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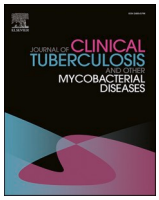

Relapse after treatment with standardized all-oral short regimens for rifampicin-resistant tuberculosis (RR-TB): A systematic review and *meta*-analysis

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A R T I C L E I N F O

Keywords:
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Short all-oral regimens
Relapse

A B S T R A C T

Background: Treatment for rifampicin-resistant tuberculosis (RR-TB) has been shortened to 12 months or less, with duration depending on the regimen used and treatment response. Treatment shortening has the potential to increase the risk of relapse, with a new episode of RR-TB after cure or completion. The proportion of relapses after standardized all-oral short (12 months or less) RR-TB regimens has not yet been systematically reviewed, which is the main objective of this review.

Methods: This is a systematic review and *meta*-analysis. PubMed, Web of Science and Google scholar databases were systematically investigated to identify studies published between January 2018 and November 2023. Characteristics of studies, demographic data, baseline clinical condition, resistance profile, and definitions used for relapse, failure, and end-of-treatment outcomes are summarized in tables and graphs. Pooled proportions are estimated for relapse.

Results: A total of ten studies were included in this review and *meta*-analysis, representing 1792 participants. Seven studies were clinical trials and two were cohorts. Five studies investigated all-oral six-month regimens composed of bedaquiline, pretomanid, and linezolid (BPaL). The remaining studies assessed other standardized all-oral short regimens, with treatment duration between 6 and 12 months. Post-treatment follow-up (PTFU) duration ranged from 6 to 30 months. The pooled proportion estimate of relapse was 2·0% (95 % CI, 1·0-3·0%) for all and BPaL-based regimens. Treatment extension due to poor treatment response was poorly documented.

Conclusion: This review showed that the proportion of relapse in RR-TB patients treated with standardized short all-oral regimens was low. The low relapse proportion is similar to what was achieved for drug-susceptible Tuberculosis patients treated with first-line rifampicin-containing regimens. However, most data came from trial settings, and in some studies the post-treatment follow-up was short. Studies of large programmatic cohorts with longer post-treatment follow-up periods are needed to confirm the low relapse rate shown in the clinical trials.

1. Introduction

Tuberculosis (TB) was the second leading infectious killer after COVID-19 in 2022 and global TB targets have either been missed or remain off track. An estimated 10·6 million people fell ill and 1·3 million people died from TB including 167·000 deaths among people with HIV in 2023 [1]. Without treatment, TB is a severe and potentially fatal disease. After five years without treatment, 50–60 % of HIV-negative pulmonary TB patients would die [2]. First-line six-month rifampicin-based regimens are highly successful in patients with rifampicin-susceptible TB (RS-TB), with only about 2·9% of cases experiencing relapse (new episode of TB after cure or treatment completion) in high incidence settings [3]. However, resistance to the main first-line TB drug (rifampicin) threatens TB control. Poor treatment completion of traditional 18–24 long regimens necessitate the potent and short second-line TB treatment regimens.

TB treatment regimens combine multiple antituberculosis drugs. Regimens should include drugs with early bactericidal effect (killing of actively replicating bacilli) to rapidly reduce the bacillary load, thus reducing the risk of transmission, resistance selection, and treatment failure. In addition, drugs with sterilizing effects are required to kill dormant bacillary populations, thus reducing the risk of relapse after

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treatment completion. Higher sterilizing activity allows shortening of treatment duration [4]. In their manuscript from 2018, Van Deun et al described anti-TB drugs based on their bactericidal, sterilizing, and resistance prevention activity. They defined the term 'core drug' as a drug that contributes most to cure, preventing treatment failure and relapse. The core drug has high bactericidal and sterilizing activity, both essential for a relapse-free cure, and is administered throughout treatment. Rifampicin (RIF), fluoroquinolones (FQs), bedaquiline (BDQ), and possibly pretomanid (Pa), have core drug characteristics [5].

Shortening the duration of treatment for those with rifampicin-susceptible tuberculosis (RS-TB) and rifampicin-resistant tuberculosis (RR-TB) is a global research goal. TB treatment has been continuously evolving over the past decade. In the 1970 s rifampicin (RIF) was added to drugs with mainly bactericidal activity, which allowed shortening treatment duration from 18 to 9 months with more than 95 % cure rates. When pyrazinamide, with excellent sterilizing activity, was added in the 1980s, the treatment duration was shortened further to 6 months, without increasing relapses [6].

Before 2016, recommendations for these long-duration regimens were the mainstay recommendations and RR-TB patients were treated for up to 24 months. Unfortunately, such regimens led to poor treatment outcomes with about 50 % of RR-TB cases being cured [7]. Since 2016, WHO guidelines for the management of RR/MDR-TB have been updated on a regularly basis [8]. Treatment guidelines for RR-TB are changing rapidly as the potential of new drugs and regimens are better understood. In 2016, the so-called "Bangladesh regimen" shortened the recommended treatment duration for some MDR-TB patients to nine months [9]. The regimen relied on the combination of a fluoroquinolone and a second-line injectable drug, plus companion drugs. Since 2018, WHO has recommended replacing the injectable drug with a new drug, bedaquiline, in the nine-month regimen, to constitute an all-oral RR-TB treatment regimen [10]. In 2022, based on the encouraging results of trials on BPaL-based regimens, the Nix-TB [11], ZeNix [12], and TB-PRACTECAL trials [13], WHO published a conditional recommendation for the use of a six-month treatment regimen, composed of bedaquiline, pretomanid, and linezolid (600 mg), plus moxifloxacin (BPaL-M) for patients with FQ-susceptible isolates, rather than nine-months or longer regimens in MDR/RR-TB cases.

Shortening treatment duration increases the risk of relapse. Relapse is defined as a new episode of active TB disease due to the re-emergence of the original infection, as determined by genotypic analysis of the prevailing tubercle bacilli [14]. Therefore, WHO recommends at least 20 months post-treatment follow-up so that relapses are diagnosed and registered [15].

Novel short all-oral recommended RR-TB regimens were evaluated in trials in relatively small cohorts, with sample sizes that fit the assessment of composite adverse outcomes. However, such relatively small study population sizes are too small to meaningfully investigate a relatively rare outcome, such as relapse. No previous review pooled the data on relapse after short oral RR-TB regimens. This systematic review and *meta*-analysis therefore aim to estimate the pooled proportion of relapse among cases treated with standardized all-oral short RR-TB treatment regimens. In addition, we will summarize other treatment outcomes, criteria for the prolongation of treatment duration, and how frequently such prolongations occurred.

