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Incentives and Support Programs to Improve Adherence to Tuberculosis Treatment

Rapid Review

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Abbreviations

CI	confidence interval
DOT	direct observed therapy
LTBI	latent tuberculosis infection
NICE	National Institute of Health and Care Excellence
OR	odds ratio
RCT	randomized controlled trial
RR	risk ratio
SR	systematic review
TB	tuberculosis

Key Messages

- Three overviews of reviews and 11 systematic reviews were identified regarding the clinical effectiveness of adherence incentives in those who require assistance to complete their tuberculosis treatment.
- Four evidence-based guidelines were identified that provided recommendations regarding the use of adherence incentives in those who require assistance completing their tuberculosis treatment.
- The reported clinical effectiveness of adherence incentives for patients with tuberculosis was mixed. There were no detrimental effects of providing incentives, but there was also no conclusive evidence pointing to a clinical benefit. The overall quality of the included reviews was moderate to high.
- The included guidelines recommended that incentives and enablers be included as a part of a patient-centred strategy for treatment and for patients with active tuberculosis or patients at high risk; however, the evidence formulating these recommendations was of low certainty or quality. Two of the included guidelines were of high methodological quality, and 2 were of lower methodological quality.

Context and Policy Issues

Tuberculosis (TB) is an infectious disease caused by the bacterium *Mycobacterium tuberculosis*.[1] Initial infection leads to latent TB, which has no active symptomology as the disease is contained by the host's immune defences. However, in a small subset of infected patients (5% to 10%), the infection can proceed to active TB, which has visible symptoms and high mortality.[2] Worldwide, TB kills more people than any other infectious disease. WHO's End TB Strategy aims to reduce TB death by 90% by 2035.[2]

TB is curable, with TB treatment given in 2 phases: initial intensive treatment and continuation treatment. In the initial phase, it is recommended that the medication be given daily; in the continuation phase, the medication can be given daily or intermittently.[3] As treatment is intensive and frequent, medication nonadherence is a problem and can lead to poorer patient outcomes and development of drug-resistant TB.[4] The intensive nature of treatment can lead to significant barriers for people attending treatment, especially those in hard-to-reach populations or those who are poorer and cannot afford to take time off work or to travel to the clinic for treatment. Therefore, a multi-faceted, patient-centred treatment strategy is often cited as an option to help overcome these barriers. Components of a patient-centred strategy could include *enablers*, such as transportation vouchers and social service assistance, and *incentives*, such as food stamps, snacks and meals, and provision of housing, stipends, coupons, or cash.[5] Incentives are generally defined as items or services that reward healthy behaviour and enablers are defined as items or services that remove barriers to accessing health care.[6]

This report is an upgrade of a previous CADTH report, *Support Programs for Tuberculosis Treatment: Clinical Utility and Guidelines*, with an updated search using broader search terms.[7] The purpose of this review is to identify clinical studies of support programs, material incentives, or material enablers in the treatment of TB, and to summarize the clinical effectiveness of these interventions. Evidence-based guidelines were also identified, and the recommendations regarding support programs and incentives were summarized.

This report is a component of a larger CADTH Condition Level Review on TB. A condition level review is an assessment that incorporates all aspects of a condition, from prevention and detection to treatment and management. For more information on CADTH's Condition Level Review of TB, please visit the TB project page on CADTH's website.

Research Questions

1. What is the clinical effectiveness of adherence incentives and support programs in those who require assistance to complete their tuberculosis treatment?
2. What are the evidence-based guidelines regarding the use of adherence incentives and support programs in those who require assistance completing their tuberculosis treatment?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were *adherence incentives* and *tuberculosis patients*. Search filters were applied to limit retrieval to health technology assessments, systematic reviews (SRs), meta-analyses, or network meta-analyses, any types of clinical trials or observational studies, and guidelines. The search was also limited to English-language documents published between January 1, 2014, and November 11, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were published before 2014. The year 2014 was chosen as the cut-off to match the search dates of the previous CADTH report.[7] Systematic reviews with all relevant studies captured in other more recent or more comprehensive SRs were excluded. Primary studies were excluded from the report due to the abundance of SRs and overviews. SRs that were retrieved by the search were excluded if they were captured in 1 or more included overviews of reviews. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools: A MeaSurement Tool to Assess Systematic Reviews 2 (AMSTAR 2)[8] for SRs, with additional considerations for overviews of reviews, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[9] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 374 citations were identified in the literature search. Following screening of titles and abstracts, 331 citations were excluded and 43 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 29 publications were excluded for various reasons, and 18 publications met the inclusion criteria and were included in this report. These comprised 3 overviews of reviews, 11 SRs, and 4 evidence-based guidelines. Appendix 1 presents the PRISMA[10] flow chart of the study selection.

Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Table 1: Selection Criteria

Criteria	Description
Population	Individuals with TB who require support to complete TB treatment
Intervention	Support programs, material incentives, or material enablers that provide assistance to improve TB treatment completion (e.g., incentive programs, provision of resources, education programs)
Comparator	Q1: Alternative support program or alternative incentive: No incentives or support Q2: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g., compliance with TB treatments, treatment completion, active TB disease, health-related quality of life) Q2: Recommendations regarding the use of support programs or material incentives or enablers to improve TB treatment compliance
Study designs	Health technology assessments, systematic reviews, evidence-based guidelines

TB = tuberculosis.

Study Design

Three overviews of reviews and 11 SRs were identified.[4,11-23] The overviews of reviews were published in 2018[11] and 2017.[12,13] The SRs were published in 2020,[14] 2019,[4,15] 2018,[16-19] 2017,[20,21] and 2016.[22,23] There were 7 SRs with meta-analyses, but not all SRs with a meta-analysis included relevant information within the meta-analyzed data (i.e., the relevant data were narratively described).[14-16,18,19,22,23] The date ranges for the overviews of reviews were up to 2017[11] and 2016.[12,13] The date ranges for the SR searches were up to 2018,[4,14] 2017,[11,15,19] 2016,[12,13,17] 2015,[18,20,21,23] and 2014.[22]

There was significant overlap between the SRs. Details on the extent of overlap in the studies is provided in Appendix 5.

The scope of the included SRs was broader than the scope of the present report, with the exception of Richterman et al. (2018).[19] This was because the majority of SRs included other interventions to promote adherence to treatment,[4,16-18,20,23] interventions to promote adherence or completion of screening,[14,21,22] or additional populations such as patients with HIV,[11,20] vulnerable populations without TB,[11] or patients in low-income countries.[12,13] Appendix 2 details how many primary studies were included in each SR and how many of those included studies that were relevant to this report.

Four guidelines were identified. Two of these guidelines were separate chapters of an overarching guideline (the Canadian Tuberculosis Standards).[3,24] The developing institutions for the identified guidelines were the WHO,[25] the National Institute for Health and Care Excellence (NICE),[26] and the Canadian Thoracic Society in collaboration with the Public Health Agency of Canada.[3,24]

A comprehensive literature search (or multiple literature searches) was used to inform the included guidelines. The authors of the WHO guideline searched for randomized controlled trials (RCTs) that had direct comparisons and used teams of experts to develop the recommendations through consensus and discussion.[25] The authors of the NICE guidelines searched for reviews, RCTs, or observational studies, and used a guideline development group who developed the recommendations through consensus.[26] The Canadian Tuberculosis Standards were not clear on the guideline development process, but noted that they included "all published evidence" on the topics of interest.[3,24]

The evidence was assessed by the publication authors using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) or a modified GRADE in all included guidelines.[3,24-26] The rating system for each guideline is reported in Appendix 2.

Country of Origin

The overviews were conducted by first authors from the UK,[11] Chile,[12] and South Africa,[13] but the remainder of the authors in each of these reviews were from a variety of different countries.

The SRs were conducted by first authors from Canada,[14,15] Spain,[4] the US,[16,17,19,20] Brazil,[18] the Netherlands,[21,23] and Sweden.[22]

The 4 guidelines were intended for use globally,[25] in the UK,[26] and in Canada.[3,24]

Patient Population

The overviews of reviews examined vulnerable populations who are food insecure or malnourished,[11] and people in low-income countries.[12,13] Only data regarding people in low-income countries or vulnerable populations who also have TB were extracted.

The SRs examined patients who have latent TB,[14,17,22] drug-resistant TB,[15] active TB,[16,18,19,21] either latent or active TB,[4,23] or patients who have TB and a co-occurring substance use disorder.[20]

For the included guidelines, the target populations were patients with drug-susceptible TB,[25] children, young people and adults with latent TB,[26] and patients with active TB.[3,24]

Interventions and Comparators

The overviews of reviews examined interventions such as community-based supplementary feeding programs,[11] alternative delivery and implementation strategies,[12] and financial arrangements, including incentives.[12,13] These interventions were compared to other strategies or no strategies or incentives.[11-13]

The SRs examined interventions such as interventions designed to promote adherence to treatment,[4,16,21,22] interventions that addressed barriers to treatment compliance,[17] material or financial incentives or support,[14,15,18,19,23] educational programs,[14,18] psychosocial or psycho-emotional support,[15,23] food incentives or support,[18] and contingency management interventions.[20] The general interventions to promote adherence or address barriers to treatment or screening included support programs, material incentives, or material enablers.[4,16,17,21,22]

The SRs compared these support programs or incentives to control groups,[4,14,15,17,20] no incentives or support,[15,17,22] other incentives or strategies,[17,18] or to usual care or standard support.[16,17,23]

The guidelines examined treatment adherence interventions[25,26] and incentives and enablers to TB treatment.[3,24]

Outcomes

The outcomes for the overviews of reviews and the SRs were treatment adherence[4,11-13,15-17,20,22,23]; mortality[11,16,18]; treatment completion, success, or failure[4,11-14,16,19,20,22,23]; cure rate or microbiologic cure[16,18,19]; weight gain[11]; quality of life (QoL)[11]; effectiveness[21,22]; sputum conversion[4,11]; loss to follow-up[15,16]; default rate[16,18]; and missed doses.[4,20]

The guidelines examined outcomes related to treatment adherence,[3,24,26] treatment success,[25] treatment completion,[25] and sputum conversion[25] and used these outcomes as metrics to develop the recommendations.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Overviews of Reviews

The overviews of reviews were of high quality. All 3 reviews were published by Cochrane and therefore followed Cochrane methodology, which was provided and detailed.[11-13]

The methods, research questions, inclusion criteria, and study details were clear. The studies used comprehensive literature searches, performed study selection and data extraction in duplicate, and provided excluded studies lists with reasons.

Pantoja et al.[12] and Wiysonge et al.[13] did not include an analysis on overlap of the primary studies examined by the included SRs. Additionally, all 3 studies did not report on the sources of funding for the studies included in the reviews.[11-13]

Systematic Reviews

The included SRs were of variable quality.[4,14-23]

All the SRs[4,14-23] included a comprehensive literature search strategy (although Alipanah et al.[16] only searched 1 database). Additionally, all the included SRs, with the exception of Herrmann et al.,[20] assessed study quality or risk of bias using validated tools, and clearly reported the quality of the included primary studies.[4,14-19,21-23]

Eight SRs performed study selection in duplicate.[4,14,18-23] Three SRs had study selection performed by only 1 reviewer, which may have led to missed studies during selection.[15-17] Additionally, for data extraction, 4 SRs did not have either duplicate extraction or single extraction with an independent verifier.[4,15-17]

Seven SRs conducted their final searches over 1.5 years before publication.[14,15,17,18,20-22] This does not necessarily mean that the conclusions presented in the SRs were erroneous, but it could mean that studies published between the search date and publication date were potentially missed. Additionally, 5 SRs only included studies in English[14,16,17,20] (with 1 including English and Spanish only[4]), which limits the potential number of included studies and relevant information, especially for SRs that focused on individuals living in lower-income countries. Although information from low-income countries with a higher TB incidence may not be as relevant to the Canadian context, many low-incidence countries have primary languages that are not English, and this limitation on language may have eliminated potentially relevant studies from those countries.

Guidelines

The critical appraisal of the guidelines was performed in previous CADTH reports.

The guidelines by WHO,[25] NICE,[26] and the Canadian Tuberculosis Standards chapter on active tuberculosis[3] were assessed in the CADTH report *Treatment of Tuberculosis: A Review of Guidelines*,[27] available at the CADTH website. The guideline from the Canadian Tuberculosis Standards chapter on identification of TB in high-risk populations[24] was assessed in the CADTH report *Identification of Tuberculosis: A Review of the Guidelines*.[28]

More details on the quality of these guidelines can be found in those reports. Briefly, the WHO guideline[25] and NICE guideline[26] were assessed to be of high quality, with clear descriptions of scope, populations, target users, and recommendations. These guidelines had a systematic approach to evidence synthesis, with evaluation of the primary literature, and transparent literature search methods and recommendation development.[25,26]

The Canadian Tuberculosis Standards chapter on active tuberculosis (chapter 5)[3] and the Canadian Tuberculosis Standards chapter on identification of TB in high-risk populations (chapter 13)[24] were assessed to be lower quality compared with other identified guidelines. They had clear recommendations but limited detail on methods, such as recommendation development, research questions, the professions involved in the development, search methods, assessment of primary study quality, or external review.[3,24]

Summary of Findings

Appendix 4 presents the main study findings and authors' conclusions.

Clinical Effectiveness of Support Programs for Treatment of Tuberculosis

Treatment adherence and completion were the most common outcomes examined by the studies.

Treatment Acceptance (Initiation of Treatment)

In 1 SR by Barss et al., acceptance of treatment (i.e., a patient starting treatment) improved with both patient incentives and patient education supports. When patients were provided with an incentive, 49 additional patients per 100 patients recommended for treatment accepted the treatment (95% confidence interval [CI], 46 to 52). With patient education support, 15 additional patients accepted treatment per 100 recommended (95% CI, 11 to 19).[14]

Treatment Adherence

Financial Incentives

In 1 cohort study identified by Herrmann et al.,[20] patients received US$15 in subway tokens per week for all doses ingested or a combination of this incentive and monthly bonuses of US$30 to US$60 for those who took more than 80% of the doses for the month. Patients who received US$15 in subway tokens per week for all doses ingested were 2.7 times more likely to take more than 80% of doses if they were given the larger incentive package. Herrmann et al.[20] also reported on an RCT that examined giving people who inject drugs either US$10 a month for adherence paid once a month for 6 months or US$10 per month for adherence paid out as a lump sum after 6 months. There was no difference in TB treatment adherence between the groups.

Non-Cash Incentives and Educational Support

In Alipanah et al.,[16] the relative risk for treatment adherence for oral and written educational material compared with standard care was 1.83 (95% CI, 1.14 to 2.92) for 1 included RCT and 1.21 (95% CI, 1.05 to 1.40) for 1 included cohort study, indicating patients who received the oral and written education were 1.83 times more likely to adhere to treatment in the included RCT and 1.21 times more likely to adhere to treatment in the included cohort study.

