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Delamanid-containing regimens and multidrug-resistant tuberculosis: A systematic review and meta-analysis

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ABSTRACT

Introduction: Multidrug-resistant tuberculosis (MDR-TB) is a life-threatening condition needing long polychemotherapy regimens. As no systematic reviews/meta-analysis is available to comprehensively evaluate the role of delamanid (DLM), we evaluated its effectiveness and safety.

Methods: We reviewed the relevant scientific literature published up to January 20, 2022. The pooled success treatment rate with 95% confidence intervals (CI) was assessed using a random-effect model. We assessed studies for quality and bias, and considered $P<0.05$ to be statistically significant.

Results: After reviewing 626 records, we identified 25 studies that met the inclusion criteria, 22 observational and 3 experimental, with 1276 and 411 patients, respectively. In observational studies the overall pooled treatment success rate of DLM-containing regimens was 80.9% (95% CI 72.6-87.2) with no evidence of publication bias (Begg's test; $P>0.05$). The overall pooled treatment success rate in DLM and bedaquiline-containing regimens was 75.2% (95% CI 68.1-81.1) with no evidence of publication bias (Begg's test; $P>0.05$). In experimental studies the pooled treatment success rate of DLM-containing regimens was 72.5 (95% CI 44.2-89.8, $P<0.001$, I^2: 95.1%) with no evidence of publication bias (Begg's test; $P>0.05$).

Conclusions: In MDR-TB patients receiving DLM, culture conversion and treatment success rates were high despite extensive resistance with limited adverse events.

Introduction

Tuberculosis (TB) continues to be a global emergency, with 10 million incident TB cases, 1.3 million HIV-negative and 0.214 million HIV-positive TB deaths and only 157,903 cases of rifampicin-resistant (RR)-TB cases detected and reported in 2020 (about one third of estimated cases) of which 150,359 were enrolled on treatment as reported by the World Health Organization (WHO) (World Health Organization, 2021).

The emergence and spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR)-TB has further complicated the clinical and public health management of the disease (World Health Organization, 2021). This is especially alarming in this temporal phase when subsequent waves of COVID-19 pandemic are affecting the whole world, causing pressure on (TB) health services (Migliori et al., 2021; Motta et al., 2020; Tadolini et al., 2020; TB/COVID-19 Global Study Group, 2021; Visca et al., 2021)

MDR-TB is caused by strains of *Mycobacterium tuberculosis* resistant to at least the two core anti-TB drugs, isoniazid (INH) and rifampicin (RIF). XDR-TB was previously defined as TB caused by MDR *Mycobacterium tuberculosis* with further resistance to any fluoroquinolone (FLQs) and at least one of the three injectable second-line drugs (kanamycin, amikacin, and/or capreomycin) (Borisov et al., 2019; Viney et al., 2021; World Health Organization, 2009). The WHO definition of XDR was recently modified focusing on resistance to Group A MDR-TB drugs: now defined as MDR plus resistance to FLQs and either linezolid (LZD) or bedaquiline (BDQ), the drugs which proved to be effective and reasonably safe (Ahmad et al., 2018; Borisov et al., 2019; Viney et al., 2021; World Health Organization, 2020).

The treatment success of MDR-TB treatment is still suboptimal, with a point estimate of 59% in the 2018 global cohort (World Health Organization, 2021), owing to difficulties to provide rapid and quality diagnosis, to design effective regimens (particularly for XDR-TB, as few drugs are still effective), and to manage frequent (and severe) adverse events. Last, but not least, the high cost of these drugs and, therefore, the difficulty for resource-limited countries to prescribe them, is still limiting the effective management of MDR- and XDR-TB at the global level (Migliori et al., 2020).

In this scenario the availability of new safe and effective drugs is of paramount importance. Among the few new anti-TB drugs, while much has been published on BDQ (Borisov et al., 2017; Hatami et al., 2022, World Health Organization, 2020), much less evidence is available on delamanid (DLM), which, for the relative paucity of available information, is presently classified among WHO Group C drugs (World Health Organization, 2020).

DLM is a promising nitro-dihydro-imidazooxazole derivative administered to treat MDR-TB. DLM inhibits the synthesis of methoxy- and keto-mycolic acid (which are components of *Mycobacterium tuberculosis* cell wall) through the F420 coenzyme mycobacteria system, while generating nitrous oxide.

Three systematic reviews investigated preliminary data on the combination of BDQ and DLM (D'Ambrosio et al., 2017; Migliori et al., 2017, Pontali et al., 2018) (one of them in children (D'Ambrosio et al., 2017)), and one systematic review described outcomes of children with MDR-TB (Harausz et al., 2018).

More recently, two systematic reviews evaluated mutations conferring resistance to BDQ and DLM (Kadura et al., 2020, Nieto Ramirez et al., 2020). A better understanding of genetic and phenotypic resistance is urgently needed to guide clinical management of DLM (Nguyen et al., 2020).

So far, no comprehensive systematic review on the efficacy/effectiveness and safety of DLM-containing regimens is available.

The aim of the present systematic review and meta-analysis is to evaluate effectiveness (bacteriological conversion and outcomes) and safety of DLM-containing regimens to manage MDR/RR-TB patients.

Methods

Search strategy

We searched Pubmed/MEDLINE, EMBASE, and Cochrane Library for studies reporting on the efficacy and effectiveness of individualized regimens containing DLM in patients with drug susceptibility testing (DST)-confirmed MDR/RR-TB, published up to January 20, 2022. The search terms were as follow: [(tuberculosis [Title/Abstract]) AND (delamanid [Title/Abstract]) OR (bedaquiline[Title/Abstract]) AND (efficacy[Title/Abstract] OR effectiveness[Title/Abstract]) OR safety[Title/Abstract]] (Appendix). Only studies written in English were selected. This study was conducted and reported in accordance with the Preferred Reporting Items

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for Systematic Reviews and Meta-Analyses statement (PRISMA) (Moher et al., 2009).

