

BMJ Open Impacts of social support on the treatment outcomes of drug-resistant tuberculosis: a systematic review and meta-analysis

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ABSTRACT

Objective To assess the effectiveness of social support on treatment success promotion or lost to follow-up (LTFU) reduction for patients with drug-resistant tuberculosis (DR-TB).

Design We searched Pubmed, Web of Science, Embase, Scopus and Medline databases until 18 June 2020 for interventional or mixed-method studies which reported social support and treatment outcomes of DR-TB patients. Two independent reviewers extracted data and disagreements were resolved by consensus with a third reviewer. Random-effects meta-analysis was performed to calculate the OR and 95% CI for the effects of social support on the improvement of treatment outcomes and the heterogeneity and risk of bias were assessed.

Setting Low-income and middle-income countries.

Participants DR-TB patients.

Outcomes Treatment success is defined as the combination of the cured and treatment completion, and LTFU is measured as treatment being interrupted for two consecutive months or more.

Results Among 173 articles selected for full-text review, 162 were excluded through independent review ($\kappa=0.87$) and 10 studies enrolling 1621 DR-TB patients in eight countries were included for qualitative analysis. In these studies, the most frequently introduced social support was material support (10 studies), followed by informational (eight studies), emotional (seven studies) and companionship support (four studies). Seven studies that reported treatment outcomes in both intervention arm and control arm are qualified for meta-analysis. An encouraging improvement on treatment success rate (OR: 2.58; 95% CI: 1.80 to 3.69) was found when material support was integrated into social support packages and no heterogeneity was observed (I^2 of 0%, Q test $p=0.72$). Reduction on LTFU rate (OR: 0.17; 95% CI: 0.05 to 0.55) was also noted when material support was available but substantial heterogeneity was found (I^2 of 80%, Q test $p=0.002$).

Conclusion Material support appeared feasible and effective to improve treatment success for DR-TB patients combined with other social support interventions.

PROSPERO registration number CRD42019140824.

Strengths and limitations of this study

- It is the first systematic review and meta-analysis revealing the positive effects of integrated social support directly on the final treatment outcomes for drug-resistant tuberculosis (DR-TB) patients.
- Social support interventions are categorised and fully described in this study, providing reasonable strategies for their further integration into DR-TB control framework.
- The major concern is lacking of studies which did not apply material support in meta-analysis.
- The variation in participants' characteristics and social support and limited quantity of relevant literature were also considered as limitations.

INTRODUCTION

The epidemic of drug-resistant tuberculosis (DR-TB) remains a major public health threat in many countries, and it has been one of the main obstacles in the success of achieving 2030 targets set in the End TB Strategy. Globally, DR-TB commonly contains three types of resistance, which are rifampicin resistance (RR-TB, resistance to rifampicin with or without resistance to other anti-TB drugs), multidrug resistance (MDR-TB, resistance to at least both isoniazid and rifampicin) and extensive drug resistance (XDR-TB, resistance to any fluoroquinolone and at least one of three second-line injectable drugs, in addition to MDR-TB).¹ Between 2016 and 2017, the number of reported MDR-TB and RR-TB cases increased by more than 30% in six of the 30 high MDR-TB burden countries.² Some studies suggested that recently transmission of MDR-strain and XDR-strain has become the dominant spread pattern, rather than the emergence of drug resistance caused by inappropriate antibiotic

use,^{3 4} which highlighted the importance of DR-TB prevention and control. As agreed by researchers from different countries,^{5 6} controlling the epidemic of DR-TB plays a vitally significant role in global TB control and public health.

WHO has published guidelines of National Tuberculosis Control Programme (NTP) to promote the management of TB and DR-TB and it has been widely applied to many countries.⁷⁻¹¹ Four-level (central, regional, district and peripheral) organisation structure is suggested to support the implementation of Directly Observed Therapy (DOT), diagnosis and treatment network.⁹ However, the total number of MDR-TB patients, still rose by approximately 20% annually from 2009 to 2017^{1 12} and the effects of DOT were also unsatisfactory to some extent.^{13 14} Control of DR-TB still encounters many intricate challenges. First, psychosocial challenges that DR-TB patients face, for example, stigma and psychological distress, have been reported widely, and cause poor adherence and treatment outcomes.¹⁵⁻¹⁷ Thus, patients with MDR-TB revealed a strong appeal of social support.^{18 19} Unlike physical interventions, psychosocial environment could affect the effectiveness of behavioural interventions.⁴ Second, the median cost for MDR-TB was US\$7141 in 2017, which was almost six times higher than drug-susceptible TB.² The direct and indirect costs for DR-TB treatment are unaffordable for many patients, but social protection has been proven to be effective to alleviate catastrophic expenses outpatient-based care with social support (such as food packages and transport vouchers) is more affordable and cost-effective than hospitalisation.²⁰⁻²² Although social support seems feasible to be integrated into NTP, the effectiveness of social support on the improvement of DR-TB treatment outcomes was rarely reported.