Unclear Incentives

Heuvelings et al. reported 1 study comparing directly observed therapy alone with directly observed therapy in combination with incentives in hard-to-reach populations and found that incentives were beneficial for treatment adherence.[21] It was unclear what these incentives were.

Treatment Completion, Success, and Failure

Pantoja et al.[12] and Wiysonge et al.[13] both included the same SR and concluded that sustained material incentives made little or no difference in treatment completion for active TB compared with no incentives, although they did not provide numerical values.

Financial Incentives

Richterman et al.[19] meta-analyzed 4 studies that examined cash incentives compared with usual care and found a significant benefit of cash incentives for treatment success (odds ratio [OR] = 1.77; 95% CI, 1.57 to 2.01). In the non–meta-analyzed studies, treatment success was more likely with a monthly cash incentive equivalent to a low civil service salary (OR = 1.19; 95% CI, 1.03 to 1.37), and treatment completion was more likely with cash incentives (OR = 3.28; 95% CI, 1.65 to 6.51).[19]

Alipanah et al.[16] included 5 RCTs and 4 cohort studies examining financial incentives compared with standard of care (directly observed therapy or self-administered therapy) and reported that the pooled risk ratio (RR) for treatment completion in the 5 RCTs significantly favoured the intervention (RR = 1.23; 95% CI, 1.15 to 1.31), but the pooled RR for the 4 cohort studies was not significantly different for treatment completion. A similar effect occurred for treatment failure; the RR for 1 RCT was significant in favour of the intervention (RR = 0.66; 95% CI, 0.50 to 0.87), but the pooled RR for 2 cohort studies was not significant. The use of financial incentives was associated with significantly higher treatment success in both pooled RCTs (3 RCTs: RR = 1.07; 95% CI, 1.03 to 1.11) and cohort studies (4 cohort studies: RR = 1.25; 95% CI, 1.09 to 1.42).

For latent TB, Riquelme-Miralles et al.[4] reported no benefit of cash incentives in people who are homeless compared with non-cash incentives, and no benefit in people who received monetary incentives compared with no incentives. Both these studies were also reported in Liu et al.[17] and Herrmann et al.[20]

In people who use drugs, an immediate incentive did not have a significant impact on treatment completion compared with a deferred incentive.[17] When providing a monetary incentive or outreach alone, the monetary incentive was more effective for increasing treatment completion (OR = 45.5; 95% CI, 9.7 to 214.6). The primary study examining outreach and incentives was also reported in Herrmann et al.[20] and Stuurman et al.[22]

In individuals who are incarcerated, the odds of treatment completion was higher with monetary incentives compared to usual care (OR = 1.07; 95% CI, 0.47 to 2.40).[17] This study was also reported in Herrmann et al.[20]

Food Supplements or Incentives

Riquelme-Miralles et al.[4] reported a benefit of food incentives for treatment completion in patients with active TB compared with standard care (98% versus 82%) in 1 study, but no benefit in a second study (76% versus 78%). No statistical results were reported.[4]

One cohort study identified by Herrmann et al.[20] reported that a US$5 grocery gift card in addition to directly observed therapy made adults or children with medication nonadherence 5.7 times more likely to complete treatment (value not reported). This study was also reported in Alipanah et al.,[16] van Hoorn et al.,[23] and Heuvelings et al.[21]

Non-Cash Incentives and Educational Support

Alipanah et al.[16] included 1 RCT that examined education supports compared with no supports and reported a higher rate of treatment completion for the intervention group (RR = 1.71; 95% CI, 1.32 to 2.22). There was no significant effect on treatment success or failure.

Stuurman et al.,[22] Liu et al.,[17] Riquelme-Miralles et al.,[4] and Herrmann et al.[20] all reported an RCT examining patients who were incarcerated with latent TB. The intervention was an informational or educational session combined with US$25 vouchers for food or transport if they attended a TB clinic within 1 month of release from incarceration compared with a control group (group receiving neither intervention). A second comparison was the informational session alone compared with a control group, which Liu et al. reported as significant (OR = 2.2; 95% CI, 1.04 to 4.72) in favour of the educational incentive. For the combination of non-cash incentive and education, the SRs[17,22] reported an OR of 1.07 (95% CI, 0.5 to 2.4) in favour of the incentives, but this was not statistically significant. However, Herrmann et al.[20] also reported this RCT, but reported opposite results: there was less treatment completion in the incentive group compared with controls. An examination of the original RCT[29] revealed that Herrmann et al. reported this incorrectly.

A study reported in Stuurman et al.[22] reported that patients with TB who injected drugs and who received support through methadone treatment and counselling had higher odds of completing treatment compared with no incentive (OR = 14.5; 95% CI, 5.0 to 42), but this evidence was of very low quality.

Combined Incentives and Support

For active TB, Riquelme-Miralles et al.[4] reported no benefit of financial incentives mixed with educational support compared with standard care over 6 to 9 months. In people with TB who use drugs, outreach mixed with incentives and incentives alone were more effective than outreach alone (52.8% versus 3.6% and 60% versus 3.6%, respectively). In adolescents, there was no benefit of peer counselling mixed with an incentive or incentives alone compared with standard of care.[4] In a general population of patients with TB, there was a benefit of education and economic incentives compared with standard care over 9 to 12 months (63.8% versus 27.1%). No statistical results were reported.[4]

van Hoorn et al.[23] meta-analyzed studies providing socioeconomic supports (e.g., food supplementation and economic support), psycho-emotional supports (e.g., counselling, psychotherapy, and the organization of self-help groups), and combined supports for the outcome of treatment success. All the RRs significantly favoured the interventions over the control groups, with 4 studies examining socioeconomic supports (pooled RR = 1.08; 95% CI, 1.03 to 1.13) and 3 studies examining combined supports (pooled RR = 1.17; 95% CI, 1.12 to 1.22). When examining the outcome of unsuccessful treatment, the interventions were also significantly favoured, with 2 studies examining socioeconomic supports (pooled RR = 0.78; 95% CI, 0.69 to 0.88) and 4 studies examining combined supports (pooled RR = 0.42; 95% CI, 0.23 to 0.75).[23]

Losses to Follow-up

Financial Support

Law et al.[15] conducted a meta-analysis of studies examining financial support (reimbursement of rent and travel expenses, and compensation of lost wages) compared with no support, and nutritional support (e.g., food baskets, provisions of basic foods, hot meals) compared with no support. In patients who received travel expenses (10 cohorts

pooled together), the proportion of patients who were lost to follow-up was 0.15 (95% CI, 0.10 to 0.24); in patients who received rent and travel expenses (4 cohorts pooled together), the proportion of patients lost to follow-up was 0.08 (95% CI, 0.06 to 0.10); and in patients who received supplemental income (3 cohorts pooled together), the proportion of patients lost to follow-up was 0.06 (95% CI, 0.00 to 0.61). For patients who received no financial support, the proportion of patient lost to follow-up was 0.24 (95% CI, 0.17 to 0.34).[15] There was a significant difference in loss to follow-up between the subgroups of travel reimbursement, travel and rent reimbursement, compensation of lost wages, and no treatment ($P < 0.01$), but there were no direct statistical comparisons provided.

In Alipanah et al.,[16] financial incentives were associated with lower loss to follow-up (1 RCT: RR = 0.74; 95% CI, 0.60 to 0.90; 5 cohort studies: pooled RR = 0.48; 95% CI, 0.28 to 0.81). There did not appear to be any primary study overlap between Alipanah et al. and Law et al. for this intervention.

Food Packages

For food support, the proportion of patients (14 pooled cohorts) who received food packages and were lost to follow-up was 0.15 (95% CI, 0.10 to 0.22). The proportion of patients (17 pooled cohorts) who received no support and were lost to follow-up was 0.18 (95% CI, 0.06 to 0.27).[15] There was no significant difference between these groups.[15]

Cure Rate and Microbiologic Changes

Material or Financial Incentives

Pantoja et al.[12] and Wiysonge et al.[13] included the same SR and concluded that sustained material incentives had little to no difference in cure rates for active TB compared with no incentives, but numerical values were not provided.

Alipanah et al. found financial incentives were associated with higher rates of cure in pooled cohort studies but not RCTs (4 cohort studies: RR = 1.13; 95% CI, 1.02 to 1.26; 1 RCT: RR = 0.92; 95% CI, 0.85 to 1.01) and sputum conversion (1 RCT: RR = 1.21; 95% CI, 1.02 to 1.43).[16]

In Muller et al.,[18] cure rates pooled from 2 RCTs were not significantly different between patients who received financial incentives and patients who received no financial incentives. One of the included RCTs in the pooled estimate from Muller et al.[18] was the RR from the RCT included in Alipanah et al.[16]

In Richterman et al.,[19] monthly cash transfer and travel reimbursement interventions and monthly cash incentives to households (through the Bolsa Família program) had higher odds of microbiologic cure compared with usual care (OR = 79.08; 95% CI, 4.42 to 1,413.33 and OR = 1.07; 95% CI, 1.04 to 1.11, respectively).

Food Supplementation

Visser et al.[11] included 1 SR of relevance to this report. This SR examined cure rates and sputum conversion in patients with TB, with or without co-occurring HIV, who received food supplementation or no supplementation. The cure rate was reported in 1 primary study and it was not significantly different for patients receiving interventions compared with control groups. Sputum conversion was also not different between the groups in 3 primary studies, but it was significantly better for patients receiving supplementation in 1 small study. The authors noted that the studies were underpowered for these outcomes.[11]

In Muller et al.,[18] cure rates pooled from 3 RCTs found no significant difference between patients who received food incentives and patients who did not.

Educational Supports

In Muller et al.,[18] cure rates pooled from 2 RCTs were higher in patients who received education or counselling (RR = 1.16; 95% CI, 1.05 to 1.29).

Mortality

Visser et al.[11] included 1 SR that examined mortality outcomes of patients who received food supplementation compared with no supplementation at 1 year of follow-up. There was no significant difference between the groups, and no subgroup differences in patients who also had HIV.[11] Alipanah et al.[16] reported that in pooling 3 cohort studies, there was a significant benefit of material or financial incentives on mortality for patients with TB (RR = 0.51; 95% CI, 0.37 to 0.71); however, in pooling 2 RCTs, there was no significant effect. Muller et al.[18] pooled 2 RCTs and found no significant difference between patients who received financial incentives or none. One RCT included in the pooled estimate for Muller et al. was also included in the pooled estimate for Alipanah et al.[16]

Quality of Life

One SR identified in Visser et al.[11] examined QoL of patients receiving food supplementation compared with no supplementation. The supplementation may have improved QoL in the first 2 months of treatment, but the authors noted the evidence was of low certainty and narratively described (no statistical comparisons).[11]

Guidelines Regarding Support Programs for Treatment of Tuberculosis

The guidelines from the WHO[25] recommended that health education and counselling for treatment adherence should be provided to patients who are on TB treatment (strong recommendation, moderate certainty in the evidence). It is also recommended providing a package of treatment adherence interventions to patients in conjunction with treatment administration (conditional recommendation, low certainty in the evidence), which could include material support to patients (conditional recommendation, moderate certainty in the evidence).[25]

The guidelines from NICE[26] recommended that the care plan identify the reasons why a patient may not attend treatment, including determining any enablers or incentives to help patients overcome barriers to treatment. This plan should also define the supports needed to address needs, such as those to acquire housing. These guidelines also recommended that multidisciplinary teams implement strategies that encourage following treatment plans, including health education counselling, tailored health education booklets, and incentives and enablers to help people follow their treatment regime.[26] During treatment, TB teams should assess living situations of patients and work with agencies to provide accommodation for those that need it.[26] Housing should be funded by local government and clinical commissioning groups for individuals who are homeless and ineligible for state-funded accommodations. All these recommendations were deemed to do more good than harm for the vast majority of patients.[26]

The Canadian Tuberculosis Standards chapter 5[3] conditionally recommended that a comprehensive, patient-centred treatment program be provided for patients initiating treatment, although this was based on weak evidence. The key elements of a program such as this would include incentives and enablers, social service support, housing support,

and provision of transportation.[3] The Canadian Tuberculosis Standards chapter 13[24] also conditionally recommended — based on weak evidence — that individuals who are homeless and with medical conditions associated with high risks of reactivation should be considered for special measures such as incentives and enablers. Those who are at the highest risk in general should also be considered for incentives and enablers.[24]

Limitations

There are limitations associated with the body of evidence and overall conclusions presented in this report.

Two of the overviews of reviews focused on low-income countries,[12,13] and therefore may not be generalizable to the Canadian context or to contexts in higher income countries with a low TB incidence. Additionally, there was a lot of heterogeneity in the studies that were included — the results from primary studies reported in the included SRs fell under the umbrella of types of supports but may have consisted of a variety of different interventions and comparators. Due to the limited reporting of many of the SRs, it was not clear exactly what were the interventions and the comparators.

This report only includes SRs and overviews of reviews; therefore, it is limited because the last search date of the SRs is the true cut-off for information from relevant primary studies. It is likely that some primary studies were missed in the analysis that were published between 2018 — the latest search date in the SRs — and 2020. Therefore, there may be key information missing from the analysis, and it is unknown if any primary studies have been published that would vastly change the clinical findings of this report.

The guidelines that were developed for the Canadian context[3,24] were of low methodological quality because of a lack of reporting of methods, and they were not specific in what incentives and enablers were recommended for individuals with TB. The other included guidelines[25,26] were of higher quality, but were not specific to the Canadian context, and therefore may have limited applicability in Canada.

Conclusions and Implications for Decision- or Policy-Making

Three overviews of reviews[11-13] and 11 SRs[4,11-23] were identified regarding the clinical effectiveness adherence incentives for those who require assistance to complete their tuberculosis treatment. Additionally, 4 guidelines[3,24-26] were identified that provided recommendations regarding the use of adherence incentives for those who require assistance completing their tuberculosis treatment. Two of these guidelines were separate chapters of an overarching guideline (the Canadian Tuberculosis Standards).[3,24]

Overall, the results were neutral to positive for financial incentives and support, food incentives and support, educational incentives and support, non-cash incentives and support, and mixed supports. No studies found a detrimental clinical effect of provision of adherence incentives. The most-reported outcomes were treatment adherence and treatment completion, and the identified populations ranged from people with active or latent TB in the general public, people in low-income countries, people who use drugs, people who were

homeless, and people who were incarcerated or newly released. There was significant overlap between the identified studies. The identified overviews of reviews concluded that sustained material incentives had little to no impact on cure rates or treatment completion for active TB,[12,13] and food incentives did not significantly affect cure rates, mortality, or sputum conversion.[11] However, there were some reported benefits of incentives, as reported in some included SRs, such as benefits of financial incentives on mortality, cure rates, and treatment success. However, these benefits were not sustained in every SR or across every primary study; therefore, it is not possible to conclusively determine a benefit of adherence incentives for treatment of TB.