Study Selection

The records found through database searching were merged, and the duplicates were removed using EndNote X7 (Thomson Reuters, Toronto, ON, Canada). Two reviewers (MZ and EA) independently screened the records by title/abstract and full text to exclude those unrelated to the study objectives. Included studies met the following criteria: (1) patients diagnosed with MDR-TB according to the WHO criteria (World Health Organization, 2021); (2) patients treated with DLM-containing regimens; (3) treatment success (sputum and culture conversion), and (4) safety of the investigated drug/regimen. Conference abstracts, editorials, reviews, study protocols, molecular or experimental studies on animal models, and articles describing TB patients recruited without a confirmed bacteriological diagnosis, or administering DLM for other diseases like leishmaniosis were excluded.

Both the old and new definition of XDR-TB were used, as defined by the authors of the articles selected (Viney et al., 2021). Pre-XDR-TB was defined according to the new definition (TB caused by *M. tuberculosis* strains that fulfill the definition of MDR/RR-TB and that are also resistant to any FLQ) as this definition did not officially exist before (Viney et al., 2021).

Treatment outcomes were recorded in accordance with those used by the authors of the original studies selected, which were in agreement with the WHO definitions (treatment success, defined as the combination of patients who were cured and those who completed treatment; death, defined as death from any cause while on treatment; and treatment failure, defined as unsuccessful treatment, as determined by positive cultures at the end of the treatment regimen) (World Health Organization, 2011).

The regimens were considered DLM- and DLM/BDQ-containing based on what appeared in the methods of the original studies selected. The analysis was performed separately for experimental and observational studies and pooling the results together.

Optimized background regimens (OBR) were concomitantly prescribed with DLM. Basically, their characteristics were decided by the attending physician based on the DST results, WHO or national guidelines in force at the time of the diagnosis, and drugs' availability. In the studies selected the best regimen was tailored on the patient's characteristics and was not standardized. However, not all selected papers disclosed in detail the therapeutic approach.

Data extraction

Two reviewers (MZ and EA) designed a data extraction form and extracted data from all eligible studies, with differences being resolved by consensus. The following data were extracted: first author's name; year of publication; study duration; type of study; country or countries where the study was conducted; number of patients with MDR-TB; patient age; treatment protocols (treatment regimens and duration of treatment); HIV history; demographics (i.e., age, sex, nationality); type of adverse events; drug resistance status; culture conversion, and treatment outcomes.

Quality assessment

Two reviewers (MZ and EA) assessed the quality of the studies using two different assessment tools. A third reviewer (MJN) was involved in case of inconsistencies.

The Newcastle-Ottawa Scale (NOS) for observational studies and the Cochrane tool for experimental studies (Higgins et al., 2011; Wells GA et al., 2012) were adopted to assess the study quality. The NOS scale evaluates the risk of bias of observational studies with three domains: (1) selection of participants, (2) comparability, and (3) outcomes. A study can be awarded a maximum of one point for each numbered item within the selection and outcome categories, and a maximum of two points can be given for comparability. Scores of 0–3, 4–6, and 7–9 were assigned for the low, moderate, and high quality of studies, respectively.

The Cochrane tool is based on; use of random sequence generation; concealment of allocation to conditions; blinding of participant and personnel; blinding of outcome assessors; completeness of outcome data and other; selective reporting and other biases. Each study was rated as at low risk of bias when there was no concern regarding bias; as high risk of bias when there was concern regarding bias; or unclear risk of bias if the information was absent.

Data analysis

Statistical analyses were performed with Comprehensive Meta-Analysis software, version 2.0 (Biostat Inc., Englewood, NJ, USA). Point estimates and 95% CIs for the proportion of patients achieving treatment outcomes were calculated. The random-effects model was used because of the estimated heterogeneity of the true effect sizes. The between-study heterogeneity was assessed by Cochran's Q test and the I2 statistic. Publication bias was assessed statistically by using Begg's test (P value <0.05 was considered indicative of statistically significant publication bias) (Begg and Mazumdar, 1994).

Results

A total of 626 records were found in the initial search; after removing duplicate articles, the titles and abstracts of 351 references were screened (Figure 1). Of these, 42 articles were selected for a full-text review. After the full-text review, 25 articles met the inclusion criteria (Auchynka et al., 2021; Chang et al., 2018; Das et al., 2020; Das et al., 2021; Dooley et al., 2021; Ferlazzo et al., 2018; Ghosh et al., 2021; Gler et al., 2012; Häcker et al., 2020; Hafkin et al., 2017, Hafkin et al., 2019; Hewison et al., 2017; Kang et al., 2020; Kim et al., 2018; Kuksa et al., 2017; Kwon et al., 2021; Lee et al., 2020; Madzgharashvili et al., 2021; Mohr-Holland et al., 2020; Mok et al., 2019; Olayanju et al., 2020; Pirmahmadzoda et al., 2021; Sarin et al., 2019; Solodovnikova et al., 2021; von Groote-Bidlingmaier et al., 2019) of which 22 were observational (with 1,276 patients) (Auchynka et al., 2021; Chang et al., 2018; Das et al., 2020; Das et al., 2021; Ferlazzo et al., 2018; Ghosh et al., 2021; Häcker et al., 2020; Hafkin et al., 2017; Hafkin et al., 2019; Hewison et al., 2017; Kang et al., 2020; Kim et al., 2018; Kuksa et al., 2017; Kwon et al., 2021; Lee et al., 2020; Madzgharashvili et al., 2021; Mohr-Holland et al., 2020; Mok et al., 2019; Olayanju et al., 2020; Pirmahmadzoda et al., 2021; Sarin et al., 2019; Solodovnikova et al., 2021;) and three experimental studies (with 411 patients) (Dooley et al., 2021; Gler et al., 2012; von Groote-Bidlingmaier et al., 2019) (Tables 1 and 2). The study period ranged from 2012 to 2021. The mean age of the patients was 36.1 years.

Overall, 591 patients were included in DLM-containing regimen group and 685 patients in the DLM/BDQ-containing regimen group.

Quality of included studies

Based on the Newcastle-Ottawa Scale, which was used to evaluate the quality of the observational studies, the mean (standard deviation [SD]) NOS score was 8.0 (0.6), which is suggestive for a high methodological quality and a low risk of bias of the included studies (Table 3).