2. Methods

2.1. Search strategy and selection criteria

For this systematic review and *meta*-analysis, we searched PubMed (Medline), Web of Science, and Google Scholar databases systematically from 10th October 2022 to November 2023. The search string for PubMed (Medline) is available in Annex 1. The review was not restricted by language. Tom Decroo remained available for articles in French or Dutch. Reviews and reference lists were screened to identify relevant literature. Trial registries were also searched to seek any data from relevant unpublished studies. In addition, the references of the chosen articles and relevant review papers were manually searched and reviewed. This study is registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number (CRD42022385493). We prepared our study protocol, performed the systematic review, and prepared the report according to the recommendation by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [16].

2.2. Selection criteria

Two reviewers (ARY and AM) independently searched the literature and examined the relevant studies for further assessment of data on relapse and treatment outcomes of standardized short all-oral regimens. Conflicts over inclusion, and data items were checked by a third reviewer (TD). A number of criteria were required for inclusion in our analysis: (I) original articles about standardized short all-oral regimens (6–12-month) for RR-TB; (II) reporting treatment outcomes and relapse during a post-treatment follow-up period of at least 6 months; (III) studies published from January 2018 until the November 2023. The rationale for selecting the years 2018 and later stems from the introduction of standardized short all-oral regimens in 2018. Exclusion criteria of studies for our analysis were: (I) non-human studies; (II) case-report and case-series. For studies still recruiting, or where recruitment status was unclear, authors were contacted and requested to provide study results related to the systematic review's outcomes of interest.

2.3. Data extraction

Data were extracted independently by two investigators (ARY and AM), and differences were resolved by discussion with a third reviewer (TD). Duplicates in the search results were detected by Rayyan, an online browser-based tool for systematic reviews. The corresponding authors of selected papers were contacted to obtain any missing data. The following data were extracted from eligible papers: first author, year of publication, country of the data collection, study year, study design, the number of participants, baseline socio-demographic, clinical and microbiological characteristics, treatment duration, post-treatment follow-up duration, definitions (relapse and failure), end-of treatment outcomes and relapse.

2.4. Assessment of study bias

We assessed risk of bias at the level of the study using Cochrane risk of bias tool Version 2·0 (*RoB*-2) [17], for randomized clinical trials (RCTs). For non-randomized clinical trials and retrospective cohort studies the Newcastle-Ottawa scale (NOS) was used [18]. We assessed the risk of bias and applicability concerns using five domains for randomized clinical trials: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. The level of risk or concern was reported as high, some concern, or low. For studies other than RCTs the NOS tool was used to assess the risk of bias and the level of risk was reported as high or low.

2.5. Statistical methods and meta-analysis

All studies which reported relapse were included in the *meta*-analysis. We calculated the pooled proportion estimates for patients who had relapse. The *meta*-analysis was done using RevMan (version 5·4·1) [19]. Random-effects model was applied for assigning weights. The random effect model was chosen because we wanted to draw an unconditional inference regarding the outcome of interest (relapse), and because the common effect size was uncertain. The heterogeneity of outcome within and between each group of studies were assessed using the Cochrane Q

test (p-value < 0·1 denoting the presence of heterogeneity) and the I^2 statistic in forest plots described by Higgins et al. [20]. The I^2 statistic estimates the percent of observed between-study variability due to heterogeneity rather than to chance and ranges from 0 % to 100 %. Values of 25 %, 50 % and 75 % were considered representing low, medium and high heterogeneity respectively. A value of 0 % indicates no observed heterogeneity while 100 % indicates significant heterogeneity. For this review we determined that I^2 values above 75 % were indicative of significant heterogeneity [21]. The outcome of interest (relapse) is measured in numbers and proportions. The pooled proportion estimate was calculated among patients who were cured or completed treatment.

2.6. Definitions

According to the recommendations of the WHO, we defined the final treatment outcome as either favorable (cured and treatment completed) or unfavorable (died, lost to follow-up, treatment failure and relapse). Relapse disease is defined as a second (or third) episode of active TB disease due to re-emergence of the original infection, as determined by genotypic analysis of the prevailing tubercle bacilli. Also, whole-genome sequencing (WGS) is required to identify minor differences which will provide the greatest insight to differentiate relapse versus re-infection [15].

2.7. Role of the funding source

There was no funding source for this study.

3. Results

In total, 145 records were identified and 36 articles were retrieved for full-text screening. Ten studies meeting the inclusion criteria were selected for this systematic review and *meta*-analysis. (Fig. 1).

Results of the risk of bias assessment using the Risk of Bias tool for the six clinical trials show an overall low risk of bias. Some concerns are identified in the areas of data missingness, measurement of the outcome, and selection of the reported results. Results of the bias assessment using the New Castle Ottawa Scale (NOS) tool show an overall low to moderate risk of bias among the two observational studies included in the review. (Annex-2).

The studies were conducted in 13 countries in Asia, Africa, Europe and United States of America. The sample size ranged between 20 and 688 participants. Six studies were randomized clinical trials [22,24–26,28–29], one non-randomized clinical trial [23], and three were cohort studies [27,30–31]. (Table 1).

The participants' age range was between 14 and 83 years old, and on average 63·7% of the participants in the studies were male. HIV coinfection ranged from 5·7% to 71·7%. Baseline smear microscopy was reported in seven studies [24,26–31], and ranged between 20·3% and 65·7%. Baseline rifampicin-resistant was reported in all studies except