The SRs were of variable quality. The SRs had comprehensive search strategies and frequently employed sound methodology, such as duplicate screening, duplicate data extraction, and assessments of risk of bias and primary study quality. However, many of the SRs had search dates that were significantly earlier than the publication dates of the report, and 5 of the SRs imposed language limitations on their searches which may have led to potentially missed studies.

The identified guidelines generally recommend the use of incentives and enablers in the provision and initiation of treatment but did not provide specific recommendations regarding which incentives should be given and to whom. Additionally, the evidence on which these recommendations were based was generally weak or of low certainty.

Implementation of policies and programs that provide incentives to individuals require suitable clinical evidence to justify the costs of operation. This report did not include questions regarding cost-effectiveness of these programs because it was not within the scope of the report; therefore, it is unclear whether the economic impact of these programs would be supported by a positive clinical impact to patients. It is necessary to consider the different needs of different populations when determining which incentives will be both appropriate and useful for patients.

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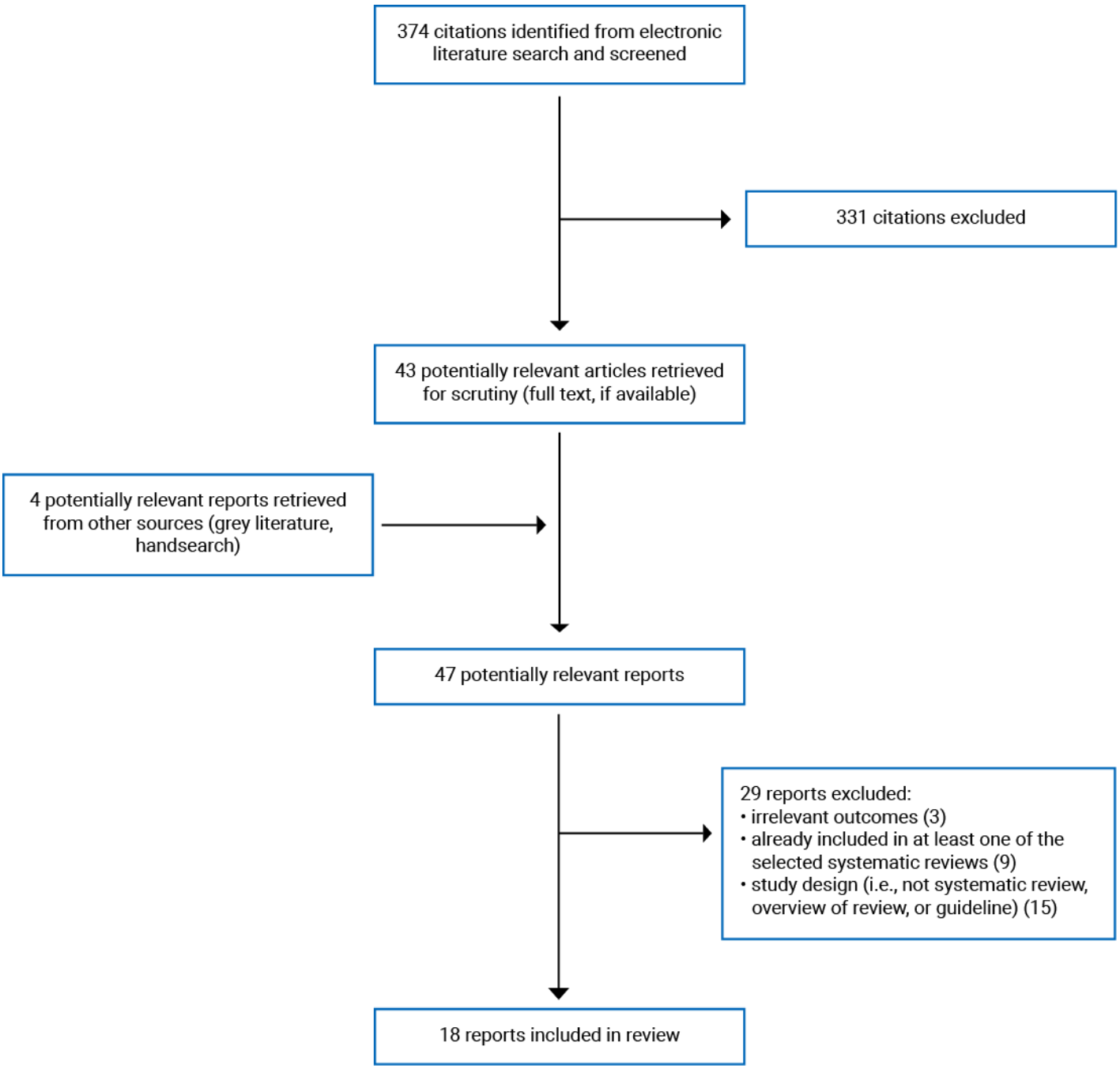
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Network Meta-Analyses

Study citation, country, funding source	Study designs, databases, and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes
Overviews of reviews (umbrella reviews)				
Visser et al. (2018)[11] **Country:** UK **Funded by:** • Cochrane collaboration • Department for International Development, UK Grant: 5242	**Eligible studies:** SRs with predetermined objectives and eligibility criteria, searched ≥ 2 data sources, (≥ 1 electronic database), and data extraction and quality assessment done independently and in duplicate **Search time frame:** Search conducted July 9, 2013, and updated January 29, 2017 **Databases:** CDSR; MEDLINE Ovid (searched from 1946), In-Process and Other Non-Indexed Citations Ovid, and Epub Ahead of Print Ovid; Embase Ovid (searched from 1980); DARE; HTA Database; Campbell Systematic Reviews; Virtual Health DoPHER; 3ie Systematic Reviews; PROSPERO **Studies:** N = 8 **Relevant studies:** n = 1	**Included populations:** • Vulnerable population (i.e., food insecure, malnourished) including pregnant people, people with TB or HIV or both, and older people • Excluded populations that required specialized therapeutic care **Relevant populations for this review:** People with active TB (with or without HIV)	**Intervention:** Community-based, supplementary feeding programs (i.e., providing more food than what was typically normal in the home, either through general feeding programs or selective feeding programs) **Comparator:** No supplements or a different supplement	**Eligible outcomes:** • Death, illness (or disease-related outcomes) • Growth in children • Nutritional status of children and adults • Adherence to treatment • School attendance, cognition tests, and educational attainment • Costs **Relevant outcomes from included studies:** • Mortality • Illness-related outcomes (cure rate, treatment completion/failure, and sputum conversion) • Weight gain • Quality of life

Study citation, country, funding source	Study designs, databases, and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes
Pantoja et al. (2017)[12] **Country:** Chile and UK **Funded by:** • Cochrane • Department of Family Medicine, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile • Institute for Clinical Effectiveness and Health Policy, Buenos Aires, Argentina • Norwegian Knowledge Centre for the Health Services, Oslo, Norway • University of Cape Town, Cape Town, South Africa • South African Medical Research Council, South Africa • Norwegian Agency for Development Cooperation (Norad), Oslo, Norway • Effective Health Care Research, UK[a]	**Eligible studies:** SRs with: • methods section and selection criteria • patient outcomes, use of health care services and resources, health care provider or social outcomes • information on low-income countries (World Bank classification) • publication date after April 2005 **Search time frame:** 2000 to 2010 (HSE); other databases up to December 17, 2016 **Databases:** HSE, CDSR, PubMed, Embase, DARE, HTA Database, CINAHL, LILACS, PsycINFO, EPPI-Centre Evidence Library, 3ie Systematic Reviews and Policy Briefs, WHO Database, Campbell Library, SURE Guides for Preparing and Using Evidence-Based Policy Briefs, European Observatory on Health Systems and Policies, DFID, NICE guidelines,[b]CDC Community Guide,[c]CADTH, Rx for Change, McMaster Plus KT+, McMaster Health Forum **Studies:** N = 39 **Relevant studies:** n = 1	**Included populations:** People in low-income countries **Relevant populations for this review:** Patients with TB in low-income countries	**Intervention:** Alternative delivery, financial and governance arrangements, and implementation strategies **Comparator:** Other strategies or no intervention (usual care)	**Eligible outcomes:** • Patient outcomes • Utilization of health care services, resource use • Health care provider outcomes • Social outcomes **Relevant outcomes from included studies:** • Adherence to anti-tuberculosis treatment • Completion of treatment for active TB

Study citation, country, funding source	Study designs, databases, and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes
Wiysonge et al. (2017)[13] **Country:** South Africa **Funded by:** • Department of Family Medicine, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile • Institute for Clinical Effectiveness and Health Policy, Buenos Aires, Argentina • South African Medical Research Council, Cape Town, South Africa • Norwegian Institute of Public Health, Oslo, Norway • National Research Foundation (CSW), South Africa • Norwegian Agency for Development Cooperation, Norway • The Effective Health Care Research Consortium, UK[a]	**Eligible studies:** SRs with: • methods section and selection criteria • patient outcomes, utilization of health care services, resource use, health care provider or social outcomes • information on low-income countries as classified by the World Bank • publication date after April 2005 **Search time frame:** 2000 to 2010 (HSE); other databases up to December 17, 2016 **Databases:** HSE, CDSR, PubMed, Embase, DARE, HTA Database, CINAHL, LILACS, PsycINFO, EPPI-Centre Evidence Library, 3ie Systematic Reviews and Policy Briefs, WHO Database, Campbell Library, SURE Guides for Preparing and Using Evidence-Based Policy Briefs, European Observatory on Health Systems and Policies, DFID, NICE guidelines,[b]CDC Community Guide,[c]CADTH, Rx for Change, McMaster Plus KT+, McMaster Health Forum **Studies:** N = 15 **Relevant studies:** n = 1	**Included populations:** People in low-income countries **Relevant populations for this review:** Patients with TB in low-income countries	**Intervention:** Financial arrangements (i.e., how funds are collected, insurance schemes, how services are purchased, and the use of targeted financial incentives or disincentives) **Comparator:** Other arrangements or no arrangements (usual care)	**Eligible outcomes:** • Patient outcomes • Utilization of health care services, resource use • Health care provider outcomes • Social outcomes **Relevant outcomes from included studies:** • Adherence to anti-tuberculosis treatment • Completion of treatment for active TB

Study citation, country, funding source	Study designs, databases, and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes
Systematic reviews				
Barss et al. (2020)[14] **Country:** Canada **Funding:** Canadian Institutes for Health Research (Ottawa, ON, Canada)	**Eligible studies:** RCTs and cohort studies with: • primary study data • LTBI treatment or diagnosis • outcomes related to 7 steps of LTBI framework • comparators • absolute numbers reported **Search time frame:** January 1990 to February 25, 2018 **Databases:** PubMed, Cochrane Library (Systematic Reviews and Trials), Embase **Studies:** N = 30 **Relevant studies:** n = 9	**Included populations:** Populations eligible for LTBI management **Relevant populations for this review:** Populations eligible for LTBI management	**Intervention:** Patient incentives and education **Comparator:** Historical or concurrent control groups	**Eligible outcomes:** Outcomes affecting the LTBI cascade framework, such as: • identification of those eligible for LTBI management • initial assessment started • initial assessment completed • medical evaluation started • medical evaluation completed • LTBI treatment recommended by provider • patient starts LTBI treatment **Relevant outcome from included studies:** Patient acceptance of treatment or completion

Study citation, country, funding source	Study designs, databases, and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes
Law et al. (2019)[15] **Country:** Canada **Funding:** Canadian Institutes of Health Research (FRN143999) Vanier Canada Graduate Scholarship	**Eligible studies:** Primary studies with: • final treatment outcomes including losses to follow-up • interventions for patients with drug-resistant TB with psychosocial, education, or material support • excluded pediatric-only studies **Search time frame:** January 2000 to December 2017 **Databases:** MEDLINE (PubMed), Embase, Embase Classic, Web of Science, Scopus, PsycINFO, Global Health, Social Work abstracts, Cochrane Central Register of Controlled Trials **Studies:** N = 25 (35 cohorts) **Relevant studies:** n = 19	**Included populations:** Patients with drug-resistant TB **Relevant populations for this review:** Patients with drug-resistant TB	**Intervention:** Psychosocial, educational, or material support **Comparator:** No comparator or controls (historical or concurrent)	**Eligible outcomes:** • Loss to follow-up, defined as treatment interruption for ≥ 2 months • Adherence **Relevant outcomes from included studies:**All noted above
Riquelme-Miralles et al. (2019)[4] **Country:** Spain **Funding:** None	**Eligible studies:** • English or Spanish RCTs or controlled clinical trials • Excluded pediatric-only studies **Search time frame:** Up to December 31, 2018 **Databases:** MEDLINE, Embase **Studies:** N = 37 (28 active, 10 latent) **Relevant studies:** n = 10	**Included populations:** People with latent or active TB **Relevant populations for this review:** People with latent or active TB	**Intervention:** Non-pharmacological interventions to increase adherence to treatment **Comparator:** Control (unclear what controls were eligible)	**Eligible outcomes:** • Treatment completion • Treatment success • Percentage of taken or missed doses • Pill count • Isoniazid in urine • Sputum smear conversion • Medication taken on time **Relevant outcomes from included studies:** As above

Study citation, country, funding source	Study designs, databases, and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes
Alipanah et al. (2018)[16] **Country:** US **Funding:** WHO	**Eligible studies:** RCTs, prospective or retrospective cohort studies **Search time frame:** Through February 3, 2018 **Databases:** MEDLINE **Studies:** N = 129 **Relevant studies:** n = 15	**Included populations:** Adults or children in any setting undergoing active TB treatment **Relevant populations for this review:** Adults or children in any setting undergoing active TB treatment	**Intervention:** Interventions to promote adherence **Comparator:** Routine practice	**Eligible outcomes:** • Cure • Treatment success • Death • Loss to follow-up • Relapse • Adherence • Development of resistance **Relevant outcomes from included studies:** • Cure • Treatment success • Death • Loss to follow-up • Relapse • Adherence
Liu et al. (2018)[17] **Country:** US **Funding:** • McMaster University (Department of HEI) • Vision 2020 Fund	**Eligible studies:** Quantitative and qualitative studies **Search time frame:** Up to June 30, 2016 **Databases:** PubMed, Embase **Studies:** N = 54 **Relevant studies:** n = 7	**Included populations:** Patients with latent TB **Relevant populations for this review:** Patients with latent TB	**Intervention:** Interventions that address barriers for treatment compliance **Comparator:** Any comparator	**Eligible outcomes:** Treatment adherence **Relevant outcomes from included studies:** Treatment adherence