A systematic review done by Thomas discussed the neurological side-effects (depression, convulsion and psychosis), emotional insecurity, stigma and reshaped psychological state, but the effects of social support interventions were unclear.¹⁵ Social support was mentioned as a part of effective strategies to reduce treatment default by Toczek and Weaver,^{23 24} while relevant information about the implementation of strategies, such as the duration, content and provider, were poorly documented. A review advanced by van Hoorn revealed the effects of psycho-emotional and social-economic support, but the research focused on drug-susceptible TB patients, instead of DR-TB patients who suffer from longer medication period, more expensive medication and severer side-effects.²⁵ In this systematic review, we sought to identify the effects of social support on DR-TB patients. We explored the direct impact of social support on final treatment outcomes, rather than on indirect treatment adherence or self-reported benefits, defined social support based strictly on the WHO DR-TB guideline,²⁶ and revealed how

these social support interventions are implemented in detail.

METHODS

Study design and search strategies

We conducted a systematic review and meta-analysis to summarise interventional studies. This systematic review was arranged in accordance with the Cochrane Handbook for Systematic Reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.^{27 28}

We searched PubMed, Web of Science, Medline, Embase and Scopus to identify relevant articles published before 19 June 2020. The combination of DR-TB (drug-resistant tuberculosis, multidrug-resistant tuberculosis, rifampicin-resistant tuberculosis, DR-TB, MDR-TB, RR-TB and so on) and social support (informational, emotional, companionship and material support) was used as search term. Information support includes health education, counselling, DR-TB brochures and so on; emotional support includes all kinds of psychological interventions and encouragement; material support refers to different kinds of sources to deal with patients' financial burden (eg, travel reimbursement, free treatment and nutrition provision) and companionship support could be the help for patients to participate in a social network (eg, peer counselling). Then, we added other relevant studies from systematic reviews of social support for DR-TB patients.^{15 24 25 29}

Definitions of social support and treatment outcomes

We identified social support by a commonly used framework advanced by the WHO,²⁶ which includes four distinct subtypes: (1) informational support: including training, education and counselling; (2) emotional support: refers to all expressions of care that strengthen self-esteem through empathy, trust, encouragement and care; (3) companionship support: defined as the help that makes a person feel that he or she belongs to the social network, and that he or she can rely on it for certain needs and (4) material support: all commodities, including financial subsidies.

According to WHO guidelines, treatment outcomes for RR-TB/MDR-TB/XDR-TB consist of cured, treatment completed, treatment failed, died, lost to follow-up (LTFU), not evaluated and treatment success.¹ Treatment success is the combination of cured and treatment completed. 'Cured' refers to treatment completed without evidence of failure and three or more consecutive cultures taken at least 30 days apart showing negative after the intensive phase, while 'treatment completion' means treatment completed without evidence of failure but no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase. 'LTFU' indicates that the treatment was interrupted for

Table 1 Risk of bias assessment on social support interventions to improve DR-TB treatment outcomes

Study	Selection bias	Design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Global rating
Li <i>et al</i> ¹¹	Strong	Moderate	Strong	Moderate	Moderate	Strong	Moderate
Yin <i>et al</i> ¹⁹	Moderate	Moderate	Strong	Moderate	Moderate	Moderate	Moderate
Luyirika <i>et al</i> ³⁸	Moderate	Weak	Weak	Weak	Moderate	Strong	Weak
Oyieng'o <i>et al</i> ³⁹	Moderate	Moderate	Weak	Moderate	Strong	Strong	Moderate
Taneja <i>et al</i> ⁴⁰	Strong	Moderate	Moderate	Moderate	Moderate	Strong	Moderate
Baral <i>et al</i> ⁴¹	Moderate	Moderate	Strong	Moderate	Moderate	Strong	Moderate
Brust <i>et al</i> ⁴²	Strong	Moderate	Weak	Moderate	Moderate	Strong	Moderate
Acha <i>et al</i> ⁴³	Strong	Moderate	Weak	Moderate	Moderate	Strong	Moderate
Mohr <i>et al</i> ⁴⁴	Moderate	Moderate	Strong	Weak	Moderate	Strong	Moderate
Sripad <i>et al</i> ⁴⁵	Strong	Moderate	Moderate	Moderate	Moderate	Strong	Moderate
Bhatt <i>et al</i> ⁴⁶	Strong	Moderate	Strong	Moderate	Moderate	Strong	Moderate