Table 1
Observational and experimental studies included in the meta-analysis (DLM-containing regimens group)

Author	Year	Country	Type of study	Meanage	HIVN (%)	Pre-treated for TB	TB disease	No. of patients receiving DLM	Other drugsincludedin regimen	Length of treatment (months)	Outcomes		
											Treatment successN (%)	FailureN (%)	DeathN (%)
Auchynka et al., 2021	2021	Belarus	RC	NR	NR	NR	MDR/Pre-XDR/XDR	105	FLQs;LZD; CFZ;CYC; IMP;PZA; AMGs	6	94(89.5%)	NR	NR
Chang et al., 2018	2018	Hong Kong	PC	48	0	6	Pre-XDR/XDR	11	FLQ;LZD	11.5	9(81.8%)	1(9%)	0
Dooley et al., 2021	2021	South Africa & Peru	RCT	32	11(39)	6	RR	24	CFZ;FLQs	6	22(91.6%)	2(8.3%)	0
Gler et al., 2012	2012	9 countries	RCT	36	NR	141	MDR	141	FLQs;AMGs;PZA; CYC;ETM;ETH	2	64(45.3%)	NR	NR
Häcker et al., 2020	2020	Germany	RC	30	1	NR	MDR/Pre-XDR/XDR	25	LZD;FLQs;TRD;CFZ	18.3	18(72%)	1(4%)	1(4%)
Hafkin et al., 2017	2017	USA	PC	32	12(15)	64	MDR Pre-XDR XDR	8 26 44	LZD;FLQs;CFZ;AMGs	6	53(67.9%)	11(14.1%)	8(10.2%)
Hewison et al., 2017	2017	7 countries[1]	RC	29.5	8(15)	49	MDR Pre-XDR XDR	10 14 27	FLQs;CFZ;LZD	6	39(76.4%)	4(7.8%)	7(13.7%)
Kuksa et al., 2017	2017	Latvia	RC	41.5	1(5.3)	13	MDR Pre-XDR XDR	2 8 9	TRD;LZD;PZA;FLQs	7.8	16(84.2%)	0	0
Madzgharashvili et al., 2021	2021	USA	RC	15.1	0	0	MDR/Pre-XDR/XDR	8	PZA;ETM;FLQs;CYC	19.6	7(87.5%)	0	0
Mohr-Holland et al., 2020	2020	South Africa	RC	NR	78(78.8)	58	RR Pre-XDR	64 35	PZA;FLQs;TRD; ETM;hINH;LZD	6.3	57(57.5%)	6(6%)	14(14.1%)
Mok et al., 2019	2019	South Korea	RC	47	0	27	MDR Pre-XDR XDR	14 27 8	FLQs;AMGs;LZD;CFZ	24	40(81.6%)	3(6.1%)	3(6.1%)
von Groote-Bidlingmaier et al., 2019	2019	7 countries[2]	RCT	32	12(5.3)	NR	MDR Pre-XDR XDR	177 39 10	Optimized background regimen (NR)	6	173(76.5%)	NR	18(7.9%)
Solodovnikova et al., 2021	2021	Belarus	RC	NR	NR	NR	RR/MDR/XDR	19	LZD;CFZ;CYC;FLQs	6	19(100%)	0	0
Kim et al., 2018	2018	South Korea	RC	48	NR	10	MDR/Pre-XDR/XDR	8	WHO-recommended regimen	5.6	8(100%)	NR	0
Kang et al., 2020	2020	South Korea	RC	47.8	1(0.9)	55	MDR Pre-XDR XDR	50 49 9	AMG;FLQs;LZD;CYC	6	95(87.9%)	1(0.9%)	8(7.4%)
Das et al., 2020	2020	India	RC	15.5	0	NR	Pre-XDR /XDR	11	LZD;CFZ	22	10(90.9%)	NR	NR

PC: prospective cohort; RC: retrospective cohort; RCT: randomized clinical trial; BDQ: bedaquiline; DLM: delamanid; FLQs: fluoroquinolones; LZD: linezolid; CFZ: clofazimine; CYC: cycloserine; AMGs: aminoglycosides; MEM/CLV: meropenem-clavulanate; TRD: terizidone; IMP: imipenem; ETH: ethionamide; hINH: high-dose isoniazid; ETM: ethambutol; PZA: pyrazinamide; PMD: pretomanid; MDR: multidrug-resistant; XDR: extensively drug-resistant; RR: rifampin-resistant; and NR: not reported. [1]: the Philippines, Peru, Latvia, Estonia, China, Japan, Korea, Egypt, the United States; [2]: Armenia, Belarus, Georgia, India, Russia, South Africa, Swaziland; [3]: Estonia, Latvia, Lithuania, Moldova, Peru, the Philippines, and South Africa

Table 2
Observational and experimental studies included in the meta-analysis (DLM and BDQ-containing regimens group)