Study citation, country, funding source	Study designs, databases, and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes
Muller et al. (2018)[18] **Country:** Brazil **Funding:** • Hospital de Clínicas de Porto Alegre Research Incentive Fund • Coordenação de Aperfeiçoamento de Pessoal de Nível Superior Programa Institucional de Bolsas de Iniciação Científica Universidade • Federal do Rio Grande do Sul, Conselho Nacional de Desenvolvimento Científico e Tecnológico	**Eligible studies:** RCTs **Search time frame:** Inception to October 2015 **Databases:** PubMed, Cochrane Central Register of Controlled Trials (Cochrane Central), LILACS, Embase **Studies:** N = 19 **Relevant studies:** n = 7	**Included populations:** Patients with TB, excluding children and latent TB **Relevant populations for this review:** Patients with TB	**Intervention:** Interventions for improving adherence, including DOTS, financial incentives, food incentives, and patient education or counselling **Comparator:** No incentives, other strategies for adherence	**Eligible outcomes:** • Cure rate • Mortality • Default rates **Relevant outcomes from included studies:** • Cure rate • Mortality • Default rates
Richterman et al. (2018)[19] **Country:** US **Funding:** WHO	**Eligible studies:** Clinical trials and observational studies **Search time frame:** Inception to August 4, 2017 **Databases:** PubMed, Embase, Cochrane Library, ClinicalTrials.gov **Studies:** N = 8 **Relevant studies:** n = 8	**Included populations:** Patients with active pulmonary TB in low- and middle-income countries **Relevant populations for this review:** Patients with active pulmonary TB	**Intervention:** Cash transfer interventions **Comparator:** NR	**Eligible outcomes:** • Treatment completion • Microbiologic cure • Treatment success **Relevant outcomes from included studies:** As above

Study citation, country, funding source	Study designs, databases, and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes
Herrmann et al. (2017)[20] **Country:** US **Funding:** NIDA T32 DA007242	**Eligible studies:** RCTs, within-subject studies, or studies with historical control cohorts **Search time frame:** Up to June 2015 **Databases:** PubMed, MEDLINE, Google Scholar **Studies:** N = 23 **Relevant studies:** n = 8	**Included populations:** Patients with hepatitis, HIV, and/or TB with a co-occurring substance use disorder **Relevant populations for this review:** Patients with TB or TB and HIV/ hepatitis	**Intervention:** Contingency management interventions for prevention, diagnosis, or treatment, with quantifiable monetary value **Comparator:** Control groups	**Eligible outcomes:** • Behaviours targeted by intervention • Medical target (e.g., treatment completion) **Relevant outcomes from included studies:** • Attendance for treatment • Treatment completion • Number of doses taken
Heuvelings et al. (2017)[21] **Country:** The Netherlands **Funding:** European Centre of Disease Prevention and Control	**Eligible studies:** RCTs or NRS **Search time frame:** January 1, 1990 to April 10, 2015 **Databases:** EMBASE, MEDLINE, MEDLINE In-Process **Studies:** N = 19 **Relevant studies:** n = 3	**Included populations:** Patients with TB, excluding latent TB, who are hard-to-reach (i.e., migrants, refugees, asylum seekers, the Roma population, people who are homeless, people who use drugs, people living with HIV, prisoners, sex workers) **Relevant populations for this review:** Patients with TB	**Intervention:** Interventions for prevention, control, identification, and management of TB **Comparator:** NR	**Eligible outcomes:** • Effectiveness • Cost-effectiveness • Adverse events • Usefulness of intervention **Relevant outcomes from included studies:** • Effectiveness • Adverse events

Study citation, country, funding source	Study designs, databases, and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes
Stuurman et al. (2016)[22] **Country:** Sweden **Funding:** ECDC	**Eligible studies:** RCTs, non-randomized prospective comparative studies, prospective longitudinal observational studies, retrospective studies **Search time frame:** Up to February 3, 2014 **Databases:** PubMed, Embase **Studies:** N = 115 **Relevant studies:** n = 4	**Included populations:** Patients with latent TB **Relevant populations for this review:** Patients with latent TB	**Intervention:** Interventions to improve LTBI treatment initiation, adherence or completion **Comparator:** No intervention to improve LTBI treatment initiation, adherence or completion	**Eligible outcomes:** • Treatment adherence • Treatment completion • Treatment initiation • Effectiveness • Acceptability • Feasibility **Relevant outcomes from included studies:** • Treatment adherence • Treatment completion • Treatment initiation • Effectiveness
Van Hoorn et al. (2016)[23] **Country:** The Netherlands **Funding:** • HIDN • USAID	**Eligible studies:** Primary studies and reviews **Search time frame:** January 1, 1990 to March 15, 2015 **Databases:** PubMed, Embase **Studies:** N = 25 **Relevant studies:** n = 21	**Included populations:** Patients taking TB treatment **Relevant populations for this review:** Patients taking TB treatment	**Intervention:** Psycho-emotional and socioeconomic interventions **Comparator:** Standard support	**Eligible outcomes:** • Treatment adherence • Treatment outcomes • Financial burden **Relevant outcomes from included studies:** As above

CDSR = Cochrane Database of Systematic Reviews; DARE = Database of Abstracts of Reviews of Effectiveness; DFID = UK Department for International Development; DoPHER = Database of Promoting Health Effectiveness Reviews; ECDC = European Centre for Disease Prevention and Control; EPPI = Evidence for Policy and Practice Information and Co-ordinating; HIDN = The Global Health Bureau, Office of Health, Infectious Disease and Nutrition; HSE = Health Systems Evidence; HTA = health technology assessment; LILACS = Literatura Latino Americana em Ciencias da Saude, Latin American and Caribbean Health Sciences Literature; LTBI = latent tuberculosis infection; NICE = National Institute for Health and Care Excellence; NIDA = National Institute on Drug Abuse; NR = not reported; SURE = Supporting the Use of Research Evidence; TB = tuberculosis; USAID = US Agency for International Development.

[a]Effective Health Care Research Consortium is funded by UK aid from the UK Government for the benefit of developing countries.

[b]Includes NICE guidelines for public health and systematic reviews.

[c]Community Guide is the CDC's Guide to Community Preventive Services.

Table 3: Characteristics of Included Guidelines

Country, funding body, developing institution	Intended users, target population	Relevant intervention and outcomes	Evidence collection and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
WHO (2017)[25]						
Country: Global **Funding:** USAID **Developing institution:** WHO	**Intended users:** Patients, clinicians, and policy-makers **Target population:** Patients with drug-susceptible TB	**Intervention:** Treatment adherence interventions **Outcome(s):** • Treatment success • Treatment completion • Sputum conversion	Evidence review focused on RCTs with direct comparisons between the intervention and comparator of interest, commissioned by independent reviewers	Evidence assessed using GRADE Recommendations of *strong* and *conditional* for patients, clinicians, and policy-makers (see Table 4)	Teams of experts assessed the evidence as part of a guideline development group using "Evidence to Decision" tables. The recommendations were created using consensus and discussions; no voting was needed in the development	The guidelines were peer reviewed by an external review group of experts and end users

Country, funding body, developing institution	Intended users, target population	Relevant intervention and outcomes	Evidence collection and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
NICE (2016)[26]						
Country: UK **Funding:** Not specified **Developing institution:** NICE	**Intended users:** • Health care professionals, TB multidisciplinary teams • Substance misuse services, prisons, and immigration removal centres, local government, TB control boards, voluntary sector workers • Public Health England and NHS England, directors of public health and public health consultants • People with TB and their carers **Target population:** Children, young people, and adults with latent TB	**Intervention:** Adherence to treatment and follow-up **Outcome(s):** Adherence to testing and treatment	Update to a previous 2011 version of the guideline Multiple SRs were conducted for the entire guideline, using comprehensive search strategies For each SR, detailed eligibility criteria were reported	NICE methodological checklists were used to critically appraise RCTs and cohort studies. GRADE evidence profiles were prepared and GRADE was used to critically appraise the body of evidence Criteria considered included risk of bias and inconsistency	Developed in accordance with the NICE manual for developing guidelines[30] The results of the meta-analyses were sent to the guideline development group before each meeting, where the findings were presented in evidence tables, excluded study tables, GRADE profiles, and evidence statements. A consensus method was used to formulate the recommendations. Specific "linking evidence to recommendation" criteria guided the development of the recommendations. The wording of the recommendations denotes the certainty: *offer*, *do not offer*, and *consider* (see Table 4)	The guideline was published online for 2 formal rounds of public and stakeholder consultation before publication, which involved responding to each comment and maintaining an audit trail

Country, funding body, developing institution	Intended users, target population	Relevant intervention and outcomes	Evidence collection and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
Canadian Tuberculosis Standards, Chapter 5 (2014)[3]						
Country: Canada **Funding:** Jointly funded by the CTS of The Lung Association, and the Public Health Agency of Canada **Developing institution:** Jointly produced by the CTS of The Lung Association, and the Public Health Agency of Canada	**Intended users:** Public health and clinical professionals **Target population:** Patients with active TB	**Intervention:** Incentives and enablers **Outcome(s):** Adherence	Developed by 1 or more authors with expertise in tuberculosis prevention and control	Modified GRADE The gradings of the recommendations were *strong* and *conditional* (see Table 4)	Not reported	External review conducted, noted to have been done by the Association of Medical Microbiology and Infectious Disease Canada and others, but the others were not specified
Canadian Tuberculosis Standards, Chapter 13 (2014)[24]						
Country: Canada **Funding:** Jointly funded by the CTS of The Lung Association, and the Public Health Agency of Canada **Developing institution:** Jointly produced by the CTS of The Lung Association, and the Public Health Agency of Canada	**Intended users:** Public health and clinical professionals **Target population:** Patients with active TB	**Intervention:** Incentives and enablers **Outcome(s):** Adherence	Developed by 1 or more authors with expertise in tuberculosis prevention and control	Modified GRADE The gradings of the recommendations were *strong* and *conditional* (see Table 4)	Not reported	External review conducted, noted to have been done by the Association of Medical Microbiology and Infectious Disease Canada and others, but the others were not specified

CTS = Canadian Thoracic Society; GRADE = Grading of Recommendations Assessment, Development and Evaluation; NICE = National Institute for Health and Care Excellence; NR = not reported; RCT = randomized controlled trial; SR = systematic review; TB = tuberculosis; USAID = United States Agency for International Development.

Table 4: Rating System for Included Guidelines

Strength of recommendation	Definition
WHO (2017)[25]	
For patients: "strong"	"Most individuals in this situation would want the recommended course of action and only a small proportion would not (p. 5)."[25]
For patients: "conditional"	"The majority of individuals in this situation would want the suggested course of action, but many would not (p. 5)." [25]
For clinicians: "strong"	"Most individuals should receive the intervention (p. 5)."[25]
For clinicians: "conditional"	"Recognize that different choices will be appropriate for individual patients, and that patients must be helped to arrive at a management decision consistent with their values and preferences (p. 5)."[25]
For policy-makers: "strong"	"The recommendation can be adopted as policy in most situations (p. 5)."[25]
For policy-makers: "conditional"	"Policy-making will require substantial debate and involvement of various stakeholders (p. 5)."[25]
NICE (2016)[26]	
"Offer/should…"	For the vast majority of patients, the intervention will do more good than harm.[30]
"Do not offer"	The intervention will not be of benefit for most patients.[30]
"Consider…"	"…recommendation for which the evidence of benefit is less certain"[30] or "…there is a closer balance between benefits and harms (activities or interventions that could be used)."[30]
Canadian Tuberculosis Standards (2014)[3,24]	
Strong	"The recommendation implies that the desirable effects clearly outweigh undesirable effects, was based on strong/moderate evidence and was considered unlikely to change with additional published evidence (p. 2)."[31]
Conditional	"The recommendation implies that the desirable effects are closely balanced with undesirable effects, and/or was based on moderate/weak/very weak evidence and was considered likely to change with additional published evidence (p. 2)."[31]

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Reviews Using AMSTAR 2[8]

Strengths	Limitations
Visser et al. (2018)[11]	
• Research questions and inclusion criteria are clear • Protocol established before conducting review • Selection of the study designs for inclusion in the review explained • Literature search strategy was comprehensive • Study selection performed in duplicate (independently and in duplicate for the first search and with 1 author screening and 1 author reviewing for the later search) • Data extraction performed by 1 author and another author checked for accuracy • List of excluded studies provided, and exclusions were justified • Overlap of primary studies assessed in the included SRs (there was no matrix, but there was limited overlap which was noted in the write up) • Included studies described in adequate detail • Methodological quality assessed of included SRs and the primary studies within these reviews • Indirect comparisons were not explored • Conflicts of interest and funding of overview reported	• Did not report on the sources of funding for the studies included in the review

Strengths	Limitations
Pantoja et al. (2017)[12]	
• Research questions and inclusion criteria are clear • Protocol established before conducting review • Review authors explained their selection of the study designs for inclusion in the review • Review authors used a comprehensive literature search strategy • Review authors performed study selection in duplicate – specifically independently and in duplicate for the titles and abstracts and with 1 author screening and 1 author reviewing for the full texts • One review author performed data extraction, and another checked for accuracy • Review authors provided list of excluded studies and justified the exclusions • Review authors assessed the methodological quality of included SRs and the primary studies within these reviews • Review authors did not explore indirect comparisons • Conflicts of interest and funding reported	• Did not report on the sources of funding for the studies included in the review • Some results missing from review (e.g., numerical results for tuberculosis treatment adherence) • No information on overlap of primary studies
Wiysonge et al. (2017)[13]	
• Research questions and inclusion criteria are clear • Established protocol before conducting review • Review authors explained their selection of the study designs for inclusion in the review • Review authors used a comprehensive literature search strategy • Review authors performed study selection in duplicate – specifically independently and in duplicate for the titles and abstracts and with 1 author screening and 1 author reviewing for the full texts • One review author performed data extraction, and another checked for accuracy • Review authors provided list of excluded studies and justified the exclusions • Review authors assessed the methodological quality of included SRs and the primary studies within these reviews • Review authors did not explore indirect comparisons • Conflicts of interest and funding reported	• Did not report on the sources of funding for the studies included in the review • Some results missing from review (e.g., numerical results for tuberculosis treatment adherence) • No information on overlap of primary studies

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; NR = not reported; RoB = risk of bias; SR = systematic review.