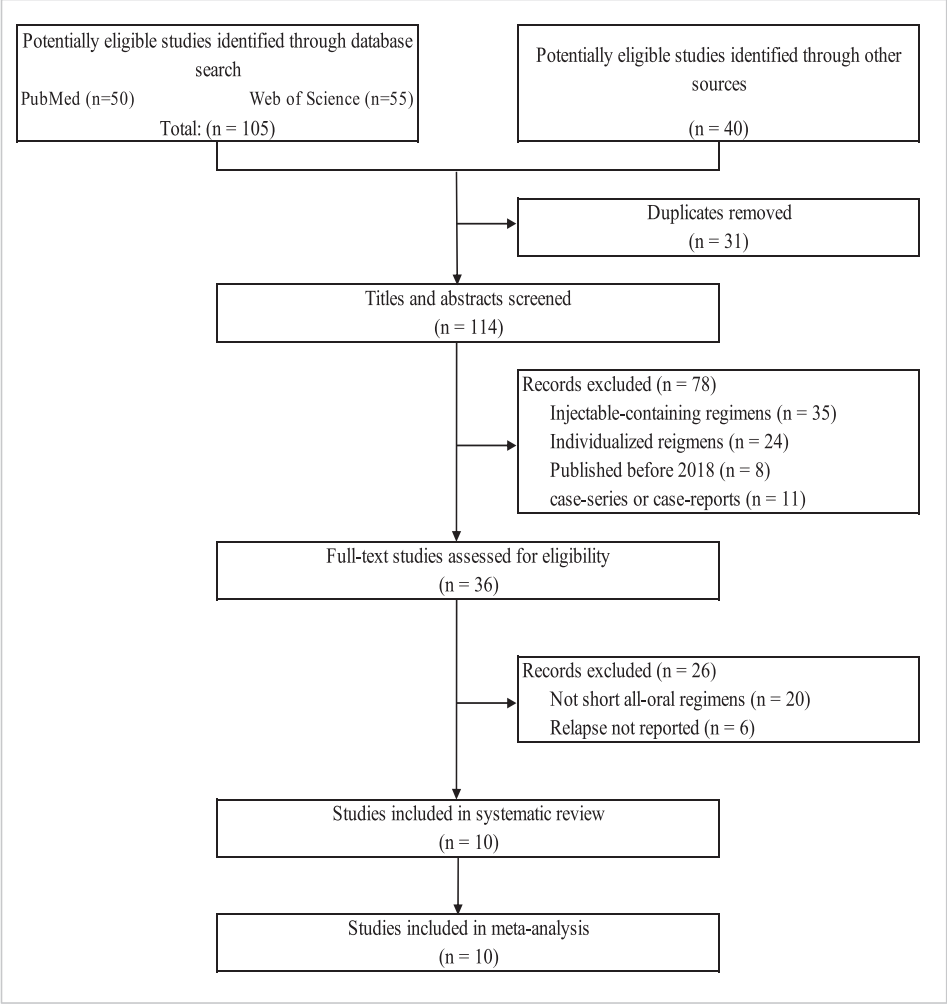

Fig. 1. Flow chart of study inclusion and exclusion.

Table 1
Characteristics of the included studies.

Author, Year	Country	Participants	Study Design
Conradie F. et al (2020) [22]	1	109	RCT
Fu L. et al (2021) [23]	2	41*	NRCT
Esmail A. et al (2022) [24]	1	49	RCT
Goodall RL. et al (2022) [25]	1, 3, 4, 5, 6, 7	196	RCT
Nyang'wa BT. et al (2022) [26]	1, 8, 9	364	RCT
Ndjeka N. et al (2022) [27]	1	688	Cohort
Conradie F. et al (2022) [28]	1, 4, 10, 11	181	RCT
Mok J. et al (2022) [29]	12	108	RCT
Goswami ND. et al (2022) [30]	13	20	Cohort
Haley C. et al (2023) [31]	13	70	Cohort

Abbreviations/acronyms: RCT: Randomized control trial, NRCT: Non-randomized clinical trial, 1: South Africa, 2: China, 3: Ethiopia, 4: Georgia, 5: India, 6: Uganda, 7: Mongolia, 8: Belarus, 9: Uzbekistan, 10: Moldova, 11: Russia, 12: South Korea, 13: United states of America, *: data of 41 patients were only reported.

one [26], and ranged between 35 and 100 %. Not considering Mok J. et al 2022, who used baseline fluoroquinolone resistance (FQR) as an exclusion criterion, baseline FQR ranged from 4·1% to 65·0%. Cavitary disease in chest radiography ranged between 7·0% and 61·8%. (Table 2).

All studies reported definition for treatment failure except three studies [25,29–30]. The definition of relapse was reported in all studies except one [30]. Having a positive culture with the baseline strain at post-treatment follow-up duration. Permanent regimen change, discontinuation, lack of culture conversion, clinical efficacy, and bacteriological reversion were among a large and varied set of criteria that defined treatment failure in different studies (Table 3).

Treatment duration was between 6 and 12 months. The shortest PTFU duration was six months [23,28], and the longest was 30 months [25]. All other studies were between 6 and 24 months [22–24,26–31]. Four studies [22,25,28,31], reported criteria for treatment extension. Only one study showed the number of patients for whom treatment duration was extended [31]. (Table 4).

Among included studies four studies had more than one interventional arm [26,23]. Favorable outcomes were achieved among a minimum of 68·4% and a maximum of 97·5% of participants. Lost to follow-up was observed among 0·9-8·6% of participants. Death was reported between 1·0% and 17·0% of cases and treatment failure was observed

Table 3
Definition of failure and relapse among included studies.

Author, Year	Definition of failure	Definition of relapse
Conradie F. et al (2020) [22]	Lack of clinical efficacy, lack of culture conversion, or bacteriological reversion	Positive culture with evidence of baseline strain at PTFU
Fu L. et al (2021) [23]	Termination or permanent change to a new regimen or treatment strategy	Positive culture with evidence of baseline strain at PTFU
Esmail A. et al (2022) [24]	Permanent regimen change (>1 group A† drug or > 2 group B‡ / C* drugs)	Positive culture with evidence of baseline strain at PTFU
Goodall RL. et al (2022) [25]	Not reported	Positive culture with evidence of baseline strain at PTFU
Nyang'wa BT. et al (2022) [26]	Termination or permanent change to a new regimen or treatment strategy	Positive culture with evidence of baseline strain at PTFU
Ndjeka N. et al (2022) [27]	Termination or discontinuation of at least 2 drugs due to intolerance, adverse event, drug resistance, failure to culture convert or culture reversion	Positive culture with evidence of baseline strain at PTFU
Conradie F. et al (2022) [28]	A change from the protocol-specified treatment due to: clinical efficacy, retreatment, or death by 26 weeks after completion of treatment	Positive culture with evidence of baseline strain at PTFU
Mok J. et al (2022) [29]	Not reported	Positive culture with evidence of baseline strain at PTFU
Goswami ND. et al (2022) [30]	Not reported	Not reported
Haley C. et al (2023) [31]	Lack of culture conversion after 4 months of BPaL or culture reversion to positive with 2 consecutive samples 30 days apart	Positive culture with same baseline strain at PTFU

Abbreviations/acronyms: PTFU: post-treatment follow-up, EOT: end-of-treatment. According to WHO 2019 consolidated multidrug-resistant tuberculosis (MDR-TB) guideline:
† Group A: levofloxacin or moxifloxacin, bedaquiline, linezolid.
‡ Group B: clofazimine, cycloserine or terizidone.
*Group C: ethambutol, delamanid, pyrazinamide, imipenem–cilastatin, amikacin, ethionamide or prothionamide, p-aminosalicylic acid.