Author	Year	Country	Type of study	Meanage	HIVN (%)	Pre-treated for TB	TB disease	No. of patients receiving DLM+ BDQ	Other drugsincludedin regimen	Length of treatment (months)	Outcomes		
											Treatment success	Failure	Death
Auchynka et al., 2021	2021	Belarus	RC	NR	NR	NR	MDR/Pre-XDR/XDR	20	FLQs;LZD; CFZ;CYC; IMP;PZA; AMGs	6	16(80%)	NR	NR
Das et al., 2021	2021	India	RC	25	1(1.4)	70	Pre-XDR XDR	28 42	LZD;CFZ	19	49(70%)	5(7.1%)	13(18.5%)
Dooley et al., 2021	2021	South Africa & Peru	RCT	34	10(36)	8	RR	20	CFZ;FLQs	6	19(95%)	1(5%)	0
Hafkin et al., 2019	2019	USA	RC	37	46(54.8)	74	MDR Pre-XDR XDR	4 18 62	LZD;PZA; CFZ;FLQs	6	51(60.7%)	4(4.7%)	10(11.9%)
Madzgharashvili et al., 2021	2021	USA	RC	15.5	0	0	MDR/Pre-XDR/XDR	2	LZD;PZA; CYC;CFZ	22	2(100%)	0	0
Kwon et al., 2021	2021	South Korea	RC	49	0	19	Pre-XDR/XDR	28	LZD;CFZ; MEM/CLV;CYC	6	23(82.1%)	2(7.1%)	1(3.5%)
Das et al., 2020	2020	India	RC	15.5	0	NR	Pre-XDR /XDR	12	LZD;CFZ	22	11(91.6%)	NR	NR
Lee et al., 2020	2020	South Korea	RC	49.8	1 (1.4)	49	MDR Pre-XDR XDR	13 41 20	FLQs; LZD;CFZ;CYC	5.5	42(56.7%)	1(1.3%)	4(5.4%)
Olayanju et al., 2020	2020	South Africa	PC	34	22 (55)	29	MDR Pre-XDR XDR	6 15 19	AMGs; FLQs;LZD;CFZ;TRD	6	27(67.5%)	NR	NR
Kang et al., 2020	2020	South Korea	RC	47.7	1 (1.5)	47	MDR Pre-XDR XDR	8 37 22	AMG;FLQs;LZD;CYC	6	58(86.5%)	3(4.4%)	3(4.4%)
Sarin et al., 2019	2019	India	PC	24	0	NR	MDR/Pre-XDR/XDR	42	FLQs;LZD;CFZ;IMP	6	25(59.5%)	NR	10(23.8%)
Kim et al., 2018	2018	South Korea	RC	50	NR	11	MDR/Pre-XDR/XDR	11	WHO-recommended regimen	11/3	7(63.6%)	NR	0
Ferlazzo et al., 2018	2018	Armenia, India, South Africa	RC	32.5	11 (39)	4	MDR Pre-XDR XDR	2 12 14	FLQs;LZD;CFZ;IMP	6	22(78.5%)	NR	1(3.5%)
Pirmahmadzoda et al., 2021	2021	Tajikistan	RC	NR	NR	NR	XDR	11	WHO-recommended regimen	20-36	11(100%)	0	0
Ghosh et al., 2021	2021	Germany	RC	35	66 (33)	169	MDR/Pre-XDR/XDR	147	WHO-recommended regimen	6	116(78.9%)	NR	NR

PC: Prospective cohort; RC: retrospective cohort; RCT: randomized clinical trial; BDQ: bedaquiline; DLM: delamanid; FLQs: fluoroquinolones; LZD: linezolid; CFZ: clofazimine; CYC: cycloserine; AMGs: aminoglycosides; MEM/CLV: meropenem-clavulanate; TRD: terizidone; IMP: imipenem; ETH: ethionamide; hINH: high-dose isoniazid; ETM: ethambutol; PZA: pyrazinamide; PMD: pretomanid; MDR: multidrug-resistant; XDR: extensively drug-resistant; RR: rifampin-resistant; NR: not reported.

Table 3
Quality assessment of the observational studies included in the meta-analysis (The NOS tool)

Author	Selection				Comparability		Outcome			
	Representativeness of Exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Adjust for the most important risk factors	Adjust for other risk factors	Assessment of outcome	Follow-up length	Lossto follow-uprate	Total quality score
Auchynka et al., 2021	1	1	1	1	1	0	1	1	1	8
Chang et al., 2018	1	1	1	1	1	1	1	1	1	9
Das et al., 2021	1	1	1	1	1	0	1	1	1	8
Häcker et al., 2020	1	1	1	1	1	1	1	1	1	9
Hafkin et al., 2017	1	1	1	1	1	0	1	1	1	8
Hafkin et al., 2019	1	1	1	1	1	0	1	1	0	7
Hewison et al., 2017	1	1	1	1	1	0	1	1	1	8
Kuksa et al., 2017	1	1	1	1	1	1	1	1	1	9
Madzgharashvili et al., 2021	1	1	1	1	1	1	1	1	1	9
Mohr-Holland et al., 2020	1	1	1	1	1	0	1	1	0	7
Mok et al., 2019	1	1	1	1	1	0	1	1	1	8
Solodovnikova et al., 2021	1	1	1	1	1	0	1	1	1	8
Kwon et al., 2021	1	1	1	1	1	0	1	1	1	8
Das et al., 2020	1	1	1	1	1	0	1	1	1	8
Lee et al., 2020	1	1	1	1	1	0	1	1	1	8
Olayanju et al., 2020	1	1	1	1	1	0	1	1	0	7
Kang et al., 2020	1	1	1	1	1	0	1	1	1	8
Sarin et al., 2019	1	1	1	1	1	0	1	1	1	8
Kim et al., 2018	1	1	1	1	1	0	1	1	1	8
Ferlazzo et al., 2018	1	1	1	1	1	0	1	1	1	8
Pirmahmadzoda et al., 2021	1	1	1	1	1	0	1	1	1	8
Ghosh et al., 2021	1	1	1	1	1	0	1	1	1	8

