Material incentives and enablers in the management of tuberculosis (Review)

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[Intervention Review]

Material incentives and enablers in the management of tuberculosis

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ABSTRACT

Background

Patient adherence to medications, particularly for conditions requiring prolonged treatment such as tuberculosis, is frequently less than ideal, and can result in poor treatment outcomes. Material incentives (given as cash, vouchers and tokens), have been used to improve adherence.

Objectives

To assess the effects of material incentives in people undergoing diagnostic testing, or receiving prophylactic or curative therapy, for tuberculosis.

Search methods

We undertook a comprehensive search of the Cochrane Infectious Diseases Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; LILACS; Science Citation Index; and reference lists of relevant publications; to 22 June 2011.

Selection criteria

Randomized controlled trials of material incentives in patients being investigated for tuberculosis, or on treatment for latent or active disease.

Data collection and analysis

At least two authors independently screened and selected studies, extracted data, and assessed the risk of bias. The effects of interventions are compared using risk ratios (RR), and presented with 95% confidence intervals (CI). The quality of the evidence was assessed using GRADE.

Main results

We identified 11 eligible studies. Ten were conducted in the USA: in adolescents (one trial), in injection drug or cocaine users (four trials), in homeless adults (three trials), and in prisoners (two trials). One additional trial recruited malnourished men receiving active treatment for tuberculosis in Timor-Leste.

Material incentives may increase the return rate for reading of tuberculin skin test results compared to normal care (two trials, 1371 participants: RR 2.16, 95% CI 1.41 to 3.29, *low quality evidence).*

Similarly, incentives probably improve clinic re-attendance for initiation or continuation of antituberculosis prophylaxis (three trials, 595 participants: RR 1.58, 95% CI 1.27 to 1.96, *moderate quality evidence*), and may improve subsequent completion of prophylaxis in some settings (three trials, 869 participants: RR 1.79, 95% CI 0.70 to 4.58, *low quality evidence).*

We currently don't know if incentives can improve long-term adherence and completion of antituberculosis treatment for active disease. Only one trial has assessed this and the incentive, given as a daily hot meal, was not well received by the population due to the inconvenience of attending the clinic at midday (one trial, 265 participants, RR 0.98, 95%CI 0.86 to 1.12, *very low quality evidence*).

Several trials have compared different forms or levels of incentive. These comparisons remain limited to single trials and robust conclusions cannot be made. In summary, cash incentives may be more effective than non-cash incentives (return for test results: one trial, 651 participants: RR 1.13, 95%CI 1.07 to 1.19, *low quality evidence*, adherence to tuberculosis prophylaxis: one trial, 141 participants: RR 1.26, 95%CI 1.02 to 1.56, *low quality evidence)* and higher amounts of cash may be more effective than lower amounts (return for test results: one trial, 404 participants: RR 1.08, 95%CI 1.01 to 1.16, *low quality evidence).*

Material incentives may also be more effective than motivational education at improving return for tuberculin skin test results (*low quality evidence*), but may be no more effective than peer counselling, or structured education at improving continuation or completion of prophylaxis (*low quality evidence*).

Authors' conclusions

There is limited evidence to support the use of material incentives to improve return rates for tuberculosis diagnostic test results and adherence to antituberculosis preventive therapy. The data are currently limited to trials among predominantly male drug users, homeless, and prisoner subpopulations in the USA, and therefore the results are not easily generalised to the wider adult population, or to low- and middle-income countries, where the tuberculosis burden is highest.

Further high-quality studies are needed to assess both the costs and effectiveness of incentives to improve adherence to long-term treatment of tuberculosis.

PLAIN LANGUAGE SUMMARY

Material incentives for improving patient adherence to tuberculosis diagnosis, prophylaxis, and treatment

Patients do not always follow the advice of health care providers if being investigated or treated for tuberculosis. Material incentives (such as cash, vouchers and tokens) may encourage them to return for the results of tests or to take prescribed treatments. This review, which analysed the results of 11 randomized controlled trials, concluded that material incentives do increase the number of patients (in certain marginalized subpopulations, mostly men) who return to the clinic to receive their test results for the diagnosis of tuberculosis, and the number of patients who go to the clinic to start treatment for tuberculosis. There was no evidence to show that incentives increase the number of patients who complete treatment for latent or active tuberculosis.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Material incentives compared to routine care for improving patient adherence to TB management

Patient or population: People engaged in tuberculosis programmes
Settings: High- and low-income settings
Intervention: Material incentives (such as cash, grocery vouchers or food)
Comparison: Routine care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Routine care	Material incentives			
Return for tuberculin skin test reading	441 per 1000	953 per 1000 (622 to 1000)	RR 2.16 (1.41 to 3.29)	1371 (2 studies)	⊕⊕◯◯ low[1,2]
Return to clinic to start or continue treatment	249 per 1000	393 per 1000 (316 to 488)	RR 1.58 (1.27 to 1.96)	595 (3 studies)	⊕⊕⊕◯ moderate[2]
Completion of TB prophylaxis	405 per 1000	725 per 1000 (283 to 1000)	RR 1.79 (0.70 to 4.58)	869 (3 studies)	⊕⊕◯◯ low[2,3]
Completion of treatment for active TB	775 per 1000	760 per 1000 (669 to 868)	RR 0.98 (0.86 to 1.12)	265 (1 study)	⊕◯◯◯ very low[4,5]

The **assumed risk** is taken from the control groups in the trials. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded by 1 for risk of bias: Neither study adequately described the method of randomization.
[2] Downgraded by 1 for indirectness: These trials were conducted in specific subpopulations from the USA and the result may not be applicable in other settings.
[3] Downgraded by 1 for inconsistency: Two studies found no suggestion of a benefit with the incentive, and just one study found a clinically and statistically significant benefit in drug users.
[4] Downgraded by 2 for indirectness: Qualitative research around this trial suggests that the form of the incentive was not appropriate as patients did not like having to attend the clinic at midday for a meal.
[5] Downgraded by 1 for imprecision: The 95% CI includes what may be clinically important benefits and no effect.

BACKGROUND

Description of the condition

Tuberculosis (TB) is an infectious disease caused by the bacteria *Mycobacterium tuberculosis* which spreads from person to person by inhalation of respiratory droplets. The burden of disease is highest in low- and middle-income countries where it is associated with poverty, overcrowding, and lowered immunity (due to poor nutrition or infection with the human immunodeficiency virus (HIV)) (WHO 2009a).

Following the initial infection, most people do not develop symptoms as the bacteria is completely controlled by the immune system, and lies dormant in a state known as 'latent TB'. Active TB, where the bacteria is no longer controlled by the immune system, can occur at any time following infection and most commonly affects the lungs, causing a chronic cough (which acts to spread the disease), loss of weight, loss of appetite, and general malaise. (Harries 2006).

The most widely used method of diagnosing latent TB is the tuberculin test (also known as the Mantoux test), which involves injecting a small amount of a purified *M. tuberculosis* protein under the skin, usually of the forearm. If the person has previously been exposed to TB, a small swelling occurs due to a localised immune response, and the size of this response is measured 48 to 72 hours later (CDC 2010). Treatment of latent TB, often called TB prophylaxis, aims to prevent the later development of active disease, and reduce transmission.

Effective treatment for both active and latent TB requires regular medication to be taken for six to twelve months, and non-adherence to this difficult and prolonged schedule is the most common cause of treatment failure (Narayanan 2003; Volmink 2000) and one of the most important obstacles to TB control globally. Non-adherence, with prolonged infectiousness, constitutes a health risk to close family and community contacts, and can lead to the development of drug resistant organisms which are more difficult and more expensive to treat (Lam 2002).

Adherence is not the sole responsibility of the patient, nor of the health system, but some combination of the two (Garner 2007), and consequently interventions aimed at reducing non-adherence may need to target both. These interventions may be classified as: technical (making the medications simpler to take, such as reducing doses and personalising packaging); behavioural (establishing a pattern of behaviour through stimuli or positive reinforcement); educational (improving patients' capacity to manage their diseases, often through a cognitive didactic approach); structural (improving the accessibility and acceptability of TB programmes); or complex (a combination of these) (WHO 2003c; Munro 2007; van Dulmen 2007; Haynes 2008). A review of direct observation has been completed indicating little added effect of direct observation (Volmink 2007), and a review of patient reminders and prompts is also available showing mixed effects (Liu 2008). A further review on patient education is currently ongoing (M'Imunya 2007).

Description of the intervention

Incentives and enablers are interventions targeted at the patient which seek to either promote or assist improved adherence (WHO 2003a; WHO 2003b; WHO 2003c). They may be given directly as cash or vouchers for groceries, or indirectly as the provision of a service for which the patient would otherwise have had to pay (for example transport to and from the clinic).

A recent overview of reviews found that material incentives improved adherence and outcomes for a number of health problems, and also increased the utilisation of health services for prevention programmes (Sutherland 2008). Conditional cash transfers, used primarily in Latin America, are essentially material incentives used on a large scale to promote healthy behaviour in poor families and individuals (Lagarde 2007). They have been particularly successful in promoting the use of health services and in improving nutritional and anthropometric outcomes in certain groups (Lagarde 2007).

How the intervention might work

Incentives are based on behavioural theories of reward for 'good' behaviour (van Dulmen 2007), and may be defined as 'any financial or material reward that patients and/or providers receive, conditional on their explicitly measured performance or behavior' (Beith 2007). Alternatively, 'enablers' assist patients to adhere by overcoming the financial barriers to treatment. In a recent qualitative review, economic constraints due to absences from work to attend appointments, or the direct and indirect costs of accessing treatment, were commonly cited by patients as important barriers to completing TB treatment (Munro 2007).

As well as potential benefits, the use of material incentives may also have unintentional negative consequences. Patients who receive incentives to adhere to one health behaviour may be reluctant to adhere to others if they are not also accompanied by incentives (Malotte 1999). This might be especially important where incentives are offered in one of several possible stages in a multi-stage treatment process such as screening for and treating TB. Further possible negative effects include: resentment in patients who do not receive the incentive (Malotte 2001); fraud and corruption, with patients manipulating the incentive system to gain more; or the creation of 'ghost' patients allowing health staff to steal incentives from the system (White 1998); or the 'perverse incentive' effect, where the incentive induces exactly the opposite behaviour to that intended, ie patients who want to continue receiving the incentive may deliberately not take medications in order to remain ill (Department of Social Development 2006).

Why it is important to do this review

In light of the increased risk of TB posed by HIV infection (Stop TB Partnership 2010), and the development of epidemics

of drug-resistant forms of TB (Wells 2007; Yang 2011), efforts to help patients complete therapy are of paramount importance. If material incentives improve adherence rates amongst patients with TB, they should be used far more widely than they are currently.

OBJECTIVES

To evaluate the effects of material incentives given to patients undergoing diagnostic testing for TB, or receiving drug therapy to prevent or cure TB.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials, where the unit of allocation is either an individual or cluster.