DR-TB, drug-resistant tuberculosis.

two consecutive months or more. In this review, treatment success and LTFU were invoked as indicators of treatment outcomes as they were most frequently reported.

Inclusion criteria

Studies were included if they met all the following criteria. (1) Study designs: interventional (randomised or non-randomised controlled trials (RCTs), quasi-experiment, before-and-after studies, prospective and retrospective cohorts) or mixed-method studies. (2) Categories of participants: DR-TB (RR-TB, MDR-TB or XDR-TB) patients were identified if they met any of the following three standards: culture-confirmed DR-TB with at least first-line drug susceptibility testing; or patients registered in DR-TB programmes or centres which meant they had previously been diagnosed; or patients were adopting DR-TB medication regimens. (3) Interventions: in addition to the supports from NTP, any one or more of the four types of social support (informational, emotional, companionship and material) were provided to patients. (4) Comparison: studies with comparison group were included for meta-analysis if patients in control arm were not provided with any type of social support other than supports from NTP (only included for meta-analysis). (5) Treatment outcomes: treatment success or LTFU.

Exclusion criteria

The following studies were excluded. (1) Studies only reporting DOT as social support intervention were excluded because it was not the priority of our interest and had been previously studied by other researchers.^{30 31} (2) Studies only conducted in short intensive phase were excluded because during hospitalisation (intensive phase), the support from physicians and nurses may confound the impacts of social support, and treatment success or LTFU of DR-TB

normally could not be observed in short intensive phase. (3) When the intervention duration was less than 6 months, studies were excluded to avoid bias towards final treatment outcomes. (4) Studies conducted in the same location during the same period were considered as potential duplicates and it was verified by contacting authors for clarification.

Data extraction

Two reviewers conducted the literature searching independently and subsequently consolidated studies together. Then they screened the titles and abstracts to extract data. For the controversial studies, the research members discussed with the third independent reviewer to reach an agreement. Endnote X8 was used to cite and manage all the data. In addition, extracted studies were recorded by a predesigned extracting Microsoft Excel form to collect information of country, duration, location, methods, number of participants, DOT involved, interventions and outcomes, and verified by a second reviewer. When study findings were uncertain or missing, we contacted the authors for details.

Methodological quality assessment

Due to the lack of RCTs, we used the Effective Public Health Practice Project,^{32 33} instead of the Cochrane Collaboration's Tool, to independently assess the risk of bias, based on selection bias (the representative of target population), design (study design), confounders (control of confounders), blinding (blinding of outcome assessors and participants), data collection methods (the validity and reliability of data collection tools), withdrawals and dropouts (follow-up rate). Specifically, global rating was assessed based on the principle that strong evidence refers to those with no weak ratings and at least four strong ratings,

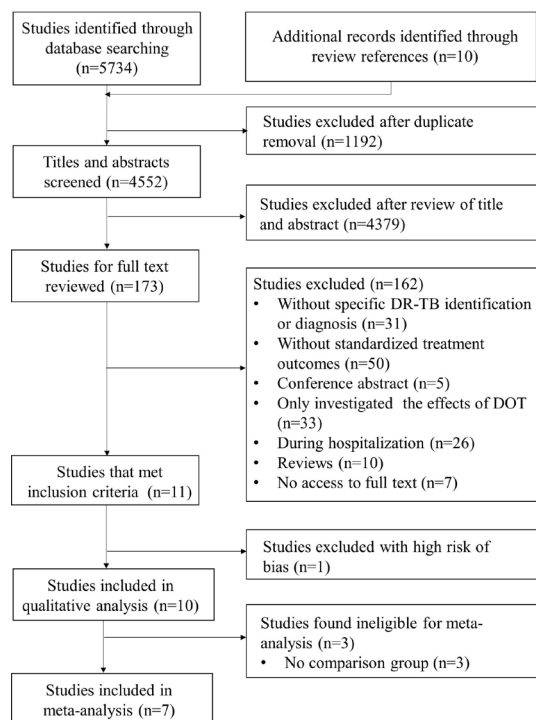


Figure 1 Flowchart showing the selection of studies on social support interventions to improve DR-TB treatment outcomes. DOT, Directly Observed Therapy; DR-TB, drug-resistant tuberculosis.

moderate evidence refers to those with less than four strong ratings and one weak rating and those with two or more weak ratings are considered weak.