NOS: The Newcastle-Ottawa Scale

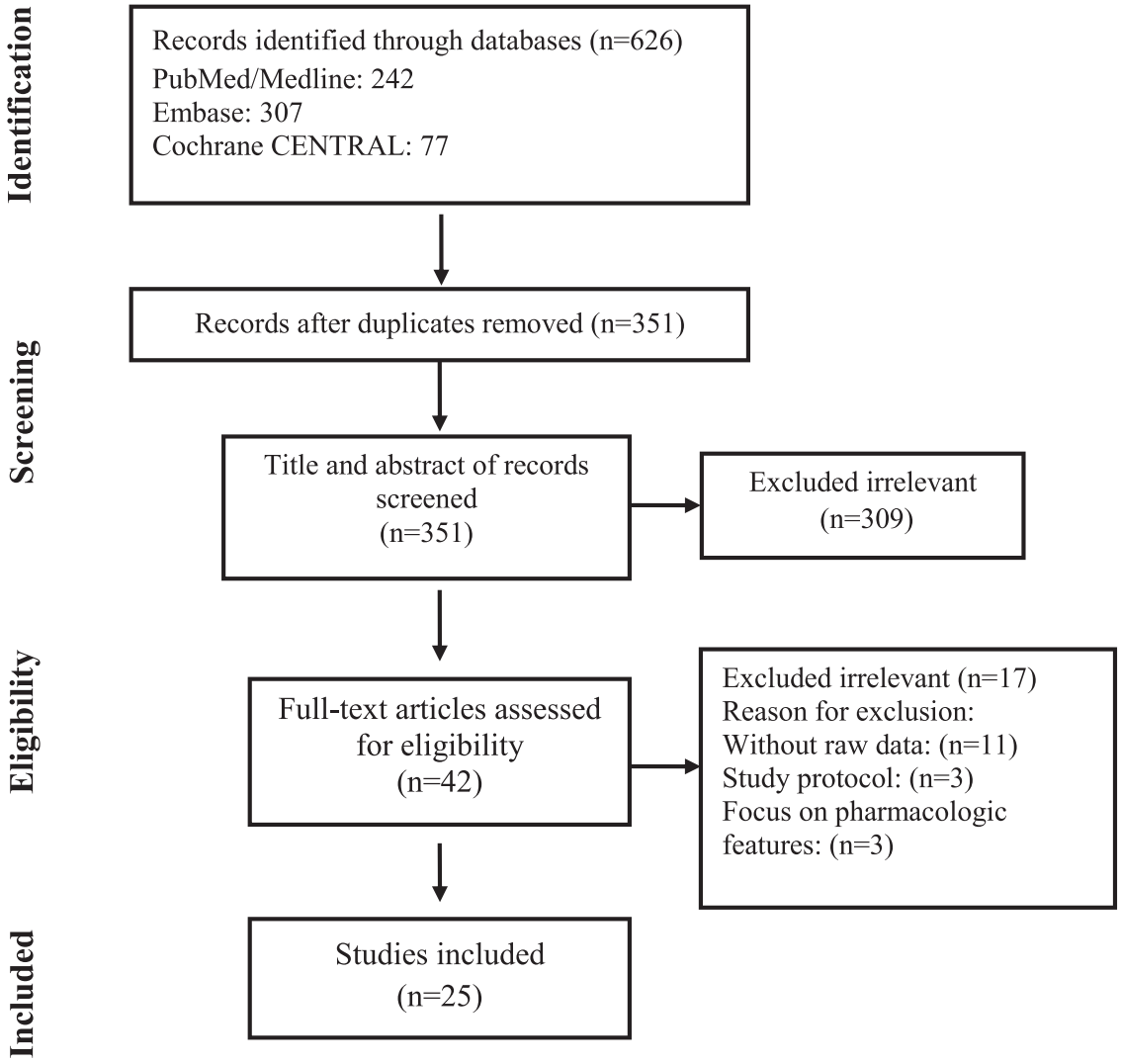

Figure 1. Flow chart of study selection for inclusion in the systematic review and meta-analysis.

Table 4
Quality assessment of the experimental studies included in the meta-analysis (the Cochrane tool)

Author	Random sequencegeneration	Allocation concealment	Blinding of participants andpersonnel	Blinding of outcomeassessment	Incomplete outcomedata	Selective reporting	Other bias
Gler et al., 2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Dooley et al., 2021	Low risk	High risk	High risk	High risk	Low risk	Low risk	Low risk
von Groote-Bidlingmaier et al., 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Only one experimental study (Dooley et al., 2021) has a high risk of bias in the cases of allocation concealment, blinding of participants, and blinding of outcome (Table 4).

Outcomes in observational studies

The overall pooled treatment success rate in DLM-containing regimens group was found to be 80.9% (95% CI 72.6-87.2, I^2: 73%) (Figure 2). There was no evidence of publication bias (Begg's test P >0.05).

The overall pooled treatment success rate in DLM- and BDQ-containing regimens group was found to be 72.8% (95% CI 65.9-78.9, I^2: 62%) (Figure 3). There was no evidence of publication bias (Begg's test P >0.05).

Outcomes in experimental studies

The pooled treatment success rate in in DLM-containing regimens group was 72.5% (95% CI 44.2-89.8, I^2: 95%) (Figure 4). The result of the Begg's test showed no evidence of publication bias (P >0.05).

Time to sputum culture conversion

The median time to sputum culture conversion ranged from 1.1 to 1.7 months in the DLM-containing regimens group (Auchynka et al., 2021; Chang et al. 2018; Das et al., 2020; Mok et al., 2019; Solodovnikova et al., 2021; von Groote-Bidlingmaier et al., 2019). In an additional study by Kim et al., 2018, reporting the information separately, the median time to cul-

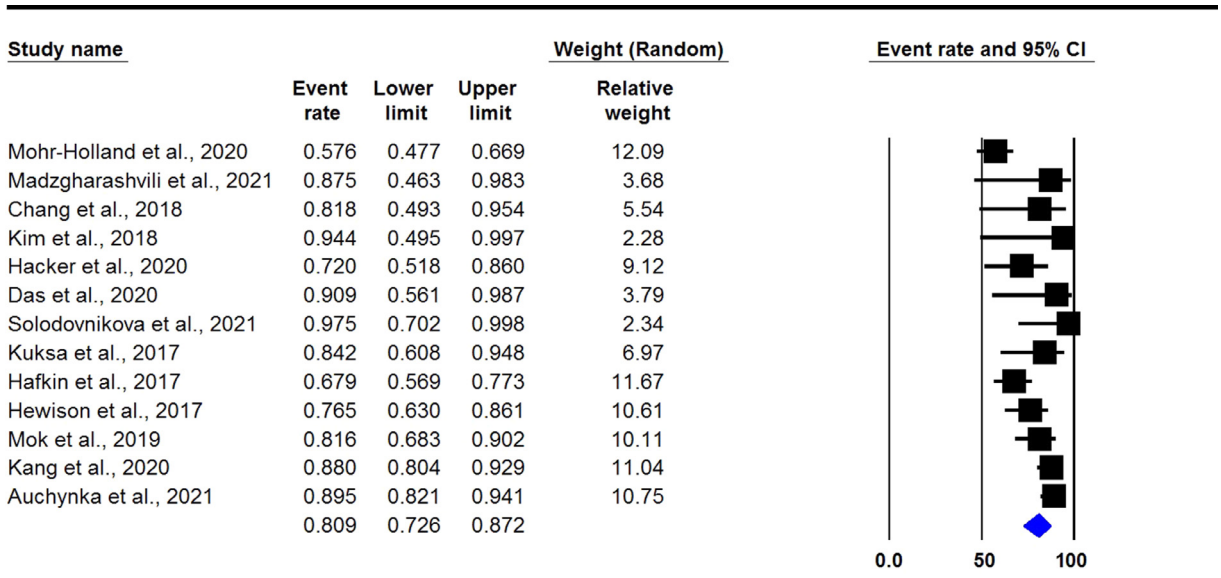

Figure 2. Treatment success rate in observational studies. (DLM-containing regimens group)
Legend: DLM: delamanid.