Types of participants

People receiving curative treatment for TB

This included smear positive cases, smear negative cases, new cases, and re-treatment cases.

People receiving preventive therapy for TB

This included patients at risk of developing active TB and taking anti-TB chemoprophylaxis (ie isoniazid preventive therapy).

People suspected of TB undergoing, and collecting results of, diagnostic tests

Diagnosis of TB infection (using tuberculin skin tests) and disease (using sputum microscopy and culture) often requires the patient to return to the health facility a few days after the test is performed to receive the results. Incentives have been used to encourage patients to do this.

Although it was originally intended to include only studies focusing on adults of 16 years and over, we decided to drop this age limitation as a few trials were found that investigated children or adolescents.

Types of interventions

Intervention

Interventions included any form of material inducement to return for TB test results, or adhere to or complete anti-TB preventive or curative treatment. These may have been direct such as cash or vouchers for groceries, or indirect such as the provision of a service for which the patient would otherwise have had to pay (for example transport to and from the clinic). Non-material incentives, such as praise from a health worker, were not considered in this review, because their economic value is difficult to quantify and the form of the incentive is difficult to standardise.

In those trials where incentives were combined with other interventions, studies were only eligible for inclusion in a meta-analysis if disaggregation of the effect of the incentive was possible. Other interventions that could be combined with incentives include health information and education, and increased access to health workers through home visits, or additional appointments. Trials were only included if the standard TB curative or preventive treatment were the same across the control and treatment arms.

Control

Controls were those patients receiving standard TB treatment or preventive treatment, or undergoing testing for suspected TB, who had no incentive or an alternative incentive or intervention.

Types of outcome measures

Primary:

For treatment of active TB

Cure and/or completion of treatment, using the following World Health Organization (WHO) definitions (WHO 2009b):

- **Cured:** A patient who was initially smear-positive and who was smear negative in the last month of treatment and on at least one previous occasion.
- **Successfully treated:** A patient who was cured or who completed treatment (WHO 2009b).

For prophylaxis

Cases of TB.

For diagnostics

Number returning to collect test results within the appropriate time frame for that test.

Secondary:

Percentage of treatment completed, appointment keeping, presence of urinary markers, and certification by direct observation of treatment.

Adverse effects

Adverse events reported in trials, such as expenditure of cash or vouchers on unhealthy items. The latter were defined as commodities that undermine the patient's chance of cure, such as tobacco products or alcohol.

Costs

Cost effectiveness of the intervention; where costs include the direct and indirect costs incurred by patients, and costs to the health system of providing and administering the incentives.

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Databases

We searched the following databases using the search terms and strategy described in Table 1: Cochrane Infectious Diseases Group Specialized Register (22 June 2011); Cochrane Central Register of Controlled Trials (CENTRAL: 22 June 2011); MEDLINE (1966 to 22 June 2011); EMBASE (1974 to 22 June 2011); LILACS (1982 to 22 June 2011); and Science Citation Index (EXPANDED) and Social Sciences Citation index (SSCI) (1956 to 22 June 2011).

We also searched the metaRegister of Controlled Trials (mRCT) using 'tuberculosis', 'incentive', 'cash transfer', 'adherence', 'compliance', and 'concordance' as search terms (1998 to 22 June 2011). In addition, we searched the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/search/en/) for ongoing trials (22 June 2011).

Researchers and organizations

We contacted researchers and other experts in the field of TB and adherence research, for unpublished and ongoing trials.

Reference lists

We checked the reference lists of related reviews (Garner 2007; Haynes 2008; Lagarde 2007; Sutherland 2008; Volmink 2000) and all full-text articles reviewed for inclusion in this review.

Data collection and analysis

Selection of studies

Elizabeth Lutge (EL) and Stephen Knight (SK) independently screened all citations and abstracts identified by the search strategy for potentially eligible studies. The full text articles of potentially relevant studies were independently assessed by the two authors using the pre-specified trial inclusion criteria. Disagreements were resolved by discussion and consensus. When a disagreement could not be resolved we sought arbitration from a third author (Charles Shey Wiysonge (CSW) or Jimmy Volmink (JV)). We excluded studies that did not meet the inclusion criteria and documented the reasons for exclusion in the table of 'Characteristics of excluded studies'.

Data extraction and management

Using a pre-designed data extraction form, EL and CSW independently extracted information from the selected trial reports on study methods used, participant characteristics, interventions, and outcomes. For all outcomes, we extracted the number of participants randomized and the number analysed. The trials identified and included in this review all randomized individual participants and reported only dichotomous outcomes. For each study, we extracted the number of participants with an outcome of interest in each group as well as the number of participants randomized to each group, and the number analysed.

Disagreements were resolved through discussion and consensus between EL and CSW initially, and with SK or JV if the disagreement was not resolved.

Assessment of risk of bias in included studies

EL and CSW independently assessed the risk of bias in each included study using the The Cochrane Collaboration's tool for assessing the risk of bias (Higgins 2011). The authors followed the guidance to assess whether adequate steps were taken to reduce the risk of bias across six specific domains, namely, random sequence generation; allocation concealment; blinding of participants, personnel and outcome assessment; incomplete outcome data; selective outcome reporting; and 'other issues'. For each included study, the two authors independently described what the trial authors reported that they did for each domain and then made a decision relating to the risk of bias for that domain by assigning a judgement of 'Low risk' of bias, 'High risk' of bias, or 'Unclear risk' of bias. The authors compared the results of their independent assessments of risk of bias and resolved any discrepancies by discussion and consensus. Any differences in opinion between the two authors was resolved by discussion and consensus; with arbitration by a third author (JV).

Assessment of reporting biases

If at least 10 studies were included in the meta-analysis for any outcome, we would have evaluated the likelihood of publication bias and other sources of bias by examining the degree of asymmetry of funnel plots. We chose this number because it has been shown that when there are fewer than 10 studies in a meta-analysis the power of funnel plot asymmetry tests is too low to distinguish chance from real asymmetry (Higgins 2011).

Data synthesis

We analysed data using Review Manager 5. We analysed trial participants in groups to which they were randomized, regardless of how much of the intended intervention they actually received.

All studies reported only dichotomous data, so we have expressed study results as the risk ratio (RR) with its 95% confidence intervals (CI) for each outcome. We used the fixed-effect model for the primary analysis. When significant statistical heterogeneity was present and it was appropriate to combine the data, we used the random-effects model. We stratified analyses according to the type of incentive and control intervention ie incentive versus routine care, immediate versus deferred incentive, cash versus non-cash incentive, and incentive versus any other intervention.

In addition, we used the GRADE approach to summarise the quality of the evidence on the effects of material incentives on each outcome (Guyatt 2008). In the GRADE system, randomized trials without important limitations constitute high quality evidence. However, the system considers five factors that can lower the quality of the evidence ie study limitations, inconsistent results across studies, indirectness of the evidence, imprecision, and publication bias. Overall, the GRADE system classifies research evidence into four categories ie high, moderate, low, or very low quality. High quality evidence implies that we "are very confident that the true effect lies close to that of the estimate of the effect", while very low quality evidence implies that the "true effect is likely to be substantially different from the estimate of effect" found in the review (Balshem 2011).

Subgroup analysis and investigation of heterogeneity

The presence of statistical heterogeneity across trials was determined by visually inspecting the forest plots to check for overlapping CIs and by means of the chi^2 test for heterogeneity with a P value of < 0.10 indicating statistical significance. Further, the I^2 statistic was used to quantify the amount of heterogeneity as low (I^2 value of 25% or less), moderate (I^2 value between 25% and 75%), or high (I^2 value of 75% or more). If we had at least 10 studies in any meta-analysis that showed significant statistical heterogeneity, we would have explored the possible sources of heterogeneity by performing subgroup analyses; with subgroups defined by age, gender, socioeconomic status, and risk of bias (ie low versus high/unclear).

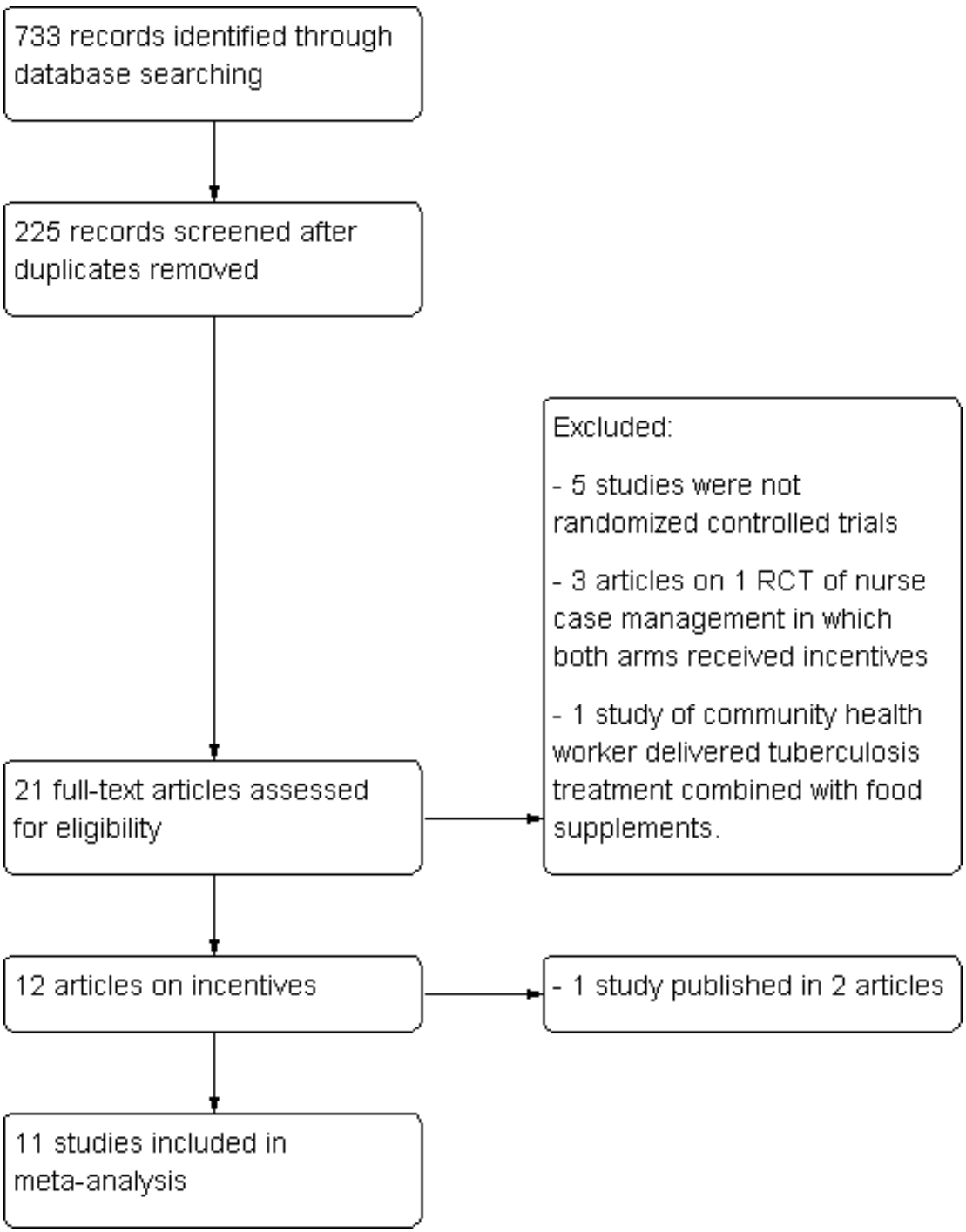
RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

