National Institute for Health and Clinical Excellence (NICE)

Evidence review on the effectiveness and cost-effectiveness of interventions aimed at managing tuberculosis in hard-to-reach groups.

July 2011

Disclaimer

In keeping with our values of integrity and excellence, Matrix has taken reasonable professional care in the preparation of this report. Although Matrix has made reasonable efforts to obtain information from a broad spectrum of sources, we cannot guarantee absolute accuracy or completeness of information/data submitted, nor do we accept responsibility for recommendations that may have been omitted due to particular or exceptional conditions and circumstances.

Confidentiality

Any enquiries about this report should be directed to

enquiries@matrixknowledge.com

Authors

Maria Rizzo, Matrix Evidence
Alison Martin, Matrix Evidence
Victoria Cliff-Matthews, Matrix Evidence
Farah Jamal, Matrix Evidence
Angela Lehmann, Matrix Evidence
Alexis Llewellyn, Matrix Evidence
Isaac Marrero-Guillamon, Matrix Evidence
Alison O'Mara, Matrix Evidence
Chris Cooper, King's College, London
Alan Gomersall, King's College, London

Acknowledgements

The review team would like to thank the team at NICE (Kay Nolan, Catherine Swann, and Paul Levay) for their support. The team is also grateful to Gillian Craig at City University London, and Andrew Hayward, the PDG Chair, who provided expert input.

Declaration of authors' competing interests

No authors have competing interests.

Contents

1.0 Executive Summary

1.1 Introduction

This evidence review is the third of four commissioned by NICE to inform the guideline on the identification and management of tuberculosis (TB) in hard-to-reach groups. The focus of this review is on the effectiveness and cost-effectiveness of strategies to manage TB in these populations. Other reviews in the series cover the identification of TB in hard-to-reach groups, the best service models to identify and manage these groups, and barriers and facilitators to screening and treatment of TB.

The primary research questions for this review were:

1) Which interventions are effective and cost-effective at managing TB in people from hard-to-reach groups?
2) What are effective case management approaches to identify those who may need support to complete treatment?

The secondary research questions were:

3) What factors impact on the effectiveness of the interventions? Specifically, does the efficacy of the intervention vary by the:
    - theories or conceptual models underpinning the interventions?
    - diversity of the population (in terms of hard-to-reach group, age, or gender)?
    - persons/organisations commissioning/delivering the interventions?
    - way in which the intervention is delivered (for example, one-to-one or group-based)?
    - involvement of the target population in the planning, design, or delivery of the intervention?
    - content of different interventions?
    - frequency, intensity, and duration of the intervention?
    - time and place that the intervention is delivered?
4) How transferable are the findings regarding effectiveness to other hard-to-reach populations, other settings, or other times? (Consider the representativeness of the sample; key characteristics of the sample compared to other hard-to-reach groups; and the appropriateness of the analyses in terms of generalisability.)
5) What are the adverse or unintended effects (e.g., decreased compliance) of TB management interventions on hard-to-reach people, if any?

1.2 Methods

To locate evidence, a range of databases and websites indexing relevant literature were searched. Study reports were included if they:

1. had a focus on TB services of any kind; and
2. were published in 1990 or later; and
3. were written in English; and
4. were conducted in an OECD country; and
5. included data from any hard-to-reach group; and
6. presented quantitative empirical data; and
7. discussed an intervention relating to one of the following: identifying TB cases; managing TB cases; design of service models; and
8. was a (cost)-effectiveness study; or
9. any other type of quantitative primary research; or
10. a systematic review.

A total of 28 studies met all these inclusion criteria and reported comparative effectiveness or economic data in the management of latent or active TB, and were included in the review.

1.3 Findings

1.3.1 Findings on the effectiveness of interventions to manage Latent TB Infection (LTBI)

Evidence statement 1: **The effectiveness of education to manage latent TB infection (LTBI).**
ES1.0 **Weak evidence from one** randomised controlled trial (RCT) (White et al., 2002 [+]) suggests that **prisoners** were statistically more likely to complete treatment for LTBI in the community if they received an educational programme about TB every two weeks while in prison to reinforce the initial education provided to all prisoners (AOR = 2.2; 95% CI 1.04-4.72). The study was limited as it did not statistically compare attendance rates at a first TB clinic appointment after release from prison (one of the study's primary outcome measures). In addition, when the education intervention was conducted outside of the RCT setting by prison discharge planners, prisoners were less likely to adhere to their first TB appointment in the community compared to when it was delivered as part of the RCT (p=0.002; White et al., 2005 [+]). However, it is not known how this compared to treatment as usual. *Applicability* Two studies were found on the effectiveness of education to manage LTBI, conducted in the USA in a prison setting. As no study was conducted in the UK, it is difficult to assess the comparability of the findings to a UK context. The evidence for effectiveness was conducted in prisoners but, as prisoners overlap with other hard-to-reach groups, the results may be extrapolated to other groups but not to other settings.

Evidence statement 2: **The effectiveness of peer support to manage LTBI.**

ES2.0 **Weak evidence from one** RCT (Chaisson et al., 2001 [+]) found that statistically more **intravenous drug users** were likely to complete treatment if they received peer support (58/101, 57%) compared with treatment as usual (49/100, 49%; p<0.001), when adherence was measured using electronic bottle caps. However, there was no significant difference when adherence was measured by self report. All participants received a $10 incentive to adhere to the research protocol, so these adherence rates might not be replicable in settings where such an incentive is not available.

ES2.1 **Inconsistent evidence** from one RCT (Kominski et al., 2007 [+]) and one before-and-after study (McCue & Afifi, 1996 [-]) limits the conclusions on the effectiveness of individual peer support among the **foreign-born** (who were adolescents) or international university students with LTBI. Kominski et al. (2007 [+]) found no difference in treatment completion rates between peer support and treatment as usual. However the study did not compare groups at baseline or at the final assessment, and the description of the intervention is limited. In contrast, McCue & Afifi's (1996 [-]) before-and-after study suggests that there was a statistically significant increase in treatment completion with peer support compared with a historical control group that received treatment as usual (p<0.001). However, there was selective reporting of results in this study; no information reported on the selected population, and baseline comparisons between groups were also not analysed.

Applicability
Three studies were identified that explored the effectiveness of peer support to manage LTBI, all of which were conducted in the USA. As there was no study conducted in the UK it is difficult to compare the applicability of the findings to the UK setting. The evidence for peer support was found for intravenous drug users and foreign-born/international students. , It is therefore not clear how this evidence translates to other hard-to-reach groups, particularly as the foreign-born participants were a very specific group of young people (adolescents and university students) who may not be as hard-to-reach as other groups.

Evidence statement 3: **The effectiveness of supervised treatment to manage LTBI.**

ES3.0 **Weak evidence from one** RCT (Matteelli et al., 2000 [+]) found that treatment completion rates in **illegal immigrants** were lower with twice-weekly supervised treatment where participants were not observed taking the medication than with unsupervised twice-weekly or usual isoniazid treatment. However the study provided limited information about the treatment conditions, so it is unclear to what extent the treatment regimens differed, and the statistical significance of the difference in results was not assessed.

Applicability
One study was found that explored the effectiveness of supervised treatment to manage LTBI, which was conducted in Italy. The description of treatment as usual is limited, therefore, it is difficult to assess whether the study is comparable to treatment

in the UK. Evidence on supervised treatment is only available for immigrants and it is not known how these results would compare for other hard-to-reach groups.

Evidence statement 4: **The effectiveness of directly observed preventive therapy (DOPT) to manage LTBI.**

ES4.0 **Inconsistent evidence from two** RCTs (Batki et al., 2002 [+]; Chaisson et al., 2001 [+]) means that the effectiveness of DOPT compared with treatment as usual is unclear in **drug users**. Batki et al. (2002 [+]) delivered DOPT daily onsite at a hospital alongside methadone maintenance in intravenous drug users and found a statistically significant difference in treatment completion in favour of DOPT compared with treatment as usual (77.1%, 95% CI 61.3% to 91.0% with DOPT vs.13.1%, CI 3.0% to 23.7% with usual care; p<0.0001). In contrast, Chaisson et al. (2001 [+]) found no statistically significant differences (p=0.86) between DOPT, delivered by a nurse outreach worker onsite at the TB clinic or in a mutually convenient location, two days per week, compared with treatment as usual.

ES4.1 **Weak evidence from one** RCT (Tulsky et al., 2000 [+]) found that DOPT delivered twice-weekly by a peer did not result in a statistically significant difference in treatment completion in the **homeless** compared with treatment as usual (DOPT = 19%, TAU = 26%; p value not reported). The generalisability of the study to the homeless population may be limited as it included participants who lived in apartments, and only included those who had already demonstrated adherence by returning within one week for their TST result.

ES4.2 **Weak evidence from one** before-and-after study (Rodrigo et al., 2002 [-]) suggests that the incidence rates for TB among **prisoners** declined when DOT was implemented (5089 per 100,000 in 1993 to 812 per 100,000 in 2000) having increased prior to the implementation of DOT (3418 per 1000,000 in 1987 to 8041 per 100,000 in 1992), the fall from start to finish of both time periods being statistically significant (p< 0.001). The findings were limited because the incidence rates for TB also declined in the general population. There was also no information reported on the sample characteristics.

Applicability

Three studies were conducted in the USA and one in Spain, two in drug users, one in the homeless and one in prisoners. This limits the applicability of the findings to a UK context and to other hard-to-reach groups.

Evidence statement 5: **The effectiveness of incentives to manage LTBI.**

ES5.0 **Moderate evidence from two** RCTs (White et al., 1998 [+]; White et al., 2002 [+]) which were combined by the report in a meta-analysis found no significant difference with one-off monetary incentives compared with treatment as usual in the likelihood that **prisoners** with LTBI would attend a first TB clinic appointment after release from prison (OR = 1.673, 95% CI 0.989 to 2.831; p=0.055). There was also no

statistically significant difference for treatment completion (OR = 1.042, 95% CI 0.48 to 2.26; p=0.917).

ES5.1 **Weak evidence from one RCT** (Kominski et al., 2007 [+]) found that adolescents (79.3% **foreign-born**) who were provided a one-off incentive at the end of treatment for LTBI were equally likely to adhere to treatment compared with treatment as usual (incentives = 73.9%, 150/203 vs. TAU = 75.9%, 148/195), however, this was not statistically compared. The study also did not compare groups at baseline, therefore, it is not known if there were any initial differences between groups.

Applicability
The three studies were all conducted in the USA, two in prisoners and one in adolescents where the majority were foreign-born. This limits the applicability of the findings to the UK and to other hard-to-reach groups.

Evidence statement 6: **Effectiveness of combined interventions to manage LTBI.**

ES6.0 **Moderate evidence from one** RCT (Nyamathi et al., 2008 [++]) found that there was a statistically significant benefit of adding case-management which included an education intervention (8 sessions over 24 weeks) to DOPT to manage LTBI in the **homeless** compared with providing DOPT alone (AOR = 3.01, 95% CI 2.15 to 4.20).

ES6.1 **Weak evidence from one** RCT (Tulsky et al., 2000 [+]) found that adding twice-weekly $5 cash incentives to attend DOPT appointments resulted in statistically greater adherence to treatment completion in the **homeless** (44%, 19/43) compared with providing DOPT provided by a peer without incentives (7/37, 19%; p=0.02) but that incentives were not significantly more effective than treatment as usual (10/38, 26%; p=0.11). The clinical significance of these differences is unclear. The generalisability of the study to hard-to-reach groups may be limited as it included participants who lived in apartments and only included those who returned for their TST results within one week.

ES6.2 **Weak evidence from one** RCT (Tulsky et al., 2004 [+]) suggested that there was no statistically significant difference in adherence to treatment completion when the **homeless** were given a $5 cash incentive plus DOPT compared with a choice of a fast-food voucher or grocery store voucher worth $5 plus DOPT (cash incentive = 89.2%, 58/65 vs. voucher incentive = 81.5%, 44/54; p=0.23). The study was limited as there were statistically significant differences between groups at baseline in factors that were predictive of treatment completion, however, these were controlled for in the analyses.

ES6.3 **Weak evidence from one** RCT (Malotte et al., 2001 [++]) suggests that there was no added benefit when adding outreach to DOPT plus a $5 incentive to manage LTBI in **drug users** (DOPT with outreach plus incentives = 60% vs. DOPT plus incentives = 52.8%; p value not reported). These differences were not statistically compared, limiting the study findings.

ES6.4 **Moderate evidence from one** RCT (Malotte et al., 2001 [++]) found that **drug users** with LTBI were statistically more likely to complete treatment when provided with incentives (regardless of whether outreach was also provided), compared with DOPT plus outreach without incentives (AOR = 45.5, 95% CI 9.7 to 214.6; p<0.0001). However, the confidence intervals are wide, reducing the precision of the results.

ES6.5 **Weak evidence from one** RCT (Kominski et al., 2007 [+]) found that there was a statistically non-significant difference in adherence to treatment completion in the **foreign-born** with LTBI among those who received peer support plus a one-off incentive at the end of treatment compared with treatment as usual (Peer support plus incentive = 83.8%, 165/197 vs.TAU = 75.9%, 148/195; p=0.51).

Applicability
Five studies combining multiple interventions to manage LTBI were all conducted in the USA, three among the homeless, one among drug users and one in the foreign-born. Although these studies cover a variety of hard-to-reach groups it is not known the specific effect of the combined interventions among prisoners and in the UK populations.

Evidence statement 7: **Effectiveness of a service model approach/social care support to manage LTBI.**

ES7.0 **Weak evidence from one** RCT (Batki et al., 2002 [+]) in **intravenous drug users** found a statistically significant increase in adherence to treatment completion when a service model approach/social care support was used (59.5%, 95% CI 43.6 to 75.3) compared with treatment as usual (13.1%, CI 3.0% to 23.7%; p<0.0001) but no difference compared with DOPT plus methadone maintenance without additional social care support (p values not reported). The study was limited due to baseline differences between groups and the generalisability of the findings was limited because different daily doses of isoniazid were prescribed.

ES7.1 **Weak evidence from one** before-and-after study (White et al., 2003[+])found a statistically significant increase in treatment completion rates in favour of service model approach/social care support compared with treatment as usual (p<0.001) in **mixed hard-to-reach groups** with LTBI (service model approach/social care support = 70.3%, 102/145 vs. TAU = 47.9%, 447/934). The study was mainly limited by baseline differences between groups and there may have been treatment contamination across the two time periods.

Applicability
The two studies were conducted in the USA, one in intravenous drug users and one in mixed hard-to-reach groups. It is not known how these results apply to any one specific hard-to-reach group, or to the UK setting which may have a different social care/support approach.

Evidence statement 8: **Economic evidence for self-administered therapy to**

manage LTBI.
ES8.0 **Weak evidence from one** study (Bandyopadhyay et al., 2002 [-]) suggests that the total cost of self-administered therapy to manage LTBI in **prisoners** was $32,866 and would result in cost-savings of $9,227 compared with no intervention. The study was limited because it did not include all important costs such as screening and two weeks of isoniazid administered in prison. The outcomes were based on a sample of 168 prisoners and adherence was measured by self-report. *Applicability* One study was found that explored self-administered therapy for LTBI which was conducted in US prisoners. Although the prison population overlaps with other hard-to-reach groups, it is not known whether similar cost-savings would be found in other populations and in other settings, including the UK.

Evidence statement 9: **Economic evidence for DOPT to manage LTBI.**
ES9.0 **Moderate evidence from one** economic study (Gourevitch et al.,1998 [+]) found that when using the most conservative estimate of isoniazid efficacy (40%), DOPT would have resulted in net savings of $284 per person screened compared with self-administered therapy in **drug users** with LTBI. Some limitations of the study are that it did not take into account multi-drug resistance and was based on a population attending a single methadone maintenance treatment programme in the USA. ES9.1 **Moderate evidence from one** economic study (Schwartzman et al., 2005 [++]) found that the total direct costs of expanding a screening programme in Mexico to include DOPT for LTBI in **immigrants** prior to immigration to the USA was $1,901 million which resulted in net savings of $84 million compared with the usual TB control efforts in Mexico. The study conducted several sensitivity analyses to test their assumptions and the programme remained cost-saving. *Applicability* Both studies investigating the economic evidence for DOPT to manage LTBI were conducted in the USA, one in drug users and the other in immigrants. It is not known how applicable these studies are to other hard-to-reach groups and to the UK setting.

Evidence statement 10: Economic evidence for combined interventions to manage LTBI
ES10.0 **Weak evidence from one** economic study (Kominski et al., 2007 [+]) in the **foreign-born** suggests that peer support and incentives resulted in higher QALYs compared with treatment as usual (0.1962) at a higher cost of $41, resulting in an ICER (Incremental Cost-effectiveness Ratio) of $209 per QALY. In a Monte Carlo microsimulation of 10,000 trials, the ICER was consistently below the willingness-to-pay threshold of $50,000. The study was limited because the author used his own assumptions about the QALYs and the intervention did not result in statistically greater adherence to treatment compared with treatment as usual.

Applicability
There was only one study on the cost-effectiveness of combined interventions and it was based in the USA in a population where 80% were foreign-born. The intervention was not specifically designed for this hard-to-reach population and it is not known how these results translate to other hard-to-reach groups and to the UK, particularly the costs of treatment.

1.3.2 Findings on the effectiveness of interventions to manage active TB

Evidence statement 11: **Effectiveness of directly observed therapy (DOT) to manage active TB.**

ES11.0 **Weak evidence from one** retrospective cohort study (Alwood, 1994 [-]) suggested that significantly more people adhered to more than six months of treatment when they received DOT (96%, 44/48) to manage active TB compared with treatment as usual (76%, 22/30; p=0.02) in a population of people with HIV co-infection of whom 64% were i**ntravenous drug users**. The findings on adherence were limited as the study only reported data on those who had adhered to 8 weeks or more of treatment.

ES11.1 **Inconsistent evidence from two** studies: one quasi-RCT (MacIntyre et al., 2003 [+]) and one before-and-after study (Chemtob et al*.,* 2003 [-]) means conclusions are uncertain about the effectiveness of DOT to manage active TB in the **foreign-born**. MacIntyre et al. (2003 [+]) found that there was statistically no significant difference in treatment completion for those who received DOT (administered by a family member; 96.5%) and treatment as usual (90.6%; RR for non-completion = 2.7, 95%CI 0.66 to14.2; p=0.11). However, the study was underpowered to detect a small difference between groups. In contrast, Chemtob et al*. (*2003 [-]) suggest that more people were cured of TB (confirmed by bacteriological confirmation) if they received DOT (78.5% in 1999; 76.9% in 2000) compared with treatment as usual (26.7%). However this may be because there was more opportunity to obtain sputum from those on full DOT compared with partial DOT. In addition, the differences were not statistically compared, limiting the conclusions.

ES11.2 **Weak evidence from one** before-and-after study (Rodrigo et al., 2002 [-]) suggests that adherence among **prisoners** who were smear-positive increased significantly over time, both before and after DOT was introduced, rising from 95 per 100 in 1993 to 100 per 100 in 2000 for those who received DOT, and from 60 per 100 in 1987 to 76 per 100 in 1992 for those who received treatment as usual. There was also no information reported on the sample characteristics.

ES11.3 **Weak evidence from one** retrospective cohort study (Deruaz & Zellweger, 2004 [-]) in **mixed hard-to-reach groups** suggests that there was statistically no significant differences in successful treatment outcomes if participants received a full course of DOT (89.5%) compared with partial DOT (89.5%) where medication was only observed for the first two months (p=1.0). There was also no statistically significant difference in successful treatment outcome when DOT was conducted onsite (92.6%)

or via social outreach (85.2%; p=0.67). The study was limited as there were differences in how outcomes were collected, with greater bias when DOT was conducted via social outreach. In addition, assignment to treatment was based on factors associated with outcome, such that those who were more likely to be non-adherent were assigned to a full course of DOT, reducing the validity of the findings.

Applicability
Four studies investigated the effectiveness of DOT to manage active TB, one in drug users, two in the foreign-born and one in mixed hard-to-reach groups. These studies were conducted in the USA, Australia, Switzerland and Israel. These studies were conducted in a variety of countries and hard-to-reach groups, increasing the applicability of the findings of DOT to manage active TB. However, the effectiveness of DOT across these groups remains unclear, which makes it difficult to generalise beyond the populations reported in these studies.

Evidence statement 12: **Effectiveness of legal detention to manage active TB.**
ES12.0 **Weak evidence from one** retrospective cohort study (Oscherwitz et al., 1997 [-]) with 81% of participants being **drug or alcohol users**, found that there was a statistically significant increase in treatment completion when participants were not detained (82%) compared to participants who were detained (20%; p<.001). However, there were statistically significant differences between the groups, such that those who were legally detained were more likely to be hard to reach, and assignment to detention was based on non-adherence which may have confounded the results. *Applicability* There was one study in the USA on drug or alcohol users. It is not known how these findings transfer to a UK context and to other hard-to-reach groups.

Evidence statement 13: **Effectiveness of combined interventions to manage active TB.**
ES13.0 **Moderate evidence from one** before-and-after study (Bock et al., 2001 [+]) found that there was a statistically significant benefit of adding incentives to DOT on treatment completion compared with DOT alone (OR = 5.73, 95% CI 2.25 to 14.84) in a population that included over 50% of **drug users**. The study was limited because DOT was compared with a retrospective cohort of patients. ES13.1 **Moderate evidence from one** before-and-after study (Juan et al., 2006 [+]) found that there was a statistically significant benefit of adding incentives to DOT on treatment completion compared with self-administered therapy (RR = 3.07, 95% CI 2.13 to 4.41; Juan et al., 2006 [+]) in **mixed hard-to-reach groups**. The study was limited because DOT was compared with a retrospective cohort of patients and there were significant differences between the cohorts in the two time periods. *Applicability* Two studies conducted in Spain and the USA investigated the effectiveness of DOT

plus incentives to manage active TB in mixed hard-to-reach groups. No study identified was conducted in the UK.

Evidence statement 14: **Effectiveness of enhanced case management for active TB.**
ES14.0 **Moderate evidence from one** RCT (Ricks, 2008 [++]) found that significantly more **drug users** completed treatment with enhanced case management provided by a former drug user peer compared with limited case management from a health worker (RR = 2.68, 95% CI 1.24 to 5.82; p=0.01). The study was limited due to small sample sizes and high dropout rates and a lack of clarity about what constituted enhanced case management. *Applicability* One study conducted in the USA explored enhanced case management conducted by peers of drug misusers to manage active TB. It is not known how these findings translate to a UK setting or for other hard-to-reach groups.

Evidence statement 15: **Effectiveness of a service model approach/social care support to manage active TB.**
ES15.0 **Weak evidence from one** retrospective cohort design (Diez et al., 1996 [-]) suggests that the annual incidence rate of TB among the **homeless** significantly decreased when a service model approach/social care support was implemented in one district of Barcelona (p=0.03) but did not decrease in other districts not implementing the programme (p=0.34). It is not known whether the decrease in the incidence was due to the service model approach/social care support programme or due to other factors present at the time. *Applicability* One study explored the management of active TB using a service model approach/social care support conducted in Spain in the homeless. It is not known how this service model approach would translate to a UK context, to other hard-to-reach groups, and to the current time period.

1.3.3 Findings on the factors that impact on the effectiveness of the interventions to manage latent or active TB

Evidence statement 16: **The effectiveness of the intervention by the diversity of the population (in terms of hard-to-reach group, age, or gender).**
ES16.0 **Moderate evidence from three** studies found that the main characteristic that was shown to be predictive of treatment completion was residing in stable housing before receiving treatment for TB in the **homeless** (Tulsky et al., 2000 [+]; Tulsky et al., 2004 [+]) and in **prisoners** (White et al., 2002[+]). Therefore, participants who live on the streets or in a shelter have poorer adherence to treatment for TB and may need additional support to maintain their adherence with treatment.

Applicability
All three studies were conducted in the USA and it is not known how this evidence translates to the UK context. There may be differences between the two countries in how people residing in the streets or shelters are cared for, which may have a different impact on adherence to treatment.

Evidence statement 17: **The effectiveness of the intervention by person delivering the intervention.**
ES17.0 **Moderate evidence from one** RCT (Ricks, 2008 [++]) found that the probability of completing treatment was statistically greater when peers delivered enhanced case management to **drug users** compared with limited case management delivered by a health care professional (RR=2.68, 95% CI 1.24 to 5.82; p=0.01). The findings are limited because the peer-led intervention also had enhanced case management. It is therefore not known whether the positive treatment outcomes are due to the professional who delivers the service and/or the intensity of case management. *Applicability* The study was conducted in the USA in drug users; it is not known how these findings translate to a UK setting or for other hard-to-reach groups.

Evidence statement 18: **The effectiveness of the intervention by the setting in which it is delivered.**
ES18.0 **Weak evidence from two** studies found that there was statistically no significant difference if DOT/DOPT was conducted on site at a health care service or in the community at a site convenient for people with active TB, in **mixed hard-to-reach groups** (Deruaz & Zellweger, 2004 [-]) and **drug users** with LTBI (Malotte et al., 2001 [++]). The studies were of varying quality. *Applicability* One study was conducted in the USA and the other in Switzerland in drug users and mixed hard-to-reach groups. It is not known how these findings translate to the UK context and to other hard-to-reach groups.

1.3.4 The adverse or unintended effects (e.g., decreased compliance) of interventions on the management of latent or active TB

Evidence statement 19: **The adverse or unintended effects (e.g., decreased compliance) of interventions on the management of TB.**
ES19.0 **Weak evidence from two** studies suggest that legal detention for active TB in **drug or alcohol users** (Oscherwitz et al., 1997 [-]) and 'supervised' treatment for LTBI where participants were not observed taking the medication (Matteeli et al., 2000 [+])

had unintended or adverse effects on compliance compared to when the intervention was not applied. Both studies had multiple limitations including that those who were legally detained (Oscherwitz et al., 1997 [-]) were selected on the basis of being non-adherent; and there was limited information about what constituted supervised treatment (Matteelli et al., 2000 [+]).

Applicability
One study was conducted in the USA and one in Italy in drug or alcohol users and illegal immigrants. It is not known how these findings translate to the UK context and to other hard-to-reach groups.

1.4 Discussion

1.4.1 Evidence gaps

Tables 1 and 2 highlight the gaps in the evidence for the different hard-to-reach groups.

Table 1: Summary of evidence for managing LTBI

	Prisoners	Drug users	Foreign-born/immigrants	Homeless	Mixed hard-to-reach
Education	Weak				
Peer support		Weak	Inconsistent		
Supervised treatment			Weak		
DOPT	Weak	Inconsistent		Weak	
Incentives	Moderate		Weak		
Peer support plus incentives			Weak		
Case management plus education				Moderate	
DOPT plus incentives		Moderate		Weak	
Service model approach/social care support		Weak			Weak

Green = statistically significant difference in favour of the intervention group; Orange = no difference between groups; Yellow = inconsistent evidence, both differences and no differences; Red = unintended effects; Grey = gaps in the evidence.

Table 2: Summary of interventions for managing active TB

	Prisoners	Drug users	Foreign-born/immigrants	Homeless	Mixed hard-to-reach
DOT	Weak	Weak	Inconsistent		Weak
Legal detention		Weak			
Enhanced case management		Moderate			
DOPT plus incentives		Moderate			Moderate
Service model approach/social care support				Weak	

Green = statistically significant different in favour of the intervention group; Orange = no difference between groups; Yellow = inconsistent evidence, both differences and no differences; Red = unintended effects; Grey = gaps in the evidence

There was no evidence identified from the UK, no cost-effectiveness studies on the management of active TB, and only limited cost-effectiveness studies on the management of LTBI.

1.4.2 Conclusions

The evidence on the management of latent and active is overwhelmingly from the USA with no comparative study identified from the UK and no cost-effectiveness study on the management of active TB and limited cost-effectiveness studies on LTBI. The review did, however, contain evidence across different hard-to-reach groups. Despite these limitations, the strongest evidence found to manage both LTBI and active TB is for case management, and for DOPT plus incentives. There is also some suggestion that it is cost-saving to manage LTBI with self-administered therapy or DOPT compared with no treatment.

2.0 Aims and background

2.1 Objectives

The National Institute for Health and Clinical Excellence (NICE) has been asked by the Department of Health (DH) to develop public health programme guidance aimed at identifying and managing tuberculosis (TB) among hard-to-reach groups. The guidance will provide recommendations for agencies in the health sector, local authorities and other public, private or third-sector bodies, particularly those working with hard-to-reach groups.

This report is the third of four systematic reviews that have been undertaken to inform the guidance. It examines the effectiveness and cost-effectiveness of interventions aimed at managing TB in hard-to-reach groups. This report systematically reviews and synthesises relevant research to inform this topic. The outcomes of interest include (but are not limited to) treatment completion, length of time participants remained adherent to treatment, decrease in active TB incidence rates and cost-savings of treatment. The remaining review will explore quantitative evidence in relation to appropriate models for TB services delivered to hard-to-reach groups.

2.2 Rationale

In 2009 in the UK, a total of 9,040 cases of tuberculosis were reported resulting in a rate of 14.6 cases per 100,000 population (95% confidence interval (CI) 14.3 to 14.9; Health Protection Agency, 2010). Compared with 2008, this was a 9% increase in the number of cases and a 4.2% increase in the rate of TB (Health Protection Agency, 2010). Certain populations are at particularly high risk, since TB infection is strongly associated with social risk factors including homelessness, imprisonment, drug use, and immigration (Story et al., 2007). Although overall rates of TB in high-income countries have steadily fallen, there remains a high prevalence among these typically hard-to-reach groups (Fujiwara, 2000). The association of TB with poverty is well documented (Lönnroth et al., 2009), and individuals with social risk factors for TB that are linked to poverty, such as homelessness and drug abuse, are typically unwilling or unable to seek and comply with medical care, and are therefore hard to reach. These high-risk groups are not only much more likely to contract TB, but are also more likely to be diagnosed at a late stage of the disease, and less likely to adhere to treatment, which typically lasts for six months or more (Health Protection Agency, 2009). This reduces the efficacy of antituberculosis therapy, and contributes to the development of drug-resistant forms of the disease, which are much more difficult and costly to treat.

The central challenge to the control and surveillance of TB is, therefore, identifying and targeting these hard-to-reach, high-risk groups. Individuals or groups who face barriers to accessing health services may benefit from targeted screening to promote early diagnosis of TB (Health Protection Agency, 2007). Ensuring compliance with treatment

is also a key aspect of TB control. The Health Protection Agency has found that only 79% of people with TB in the UK complete treatment, below the World Health Organisation target of 85% (Health Protection Agency, 2009). Currently 6.8% of cases in the UK are resistant to at least one first-line drug, and 1.1% have multi-drug resistant infection (Health Protection Agency, 2009).

While the highest proportion of cases of TB occur in foreign-born patients (75% of people with TB in London were born abroad (Health Protection Agency, 2009)), evidence from a large outbreak of drug-resistant tuberculosis points to ongoing active transmission among marginalised groups (Antoine et al., 2006). Studies of the spread of TB in prisons have concluded that improving prison conditions is a priority for any effective programme to control TB and reduce its spread back into the hard-to-reach communities from which prisoners are disproportionately derived (Levy et al., 2000). There is also evidence of substantial transmission within UK-born minority ethnic populations (French et al., 2007).

The impact of TB is exacerbated when it occurs in people concurrently infected with HIV, in particular, in groups at high risk of both infections such as drug users (Rodwell et al., 2010) and immigrants (World Health Organization, 2010). Globally, TB is a leading cause of death among people with HIV, and it is estimated that one third of the 40 million people living with HIV worldwide are co-infected with TB (World Health Organization, 2010). In the UK, Ahmed et al.'s (2007) study found that 5.7% of people with TB were infected with HIV, with a substantial year-on-year increase over the period of their study (from 3.1% in 1999 to 8.3% in 2003). A further serious problem is the stigma connected with HIV and AIDS, which also leads to delayed treatment-seeking and poor adherence to treatment (Grange et al., 2001). Programmes that aim to increase the identification and management of TB must, therefore, address hard-to-reach groups at risk of HIV such as intravenous drug users (IDUs), prisoners, and sex workers.

In recent years, the emphasis has moved away from a traditional top-down model of TB control to community- and patient-centred health services which are based on analysis of local factors affecting case-finding and adherence to treatment (Grange et al., 2001), and from a reactive model to one emphasising proactive approaches to locating and treating cases. For example, the Department of Health established the Find and Treat service which supports the detection, diagnosis and treatment of TB in hard-to-reach groups in London using mobile digital X-ray machines, advice and support services and follow-up care (Health Protection Agency, 2007).

2.3 Research questions

The primary research questions for this review were:

1. Which interventions are effective and cost effective at managing TB in people from hard-to-reach groups?

2. What are effective case management approaches to identify those who may need support to complete treatment?

The secondary research questions were:

3. What factors impact on the effectiveness of the interventions? Specifically, does the efficacy of the intervention vary by the:
   - theories or conceptual models underpinning the interventions?
   - diversity of the population (in terms of hard-to-reach group, age, or gender)?
   - persons/organisations commissioning/delivering the interventions?
   - way in which the intervention is delivered (for example, one-to-one or group-based)?
   - involvement of the target population in the planning, design, or delivery of the intervention?
   - content of different interventions?
   - frequency, intensity, and duration of the intervention?
   - time and place that the intervention is delivered?
4. How transferable are the findings regarding effectiveness to other hard-to-reach populations, other settings, or other times? (consider the representativeness of the sample; key characteristics of the sample compared to other hard-to-reach groups; and the appropriateness of the analyses in terms of generalisability).
5. What are the adverse or unintended effects (e.g., decreased compliance) of TB management interventions on hard-to-reach people, if any?

3.0 Methods

The review was conducted in accordance with the methodology laid out in the second edition of *Methods for the development of NICE public health guidance* (NICE, 2009). In addition to the usual procedures outlined in the public health guidance, this review conducted one large search across the three quantitative reviews on identification, management and service models to manage TB in hard-to-reach groups. This review also combined the evidence tables for quantitative and economic evaluation studies (Appendix C).

3.1 Searching

The following databases were searched for this review and for the other two quantitative reviews from 1990 to October 2010:

- Assia
- British Nursing Index
- CRD (DARE, HTA, NHS EED)
- CINAHL

- Cochrane Library (for systematic reviews)
- Current Contents
- ECONLIT
- EMBASE
- ERIC
- HMIC
- Medline
- Medline In-Process
- PsycINFO
- SPP
- Soc Abs
- Social Services Abstracts
- Web of Science

The full search strategy and the results of the searches can be found in Appendix A. The search strategy was written to locate references relevant across the three quantitative effectiveness reviews.

The following websites and databases were searched manually for relevant literature:

- Action - Advocacy to Control TB Internationally
- British Infection Association
- Centers for Disease Control and Prevention (resources on TB)
- Centers for Disease Control TB-Related News and Journal Items Weekly Update mailing list archives
- Centers for Disease Control National Prevention Information Network
- NICE, including former Health Development Agency
- NHS Evidence
- Stop TB Partnership
- TB Alert
- UK Coalition to Stop TB
- World Health Organization
- WHO Global Health Atlas
- Health Protection Agency
- British Thoracic Society
- Public Health Observatories
- BL Direct
- Community Abstracts via Oxmill
- Google Scholar
- National Research Register archive site
- UK Clinical Research Network

To supplement the database and website searches, the review also identified additional potential relevant records using the following methods:

- scanning of citation lists of included studies obtained through database searching;
- 'forward' citation chasing of included studies using ISI Web of Knowledge, locating studies which cited them;
- scanning lists of included studies from all systematic reviews which met the inclusion criteria at the full text screening stage; and
- a call for evidence from all stakeholders, organised by NICE.

3.2 Screening

All records identified by the searches were uploaded into a database and duplicate records were removed. Inclusion criteria were developed (see below) to identify relevant studies for the three reviews. Initially, the records were screened on title and abstract. Where no abstract was available, a web search was first undertaken to locate one; if no abstract could be found, records were screened on title alone. A round of pilot screening was conducted on a random sample of ten abstracts to test and refine the inclusion criteria. Once the inclusion criteria were agreed upon, records were screened by four reviewers independently using the abstract inclusion checklist in Appendix B. Double screening was conducted on 10% of the records; any differences were resolved by discussion and, if necessary, with the input of a third reviewer. Agreement before reconciliation for the abstract screening was 96.48% (N=2,165) and inter-rater reliability (Cohen's kappa) was κ=0.535 (95% CI 0.432 to 0.637).[1]

The inclusion criteria across the three quantitative reviews were the following:

- the study has a focus on TB services of any kind; and
- was published in 1990 or later; and
- is written in English; and
- was conducted in an OECD country; and
- includes data from any hard-to-reach group; and
- presents quantitative empirical data; and
- discusses an intervention relating to one of the following: identifying TB cases; managing TB cases; design of service models; and
- is a (cost)-effectiveness study; or
- any other type of quantitative primary research; or
- a systematic review.

For this review we focused on studies that discussed an intervention relating to managing TB cases.

[1] It has been argued that Cohen's kappa or similar measures may under-rate reliability where scores are highly asymmetrical, i.e. numbers for one code (e.g. exclude) are much higher than for the other(s) (e.g. include) (Feinstein and Cicchetti 1990). This is the case here, because inclusion rates were fairly low, and hence there were many more studies excluded than included. For this reason, the kappa score is slightly lower than standard guidance would indicate is acceptable, even though rates of agreement were high.

The review also included studies where 50% or more of the participants had characteristics that met the review's definition of hard to reach. The full screening checklist is presented in Appendix B.

3.3 Quality assessment

All included studies were quality assessed using the tools in Appendix F (effectiveness studies) and Appendix I (cost-effectiveness) of the *Methods for the development of NICE public health guidance* (NICE, 2009). On the basis of the answers to the questions within these tools, and in line with the NICE guidance manual, each study was given an overall quality rating: [++] for high quality; [+] for medium quality; or [-] for low quality. The tool was completed independently by two reviewers for a randomly selected sample of 10% of records relevant to the management review (N=2). For the other records, the tool was completed by one reviewer and checked by another, with any disagreements resolved by discussion. The results of the quality assessment are presented in section 4.3 below; two examples of completed quality assessment forms are presented in Appendix E.

3.4 Data extraction

Data were extracted from included studies using combined (cost)-effectiveness evidence tables (see Appendix K in NICE (2009)). The tool was completed independently by two reviewers for a randomly selected sample of 10% of records relevant to management (N=2). For the other records, the tool was completed by one reviewer and checked by another, with any disagreements resolved by discussion or reference to a third researcher. Data for each included study were extracted and are presented in the evidence tables (Appendix C).

3.5 Data synthesis and presentation

In most cases, the studies of effectiveness did not support meta-analysis and were reported narratively, as were the cost-effectiveness studies. Information on the study characteristics were first summarised and then the results were discussed taking into account the risk of bias for each individual study as determined by the results of the quality assessment (Section 4.3).

The results of the studies were synthesised into evidence statements. In addition to assessing the quality of the individual studies, the overall strength of the evidence statements took into account the quality, quantity, and consistency of the evidence. The evidence statements reflect the strength of the conclusions made by the studies, the quality of the studies (as determined in the quality assessment), and any inconsistencies in the findings across studies. The summaries used are those described in NICE (2009):

- **no evidence** – no evidence or clear conclusions from any studies;

- **weak evidence** – no clear or strong evidence/conclusions from high quality studies and only tentative evidence/conclusions from moderate quality studies or clear evidence/conclusions from low quality studies;
- **moderate evidence** – tentative evidence/conclusions from multiple high quality studies, or clear evidence/conclusions from one high quality study or multiple medium quality studies, with minimal inconsistencies across all studies;
- **strong evidence** – clear conclusions from multiple high quality studies that are not contradicted by other high quality or moderate quality studies; and
- **inconsistent evidence** – mixed or contradictory evidence/conclusions across studies.

When a meta-analysis was possible (in one case), when more than one study explored a similar intervention and comparison group with similar outcomes for the same hard-to-reach group, data was first extracted into the evidence table (Appendix C) and then into STATA 8 (StataCorp, 2003). Odds ratios were calculated for dichotomous data, based on an intention-to-treat analysis with last observation carried forward (LOCF), where available. Heterogeneity was tested using the Q-test which determined the absence or presence of heterogeneity. Data from pooled studies where heterogeneity was not statistically significant were combined using a fixed-effects model using the method of Mantel and Haenszel. When there was statistically significant heterogeneity, results were combined using a random-effects model using the DerSimonian & Laird method of analysis. Publication bias was assessed using a visual inspection of the funnel plot and no bias was present in the one meta-analysis conducted. Outcome data were assessed for clinical importance, taking into account both the point estimate of the effect and the associated 95% confidence interval.

4.0 Summary of included studies

4.1 Flow of literature through the review

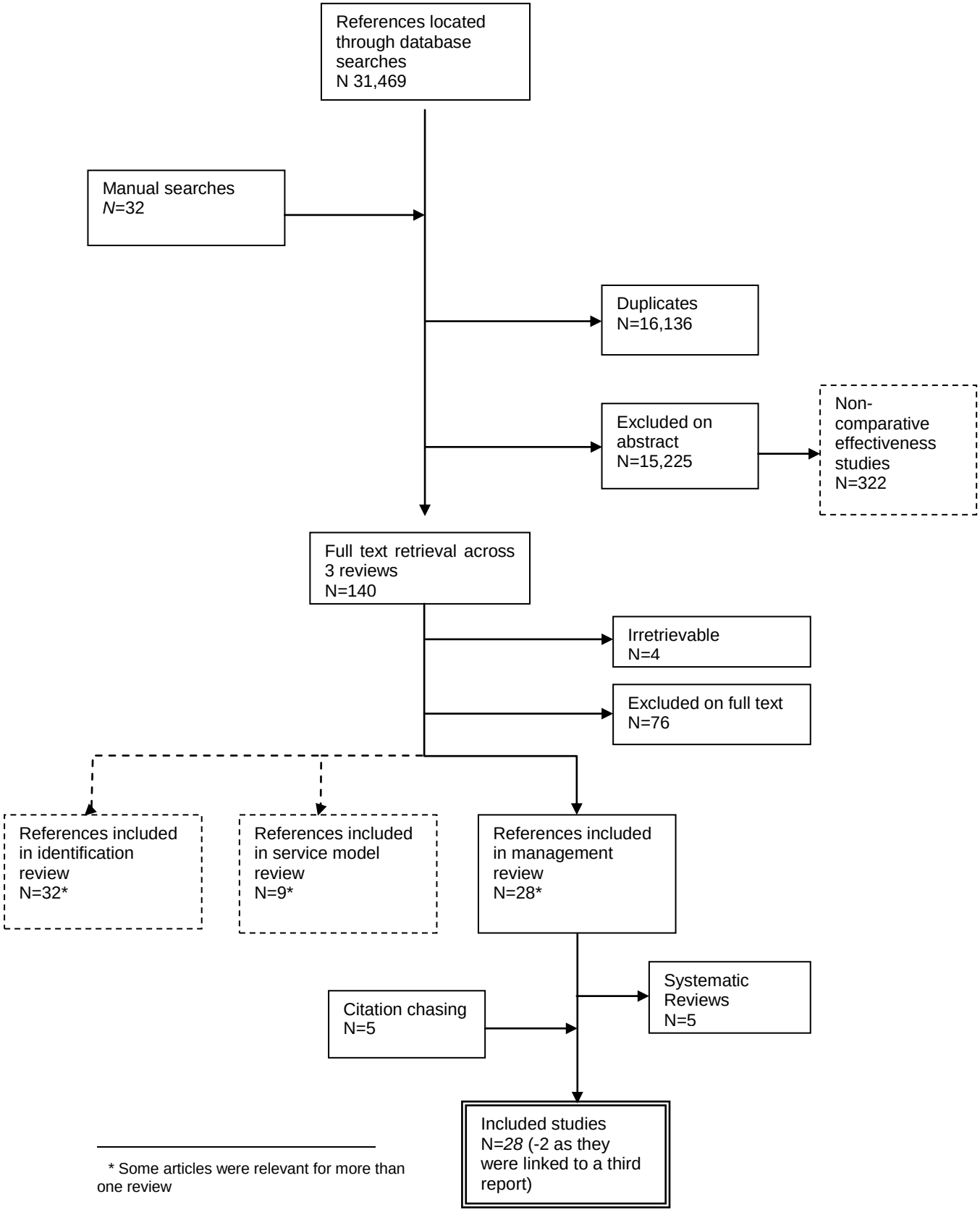
Database searches were conducted to locate references relevant for the three reviews, and 31,469 records were found. A further 32 records were located through manual searching. Of these, 16,136 were duplicate records and were removed. The remaining 15,333 abstracts were screened for inclusion in the three reviews.

A total of 15,225 references were excluded following screening of titles and abstracts. After conversation with NICE, non-comparative studies were excluded from the reviews. Full texts of the remaining 140 references were ordered. Four references were irretrievable and 76 excluded, the remaining 60 studies were included across the three reviews.

For the purpose of this review, 28 were relevant. Five systematic reviews that met the inclusion criteria were disaggregated for citation chasing but were not included in the review. Backward and forward citation chasing from the included studies yielded five additional references, for a total of 28 included references. Three of these reported

findings from the same project and were therefore treated as one study (Nyamathi et al., 2006; 2007; 2008). The flow of literature through the review is illustrated in Figure 1, and Section 7 lists the citation details of all included studies.

Figure 1. Flow of literature



* Some articles were relevant for more than one review

4.2 Summary of the included studies

The 28 included references report on 26 unique studies conducted in the following countries:

- 19 in the USA;
- 3 in Spain;
- 1 in Italy;
- 1 in Israel;
- 1 in Switzerland;
- 1 in Australia.

Study population characteristics consisted of the following:

- 7 on drug users;
- 5 on homeless people;
- 6 on immigrants or foreign-born;
- 4 on prisoners;
- 4 on mixed hard-to-reach groups.

The type of studies were as follows:

- 22 effectiveness studies;
- 4 economic evaluations

A summary of the number of studies identified by type of TB infection for each hard-to-reach population is given in Table 3.

Table 3. Summary of studies included for each hard-to-reach group

Type of infection	Drug users	Homeless	Immigrant/ foreign-born	Prisoners	Mixed	Total
LTBI	4	4	5	3	1	17
Active TB	3	1	0	0	3	7
Unclear	0	0	0	1	0	1
Both active and LTBI	0	0	1	0	0	1
Total	7	5	6	4	4	26

A summary of the included studies is provided in Table 4. Full study details are presented in the evidence tables (Appendix C).

Table 4. Summary of included studies

	Aim	Study design	HTR group/s	TB	Location	Quality score
Alwood et al. (1994)	To evaluate the effectiveness of supervised intermittent therapy for TB in patients with HIV infection.	Retrospective cohort	Intravenous drug users	Active TB	USA	-
Bandyopadhyay et al. (2002)	To review the outcome of individuals referred for continuation of isoniazid preventive therapy (IPT) from short-term correctional facilities to the City of Hartford Health Department Chest Clinic. The authors assessed adherence to IPT and estimated the cost effectiveness of the program.	Cost-effectiveness	Prisoners	LTBI	USA	-
Batki et al. (2002)	To compare the completion rates for isoniazid preventive therapy (IPT) for Intravenous drug users randomly assigned to methadone treatment combined with directly-observed preventive treatment (DOPT) versus those assigned to routine TB clinic referral without methadone treatment.	RCT	Intravenous drug users	LTBI	USA	+
Bock et al. (2001)	To evaluate whether incentives increase adherence to DOT for TB in non-adherent patients.	Before-and-after	Drug users	Active TB	USA	+
Chaisson et al. (2001)	To determine the effect of several interventions on adherence to TB preventive therapy.	RCT	Intravenous drug users	LTBI	USA	+
Chemtob et al. (2003)	To describe the TB control programme in Israel and to compare the outcome of treatment before-and-after its launch in 1997.	Before-and-after	Foreign-born	Active and latent TB	Israel	-
Déruaz &. Zellweger (2004)	To evaluate the effect of duration/intensity and location of DOT on clinical outcomes.	Retrospective cohort	Mixed hard-to-reach	Active TB	Switzerland	-
Diez et al. (1996)	To compare the TB incidence rate in Ciutat Vella, Barcelona, where a social support TB programme including DOT was implemented, with other districts in Barcelona where the programme was not implemented.	Retrospective cohort	Homeless	Active TB	Spain	-

Gourevitch et al. (1998)	To assess the cost-effectiveness of providing DOPT to drug users on methadone maintenance with and without HIV infection by comparing the costs of ensuring adherence to and completion of chemoprophylaxis of TB with those of treating active disease.	Cost-effectiveness	Drug users	LTBI	USA	+
Juan et al. (2006)	To compare DOT through pharmacies versus self-administered treatment (SAT) for TB patients at risk of non-adherence.	Before-and-after	Mixed hard-to-reach	Active TB	Spain	+
Kominski et al. (2007)	To assess the costs and cost-effectiveness of three interventions (peer support, contingency contracting and the two combined) compared with usual care on adolescent compliance with treatment for LTBI.	Cost-effectiveness	Foreign-born	LTBI	USA	+
MacIntyre et al. (2003)	To evaluate the effectiveness of a family-based programme of DOT for TB, in comparison to supervised but non-observed, treatment.	Quasi-RCT	Foreign-born	LTBI	Australia	+
Malotte et al. (2001)	To compare the independent and combined effects of monetary incentives and outreach worker provision of DOT (for LTBI) in active drug users.	RCT	Drug users	LTBI	USA	++
Matteelli et al. (2000)	To assess adherence to one supervised, medical service-based, twice-weekly regimen of isoniazid in illegal migrants in Northern Italy.	RCT	Illegal immigrants	LTBI	Italy	+
McCue & Afifi (1996)	To compare the treatment completion rates before and after 1992, when a peer-support programme was implemented in international university students.	Before-and-after	International students	LTBI	USA	-
Nyamathi et al. (2006; 2007; 2008)	To evaluate the effectiveness of a validated nurse case-management and an enhanced educational programme with tracking standard brief educational programme to improve adherence to latent TB infection treatment among homeless persons.	Cluster RCT	Homeless	LTBI	USA	++
Oscherwitz et al. (1997)	To evaluate in persistently non-adherent TB patients who were legally detained, how many completed treatment compared with patients who were not legally detained.	Retrospective cohort	Drug or alcohol users	Active TB	USA	-
Ricks (2008)	To compare the effectiveness of the Indigenous Leader Outreach Model (ILOM) versus standard TB control among substance users.	RCT	Drug users	Active TB	USA	++

Rodrigo et al. (2002)	To evaluate a TB programme with DOT in prisons in Barcelona.	Before-and-after	Prisoners	Unclear	Spain	-
Schwartzman et al. (2005)	To investigate the health-related outcomes and costs of adding a directly-observed treatment, short course (DOTS) programme in Mexico or a TST to the standard radiographic screening of immigrants in the USA.	Cost- saving	Immigrants	LTBI	USA	++
Tulsky et al. (2000)	To compare the effectiveness of twice-weekly DOPT plus cash incentives versus DOPT plus case management by peer health advisers, versus standard care in the homeless with LTBI.	RCT	Homeless	LTBI	USA	+
Tulsky et al. (2004)	To compare the effects of DOPT plus $5 cash inventive with DOPT plus vouchers worth $5 among the homeless on completion of treatment and time spent to follow-up participants.	RCT	Homeless	LTBI	USA	+
White et al. (1998)	To compare a $5 cash incentive plus standardised TB education with standardized TB education alone in encouraging released inmates to make a first visit to the TB Clinic.	RCT	Prisoners	LTBI	USA	+
White et al. (2002)	To evaluate two interventions aimed at improving adherence to treatment of persons with latent tuberculosis infection after release from jail.	RCT	Prisoners	LTBI	USA	+
White et al. (2003)	To examine therapy completion for latent TB infection before-and-after the implementation of a DOPT programme.	Before-and-after	Mixed hard-to-reach	LTBI	USA	+
White et al. (2005)	To compare rates of first visit to the TB clinic after release from jail, as well as completion of therapy, in inmates with LTBI who participated in a randomised trial versus inmates who were counselled and educated after the end of the clinical trial using the same protocol, delivered by jail health workers. A secondary aim was to examine the relationship between the nature of the educational sessions and participant outcomes for participants who received education from jail discharge planners.	Before-and-after	Homeless	LTBI	USA	+

HTR = hard-to-reach; LTBI = latent TB infection; IDU = intravenous drug user; RCT = randomised controlled trial; IPT = isoniazid preventive therapy; DOPT = Directly Observed Preventive Therapy; DOT = Directly Observed Therapy; DOTS = Directly Observed Therapy Short Course; SAT = self-administered therapy.