Table 2
Baseline demographic and clinical characteristics of study participants.

Author, Year	Age	Male	Sample	HIV	Smear	RR	FQR	Cavity
Conradie F. et al (2020) [22]	35 (17–60)	52·0%	109	56 (51.0 %)	_	38 (35.0 %)	71 (65.0 %)	51 (46.7 %)
Fu L. et al (2021) [23]	38 (15–78)	73·0%	41	_	_	49 * (47.5 %)	32* (31.0 %)	51* (49.5 %)
Esmail A. et al (2022) [24]	37 (31–43)	69·0%	49	27 (55.0 %)	30 (61.2 %)	44 (89·7%)	2 (4·1%)	26 (53·0%)
Goodall RL. et al (2022) [25]	33 (15–65)	63·0%	196	27 (13·7%)	_	196 (100 %)	0 (0·0%)	13 (7·0%)
Nyang'wa BT. et al (2022) [26]	34 (18–62)	57·7%	364	101 (28·0%)	238 (65·7%)	_	79 (21·7%)	218 (60·0%)
Ndjeka N. et al (2022) [27]	42 (33–51)	61·0%	688	493 (71·7%)	297 (43·1%)	688 (100 %)	_	_
Conradie F. et al (2022) [28]	36 (26–44)	68·0%	181	36 (20·0%)	88 (48·6%)	160 (88·3%)	75 (41·4%)	112 (61·8%)
Mok J. et al (2022) [29]	49 (39–57)	67·1%	108	0 (0·0%)	17 (20·3%)	108 (100 %)	0 (0·0%)	38 (48·1%)
Goswami ND. et al (2022) [30]	42 (23–76)	60·0%	20	_	12 (60·0%)	8 (40·0%)	10 (50·0%)	7 (35·0%)
Haley C. et al (2023) [31]	37 (14–83)	65·7%	70	4 (5·7%)	34 (54·0%)	43 (61·4%)	10 (14·3%)	29 (46·0%)

Abbreviations/acronyms: Med: median, IQR: interquartile range, HIV: human immunodeficiency virus, RR: rifampicin-resistant, FQR: fluoroquinolone-resistant, CXR: chest radiography.
* The study sample size was 103 patients by the time they published the primary results the only 41 patients had completed the treatment.

Table 4
Treatment duration, post-treatment follow-up duration, and criteria for extension.

Author, Year	TD	PTFU	Criteria for extension
Conradie F. et al (2020) [22]	6	24	If positive culture at week 16, extend to 39 weeks
Fu L. et al (2021) [23]	9–12	6	Not reported
Esmail A. et al (2022) [24]	6–9	15–18	Not reported
Goodall RL. et al (2022) [25]	9	30	If delayed smear conversion (timepoint of conversion assessment not specified), add 8 more weeks of treatment
Nyang'wa BT. et al (2022) [26]	6	16	Not reported
Ndjeka N. et al (2022) [27]	9–12	24	Not reported
Conradie F. et al (2022) [28]	6	6	If suspicion of active disease between 16 and 26 weeks, extend to 39 weeks
Mok J. et al (2022) [29]	9	12	Not reported
Goswami ND. et al (2022) [30]	6	12	Not reported
Haley C. et al (2023) [31]	6	24	If bone involvement, extensive tuberculosis disease, delayed culture conversion, and non-adherence extend to more than 39 weeks

Abbreviations/acronyms: TD: Treatment duration, PTFU: post-treatment follow-up, treatment, and post-treatment follow-up durations are reported in months.

between 0·7% and 9·2% of participants. Overall, 1792 patients were treated with standardized all-oral short regimens. Among them, 744 (41.5 %) patients were treated with BPaL regimens and 1048 (58.5 %) with other standardized short-oral regimens. A total number of 1445 (80.6 %) patients achieved a favorable outcome. Among 1445 patients with a favorable outcome, 25 cases of relapse were reported, 17 cases were patients whom received BPaL regimens and eight patients were those whom received other standardized short all-oral regimens. For one study, although 103 patients were enrolled in one study, outcomes data for only 41 of the patients were published. Despite emailing the corresponding author, we did not get outcome data for all 103 patients [23] (Table 5).

For relapse, the pooled proportion was calculated for all regimens and for BPaL regimens. Studies with no relapses were excluded from *meta*-analysis, as the effect was not estimable. The pooled proportion of relapse among all regimens was 2·0% (95 % CI, 1·0-3·0%) with a chi-square of 9·48, low heterogeneity of $I^2 = 26$ % and overall effect size of Z = 3·66. (Fig. 2).

For BPaL regimens, the pooled proportion of relapse was also 2·0% (95 % CI, 1·0-3·0%) with a chi-square of 5·88, heterogeneity with $I^2 = 0$ % and overall effect size of Z = 3·44. As the test for heterogeneity $I^2 = 0$ %, the occurrence of the effect size by chance or sampling error cannot be excluded. (Fig. 3)

4. Discussion

This review demonstrates a relatively low frequency of relapse (overall: 2·0%; 95 % CI, 1·0-3·0%) and high treatment success (overall: range between 68·4% and 97·5%) for standardized short all-oral RR-TB treatment regimens. This is a major improvement, considering that before the introduction of short regimens, the RR-TB treatment success rate was around 60·0% globally [32], with relapses occurring in about 8·5% of patients [33]. The results of this study indicate that relapse after standardized all-oral short regimens is similar compared to relapse after highly effective rifampicin-based treatment for RS-TB with only about 2·9% of cases experiencing relapse [34].