We obtained 733 titles and abstracts from the electronic search of databases, and no additional articles from contacting researchers or screening reference lists. After removal of duplicates, 225 records remained. Following discussion and consensus, we obtained 21 potentially eligible articles. Five of these articles were not randomized controlled trials (Cheng 1997; Filho 2009; FitzGerald 1999; Morisky 1990; Yao 2008), three were published reports of a trial of nurse case-management of latent TB in which both study arms received the same material incentive (Nyamathi 2006), and one was a trial of community health worker delivered TB treatment combined with food supplements (Jahnavi 2010). All nine articles were excluded. Eleven randomized controlled trials met our inclusion criteria (Chaisson 2001; Malotte 1998; Malotte 1999; Malotte 2001; Martins 2009; Morisky 2001; Pilote 1996; Tulsky 2000; Tulsky 2004; White 1998; White 2002), and were included in the review. The final article (Kominski 2007) was a cost-effectiveness analysis of an included study (Morisky 2001). The search and selection of studies is shown in Figure 1.

Figure 1. PRISMA diagram showing the search and selection of studies



Included studies

Ten of the 11 included trials were conducted in the USA, and only one is from a low- or middle-income country (Martins 2009: Timor-Leste).

Studies varied in size from 79 to 1078, with a mean of 430 participants, and most studies focused on very specific patient subgroups. Four studies were conducted among injection drug or cocaine users (Malotte 1998; Malotte 1999; Chaisson 2001; Malotte 2001), three on homeless or marginally housed adults (Pilote 1996; Tulsky 2000; Tulsky 2004), two studies on prisoners (White 1998; White 2002), and one assessed incentives given to adolescents aged 11 to 19 years (Morisky 2001). Only one study involved members of the general adult population with TB, and this focused on malnourished men living close to the study clinics (Martins 2009).

The studies assessed adherence to different stages of TB management. Some investigated the use of incentives in improving return for reading of tuberculin skin test results (Malotte 1998; Malotte 1999) while others focused on improving attendance at the clinic for initiation of treatment (Pilote 1996), adherence to preventive TB treatment (White 1998; Tulsky 2000; Chaisson 2001; Malotte 2001; Morisky 2001; White 2002; Tulsky 2004) and just one looked at adherence to treatment for active TB (Martins 2009).

The trials investigated various types of incentives, and several trials had multiple study arms receiving different forms of both material and non-material incentives. Eight studies included a study arm given cash in values of US $5 or US $10 (Pilote 1996, Malotte 1998, White 1998, Malotte 1999, Tulsky 2000, Chaisson 2001, Malotte 2001, Tulsky 2004). Three studies gave vouchers which could be redeemed for groceries, food, transport, meals at fast food outlets or phone calls (Malotte 1999, White 2002, Tulsky 2004), and one study gave food as a hot daily meal (Martins 2009). In one study, adolescent patients negotiated the incentive they received from their parents (Morisky 2001). Common choices included special meals at home, going to a movie or renting a video.

These material incentives were compared with routine care, and in multi-arm trials also with motivational education (Malotte 1998; Malotte 1999), peer counselling (Morisky 2001; Pilote 1996; Tulsky 2000), and standardised education sessions (White 1998; White 2002). In addition, one study compared different levels of incentive (Malotte 1998), one study compared an immediate incentive, given monthly throughout treatment, with a lump sum given on completion (Chaisson 2001), and two studies compared different forms of incentive (Malotte 1999; Tulsky 2004).

Excluded studies

One study was excluded because in both arms of the trial, patients were given the same incentive (Nyamathi 2006). Two other trials were excluded from this review because they were quasi-randomized; in one, randomization was done by day of the week (Cheng 1997) and in the other it was done by the last digits in the participants' clinic record numbers (Morisky 1990). Three trials were excluded because they were two cross sectional studies where one group was given the incentive and the other was not (Filho 2009, FitzGerald 1999, Yao 2008), and another was excluded because the main intervention was community health-worker delivered TB treatment combined with food supplements (Jahnavi 2010).

Risk of bias in included studies

Our judgements about the risk of bias in each included study are summarised in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

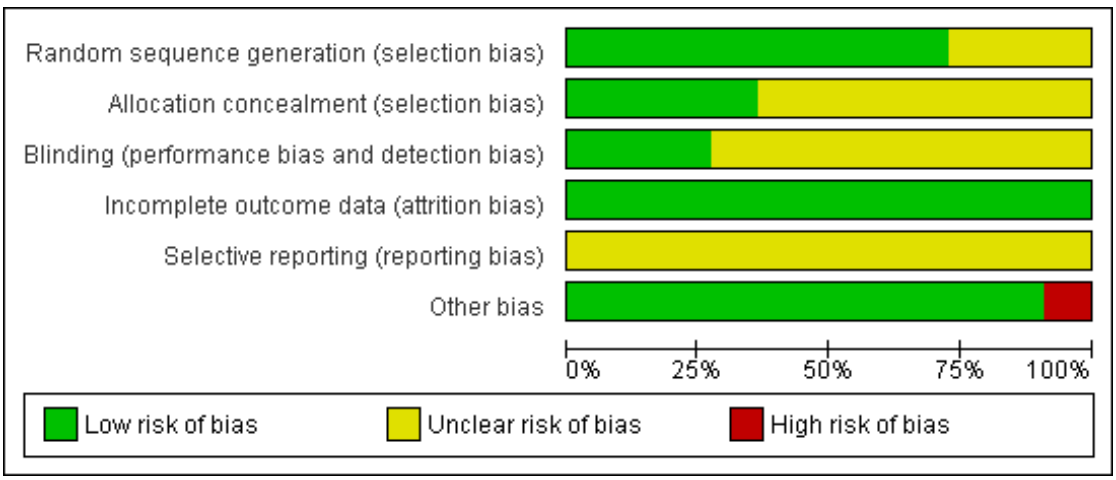
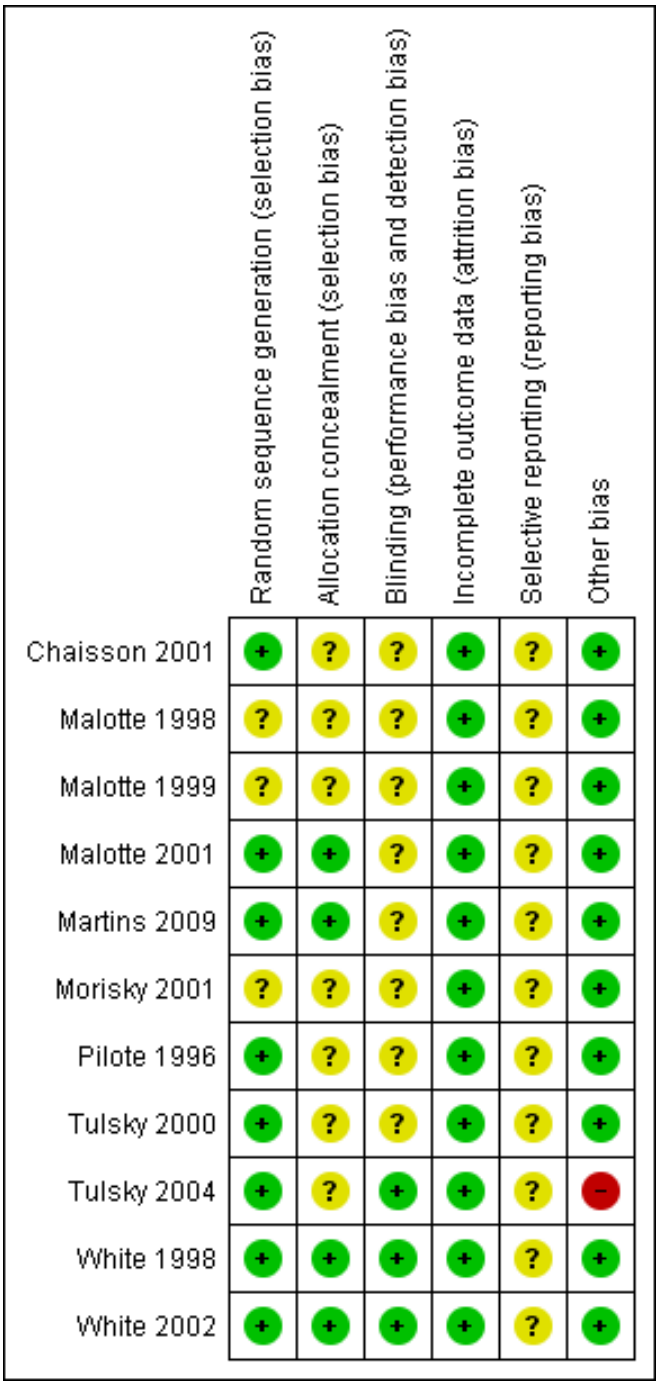


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The generation of the randomization sequence was judged to be adequate in eight trials (Pilote 1996; White 1998; Tulsky 2000; Chaisson 2001; Malotte 2001; White 2002; Tulsky 2004, Martins 2009) and unclear risk in the remainder (Malotte 1998; Malotte 1999; Morisky 2001). The allocation concealment was judged to be adequate in four trials (White 1998; Malotte 2001; White 2002, Martins 2009) and unclear risk in the rest.

Blinding

The blinding of outcome assessors was adequate in three trials (White 1998; White 2002; Tulsky 2004) and unclear in the rest.

Incomplete outcome data

All the included trials addressed incomplete outcome data adequately.

Selective reporting

It was unclear to us if any of the included studies was free of selective outcome reporting; since the study protocols were not available and there was no earlier methods paper listing the prespecified outcomes for any of the studies

Other potential sources of bias

Our assessment indicated that studies to be free of other biases; except Tulsky 2004. The trial compared the effects of cash and non-cash incentives among homeless adults on adherence to treatment for latent TB infection as well as the length of time needed to look for participants who missed their dose of medications. Although the participants were described as homeless, the study groups were not the same with respect to their primary housing in the year prior to the study. In the cash incentive arm, 23% had lived in a shelter or on the street, whilst 41% of the non-cash incentive arm had done so (Tulsky 2004). This baseline difference had the potential to introduce systematic differences in study outcomes.