Table 6: Strengths and Limitations of Systematic Reviews Using AMSTAR 2[8]

Strengths	Limitations
Barss et al. (2020)[14]	
• Research questions and inclusion criteria are clear • The review authors explained their selection of the study designs for inclusion in the review • Details of the interventions in the primary studies clear (supplementary data) • All forest plots reported • The review authors used a comprehensive literature search strategy • The review authors performed study selection and data extraction in duplicate • RoB assessed in individual studies • Random effects used for meta-analysis with inverse variance weighting method • Conflicts of interest and funding reported	• The inclusion criteria are not clear with regards to the comparators and interventions, and the population is not stated clearly • Search performed more than 1.5 years before publication, with no updates to the search • No established protocol before conducting review • No provided list of excluded studies and justification of exclusions • High heterogeneity in the pooled studies • No discussion of quality of studies or risk of bias • Limited to English-only studies
Law et al. (2019)[15]	
• Research questions and inclusion criteria are clear • Established protocol registered ahead of time in PROSPERO • The review authors explained their selection of the study designs for inclusion in the review • Details of the interventions in the primary studies clear (main report and supplementary data) • The review authors used a comprehensive literature search strategy • RoB assessed in individual studies • Conflicts of interest and funding reported	• One reviewer performed data extraction • One reviewer performed screening for titles and abstracts • No list of excluded studies • Search performed more than 1.5 years before publication, with no updates to the search • High heterogeneity in the pooled studies

Strengths	Limitations
Riquelme-Miralles et al. (2019)[4]	
• Eligible outcomes are clearly stated • The review authors explained their selection of the study designs for inclusion in the review • Details of the interventions in the primary studies clear (supplementary data) • No list of excluded studies, but studies and reasons for exclusion provided in text with references • The review authors used a comprehensive literature search strategy • The review authors performed study selection in duplicate • RoB assessed in individual studies • Conflicts of interest and funding reported	• Research questions and inclusion criteria were not clear for all aspects • Population is unclear; it appears to be all individuals with TB in the methods, but studies exclusively on children were excluded and the reason for exclusion was not mentioned until the discussion • Unclear if data extraction was also performed in duplicate • Authors found that despite using more than 1 database, a significant portion of the included studies came from the reference lists of other SRs, which may indicate that keywords or databases used were not sufficient to capture the relevant studies • Statistical results not reported
Alipanah et al. (2018)[16]	
• Research questions and inclusion criteria are clear • The review authors explained their selection of the study designs for inclusion in the review • Details of the interventions in the primary studies clear (supplementary data) • Full-text selection performed in duplicate • Publication bias assessed for cohort studies • RoB assessed in individual studies • Conflicts of interest and funding reported	• Abstract selection not performed in duplicate • No list of excluded studies • Only 1 database searched • Only English-language studies included (except for 2 foreign language studies that had already been abstracted by other reviews) • High heterogeneity in some meta-analyzed data • Unclear if data were abstracted in duplicate

Strengths	Limitations
Liu et al. (2018)[17]	
• Research questions and inclusion criteria are clear • The review authors explained their selection of the study designs for inclusion in the review • The review authors used a comprehensive literature search strategy • Full-text selection performed in duplicate • RoB assessed in individual studies • Conflicts of interest and funding reported	• Search performed more than 1.5 years before publication, with no updates to the search • Study selection performed by 1 reviewer • Data were extracted by 1 reviewer (except for a 10% subset for verification) • Only English-language studies included, with some relevant non-English studies identified but not included in the results • No list of excluded studies • Details of the interventions in the primary studies unclear (written as "strategies to improve adherence" or "predictors and barrier for compliance or adherence") • Results from some studies were not reported (e.g., the study was noted in text as including incentive strategies, but there were no numerical results regarding incentives) • Some conclusions did not seem to follow from the results reported (e.g., concluding that incentives significantly increased completion of treatment, but the numerical results reported did not follow this pattern)
Muller et al. (2018)[18]	
• Research questions and inclusion criteria are clear • The review authors explained their selection of the study designs for inclusion in the review • Abstract selection and full-text selection performed in duplicate • The review authors used a comprehensive literature search strategy • Data were abstracted in duplicate • No limitation on language • Lower heterogeneity in meta-analyzed data, likely due to inclusion of only RCTs • Details of the interventions in the primary studies clear • RoB assessed in individual studies • Conflicts of interest and funding reported	• Search performed more than 1.5 years before publication, with no updates to the search • No list of excluded studies

Strengths	Limitations
Richterman et al. (2018)[19]	
• Protocol established before review and noted as available • Research questions and inclusion criteria are clear • Literature search strategy was comprehensive • Abstract selection and full-text selection performed in duplicate • Data were abstracted in duplicate into a standardized form • Publication bias assessed for meta-analyzed data • Lower heterogeneity in meta-analyzed data • Details of the interventions in the primary studies clear • RoB assessed in individual studies • Conflicts of interest reported	• Eligible comparators not clear • Funding source unclear (assumed to be WHO)
Herrmann et al. (2017)[20]	
• Research questions are clear • Abstract selection and full-text selection performed in triplicate • Literature search strategy was comprehensive • Data were abstracted in triplicate • Details of the interventions in the primary studies clear • Conflicts of interest and funding reported	• Search performed more than 1.5 years before publication, with no updates to the search • The review authors do not explain their selection of the study designs for inclusion in the review • Did not assess quality of included studies • Eligible comparators not clear • Only English-language studies included

Strengths	Limitations
Heuvelings et al. (2017)[21]	
• Established protocol registered ahead of time in PROSPERO • Inclusion criteria and research questions are clear (supplementary information) • Abstract selection and full-text selection performed in duplicate • Data were abstracted with independent checking by a second author using a pre-specified extraction form • Details of the interventions in the primary studies clear in evidence tables • RoB assessed in individual studies • No language restrictions on search • Conflicts of interest and funding reported	• Search performed more than 1.5 years before publication • No list of excluded studies • Eligible comparators not clear • Did not include some results from primary studies; required to get results from a previous review by another group
Stuurman et al. (2016)[22]	
• Protocol established before review and noted as available • Inclusion criteria and research questions are clear (supplementary information) • No geographical, time, or language restrictions on search • The review authors used a comprehensive literature search strategy • Abstract selection and full-text selection performed in duplicate • Details of primary studies clear • RoB assessed in individual studies • Data were abstracted in duplicate with a third author independently checking accuracy • Conflicts of interest and funding reported	• Search performed more than 1.5 years before publication, with no updates to the search • Results in text do not appear to match results in evidence tables • No list of excluded studies

Strengths	Limitations
Van Hoorn et al. (2016)[23]	
• Inclusion criteria and research questions are clear • Literature search strategy was comprehensive • Abstract selection performed in duplicate • Data were abstracted with a second author independently checking accuracy • Details of primary studies clear • RoB assessed in individual studies • Funding of primary studies reported • Conflicts of interest and funding reported	• Full-text screening was done by 1 reviewer • No list of excluded studies • No protocol available • High heterogeneity in some meta-analyzed data • Text is not well referenced, making it difficult to determine which studies the results are referring to

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; NR = not reported; RoB = risk of bias.

Table 7: Strengths and Limitations of Guidelines Using AGREE II[9]

Item	WHO guideline for drug-susceptible TB (2017)[25]	NICE (2016)[26]	PHAC Identification High-Risk (2014)[24]	PHAC Treatment Active TB (2014)[3]
Domain 1: Scope and Purpose				
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes	No	No
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes	No	No
3. The population (e.g., patients, public) to whom the guideline is meant to apply is specifically described.	Partially	Yes	Yes	No
Domain 2: Stakeholder Involvement				
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes	Partially	Partially
5. The views and preferences of the target population (e.g., patients, public) have been sought.	Partially	Yes	No	No
6. The target users of the guideline are clearly defined.	Yes	Yes	Partially	Partially
Domain 3: Rigour of Development				
7. Systematic methods were used to search for evidence.	Yes	Yes	No	No
8. The criteria for selecting the evidence are clearly described.	Yes	Yes	No	No
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Yes	No	No
10. The methods for formulating the recommendations are clearly described.	Yes	Yes	No	No
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes	Partially	Partially
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes	No	No
13. The guideline has been externally reviewed by experts before its publication.	Yes	Yes	Partially	Partially
14. A procedure for updating the guideline is provided.	Yes	Yes	No	No
Domain 4: Clarity of Presentation				
15. The recommendations are specific and unambiguous.	Yes	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes	Yes	Yes

Item	WHO guideline for drug-susceptible TB (2017)[25]	NICE (2016)[26]	PHAC Identification High-Risk (2014)[24]	PHAC Treatment Active TB (2014)[3]
Domain 5: Applicability				
18. The guideline describes facilitators and barriers to its application.	Partially	No	No	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes	Partially	No	No
20. The potential resource implications of applying the recommendations have been considered.	Partially	Yes	No	No
21. The guideline presents monitoring and/or auditing criteria.	Yes	Yes	No	No
Domain 6: Editorial Independence				
22. The views of the funding body have not influenced the content of the guideline.	Yes	Partially	Partially	Partially
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes	No	No

AGREE II = Appraisal of Guidelines for Research and Evaluation II; NICE = National Institute for Care and Health Excellence; PHAC = Public Health Agency of Canada; WHO = WHO.

Appendix 4: Main Study Findings and Authors' Conclusions

Summary of Findings From Included Overviews of Reviews

Visser et al. (2018)[11]

Main Study Findings

- One included SR
  - Patients with TB with or without HIV
  - Included interventions of oral nutritional supplement given for more than 4 weeks
  - Intervention: 60 days to 6 months long
  - Follow-up: 8 weeks to 1 year
- Quality of life
  - 2 primary studies with 134 participants
  - Conclusion: "supplementation may have increased QoL scores during the first 2 months of treatment (low-certainty evidence) (p. 17)."
- Nutritional status of adults
  - Weight gain (kg) increase at
    - 6 weeks: mean difference = 1.73 (95% CI, 0.81 to 2.65) (1 primary study with 34 participants)
    - 12 weeks: mean difference = 2.60 (95% CI, 1.74 to 3.46) (1 primary study with 100 participants)
    - 32 weeks: mean difference = 2.60 (95% CI, 0.52 to 4.68) (1 primary study with 265 participants)
  - Weight gain did not change in 1 primary study with patients co-infected with HIV
  - Conclusion: probably a modest increase in weight, but not consistent (moderate-certainty evidence)
- Illness (or disease-related outcomes)
  - No difference in disease outcomes, but studies underpowered for free food or high-energy supplements versus no supplementary feeding
    - Cure rate: RR = 0.91 (95% CI, 0.59 to 1.41) (1 primary study with 102 participants)
    - Sputum negative at 8 weeks results: RR = 1.08 (95% CI, 0.86 to 1.37) (3 primary studies with total of 222 participants)
  - One primary study found significant benefit for treatment completion and sputum conversion
  - Conclusion: very low-certainty evidence for all
- Mortality
  - Death at 1-year follow-up
    - RR = 0.34 (95% CI, 0.10 to 1.20)
    - No subgroup differences for patient with or without HIV
    - Conclusion: very low-certainty evidence

Authors' Conclusion

"Mortality data were limited and underpowered in meta-analysis in all populations (children with MAM, in children with HIV, and in adults with tuberculosis) … In adults with tuberculosis, one small trial found a significant benefit on treatment completion and sputum conversion rate. There were also significant but modest benefits in terms of weight gain (up to 2.60 kg) during active tuberculosis (p. 2)."

Pantoja et al. (2017)[12] and Wiysonge et al. (2017)[13]

Pantoja et al. (2017)[12]and Wiysonge et al. (2017)[13] included the same SR (Lutge et al. [2015][6]). They also provided identical results for the review.

Main Study Findings

- One included SR
  - Patients receiving drug therapy to cure TB
  - Included 11 primary studies; 2 studies were on adherence to treatment
  - Comparisons included:
    - Immediate versus deferred incentives
    - Cash versus non-cash incentives
    - Different levels of cash incentives
    - Incentives versus other interventions

"Sustained material incentives may lead to little or no difference in cure or completion of treatment for active TB, compared to no incentive (p. 42)."

"Compared to a non-cash incentive, cash incentives may slightly increase the number of people who return to a clinic for reading of their tuberculin skin test and may increase the number of people who complete TB prophylaxis (p. 42)."

"Compared to counselling or education interventions, material incentives may increase the number of people who return to a clinic for reading of their tuberculin skin test (p. 42)."

"Compared to counselling or education interventions, material incentives may lead to little or no difference in the number of people who return to a clinic to start or continue TB prophylaxis or in the number of people who complete TB prophylaxis (p. 43)."

"Higher cash incentives may slightly improve the number of people who return to a clinic for reading of their tuberculin skin test, compared to lower cash incentives (p. 43)."

Authors' Conclusion

"Compared to routine care, cash-and non-cash incentives probably increase health service utilization (return visits for tuberculin skin test reading, start or continuation of treatment) (low- to moderate-certainty evidence). They may not improve completion of TB prophylaxis (low-certainty evidence), and it is uncertain if they improve completion of treatment for active TB (very low-certainty evidence). Cash incentives may slightly improve patient return for tuberculin skin test reading and completion of TB prophylaxis compared to non-cash incentives (low-certainty evidence). Immediate (compared to deferred) incentives may not improve adherence to anti-tuberculosis treatment (low-certainty evidence) (p. 14)."

Summary of Findings From Included Systematic Reviews

Barss et al. (2020)[14]

Main Study Findings

N = 9 total primary studies

- Completion of initial assessments
  - Improved with financial and non-financial incentives: risk difference = 42 (95% CI, 34 to 51) additional patients completing initial assessment per 100 starting, 9 studies or cohorts, I^2 = 89%
  - Did not significantly improve with patient education: risk difference = 22 (95% CI, 6 to 49 per 100 people), 5 studies or cohorts, I^2 = 97%
- Completion of medical evaluations
  - improved significantly with patient incentives (risk difference = 48; 95% CI, 15 to 81 additional patients completing medical evaluation per 100 starting), 2 studies or cohorts, I^2 = 93%
- Acceptance of treatment
  - improved with patient incentives (risk difference = 49; 95% CI, 46 to 52) additional patients accepting treatment per 100 recommended), 1 study or cohort
  - improved with patient education (risk difference = 15; 95% CI, 11 to 19) additional per 100), 1 study or cohort
- One study included patient incentives but the results for incentives were not reported

Authors' Conclusion

"Step 7: In single studies, patient incentives (49 [95% CI, 46–52] additional patients accepting treatment per 100 recommended) and patient education (15 [95% CI, 11–19] additional per 100) improved the rates of patient acceptance of LTBI [latent tuberculosis infection] treatment (p. 105)."