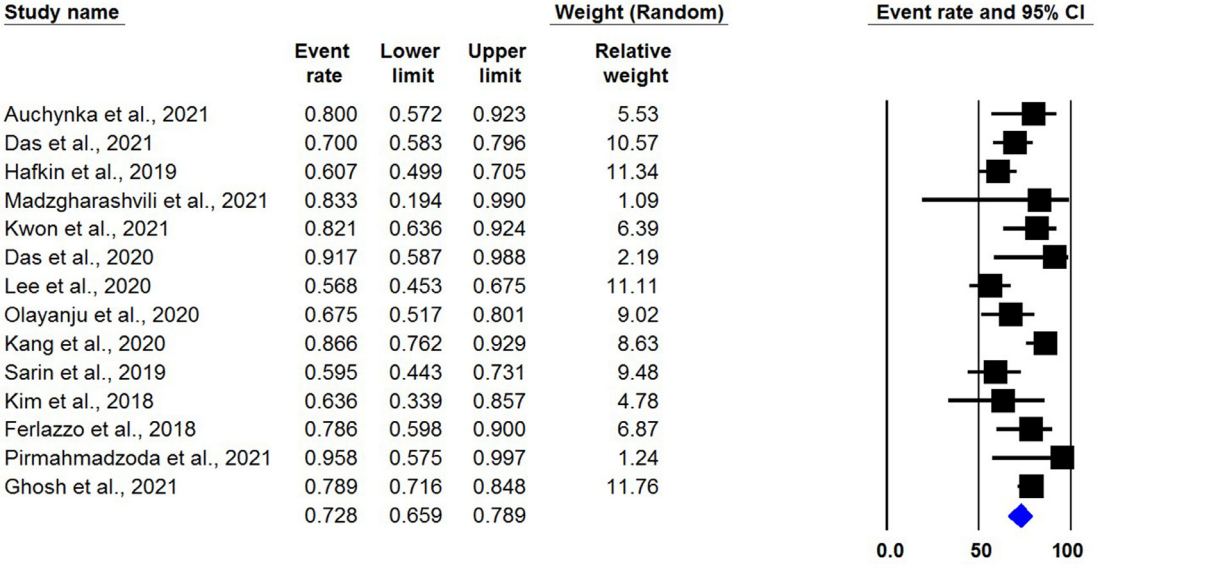

Figure 3. Treatment success rate in observational studies. (DLM and BDQ-containing regimens group)
DLM: delamanid; BDQ: bedaquiline.

ture conversion for DLM-containing regimens was 4.1 months and for DLM plus BDQ-containing regimens it was 10.3 months.

The pooled death rate and treatment failure in DLM-containing regimens group was found to be 7.8% (95% CI 5.5-11.0, I^2: 13.0%) and 9.2% (95% CI 7.2-11.6, I^2: 0.0%), respectively.

Adverse events

In the DLM-containing regimens group only 4/165 (2.4%) patients had QTcF prolongation (Fridericia correction, as reported by the original studies selected) definitely attributed to DLM. Also 2/127 (1.5%) patients with gastrointestinal symptoms and 1/27 (3.7%) patient with dermatologic symptoms were reported in this group (Table 5). Most of the adverse events potentially attributed to DLM and BDQ-containing regimens group (Table 6) were QTcF prolongation (12.8%, 55/427), psychiatric disorders (7.1%, 2/28), gastrointestinal symptoms (4.5%, 12/267), peripheral neuropathy (3.5%, 1/28), renal failure/ increased creatinine (2%, 2/102), and hepatic disorders/elevated liver enzymes (1.4%, 1/70).

Table 5
Adverse effects in included studies (DLM-containing regimens group)

Author	Number of patients	QTcF prolongation	Hepatic disorder/ Elevated liver enzyme	Renal failure/ Increased creatinine	Optic neuropathy/ Blurred vision	Ototoxicity/ Hearing loss	Hematological disorders (Anemia, thrombocytopenia, eosinophilia)	Gastrointestinal symptoms (Diarrhea, vomiting, nausea, abdominal pain)	Peripheral neuropathy	Electrolyte disturbance	Arthralgia	Psychiatric disorder	Dermatologic symptoms
Auchynka et al., 2021	105	-	-	-	-	-	-	-	-	-	-	-	-
Chang et al., 2018	11	0	-	-	-	-	-	-	-	-	-	-	-
Dooley et al., 2021	24	-	-	-	-	-	-	-	-	-	-	-	-
Gler et al., 2012	141	-	-	-	-	-	-	-	-	-	-	-	-
Häcker et al., 2020	25	-	-	-	-	-	-	-	-	-	-	-	-
Hafkin et al., 2017	78	-	-	-	-	-	-	-	-	-	-	-	-
Hewison et al., 2017	51	-	-	-	-	-	-	-	-	-	-	-	-
Kuksa et al., 2017	19	0	0	0	0	0	0	0	0	0	0	0	0
Madzgharashvili et al., 2021	8	0	-	-	-	-	-	-	-	-	-	-	-
Mohr-Holland et al., 2020	99	-	-	-	-	-	-	-	-	-	-	-	-
Mok et al., 2019	49	-	-	-	-	-	-	-	-	-	-	-	-
von Groote-Bidlingmaier et al., 2019	226	-	-	-	-	-	-	-	-	-	-	-	-
Solodovnikova et al., 2021	19	-	-	-	-	-	-	-	-	-	-	-	-
Kim et al., 2018	8	1	-	-	-	-	-	-	-	-	-	-	1
Kang et al., 2020	108	2	-	-	-	-	-	2	-	-	-	-	-
Das et al., 2020	11	1	-	-	-	-	-	-	-	-	-	-	-