Effects of interventions

See: **Summary of findings for the main comparison** Material incentives compared to routine care for improving patient adherence to TB management

Incentives versus routine care

Return to clinic for tuberculin skin test reading

Two studies in drug users from the USA compared material incentives ($5-$10) with routine care alone (Malotte 1998; Malotte 1999).

Material incentives significantly increased the proportion of people who returned for reading of the tuberculin skin test (two trials, 1371 participants: RR 2.16, 95% CI 1.41 to 3.29; Analysis 1.1). Although there was significant heterogeneity between these studies (I^2 = 86%), the heterogeneity relates to the magnitude of the observed effect, and not the direction or significance of the result. Both studies demonstrated a clinically important benefit.

Return to clinic for initiation or continuation of TB prophylaxis

Three studies from the USA compared material incentives with routine care alone (Pilote 1996; White 1998; White 2002). Pilote 1996 gave $5 to homeless people on return to a clinic after a positive tuberculin skin test, White 1998 gave $5 when recently released prisoners attended a community clinic for continuation of TB prophylaxis, and White 2002 gave recently released prisoners food or transportation vouchers worth $25 upon presentation at a TB clinic.

Incentives significantly increased clinic attendance for initiation or continuation of treatment for latent TB infection (three trials, 595 participants: RR 1.58, 95% CI 1.27 to 1.96; Analysis 1.2). Although heterogeneity between the relative effects was low (I^2 = 0%), there was a wide variation in the absolute benefit achieved with incentives. In the two trials in prisoners, attendance at clinic remained lower than 25% even in the intervention groups.

Completion of TB prophylaxis

Three studies, again from the USA, examined the effect of incentives on completion of TB prophylaxis. Malotte 2001 gave a $5 cash incentive to drug users on attendance for twice weekly directly observed treatment, White 2002 gave recently released prisoners transportation vouchers worth $25 upon first presentation at a TB clinic, and Morisky 2001 established an incentive agreement between adolescents aged 11 to 19 years and their parents, where parents provided cash or treats at various stages in the treatment process.

Incentives had no statistically significant effect on the completion of TB prophylaxis (three trials, 869 participants: RR 1.79, 95%

CI 0.70 to 4.58, Analysis 1.3). However, there was significant heterogeneity in these results (I^2 = 90%). Malotte 2001 found a statistically significant benefit with incentives (RR 14.53, 95% CI 3.64 to 57.98), but adherence in the control group was extremely low (3.6%). In Morisky 2001 completion of treatment was reasonable in the control group (77.8%), and did not significantly change with the incentive (76.4%), while in White 2002 completion remained low in both groups despite the intervention (13.8% control vs 14.1% intervention).

Completion of treatment for active TB

One trial compared incentives given as food (in the form of hot meals at the clinic during the intensive phase of treatment followed by monthly food parcels) to nutritional advice alone (Martins 2009). Both arms received usual TB care.

There was no significant difference in treatment completion rates between participants given nutritional supplements and those receiving nutritional advice alone (one trial, 265 participants, RR 0.98, 95% CI 0.86 to 1.12, Analysis 1.4). Treatment completion was below 80% in both the control (77.5%), and intervention groups (75.7%); TB cure was not reported.

Immediate versus deferred incentive

Completion of TB prophylaxis

One study, (Chaisson 2001) compared the effects of an immediate incentive ($10 for each monthly appointment attended) with the promise of a deferred lump sum ($10 for each appointment attended) on completion of TB prophylaxis.

The participants who received the immediate incentives completed treatment more often than those whose incentives were deferred (83% vs 75%), but the difference was not statistically significant (one trial, 300 participants: RR 1.11, 95% CI 0.98 to 1.24; Analysis 2.1).

Cash versus non-cash incentives

Return to clinic for tuberculin skin test reading

One study amongst injection drug and crack cocaine users (Malotte 1999), directly compared a cash incentive ($10) with non-cash incentives (grocery store coupons, bus tokens and fast food coupons equivalent in value to $10).

The cash incentive was significantly more effective at increasing return for reading of tuberculin skin tests than any of the non-cash incentives (one trial, 651 participants: RR 1.13, 95% CI 1.07 to 1.19; Analysis 3.1).

Completion of TB prophylaxis

One study among homeless and marginally housed adults with latent TB infection (Tulsky 2004) compared a cash incentive ($5), with non-cash incentives (patients could choose between fast food or grocery store coupons, phone cards or bus tokens equivalent to $5).

Again, the cash incentive was significantly more effective than the non-cash incentives (one trial, 141 participants: RR 1.26, 95% CI 1.02 to 1.56; Analysis 3.2).

Different values of cash incentive

Return to clinic for tuberculin skin test reading

One trial (Malotte 1998), also compared different values of cash incentive ($10 versus $5).

The $10 incentive significantly increased the proportion of patients returning to clinic to collect their diagnostic TB test result compared to the $5 incentive (one trial, 404 participants: RR 1.08, 95% CI 1.01 to 1.16; Analysis 4.1).

Incentives versus any other intervention

Return to clinic for tuberculin skin test reading

The two trials among drug users in the USA (Malotte 1998; Malotte 1999), also had a treatment arm which received 5 to 10 minutes of motivational education .

The material incentives ($5 to $10) significantly increased the rate of return for tuberculin skin test reading compared to motivational education alone (two trials, 1366 participants:RR 2.16, 95% CI 1.56 to 3.00; Analysis 5.1).

Return to clinic for initiation or continuation of TB prophylaxis

Two trials assessing return to clinic for TB prophylaxis compared material incentives with education or counselling. Both are from the USA; Pilote 1996 used peer counsellors to encourage homeless men and women to attend clinic after a positive test result, and White 2002 gave education sessions every two weeks to jail inmates to encourage attendance at a community clinic upon release.

There was no significant difference between material incentives and education or peer counselling (two trials, 535 participants: RR 1.10, 95% CI 0.92 to 1.31; Analysis 5.2).

Completion of TB prophylaxis

Three trials also used peer counselling or education sessions to promote completion of TB prophylaxis: one among jail inmates (White 2002), one amongst homeless adults (Tulsky 2000), and one among adolescents (Morisky 2001).

The results were mixed. In adolescents, completion rates were high in both groups and with no significant difference between groups (one trial, 387 participants: RR 0.95, 95% CI 0.86 to 1.06). Among the homeless, the cash incentive appeared more effective than counselling but completion remained low in both groups (one trial, 80 participants: RR 2.34, 95% CI 1.11 to 4.93), and among jail inmates the trend was towards a benefit with counselling (one trial, 370 participants: RR 0.58, 95% CI 0.31 to 1.09).

Potential effect modifiers

The only potential effect modifier to be reported was educational status. Six trials assessed this and no effect on outcomes was noted (Pilote 1996; Malotte 1998; Malotte 1999; Malotte 2001; White 2002; Tulsky 2004).

None of the studies reported their results subgrouped by HIV status. In three studies it was noted that HIV positive patients were included (Malotte 1998; Malotte 1999; Malotte 2001), in one study it was noted that the population from which the study sample was drawn had a generally low prevalence of HIV (Martins 2009), and in a further three trials HIV positive patients were actively excluded (Tulsky 2000; White 2002; Tulsky 2004).

Adverse events

Although adverse events due to the anti-TB drugs administered (such as isoniazid) were noted, adverse effects of the incentives themselves were not. No study documented what patients chose to purchase with the cash or vouchers, and no study recorded incidents of theft, fraud or perverse incentive effect.

Cost effectiveness

We found one paper reporting a cost analysis (Kominski 2007), which related to an included trial (Morisky 2001). This trial involved the administration of an incentive to adolescents with latent TB (in the form of a "contingency contract" with their parents).

As this trial failed to demonstrate any clinical benefit with the use of incentives, any further appraisal of the cost component is inappropriate, and this particular intervention unlikely to be cost effective in this setting.

DISCUSSION

Summary of main results

When given as cash, incentives may increase the return rate for reading of tuberculin skin test results compared to normal care (*low quality evidence*), and probably improve clinic re-attendance for initiation or continuation of anti-TB prophylaxis (*moderate quality evidence*).

Cash incentives may also be more effective than non-cash incentives (*low quality evidence*), and higher amounts of cash may be more effective than lower amounts (*low quality evidence*).

We currently don't know if material incentives can improve long-term adherence and completion of anti-TB treatment for active disease. Only one trial has assessed this and the incentive, given as a daily hot meal, was not well received by the population due to the inconvenience of attending the clinic at midday (*very low quality evidence*).

Material incentives may be more effective than motivational education at improving return tuberculin skin test results (*low quality evidence*), but may be no more effective than peer counselling, or structured education at improving continuation or completion of prophylaxis (*low quality evidence*).

Overall completeness and applicability of evidence

All but one of the studies included in this review were conducted in the USA, and in all but two the participants belonged to special groups (injecting drug users, homeless people, prison inmates, and adolescents). The applicability of these results to the broader adult population, especially in low- and middle-income countries where the burden of TB is highest, is therefore questionable. It is possible that these subpopulations have different relationships with material incentives, than the general population, and a greater potential for misuse.

One important consideration in extrapolating these results to other populations is HIV. It is possible that HIV co-infection may affect adherence to anti-TB medications, either positively (for example through adherence education received in the HIV programme), or negatively (for example because illness prevents patients from attending the clinic, or because patients are already taking a number of medications for HIV). However, HIV was not considered in most of these studies. Since the risk of developing TB among patients with HIV is far higher than in those who are HIV negative (WHO 2009a), future studies on incentives for TB should specifically investigate the effect of HIV status on outcomes.

In some settings, health workers and managers may be concerned about giving cash to patients. Indeed, this was the rationale for the inclusion of non-cash incentives in one of the trials in this review (Malotte 1999). The reason for this concern was not described in the trial, but could be related to the expenditure of cash on unhealthy purchases. Vouchers for specified goods cannot be spent on such items and in fact were demonstrated by this trial to have

a beneficial effect on return for tuberculin skin testing. None of the studies however investigated what purchases were made with cash or voucher incentives.

A further objection to the use of incentives may be to the rationale of 'paying the patient' to behave in a healthy way (when it is considered the patients' responsibility to do so). However, in poor settings, it may be difficult, if not impossible, for the patient to access the clinic or pay for medicines (McIntyre 2006). This acknowledgement underlies the Opportunidades Programme (now Progressa Programme) in Mexico, where patients are assisted financially in return for behaviours that will promote the health of families (Lagarde 2007). This programme has been shown to have benefits in a poor population (Lagarde 2007), as well as in groups of vulnerable patients in wealthier settings (such as homeless people in the USA) (Pilote 1996). However, the ethics of "paying patients" who are not poor or vulnerable is beyond the scope of this review.

Quality of the evidence

The quality of evidence provided by this review has been assessed using the GRADE methods, and is presented in five summary of findings tables (Summary of findings for the main comparison, Appendix 1, Appendix 2, Appendix 3, Appendix 4). The evidence is generally considered to be of low or very low quality which indicates that further research is very likely to change these estimates of effect.