Law et al. (2019)[15]

Main Study Findings

N = 19

Losses to follow-up

- Financial support
  - Financial support offered in 12 studies, and included reimbursement of rent and travel expenses, and compensation of lost wages
  - Financial support associated with fewer losses to follow-up
  - Pooled proportions of patients lost to follow-up
    - Covering travel expenses (10 cohorts) was associated with less loss to follow-up: 0.15 (95% CI, 0.10 to 0.24; I^2 = 94%)
    - Covering rent and travel expenses (4 cohorts) associated with less loss to follow-up: 0.08 (95% CI, 0.06 to 0.10; I^2 = 0%)
    - Providing supplemental income (3 cohorts) associated with less loss to follow-up: 0.06 (95% CI, 0.00 to 0.61; I^2 = 96%)
    - No financial support (14 cohorts): 0.24 (95% CI, 0.17 to 0.34; I^2 = 95%)

        - Cochran Q test: P < 0.01
    - In patients who received twice daily or daily direct observed therapy (DOT) (proportion of patients lost to follow-up)
        - Covering travel expenses (8 cohorts) was associated with less loss to follow-up: 0.14 (95% CI, 0.07 to 0.24; I^2 = 94%)
        - Covering rent or travel expenses (4 cohorts) associated with less loss to follow-up: 0.08 (95% CI, 0.06 to 0.10; I^2 = 0%)
        - Providing supplemental (2 cohorts) associated with less loss to follow-up: 0.01 (95% CI, 0.00 to 0.68; I^2 = 88%)
        - No financial support (10 cohorts): 0.21 (95% CI, 0.14 to 0.30; I^2 = 94%)
        - Cochran Q test: P < 0.01
- Food packages
    - Food packages provided in 15 studies
    - Food package included food baskets, provisions of basic foods, hot meals, and more
        - weak evidence of an association with lower losses to follow-up
    - Pooled proportions of patients lost to follow-up
        - Food packages (14 cohorts) associated with less loss to follow-up: 0.15 (95% CI, 0.10 to 0.22I^2 = 95%)
        - No food packages: 0.18 (95% CI, 0.11 to 0.29; I^2 = 96%)
        - Cochran Q test: P = 0.51
    - In patients who received twice daily or daily DOT (proportion of patients lost to follow-up)
        - Food packages (13 cohorts) associated with less loss to follow-up: 0.13 (95% CI, 0.09 to 0.19; I^2 = 94%)
        - No food packages: 0.13 (95% CI, 0.06 to 0.27; I^2 = 97%)
        - Cochran Q test: P = 1.00

Authors' Conclusion

"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 (p. 7)."

Riquelme-Miralles et al. (2019)[4]

Main Study Findings

N = 8

Completion (%)

- Food supplements and incentives
    - Active TB
        - 1 study (food supplements versus standard care) found benefit in adherence (98% versus 82%)
        - 1 study (food incentives versus standard care) found no benefit in adherence over 8 months (76% versus 78%)

- Education and economic incentives
  - Active TB
    - 1 study (economic and education incentive versus standard care) found no benefit over 6 months to 9 months (97.7% versus 91.1%)
  - Latent TB, patients who were homeless
    - 1 study (cash incentives versus non-cash incentives) found no benefit over 6 months (89.2% versus 81.5%)
    - 1 study (monetary incentives versus standard care) found benefit over 6 months (44% versus 26%, P not reported, but reported as not significant in other SRs)
  - Latent TB, inmates
    - 1 study (non-cash incentive versus standard care) found benefit over 6 months (23% versus 12%), but no benefit over 6 months for education versus standard care (12% versus 12%)
  - Latent TB, people who use drugs
    - 1 study (outreach plus incentive versus outreach alone and incentive alone versus outreach alone) found benefit for incentives and outreach and incentives alone over 6 to 12 months (52.8% versus 3.6% and 60% versus 3.6%, respectively)
  - Latent TB, adolescents
    - 1 study (peer counselling and incentive versus standard care and incentive contract versus standard care) found no benefit for either peer counselling plus incentive or incentives alone over 6 months (84.8% versus 77.8% and 76.4% versus 77.8%, respectively)
  - Latent TB, general
    - 1 study (education and economic incentives versus standard care) found benefit for incentives and outreach and incentives alone over 9 months to 12 months (63.8% versus 27.1%)

Authors' Conclusion

"The studies found are in reality very different from each other. There is too much variability in studies on therapeutic adherence, both in the active tuberculosis and in the latent infection treatment groups, to be able to compare strategies for identifying interventions, objectives and effects. In addition, the designs generally have methodological flaws, preventing us from accurately determining which interventions we could apply in clinical practice for our patients. Accordingly, we encourage other authors to continue researching in this line, by developing new clinical trials, following the current recommendations that minimise the risk of bias, and all of this with a sample size that is adequate for its objective. Once several studies of this nature have been carried out, we will be in a position to reassess the clinical question posed in this systematic review (p. 459)."

Alipanah et al. (2018)[16]

Main Study Findings

N = 15 total

- Patient education (oral and written educational material) plus standard care versus standard care alone
  - 4 RCTs, 1 cohort study

- Associated with a higher rate of treatment completion (1 RCT: RR = 1.71; 95% CI, 1.32 to 2.22)
- Associated with a higher rate of treatment adherence (1 RCT: RR = 1.83, 95% CI, 1.14 to 2.92; 1 cohort study: RR = 1.21; 95% CI, 1.05 to 1.40)
- Associated with a higher rate of cure (1 RCT: RR = 2.15, 95% CI, 1.58 to 2.92)
- No significant effect on rates of mortality, treatment success, failure, or loss to follow-up

- Patient incentives and enablers plus standard care versus standard care alone
  - 4 RCTs, 11 cohort studies
  - Associated with lower rates of mortality (3 cohort studies: RR = 0.51; 95% CI, 0.37 to 0.71; 2 RCTs: RR = 0.93; 95% CI, 0.41 to 2.09)
  - Associated with lower rates of treatment failure (1 RCT: RR = 0.66; 95% CI, 0.50 to 0.87; 2 cohort studies: RR = 0.18; 95% CI, 0.02 to 2.10)
  - Associated with lower loss to follow-up (1 RCT: RR = 0.74; 95% CI, 0.60 to 0.90; 5 cohort studies: RR = 0.48; 95% CI, 0.28 to 0.81)
  - Associated with higher rate of treatment success (3 RCTs: RR = 1.07; 95% CI, 1.03 to 1.11; 4 cohort studies: RR = 1.25; 95% CI, 1.09 to 1.42)
  - Associated with higher rates of treatment completion (5 RCTs: RR = 1.23; 95% CI, 1.15 to 1.31; 4 cohort studies: RR = 1.18; 95% CI, 0.97 to 1.43)
  - Associated with higher rates of cure (4 cohort studies: RR = 1.13; 95% CI, 1.02 to 1.26; 1 RCT: RR = 0.92; 95% CI, 0.85 to 1.01)
  - Associated with higher rate of sputum conversion at 2 months (1 RCT: RR = 1.21, 95% CI, 1.02 to 1.43)

Authors' Conclusion

"The addition of other adherence interventions to DOT, such as education (for staff or patients), material or psychological support, or reminder systems (including SMS technology and phone reminders), correlated with reduced rates of mortality and loss to follow-up and higher rates of treatment success and cure (p. 22)."

Liu et al. (2018)[17]

Main Study Findings

N = 7

- Incentive strategies
  - Monetary or cash incentives and non-cash incentives significantly increased completion of treatment in some studies
  - Homeless adults (2 studies):
    - Cash incentive versus non-cash: 89.2% versus 81.5%
    - Cash incentive versus none: adjusted OR = 1.94 (95% CI, 0.65 to 5.83; P = 0.24)
    - Completion with monetary incentive versus none: OR = 2.57 (95% CI, 1.11 to 5.94)
    - Monetary incentive versus peer health advisor only versus usual care: 44% versus 19% versus 26%; P = 0.02 for monetary incentive versus peer health and P = 0.11 for monetary incentive versus usual care
  - People who use drugs (2 studies):
    - Immediate incentive versus deferred incentive: 83% versus 75% (P = 0.09)

        - Monetary incentive versus outreach alone: adjusted OR = 45.5 (95% CI, 9.7 to 214.6); monetary incentive plus outreach: adjusted OR = 29.7 (95% CI, 6.4 to 137.5)
    - Inmates (1 study):
        - Incentive versus none: OR = 1.07 (95% CI, 0.47 to 2.40)
- Education
    - Inmates (1 study):
        - Incentive versus none: OR = 2.2 (95% CI, 1.04 to 4.72)
- Results from 4 studies regarding incentives (cash or non-cash) were not reported

Authors' Conclusion

"Incentive strategies, including cash or monetary incentives and noncash incentives (e.g., toys for children, free lunch, grocery store coupons, and phone cards or bus tokens), significantly increased completion rates among LTBI patients. For example, Tulsky et al. found an 18% increase in completion among homeless adults in the United States. Chaisson et al. found that patients receiving immediate incentives had higher completion rates than patients receiving deferred incentives among drug users (83% vs 75%) (p. e427)."

Muller et al. (2018)[18]

Main Study Findings

N = 7

- Education and counselling
    - Patient education/counselling versus no education/counselling
        - Cure rates: 2 RCTs (1,106 patients), patient education or counselling led to better cure rates (RR = 1.16; 95% CI, 1.05 to 1.29; P = 0.004; I^2 = 0%)
        - Default rate: 2 RCTs, decreased in patients receiving education by 13% (RR = 0.87; 95% CI, 0.77 to 0.98; P = 0.03; I^2 = 0%)
- Food incentives
    - Food incentives versus no food incentives
        - Cure rates: 3 RCTs found no significant difference (434 patients: RR = 1.07; 95% CI, 0.95 to 1.21; P = 0.27; I^2 = 50%)
- Financial incentives
    - Financial incentives versus no financial incentives
        - Cure rates: 2 RCTs, no significant difference between the use of financial incentives and no financial incentives (4,214 patients, RR = 1.00; 95% CI, 0.81 to 1.23; P = 0.99; I^2 = 67%)
        - Mortality: 2 RCTs, patients receiving financial incentive versus none (RR = 1.02; 95% CI, 0.82 to 1.27; P = 0.85) (Note: RR was written as "1.2" in text, but "1.02" in forest plots)
        - Default rate: 2 RCTs, decreased by 26% for patients receiving financial incentive (RR = 0.74; 95% CI, 0.61 to 0.90; P = 0.002; I^2 = 0%)
- The quality of evidence for cure rates, default rates, and mortality was low

Authors' Conclusion

"In addition, the default rate decreased by respectively 49%, 26% and 13% with DOTS, financial incentives and patient education and counselling. There was no significant reduction in

mortality rates with the use of these interventions. Assuming an appropriate drug regimen is prescribed, treatment success depends largely on the patient's adherence to the regimen. Without adequate support, a significant proportion of patients with TB discontinue treatment before the end of the planned period or take medication irregularly (p. 737)."

Richterman et al. (2018)[19]

Main Study Findings

N = 8

- Meta-analysis
  - Likelihood of treatment success with cash incentives versus usual care
    - 4 studies meta-analyzed: OR = 1.77 (95% CI, 1.57 to 2.01; I^2 = 0%)
- Non–meta-analyzed studies
  - Treatment success
    - Monthly cash equivalent to low civil service salary versus usual care: OR = 1.19 (95% CI, 1.03 to 1.37)
  - Treatment completion
    - Cash transfer for transport, poverty reduction, and other costs versus usual care: OR = 3.28 (95% CI, 1.65 to 6.51)
  - Microbiologic cure
    - Monthly cash transfer and travel reimbursement versus usual care: OR = 79.08 (95% CI, 4.42 to 1,413.33)
    - Monthly cash to female head of household versus usual care: OR = 1.07 (95% CI, 1.04 to 1.11)
  - Weight gain
    - Monthly cash transfer and travel reimbursement versus usual care: 10.4 lbs versus 1.7 lbs (P not reported)
  - Return to work after 1 year
    - Monthly cash transfer and travel reimbursement versus usual care: 93% versus 47% (P not reported)
  - Mortality
    - Monthly cash transfer and travel reimbursement versus usual care: 0% versus 10% (P not reported)
    - Monthly cash transfer equivalent to median direct cost for tuberculosis care versus usual care: 7% versus 6% (P not reported)
    - Monthly cash, cash at treatment completion, transport reimbursement versus usual care: 5% versus 6%, (P not reported)
    - Cash transfers throughout treatment, approximately 10% household income versus usual care: 4% versus 4% (P not reported)
  - Treatment failure
    - Monthly cash, cash at treatment completion, transport reimbursement versus usual care: 2% vs 5% (P not reported)
  - Loss to follow-up

        - Monthly cash, cash at treatment completion, transport reimbursement versus usual care: 5% vs 10% (P not reported)
        - Monthly cash transfer equivalent to median direct cost for tuberculosis care versus usual care: 5% vs 20% (P not reported)
    - Sputum positivity after 6 months
        - Monthly cash transfer and travel reimbursement versus usual care: 0% versus 13% (P not reported)
    - Negative smear at 2 months
        - Monthly cash transfer equivalent to median direct cost for tuberculosis care versus usual care: 88% versus 92% (P not reported)

Authors' Conclusion

"In conclusion, we found some evidence that cash transfer interventions improve treatment outcomes in patients with active pulmonary tuberculosis in low- and middle-income countries, although the overall quality of this evidence is low. These findings support calls by WHO and others to incorporate cash transfer interventions into social protection schemes within tuberculosis treatment programmes (p. 480)."

Herrmann et al. (2017)[20]

Main Study Findings

N = 8

- Education and financial incentives (≥ 33% population are people who use drugs)
    - Inmates:
        - 1 RCT, education plus US$5 for visit versus education alone: 26% attendance versus 23% attendance (P = 0.82)
        - 1 RCT, informational session plus US$25 vouchers for food or transport if attending TB clinic within 1 month of release versus informational session alone versus control: 37% (incentive group) versus 37% (education group) versus 24% (control group) attendance, 12% (incentive group) versus 23% (education group) versus 12% (control group) treatment completion (P = NR) (Note: Herrmann et al[20] originally wrote this as 23% completion in the control group and 12% completion in incentive group. This was erroneously reported upon review of the original primary study)
    - People who are homeless:
        - 1 RCT, US$5 per dose (observed) versus no money (self-administered): 44% versus 26% (P = 0.11)
        - 1 RCT, US$5 per dose versus US$5 non-cash incentive per dose: 89% completion versus 81% completion (P = 0.23)
    - General population:
        - 1 cohort study, US$15 in subway tokens per week for all doses ingested versus US$15 in subway tokens per week for all doses ingested and monthly bonuses of US$30 to US$60 for 80% or more of doses taken in the month: 2.7 times more likely to take 80% or more of doses with bigger incentive package
    - People who inject drugs:

        - 1 RCT, US$10 a month for adherence paid once a month for 6 months versus US$10 per month for adherence paid out as a lump sum after 6 months: 84% completion versus 75% (P = 0.09)
        - 1 RCT, DOT plus US$5 per dose versus DOT alone: 53% completion versus 4% (P = NR)
    - Adults (56% with substance use disorder) or children with medication nonadherence:
        - 1 cohort study, US$5 grocery gift card plus DOT or physician visit versus DOT alone: 5.7 times more likely to complete treatment with incentive, 60% completion versus 19% (P = NR)

Authors' Conclusion

"In summary, the present review demonstrates that there is compelling evidence that incentive-based interventions improve adherence to vaccinations, diagnostic tests and pharmacotherapies critical for the control of hepatitis, HIV and TB among individuals with SUDs [substance use disorders]. The parameters that moderate the efficacy of these interventions appear consistent with those shown to influence outcomes of CM [contingency management] for the treatment of SUDs. Incentives are a valuable tool that can be used to improve public health outcomes related to infectious disease (p. 10-11)."

