Interventions to improve retention-in-care and treatment adherence among patients with drug-resistant tuberculosis: a systematic review

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To effectively improve retention rates in the treatment of drug-resistant tuberculosis, psychosocial support, provided through one-on-one counselling and home visits, should be provided throughout treatment, rather than only during the intensive phase http://ow.ly/Yiyf30lXxPW

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ABSTRACT The global loss to follow-up (LTFU) rate among drug-resistant tuberculosis (DR-TB) patients remains high at 15%. We conducted a systematic review to explore interventions to reduce LTFU during DR-TB treatment.

We searched for studies published between January 2000 and December 2017 that provided any form of psychosocial or material support for patients with DR-TB. We estimated point estimates and 95% confidence intervals of the proportion LTFU. We performed subgroup analyses and pooled estimates using an exact binomial likelihood approach.

We included 35 DR-TB cohorts from 25 studies, with a pooled proportion LTFU of 17 (12–23)%. Cohorts that received any form of psychosocial or material support had lower LTFU rates than those that received standard care. Psychosocial support throughout treatment, *via* counselling sessions or home visits, was associated with lower LTFU rates compared to when support was provided through a limited number of visits or not at all.

Our review suggests that psychosocial support should be provided throughout DR-TB treatment in order to reduce treatment LTFU. Future studies should explore the potential of providing self-administered therapy complemented with psychosocial support during the continuation phase.

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Introduction

Approximately 15% of 1.67 million annual global deaths due to tuberculosis (TB) are from rifampicin-resistant (RR) or multidrug-resistant (MDR)-TB, a strain resistant to at least rifampicin and isoniazid, the two most effective first-line anti-TB drugs [1]. Treating RR-/MDR-TB with second-line drugs is significantly costlier, more toxic, less effective and takes longer than treating drug-susceptible TB. Thus, rates of treatment noncompletion and interruption rates in RR-/MDR-TB are significantly higher. Approximately 15% of all RR-/MDR-TB patients are lost to follow-up from treatment, defined as interrupting treatment for >2 months, and only half are treated successfully [1].

Treatment nonadherence and interruption diminish the quality of life of people living with RR-/MDR-TB [2] and increase disease transmission. Developing effective interventions to improve adherence and retention in RR-/MDR-TB care is crucial. A systematic review [3] found that MDR-TB treatment strategies that used a more comprehensive approach, including financial and nutritional support, tended to have fewer losses to follow-up. However, the review, which included 75 studies, did not identify any nonobservational experimental trials for inclusion, and thus was subject to a high risk of confounding bias.

In light of increased global efforts to improve treatment and management for RR-/MDR-TB, we have synthesised new evidence, including observational and quasi-experimental studies published since the earlier systematic review, on the effectiveness of interventions in RR-/MDR-TB treatment that include various combinations of psychosocial, educational or material support. We describe and assess these interventions, their effectiveness in reducing losses to follow-up and improving adherence, and issues affecting their implementation.

Methods

This review is reported according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement [4], registered on the PROSPERO database (#CRD42016052854) and analysed according to MOOSE (meta-analyses of observational studies in epidemiology) guidelines [5].

Search strategy

We searched MEDLINE (PubMed), Embase and Embase Classic, Institute for Scientific Information Web of Science, Scopus, PsycINFO, Global Health, Social Work abstracts and the Cochrane Central Register of Controlled Trials, for studies published between 2000 (the year the World Health Organization (WHO) first launched DOTS-Plus pilot projects for treatment and management of MDR-TB [6]) and December 14, 2017. Our search strategy combined the following concepts: 1) tuberculosis; 2) adherence/compliance/default/drop-out; 3) concordance or contract; 4) linkage/referral/tracing; 5) reminder/monitor; 6) training/education/counselling; 7) motivational/behavioural/social support; 8) patient-centred care/retention; 9) health system/services intervention/programme/strategy; 10) cash/reimbursement/refund/reward/incentives; 11) dietary/nutritional supplement or food; 12) directly observed therapy (DOT); and 13) evaluation (online supplementary table S1 presents search details). No geographical or language restrictions were applied. We identified additional articles from reference lists of identified original articles and four recent systematic reviews on strategies for reducing MDR-TB patient losses to follow-up [3]; decentralised models of MDR-TB care [7]; community-based MDR-TB treatment [8]; and DOT in MDR-TB treatment [9].

Study screening and eligibility criteria

We included primary studies that 1) reported final treatment outcomes including losses to follow-up; and 2) examined a health services intervention targeting patients with RR-/MDR-TB that included at least some form of psychosocial, educational or material support. We defined each as any support provided to address psychological or social issues; any education or counselling provided pertaining to TB treatment; and any nutritional (*e.g.* food package or hot meals) or financial (*e.g.* reimbursement for treatment-related expenses and lost wages) support. Studies only examining surgical or drugs-related interventions were not included; other exclusion criteria included 1) <10 cases of RR-/MDR-TB; 2) only children (aged <18 years) included, due to their likely dependence on adult caregivers for adherence; 3) only interim outcomes reported (defined as outcomes, such as 6-month sputum conversion, that occurred before the planned end of treatment); 4) no details on drug susceptibility testing for at least rifampicin; or 5) no treatment with second-line drugs. One reviewer (SL) screened all titles and abstracts, and two independent reviewers (SL and AD) screened full reports of potentially relevant studies; discrepancies were resolved by discussion. We contacted authors of published abstracts and studies to obtain further information when necessary.

Types of outcome measures

Our primary outcome of interest was loss to follow-up, defined as treatment interruption for ⩾2 months [1]. Secondary outcomes included any measures of treatment adherence.

Data extraction and analysis

One reviewer (SL) extracted outcomes data, participant characteristics, details on study interventions and information necessary to assess study quality. We used the ROBINS-I tool [10] to assess the quality of cohort studies, and the Cochrane Risk of Bias Tool [11] for quasi-experimental trials. All extracted data were entered into Excel (Microsoft Corporation, Redmond, WA, USA).