The main reason for downgrading quality was the indirectness of the evidence, with only one trial from the general adult population of low and middle income countries.

Potential biases in the review process

We minimised potential biases in the review process by adhering to the guidelines of the Cochrane Collaboration (Higgins 2011). We conducted comprehensive searches of both peer-reviewed and grey literature, without limiting the searches to a specific language. Two independent authors assessed study eligibility, extracted data, and assessed the risk of bias in each included study.

Agreements and disagreements with other studies or reviews

Consistent with the findings of relevant previous reviews (Lagarde 2007; Haynes 2008; Sutherland 2008), we found that material incentives may promote the uptake of health services in certain settings. However, to the best of our knowledge, our review is the most comprehensive synthesis of existing evidence on the effects of material incentives in patients undergoing diagnostic testing for TB or receiving drug therapy to prevent or cure TB.

AUTHORS' CONCLUSIONS

Implications for practice

There is some evidence to support the use of material incentives to improve return rates for TB diagnostic test results and adherence to anti-TB preventive therapy. The data is currently limited to trials among predominantly male drug users, homeless, and prisoner subpopulations in the USA, and therefore the results are not easily generalised to the wider adult population, or to low- and middle-income countries, where the TB burden is highest.

Implications for research

Further high-quality studies are needed to assess the effects and costs of incentives to improve adherence to the long-term treatment of active TB.

Future studies should specifically investigate the role of HIV and socioeconomic status in modifying the effects of incentives for TB treatment. The possible adverse effects of incentives such as misuse of incentives, fraudulent practices, the effect of incentives on non-recipients, and the perverse incentive effect, should also be considered.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chaisson 2001

Methods	Individually randomized controlled trial, factorial design Duration of enrolment: June 1995 - August 1997
Participants	Number enrolled: 300 Inclusion criteria: Injection drug users over 18 years old, with tuberculin skin test reading of more than 5 mm induration if HIV positive or 10 mm if HIV negative, on preventive treatment for TB Exclusion criteria: evidence of active TB, history of serious adverse reaction to INH (isoniazid) treatment, previous INH treatment for 6 months or longer, serum ALT elevated more than 5 times normal levels, or HIV disease with CD4 count of less than 200/mm3. (Isoniazid is a standard TB medication used for both prophylaxis and treatment of active TB)
Interventions	All participants were randomly assigned to receive either: 1. A an immediate $10 stipend per month (for each monthly appointment kept), or 2. A deferred amount, equal to $10 for each monthly appointment kept The immediate payment was given at the end of each month when the patient had completed a routine assessment for adherence and drug toxicity. The deferred payment was credited each month a patient in this group completed assessment for adherence and toxicity, but payment was made when treatment was completed or when the patient withdrew from the study Each arm was on prophylaxis for TB.
Outcomes	Completion of 6 months of INH preventive treatment (reporting for each of 6 monthly visits and taking at least 80% of medication)
Notes	Independent of the material incentive, all patients were randomly assigned to directly observed preventive therapy (ie outreach meeting with a nurse twice a week; peer support counselling (ie monthly support group meetings); or routine care (ie monthly clinic visits) Trial location: Baltimore, United States Setting: Community based tuberculosis clinic Source of funding:National Institute on Drug Abuse (DA 08992) and the National Institute of Allergy and Infectious Diseases (AI 01637)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generation performed by computer algorithm.

Chaisson 2001 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment was given.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not known if outcome assessors were blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers presented for whole group and each arm, intention to treat analysis. Withdrawals included "failure to return (37 patients), voluntary withdrawal (4)...and other reasons (13)". These do not seem to be related to the material incentives
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and there is no earlier methods paper listing the pre-specified outcomes
Other bias	Low risk	The study appears to be free of other bias.

Malotte 1998

Methods	Individually randomized controlled trial Duration: April 1994 to August 1995.
Participants	Number enrolled: 1004 Inclusion criteria: Injection drug and crack cocaine users, who had tuberculin skin tests and were required to return for the reading Exclusion criteria: None stated
Interventions	Participants were divided into 6 arms, which received the following interventions: 1. 5-10 minute session of motivational education 2. 5-10 minute session of motivational education plus $10 on return for tuberculin skin test reading 3. 5-10 minute session of motivational education plus $5 on return for tuberculin skin test reading 4. $10 on return for tuberculin skin test reading 5. $5 on return for tuberculin skin test reading 6. Routine care.
Outcomes	Return for tuberculin skin test reading within 96 hours.
Notes	Trial location: Long beach, California, United States Setting: Urban research clinic Source of funding: National Institute on Drug Abuse (grant RO1-DA08799)
Risk of bias	

Malotte 1998 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No omissions from final analysis. 1004 enrolled, intention to treat analysis.
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and there is no earlier methods paper listing the pre-specified outcomes
Other bias	Low risk	The study appears to be free of other bias.

Malotte 1999

Methods	Individually randomized controlled trial Duration: September 1995 to September 1997
Participants	Number enrolled: 1078 Inclusion criteria: Injection drug and crack cocaine users who had tuberculin skin tests and were required to return for the reading (age restrictions not specifically stated but all participants were over age of 18 years) Exclusion criteria: Participation in group's previous studies
Interventions	1. $10 on return for tuberculosis skin test reading. 2. grocery store coupons worth $10 on return for tuberculosis skin test reading 3. patient's choice of bus passes or coupons for fast food restaurant worth $10 on return for tuberculosis skin test reading 4. Motivational education session of 5 - 10 minutes. 5. Routine care.
Outcomes	Return for tuberculosis skin test reading within 96 hours.
Notes	Study was a follow up to Malotte 1998 - authors wanted to test effectiveness of non-cash incentives, as they felt health departments might object to giving cash out to patients as this was considered controversial Trial location: Long beach, California, United States Setting:Urban research clinic Source of funding: National Institute on Drug Abuse (grant RO1-DA08799)

Malotte 1999 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description of method of randomization.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No omissions from final analysis. 1078 randomized, intention to treat analysis
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and there is no earlier methods paper listing the prespecified outcomes
Other bias	Low risk	The study appears to be free of other bias.

Malotte 2001

Methods	Individually randomized controlled trial Duration: April 1994 to September 1997 (recruitment period).
Participants	Number enrolled: 169 Inclusion criteria: Injection drug or crack cocaine users, needing INH treatment for TB prophylaxis Exclusion criteria: Active TB or medical contraindications to the use of isoniazid
Interventions	1. Twice weekly directly observed therapy (DOT) by study outreach worker at location chosen by patient, plus $5 per visit 2. Twice weekly DOT by study outreach worker at location chosen by patient 3. Twice weekly DOT at study site plus $5 per visit. Participants in both arms received INH prophylaxis.
Outcomes	Completion of course of INH (6 months if patient HIV negative, 12 months if patient HIV positive). Also percentage of medications taken on time (all doses in all arms were directly observed)
Notes	Trial location: Long beach, California, United States Setting:Urban research clinic Source of funding: National Institute on Drug Abuse (grant RO1-DA08799)
Risk of bias	

Malotte 2001 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization in blocks of 18, assumed to have been done by computer
Allocation concealment (selection bias)	Low risk	Allocation was kept in "numbered, opaque, sealed envelopes" and "staff ... were unaware of block size"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	169 patients randomized. Six excluded from analysis for medical reasons which were unlikely to have been related to the study outcome. Intention to treat analysis
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and there is no earlier methods paper listing the prespecified outcomes
Other bias	Low risk	The study appears to be free of other bias.

Martins 2009

Methods	Individually randomized controlled trial conducted at three sites in Dili, Timor Leste Duration: Enrollment 16 March - 9 November 2005; Follow up continued until July 2006
Participants	Patients with newly diagnosed pulmonary tuberculosis, both positive and negative results on sputum tests Eligible: 833 (563 excluded) Randomized: 270 (133 control, 137 intervention group). Most participants were poor, malnourished men living close to the clinics
Interventions	1. Nutritious, culturally appropriate daily meal (weeks 1-8) and food packages (weeks 9-32) 2. Control group given nutritional advice. Both groups received standard TB treatment.
Outcomes	Primary outcomes: Completion of treatment, including cure Secondary outcomes: Adherence to treatment, weight gain, and clearance of sputum smears
Notes	Outbreak of civil conflict in the country three months before completion of study disrupted service delivery and access of patients to health care (70% of the population were displaced). However, it is likely that this affected intervention and control groups

	similarly Most participants were poor and malnourished men who lived close to the clinics and this may limit the external generalisability of the study Substantial missing data for intermediate outcomes implies that participants did not attend clinics regularly. Also, intervention was not well received by many participants as it was inconvenient to attend the clinics at midday for the meal (this was also the reason for a high number of patients' refusal to participate in the trial). 70% of participants had negative smear results, which means that cure could not be objectively verified. Adherence was not objectively assessed Adverse events: None necessitated stopping treatment. Itch with or without rash was more than twice as likely to occur in the intervention group (RR 2.27; 95% CI 1.20-4. 26)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated random allocation sequence with randomly varying block sizes (done by independent statistician using STATA). Allocation was stratified by community health clinic and by diagnosis of TB (positive or negative smear)
Allocation concealment (selection bias)	Low risk	Concealed from all investigators with sequentially numbered opaque sealed envelopes prepared distant from study site
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding of participants and treatment providers not done, but independent observer who determined the primary outcome was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants received allocated intervention and loss to follow up (transfer to another clinic during treatment) was very small (1% in intervention group and 4% in control group). Intention to treat analysis
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and there is no earlier methods paper listing the prespecified outcomes
Other bias	Low risk	The study appears to be free of other bias.