4.3 Quality of the included studies

The results of quality assessment are presented in Tables 5 and 6. Four studies were judged to be of high quality [++], fourteen of medium quality [+], and eight of low quality [-], as follows:

Hard-to-reach group	High quality [++]	Medium quality [+]	Low quality [-]
Drug users	Malotte et al. (2001) Ricks (2008)	Batki et al. (2002) Bock et al. (2001) Chaisson et al. (2001) Gourevitch et al. (1998)	Alwood et al. (1994) Oscherwitz et al. (2007)
Homeless	Nyamathi et al. (2008)	Tulsky et al. (2000) Tulsky et al. (2004) White et al. (2005)	Diez et al. (1996)
Immigrant / foreign-born	Schwartzman et al. (2005)	Kominski et al. (2007) MacIntyre et al. (2003) Matteelli et al. (2000)	Chemtob et al. (2003) McCue & Afifi (1996)
Prisoners		White et al. (1998) White et al. (2002)	Bandyopadhya et al. (2002) Rodrigo et al. (2002)
Mixed		Juan et al. (2006) White et al. (2003)	Déruaz &. Zellweger (2004)

.

Table 5. Quality of the included studies (effectiveness)

First author	Population					Method of allocation to intervention/comparison									Outcomes							Analysis				Summary		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Alwood (1994)	+	+	++	-	+	NA	NA	-	++	NR	-	+	+	+	++	+	++	++	++	-	-	NR	++	+	+	-	-	-
Batki (2002)	++	+	++	++	++	NR	NA	++	+	NR	++	+	+	++	++	++	++	++	++	+	++	NR	++	++	+	++	+	+
Bock (2001)	+	+	++	++	+	++	NA	++	++	NR	++	+	+	++	++	+	++	++	++	+	++	NR	++	++	++	++	+	+
Chaisson (2001)	++	+	++	++	++	NR	NA	-	++	NR	++	+	+	++	++	++	++	++	++	++	++	NR	++	++	+	++	+	+
Chemtob (2003)	++	+	-	NA	+	NA	NA	++	++	NR	++	+	+	+	++	+	++	NR	NR	NR	-	NR	-	-	-	-	+	-
Deruaz (2004)	++	+	+	-	+	-	-	+	-	NR	++	+	+	-	++	++	++	++	++	-	-	NR	-	++	+	-	+	-
Diez (1996)	+	+	-	-	-	NA	NA	NR	NR	NR	NA	+	+	-	NA	-	+	++	++	NR	NA	NR	-	+	++	-	-	-
Juan (2006)	++	+	+	-	++	NA	NA	++	++	NR	++	+	+	++	++	+	++	++	++	+	-	NR	++	++	++	+	+	+
MacIntyre (2003)	+	+	+	++	++	NR	NA	+	++	NR	++	+	+	+	++	+	++	++	++	NR	++	-	+	+	+	+	+	+
Malotte (2001)	++	+	+	+	++	++	NA	++	++	NR	++	+	+	++	++	++	++	++	++	++	++	NR	++	++	++	++	+	++
Matteelli (2000)	++	+	++	++	++	NR	NA	++	++	NR	++	+	+	++	++	++	++	++	++	++	++	NR	+	++	-	+	+	+
McCue (1996)	++	+	NR	NA	+	NA	NA	++	++	NR	NR	+	+	NR	++	++	++	++	++	NR	-	NR	-	-	-	-	+	-
Nyamathi (2008)	++	+	+	++	++	NR	NA	++	++	NR	++	+	+	++	++	+	++	++	++	++	++	++	+	++	++	++	+	++
Oscherwitz (1997)	+	+	+	NA	+	NA	NA	++	++	NR	++	+	+	+	++	++	++	NR	NR	-	+	NR	-	++	+	-	+	-
Ricks (2008)	++	+	++	++	++	++	NA	++	++	NR	++	+	+	+	++	++	++	++	++	++	++	+	++	++	++	++	+	++
Rodrigo (2002)	+	++	NR	NA	+	NA	NA	++	++	NR	++	+	+	+	++	++	++	NR	NR	NR	-	NR	-	++	+	-	+	-
Tulsky (2000)	++	+	+	++	++	++	NA	+	+	NR	++	+	+	+	+	+	++	++	++	++	-	NR	-	++	++	+	+	+
Tulsky (2004)	++	+	+	++	++	++	NA	++	+	NR	++	+	+	+	+	+	++	++	++	+	-	-	++	++	++	+	+	+
White (1998)	++	+	++	++	+	++	NA	++	++	NR	++	+	+	++	++	+	++	++	++	NR	-	NR	+	+	+	+	+	+

White (2002)	++	+	++	++	++	++	NA	++	+	-	++	+	+	+	++	+	++	++	++	++	++	++	++	++	++	+	+
White (2003)	+	+	++	+	++	NA	NA	+	++	NR	++	+	+	+	+	++	++	++	++	+	-	NR	++	++	++	+	+	+
White (2005)	++	+	+	-	+	NA	NA	++	++	NR	++	+	+	++	++	++	++	++	++	+	++	NR	++	++	++	+	+	+

Key: ++ The study has been designed/conducted in such a way as to minimise the risk of bias; + Either the answer to the checklist question is not clear from the way the study is reported, or the study may not have addressed all potential sources of bias; - Significant sources of bias may persist; NR The study fails to report this particular question; NA given the study design.

Key to questions:

1. Is the source population or source area well described?
2. Is the eligible population or area representative of the source population or area?
3. Do the selected participants or areas represent the eligible population?
4. How was confounding minimised?
5. Were interventions (and comparisons) well described and appropriate?
6. Was the allocation concealed?
7. Were participants and/or investigators blind to exposure and comparison?
8. Was the exposure to the intervention and comparison adequate?
9. Was contamination acceptably low?
10. Were other interventions similar in both groups?
11. Were all participants accounted for at study conclusion?
12. Did the setting reflect usual UK practice?
13. Did the intervention or control comparison reflect usual UK practice?
14. Were the outcome measures reliable?
15. Were all outcome measurements complete?
16. Were all important outcomes assessed?
17. Were outcomes relevant?
18. Were there similar follow-up times in exposure and comparison groups?
19. Was follow-up time meaningful?
20. Were exposure and comparison groups similar at baseline? If not, were these adjusted?
21. Was Intention to Treat (ITT) analysis conducted?
22. Was the study sufficiently powered to detect an intervention effect (if one exists)?
23. Were the estimates of effect size given or calculable?
24. Were the analytical methods appropriate?
25. Was the precision of intervention effects given or calculable? Were they meaningful?
26. Are the study results internally valid? (i.e. unbiased)
27. Are the study results generalisable to the source population? (i.e. externally valid)
28. Final quality score.

Key to answers 26-27:

++ All or most of the checklist criteria have been fulfilled; where they have not been, the conclusions are very unlikely to alter

+ Some of the checklist criteria have been fulfilled, where they have not, or not adequately described, the conclusions are unlikely to alter

- Few or no checklist criteria have been fulfilled and the conclusions are likely to alter

Table 6. Quality of the included studies (economic evaluations)

First author	Applicability (relevance to the specific topic)									Study limitations (level of methodological quality)											
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Bandyopadhyay (2002)	Y	Y	PA	N	N	N	N	Y	PA	PA	Y	Y	PA	PA	N	PA	PA	N	N	U/C	Very serious limitations [-]
Gourevitch (1998)	Y	Y	PA	PA	N	N	N	PA	PA	PA	Y	Y	PA	PA	PA	PA	PA	N	N	U/C	Potentially serious limitations [+]
Kominski (2007)	PA	Y	PA	Y	Y	PA	Y	Y	PA	Y	Y	Y	PA	PA	Y	PA	PA	Y	Y	U/C	Potentially serious limitations [+]
Schwartzman (2005)	Y	Y	PA	Y	Y	PA	N	Y	PA	PA	Y	Y	PA	PA	Y	PA	PA	N	Y	U/C	Minor limitations [++]

Y= Y; N=no; PA=partially; U/C= unclear ; D/A Directly Applicable

Key to questions:

1. Is the study population appropriate for the topic being evaluated?
2. Are the interventions appropriate for the topic being evaluated?
3. Is the system in which the study was conducted sufficiently similar to the UK context?
4. Were the perspectives clearly stated?
5. Are all direct health effects on individuals included, and are all other effects included where they are material?
6. Are all future costs and outcomes discounted appropriately?
7. Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?
8. Are costs and outcomes from other sectors fully and appropriately measured and valued?
9. Overall judgement (no need to continue if NA).
10. Does the model structure adequately reflect the nature of the topic under evaluation?
11. Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?
12. Are all important and relevant outcomes included?
13. Are the estimates of baseline outcomes from the best available source?
14. Are the estimates of relative "treatment" effects from the best available source?
15. Are all important and relevant costs included?
16. Are the estimates of resource use from the best available source?
17. Are the unit costs of resources from the best available source?
18. Is an appropriate incremental analysis presented or can it be calculated from the data?
19. Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?
20. Is there any potential conflict of interest?
21. Overall assessment.

4.4 Applicability

None of the included studies were conducted in the UK; most of the studies (19/26) were conducted in the USA, six in Europe and one in Australia. This raises some issues regarding the applicability of findings to the UK. Although these studies cover similar interventions and population groups to those relevant to the UK context, the effectiveness and cost-effectiveness of the interventions here evaluated may be influenced by differences in overall health and social services provided.

There were a range of hard-to-reach groups participating in the included studies, with seven in drug users; six in immigrants or the foreign-born; five in homeless people; four in prisoners; and four in mixed hard-to-reach groups. However, given the range of interventions explored in the review, the applicability of the findings for some hard-to-reach groups may be limited. The applicability of the findings to the UK context and to different hard-to-reach groups is explored in more detail in the evidence statements and conclusions.

5.0 Study findings

The study findings were divided by those interventions aimed at managing LTBI and those aimed at managing active TB. The effectiveness and cost-effectiveness review were reported separately for each type of intervention and separated for each hard-to-reach group. When a study was reported on more than one occasion, for example, if it had more than one intervention arm, then, in the first instance, full details of the study characteristics were reported. Thereafter, only brief details and any new results were reported to avoid repetition. Full study characteristics can be found in Appendix C.

5.1 Interventions for managing latent tuberculosis Infection (LTBI)

5.1.1 Effectiveness review

Education

Education intervention: any intervention that includes the sharing of information with patients with the aim of increasing their knowledge of TB.

Study id	Study design	Country	Population	Comparisons*	Delivery	Setting	Professional
White et al. (2002 [+])	RCT	USA	Prisoners	Educational intervention Treatment as usual	Individual, every 2weeks	TB clinic	Not reported
White et al. (2005 [+])	Before-and-after study	USA	Prisoners	Educational intervention delivered within a RCT. Educational intervention delivered in non-trial clinical settings.	Individual, every 2 weeks	Prison	Prison discharge planners

*Note: some studies included more than one intervention other than education; these have not been extracted here.

Prisoners

White et al. (2002 [+]; Educational intervention =107; Treatment as usual = 104) explored the effect of enhanced educational sessions on management of LTBI in prisoners in the USA. Treatment as usual in this RCT received an education session

that included details on LTBI, side effects of medication, availability of free care after release from prison, transportation details, and opening hours of the TB clinic. Medication for LTBI was a six-month supply of isoniazid treatment. The intervention group also received education sessions every two weeks while they were in prison to reinforce the initial educational information. The main outcome of interest was how many prisoners attended their first TB clinic appointment in the community. The study also included a third comparison arm (N=114) reported elsewhere in the section on incentives.

The study found that adherence to the first TB clinic appointment was 37% (40/107) in the additional education group compared with 24% (25/104) in treatment as usual group. The study did not statistically compare adherence to the first TB clinic appointment, which limited the study's findings. Completion of a full course of isoniazid treatment was 23% in the education group (24/106) and 12% (12/103) in treatment as usual (p=0.04). Prisoners were twice as likely to complete a full course of treatment if they received the additional educational intervention while in prison compared to those who received treatment as usual (adjusted odds ratio [AOR] = 2.2, 95% CI 1.04-4.72). Another predictor of treatment completion was residing in stable housing before being sent to prison (AOR = 2.94, 95% CI 1.01-8.58; p=0.05). No other tested predictors had a statistically significant effect on clinic attendance.

The same sample of prisoners who received the additional educational intervention (White et al. (2002 [+]) were later compared with a group receiving the same education intervention (N=104) but delivered outside of the RCT as part of usual care (N=164; White et al., 2005 [+]). In the usual care group, the prison's discharge planners delivered the educational intervention. It was not clear why the numbers in the educational intervention from White et al. (2002 [+]) (N=107) differed from the numbers reported in White et al. (2005 [+]; N=104). The study found that the usual care group had a 10% rate of first attendance at the TB clinic in the community (16/164). This was statistically significantly lower than attendance rate in the RCT intervention group reported in White et al. (2002 [+]; p=0.002).The authors note that there may have been limitations in the comparisons as there were differences in the study periods which may have confounded the results. For example, as part of the RCT, prisoners had greater contact with research personnel and reimbursement was paid if they adhered to the research procedures. These factors limit the conclusions which can be drawn from the study.

Evidence statement 1: **The effectiveness of education to manage LTBI.**
ES1.0 **Weak evidence from one** RCT (White et al., 2002 [+]) suggests that **prisoners** were statistically more likely to complete treatment for LTBI in the community if they received an educational programme about TB every two weeks while in prison to reinforce the initial education provided to all prisoners (AOR = 2.2; 95% CI 1.04-4.72). The study was limited as it did not statistically compare attendance rates at a first TB clinic appointment after release from prison (one of the study's primary outcome measures). In addition, when the education intervention was conducted outside of the

RCT setting by prison discharge planners, prisoners were less likely to adhere to their first TB appointment in the community compared to when it was delivered as part of the RCT (p=0.002; White et al., 2005 [+]). However, it is not known how this compared to treatment as usual.

Applicability
Two studies were found on the effectiveness of education to manage LTBI, conducted in the USA in a prison setting. As no study was conducted in the UK, it is difficult to assess the comparability of the findings to a UK context. The evidence for effectiveness was conducted in prisoners but, as prisoners overlap with other hard-to-reach groups, the results may be extrapolated to other groups but not to other settings.

Peer support

Peer support: any intervention, individual- or group-based that is led by a member of the same hard-to-reach group as the patient's with the emphasis on providing support to the patient, and may include sharing of information about TB.

Study id	Study design	Coun-try	Population	Comparisons*	Delivery	Setting	Profess-ional
Chaisson et al. (2001 [+])	RCT	USA	Intravenous drug users	Peer-support; Treatment as usual (TAU).	Individual and group, every 2 weeks.	TB clinic	Former Intravenous drug users who completed treatment for TB.
Kominski et al. (2007 [+])	RCT (cost-effectiveness study)	USA	Foreign-born adolescents	Peer-support; TAU	Individ-ual, frequency unclear.	Public health clinics	Adolescents who completed treatment for TB.
McCue & Afifi (1996 [-])	Before-and-after	USA	Internat-ional students	Peer support; TAU	Individual, weekly for 6 months.	Health clinic, University	International students from countries with a high prevalence of TB.

*Note: some studies included more than one intervention other than peer support; these have not been extracted here.

<u>Drug users</u>
Chaisson et al. (2001 [+]) randomised drug users with LTBI in the USA to peer support (N=101) or to treatment as usual (N=100) in a hospital (Chaisson et al., 2001 [+]). The

peer-support group received counselling from a peer twice during the first month of therapy and once a month thereafter. Patients were also asked to attend monthly peer-support group meetings where lunch was provided. The peers delivering the treatment were former intravenous drug users who had completed isoniazid preventive therapy and were trained in counselling patients with TB and HIV about health promotion, prevention, treatment adherence and life-coping strategies. The intervention took place in a TB clinic. Treatment as usual consisted of standard treatment of a six-month course of isoniazid therapy, with patients making monthly visits to the hospital for each 30-day supply of the medication. Patients also received an initial counselling session with the nurse and were encouraged to ask questions about their treatment. All participants received either an immediate or deferred $10 stipend for adhering to monthly study procedures such as routine assessments.

The study found that treatment completion (defined as taking 80% of prescribed medication and reporting for monthly visits for six months) was 78% (79/101) for those who received peer-support and 79% (79/100) for those in routine care; the p-value was not reported. Adherence to at least 80% of doses taken was 71% in the peer group (72/101) compared with 90% (90/100) with treatment as usual; this was not statistically compared. The study had a third treatment arm involving DOPT, which is reported in more detail in the section on DOPT. There was also no statistically significant difference in treatment completion rates between DOPT and peer support (p=0.73).

In this study, the reliability of the outcome measure changed over time. For both groups, treatment completion was first measured by self-report and then by electronic caps on medication bottles which monitor when the medication bottles are opened. When more reliable methods were used there was a statistically significant difference in treatment completion in favour of peer support (58/101, 57%) compared with treatment as usual (49/100, 49%; p<0.001).

In addition to the limitations noted above, the use of the $10 stipend may have increased adherence to treatment among those in the treatment as usual group than normally would have been the case with standard care.

Foreign-born/International students

Kominski et al. (2007 [+]; N=394) in a RCT in the USA examined the effectiveness of providing peer support to adolescents, just under 80% of whom were foreign-born, compared with treatment as usual. Peer support was delivered by an adolescent who had successfully completed treatment, who stressed the importance of taking medication and adhering to clinic appointments; no further information was provided in the paper about the intervention. Treatment as usual consisted of a standard course of at least six months of isoniazid treatment for LTBI plus the standard educational material routinely provided to all patients.

The study found similar adherence rates for those who received peer support (150/199, 75.4%) and usual care (148/195, 75.9%). The difference between the groups was not

statistically compared. The study also did not statistically compare the groups at baseline, making it difficult to determine whether there were any important differences between the two groups. In addition, the description of peer support was limited, making it difficult to draw conclusions from the study.

McCue & Afifi (1996 [-]) assessed the effectiveness of a peer-support (N=165) programme to manage LTBI among international students in the USA compared with a historical control group who had received treatment as usual (N=197). Peer support was delivered by an international student from a country with a high prevalence of TB who had lived in the USA for at least 18 months. The peer acted as patient advocate, providing information and suggestions to the students and passed information between students and the medical staff. They explained the meaning of a positive PPD skin test and stressed the importance of the prevention of active TB. In the treatment as usual group, patients did not receive peer support, but had advice from the medical officer, explaining TB and the importance of prevention. Medication for LTBI in both groups was six months of isoniazid therapy; no further information was provided.

The study found that treatment compliance (no definition was provided) ranged from 62% (26/42) in autumn 1992 to 71% (64/90) in autumn 1993 in the peer-support group. In the treatment as usual group, treatment compliance ranged from 6% (6/94) in autumn 1990 to 14% (9/65) in autumn 1991. The study found a statistically significant difference between peer support (in autumn 1993) and treatment as usual (in autumn 1991; $p<0.001$). No other time periods were tested.

The study was limited because it did not include information on the sample characteristics specific to the selected population, but only to the international university students as a whole. Therefore it is not known how generalisable the selected sample is to the source population. There was also no statistical comparison conducted between the selected students in the two time periods making it unclear whether there were differences in the time periods that may have contributed to different completion rates. Lastly, although treatment compliance rates were provided for each teaching term for two years, the study only statistically compared the completion rates in autumn 1993 with autumn 1991, which was the term time with the highest completion rate for the peer support group. This may have led to a bias in the reporting of the results, reducing the internal validity of the study.

Evidence statement 2: **The effectiveness of peer support to manage LTBI.**
ES2.0 **Weak evidence from one** RCT (Chaisson et al., 2001 [+]) found that statistically more **intravenous drug users** were likely to complete treatment if they received peer support (58/101, 57%) compared with treatment as usual (49/100, 49%; $p<0.001$), when adherence was measured using electronic bottle caps. However, there was no significant difference when adherence was measured by self report. All participants received a $10 incentive to adhere to the research protocol, so these adherence rates might not be replicable in settings where such an incentive is not

available.

ES2.1 **Inconsistent evidence from** one RCT (Kominski et al., 2007 [+]) and one before-and-after study (McCue & Afifi, 1996 [-]) limits the conclusions on the effectiveness of individual peer support among the **foreign-born** (who were adolescents) or international university students with LTBI. Kominski et al. (2007 [+]) found no difference in treatment completion rates between peer support and treatment as usual. However the study did not compare groups at baseline or at the final assessment, and the description of the intervention is limited. In contrast, McCue & Afifi's (1996 [-]) before-and-after study suggests that there was a statistically significant increase in treatment completion with peer support compared with a historical control group that received treatment as usual ($p<0.001$). However, there was selective reporting of results in this study, no information reported on the selected population, and baseline comparisons between groups were also not analysed.

Applicability
Three studies were identified that explored the effectiveness of peer support to manage LTBI, all of which were conducted in the USA. As there was no study conducted in the UK it is difficult to compare the applicability of the findings to the UK setting. The evidence for peer support was found for intravenous drug users and the foreign-born/international students; therefore, it is not clear how this evidence translates to other hard-to-reach groups, particularly as the evidence on the foreign-born was for a very specific group of young people (adolescents and university students) who may not be as hard-to-reach as other groups.

Supervised treatment

Supervised treatment: medication for TB is supervised but without observing patients swallowing their medication. Supervised treatment can involve monthly follow-up visits, questioning about pill-taking practices, counselling regarding pill taking, or testing of urinary isoniazid (INH) levels if non-compliance is suspected.

Study id	Study design	Country	Population	Comparisons*	Setting	Professional
Matteelli et al. (2000 [+])	RCT	Italy	Illegal immigrants	Supervised treatment of 900 mg of isoniazid; Unsupervised treatment of 900 mg of isoniazid; Treatment As	Onsite at TB clinic or specialist clinic for immigrants.	Not reported

Usual.

Illegal immigrants

In a RCT, Matteelli et al. (2000 [+]) investigated the efficacy of providing supervised treatment (N=82) of twice-weekly isoniazid in immigrants with LTBI, compared with twice-weekly, self-administered isoniazid (N=73), and with 'usual' isoniazid therapy (N=53). Participants had migrated to Italy within the five years prior to recruitment from countries with an estimated TB incidence of 50/100,000 or more. The twice-weekly, supervised and unsupervised groups were given 900 mg of isoniazid twice weekly for six months. Supervision took place on site at the relevant clinic where participants were recruited. The professional who delivered the intervention was not reported. Supervised treatment in this study appears to be different from DOPT as the professional did not directly observe the patient consume the medication, but counted the number of pills in the bottle when participants returned to the clinic. Treatment as usual was standard treatment of a six-month course of isoniazid therapy; no further information on dose was provided. It is not known if the unsupervised participants received their medication in monthly supplies.

The study assessed treatment completion, which was defined as 80% or more of prescribed medication taken. In the supervised group, this was measured by counting the number of pills in the bottles when participants returned to the clinic; in the unsupervised groups, urine samples were taken at each clinic visit. The study found that 7.3% (6/82) of immigrants in the supervised group completed treatment compared with 26% (19/73) in the unsupervised twice-weekly group and 41% (22/53) with treatment as usual. The adherence rates were not statistically compared across groups but were lowest with supervised treatment and highest with treatment as usual.

The study did not include a detailed description on the interventions, making it difficult to understand what was conducted and to compare the interventions with other studies. In addition, treatment completion was not statistically compared, which limited the study's findings. In addition, treatment completion was measured differently in both groups; pill counting in the treatment group and urine samples in the control groups.

Evidence statement 3: **The effectiveness of supervised treatment to manage LTBI.**
ES3.0 **Weak evidence from one** RCT (Matteelli et al., 2000 [+]) found that treatment completion rates were lower with twice-weekly supervised treatment in **illegal immigrants** where participants were not observed taking the medication than with unsupervised twice-weekly or usual isoniazid treatment. However, the study provided limited information about the treatment conditions, so it is unclear to what extent the treatment regimens differed, and the statistical significance of the difference in results was not assessed. *Applicability* One study was found that explored the effectiveness of supervised treatment to manage LTBI, which was conducted in Italy. The description of treatment as usual is

limited, therefore, it is difficult to assess whether the study is comparable to treatment in the UK. Evidence on supervised treatment is only available for immigrants and it is not known how these results would compare for other hard-to-reach groups.

Directly-observed preventive therapy (DOPT)

Directly Observed Preventive Therapy (DOPT): any intervention that involves the observation of participants ingesting their prescribed doses for LTBI.

Study id	Study design	Country	Population	Comparisons*	Frequency	Setting	Professional
Batki et al. (2002 [+])	RCT	USA	Intravenous drug users	DOPT; TAU.	Daily for 6 months	Onsite at hospital where they received methadone treatment.	Unclear
Chaisson et al. (2001 [+])	RCT	USA	Intravenous drug users	DOPT; Peer support; TAU.	Daily for 3 to 8 weeks and then twice-weekly for 18 to 36 weeks.	Outreach at a site chosen by the participant.	Nurse
Rodrigo et al. (2002 [-])	Before-and-after	Spain	Prisoners	DOT; TAU	Unclear	Prison (could be continued in the community)	Health worker
Tulsky et al. (2000 [+])	RCT	USA	Homeless	DOPT by peer; TAU.	Twice weekly for 6 months	Onsite at TB clinic	Lay person (researcher); Peers who were currently or previously homeless.

*Note: some studies included more than one intervention other than DOPT; these have not been extracted here.

<u>Drug users</u>

Batki et al. (2002 [+]; DOPT=35; TAU=39 explored the effectiveness of providing DOPT to intravenous drug users undergoing methadone maintenance treatment in the USA. DOPT was in the form of 300 mg of isoniazid treatment and 50 mg of pyridoxine administered seven days per week for six months. Participants also received

methadone for the co-morbid drug problem. DOPT was delivered onsite in the same hospital as the methadone maintenance treatment. The professional who delivered the DOPT was not reported. Treatment as usual was standard treatment of a six-month course of isoniazid therapy, with participants making monthly visits to the hospital for each 30-day supply of isoniazid. Methadone maintenance was not specifically delivered to those in the treatment as usual group, but participants could seek this elsewhere. The study also included a third comparison arm (N=37) in the section on combined interventions.

The study found that 77.1% (95% CI 61.3% to 91.0%) of participants receiving DOPT completed treatment compared with 13.1% (95% CI 3.0% to 23.7%) with treatment as usual; this difference was statistically significant ($p<0.0001$). Treatment completion was assessed from a review of clinical records which recorded by the physician whether treatment was completed. Participants who received DOPT also had a greater mean duration of treatment (5.7 months) compared with treatment as usual (1.6 months; $p<0.0001$).

The study was limited because there were statistically significant differences at baseline between the comparison groups on the Addiction Severity Index ($p=0.022$) and the Beck Depression Inventory ($p=0.022$) such that the scores were lowest for those who received DOPT. This may have exaggerated the apparent benefit of DOPT. Another limitation is that, in addition to participants receiving DOPT, the treatment group also received methadone maintenance therefore it is not known how much of the adherence to treatment was due to methadone maintenance or directly-observed isoniazid treatment. The study may also be limited in its generalisability as the treatment was based on daily doses of isoniazid therefore the adherence rate may not be comparable to less frequent doses of treatment. However, it is harder to comply with daily doses therefore this may have reduced the apparent different between DOPT and the comparison groups. The study excluded participants who were HIV-positive.

A second RCT (also reported in the section above on peer support) compared DOPT (N=99) with peer support (N=101) and with treatment as usual (N=100) in intravenous drug users who were seeking treatment for LTBI in a hospital in the USA (Chaisson et al., 2001 [+]). DOPT was given in the form of 900 mg of isoniazid, twice weekly for six months. DOPT was delivered by a nurse who was an outreach worker and therefore the observation of treatment took place in either the hospital or in the community at a mutually convenient location. All participants received a $10 stipend to adhere to appointments. Treatment as usual was standard treatment of a six-month course of self-administered isoniazid therapy. The study found that 80% of participants adhered to at least 80% of their prescribed doses given via DOPT, compared with 79% with treatment as usual, resulting in no statistically significant differences between groups ($p=0.86$). There was also no statistically significant difference between DOPT and peer support ($p=0.73$). Although there were no differences found, the study was limited because $10 incentives were offered to all participants to complete monthly research procedures. In addition, adherence was measured by self-report in the treatment as

usual group and only later was changed to the more reliable method of electronic caps on medication bottles.

Although these studies compared similar interventions with treatment as usual, they were too heterogeneous to combine in a meta-analysis (Batki et al., 2002 [+]; Chaisson et al., 2001 [+]). The two studies reporting different effect sizes with no overlap between the confidence intervals. Some possible explanations for the different effect sizes were that Batki et al. (2002 [+]) delivered DOPT daily alongside methadone maintenance in a setting specifically designed for drug users, and reported positive treatment outcomes based on clinical records of adherence. In contrast, Chaisson et al. (2001 [+]) offered a $10 incentive to all participants regardless of assignment to group, DOPT was administered by an outreach nurse in the community or at the hospital, and adherence was measured either with electronic caps or with self-reporting.

Homeless

Tulsky et al. (2000 [+]) in a RCT compared DOPT delivered by a peer (N=37) with treatment as usual (N=38) to manage LTBI in the homeless in the USA. The homeless included those who were marginally housed residing in either an emergency shelter or any other outdoor public space, or those temporarily residing in low cost hotels. DOPT consisted of 900 mg of isoniazid twice weekly for six months. A peer health advisor, who was currently or previously homeless, administered and observed the participants take the medication. If a patient missed an appointment then the peer was required to spend the allotted time to locate the individual. This regimen was compared with treatment as usual which consisted of a six-month course of isoniazid therapy, collected at monthly visits to the TB clinic for a 30-day supply. If a patient missed an appointment then the staff were required to send up to three letters or to make up to three telephone calls to locate the individual. The study also included a third comparison arm (N=43) reported in the section on combined interventions.

The study found that 19% (7/37) of participants completed treatment when DOPT was provided by a peer health adviser compared with 26% (10/38) when medication was self-administered; this difference was not statistically significant (p value not reported). The median number of months that isoniazid was dispensed was two months for both the treatment and control group. The results suggest that there is no statistically significant effect on adherence if a peer provides DOPT compared with self-administered therapy in this homeless population.

The generalisability of the study to the wider homeless population may be limited as it included participants who lived in apartments but were recruited into the study because they attended food shelters. In addition, the study only included those who returned for their TST results within one week, therefore, the sample may include those more likely to be adherent than the general hard-to-reach population.

Prisoners

Rodrigo et al. (2002 [-]); N=NR) explored the implementation of DOT (between 1993 and 2000) to manage TB among prisoners in short- and long-term incarceration facilities compared to a historical control group given treatment as usual prior to the implementation of DOT (between 1987 and 1992). The paper suggests that it included both active and latent TB, however, this was not clearly reported. DOT was conducted by a health worker onsite in the prison, however, prisoners could continue DOT in the community at various sites after their release. The programme also conducted contact tracing investigations. Limited information was provided about the comparison group, other than they received standard services that were available before the implementation of DOT, but no details were reported of the treatment regimens provided for either group. The study also reported outcomes relating to smear-positive cases which have been reported in the section on active TB.

The study found that the incidence rates for TB significantly declined from the year 1993 (5089 per 100,000) to the year 2000 (812 per 100,000; p<0.001) when DOT was implemented compared with the incidence rates prior to the implementation of DOT, which significantly increased between 1987 (3418 per 100,000) and 1992 (8041 per 100,000; p<0.001). The authors noted that the trend in incidence rates were statistically significant for both time periods (p<0.0001), no further information was reported. There was no statistically significant difference diagnostic delay and treatment adherence (for smear-positive and smear-negative cases) for both time periods (1993 to 2000; 1987 to 1992). Outcomes relating to smear-positive cases are reported in the section on managing active TB.

The study was limited because there was no information on the characteristics of the sample making it difficult to determine the generalisability of the included population and to compare it with other studies. It is also not known whether the differences in the TB incidence rates were caused by the implementation of DOT or other confounding factors. The study demonstrates that there was a decline in incidence of TB in the general population similar to the decline in prisoners. Therefore the decline may not be specific to DOT but a natural decline in incidence rates due to other factors.

Evidence statement 4: **The effectiveness of DOPT to manage LTBI.**
ES4.0 **Inconsistent evidence from two** RCTs (Batki et al., 2002 [+]; Chaisson et al., 2001 [+]) on the effectiveness of DOPT compared with treatment as usual is unclear in **drug users**. Batki et al. (2002 [+]) delivered DOPT daily onsite at a hospital alongside methadone maintenance in intravenous drug users and found a statistically significant difference in treatment completion in favour of DOPT compared with treatment as usual (77.1%, 95% CI 61.3% to 91.0% with DOPT vs.13.1%, CI 3.0% to 23.7% with usual care; p<0.0001). In contrast, Chaisson et al. (2001 [+]) found no statistically significant differences (p=0.86) between DOPT, delivered by a nurse outreach worker onsite at the TB clinic or in a mutually convenient location, two days per week, compared with treatment as usual.

ES4.1 **Weak evidence from one** RCT (Tulsky et al., 2000 [+]) found that DOPT delivered twice-weekly by a peer did not result in a statistically significant difference in treatment completion in the **homeless** compared with treatment as usual (DOPT = 19%, TAU = 26%; p value not reported). The generalisability of the study to the homeless population may be limited as it included participants who lived in apartments, and only included those who had already demonstrated adherence by returning within one week for their TST result. To increase the generalisability of the study it could allow for more time for participants to return for their TST results.

ES4.2 **Weak evidence from one** before-and-after study (Rodrigo et al., 2002 [-]) suggests that the incidence rates for TB among **prisoners** declined when DOT was implemented (5089 per 100,000 in 1993 to 812 per 100,000 in 2000) having increased prior to the implementation of DOT (3418 per 1000,000 in 1987 to 8041 per 100,000 in 1992), the fall from start to finish of both time periods being statistically significant ($p<0.001$). The findings were limited because the incidence rates for TB also declined in the general population. There was also no information reported on the sample characteristics.

Applicability
Three studies were conducted in the USA and one in Spain, two in drug users, one in the homeless and one in prisoners. This limits the applicability of the findings to a UK context and to other hard-to-reach groups.

Incentives

Incentives: any intervention that uses cash or a voucher with a monetary value to encourage desired behaviour in the patient. These can be one-off incentives at the start or end of treatment, or offered at regular intervals throughout the duration of the intervention.

Study id	Study design	Country	Population	Comparisons*	Frequency	Setting
Kominski et al. (2007 [+])	RCT (cost-effectiveness study)	USA	Foreign-born adolescents	Incentives: agreed between parent and child. TAU	Once at the end of treatment.	Public health clinics
White et al. (1998 [+])	RCT	USA	Prisoners	Cash incentive: $5 TAU	Once at their first TB appointment in the community.	TB clinic
White et al. (2002	RCT	USA	Prisoners	Voucher incentive: $25	Once at their first TB	TB clinic

[+])	TAU	appointment in the community.

Prisoners

White et al. (1998 [+]; Incentive = 61; Treatment as usual = 30) provided prisoners with $5 cash incentive at their first visit to the TB clinic and, like the treatment as usual group, they received a standardised TB educational programme in prison. The medication treatment provided to the treatment and control group was not reported. The study found that prisoners' adherence to their first visit to the TB clinic after release from prison was 25.8% in the incentive group and 23.3% in treatment as usual group. This difference was not statistically significant (OR = 1.43, 95% CI 0.35 to 3.71). Among those who visited the TB clinic, 25% (2/8) in the incentive group and 32% (2/7) in treatment as usual group completed treatment for LTBI; the groups were not statistically compared.

The results were limited because data on treatment completion was not provided for those who did not attend the TB clinic, although some of these might have obtained treatment elsewhere. In addition, over 70% of participants randomised into the study could not be analysed as they were not released from prison in time. The study was also underpowered to detect differences between the two groups. In the study's power calculation, 40 individuals were required in each group in order to detect a difference; the final sample size was 61.

In a similar study, White et al. (2002 [+]; Incentives = 114; Treatment as usual = 104) provided prisoners with food or transportation vouchers equivalent to $25 at their first visit to the TB clinic. Like the treatment as usual group, they were prescribed standard treatment of a six-month course of isoniazid therapy. The study also included a third comparison arm (N=107) reported in the section on educational interventions. The study found that 37% (40/107) in the incentive group and 24% (25/104) in the treatment as usual group made a first TB clinic visit within one month after release from prison; a statistical comparison between the groups was not conducted. Completion of treatment for LTBI was 12% in both the incentive and treatment as usual group. This difference was not statistically significant (AOR = 1.07, 95% CI 0.47 to 2.40).

In a fixed-effects meta-analysis carried out for this report, combining the two studies (White et al., 1998 [+]; White et al., 2002 [+]; N=179) found no significant difference in adherence to initial TB clinic visits for released prisoners with incentives compared with usual care (OR = 1.673, 95% CI 0.989 to 2.831; p=0.055), however, this was only marginally statistically non-significant. There was also no statistically significant difference when one-off incentives were provided for treatment completion (OR = 1.042, 95% CI 0.48 to 2.26; p=0.917).

Foreign-born

Kominski et al. (2007 [+]; Incentives = 203; Treatment as usual = 195) in a RCT examined the effectiveness of providing incentives in the form of contingency contracting with adolescents with LTBI in the USA, 79.3% of whom were foreign-born. Contingency contracting was a reward negotiated between the parent and adolescent. The reward was exchanged if the adolescent completed treatment. This was compared with treatment as usual, which was a standard course of at least six months of isoniazid treatment for LTBI plus the standard educational material routinely provided to all patients. A third comparison arm (N=199) was also evaluated and is reported in the section on peer support. The study found that 73.9% (150/203) of adolescents in the contingency contracting group completed six months of isoniazid treatment compared with 75.9% (148/195) with treatment as usual. The difference between the groups was not statistically compared, limiting the study's findings. The study also did not statistically compare the groups at baseline, making it difficult to determine the comparability of participants in the groups.

Evidence statement 5: **The effectiveness of incentives to manage LTBI.**
ES5.0 **Moderate evidence from two** RCTs (White et al., 1998 [+]; White et al., 2002 [+]) which were combined by the report in a meta-analysis found no significant difference with one-off monetary incentives compared with treatment as usual in the likelihood that **prisoners** with LTBI would attend a first TB clinic appointment after release from prison (OR = 1.673, 95% CI 0.989 to 2.831; p=0.055). There was also no statistically significant difference for treatment completion (OR = 1.042, 95% CI 0.48 to 2.26; p=0.917). ES5.1 **Weak evidence from one RCT** (Kominski et al., 2007 [+]) found that adolescents (79.3% **foreign-born**) who were provided a one-off incentive at the end of treatment for LTBI were equally likely to adhere to treatment compared with treatment as usual (incentives = 73.9%, 150/203 vs. TAU = 75.9%, 148/195), however, this was not statistically compared. The study also did not compare groups at baseline, therefore, it is not known if there were any initial differences between groups. *Applicability* The three studies were all conducted in the USA, two in prisoners and one in adolescents where the majority were foreign-born. This limits the applicability of the findings to the UK and to other hard-to-reach groups.

Combined interventions

The following studies explored combining more than one discrete intervention to manage LTBI.

Study id	Study design	Country	Population	Comparisons*	Setting	Frequency	Professional
Kominski et al.	RCT	USA	Foreign-born	Peer support plus	Public health	Frequency of peer	Adolescents who

(2007 [+])				incentives; Incentives; Peer support; TAU.	clinics	support was unclear; Incentives were provided once at the end of treatment.	completed treatment for TB.
Malotte et al. (2001 [++])	RCT	USA	Drug users	DOPT and monetary incentives ($5) with outreach work; DOPT with outreach work; DOPT and monetary incentives with no outreach work.	Outreach: at a site chosen by the participant. No outreach: onsite at drug users' service.	Bi-weekly at each DOPT appointment.	Outreach worker
Nyamathi et al. (2008 [++])	Cluster RCT	USA	Homeless	DOPT plus enhanced case management and education; DOPT.	Community health clinic	8 sessions, 24 weeks.	Nurse outreach worker
Tulsky et al. (2000 [+])	RCT	USA	Homeless	DOPT and monetary incentives; DOPT delivered by peer; TAU.	Onsite at TB clinic	Bi-weekly at each DOPT appointment.	Lay person (researcher) for DOPT and incentives. Peers who were homeless for DOPT delivered by peer.
Tulsky et	RCT	USA	Homeless	DOPT and	Drug users	Bi-weekly at	Unclear

al.(2004 [+])	voucher incentives; DOPT and cash incentives.	service, community	each DOPT appointment.

DOPT plus enhanced case management and education (homeless)

In a RCT, Nyamathi et al. (2008 [++]) compared the efficacy of an educational intervention plus nurse case management (N=279) with DOPT alone (N=241) to manage LTBI in a homeless population. The educational intervention involved eight sessions over 24 weeks, delivered in groups of four to five, by a nurse outreach worker. The sessions covered self-esteem, HIV risk reduction, communication skills, social and cognitive problem solving, and developing social networks (to maintain behaviour change). Both groups received DOPT of 900 mg of isoniazid twice weekly and incentives were paid to the participants for each dose taken. Participants who missed appointments for the isoniazid medication were also actively searched for by the outreach worker to re-engage the participant in the treatment programme. Treatment as usual was one 20-minute session on TB and HIV, with no outreach work for those who missed their isoniazid appointments.

Treatment completion, defined as 100% of the 52 doses taken (measured by direct observation), was 61.5% (172/279) with enhanced case management plus DOPT and 39.3% (94/241) DOPT alone ($p<0.001$). When adjusting for the baseline differences found in the study (see limitations), those in the combined intervention group were three times more likely to complete treatment compared with those receiving DOPT alone (AOR = 3.01, 95% CI 2.15 to 4.20). Enhanced case-management plus DOPT was most effective for daily alcohol users (AOR = 10.41, 95% CI 2.48 to 43.68) and females (AOR = 5.80, 95% CI 1.72 to 19.5); and also led to better treatment compared with control group among males (AOR 2.51, 95% CI 1.60 to 3.93), daily drug users (AOR = 3.27, 95% CI 1.30 to 8.25) and homeless shelter recruits (AOR = 2.76, 95% CI 1.80 to4.23). There was no difference in treatment outcomes for lifetime intravenous drug users in the treatment and control groups (AOR = 2.20, 95% CI 0.85 to 5.67).

The study was limited because there were statistically significant differences between the treatment and control group at baseline. In the treatment group, there were more males ($p<0.001$) and more participants recruited from emergency shelters, and fewer from drug recovery sites ($p<0.001$) compared with treatment as usual. There was also fewer people with a history of intravenous drug use at any time in their life ($p<0.001$) and fewer drug or alcohol users ($p<0.05$) in the intervention group compared with the treatment as usual group. However, these differences were taken into account in the analyses.

DOPT plus incentives

Tulsky et al. (2000 [+]) explored the efficacy of the combined treatment of DOPT plus incentives (N=43) to manage LTBI in the homeless in an RCT. This was compared with DOPT delivered by peers (N=37) and with self-administered treatment as usual (N=38). In the DOPT plus incentive treatment arm, participants received 900 mg of isoniazid twice weekly for six months and $5 cash for every appointment attended. The study found that treatment completion was 44% (19/43) in the combined intervention of DOPT plus incentives; this was statistically greater than DOPT provided by a peer (7/37, 19%; p=0.02) but not greater than usual care (10/38, 26%; p=0.11). The median number of months that isoniazid was dispensed was five months in the combined DOPT plus incentive arm. This was statistically higher than DOPT delivered by a peer (two months; p=0.005) or usual care (two months; p=0.04).

The study combined the results from DOPT (delivered by peers) and treatment as usual and compared this with the combined intervention of DOPT plus incentives to explore significant predictors of treatment completion at six months. The study found that the homeless were more than twice as likely to complete treatment if they received incentives in addition to DOPT compared with the control group (treatment as usual and DOPT provided by peers; OR = 2.57, 95% CI 1.11 to 5.94). Other significant predictors of treatment completion were being a resident in a hotel or other stable housing compared with living on the street or in a shelter (OR= 2.33; 95% CI 1.00 to 5.47).

Tulsky et al. (2004 [+]) in a RCT explored the combination of providing a homeless population in the USA a cash or voucher incentive plus DOPT. In addition to DOPT, the homeless were given either $5 cash incentive (N=72) or a choice of a fast-food voucher or grocery store voucher worth $5 (N=69). Across groups, incentives were paid twice-weekly at each onsite medical appointment attended where they were observed taking their medication. Medication was either 900 mg of isoniazid twice weekly for six months or 600 mg of rifampin plus 300 mg of isoniazid for four months. As DOPT was only provided twice weekly, those participants on rifampin were required to self-medicate on the non-clinic days. The number of participants prescribed each medication regime in each incentive group was not reported. Outreach efforts were made if a participant missed more than one appointment; three outreach efforts were made in the first month and were reduced to one subsequently.

The study found that 89.2% (58/65) completed treatment in the cash incentive group compared with 81.5% (44/54) in the voucher incentive group; this difference was not statistically significant (p=0.23). The study was limited because there was a difference between treatment groups at baseline in the numbers living on the street or in shelters: 41% in the voucher incentive group compared with 23% in the cash incentive group, (p=0.04). Being a resident in a low-cost residential hotel (92%) compared with living on the streets or in shelters (79%) was a statistically significant predictor of treatment completion (p=0.04). However, even when adjusting for this difference in a multivariate

analysis, group assignment was still not independently predictive of treatment completion (AOR = 1.94, 95% CI 0.65 to 5.83).

DOPT plus outreach (drug users)

Malotte et al. (2001 [++]) compared three combinations of treatment for a population of drug users with LTBI in the USA. All three treatment arms incorporated DOPT but also included (1) outreach (N=55); (2) incentives (N=55); or (3) incentives plus outreach (N=53). Across comparison groups DOPT included 900 mg isoniazid twice weekly for six months for those without HIV and 12 months for those with a positive HIV status. The outreach component included DOPT provided by an outreach worker at a location chosen by the participant. In the treatment group without outreach, DOPT was conducted at a drug users' service in the community. In the incentive groups, drug users received $5 cash for each appointment attended.

The study found that 60% (33/55) of the drug users completed treatment when DOPT plus incentives were provided onsite in a drug services facility compared with 52.8% (28/53) when DOPT plus incentives were provided by an outreach worker at a site convenient for the participant. These differences were not statistically compared, limiting the study findings. There appears to be no added benefit for adding outreach to DOPT plus incentives for treatment completion. However, the added benefit of outreach may be limited in this study as both groups were offered convenient locations for drug users to attend. In the group without outreach, DOPT occurred onsite at a drug services facility specifically designed for the hard-to-reach group, rather than a specialist TB clinic or hospital setting.

The study also found that drug users were statistically more likely to complete treatment in the two treatment groups where incentives were provided compared to DOPT plus outreach without such incentives (AOR = 45.5, 95% CI 9.7 to 214.6; $p<0.0001$). The percentage of medication taken on time was 12% among those who received DOPT plus outreach (without incentives); this was statistically lower that the proportions found in the two treatment groups where incentives were provided (72% for outreach plus monetary incentives; 69% for monetary incentives; $p<0.001$). The absolute numbers were not reported for this outcome, only percentages. These results suggest that regardless of the added outreach, there appears to be a benefit from adding incentives to DOPT.

Peer support plus incentives (foreign born)

Kominski et al. (2007 [+]; Combined intervention = 203; Treatment as usual= 195) in a RCT in the USA examined the effectiveness of combining peer support and incentives in the form of contingency contracting to adolescents with LTBI, of whom 79.3% were foreign-born. The results of the single intervention groups have been reported earlier in this report. The study found that treatment completion among those who received peer support plus contingency contracting was 83.8% (165/197). Compared with treatment as usual, which was a standard course of self-administered isoniazid therapy (75.9%, 148/195), the difference was statistically non-significant ($p=0.051$). The study did not

statistically compare the combined intervention with either peer support alone or contingency contracting alone, therefore, it is not known what the added benefit is of combining the interventions, limiting the study's findings.

Evidence statement 6: **Effectiveness of combined interventions to manage LTBI.**
ES6.0 **Moderate evidence from one** RCT (Nyamathi et al., 2008 [++]) found that there was a statistically significant benefit of adding case management which included an education intervention (eight sessions over 24 weeks) to DOPT to manage LTBI in the **homeless** compared with providing DOPT alone (AOR = 3.01, 95% CI 2.15 to 4.20). ES6.1 **Weak evidence from one** RCT (Tulsky et al., 2000 [+]) that adding twice-weekly $5 cash incentives to attend DOPT appointments resulted in statistically greater adherence to treatment completion in the **homeless** (44%, 19/43) compared with providing DOPT provided by a peer without incentives (7/37, 19%; p=0.02) but was not significantly more effective than treatment as usual (10/38, 26%; p=0.11). The clinical significance of these differences is unclear. The generalisability of the study to hard-to-reach groups may be limited as it included participants who lived in apartments and only included those who returned for their TST results within one week. ES6.2 **Weak evidence from one** RCT (Tulsky et al., 2004 [+]) suggested that there was no statistically significant difference in adherence to treatment completion when the **homeless** were given a $5 cash incentive plus DOPT compared with a choice of a fast-food voucher or grocery store voucher worth $5 plus DOPT (cash incentive = 89.2%, 58/65 vs. voucher incentive = 81.5%, 44/54; p=0.23). The study was limited as there were statistically significant differences between groups at baseline in factors that were predictive of treatment completion, however, these were controlled for in the analyses. ES6.3 **Weak evidence from one** RCT (Malotte et al., 2001 [++]) suggests that there was no added benefit when adding outreach to DOPT plus a $5 incentive to manage LTBI in **drug users** (DOPT with outreach plus incentives = 60% vs. DOPT plus incentives = 52.8%; p value not reported). These differences were not statistically compared, limiting the study findings. ES6.4 **Moderate evidence from one** RCT (Malotte et al., 2001 [++]) found that **drug users** with LTBI were statistically more likely to complete treatment when provided with incentives (regardless of whether outreach was also provided), compared with DOPT plus outreach without incentives (AOR = 45.5, 95%CI 9.7 to 214.6; p<0.0001). However, the confidence intervals are wide, reducing the precision of the results. ES6.5 **Weak evidence from one** RCT (Kominski et al., 2007 [+]) found that there was a statistically non-significant difference in adherence to treatment completion in the **foreign-born** with LTBI among those who received peer support plus a one-off incentive at the end of treatment compared with treatment as usual (Peer support plus incentive = 83.8%, 165/197 vs.TAU = 75.9%, 148/195; p=0.51).

Applicability
Five studies combining multiple interventions to manage LTBI were all conducted in the USA, three among the homeless, one among drug users and one in the foreign-born. Although these studies cover a variety of hard-to-reach groups it is not known the specific effect of the combined interventions among prisoners and in the UK populations.

Service model approach/social care support

Service model approach/social care support: any intervention that goes beyond the treatment of TB to also offer, for example, access to other medical and mental health services and social care support. Social care support can include, but is not limited to, social work referrals, food and clothing, and housing and financial support.

Study id	Study design	Country	Population	Comparisons*	Components	Setting	Professional
Batki et al. (2002 [+])	RCT	USA	Intravenous drug users	Service model approach / social care support (with DOPT and methadone maintenance); DOPT (with methadone maintenance); TAU.	DOPT; Methadone maintenance; Counselling; Medical services; Psychiatric services; Social work referrals.	Onsite at hospital where they received methadone treatment.	Unclear
White et al. (2003 [+])	RCT	USA	Mixed hard-to-reach groups	Service model approach / social care support; TAU.	DOPT; Incentives; Outreach work; Case management; Access to social care services (and food and clothing); Medical services; Mental health services; Substance abuse services.	Onsite at a Tuberculosis Outreach Prevention Services	MDT

Intravenous drug users

Batki et al. (2002 [+]) explored the effectiveness of providing drug users undergoing methadone maintenance treatment in the USA with a service model approach/social care support (N=37) that included DOPT and other services to care for the individual beyond the management of LTBI, such as methadone maintenance for the co-morbid drug problem, psychosocial support (twice-monthly counselling sessions), medical services, psychiatric treatment as needed, and social work referrals. This approach was compared with DOPT and methadone maintenance without any other additional services (N=35). A third comparison arm (N=39) was also included which was self-administered isoniazid therapy (further details reported earlier in this report in the section on DOPT).

The study found that treatment completion (defined as 80% or more of doses taken) was 59.5% (22/37; 95% CI 43.6 to 75.3) for those who received a service model approach/social care support. This was statistically greater than treatment as usual (5/39; 13.1%, CI 3.0% to 23.7%; p<0.0001) but not statistically greater than DOPT plus methadone maintenance without additional social care support (p values not reported). The study also found that the median length of treatment was 5.0 months (95% CI: 4.5 to 5.5) for those who received the service model approach/social care support. This was statistically greater than treatment as usual (1.6 months; p<0.001) but not greater than DOPT plus methadone maintenance (p value not reported). This suggests that there was no added benefit when additional social care support was added to DOPT plus methadone maintenance in terms of adherence to treatment of LTBI. However, it is not known if there were added benefits other than adherence. The study was limited due to baseline differences between groups, and the generalisability of the findings due to daily doses of isoniazid being prescribed.