Statistical analysis

We introduced a narrative synthesis to demonstrate the characteristics of all included studies. For seven studies that set comparison groups, meta-analysis was applied to describe the impacts of social support by forest plots. Mantel-Haenszel model and random-effects method were used to obtain the ORs and 95% CIs for the unadjusted treatment success rates and LTFU rates. Subgroup analysis was performed to adjust the effects of material support; we assumed material support was essential in social support packages because treatment for MDR-TB or XDR-TB was a catastrophic expenditure, costing up to 25 times as much as for drug-susceptible TB^{34 35} and many reviews revealed the effectiveness and importance of monetary incentives.^{23 36 37}

Between-group difference was tested by Q statistics and p-value. A p-value less than 0.05 indicated a significant difference. Heterogeneity across studies under each category was assessed by I^2 statistic and p-value; an I^2 was greater than 50% with $p < 0.05$ indicated the existence of significant heterogeneity across studies. Resources of the heterogeneity, including HIV prevalence, the application of DOT and the classification of DR-TB were not analysed, as there was not sufficient information available to complete a meta-regression model that used any of these variables. Sensitivity analyses were completed by

excluding one primary study at a time and assessing the new pooled treatment success rate and LTFU rate. Publication bias was not assessed because only seven studies were available. All meta-analyses were carried out by using Review Manager V.5.3 (Cochrane Collaboration, Copenhagen, Denmark).

Patient and public involvement

No patient involved.

RESULTS

In total, we identified 5734 studies from e-journal databases, among which 173 records were identified as potentially relevant by abstract screening, and 162 records were excluded through independent full-text review ($\kappa = 0.87$, high agreement). A total of 11 studies met the inclusion criteria and corresponding researchers were contacted to request clarification if needed. The quality of each study is presented in table 1 and one case study was excluded due to the weak global rating, as there was only one participant and the control of confounders and the blinding were missed.³⁸ Therefore, 10 studies with 1621 DR-TB patients were finally included in the analysis. Figure 1 shows the selection process.

Characteristics of the included studies

Among the 10 studies published between 2007 and 2019, five were conducted in Asia (China, India and Nepal), three in Africa (South Africa and Kenya) and two in South America (Ecuador and Peru). Six studies^{19 39–43} focused on MDR-TB, one⁴⁴ only involved RR-TB patients, three^{11 45 46} involved all types of DR-TB.⁴² Four studies^{11 19 42 46} clearly gave information about the arrangement of drug susceptibility tests, and three other studies clarified the DR-TB medication intake^{39 43 44} and the rest recruited patients enrolled in TB programmes: NTP in Ecuador,⁴⁵ China,¹¹ Nepal⁴¹ and Revised NTP in India.^{40 46} Seven studies^{11 19 39 42–45} performed DOT, two studies^{41 46} mentioned patients were chosen from DOTS centres but did not illustrate if DOT was provided for full course of treatment and one study⁴⁰ did not apply DOT for the social support group (table 2). Final treatment outcomes of DR-TB patients were shown in table 3.

Social support interventions

While eight of the 10 studies implemented integrated social support interventions,^{19 39–44 46} two other studies only provided single intervention in form of monetary incentives.^{11 45} Table 4 shows the details of social support strategies. Among the four subcategories of social support interventions, the most frequently introduced intervention was material support as 10 studies implemented it, followed by informational support (eight studies), emotional support (seven studies) and companionship support (four studies).