Several reasons may explain the good treatment outcomes for short all-oral regimens. In the past, regimens were often individualized, targeting the inclusion of a minimum number of "likely active TB drugs", but ignoring the need for complementary action of included anti-TB medications [35]. Short all-oral regimens reported in this review were standardized, usually included multiple core drugs (most studied regimens had at least two of FQ, BDQ, and Pa), and assured both high bactericidal and sterilizing activity, thus less treatment failure and relapse [36]. All included studies, except Mok j. et al 2022, included BDQ in their regimens. BDQ is associated with higher rates of culture conversion and a significant reduction in all-cause death [37]. BDQ also has a weakness, as its bactericidal activity during the first week of chemotherapy is minimal [38]. Including other drugs with high early bactericidal activity might mitigate this weakness [39]. In BPaL regimens, the presence of Pa probably explains the high frequency of favorable end-of-treatment outcomes. Previous studies demonstrated that Pa-containing regimens were superior to standard treatments when a daily change in colony-forming units and time-to-culture conversion were compared [40], improving the bactericidal activity and probably also the resistance-preventing and sterilizing activity of the regimen [41].

Definitive relapse-free cure remains the main goal for RR-TB. However, the included studies did not show RR-TB retreatment outcomes after treatment failure or relapse. While including two or more core

Table 5
Treatment regimens, end-of-treatment outcomes, and relapse.

Author, Year	Regimen composition	End-of-treatment outcomes *n* (%)				Relapse *n* (%)
		Favorable	LTFU	Died	Failure	
Conradie F. et al (2020) [22]	BDQ, Pa, LZD	98/109 (89·9%)	1/109 (0·9%)	7/109 (6·4%)	1/109 (0·9%)	2/98 (2·0%)
Fu L. et al (2021) [23]	LZD, FQ, BDQ / CFZ, CS, Z	40/41 (97·5%)	NA	NA	1/41 (2·4%)	0/40 (0·0%)
Esmail A. et al (2022) [24]	BDQ, LFX, LZD, Z, INH/ Trd/ Eto	33/44 (75·0%)	3/44 (6·8%)	4/44 (9·1%)	3/44 (6·8%)	1/33 (3·0%)
Goodall RL. et al (2022) [25]	BDQ, LFX, CFZ, E, Z	162/196 (82·6%)	8/196 (4·1%)	3/196 (1·5%)	18/196 (9·2%)	5/162 (3·1%)
Nyang'wa BT. et al (2022) [26]						
	BDQ, Pa, LZD, MFX	121/138 (87·7%)	4/138 (2·9%)	0/138 (0·0%)	0/138 (0·0%)	1/121 (0·8%)
	BDQ, Pa, LZD, CFZ	88/115 (76·5%)	9/115 (7·8%)	1/115 (0·8%)	1/115 (0·8%)	5/88 (5·7%)
	BDQ, Pa, LZD	96/111 (86·4%)	0/111 (0·0%)	1/111 (0·9%)	0/111 (0·0%)	3/96 (3·1%)
Ndjeka N. et al (2022) [27]	BDQ, CFZ, MFX/LFX, Z, E, Eto, INH	507/688 (73·7%)	59/688 (8·6%)	117/688 (17·0%)	5/688 (0·7%)	1/507 (0·2%)
Conradie F. et al (2022) [28]						
	BDQ, Pa, LZD x 1200 mg x 26 weeks	41/45 (91·1%)	1/45 (2·2%)	0/45 (0·0%)	0/45 (0·0%)	0/41 (0·0%)
	BDQ, Pa, LZD x 1200 mg x 9 weeks	40/46 (86·9%)	0/46 (0·0%)	1/46 (2·2%)	0/46 (0·0%)	2/40 (5·0%)
	BDQ, Pa, LZD x 600 mg x 26 weeks	41/45 (91·0%)	0/45 (0·0%)	0/45 (0·0%)	0/45 (0·0%)	1/41 (2·4%)
	BDQ, Pa, LZD x 600 mg x 9 weeks	37/45 (82·2%)	1/45 (2·2%)	0/45 (0·0%)	1/45 (2·2%)	1/37 (2·7%)
Mok et al (2022) [29]	DLM, LFX, LZD, Z	54/79 (68·4%)	1/79 (1·3%)	2/79 (2·5%)	5/79 (6·3%)	1/54 (1·85 %)
Goswami ND. et al (2022) [30]	BDQ, Pa, LZD	19/20 (95·0%)	1/20 (5·0%)	0/20 (0·0%)	0/20 (0·0%)	0/19 (0·0%)
Haley C. et al (2023) [31]	BDQ, Pa, LZD	68/70 (97·1%)	5/70 (7·1%)	2/70 (2·8%)	0/70 (0·0%)	2/68 (2·9%)

Abbreviations/acronyms: BPaL: bedaquiline (BDQ), pretomanid (Pa), linezolid (LZD), LTFU: lost to follow-up, FQ: fluoroquinolone, CFZ/C: clofazimine, CS: cycloserin, Z: pyrazinamide, LFX: levofloxacin, Trd: terizidone, E: ethambutol, Eto: ethionamide, MFX: moxifloxacin, INH: isoniazid, NA: Not available.

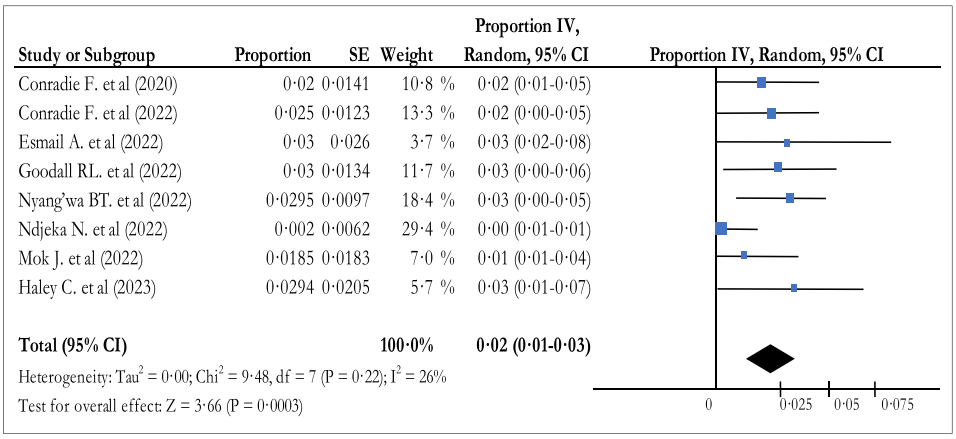

Fig. 2. Pooled proportion of relapse among all studies.