Heuvelings et al. (2017)[21]

Main Study Findings

N = 3

- Screening adherence
    - People who are homeless:
        - 1 RCT, incentives versus usual care: "improves tuberculosis… screening (p. e177)"
        - From original NICE review[32]: 84% versus 53% (OR = 4.7; 95% CI, 2.2 to 9.8)
- Tuberculosis management
    - People who use drugs:
        - DOT plus incentives versus DOT alone: "DOT increases successful treatment outcomes and improves treatment adherence among several hard-to-reach populations, especially when combined with incentives (p. 3155)"
        - From original NICE review[32]: at 32 weeks, 60% versus 19% (OR = 5.73; 95% CI, 2.25 to 14.84)
        - From original NICE review[32]: at 52 weeks, 89% versus 52% (OR = 7.29; 95% CI, 2.45 to 22.73)
    - Migrants, homeless people, people who use drugs, people with HIV:
        - DOT plus incentives versus DOT alone: "DOT increases successful treatment outcomes and improves treatment adherence among several hard-to-reach populations, especially when combined with incentives (p. e155)"
        - From original NICE review[32]: 75.2% versus 26.7% (RR = 3.069; 95% CI, 2.133 to 4.414; P < 0.0001)

Authors' Conclusion

"The NICE review found that DOT increases successful treatment outcomes and improves treatment adherence among several hard-to-reach populations, especially when combined with incentives (p. e155)."

Stuurman et al. (2016)[22]

Main Study Findings

N = 4

- People who inject drugs:
  - Higher completion rates for patients receiving monetary incentives versus no incentive: adjusted OR = 32.0 (95% CI, 7.1 to 145); moderate quality
  - Higher completion rates for patients receiving methadone treatment and substance use disorder counselling versus no incentive: OR = 14.5 (95% CI, 5.0 to 42); very low quality
- Inmates:
  - Food or transport vouchers if attending clinic 1 month after release versus no vouchers: OR = 1.07 (95% CI, 0.5 to 2.4), moderate quality
- People who are homeless
  - Cash incentives versus non-cash incentives: OR = 1.7 (95% CI, 0.7 to 4.3); low quality

Authors' Conclusion

"Overall, however, the evidence was inconclusive and recommendations on the best interventions to improve uptake of LTBI medication are hampered by the heterogeneity of the studies. The benefit of interventions to improve treatment completion, such as incentives and DOT, appears to be population and setting dependent. Specific needs of the different populations with LTBI should be addressed taking into consideration the local context, specific settings and conditions in which the LTBI treatment programme is implemented (p. 15)."

Van Hoorn et al. (2016)[23]

Main Study Findings

N = 21

- Meta-analysis: treatment success (9 RCTs)
  - Psycho-emotional supports
    - 3 studies: pooled RR = 1.37 (95% CI, 1.08 to 1.73; I^2 = 78%)
    - Omission of 1 study with high risk of bias: RR = 1.20 (95% CI, 1.07 to 1.35; I^2 = 0%)
  - Socioeconomic supports
    - 4 studies: pooled RR = 1.08 (95% CI, 1.03 to 1.13; I^2 = 14.4%)
  - Combined supports
    - 3 studies: pooled RR = 1.17 (95% CI, 1.12 to 1.22; I^2 = 0%)
  - Overall
    - Pooled RR = 1.17 (95% CI, 1.09 to 1.25; I^2 = 72.8%)
  - All favoured intervention over control
- Meta-analysis: unsuccessful treatment outcomes (9 studies)

    - Psycho-emotional supports
        - 4 studies: pooled RR = 0.46 (95% CI, 0.22 to 0.96; I^2 = 85%)
        - Omission of 1 study with high risk of bias: RR = 0.33 (95% CI, 0.22 to 0.50; I^2 = 0%)
    - Socioeconomic supports
        - 2 studies: pooled RR = 0.78 (95% CI, 0.69 to 0.88; I^2 = 0%)
    - Combined supports
        - 4 studies: pooled RR = 0.42 (95% CI, 0.23 to 0.75; I^2 = 64%)
    - Overall
        - Pooled RR = 0.53 (95% CI, 0.41 to 0.70; I^2 = 80.2%)
- Treatment adherence (3 RCTs)
    - Socioeconomic supports
        - 1 study: RR = 1.01 (95% CI, 0.85 to 1.33)
    - Combined supports
        - 1 study: RR = 1.11 (95% CI, 0.92 to 1.33)
- Non–meta-analyzed data
    - Studies excluded from meta-analysis
        - Treatment adherence
            - Historically controlled study, indirect economic support versus usual care: 32 weeks or less OR = 5.73 (95% CI, 2.25 to14.84); 52 weeks or less OR = 7.29 (95% CI, 2.45 to 22.73)
            - Case-control study, indirect economic support versus usual care: The odds patient will adhere is 2.7 times as great as person receiving the basic incentive package
            - Before-and-after study, direct economic support versus usual care: default rates reduced (11% versus 1%; P = 0.03) in favour of intervention
    - Non-randomized studies
        - 7 non-randomized studies reported some effect of socioeconomic supports on treatment success (RR range from 1.03 to 2.51; 95% CI, 0.96 to 2.99); 5 of 7 studies reported significant RR in favour of intervention
        - 6 non-randomized studies reported some effect of socioeconomic supports on treatment failure (RR range from 0.32 to 0.96; 95% CI, 0.18 to 3.49); 5 of 6 studies reported significant RR in favour of intervention
        - 2 case-control studies reported significant beneficial effects of socioeconomic supports on treatment failure (RR = 0.51; 95% CI, 0.37 to 0.70 and RR = 0.10; 95% CI, 0.05 to 0.20)

Authors' Conclusion

"This review found that PE [psycho-emotional] and SE [socioeconomic] support did improve treatment outcomes across a variety of settings and patient populations, with a tendency towards better outcomes with PE interventions or a combined approach. However, the quality of evidence was classified as "very low" under the GRADE approach. Food supplementation and counselling were commonly included in the package of support. PE, SE and combined interventions improved treatment outcomes; only for interventions including SE support exclusively there was no significant improvement in treatment success. Overall, support interventions were associated with significantly higher treatment success (overall RR 1.08; CI

1.03 to 1.13) and reductions in unsuccessful treatment outcomes (overall RR 0.53; CI 0.41 to 0.70) (p. 21)."

Table 8: Summary of Recommendations in Included Guidelines

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
WHO (2017)[25]	
"Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment (p. 20)."	Strong recommendation, moderate certainty in the evidence
"A package of treatment adherence interventions may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option (p. 20)."	Conditional recommendation, low certainty in the evidence
"One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health-care providers: • tracers and/or digital medication monitor • material support[a] to patient • psychological support to patient • staff education (p. 20)."	• Conditional recommendation, very low certainty in the evidence • Conditional recommendation, moderate certainty in the evidence • Conditional recommendation, low certainty in the evidence • Conditional recommendation, low certainty in the evidence
NICE (2016)[26]	
Improving adherence: case management including directly observed therapy "TB case managers should ensure the health and social care plan (particularly if directly observed therapy is needed) identifies why a person may not attend for diagnostic testing or follow a treatment plan, and how they can be encouraged to do so. It should also include ways to address issues such as fear of stigmatisation, support needs and/or cultural beliefs, and may include information on…any enablers or incentives to overcome anything that is stopping diagnosis or treatment [2012, amended 2016] (p. 57-58)."	Offer/should = for the vast majority of patients, the intervention will do more good than harm[30]
"The health and social care plan should define the support needed to address any unmet health and social care needs (for example, support to gain housing or other benefits, or to help them access other health or social care services) [2012, amended 2016] (p. 58)."	Offer/should = for the vast majority of patients, the intervention will do more good than harm[30]
Other strategies to encourage people to follow their treatment plan "Multidisciplinary TB teams should implement strategies for active and latent TB to encourage people to follow the treatment plan and prevent people stopping treatment early. These could include: • health education counselling and patient-centred interviews [2006, amended 2016] • tailored health education booklets from quality sources (see section 1.1.2) [2006, amended 2016] • incentives and enablers to help people follow their treatment regimen [new 2016] (p. 59)."	Offer/should = for the vast majority of patients, the intervention will do more good than harm[30]

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
Accommodation during treatment • "Multidisciplinary TB teams should assess the living circumstances of people with TB. Where there is a housing need they should work with allied agencies to ensure that all those who are entitled to state-funded accommodation receive it as early as possible during their treatment, for example, as a result of a statutory homelessness review and identified need. [2012, amended 2016] • Multidisciplinary TB teams, commissioners, local authority housing lead officers and other social landlords, providers of hostel accommodation, hospital discharge teams, Public Health England and the Local Government Association should work together to agree a process for identifying and providing accommodation for homeless people diagnosed with active pulmonary TB who are otherwise ineligible for state-funded accommodation. This includes people who are not sleeping rough but do not have access to housing or recourse to public funds. The process should detail the person's eligibility and ensure they are given accommodation for the duration of their TB treatment. [2012, amended 2016] • Local government and clinical commissioning groups should fund accommodation for homeless people diagnosed with active TB who are otherwise ineligible for state-funded accommodation. Use health and public health resources, in line with the Care Act 2014. [2012, amended 2016] • Public Health England, working with the Local Government Association and their special interest groups, should consider working with national housing organisations such as the Chartered Institute of Housing, Homeless Link, Sitra and the National Housing Federation to raise the profile of TB. This is to ensure people with TB are considered a priority for housing [new 2016] (p. 76-77)."	Offer/should = for the vast majority of patients, the intervention will do more good than harm[30]
Canadian Tuberculosis Standards, Chapter 5 (2017)[3]	
"The decision by a care provider to initiate treatment of active TB implies a commitment to ensure that all the recommended doses are taken without interruption. The goal of active TB treatment is to take 100% of prescribed doses. This is best done by providing a comprehensive, patient-centred treatment program[b] (p. 15)."	Conditional recommendation, based on weak evidence
Canadian Tuberculosis Standards, Chapter 13 (2017)[24]	
"Homeless people with medical conditions associated with a high risk of reactivation should be considered for special measures to enhance adherence, such as directly observed LTBI treatment and/or incentives and enablers (p. 16)."	Conditional recommendation, based on weak evidence
"Those at highest risk of reactivation should be considered for special measures to enhance adherence, such as directly observed LTBI treatment and/or incentives and enablers (p. 17)."	Conditional recommendation, based on weak evidence

TB = tuberculosis; LTBI = latent tuberculosis infection; NR = not reported.

[a]"Material support can be food or financial support: meals, food baskets, food supplements, food vouchers, transport subsidies, living allowance, housing incentives, or financial bonus. This support addresses indirect costs

incurred by patients or their attendants in order to access health services and, possibly, tries to mitigate consequences of income loss related to the disease (p. 20)."

[b]This program includes the use of use of incentives and enablers as well as social service support (e.g., childcare, housing assistance, referral for treatment of substance abuse, and providing transportation).

Appendix 5: Overlap Between Included Systematic Reviews

Table 9: Overlap in Relevant Systematic Reviews Between Included Overviews of Reviews

Systematic review citation	Visser et al. (2018)[11]	Pantoja et al. (2017)[12]	Wiysonge et al. (2017)[13]
Grobler L, et al. Cochrane Database of Systematic Reviews; 2016, Issue 6	Yes	No	No
Lutge EE, et al. Cochrane Database of Systematic Reviews; 2015, Issue 9	No	Yes	Yes

Table 10: Overlap in Relevant Primary Studies Between Included Systematic Reviews

Primary study citation	Barss et al. (2020)[14]	Law et al. (2019)[15]	Riquelme-Miralles et al. (2019)[4]	Alipanah et al. (2018)[16]	Liu et al. (2018)[17]	Muller et al. (2018)[18]	Richterman et al. (2018)[19]	Herrmann et al. (2017)[20]	Heuvelings et al. (2017)[21]	Stuurman et al. (2016)[22]	van Hoorn et al. (2016)[23]
Alvarez Gordillo GDC, et al. Rev Panam Salud Publica 2003; 14: 402–408.	No	No	No	No	No	Yes	No	No	No	No	No
Baral SC, et al. BMC Public Health 2014; 14: 46.	No	Yes	No	No	No	Yes	No	No	No	No	Yes
Bastard M, et al. J Infect Dis 2015; 211: 1607–1615.	No	Yes	No	No	No	No	No	No	No	No	No
Batki SL, et al. Drug Alcohol Depend. 2002;66:283–93.	No	No	No	No	No	No	No	No	No	Yes	No
Bock NN, et al. Int J Tuberc Lung Dis. 2001; 5(1):96-8.	No	No	No	Yes	No	No	No	Yes	Yes	No	Yes
Cantalice Filho JP, et al. J Bras Pneumol. 2009; 35(10):992-7.	No	No	No	Yes	No	No	No	No	No	No	Yes
Chaisson RE. Am J Med. 2001;110(8):610-615.	No	No	No	No	Yes	No	No	Yes	No	No	No
Cheng TL, et al. Pediatrics 1997; 100(2 Pt 1): 210–213.	Yes	No	No	No	No	No	No	No	No	No	No