Mixed hard-to-reach groups

In a before-and-after study, White et al. (2003 [+]) compared the implementation of a service model approach/social care support to manage LTBI in 1997 through to June 1998 (N=145), with standard care of self-administered therapy implemented in 1993 through to 1994 (N=619) and through 1991 to 1998 (N=315) in mixed hard-to-reach groups. The participants included the homeless, prisoners, drug users, new entrants or those with HIV infection, and were all in the USA. During the treatment period, the clinicians made a judgement on whether the patient was at risk for non-adherence to treatment and therefore required DOPT, or whether self-administered therapy was appropriate. DOPT was in the form of 900 mg of isoniazid with 50 mg of vitamin B6, twice weekly for six months, administered by a health worker or nurse. The observation of medication was either onsite at the main TB clinic, a Tuberculosis Outreach Prevention Service or in another site convenient for the patient. The patient was managed by a multi-disciplinary team including outreach workers that met twice weekly to review the patient's progress and considered the needs of the patient beyond TB, such as access to social services, food, clothing and any other medical and mental health needs, including services for substance abuse. Incentives were also offered to

all patients and usually consisted of lunch, a meal coupon and a bus token. Additional incentives were also considered on a case-by-case basis by the multi-disciplinary team. Prior to the implementation of the service model approach/social care support, all patients received self-administered therapy which was the standard treatment, consisting of a six-month course of isoniazid therapy, collected at monthly visits to the hospital. No further information was provided about treatment as usual.

The study found that treatment completion, defined by professionals in the medical records, was 70.3% (102/145) for those who received a service model approach/social care support compared with 47.9% (447/934) for those who self-administered therapy; this difference was statistically significant ($p<0.001$). The study also found a statistically significant difference in mean length of treatment in favour of the service model approach/social care support (8.0 months; S.D. 3.0) compared with treatment as usual, in 1997 and 1998 (7.6 months; S.D. 3.7); and in 1993 and 1994 (9.5 months; S.D. = 9.1; $p<0.001$).

The authors noted some limitations in the study which included the use of a before-and-after study design as there may have been other differences in the management of LTBI in the time periods. There were also statistically significant differences between groups for some baseline comparisons, including fewer African Americans and more Latino Americans in the service model approach/social care support group ($p=0.002$) with more participants who were foreign-born ($p<0.001$). There may have also been treatment contamination as participants assigned to the service model approach/social care support may have received self-administered therapy and not DOPT, as the choice of treatment was made by the clinician. All these limitations may have underestimated the differences found between the comparison groups.

Evidence statement 7: **Effectiveness of a service model approach/social care support to manage LTBI.**
ES7.0 **Weak evidence from one** RCT (Batki et al., 2002 [+]) in **intravenous drug users** found a statistically significant increase in adherence to treatment completion when a service model approach/social care support was used (59.5%, 95% CI 43.6 to 75.3) compared with treatment as usual (13.1%, CI 3.0% to 23.7%; $p<0.0001$) but no difference compared with DOPT plus methadone maintenance without additional social care support (p values not reported). The study was limited due to baseline differences between groups and the generalisability of the findings due to different daily doses of isoniazid prescribed. ES7.1 **Weak evidence from one** before-and-after study (White et al., 2003 [+]) found a statistically significant increase in treatment completion rates in favour of service model approach/social care support compared with treatment as usual ($p<0.001$) in **mixed hard-to-reach groups** with LTBI (service model approach/social care support = 70.3%, 102/145 vs. TAU = 47.9%, 447/934). The study was mainly limited by baseline differences between groups and there may have been treatment contamination across the two time periods.

Applicability
The two studies were conducted in the USA, one in intravenous drug users and one in mixed hard-to-reach groups. It is not known how these results apply to any one specific hard-to-reach group, or to the UK setting which may have a different social care/support approach.

5.1.2 Cost-effectiveness review

Self-administered therapy

Study id	Economic analysis	Country	Population	Comparisons	Setting
Bandyopadhyay et al. (2002 [-])	Cost-saving	USA	Prisoners	Self-administered therapy; No intervention.	Community

Bandyopadhyay et al. (2002 [-]; N=168) examined the cost-savings of providing prisoners released from short-term correctional facilities in the US isoniazid to manage LTBI in the community, compared with no intervention. Prisoners were given a two-week supply of isoniazid while in a short-term prison and were referred to a chest clinic after release. At the clinic, six months of self-supervised isoniazid was prescribed (300 mg/day) for six or 12 months depending on HIV status. Patients were seen monthly to assess adherence and tolerance to the medication. To calculate costs, the study used published data and clinic records. Discount rate and the economic perspective for the study were not reported.

The study found that the total cost of self-administered therapy to manage LTBI in prisoners was $32,866 and would result in cost-savings of $9,227 (based on cases of active TB prevented) compared with no intervention. The study had marked limitations including that the cost of screening and isoniazid administered in prison was not included in the analysis. Other important and relevant costs were not addressed, such as the cost of non-adherence and of adverse effects of treatment. The outcomes were based on a sample of 168 prisoners, reducing the generalisability of the study, and adherence was measured by self-report, limiting the validity of the findings.

Evidence statement 8: **Economic evidence for self-administered therapy to manage LTBI.**
ES8.0 **Weak evidence from one** study (Bandyopadhyay et al., 2002 [-]) suggests that the total cost of self-administered therapy to manage LTBI in **prisoners** was $32,866 and would result in cost-savings of $9,227 compared with no intervention. The study was limited because it did not include all important costs such as screening and two

weeks of isoniazid administered in prison. The outcomes were based on a sample of 168 prisoners and adherence was measured by self-report.

Applicability
One study was found that explored self-administered therapy for LTBI which was conducted in US prisoners. Although the prison population overlaps with other hard-to-reach groups, it is not known whether similar cost-savings would be found in other populations and in other settings, including the UK.

Directly-observed preventive therapy (DOPT)

Study id	Economic analysis	Country	Population	Comparisons*	Setting	Professional
Gourevitch et al. (1998 [+])	Cost-savings	USA	Drug users	DOPT; Self-administered therapy.	Methadone clinic	Nurse
Schwartzman et al. (2005 [++])	Cost-saving	USA	Immigrants	DOPT; Screening only.	Pre-immigration.	Not reported.

Gourevitch et al. (1998 [+]; N=151) explored the cost-savings of providing drug users with DOPT to manage LTBI in a controlled trial. Drug users enrolled in a methadone maintenance clinic in the USA received a choice of either DOPT or self-administered therapy. DOPT consisted of isoniazid 300 mg/day and pyridoxine, 50 mg/day. A nurse directly observed the medication on site at the methadone clinic, alongside the administration of daily methadone doses. This was compared with self-administered therapy; no further information was reported. The study obtained direct medical costs of providing DOPT and prevalence of TB reactivity, other data was gathered from published sources. Net savings included the costs of screening 507 patients for TB for whom there was available data (of these, 184 were eligible for treatment) and the costs of the treatment for the 151 drug users who started treatment. Discount rates were not used but the costs were adjusted to take into account the 1996 US dollar. A five-year time horizon was used.

The study found that the total cost of treatment without DOPT was $24,050.40 which was $159.27 per person treated. The cost of treatment with DOPT was $74,958.40 which was $496.41 per person treated. If isoniazid was 40% effective at preventing active TB, this would have resulted in a net saving of $143,778 ($284 per person screened); at 65% efficacy this amounted to a savings of $285,284 ($563 per person screened); and at 90% efficacy, a savings of $465,217 (£918 per person screened).

The authors noted that the study was limited because it did not explore the cost-savings beyond five years and that the base model did not take into account multi-drug resistance, multiple hospitalisations per case of tuberculosis, outpatient costs of

tuberculosis care, and the cost of treating and preventing secondary infections. Lastly, the model is based on analysis of the population attending a single methadone maintenance treatment programme in the USA and therefore not necessarily generalisable to other settings.

Immigrants

Schwartzman et al. (2005 [++]) examined the cost-savings of providing DOPT to immigrants in Mexico after screening for LTBI before entry in the USA. The study used a hypothetical sample of legal immigrants, undocumented migrants and temporary visitors and compared chest X-ray screening plus DOPT to manage LTBI compared with chest X-ray screening and standard TB control in Mexico. Data came from published sources, and costs to provide DOPT in Mexico were paid for by the US government and derived from the costs of an equivalent expansion project in Ecuador. The study used a 20-year horizon and a 3% discount rate.

The study found that the total direct costs were $1,901 million, which resulted in net savings of $84 million compared with no DOPT. The study also considered the indirect costs incurred, which were considered to be out-of-pocket expenditures by patients and their families and lost wages due to death, disability, or provision of care. This was estimated to be $608 million and DOPT was calculated to result in net savings of $24 million compared with no DOPT. In a sensitivity analysis, the study demonstrated that DOPT would have resulted in net savings even if the US government doubled its initial investment for the programme, or paid for the medication to manage TB for all new and retreated cases in Mexico for the entire 20 years. In addition, if the number of migrants entering the USA, or the prevalence of HIV infection, LTBI or drug resistance was higher than originally estimated, DOPT would have resulted in greater net savings.

The authors noted that there were some limitation in their study due to the uncertainty of the parameters used in the economic model, however, these were tested in sensitivity analyses and DOPT remained cost-saving. Other limitations were that the model did not include secondary transmissions of TB. However, this would have resulted in greater net savings for DOPT.

Evidence statement 9: **Economic evidence for DOPT to manage LTBI.**
ES9.0 **Moderate evidence from one** economic study (Gourevitch et al.,1998 [+]) found that when using the most conservative estimate of isoniazid efficacy (40%), DOPT would have resulted in net savings of $284 per person screened compared with self-administered therapy in **drug users** with LTBI. Some limitations of the study are that it did not take into account multi-drug resistance and was based on a population attending a single methadone maintenance treatment programme in the USA. ES9.1 **Moderate evidence from one** economic study (Schwartzman et al., 2005 [++]) found that the total direct costs of expanding a screening programme in Mexico to include DOPT for LTBI in **immigrants** prior to immigration to the USA was $1,901 million, which resulted in net savings of $84 million compared with the usual TB control

efforts in Mexico. The study conducted several sensitivity analyses to test their assumptions and the programme remained cost-saving.

Applicability
Both studies investigating the economic evidence for DOPT to manage LTBI were conducted in the USA, one in drug users and the other in immigrants. It is not known how applicable these studies are to other hard-to-reach groups and to the UK setting.

Combined interventions

Foreign-born
Kominski et al. (2007 [+]; Combined intervention = 197; Treatment as usual = 195) in a RCT in the USA examined the cost-effectiveness (and effectiveness, reported elsewhere in this report) of combining peer support and incentives in the form of contingency contracting to adolescents with LTBI, of whom 79.3% were foreign-born compared with treatment as usual, which was a standard course of self-administered isoniazid therapy. The study used actual utilisation of services and cost of resource use was obtained from Medicare charges in 1999. The author also estimated some assumptions including QALY values for being healthy, having a positive skin test but incomplete treatment, and for active TB.

The study found that the combined intervention of peer support plus incentives resulted in higher QALYs compared with treatment as usual (0.1962) at a higher cost of $41. This resulted in an incremental cost-effectiveness ration (ICER) of $209 per QALY. In a Monte Carlo microsimulation of 10,000 trials, costs were higher in the peer counselling plus contingency contracting group in 89.75% of the trials, without any additional improvement in QALYs. However, in all trials, the ICER was below the willingness-to-pay threshold of $50,000.

The study was limited because the author used his own judgement for some of the assumptions regarding the QALYs, reducing the validity of the findings. In addition, the study stated that cost-effectiveness analysis would only be conducted for those treatment groups that had statistically significant differences in adherence when compared to usual care. However, peer counselling and contingency contracting was marginally statistically non-significant (p=0.051). This was not acknowledged in the report.

Evidence statement 10: Economic evidence for combined interventions to manage LTBI
ES10.0 **Weak evidence from one** economic study (Kominski et al., 2007 [+]) in the **foreign-born** suggests that peer support and incentives resulted in higher QALYs compared with treatment as usual (0.1962) at a higher cost of $41, resulting in an ICER of $209 per QALY. In a Monte Carlo microsimulation of 10,000 trials the ICER was consistently below the willingness-to-pay threshold of $50,000. The study was limited because the author used his own assumptions about the QALYs and the intervention

did not result in statistically greater adherence to treatment compared with treatment as usual.

Applicability
There was only one study on the cost-effectiveness of combined interventions and it was based in the USA in a population where 80% were foreign-born. The intervention was not specifically designed for this hard-to-reach population and it is not known how these results translate to other hard-to-reach groups and to the UK, particularly the costs of treatment.

5.2 Interventions for managing active TB

5.2.1 Effectiveness review

Directly Observed Therapy (DOT)

Directly Observed Therapy (DOT): any intervention that involves the observation of patients ingesting their prescribed doses for active TB. NICE (2006) currently recommends the use of DOT for active TB in patients at risk for non-adherence to treatment using a thrice-weekly dosing regimen. None of the studies identified for this review used this dosing regimen.

Study id	Study design	Country	Popul-ation	Compar-isons	Frequ-ency	Setting	Professional
Alwood (1994 [-])	Retrospect-ive cohort	USA	Drug users HIV co-infection	DOT; TAU	Twice-weekly for 9 months.	Chest clinic	Nurse
Deruaz and Zellweger (2004 [-])	Retrospective cohort	Switzerland	Mixed hard-to-reach	Full DOT; Partial DOT. DOT onsite; DOT outreach.	Daily for 6 months.	TB clinic or social outreach.	Nurses
Chemtob et al. (2003 [-])	Before-and-after	Israel	Foreign-born	DOT; TAU.	Unclear	TB clinic	Unclear
MacIntyre et al. (2003 [+])	Quasi-RCT	Australia	Foreign-born	DOT (delivered by family member);	Daily doses, 6 months.	Home	Family member

				TAU.			
Rodrigo et al. (2002 [-])	Before-and-after	Spain	Prisoners	DOT; TAU.	Unclear	Prison (could be continued in the community)	Health worker

Drug users

Alwood (1994 [-]; DOT = 48; Treatment as usual = 30) in a retrospective cohort study in the USA, explored the efficacy of DOT to manage active TB in patients with HIV co-infection, 64% of whom were intravenous drug users. This intervention was compared with treatment as usual, which was reported as self-administration of medication that could have been partly supervised if it was given in a supervised setting or a combination of partial supervision and self-administration. The medication regime provided to both treatment and control groups was isoniazid 300 mg, rifampin 600 mg, ethambutol 15 to 25 mg/kg and pyrazinamide 25 mg/kg daily for 3 to 8 weeks, followed by twice-weekly isoniazid 15 mg/kg plus rifampin 600mg for 18 to 36 weeks. The recommended treatment length was 9 months. In the treatment group, patients were observed swallowing their medication by a nurse. No further details were reported.

The results reported in the study were for only those who completed at least 8 weeks of treatment. This limits the study's findings on adherence by removing those who were non-adherent in the first 8 weeks. Despite this initial selection for more adherent participants, the study found that statistically more people completed six months or more of treatment when they received DOT (96%, 44/48) compared with treatment as usual (76%, 22/30; p=0.02). Participants receiving DOT were significantly more likely to be alive at the end of treatment, 85% (41/48) in the DOT group compared with 57% (17/30) in the treatment as usual group, (p=0.01). TB was the cause of death in 10% (5/48) of the cases who received DOT and 37% of the cases (11/30) who received treatment as usual. This difference was statistically significant in favour of DOT (p=0.01).

The study was also limited due to the potential contamination of treatment. Those receiving treatment as usual could have received medication that was supervised, which may have been similar to DOT. This would have underestimated the treatment differences between the comparison groups. The study design was also limited as it was a retrospective cohort study.

Foreign-born

In a quasi-RCT in Australia, MacIntyre et al. (2003 [+]; DOT = 87; Treatment as usual = 86) compared DOT delivered by a family member with treatment as usual. In the study population 81.5% were born outside of Australia. DOT therapy included the medication regimen provided by their physician, but the patients were directly observed taking the medication daily by a family member who recorded every dose taken. The family member was nominated by the patient and received appropriate training in order to

deliver DOT. Treatment as usual consisted of the medication regimen prescribed by the patient's physician and monthly visits to the clinic.

In an intention-to-treat analysis, compliance with treatment, measured by six random urinary isoniazid levels over a six-month period, was not statistically significantly different between those who received DOT administered by a family member (65/87, 74.7%) and those receiving treatment as usual (67/86, 77.9%; RR for non-compliance = 1.04, 95%CI 0.88 to1.23). This analysis included 42% of patients assigned to DOT who did not receive the intervention. The main reason for attrition was that participants could not identify a suitable family member to administer DOT. In a per protocol analysis including only those who received DOT, similar non-significant results were found (RR for non-compliance = 0.96, 95%CI 0.75 to 1.23). There was also no statistically significant difference found for completion of treatment, defined as completing the prescribed course of medication as measured by recorded clinic attendances and collection of prescribed medications. In the DOT group 96.5% (84/87) completed treatment compared with 90.6% (78/86) with treatment as usual (RR for non-completion = 2.7, 95%CI 0.66 to14.2; p = 0.11).

The author of the study noted several limitations, including that it only had a 60% power to detect a difference in adherence between groups. The authors also noted the insensitivity of urinary isoniazid tests to detect non-compliance, as isoniazid can be detected up to 24 hours after taking the last dose and therefore may not detect a missed daily dose. The study was also marked with high attrition rates as described earlier.

Chemtob et al. (2003 [-]; DOT = 671; Treatment as usual = 206) examined a DOT programme implemented between 1999 and 2000, to manage active and latent TB, in a before-and-after study, with treatment as usual in 1990 to 1992, before the implementation of the DOT programme in Israel (no further details were provided on treatment as usual). Although the demographics of the study population were not reported, the study noted that typically 85% of Israel's population with TB were foreign-born, from the former Soviet Union and Ethiopia. However the exact number of foreign-born cases in this study was not reported, making it unclear how generalisable the included population is to hard-to-reach populations. The study did not report what medication was provided to manage TB but noted that DOT was administered on site at a single community-based centre and was conducted in a culturally sensitive manner. It was not clear which professional conducted DOT or the length and frequency of treatment.

The study found that the proportion of patients who received DOT and were cured at end of treatment was 78.5% (255/325) for those treated in 1999 and 76.9% (266/346) for those treated in 2000. Before the implementation of DOT, 26.7% had successful treatment outcomes, which included people who were either cured or who had completed treatment. The difference in successful treatment outcomes before-and-after implementation of DOT was not statistically compared, limiting the conclusions which

can be drawn from this study. It was also unclear why the results were reported separately for DOT in 1999 and 2000. Other limitations include the lack of demographics reported for the sample and that the outcomes were categorised differently in the two time periods, making it difficult to compare the results.

Prisoners

Rodrigo et al. (2002 [-]); N=NR) explored the implementation of DOT (between 1993 and 2000) to manage TB among prisoners in short- and long-term incarceration facilities compared to a historical control group given treatment as usual prior to the implementation of DOT (between 1987 and 1992). The paper suggests that it included both latent and active TB, although this was not clearly reported. Only those outcomes related to smear-positive cases are reported here, the remaining results and further study details are reported in the section on managing LTBI.

The study found that treatment adherence for smear-positive cases increased significantly over time, both before and after DOT was introduced, rising from 95 per 100 in 1993 to 100 per 100 in 2000 for those who received DOT, and from 60 per 100 in 1987 to 76 per 100 in 1992 for those who received treatment as usual. There was no statistically significant difference for smear-positive incidence rates, for both time periods (1993 to 2000; 1987 to 1992).

The study was limited because there was no information on the characteristics of the sample making it difficult to determine the generalisability of the included population and to compare it with other studies..

Mixed hard-to-reach groups

In a retrospective cohort study, Deruaz & Zellweger (2004 [-]; N=54) compared providing a full course of DOT to manage active TB with partial DOT which consisted of only two months of direct observation, among mixed hard-to-reach groups in Switzerland. The selected population included refugees, alcohol or drug users, homeless people and prisoners. Assignment to either full or partial DOT was based on the needs of the patients and was decided by the medical supervisor. Those who were assigned to a full course of DOT were typically refugees, asylum seekers or illegal immigrants; re-treatment drug resistant; or had a history of non-adherence. Those who were assigned to partial DOT were typically considered compliant with stable social conditions. DOT was conducted by a nurse and the medication consisted of daily doses of isoniazid, rifampicin, pyrazinamide and ethambutol for two months and continuation with isoniazid and rifampicin for four months.

The study also compared, regardless of assignment to full or partial DOT, the effectiveness of DOT when it was conducted on site at a TB clinic compared with a social outreach site. For those who received DOT on site, it was conducted at a dispensary unit for TB. Asylum seekers received a bus fare to attend the clinic. For those who received DOT via social outreach, it occurred either in a social care centre,

where needs other than those concerning TB could be addressed, at home, or at any other convenient location for the patient.

The study found that for those assigned to a full course of DOT, 38% (14/36) were cured of active TB (based on bacteriological confirmation) at end of treatment and 50% (18/36) completed treatment compared with partial DOT where 17% (3/18) were cured of active TB and 72% (13/18) completed treatment. There was statistically no significant differences in all successful treatment outcomes (defined as either cured or completed treatment) between those treated with a full course of DOT (89.5%, 32/36) compared with partial DOT (89.5%, 16/18; p=1.0). It was not clear why in full DOT more people were likely to be cured of DOT but were less likely to complete treatment compared with partial DOT where the opposite was found. This may be due to the number of samples tested for bacteriological confirmation.

For those who received treatment on site, 38% (10/27) were cured of active TB at end of treatment and 55% (15/27) completed treatment, compared with DOT conducted by social outreach, 26% (7/27) were cured of active TB and 60% (16/27) completed treatment. There was statistically no significant differences in all successful treatment outcomes when DOT was delivered on site (92.6%, 25/27) compared to when it was delivered via outreach (85.2%, 23/27; p=0.67).

The study was limited because there were systematic differences between groups in how treatment outcomes were collected. When DOT was conducted on site, adherence to treatment was recorded systematically by the nurse, but when it was conducted via social outreach, adherence was not routinely recorded. In order to collect the data, information was provided orally by professionals who conducted DOT via social outreach at least six months after treatment completion. This reduces the validity of the findings as it may have been subject to observer and/or recall bias. The findings were further limited as assignment to groups (full or partial; on site or outreach) was based on factors that may have been associated with treatment outcomes. For example, patients were assigned to full DOT if they were more likely to have problems with adherence. With more people in one group likely to adhere to treatment, this may have underestimated the differences between the groups.

Evidence statement 11: **Effectiveness of DOT to manage active TB.**
ES11.0 **Weak evidence from one** retrospective cohort study (Alwood, 1994 [-]) suggested that significantly more people adhered to more than six months of treatment when they received DOT (96%, 44/48) to manage active TB compared with treatment as usual (76%, 22/30; p=0.02) in a population of people with HIV co-infection of whom 64% were i**ntravenous drug users**. The findings on adherence were limited as the study only reported data on those who had adhered to eight weeks or more of treatment. ES11.1 **Inconsistent evidence from two** studies, one quasi-RCT (MacIntyre et al., 2003 [+]) and one before-and-after study (Chemtob et al., 2003 [-]) means conclusions

are uncertain about the effectiveness of DOT to manage active TB in the **foreign-born**. MacIntyre et al. (2003 [+]) found that there was statistically no significant difference in treatment completion for those who received DOT (administered by a family member; 96.5%) and treatment as usual (90.6%; RR for non-completion = 2.7, 95%CI 0.66 to14.2; p=0.11). However, the study was underpowered to detect a small difference between groups. In contrast, Chemtob et al*. (*2003 [-]) suggest that more people were cured of TB (based on bacteriological confirmation) if they received DOT (78.5% in 1999; 76.9% in 2000) compared with treatment as usual (26.7%). However, this may be because there was more opportunity to obtain sputum from those who received DOT compared with treatment as usual. In addition, the differences were not statistically compared, limiting the conclusions.

ES11.2 **Weak evidence from one** before-and-after study (Rodrigo et al., 2002 [-]) suggests that adherence among **prisoners** who were smear-positive increased significantly over time both before and after DOT was introduced, rising from 95 per 100 in 1993 to 100 per 100 in 2000 for those who received DOT, and from 60 per 100 in 1987 to 76 per 100 in 1992 for those who received treatment as usual. There was also no information reported on the sample characteristics.

ES11.3 **Weak evidence from one** retrospective cohort study (Deruaz & Zellweger, 2004 [-]) in **mixed hard-to-reach groups** suggests that there was statistically no significant differences in successful treatment outcomes if participants received a full course of DOT (89.5%) compared with partial DOT (89.5%) where medication was only observed for the first two-months (p=1.0). There was also no statistically significant difference in successful treatment outcome when DOT was conducted on site (92.6%) or via social outreach (85.2%; p=0.67). The study was limited as there were differences in how outcomes were collected, with greater bias when DOT was conducted via social outreach. In addition, assignment to treatment was based on factors associated with outcome, such that those who were more likely to be non-adherent were assigned to a full course of DOT, reducing the validity of the findings.

Applicability
Four studies investigated the effectiveness of DOT to manage active TB, one in drug users, two in the foreign-born and one in mixed hard-to-reach groups. These studies were conducted in the USA, Australia, Switzerland and Israel. These studies were conducted in a variety of countries and hard-to-reach groups, increasing the applicability of the findings of DOT to manage active TB. However, the effectiveness of DOT across these groups remains unclear, which makes it difficult to generalise beyond the populations reported in these studies.

Legal detention

Legal detention: any intervention that enforces legal sanction/detention to manage TB.

Oscherwitz et al. (1997 [-]), in a retrospective cohort study, compared the effectiveness of managing active TB through the use of legal detention (N=67) compared with not using such sanctions (N=4258) in a sample where 81% were drug or alcohol users in the USA. Legal detention was implemented in the study between 1994 and 1995 for non-adherent patients who were contagious, when participants were released from legal detention but had not necessarily completed treatment; participants were under no obligation to continue medication for TB. This sample was compared with a cohort who were not legally detained in the same time period but had different demographic characteristics (see limitations).

The study found that there was a statistically significant difference in favour of not enforcing legal detention on participants. For those who were legally detained, 20% (20/49; excluding those who died or moved) completed treatment compared with 82% (denominator not known) when they were not legally detained ($p<0.001$). The conclusions drawn from this study are limited because those who were legally detained were statistically more likely to be hard o reach compared to those who were not legally detained (i.e. the former were more likely to be foreign-born, homeless, drug users, or diagnosed with TB in prison; $p<0.001$). Therefore the differences may not be due to the use of legal detention but due to differences in sample characteristics. Assignment to legal detention was also based on non-adherence, therefore, participants in this group may be more likely to be non-adherent regardless of the intervention. In addition, although 81% of the population were drug or alcohol users, the control group only had a small percentage of hard-to-reach characteristics, limiting the generalisability of the findings to the review question.

Evidence statement 12: **Effectiveness of legal detention to manage active TB.**
ES12.0 **Weak evidence from one** retrospective cohort study (Oscherwitz et al., 1997 [-]) with 81% of participants being **drug or alcohol users**, found that there was a statistically significant increase in treatment completion when participants were not detained (82%) compared to participants who were detained (20%; $p<.001$). However, there were statistically significant differences between the groups, such that those who were legally detained were more likely to be hard to reach, and assignment to detention was based on non-adherence, which may have confounded the results. *Applicability* There was one study in the USA on drug or alcohol users. It is not known how these findings transfer to a UK context and to other hard-to-reach groups.

Combined interventions

Study id	Study design	Country	Population	Comparisons*	Frequency	Setting	Professional
Bock et al. (2001 [+])	Before-and-after	USA	Drug users	DOT plus incentives; DOT.	Incentives given at each DOT	Unclear	Unclear

					appointment.		
Juan et al. (2006 [+])	Before-and-after	Spain	Mixed hard-to-reach groups	DOT plus incentives; TAU.	Incentives given at each DOT appointment.	Pharmacy	Pharmacist

Drug users

In a before-and-after study in the USA, Bock et al. (2001 [+]), compared the efficacy of adding incentives to DOT (N=55) to manage active TB with providing DOT alone (N=57) in participants with a history of non-adherence, of whom over 50% of the sample were drug users. Participants were prospectively selected for the combined intervention if they missed more than 25% of their DOT appointments which defined them as being non-adherent. They received a $5 grocery voucher for each DOT appointment attended. This group was compared with a historical cohort of patients who received DOT before implementation of incentives. To have a comparable group of patients, the study only selected historical cohorts who had also missed at least 25% of their DOT appointments. No further details about the treatment and control groups were provided, therefore, it is not clear which professional and in which setting the treatments were provided. In addition it is not known which medication regimen was used for DOT, or the treatment length.

The study found that treatment completion at 32 weeks was significantly higher in the combined incentives plus DOT group 60% (33/55) compared with 19% (10/52) in the historical control group. (OR = 5.73, 95%CI 2.25 to14.84). Similar results were found at 52 weeks; 89% (49/55) completed treatment when incentives were added compared to 52% (27/52) when no incentives were offered (OR 7.29, 95%CI 2.45 to 22.73). The study was limited because details of the treatment conditions were not clear, there was also no detailed information on how treatment completion as defined. The analysis did not include those who transferred to another programme (who may or may have not completed treatment) or those whose records were lost or deemed uncooperative. It was not clear how an uncooperative patient was defined but this may have excluded patients who were least likely to complete treatment. Lastly, the study design was a before-and-after study where there may have been differences in the population or management of active TB other than the addition of incentives.

Mixed hard-to-reach groups

Juan et al. (2006 [+]), in a before-and-after study in Spain, compared the combination of a pharmacy-based DOT programme plus incentives (N=101) with treatment as usual (N=112) among mixed hard-to-reach groups. Patients were defined as hard to reach because they met one or more of the following criteria: alcohol misuse (>280 g/week for men or >168 g/week for women); illicit (injection or non-injection) drug use; immigrant status; homelessness; or previous failure to complete TB treatment (or HIV infection). Patients in the combined intervention were prospectively allocated to treatment between 1999 and 2002. DOT was conducted at the district pharmacy closest to the patient's residence. Delivery of the TB medications along with incentives

was carried out by a trained pharmacist. Combined treatment was compared with a retrospective cohort of patients who received standard, self-administration of treatment for active TB between 1996 and 1998 in the same district as the treatment group with similar hard-to-reach characteristics.

The study found that 75.2% (76/101) of patients who received both pharmacy-based DOT and incentives did not miss more than two consecutive doses compared with 26.7% (30/112) with treatment as usual. The difference in treatment completion was statistically significant in favour of the combined intervention (RR = 3.069, 95% CI 2.133 to4.414; p<0.0001). The study had limitations including statistically significant baseline differences between groups, which may have confounded the results. These differences included more Illicit drug users (p=0.0001) and males (p<.0001) in the historical treatment as usual group, and more immigrants in the combined treatment group (p=0.0006). These baseline differences were not adjusted for in the analysis. In addition, there may have been other differences between groups in the two time points as the study was a before-and-after study design.

Evidence statement 13: **Effectiveness of combined interventions to manage active TB.**
ES13.0 **Moderate evidence from one** before-and-after study (Bock et al., 2001 [+]) found that there was a statistically significant benefit of adding incentives to DOT on treatment completion compared with DOT alone (OR = 5.73, 95%CI 2.25 to14.84) in a population that included over 50% of **drug users**. The study was limited because DOT was compared with a retrospective cohort of patients ES13.1 **Moderate evidence from one** before-and-after study (Juan et al., 2006 [+]) found that there was a statistically significant benefit of adding incentives to DOT on treatment completion compared with self-administered therapy (RR = 3.07, 95% CI 2.13 to4.41; Juan et al., 2006 [+]) in **mixed hard-to-reach groups**. The study was limited because DOT was compared with a retrospective cohort of patients and there were significant differences between the cohorts in the two time periods. *Applicability* Two studies conducted in Spain and the USA investigated the effectiveness of DOT plus incentives to manage active TB in mixed hard-to-reach groups. No study identified was conducted in the UK.

Enhanced case management

Case management: involves an individual health care professional taking responsibility for the co-ordination of care of a patient.

Study id	Study design	Country	Population	Comparisons*	Setting	Professional
Ricks (2008 [++])	RCT	USA	Drug users	Enhanced case management by peers; Limited case management by non-peers.	TB clinic	Peer outreach worker; Health worker and nurse case manager.

Ricks (2008 [++]), in a RCT in the USA, examined the effectiveness of enhanced case management delivered by former drug users (N=48) compared with limited case management (N=46) conducted by health care professionals. Enhanced case management consisted of an Indigenous Leader Outreach Worker who was a former substance user to deliver DOT. The peer outreach workers facilitated patients' attendance at appointments, provided incentives (cash and voucher incentives) and transportation, and advocated for patients with their health care provider at medical appointments. The comparator group consisted of a public health worker who delivered DOT but with limited case management provided by a nurse case manager. The nurses were responsible for all case management services, and for developing referral relationships with social service and health care providers. Patients were also provided with monetary incentives and tokens for transportation were given to patients at risk of non-adherence. No further information was provided on what constituted enhanced or limited case management.

The study found that treatment completion, defined by the physician and based on the percentage of doses taken and the timing (typically defined as 80% of medication at end of treatment), was 85% (41/48) for those who received enhanced case management and 61% (28/46) for those who received limited case management. The probability of completing treatment was statistically greater with enhanced case management compared with limited case management (RR=2.68, 95% CI 1.24 to 5.82; p=0.01). There was also a statistically significant difference found for treatment compliance defined as taking 80% of medication while undergoing treatment. For those in enhanced case management 84% (38/48) complied with treatment compared with 68% (25/46) in limited case management (RR=2.51, 95% CI 1.15 to 5.48, p=0.016). The mean number of missed DOT appointments was not statistically significant (limited case management =7.64; enhanced case management = 4.11; p=0.13). The authors noted that the study was limited due to small sample sizes and high dropout rates, which may have prevented other small but significant changes for being detected.

Evidence statement 14: **Effectiveness of enhanced case management for active TB.**
ES14.0 **Moderate evidence from one** RCT (Ricks, 2008 [++]) found that significantly more **drug users** completed treatment with enhanced case management provided by a former drug user peer compared with limited case management from a health worker (RR=2.68, 95% CI 1.24 to 5.82; p=0.01). The study was limited due to small sample sizes and high dropout rates and a lack of clarity about what constituted enhanced case management. *Applicability* One study conducted in the USA explored enhanced case management conducted by peers of drug misusers to manage active TB. It is not known how these findings translate to a UK setting or for other hard-to-reach groups.

Service model approach/social care support

Service model approach/social care support: any intervention that goes beyond the treatment of TB to also offer, for example, access to other medical and mental health services and social care support. Social care support can include, but is not limited to, social work referrals, food and clothing, and housing and financial support.

Study id	Study design	Country	Population	Comparisons*	Components	Setting	Professional
Diez et al. (1996 [-])	Retrospective cohort	Spain	Homeless	Service model approach /social care support; TAU.	DOT; MDT; Outreach work; Medical services; Social care (pensions, benefits).	Residential facility, community.	MDT

Diez et al. (1996 [-]; Service model approach/social care support = 240; Control = NR), in a retrospective cohort study, compared the TB incidence in a district of Barcelona where a service model approach/social care support was implemented, with incidence in other districts in Barcelona that did implement this programme. The service model approach/social care support was implemented between 1987 and 1992 and included a MDT of nurses and social workers. Nurses conducted home visits and promoted adherence to therapy. Social workers procured health care, arranged pensions and helped to re-establish benefits and co-ordinate the stay of the patients in the residential facility. Active TB was managed using DOT. All participants spent the first 15 days prior to DOT treatment in district hospital to confirm the diagnosis of active TB, to start treatment and to isolate the patient during infectious period. Subsequent treatment took place in a residential facility in the community. The types of services used to manage active TB in the other districts of Barcelona were not reported.

In the district where the service model approach/social care support was implemented, the annual incidence rate of TB among the homeless significantly decreased during the programme implementation (p=0.03) but did not significantly decrease in the other districts of Barcelona (p=0.34). The study had several limitations including the validity of the study findings. It is not known whether the decrease in the incidence of TB was due to the service model approach/social care support programme or due to other factors present in that district of Barcelona. There were also no details about the interventions given to the comparison groups and no demographics reported for the entire sample. Lastly, less than a quarter of the eligible population were included in the programme, reducing the generalisability of the findings.

Evidence statement 15: **Effectiveness of a service model approach/social care support to manage active TB.**
ES15.0 **Weak evidence from one** retrospective cohort design (Diez et al., 1996 [-]) suggests that the annual incidence rate of TB among the **homeless** significantly decreased when a service model approach/social care support was implemented in one district of Barcelona (p=0.03) but did not decrease in other districts not implementing the programme (p=0.34). It is not known whether the decrease in the incidence was due to the service model approach/social care support programme or due to other factors present at the time. *Applicability* One study explored the management of active TB using a service model approach/social care support conducted in Spain in the homeless. It is not known how this service model approach would translate to a UK context, to other hard-to-reach groups, and to the current time period.

5.2.2 Cost-effectiveness review

No studies were identified that explored the cost-effectiveness of managing active TB in hard-to-reach groups.

6.0 Discussion and summary

The primary research questions for this review were:

Which interventions are effective and cost effective at managing TB in people from hard-to-reach groups?
All the studies identified for this review primarily answered this research question and are summarised in the section on key findings.

What are effective case management approaches to identify those who may need support to complete treatment?
No comparative studies were identified for this review that specifically addressed this research question. However, there were three studies that explored the effectiveness of case management to improve adherence to TB treatment (Nyamathi et al., 2008 [++]; Ricks, 2008 [++]; White et al., 2003 [+]). The main selection criteria used in these studies to identify individuals for both case management and the control conditions were:

- No previous treatment:
  - no self-reported history of having already completed LTBI therapy (Nyamathi et al., 2008 [++]);
  - first-time visit to the TB clinic (White et al., 2003 [+]);
- Adult:
  - aged between 18 and 55 years, or over the age of 55 if they had other risk factors for developing active TB, such as intravenous drug use or taking immune suppressing medications;
  - 18 years or more (Ricks, 2008 [++]);
- Member of a hard-to-reach group:
  - homeless (Nyamathi et al., 2008 [++]);
  - used illicit drugs and/or daily use of alcohol in the previous six months (Ricks, 2008[++]);
  - considered high risk for non-adherence because were either homeless, prisoners, drug users, migrants, or those with HIV infection (White et al., 2003 [+]).

However, none of the three studies tested how effective these criteria were to identify those who many need support to complete treatment. The criteria were also relevant for the control condition and not specific to case management. More comparative research is needed in this area.

The secondary research questions for this review were:

What factors impact on the effectiveness of the interventions? Specifically, does the efficacy of the intervention vary by the:

- Theories or conceptual models underpinning the interventions?

The theories which underpinned the interventions were not regularly reported in the studies. This information would have been helpful in understanding the theory behind the interventions and how they might be expected to bring about change and improve adherence in hard-to-reach groups.

- Diversity of the population (in terms of hard-to-reach group, age, or gender)?
  There were several studies that explored the population characteristics that were associated with treatment completion. Regardless of the treatment that the participant received, the main variable that was shown to be predictive of treatment completion was residing in stable housing before receiving treatment for TB in the homeless (Tulsky et al., 2000 [+]; Tulsky et al., 2004 [+]) and in prisoners (White et al., 2002 [+]). Therefore, participants who live on the streets or in a shelter have poorer adherence to treatment for TB and may need additional support to maintain their adherence with treatment.

- Persons/organisations commissioning/delivering the interventions?
  The studies included a range of professionals delivering the interventions, including researchers (for example, Tulsky et al., 2000 [+]), peers from the same hard-to-reach group as the participants (for example, Ricks, 2008 [++]), family members (for example, MacIntyre et al., 2003 [+]) nurses (for example, Chaisson et al., 2001 [+]) and multidisciplinary teams (for example, Diez et al., 1996 [-]). However, only one study directly compared the effectiveness of the intervention by varying the professional (Ricks, 2008 [++]). The study found that the probability of completing treatment was statistically greater when peers delivered enhanced case management compared with limited case management delivered by a health care professional (RR=2.68, 95% CI 1.24 to 5.82; p=0.01). The conclusions which can be drawn from this study are limited because the peer-led intervention also had enhanced case management, therefore, it is not known whether the positive treatment outcomes are due to the professional who delivers the service and/or the intensity of case management. The third quantitative review in this series on service models will explore in more detail the effective components of service delivery, including the type of professional delivering the intervention.

- Way in which the intervention is delivered (for example, one-to-one or group-based)?
  The majority of interventions were individual-based but two studies included both an individual- and group-based treatment (Chaisson et al., 2001 [+]; Nyamathi et al., 2008 [++]).In Nyamathi et al. (2008 [++]) these were a group-based education programme and individual case-management sessions. In Chaisson et al. (2001 [+]) these were individual counselling sessions and group-based, peer-support programme. There was no study that directly assessed the effectiveness of the delivery of the intervention on adherence to treatment.

- Involvement of the target population in the planning, design, or delivery of the

intervention?

There was no study that clearly reported involving the target population in the planning or design of the intervention. Five studies included peers in the delivery of the following interventions: peer support (Chaisson et al., 2001 [+]; Kominski et al., 2007 [+]; McCue & Afifi, 1996 [-]); DOPT (Tulsky et al., 2000 [+]), and case management (Ricks, 2008 [++]). Only one of these studies directly compared the effectiveness of delivering the intervention by a peer compared with a non-peer (Ricks, 2008 [++], reported above). However, the findings are limited because the intervention delivered by the two groups of practitioners was different.

Content of different interventions?

The review excluded studies that directly compared different treatment regimens (for example six months of medication treatment with nine months of treatment), and the differences in the components of the interventions are described in the relevant sections in the study findings.

- Frequency, intensity, and duration of the intervention?

  There was no study that directly compared the frequency, intensity or duration of the intervention on adherence to treatment for non-pharmacological interventions. There were studies that compared the different duration of medication for TB, however, these were outside the scope of the review. The duration of treatment in the included studies typically represented a standard course of medication regimen for TB which varied depending on HIV status from six to 12 months. However, the frequency on treatment varied.

  The frequency of the dosing regimen in directly-observed therapy varied from daily doses (for example, Batki et al., 2002 [+]), to twice-weekly doses (for example, Tulsky et al., 2000 [+]). There was no included study that administered thrice-weekly doses, which is the currently recommended by NICE (2011), limiting the applicability of the research findings to the UK context.

  The frequency of incentives varied from one-off incentives when participants attended their first TB clinic appointment (for example, White et al., 1998 [+]); once at the end of treatment (for example, Kominski et al., 2007 [+]); or at each twice-weekly DOPT appointment attended (for example, Tulsky et al., 2000 [+]). There was moderate evidence for the combined intervention of DOPT plus incentives while only weak evidence for incentives on their own.

- Time and place that the intervention is delivered?

  There were two studies that directly compared the impact of the setting for DOT/DOPT on adherence to treatment, both including people with active TB, in mixed hard-to-reach groups (Deruaz & Zellweger, 2004 [-]) and drug users with LTBI (Malotte et al., 2001 [++]). Both studies found that there was statistically no significant difference if treatment was conducted on site at a health care service or in the community at a site convenient for the participant. The third

quantitative review will explore in more detail the effective components of service delivery including where the intervention was delivered.

How transferable are the findings regarding effectiveness to other hard-to-reach populations, other settings, or other times? (Consider the representativeness of the sample; key characteristics of the sample compared to other hard-to-reach groups; and the appropriateness of the analyses in terms of generalisability.)
Tables 5 and 6 highlight the gaps in the evidence which question the applicability of the findings to some hard-to-reach groups. This is discussed in further detail in the section on the gaps in the evidence.

What are the adverse or unintended effects (e.g., decreased compliance) of TB management interventions on hard-to-reach people, if any?
There were two studies that had unintended or adverse effects on compliance to treatment for TB (Matteeli et al., 2000 [+]; Oscherwitz et al., 1997 [-]). Oscherwitz et al. (1997 [-]) found that there was a statistically greater non-compliance with TB treatment when legal detention was used (20%, 20/49) compared to when it was not used (82%, denominator not known; $p<0.001$). Matteelli et al. (2000 [+] also found that treatment completion rates were lower in immigrants who received twice-weekly 'supervised' treatment where participants were not observed taking the medication, compared with unsupervised twice-weekly isoniazid treatment. Both studies had multiple limitations. Those who were legally detained were selected on the basis of being likely to be non-adherent, and were statistically different from the control group in variables associated with non-adherence (Oscherwitz et al., 1997 [-]). In addition, there was limited information about what constituted supervised treatment and the statistical significance of the difference in results was not assessed (Matteelli et al., 2000 [+]).

Evidence statement 16: **The effectiveness of the intervention by the diversity of the population (in terms of hard-to-reach group, age, or gender).**
ES16.0 **Moderate evidence from three** studies found that the main characteristic that was shown to be predictive of treatment completion was residing in stable housing before receiving treatment for TB in the **homeless** (Tulsky et al., 2000 [+]; Tulsky et al., 2004 [+]) and in **prisoners** (White et al., 2002 [+]). Therefore, participants who live on the streets or in a shelter have poorer adherence to treatment for TB and may need additional support to maintain their adherence with treatment. *Applicability* All three studies were conducted in the USA and it is not known how this evidence translates to the UK context. There may be differences between the two countries in how people residing in the streets or shelters are cared for, which may have a different impact on adherence to treatment.

Evidence statement 17: **The effectiveness of the intervention by person delivering the intervention.**
ES17.0 **Moderate evidence from one** RCT (Ricks, 2008 [++]) found that the probability of completing treatment was statistically greater when peers delivered enhanced case management to **drug users** compared with limited case management delivered by a health care professional (RR=2.68, 95% CI 1.24 to 5.82; p=0.01). The findings are limited because the peer-led intervention also had enhanced case management. It is therefore not known whether the positive treatment outcomes are due to the professional who delivers the service and/or the intensity of case management. *Applicability* The study was conducted in the USA in drug users; it is not known how these findings translate to a UK setting or for other hard-to-reach groups.

Evidence statement 18: **The effectiveness of the intervention by the setting in which it was delivered.**
ES18.0 **Weak evidence from two** studies found that there was statistically no significant difference if DOT/DOPT was conducted on site at a health care service or in the community at a site convenient for people with active TB, in **mixed hard-to-reach groups** (Deruaz & Zellweger, 2004 [-]) and **drug users** with LTBI (Malotte et al., 2001 [++]). Both studies were of varying quality. *Applicability* One study was conducted in the USA and the other in Switzerland in drug users and mixed hard-to-reach groups. It is not known how these findings translate to the UK context and to other hard-to-reach groups.

Evidence statement 19: **The adverse or unintended effects (e.g., decreased compliance) of interventions on the management of TB.**
ES19.0 **Weak evidence from two** studies suggested that legal detention for active TB in **drug or alcohol users** (Oscherwitz et al., 1997 [-]) and 'supervised' treatment for LTBI where participants were not observed taking the medication (Matteeli et al., 2000 [+]) had unintended or adverse effects on compliance compared to when the intervention was not applied. Both studies had multiple limitations including that those who were legally detained (Oscherwitz et al., 1997 [-]) were selected on the basis of being non-adherent; and there was limited information about what constituted supervised treatment (Matteelli et al., 2000 [+]). *Applicability* One study was conducted in the USA and one in Italy in drug or alcohol users and illegal immigrants. It is not known how these findings translate to the UK context and to other hard-to-reach groups.

6.1 Key findings

6.1.1 Interventions for managing latent tuberculosis infection (LTBI)

A summary of the key findings for interventions to manage LTBI is demonstrated in Table 1. The evidence highlighted in green represent interventions that significantly improved adherence to treatment compared with a control group(s). The text reflects the strength of the evidence for each category. These key findings are summarised in further detail below.

Table 1: Summary of evidence for managing LTBI

	Prisoners	Drug users	Foreign-born/immigrants	Homeless	Mixed hard-to-reach
Education	Weak				
Peer support		Weak	Inconsistent		
Supervised treatment			Weak		
DOPT	Weak	Inconsistent		Weak	
Incentives	Moderate		Weak		
Peer support plus incentives			Weak		
Case management plus education				Moderate	
DOPT plus incentives		Moderate		Weak	
Service model approach/social care support		Weak			Weak

Green = statistically significant different in favour of the intervention group; Orange = no difference between groups; Yellow = inconsistent evidence, both differences and no differences; Red = unintended effects; Grey = gaps in the evidence

There was moderate evidence suggesting that case management plus education significantly improved treatment completion in the homeless compared with DOPT (AOR = 3.01, 95% CI 2.15 to 4.20; Nyamathi et al., 2008 [++]).There were statistically significant differences between groups at baseline but these were controlled for in the analyses.

There was moderate evidence to suggest that DOPT plus incentives (44%, 19/43) compared with DOPT alone (7/37, 19%) resulted in significantly greater treatment completion in the homeless (p=0.02; Tulsky et al., 2000 [+]) and in drug users (AOR = 45.5, 95%CI 9.7 to 214.6; p<0.001; Malotte et al., 2001 [++]). However, in one of these

studies, DOPT plus incentives was not more effective than treatment as usual (10/38, 26%; p=0.11; Malotte et al., 2001 [++]).

There was weak evidence suggesting that education provided every two weeks while in prison significantly improved treatment completion for LTBI compared with providing a one-off educational session to all prisoners at the start of treatment (AOR = 2.2; 95% CI 1.04-4.72; White et al., 2002 [+]). However prisoners were less likely to adhere to their first TB appointment in the community when the intervention was delivered outside of an RCT context, compared to when it was delivered as part of the RCT (p=0.002; White et al., 2005 [+]).

There was weak evidence suggesting that peer-support (58/101, 57%) compared with treatment as usual (49/100, 49%) significantly improved treatment completion in intravenous drug users as measured by electronic bottle caps (p<0.001; (Chaisson et al., 2001 [+]). However, there were no significant differences between groups when adherence was measured by self report. The evidence for peer support in the foreign-born is less certain as there was inconsistent evidence from two studies (Kominski et al., 2007 [+]; McCue & Afifi, 1996 [-]).

There was weak evidence to suggest that a service model approach/social care support compared with treatment as usual resulted in greater treatment completion in intravenous drug users (59.5% vs. 13.1%; p<0.0001; Batki et al., 2002 [+]) and mixed hard-to-reach groups (70.3%, 102/145 vs. 47.9%, 447/934; White et al., 2003 [+]). However, in drug users, the intervention was not statistically more effective compared with DOPT plus methadone maintenance without the additional social care support (p values not reported; Batki et al., 2002 [+]).

The remaining interventions (DOPT and incentives) either had inconsistent evidence or did not demonstrate any statistically significant difference in adherence to treatment for LTBI compared with the control group(s). One study demonstrated a statistically significant increase in treatment completion in drug users with DOPT compared with treatment as usual (Batki et al., 2002 [+]). However, there was not statistically significant difference in other studies on drug users (Chaisson et al., 2001 [+]) and in the homeless (Tulsky et al., 2000 [+]). There was also limited conclusions that could be drawn on the effectiveness of DOPT in prisoners (Rodrigo et al., 2002 [-]).

One-off incentives provided to prisoners to attend their first TB appointment in the community produced no statistically significant difference in adherence compared with treatment as usual when no incentives were provided (White et al., 1998 [+]; White et al., 2002 [+]). This was also found in the foreign-born when one-off incentives were provided at the end of treatment (Kominski et al., 2007 [+]). However, there is some inconsistent evidence to support the use of combined DOPT plus incentives in the homeless and drug users (as described above).

There was limited data on the cost-effectiveness of managing LTBI in hard-to-reach groups. For self-administered therapy in prisoners there was weak evidence that suggests that treating LTBI was cost-saving ($9,227) compared with not treating LTBI (Bandyopadhyay et al., 2002 [-]).There was moderate evidence to suggest that applying DOPT to the usual TB control efforts in Mexico before immigration to the USA resulted in cost-savings compared with treatment as usual, which included screening and self-administered treatment prior to immigration (Schwartzman et al., 2005 [++]). Moderate evidence was also found for the cost-savings ($284 per person screened) of managing LTBI with DOPT in drug users (Gourevitch et al.,1998 [+]). There was some evidence on the cost-effectiveness of providing a combined intervention of peer-support with incentives ($209 per QALY), however, the intervention did not result in greater adherence to treatment compared with treatment as usual (Kominski et al., 2007 [+]).

Overall, the evidence for the management of LTBI in hard-to-reach groups is weak with the exception of the evidence for case management plus education in the homeless (Nyamathi et al., 2008 [++]) and DOPT plus incentives in drug users (Malotte et al., 2001 [++]). There is also some moderate evidence on the cost-savings of self-administered therapy in prisoners (Bandyopadhyay et al., 2002 [-]) and DOPT in immigrants (Schwartzman et al., 2005 [++]) and drug users (Gourevitch et al., 1998 [+]). The applicability of the research is also limited as none of the studies was conducted in the UK.

6.1.2 Interventions for managing active TB

There was a smaller evidence base for the management of active TB in hard-to-reach groups as demonstrated in Table 2. The key findings for this evidence are summarised below.

Table 2: Summary of interventions for managing active TB

	Prisoners	Drug users	Foreign-born/immigrants	Homeless	Mixed hard-to-reach
DOT	Weak	Weak	Inconsistent		Weak
Legal detention		Weak			
Enhanced case management		Moderate			
DOPT plus incentives		Moderate			Moderate
Service model approach/social care support				Weak	

Green = statistically significant different in favour of the intervention group; Orange = no difference between groups; Yellow = inconsistent evidence, both differences and no differences; Red = unintended effects; Grey = gaps in the evidence

With the exception of legal detention, all the interventions demonstrated some evidence of improved adherence to treatment compared with a control group(s).