We estimated unadjusted risk ratios and 95% confidence intervals to compare the proportions lost to follow-up in each arm/cohort in comparative studies. We conducted pooled analyses of all study cohorts to analyse the association between different types of support and losses to follow-up. We used the exact binomial likelihood approach, including a random effect to account for between-study heterogeneity, to estimate pooled proportions lost to follow-up and 95% confidence intervals. This approach produces less-biased estimates of the pooled effect and the between-study variability than normal approximation approaches [12]. We investigated heterogeneity using the I^2 statistic *via* subgroup analyses, and explored differences in geographic regions, extensively drug-resistant (XDR) status, HIV prevalence, previous treatment, treatment delivery methods and types of adherence support. Cochran's Q test was performed to test for subgroup differences. In our main analyses, we excluded patients who died or failed treatment (to exclude from the denominator patients who could not have experienced the outcome of lost to follow-up) and patients who were transferred out or not evaluated for final treatment outcomes. We conducted sensitivity analyses in which we considered patients who were transferred out or not evaluated, or those who died, as patients lost to follow-up. All statistical analyses were performed in R (www.r-project.org).

Results

Description of included studies

Our search strategy identified 5911 studies; of these we included 23 cohort studies and two quasi-experimental trials [13–37] in our analyses (figure 1). These 25 studies included 35 different cohorts of RR-/MDR-TB patients, distinguished by the different types and levels of adherence support. The types of treatment support provided to the included cohorts are summarised in table 1. All but three studies [20, 22, 37] were conducted in high-burden TB/MDR-TB countries [1].

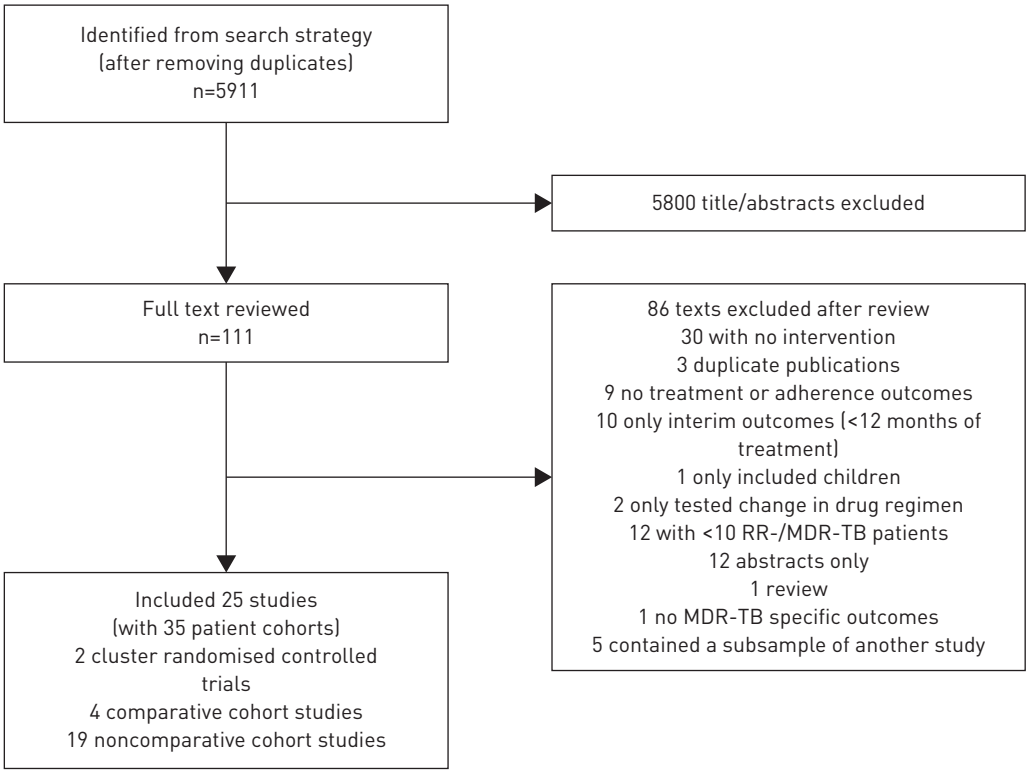

FIGURE 1 Flow diagram of literature search and study selection. RR: rifampicin-resistant; MDR: multidrug-resistant; TB: tuberculosis.