QTcF: corrected QT with the Fredericia formula; DLM: delamanid

Table 6
Adverse effects in included studies (DLM and BDQ-containing regimens group)

Author	Number of patients	QTcF prolongation	Hepatic disorder/ Elevated liver enzyme	Renal failure/ Increased creatinine	Optic neuropathy/ Blurred vision	Ototoxicity/ Hearing loss	Hematological disorders (Anemia, thrombocytopenia, eosinophilia)	Gastrointestinal symptoms (Diarrhoea, vomiting, nausea, abdominal pain)	Peripheral neuropathy	Electrolyte disturbance	Arthralgia	Psychiatric disorder	Dermatologic symptoms
Auchynka et al., 2021	20	-	-	-	-	-	-	-	-	-	-	-	-
Das et al., 2021	70	5	1	-	-	-	-	3	-	-	-	-	-
Hafkin et al., 2019	84	-	-	-	-	-	-	-	-	-	-	-	-
Madzgharashvili et al., 2021	2	0	-	-	-	-	-	-	-	-	-	-	-
Dooley et al., 2021	20	-	-	-	-	-	-	-	-	-	-	-	-
Kwon et al., 2021	28	17	-	-	-	-	-	1	-	-	-	-	-
Das et al., 2020	12	1	-	-	-	-	-	-	-	-	-	-	-
Lee et al., 2020	74	23	-	1	-	-	-	4	-	-	-	-	-
Olayanju et al., 2020	40	-	-	-	-	-	-	-	-	-	-	-	-
Kim et al., 2018	11	2	-	-	-	-	-	-	-	-	-	-	-
Ferlazzo et al., 2018	28	4	-	1	-	-	-	1	1	-	-	2	-
Kang et al., 2020	67	-	-	-	-	-	-	3	-	-	-	-	-
Sarin et al., 2019	42	-	-	-	-	-	-	-	-	-	-	-	-
Pirmahmadzoda et al., 2021	11	-	-	-	-	-	-	-	-	-	-	-	-
Ghosh et al., 2021	147	3	-	-	-	-	-	-	-	-	-	-	-

QTcF: corrected QT with the Fredericia formula; DLM: delamanid; BDQ: bedaquiline

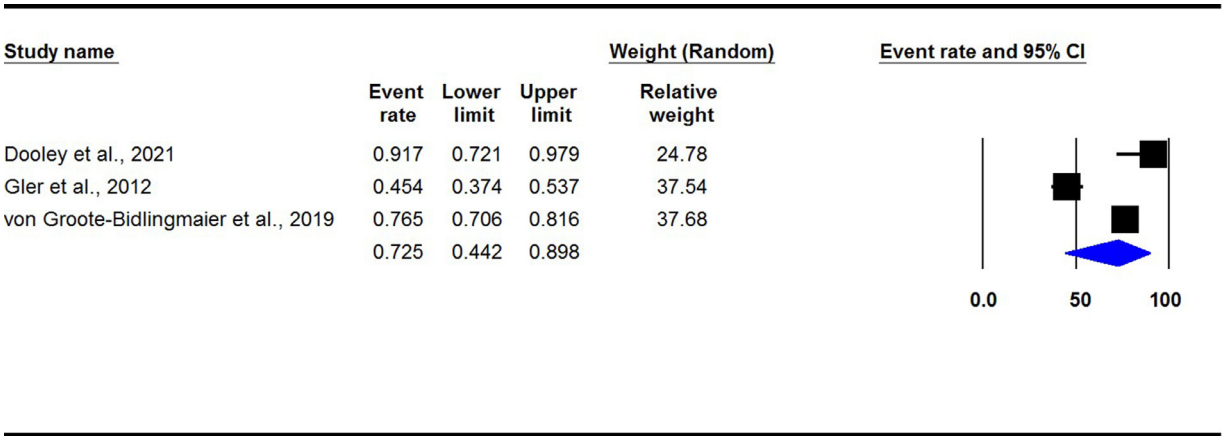

Figure 4. Treatment success rate in experimental studies. (DLM-containing regimens group)
DLM: delamanid.

Table 7
Pooled treatment success rate among subgroups of studies in DLM group

Subgroups	No. of study	No. of patients	Treatment success %(95 % CI)	Heterogeneityl2 (%)	Begg's testP-value
Type of study:					
Observational studiesExperimental studies	13 studies3 studies	591391	80.9 (72.6-87.2)72.5 (44.2-89.8)	7395	0.160.90
Age:					
≤40>40	8 studies5 studies	564195	74.2 (61.3-84)85.6 (79.9-89.9)	85.40.0	0.711.00
Sex:					
MaleFemale	3 studies3 studies	2315	80.7 (59.7-92.1)83.6 (56.5-95.2)	0.00.0	1.001.00
Children/adult:					
Children/adolescentAdult	2 studies14 studies	19963	89.4 (66.0-97.0)78.4 (69.3-85.4)	0.086.0	NA*0.45

* There must be at least three studies to run publication bias.DLM: delamanid; CI: confidence interval

Subgroup analysis

The treatment success rate in patients aged ≤40 and >40 in DLM containing regimens was 74.2% and 85.6%, respectively (Table 7), whereas in males and females was found to be 80.7% and 83.6%, respectively. The treatment success rate in children and adults was found to be 89.4% and 78.4%, respectively.

Discussion

Our study was aimed at evaluating efficacy/effectiveness and safety of DLM-containing regimens to manage MDR/RR-TB. The results of our study show that culture conversion and treatment success rates were high despite extensive drug resistance patterns. Overall, DLM-containing regimens achieved a treatment success exceeding 80%, being lower when both DLM and BDQ were prescribed. Unfortunately, the details provided in the different studies on the resistance profile and, specifically, on BDQ resistance did not allow to perform additional analyses to determine why outcomes in the latter group was worse.

In observational studies on BDQ the results of 3,536 patients were analyzed (Hatami et al., 2022), with a success rate of 74.7%, while 591 patients undergoing treatment with DLM achieved a success rate of 80.9%. In experimental studies on BDQ, 441 patients achieved a success rate of 86.1%, whereas the 391 patients treated with DLM had a success rate of 72.5%.