There was moderate evidence that enhanced case management delivered by a peer resulted in significantly greater treatment completion compared with limited case management delivered by a health care professional (RR=2.68, 95% CI 1.24 to 5.82; p=0.01; Ricks, 2008 [++]). However there was limited detail on what constituted enhanced case management, making it difficult to know how the findings of the study might apply to other settings.

There was moderate evidence that DOT plus incentives resulted in statistically greater treatment completion compared with self-administered therapy in mixed hard-to-reach groups (RR = 3.07, 95% CI 2.13 to 4.41; Juan et al., 2006 [+]) and compared with DOT alone in drug users (OR = 5.73, 95%CI 2.25 to14.84; Bock et al., 2001 [+]).

There was weak evidence that DOT compared with treatment as usual resulted in greater adherence to treatment in intravenous drug users (Alwood, 1994 [-]) but limited evidence for other hard-to-reach groups. There was inconsistent evidence in the foreign-born, with one study demonstrating higher adherence rates when DOT was delivered by a health care professional (statistical comparisons were not conducted; Chemtob et al*.,* 2003 [-]) but no statistically significant difference when DOT was delivered by a family member (RR for non-completion = 2.7, 95%CI 0.66 to14.2; p=0.11; MacIntyre et al., 2003 [+]).There were also limited conclusions which could be drawn from the evidence for DOT in prisoners (Rodrigo et al., 2002 [-]). Lastly, a final study in mixed hard-to-reach groups found that there was no statistically significant difference when a full course of DOT was delivered compared with a partial course of DOT, and no difference in adherence when the intervention was delivered on site or via outreach services (Deruaz & Zellweger, 2004 [-]). However, the majority of the studies exploring DOT were of low quality [-].

There was also weak evidence (Diez et al., 1996 [-]) that the service model approach/social care support resulted in a statistically significant decrease in the annual incidence rate of TB among the homeless when the intervention was implemented in one district of Barcelona (p=0.03), with no corresponding decrease in other districts, where the programme was not implemented (p=0.34). It is not known whether the decrease in the incidence was due to the service model approach/social care support programme or due to other factors present at the time.

Overall, the evidence for the management of active TB was weak or inconsistent except for the evidence on the effectiveness of case management (Ricks, 2008 [++]) and DOPT plus incentives (Bock et al., 2001 [+]; Juan et al., 2006 [+]). The applicability of the evidence to a UK context is limited as none of the studies were conducted in the UK. In addition, there were no studies identified on the cost-effectiveness of managing active TB.

6.2 Strengths and weaknesses of the review

This review was conducted according to full systematic review standards and in accordance with NICE's methods manual for public health reviews. Searches were highly sensitive and encompassed a wide range of sources, and safeguards to ensure reliability were in place throughout the process of screening, data extraction and quality assessment, and data synthesis.

For the effectiveness review, the criteria regarding study methodology were inclusive. Any study that used either a comparison or control group (randomised or non-randomised), or presented data from before-and-after the intervention, was included. Only studies that were limited to both a single group and a single time point were excluded on the grounds of methodology. This allowed the review to focus on the effectiveness and cost-effectiveness of managing TB in hard-to-reach groups.

The main weakness of the review is the lack of data from studies conducted in the UK. The majority of the studies were from the USA, limiting the applicability of the review to the UK. There was also no strong evidence found for any of the interventions to manage latent or active TB. For evidence statements to be classified as strong there needs to be clear conclusions from multiple high quality studies that are not contradicted by other high quality or moderate quality studies.

6.3 Gaps in the evidence

The main gap in the evidence is that there were no comparative studies conducted in the UK on the management of latent or active TB in hard-to-reach groups, limiting the applicability of the review to a UK setting.

There were also gaps identified for some interventions in the different hard-to-reach groups demonstrated in Tables 5 and 6. For instance, although case management had moderate evidence to support its efficacy in the homeless with LTBI and drug users with active TB, it is not known how this evidence applies to other hard-to-reach groups. Similarly, it is not known how DOPT plus incentives applies to other hard-to-reach groups than drug users and the homeless with LTBI, or drug users and mixed hard-to-reach groups with active TB.

There were few cost-effectiveness studies on interventions to manage LTBI and none on interventions to manage active TB. More high quality studies are needed on the clinical and cost-effectiveness of interventions to manage latent and active TB in hard-to-reach groups in the UK.

6.4 Conclusions

The evidence on the management of latent and active TB is overwhelmingly from the USA with no comparative study identified from the UK; no cost-effectiveness study on the management of active TB; and limited cost-effectiveness studies on LTBI. The review did, however, contain evidence across different hard-to-reach groups. This differed to the first of the quantitative reviews conducted for NICE on the identification of TB among hard-to-reach groups that included comparative studies from the UK, the majority of which were cost-effectiveness studies, however, without a range of literature across different hard-to-reach groups.

The conclusions which can be drawn from this review are limited as the majority of the evidence is weak. However, the strongest evidence supported the use of case management, and DOPT plus incentives for people with LTBI or active TB. There is also some suggestion that it is cost-saving to manage LTBI with self-administered therapy and DOPT.

6.5 Implications identified by the review team

The conclusions drawn from the first qualitative review of barriers and facilitators in the identification and management of TB found that members of hard-to-reach groups frequently report incomplete or inaccurate knowledge about the cause and transmission of TB. However, there was limited evidence found in the quantitative reviews on the use of educational interventions as part of the identification and management of TB. In the management review, there is evidence that suggests educating prisoners in TB improves adherence to treatment (White et al., 2002 [+]). Therefore, in addition to participants expressing a lack of knowledge about TB, there is some evidence to suggest that improving their knowledge can improve outcomes in the management of TB.

The qualitative review also identified many potential barriers to the identification and management of TB, including participants' fear and anxiety towards TB; the stigma associated with the condition; and the language and culture barriers to care, but it is not always evident how interventions to manage TB take into account these concerns.

The quantitative review of the identification of TB found the use of incentives and peer support could improve the coverage and yield of active case-finding in hard-to-reach groups. There was some support for the use of incentives in the management of TB but only in conjunction with providing DOT or DOPT. There was also some evidence in the management review of improved outcomes with the use of peer support for LTBI, however, the evidence-base was weak. The quantitative review on identification also found some cost-effectiveness data on the use of contact tracing to identify TB among household contacts of patients. However, no studies were identified on the management of TB in hard-to-reach contacts..

Service providers should consider the range of research found across the qualitative and quantitative evidence in the identification and management of TB when planning and providing health care to hard-to-reach groups with TB.

7.0 Glossary

Active TB: TB that is symptomatic and may be contagious, typically confirmed by sputum cultures. The management of active TB typically involves multiple drug therapy for six months or 12 months for those who are HIV positive.

Case management: involves an individual health care professional taking responsibility for the co-ordination of care of a patient.

CXR—Chest X-ray

DOPT —Directly Observed Preventive Therapy: any intervention that involves the observation of participants ingesting their prescribed doses for LTBI.

DOT—Directly Observed Therapy: any intervention that involves the observation of patients ingesting their prescribed doses for active TB. NICE (2006) currently recommend the use of DOT for active TB in patients at risk for non-adherence to treatment using a thrice-weekly dosing regimen. None of the studies identified for this review used this dosing regimen.

DOTS—Directly Observed Therapy Short Course

Drug users: individuals who take any illegal recreational drug.

Education intervention: any intervention that includes the sharing of information with patients with the aim of increasing their knowledge of TB.

Foreign-born: people who were born outside the country in which they are currently living. It includes both permanent residents and temporary visitors on a work or student visa.

HTR—Hard-to-reach groups: any group that has difficulty accessing or remaining in services for TB.

ICER—Incremental Cost-Effectiveness Ration

IDU—Intravenous Drug Users: includes drug users who primarily take intravenous illicit drugs.

ILOM—Indigenous Leader Outreach Model

Immigrants: a person who has come into a foreign country to live there permanently, not as a tourist or visitor.

Incentives: any intervention that uses cash or a voucher with a monetary value to encourage desired behaviour in the patient. These can be one-off incentives at the start or end of treatment, or offered at regular intervals throughout the duration of the intervention.

INH—Urinary Isoniazid Therapy

IPT—Isoniazid Preventive Therapy

ITT—Intention to Treat

Legal detention: any intervention that enforces legal sanction/detention to manage TB.

LOCF—Lost Observation Carried Forward

LTBI —Latent Tuberculosis Infection: TB that is asymptomatic, but can convert to active disease over time. Identification based on active or passive screening, usually with TST, QFT-G. Management of LTBI typically involves monotherapy with isoniazid for six months.

MDT—Multi-Disciplinary Team

NA—Not Applicable

NR—Not Report

Peer support: any intervention, individual- or group-based that is led by a member of the same hard-to-reach group as the patient's with the emphasis on providing support to the patient, and may include sharing of information about TB.

Prisoners: people residing in a prison for either a remand period or for a convicted offence. This population also overlaps with other hard-to-reach groups as prisoners are disproportionately derived from hard-to-reach communities, for example, drug users.

PPD—Purified Protein Derivative

QUALYs—Quality-Adjusted Life Years

RCT—Randomised Controlled Trial

RR—Relative Risk

SAT—Self-Administered Therapy

Service model approach/social care support: any intervention that goes beyond the treatment of TB to also offer, for example, access to other medical and mental health services and social care support. Social care support can include, but is not limited to, social work referrals, food and clothing, and housing and financial support.

Supervised treatment: medication for TB is supervised but without observing patients swallowing their medication. Supervised treatment can involve monthly follow-up visits, questioning about pill-taking practices, counselling regarding pill taking, or testing of urinary isoniazid (INH) levels if non-compliance is suspected.

TAU—Treatment as Usual

TST—Tuberculin Skin Test

8.0 References

8.1 Studies included in the review

Studies included in the review (N=29 + 2 linked references)

Alwood, K., Keruly, J., Moore-Rice, K., Stanton, D., L., Chaulk, C., P., & Chaisson, R., E. (1994). Effectiveness of supervised, intermittent therapy for tuberculosis in HIV-infected patients. *Aids*, *8*(8), 1103-1108.

Bandyopadhyay, T., Murray, H., & Metersky, M., L. (2002). Cost-effectiveness of Tuberculosis Prophylaxis After Release From Short-term Correctional Facilities. *Chest*, *121*(6), 1771-1775.

Batki, S., L., Gruber, V., A., Bradley, J., M., Bradley, M., & Delucchi, K. (2002). A controlled trial of methadone treatment combined with directly observed isoniazid for tuberculosis prevention in injection drug users. *Drug and Alcohol Dependence*, *66*(3), 283–293.

Bock, N., N., Sales, R., M., Rogers, T., & DeVoe, B. (2001). A spoonful of sugar...: improving adherence to tuberculosis treatment using financial incentives. *The International Journal of Tuberculosis and Lung Disease*, *5*(1), 96–98.

Chemtob, D., Leventhal, A., Berlowitz, Y., & Weiler-Ravell, D. (2003). The new National Tuberculosis Control Programme in Israel, a country of high immigration. *The International Journal of Tuberculosis and Lung Disease*, *7*(9), 828–836.

Chaisson, R., E., Barnes, G., L., Hackman, J., Watkinson, L., Kimbrough, L., P., N., et al. (2001). A randomized, controlled trial of interventions to improve adherence to isoniazid therapy to prevent tuberculosis in injection drug users. *The American Journal of Medicine*, *110*(8), 610–615.

Dèruaz, J., & Zellweger, J., P. (2004). Directly observed therapy for tuberculosis in a low prevalence region: first experience at the Tuberculosis Dispensary in Lausanne. *Swiss Medical Weekly*, *134*, 552–558.

Diez, E., Clavería, J., Serra, T., Caylą, J., A., Jansą, J., M., Pedro, R., & Villalbi, J., R. (1996). Evalution of a social health intervention among homeless tuberculosis patients. *Tubercle and Lung Disease*, *77*(5), 420–424.

Gourevitch, M., N., Alcabes, P., Wasserman, W., C., & Arno, P., S. (1998). Cost-effectiveness of directly observed chemoprophylaxis of tuberculosis among drug users at high risk for tuberculosis. *The International Journal of Tuberculosis and Lung Disease*, *2*(7), 531–540.

Juan, G., Lloret, T., Perez, C., Lopez, P., Navarro, R., Ramón, M., Cortijo, J., et al. (2006). Directly observed treatment for tuberculosis in pharmacies compared with self-administered therapy in Spain. *The International Journal of Tuberculosis and Lung Disease*, *10*(2), 215–221.

Kominski, G., F., Varon, S., F., Morisky, D., E., Malotte, C., K., Ebin, V., J., Coly, A., & Chiao, C. (2007). Costs and cost-effectiveness of adolescent compliance with treatment for latent tuberculosis infection: results from a randomized trial. *Journal of Adolescent Health*, *40*(1), 61-68.

MacIntyre, C., R., Goebel, K., Brown, G., V., Skull, S., Starr, M., & Fullinfaw, R., O. (2003). A randomised controlled clinical trial of the efficacy of family-based direct observation of anti-tuberculosis treatment in an urban, developed-country setting. *The International Journal of Tuberculosis and Lung Disease*, *7*(9), 848–854.

Malotte, C., K., Hollingshead, J., R., & Larro, M. (2001). Incentives vs outreach workers for latent tuberculosis treatment in drug users. *American Journal of Preventive Medicine*, *20*(2), 103–107.

Matteelli, A., Casalini, C., Raviglione, M., C., El-Hamad, I., Scolari, C., Bombana, E., Bugiani, M., et al. (2000). Supervised preventive therapy for latent tuberculosis infection in illegal immigrants in Italy. *American Journal of Respiratory and Critical Care Medicine*, *162*(5), 1653.

McCue, M., & Afifi, L., A. (1996). Using peer helpers for tuberculosis prevention. *Journal of American College Health*, *44*(4), 173.

Nyamathi, A., Nahid, P., Berg, J., Burrage, J., Christiani, A., Aqtash, S., Morisky, D., et al. (2008). Efficacy of nurse case-managed intervention for latent tuberculosis among homeless subsamples. *Nursing Research*, *57*(1), 33-39.

Nyamathi, A., Stein, J., A., Schumann, A., & Tyler, D. (2007). Latent variable assessment of outcomes in a nurse-managed intervention to increase latent tuberculosis treatment completion in homeless adults. *Health Psychology*, *26*(1), 68–76.

Nyamathi, A., M., Christiani, A., Nahid, P., Gregerson, P., & Leake, B. (2006). A randomized controlled trial of two treatment programs for homeless adults with latent tuberculosis infection. *The International Journal of Tuberculosis and Lung Disease*, *10*(7), 775–782.

Oscherwitz, T., Tulsky, J., P., Roger, S., Sciortino, S., Alpers, A., Royce, S., & Lo, B. (1997). Detention of persistently nonadherent patients with tuberculosis. *The Journal of the American Medical Association*, *278*(10), 843.

Ricks, P., M. (2008). Tuberculosis control among substance users: The indigenous leadership outreach model vs. standard care (PhD Thesis). Chicago, Illinois: University of Illinois at Chicago.

Rodrigo, T., Caylà, J., A., Garcia, O., P., Brugal, M., T., Jansà, J., M., Guerrero, R., Marco, A., et al. (2002). Effectiveness of tuberculosis control programmes in prisons, Barcelona 1987-2000. *The International Journal of Tuberculosis and Lung Disease*, *6*(12), 1091–1097.

Schwartzman, K., Oxlade, O., Barr, R., G., Grimard, F., Acosta, I., Baez, J., Ferreira, E., et al. (2005). Domestic Returns from Investment in the Control of Tuberculosis in Other Countries. *New England Journal of Medicine*, *353*(10), 1008-1020.

Tulsky, J., P., Pilote, L., Hahn, J., A., Zolopa, A., J., Burke, M., Chesney, M., & Moss, A., R. (2000). Adherence to isoniazid prophylaxis in the homeless: a randomized controlled trial. *Archives of Internal Medicine*, *160*(5), 697-702.

Tulsky, J., P., Hahn, J., A., Long, H., L., Chambers, D., B., Robertson, M., J., Chesney, M., A., & Moss, A., R. (2004). Can the poor adhere? Incentives for adherence to TB prevention in homeless adults. *The International Journal of Tuberculosis and Lung Disease*, *8*(1), 83–91.

White, M., C., Tulsky, J., P., Goldenson, J., Portillo, C., J., Kawamura, M., & Menendez, E. (2002). Randomized controlled trial of interventions to improve follow-up for latent tuberculosis infection after release from jail. *Archives of Internal Medicine*, *162*(9), 1044-1050.

White, M., C., Gournis, E., Kawamura, M., Menendez, E., & Tulsky, J., P. (2003). Effect of directly observed preventive therapy for latent tuberculosis infection in San Francisco. *The International Journal of Tuberculosis and Lung Disease*, *7*(1), 30–35.

White, M., C., Tulsky, J., P., Menendez, E., Arai, S., Goldenson, J., & Kawamura, L., M. (2005). Improving tuberculosis therapy completion after jail: translation of research to practice. *Health Education Research*, *20*(2), 163-174.

White, M., C., Tulsky, J., P., Reilly, P., McIntosh, H., W., Hoynes, T., M., & Goldenson, J. (1998). A clinical trial of a financial incentive to go to the tuberculosis clinic for isoniazid after release from jail. *The International Journal of Tuberculosis and Lung Disease*, *2*(6), 506–512.

8.2 Other works cited

Ahmed, A., B., Abubaker, I., Delpech, V. et al. (2007) The growing impact of HIV infection on the epidemiology of tuberculosis in England and Wales: 1999–2003. *Thorax 62*(8):672-676.

Antoine, D., Maguire, H., & Story, A. (2006). Epidemiology and response to the growing problem of tuberculosis in London. *Eurosurveillance 11*(3): 25-28.

Delpech, V., Antoine, D., Forde, J., et al. (2004). HIV and Tuberculosis (TB) co-infections in the United Kingdom (UK): Quantifying the problem. Paper

presented at the 15th International AIDS Conference, Bangkok, 11-16 July 2004.

Department of Health (2007) *Tuberculosis prevention and treatment: a toolkit for planning, commissioning and delivering high quality services in England*. London: Department of Health.

French, C., E., Antoine, D., Gelb, D., et al. (2007). Tuberculosis in non-UK-born persons, England and Wales, 2001-2003. *International Journal of Tuberculosis and Lung Diseases 11*(5): 577-584.

Fujiwara, P., I. (2000). Tide pools: What will be left after the tide has turned? *International Journal of Tuberculosis and Lung Disease 4*(12 suppl. 2): S111-S116.

Grange, J., Story, A. & Zulma, A. (2001). Tuberculosis in disadvantaged groups. *Current Opinion in Pulmonary Medicine 7*(3):160-164.

Health Protection Agency (2007). *Mobile targeted digital radiography in the control of tuberculosis amongst hard to reach groups: key findings*. London: Department of Health.

Health Protection Agency (2009) *Tuberculosis in the UK. Annual report on tuberculosis surveillance in the UK*. London: Health Protection Agency.

Health Protection Agency (2010) *Tuberculosis in the UK. Annual report on tuberculosis surveillance in the UK*. London: Health Protection Agency.

Levy, M., H., Reyes, H. & Coninx, R. (2000). Overwhelming consumption in prisons: Human rights and tuberculosis control. *Health and Human Rights 4*(1)*:*166-191.
Jones, T., F., Craig, A., S., Valway, S., E., et al. (1999) Transmission of tuberculosis in a jail. *Annals of Internal Medicine 131*(8): 557-563.

Lönnroth, K., Jaramillo, E., Williams, B., G. et al. (2009) Drivers of tuberculosis epidemics: the role of risk factors and social determinants. *Social Science and Medicine 68*(12): 2240–2246.

Rodwell, T., C., Barnes, R., F., W., Moore, M., et al (2010) HIV–tuberculosis coinfection in Southern California: Evaluating disparities in disease burden. *American Journal of Public Health,* advance online publication.

Story, A., Murad, S. Roberts, W. et al. (2007). Tuberculosis in London: the importance of homelessness, problem drug use and prison. *Thorax 62*(8): 667-671.
Lönnroth, K., Jaramillo, E., Williams, B., G., et al. (2009) Drivers of tuberculosis epidemics: the role of risk factors and social determinants. *Social Science and Medicine 68*(12): 2240–2246.

World Health Organisation (2010). *Tuberculosis and HIV: Factsheet*. www.who.org. Accessed 9th March 2010.

8.3 Studies excluded on full text

Systematic reviews not included in the review, but used for citation chasing (N=5)

Hirsch-Moverman, Y., Daftary, A., Franks, J., & Colson, P., W. (2008). Adherence to treatment for latent tuberculosis infection: systematic review of studies in the US

and Canada [Review article]. *The International Journal of Tuberculosis and Lung Disease*, *12*(11), 1235–1254.

Hwang, S., W., Tolomiczenko, G., Kouyoumdjian, F., G., & Garner, R., E. (2005). Interventions to Improve the Health of the Homeless: A Systematic Review. *American Journal of Preventive Medicine*, *29*(4), 311-311.e75.

Liu, Q., Abba, K., Alejandria, M., M., Balanag, V., M., Berba, R., P., & Lansang, M., A. D. (2008). Reminder systems and late patient tracers in the diagnosis and management of tuberculosis. *Cochrane Database of Systematic Reviews*, (4), CD006594.

Volmink, J., & Garner, P. (2007). Directly observed therapy for treating tuberculosis. *Cochrane Database of Systematic Reviews*, (4), CD003343.

Volmink, J., & Garner, P. (1997). Systematic review of randomised controlled trials of strategies to promote adherence to tuberculosis treatment. *BMJ*, *315*(7120), 1403 -1406.

Studies excluded on full text (N=76)

Andre, M., Ijaz, K., Tillinghast, J., D., Krebs, V., E., Diem, L., A., Metchock, B., Crisp, T., et al. (2007). Transmission network analysis to complement routine tuberculosis contact investigations. *American Journal of Public Health*, *97*(3), 470-477.

Badiaga, S., Raoult, D., & Brouqui, P. (2008). Preventing and controlling emerging and reemerging transmissible diseases in the homeless. *Emerging Infectious Diseases*, *14*(9), 1353-1359.

Barnes, P., F., & Barrows, S., A. (1993). Tuberculosis in the 1990s. *Annals of Internal Medicine*, *119*(5), 400-410.

Burgos, J., L., Kahn, J., G., Strathdee, S., A., Valencia-Mendoza, A., Bautista-Arredondo, S., Laniado-Laborin, R., Castaneda, R., et al. (2009). Targeted screening and treatment for latent tuberculosis infection using QuantiFERON - TB Gold is cost-effective in Mexico. *International Journal of Tuberculosis & Lung Disease*, *13*(8), 962-968.

Burgos, M., Gonzalez, L., C., Paz, E., A., Gournis, E., Kawamura, L., M., Schecter, G., Hopewell, P., C., et al. (2005). Treatment of multidrug-resistant tuberculosis in San Francisco: an outpatient-based approach. *Clinical Infectious Diseases*, *40*(7), 968-975.

Burns, A., D., & Harrison, A., C. (2007). Costs of investigating and managing non-residents with possible tuberculosis: New Zealand experience of an international problem. *Respirology*, *12*(2), 262-266.

Carr, T. (1998). Return of school forms and nurse home visits increased adherence with follow up reading of tuberculosis tests in children [commentary on Cheng TL, Ottolini MC, Baumhaft K, et al.] Strategies to increase adherence with tuberculosis test reading in a high-ri. *Evidence-Based Nursing*, *1*(3), 78.

Casal, M., Vaquero, M., Rinder, H., Tortoli, E., Grosset, J., Rusch-Gerdes, S., Gutierrez, J., et al. (2005). A case-control study for multidrug-resistant

tuberculosis: risk factors in four European countries. *Microbial Drug Resistance-Mechanisms Epidemiology & Disease*, *11*(1), 62-67.

Chang, S., Wheeler, L., S. M., & Farrell, K., P. (2002). Public health impact of targeted tuberculosis screening in public schools. *American Journal of Public Health*, *92*(12), 1942.

Chaulk, C., P., Friedman, M., & Dunning, R. (2000). Modeling the epidemiology and economics of directly observed therapy in Baltimore. *International Journal of Tuberculosis & Lung Disease*, *4*(3), 201-207.

Chaulk, C., P., Moorerice, K., Rizzo, R., & Chaisson, R., E. (1995). 11 Years of Community-Based Directly Observed Therapy for Tuberculosis. *The Journal of the American Medical Association*, *274*(12), 945-951.

Clark, P., M., Karagoz, T., Apikoglu-Rabus, S., & Izzettin, F. V. (2007). Effect of pharmacist-led patient education on adherence to tuberculosis treatment. *American Journal of Health-System Pharmacy*, *64*(5), 497-506.

Clark, R., C., & Mytton, J. (2007). Estimating infectious disease in UK asylum seekers and refugees: a systematic review of prevalence studies. *Journal of Public Health*, *29*(4), 420-428.

Codecasa, L., R., & Besozzi, G. (1998). Acceptance of isoniazid preventive treatment by close contacts of tuberculosis cases: a 692-subject Italian study. *International Journal of Tuberculosis & Lung Disease*, *2*(3), 208-212.

Coker, R., J. (2003). Public health impact of detention of individuals with tuberculosis: systematic literature review. *Public Health*, *117*(4), 281-287.

Davidson, B., L. (1998). A controlled comparison of directly observed therapy vs self-administered therapy for active tuberculosis in the urban United States. *Chest*, (5), 1239-43.

Diel, R., & Niemann, S. (2003). Outcome of tuberculosis treatment in Hamburg: a survey, 1997-2001. *International Journal of Tuberculosis & Lung Disease*, *7*(2), 124-131.

Elk, R., Grabowski, J., Rhoades, H., Spiga, R., Schmitz, J., & Jennings, W. (1993). Compliance with tubercolosis treatment in methadone-maintained patients: Behavioral interventions. *Journal of Substance Abuse Treatment*, *10*(4), 371–382.

Fallab-Stubi, C., L., Zellweger, J., P., Sauty, A., Uldry, C., Iorillo, D., & Burnier, M. (1998). Electronic monitoring of adherence to treatment in the preventive chemotherapy of tuberculosis. *International Journal of Tuberculosis & Lung Disease*, *2*(7), 525-530.

Faustini, A., Hall, A., J., & Perucci, C., A. (2005). Tuberculosis treatment outcomes in Europe: a systematic review. *European Respiratory Journal*, *26*(3), 503-510.

Floyd, K. (2003). Costs and effectiveness: the impact of economic studies on TB control (Brief record). *Tuberculosis*, (1-3), 187-200.

Fraser, A., Paul, M., Attamna, A., & Leibovici, L. (2006). Treatment of latent tuberculosis in persons at risk for multidrug-resistant tuberculosis: systematic review. *International Journal of Tuberculosis & Lung Disease*, *10*(1), 19-23.

Furin, J. (2007). The clinical management of drug-resistant tuberculosis. *Current Opinion in Pulmonary Medicine*, *13*(3), 212-217.

Gonzalez-Ochoa, E., Brooks, J., L., Matthys, F., Caliste, P., Armas, L., & Van der Stuyft, P. (2009). Pulmonary tuberculosis case detection through fortuitous cough screening during home visits. *Tropical Medicine & International Health*, *14*(2), 131-135.

Gourevitch, M., N, Wasserman, W., Panero, M., S., & Selwyn, P., A. (1996). Successful adherence to observed prophylaxis and treatment of tuberculosis among drug users in a methadone program. *Journal of Addictive Diseases*, *15*(1), 93–104.

Gruber, V., A., Delucchi, K., L., Kielstein, A., & Batki, S., L. (2008). A randomized trial of 6-month methadone maintenance with standard or minimal counseling versus 21-day methadone detoxification. *Drug & Alcohol Dependence*, *94*(1-3), 199-206.

Guzman-Montes, G., Y., Ovalles, R., H., & Laniado-Laborin, R. (2009). Indirect patient expenses for antituberculosis treatment in Tijuana, Mexico: is treatment really free?. *Journal of Infection in Developing Countries*, *3*(10), 778-782.

Haynes, R., B., Ackloo, E., Sahota, N., McDonald, H., P., & Yao, X. (2008). Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews*, (2), CD000011.

Horsburgh, C., R., Goldberg, S., Bethel, J., Chen, S., Colson, P., W., Hirsch-Moverman, Y., Hughes, S., et al. (2010). Latent TB infection treatment acceptance and completion in the United States and Canada. *Chest*, *137*(2), 401-409.

Jasmer, R., M., Seaman, C., B., Gonzalez, L., C., Kawamura, L., M., Osmond, D., H., & Daley, C., L. (2004). Tuberculosis treatment outcomes: directly observed therapy compared with self-administered therapy. *American Journal of Respiratory & Critical Care Medicine*, *170*(5), 561-566.

Jasmer, R., M., Snyder, D. ,C., Chin, D., P., Hopewell, P., C., Cuthbert, S., S., Antonio Paz, E., & Daley, C., L. (2000). Twelve months of isoniazid compared with four months of isoniazid and rifampin for persons with radiographic evidence of previous tuberculosis: an outcome and cost-effectiveness analysis. *American Journal of Respiratory & Critical Care Medicine*, *162*(5), 1648-1652.

Khan K., Muennig P., Behta M., Zivin J., G. (2002) Global drug-resistance patterns and the management of latent tuberculosis infection in immigrants to the United States. *N. Engl. J. Med. 5*; 347(23):1850-1859.

Kimerling, M., E., Shakes, C., F., Carlisle, R., Lok, K., H., Benjamin, W., H., & Dunlap, N., E. (1999). Spot sputum screening: evaluation of an intervention in two homeless shelters. *The International Journal of Tuberculosis and Lung Disease*, *3*(7), 613–619.

Kong, P., M., Tapy, J., Calixto, P., Burman, W., J., Reves, R., R., Yang, Z., & Cave, M., D. (2002). Skin-test screening and tuberculosis transmission among the homeless. *Emerging Infectious Diseases*, *8*(11), 1280-1284.

Kranzer, K., Houben, R., M., Glynn, J., R., Bekker, L., G., Wood, R., & Lawn, S., D. (2010). Yield of HIV-associated tuberculosis during intensified case finding in resource-limited settings: a systematic review and meta-analysis. *The Lancet Infectious Diseases*, *10*(2), 93-102.

Lincoln, T., Brannan, G., L., Lynch, V., Conklin, T., J., Clancey, T., Rose, D., N., & Tuthill, R., J. (2004). Completing tuberculosis prophylaxis in jail: targeting treatment and comparison of rifampin/pyrazinamide with isoniazid regimens. The International Journal of Tuberculosis and Lung Disease, 8(3), 306–311.

Long, R., Zielinski, M., Kunimoto, D., & Manfreda, J. (2002). The emergency department is a determinant point of contact of tuberculosis patients prior to diagnosis. *International Journal of Tuberculosis and Lung Disease*, *6*(4), 332-339.

Lorvick, J., Thompson, S., Edlin, B., R., Kral, A., H., Lifson, A., R., & Watters, J., K. (1999). Incentives and accessibility: a pilot study to promote adherence to TB prophylaxis in a high-risk community. *Journal of Urban Health*, *76*(4), 461–467.

Lucas, G., M., Mullen, B., A., McCaul, M., E., Weidle, P., J., Hader, S., & Moore, R., D. (2007). Adherence, drug use, and treatment failure in a methadone-clinic-based program of directly administered antiretroviral therapy. *AIDS Patient Care & Stds*, *21*(8), 564-574.

MacIntyre, C., R., Ansari, M., Z., Carnie, J., & Hart, W., G. (2000). No evidence for multiple-drug prophylaxis for tuberculosis compared with isoniazid alone in Southeast Asian refugees and migrants: completion and compliance are major determinants of effectiveness. *Preventive Medicine*, *30*(5), 425-432.

MacIntyre, C., R., & Plant, A., J. (1998a). Tuberculosis in South-East Asian refugees after resettlement–can prevention be improved by better policy and practice? *Preventive Medicine*, *27*(6), 815-820.

MacIntyre, C., R., & Plant, A., J. (1998b). Preventability of incident cases of tuberculosis in recently exposed contacts. *International Journal of Tuberculosis & Lung Disease*, *2*(1), 56-61.

MacNeil, J., R., Lobato, M., N., & Moore, M. (2005). An unanswered health disparity: tuberculosis among correctional inmates, 1993 through 2003. *American Journal of Public Health*, *95*(10), 1800-1805.

Malmborg, R., Mann, G., Thomson, R., & Squire, S., B. (2006). Can public-private collaboration promote tuberculosis case detection among the poor and vulnerable? *Bulletin of the World Health Organization*, *84*(9), 752-758.

McNabb, S., J., Surdo, A., M., Redmond, A., Cobb, J., Wiley, J., Chakrabarti, S., Duncan, H., et al. (2004). Applying a new conceptual framework to evaluate tuberculosis surveillance and action performance and measure the costs, Hillsborough County, Florida, 2002. *Annals of Epidemiology*, *14*(9), 640-645.

Menendez, E., White, M., C., & Tulsky, J., P. (2001). Locating study subjects: predictors and successful search strategies with inmates released from a US county jail. *Controlled Clinical Trials*, *22*(3), 238-247.

Mohle-Boetani, J., C., Miguelino, V., Dewsnup, D., H., Desmond, E., Horowitz, E., Waterman, S., H., & Bick, J. (2002). Tuberculosis outbreak in a housing unit for human immunodeficiency virus-infected patients in a correctional facility: transmission risk factors and effective outbreak control. *Clinical Infectious Diseases*, *34*(5), 668-676.

Moore, R., D, Chaulk, C., P, Griffiths, R., Cavalcante, S., & Chaisson, R., E. (1996). Cost-effectiveness of directly observed versus self-administered therapy for

tuberculosis. *American Journal of Respiratory and Critical Care Medicine*, *154*(4), 1013.

Morisky, D., E, Malotte, C., K, Choi, P., Davidson, P., Rigler, S., Sugland, B., & Langer, M. (1990). A patient education program to improve adherence rates with antituberculosis drug regimens. *Health Education & Behavior*, *17*(3), 253.

NoY, J., & Popay, J. (2007). Directly observed therapy and tuberculosis: how can a systematic review of qualitative research contribute to improving services? A qualitative meta-synthesis. *Journal of Advanced Nursing*, *57*(3), 227-243.

Orlando, G., Merli, S., Cordier, L., Mazza, F., Casazza, G., Villa, A., M., Codecasa, L., et al. (2010). Interferon-gamma releasing assay versus tuberculin skin testing for latent tuberculosis infection in targeted screening programs for high risk immigrants. *Infection*, *38*(3), 195-204.

Oxlade, O., Schwartzman, K., & Menzies, D. (2007). Interferon-gamma release assays and TB screening in high-income countries: a cost-effectiveness analysis. *The International Journal of Tuberculosis and Lung Disease*, *11*(1), 16–26.

Pillaye, J., & Clarke, A. (2003). An evaluation of completeness of tuberculosis notification in the United Kingdom. *BMC Public Health*, *3*, 31.

Porco, T., C., Lewis, B., Marseille, E., Grinsdale, J., Flood, J., M., & Royce, S., E. (2006). Cost-effectiveness of tuberculosis evaluation and treatment of newly-arrived immigrants. *BMC Public Health*, *6*(1), 157.

Rendleman, N., J. (1999). Mandated tuberculosis screening in a community of homeless people. *American Journal of Preventive Medicine*, *17*(2), 108–113.

Rose, D., N. (2000). Benefits of screening for latent Mycobacterium tuberculosis infection. *Archives of Internal Medicine*, *160*(10), 1513-1521.

Rozovsky-Weinberger, J., Parada, J., P., Phan, L., Droller, D., G., Deloria-Knoll, M., Chmiel, J., S., & Bennett, C., L. (2005). Delays in suspicion and isolation among hospitalized persons with pulmonary tuberculosis at public and private US hospitals during 1996 to 1999. *Chest*, *127*(1), 205-212.

Schumann, A., Nyamathi, A., & Stein, J., A. (2007). HIV risk reduction in a nurse case-managed TB and HIV intervention among homeless adults. *Journal of Health Psychology*, *12*(5), 833-843.

Selwyn, P., A., Budner, N., S., Wasserman, W., C., & Arno, P., S. (1993). Utilization of on-site primary care services by HIV-seropositive and seronegative drug users in a methadone maintenance program. *Public Health Reports*, *108*(4), 492-500.

Smieja, M., J., Marchetti, C., A., Cook, D., J., & Smaill, F., M. (2000). Isoniazid for preventing tuberculosis in non-HIV infected persons. *Cochrane Database of Systematic Reviews*, (2), 001363.

Snyder, D., C., Paz, E., A., Mohle-Boetani, J., C., Fallstad, R., Black, R., L., & Chin, D., P. (1999). Tuberculosis prevention in methadone maintenance clinics. Effectiveness and cost-effectiveness. *American Journal of Respiratory & Critical Care Medicine*, *160*(1), 178-185.

Solsona, J., Cayla, J., A., Nadal, J., Bedia, M., Mata, C., Brau, J., Maldonado, J., et al., others. (2001). Screening for tuberculosis upon admission to shelters and free-meal services. *European Journal of Epidemiology*, *17*(2), 123–128.

Spyridis, P., Tsolia, M., Gelesme, A., Moustaki, M., Spyridis, N., Sinaniotis, C., & Karpathios, T. (2003). The impact of Greece's childhood tuberculosis screening programme on the epidemiological indexes in the greater Athens area. *International Journal of Tuberculosis & Lung Disease*, *7*(3), 248-253.

Sreeramareddy, C., T., Panduru, K., V., Menten, J., & Van den Ende, J. (2009). Time delays in diagnosis of pulmonary tuberculosis: a systematic review of literature. *BMC Infectious Diseases*, *9*, 91.

Stevens, A., Bickler, G., Jarrett, L., & Bateman, N. (1992). The public health management of tuberculosis among the single homeless: is mass miniature X-ray screening effective? *British Medical Journal*, *46*(2), 141.

Storla, D., G., Yimer, S., & Bjune, G., A. (2008). A systematic review of delay in the diagnosis and treatment of tuberculosis. *BMC Public Health*, *8*, 15.

Tanke, E., D., & Leirer, V., O. (1994). Automated telephone reminders in tuberculosis care. *Med Care*, (4), 380-389.

Taylor, Z., Marks, S., M., Rios Burrows, N., M., Weis, S., E., Stricof, R., L., & Miller, B. (2000). Causes and costs of hospitalization of tuberculosis patients in the United States. *International Journal of Tuberculosis & Lung Disease*, *4*(10), 931-939.

Thomas, R., E. (1997). Mantoux (tuberculosis) testing. Evaluation of guidelines for testing in Canadian institutions. *Canadian Family Physician*, *43*, 933-938.

Umbricht-Schneiter, A., Ginn, D., H., Pabst, K., M., & Bigelow, G., E. (1994). Providing medical care to methadone clinic patients: referral vs on-site care. *American Journal of Public Health*, *84*(2), 207-210.

Underwood, B., R., White, V., L., Baker, T., Law, M., & Moore-Gillon, J., C. (2003). Contact tracing and population screening for tuberculosis–who should be assessed? *Journal of Public Health Medicine*, *25*(1), 59-61.

Walker, D, M., R. (2000). An incremental cost-effectiveness analysis of the first, second and third sputum examination in the diagnosis of pulmonary tuberculosis. *International Journal of Tuberculosis and Lung Disease*, *4(3)*, 246-251.

Weis, S., E., Slocum, P., C., Blais, F., X., King, B., Nunn, M., Matney, G., B., Gomez, E., et al. (1994). The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. *New England Journal of Medicine*, *330*(17), 1179-1184.

White, M., C., Duong, T., M., Cruz, E., S., Rodas, A., McCall, C., Menendez, E., Carmody, E., R., et al. (2003). Strategies for effective education in a jail setting: the Tuberculosis Prevention Project. *Health Promotion Practice*, *4*(4), 422-429.

White, M., C., Tulsky, J., P., Menendez, E., Goldenson, J., & Kawamura, L., M. (2005). Incidence of TB in inmates with latent TB infection: 5-year follow-up. *American Journal of Preventive Medicine*, *29*(4), 295-301.

White, M., C., Cuttler, S., & Zhao, X. (2007). Linking released inmates to TB clinic for treatment of latent tuberculosis infection: Why is it so difficult? *Journal of Correctional Health Care*, *13*(3), 206-215.

Winje, B., A., Oftung, F., Korsvold, G., E., Mannsaker, T., Jeppesen, A., S., Harstad, I., Heier, B., T., et al. (2008). Screening for tuberculosis infection among newly

arrived asylum seekers: comparison of QuantiFERONTB Gold with tuberculin skin test. *BMC Infectious Diseases*, *8*, 65.

Studies already included in the previous review:

Bothamley, G., H., Rowan, J., P., Griffiths, C., J., Beeks, M., McDonald, M., Beasley, E., Bosch, C. van den, et al. (2002). Screening for tuberculosis: the port of arrival scheme compared with screening in general practice and the homeless. *Thorax*, *57*(1), 45-49.

Brassard, P., Steensma, C., Cadieux, L., & Lands, L., C. (2006). Evaluation of a school-based tuberculosis screening program and associate investigation targeting recently immigrated children in a low-burden country. *Pediatrics*, *117*(2), e148-156. doi:10.1542/peds.2005-1534

Chaisson, R., E., Keruly, J., C., McAvinue, S., Gallant, J., E., & Moore, R., D. (1996). Effects of an incentive and education program on return rates for PPD test reading in patients with HIV infection. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *11*(5), 455-459.

Citron, K., M., Southern, A., & Dixon, M. (1995). Out of the shadow Detecting and treating tuberculosis amongst single homeless people. London: Crisis.

Dasgupta, K., & Menzies, D. (2005). Cost-effectiveness of tuberculosis control strategies among immigrants and refugees. *European Respiratory Journal*, *25*(6), 1107-1116.

Dasgupta, K., Schwartzman, K., Marchand, R., Tennenbaum, T., N., Brassard, P., & Menzies, D. (2000). Comparison of cost-effectiveness of tuberculosis screening of close contacts and foreign-born populations. *American Journal of Respiratory & Critical Care Medicine*, *162*(6), 2079-2086.

El-Hamad, I., Casalini, C., Matteelli, A., Casari, S., Bugiani, M., Caputo, M., Bombana, E., et al. (2001). Screening for tuberculosis and latent tuberculosis infection among undocumented immigrants at an unspecialised health service unit. *International Journal of Tuberculosis & Lung Disease*, *5*(8), 712-716.

FitzGerald, J., M., Patrick, D., M., Strathdee, S., Rekart, M., Elwood, R., K., Schecter, M. ,T., Montaner, J., et al., Vancouver Injection Drug Use Study Group. (1999). Use of incentives to increase compliance for TB screening in a population of intravenous drug users. *International Journal of Tuberculosis and Lung Disease*, *3*(2), 153-155.

Hardy, A., B., Varma, R., Collyns, T., Moffitt, S., J., Mullarkey, C., & Watson, J., P. (2010). Cost-effectiveness of the NICE guidelines for screening for latent tuberculosis infection: the QuantiFERON-TB Gold IGRA alone is more cost-effective for immigrants from high burden countries. *Thorax*, *65*(2), 178-180.

Jones, T., F., & Schaffner, W. (2001). Miniature chest radiograph screening for tuberculosis in jails: a cost-effectiveness analysis. *American Journal of Respiratory & Critical Care Medicine*, *164*(1), 77-81.

Kumar, D., Citron, K., M., Leese, J., & Watson, J., M. (1995). Tuberculosis among the homeless at a temporary shelter in London: report of a chest X-ray screening programme. *British Medical Journal, 49*(6), 629-633.

Laifer, G., Widmer, A., F., Simcock, M., Bassetti, S., Trampuz, A., Frei, R., Tamm, M., et al. (2007). TB in a low-incidence country: differences between new immigrants, foreign-born residents and native residents. *American Journal of Medicine*, *120*(4), 350-356.

Lavender, M. (1997). Screening immigrants for tuberculosis in Newcastle upon Tyne. *Journal of Public Health*, *19*(3), 320.

Marra, F., Marra, C., A., Sadatsafavi, M., Morán-Mendoza, O., Cook, V., Elwood, R., K., Morshed, M., et al. (2008). Cost-effectiveness of a new interferon-based blood assay, QuantiFERON-TB Gold, in screening tuberculosis contacts. *The International Journal of Tuberculosis and Lung Disease*, *12*(12), 1414-1424.

Malotte, C., K., Hollingshead, J., R., & Rhodes, F. (1999). Monetary versus nonmonetary incentives for TB skin test reading among drug users. *American Journal of Preventive Medicine*, *16*(3), 182-188.

Malotte, C., K., Rhodes, F., & Mais, K., E. (1998). Tuberculosis screening and compliance with return for skin test reading among active drug users. *American Journal of Public Health*, *88*(5), 792-796.

Miller, T., L., Hilsenrath, P., Lykens, K., McNabb, S., J., Moonan, P., K., & Weis, S., E. (2006). Using cost and health impacts to prioritize the targeted testing of tuberculosis in the United States. *Annals of Epidemiology*, *16*(4), 305-312.

Monney, M., & Zellweger, J., P. (2005). Active and passive screening for tuberculosis in Vaud Canton, Switzerland. *Swiss Medical Weekly*, (135), 469–474.

Mor, Z., Lerman, Y., & Leventhal, A. (2008). Pre-immigration screening process and pulmonary tuberculosis among Ethiopian migrants in Israel. *European Respiratory Journal*, *32*(2), 413-418.

Ormerod, L., P. (1998). Is new immigrant screening for tuberculosis still worthwhile?. *Journal of Infection*, *37*(1), 39-40.

Pareek, M., White, P., J., Lalvani, A., & Garnett, G., P. (2009). Modelling the health impact and cost-effectiveness of screening new entrants to the UK for latent tuberculosis infection. *Journal of Infection*, *59*(6), S442.

Perlman, D., C., Gourevitch, M., N., Trinh, C., Salomon, N., Horn, L., & Des Jarlais, D., C. (2001). Cost-effectiveness of tuberculosis screening and observed preventive therapy for active drug injectors at a syringe-exchange program. *Journal of Urban Health*, *78*(3), 550–567.

Perlman, D., C., Friedmann, P., Horn, L., Nugent, A., Schoeb, V., Carey, J., Salomon, N., et al. (2003). Impact of monetary incentives on adherence to referral for screening chest x-rays after syringe exchange-based tuberculin skin testing. *Journal of Urban Health*, *80*(3), 428-437.

Puisis, M., Feinglass, J., Lidow, E., & Mansour, M. (1996). Radiographic screening for tuberculosis in a large urban county jail. *Public Health Reports*, *111*(4), 330-334.

Schwartzman, K., & Menzies, D. (2000). Tuberculosis screening of immigrants to low-prevalence countries. A cost-effectiveness analysis. *American Journal of Respiratory & Critical Care Medicine*, *161*(3), 780-789.

Sciortino, S., Mohle-Boetani, J., Royce, S., E., Will, D., & Chin, D., P. (1999). B notifications and the detection of tuberculosis among foreign-born recent

arrivals in California. *International Journal of Tuberculosis & Lung Disease*, *3*(9), 778-785.

Tan, M., C., Marra, C., A., Sadatsafavi, M., Marra, F., Moran-Mendoza, O., Moadebi, S., Elwood, R., K., et al. (2008). Cost-effectiveness of LTBI treatment for TB contacts in British Columbia. *Value in Health*, *11*(5), 842-852.

Verver, S., Bwire, R., & Borgdorff, M., W. (2001). Screening for pulmonary tuberculosis among immigrants: estimated effect on severity of disease and duration of infectiousness. *International Journal of Tuberculosis & Lung Disease*, *5*(5), 419-425.

Watson, J., M., Abubaker, I., Story, A., Welfare, R., White, P., Garnett, G., Mugford, M., et al., others. (2007). *Mobile targeted digital chest radiography in the control of tuberculosis among hard to reach groups.* London: Health Protection Agency Centre for Infections; Department of Health.

Yates, S., Story, A., & Hayward, A., C. (2009). Screening prisoners for Tuberculosis: What should the UK do? [Poster]. *Thorax*, 64(Suppl 4), A105-105.

9.0 Appendix A: Search strategies and results

9.1 Database searches

The search strategy was written at the Centre for Evidence and Policy, King's College, London, in partnership with Matrix Reviews, Dr Gill Craig of City University, London, and NICE. All results were imported into a bibliographic management tool for screening and management.

The search approach was systematic and exhaustive. One comprehensive strategy was written to locate references relevant to the three quantitative reviews (see section 8.1.1 below). Additional, targeted searches were conducted subsequently in four databases (see section 8.1.2 below).

Table A1. Database searches results

Database	Hits
1. Assia*	658
2. British Nursing Index	48
3. CRD (DARE, HTA, NHS EED)	200
4. CINAHL	2,023
5. Cochrane Library (Reviews)	683
6. Current Contents	3,147
7. ECONLIT	99
8. EMBASE*	10,359
ERIC	58
HMIC	171
Medline*	7,574
Medline In-Process	352
PsycINFO	373
SPP	50
Soc Abs*	431
Social Services Abstracts	102
Web of Science	5,141
Total	*31,469*

*Additional searches were conducted in these databases.

Note: After de-duplication, there were a total of 15,354 unique studies.

9.1.1 Searching of electronic databases: strategy

1. exp Tuberculosis/ or (tuberculosis or tb).ti,ab.

2. ((hard$ adj2 reach) or (hard$ adj2 locate) or (hard$ adj2 find) or (hard$ adj2 treat) or (difficult adj2 locate) or (difficult adj2 engage) or social$ exclu$ or social inequalit$ or (difficult$ adj2 reach) or (difficult$ adj2 find) or (difficult$ adj2 treat)).ti,ab.
3. (geograph$ or transport$ or physical and (barrier$)).ti,ab.
4. (low$ or poor$ or negative and (quality adj2 life)).ti,ab.
5. ((vulnerable or disadvantaged or at risk or high risk or low socioeconomic status or neglect$ or affected or marginal$ or forgotten or non-associative or unengaged or hidden or excluded or transient or inaccessible or underserved or stigma$ or inequitable) and (people or population$ or communit$ or neighbourhood$1 or neighborhood$1 or group$ or area$1 or demograph$ or patient$ or social$)).ti,ab. or Vulnerable populations/
6. poverty area/
7. (refuser$1 or nonuser$1 or non-user$1 or non user$1 or discriminat$ or shame or prejud$ or racism or racial discriminat$).ti,ab.
8. social support/ or *social conditions/ or stigma/ or Social Isolation/ or *quality of life/ or Prejudice/ or Socioeconomic Factors/
9. prisoner$1.ti,ab.
10. (recent$ adj2 release$ adj2 (inmate$ or prison$ or detainee$ or felon$ or offender$ or convict$ or custod$ or detention or incarcerat$ or correctional or jail$ or penitentiar$)).ti,ab.
11. ((prison$ or penal or penitentiar$ or correctional facilit$ or jail$ or detention centre$ or detention center$) and (guard$1 or population or inmate$ or system$ or remand or detainee$ or felon$ or offender$1 or convict$ or abscond$)).ti,ab.
12. (parole or probation).ti,ab.
13. *prisoners/
14. ((custodial adj (care or sentence)) or (incarceration or incarcerated or imprisonment)).ti,ab.
15. (immobile or (disabled and (house bound or home bound)) or (house or home adj3 (bound))).ti,ab. or Homebound Persons/
16. ((hous$ and (quality or damp$ or standard$ or afford$ or condition$ or dilapidat$)) or (emergency or temporary or inadequate or poor$ or overcrowd$ or over-crowd$ or over-subscribed and (hous$ or accommodation or shelter$ or hostel$ or dwelling$))).ti,ab. or housing/ st
17. (rough sleep$ or runaway$1 or (homeless$ or street or destitut$ and (population or person$1 or people or group$ or individual$1 or shelter$ or hostel$ or accommodation$1))).ti,ab. or exp homeless persons/
18. (drug$ or substance and (illegal or misus$ or abuse or intravenous or IV or problem use$ or illicit use$ or addict$ or dependen$ or dependant or delinquency)).ti,ab. or *Substance-Related Disorders/ or Drug users/ or Substance Abuse, Intravenous/
19. ((alcohol$ and (misus$ or abuse or problem$ use$ or problem drink$ or illicit use$ or addict$ or dependen$ or dependant or delinquency)) or alcoholic$1).ti,ab. or *Alcohol-Related Disorders / or Alcoholics/

20. (prostitution or sex work$ or transactional sex$ or prostitute$1).ti,ab. or Prostitution/
21. (poverty or deprivation or financial hardship$).ti,ab.
22. (low-income or low income or low pay or low paid or poor or deprived or debt$ or arrear$ and (people or person$1 or population$1 or communit$ or group$ or social group$ or neighbourhood$1 or neighborhood$1 or famil$)).ti,ab.
23. poverty/
24. (low$ and (social class$)).ti,ab.
25. (traveller$1 or Gypsies or Gypsy or Gipsy or Romany or Roma).ti,ab. or gypsies/
26. (mental$ and (health or ill or illness)).ti,ab. or *mental health/ or Mentally Ill Persons/
27. (health care worker$1 or (health care adj2 service provi$) or (health-care adj2 provi$)).ti,ab.
28. (complex adj2 (patient$ or Need$)).ti,ab.
29. (outreach adj2 worker$1).ti,ab. or Community health aides/
30. (support adj2 worker$1).ti,ab.
31. (case adj2 worker$1).ti,ab.
32. (social adj2 worker$1).ti,ab.
33. social care professional$1.ti,ab.
34. ((social care adj2 service provi$) or (social-care adj2 provi$)).ti,ab.
35. ((language$ or communicat$ and (barrier$ or understand$ or strateg$ or proficien$)) or translat$ or interpret$ or (cultur$ and (competen$))).ti,ab. or Communication Barriers/ or *Language/
36. (immigrant$ or migrant$ or asylum or refugee$ or undocumented or foreign born or UK born or non-UK born or non UK born or (born adj overseas) or (displaced and (people or person$1))).ti,ab. or "Emigration and Immigration"/ or refugees/
37. "Transients and Migrants"/
38. "Emigrants and Immigrants"/
39. or/2-38
40. (Intervention$).ti,ab. or Crisis Intervention/
41. ((early or primary) adj2 Intervention$).ti,ab.
42. (person$ or individual or local$ or community or cultural or structural or supported or indicated or target$ or multi?component or comprehensive or pilot or media and (Intervention$)).ti,ab.
43. ((midstream or mid-stream) and intervention$).ti,ab.
44. (Identify$ or find or finding or locat$ or trac$ or contact$ or discover$ or detect or recruit$ or attract$).ti,ab.
45. (case finding or (active or passive adj3 (case finding))).ti,ab.
46. (program$ or scheme$1 or service$1 or campaign$ or mobili?ation or strateg$ or measure or policy or policies and (tuberculosis or tb)).ti,ab.