TABLE 1 Description of treatment support provided in included study cohorts

First author, year [ref.]	Subjects n	Country, study period	DOT frequency (intensive/ continuation phase)	DOT location	Individual counselling	Home visits available	Financial support offered	Food packages provided	Group counselling	Counselling/ education offered to family
Studies with two or more patient cohorts										
Baral, 2014 [13] (control)¶	33	Nepal, 2008	Daily/daily	Clinic	No	No	No	No	No	NS
Baral, 2014 [13] (arm 1)	33	Nepal, 2008	Daily/daily	Clinic	2–5 tailored sessions by trained nurse	No	No	No	Every 2–3 weeks	NS
Baral, 2014 [13] (arm 2)	42	Nepal, 2008	Daily/daily	Clinic	2–5 tailored sessions by trained nurse	No	NPR 2000 per month	No	Every 2–3 weeks	NS
Cox, 2014 [14] (control)¶	216	South Africa, 2005–2010	Daily/daily	In-patient, hospital/clinic	NS	No	No	No	No	No
Cox, 2014 [14] (intervention)¶	571	South Africa, 2005–2010	Daily/daily	Clinic	Routine counselling at start of treatment	No, but home assessment performed by CHW at start of treatment	No	No	Weekly peer support groups	NS
Huerga, 2017 [15] (Homa Bay)	28	Kenya, 2006–2012	Twice daily/twice daily	Clinic/home	Weekly to monthly counselling sessions, and as needed	Daily home visits by CHW	Rent and travel	No	No	NS
Huerga, 2017 [15] (Mathare)	70	Kenya, 2006–2012	Daily/daily	Clinic	Weekly to monthly counselling sessions, and as needed	No	Rent and travel expenses	Daily hot meal and monthly food basket	No	NS
Huerga, 2017 [15] (Nairobi)	71	Kenya, 2006–2012	Daily/daily	Clinic	Counselling by nurses on request by doctors	No	Rent and travel expenses	No	No	NS
Loveday, 2015 [16] (hospital)¶	813	South Africa, 2008–2010	Daily/none	In-patient, hospital	NS	No	No	No	No	NS
Loveday, 2015 [16] (site 1)	125	South Africa, 2008–2010	Daily/daily	Clinic/home	Weekly educational sessions	Daily home visits by CHW	Travel expenses	No	No	Yes
Loveday, 2015 [16] (sites 2 and 3)	350	South Africa, 2008–2010	Daily/none	Clinic/home	Unspecified frequency and duration	No	Travel expenses	No	No	Yes
Loveday, 2015 [16] (site 4)	261	South Africa, 2008–2010	Daily/none	Clinic	Unspecified frequency and duration	No	Travel expenses	No	No	Yes
Mohr, 2017 [17] (SAT)	244	South Africa, 2010–2014	Daily/none	Clinic	4 standardised sessions during intensive phase, and 1 at start of continuation phase	Weekly visits by CHW at the start of continuation phase, monthly after	No	No	No	NS
Mohr, 2017 [17] (SOC)	160	South Africa, 2010–2014	Daily/daily	Clinic	4 standardised sessions during intensive phase	No	No	No	No	NS
Taneja, 2017 [18] (control)	50	India, 2014	Thrice weekly/ none	Health facility (public/private/ NGO)	Thrice weekly during intensive phase, weekly thereafter	No	No	No	No	NS
Taneja, 2017 [18] (intervention)	50	India, 2014	Thrice weekly/ none	Health facility (public/private/ NGO)	Fortnightly at home and thrice weekly at clinic during intensive phase, weekly at clinic and every 45 days at home thereafter	Fortnightly visits from homecare team during intensive phase, and every 45 days thereafter	No	Daily provision of eggs and multigrain biscuits	No	Yes
Studies with a single patient cohort										
Alene, 2017 [19]	481	China, 2011–2014	Daily/daily	Clinic/home	Throughout initial hospitalisation (1–2 months)	None specified	No	No	No	Yes
Bastard, 2015 [20]	403	Armenia/ Georgia, 2002–2010	Daily/daily	Clinic/home	Routine sessions	Daily by health personnel or CHW	Travel expenses	Yes, unspecified	Yes, unspecified	NS
Cox, 2007 [21]	87	Uzbekistan, 2003–2005	Daily/daily	Clinic	Daily counselling, or as needed	No	Travel expenses	4 meals daily during hospitalisation; monthly food parcels after	No	NS
	25		Daily/none			No	No	No	No	NS

Continued

TABLE 1 Continued

First author, year [ref.]	Subjects n	Country, study period	DOT frequency (intensive/ continuation phase)	DOT location	Individual counselling	Home visits available	Financial support offered	Food packages provided	Group counselling	Counselling/ education offered to family
Escudero, 2006 [22]		Spain, 1998–2000		In-patient, hospital	Repeatedly during hospitalisation, monthly thereafter, by clinician/ psychologist					
Gelmanova, 2011 [23]	38	Russia, 2006–2008	Twice daily/twice daily	Hospital/Home	Daily counselling, or as needed, by nurses and psychologist	Twice daily by a team of two nurses	Travel passes	Daily food parcels	No	Yes
Isaakidis, 2011 [24]	35	India, 2007–2011	Twice daily/twice daily	Health facility (public/private/ NGO)	Monthly psychosocial follow-up	No	No	No	No	NS
Joseph, 2011 [25]	38	India, 2006–2007	Daily/daily	Health facility (public/private/ NGO)	Initial education by medical officer and social worker, followed by daily adherence advice from trained DOT provider	No	No	No	No	Yes
Keshavjee, 2008 [26]	608	Russia, 2000–2004	Daily/daily	In-patient, hospital; clinic/ rural health outpost	Daily counselling, or as needed	No	No	Monthly food packages and meals for adherent patients	No	NS
Kliiman, 2009 [27]	235	Estonia, 2003–2005	Daily/daily	In-patient, hospital; clinic	NS	No	Travel expenses	Yes, unspecified	No	NS
Meressa, 2015 [28]	612	Ethiopia, 2009–2014	Daily/daily	Clinic/home	Monthly counselling	Monthly visits by outpatient team	Rent and travel expenses	Monthly food baskets	No	Yes
Mitnick, 2003 [29]	75	Peru, 1996–1999	Daily/daily	Clinic/home	Daily counselling, or as needed	Daily by CHW	Travel expenses	Yes, unspecified	Weekly, bimonthly social support groups	Yes
Mitnick, 2008 [30]	650	Peru, 1999–2002	Daily/daily	Clinic/home	Daily counselling, or as needed	Daily by CHW	Travel expenses	Yes, unspecified	Weekly, bimonthly social support groups	Yes
Mohr, 2015 [31]	853	South Africa, 2008–2012	Daily/daily	Clinic	3 sessions in intensive phase and 1 in continuation phase	No	No	Yes, unspecified	Weekly peer-support groups	Yes
Satti, 2012 [32]	134	Lesotho, 2008–2009	Twice daily/twice daily	Home	Daily counselling, or as needed	Twice daily by trained CHW	Travel expenses	Monthly food packages	No	Yes
Shin, 2006 [33]	244	Russia, 1998–2000	Daily/daily	Clinic/rural health outpost	Daily counselling, or as needed	No	No	Monthly food packages/ meals for adherent patients	No	NS
Suárez, 2002 [34]	298	Peru, 1997–1999	Daily/daily	Clinic	NS	No	No	Weekly food parcels	NS	No
Thomas, 2007 [35]	66	India, 1999–2003	Thrice weekly/ thrice weekly	Health facility (public/private/ NGO)	Monthly sociological counselling	No	Monthly compensation for lost wages and travel expenses	No	No	NS
Vaghela, 2015 [36]	101	India, 2009–2010	Daily/daily	Health facility (public/private/ NGO)	Every 15 days during intensive phase, every 45 days thereafter	Visits by CHW every 15 days during intensive phase, every 45 days thereafter	None	Daily provision of eggs and multigrain biscuits	No	Yes
Yu, 2015 [37]	126	Taiwan, 2007–2009	Twice daily/twice daily	Clinic/home	Daily counselling, or as needed	Daily visits by medical team	Monthly income	No	No	Yes

DOT: directly observed therapy; SAT: self-administered therapy; SOC: standard of care; NS: none specified; NPR: Nepalese rupee; CHW: community health worker; NGO: nongovernmental organisation. #: studies with more than one arm/cohort (each arm shown separately); ¶: included in comparative analysis, but excluded from pooled analysis (see text for details).