Material support included monetary incentives and basic necessities. The monetary incentives was mentioned

Table 2 Studies on social support interventions to improve treatment outcome for DR-TB

Study	Study design	Region	Economies*	Research objects	% Male HIV		Sample size		Interventions			Social support		
					Male	HIV	(Intervention/total)	DOT	Intervention arm	Comparison arm	Material support	Emotional support	Informational support	Companion-ship support
Li <i>et al</i> ¹¹	Before-and-after Study	China	UMIC	DR-TB	72	0‡	172/198	+	NTP+SS	NTP	+	-	-	-
Yin <i>et al</i> ¹⁹	Retrospective Cohort Study	China	UMIC	MDR-TB	70	0	118/218	+	SS	NI	+	-	+	-
Oyieng'o <i>et al</i> ³⁹	Prospective Cohort Study	Kenya	LMIC	MDR-TB	50	50	8/8	+	SS	-	+	+	+	+
Taneja <i>et al</i> ⁴⁰	Quasi-experimental Study	India	LMIC	MDR-TB	59	NR	32/70	-	NTP+SS	NTP	+	+	+	-
Baral <i>et al</i> ⁴¹	Mixed-Method Study†	Nepal	LIC	MDR-TB	65	NR	75/156	NR	NTP+SS	NTP	+	-	+	-
Brust <i>et al</i> ⁴²	Retrospective Cohort	South Africa	UMIC	MDR-TB	38	83	80/80	+	SS	-	+	+	+	+
Acha <i>et al</i> ⁴³	Prospective Cohort Study	Peru	UMIC	MDR-TB	52	NR	285/285	+	SS	-	+	+	+	+
Mohr <i>et al</i> ⁴⁴	Prospective Cohort Study	South Africa	UMIC	RR-TB	55	72	174/292	+	SS	NI	-	+	+	+
Sripad <i>et al</i> ⁴⁵	Non-randomised Trial	Ecuador	UMCI	DR-TB	52	6	105/191	+	NTP+SS	NTP	+	-	-	-
Bhatt <i>et al</i> ⁴⁶	Retrospective Cohort Study	India	LMIC	DR-TB	54	2‡	60/123	NR	NTP+SS	NTP	+	+	+	-

*World Bank list of economies (June 2019).

†Formative qualitative study, pilot intervention study and explanatory qualitative study.

‡Self-report.

DOT, Directly Observed Therapy; DR-TB, drug-resistant tuberculosis; LIC, low-income country; LMIC, lower-middle-income country; MDR-TB, multidrug resistance tuberculosis; NI, no intervention was applied in comparison arm to improve patients' treatment outcomes; NR, not report; NTP, National Tuberculosis Programme; RR-TB, rifampicin resistance tuberculosis; SS, social support; UMIC, upper-middle-income country.

**Table 3** Treatment outcomes of DR-TB patients for social support interventions

Study	Treatment success				Loss to follow-up			
	Intervention arm		Comparison arm		Intervention group		Comparison group	
	Treatment success	Total sample	Treatment success	Total sample	LTFU	Total sample	LTFU	Total sample
Li <i>et al</i> ¹¹	–	–	–	–	3	172	12	26
Yin <i>et al</i> ¹⁹	92	118	52	100	–	–	–	–
Oyeng'o <i>et al</i> ³⁹	6	8	–	–	–	–	–	–
Taneja <i>et al</i> ⁴⁰	20	32	14	38	–	–	–	–
Baral <i>et al</i> ⁴¹	60	75	54	81	8	75	15	81
Brust <i>et al</i> ⁴²	59	80	–	–	4	80	–	–
Acha <i>et al</i> ⁴³	171	285	–	–	10	285	–	–
Mohr <i>et al</i> ⁴⁴	99	174	66	118	31	174	25	118
Sripad <i>et al</i> ⁴⁵	–	–	–	–	10	105	23	86
Bhatt <i>et al</i> ⁴⁶	39	60	29	63	3	60	15	63

DR-TB, drug-resistant tuberculosis; LTFU, lost to follow-up.

in nine studies, commonly in form of travel reimbursement^{11 19 39 41 42 44 46} and nutrition bonus;^{39 40 46} and monetary incentives were mostly supplied on a monthly basis, from US\$15.5¹⁹ to US\$240.⁴⁵ One study offered monthly bonus as a reward to stimulate patients if they took medication at least 26 days per month.⁴⁵ Free treatment⁴⁵ and service packages which covered up to 90% of the treatment costs were also mentioned to alleviate the heavy financial burden brought by the medication regimen. Food was distributed to DR-TB patients as the main necessities,^{39 40 46} for example, eggs, grains, milk and cooking oil.