47. ((case adj3 management) or case-managed).ti,ab. or Case Management/ or Patient Care Planning/ or Managed Care Programs/ or Patient care management/
48. (case adj3 manag$ adj3 strategy).ti,ab. or continuity of patient care/
49. (treat$ or diagnosis and (management)).ti,ab.
50. (active or passive and (Case adj3 Management)).ti,ab.
51. (risk assess$ or risk profile or risk Indicator or care plan$).ti,ab.
52. ((service and (model$ or deliver$))).ti,ab. or delivery of health care/ or *health services/ or Urban health services/
53. ((primary adj3 healthcare) or (primary adj3 health$ or care)).ti,ab. or exp Primary Health Care/
54. (nurse or ((general or family) adj3 (practice$ or practitioner$ or physicians$ or doctor$))).ti,ab. or Nurses/ or 1/ or Family practice/ or Physicians, Family/
55. ((health or extension or multi-disciplinary or multidisciplinary) and (professional$ or personal$ or practitioner or worker$ or partner$ or promot$ or provider or care team or care provider or unit or casework$ or (case adj2 work$))).ti,ab. or *Health Personnel/ or Nurses' Aides/
56. (social adj2 (work$ or Support$ or Outreach)).ti,ab. or social work/ or Social Support/
57. (lay or allied or link and (professional$ or practitioner$1 or worker$1 or advocate$1 or personnel)).ti,ab. or Allied Health Personnel/
58. (volunteer$ or voluntary or charit$ or third sector).ti,ab. or Voluntary Workers/ or exp Voluntary health agencies/
59. (health adj1 (center$1 or centre$1 or facilit$ or service$ or clinic$1 or hospital$1 or program$1)).ti,ab or Community Health/ or "Catchment Area (Health)"/
60. ((day adj2 (care or hospital$ or patient$)) or workshop$).ti,ab. or day care/
61. (rehab$).ti,ab. or rehabilitation centers/
62. (dedicated or permanent or rapid access or fixed or TB or tuberculosis and (clinic$1 or centre$1 or center$1 or program$)).ti,ab.
63. ((((drug adj2 dependency) or substance abuse or HIV) and (unit$ or clinic$1 or centre$1 or center$1 or program$) and (tuberculosis or tb))).ti,ab. or Substance Abuse Treatment Centers/
64. (pharmac$ or dispensary).ti,ab. or Pharmacies/ or Community Pharmacy Services/
65. (communit$ or (support$ adj2 communit$)).ti,ab. or *Community Health Services / or *Community Networks / or Community Health Aides/ or *Community-Institutional Relations/ or community hospital/ or Community Health Nursing/
66. (directly observed treatment or directly observed therapy or (supervised adj2 treatment) or (coerc$ adj2 (treat$ or therapy))).ti,ab. or Directly Observed Therapy/
67. (ambulatory adj2 care).ti,ab. or ambulatory care/ or Ambulatory Care Facilities/

68. ((mobile or travel$ or transport$ or workplace or work-place or tertiary) and (health adj3 (care or work$ or practitioner$ or professional$ or service$ or center$1 or centre$1 or unit$1 or program$))).ti,ab. or Mobile Health Units/
69. ((mobile or travel$ or transport$ or workplace or work-place or tertiary) and (nurs$ or doctor$)).ti,ab.
70. ((out adj3 hours) or (after adj3 hours) or telephone or telemedicine).ti,ab. or after-hours care/ or Telemedicine/
71. ((walk-in or walkin or walk in) adj2 (center$1 or centre$1 or service or program$ or Clinic$1 or Session or Assesment$1)).ti,ab.
72. ((drop$ adj1 in) adj2 (center$1 or centre$1 or service or program$ or clinic$1 or session or meeting or assesment$1)).ti,ab.
73. (((health or home$ or house$) and (call$ or visit$)) or (home-care or home-based or (support$ adj1 hous$))).ti,ab. or Home Health Aides/ or home care services/ or *House Calls/
74. ((early adj2 discharge) or (recent$ adj2 discharged) or (out adj2 patient)).ti,ab. or patient care/ or outpatient clinics, hospital/ or patient care team/
75. (counselling or counseling or counsellor or counselor or (integrated counselling adj1 testing centre$1) or (integrated counselling adj1 testing center$1) or ICTC).ti,ab. or Counseling/ or Directive Counseling/
76. ((help adj2 group$) or (self adj2 help) or support$ or (peer adj2 peer)).ti,ab. or Self-Help Groups/
77. (collaborat$ or shared or (integrated adj1 care$) or ICP or network$ or co-locat$ or (one adj1 stop)).ti,ab. or "delivery of health care, integrated"/
78. ((health adj2 education) or (skill adj2 mix) or (role adj2 develop$) or leadership or (interdisciplinary or inter-team or Professional or team adj2 (communicate$))).ti,ab. or exp Health Education/ or Interdisciplinary Communication/ or Leadership/
79. (outreach or mobile$ or satellite$ or hub or spoke or rural or urban or street or pavement$1 or sidewalk$1 or corner or shelter or hostel or sanatorium or sanitorium or sanitarium and (tuberculosis or tb)).ti,ab.
80. or/40-79
81. (test$).ti,ab.
82. (examination$1 or assessment$1 or identification or assay$ or detection).ti,ab.
83. (diagnosi$).ti,ab. or *diagnostic tests, routine/
84. ((chest adj2 x?ray) or chest radiograph or MXU).ti,ab. or Mass Chest X-Ray/
85. (screen$ or (new$ adj1 screen$)).ti,ab.
86. (monitor$ or sampling).ti,ab.
87. (target$ or focus$ or community or population or individual$ or person$ or opportunistic or coerc$ or voluntary or initiated and (test$ or diagnosis or screen$ or assay$ or detection)).ti,ab.
88. PIT.ti,ab.
89. provider initiated test$.ti,ab.

90. ((rapid or prompt or quick$ or earl$ or (point adj2 care)) and (test$ or screen$ or diagnosi$ or assay$ or detection)).ti,ab.
91. ((provider or anonymous or accurate or support$ or incentiv$ or counsel$) and (test$ or diagnosis or screen$ or assay$)).ti,ab. or Anonymous Testing/
92. (test$ adj2 (center$1 or centre$1 or unit$1 or setting)).ti,ab.
93. or/81-92
94. (acceptability or acceptable or attend$ or access$ or availab$ or non-attend$ or increas$ or promot$ or opt$ or particip$ or adhere$ or involvement or uptake or take-up or utiliz$ or utilis$ or refus$ or referr$ or self-referr$ or self-report$ or barrier$ or decreas$ or isolation or interven$ or aware$ or opportunit$ or advice or information or incentiv$ or recruit$ or find or finding or compliance or comply or retain or retention or provision or encour$ or usage).ti,ab.
95. (socio sanitary support or reimburs$ or (social adj2 support) or (cash or financial or money or monetary or economic or voucher or credit or drug$1 or methadone or telephone adj2 (benefit$ or support or incentive or assist$ or credit))).ti,ab. or Reimbursement, Incentive/
96. (((lifestyle or behavio?r) adj2 (therapy or modif$ or chang$ or adapt$ or adopt$)) and (tuberculosis or tb)).ti,ab. or social marketing/
97. "Marketing of Health Services"/
98. Attitude to health/
99. Health Services Accessibility/
100. Access to information/
101. Confidentiality/
102. Health education/
103. Health promotion/
104. Patient acceptance of health care/
105. Patient compliance/
106. Motivation/
107. Stigma.ti,ab.
108. prevalence/
109. *Consumer Participation/
110. or/94-109
111. (treat$).ti,ab. or Treatment Outcome/
112. (directly observed treatment or directly observed therapy or (supervised adj2 treatment) or (coerc$ adj2 (treat$ or therapy))).ti,ab. or Directly Observed Therapy/
113. (disease management or (treat$ and (management or control))).ti,ab.
114. ((adherence or compli$ or non-compli$ or default$ or finish$ or Retention or attrition or (drop adj1 out) or disappear$ or abscond$) and (treat$)).ti,ab. or exp Patient Compliance/
115. ((referr$ or self-referr$ or (self adj diagnos$)) and (treat$)).ti,ab.
116. ((suitab$ or eligib$) and (treat$)).ti,ab.
117. ((follow adj1 up) or (discharge)).ti,ab. or Follow-Up Studies/
118. ((positive or negative) and (test)).ti,ab.

119. ((interrupt$ or relapse$ or stop$ or cessation or with?ld$ or avoidance or (lost adj2 follow)) and (treat$)).ti,ab. or *Withholding Treatment/
120. ((medicine$1 or drug or treat$) and (regimen or adherence)).ti,ab.or exp self care/
121. (treat$ and (appointment$ or Schedule$)).ti,ab. or "Appointments and Schedules"/
122. ((care adj2 seeking) and (pathway$)).ti,ab.
123. (case adj3 management or case-managed).ti,ab. or Case Management/ or Patient Care Planning/ or Managed Care Programs/ or Patient care management/
124. (case adj3 manag$ adj3 strategy).ti,ab. or continuity of patient care/
125. ((case or treat$ or diagnosis) and (management)).ti,ab.
126. ((active or passive) and (case adj3 management)).ti,ab.
127. ((risk assessment or care plan$) and (case adj3 management)).ti,ab.
128. or/111-127
129. (1 AND 39 AND (80 OR (93 AND (110 OR 128))))
130. limit 129 to yr="1990 -Current"
131. limit 130 to “English Language”
132. (animal$ or badger$ or Cow$ or Cattle or bovine).ti,ab. or (animals/ not humans/)
133. 131 not 132

9.1.2 Additional searches: strategy

Additional searches were conducted in PubMed, Medline, ASSIA and SocAbs, following discussion on an earlier review with the PDG. These searches specifically targeted four topics:

1. religion/religious groups as a hard-to-reach group;
2. illiteracy and benefits as a poverty term;
3. engaging community leaders/champions/advocates; and
4. patient and professional relationships.

The following clusters were added to the tuberculosis line described above (exp Tuberculosis/ or (tuberculosis or tb).ti,ab.):

For topic 1:

(christian* or church* or chapel* or priest* or vicar* or catholic* or catholicism or protestant* or methodist* or baptist* or Jehovah* or presbyterian* or anglican* or pentecostal*).ti,ab.
(muslim* or islam* or mosque* or imam*).ti,ab.or jews/ or (jew* or judaism* or synagogue*).ti,ab.

exp religion/ or (christian* or church* or chapel* or priest* or vicar* or catholic* or catholicism or protestant* or methodist* or baptist* or Jehovah* or presbyterian* or anglican* or pentecostal*).ti,ab.
jews/ or (jew* or judaism* or synagogue*).ti,ab.
(sikh* or hindu* or buddhis* or temple*).ti,ab.
((religion* or religious* or faith*) and (people* or person* or group* or population or neighbour* or neighbor* or patient* or communit*)).ti,ab.
For topic 2:

(illitera$ or welfare benefit$ or social benefit$)

For topic 3:

(community adj1 leader$ or community adj1 Manag$ or advocat$ or champion$) and (engag$ or involv$)

For topic 4:

professional-family relations/ or professional-patient relations/ or nurse-patient relations/ or physician-patient relations/ or patient relationships

9.2 Website searches

The following websites and databases were searched manually for relevant literature:

Table A2. Website searching details

Website	Web-link	Notes	Included on abstract
Action - Advocacy to Control TB Internationally	www.action.org	-	0
British Infection Association	www.britishinfection.org	-	0
Centers for Disease Control and Prevention	www.cdc.gov/tb	Searched for resources on TB	4
Centers for Disease Control TB-Related News and Journal Items Weekly Update mailing list archives	www.cdcnpin.org/lyris/ui/listservs.aspx	-	0
Centers for Disease Control National Prevention Information Network	www.cdcnpin.org/scripts/tb/index.asp	-	0
NICE, including former Health Development Agency	www.nice.org.uk	Searched for (TB or tuberculosis)	0
NHS Evidence	www.evidence.nhs.uk	Searched for (TB or tuberculosis)	2
Stop TB Partnership	www.stoptb.org	-	0
TB Alert	www.tbalert.org	-	0
UK Coalition to Stop TB	www.stoptbuk.org	-	0
World Health Organization	http://www.who.int/tb/en/	Searched the WHO Library database	0
WHO Global Health Atlas	http://apps.who.int/globalatlas/dataQuery/default.asp	-	0
Health Protection Agency	www.hpa.org.uk	Tuberculosis (publications)	0
British Thoracic Society	www.brit-thoracic.org.uk	Tuberculosis (all fields)	2
Public Health Observatories	www.apho.org.uk/resource/searchoptions.aspx	Tuberculosis (all fields)	0
BL Direct*	Database	tuberculosis (all fields; one week date limit)	0
Community Abstracts via Oxmill*	Database	Tuberculosis (all fields)	3
Google Scholar*	Database	tuberculosis AND (identifying OR managing OR "at risk" OR "hard to reach" OR "service models" OR immigrant OR migrant OR prisoner OR asylum OR refugee OR "drug use" OR homeless)	22
National Research Register archive site*	Database	Tuberculosis (all fields)	1
UK Clinical Research Network*	Database	Tuberculosis	0

*These databases were treated as hand-searching

9.3 Other sources

We requested recommendations from our expert advisor, Dr Gillian Craig, and the PDG Chair, Andrew Hayward. As part of the guidance development process, NICE also carried out a call for evidence (see section 8.4, below).

9.4 Call for evidence

Table A3. Additional studies included after the call for evidence

Full Reference **(E.g. Author, date of publication, full title of paper/report and where a copy can be obtained)**	**Screening code**
Bodenmann, P., Vaucher, P., Wolff, H., Favrat, B., Tribolet, F., Masserey, E., Zellweger, J.,P. (2009). Screening for latent tuberculosis infection among undocumented migrants in Swiss healthcare centres; a descriptive exploratory study. *BMC Infect Dis*, *9(*1):34.	Non-comparative
Carr, R., & Dukes, R. (2009). *Report, findings and recommendations from a consultation with newly arrived people focused on ways to improve uptake of and increase general awareness of Tuberculosis and Tuberculosis screening in Leeds*.	Non-comparative
Peterborough TB Awareness Pilot Programme 2008/09 Report; produced by McGuire C and Pankhania G, Public Health, NHS Peterborough, April 2009.	Non-comparative

9.5 Citation chasing

After full-text screening was completed, the citation lists of included studies and relevant systematic reviews were scanned for relevant titles, which were then screened for inclusion. This yielded four new included studies. Forward citation-chasing was conducted for all included studies using Google Scholar. This yielded 247 references, of which, one reference was included in this review.

10.0 Appendix B. Screening checklist

Table B1. Screening checklist

Q	Question	Hierarchy	Code	Notes
1.	Does the study have a focus on **TB services** of any kind?	YES/ UNCLEAR – go to Q2	NO – exclude **1_EX.TB**	Studies need not focus on TB services exclusively, but must present data relating to TB services (preventing, screening, treating). Abstracts regarding infectious diseases in general, which do not mention TB, should be excluded. Studies on the following should also be excluded: • epidemiological research (prevalence of TB, mapping of spread); • the microbiology of TB; • the pharmacology of specific treatments, without reference to services; • preventive TB vaccine (e.g. BCG); • the effectiveness of different tests for diagnosing active and latent TB; • drug treatment regimens (drugs used, dosage, frequency, and duration); • clinical effectiveness of drug treatment and/or surgery.
2.	Was the study published in **1990 or later**?	YES/ UNCLEAR – go to Q3	NO – exclude **2_EX.DATE**	
3.	Is the study report in **English**?	YES/ UNCLEAR – go to Q4	NO – exclude **3_EX.NON-ENG**	
4.	Was the study conducted in an **OECD country**?	YES/ UNCLEAR – go to Q5	NO – exclude **4_EX.OECD**	OECD countries are taken to include: Australia; Austria; Belgium; Canada; Chile; Czech Republic; Denmark; Finland; France; Germany; Greece; Hungary; Iceland; Ireland; Israel; Italy; Japan; Luxembourg; Mexico; the Netherlands; New Zealand; Norway; Poland; Portugal; South Korea; Slovakia; Slovenia; Spain; Sweden; Switzerland; Turkey; the UK; and the USA.
5.	Does the study include data from any **hard-to-reach group**?	YES/ UNCLEAR – go to Q6	NO – exclude **5_EX.POP**	Hard-to-reach groups at risk of TB: children, young people and adults whose social circumstances or lifestyle, or those of their parents or carers, make it difficult to: • recognise the clinical onset of tuberculosis; • access diagnostic and treatment services; • self-administer treatment (or, in the case of children and young people, have treatment administered by a parent or carer); or • attend regular appointments for clinical follow-up. Hard-to-reach groups include, but are not limited to: prisoners; problem drug users or people with alcohol problems; homeless people or people in temporary accommodation; asylum-seekers, refugees, and recent immigrants; Gypsies/travellers/Romas; and sex workers. Groups such as Aboriginal peoples or migrant populations that are not particularly relevant in the UK

				setting (e.g., Latino/Hispanic samples in the USA) are not considered hard to reach for this review. This criterion should be applied inclusively at abstract stage, i.e. any paper not specifically excluding such groups should be included.
6.	Does the study present any **quantitative empirical data**?	YES/ UNCLEAR – go to Q7	NO – exclude **6_EX.NON-EMP**	Include studies with quantitative empirical data. Exclude think pieces, policy documents, practice guidelines, non systematic reviews, etc.
7.	Does the study discuss an **intervention** relating to one of the following**:** **Identifying** **Managing** **Service models**	YES/ UNCLEAR - go to next section *Note which review using the tick boxes*	NO – exclude **7_EX.TOPIC**	IF INCLUDED, ALWAYS TICK A BOX. Exclude studies about interventions on the prevention of TB for people who do not have TB (latent or active). **Interventions** regarding **raising awareness** of TB or **identifying** people with TB (diagnosis/screening). nclude: • interventions aiming to increase the uptake of diagnostic services, such as advice and information from clinicians or other professionals, or educational interventions to raise awareness of the symptoms of TB or of the availability of diagnostic services; • outreach services targeted at particular groups, such as mobile clinics or diagnosis (e.g., mobile X-ray units) and referral services; • diagnostic completion (that is, that once TB is suspected, the diagnosis is confirmed). Exclude studies of the effectiveness of different tests for diagnosing active and latent TB. **Interventions** regarding **managing** TB, including **case management** and treatment compliance. Include: • interventions aiming to increase the uptake of treatment services, such as advice and information from clinicians or other professionals, or educational interventions to raise awareness of treatment services; • outreach treatment services targeted at particular groups, such as mobile clinics; • interventions aiming to identify people in need of additional support, or to support people to complete TB treatment. This may include, for example: case management approaches led by clinicians, multi-disciplinary teams or specialist caseworkers; educational or psychosocial interventions to promote treatment adherence; interventions with professionals or patients to promote directly-observed therapy (DOT); or interventions to identify people who have commenced treatment in the past, but are not known to have completed the full course of treatment. **Interventions** regarding **service models** and service structures for supporting TB identification and

				management. Include any organisational-level intervention aimed at improving TB diagnosis or treatment among hard-to-reach groups. This may include, for example: • the provision of new services, such as outreach clinics; • changes to service delivery or accessibility to reduce barriers to accessing TB services; • the provision of services in new settings or by different providers; • the adoption of new information or knowledge management schemes to facilitate service delivery; and • professional development and education, or • other interventions to raise clinicians' and other professionals' awareness of TB.
8	Is it a **(cost)-effectiveness study**?	YES/ UNCLEAR – 8_IN.EFF	NO – go to next section	Include if study presents effectiveness or cost-effectiveness data, which comes from one or more of the following study designs: • RCTs, non-randomised controlled trials; • one-group (pre-test – post-test), or two-groups designs (other than RCT or non-RCT); • any economic analysis (cost-benefit, cost-effectiveness, cost-utility analyses, cost evaluation or other cost analyses). If the study does not compare the intervention group with another group or time point, go to Q9. If the study is a systematic review or meta-analysis, go to Q10.
9	Is it **any other** type of quantitative primary research?	YES/ UNCLEAR – 9_IN.OTHER	NO – go to next section	
10	Is the study a **systematic review**?	YES/ UNCLEAR – 0_IN.SR	END	Include if the study is a systematic review or meta-analysis.
Flag	What hard-to-reach population is it?	Tick all boxes that apply		IF INCLUDED, ALWAYS TICK A BOX. • Recent immigrant/asylum-seeker/refugee; • homeless; • drug misuse; • prisoner; • all other (e.g., sex worker, gypsy/traveller/Roma) – please note; • unclear/undefined.

For cases where inclusion is unclear, code as **Q_QUERY** and save to discuss with screening team.

11.0 Appendix C: Evidence tables

Study details	Population and setting	Method of allocation to intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Alwood **Year:** 1994 **Citation:** Alwood, K., Keruly, J., Moore-Rice, K., Stanton, D., L., Chaulk, C., P., & Chaisson, R., E. (1994). Effectiveness of supervised, intermittent therapy for tuberculosis in HIV-infected patients. *Aids*, *8*(8), 1103-1108. **Aim of study:** To evaluate the effectiveness of directly	**Source population/s:** Patients with active TB and HIV co-infection (65% drug users), USA. **Eligible population:** Patients with TB and HIV co-infection in Baltimore, Maryland. **Selected population:** All patients with verified diagnoses of TB and HIV infection between January 1984 and June1992. Cases were found by cross matching records from the Baltimore City Health Department Chest Clinic, the	**Method of allocation:** Non-randomised; treatment regimen was determined by the treating physician and chest clinic staff. **Intervention/s description:** DOT: isoniazid 300 mg, rifampin 600 mg, ethambutol 15-25 mg/kg and pyrazinamide 25 mg/kg daily for 3-8 weeks, followed by twice weekly isoniazid 15 mg/kg and rifampin 600mg for 18-36 weeks. Medication was administered by a nurse who watched the patient swallow the pills. Recommended treatment length was 9 months. **Comparator/control/s description:**	**Primary outcomes:** Length of treatment: dichotomised for those receiving less than 6 months of treatment and those receiving 6 months or more of treatment. Overall survival: those alive at the end of treatment (recommended treatment length was 9 months). **Secondary outcomes:** Variables that predicted survival: Looked at which independent variables predicted survival. **Method of**	**Primary results:** Length of treatment ≥ 6months: DOT = 44/48 (96%); Indirect treatment = 22/30 (76%); p = 0.02. Length of treatment < 6 months: DOT = 2/48 (4%); Indirect treatment = 7/30 (24%); p = 0.01. Overall survival: DOT = 41/48 (85%); Indirect treatment = 17/30 (57%); p =0.01. TB as cause of death: DOT = 5/48 (10%); Indirect treatment = 11/30 (37%); p =0.01. Variables that significantly predicted survival (OR of death): DOT = OR 0.28 (95% CI 0.08-0.96; p = 0.04); Age = OR 1.10 (95% CI 1.01-1.91; p = 0.03)	**Limitations identified by author:** The study was a non-randomised, retrospective study. **Limitations identified by review team:** Control group included several different treatment strategies some of which caused slight contamination of therapy as some patients could have received medication that was supervised, similar to DOT. This would have underestimated the treatment differences between the comparison groups. Only those patients who completed more than 8 weeks of drug treatment were included in the analysis (73%). Dropout rates prior to 8 weeks are not reported for each group. This limits the external and internal validity

observed therapy for TB in patients with HIV co-infection. **Study design:** Retrospective cohort study. **Type of economic analysis:** NA **Economic perspective:** NA **Quality appraisal effectiveness studies:** - **Internal validity: -** **External validity: -** **Quality appraisal economic studies:** NA **Quality score:** **Applicability:**	AIDS registry, and the John Hopkins Hospital AIDS clinic. **Excluded population:** NA **Setting:** Baltimore City Health Department Chest Clinic, Maryland, USA. **Sample characteristics:** <u>Total group (N = 107)*:</u> 78% male; mean age = 35; 91% African American; 88% on Medicaid or no health insurance; 7% homeless; 73% unemployed; 18% prior incarceration; 64% IDU, 48% alcohol use. **Economic analysis data sources:** NA	<u>Indirect therapy</u>: included the same agents in daily doses. Medication was self-administered, partly supervised if given in another supervised setting or a combination of the above. Patients in this group were generally followed in drug treatment programmes, HIV clinics, or other clinical settings. **Sample sizes:** **Total: ***N =107; of which 78 completed more than 8 weeks of treatment and were included in the analysis. **Intervention:** 48/78 **Control:** 30/78 **Baseline comparisons:** No significant differences in gender, or proportion with TB but not AIDS compared to those with AIDS prior to TB diagnosis, or with AIDS and TB.	**analysis:** Chi-square tests; Fisher's exact test, two-tailed t tests; logistic regression. Patients who died before receiving any TB treatment were excluded from the analysis. **Modelling method and assumptions:** NA **Time horizon:** NA	AIDS diagnosis before death = OR 5.03 (95% CI 1.01-24.9; p = 0.05). Note: the study did not specify in which way age and AIDS status interacted with survival. **Secondary results:** NR **Sample selection and attrition details:** 16 patients died prior to receiving any treatment, 10 died during induction and 20 died during the continuation phase. 78/107 (73%) received treatment beyond 8 weeks, and the analysis did not include those who completed less than 8 weeks treatment. Dropout rates prior to 8 weeks for each group are not reported.	of the findings. **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** NR

NA		However, patients in the DOT group were significantly more likely to be African American (96% vs. 80%, p=0.02). No differences in the other ethnicity (White) were reported. **Study sufficiently powered?** NR			

Study details	**Population and setting**	**Method of allocation to intervention/ comparator**	**Outcomes and methods of analysis:**	**Results**	**Notes**
Authors: Bandyopadhyay et al. **Year:** 2002 **Citation:** Bandyopadhyay, T., Murray, H., & Metersky, M., L. (2002). Cost-effectiveness of tuberculosis prophylaxis after release from short-term correctional facilities. *Chest*, *121*(6), 1771-	**Source population/s:** Prisoners with LTBI, US. **Eligible population:** Prisoners referred to the City of Hartford Chest Clinic after release from short-term correctional facilities in Connecticut between January 1993 and July 1997.	**Method of allocation:** NA **Intervention/s description:** <u>Self-administered therapy</u>: prisoners were given a 2-week supply of INH and were asked to follow-up with treatment after release into the community, in a chest clinic. At the clinic, 6 months of self-supervised INH, 300 mg/day, was prescribed for participants without HIV infection and 12	**Primary outcomes:** <u>Total cost of the intervention</u>: during study period, 4 years and 6 months. **Secondary outcomes:** NA **Method of analysis:** NA **Modelling method and assumptions:** The estimated cost and adherence rates were based on a sample of	**Primary results:** <u>Total cost of the intervention</u> = $32,866 <u>Cost saving</u> = $9,227; over 4 years and 6 months based on the assumption that 2.68 cases of active TB were prevented, costingthe health care system $42,093 to treat. **Secondary results:** NA **Sample selection and attrition details:**	**Limitations identified by author:** As all therapy was self-supervised and pill counts and urine tests for isoniazid were not routinely performed, adherence may have been lower than reported. Cost-effectiveness analysis is based on prior published estimates, which may not be applicable to all settings. In this patient population with a high risk of HIV, it is likely that future risk of developing active TB was

1775. **Aim of study:** To review the outcome of individuals referred for continuation of isoniazid preventative therapy from short-term correctional facilities to the City of Hartford Health Department Chest Clinic. The authors assessed adherence to IPT and estimated the cost-effectiveness of the programme. **Study design:** NA **Type of economic analysis:** Cost-saving. **Economic**	**Selected population:** Prisoners eligible and consenting to screening who had a positive TST result indicative of LTBI and started treatment on INH. **Excluded population:** Inmates who were instructed to follow-up at other tuberculosis Clinics, apart from Hartford Chest Clinic. **Setting:** Chest Clinic, Connecticut, US. **Sample characteristics:** **Economic analysis data source:** Published data and clinic records.	months' for those with HIV infection. Patients were seen monthly to assess adherence and tolerance to medication. Limited attempts were made to contact participants if they did not contact the clinic. Attempts included telephoning, sending postcard reminders and, rarely, conducting home visits. **Comparator/control/s description:** No intervention: no further information provided. **Sample sizes:** **Total:** N **=** 168; **Intervention:** N **=** 168; **Control**: NA. **Baseline comparisons:** NA **Study sufficiently powered?** NA	prisoners used in this study. Cost savings were based on the estimated number of cases of TB prevented and the cost of treating these potential cases and their contacts. The number of cases of active TB prevented was calculated assuming an 0.1% reactivation rate per year for untreated patients with an unknown length of time since tuberculosis exposure. Survival age was arbitrarily designated at 75 years. Assumed 85% efficacy of a completed course of IPT in preventing reactivation of TB. Assumed that each case of reactivation	NA	underestimated. Therefore, cost-effectiveness may be higher than reported. The cost of screening and INH in correctional facilities was not included in the analysis. **Limitations identified by review team:** Important and relevant costs are not addressed, such as cost of non-adherence and adverse effects of treatment. Treatment adherence outcomes are based on a single study, with a sample of N=168, and their reliability may be questionable (self-reported), which may limit the validity of the findings. Discount rate and the economic perspective were not reported. The economic analysis did not include a sensitivity analysis. **Evidence gaps and/or recommendations for future research:** NR

perspective: NR **Quality appraisal non-economic studies:** NA **Internal validity:** NA **External validity:** NA **Quality appraisal economic studies:** - **Quality score** **Applicability:** +			of TB would result in a mean of 1.2 further cases of active TB that would require treatment. The cost of treating a case of reactivated TB was based on published sources. **Time horizon:** Total costs based on the period of the study (1993-1997), 4 years and 6 months.		**Source of funding:** NR

Study details	Population and setting	Method of allocation to intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Batki et al. **Year:** 2002 **Citation:** Batki, S., L., Gruber, V., A., Bradley, J., M., Bradley, M., & Delucchi,	**Source population/s:** IDUs with LTBI, USA. **Eligible population:** Heroin-dependent IDUs entering the 21-day methadone detoxification clinic at San Francisco	**Method of allocation:** Random assignment to groups. Allocation concealment with the use of individually sealed envelopes. **Intervention/s description:** Service model approach/social care support: standard	**Primary outcomes:** Treatment completion: defined as 80% or more of doses taken in the 6-month course of INH treatment. For the treatment groups this was measured by DOPT; for routine care this	**Primary results:** Treatment completion: Service model/social care support = 22/37 (59.5%; CI 43.6 - 75.3); DOPT = 27/35 (77.1%; CI 61.3 - 91.0); RC = 5/39 (13.1%; CI 3 - 23.7). Note: 2 cases had been admitted to methadone	**Limitations identified by author:** The lack of a treatment group which provided observed INH administration without methadone makes it difficult to evaluate the relative impact on adherence of either methadone alone or observed INH administration alone. It is therefore not known how

K. (2002). A controlled trial of methadone treatment combined with directly observed isoniazid for tuberculosis prevention in injection drug users. *Drug and alcohol dependence*, *66*(3), 283–293. **Aim of study:** To compare the completion rates for isoniazid (INH) preventive therapy for IDUs randomly assigned to methadone treatment combined with directly observed preventive treatment (DOPT)	General Hospital (SFGH). **Selected population:** From March 1995 to December 1996, those who met the following inclusion criteria were included: 1) latent tuberculosis infection as demonstrated by a positive PPD test (10 mm or greater in duration), a negative chest x-ray, and approval by a tuberculosis clinic physician; 2) a DSM-III-R diagnosis of opioid dependence; 3) age between 21 and 59 years; 4) willing to receive 6 months of INH preventive therapy and methadone treatment. 115 individuals consented to participate, of whom 4 were later	methadone treatment where participants received DOPT in the form of daily observed doses of INH (300 mg) and pyridoxine (50 mg) in addition to daily methadone doses in the 60-90 mg range. Drugs were administered 7 days per week for 6 months, followed by a 6-week tapering of methadone. Participants also received twice-monthly counselling sessions, weekly random observed urine samples, medical services, psychiatric treatment as needed, and social work referrals. DOPT: minimal methadone treatment where participants received the same DOPT + methadone strategy, but without counselling or any other services. **Comparator/control/s description:**	was measured by reviewing patient records which documented the collection of prescriptions. Mean duration of treatment: Mean INH treatment retention (in months) and duration of INH (in weeks) Adverse effects: total number across the groups. **Secondary outcomes:** NR **Method of analysis:** ITT analysis; one way analysis of variance; Pearson chi-square tests; Kruskal-Wallis one-way non-parametric test. **Modelling method and assumptions:** NA	maintenance treatment elsewhere and had received DOPT for INH outside of the study. The two methadone treatment groups had significantly higher treatment completion rates compared to the RC group (Pearson chi-square = 33.1, p<.0001). There was no significant difference between the two methadone groups in the rate of INH completion; p value not reported. Mean duration of treatment: Mean INH treatment retention (in months): Service model/social care support = 5.0 months (CI: 4.5-5.5); MMT= 5.7 months (CI: 5.4-6.0); RC = 1.6 months (CI: 0.9 - 2.25); The two methadone treatment groups stayed significantly longer in treatment compared with routine	much of adherence is attributable to directly observed INH dosing. Also, the study was based on daily INH dose, and completion rates may be different for newer methods of providing TB preventive medications with less frequent dosing or shorter duration requirements. The study also excluded HIV-positive IDUs which limits the generalisability of the study to the source population. **Limitations identified by review team:** Significant differences in baseline characteristics of the three groups limit the study's internal validity. **Evidence gaps and/or recommendations for future research:** A key evidence gap is the effect of DOPT plus methadone maintenance compared with DOPT without methadone maintenance or other incentives such as vouchers

compared with those assigned to routine TB clinic referral without methadone treatment or DOPT. **Study design:** RCT. **Type of economic analysis:** NA **Economic perspective:** NA **Quality appraisal effectiveness studies:** + **Internal validity:** ++ **External validity:** + **Quality appraisal economic studies:** NA **Quality score**	excluded (see attrition details). **Excluded population:** Patients could not participate if they were: 1) pregnant (pregnant patients were immediately admitted to the regular methadone maintenance programme), 2) HIV positive (also immediately admitted to methadone maintenance), or 3) had evidence of active liver disease (e.g. aspartate transaminase (AST) greater than three times the upper limit of the normal range). **Setting:** San Francisco General Hospital, USA. **Sample characteristics:** Average age =	Routine Care (RC): No methadone treatment or DOPT. Participants only received a 6-month course of INH preventive therapy consisting of monthly visits for 30-days' supply of INH. Note: all interventions took part in a TB clinic in the same hospital where participants were given methadone maintenance. **Sample sizes:** **Total:** N = 111 **Intervention:** **DOPT:** N = 35 **Service model approach/social care support**: N = 37 **Control:** N = 39 **Baseline comparisons:** There were significant differences between the three groups on age (p = .047); Addiction Severity Index (ASI) psychiatric composite score (p=0.027); and Beck	**Time horizon:** NA	care (p<0001). Duration of INH (in weeks): RC = not reported; DOPT plus psychosocial intervention = 21.6 (CI: 19.4 - 23.9); DOPT = 24.6 (CI: 23.2 - 25.9]); p =0.1924). Adverse effects: 13/72 (18%) subjects in the two methadone groups experienced adverse effects (raised AST levels) which led to temporary discontinuation of treatment. All 13 were re-challenged with INH following the advice of the tuberculosis clinic physicians. 8/13 were able to resume and continue treatment. **Secondary results:** The study did not find: current diagnosis of alcohol abuse or dependence; the number of days of alcohol use in the past	for goods and services, and compared with DOPT alone. Effects of these interventions should be evaluated using TB preventive medications with different dosing requirements. Also, cost effectiveness of methadone plus DOPT remains to be determined through research designed specifically to measure that outcome. **Source of funding:** National Institute on Drug Abuse.

applicability: NA	40.2-43.0 years; Years of heroin use = 0 (routine care), 14.5-19.1 (treatment groups); Risk of AIDS-related behaviours relating to drug use = 5.3-6.3; Risk of AIDS-related behaviours relating to sex behaviour = 2.1-3.2. **Economic analysis data sources:** NA	Depression Inventory(BDI) scores (p=0.022). For both the ASI psychiatric composite and the BDI, scores were lowest in the DOPT group and highest in RC. Age was lowest in DOPT plus psychosocial intervention and highest in RC. **Study sufficiently powered?** NR		30 days; current cocaine abuse or dependence; and homelessness to be statistically significantly related to treatment completion. **Sample selection and attrition details:** Of the 115 individuals who were eligible and who consented to participate in the study, 4 subjects were excluded prior to completion of the baseline assessments and before treatment was started (1 was found to have past history of INH intolerance, 2 were judged to have active TB, and 1 dropped out).	

Study details	Population and setting	Method of allocation to intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Bock et al. **Year:** 2001	**Source population/s:** Non-adherent group (over 50% drug	**Method of allocation:** Patients assigned to incentive treatment prospectively between	**Primary outcomes:** Treatment completion: at 32 and 52 weeks. No	**Primary results:** Treatment completion at 32 weeks: Incentive DOT	**Limitations identified by author:** The incentive programme was compared with a

Citation: **Aim of study:** To evaluate whether incentives increase adherence to DOT for TB in non-adherent patients. **Study design:** Before and after. **Type of economic analysis:** NA **Economic perspective:** NA **Quality appraisal effectiveness studies:** + **Internal validity:** ++ **External validity:** + **Quality**	users) with active TB, USA. **Eligible population:** Patients defined as being non-adherent to TB treatment in Fulton County, Georgia, USA. **Selected population:** Patients who missed at least 25% of DOT appointments, between 1 November 1996 and 31 October 1997. **Excluded population:** NR **Setting:** TB programme, Fulton County, Georgia. **Sample characteristics:** No significant differences between groups in: Median age = 36-38 years;	November 1996 and October 1997. Patients assigned to the control group were a historical cohort of patients who met the same inclusion criteria as the treatment group but did not receive the incentive programme, from April 1995 through to March 1996. **Intervention/s description:** <u>Incentive programme</u>**:** patients were given a coupon redeemable for $5 at a regional chain of grocery stores at each DOT appointment attended. If the patient was a child then the parent or guardian who was responsible for bringing the child to the DOT appointment was given a voucher. No further details reported. **Comparator/control/s description:** <u>Usual care:</u> historical cohort of patients who would have been	further details provided on how completion was defined. The length of treatment not reported. **Secondary outcomes:** NR **Method of analysis:** Odds ratios; Cornfield 95% confidence intervals p-value. Patients who died during treatment, transferred to another programme prior to completing treatment, or whose records were closed as lost or were deemed uncooperative were excluded from the analysis. **Modelling method and assumptions:** NA **Time horizon:** NA	programme = 33/55 (60%); Usual care = 10/52 (19%); OR = 5.73 (95%CI 2.25–14.84) (p-value not reported). <u>Treatment completion at 52 weeks</u>: Incentive DOT programme = 49/55 (89%); Usual care = 27/52 (52%); OR 7.29 (95%CI 2.45–22.73) (p-value not reported). Patients in the incentive group who had not completed treatment by 32 weeks (16/22, 72%) were more likely to have completed treatment by 52 weeks compared with patients in usual care (17/42, (40%); OR = 3.92 (95%CI 1.13–14.15, p<0.02). **Secondary results:** NR **Sample selection and attrition details:**	historical cohort. **Limitations identified by review team:** It was unclear what treatment the usual care group received, therefore it is not known whether the control group also received DOT. The paper suggests that this was the case although it was not clearly stated. The analysis did not include those who transferred to another programme (who may or may have not completed treatment) or those whose records were lost or deemed uncooperative. It was not clear how an uncooperative patient was defined. All patients who started treatment should have been included in the analysis in an ITT to have a more conservative estimate of treatment effects. **Evidence gaps and/or recommendations for future research:** NR **Source of funding:**

appraisal economic studies: NA **Quality score applicability:** NA	African American = 81%-84%; Male = 53%-63%; HIV-positive = 33%-35%; Homeless = 12.5-25%); Drug abuse = 51%-61%. **Economic analysis data sources:** NA	eligible for the programme but did not receive incentives. No further information was provided. **Sample sizes:** **Total:** N = 107 **Intervention:** N = 55 **Control:** N = 57 **Baseline comparisons:** There were significant differences between groups for those who were mono-resistant to INH; 13% in the control group and 4% in intervention group (p<0.003). No significant difference in any other baseline comparisons. **Study sufficiently powered?** NR		194 patients began treatment from April 1995 through to March 1996, 52 (28%) of whom met the eligibility criteria and were included as the historical cohort. 185 patients began treatment in November 1996 through to October 1997, 55 (30%) of whom were enrolled in the incentive programme.	American Lung Association, Georgia Chapter.

Study details	**Population and setting**	**Method of allocation to intervention/ comparator**	**Outcomes and methods of analysis:**	**Results**	**Notes**
Authors: Chaisson et al. **Year:** 2001	**Source population/s:** IDUs with LTBI, USA.	**Method of allocation:** Randomisation was performed by computer algorithm. Allocation	**Primary outcomes:** <u>Treatment completion</u>: defined as taking 80% of medication and	**Primary results:** <u>Treatment completion:</u> DOPT = 72/99 (80%); Peer support = 79/101 (78%);	**Limitations identified by author:** NR **Limitations identified by**

Citation: Chaisson, R., E., Barnes, G., L., Hackman, J., Watkinson, L., Kimbrough, L., P. N., et al. (2001). A randomized, controlled trial of interventions to improve adherence to isoniazid therapy to prevent tuberculosis in injection drug users. *The American Journal of Medicine*, *110*(8), 610–615. **Aim of study:** To determine the effect of several interventions on adherence to tuberculosis preventive therapy.	**Eligible population:** IDUs seeking treatment for TB in the Baltimore City Health Department tuberculosis clinic between June 1995 and September 1997. **Selected population:** Patients who were at least 18 years old; used injection drugs; had a positive TST result; and were candidates for INH preventive therapy. **Excluded population:** Patients who had active TB; a history of serious adverse reactions to INH; previous INH therapy for 6 months or longer; serum alanine aminotransferase level more than 5 times normal; or	concealment was not reported. **Intervention/s description:** DOPT: Patients were assigned to an outreach worker - a nurse who met with them twice weekly and administered INH 900 mg for 6 months per visit, and observed the patient swallow the medication. Arrangements were made for treatment to be given at the clinic or at a mutually convenient community location. Patients assigned to DOPT therapy were monitored for adherence using a log of all doses of medication that were scheduled and administered. Peer group: patients received self-administered therapy in monthly supplies of 300mg/day of INH for	reporting for 6-monthly visits. For DOPT group this was observed, for the peer group and routine care this was self-reported by asking monthly how many doses were missed, and a pill count was made. After 200 patients were enrolled in the study, the study changed its protocol and adherence in the unsupervised groups was monitored using electronic caps on their medication bottles. **Secondary outcomes:** NA **Method of analysis:** Categorical variables were compared with the continuity-corrected x^2 test or Fisher's exact test.	Routine care = 79/100 (79%). DOPT vs. peer support: p = 0.73; DOPT vs. routine care: p = 0.86. Peer support vs. routine care: p-value not reported. Treatment completion, took at least 80% of doses: DOPT = 81/99 (82%); Peer support = 72/101 (71%); Routine care = 90/100 (90%). DOPT vs. peer support: p = 0.08; DOPT vs. routine care: p = 0.10. Peer support vs. routine care: p-value not reported. Took at least 90% of doses: DOPT =79/99 (80%); Peer support = 5/101 (51%); Routine care = 77/100 (77%).	**review team:** Across groups, all patients received either an immediate or deferred $10 stipend for adhering to the monthly study procedures. This may have increased adherence to the study protocol and thus adherence to TB treatment, minimising any differences between groups. The p-value for any statistical comparison between peer support and routine care was not consistently reported. The reliability of the outcome was changed over time: for peer support and routine care, it was first measured by self-report and then by electronic caps on medication bottles. When more reliable methods were used there was a statistically significant difference in treatment completion between peer support and routine care groups. **Evidence gaps and/or recommendations for future research:** NR

Study design: RCT **Type of economic analysis:** NA **Economic perspective:** NA **Quality appraisal non-economic studies:** + **Internal validity:** ++ **External validity:** + **Quality appraisal economic studies:** NA **Quality score applicability:** NA	HIV disease with a CD4 cell count of less than 200/mm. **Setting:** TB clinic, Baltimore, USA. **Sample characteristics:** Range of baseline characteristics across groups: Age, mean: 41.7 to 42.8 years; Gender, female: 26% to 27%. **Economic analysis data source:** NA	6 months. They were required to return monthly for a refill and a nursing visit. Patients also received peer counselling twice during the first month of therapy and once a month thereafter. Patients were also asked to attend monthly support group meetings where lunch was provided. Peers were former IDUs who had completed INH preventive therapy and were trained in counselling patients with TB and HIV about health promotion, prevention, treatment adherence and life-coping strategies. **Comparator/controls/ description:** Routine care: Patients received a monthly supply of INH, 300mg/day. Patients had an initial counselling session	Continuous variables were compared using Student's *t* test or the Wilcoxon rank sum test. The categorical variable for isoniazid urine test result was given a weighted summary score with adjustment for repeated measures. Potential interactions between the primary interventions and the financial incentive were analysed with a log linear model. **Modelling method and assumptions:** NA **Time horizon:** NA	DOPT vs. peer support: p <0.001; DOPT vs. routine care: p-value= 0.63. Took 100% of the doses: DOPT = 76/99 (77%); Peer support = 6/101 (6%); Routine care = 10/100 (10%). DOPT vs. peer support: p <0.001; DOPT vs. routine care: p <0.001. Doses taken, as ascertained by electronic monitoring of pill bottle caps: DOPT = not used. Peer support = 58/101 (57%); Routine care = 49/100 (49%); Peer support vs. routine care: p <0.001. **Secondary results:** NA **Attrition details:** DOPT: 11 patients lost to follow up; 9	**Source of funding:** NR

		with the nurse, were encouraged to ask questions about their treatment, and were scheduled for a monthly assessment at the clinic where they were asked about adherence. For those patients in the peer support and in the routine care groups, isoniazid was provided in bottles equipped with an electronic cap that recorded the time and date the bottle was opened. These patients were also asked to provide urine samples at each monthly visit. Note: all patients across groups received either an immediate or a deferred $10 stipend for each month they adhered to study procedures such as the routine assessments on adherence and drug		withdrawn for other reasons. Peer support: 15 lost to follow up; 7 withdrawn for other reasons. Routine care: 10 lost to follow up; 11 withdrawn for other reasons. All patients included in intention to treat analysis.	

		toxicity. Patients were considered adherent to therapy if a dose was administered by an outreach nurse or if the patient had taken more than 80% of prescribed doses during a month. **Sample sizes:** **Total =** 300 injection drug users **Intervention** DOT: N = 99 Peer: N = 101 **Control** Routine: N = 100 **Baseline comparisons:** Note: There were no statistically significant baseline differences between groups. **Study sufficiently powered?** NR			

Study details	Population and setting	Method of allocation to intervention/ comparator	Outcomes and methods of analysis:	Results	Notes

Authors: Chemtob et al. **Year:** 2003 **Citation:** Chemtob, D., Leventhal, A., Berlowitz, Y., & Weiler-Ravell, D. (2003). The new National Tuberculosis Control Programme in Israel, a country of high immigration. *The International Journal of Tuberculosis and Lung Disease*, *7*(9), 828–836. **Aim of study:**	**Source population/s:** Foreign born patients with active and LTBI, Israel **Eligible population:** Patients treated for TB in Israel between January 1990 and September 1992 (cohort 1) and between 1999 and 2000 (cohort 2). No further information provided. **Selected population:** NR **Excluded population:** NR **Setting:** TB centre. **Sample characteristics:** Typically, 85% of patients with TB in Israel are foreign-born and	**Method of allocation:** Natural allocation of cohort of TB patients before (1990-1992) and after the introduction of a TB programme (1999-2000). **Intervention/s description:** <u>TB Programme:</u> Incorporates five elements of the DOTS strategy recommended by the World Health Organization: 1) political commitment; 2) laboratory diagnostic facilities; 3) directly-observed treatment (DOT); 4) a consistent drug supply; and 5) a permanent reporting system. The programme also has four unique features: 1) DOT is universally applied, with absolutely no exceptions and for the full duration of treatment; 2) DOT is administered	**Primary outcomes:** <u>Treatment outcomes:</u> categorised between 1990 and 1992 as either 'successful', defined as cured or treatment completed; or 'potentially unsatisfactory', defined as all other cases that did not result in a successful outcome (as defined above) or death. Between 1999 and 2000 treatment outcomes were presented separately for those who were cured or completed treatment, representing successful outcomes; and for those who died, defaulted, transferred or were not evaluated, representing unsuccessful outcomes.	**Primary results:** <u>Treatment outcome:</u> *Treatment as usual:* *New cases (N = 196):* successful outcome = 24.5%; died = 5.6%; potentially unsatisfactory outcome = 69.9%. *Re-treated cases (N = 10):* successful outcome = 70%; died = 10%; potentially unsuccessful outcome = 20%. *Total (N = 206):* successful outcome = 26.7%; died = 5.8%; potentially unsuccessful outcome = 67.5%. *TB programme in 1999:* *New cases (N = 289):* cured = 73%; completed = 9.0%; died = 10.4%; failed = 2.1%; defaulted = 2.8%; transferred = 1.7%; not evaluated = 0.1%.	**Limitations identified by author:** NR **Limitations identified by review team:** The study does not report sufficient detail on the demographics of patients in the two cohorts therefore it is difficult to judge the generalisability of the sample and the relevance of the population to this review. It is not known how many patients were hard to reach but the study states that, typically, 85% of TB patients in Israel are foreign-born. It is also not clear how the cohorts were selected. As there was no baseline demographics reported it is unclear how comparable the patients in the two cohorts were with each other and whether there were statistically significant differences that may have contributed to differences in outcomes. For example, it is unclear whether the proportion of participants with active TB compared with LTBI was consistent

To describe the tuberculosis control programme in Israel and to compare the outcome of treatment before and after its launch in 1997. **Study design:** Before and after study. **Type of economic analysis:** NA **Economic perspective:** NA **Quality appraisal non-economic studies:** - **Internal validity: - External validity:**	from the former Soviet Union and Ethiopia. **Economic analysis data source:** NA	using a community-based strategy at central and local level; 3) screening procedures (skin testing and radiography when appropriate), case investigation and treatment of latent infection are performed routinely, particularly for the new immigrant population; and 4) original research was conducted into the cultural-anthropological needs of the immigrants from Ethiopia and the relevant findings were applied in the programme. **Comparator/control/s description:** <u>Treatment as usual:</u> standard care provided prior to the implementation of the new TB programme between January 1990 and September 1992. Standard care did not include the unique features that the new	**Secondary outcomes:** NR **Method of analysis:** NR **Modelling method and assumptions:** NA **Time horizon:** NA	Re-treated cases (N = 36): cured = 50%; completed = 0%; died = 11.1%; failed = 22.3%; defaulted = 8.3%; transferred = 8.3%; not evaluated = 0%. Total (N = 325): cured = 78.5%; completed = "-"; died = 10.5%; failed = 4.3%; defaulted = 3.4%; transferred = 2.4%; not evaluated = 0.9%. *TB programme in 2000* New cases (N = 320): cured = 67.2%; completed = 10.3%; died = 10.6%; failed = 0.9%; defaulted = 2.8%; transferred = 6.9%; not evaluated = 1.3%. Re-treated cases (N = 26): cured = 23.1%; completed = 46.1%; died = 3.8%; failed = 3.8%; defaulted = 3.8%; transferred = 7.9%;	across the groups, as this would have had an impact on the likelihood of a successful outcome. The outcomes reported in the two cohorts were classified differently therefore making the comparisons of outcomes difficult. In addition the outcomes were not statistically compared, limiting the conclusions which can be drawn from this study. It is not clear why the outcomes were reported separately in 1999 and 2000. **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** NR

+ **Quality appraisal economic studies:** NA **Quality score applicability:** NA		TB programme contained. No further information provided. **Sample sizes:** **Total:** N = 877; **Intervention:** N = 671; **Control:** N = 206. **Baseline comparisons:** NR **Study sufficiently powered?** NR		not evaluated = 11.5%. Total (N = 346): cured = 76.9%; completed = "-"; died = 10.1%; failed = 1.2%; defaulted = 2.9%; transferred = 6.9%; not evaluated = 2%. Statistical significance of the differences between groups was not reported. **Secondary results:** NR **Attrition details:** NR	

Study etails	**Population and setting**	**Method of allocation to intervention/ comparator**	**Outcomes and methods of analysis:**	**Results**	**Notes**
Authors: Déruaz &. Zellweger **Year:** 2004 **Citation:** Dèruaz, J., & Zellweger, J., P.	**Source population/s:** Mixed hard-to-reach groups with active TB, Switzerland. **Eligible population:** All the patients who	**Method of allocation:** Natural allocation conducted retrospectively. Patients were assigned by the medical supervisor to full DOT (whole duration of treatment), or partial DOT (intensive phase	**Primary outcomes:** <u>Treatment outcome:</u> Successful outcomes were those *cured* (with bacteriological confirmation) and those who had *completed* a full	**Primary results:** <u>Treatment outcome by intensity of DOT:</u> *Full DOT:* Cured = 38% (14/36); Treatment completed = 50% (18/36); Default = 5% (2/36); Transfer out = 5% (2/36); Death = 0%	**Limitations identified by author:** There was a problem with communicating with the non-French speaking patients about the treatment regimen. In addition, there was a lack of communication between the TB dispensary unit and the

(2004). Directly-observed therapy for tuberculosis in a low prevalence region: first experience at the Tuberculosis Dispensary in Lausanne. *Swiss Medical Weekly*, *134*, 552–558. **Aim of study:** The aim of the study was to evaluate a DOT programme for outcomes given the duration/intensity and location of DOT. **Study design:** Retrospective cohort **Type of economic analysis:** NA **Economic perspective:** NA	started in the DOT programme from October 1997 to March 2000 and had ended treatment by March 2001. **Selected population:** Immigrants or patients with severe psychiatric comorbidities (psychosis etc.), alcohol or drug abusers, patients presenting with social problems (homeless, illegal immigrants, prison inmates), HIV-infected patients; and retreatment cases, intermittent treatment cases and all drug-resistant TB. **Excluded population:** NR **Setting:** Onsite at a TB	only, i.e. 2 months) followed by SAT, depending on individual needs; and were either treated onsite at a TB centre (onsite DOT); or via social outreach, in a convenient location for the participant or in a centre that could address their social needs (outreach DOT). **Intervention/s description:** <u>Full DOT:</u> Patients underwent directly-observed treatment for the whole treatment regimen for active TB. Patients allocated to a full course of DOT were typically refugees, asylum seekers, or illegal immigrants (74%); had language problems; were undergoing intermittent therapy or retreatment; had drug-resistant TB; or had a history of non-adherence.	course of treatment (without bacteriological confirmation of cure). Unsuccessful outcomes were presented as *failure* (sputum still positive after 5 months of treatment); *defaulters* (interruption of treatment for more than 2 months); *death* (whatever the cause); *transfer* (patient transferred out of the health care system and lost to follow-up); and *relapse* (new diagnosis of TB in a patient who was declared cured or who had completed a full course of treatment). **Secondary outcomes:** NA **Method of analysis:**	(0/36); Failure = 0% (0/36). *Partial DOT:* Cured = 17% (3/18); Treatment completed = 72% (13/18); Default = 5% (1/18); Transfer out = 0% (0/18); Death = 5% (1/18); Failure = 0% (0/18). There was no statistically significant difference in successful treatment outcomes (89.5% in both groups) for full DOT (32/36) versus partial DOT (16/18; p = 1.00). <u>Outcome by type of supervision:</u> *On site (only) DOT:* Cured = 38% (10/27); Treatment completed = 55% (15/27); Default = 4% (1/27); Transfer out = 0% (0/27); Death = 4% (0/27); Failure = 0% (0/27). *Outreach, DOT:*	external structures. For example, 1 pharmacy did not report bad adherence to the dispensary and 1 patient was lost to follow-up. There may have been a measurement bias as outcomes for patients who received DOT on site were recorded systematically by the nurse. However for those who received DOT via social outreach efforts, this was not always recorded and therefore information was given orally by professionals. As data was collected at least 6 months after treatment completion, the accuracy of the outcomes is uncertain, reducing the validity of the findings. **Limitations identified by review team:** In addition to the limitations noted above, the study was unable to provide interpreters for non-French speaking patients (which accounted for the majority of participants), which may have affected the results.