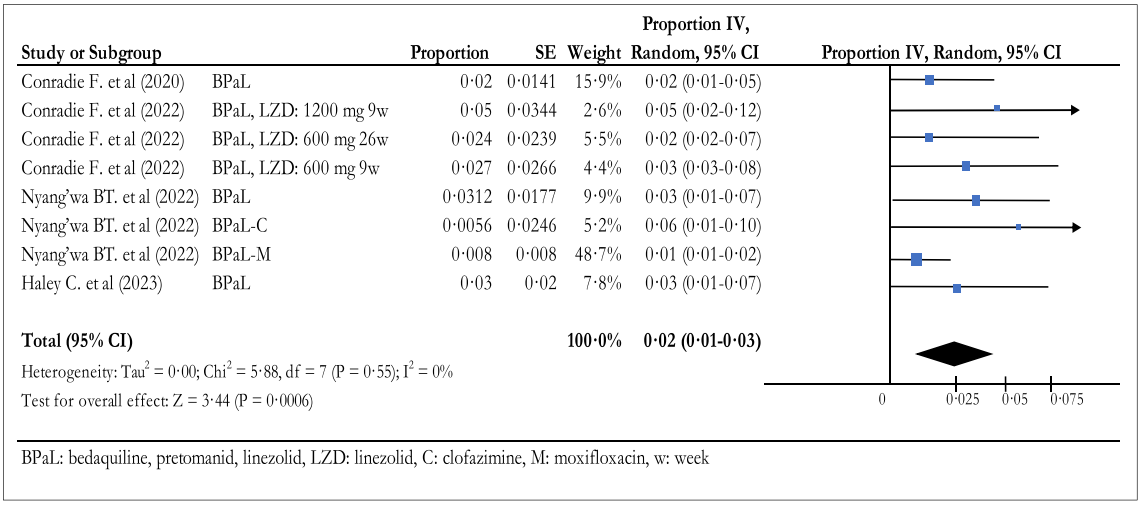

Fig. 3. Pooled proportion of relapse among BPal regimens.

drugs can strengthen the regimen, it may reduce the chances of successfully treating patients after treatment failure or relapse. Such patients are at risk of having TB resistant to multiple core drugs, e.g., XDR-TB (TB resistant to FQ, and also BDQ or LZD). How to retreat RR-TB remains unknown. Studies are needed to compare an "upfront potent approach", combining the most potent second-line drugs in a first RR-TB treatment, with a "cascade of regimens approach", in terms of definitive relapse-free cure [42]. The latter approach relies on one core drug per treatment regimen and assures more robust re-treatment options and probably a higher proportion of patients with definitive relapse-free cure overall [43].

Another threat to achieving relapse-free cure is the empiric use of most new second-line drugs. Indeed, in most settings drug susceptibility testing (DST) for BDQ, Pa, or LZD is not widely available. In patients treated first time for RR-TB, the pooled frequency of LZD resistance was 4·2% [44]. Acquired bedaquiline resistance (ABR) was assessed based on predefined MIC thresholds and genotypic ABR based on the emergence of resistance-associated variants. The median (IQR) frequency of phenotypic ABR was 2.2 % (1.1 %-4.6 %) and 4.4 % (1.8 %-5.8 %) for genotypic ABR [45]. BDQ resistance is even more frequent (up to 20·0%) in patients with baseline FQ resistance [46]. Considering that FQ-resistant RR-TB (pre-XDR-TB) is an indication for BPaL, a three-drug regimen, and the lack of access to BDQ DST, the chances of pre-XDR-TB patients being treated with two active drugs only (Pa and LZD) may be not negligible. This increases the risk of poor outcomes and additional resistance acquisition. Therefore, the introduction of these new regimens needs to be accompanied by improved access to DST for new drugs.[47].

Individual studies included in this review were powered to assess a composite endpoint, combining multiple outcomes, [48] but not to estimate the frequency of relapse. This review filled this gap, combining data from multiple individual studies, mainly clinical trials, to show the proportion of relapse with good precision. For BPaL-based regimens, data from 744 patients were pooled, of whom 17 experienced relapses, showing 2·0% (95 % CI, 1·0-3·0%) relapse after cure or treatment completion· Studies of large programmatic cohorts, including systematic post-treatment follow-up, are needed to assess relapse in routine care, usually with less stringent follow-up and less patient support than under trial conditions.

This systematic review has several limitations. Most of the studies in this systematic review followed participants for less than two years after their treatment completion. Even though most relapses occur within the first year after treatment completion, a too-short follow-up time probably underestimates the true extent of relapse.[49] WHO recommends post-treatment systematic follow up for 24 months post-treatment.[50] In addition, studies were conducted in very few countries which leaves our findings non-representative for all high RR-TB burden countries, as patient-level factors may differ, as well as baseline resistance to second-line drugs. Not all studies reported baseline co-morbidities, culture results, and criteria for treatment extension. Attempts to get results from authors were unsuccessful. The secondary objective of this review was to estimate the proportion of participants who required treatment duration

extension. Since none of the studies did report the frequency of treatment extension, we were unable to achieve this objective. Despite difference in duration of PTFU, the definition of relapse was similar across studies, which allowed us to estimate the pooled proportion estimates for relapse for all regimens, and separately for BPaL regimens. For having a favorable treatment outcome, because of the very high heterogeneity ($I^2 > 90$ %; probably due to the diversity in primary endpoint definitions), we choose not to proceed with pooled estimates for favorable outcomes.

5. Conclusion

The results of this study indicate that relapse after standardized all-oral short regimens is similar compared to relapse after highly effective rifampicin-based treatment for rifampicin-susceptible TB. However, the overall number of patients who received studied treatment regimens is still rather small for a relatively rare outcome such as relapse. Moreover, the duration of post-treatment follow-up was insufficient in most studies. The scale-up of studied short RR-TB regimens, especially BPaL-based regimens, under programmatic conditions should be accompanied by systematic post-treatment follow-up to obtain a reliable estimate of relapse in real-life settings.

CRediT authorship contribution statement

Ahmad Reza Yosofi: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Anita Mesic:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Tom Decroo:** Writing – review & editing, Validation, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2024.100426.

