmonary tuberculosis: a multicenter study in China. *Front Public Health* 2023; 11: 1039399.
30 Turkova A, Wills GH, Wobudeya E, *et al.* Shorter treatment for nonsevere tuberculosis in African and Indian children. *N Engl J Med* 2022; 386: 911–922.
31 Paton NI, Cousins C, Suresh C, *et al.* Treatment strategy for rifampin-susceptible tuberculosis. *N Engl J Med* 2023; 388: 873–887.
32 Jindani A, Atwine D, Grint D, *et al.* Four-month high-dose rifampicin regimens for pulmonary tuberculosis. *NEJM Evid* 2023; 2: EVIDoa2300054.
33 Rosu L, Madan JJ, Tomeny EM, *et al.* Economic evaluation of shortened, bedaquiline-containing treatment regimens for rifampicin-resistant tuberculosis (STREAM stage 2): a within-trial analysis of a randomised controlled trial. *Lancet Glob Health* 2023; 11: e265–e277.

34 Li R, Ma J-B, Yang H, *et al.* Effects of bedaquiline combined with fluoroquinolone and/or clofazimine on QT interval in patients with multidrug-resistant tuberculosis: a retrospective study. *Microbiol Spectr* 2023; 11: e0104823.

35 Kushemererwa O, Nuwagira E, Kiptoo J, *et al.* Adverse drug reactions and associated factors in multidrug-resistant tuberculosis: a retrospective review of patient medical records at Mbarara Regional Referral Hospital, Uganda. *SAGE Open Med* 2023; 11: 20503121231171350.

36 Mpoh MM, Deli V, Daniel TT, *et al.* Safety of antituberculosis agents used for multidrug-resistant tuberculosis among patients attending the Jamot Hospital of Yaounde, Cameroon. *Int J Mycobacteriol* 2023; 12: 168–174.

37 Duga AL, Salvo F, Kay A, *et al.* Safety profile of medicines used for the treatment of drug-resistant tuberculosis: a descriptive study based on the WHO database (VigiBase®). *Antibiotics (Basel)* 2023; 12: 811.

38 Hewison C, Khan U, Bastard M, *et al.* Safety of treatment regimens containing bedaquiline and delamanid in the endTB cohort. *Clin Infect Dis* 2022; 75: 1006–1013.

39 Kohler S, Sitali N, Achar J, *et al.* Programme costs of longer and shorter tuberculosis drug regimens and drug import: a modelling study for Karakalpakstan, Uzbekistan. *ERJ Open Res* 2022; 8: 00622-2021.

40 Kohler S, Sitali N, Achar J, *et al.* Costs and import costs of past, present, and future TB drug regimens: a case study for Karakalpakstan, Uzbekistan. *J Public Health* 2023; 45: 481–487.

41 Mulder C, Rupert S, Setiawan E, *et al.* Budgetary impact of using BPaL for treating extensively drug-resistant tuberculosis. *BMJ Glob Health* 2022; 7: e007182.

42 Muniyandi M, Ramesh PM, Wells WA, *et al.* The cost-effectiveness of the BEAT-TB regimen for pre-extensively drug-resistant TB. *Trop Med Infect Dis* 2023; 8: 411.

43 Muniyandi M, Karikalan N, Velayutham B, *et al.* Cost effectiveness of a shorter moxifloxacin based regimen for treating drug sensitive tuberculosis in India. *Trop Med Infect Dis* 2022; 7: 288.

44 World Health Organization. Key updates to the treatment of drug-resistant tuberculosis: rapid communication, June 2024. Geneva, World Health Organization, 2024.

45 World Health Organization. WHO consolidated guidelines on tuberculosis. Module 5: Management of tuberculosis in children and adolescents. Geneva, World Health Organization, 2022. https://iris.who.int/bitstream/handle/10665/352522/9789240046764-eng.pdf

46 Laurence YV, Griffiths UK, Vassall A. Costs to health services and the patient of treating tuberculosis: a systematic literature review. *Pharmacoeconomics* 2015; 33: 939–955.

47 Pai H, Ndjeka N, Mbuagbaw L, *et al.* Bedaquiline safety, efficacy, utilization and emergence of resistance following treatment of multidrug-resistant tuberculosis patients in South Africa: a retrospective cohort analysis. *BMC Infect Dis* 2022; 22: 870.

Suggested answers

1. All-oral, shorter regimens for DR-TB improve safety and effectiveness and have been associated with fewer AEs.
2. Several studies showed that regimens incorporating novel drugs, such as Bdq, Pa, and Lzd, are not only non-inferior but often superior to standard treatments, with fewer AEs and shorter treatment durations. Dlm and Cfz are also identified as valuable drugs in combination therapies.
3. The main limitations are: the scarcity of studies; the fact that paediatric treatment guidelines are frequently extrapolated from adult data, which may not adequately represent younger populations; lack of subgroup analysis.
4. In the past 2 years, there have been few developments in DS-TB, with the majority of studies focusing on DR-TB. The majority of studies tried to increase core drug dosages, repurpose drugs used in DR-TB, or shorten treatment duration. There was little evidence of resistance promotion in the second and only the first two demonstrated non-inferiority to a conventional regimen.