Quality appraisal non-economic studies: - **Internal validity: -** **External validity:** + **Quality appraisal economic studies:** NA **Quality score applicability:** NA	dispensary unit or outreach in a social health service or convenient location for the patient, Canton of Vaud, Switzerland. **Sample characteristics:** Males =5 7.4%; Females = 42.6%; Swiss nationality = 5.6%; foreign-born residents = 24.1%; asylum seekers and refugees = 62.9%; illegal immigrants 7.4%. **Economic analysis data source:** NA	<u>Partial DOT:</u> Patients were typically directly observed only during the intensive phase of treatment for the first 2 months. Patients were generally allocated this treatment if they were considered compliant with negative cultures and stable social conditions. <u>Onsite DOT:</u> DOT occurred entirely on site, at a single institution where TB medication was dispensed. Patients visited the site daily to take their medication. Asylum seekers received bus fare reimbursement to attend the dispensary. <u>Social outreach DOT:</u> DOT occurred either in a social care centre so patients with additional needs could be cared for, with nurses visiting the patients at home or patients coming to the	Comparison of results between different subgroups was calculated by Fisher's exact test. **Modelling method and assumptions:** NA **Time horizon:** Data was collected retrospectively, at least 6 months after completion of treatment.	Cured = 26% (7/27); Treatment completed = 60% (16/27); Default = 7% (2/27); Transfer out = 8% (2/27); Death = 0% (0/27); Failure = 0% (0/27). There was no statistically significant difference in successful treatment outcomes for DOT delivered on site (92.6%, 25/27) versus when it was delivered by outreach (85.2%, 23/27; p = 0.67). Note: results are extracted from graphs and therefore only an approximation. **Secondary results:** NA **Attrition details:** 1 patient was lost to follow-up.	Intervention groups have been contaminated, as many treatments were started in the dispensary and later moved to another supervision structure. For example, 10 patients received DOT on site at the TB dispensary centre as well as in a social outreach location (pharmacy, family, prison, social health structures). Allocation to treatment group was based on factors associated with the outcomes. For instance, those who were assigned to partial DOT were more likely to be compliant and a treatment outcome was compliance to treatment. Likewise those administered a full course of DOT were more likely to be non-compliant. In addition, it is not known within each group (i.e. full DOT and partial DOT) how many patients were treated on site or via social outreach. The effects attributable to DOT by duration/intensity are not

		centre. Social centres included health centres for refugees and asylum seekers, shelters with nurses or social workers supervising treatment, general practitioner surgeries, pharmacies. Daily supervision could also be by a family member, with the patient collecting the drugs weekly from the dispensary, or drug distribution in prison. Where possible, patients were seen at a site located near the patient's home or workplace. Female patients with small children were usually visited at home by a nurse. Note: across groups treatment consisted of a 2-month intensive phase with isoniazid, rifampicin, pyrazinamide, plus ethambutol) followed			precisely known as the results may have been confounded by the distribution of social outreach or onsite TB administration. **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** NR

		by a 4-month continuation phase with isoniazid and rifampicin, and was adapted if necessary according to drug sensitivity, side effects and contra-indications. The mean duration of treatment was 6.5 months. Patients were observed taking all medication by a nurse. **Comparator/control/s description:** NA **Sample sizes:** **Total:** N = 54 **Intervention:** Full DOT: N = 36 Partial DOT: N = 18 Onsite DOT: N = 27 Social outreach DOT: N = 27. Note: sub-group analyses were carried out by splitting the total study population first into those who received full or partial			

		DOT, and second by whether it occurred on site or via social outreach. **Control:** NA **Baseline comparisons:** NR **Study sufficiently powered?** NR			

Study details	Population and setting	Method of allocation to intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Diez et al. **Year:** 1996 **Citation:** Diez, E., Clavería, J., Serra, T., Caylą, J., A., Jansą, J., M., Pedro, R., & Villalbi, J., R. (1996). Evalution of a social health intervention	**Source population/s:** Homeless with active TB, Spain. **Eligible population:** Marginal or poor patients who met enrolment criteria for the social support TB programme and the entire homeless population in Barcelona	**Method of allocation:** Naturalistic allocation of participants who met eligibility for entry into a treatment programme in one district of Spain. This group was compared to the incidence rate of the homeless with TB from other districts in Barcelona, Spain. **Intervention/s description:**	**Primary outcomes:** <u>Decrease in TB incidence rate:</u> in the district of Barcelona where treatment was conducted compared with other districts in Barcelona. Note: other outcomes reported but these were non-comparative and therefore not extracted here.	**Primary results:** <u>Decrease in TB incidence</u>: During the programme period (between 1987 and 1992) the annual incidence of TB among the homeless significantly decreased in the district, Ciutat Vella where the treatment programme was implemented (32.4 per 10^5 inhabitants in 1988, to 19.8 per $l0^5$ in 1992, p = 0.03). This rate did	**Limitations identified by author:** NR **Limitations identified by review team:** It is not known if the decrease in TB incidence rate in Ciutat Vella was due to the programme or due to other confounding factors. For example, less than a quarter of the eligible homeless population of Ciutat Vella were included in the programme, yet overall TB incidence rate in the district fell significantly, despite most of the homeless population

among homeless tuberculosis patients. *Tubercle and Lung Disease*, *77*(5), 420–424. **Aim of study:** To compare the TB incidence rate in Ciutat Vella, Barcelona where a social support tuberculosis programme (SSTP) containing DOT was implemented, with other districts in Barcelona where the programme was not implemented. **Study design:** Retrospective cohort design **Type of**	identified with TB between 1987 and 1992. **Selected population:** Enrolment criteria for the social support TB programme included unemployment (without benefit incomes), alcoholism, IDUs, structural family problems and lack of stable housing. Comparison group was anyone with TB and homeless; no further information provided. **Excluded population:** NR **Setting:** Treatment arm was a residential facility in the community. No information on the setting for the comparison arm.	Social support TB programme (SSTP): provided treatment between 1987 and 1992. Included a MDT of nurses and social workers. Nurses conducted home visits and promoted adherence to therapy. Social worker procured health care, arranged pensions and helped to re-instigate benefits and co-ordinate the stay of the patients in the residential facility. Treatment included DOT. Note: All participants spent the first 15 days prior to DOT treatment in district hospital to confirm diagnosis of active TB, to start treatment and isolate the patient during infectious period. **Comparator/control/s description:** No	**Secondary outcomes:** Cost-savings of treatment: from pre-implementation of the programme (estimated from costs in1986) with cost of the programme between 1987 and 1992. **Method of analysis:** To assess impact of SSTP intervention, X^2 test was used to evaluate trends of cases in a) Ciutat Vella (where SSTP is used), b) other districts and c) city as a whole. **Modelling method and assumptions:** Economic evaluation measured the change in the number of hospital admissions and the length of days stayed in hospital	not significantly decrease in the other districts of Barcelona (1.6 per 10^5 inhabitants in 1988, 1.7 per 10^5 in 1992, p = 0.34). **Secondary results:** Cost-savings of treatment: The total cost of the programme in the 6 years it was implemented was $750,505. Based on the estimated cost from data in 1986, the programme was expected to have a saving of $1,514,030. **Attrition details:** NR	not participating in the programme. Due to the design of the study there were no details about the comparison group including the type of intervention available and the demographics of the entire sample. Therefore it is not known if there were any differences between the population and the sort of treatment received in the other districts. There was limited information on the cost calculations, making it difficult to draw conclusions from the data. **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** Treatment programme funded by the Barcelona City Council and the Generalitat of Catalonia.

economic analysis: NA **Economic perspective:** NA **Quality appraisal non-economic studies: - Internal validity:** + **External validity:** - **Quality appraisal economic studies:** NA **Applicability:** NA	**Sample characteristics:** Treatment arm included 10-21% of all TB cases in the district; Male: 92.4%; Age, mean: 42 years; Alcoholism: 143 (68%); Homelessness: 100 (48%); IDU (not active): 24 (11%). No details on the sample characteristic of the comparison arm. **Economic analysis data source:** Hospital discharge files.	information provided. Comparison arm were individuals identified with TB and who were homeless in other districts in Barcelona where the treatment service was not provided. **Sample sizes: Total:** NR **Intervention:** N =210 **Control:** NR **Baseline comparisons:** NR **Study sufficiently powered?** NR	due to TB at the Hospital del Mar (district hospital). **Time horizon:** NA		

Study details	**Population and setting**	**Method of allocation to intervention/ comparator**	**Outcomes and methods of analysis:**	**Results**	**Notes**
Authors: Gourevitch et al.	**Source population/s:**	**Method of allocation:** Participants enrolled at	**Primary outcomes:** Total cost of	**Primary results:** Total cost of	**Limitations identified by author:**

Year: 1998 **Citation:** Gourevitch, M., N., Alcabes, P., Wasserman, W., C., & Arno, P., S. (1998). Cost-effectiveness of directly observed chemoprophylaxis of tuberculosis among drug users at high risk for tuberculosis. *The International Journal of Tuberculosis and Lung Disease*, *2*(7), 531–540. **Aim of study:** To assess the cost-effectiveness of providing DOPT to drug users with and without HIV infection by comparing the costs of ensuring adherence to and completion	Drug users with LTBI, US. **Eligible population:** Drug users enrolled in a methadone maintenance treatment programme in the Bronx, New York, USA. **Selected population:** Those eligible for chemoprophylaxis who volunteered to receive DOPT. **Excluded population:** NR **Setting:** Primary medical care services, New York, USA (for screening). Methadone maintenance clinic for DOPT. **Sample**	the methadone maintenance clinic were offered either DOPT or SAT. Treatment choice was completely voluntary. **Intervention/s description:** <u>DOPT:</u> Nurse directly-observed chemoprophylaxis (INH 300 mg/day and pyridoxine, 50 mg/ day) on site at the methadone clinic, alongside their daily methadone dose. Treatment was prescribed for 6 months for those who were HIV-seronegative and 12 months for those who were HIV-seropositive. When patients were not scheduled to receive methadone, they were given pre-packaged doses of medication to take home. Records completed by	<u>treatment</u> <u>Net savings generated by the DOPT programme:</u> compared the costs of providing DOPT with not providing DOPT, taking into account the cost of screening, observed chemoprophylaxis treatment and monitoring. Costs were derived from the 507 patients who were screened for TB and had data available on anergy and HIV status (not just the 187 who started treatment). **Secondary outcomes:** NA **Method of analysis:** X^2 or Fisher's exact test. **Modelling method and assumptions:** Modelling the number of active TB	<u>treatment:</u> Without DOPT = $24,050.40; $159.27 per person treated. With DOPT = $ 74,958.40; $496.41 per person treated. <u>Net savings generated by DOPT by effectiveness of INH:</u> 40% = $143,778, $284 per person screened; 65% = $285 284, $563 per person screened; 90% = $465,217, £918 per person screened. **Secondary results:** NA **Sample selection and attrition details:** NR 537 participants enrolled; data was available for 507 (94%). 184 participants were eligible for chemoprophylaxis;	The authors did not model the impact of chemoprophylaxis beyond 5 years of follow up. The base model did not take into account multi-drug resistance, multiple hospitalizations per case of tuberculosis, outpatient costs of tuberculosis care, and the cost of treating secondary infections and cases that could have been averted by chemoprophylaxis. The model is based on analysis of the population attending a single methadone maintenance treatment programme in the Bronx and therefore not necessarily generalisable to other settings. **Limitations identified by review team:** None in addition to the above. **Evidence gaps and/or**

of chemoprophylaxis for TB among drug users in the absence of DOPT. **Study design:** NA **Type of economic analysis:** Cost-savings. **Economic perspective:** Perspective of a methadone maintenance treatment programme with an on-site primary care and TB control and prevention programme. **Quality appraisal non-economic studies:** NA **Internal validity:** NA **External validity:** NA **Quality appraisal economic studies:**	**characteristics:** Range of baseline characteristics among those who were HIVseropositive (N = 159) and HIV-seronegative (N= 348): Gender, Male: HIV seropositive: 92 (58%) and HIV seronegative: 205 (59%); PPD-positive: HIV-seropositive: 25 (16%) and HIV-seronegative: 100 (29%). **Economic analysis data source:** Direct medical costs of providing DOPT and prevalence of TB reactivity and cutaneous anergy. Time spent by medical and nursing staff to screen, treat and monitor patients were estimated	the nursing staff indicated whether medication was taken each day. **Comparator/control/s description:** SAT: Self-administered chemoprophylaxis. **Sample sizes:** **Total:** N = 151 **Intervention:** NA; **Control:** NA. **Baseline comparisons:** NR **Study sufficiently powered?** NA	cases that would have arisen in a sample over a period of 5 years in the absence of DOPT. The model took into account the prevalence of HIV and mortality rates among drug users. Sensitivity analyses: effect of incorporating different values for parameters such as HIV prevalence and INH effectiveness. Included the costs of screening and drug treatment. Costs directly attributable to DOPT were the costs of the nurse's time to deliver the medication and directly observe ingestion and the administrative costs associated with treatment.	151 accepted treatment.	**recommendations for future research:** NR **Source of funding:** National Institute of Drug Abuse; NY State AIDS Institute; New York City Department of Health.

+ **Quality score** **Applicability:** +	based on interview and observation. Other data from published sources.		Outpatient TB treatment costs and additional costs of detecting, preventing or treating active disease resulting from 'secondary' cases of TB were excluded. Discount rates not used. Costs adjusted to take into account the 1996 US dollar. Other assumptions were that no case of TB developed during INH administration; and that cases with active TB were sensitive to all anti-TB drugs. **Time horizon:** 5 years.		

Study details	**Population and setting**	**Method of allocation to intervention/ comparator**	**Outcomes and methods of analysis:**	**Results**	**Notes**
Authors: Juan et al.	**Source population/s:** Mixed hard-to-	**Method of allocation:** Allocation to DOT was conducted	**Primary outcomes:** <u>Treatment completion:</u>	**Primary results:** <u>Treatment completion:</u> DOT group = 76/101	**Limitations identified by author:** Comparison made with a retrospective cohort.

Year: 2006 **Citation:** Juan, G., Lloret, T., Perez, C., Lopez, P., Navarro, R., Ramón, M., Cortijo, J., et al. (2006). Directly observed treatment for tuberculosis in pharmacies compared with self-administered therapy in Spain. *The International Journal of Tuberculosis and Lung Disease*, *10*(2), 215–221. **Aim of study:** To compare DOT provided through pharmacies	reach groups with active TB, Spain. **Eligible population:** TB patients within Valencia's Health District no. 8. **Selected population:** Inclusion criteria were: 1) TB diagnosis; 2) one or more of the following: HIV infection, alcoholism (>280 g/week for men or >168 g/week for women), illicit (injection or non-injection) drug use, immigrant status, homelessness or previous failure to complete TB treatment. Inclusion was fully voluntary. **Excluded population:** NR **Setting:** Health District no. 8,	prospectively for those who consented to treatment beween1999 and 2002. Allocation to SAT was done retrospectively for those treated for TB between 1996 and 1998 from the same district as the treatment group with similar characteristics of non-adherence. **Intervention/s description:** <u>Pharmacy-based DOT:</u> Between 1999 and 2002 a social worker at the hospital assigned each patient to the district pharmacy closest to the patient's residence. Delivery of the TB medications along with socio-sanitary support and incentives was carried out at the assigned pharmacy by a trained pharmacist. Out-patients followed a treatment protocol decided by their	Different definitions of completion used in results with no clear definition of the term. Completion measured by DOT for the treatment group whilst unclear how it was measured for the control group. <u>Missed appointments.</u> <u>Differential costs in treatment.</u> **Secondary outcomes:** NR **Method of analysis:** For categorical outcomes, relative risks were calculated and differences tested using Fisher's exact test. For means, the t-test was used. **Modelling method and assumptions:** NA	(75.2%), defined as number who did not miss more than 2 consecutive doses; SAT group = 30/112 (26.7%) (no clear definition of completion used for control group). The difference was statistically significant (RR = 3.069, 95% CI 2.133-4.414; p<0.0001). <u>Missed appointments:</u> DOT group: 69/101 (68.3%) did not miss any appointments; 32/101 (31.6%) missed some appointments. Of these 32, 12 were traced by the programme and continued treatment. Data was not provided for SAT. <u>Differential costs:</u> No difference in hospital costs between the groups. Different costs were incurred in the drugs dispensed, €102 per patient for DOT compared with € 217for SAT; and the	**Limitations identified by review team:** It was not clear what definition was used for treatment completion and whether the same definition criteria were used across treatment conditions. For example, in the comparison of treatment completion where a relative risk was reported, the definition for treatment completion was missing more than 2 consecutive appointments for the treatment arm. It is not known whether this was also the same definition criteria used in the control group. Different criteria of completion may have contributed to differences in adherence outcomes. Due to the nature of the intervention, the collection of data on adherence would have been more reliable in the treatment arm as it used DOT. It was not clear how completion was measured in the control arm but as it was collected retrospectively from SAT, it may be assumed that it was measured less reliably than the treatment arm.

with self-administered treatment (SAT) for TB patients at risk of non-adherence. **Study design:** Before and after. **Type of economic analysis:** NA **Economic perspective:** NA **Quality appraisal effectiveness studies:** + **Internal validity:** + **External validity:** + **Quality appraisal economic studies:** NA **Quality score Applicability:**	Valencia, Spain. **Sample characteristics:** Male = 67.3-78.6%; average age = 28-34; HIV-positive = 66.3-75.0%; alcohol abuse = 32.7-37.5%; illicit drug use = 37.6-64.3%; homeless = 13.9-18.7%; immigrant = 3.6-17.8% **Economic analysis data sources:** NA	physician in accordance with standard guidelines: INH (15mg/kg, max 900 mg) and RMP (10 mg/kg, max 600 mg) twice weekly for 6 months (9 months for HIV-positive patients), with the addition of PZA (50–570 mg/kg, max 4 g) and EMB (50 mg/kg, max 2.5 g) for the first 6 weeks of treatment. In addition to DOT, reinforcement and support was provided in each visit. **Comparator/control/s description:** SAT: Between January 1996 to 31 December 1998 (retrospective) patients in the same health district and hospital with similar demographic and clinical characteristics, and with a similar risk level for non-adherence based on sample characteristics (see selected population), were	**Time horizon:** NA	stipends for personnel (physician, social worker, pharmacists) in the supervision phase, € 515 per patient for DOT compared with €115 for SAT. **Secondary results:** NR **Sample selection and attrition details:** Of 483 patients diagnosed with TB (1999–2002), 131 met the criteria to be included in DOT. Of these, 30 preferred SAT, and the remaining 101 entered the DOT programme. 20 patients, who interrupted their treatment for more than two consecutive doses, were lost to follow-up.	The study used a before and after design and there were statistically significant differences between groups which may have confounded the results. These baseline differences were not adjusted for in the analysis. In addition, there may have been other differences between groups not measured by the study that may have impacted on the results. **Evidence gaps and/or recommendations for future research:** Additional research in this and other communities is required for further validation and replication of the effects of DOT in Spain. **Source of funding:** NR

NA		treated with conventional SAT. **Sample sizes:** **Total:** N = 212; **Intervention:** N = 101; **Control:** N = 112. **Baseline comparisons:** Illicit drug users were more frequent among patients on SAT (p = 0.0001), while more patients on DOT were immigrants (p = 0.0006). Patients on SAT were more likely to be male (p <.0001). No significant differences were found for the remaining variables. **Study sufficiently powered?** NR			

Study details	**Population and setting**	**Method of allocation to intervention/ comparator**	**Outcomes and methods of analysis:**	**Results**	**Notes**
Authors: Kominski et al. **Year:** 2007.	**Source population/s:** Adolescents (80% foreign-born) with LTBI, US.	**Method of allocation:** Block randomised by three age groups and gender between 1995 and 1998.	**Primary outcomes:** Adherence to isoniazid preventive therapy: completion of the 6-month	**Primary results:** *Effectiveness outcomes:* Adherence to isoniazid preventive therapy:	**Limitations identified by author:** NR **Limitations identified by review team:** The study did

Citation: Kominski, G., F., Varon, S., F., Morisky, D., E., Malotte, C., K., Ebin, V., J., Coly, A., & Chiao, C. (2007). Costs and cost-effectiveness of adolescent compliance with treatment for latent tuberculosis infection: results from a randomized trial. *Journal of Adolescent Health*, *40*(1), 61-68. **Aim of study:** To assess the costs and cost-effectiveness of three interventions (peer-support, contingency contracting and	**Eligible population:** Adolescents referred to TB clinics that treat a large proportion of new entrants. **Selected population:** Adolescents (11- to 19-year-olds) screened for TB at school with LTBI confirmed by TST, and referred to clinic. **Excluded population:** NR **Setting:** Public health clinics. **Sample characteristics:** Total group: 79.3% foreign-born; 51.4% male; mean age 15.4 years. **Economic**	**Intervention/s description:** Peer counselling: an adolescent who had successfully completed treatment was used as a peer counsellor and stressed the importance of taking medication and adhering to clinic appointments. The study did not provide information on when the peer stressed this importance and how often this was done. Contingency contracting: reward negotiated between parent and adolescent in exchange for compliant behaviour and completion of care. Rewards included any tangible item or any other type of privilege that was valued by the adolescent. Costs paid for by the parent but included in economic analysis.	course of treatment documented in medical records as confirmed by a health care professional. Clinic attendance at 6 months to report completion was a condition of adherence. Total cost of LTBI treatment. Average lifetime TB-related costs. ICER/QALYs: lifetime TB-related costs and health benefits relative to usual care. **Secondary outcomes:** NR **Method of analysis:** Multivariate logistic regression: to measure predicted compliance controlling for income, gender, student status, age, place of birth, health	Peer counselling plus contingency contracting = 165/197 (83.8%) Peer counselling = 150/199 (75.4%) Contingency contracting: 150/203 (73.9%) Usual care = 148/195 (75.9%). The difference in adherence rate between peer counselling + contingency contracting and usual care was of borderline statistical significance (p = 0.051). Statistical comparisons for the other treatment groups with usual care were not reported. *Economic outcomes:* Total cost of LTBI treatment mean (SD): Peer counselling plus contingency contracting = $341 ($63) Peer counselling = $277 ($37) Contingency	not report any statistical comparison between groups on baseline demographics making it difficult to judge if there were any known differences between the groups. However all variables were controlled for in the analysis. The p values for the difference between the treatment groups with usual care were not reported, except for comparison with peer counselling + contingency contracting. The study stated that cost-effectiveness analysis would only be conducted for those treatments groups that had statistically significant differences in adherence when compared to usual care. However, this was conducted for peer counselling + contingency contracting although it had a p-value greater than 0.05 (albeit only marginally, 0.051). This was not acknowledged in the report. The author used his own judgement for the

combined peer support and contingency contracting) compared with usual care on adolescent compliance with treatment for LTBI. **Study design:** RCT. **Type of economic analysis:** Cost-effectiveness. **Economic perspective:** Societal perspective. **Quality appraisal non-economic studies:** NA **Internal validity:** NA **External validity:** NA **Quality appraisal**	**analysis data source:** Actual utilisation of services derived from study. Cost of resource use obtained from Medicare charges in 1999. Published sources were consulted and author made some assumptions.	<u>Peer counselling plus contingency contracting</u>: received both peer counselling and contingency contracting. **Comparator/control/s description:** <u>Usual care</u>: received the treatment and educational material routinely provided to patients. Note: all participants received treatment and medical follow-up visits according to standard procedures including monthly supplies of isoniazid for at least 6 months. **Sample sizes:** **Total:** N=794 **Intervention:** <u>Peer counselling</u>: N=199; <u>Contingency contracting</u>: N=203; <u>Peer counselling plus contingency</u>	status, difficulty in getting to clinic, travel time to clinic, living arrangements, length of time waited to see nurse. <u>Multivariate linear regression of compliance</u>: to measure costs using predicted compliance as independent variable to determine the costs of treatment after controlling for factors that significantly affected compliance. **Modelling method and assumptions:** Markov model used for cost-effectiveness analysis. Monte Carlo microsimulation using 10,000 trials for ICER. Cost-effectiveness was only calculated	contracting = $326 ($67) Usual care = $199 ($43); Peer counselling plus contingency contracting vs. peer counselling: p = 0.001. Peer counselling vs. contingency contracting: p = 0.001. Contingency contracting vs. usual care: p = 0.001 Note: cost-effectiveness was only calculated for peer counselling plus contingency contracting compared with usual care. <u>QALYs</u>: Peer counselling plus contingency contracting = 24.3968; Usual care = 24.2006; Incremental effectiveness in QALYs: 0.1962. <u>Average lifetime TB-related costs</u>: Peer counselling plus contingency	assumptions in the QALY for being healthy, having a positive skin test but incomplete treatment, and for active TB. **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** National Heart, Lung and Blood Institute.

economic studies: + **Applicability:** +		contracting: N=197; **Control:** Usual care: N = 195. **Baseline comparisons:** The authors state that the groups were "relatively" consistent however it is not clear if this was confirmed statistically. **Study sufficiently powered?** NR	for the treatment groups that had statistically significant higher completion rates compared with usual care. Included only direct costs of the intervention and not indirect costs such as time and cost of travel. Discount rate of 3% used. Costs included data from the study on counts of: clinic visits, chest x-rays, TSTs, isoniazid prescriptions, missed appointments. Other costs included: costs of letters sent to adolescents, the cost of hiring peer counsellors, an incentive paid to the adolescent, taking the average	contracting = $767; Usual care = $808; Incremental cost: $41. ICER: $209 per QALY. In a Monte Carlo microsimulation using 10,000 trials, in 89.75% of the trials, costs were higher in the peer counselling plus contingency contracting group without any additional improvement in QALYs. In all trials, the ICER was below $50,000. **Secondary results:** NR **Attrition details:** 88% of the eligible population consented to take part in the study; there were no statistically significant differences between those who consented and those who did not.	

			payment made by parents and the costs of using staff from each site. Published sources were used for assumptions of efficacy and hepatoxicity of isoniazid treatment, cost of treating active TB, the prevalence and fatality rate of TB and hepatitis fatality rate. Author used his own judgement to make assumptions about the QALY for being healthy, having a positive skin test but incomplete treatment, and for active TB. **Time horizon:** life-time TB-related costs.		

Study details	**Population and setting**	**Method of allocation to intervention/ comparator**	**Outcomes and methods of analysis:**	**Results**	**Notes**

Authors: MacIntyre et al. **Year:** 2003 **Citation:** MacIntyre, C., R., Goebel, K., Brown, G., V., Skull, S.,, Starr, M., & Fullinfaw, R., O. (2003). A randomised controlled clinical trial of the efficacy of family-based direct observation of anti-tuberculosis treatment in an urban, developed-country setting. *The International Journal of Tuberculosis and Lung Disease*, *7*(9), 848–854.	**Source population/s:** Patients (80% foreign-born) with active (81.5%) and LTBI, Australia. **Eligible population:** TB patients in the North-Western Health Care Network, Victoria, Australia. **Selected population:** All TB patients in two clinics, who started treatment between 30 January 1998 and 11 July 2000, who agreed to participate, with the exceptions below. **Excluded population:** Patients with multidrug-resistant TB and patients with relapsed TB who were already receiving nurse-	**Method of allocation:** Quasi-randomised assignment such that the first patient was assigned to the control arm and every second patient assigned to treatment. There was no allocation concealment. **Intervention/s description:** Family-based directly observed treatment (FDOT): A suitable family member, nominated by the patient, was educated and trained to observe and record pill taking daily. All patients received the drug regimen prescribed by their treating physician. Medication was administered daily. **Comparator/control/s description:** Standard Treatment (ST): Treatment supervised at monthly clinic visits, but did not include DOT.	**Primary outcomes:** Completion of treatment: defined as completing the prescribed regimen and measured by recorded clinic attendances and collection of prescribed medications. Compliance with treatment: measured by six random urinary INH levels over a 6-month period. The study nurse visited all TB patients (receiving both FDOT and ST) once a month to collect urine specimens for INH levels. Visits were random and with 1 hour's notice. Urine samples were collected by investigators who were blinded to participants' assignment to group. **Secondary**	**Primary results:** Compliance with treatment: ITT analysis: FDOT = 65/87 (74.7%); ST = 67/86 (77.9%); RR for non-compliance =1.04 (95%CI 0.88–1.23). Note: this included participants assigned to FDOT who didn't receive the intervention (see attrition details below) Per protocol analysis (based on treatment actually received): FDOT =38/50; ST = 67/86; RR for non-compliance = 0.96 (95%CI 0.75–1.23). Completion of treatment: ITT analysis: ST = 78/86 (90.6%); FDOT = 84/87(96.5%); RR for non-completion = 2.7 (95%CI 0.66–14.2, p = 0.11). **Secondary results:**	**Limitations identified by author:** The study was not powered to detect less than a 60% reduction in non-compliance (from 25% to 10%). The urinary INH test is an insensitive measure of compliance, since INH may be detected up to 24 hours after a dose, therefore, if a patient missed a dose, this would not be detected. **Limitations identified by review team:** The study used a weak randomisation procedure with no allocation concealment. These processes could have allowed for any investigator to influence the randomisation procedure, although there is no reason to suggest that this was the case. **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** NR

Aim of study: To evaluate the effectiveness of a family-based programme of DOT for TB, in comparison to non-observed, supervised treatment. **Study design:** Quasi-RCT **Type of economic analysis:** NA **Economic perspective:** NA **Quality appraisal effectiveness studies:** + **Internal validity:** + **External validity:** + **Quality appraisal economic studies:** NA	administered DOT: patients with HIV co-infection or non-tuberculous mycobacterial (NTM) infections. **Setting:** North-Western Health Care Network, Victoria, Australia. **Sample characteristics:** <u>Total group:</u> Mean age = 41 years (median 38 years, range 14–83); Male = 51% (89/173); Foreign-born = 80% (the most frequent countries of birth were Vietnam [29%], Somalia [10.4%], China [5.2%] and Ethiopia [3.5%]); Employment: 26% (45/173) paid employment, 24% (41/173) were home carers and 30% (52/173) were students.	**Sample sizes:** **Total:** N = 173; **Intervention:** N = 87; **Control:** N = 86. **Baseline comparisons:** NR **Study sufficiently powered?** No. Sample of 224 was needed for 80% power; actual sample was 173.	**outcomes:** NR **Method of analysis:** Intention-to-treat analysis; Poisson regression analysis. **Modelling method and assumptions:** NA **Time horizon:** NA	NR **Sample selection and attrition details:** 42% (37/87) of those allocated to FDOT did not receive the intervention. The main reason was living alone and therefore not having a family member to administer FDOT (60%, 22/37). Refusal to accept FDOT (8/37) and other reasons (7/37) comprised the remainder (family dynamics and hierarchy, having work hours that did not coincide with those of other family members and wanting to prove ability to remember medicines).	

Quality score applicability: NA	**Economic analysis data sources:** NA				

Study details	Population and setting	Method of allocation to intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Malotte et al. **Year:** 2001 **Citation:** Malotte, C., K., Hollingshead, J., R., & Larro, M. (2001). Incentives vs outreach workers for latent tuberculosis treatment in drug users. *American Journal of Preventive Medicine*, *20*(2), 103–	**Source population/s:** Drug users with LTBI, US. **Eligible population:** Participants with a positive tuberculin skin test and no evidence of active disease or major contraindications to isonazid.. **Selected population:** 169 participants agreed to participate. **Excluded population:** **Setting:** Community,	**Method of allocation:** Randomisation to one of three groups within blocks of 18. Allocation concealment using numbered, opaque, sealed envelopes. **Intervention/s description:** <u>Outreach DOPT plus monetary incentives (Condition 1)</u>: twice weekly DOPT supplied by an outreach worker at a location chosen by the participant, plus a $5 per visit incentive. <u>Outreach DOPT (Condition 2):</u> twice-weekly DOT by an outreach worker at a site chosen by the participant but with no	**Primary outcomes:** <u>Percentage of medication taken on time</u>: number of doses taken on time divided by the total number of doses taken on time, late and/or missed. Minimum number of doses in the denominator was 52 (two per week for 26 weeks) unless the medication was stopped by a health professional. Those lost to follow-up were assumed to have missed doses (all doses from the last dose taken up to 52 doses were counted as missed). <u>Completion of</u>	**Primary results:** <u>Completion of treatment:</u> Outreach DOPT plus monetary incentives (Condition 1) = 28/53 (52.8%). Outreach DOPT (Condition 2) = 2/55 (3.6%). DOPT plus monetary incentives (Condition 3) = 33/55 (60%). Adjusted Odds Ratio (AOR) for outreach DOPT plus incentive compared with outreach DOPT alone = 29.7 (95% CI 6.4-137.5), p<0.0001. AOR (for DOPT plus incentive compared	**Limitations identified by author:** None. **Limitations identified by review team:** In the comparisons of the different treatment groups, condition 1 and condition 3 were only compared with condition 2. It was not clear from the methods that condition 2 was the 'control condition'. Comparisons should have also been conducted between condition 1 and 3 to understand whether the inclusion of an outreach worker to administer DOPT improved treatment completion compared with standard DOPT. **Evidence gaps and/or recommendations for future research:** NR

107. **Aim of study:** To compare the independent and combined effects of monetary incentives and outreach worker provision of DOT (for LTBI) treatment in a sample of active drug users. **Study design:** RCT **Type of economic analysis:** NA **Economic perspective:** NA **Quality appraisal non-economic studies:** ++ **Internal validity:** ++	storefront facility that housed both research and service programmes for drug users, California, USA. **Sample characteristics:** Mean age: 42 years, range 23 to 69 years); male: 82%; crack cocaine use: 68%; IDUs:13%; alcohol consumption: 81%. living in own home: 41.7%. **Economic analysis data source:** NA	monetary incentive. <u>DOPT plus monetary incentives (Condition 3)</u>: twice-weekly DOPT, conducted at the study's community site. Participants in this group were paid $5 per scheduled visit attended. Note: all participants were prescribed INH, 15 mg/kg, with a maximum dose of 900 mg, twice per week (Monday and Thursday or Tuesday and Friday). Length of treatment was 6 months or 12 months depending on HIV status. All participants were informed of the importance of treatment completion and possible side effects of medication. Participants were observed swallowing	<u>treatment</u>: no further definition provided. Did not include those whose medication was stopped for medical reasons. **Secondary outcomes:** NA **Method of analysis:** Baseline differences were assessed using analysis of variance (ANOVA) for continuous variables and contingency table analysis (x^2) for categorical variables. Univariate relationships of treatment completion with treatment condition, demographic characteristics, and drug use characteristics were tested using x^2 analyses with	with outreach DOPT alone = 45.5 (95% CI 9.7-214.6); p<0.0001. <u>Percentage of medication taken on time:</u> Outreach DOPT plus monetary incentives (Condition 1) = 72%; p < 0.001 compared with condition 2. Outreach DOPT (Condition 2) = 12%. DOPT plus monetary incentives (Condition 3) = 69%; p < 0.001 compared with condition 2. Note: absolute numbers were not reported for this outcome, only percentages. **Secondary results:** <u>Variables associated with increased treatment completion:</u> No binge drinking in the past 30 days compared with some: AOR = 2.1 (95% CI 0.9-4.4, p=0.07).	**Source of funding:** National Institute on Drug Abuse.

External validity: + **Quality appraisal economic studies:** NA **Quality score applicability:** NA		all medications. If the participant did not appear or could not be found, medication could be given the following day. If the dose was not provided the following day, it was considered missed. **Comparator/control/s description:** NA **Sample sizes:** **Total =** 163 **Intervention:** Outreach DOPT plus monetary incentives (Condition 1): N = 53; Outreach DOPT (Condition 2): N = 55; DOPT plus monetary incentives (Condition 3): N = 55. **Control** = NA **Baseline comparisons:** No statistically significant differences at baseline.	continuity correction where appropriate. Intervention effects were tested in both univariate and multivariate logistic regression analyses, on an intention-to-treat basis. In addition to treatment condition, the multivariate analysis included as covariates all variables that were related (p<0.10) to treatment completion in univariate comparisons. Analysis on treatment completion did not include those whose medication was stopped for clinical reasons (N = 6). If a participant was lost to follow-up (moved or imprisoned), all doses after the last dose taken were	Recruitment status Prior study participants compared with newly recruited participants: AOR = 2.5 (95% CI 1.1-5.7, p=0.03). **Sample selection and attrition details:** 202 were eligible, 169 consented to take part in the study. 14 individuals were not eligible for INH due to evidence of potential active disease or medical contraindications, 2 were followed by the health department and 6 did not return for assessment results. 6 individuals were not included in the analysis: 2 had a previous history of INH therapy; 3 had prolonged elevated liver function tests; and 1 was referred to the health department for multiple medications due to a	

		Study sufficiently powered? NR	counted as missed. **Modelling method and assumptions:** NA **Time horizon:** NA	positive sputum test.	

Study details	**Population and setting**	**Method of allocation to intervention/ comparator**	**Outcomes and methods of analysis:**	**Results**	**Notes**
Authors: Matteelli et al., **Year:** 2000 **Citation:** Matteelli, A., Casalini, C., Raviglione, M., C., El-Hamad, I., Scolari, C., Bombana, E., Bugiani, M., et al. (2000). Supervised preventive therapy for latent tuberculosis infection in illegal	**Source population/s:** Illegal immigrants with LTBI, Italy. **Eligible population:** Immigrants treated in a TB clinic in Brescia and those who applied for housing in dormitories and therefore required to be screened for TB on site, in Turin, Italy. **Selected population:** Participants who came from countries with an estimated TB	**Method of allocation:** Participants randomised to study groups; method of randomisation not reported. Allocation concealment also not reported. **Intervention/s description:** <u>Supervised treatment of 900mg of INH (Regimen A):</u> Supervised isoniazid at a dose of 900 mg twice weekly for 6 months. Supervised treatment included participants reporting twice weekly to the clinical service sites (either the tuberculosis clinic or the clinic for	**Primary outcomes:** <u>Treatment completion</u>: Defined as 80% or more of prescribed medication taken. In the supervised group (Regimen A) this was measured by counting the number of pills in the bottles when participants returned to the clinic. In the unsupervised groups (Regimens B and C) urine samples were taken at each clinic visit. <u>Probability of continuing treatment throughout the 26-week study period</u>.	**Primary results:** <u>Treatment completion:</u> Supervised treatment of 900mg of INH (Regimen A) = 7.3% (6/82). Unsupervised treatment of 900mg of INH (Regimen B) = 26% (19/73). Unsupervised treatment of 300mg INH (Regimen C) = 41% (22/53). Adherence rates across groups were not statistically compared. Note: only percentages presented and it was not clear which	**Limitations identified by author:** NR **Limitations identified by review team:** *p-value*The exact numbers of participants continuing treatment were not clearly stated and difficult to extrapolate as they were only presented graphically. Details of the interventions were limited therefore it is difficult to understand what occurred in each of the intervention arms and to compare with other studies. **Evidence gaps and/or recommendations for future research:** Future studies should

immigrants in Italy. *American Journal of Respiratory and Critical Care Medicine*, *162*(5), 1653. **Aim of study:** To assess adherence to one supervised, medical service-based, twice-weekly regimen of isoniazid in illegal migrants in Northern Italy. **Study design:** RCT. **Type of economic analysis:** NA **Economic perspective:**	incidence of 50/100,000 or more; had a history of immigration of less than 5 years; and development of a skin induration > 10 mm using TST. **Excluded population:** Participants were excluded if they were pregnant, older than 35 years, and had liver enzymes (AST, ALT) five times or more than the upper normal values, or diagnosed with active TB. **Setting:** TB clinic for participants recruited and treated in Brescia and specialised clinic for migrants for those recruited and treated in Turin.	migrants) to collect drugs. It was also unclear what type of supervision occurred when participants collected drugs. All patients were provided with free drugs, but no incentives or enablers were provided. The professional who delivered DOPT was not reported. <u>Unsupervised treatment + 900mg of INH (Regimen B):</u> unsupervised IPT 900 mg twice weekly for 6 months, self-administered. <u>Unsupervised treatment + 300mg of INH (Regimen C):</u> Unsupervised INH regimen of 300 mg daily for 6 months; standard treatment. No further information provided on unsupervised treatment. It was not clear whether participants received	<u>Mean time to drop out from treatment</u>. **Secondary outcomes:** NA **Method of analysis:** Continuous data were compared using Student's *t* test; Categorical data was analysed by means of the chi-squared test with Mantel-Haenszel stratified analysis. Probabilities of completing treatment were compared by means of the Kaplan-Meier plots and the Mantel-Haenszel Log rank test. **Modelling method and assumptions:** NA **Time horizon:** NA	denominator was used to calculate these figures. <u>Probability of continuing treatment throughout the study period:</u> Participants who received supervised treatment + 900mg of INH (Regimen A) had a significantly lower probability of completing treatment than did participants who received unsupervised treatment of 300mg (Regimen C; p = 0.001) and unsupervised treatment of 900mg of INH (Regimen B; p = 0.006). <u>The mean time to dropout from treatment</u>: Across groups = 5weeks (range, 1 to 19 weeks). This was statistically significantly shorter for participants in Regimen A (3.8 weeks) compared with subjects in Regimen B (6 weeks) and	evaluate the efficacy of short-term multidrug regimens delivered through outreach DOPT to illegal immigrants in industrialised countries. **Source of funding:** NR

NA **Quality appraisal non-economic studies:** + **Internal validity:** + **External validity:** + **Quality appraisal economic studies:** NA **Quality score** **Applicability:** NA	**Sample characteristics:** Sex, male: Regimen A: 58.5%; Regimen B: 65.7%; Regimen C: 60.3%. Age, 15-24 years: Regimen A: 31.7%; Regimen B: 30.2%; Regimen C: 30.2%. The remaining participants were 25-35 years old. Country of origin, Africa: Regimen A: 73.2%; Regimen B: 68.5%; Regimen C: 69.8%. The remaining participants were classified as 'other'. Religion, Muslim: Regimen A: 50%; Regimen B: 53.4%; Regimen	their medication in monthly supplies or not. **Comparator/control/s description:** NA **Sample sizes:** **Total** = 208 **Intervention** Supervised treatment of 900mg of INH: N = 82; Unsupervised treatment of 900mg of INH: N =73; Unsupervised treatment of 300mg of INH: n = 53. **Control:** NA **Baseline comparisons:** There were no statistically significant differences reported at baseline. **Study sufficiently powered?** NR		Regimen C (6.2 weeks) (p = 0.003). **Secondary results:** NA **Attrition details:** 156 participants did not complete treatment: 127 were lost to follow-up, 21 decided to stop treatment, six moved away from the study areas, one became pregnant, one was imprisoned, and five developed adverse events. It was not clear whether these were included in the analyses.	

	C: 41.5%. The remaining participants were classified as 'other'. Alcohol/drug abuse: Regimen A: 9.7%; Regimen B: 9.6%; Regimen C: 13.2%. **Economic analysis data source:** NA				

Study details	**Population and setting**	**Method of allocation to intervention/ comparator**	**Outcomes and methods of analysis:**	**Results**	**Notes**
Authors: McCue & Afifi **Year:** 1996 **Citation:** McCue, M., & Afifi, L., A. (1996). Using peer helpers for tuberculosis prevention. *Journal of American College*	**Source population/s:** International students with LTBI, USA. **Eligible population:** International students with positive PPD skin test at the University of Iowa. **Selected population:** N/A **Excluded population:** N/A	**Method of allocation:** Natural allocation, patients who received peer support in 1992 when it was implemented compared with a cohort of patients who received treatment as usual before the implementation of the programme (1990 to 1992). **Intervention/s description:** Peer	**Primary outcomes:** Treatment compliance: no further information provided on definition or on how the data was collected. **Secondary outcomes:** NR **Method of analysis:** NR	**Primary results:** Treatment compliance: *Peer support*: Autumn 1992 = 26/42 (62%); Spring 1993 = 26/33 (79%); Autumn 1993 = 64/90 (71%); Spring 1994 = no data available as too few peers. *Treatment as usual*: Autumn 1990 = 6/94	**Limitations identified by author:** NR **Limitations identified by review team:** The information on the sample characteristics were not specific to the selected population but to the international university students as a whole. Therefore it is not known how generalisable the selected sample is to the source population.