The success rate on the 292 patients undergoing combined treatment with BDQ and DLM was 73.9%, with patients likely to harbor strains of *Mycobacterium tuberculosis* with a more challenging drug resistance pattern (Pontali et al., 2018).

Few adverse events were reported overall, especially in the studies containing DLM without BDQ. Although under-reporting of adverse events is likely, they seemed to be rare.

A parallel recent systematic review and meta-analysis conducted on BDQ (Hatami et al., 2022) allows to compare effectiveness and safety with those found for DLM.

Overall, more studies were available on BDQ (1,946 identified and 29 selected) (Hatami et al., 2022) than for DLM (351 and 25, respectively). DLM-containing regimens achieved higher success rate than BDQ-containing ones in observational studies and lower in experimental studies.

In terms of adverse events, in DLM-containing regimen a lower proportion of QTcF prolongation was observed (2.4%) than in BDQ-containing regimens (10.4%), as well as a lower frequency of gastro-intestinal adverse effects (1.8% vs. 15.3%). In BDQ-containing regimens peripheral neuropathy (13.8%) and hematological disorders (13.6%) were also noted (Pontali et al., 2018), but there were no such reports for DLM-containing regimens.

More adverse events were identified among the 225 patients undergoing combined treatment with BDQ and DLM: QTcF prolongation 12.8%, psychiatric disorders 7.1%, gastrointestinal effects 4.5%, peripheral neuropathy 3.5%, renal failure/increased creatinine 2%, and hepatic disorders/elevated liver enzyme 1.4%. The authors of the different studies reporting combined BDQ and DLM regimens were unable to assign the adverse events to a specific drug.

No evidence of publications bias was identified in our study as well as in the BDQ study (Pontali et al., 2018).

Several studies not reporting both effectiveness and safety of DLM have been published, supporting the results of our systematic review and meta-analysis. An early bactericidal activity (EBA) trial demonstrated that DLM in monotherapy was able to lower Colony Forming Units from baseline over 14 days of daily treatment (Diacon et al., 2011). DLM added to an optimized background regimen (OBR) in adult MDR-TB patients increased sputum culture conversion rates after 2 months (phase IIb, randomized, placebo-controlled, multinational clinical trial) (Gler et al., 2012). Other phase IIb trials demonstrated that DLM-containing

regimens improved treatment outcomes and reduced mortality (Skripconoka et al., 2013; Wells et al., 2015). Conversely, the results of another trial included in our analysis, (von Groote-Bidlingmaier et al., 2019) in which the reduction in median time to sputum culture conversion over 6 months was not significant in the DLM arm, although the strong OBR with placebo was highly effective; possibly the study was not powered sufficiently to see a discernible difference with a very effective OBR and placebo arm.

A large prospective study by Global Tuberculosis Network (GTN) (Koirala et al., 2021), not included in this meta-analysis (no separate outcomes for patients treated with DLM only), reported interesting results on regimens including BDQ and/or DLM. It included 883 consecutive patients treated with BDQ and/or DLM from 52 centres in 29 countries. Of the 477 patients treated with BDQ and/or DLM and completing treatment, 344 (72.1%) achieved treatment success. Of 383 patients treated with BDQ but not DLM, 284 (74.2%) achieved treatment success, while 25 (6.5%) died, 11 (2.9%) failed and 63 (16.5%) were lost to follow-up. In this cohort the drug-resistance pattern of the patients was severe (>30% with XDR-TB; median number of resistant drugs and 6 (4–8) among patients with a final outcome). The small number of paediatric patients involved prevented the authors to conduct specific analyses.

In terms of safety, the proportion of serious adverse events was low in the first trials (Diacon et al., 2011; Skripconoka et al., 2013), and the few patients with prolonged QTcF interval had no clinical cardiac events (Skripconoka et al., 2013).

Evidence in children is modest. In a study that enrolled 16 children treated with DLM on compassionate basis, no adverse event was reported in fifteen children, while one child treated with a combination of DLM, capreomycin, ethionamide, cycloserine, clofazimine, imipenem, amoxicillin/clavulanate, and pyrazinamide experienced vomiting, renal impairment, electrolyte disturbances, and prolonged QTcF (Tadolini et al., 2016). In a recent study (Sasaki et al., 2021) the cardiac safety of DLM administered according to the recommended dosing was further emphasized. Other case series confirmed the safety of DLM in the pediatric age group (Esposito et al., 2014; Hewison et al., 2017; Kuksa et al., 2017; Mohr et al., 2018; Shah et al., 2020).

Our systematic review and meta-analysis updates the available evidence on DLM efficacy/effectiveness and safety, showing the drug has a promising profile. DLM is presently included among WHO Group C drugs, mainly because of previous lack of data and its non-inclusion in the large individual data meta-analysis which informed the new WHO classification of the drugs to manage MDR-TB (Ahmad et al., 2018). Similarly, the priority of DLM is rather low in the ATS/CDC/ERS/IDSA guidelines (Nahid et al., 2019).

Our study has some limitations as it does not evaluate adherence to treatment regimens containing DLM (an important outcome determinant) and different patient characteristics exist across studies.

Although a population pharmacokinetic analysis of available trial data suggests that DLM exposure is not affected by age, mild or moderate renal impairment, HIV, or CYP3A4 inhibitors or inducers (Wang et al., 2020) subgroup analyses are needed to better understand the role played by some confounders (e.g., levels of drug resistance, setting and adherence)

Furthermore, another confounding factor could be the OBR prescribed to the recruited patients. Its characteristics are based on patient's needs (e.g., DST results, available drugs) and could have varied following updates of international (e.g., WHO and international scientific societies) and national guidelines. Missing information on the details on which the OBRs were designed can hinder the between-study comparison, increasing the risk of over- or under-estimation of the efficacy/effectiveness and safety profiles of the regimens.

In conclusion, the results of this study and the direct comparison with a recent study focused on BDQ (Hatami et al, 2022) suggest that DLM-containing regimens are effective and safe to treat MDR-TB patients.

Conflict of interest

The authors declare no conflicts of interest.

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Ethical approval

Not applicable.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.02.043.

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