References

[1] Global tuberculosis report 2023 [Internet]. Who.int. [cited 2024 Jan 22]. Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023.
[2] Ulasi A, Nwachukwu N, Onyeagba R, Umeham S, Amadi A. Prevalence of rifampicin resistant tuberculosis among pulmonary tuberculosis patients In Enugu, Nigeria. Afr Health Sci [Internet] 2022;22(2):156–61. https://doi.org/10.4314/ahs.v22i2.18 [cited 2023 Jul 21].
[3] Jo K-W, Yoo J-W, Hong Y, Lee JS, Lee S-D, Kim WS, et al. Risk factors for 1-year relapse of pulmonary tuberculosis treated with a 6-month daily regimen. Respir Med 2014;108:654–9. https://doi.org/10.1016/j.rmed.2014.01.010.
[4] Mishra S, Saito K. Clinically encountered growth phenotypes of tuberculosis-causing bacilli and their in vitro study: A review. Front Cell Infect Microbiol [Internet] 2022;12. https://doi.org/10.3389/fcimb.2022.1029111.
[5] Van Deun A, Decroo T, Piubello A, de Jong BC, Lynen L, Rieder HL. Principles for constructing a tuberculosis treatment regimen: the role and definition of core and companion drugs. Int J Tuberc Lung Dis [Internet] 2018;22(34):239.
[6] Aung KJM, Van Deun A, Declercq E, Sarker MR, Das PK, Hossain MA, et al. Successful "9-month Bangladesh regimen" for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis [Internet] 2014;18(10):1180–7.
[7] Nix-TB [Internet]. TB Alliance. 2015 [cited 2023 Jul 21]. Available from: https://www.tballiance.org/portfolio/trial/5089.
[8] WHO 2022 DR-TB Guidelines [Internet]. Who.int. [cited 2023 Jul 21]. Available from: https://apps.who.int/iris/rest/bitstreams/1211676/retrieve.
[9] Various Doses and Durations of Linezolid Plus Bedaquiline & Pretomanid in Participants With Drug Resistant Tuberculosis - Full Text View - Clinicaltrials.gov [Internet]. Clinicaltrials.gov. [cited 2023 Jul 21]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT03086486.
[10] Conradie F, Bagdasaryan TR, Borisov S, Howell P, Mikiashvili L, Ngubane N, et al. Bedaquiline–pretomanid–linezolid regimens for drug-resistant tuberculosis. N Engl J Med 2022;387:810–23. https://doi.org/10.1056/nejmoa2119430.
[11] TB PRACTECAL [Internet]. TB Alliance. [cited 2023 Jul 21]. Available from: https://www.tballiance.org/portfolio/trial/12869.
[12] McIvor A, Koornhof H, Relapse KBD. re-infection and mixed infections in tuberculosis disease [cited 2023 Jul 21];75(3):ftx020. Available from: Pathog Dis [Internet] 2017. https://academic.oup.com/femspd/article/75/3/ftx020/3003284.
[13] Moher D, Liberati A, Tetzlaff J, Altman DG. for the PRISMA group. preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535–. https://doi.org/10.1136/bmj.b2535.
[14] RoB 2: A revised Cochrane risk-of-bias tool for randomized trials [Internet]. Cochrane.org. [cited 2023 Jul 21]. Available from: https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials.
[15] Carson Ka-Lok Lo, Dominik Mertz, Mark Loeb. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. BMC Medical Research Methodology 2014;14:45.
[16] RevMan: Systematic review and meta-analysis tool for researchers worldwide. Cochrane.org n.d. https://revman.cochrane.org/info (accessed November 17, 2023).
[17] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003 Sep 6;327(7414):557–60. https://doi.org/10.1136/bmj.327.7414.557. PMID: 12958120; PMCID: PMC192859.
[18] Aslam M. Cochran's Q test for analyzing categorical data under uncertainty. J Big Data 2023;10. https://doi.org/10.1186/s40537-023-00823-3.
[19] Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM, et al. Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med [Internet] 2020;382(10):893–902. https://doi.org/10.1056/nejmoa1901814.
[20] Fu L, Weng T, Sun F, Zhang P, Li H, Li Y, et al. Insignificant difference in culture conversion between bedaquiline-containing and bedaquiline-free all-oral short regimens for multidrug-resistant tuberculosis. Int J Infect Dis [Internet] 2021;111:138.
[21] Esmail A, Oelofse S, Lombard C, Perumal R, Mbuthini L, Goolam Mahomed A, et al. An all-oral 6-month regimen for multidrug-resistant tuberculosis: A multicenter, randomized controlled clinical trial (the NExT study). Am J Respir Crit Care Med [Internet]. 2022;205(10):1214–27 [cited 2023 Jul 21], https://pubmed.ncbi.nlm.nih.gov/35175905/.
[22] Goodall RL, Meredith SK, Nunn AJ, Bayissa A, Bhatnagar AK, Bronson G, 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 [Internet]. 2022;400(10366):1858–68 [cited 2023 Jul 21].
[23] Nyang'wa B-T, Berry C, Kazounis E, Motta I, Parpieva N, Tigay Z, et al. A 24-week, all-oral regimen for rifampin-resistant tuberculosis. N Engl J Med [Internet]. 2022;387(25):2331–43 [cited 2023 Jul 21].
[24] Ndjeka N, Campbell JR, Meintjes G, Maartens G, Schaaf HS, Hughes J, et al. Treatment outcomes 24 months after initiating short, all-oral bedaquiline-containing or injectable-containing rifampicin-resistant tuberculosis treatment regimens in South Africa: a retrospective cohort study [cited 2023 Jul 21] Lancet Infect Dis [Internet]. 2022;22(7):1042–51. https://pubmed.ncbi.nlm.nih.gov/35512718/.
[25] Conradie F, Bagdasaryan TR, Borisov S, Howell P, Mikiashvili L, Ngubane N, et al. Bedaquiline–pretomanid–linezolid regimens for drug-resistant tuberculosis [cited 2023 Jul 21] N Engl J Med [Internet]. 2022;387(9):810–23. https://pubmed.ncbi.nlm.nih.gov/36053506/.
[26] Mok J, Lee M, Kim DK, Kim JS, Jhun BW, Jo K-W, 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. Available from Lancet [Internet] 2022;400(10362):1522–30. https://www.sciencedirect.com/science/article/pii/S0140673622018839.
[27] Goswami ND, Ashkin D, Haley CA. BAM Project Team Pretomanid in the treatment of patients with tuberculosis in the United States. N Engl J Med 2022 Sep 1;387(9):850–2. https://doi.org/10.1056/NEJMc2119461. PMID: 36053513.
[28] Haley CA, Schechter MC, Ashkin D, Peloquin CA, Peter Cegielski J, Andrino BB, et al. BPaL implementation group. implementation of bedaquiline, pretomanid, and linezolid in the United States: experience using a novel all-Oral treatment regimen for treatment of rifampin-resistant or rifampin-intolerant tuberculosis disease. Clin Infect Dis 2023 Oct 5;77(7):1053–62. https://doi.org/10.1093/cid/ciad312. PMID: 37249079.
[29] Field SK. Bedaquiline for the treatment of multidrug-resistant tuberculosis: great promise or disappointment? Ther Adv Chronic Dis [Internet] 2015;6(4):170–84. https://doi.org/10.1177/2040622315582325.