Quality of studies

We did not exclude any study based on our assessment of quality (see online supplementary tables S4 and S5 for summaries and online supplementary tables S9 and S10 for details). All included studies used routinely collected data within local TB systems to ascertain treatment outcomes. Reporting of intervention details varied across studies, and it was difficult to evaluate the fidelity of intervention implementation and delivery in three studies [19, 20, 25]. Some studies did not provide important patient characteristics, such as any previous TB treatment (n=2), previous treatment with second-line drugs (n=13), XDR status (n=6) and HIV status (n=6); these studies were conducted in settings where <10% of TB patients are infected with HIV) (online supplementary table S2).

Five cohort studies included two or more separate cohort groups [14–17, 37], which allowed for comparison of outcomes. However, we excluded the control cohort in the study by Yu *et al.* [37] because we were not able to obtain adequate details on the care provided, nor the number of patients lost to follow-up. Of the remaining four studies, two compared patient cohorts before and after implementation of an intervention [14, 17] and two analysed concurrent cohort groups receiving different types of care [15, 16]. None of the studies provided adjusted estimates for the effect of intervention on loss to follow-up rates to account for potential confounding. All four studies were considered to have serious risks of biases due to confounding and two were considered to have moderate risks of bias due to missing data (patients who were transferred out or not evaluated for final treatment outcomes) (online supplementary table S4).

Two trials were included in our analysis [13, 18]. Both were cluster randomised trials where healthcare facilities were randomised to provide routine care or the study interventions. The overall risk of performance bias was high for both studies, because sites selected to implement the intervention were unblinded (online supplementary table S5). This could have a spillover effect and positively affect standard elements of care, thereby possibly overestimating the benefit of the intervention. However, sites providing routine care could have improved their care to compensate for the absence of an intervention, thereby underestimating the benefit. Furthermore, due to the small number of clusters randomised in each study, patient and site characteristics were not balanced between the intervention and control arms, which could lead to residual confounding. Baral *et al.* [13] adjusted for age and sex, but neither study accounted for clustering by site or other important baseline confounders.

Results of head-to-head comparisons

The results from comparative cohort studies and trials are shown in figure 2. The standard of care (study control) varied across the studies (see table 1 and online supplementary table S8 for details). Given the variation in the control groups as well as the types of support provided in the intervention groups, pooling of intervention effects was not possible. Patients who received some form of psychosocial, educational or material support, in addition to the standard care, were less likely to be lost to follow-up, with the exception of the study by Cox *et al.* [14]. In their pilot intervention study, Cox *et al.* [14] found no difference (risk ratio 1.04, 95% CI 0.83–1.32) between the control group, which received hospital-initiated MDR-TB treatment, and the intervention group, which received community-based, clinic-initiated

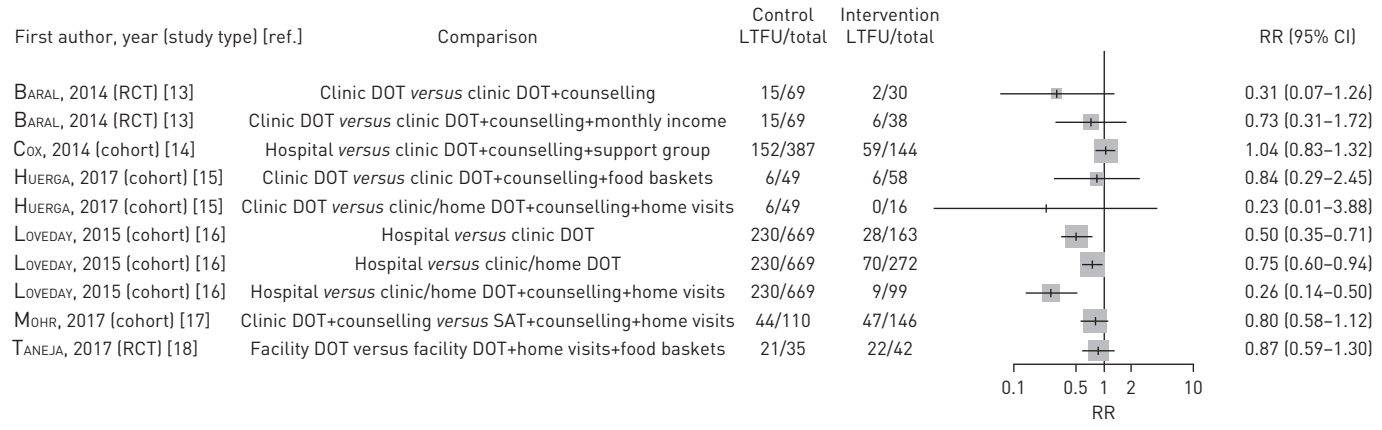

FIGURE 2 Forest plot of unadjusted risk ratios (RR) comparing proportions lost to follow-up (LTFU) between control and intervention arms in comparative studies (two or more patient cohorts). The size of the square is proportional to the size of the study sample. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated were excluded from the denominator. See table 1 and online supplementary table S8 for details of treatment delivery and management for each study. Data are presented as n unless otherwise stated. DOT: directly observed therapy; SAT: self-administered therapy.

treatment with routine counselling sessions and access to a peer-support group. The greatest reduction in losses to follow-up was seen in two cohorts that received support through daily home visits by community health workers, as well as home-based DOT, when compared to the standard of care [15, 16]. In the cluster randomised trial by Baral *et al.* [13], the addition of individually tailored counselling sessions provided by nurses reduced the risk of lost to follow-up by 70%, but this estimate was very imprecise (risk ratio 0.31, 95% CI 0.07–1.26), and adding a monthly income supplement did not improve the effect (risk ratio 0.73, 95% CI 0.31–1.72).