Health: 44(4), 173. **Aim of study:** To compare the treatment completion rates before and after 1992, when a peer-support programme was implemented, for international university students. **Study design:** Before and after **Type of economic analysis:** NA **Economic perspective:** NA **Quality appraisal non-**	**Setting:** Health clinic, University of Iowa. **Sample characteristics:** <u>All international students of the University of Iowa, Autumn 1993</u>: N = 1,874; Country of origin = China: 38.3% Southeast Asia: 18.7% Korea: 13.0% Japan/Western Europe/Australia/Canada: 12.5% Eastern Europe/Middle East: 8.7% Latin America: 4.3% sub-Saharan Africa: 3.7% Pacific Islander/unspecified other < 1.0. Only 165 of these were included in the study, demographic profile of participants not reported. Note: no other demographics reported. **Economic analysis data source:** NA	<u>support:</u> peers were foreign students at the university who had lived in Iowa for 18 to 24 months and who had come from countries with the highest prevalence of TB. Peers served as patient advocates, communicating information and suggestions between students and medical staff. They explained the meaning of a positive PPD test and stressed the importance of TB prevention. They worked individually with a case load of 2 to 4 students, with whom they met weekly for the full 6 months of treatment. LTBI treatment was 6 months of INH. Peers received 16 hours of training on	**Modelling method and assumptions:** NA **Time horizon:** NR	(6%); Spring 1991 = 2/16 (12%); Autumn 1991 = 9/65 (14%); Spring 1992 = 1/22 (5%). The study compared completion rates in Autumn 1993 (unclear which time period it was compared with) and found a statistically significant difference between peer support and treatment as usual (prior to the implementation of the programme); p < 0.0001. **Secondary results:** NA **Attrition details:** NR	There was also no statistical baseline comparison conducted between the selected students in the two groups. Therefore it is not known whether there were any statistically significant baseline differences that may have contributed to different completion rates. The study only statistically compared the completion rates in Autumn 1993, which was the term time with the highest completion rate for the peer support group. This may have led to a bias in results, reducing the internal validity of the study. **Evidence gaps and/or recommendations for future research:** Further investigation into which components are most effective and in which areas efficiency can be improved. **Source of funding:** NR

economic studies: - **Internal validity: - External validity:** + **Quality appraisal economic studies:** NA **Quality score applicability:** NA		communication skills, TB knowledge and medication. **Comparator/control/s description:** Treatment as usual: no peer support, medical staff explained the importance of TB medication and prevention. Students with positive PPD tests were given INH treatment. **Sample sizes: Total:** N = 362**; Intervention:** N =165; **Control:** N =197. Note: these are the number of participants who agreed to start INH treatment. **Baseline comparisons:** NR? **Study sufficiently powered? NR**			

Study details	Population and setting	Method of allocation to intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Nyamathi et al. **Year:** 2008 Data was also extracted from the linked papers, Nyamathi et al. (2006; 2007). **Citation:** Nyamathi, A., Nahid, P., Berg, J., Burrage, J., Christiani, A., Aqtash, S., Morisky, D., et al. (2008). Efficacy of nurse case-managed intervention for latent tuberculosis among homeless	**Source population/s:** Homeless persons with LTBI, USA. **Eligible population:** Homeless adults with LTBI in homeless shelters and residential recovery programs in the Skid Row region of downtown Los Angeles between 1998 and 2003. **Selected population:** The inclusion criteria were as follows: (a) having spent the previous night in 1 of the 12 selected sites; (b) having no self-reported history of completing LTBI therapy; (c) being between the ages of 18 and 55 years,	**Method of allocation:** Sites were randomised to the intervention programme or standard programme. **Intervention/s description:** Nurse Case Management (NCM): in addition to standard care, participants received eight comprehensive educational and skills training modules over 24 weeks in small groups of 4 to 5. The programme was delivered before the treatment dose by research nurses and outreach workers in a culturally competent and tailored manner. Participants were not reimbursed for attending the educational sessions. Intervention components: (a)	**Primary outcomes:** Treatment completion: Defined as 100% compliance to 52 doses of INH, recorded twice weekly by the DOT nurse. Data presented for sub-group characteristics of the population. Note: the study reported other outcomes not relevant to the review such as outcomes relating to depression and TB knowledge, which have not been extracted here. **Secondary outcomes:** **Method of analysis:** chi-square tests; relative risks; zero-order correlations;	**Primary results:** Treatment completion: Treatment group = 172/279 (61.5%); Control group = 94/241 (39.3%); (p<0.001). Adjusting for differences in baseline demographics, treatment completion for the the treatment group compared with control was: AOR = 3.01 (95% CI 2.15-4.20). Treatment completion for intervention vs. control in selected subgroups: Males = Adjusted odds-ratio (AOR) 2.51 (95% CI 1.60-3.93). Females = AOR 5.80 (95% CI 1.72-19.5); Lifetime IDU use = AOR 2.20 (95% CI 0.85-5.67); Daily alcohol use = AOR 10.41; (95% CI 2.48-43.68); Daily drug use = AOR 3.27 (95% CI 1.30-8.25); Homeless shelter recruits =AOR 2.76 (95% CI 1.80-	**Limitations identified by author:** Study not powered to detect disparities in certain subgroups of participants. Sample and setting may not be representative of other contexts. Assessment of drug and alcohol use relied on self-reports only -although strong correlations between these and objective measures had been found in previous research. **Limitations identified by review team:** Participants varied in the treatment and control groups on several demographic variables, however these are controlled for in the analyses. **Evidence gaps and/or recommendations for future research:** "Further research is needed to better

subsamples. *Nursing Research*, *57*(1), 33-39. **Aim of study:** To evaluate the effectiveness of a validated nurse case-managed intervention with incentives and tracking to improve adherence to latent TB infection treatment among homeless persons. **Study design:** Cluster RCT. **Type of economic analysis:** NA	or over the age of 55 years and having reported risk activation factors for active TB, such as IDU or taking immunosuppressing medications; and (d) being Tuberculin Skin Test (TST) positive via the Mantoux method, with at least 10 mm of induration (5 mm if HIV positive). **Excluded population:** Demonstrated cognitive impairment, such as active hallucinations or stupor. **Setting:** Recruitment and screening conducted in 8 homeless shelters and 4 residential recovery programmes in Skid Row, Los Angeles. Treatment occurred	changing context activities related to self-esteem, future-oriented planning, and attitudinal readiness for change; (b) TB and HIV risk reduction education; (c) training in coping, self management, and communication skills; (d) training in social and cognitive problem solving to implement behaviour change; and (e) developing relationships and social networks to maintain behaviour change. Participants who missed appointments for the INH dose or the NCM program were actively tracked and reengaged in the programme by the outreach staff using the detailed locator guides. Intervention based on the Comprehensive Health Seeking and Coping Paradigm	logistic regression; adjusted odds ratios. **Modelling method and assumptions:** NA **Time horizon:** NA	4.23). Across groups, treatment completion was significantly and positively associated with assignment to nurse case management (r = 0.22, p = 0.001); older age, and less heroin or cocaine use. Nurse case management also predicted greater TB knowledge, greater ease of treatment (taking INH, keeping appointments), and more satisfaction with treatment. **Secondary results:** NR **Sample selection and attrition details:** 5,442 homeless persons were screened: 1,483 did not meet inclusion criteria; 5 refused TST and 277 were excluded for other reasons; 2,697/3,959 were PPD negative, 40 refused CXR or were not eligible for it; 199 refused or missed physical exam; 195 were screened out by doctor; 26 refused DOT. In total, 4,902/5,442 were excluded. In the intervention group,	delineate adherence to medication regimens among high-risk subgroups so that resources can be distributed to individuals in these subgroups who are at highest risk of treatment failure." Assessment of the cost-effectiveness of different programmes should be determined. **Source of funding:** National Institute of Health (NIH) through the National Institute on Drug Abuse DA11145 and the NIH Roadmap for Medical Research

Economic perspective: NA **Quality appraisal effectiveness studies:** ++ **Internal validity:** ++ **External validity:** + **Quality appraisal economic studies:** NA **Quality score applicability:** NA	in Wesley Community Health Medical Clinic at the Weingart Center. **Sample characteristics:** Total group: 79.6% male; 81% Black; 90% unemployed; mean age = 42 years (SD = 8.5 years); 72.5% had completed high school; 55.6% never married; 28.3% partnered; 75.4% uninsured; 11.4% recent IDU; 16.0% daily alcohol use; 26.2% daily drug use; 33.1% daily alcohol/drug use. **Economic analysis data sources:** NA	(CHSCP) which includes promotion of health seeking behaviour such as completion of LTBI, and reducing substance use and high-risk sexual activity through direct health education, psychosocial support and linkage to medical and social services. **Comparator/control/s description:** Control group: one 20-minute TB and HIV education session was delivered, no outreach tracking was conducted for those who missed INH treatment. Note: in both treatment and control group, homeless adults were required to present to the clinic twice a week over a period of 6 months to receive DOT of 900 mg of INH with 50 mg Vitamin B6. Incentives of $5 were		11/279 participants were lost to follow-up and 57/279 dropped out of intervention but completed 6-month follow-up survey. In the control group, 11/279 participants were lost to follow-up and 97/279 dropped out of intervention but completed 6-month follow-up survey.	

		paid to the participants for each dose taken. Both groups were tracked for completion of the 6-month questionnaire. **Sample sizes:** **Total:** N = 520 **Intervention:** N = 279 **Control:** N = 241 **Baseline comparisons:** There were significant differences between groups in: Gender: more males in the treatment am ($p<0.001$); Recruitment site: more people recruited from emergency shelters and fewer recruited from drug recovery shelters in the treatment arm ($p<0.001$); Lifetime IDU: fewer people with lifetime history of IDU in treatment arm ($p<0.001$); Daily drug use: fewer people taking illicit drugs daily in the			

		treatment arm (p<0.05); Daily alcohol or drug use: fewer people taking alcohol or illicit drugs daily in the treatment arm (p<0.05). **Study sufficiently powered?** Yes.			

Study details	Population and setting	Method of allocation to intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Oscherwitz et al. **Year:** 1997 **Citation:** Oscherwitz, T., Tulsky, J., P., Roger, S., Sciortino, S., Alpers, A., Royce, S., & Lo, B. (1997). Detention of persistently non-adherent patients with tuberculosis. *JAMA 278*(10), 843.	**Source population/s:** Non-adherent patients with active TB in the USA, 81% of whom were drug or alcohol users. **Eligible population:** Patients who were legally detained because of non-adherence to TB treatment in 1994 or 1995; compared with adult patients with TB aged 15 to 69 who were not legally detained.	**Method of allocation:** Natural allocation based on documentation that a TB patient was legally detained compared with patients in the same period who were not legally detained. **Intervention/s description:** Legal detention: non-adherent patients who were contagious were legally detained; treatment could have been discontinued by the patient when they were released from detention. No	**Primary outcomes:** Treatment completion: determined by clinical records; those who detained patients were also contacted to determine the status of patients who were still in treatment when clinical records were reviewed. Treatment completion within 12 months: **Secondary outcomes:** NA	**Primary results:** Treatment completion: Legal detention (intent-to-treat) = 44/67(66%); Legal detention (excluding those who died or moved) = 41/49 (84%); Data not reported for the comparison group. Treatment completion within 12 months: Legal detention (excluding those who died or moved = 20/49 (20%); Control group = 82% (not clear how many people were included);	**Limitations identified by author:** NR **Limitations identified by review team:** There were statistically significant differences between the treatment and control group in factors that may have impacted on treatment completion as more participants who were detained were hard to reach (more likely to be drug users, homeless, foreign-born and diagnosed with TB in prison compared with the control group). The intervention group were selected for being non-

Aim of study: The aim of the study relevant to this review was in persistently non-adherent TB patients who were legally detained, how many of these completed treatment compared to a cohort of patients who were not legally detained? **Study design:** Retrospective cohort **Type of economic analysis:** NA **Economic perspective:** NA **Quality**	**Selected population:** NA **Excluded population:** In the treatment group, those who were only issued orders of examination or isolation were excluded. In the control group, those who died, moved, remained in therapy or had unknown reasons for stopping therapy were excluded. **Setting:** NR **Sample characteristics:** Age, mean: 34.7 (legal detention) to 41.8 (control group) years old; and Male: 68.8% (legal detention) to 67.4% (control group). **Economic analysis data**	information was reported on how long legal detention lasted. **Comparator/control/s description:** Control group: patients who received the same treatment regimen as the treatment group but without detention. No further information was reported. **Sample sizes:** **Total:** N = 4325 **Intervention:** N = 67 **Control:** N = 4258 **Baseline comparisons:** There was a statistically significant difference between treatment and control groups at baseline such that the treatment group was more likely to be hard to reach for all the characteristics below ($p < 0.001$): Foreign-born: 76.6% (detained) vs. 34.6% (control); Homeless: 45.6%	**Method of analysis:** Two-tailed *t* test for continuous data and x^2 test for categorical data. **Modelling method and assumptions:** NA **Time horizon:** NR	$P < 0.001$. **Secondary results:** NA **Attrition details: NR?**	adherent which was not the case for the control group, therefore, similar groups are not being compared. The study met the inclusion criteria for the review because over 50% of the sample was drug or alcohol users. However, the majority (80.81%) of drug users were in the treatment group. This means that the control group were not hard to reach limiting the applicability of the review to the research question. The treatment and control group also had different exclusion criteria and additional measurement of treatment completion (additional data provided for the treatment group via the professional who detained the patient) **Evidence gaps and/or recommendations for future research:** The effect of legal detention on adherence rates remains unknown, as the intervention group were selected for initial non-compliance, compared

appraisal non-economic studies: - **Internal validity: - External validity:** + **Quality appraisal economic studies:** NA **Quality score applicability:** NA	**source:** NA	(detained) vs. 12.3% (control); IDUs: 39.6% (detained) vs. 7.6% (control); Non-injection drug user: 55.8% (detained) vs. 13.5% (control); Alcohol abuse: 66.0% (detained) vs. 20.8% (control); Drugs or alcohol abuse: 80.8%(detained) vs. 26.3% (control); Diagnosed with TB in prison: 18.6% (detained) vs. 6.1% (control). **Study sufficiently powered?** NR			with the control group which were presumably more compliant at baseline **Source of funding:**

Study details	Population and setting	Method of allocation to intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Ricks **Year:** 2008 **Citation:** Ricks, P., M.	**Source population/s:** Drug users with active TB, USA. **Eligible population:**	**Method of allocation:** Participants randomly assigned to intervention/control using a random number sequence and allocated using	**Primary outcomes:** TB treatment completion: decided by the physician and based on the percentage of doses taken and the	**Primary results:** Treatment completion: intervention group = 41/48 (85%); control group = 28/46 (61%); RR = 2.68, 95% CI 1.24 - 5.82 (p = 0.01).	**Limitations identified by author:** small sample size and high dropout rate limited the ability to detect changes that may have been small but significant. However, the study did manage to find

(2008). *Tuberculosis control among substance users: The indigenous leadership outreach model vs. standard care (PhD Thesis)*. Chicago, Illinois: University of Illinois at Chicago. **Aim of study:** To compare the effectiveness of the Indigenous Leader Outreach Model (ILOM) vs standard TB management among substance users. **Study design:** RCT	Substance users undergoing TB treatment in Chicago. **Selected population:** Inclusion criteria: 1) was assigned to West Garfield TB nursing station, which was where the primary Chicago Department of Public Health (CDPH) case management nurse was located, 2) was at least 18 years of age, 3) had used an illicit drug in the 6 months prior to enrolment and/or daily use of alcohol in the 6 months prior to enrolment, 4) had active TB and DOT was ordered by the CDPH physician, 5) agreed to complete baseline and follow-up interviews, 6) agreed to provide blood samples for	sequentially numbered envelopes. **Intervention/s description:** Enhanced model: two person mixed-gender team of Indigenous Leader Outreach Workers (ILOWs) (former substance users) who provided DOT. Patients were seen every 30 days for medical evaluation. ILOWs facilitated client attendance at scheduled medical exam appointments by reminding clients of their appointments, providing incentives (monetary and non-monetary, such as tokens), providing transportation, and advocating/translating for clients with the health care provider at the appointment. The ILOWs also provided the client with comprehensive health information regarding infectious diseases, strategies for reducing	timing. This was typically defined as the patient taking 80% of their medication from the DOT worker. Treatment compliance: having taken at least 80% of prescribed doses of TB medication, *whilst under treatment*. People who missed taking medication from their DOT worker may have been considered compliant, if it was verified that they received treatment from another source, such as a hospital or jail. Missed DOT appointments: missing a scheduled DOT appointment. Consecutively missed appointments. **Secondary**	Treatment compliance: intervention group = 38/48 (84%); control group = 25/46 (68%) (RR=2.51, 95% CI 1.15-5.48, p = 0.016). Missing DOT appointments: control group = 7.64 (mean); treatment group = 4.11 (p = 0.13). Consecutively missed DOT appointments: comparison group = 3.82 (mean); treatment group = 3.96 (p = 0.57). **Secondary results:** NA. **Sample selection and attrition details:** 100/549 suspected cases were eligible and consented to participate. Of these, 6 were found after randomisation to not have active TB and thus were removed from the analysis. Among the remaining	some statistically significant differences. **Limitations identified by review team:** The aim of the study was to examine whether using peers from similar hard-to-reach groups was more effective than using non-peer health workers. However, in the treatment group participants also received intensive case management. This made it difficult to determine which component of the intervention led to improved outcomes. **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** NR

Type of economic analysis: NA **Economic perspective:** NA **Quality appraisal effectiveness studies: ++** **Internal validity:** ++ **External validity:** + **Quality appraisal economic studies:** NA **Quality score applicability:** NA	HIV-testing after each interview. **Excluded population:** Potential participants who failed to meet one of the criteria above. **Setting:** Chicago, October 1996 to July 2000 **Sample characteristics:** 61% African American male; 58% had never been married; 61% lived with other people; 3% had private insurance; 57% spent most nights in the preceding 6 months at their own or partner's house or apartment; leading source of income (20%) was benefits from the Veterans Affairs, disability, and Supplemental	specific risk behaviours, and prevention materials. **Comparator/control/s description:** Standard CDPH approach: one public health worker who performed DOT, with limited case management provided by a nurse case manager. Patients were seen every 30 days for medical evaluation. The nurses were responsible for all case management services, and for developing referral relationships with social service and health care providers. The CDPH was able to provide monetary incentives and tokens for transportation to patients with adherence issues. **Sample sizes:** **Total** 94 **Intervention** 48 **Control** 46 **Baseline**	**outcomes:** Changing HIV and TB risk behaviours, TB knowledge, and sense of TB stigmatisation among adult substance users with TB in Chicago. [not extracted] **Method of analysis:** Modified intention-to-treat analysis (participants who after randomisation were found to not have TB were excluded from analysis); Fishers t-test; Wilcoxon rank-sum tests. **Modelling method and assumptions:** NA **Time horizon:** NA	94, 6 died or were transferred before DOT, 2 withdrew from the study and 7 refused to be interviewed. Overall, 36/46 (78%) cases completed the study in the control group, and 43/48 in the intervention group (90%).	

	Security Income; mean monthly income from all sources was $746 (median $511); 56% had a chest X-ray at time of diagnosis that was consistent with active TB; injecting drug use was low (5%), freebasing cocaine or crack, smoking marijuana, and non-injecting heroin use were the three most frequently used illicit drugs; 74% reported multiple drug use; alcohol use was the most common (70%); 45% had a regular sexual partner. **Economic analysis data sources:** NA	**comparisons:** No significant differences in gender, race, education, risk behaviours, TB knowledge, or TB stigma. **Study sufficiently powered?** The final sample had 76% power to detect a 20% difference in completion rates between the two groups.			

Study details	**Population and setting**	**Method of allocation to intervention/ comparator**	**Outcomes and methods of analysis:**	**Results**	**Notes**
Authors:	**Source population/s:**	**Method of allocation:**	**Primary outcomes:**	**Primary results:**	**Limitations identified by**

Rodrigo et al. **Year:** 2002 **Citation:** Rodrigo, T., Caylà, J., A., Garcia, O., P., Brugal, M., T., Jansà, J., M., Guerrero, R., Marco, A., et al. (2002). Effectiveness of tuberculosis control programmes in prisons, Barcelona 1987-2000. *The International Journal of Tuberculosis and Lung Disease*, *6*(12), 1091–1097. **Aim of study:** To evaluate a TB programme	Prisoners (unclear which type of TB), Spain. **Eligible population**: Any prisoner who had been incarcerated at any time during their TB treatment between 1987 and 2000. **Selected population:** NA **Excluded population:** Those who had emigrated or been transferred to prisons not included in the study; those who died (as it was not known if they had completed treatment). **Setting:** Prison (long- and short-term), and in some cases the continuation of treatment in the community. **Sample characteristics:** NR **Economic analysis data source:** NA	Natural allocation comparing those who received treatment with DOT which started in 1993 compared with a historical cohort in prison between 1987 and 1992, who did not receive DOT. **Intervention/s description:** DOT: direct observation by a health worker of the patient swallowing the pills. Prisoners were offered the opportunity to continue treatment in various sites in the community once realised from prison: methadone maintenance clinic, outpatient services, or shelter facilities. DOT was provided for 6.5% of patients initially, increasing to 84.6% in 1995 and 100% in 2000. Contact tracing was also conducted.	Incidence rates: number of cases treated in prison for TB each year, divided by the annual average prison population. Unclear whether this related to active or LTBI. Smear-positive incidence rates: number of smear-positive cases treated in prison each year, divided by the annual average prison population. Diagnostic delay: median number of days between the start of treatment and the date of onset of symptoms; this was restricted to smear-positive cases. Treatment adherence: correctly followed treatment regimen during the indicated time not	Incidence rates: *TAU* 1987 = 3418 per 100,000; 1992 = 8041 per 100,000. *DOT* 1993 = 5089 per 100,000; 2000 = 812 per 100,000. The author reports that incidence rates rose significantly during the TAU years (1987 to 1992), then fell significantly during the DOT years (1993 to 2000) ($p < 0.0001$). Smear-positive incidence rates: *TAU* 1987 = 1227 per 100,000; 1992 = 2056 per 100,000. *DOT* 1993 = 1398 per 100,000; 2000 = 174 per 100,000. Diagnostic delay (median days): *TAU* 1987 = 67 days;	**author:** NR **Limitations identified by review team:** There was no information on the characteristics of the sample investigated in the study and whether there were any differences in the population between the two time periods. This makes it difficult to determine the generalisability of the included population to compare with other studies and in understanding the validity of the findings. Given the design of the study, it is not known whether the differences in the incidence rates were due to the implementation of DOT or due to other factors. The study demonstrated graphically that there was also a decline in incidence of TB in the general population similar to the decline in prison. Therefore the decline may not be specific to DOT but a natural decline in incidence rates due to other factors. **Evidence gaps and/or**

with DOT in prisons in Barcelona. **Study design:** Before and after **Type of economic analysis:** NA **Economic perspective:** NA **Quality appraisal non-economic studies:** - **Internal validity: -** **External validity:** + **Quality appraisal economic studies:** NA **Quality score applicability:**		No details given on the medication prescribed. **Comparator/control/s description:** Treatment as usual: before the implementation of DOT in prison. No further information provided. **Sample sizes:** **Total:** NR **Intervention:** NR **Control:** NR **Baseline comparisons:** NR **Study sufficiently powered?** NR	specifically for DOT; non-adherence: abandoning treatment for more than 60 days and not returning for recommencement. DOT treatment adherence: correctly followed treatment regimen for DOT. **Secondary outcomes:** NR **Method of analysis:** Mantel-Haentzel **Modelling method and assumptions:** NR **Time horizon:** NR	1992 = 30 days. *DOT* 1993 = 31 days; 2000 = 32 days. Treatment adherence: *DOT* *TAU* 1987 = 43 per 100; 1992 = 67 per 100. 1993 = 90 per 100; 2000 = 63 per 100. Treatment adherence for smear-positive cases: *TAU* 1987 = 60 per 100; 1992 = 76 per 100. This increase was statistically significant ($p < 0.001$) *DOT* 1993 = 95 per 100; 2000 =100 per 100. This increase was statistically significant ($p < 0.001$) DOT treatment adherence (and	**recommendations for future research:** NR **Source of funding:** NR

NA				percentage on DOT): *DOT* 1993 = 100% (6.5%); 1994 = 83.3% (16.7%); 1995 = 93.8% (95.5%); 1996 = 92.2% (84.6%); 1997 = 95.8% (88.3%); 1998 = 100% (88%); 1999 = 78.9% (100%); 2000 = 83.3% (92.9%). The author reports that the proportion of patients undergoing DOT treatment increased significantly over time between 1993 and 2000($p < 0.0001$). **Secondary results:** NR **Attrition details:** NR	

Study details	**Population and setting**	**Method of allocation to intervention/ comparator**	**Outcomes and methods of analysis:**	**Results**	**Notes**
Authors: Schwartzman et al. **Year:** 2005	**Source population/s:** Immigrants with LTBI, USA. **Eligible**	**Method of allocation:** NA **Intervention/s description:** DOPT expansion:	**Primary outcomes:** Costs: direct and indirect. Direct costs were borne by the US government and health care system	**Primary results:** DOPT expansion: Cases of TB averted (compared with radiographic screening	**Limitations identified by author:** The authors state that there was some uncertainty surrounding some parameters used in the model. These included

Citation: Schwartzman, K., Oxlade, O., Barr, R., G., Grimard, F., Acosta, I., Baez, J., Ferreira, E., et al. (2005). Domestic returns from investment in the control of tuberculosis in other countries. *New England Journal of Medicine*, *353*(10), 1008-1020. **Aim of study:** To investigate the health-related outcomes and costs of adding a directly observed treatment, short-course (DOTS) programme in	**population:** NA **Selected population:** NA **Excluded population:** NA **Setting:** NR **Sample characteristics:** Modelling assumptions for the sample from Mexico: mean age of 27 years for legal immigrants, 29 years for undocumented migrants and 35 years for temporary visitors; prevalence of LTBI was 6.3% for legal immigrants, 6.3% for undocumented migrants and 6.9% for temporary visitors; prevalence of HIV infection was 0% in legal immigrants and 0.3% for undocumented migrants and	aUS-funded expansion of a DOPT programme with X-ray screening in Mexico,plus radiographic screening when entering the USA. The DOTS strategy in Mexico was expanded in order to reach100% coverage of the population. Note: there was another intervention relevant to the identification review that was not extracted here (TST screening plus radiographic screening). **Comparator/control/s description:** No DOPT: Radiographic screening: current practice of radiographic screening and TB control in Mexico. **Sample sizes:** **Total:** estimated that over the 20-year period 35.4 million migrants would enter the USA	for the expansion of the DOTS strategy and TB screening and health care. Indirect costs are out-of-pocket expenditures by patients and their families and lost wages due to death, disability, or provision of care. **Secondary outcomes:** NR **Method of analysis:** NA **Modelling method and assumptions:** Decision-analysis model using multiple Markov processes. 3% discount rate. 2003 US dollars. Modelling cost of radiographic screening: cost of screening per person, $16.73; cost of medical evaluation per	alone): 2,591. Deaths prevented: 349. Total direct costs: $1,901 million. Net savings on direct costs (compared with radiographic screening alone): $84 million. Total indirect costs: $608 million. Net savings on indirect costs (compared with radiographic screening alone): $24 million. Net savings on indirect and direct costs: $108 million. Sensitivity analyses demonstrated that net savings would have occurred even if the US government doubled its initial investment for the DOPT programme, or paid for antituberculosis drugs for all new and retreated cases in Mexico for all 20 years,	the assumption that the incidence of TB would decrease by 6% annually. This figure was taken from the rate of decline found in Peru after expansion of a DOPT programme. However, the expansion of the DOPT programme would have remained cost-saving unless the decline was less than 1.2% annually. Another uncertainty noted by the authors was that the patterns of migration would remain constant over 20 years. However, a sensitivity analysis demonstrated that the prevalence of migrants could have dropped to one third of the estimated values and the expansion of the DOPT programme would have remained cost-saving. The model did not consider the secondary spread of TB, however, by excluding this, it would have underestimated the cost-savings of the DOPT programme. Lastly, the costs of the DOPT programme were uncertain but were taken

Mexico or a TST to the standard radiographic screening to immigrants in the USA. **Study design:** NA **Type of economic analysis:** cost-saving. **Economic perspective:** societal (direct costs by US government, indirect costs by immigrants and their families). **Quality appraisal non-economic studies:** NA **Internal validity:** NA **External validity:** NA	temporary visitors; prevalence of underlying MDR infection was 2.4% for all the groups; and average income in the 5th year after entry was $18,054 for legal immigrants, $14,443 for undocumented migrants and $0 for temporary visitors. **Economic analysis data source:** Various published resources for characteristics of the sample. Costs for the DOT expansion came from those derived from an equivalent expansion project in Ecuador; drugs expenditure from WHO incidence estimates and drug prices in the Global Drug Facility.	from Mexico. **Intervention:** NR **Control:** NR **Baseline comparisons:** NA **Study sufficiently powered?** NA	person if result abnormal, $144.36 Modelling cost of TST: cost of screening per person, $16.51; cost of medical evaluation per person if test is positive, $100.44. Modelling cost of treatment of LTBI per person, $281.69. Modelling costs of initial DOTS expansion: $34.9 million; costs of antituberculosis drugs in Mexico for 20 years, $2.8 million. Modelling costs of active TB following migration: direct costs per person $36,045; and indirect costs $2,262. Sensitivity analyses varied all the modelling	or if the number of migrants was only 33% of the current levels. Likewise, if the number of migrants entering the USA or the prevalence of HIV infection, LTBI or drug resistance was higher than estimated, net savings would have been greater. **Secondary results:** <u>DOPT expansion:</u> Cases of TB prevented (compared with radiographic screening alone): 342 from Haiti and 248 from Dominican Republic. Net savings on direct cost (compared with radiographic screening alone): $9 million for migrants from Haiti and $5 million for migrants from Dominican Republic. Net savings on indirect costs (compared with radiographic screening	from the costs of a similar programme in Ecuador, and the effects of varying these costs were calculated in a sensitivity analysis. **Limitations identified by review team:** none in addition to the above. **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** grant from the Rockefeller Foundation.

Quality appraisal economic studies: ++ **Applicability:** +			assumptions. Subgroup analyses to see if similar results were found if the programme was impletemented in Haiti or the Dominican Republic. A full list of assumptions and costs for providing a similar programme in Haiti or the Dominican Republic are provided by the authors in an appendix. **Time horizon:** 20 years.	alone): $4 million for migrants from Haiti and $2 million for migrants from Dominican Republic. Net savings on indirect and direct costs (compared with radiographic screening alone): $13 million for migrants from Haiti and $7 million for migrants from Dominican Republic. **Attrition details:** NA	

Study details	Population and setting	Method of allocation to intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Tulsky et al. **Year:** 2000 **Citation:** Tulsky, J., P.,	**Source population/s:** Homeless with LTBI, USA. **Eligible population:**	**Method of allocation:** Block randomisation where one third of participants were randomly assigned to each arm; from June 1992 to December	**Primary outcomes:** <u>Adherence: 6 months' completion of isoniazid preventive therapy:</u> collected from review of medical	**Primary results:** <u>Adherence: 6 months' completion of isoniazid preventive therapy:</u> Overall: 36/118 (31%) Monetary incentive: 19/43 (44%)	**Limitations identified by author:** NR. **Limitations identified by review team:** The generalisability of the sample may be limited as it

Pilote, L., Hahn, J., A., Zolopa, A.,J., Burke, M., Chesney, M., et al. (2000). Adherence to isoniazid prophylaxis in the homeless: a randomized controlled trial. *Arch Intern Med 160*(5), 697-702. **Aim of study:** To compare the effectiveness of bi-weekly DOPT plus cash incentives and DOPT plus case management by peer health advisers with standard care on treatment adherence for homeless people with LTBI.	People with LTBI who were homeless or marginally housed residing in either an emergency shelter or any other outdoor public space or those temporarily residing in low-cost hotels. **Selected population:** Participants who: 1) had a positive TST result according to the Centers for Disease Control and Prevention criteria and/or had a credible history of a prior positive TST result without any follow-up in the previous 6 months; 2) were fluent in spoken English or Spanish; 3) completed a visit to the TB clinic and agreed to take isoniazid preventive therapy for 6	1994. Allocation was concealed as participants made a blinded selection of labelled coins from a bag. **Intervention/s description:** <u>DOPT plus cash incentives</u>: Participants were given 900mg of isoniazid, twice weekly for 6 months and received $5.00 for each visit. Each dose taken was observed by a research assistant (lay persons trained by the study physician) who also monitored side effects. If a dose of isoniazid was missed then attempts to contact the participant was made. <u>DOPT plus case management by peer health adviser</u>: Participants given	charts; observed dose taken and recorded for treatment arms, but was reliant on self-report for control arm. <u>Median number of months isoniazid dispensed</u>: this included subjects who interrupted and re-entered treatment. The exact number who re-entered is not reported. <u>Probability of receiving at least 3 months of isoniazid treatment.</u> **Secondary outcomes:** NR **Follow-up:** 6 months from treatment initiation to completion. **Method of analysis:** Wilcoxon rank sum tests to test for	Peer health adviser: 7/37 (19%) Usual care: 10/38 (26%). Monetary incentive vs. peer health adviser: p = 0.02, Monetary incentive vs. usual care: p = 0.11 Peer health adviser vs usual care: ns (p-value not reported). <u>Significant predictors of treatment completion at 6-months:</u> Monetary incentive compared with peer adviser/control: OR = 2.57 (95% CI 1.11 to 5.94); Residence in a hotel or other stable housing compared with residence on the street or in a shelter: OR: 2.33 (95% CI 1.00-5.47). <u>Median number of months isoniazid dispensed:</u> Monetary incentive group: 5 months; Peer health adviser =	included only those who returned for TST results within one week of the initial appointment. In addition, the sample included some participants who lived in apartments but were picked up in food shelters. Due to the nature of the intervention there was a difference in measurement of adherence, one being more reliable than the other. For the treatment arms adherence was via DOT while for the control arm it was an indirect measure of dosage taking through collection of medication. The protocol was changed so that all participants received a $5 incentive to return for their initial appointment, causing contamination of intervention which would have underestimated the differences between the groups. However, the change happened at a later stage of the study, and there were no observed significant demographic differences

Study design: RCT **Type of economic analysis:** NA **Economic perspective:** NA **Quality appraisal non-economic studies:** + **Internal validity:** + **External validity:** + **Quality appraisal economic studies:** NA **Applicability:** NA	months or more; 4) people in whom isoniazid treatment was delayed pending further evaluation but who eventually received it. **Excluded population:** Those individuals receiving prophylaxis or treatment for active TB or individuals who were HIV positive. **Setting:** TB clinic, USA. **Sample characteristics:** All participants: Male: 86%, N =101; Age, median: 37 years; African American: 52%, N = 61; White: 25%, N = 21 Hispanic: 27%, N = 32; Homeless > 1 year: 50%, N = 59; Ever in prison/jail:	900mg of isoniazid, twice weekly for 6 months. Peer health adviser provided isoniazid treatment, observing participants taking each dose and monitoring side effects before each dose of INH. Any potential side effects were referred to a physician. If participant missed an appointment then the peer health adviser spent allotted time to locate the individual. Each participant was assigned 1 peer health advisor for the duration of their treatment course. Those whose drug treatment was not dispensed immediately by the TB clinic pending the results of additional testing were visited twice weekly by a health adviser for a review of TB symptoms.	baseline differences. X^2 tests or Fisher exact tests were used for the analysis of categorical variables. Probability of adherence estimated using Kaplan-Meier methods. Variables associated with increased adherence ($p < 0.10$) in bivariate analysis were included in a forward stepwise logistic regression model. Compared monetary incentive arm with other two arms (treatment and control) due to insufficient numbers to conduct a multivariate analysis comparison groups. Did not include 3	2 months; Usual care = 2 months. The difference was statistically significant in the monetary incentive arm compared with the peer adviser arm ($p = 0.005$) and usual care ($p = 0.04$). Probability of receiving at least 3 months of isoniazid treatment: Monetary incentive arm = 71% (95% CI 59%-86%); Peer health adviser = 42% (95% CI 29%-61%); Usual care = 45% (95% CI 31%-64%). **Secondary results:** NR **Sample selection and attrition details:** N = 3 due to adverse effects (the number dropped out in each comparison was not reported). 330/2158 participants	between groups before and after this change. **Evidence gaps and/or recommendations for future research:** The role of different types of incentives should be discussed for active TB and preventive therapy. **Source of funding:** NR

	59%, N = 70; Injection of drugs (past 30 days): 11%, N = 13; Crack cocaine use (past 30 days): 36%, N = 42; Living in street or shelter: 67%, N = 79; Living in hotel, apartment or other: 33%, N = 39; Ever hospitalised formental illness: 15%, N = 18. **Economic analysis data source:** NA	Peer health advisors worked 12 hours a week for $8.98 per hour; had to be homeless at the time of hire or during the previous year of hire. The peer health adviser accompanied his/her client to the clinic for monthly refill appointments. **Comparator/control/s description:** <u>Usual care:</u> 300mg of isoniazid daily for 6 months. Participants were given 1 month's supply of medication and asked to return monthly for 6 months. If an appointment was missed, staff sent up to 3 letters or made 3 telephone calls to locate the individual. Participants were considered adherent to treatment if they picked	individuals in analysis as treatment was stopped due to adverse effects (analysis therefore not ITT). **Modelling method and assumptions:** NA **Time horizon:** NA	were screened and eligible. 121/330 participants were prescribed isoniazid treatment after confirmation of LTBI after further testing with sputum cultures. 3/121 participants were excluded from analysis due to adverse effects from isoniazid treatment.	

		up their monthly refill (rather than by direct observation). Note: all participants were monitored monthly and provided with isoniazid refills. There was also a change in protocol where one-off $5 incentives were given to all participants to attend the first clinic appointment (rather than only to the monetary incentive group during the course of study). This change took place after 91 of the 118 had been recruited in the study. No significant differences in demographic characteristics or adherence behaviour were observed between those recruited before and after this change in protocol. **Sample sizes:**			

		Total: N **=** 118 **Intervention:** DOPT plus case management by peer health adviser: N = 37 DOPT plus cash incentives: N = 43 **Control:** N = 38 **Baseline comparisons:** There were no significant baseline differences between the three comparison arms. **Study sufficiently powered?** NR			

Study details	**Population and setting**	**Method of allocation to intervention/ comparator**	**Outcomes and methods of analysis:**	**Results**	**Notes**
Authors: Tulsky et al. **Year:** 2004 **Citation:** Tulsky, J., P., Hahn, J., A., Long, H., L., Chambers,	**Source population/s:** Homeless with LTBI, USA. **Eligible population:** Those living on the street and in shelters and those marginally housed in hotels	**Method of allocation:** Randomisation from a list of randomly generated numbers that had been previously sealed into envelopes (allocation concealment). **Intervention/s description:**	**Primary outcomes:** <u>Completion of 6 months' preventive therapy</u>: collected from review of medical charts, participants were directly observed while taking medication.	**Primary results:** <u>Completion of 6 months' preventive therapy</u>: 58/65 (89.2%) completed therapy in the cash incentive group; 44/54 (81.5%) completed therapy in the voucher incentive	**Limitations identified by author:** NR **Limitations identified by review team:** For participants on the daily 600 mg of rifampin and 300 mg of isoniazid regimen, DOPT was only carried out 2 days a week, with self-

D., B., Robertson, M., J.Chesney, M., A., & Moss, A. R. (2004). Can the poor adhere? Incentives for adherence to TB prevention in homeless adults. *The International Journal of Tuberculosis and Lung Disease*, *8*(1), 83–91. **Aim of study:** To compare the effect of DOPT plus a $5 cash incentive compared with DOPT plus vouchers worth $5 on completion of treatment.	from May 1996 to December 1997. **Selected population:** Those with a new positive TST result, or who clearly described a past positive TST result and had not had a chest X-ray in the last 6 months (it was not reported whether those with previous test had previously been treated). **Excluded population:** Those with HIV and those assumed to have active TB. **Setting:** Community, storefront setting in inner-city San Francisco. **Sample characteristics:** <u>All participants</u>: Age, median: 41 years (range 21-	<u>Cash incentives</u>: $5payment for keeping each twice-weekly medication appointment. **Comparator/control/s description:** <u>Voucher incentives</u>: a choice of fast-food or grocery store coupons worth £5 given for keeping each twice-weekly medication appointment. Note: For both groups, participants were observed taking their medication on study site. Participants were escorted monthly to a nearby TB clinic to review symptoms and refill medication. Medication was either 900 mg isoniazid twice weekly for 6 months or 600 mg of rifampin plus 300mg of isoniazid daily for 4 months. DOPT only occurred twice weekly therefore participants on rifampin self-administered their	<u>Hours of follow-up needed for participants who missed appointments.</u> **Secondary outcomes:** <u>Cost of treatment per participant:</u> included the cost of the incentive plus staff time averaging $13.39 per hour. The cost of rent, office supplies, phone lines and medication was not included as the author states that this would be necessary in any setting for treatment of LTBI. <u>Cost of follow-up per participant:</u> **included** the costs listed above, and assumed that follow-up would take 1 hour per participant for outreach efforts and 10 minutes for each phone call or letter.	group; p = 0.23. Being a resident in hotels (92%) compared with living in the streets/shelters (79%) was statistically significantly predictive variable of completing treatment (p = 0.04). There were differences between groups in this variable. In a multiple regression analysis, being male (OR = 5.65, 95% CI 1.36-23.50) and staying in a hotel/other (OR = 4.86, 95% CI 1.32-17.94) were independently predictive of completing treatment. Assignment to cash incentive group was not independently predictive of treatment completion (OR = 1.94, 95% CI 0.65-5.83). <u>Hours of follow-up needed for participants who missed appointments:</u>	administration on the remaining 5 days. There is no reason to suggest that the numbers who were prescribed this medication were different between groups. However, the numbers were not reported. Adherence with a daily regimen for 4 months may well be different from a twice-weekly, 6-month regimen, making it difficult to interpret these data. There were significant differences at baseline: there were a greater number of participants residing in shelters and on the streets in the voucher incentive arm compared with the cash incentive arm. This demographic was predictive of not completing treatment and therefore would have confounded any differences between the groups caused by the different incentives. This baseline difference was only adjusted for in the multivariate analysis and when controlling for this factor, group assignment was not independently

Study design: RCT **Type of economic analysis:** NA **Economic perspective:** NA **Quality appraisal non-economic studies:** + **Internal validity:** + **External validity:** + **Quality appraisal economic studies:** NA **Applicability:** NA **Quality score:** NA	79); African American: 47% Caucasian: 32% Other ethnicity: 21% Lifetime history of crack cocaine use: 51% Living in shelter or on the street: 49% **Economic analysis data source:** NA	medication on the non-clinic days. The number of participants prescribed each medication regimen was not reported, and so it is unclear whether there were significant differences in regimen use between groups. All participants were followed up after missed appointments. After the first missed appointment, staff made phone calls and sent reminder letters. After the second missed appointment, outreach efforts were made including visits to the known address, the free meal programmes visited by participant, and other known locations. 3 outreach efforts were made in the first month after a missed appointment, 1 outreach effort after the first month. If the participant did not take any preventative therapy	**Method of analysis:** X^2 or Fisher's exact test for categorical variables. Mann-Whitney test for continuous variables. Multivariate analysis using stepwise logistic regression. **Modelling method and assumptions:** NA **Time horizon:** NA	Median and mean follow-up hours were 0.5 and 2.0 in the cash arm compared to 1.7 and 4.5 in the non-cash arm. In a multivariate analyis, cash incentive (OR=2.67, 95% CI 1.13-6.31, P=0.02), no history of crack cocaine use (OR=2.56, 95% CI 1.08-6.07, P=0.03), and a prior history of isoniazid treatment (OR=3.51, 95% CI 0.98-12.5, P=0.05) were independent predictors of needing less time (< 1 hour) for follow-up. **Secondary results:** Cost of treatment per participant: $460.90 for the cash incentive group and $494.45 in the voucher incentive group taken into account the cost of treatment across groups (434.20 plus the follow-up costs below).	predictive of treatment completion. The study was also not sufficiently powered to detect a 20% difference or less between groups. **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** Supported by grants from the National Heart, Lung, and Blood Institute and the National Institute of Mental Health.

		for 1 month, they were dropped from the study and considered lost to follow up. **Sample sizes:** **Total:** N = 141 **Intervention:** N = 72 **Control:** N = 69 **Baseline comparisons:** There were significant differences between groups: more participants lived in a shelter/street in the voucher incentive group (41%) compared with the cash incentive group (23%; p = 0.04). **Study sufficiently powered?** The study was underpowered given the sample it included in the study as it needed 86% power, with 85 participants per arm to detect a difference of 0.20 between groups. The study only had 67% power with the		<u>Cost of follow-up per participant:</u> In the cash incentive arm, participants required an average of 2 hours of follow-up which cost $26.78 per participant. For the voucher incentive arm, participants required 4.5 hours of follow-up which cost an average of $60.26 per participant. **Sample selection and attrition details:** <u>Sample selection:</u> 488/2570 of those screened were eligible for referral to TB clinic. 212/488 attended clinic; there was significant difference between those who did and did not attend the clinic such that they were more likely to be US born, or to have a history of daily drinking and injection drug use. 141/212 met inclusion criteria and consented to randomisation.	

		final sample size.		Attrition: 5 participants stopped medication due to adverse events, 1 died in a hotel fire.	

Study details	Population and setting	Method of allocation to intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: White et al. **Year:** 1998 **Citation:** White, M., C., Tulsky, J., P., Reilly, P., McIntosh, H., W., Hoynes, T., M., & Goldenson, J., (1998). A clinical trial of a financial incentive to go to the tuberculosis clinic for isoniazid after release	**Source population/s:** Prisoners with LTBI, USA. **Eligible population:** Prisoners in San Francisco City and County Jails in 1996 with LTBI who agreed to begin therapy in jail and were released into the community while still undergoing therapy. . **Selected population:** Inmates screened for TB who agreed to take INH preventive therapy	**Method of allocation:** Random allocation using previously sealed envelopes in which group assignment was indicated using a table of random numbers. **Intervention/s description:** Incentive: $5 cash incentive provided at the time of first visit to the TB clinic in addition to standardised TB education given at the time INH was started in the jail. **Comparator/control/s description:** Control: standardised TB education alone. Note: the medication	**Primary outcomes:** Adherence to first visit to the TB Clinic: measured whether, after release from jail, prisoners made a visit to the TB clinic. The date of the first visit was noted. Treatment completion: noted in the patient medical records whether treatment was completed. However, this was only available for those who visited the clinic. **Secondary outcomes:** Note: The review did not extract reasons	**Primary results:** Adherence to first visit to the TB Clinic: Incentive = 8/31 (25.8%); Control = 7/30 23.3%); OR = 1.43 (95% CI 0.35-3.71; p = 0.82). Treatment completion (among those who visited TB clinic at least once): Incentive = 2/8 (25%); Control = 2/7 (32%). Note: the difference was not statistically compared. **Secondary results:** NA **Sample selection and attrition details:** Sample selection: 20 inmates who were	**Limitations identified by author:** **Limitations identified by review team:** The study was underpowered - the authors noted that 40 individuals were required per group but the study groups included only 30 in the control group and 31 in the treatment group. The study did not statistically compare treatment completion outcomes between study groups as the reviewers acknowledged that there were no appreciable difference across study groups and that the numbers completing treatment were too small to analyse. The study relied on the

from jail. *The International Journal of Tuberculosis and Lung Disease*, *2*(6), 506–512. **Aim of study:** To compare a $5 cash incentive plus standardised TB education with standardised TB education alone in encouraging released inmates to make a first visit to the TB clinic. **Study design:** RCT **Type of economic analysis:** NA **Economic perspective:**	as recommended by jail physicians for TB. **Excluded population:** Those inmates who did not speak English or Spanish; and those who were sequestered from the jail population due to mental illness or violence. **Setting:** Jail setting for education intervention and TB Clinic for receiving cash incentive and checking adherence. **Sample characteristics:** Male= 98.4%; Age (mean) = 32; years; Foreign born = 54.1%; Physician visit or hospitalisation for mental health problems = 27.9%;	treatment provided to the treatment and control group was not reported. **Sample sizes:** **Total:** N = 61 **Intervention:** N = 31 **Control:** N = 30 **Baseline comparisons:** There were no significant differences in the study groups on any baseline variables. **Study sufficiently powered?** Power calculation not reported, however the sample size was calculated as needing 40 participants per group. Final sample consisted of 30 per group.	for why participants did or did not attend their first visit to the TB Clinic as the data was not comparative because it was collapsed across treatment and control groups. **Method of analysis:** Fisher's exact test for dichotomous data; X^2 for categorical data; *t*-tests for normally distributed continuous variables; and Mann-Whitney for ordinal data. **Modelling method and assumptions:** NA **Time horizon:** 9-months' follow-up from the point of study inclusion to allow for sufficient time for treatment completion.	prescribed INH were excluded from the study: nine were released from jail before authors could discuss participation with them; four were determined by jail personnel to be security risks, three spoke neither English nor Spanish; two were hospitalised, and two were no longer taking INH when researchers approached them. Attrition: Of the 79 inmates enrolled in the study, 18 (22.8%) remained in jail or were sent to prison for the full time period of INH prophylaxis. Only the 61 (77.2%) who were released from jail prior to completion of INH were included in the study sample.	review of TB clinic records to measure treatment completion. As not every individual released from prison attended the clinic, treatment completion could not be ascertained for the majority of the sample (74.2% in the treatment group and 76.7% in the control group). This reduces the validity of the findings regarding treatment completion. **Evidence gaps and/or recommendations for future research:** Further work is needed to determine if a financial incentive is valuable in this population, and what amount would be reasonable to influence follow-up at the TB Clinic. **Source of funding:** University of California, Academic Senate

NA **Quality appraisal non-economic studies:** + **Internal validity:** + **External validity:** + **Quality appraisal economic studies:** NA **Quality score applicability:** NA	Ever taken non-prescription drugs = 73.8%; Reported alcohol or drug abuse= 78.7%; Received INH before = 34.4% (does not specify if this indicates failure to complete previous treatment)**.** **Economic analysis data source:** NA				

Study Details	**Population and setting**	**Method of allocation to intervention/ comparator**	**Outcomes and methods of analysis:**	**Results**	**Notes**
Authors: White et al. **Year:** 2002 **Citation:** White, M. C., Tulsky, J. P., Goldenson, J., Portillo,	**Source population/s:** Prisoners with LTBI, USA. **Eligible population:** Jail inmates with LTBI who agreed to begin therapy in jail and were	**Method of allocation:** Randomisation using random numbers. Allocation concealment: sealed envelopes. **Intervention/s description:** <u>Education group:</u> Education, provided	**Primary outcomes:** <u>First visit to the TB Clinic within 1 month after release from jail</u>: completion of therapy was determined by clinicians at the TB clinic. <u>Characteristics</u>	**Primary results:** <u>First visit to the TB Clinic within 1 month of release from jail:</u> Total = 107/325 (33%) Education group: 37% (40/107) Incentive group: 37% (42/114) Control group: 24% (25/104).	**Limitations identified by author:** The authors noted that the exclusion of inmates who were non-English-speaking Asian/Pacific Islanders may have limited the generalisability of the findings as, 5.2% of annual jail bookings in 1998 were Asian/ Pacific Islanders.

C. J., Kawamura, M., & Menendez, E. (2002). Randomized controlled trial of interventions to improve follow-up for latent tuberculosis infection after release from jail. *Archives of Internal Medicine*, *162*(9), 1044-1050. **Aim of study:** To evaluate two interventions aimed at improving adherence to treatment of persons with LTBI after release from jail.	released into the community while still undergoing therapy. **Selected population:** All eligible inmates were approached for recruitment (release date and location was unknown at study recruitment, so consecutive inmates were selected initially). **Excluded population:** Inmates who stayed in prison or remained in custody for the duration of treatment; did not speak English or Spanish; considered violent by prison staff or to have serious psychiatric illnesses; known HIV positive and under care of	every 2 weeks while in jail, to reinforce the information initially provided to all subjects. Information included: details of LTBI, therapy, adverse effects, availability of free care after release, and location of, transportation to, and hours of the TB Clinic. Incentive group: Promise of an incentive ($25 equivalent in food or transportation vouchers) offered at the first visit to the TB Clinic following release. No further contact with study personnel in jail. **Comparator/control/s description:** Usual care: 6 months' INH was provided. Jail electronic medical records were reviewed daily and standard information was provided once therapy was started. Information which was	associated with completion of first visit to the TB clinic. Completion of a 6-month treatment regimen: full course of INH therapy. Note: after the first outcome (visit to the TB clinic 1 month after release), follow-up interviews were conducted with participants from all three groups who could be contacted. **Secondary outcomes:** NR **Follow-up periods:** 1 month after release for attending first visit to the TB Clinic. Follow-up time for completion of therapy was not explicitly reported. However, it was indicated that participants	Pooled intervention groups' (education and incentive) results for first visit to TB Clinic compared to control group: p=0.02. Characteristics associated with completion of the first visit to the TB clinic (N = 325 who were released from jail): Education or incentive group versus control: Adjusted Odds Ratio (AOR) = 1.85 (95% CI 1.04-3.28; p=0.04). Time since arrival ≤ 5 years compared with non-foreign-born: AOR = 0.34 (95% CI 0.12-0.95; p=0.4). Time since arrival > 5 year compared with non-foreign-born: AOR = 1.28; (95% CI 0.63-2.60); p=0.50. Visits to a physician or nurse practitioner in the past 12 months: AOR = 1.07 (95% CI,	**Limitations identified by review team:** The study merged the results for the two treatment groups (incentives and education) in their statistical comparisons against treatment as usual. This limits our understanding of the efficacy of the individual treatment groups on their own. **Evidence gaps and/or recommendations for future research:** The authors noted that similar research should be conducted including prisoners who are Asian/Pacific Islanders as these participants were excluded from the study. **Source of funding:** National Institute of Nursing Research, National Institutes of Health, Bethesda, Md.

Study design: RCT. **Type of economic analysis:** NA **Economic perspective:** NA **Quality appraisal non-economic studies:** + **Internal validity:** ++ **External validity:** + **Quality appraisal economic studies:** NA **Quality score Applicability:** NA	Forensic AIDS project. **Setting:** San Francisco city and county prison for sample recruitment and initial therapy provision. San Francisco County Tuberculosis Clinic after release from prison. **Sample characteristics:** Male, sex: 86% (Education); 90% (Incentive); 91% (Control). Age, median, years: 29.5 (Education); 28.5 (Incentive); 29.7 (Control). Foreign birth: 66% (Education); 64% (Incentive); 67% (Control). Stable housing before jail (vs. unstable): 86% (Education); 82%	provided to all participants in the treatment and control group was offered on LTBI, adverse effects, availability of free care after release, and location of, transportation to, and hours of the TB Clinic. 1-month supply of isoniazid was offered at release. However, the drug supply could not always be offered at release, and there was no record of who eventually received it. Follow-up interviews were conducted with all participants who could be located 1 month after release into the community. **Sample sizes:** **Total:** N = 325 **Intervention:** Education: N =107 Incentive: N = 114 **Control:** N **=**104	underwent 6 months of therapy. **Method of analysis:** Analysis of treatment completion included only those subjects who attended the TB clinic at 1 month, whose treatment had not been stopped due to adverse effects. X^2 and *t* tests or Mann-Whitney tests were used to test group status and other covariates against the two outcome measures. To assess the effect of group status while adjusting for multiple covariates, a separate logistic regression model was designed for each outcome, using significant variables (α=0.10) from bivariate	0.96-1.19); p =0.22. <u>Completion of a full course of isoniazid therapy):</u> Education group = 24/106 (23%); AOR 2.2 (95% CI 1.04-4.72); p = 0.04. Incentive group = 14/113 (12%); AOR 1.07 (95% CI 0.47-2.40); ns. Control group: 12/103 (12%), reference group in AORs. <u>Characteristics associated with INH completion:</u> (Only includes the 104 subjects who attended the TB clinic within 1 month and had no discontinued treatment): Education group = AOR 1.99 (95% CI 0.63-6.22); p = 0.24. Incentive group = AOR 0.43; (95% CI 0.14-1.31); p = 0.14. Control group = reference.	