Informational consultations were held regularly in the clinic or at patients' home to assist patients in coping with the complications or adverse effects of medicine and provide health education.^{19 40–44 46} The counsellors could also persuade patients to keep taking medication,^{19 40 44} review the issue pillbox⁴⁴ and remind medicine renewal.¹⁹

Emotional support was divided into home visit and psychological support to fuel patients' medical and psychological needs. It was delivered by trained healthcare workers such as nurses and community healthcare workers^{39 40 42 44 46} to motivate and inform patients and more importantly, to administer injection,^{39 42} oral medication intake,^{39 42} side effects monitor^{40 42} and physical and social assessment.^{40 44} Psychological support was applied in different methods, such as, mental and vocational rehabilitation,⁴⁰ psychological profile evaluation and supporters group sessions.⁴³

Companionship support was commonly provided in the form of support from family treatment supporter or social groups that held various activities to meet patients' social needs and rebuilt patients' confidence to recover. Patients' family members, relatives or friends were arranged to be treatment supporters and supervised the medication intake.^{39 42 44} Group activities, including

outdoor exercises (excursions) and indoor celebrations for treatment completion, patients' birthdays and international TB days were organised.⁴³

Meta-analysis

Seven studies with control arm were included in the meta-analysis, enrolling a total of 1248 DR-TB patients. Data from five studies^{19 40 41 44 46} were synthesised to conduct meta-analysis regarding treatment success rate (figure 2), and five studies^{11 41 44–46} to conduct LTFU rate meta-analysis (figure 3).

We performed stratified analysis according to whether material support was involved or not. An encouraging improvement on treatment success rate (OR: 2.58; 95% CI: 1.80 to 3.69) was found as material support was integrated into social support packages, and no heterogeneity was observed (I^2 of 0%, Q test $p=0.72$). Sensitivity analysis for treatment success meta-analysis did not modify the heterogeneity and effect size when studies were dismissed from the analysis one by one. Reduction on LTFU rate (OR: 0.17; 95% CI: 0.05 to 0.55) was also noted when material support was available. However, substantial heterogeneity was found (I^2 of 80%, Q test $p=0.002$); we performed sensitivity analysis and found that omitting one study¹⁰ would remove heterogeneity (I^2 of 6%, $p=0.35$) (data not shown). For patients not receiving material support, there were no significant differences in treatment success rates (OR: 1.04; 95% CI: 0.65 to 1.67) and LTFU rates (OR: 0.81; 95% CI: 0.45 to 1.45) compared with the control group.

DISCUSSION

The findings of this review are consistent with WHO's suggestions that treatment adherence among TB patients could be influenced by factors at individual, economic, health system and social levels, and that most if not all the factors associated

Table 4 Types of social support interventions to improve treatment outcome for DR-TB

Study	Material support	Emotional support	Informational support	Companionship support
Li <i>et al</i> ¹¹	Monetary incentives 1. US\$15.5 cash bonus for transportation and nutritional supplements 2. Out-of-pocket payment reduction to 10% of the charge for the treatment services by government insurance funding and project subsidies			1. Community care workers (CCWs) identified a treatment supporter for the patients
Yin <i>et al</i> ¹⁹	Commodities 1. US\$10 transport reimbursement per month 2. US\$10 nutrition support per month		1. Reminding medications renewal 2. Methods to cope with adverse events 3. The importance of adherence	
Oyieng'o <i>et al</i> ³⁹	Monetary incentives 1. Transport incentives Commodities 2. Food supply	Home visit 1. Nurses gave medication and injection administration at patients' home or the nearest healthcare facility at patients' will		1. A household member supervised the evening oral dose
Taneja <i>et al</i> ⁴⁰	Commodities 1. Eggs and nutritious multigrain provision	Home visit 1. Providers: trained homecare teams visit patients' home every fortnight in intensive phase and every 45 days during continuation phase 2. Content: physical assessment by body weight, side-effects of medicine and complications; motivating patients to take sputum microscopy Psychological support 1. Addressing emotional needs 2. Providing mental and vocational rehabilitation-getting readmission to schools or encouraging them to work	1. Disease information 2. Importance of treatment adherence 3. Health education about coughing etiquettes	
Baral <i>et al</i> ⁴¹	Monetary incentives 1. US\$28 per month to cover local transport, food and rental costs		1. Small group counselling led by trained public health nurses every 2–3 weeks	
Brust <i>et al</i> ⁴²	Monetary incentives 1. Travel reimbursement for patients and family members	Home visit 1. Weekly side effects monitor by nurses or community health workers (CHWs) 2. Intensive phase: daily home visit by a nurse and a driver (injection team) 3. Continuation phase: daily visits by CHWs for DOTs	1. Weekly education sessions about MDR-TB and HIV for patients and treatment supporters in clinic	1. Family members or friends to be treatment supporters
Acha <i>et al</i> ⁴³	Monetary incentives 1. Transportation subsidy	Psychological support 1. Support group sessions convened bimonthly with 8–12 patients, one or two cured patients and health workers (psychiatrists, nurses, social workers and health workers)	1. Family workshops to increase the awareness about the disease and treatment	1. Daytime recreational excursions several times a year 2. Symbolic celebrations for patients' birthdays, treatment completion, international TB day and other festivals