Pooled results across studies

Results from all study cohorts, in both comparative and noncomparative studies, that received any form of psychosocial, educational or material support were pooled in the following analysis (online supplementary table S2 presents the characteristics of included study cohorts). We excluded the standard of care or control groups in two studies that did not provide any psychosocial, educational or material support [13, 16], as well as one comparative cohort study [14] because its intervention group was a subsample of a larger single-cohort study [31].

Final treatment outcomes were reported for a total of 6655 RR-/MDR-TB patients in 31 included study cohorts (online supplementary table S3). After excluding patients who died, failed treatment or were transferred out or not evaluated for final treatment outcomes, there remained a total of 5114 patients (median of 84 patients per study cohort). The pooled proportion lost to follow-up was 17% (95% CI 12–23%), as seen in the forest plot (figure 3). Study heterogeneity was high across all included study cohorts (I^2=96%), and remained high in subgroup analyses by WHO region (except in the Americas region, probably because all three cohorts were largely based in Lima, Peru, within approximately the same period), HIV infection rate, proportion of patients with XDR-TB, previous TB treatment (with or without second-line drugs) and start year of the study (figure 4).

In subgroup analyses, study cohorts with more frequent contact with health workers throughout treatment (in the form of DOT visits, home visits or individual counselling sessions) tended to have fewer losses to follow-up (figure 5). Additionally, provision of financial support to reimburse rent or travel expenses, as well as to compensate lost wages during treatment, was associated with fewer losses to follow-up. There was weak evidence of any association between providing food packages, group counselling or counselling to family members and losses to follow-up. In order to distinguish the effect of frequent DOT from that of adherence support, subgroup analyses according to types of support provided were restricted to study cohorts that received either twice-daily or daily DOT throughout treatment (figure 6). Within these cohorts, those that received individual counselling throughout treatment [15, 16, 21, 23–26, 28–30, 32, 33, 36, 37] had fewer losses to follow-up than those that received a fixed [13, 17, 19, 20, 31] or unspecified [15, 27, 34] number of individual counselling sessions at the start of treatment. Similarly, those that received any home visits by health workers had fewer losses to follow-up [15, 16, 20, 23, 29, 30, 32, 37]. Sensitivity analyses where patients who were transferred out (online supplementary figures S20–S22), or who died (online supplementary figures S23–S25) were considered as lost to follow-up yielded similar results. Furthermore, the findings remained consistent across strata of study cohorts stratified by prevalence of HIV co-infection (online supplementary figures S26–S29) and previous TB treatment (online supplementary figures S30–S33).

Other adherence outcomes

Three studies additionally reported the proportion of doses taken (or missed) by patients (online supplementary table S6), two of which did not include a comparison control group. In comparing treatment adherence before and after patients were enrolled into the study intervention, Gelmanova *et al.* [23] found an increase in proportion of doses taken from 52.2% (95% CI 47.5–56.9%) to 81.4% (95% CI 76.8–86.0%). These patients received increased staff time from nurses, as well as expanded access to psychosocial support, after study enrolment.

Feasibility of implementation of interventions

A summary of feasibility and implementation issues associated with study interventions is provided in online supplementary table S7. Reported issues included reluctance from health providers to follow new intervention-directed procedures [16, 17]; difficulties identifying and training support workers [29, 35]; and lack of clarity in intervention implementation [16]. Among studies that reported on cost-effectiveness, all found that the study intervention reduced losses to follow-up and was more cost-effective than the standard treatment practices in their respective setting [23, 29, 34].