Morisky 2001

Methods	Individually randomized controlled trial. Duration: Not stated
Participants	Number enrolled: 794. Inclusion criteria: Adolescents aged 11 - 19 years who needed treatment for latent TB infection Exclusion criteria: Not stated
Interventions	1. Peer counselling (at least once every two weeks) 2. Incentive (participant-parent contingency contract, where parent and patient negotiated a reward for adherence to treatment. This was provided by the parent and given at a frequency negotiated by the parent and participant). Examples of incentives included a special meal at home, going out to eat, clothing, going to movies or renting a video, or anything agreeable to both parent and adolescent 3. Combined peer counselling and incentive (participant-parent contingency contract) 4. Usual care. Participants in intervention and control arms received INH prophylaxis
Outcomes	Completion of 6 months of INH prophylaxis; measured using the discharge summary recorded in the patient's medical chart
Notes	Trial location: Los Angeles County, United States Setting: Urban community based clinics Source of funding: National Heart, Lung and Blood Institute (ROI-55770)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Authors state that intention to treat model was used (pg 570). 794 adolescents enrolled and analysed. No omissions from final analysis
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and there is no earlier methods paper listing the prespecified outcomes

Morisky 2001 (*Continued*)

Other bias	Low risk	Over and above the interventions described above, patients were interviewed three times during the study and at each interview received $15. The additional interest in the participants, plus the cash which may have acted as a further incentive to adhere, may be regarded as interventions in themselves. However, this applied to all participants and would not have introduced bias

Pilote 1996

Methods	Individually randomized controlled trial. Duration: June 1992 to April 1994.
Participants	Number enrolled: 244 Inclusion criteria: Homeless "men and women", age not specified (but all over 18 years in results), who had a tuberculin skin test and were required to attend a clinic to initiate treatment for latent or active TB Exclusion criteria: Recent investigation for TB.
Interventions	1. Peer health advisers plus usual care (advisers accompanied patients to clinics and assisted with filling out forms etc) 2. Incentive of $5 cash if participant came to clinic within 3 weeks of randomisation plus usual care 3. Usual care (appointment at TB clinic plus a bus token for transport to clinic)
Outcomes	Attendance at clinic appointment within three weeks of positive reading of tuberculin skin test
Notes	Second phase of this study reported in Tulsky et al 2000. Trial location: San Fransisco, California, United States Setting:Urban community based TB clinic (attached to San Fransisco General Hospital) Source of funding: Kaiser Family Foundation, AcqUired Immunodeficiency Syndrome Clinical Research Center, San Francisco, Calif; Universitywide Acquired Immunodeficiency Syndrome Research Program, University of California; and by grant R01-DA04363-07 from the National Institute on Drug Abuse, Bethesda, MD

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"treatment group was assigned by sampling without replacement from blocks of nine". Assumed to be done by computer

Pilote 1996 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	244 patients randomized, 244 analysed.
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and there is no earlier methods paper listing the pre-specified outcomes
Other bias	Low risk	The study appears to be free of other bias.

Tulsky 2000

Methods	Individually randomized controlled trial Duration: June 1992 to May 1995 (recruitment period June 1992 to December 1994, plus 6 months of patient follow up time)
Participants	Number enrolled: 118 Inclusion criteria: Homeless adults, with positive tuberculin skin test or credible history of prior positive tuberculin skin test but no follow up for this in the 6 months prior to the study Exlusion criteria: Receiving treatment or prophylaxis for TB at the time of the study, or HIV positive
Interventions	1. Usual care (self-supervised daily dosing with INH and monthly clinic visits for assessment and refill of tablets) 2. Taking of 900 mg INH directly observed at each of two weekly visits to study site; plus an incentive of $5 cash 3. Peer health advisor (who directly supervised taking of treatment twice weekly, accompanied patient to clinic and looked for the patient if lost to follow up) Participants in intervention and control arms received INH prophylaxis
Outcomes	Completion of 6 months of INH preventive treatment as documented in patients' clinic charts; number of months of INH dispensed
Notes	Trial location: San Fransisco, California, United States Setting: Community-based TB clinic Source of funding: Not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Tulsky 2000 (*Continued*)

Random sequence generation (selection bias)	Low risk	Block randomization used, therefore allocation sequence assumed to have been generated by computer
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 330 patients randomized, 195 found to require further evaluation and 37 needed further diagnostic tests (sputum cultures and liver function tests). Of 121 who were prescribed INH, 118 were analysed - 3 were excluded from study because of "toxic effects of INH". These reasons unlikely to be related to final outcome
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and there is no earlier methods paper listing the prespecified outcomes
Other bias	Low risk	The study appears to be free of other bias.

Tulsky 2004

Methods	Individually randomized controlled trial. Duration: May 1996 to May 1998 (based on recruitment period of May 1996 to December 1997, plus 6 months for patient follow up)
Participants	Number enrolled: 119 (85% male; median age 41 years [range 21-79]) Inclusion criteria: Homeless adults who were eligible for preventive TB treatment. Adults who were "truly homeless" (living in street and shelter dwellings) and those who were "marginally housed" (living in residential hotels) were recruited into the study Exclusion criteria: active TB or HIV positive.
Interventions	1. $5 cash incentive for each twice weekly appointment kept. 2. Non-cash incentive with face value of $5 for each twice weekly appointment kept (patients could choose between fast food or grocery store coupons, phone cards or bus tokens) Participants in intervention and control arms received INH prophylaxis
Outcomes	1. Completion of preventive treatment (assessed by reviewing TB clinic records) 2. Length of time needed to look for participants who had missed scheduled appointments and didn't respond to letters or phone calls. (A tracking form including names and mailing addresses of family, friends, and case workers was completed for each participant. After the first missed appointment, staff made phone calls and sent reminder letters. If

	the participant did not attend the next scheduled visit, outreach efforts were initiated and were guided by the information on the tracking form.)
Notes	Because the cash incentive arm did so much better than the non incentive arm in the study performed by this group previously (Tulsky 2000), the authors felt it would be unethical to continue to randomize one group to no incentive Trial location: San Fransisco, California, United States Setting: Urban, community-based TB clinic Source of funding: National Heart, Lung, and Blood Institute (grant HL55729) and the National Institute of Mental Health (grant MH54907)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence was generated "...from a list of randomly generated numbers"
Allocation concealment (selection bias)	Unclear risk	"...numbers previously sealed into individual envelopes and selected in consecutive order". Not clear if these envelopes were opaque
Blinding (performance bias and detection bias) All outcomes	Low risk	"TB clinic physicians were blinded with respect to the results of the randomisation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	141 patients randomized but 16 not prescribed INH (4 in cash incentive arm, 12 in non-cash incentive arm). Reasons for exclusion clinical and unlikely to be related to allocation. 6 patients censored (5 for clinical reasons, 1 because died in hotel fire). Again, reasons for exclusion unlikely to be related to allocation or outcome. 119 patients analysed
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and there is no earlier methods paper listing the prespecified outcomes
Other bias	High risk	The study groups were not the same with respect to their primary housing in the year prior to the study. In the cash incentive arm, 23% had lived in a shelter or on the street, whilst 41% of the non-cash incentive arm had done so

White 1998

Methods	Individually randomized controlled trial Duration: One year (1996)
Participants	Number enrolled: 79 (98% male, mean age 32.0 years) Inclusion criteria: Jail inmates eligible for INH prophylaxis for latent TB infection Exclusion criteria: Unable to speak English or Spanish, or sequestration from jail population due to violence or mental illness
Interventions	1. Promise of $5 cash incentive (to be provided) on making first visit to community TB clinic to continue INH prophylaxis after release from jail plus standardised TB education 2. Standardised TB education (about TB and the importance of taking INH prophylaxis) Participants in intervention and control arms received INH prophylaxis
Outcomes	Attendance at first visit to community TB clinic to continue INH prophylaxis after release from jail
Notes	Trial location: San Fransisco, California, United States Setting: Prison Source of funding: Academic Senate of the University of California, San Francisco

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization done using table of random numbers.
Allocation concealment (selection bias)	Low risk	Previously sealed, ordered, opaque envelopes used.
Blinding (performance bias and detection bias) All outcomes	Low risk	Research assistants collecting clinic data (as to whether participant attended first appointment or not) were blinded as to participants' assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 79 inmates enrolled in the study, 18 remained in prison for the full duration of their INH treatment (and so were never required to present at a community TB clinic). 61 were analysable, and there were no differences between treatment allocations in this group. "Data were rechecked for internal validity and there were no differences by study group in any of the variables collected for this analytic sample of 61 persons" (pg 508)

White 1998 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Study protocol not available and there is no earlier methods paper listing the pre-specified outcomes
Other bias	Low risk	The study appears to be free of other bias.

White 2002

Methods	Individually randomized controlled trial Duration of enrolment: 1 March 1998 to 31 May 1999.
Participants	Number enrolled: 558 (82% male; median age 28.5 years in incentive arm, 29.7 years in routine care arm, and 29.5 years in education arm) Inclusion criteria: Jail inmates with latent TB infection, eligible for and agreeable to INH prophylaxis Exclusion criteria: HIV positive, not able to speak English or Spanish, assessed by Sheriff's personnel to be violent, or by mental health staff to have a serious psychiatric illness
Interventions	1. Promise of incentive ($25 equivalent in food or transportation vouchers), provided at the first visit to the community TB clinic after release from jail 2. Education, provided every two weeks whilst in jail 3. Usual care (neither intervention).
Outcomes	1. Attendance at first visit to community TB clinic to continue INH prophylaxis within one month after release from jail; 2. Completion of full course of INH treatment.
Notes	HIV positive patients on INH prophylaxis receive very different programme of treatment, including incentives Trial location: San Fransisco, California, United States Setting: Prison Source of funding: National Institute of Nursing Research, National Institutes of Health, Bethesda, Md. (grant R01 NR04456)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization done using table of random numbers.
Allocation concealment (selection bias)	Low risk	Ordered, opaque, sealed envelopes used.
Blinding (performance bias and detection bias) All outcomes	Low risk	Research assistants collecting clinic data (as to whether participant attended first appointment or not) were blinded as to participants' assignments

Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 558 inmates enrolled, 48 discontinued INH treatment whilst in jail, and 185 completed INH treatment whilst in jail. Thus 325 were eligible for analysis. There were no differences between study group in either the 325 analysable patients or 558 initially enrolled patients. Reasons for exclusion from analysis not likely to be related to final outcome. Intention to treat analysis for those released while taking INH
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and there is no earlier methods paper listing the prespecified outcomes
Other bias	Low risk	The study appears to be free of other bias.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Cheng 1997	Not a randomized controlled trial, as allocation to treatment interventions was done by day of the week
Filho 2009	Not a randomized controlled trial; essentially two cross-sectional studies where first group was not given incentive and second group was
FitzGerald 1999	Not a randomized controlled trial; essentially two cross-sectional studies where first group was not given incentive and second group was
Jahnavi 2010	A trial of community health worker delivered tuberculosis treatment combined with food supplements; and not a trial of food incentives per se
Morisky 1990	Not a randomized controlled trial, as allocation to treatment interventions was done by the last digits of the participants' clinic numbers
Nyamathi 2006	Both the intervention and control arms received a $5 cash incentive for each dose of INH prophylaxis taken. It was therefore not possible to assess the effect of the incentive in this study. The main intervention was a nurse case management programme
Yao 2008	Quasi-experimental study (controlled before-after study), with no evidence of randomisation to control or intervention groups. Incentives were provided to health care workers as well as patients, and the effect of patients' incentives only is not disaggregated

DATA AND ANALYSES

Comparison 1. Incentive versus routine care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Return for tuberculin skin test results	2	1371	Risk Ratio (M-H, Random, 95% CI)	2.16 [1.41, 3.29]
2 Clinic visit to start or continue TB prophylaxis	3	595	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.27, 1.96]
3 Completion of TB prophylaxis	3	869	Risk Ratio (M-H, Random, 95% CI)	1.79 [0.70, 4.58]
4 Completion of treatment for active TB	1	265	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.86, 1.12]

Comparison 2. Immediate versus deferred incentive

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Completion of TB prophylaxis	1	300	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.98, 1.24]

Comparison 3. Cash incentive versus non-cash incentive

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Return for tuberculin skin test reading	1	652	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [1.07, 1.19]
2 Completion of TB prophylaxis	1	141	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [1.02, 1.56]

Comparison 4. Different values of cash incentive

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Return for tuberculin skin test reading	1	404	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [1.01, 1.16]

Comparison 5. Incentives versus any other intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Return for tuberculin skin testing	2	1366	Risk Ratio (M-H, Random, 95% CI)	2.16 [1.56, 3.00]
2 Clinic visit to start or continue TB prophylaxis	2	535	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.92, 1.31]
3 Completion of TB prophylaxis	3	837	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.59, 1.83]

Analysis 1.1. Comparison 1 Incentive versus routine care, Outcome 1 Return for tuberculin skin test results.