Primary study citation	Barss et al. (2020)[14]	Law et al. (2019)[15]	Riquelme-Miralles et al. (2019)[4]	Alipanah et al. (2018)[16]	Liu et al. (2018)[17]	Muller et al. (2018)[18]	Richterman et al. (2018)[19]	Herrmann et al. (2017)[20]	Heuvelings et al. (2017)[21]	Stuurman et al. (2016)[22]	van Hoorn et al. (2016)[23]
Chirico MC, et al. Salud i Ciencia. 2011;17(8):798–801.	No	No	No	No	No	No	Yes	No	No	No	No
Chua AP, et al. Singapore Med J. 2015; 56(5):2749.	No	No	No	Yes	No	No	No	No	No	No	No
Ciobanu A, et al. Public Health Action. 2014 Oct 21;4 Suppl 2:S59–63.	No	No	No	No	No	No	Yes	No	No	No	No
Cox HS, et al. PLoS One 2007; 2: E1126.	No	Yes	No	No	No	No	No	No	No	No	No
Davidson H, et al. The International Journal of Tuberculosis and Lung Disease. 2000; 4:860–865.	No	No	No	No	No	No	No	Yes	No	No	Yes
Dobler CC, et al. Int J Tuberc Lung Dis. 2015; 19 (6):657-62.	No	No	No	Yes	No	No	No	No	No	No	No
Drabo M et al. Sante Publique 21: 485–497.	No	No	No	No	No	No	No	No	No	No	Yes
Farmer P, et al. Semin Respir Infect. 1991 Dec;6(4):254–60.	No	No	No	No	No	No	Yes	No	No	No	Yes
Fitzgerald JM, et al. Int J Tuberc Lung Dis 1999; 3(2): 153–155.	Yes	No	No	No	No	No	No	No	No	No	No

Primary study citation	Barss et al. (2020)[14]	Law et al. (2019)[15]	Riquelme-Miralles et al. (2019)[4]	Alipanah et al. (2018)[16]	Liu et al. (2018)[17]	Muller et al. (2018)[18]	Richterman et al. (2018)[19]	Herrmann et al. (2017)[20]	Heuvelings et al. (2017)[21]	Stuurman et al. (2016)[22]	van Hoorn et al. (2016)[23]
Garden B, et al. Scand J Caring Sci 27: 117–122.	No	No	No	No	No	No	No	No	No	No	Yes
Gelmanova IY, et al. Int J Tuberc Lung Dis 2011; 15: 1373–1379.	No	Yes	No	No	No	No	No	No	No	No	Yes
Goldberg SV, et al. Int J Tuberc Lung Dis 2004; 8(1): 76–82.	Yes	No	No	No	No	No	No	No	No	No	No
Huerga H, et al. Int J Tuberc Lung Dis 2017; 21: 314–319.	No	Yes	No	No	No	No	No	No	No	No	No
Jahnavi G, et al. Singapore Med J. 2010;51:957–962.	No	No	Yes	Yes	No	Yes	No	No	No	No	Yes
Jakubowiak WM, et al. Int J Tuberc Lung Dis 11: 46–53.	No	No	No	No	No	No	No	No	No	No	Yes
Janmeja AK, et al. Respiration 72: 375–380.	No	No	No	No	No	No	No	No	No	No	Yes
Juan G, et al. Int J Tuberc Lung Dis 2006; 10: 215–21.	No	No	No	No	No	No	No	No	Yes	No	No
Keshavjee S, et al. Lancet 2008; 372: 1403–1409.	No	Yes	No	No	No	No	No	No	No	No	No
Kliman 2009	No	Yes	No	No	No	No	No	No	No	No	No

Primary study citation	Barss et al. (2020)[14]	Law et al. (2019)[15]	Riquelme-Miralles et al. (2019)[4]	Alipanah et al. (2018)[16]	Liu et al. (2018)[17]	Muller et al. (2018)[18]	Richterman et al. (2018)[19]	Herrmann et al. (2017)[20]	Heuvelings et al. (2017)[21]	Stuurman et al. (2016)[22]	van Hoorn et al. (2016)[23]
Kominski GF, et al. J Adolesc Health. 2007;40(1):61-68.	No	No	No	No	Yes	No	No	No	No	No	No
Liefooghe R, et al. Int J Tuberc Lung Dis 1999; 3: 1073–1080.	No	No	No	No	No	Yes	No	No	No	No	Yes
Loveday M, et al. Int J Tuberc Lung Dis 2015; 19: 163–171.	No	Yes	No	No	No	No	No	No	No	No	No
Lu H, et al. Western Pac Surveill Response J. 2013; 4(1):19-24.	No	No	No	Yes	No	No	Yes	No	No	No	Yes
Lutge E, et al. Trials. 2013; 14:154.	No	No	No	Yes	No	Yes	No	No	No	No	Yes
Malotte CK, et al. Am J Public Health 1998; 88(5): 792–796.	Yes	No	No	No	No	No	No	No	No	No	No
Malotte CK, et al. Am J Prev Med 1999; 16(3): 182–188.	Yes	No	No	No	No	No	No	No	No	No	No
Malotte CK, et al. Am J Prev Med. 2001;20:103–107.	No	No	Yes	No	Yes	No	No	Yes	No	Yes	No
Martins N, et al. BMJ. 2009;339:b4248.	No	No	Yes	Yes	No	Yes	No	No	No	No	Yes
Meressa D, et al. Thorax 2015; 70: 1181–1188.	No	Yes	No	No	No	No	No	No	No	No	No

Primary study citation	Barss et al. (2020)[14]	Law et al. (2019)[15]	Riquelme-Miralles et al. (2019)[4]	Alipanah et al. (2018)[16]	Liu et al. (2018)[17]	Muller et al. (2018)[18]	Richterman et al. (2018)[19]	Herrmann et al. (2017)[20]	Heuvelings et al. (2017)[21]	Stuurman et al. (2016)[22]	van Hoorn et al. (2016)[23]
Mitnick C, et al. New Engl J Med 2003; 348: 119–128.	No	Yes	No	No	No	No	No	No	No	No	No
Mitnick CD, et al. N Engl J Med 2008; 359: 563–574.	No	Yes	No	No	No	No	No	No	No	No	No
Mohr E, et al. PLoS One 2017; 12: e0178054.	No	Yes	No	No	No	No	No	No	No	No	No
Morisky DE, et al. Health Educ Q. 1990;17:253–267.	No	No	Yes	No	No	No	No	No	No	No	Yes
Morisky DE, et al. Public Health Rep. 2001;116:568–574.	No	No	Yes	No	Yes	No	No	No	No	No	No
Ngamvithayapong-Yanai J, et al. Western Pac Surveill Response J. 2013; 4(1):34-8.	No	No	No	Yes	No	No	No	No	No	No	No
Nyamathi AM, et al. Int J Tuberc Lung Dis. 2006;10:775–782.	No	No	Yes		Yes	No	No	No	No	No	No
Perlman L, et al. J Urban Health: Bull NY Acad Med 2003; 80(3): 428–437.	Yes	No	No	No	No	No	No	No	No	No	No
Pilote L et al., Arch Intern Med 1996; 156(2): 161–165.	Yes	No	No	No	No	No	No	No	Yes	No	No

Primary study citation	Barss et al. (2020)[14]	Law et al. (2019)[15]	Riquelme-Miralles et al. (2019)[4]	Alipanah et al. (2018)[16]	Liu et al. (2018)[17]	Muller et al. (2018)[18]	Richterman et al. (2018)[19]	Herrmann et al. (2017)[20]	Heuvelings et al. (2017)[21]	Stuurman et al. (2016)[22]	van Hoorn et al. (2016)[23]
Rocha C, et al. Int J Tuberc Lung Dis. 2011 Jun;15(6) Suppl 2:50–7.	Yes	No	No	No	No	No	Yes	No	No	No	No
Satti H, et al. PLoS One 2012; 7: e46943.	No	Yes	No	No	No	No	No	No	No	No	No
Shin SS, et al. Int J Tuberc Lung Dis 2006; 10: 402–408.	No	Yes	No	No	No	No	No	No	No	No	No
Soares EC, et al. Int J Tuberc Lung Dis 17: 1581–1586.	No	No	No	No	No	No	No	No	No	No	Yes
Sripad A, et al. Int J Tuberc Lung Dis. 2014; 18 (1):44-8.	No	No	No	Yes	No	No	No	No	No	No	Yes
Suarez PG, et al. Lancet 2002; 359: 1980–1989.	No	Yes	No	No	No	No	No	No	No	No	No
Sudardanam TD, et al. Trop Med Int Health. 2011; 16(6):699- 706	No	No	No	Yes	No	Yes	No	No	No	No	Yes
Taneja N, et al. J Clin Diagn Res 2017; 11: LC05–LC08.	No	Yes	No	No	No	No	No	No	No	No	No
Taubman D, et al. J Epidemiol Glob Health; 2013 3(4): 253-260.	Yes	No	No	No	No	No	No	No	No	No	No

Primary study citation	Barss et al. (2020)[14]	Law et al. (2019)[15]	Riquelme-Miralles et al. (2019)[4]	Alipanah et al. (2018)[16]	Liu et al. (2018)[17]	Muller et al. (2018)[18]	Richterman et al. (2018)[19]	Herrmann et al. (2017)[20]	Heuvelings et al. (2017)[21]	Stuurman et al. (2016)[22]	van Hoorn et al. (2016)[23]
Thomas A, et al. Indian J Tuberc 2007; 54: 117–124.	No	Yes	No	No	No	No	No	No	No	No	No
Torrens AW, et al. Trans R Soc Trop Med Hyg.; 2016, 110(3):199–206.	No	No	No	Yes	No	No	Yes	No	No	No	No
Tsai WC, et al. J Infect. 2010; 61(3):235-43.	No	No	No	Yes	No	No	No	No	No	No	No
Tulsky JP, et al. Arch Intern Med. 2000;160:697–702.	No	No	Yes	No	Yes	No	No	Yes	No	No	No
Tulsky JP, et al. Int J Tuberc Lung Dis. 2004;8:83–91.	No	No	Yes	No	Yes	No	No	Yes	No	Yes	No
Ukwaja KN, et al. J Tuberc Lung Dis. 2017 05 1;21(5):564–70.	No	No	No	No	No	No	Yes	No	No	No	No
Vaghela JF, et al. Indian J Tuberc 2015; 62: 91–96.	No	Yes	No	No	No	No	No	No	No	No	No
Wei X, et al. Infect Dis Poverty. 2012; 1(1):9.	No	No	No	Yes	No	No	No	No	No	No	Yes
White MC, et al. The International Journal of Tuberculosis and Lung Disease. 1998; 2:506–512.	No	No	No	No	No	No	No	Yes	No	No	No

Primary study citation	Barss et al. (2020)[14]	Law et al. (2019)[15]	Riquelme-Miralles et al. (2019)[4]	Alipanah et al. (2018)[16]	Liu et al. (2018)[17]	Muller et al. (2018)[18]	Richterman et al. (2018)[19]	Herrmann et al. (2017)[20]	Heuvelings et al. (2017)[21]	Stuurman et al. (2016)[22]	van Hoorn et al. (2016)[23]
White MC, et al. Arch Intern Med. 2002;162: 104450.	No	No	Yes	No	Yes	No	No	Yes	No	Yes	No
Wingfield T, et al. Bull World Health Organ. 2017 Apr 1;95(4):270–80.	No	No	No	No	No	No	Yes	No	No	No	No
Yu MC, et al. Eur Respir J 2015; 45: 272–275.	No	Yes	No	No	No	No	No	No	No	No	No
Zou G, et al. Int J Tuberc Lung Dis 17: 1056–1064. (8):1056-64.	No	No	No	Yes	No	No	No	No	No	No	Yes

Appendix 6: Further Information

Systematic Reviews Included Within Overviews of Reviews

Grobler L, Nagpal S, Sudarsanam TD, Sinclair D. Nutritional supplements for people being treated for active tuberculosis. *Cochrane Database Syst Rev.* 2016(6):CD006086. Medline

Lutge EE, Wiysonge CS, Knight SE, Sinclair D, Volmink J. Incentives and enablers to improve adherence in tuberculosis. *Cochrane Database Syst Rev.* 2015(9):CD007952. Medline

Excluded Primary Studies (Due to Volume of Literature)

Cocozza AM, Linh NN, Nathavitharana RR, et al. An assessment of current tuberculosis patient care and support policies in high-burden countries. *Int J Tuberc Lung Dis.* 2020;24(1):36-42. Medline

Rohit A, Kumar AMV, Thekkur P, et al. Does provision of cash incentive to HIV-infected tuberculosis patients improve the treatment success in programme settings? A cohort study from South India. J. 2020;9(8):3955-3964.

Watthananukul T, Liabsuetrakul T, Pungrassami P, Chongsuvivatwong V. Effect of Global Fund financial support for patients with multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis.* 2020;24(7):686-693. Medline

Benzekri NA, Sambou JF, Tamba IT, et al. Nutrition support for HIV-TB co-infected adults in Senegal, West Africa: A randomized pilot implementation study. *PLoS ONE.* 2019;14(7):e0219118. Medline

Bhatt R, Chopra K, Vashisht R. Impact of integrated psycho-socio-economic support on treatment outcome in drug resistant tuberculosis - A retrospective cohort study. *Indian J.* 2019;66(1):105-110. Medline

Carter DJ, Daniel R, Torrens AW, et al. The impact of a cash transfer programme on tuberculosis treatment success rate: a quasi-experimental study in Brazil. BMJ glob. 2019;4(1):e001029.

Kim H, Choi H, Yu S, et al. Impact of Housing Provision Package on Treatment Outcome Among Homeless Tuberculosis Patients in South Korea. *Asia Pac J Public Health.* 2019;31(7):603-611. Medline

Klein K, Bernachea MP, Irribarren S, Gibbons L, Chirico C, Rubinstein F. Evaluation of a social protection policy on tuberculosis treatment outcomes: A prospective cohort study. *PLoS Med.* 2019;16(4):e1002788. Medline

Yuen CM, Millones AK, Contreras CC, Lecca L, Becerra MC, Keshavjee S. Tuberculosis household accompaniment to improve the contact management cascade: A prospective cohort study. *PLoS ONE.* 2019;14(5):e0217104. Medline

Mansour O, Masini EO, Kim BJ, Kamene M, Githiomi MM, Hanson CL. Impact of a national nutritional support programme on loss to follow-up after tuberculosis diagnosis in Kenya. *Int J Tuberc Lung Dis.* 2018;22(6):649-654. Medline

Priedeman Skiles M, Curtis SL, Angeles G, Mullen S, Senik T. Evaluating the impact of social support services on tuberculosis treatment default in Ukraine. *PLoS ONE.* 2018;13(8):e0199513. Medline

Verdecchia M, Keus K, Blankley S, et al. Model of care and risk factors for poor outcomes in patients on multi-drug resistant tuberculosis treatment at two facilities in eSwatini (formerly Swaziland), 2011-2013. *PLoS ONE.* 2018;13(10):e0205601. Medline

Samuel B, Volkmann T, Cornelius S, et al. Relationship between Nutritional Support and Tuberculosis Treatment Outcomes in West Bengal, India. J. 2016;4(4):213-219.

Kliner M, Canaan M, Ndwandwe SZ, et al. Effects of financial incentives for treatment supporters on tuberculosis treatment outcomes in Swaziland: a pragmatic interventional study. *Infect.* 2015;4:29. Medline