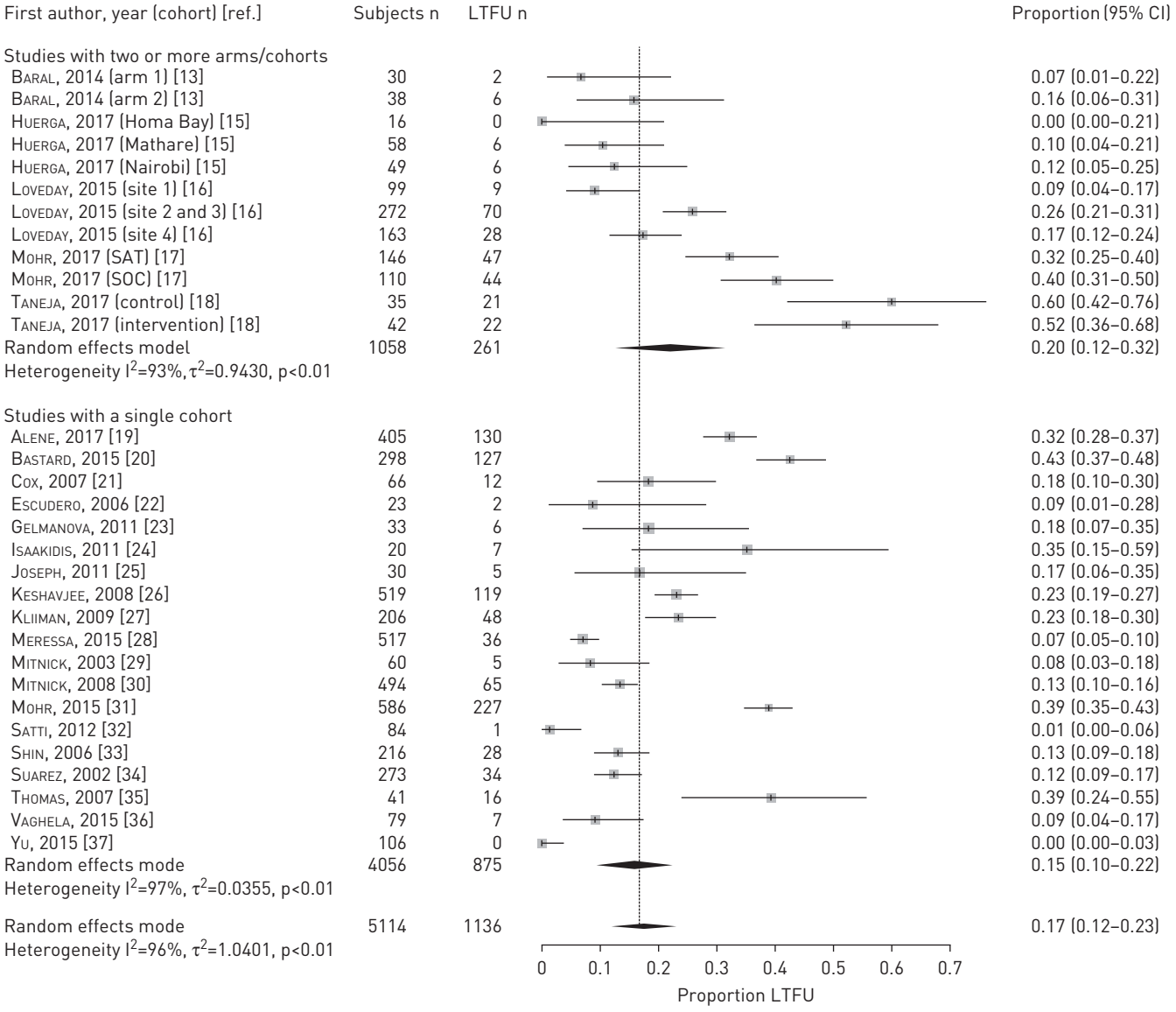

FIGURE 3 Forest plot of proportions lost to follow-up (LTFU) across all study cohorts. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated were excluded. In studies with more than one cohort, each cohort is shown separately. SAT: self-administered therapy; SOC: standard of care.

Discussion

Strategies to improve retention-in-care and treatment adherence among disease-resistant TB patients are greatly needed to increase treatment success rates globally. This review found a broad range of adherence support interventions, all of which included some degree of educational and psychosocial counselling, as well as a variety of material support. However, very few studies reported on adherence outcomes in addition to patient losses to follow-up.

Our review found individual counselling support and home visits by health workers, provided throughout treatment, were associated with fewer losses to follow-up than when they were provided only at the start of treatment, or not at all. This association remained even after restricting the analyses to studies that provided daily DOT throughout treatment. Thus, although our study found lower rates of loss to follow-up among studies that provided more frequent DOT, this could be conflated with the associated frequency of contact with providers as well as psychosocial or educational support. This is supported by findings from Mohr *et al.* [17], which showed that self-administered therapy, supplemented with routine home visits by community health workers during the continuation phase yielded a similar rate of loss to follow-up compared to daily clinic-based DOT without home visits. Furthermore, Gelmanova *et al.* [23] showed significant improvements in treatment adherence rates among MDR-TB patients when staff time