Review: Material incentives and enablers in the management of tuberculosis

Comparison: 1 Incentive versus routine care

Outcome: 1 Return for tuberculin skin test results

Study or subgroup	Any incentive n/N	Routine care n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Malotte 1998	361/404	33/100		45.8 %	2.71 [2.04, 3.59]
Malotte 1999	572/652	106/215		54.2 %	1.78 [1.55, 2.04]
Total (95% CI)	**1056**	**315**		**100.0 %**	**2.16 [1.41, 3.29]**

Total events: 933 (Any incentive), 139 (Routine care)

Heterogeneity: Tau?? = 0.08; Chi?? = 7.29, df = 1 (P = 0.01); I?? =86%

Test for overall effect: Z = 3.57 (P = 0.00035)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Incentive versus routine care, Outcome 2 Clinic visit to start or continue TB prophylaxis.

Review: Material incentives and enablers in the management of tuberculosis

Comparison: 1 Incentive versus routine care

Outcome: 2 Clinic visit to start or continue TB prophylaxis

Study or subgroup	Any incentive n/N	Routine care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Pilote 1996	69/82	42/79		57.3 %	1.58 [1.26, 1.99]
White 1998	8/31	7/30		9.5 %	1.11 [0.46, 2.67]
White 2002	42/185	25/188		33.2 %	1.71 [1.09, 2.68]
Total (95% CI)	**298**	**297**		**100.0 %**	**1.58 [1.27, 1.96]**

Total events: 119 (Any incentive), 74 (Routine care)

Heterogeneity: Chi?? = 0.74, df = 2 (P = 0.69); I?? =0.0%

Test for overall effect: Z = 4.16 (P = 0.000032)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Incentive versus routine care, Outcome 3 Completion of TB prophylaxis.

Review: Material incentives and enablers in the management of tuberculosis

Comparison: 1 Incentive versus routine care

Outcome: 3 Completion of TB prophylaxis

Study or subgroup	Any incentive n/N	Routine care n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Malotte 2001	28/53	2/55		21.8 %	14.53 [3.64, 57.98]
Morisky 2001	152/199	147/189		41.2 %	0.98 [0.88, 1.09]
White 2002	26/185	26/188		37.0 %	1.02 [0.61, 1.68]
Total (95% CI)	**437**	**432**		**100.0 %**	**1.79 [0.70, 4.58]**

Total events: 206 (Any incentive), 175 (Routine care)

Heterogeneity: Tau?? = 0.55; Chi?? = 20.12, df = 2 (P = 0.00004); I?? =90%

Test for overall effect: Z = 1.21 (P = 0.22)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Incentive versus routine care, Outcome 4 Completion of treatment for active TB.

Review: Material incentives and enablers in the management of tuberculosis

Comparison: 1 Incentive versus routine care

Outcome: 4 Completion of treatment for active TB

Study or subgroup	Incentive n/N	Routine care n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Martins 2009	103/136	100/129		100.0 %	0.98 [0.86, 1.12]
Total (95% CI)	**136**	**129**		**100.0 %**	**0.98 [0.86, 1.12]**

Total events: 103 (Incentive), 100 (Routine care)
Heterogeneity: not applicable
Test for overall effect: Z = 0.34 (P = 0.73)
Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Immediate versus deferred incentive, Outcome 1 Completion of TB prophylaxis.

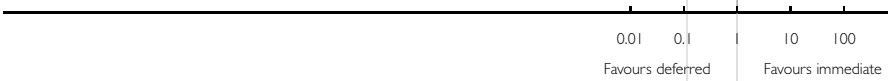
Review: Material incentives and enablers in the management of tuberculosis

Comparison: 2 Immediate versus deferred incentive

Outcome: 1 Completion of TB prophylaxis

Study or subgroup	Immediate incentive n/N	Deferred incentive n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Chaisson 2001	126/152	111/148		100.0 %	1.11 [0.98, 1.24]
Total (95% CI)	**152**	**148**		**100.0 %**	**1.11 [0.98, 1.24]**

Total events: 126 (Immediate incentive), 111 (Deferred incentive)
Heterogeneity: not applicable
Test for overall effect: Z = 1.67 (P = 0.096)
Test for subgroup differences: Not applicable

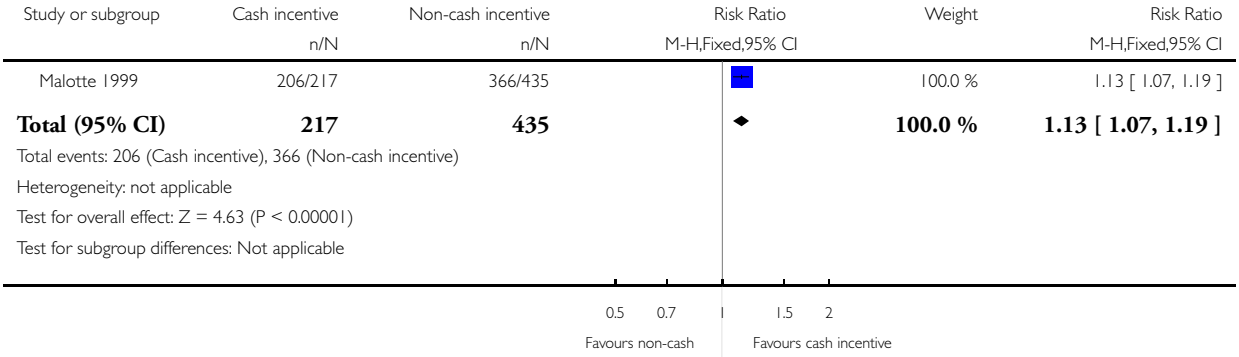


Analysis 3.1. Comparison 3 Cash incentive versus non-cash incentive, Outcome 1 Return for tuberculin skin test reading.

Review: Material incentives and enablers in the management of tuberculosis

Comparison: 3 Cash incentive versus non-cash incentive

Outcome: 1 Return for tuberculin skin test reading

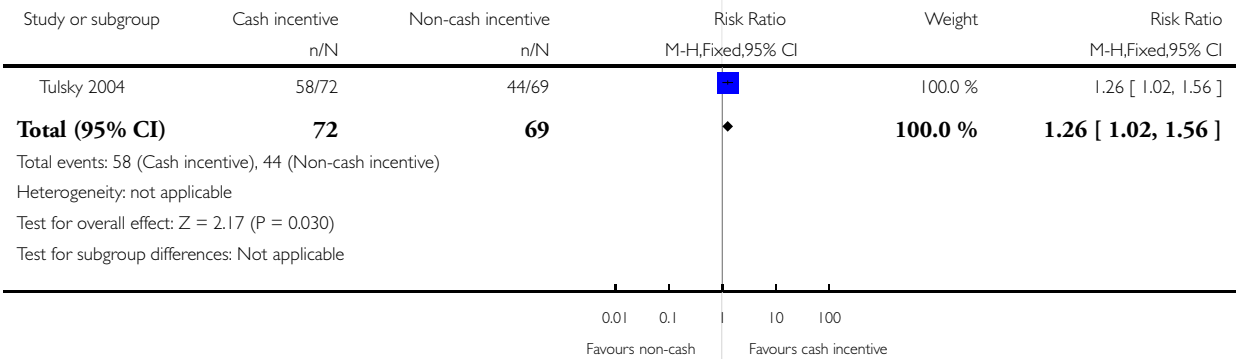


Analysis 3.2. Comparison 3 Cash incentive versus non-cash incentive, Outcome 2 Completion of TB prophylaxis.

Review: Material incentives and enablers in the management of tuberculosis

Comparison: 3 Cash incentive versus non-cash incentive

Outcome: 2 Completion of TB prophylaxis

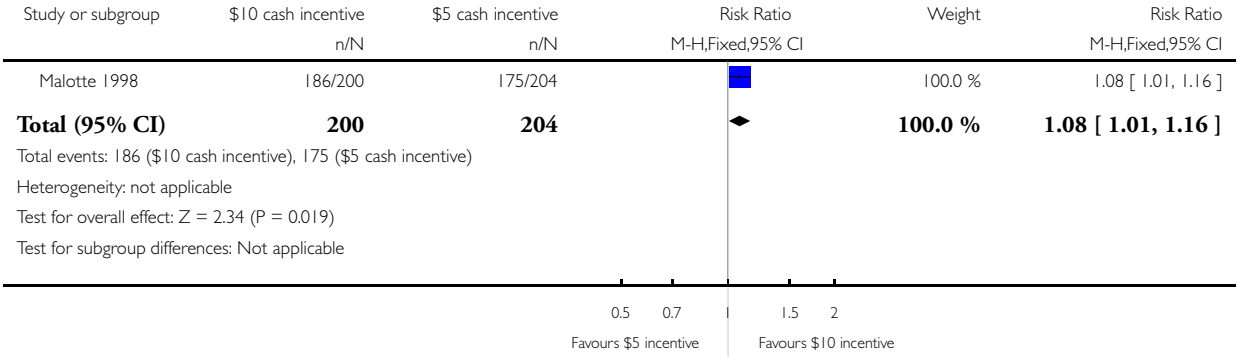


Analysis 4.1. Comparison 4 Different values of cash incentive, Outcome 1 Return for tuberculin skin test reading.