[30] Gils T, Lynen L, de Jong BC, Van Deun A, Decroo T. Pretomanid for tuberculosis: a systematic review [cited 2023 Jul 21] Clin Microbiol Infect [Internet]. 2022;28(1): 31–42. https://pubmed.ncbi.nlm.nih.gov/34400340/.
[31] Turkova A, Wills GH, Wobudeya E, Chabala C, Palmer M, Kinikar A, et al. Shorter treatment for nonsevere tuberculosis in African and Indian children. N Engl J Med [Internet] 2022;386(10):911–22. https://doi.org/10.1056/nejmoa2104535.
[32] Lyu X-L, Lin T-T, Gao J-T, Jia H-Y, Zhu C-Z, Li Z-H, et al. Effects of bedaquiline on antimicrobial activity and cytokine secretion of macrophages infected with multidrug-resistant Mycobacterium tuberculosis strains [cited 2023 Jul 21] Can J Infect Dis Med Microbiol [Internet]. 2022;2022:2703635. https://www.hindawi.com/journals/cjidmm/2022/2703635/.
[33] Lyons MA. Pharmacodynamics and bactericidal activity of bedaquiline in pulmonary tuberculosis. Antimicrob Agents Chemother [Internet] 2022;66(2): e0163621. https://doi.org/10.1128/AAC.01636-21.
[34] Li Y, Sun F, Zhang W. Bedaquiline and delamanid in the treatment of multidrug-resistant tuberculosis: promising but challenging. Drug Dev Res 2019;80:98–105. https://doi.org/10.1002/ddr.21498.
[35] Donald PR, Diacon AH. The early bactericidal activity of anti-tuberculosis drugs: a literature review [cited 2023 Jul 21] Tuberculosis (Edinb) [Internet]. 2008;88 (Suppl 1):S75–83. https://pubmed.ncbi.nlm.nih.gov/18762155/.
[36] Xu J, Li S-Y, Almeida DV, Tasneen R, Barnes-Boyle K, Converse PJ, et al. Contribution of pretomanid to novel regimens containing bedaquiline with either linezolid or moxifloxacin and pyrazinamide in Murine models of tuberculosis. Antimicrob Agents Chemother [Internet] 2019;63(5).
[37] Fekadu G, Tolossa T, Turi E, Bekele F, Fetensa G. Pretomanid development and its clinical roles in treating tuberculosis. Available from J Glob Antimicrob Resist [Internet] 2022;31:175–84. https://www.sciencedirect.com/science/article/pii/S2213716522002168.
[38] Decroo T, de Jong BC, Piubello A, Lynen L, Van Deun A. Tuberculosis treatment: one-shot approach or cascade of regimens? Lancet Respir Med 2020;8:e4–5. https://doi.org/10.1016/s2213-2600(19)30473-4.
[39] Souleymane MB, Decroo T, Mamadou S, Soumana A, Lawan IM, Gagara-Issoufou A, et al. Definitive outcomes in patients with rifampicin-resistant tuberculosis treated in Niger from 2012 to 2019: a retrospective cohort study. Int Health 2023;15: 258–64. https://doi.org/10.1093/inthealth/ihac016.
[40] Azimi T, Khoshnood S, Asadi A, Heidary M, Mahmoudi H, Kaviar VH, et al. Linezolid resistance in multidrug-resistant mycobacterium tuberculosis: a systematic review and meta-analysis. Front Pharmacol 2022;13. https://doi.org/10.3389/fphar.2022.955050.
[41] Mallick JS, Nair P, Abbew ET, Van Deun A, Decroo T. Acquired bedaquiline resistance during the treatment of drug-resistant tuberculosis: a systematic review. JAC-Antimicrobial Resistance 2022;4(2). https://doi.org/10.1093/jacamr/dlac029.
[42] Derendinger B, Dippenaar A, de Vos M, Huo S, Alberts R, Tadokera R, et al. High frequency of bedaquiline resistance in programmatically treated drug-resistant TB patients with sustained culture-positivity in Cape Town, South Africa. 2022.11.14.22282167 BioRxiv 2022. https://doi.org/10.1101/2022.11.14.22282167.
[43] Migliori GB, Lienhardt C, Weyer K, van der Werf MJ, Blasi F, Raviglione MC. Ensuring rational introduction and responsible use of new TB tools: outcome of an ERS multisector consultation. Eur Respir J 2014;44:1412–7. https://doi.org/10.1183/09031936.00132114.
[44] Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials: greater precision but with greater uncertainty?: Greater precision but with greater uncertainty? [cited 2023 Jul 27] JAMA [Internet]. 2003; 289(19):2554–9. https://pubmed.ncbi.nlm.nih.gov/12759327/.
[45] Luzze H, Johnson DF, Dickman K, Mayanja-Kizza H, Okwera A, Eisenach K, Cave MD, Whalen CC, Johnson JL, Boom WH, Joloba M. Tuberculosis Research Unit. Relapse more common than reinfection in recurrent tuberculosis 1–2 years post treatment in urban Uganda. Int J Tuberc Lung Dis. 2013 Mar;17(3):361–7. https://doi.org/10.5588/ijtld.11.0692. PMID: 23407224; PMCID: PMC6623981.
[46] Programme GT. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Who.int 2022. https://www.who.int/publications/i/item/9789240063129 (accessed October 18, 2023).