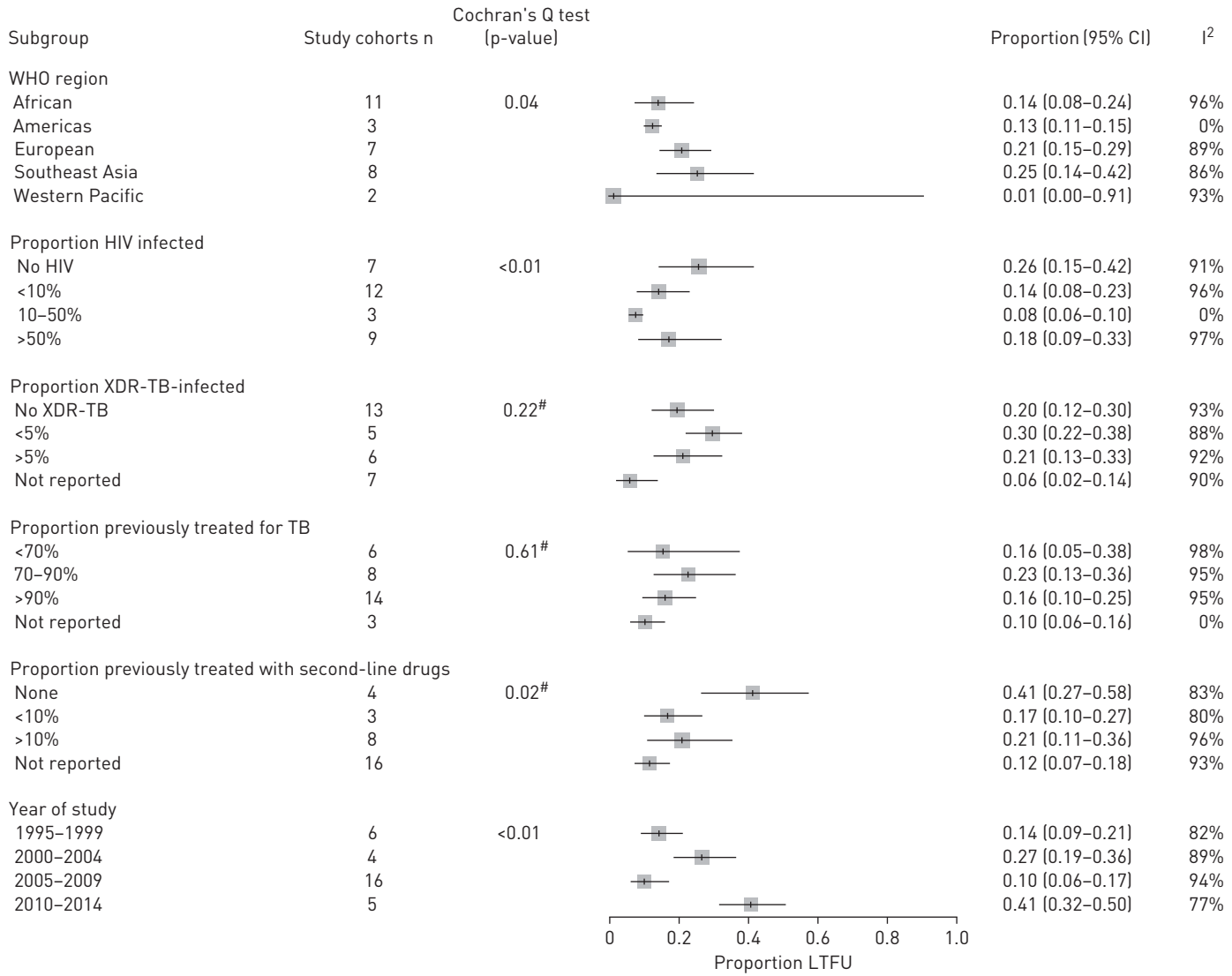

FIGURE 4 Forest plot of pooled proportions lost to follow-up (LTFU) stratified by study cohort characteristics. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated were excluded. WHO: World Health Organization; XDR: extensively drug-resistant; TB: tuberculosis. #: study cohorts that did not report a given characteristic were excluded from Cochran's Q-test for subgroup differences.

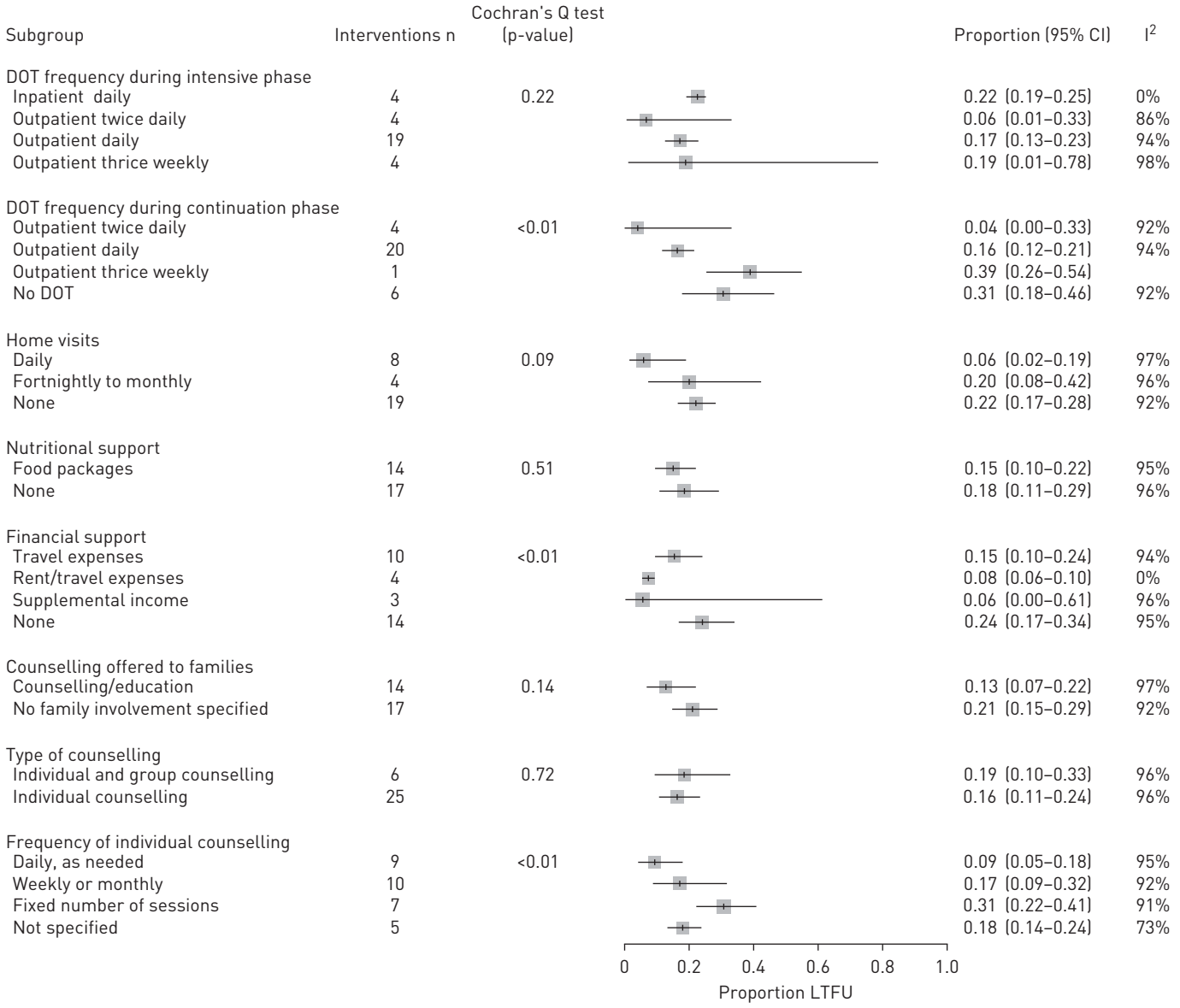

FIGURE 5 Forest plot of pooled proportions lost to follow-up (LTFU) stratified by frequency of directly observed therapy (DOT) during the intensive and continuation phase, and by type of adherence support provided during treatment. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated were excluded.

allocated to each patient was increased. These findings are consistent with those reported in a recent Cochrane systematic review [38], which found that daily DOT did not improve TB cure rates, compared to self-administered therapy, when the frequency of contact with providers increased from monthly to every 2 weeks or more.

In addition, this review provides evidence to support the effectiveness of financial compensation for rent or travel expenses, as well as lost wages, but not of group counselling, involvement of family in counselling sessions or nutritional support, on improving retention in care. The lack of effectiveness of those strategies could be due to residual confounding. For example, Cox *et al.* [14] found no effect of a community-based pilot intervention (which provided routine counselling and access to a peer support group), and suggested that this may be due to the higher numbers of patients who initiated treatment under intervention, who otherwise would not have received treatment. Furthermore, very few studies reported on implementation issues and fidelity of intervention delivery [16, 17, 23, 28, 29, 34, 35]. Thus, the reported intervention effectiveness may reflect issues with delivery, such as low engagement of patients and families in support groups [39]; lack of buy-in from health workers [16, 17, 32, 40]; or providers selectively providing adherence incentives, such as food packages, to patients deemed most worthy [41]. Future research should explore these issues through process evaluations [42].