Continued

Table 4 Continued

Study	Material support	Emotional support	Informational support	Companionship support
Mohr <i>et al</i> ⁴⁴		Home visit 1. Social situation assessment by CCWs 2. Adherence barriers identification by CCWs	1. A Médecins Sans Frontières counsellor reviewed the medication, issued a pillbox and addressed the adherence barriers in clinic	
Sripad <i>et al</i> ⁴⁵	Monetary incentives 1. US\$240 bonus each month after taking medications at least 26 days per month for up to 24 months			
Bhatt <i>et al</i> ⁴⁶	Monetary incentives 1. Cash handouts 2. Reimbursement of conveyance Commodities 1. Nutritional supplements: milk, eggs, grains, pulses, jaggery, biscuits and cooking oil	1. Motivation	1. Patient-provider group meetings	

DOTs, Directly Observed Therapy; DR-TB, drug-resistant tuberculosis; MDR-TB, multidrug resistance tuberculosis.

with poor adherence can be addressed by providing social support to patients.²⁶ Most studies with social support showed significantly improved treatment success rates and the results were in line with other studies that mentioned the positive impacts of social support or part of its interventions on TB^{23 25 36 47 48} and DR-TB patients.^{18 24} It could be reasonable to integrate social support into traditional DOTs scheme as it emphasises giving due consideration to patients' values and needs which embodies the patient-centred care approach proposed by the WHO,²⁹ while the unified DOT constraint on patients conflicts with patients' autonomy, dignity and integrity.⁴⁹

As the effectiveness of material support in TB patients was widely reported,^{21 50–53} this systematic review found that material incentives could be a critical part of social support

for DR-TB patients and material support with other social support was an effective strategy for countries at different levels of economic development. The potential mechanism could be that integrated social support with material stimulations contributed to assisting DR-TB patients to better utilise other social support, and complete other social support better.⁴¹ Patients would be better motivated if they have access to more sufficient material support because they are mostly the poor people in both impoverished and wealthy countries. Although emotional, informational and companionship support were provided, the performance of self-administered treatment was poorer than standard care when DR-TB patients did not have access to material reimbursement;⁴⁴ perhaps, only when patients' heavy financial burden was alleviated to some extent could other social support have the

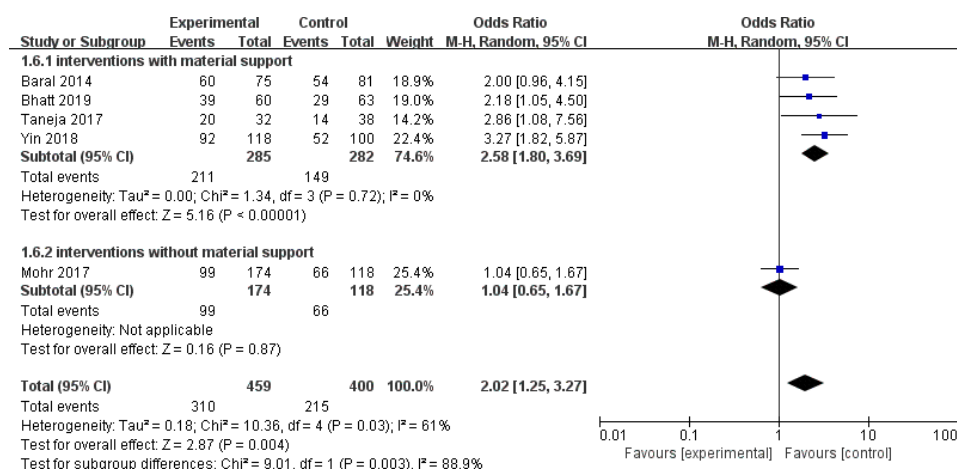


Figure 2 Likelihood of treatment success rate for social support interventions to improve DR-TB clinical outcomes. DR-TB, drug-resistant tuberculosis.