Review: Material incentives and enablers in the management of tuberculosis

Comparison: 4 Different values of cash incentive

Outcome: 1 Return for tuberculin skin test reading

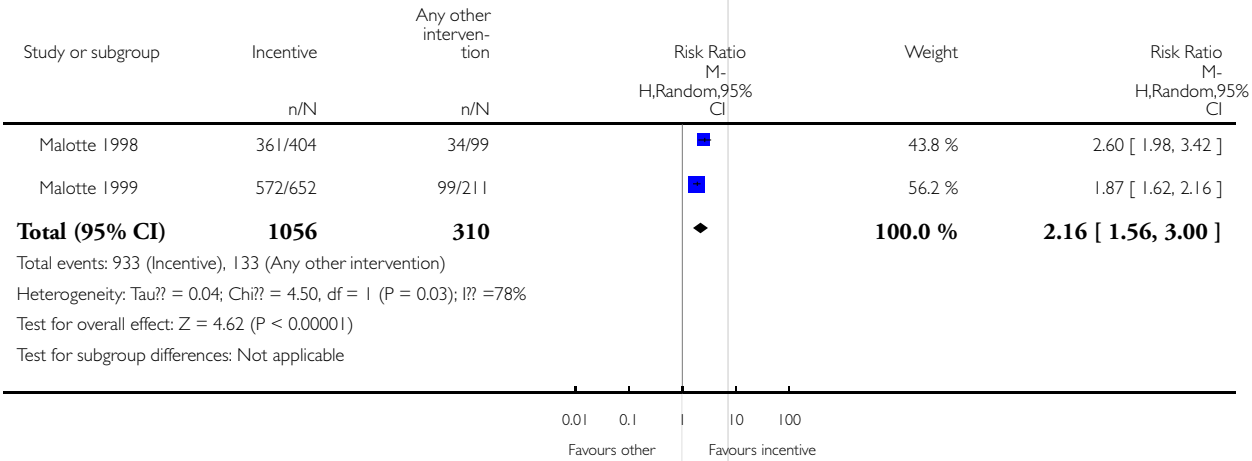


Analysis 5.1. Comparison 5 Incentives versus any other intervention, Outcome 1 Return for tuberculin skin testing.

Review: Material incentives and enablers in the management of tuberculosis

Comparison: 5 Incentives versus any other intervention

Outcome: 1 Return for tuberculin skin testing



Analysis 5.2. Comparison 5 Incentives versus any other intervention, Outcome 2 Clinic visit to start or continue TB prophylaxis.

Review: Material incentives and enablers in the management of tuberculosis

Comparison: 5 Incentives versus any other intervention

Outcome: 2 Clinic visit to start or continue TB prophylaxis

Study or subgroup	Incentive n/N	Any other intervention n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Pilote 1996	69/82	62/83		60.6 %	1.13 [0.96, 1.32]
White 2002	42/185	40/185		39.4 %	1.05 [0.72, 1.54]
Total (95% CI)	**267**	**268**		**100.0 %**	**1.10 [0.92, 1.31]**

Total events: 111 (Incentive), 102 (Any other intervention)

Heterogeneity: Chi?? = 0.16, df = 1 (P = 0.69); I?? =0.0%

Test for overall effect: Z = 1.03 (P = 0.31)

Test for subgroup differences: Not applicable

Analysis 5.3. Comparison 5 Incentives versus any other intervention, Outcome 3 Completion of TB prophylaxis.

Review: Material incentives and enablers in the management of tuberculosis

Comparison: 5 Incentives versus any other intervention

Outcome: 3 Completion of TB prophylaxis

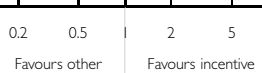
Study or subgroup	Incentive n/N	Any other intervention n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Morisky 2001	152/199	151/188		45.1 %	0.95 [0.86, 1.06]
Tulsky 2000	19/43	7/37		25.5 %	2.34 [1.11, 4.93]
White 2002	14/185	24/185		29.4 %	0.58 [0.31, 1.09]
Total (95% CI)	**427**	**410**		**100.0 %**	**1.04 [0.59, 1.83]**

Total events: 185 (Incentive), 182 (Any other intervention)

Heterogeneity: Tau?? = 0.18; Chi?? = 7.90, df = 2 (P = 0.02); I?? =75%

Test for overall effect: Z = 0.12 (P = 0.90)

Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Detailed search strategies

Search set	CIDG SR^	CENTRAL	MEDLINE^^	EMBASE^^	LILACS^^	SCI-EXPANDED and SSC
1	tuberculosis	tuberculosis	tuberculosis	tuberculosis	tuberculosis	tuberculosis
2	adherence	PATIENT COMPLIANCE	PATIENT COMPLIANCE	PATIENT-COMPLIANCE	adherence	adherence
3	compliance	PATIENT DROPOUTS	PATIENT DROPOUTS	TREATMENT-REFUSAL	compliance	compliance
4	Monitor*	MOTIVATION	MOTIVATION	MOTIVATION	Monitor$	Monitor*
5	Incentive*	SOCIAL SUPPORT	SOCIAL SUPPORT	SOCIAL SUPPORT	Incentive$	Incentive*
6	Reward*	CONTRACTS	CONTRACTS	COMPENSATION	Reward$	Reward*
7	Voucher*	Adherence	Adherence	Adherence	Voucher$	Voucher*
8	Payment*	Incentive*	Incentive*	Incentive$	Payment$	Payment*
9	Reimbursement*	Reward*	Reward*	Reward$	Reimbursement$	Reimbursement*
10	Concordance	Voucher*	Voucher*	Voucher$	Concordance	Concordance
11	Cash transfer*	Payment*	Payment*	Payment$	Cash transfer$	Cash transfer*
12	2-11/OR	Reimbursement*	Reimbursement*	Reimbursement$	2-11/OR	2-11/OR
13	1 AND 12	Concordance	Concordance	Concordance	1 AND 12	1 AND 12
14		Cash transfer*	Cash transfer*	Cash transfer$		
15		2-14/OR	2-14/OR	2-14/OR		
16		1 AND 15	1 AND 15	1 AND 15		
17			Limit 16 to Human	Limit 16 to Humans		
18						

Table 1. Detailed search strategies (*Continued*)

19	^ Cochrane Infectious Diseases Group Specialized Register		^^Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2006); Upper case: MeSH or EMTREE heading; Lower case: free text term			
20						

APPENDICES

Appendix 1. Summary of findings table: Immediate versus deferred incentive

Immediate compared to deferred incentive for improving patient adherence to TB management					
Patient or population: People at high risk of developing TB **Settings:** High- and low-income settings **Intervention:** Immediate incentive (received on a regular basis during treatment) **Comparison:** Deferred incentive (received only at end of treatment).					
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**
	Assumed risk	**Corresponding risk**			
	deferred incentive	**immediate**			
Completion of TB prophylaxis	**750 per 1000**	**832 per 1000** (735 to 930)	**RR 1.11** (0.98 to 1.24)	300 (1 study)	⊕⊕◯◯ **low**[1,2]
The **assumed risk** is taken from the control group in the trial. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio;					

(*Continued*)

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded by one for indirectness: This trial was conducted in specific subpopulations from the USA and the result may not be applicable in other settings.

[2] Downgraded by one for imprecision:The 95% CI of the estimate of effect includes both clinically important benefit and no effect.

Appendix 2. Summary of findings table: Cash versus non-cash incentive

Cash compared to non-cash incentive for improving patient adherence to TB management

Patient or population: People at high risk of developing TB
Settings: High- and low-income settings
Intervention: Cash incentive
Comparison: Non-cash incentive

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	non-cash incentive	cash			
Return for tuberculin skin test reading	**841 per 1000**	**950 per 1000** (900 to 992)	**RR 1.13** (1.07 to 1.18)	652 (1 study)	⊕⊕◯◯ **low**[1]
Completion of TB prophylaxis	**638 per 1000**	**804 per 1000** (651 to 995)	**RR 1.26** (1.02 to 1.56)	141 (1 study)	⊕⊕◯◯ **low**[1]

The **assumed risk** is taken from the control group in the trial. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to

(*Continued*)

change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded by two for indirectness: These trials were conducted in specific subpopulations from the USA and the results may not be applicable in other settings.

Appendix 3. Summary of findings table: Comparison of different values of cash incentives

Comparison of different values of cash incentives for improving patient adherence to TB management

Patient or population: People at high risk of developing TB
Settings: High- and low-income settings
Intervention: Higher cash value ($10)
Comparison: Lower cash value ($5)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	lower cash value	higher cash value			
Return for tuberculin skin test reading	**858 per 1000**	**927 per 1000** (867 to 995)	**RR 1.08** (1.01 to 1.16)	404 (1 study)	⊕⊕◯◯ **low**[1]

The **assumed risk** is taken from the control group in the trial. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded by two for indirectness: This trial was conducted in a specific subpopulation from the USA and the result may not be applicable in other settings.

Appendix 4. Summary of findings table: Material incentives versus educational or motivational interventions

Incentives compared to educational or motivational interventions for improving patient adherence to anti-TB treatment

Patient or population: Patients at high risk of developing TB
Settings: High- and low-income settings
Intervention: an incentive
Comparison: any educational or motivational intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	any other intervention	material incentives			
Return for tuberculin skin test reading	**429 per 1000**	**927 per 1000** (669 to 1000)	**RR 2.16** (1.56 to 3.00)	1366 (2 studies)	⊕⊕◯◯ **low**[1,2]
Return to clinic to start or continue treatment	**381 per 1000**	**419 per 1000** (351 to 499)	**RR 1.10** (0.92 to 1.31)	535 (2 studies)	⊕⊕◯◯ **low**[2,3]
Completion of prophylaxis for latent TB	**444 per 1000**	**462 per 1000** (262 to 813)	**RR 1.04** (0.59 to 1.83)	837 (3 studies)	⊕⊕◯◯ **low**[2,4]

The **assumed risk** is taken from the control group in the trial. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded by 1 for risk of bias: Neither study adequately described the method of randomisation.
[2] Downgraded by 1 for indirectness: These trials were conducted in specific subpopulations from the USA and the result may not be applicable in other settings.
[3] Downgraded by 1 for imprecision: The 95% CI includes what may be clinically important benefits and no effect.
[4] Downgraded by 1 for inconsistency: Two studies found no suggestion of a benefit with the incentive, and just one study found a clinically and statistically significant benefit in drug users.

HISTORY

Protocol first published: Issue 3, 2009

Review first published: Issue 1, 2012

CONTRIBUTIONS OF AUTHORS

All four authors contributed to the review, with EL taking primary responsibility. EL, SK and CSW participated in study selection, data extraction and analysis, and writing of the report. JV resolved any disputes arising during the selection of trials to include in the review, as well as assisted with data analysis and report writing.

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original protocol stipulated that only trials of adult participants would be included in this review. However, because TB is an important but neglected disease in children and adolescents, and because only few trials were identified among the adult population, it was decided to include the trials on children and adolescents that were identified in the searches.

CSW has been included as a co-author of the review because of his substantial contribution to the study selection; data extraction, analysis and interpretation; and the writing of the review.

The protocol title only referred to 'anti-tuberculosis treatment' and to incentives in general. However, since the review covers only material incentives.and includes returning for tuberculin skin test reading as well as adherence to TB prophylaxis and curative treatment adherence, we have altered the title to take these into account.

INDEX TERMS

Medical Subject Headings (MeSH)

*Motivation; *Token Economy; Homeless Persons; Medication Adherence [psychology; statistics & numerical data]; Patient Compliance [*psychology; statistics & numerical data]; Prisoners; Randomized Controlled Trials as Topic; Substance-Related Disorders [complications]; Tuberculin Test [*psychology]; Tuberculosis, Pulmonary [diagnosis; drug therapy; *psychology]

MeSH check words

Adolescent; Adult; Child; Humans; Male; Young Adult