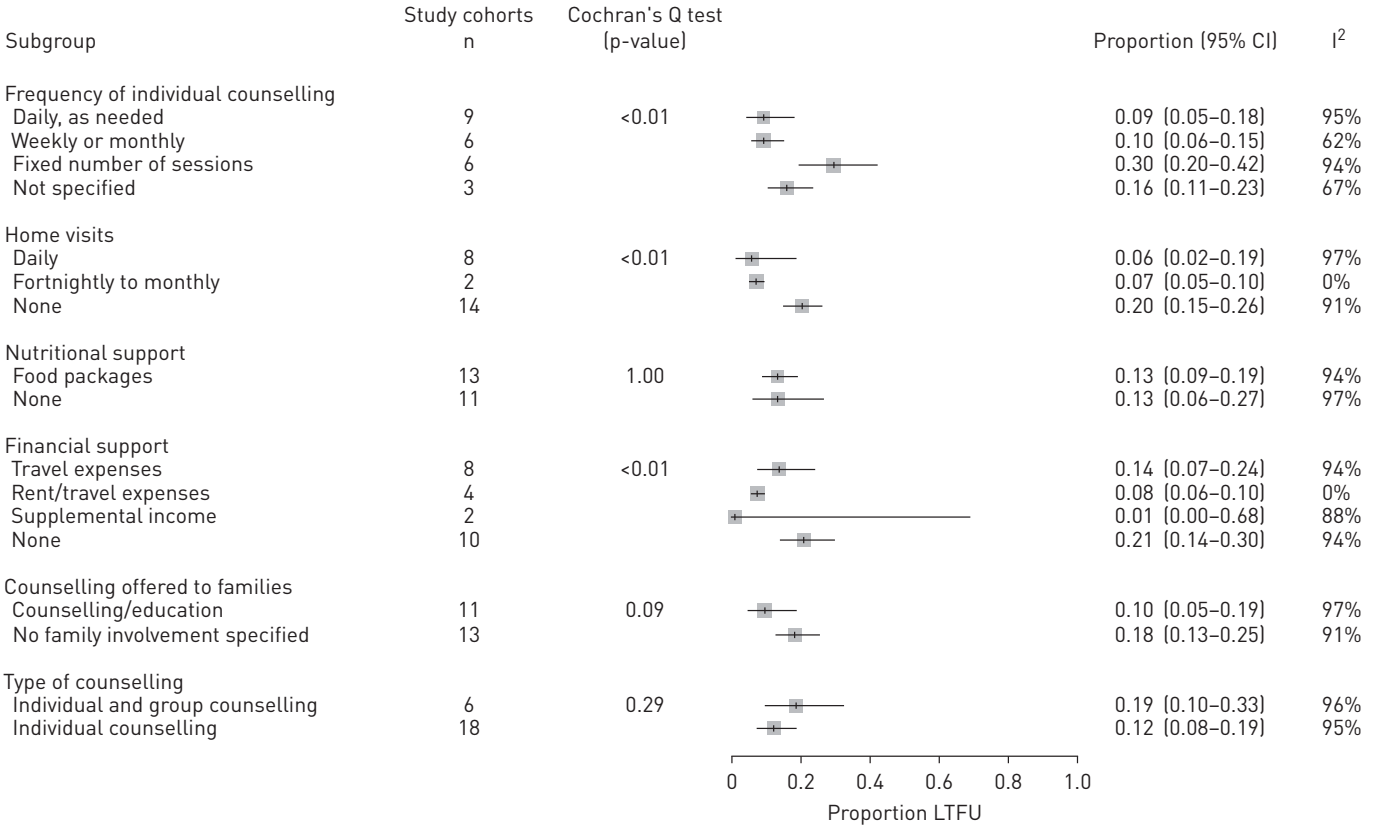

FIGURE 6 Forest plot of proportions lost to follow-up (LTFU) stratified by type of adherence support provided during treatment; this analysis compares cohorts across studies, but is restricted to cohorts that received twice-daily or daily directly observed therapy throughout treatment. Patients who died, failed treatment, who transferred out or whose treatment outcome was not evaluated were excluded.

One major limitation of this review was the sparse descriptions of interventions provided by many studies. We made extensive efforts to contact authors for details, although we were not always successful. Among studies for which we were able to acquire sufficient details, we observed a wide variation in the educational and psychosocial support provided. Although nearly all studies provided individual counselling to patients, the specifics of the counselling were not often described sufficiently to gauge whether it encompassed social and emotional support and/or treatment education. Thus, we considered individual counselling to broadly include any one-on-one time spent between patients and health workers to address psychological, social or treatment-related issues, which could include both psychosocial and educational support, and was identified by the authors as beyond the current standard of care at the study sites. The observed benefit from these forms of support could therefore have resulted from added interactions between patients and their providers, beyond DOT and routine medical check-ups. However, it is difficult to assess the degree or depth of these interactions. Additionally, the benefit could be underestimated due to the lack of training provided in some studies compared to others.

Despite these limitations, the review provides a timely update on strategies to improve MDR-TB treatment retention in care, including results of two recent cluster randomised trials [13, 18]. Unlike the earlier review [3], which included all studies reporting treatment outcomes for RR-/MDR-TB patients, we restricted our analysis to only those studies that explicitly provided patients with some form of psychosocial, educational or material support, allowing a more nuanced analysis comparing the effectiveness of different types of support. Notably, no interventions utilised e-health tools to promote adherence to RR-/MDR-TB treatment.

Our review provides the motivation for further examination of adherence interventions in RR-/MDR-TB, preferably through randomised controlled trials that compare the effectiveness of DOT to self-administered therapy, coupled with increased psychosocial and economic support throughout the treatment course. As evidenced by some recent cohort studies, and supported by expert commentaries [43, 44], a shift to self-administered therapy has the potential to relieve health worker burden so that their time and resources may be utilised to build health literacy, empower patients and deliver higher quality, patient-centred care.

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