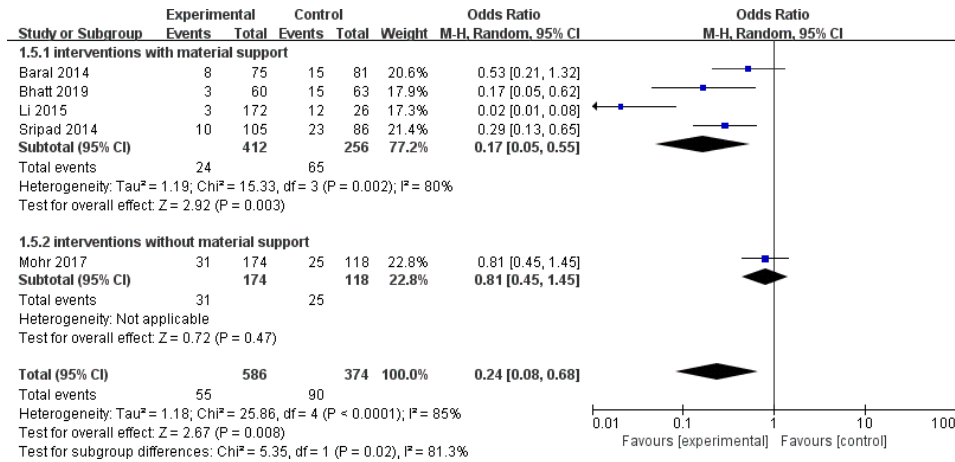


Figure 3 Likelihood of LTFU rate for social support interventions to improve DR-TB clinical outcomes. DR-TB, drug-resistant tuberculosis; LTFU, lost to follow-up.

potential to play their role in promoting patients to complete the treatment. Therefore, if possible, it was suggested that material support be prioritised when social support was arranged. However, caution should be taken when generalising the results, because potential sources of heterogeneity such as the coinfection of HIV were not evaluated.

We noticed that both small^{19 40 41} and large amount of subsidies^{11 45} for DR-TB patients can achieve greater improvement on treatment outcomes when other social supports were provided. Thus, how to utilise limited material support combined with emotional support, psychological support and companionship support and design a cost-effective social support package could be worth exploring in the future, especially for low-income and middle-income countries, many of whom mainly received TB treatment fund from international donors.⁵⁴ As funding programmes came to an end successively, the scale-up of DR-TB programmes in these countries may be impacted.⁵⁴ Apart from material support, other social support interventions would be indispensable to promote social protection for DR-TB patients. The benefits of emotional,^{55 56} informational^{57–59} and companionship support^{60–62} were widely reported in the patient management of diabetes, hypertension and HIV.

There are still some limitations in this systematic review. First, there was no RCT that met the inclusion criteria. Therefore, there is insufficient evidence to recommend the widespread integration of social support into DR-TB control framework. We call for adequately powered, good-quality, RCTs to evaluate the potential of social support for DR-TB patients. Second, in meta-analysis, there was only one study in the subgroup that did not apply material support. And there could also be heterogeneity in control group as the implementation of NTP could not be completely same in different countries. Therefore, I^2 could be bias in this small meta-analysis,⁶³ and more well-designed studies are needed to figure out the relationship between material support and other social support, namely emotional support, informational support and companionship support. Third, no sufficient information

available about HIV, DOT and socioeconomic status might also introduce heterogeneity, as these factors may relate to individual demand of social support. Finally, plausible heterogeneity was observed in LTFU meta-analysis, but we retained the study¹¹ that caused heterogeneity and did not exclude studies on the basis of heterogeneity only, as this might introduce bias.

We hope this study will provide important information for policy-makers that social support interventions have great potential to be effective methods to improve treatment outcomes for DR-TB patients. Limited material support combined with extra social support seems to be a cost-effective approach to promote treatment outcomes, especially for low-income and middle-income countries.

Contributors JY and QS conceptualised the research, provided guidance for SW to develop the protocol. JY and SW conducted the literature search, assessed potentially relevant studies for inclusion into the review, assessed the methodological quality of the included studies, independently extracted the data. SW performed the statistical analysis, drafted the manuscripts and wrote the final manuscript with the assistance of QS and JY. JY, QS and SW performed critical revisions of the manuscript. All authors reviewed the final manuscript.

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