	(Incentive); 81% (Control). Employed during the 3 months before jail: 58% (Education); 49% (Incentive); 61% (Control). Alcohol or other drug Problem: 55% (Education); 56% (Incentive);54% (Control). Any medical insurance: 20% (Education); 19% (Incentive); 24% (Control). Received isoniazid before: 24% (Education); 25% (Incentive); 19% (Control). Differences between groups in baseline characteristics were not statistically compared.	**Baseline comparisons:** NR: differences between groups in baseline characteristics were not statistically compared. **Study sufficiently powered?** Sample size calculations indicated that 86 participants in each study group would provide sufficient power (p > 0.8) to detect a 20% difference in adherence, based on previous work.	analyses. **Modelling method and assumptions:** NA **Time horizon:** NA	Stable housing before jail = AOR 2.94 (95% CI 1.01-8.58); p=0.05. Time since arrival ≤ 5 years = AOR 2.81 (95% CI 0.54-14.45); p=0.22. Time since arrival > 5 years = AOR 1.37 (95% CI (0.55-3.41; p = 0.5). Stated they would "definitely" complete isoniazid therapy = AOR 11.37 (95% CI 1.12-115.81); p =.04. **Secondary results:** <u>Number of educational sessions and time in jail:</u> Participants randomised to the education intervention received different numbers of education sessions ranging from 0 (released before education session could be provided) to more than 4. There was no significant difference in time spent	

	Economic analysis data source: NA			in jail (to receive educational sessions) and completing treatment (p=0.42). <u>Follow-up interviews effect:</u> Following the follow-up interviews after the first visit to the TB clinic following release, completion rates increased to: Education group = 48%; Incentive group = 46%; Control group: 31%. **Sample selection and attrition details:** <u>Sample selection</u>: 648 were eligible for inclusion, 558 randomised (90 refused). <u>Attrition details:</u> Did not complete first TB clinic visit following release: education group: 67/107; incentive group: 72/114; and control group:79/104. Discontinued INH	

				treatment by clinic staff due to adverse effects: education group, n =3; incentive group n = 0; and control group, n = 0. INH treatment not completed out of those who completed the first visit to the TB clinic (and had no discontinued treatment): education group, 13/37; incentive group: 28/42; and control group, 13/25.	

Study details	Population and setting	Method of allocation to intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: White et al. **Year:** 2003 **Citation:** White, M., C., Gournis, E., Kawamura, M., Menendez, E., & Tulsky, J., P. (2003).	**Source population/s:** Mixed hard-to-reach groups with LTBI, USA **Eligible population:** TB patients attending the San Francisco TB Clinic who were high risk referrals for non-adherence.	**Method of allocation:** After programme implementation (1997 to June 1998) clinicians made a judgement to offer either DOPT or SAT to patients. Prior to programme implementation (1993 to 1994) participants received SAT. **Intervention/s description:**	**Primary outcomes:** Treatment completion:≥ 80% of 6-month course taken. Incompletion could be due to: lost to follow-up, patient stopped treatment, treatment discontinued due to medical decision/adverse effects, or management	**Primary results:** Treatment completion: DOPT plus case management plus incentives group = 102/145 (70.3%); SAT group: 447/934 (47.9%); p < 0.001. Predictors that were significant in the bivariate analyses of therapy completion were sex, age,	**Limitations identified by author:** Comparisons were made with a historical cohort. There were also significant differences between groups for some baseline comparisons. **Limitations identified by review team:** Significant baseline differences in ethnicity and birth place. Assignment to intervention

Effect of directly observed preventive therapy for latent tuberculosis infection in San Francisco. *The International Journal of Tuberculosis and Lung Disease*, *7*(1), 30–35. **Aim of study:** To examine therapy completion for latent TB infection before and after the implementation of a DOPT programme. **Study design:** Before and after. **Type of**	**Selected population:** Patients who were considered high risk were defined as being from sites and/or screening programmes serving the homeless, prisoners, drug users, migrants or those with HIV infection. These patients were included if they were seen at the clinic for the first time; had a TB clinic chart opened and were prescribed INH therapy for LTBI during 1993 to 1994 (24 months) or 1997 to 1998 (18 months); and were followed to completion of care, treatment discontinuation because of toxicity, treatment discontinuation by physician for other	<u>Service model/social care support</u>: 1997 to June 1998 cohort: patients were given 900 mg of INH with 50 mg of vitamin B6 twice weekly for 6 months, or until 80% of total doses had been taken. A health worker or nurse supervised administration of all INH doses. Outreach workers were matched whenever possible to the ethnic and cultural backgrounds of the patients. Treatment was provided on site at a Tuberculosis Outreach Prevention Services. Case management team met weekly to review patients' progress and included a MDT. The team used a patient-centred approach based on a harm reduction model that attended to needs beyond TB, including access to social	decision for any other reason. <u>Completion time</u>: mean number of months needed to complete 80% of prescribed treatment. Note: outcomes extracted retrospectively from the electronic clinic records. **Secondary outcomes:** NR **Method of analysis:** Univariate tests (*t*-tests or x^2); logistic regression. Those who died or moved were not included in the analysis. **Modelling method and assumptions:** NA **Time horizon:** NA	race/ethnicity, and treatment group. Controlling for these variables, patients on DOPT were more likely to complete therapy (OR 1.93, 95%CI 1.25–3.00) than patients on SAT. <u>Completion time (mean number of months, SD)</u>: DOPT = 8.0 (3.0); SAT 1997-1998 = 7.6 (3.7); SAT 1993-1994 = 9.5 (9.1); DOPT or SAT 1997-1998 vs. SAT 1993-1994: $p < 0.001$. **Secondary results:** NR **Sample selection and attrition details:** NR	or control was not random, but based on medical judgement. Criteria for allocation to intervention and control are not reported. **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** NR

economic analysis: NA **Economic perspective:** NA **Quality appraisal effectiveness studies:** + **Internal validity:** + **External validity:** + **Quality appraisal economic studies:** NA **Quality score applicability:** NA	non-specified reasons, patient refusal of further treatment, or loss to follow-up (defined as not being located for 2 months). **Excluded population:** NR **Setting:** TB clinic, San Francisco, USA. **Sample characteristics: (SAT 1993-1994, SAT 1997-1998, DOPT 1997-1998)** Male(%) = 77.5, 77.8,-85.5%; Mean age = 34, 31.2, 38.6 years; Ethnicity(%): African American = 37.6 23.5, 36.6; White = 24.7, 20.0, 29.7; Latino = 24.4-32.7, 24.1; Asian = 9.0,17.1, 6.2; US born = 66.1, 46.7, 62.1. **Economic**	services, food, clothing, and other medical needs such as mental health and substance abuse. Incentives offered to all DOPT patients included lunch; a meal coupon; and a bus token. Selected patients deemed to be at higher risk for progressing to active TB disease (e.g., those who were HIV-positive) were offered additional incentives on a case-by-case basis, such as movie passes or food vouchers. **Comparator/control/s description:** SAT: Considered usual care where patients received SAT (300 mg of INH daily) and visited the clinic monthly for a medication refill and sign and symptom review until 6 months of therapy was completed. **Sample sizes:** **Total:** N = 1079;			

	analysis data sources: NA	**Intervention:** N = 145; **Control:** N = 934 (SAT 1993-1994 = 619; SAT 1997-1998 = 315. **Baseline comparisons:** Significant differences were found in ethnicity and birthplace. **Study sufficiently powered?** NR			

Study details	**Population and setting**	**Method of allocation to intervention/ comparator**	**Outcomes and methods of analysis:**	**Results**	**Notes**
Authors: White et al. Note: one intervention group from this study was previously reported in White et al. (2002). **Year:** 2005 **Citation:** White, M., C., Tulsky, J., P., Menendez, E.,	**Source population/s:** Prisoners with LTBI, USA. **Eligible population:** **Selected population:** English or Spanish speaking inmates; not under special security. **Excluded population:** NA	**Method of allocation:** Natural allocation from two cohorts: 1998 to1999 who participated in previous RCT in the education intervention arm; and 2002 to 2003, prisoners with LTBI who received an education intervention, who were used as a comparison group. **Intervention/s description:** Educational intervention, RCT: Education, provided	**Primary outcomes:** Completion of treatment: patient records at the at the TB Clinic were reviewed to determine completion of therapy for LTBI. Results only presented for those who went to clinic at any point after release. Adherence to first visit to TB clinic at any time after release.	**Primary results:** Adherence to first visit to TB clinic within 30 days of release: Total: N = 41/268 (15%) Educational intervention, RCT: N = 25/104 (24%); Educational intervention, usual care: N = 16/164 (10%); p = 0.002. Adherence to first visit to TB clinic at any time after release: Total: N = 57/268 (21%);	**Limitations identified by author:** There is an inherent difficulty in comparing the results of a tightly controlled randomised trial to an analysis of usual care using observational data. Differences in study periods (1998-1999 and 2002-2003) and differential refusal rates suggest that there may have been a selection bias. Inmates who agreed to be in the RCT may have been more likely to go to clinic due to the combined effects of the education, contact with

Arai, S., Goldenson, J., & Kawamura, L., M. (2005). Improving tuberculosis therapy completion after jail: translation of research to practice. *Health Education Research*, *20*(2), 163-174. **Aim of study:** To explore how research translates into usual clinical practice. The authors reported the effectiveness of an educational intervention for prisoners given the intervention as part of a RCT, compared with the	**Setting:** Prison, San Francisco, USA. **Sample characteristics:** Gender, male: study group: 95 (91.3%); usual care group: 149 (90.9%); total: 244 (91.0%). Age, mean: study group: 30.5; usual care group: 31.4; total: 31.1 Born outside the USA: Study group: 67 (66.3%); usual care: 87 (68.5%); total: 154 (67.5%). **Economic analysis data source:** NA	every 2 weeks while in jail, to reinforce the information initially provided to all subjects as part of a RCT. Information included: details of LTBI, therapy, adverse effects, availability of free care after release, and location of, transportation to, and hours of the TB Clinic (description taken from White et al., 2002). Information provided in brochure. After the study personnel conducted the single education session, no further contact was received by inmates until they completed a clinic visit within 30 days after release. **Comparator/control/s description:** <u>Educational intervention, usual care:</u> the same educational intervention delivered in the intervention	<u>Adherence to first visit to TB clinic within 30 days of release.</u> **Secondary outcomes:** Not extracted for this review. **Method of analysis:** Descriptive data on each cohort were compared using univariate analyses. Logistic regression analyses were used to estimate relative risk of completion in the usual care group as compared to the study group. Only those variables with at least a p-value of 0.1 were included for inclusion in the multiple regression. A p-value of 0.05 was used to determine statistical significance.	Educational intervention, RCT: N = 34/104 (33%); Educational intervention, usual care: N = 25/164 (15%); p = 0.001. <u>Completion of treatment (among those who went to the clinic any time after release:</u> Total: N = 23/59 (39%): Educational intervention, RCT: N =16/34 (47%); Educational intervention, usual care: N = 7/25 (28%) (p-value not reported). <u>Other outcomes for those who went to the TB clinic:</u> *Received INHtherapy previously:* Total: N =7/59 (12%); Educational intervention, RCT: N = 1/34 (3%); Educational intervention, usual care: N = 6/25 (27%) (p-value not reported).	the inmate after release by the researcher and reimbursement for interviews. Inmates in the usual care period were not informed about the study, as it was conducted by record review; they did not receive reimbursement, and may not have believed they could refuse education by Jail Discharge Planners. **Limitations identified by review team:** The analysis for treatment completion only included 59/268 participants who went to the TB clinic at any point after release from prison, due to way in which treatment completion was recorded. Treatment completion could only be noted for those who visited the TB clinic as the outcome was measured by reviewing the clinic's medical record. Due to this limitation, the findings do not represent the entire sample who received the educational intervention and were released from jail. This limits the validity and generalisability of the findings.

effectiveness in those given the intervention as part of usual practice by jail staff. Note: there was a second aim to the study that was not relevant to this review and therefore not extracted: to examine the relationship between the nature of the educational sessions and participant outcomes for participants who received education by jail discharge planners. **Study design:** Before and after study. **Type of**		group was used. However it was conducted outside of the RCT by the prisons' Discharge Planners, who met with the prisoners as part of usual care. **Sample sizes:** **Total:** N = 268 **Intervention:** N = 104 **Control:** N = 164 **Baseline comparisons:** Statistically significant baseline differences Race/Ethnicity(p = 0.004): Latino: study group: 63 (60.6%); usual care group: 110 (69.2%); total: 173 (65.8%). Black: study group: 20 (19.2%); usual care group: 26 (16.4%); total: 46 (17.5%). White: study group: 6 (5.8%); usual care group: 13 (8.2%); total: 19 (7.2%). Time in jail on INH, means days, p = 0.045: Study group: 51; usual	Analysis of treatment completion included only those participants who attended the TB clinic at any point. **Modelling method and assumptions:** NA **Time horizon:** NA	*Still on therapy*: Total: N = 1/59 (2%); Educational intervention, RCT: N = 1/34 (3%); Educational intervention, usual care: N = 0/25 (0%). (p-value not reported). *Taken off medication due to side effects*: Total: N = 3/59 (5%); Educational intervention, RCT: N = 3/34 (9%); Educational intervention, usual care: N = 0/25 (0%). (p-value not reported). *Moved, referred*: Total: N =1 (2%); Educational intervention, RCT: N = 0; Educational intervention, usual care: N = 1/25 (4%). (p-value not reported). *Self-stopped, lost to follow-up:* Total: N = 24 (41%); Educational intervention, RCT: N =	**Evidence gaps and/or recommendations for future research:** Further gains may be realised by multiple strategies for intervention and study, at the individual and the system level. **Source of funding:** Agency for Healthcare Research and Quality.

economic analysis: NA **Economic perspective:** NA **Quality appraisal non-economic studies:** + **Internal validity:** + **External validity:** + **Quality appraisal economic studies:** NA **Quality score applicability:** NA		care group: 61.7; total: 57.5 <u>Time, isoniazid start to education, mean days, P = <0.0005</u> *S*tudy group: 3.2; usual care group: 10.4; total: 7.6 **Study sufficiently powered?** NR		13 (38%); Educational intervention, usual care: N = 11 (44%). (p-value not reported). **Secondary results:** Note: results relating to the secondary aim of the study were not extracted here. **Sample selection and attrition details:** <u>Missed for consent:</u> Educational intervention, usual care: due to ineligibility (N = 31, 4%) or released/sent to another facility (N =98, 12.6%). Educational intervention, usual care: Released/sent to another facility (N = 157, 41.4%) (p-value not reported). <u>Sent to another facility after education intervention:</u> Educational intervention, RCT: N = 51 (27.1%); Educational	

				intervention, usual care: N =15(6.8%) (p-value not reported).. <u>Refused participation:</u> Study group: no inmates who refused participation were included in the findings for this group. Usual care group: includes those who might have refused participation.	

12.0 Appendix D. Studies excluded at full text stage

Table D1. Studies excluded after full text screening (N=77)

NOTE: studies that appear as "8_IN.EFF" were excluded from the current review but preliminarily included for the subsequent reviews (management and service models). Studies labelled as "9_IN.OTHER" are non-comparative studies and have been excluded from the initial draft of this review.

For exclusion codes see Appendix B.

Reference details	Abstract	Exclusion Code
Andre, M. et al., (2007). Transmission network analysis to complement routine tuberculosis contact investigations. *American Journal of Public Health*, *97*(3), 470-477.	OBJECTIVE: We examined the feasibility and value of network analysis to complement routine tuberculosis (TB) contact investigation procedures during an outbreak. METHODS: We reviewed hospital, health department, and jail records and interviewed TB patients. Mycobacterium tuberculosis isolates were genotyped. We evaluated contacts of TB patients for latent TB infection (LTBI) and TB, and analyzed routine contact investigation data, including tuberculin skin test (TST) results. Outcomes included number of contacts identified, number of contacts evaluated, and their TST status. We used network analysis visualizations and metrics (reach, degree, betweenness) to characterize the outbreak. RESULTS: secondary TB patients and more than 1200 contacts. Genotyping detected a 21-band pattern of a strain W variant. No HIV-infected patients were diagnosed. Contacts prioritized by network analysis were more likely to have LTBI than nonprioritized contacts (odds ratio=7.8; 95% confidence interval=1.6, 36.6). Network visualizations and metrics highlighted patients central to sustaining the outbreak and helped prioritize contacts for evaluation. CONCLUSIONS: A network-informed approach to TB contact investigations provided a novel means to examine large quantities of data and helped focus TB control.	5_EX.POP
Badiaga, S., Raoult, D. & Brouqui, P. (2008). Preventing and controlling emerging and reemerging transmissible diseases in the homeless. *Emerging Infectious Diseases*, *14*(9), 1353-1359.	Homelessness is an increasing public health problem. Because of poor living conditions and limited access to healthcare systems, homeless persons are exposed to many communicable infections. We summarize the intervention measures reported to be efficient for the control and the prevention of common transmissible infections among homeless populations. Evidence suggests that appropriate street- or shelter-based interventions for targeted populations are the most efficient methods. Depending on the populations targeted, these interventions may include education, free condom distribution, syringe and needle prescription programs, chest radiography screening for tuberculosis, directly observed therapy for tuberculosis treatment, improvement of personal clothing and bedding hygiene, and widespread use of ivermectin for scabies and body louse infestation. Systematic vaccination against hepatitis B virus, hepatitis A virus, influenza, Streptococcus pneumoniae, and diphtheria is strongly recommended. National public health programs specific to homeless populations are required.	6_EX.NON-EMP
Barnes, P., F. & Barrows, S., A., (1993).	PURPOSE: To summarize major recent developments in tuberculosis and current approaches to its treatment and prevention.	6_EX.NON-EMP

Tuberculosis in the 1990s. *Annals of Internal Medicine*, *119*(5), 400-410.	DATA IDENTIFICATION: Articles published since 1987 that addressed important issues in tuberculosis were identified by searching the MEDLINE database and bibliographies of relevant articles. STUDY SELECTION: One hundred one references were selected that were judged by the authors to contain information most relevant to practicing internists. RESULTS: Recent increases in tuberculosis morbidity in the United States are concentrated in racial and ethnic minorities, the foreign-born, and persons with human immunodeficiency virus infection. Amplification of Mycobacterium tuberculosis DNA by polymerase chain reaction allows rapid diagnosis of tuberculosis, and "DNA fingerprinting" of individual M. tuberculosis strains allows delineation of patterns of tuberculosis transmission. These techniques are available in research laboratories and are promising clinical tools for the future. Treatment regimens for drug-susceptible tuberculosis yield cure rates of more than 95%. Failure to ensure compliance with antituberculosis medications has resulted in an increasing prevalence of multiple-drug-resistant tuberculosis that responds poorly to therapy. Guidelines for isoniazid chemoprophylaxis have been modified in the past 5 years and are summarized. CONCLUSION: Control of tuberculosis in the United States will require improved implementation of established techniques to diagnose, treat, and prevent tuberculosis, with renewed emphasis on ensuring compliance with therapy. [References: 102]	
Burgos, J., L. et al., (2009). Targeted screening and treatment for latent tuberculosis infection using QuantiFERON - TB Gold is cost-effective in Mexico. *International Journal of Tuberculosis & Lung Disease*, *13*(8), 962-968.	OBJECTIVE: To assess the cost-effectiveness of screening for latent tuberculosis infection (LTBI) using a commercially available detection test and treating individuals at high risk for human immunodeficiency virus (HIV) infection in a middle-income country. DESIGN: We developed a Markov model to evaluate the cost per LTBI case detected, TB case averted and quality-adjusted life year (QALY) gained for a cohort of 1000 individuals at high risk for HIV infection over 20 years. Baseline model inputs for LTBI prevalence were obtained from published literature and cross-sectional data from tuberculosis (TB) screening using QuantiFERON-TB Gold In-Tube (QFT-GIT) testing among sex workers and illicit drug users at high risk for HIV recruited through street outreach in Tijuana, Mexico. Costs are reported in 2007 US dollars. Future costs and QALYs were discounted at 3% per year. Sensitivity analyses were performed to evaluate model robustness. RESULTS: Over 20 years, we estimate the program would prevent 78 cases of active TB and 55 TB-related deaths. The incremental cost per case of LTBI detected was US$730, cost per active TB averted was US$529 and cost per QALY gained was US$108. CONCLUSIONS: In settings of endemic TB and escalating HIV incidence, targeting LTBI screening and treatment among high-risk groups may be highly cost-effective.	5_EX.POP
Burgos, M., et al. (2005). Treatment of multidrug-resistant tuberculosis in San Francisco: an outpatient-based approach. *Clinical Infectious Diseases*, *40*(7), 968-975.	BACKGROUND: Treatment of patients with multidrug-resistant tuberculosis requires prolonged therapy, often involving long hospital stays. Despite intensive and costly therapy, cure rates are relatively low. METHODS: We reviewed the outcomes for all patients with multidrug-resistant tuberculosis treated in San Francisco, California, during 1982-2000 and identified billing charges for patients treated during 1995-2000. Mycobacterium tuberculosis isolates were genotyped by IS6110-based restriction fragment-length polymorphism analysis. RESULTS: Forty-eight cases were identified with resistance to a median of 3 drugs (range, 2-9 drugs). The median age of the patients was 49.5 years (range, 22-78 years); 36 (75%) of 48 patients were foreign born, 11 (23%) were human immunodeficiency virus (HIV) seropositive, and 45 (94%) had pulmonary tuberculosis. Thirty-two (97%) of the 33 HIV-seronegative	7_EX.TOPIC

	patients were cured, with only 1 relapse occurring 5 years after treatment. All 11 HIV-seropositive patients died during observation. Twenty-one patients (44%) required hospitalization, with a median duration of stay of 14 days (range, 3-74 days). The estimated inpatient and outpatient aggregate cost for the 11 patients treated after 1994 was $519,928, with a median cost of $27,752 per patient. No secondary cases of multidrug-resistant tuberculosis were identified through population-based genotyping. CONCLUSIONS: Treatment of multidrug-resistant tuberculosis in HIV-seronegative patients largely on an outpatient basis was feasible and was associated with high cure rates and lower cost than in other published studies. Patients with underlying HIV infection had very poor outcomes.	
Burns, A., D., & Harrison, A., C. (2007). Costs of investigating and managing non-residents with possible tuberculosis: New Zealand experience of an international problem. *Respirology*, *12*(2), 262-266.	BACKGROUND AND OBJECTIVE: This study's aims were to identify the diagnoses, the public hospital costs and payments for non-New Zealand (non-NZ) patients referred because of possible tuberculosis (TB). There have been no previous financial studies in this area. Funding arrangements for these patients were also reviewed. METHODS: A systematic, retrospective review was performed to identify the costs of investigating and managing non-NZ patients referred to the adult TB unit of a large, teaching hospital in Auckland, NZ. Patients were enrolled between 1 July 2002 and 30 June 2003. RESULTS: Forty-five non-NZ patients were studied. The mean age was 33.8 (+/-13.4) years. Thirty-four (75.5%) were managed under compulsion through Section 9 of the NZ TB Act. Thirty-two (71%) patients received TB treatment: 11 (24%) had infectious pulmonary TB and four had active extra-pulmonary TB. There were no multi-drug-resistant isolates. Three TB cases accounted for 250 (39%) inpatient days. One patient with rifampicin-resistant TB was responsible for 117 (29%) day-patient ward visits. Four (13%) infectious TB cases were managed as inpatients for more than 6 weeks. The total cost of services (US dollars) for the 45 patients was 350,236 dollars. The cost range was 544-43,513 dollars per patient. Four patients incurred costs over 25,000 dollars. CONCLUSIONS: TB in non-residents is a costly problem in NZ. Current policy applying to this area and the ability to determine its cost-effectiveness are in need of review.	7_EX.TOPIC
Carr, T. (1998). Return of school forms and nurse home visits increased adherence with follow up reading of tuberculosis tests in children [commentary on Cheng TL, Ottolini MC, Baumhaft K, et al. Strategies to increase adherence with tuberculosis test reading in a high- risk population. *Pediatrics*, 100, 210-213.] *Evidence-Based Nursing*, *1*(3), 78.	Question: In high risk children, can strategies of verbal and written instructions, telephone follow up, transportation tokens and a toy, education, or withholding school forms (proof of immunisation status) improve the rate of adherence with follow up reading of tuberculosis tests? Design: Randomised controlled trial. Setting: Outpatient department of an urban children's hospital in Washington, DC, USA. Participants: 627 consecutive children aged 1 to 12 years (91% African American, 74% Medicaid recipients) who were healthy and had no recent history of tuberculosis contact. 45% of participants had >/= 1 risk factor for tuberculosis (born in a country with a high prevalence of tuberculosis or contact with people who were homeless, street drug abusers, incarcerated, from high prevalence areas, or had HIV infection). Intervention: Participants and their families were given routine verbal and written instructions and randomised by day of the week to 1 of 5 strategies to improve adherence to follow up tuberculosis test reading at 48-72 hours after the Mantoux test: (1) no additional intervention (control group) (n = 121); (2) a reminder telephone call (n = 125); (3) transportation tokens and toy on return (positive reinforcement) (n = 121); (4) withholding of school forms until time of reading and information that the test would be repeated if not read within 48-72 hours (negative reinforcement) (n = 162); (5) parents taught to read the induration	5_EX.POP

	and a nurse home visit was scheduled to verify the results (n = 98). All children did not have school forms to complete; and for those who did, the form was not necessary for school attendance. Main outcome measure: Rate of adherence with follow up reading of tuberculosis test Main results: The adherence rates in the 5 groups were 58%, 70%, 67%, 70%, and 72%, respectively. Withholding school forms and advising parents that the test would be repeated (group 4, p = 0.03) and nurse home visits (group 5, p = 0.04) improved adherence for test reading compared with routine instructions alone (group 1). A reminder telephone call (group 2) showed a trend towards improvement and transportation tokens plus a toy (group 3) did not increase adherence for test reading compared with routine instructions alone. Conclusion: Withholding school forms until the time of tuberculosis test reading and nurse home visits were effective strategies for increasing the rate of adherence with follow up reading of tuberculosis tests in high risk children.	
Casal, M., et al. (2005). A case-control study for multidrug-resistant tuberculosis: risk factors in four European countries. *Microbial Drug Resistance-Mechanisms Epidemiology & Disease*, *11*(1), 62-67.	The aim of this study was to detect risk factors for multidrug resistance in patients with pulmonary tuberculosis in four European Union countries: France, Germany, Italy, and Spain. A prospective epidemiological case control study was conducted, made up of patients with clinically diagnosed and microbiologically confirmed pulmonary tuberculosis in the four countries between 1997 and 2000. A total of 138 cases and 276 controls were studied. Considering the four countries as a whole, the most statistically significant risk factors were as follows: intravenous drug use (OR 4.68); asylum-seeker support (OR 2.55) as income factor; living in a nursing home (OR 2.05); previous tuberculosis (OR 2.03) with pulmonary location; prison (OR 2.02); known tuberculosis contacts (OR 2.01); immunosuppression other than human immunodeficiency virus (HIV) (OR 1.96); acquired immunodeficiency syndrome (AIDS) (OR 1.96); current tuberculosis with pulmonary location (OR 1.77); and health-care worker (OR 1.69). These risk factors will have to be taken into account in the European Union as a whole, as well as in each individual country, to establish a health policy of monitoring and control for these cases of multidrug resistance. Although rare, their seriousness makes them particularly important.	1_EX.TB
Chang, S., Wheeler, L., S., M., & Farrell, K., P., (2002). Public health impact of targeted tuberculosis screening in public schools. *American Journal of Public Health*, *92*(12), 1942.	Not available	9_IN.OTHER
Chaulk, C., P., et al. (1995). Eleven years of community-based directly observed therapy for tuberculosis. *JAMA*, *274*(12), 945-951.	OBJECTIVE: To evaluate community-based directly observed therapy (DOT) for tuberculosis (TB) control. DESIGN: Ecological study. METHODS: Three comparisons were made in this descriptive study. (1) An 11-year retrospective comparison of TB case rates, sputum conversion rates (SCRs), rates of therapy completion, and confounding factors (acquired immunodeficiency syndrome [AIDS], immigration, unemployment, and poverty) in Baltimore, Md, with those of the five major US cities having the highest TB incidence in 1981 but which did not have comprehensive DOT programs. (2) An 11-year trend of TB in Baltimore and the 19 major US cities with the highest TB incidence in 1981. (3) A 7-year trend in TB in both city groups between 1985 and 1992. SETTING: Twenty US metropolitan cities with more than 250,000 residents. RESULTS: Since 1981, Baltimore experienced the greatest decline in TB incidence (35.6 cases per 100,000 population, 1981; 17.2 cases per 100,000	5_EX.POP

	population, 1992 [-51.7%]), and city rank for TB (sixth in 1981, 28th in 1992). Conversely, the average incidence of TB increased 2.1% in the five-city cohort and increased 1.8% in the 19-city cohort. Since 1985, TB incidence increased 35.3% in the five-city cohort and 28.5% in the 19-city cohort, but declined 29.5% in Baltimore. From 1986 through 1992, Baltimore's DOT-managed cases had the highest annual SCRs at 3 months (mean, 90.7%), and the highest completion rates for standard anti-TB therapy (mean, 90.1%) when compared with the five cities. These trends could not be attributed to differentials in AIDS, immigration, poverty, or unemployment. Increasingly, more Baltimore cases were treated under DOT (86.5%, 1993) over time. Disease relapse rates remained low, even among HIV-infected patients. Within Baltimore, the documented SCR was significantly higher among DOT-managed cases compared with non-DOT-managed cases (P < .05); multidrug resistance remains rare (0.57%). Within Maryland, Baltimore accounted for 44.4% of all TB cases in 1981, compared with 28.7% in 1992 (P < .001). CONCLUSIONS: In contrast to the national TB upswing during the 1980s, Baltimore experienced a substantial decline in TB following implementation of community-based DOT, despite highly prevalent medicosocial risk factors. Directly observed therapy facilitated high treatment completion rates and bacteriologic evidence of cure. Directly observed therapy could help reduce TB incidence in the United States, particularly in cities with high case rates.	
Chaulk, C., P., Friedman, M., & Dunning, R. (2000). Modeling the epidemiology and economics of directly observed therapy in Baltimore. *International Journal of Tuberculosis & Lung Disease*, 4(3), 201-207.	SETTING: From 1958 to 1978, Baltimore maintained one of the highest pulmonary tuberculosis (TB) rates in the US. But, from 1978 to 1992 its TB rate declined by 64.3% and its ranking for TB fell from second highest among large US cites to twenty-eighth. This TB trend coincided with the implementation of an aggressive directly observed therapy (DOT) program by Baltimore's Health Department. OBJECTIVES: We used modeling to estimate the range of TB cases prevented in Baltimore under DOT. Case estimates equal the difference between the observed number of TB cases in Baltimore versus the expected number if Baltimore's TB trend was replaced by the TB trend for the US (low estimate) or the TB trend for all US cities with over 250,000 residents (high estimate). Economic savings are estimated. RESULTS: Without DOT we estimate there would have been between 1,577 (53.6%) and 2,233 (75.9%) more TB cases in Baltimore, costing $18.8 million to $27.1 million. Cases prevented and expenditures saved increased with increased DOT participation. CONCLUSION: Our model predicts that Baltimore's TB decline accompanying DOT resulted in health care savings equal to twice the city's total TB control budget for this period. These results are most plausibly due to DOT, since it was the only major change in Baltimore's TB control program, and rising TB risk factors-AIDS, injection drug use, poverty-in a city where TB had been epidemic should have triggered a TB increase as in comparable US cities, rather than the observed decline. As national TB rates continue to decline it will be important to identify ways to capture and reinvest these savings to support effective TB control programs.	5_EX.POP
Clark, P., M. et al. (2007). Effect of pharmacist-led patient education on adherence to tuberculosis treatment. *American Journal of Health-System Pharmacy*, *64*(5), 497-506.	PURPOSE: The purpose of this study was to assess the effect of a clinical pharmacist-directed patient education program on the therapy adherence of first-time tuberculosis (TB) patients and to identify the major pharmaceutical care needs and issues of first-time TB and multidrug-resistant (MDR)-TB patients. METHODS: In the first part of the study, first-time TB patients were randomized either to the No EDU group (n = 58) where patients received routine medical and nursing care or to the EDU group (n = 56) where patients were also provided with clinical pharmacist-directed patient education. The	5_EX.POP

	patient's adherence to treatment was evaluated by attendance at scheduled visits, medication counting, and urine analysis for the presence of isoniazid metabolites. In the second part of the study, the pharmaceutical care needs and issues were determined for first-time TB patients and for MDR-TB patients (n = 40). RESULTS: The adherence of patients who received pharmacist-directed patient education was greater than that of patients who did not. The attendance at scheduled visits and urine analysis for the presence of isoniazid metabolites yielded better results in respect to adherence for the EDU group ($p < 0.05$), while medication counting did not differ between the two groups. The major pharmaceutical care needs of first-time TB patients were for pain control, nutrient replacement, appropriate prescribing, respiratory control, and diabetic control. Similar findings were recorded for MDR-TB patients. CONCLUSION: Patients' adherence to TB treatment improved when a pharmacist provided patient education on medication use and addressed patients' pharmaceutical care issues.	
Clark, R., C., & Mytton, J. (2007). Estimating infectious disease in UK asylum seekers and refugees: a systematic review of prevalence studies. *Journal of Public Health*, *29*(4), 420-428.	BACKGROUND: The prevalence of infectious diseases such as tuberculosis (TB), HIV and hepatitis B in the UK asylum seeker and refugee population is currently uncertain. METHODS: Systematic review of published and unpublished studies. RESULTS: Five studies met the inclusion criteria. Three studies reported the prevalence of TB with rates ranging from 1.33 to 10.42 per 1000. The three studies reporting hepatitis B estimated rates from 57 to 118 per 1000. One study reported a prevalence rate for HIV of 38.19 per 1000. CONCLUSION: A small number of studies have been identified reporting prevalence rates for TB, hepatitis B and HIV that vary widely where comparisons are available. These differences may reflect true variation in risk between study populations, but are likely to be affected by sampling difficulties encountered when researching these population groups. Efforts are required to improve these difficulties which are currently limiting the validity of prevalence findings and generalizability to comparable asylum seeker and refugee populations. [References: 29]	1_EX.TB
Codecasa, L., R., & Besozzi, G. (1998). Acceptance of isoniazid preventive treatment by close contacts of tuberculosis cases: a 692-subject Italian study. *International Journal of Tuberculosis & Lung Disease*, *2*(3), 208-212.	SETTING: Villa Marelli Institute, Lombardy Regional Reference Centre for Tuberculosis. OBJECTIVE: To evaluate acceptance of and adherence to isoniazid preventive treatment (IPT) of close contacts of contagious tuberculosis (TB) cases (CC); comparison of Italian and immigrant patients. METHODS: A retrospective study of a consecutive series of 692 subjects (474 Italians and 218 immigrants from developing countries) exposed to contagious TB cases, who were offered IPT after tuberculin skin testing and chest X-ray, according to the Lombardy Regional Protocol for TB control. RESULTS: Of 692 CCs, 36 (5.2%) subjects refused IPT, 522 (75.5%) completed the treatment as prescribed, 23 (3.3%) suspended IPT because of adverse effects, 14 (2.0%) spontaneously discontinued IPT against our advice, 93 (13.4%) were lost to follow up, and seven (0.6%) were still in treatment when the present data were evaluated. Italian CCs had a completion rate significantly higher than the immigrants (81.0% vs 63.3%, $P < 0.01$). CONCLUSION: The rate of acceptance and completion of IPT in our population proved higher than many previously reported data, and the better results among Italian subjects reflect the importance of a complete comprehension of IPT that may not always be achieved with immigrant patients.	9_IN.OTHER
Coker, R., J. (2003). Public health impact of detention of individuals with tuberculosis: systematic literature	As the world witnesses ever-increasing rates of tuberculosis, particularly of drug-resistant strains affecting some of society's most marginalized individuals, policy makers and Legislators may again visit the statute books in order to strengthen their armamentarium of tools to protect public health. This paper assesses the evidence in	6_EX.NON-EMP

review. *Public Health*, *117*(4), 281-287.	support of the sanction to detain those with tuberculosis who are perceived as posing a public heath threat, and shows that Little research has been conducted to inform policy, probably because traditional epidemiological methods used to assess the impact of interventions are not feasible.	
Davidson, B., L. (1998). A controlled comparison of directly observed therapy vs. self-administered therapy for active tuberculosis in the urban United States. *Chest*, (5), -43.	STUDY OBJECTIVES: To compare treatment completion rates at 8 and 12 months after treatment initiation for patients with active TB treated with either directly observed therapy (DOT) or self-administered therapy (SAT). DESIGN: Retrospective comparison study of DOT and SAT concurrent patient cohorts. SETTING: Urban Tuberculosis Control Program within a Department of Public Health. PATIENTS: Three hundred nineteen patients confirmed to have active TB between July 1, 1994, and June 30, 1995, who began outpatient drug therapy. INTERVENTIONS: Patients and/or their physicians chose to receive their anti-TB drug therapy by DOT (n=113) or SAT (n=206) and were assessed for treatment completion at prospectively determined times, 8 and 12 months. MEASUREMENTS AND RESULTS: Proportions of patients who completed treatment at 8 and 12 months without crossing over to the other group were compared. At 8 months, 52% of DOT and 35% of SAT patients had completed treatment (relative superiority of DOT, 49%; p=0.003). At 12 months, completion rates were 70% for DOT patients and 53% for SAT patients (relative superiority of DOT, 30%; p=0.006). CONCLUSIONS: In our setting, patients receiving DOT were much more likely to complete treatment earlier than those receiving SAT. Even with DOT, only 52% of patients had completed treatment by 8 months.	5_EX.POP
Diel, R., & Niemann, S. (2003). Outcome of tuberculosis treatment in Hamburg: a survey, 1997-2001. *International Journal of Tuberculosis & Lung Disease*, *7*(2), 124-131.	SETTING: Federal State of Hamburg, Germany, 1997-2001. OBJECTIVE: To determine risk factors affecting the treatment outcome for tuberculosis according to the WHO/IUATLD classification. DESIGN: Prospective evaluation among patients with culture-confirmed pulmonary disease due to Mycobacterium tuberculosis during the period 1997-1999. RESULTS: Five hundred and eighteen (467 new and 51 re-treatment) cases started a course of treatment (average duration 36.1 +/- 15.5 weeks), resulting in cure for 416 (80.3%) and treatment completed for three (0.6%) patients; 449 patients (86.7%) initially received a three-drug regimen. Treatment interruption occurred in 54 (10.4%), and failure in 12 (2.3%) cases; 32 (6.2%) patients died (irrespective of cause). Alcohol dependence appeared to be the strongest risk factor for persistence of disease, followed by homelessness and unemployment. The risk of treatment interruption was six times higher among alcoholics (OR = 6.0), five times higher among drug abusers (OR = 5.2) and three times higher among the homeless (OR = 3.0) than in other patients. CONCLUSION: Although the current treatment management in Hamburg is considered to be effective, a further improvement in the proportion of patients who complete treatment can be achieved by increased public health surveillance of subpopulations with the above-mentioned risk factors.	7_EX.TOPIC
Elk, R., et al. (1993). Compliance with tuberculosis treatment in methadone-maintained patients: Behavioral interventions. *Journal of Substance Abuse Treatment*, *10*(4), 371–382.	Tuberculosis has increased dramatically in the United States. Noncompliance with treatment is high. The purpose of this investigation was to achieve compliance with prophylactic TB treatment and simultaneously decrease drug use in a high-risk group of intravenous drug users. Two studies were conducted. Study 1: Subjects were 9 chronic opiate users who tested positive for tuberculosis and were placed on isoniazid (INH) and methadone. Methadone was dispensed contingent upon INH ingestion throughout. A within-subject, A-B design with contingency management interventions on drug use was implemented. Results:	9_IN.OTHER

	Compliance with INH was 100% in 8 patients. Cocaine use remained high. Study 2: Two patients, meeting same criteria as Study 1, participated in a within-subject A-B multiple baseline design. Methadone was dispensed contingent upon INH ingestion throughout. Successive decreases in cocaine use were reinforced in the contingent phase. Results: Compliance with INH was high. During contingency, both patients had over 40% cocaine-free urine samples compared with 0% at baseline. This investigation serves as a model for achieving compliance with TB treatment in opiate users.	
Fallab-Stubi, C., L., et al. 1998. Electronic monitoring of adherence to treatment in the preventive chemotherapy of tuberculosis. *International Journal of Tuberculosis & Lung Disease*, *2*(7), 525-530.	SETTING: Non-adherence to treatment is a frequent problem in the preventive chemoprophylaxis of tuberculosis. OBJECTIVE: To evaluate the usefulness of the Medication Event Monitoring System (MEMS) for following and improving patient adherence to 6-month treatment with isoniazid. DESIGN: Three methods of monitoring compliance, MEMS, pill count and a urine test for isoniazid, were compared prospectively in 30 patients. The efficacy of a combined intervention by the physician and the pharmacist was evaluated in non-compliant patients. RESULTS: According to the MEMS data, overall adherence to isoniazid therapy was 91.5%, and 86% of the patients were considered compliant throughout the period of observation. The pill count and the urine test tended to overestimate the overall compliance when compared to the MEMS. The combined intervention of the physician and pharmacist allowed drug adherence to be enhanced in non-compliant patients, but the effect was only transient if this was not repeated every month. CONCLUSION: Our results suggest that the MEMS system is a useful approach for monitoring and improving compliance with preventive chemotherapy for tuberculosis.	5_EX.POP
Faustini, A., Hall, A., J., & Perucci, C., A. (2005). Tuberculosis treatment outcomes in Europe: a systematic review. *European Respiratory Journal*, *26*(3), 503-510.	In order to facilitate the control of tuberculosis (TB), the World Health Organization (WHO) has defined a standardised short-course chemotherapy and a strategy, directly observed therapy. In 2000, WHO surveillance of TB treatments in Europe recorded a successful outcome rate of 77%. The aim of this report is to estimate treatment outcomes in European countries based on published studies and to identify their determinants. A systematic review was conducted of published reports of TB treatment outcomes in Europe. Meta-analysis, meta-regression and subgrouping were used to pool treatment outcomes and analyse associations with mean age, sex, immigration status and multidrug resistance. Of the 197 articles identified in the search, 26 were eligible for the review; 74.4% of outcomes were successful, 12.3% were unsuccessful and 6.8% of patients died. Heterogeneity was high for all outcomes. National estimates were possible for six countries. Multidrug resistance was inversely associated with successful outcome, which were fewer in populations with >9% multidrug-resistant TB, and in patients aged <44 yrs. Successful tuberculosis treatment outcomes were below the 85% threshold suggested by the World Health Organization. There was an inverse association with levels of multidrug-resistant tuberculosis. The unexplained heterogeneity between the studies for unsuccessful outcomes seems to be due to differing interpretations given to World Health Organization definitions. [References: 45]	7_EX.TOPIC
Floyd, K. (2003). Costs and effectiveness: the impact of economic studies on TB control (Brief record). *Tuberculosis*, (1-3), 187-200.	This paper assesses the impact of economic studies on TB control during the period 1982–2002, with a focus on cost and cost-effectiveness studies. It begins by identifying broad categories of economic study relevant to TB control, and how economic studies can, theoretically, have an impact on TB control. The impact that economic studies of TB control have had in practice is then analysed through a systematic review of the literature on cost and cost-effectiveness studies related to TB control, and three case studies	5_EX.POP

	(one cost study and two cost-effectiveness studies). The results show that in the past 20 years, 66 cost-effectiveness studies and 31 cost studies have been done on a variety of important TB control topics, with a marked increase occurring after 1994. In terms of numbers, these studies have had most potential for impact in industrialized countries, and within industrialized countries are most likely to have had an impact on policy and practice related to screening and preventive therapy. In developing countries with a high burden of tuberculosis, far fewer studies have been undertaken. Here, the main impact of economic studies has been influencing policy and practice on the use of short-course chemotherapy, justifying the implementation of community-based care in Africa, and helping to mobilize funding for TB control based on the argument that short-course treatment for TB is one of the most cost-effective health interventions available. For the future, cost and cost-effectiveness studies will continue to be relevant, as will other types of economic study.	
Fraser, A., et al. (2006). Treatment of latent tuberculosis in persons at risk for multidrug-resistant tuberculosis: systematic review. *International Journal of Tuberculosis & Lung Disease*, *10*(1), 19-23.	SETTING: The emergence and spread of multidrug-resistant tuberculosis (MDR-TB), caused by Mycobacterium tuberculosis resistant to at least isoniazid (INH) and rifampicin, is a threat to global TB control. OBJECTIVE: To appraise evidence of the effectiveness of treatment of latent TB infection (LTBI) in people at risk for developing active MDR-TB. DESIGN: Systematic review of comparative studies of people treated and not treated for LTBI following exposure to MDR-TB. DATA SOURCES: PubMed, EMBASE, LILACS and the Cochrane Library (December 2004). RESULTS: Two observational studies met inclusion criteria. A prospective cohort study found individualised tailored treatment to be effective for preventing active TB in children (OR = 0.20, 95%CI 0.04-0.94), while a retrospective cohort study found INH not to be effective (OR = 0.46, 95%CI 0.07-2.32). CONCLUSION: Evidence of the effects of treatment of LTBI in people exposed to MDR-TB is extremely limited in both quantity and quality. The increasing global spread of MDR-TB and the difficulties in treating it emphasise the need for effective preventive measures. Ideally, this issue should be addressed in a randomised controlled trial. Until such a trial is conducted, routine clinical data collected as part of existing TB control programmes could be useful and can be generated relatively easily.	1_EX.TB
Furin, J. (2007). The clinical management of drug-resistant tuberculosis. *Current Opinion in Pulmonary Medicine*, *13*(3), 212-217.	PURPOSE OF REVIEW: Drug-resistant tuberculosis is a growing problem, with almost half a million cases worldwide. In spite of the difficulty in its management, drug-resistant tuberculosis can be successfully treated, even in poor settings. RECENT FINDINGS: This article will review key findings in the areas of epidemiology, diagnosis and management of drug-resistant tuberculosis, including new antituberculous drugs. The issue of extensively drug-resistant tuberculosis will also be reviewed and discussed. Finally, novel approaches to the management of drug-resistant tuberculosis in populations with HIV, as well as in pediatric populations, among pregnant women, and among patients requiring surgical therapy, will be reviewed. SUMMARY: New advances in the diagnosis and management of drug-resistant tuberculosis allow for excellent clinical outcomes to be achieved, even in difficult-to-treat populations. This is possible with timely diagnosis of disease and rapid initiation of appropriate therapy in supported settings. [References: 44]	6_EX.NON-EMP
Gonzalez-Ochoa, E., et al. (2009). Pulmonary tuberculosis case detection through	OBJECTIVE: To compare the yield of active tuberculosis (TB) case detection among risk groups during home visits with passive detection among patients at health services. METHODS: In April 2004, in a first phase, we introduced, active screening for coughing	4_EX.OECD

fortuitous cough screening during home visits. *Tropical Medicine & International Health*, *14*(2), 131-135.	among all family members of patients that were visited at home by their family doctor or nurse for other reasons. Subsequently, from October 2004 onwards, active screening was restricted to family members belonging to groups at risk of TB. RESULTS: The overall detection rate of TB increased from 6.7/100,000 during passive detection at health services before the intervention to 26.2/100,000 inhabitants when passive detection was complemented by active case finding. Active screening among risk groups yielded 35 TB cases per 1000 persons screened compared to 20 TB cases per 1000 persons passively screened at health services. Active case finding was particularly efficient in those coughing for 3 weeks or more (107/1000 screened). CONCLUSION: This study demonstrates that active case finding in groups at risk during home visits increases the case detection rate in the population and permits the identification of cases that may not be detected through passive case finding at health facility level.	
Gourevitch, M., N., et al. (1996). Successful adherence to observed prophylaxis and treatment of tuberculosis among drug users in a methadone program. *Journal of Addictive Diseases*, *15*(1), 93–104.	Incomplete antituberculous chemoprophylaxis and treatment are major causes of the resurgence of tuberculosis, often drug-resistant, among drug users. We offered directly observed antituberculous chemoprophylaxis (n = 102) or treatment (n = 12) to tuberculous chemoprophylaxis (n = 102) or treatment (n = 12) to eligible methadone maintenance treatment patients. Methadone dosing was not contingent upon ingestion of antituberculous medication(s). No material incentives were provided. Ninety (88%) prophylaxis and 9 (75%) treatment patients were administered > or = 5 weekly doses of antituberculous medications during > or = 80% of 4740 patient-weeks. The majority of patients were HIV-seropositive. Active substance abuse was not associated with diminished adherence. Over 80% of patients completed or were still receiving therapy at the end of the study. Adherence to and completion of directly observed antituberculous therapy can thus be attained by drug users in treatment, despite ongoing drug misuse. Substance abuse treatment programs provide opportunities for enhanced compliance, and should thus be viewed as critical components of strategies to address the tuberculosis epidemic in drug users.	9_IN.OTHER
Gruber, V., A., et al. (2008). A randomized trial of 6-month methadone maintenance with standard or minimal counseling versus 21-day methadone detoxification. *Drug & Alcohol Dependence*, *94*(1-3), 199-206.	BACKGROUND: Important questions remain regarding the necessary duration and intensity for methadone treatment to be effective. METHODS: As part of a clinical trial of tuberculosis chemoprophylaxis [Batki, S.L., Gruber, V.A., Bradley, J.M., Bradley, M., Delucchi, K., 2002. A controlled trial of methadone treatment combined with directly observed isoniazid for tuberculosis prevention in injection drug users. Drug Alcohol Depend. 66 283-293. doi:10.1016/S0376-8716(01)00208-3], patients with opioid dependence were recruited from an outpatient 21-day methadone detoxification program and were randomly assigned to one of three treatment conditions: (1) continuation in 21-day methadone detoxification; (2) transfer to 6-month methadone maintenance with only minimal counseling; or (3) transfer to 6-month methadone maintenance with standard twice monthly counseling and as-needed social work and psychiatric services. Both the 6-month maintenance treatments were followed by 1.5 months of detoxification. Urine drug tests and self-report measures were collected at baseline, months 1-6, and month 8.5. RESULTS: Compared to 21-day methadone detoxification, 6-month methadone maintenance with either minimal or standard counseling resulted in fewer opiate positive urine tests and days of self-reported heroin and alcohol use. There was no change in cocaine use or other outcome measures. The increased counseling available in the standard counseling condition did not appear to reduce heroin use further than the minimal counseling	7_EX.TOPIC

	condition, in contrast to the effect found for more structured counseling in long-term methadone maintenance (McLellan et al., 1993). CONCLUSIONS: Six months of methadone maintenance, even with minimal counseling, reduces heroin and alcohol use more than 21-day methadone detoxification.	
Guzman-Montes, G., Y., Ovalles, R., H., & Laniado-Laborin, R. (2009). Indirect patient expenses for antituberculosis treatment in Tijuana, Mexico: is treatment really free? *Journal of Infection in Developing Countries*, *3*(10), 778-782.	BACKGROUND: One of the main problems faced by the Mexican National Tuberculosis Program is the high rate of patients abandoning treatment. This study aimed to determine the magnitude of unaccounted costs of tuberculosis (TB) treatment in Tijuana, Mexico. METHODOLOGY: Subjects were recruited at 21 health centres. Patients had confirmed active pulmonary TB, had been on treatment for more than 12 weeks, and were aged 18 years and older. The questionnaire provided information about demographics, past and current episodes of TB, and various categories of expenses. RESULTS: The study included 180 patients as follows: 48 had been diagnosed with tuberculosis in the past (26.6%) and had either currently relapsed or failed treatment; 160 (88.8%) were under directly observed therapy (DOT); 131 (72.8%) attended a health centre; and the rest received directly observed treatment at home. The daily cost of transportation to the health centre was MXN $25.88 +/- 3.22 (1 USD = 13 MXN). Thirty-two patients (17.8%) had to buy medication at least once, with a monthly medication expense of MXN $440.5 +/- 40.3. Patients receiving DOT at the health centre reported daily food and beverages expenses, spending MXN $56.5 +/- 10.1. Forty-two patients reported laboratory testing expenses, on average MXN $558.8 +/- 85.8 per month. Eighty patients (42.4%) reported expenses on radiographic/ultrasound studies, on average MXN $562.9 +/- 72.1 per six-month regimen. Conclusions TB diagnosis and treatment posed a significant economic burden on patients in terms of both cost and affordability; clinic-based DOT may contribute disproportionately to the costs incurred by patients.	7_EX.TOPIC
Haynes, R., B., et al. (2008). Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews*, (2), p.CD000011.	Background People who are prescribed self- administered medications typically take less than half the prescribed doses. Efforts to assist patients with adherence to medications might improve the benefits of prescribed medications, but also might increase their adverse effects. Objectives To update a review summarizing the results of randomized controlled trials (RCTs) of interventions to help patients follow prescriptions for medications for medical problems, including mental disorders but not addictions. Search strategy We updated searches of The Cochrane Library, MEDLINE, CINAHL, EMBASE, International Pharmaceutical Abstracts (IPA), PsycINFO (all via OVID) and Sociological Abstracts (via CSA) in January 2007 with no language restriction. We also reviewed bibliographies in articles on patient adherence and articles in our personal collections, and contacted authors of relevant original and review articles. Selection criteria Articles were selected if they reported an unconfounded RCT of an intervention to improve adherence with prescribed medications, measuring both medication adherence and treatment outcome, with at least 80% follow- up of each group studied and, for long- term treatments, at least six months follow- up for studies with positive initial findings. Data collection and analysis Study design features, interventions and controls, and results were extracted by one review author and confirmed by at least one other review author. We extracted adherence rates and their measures of variance for all methods of measuring adherence in each study, and all outcome rates and their measures of variance for each study group, as well as levels of statistical significance for differences between study groups, consulting authors and verifying or correcting analyses as needed. The studies differed widely according to	5_EX.POP

	medical condition, patient population, intervention, measures of adherence, and clinical outcomes. Therefore, we did not feel that quantitative analysis was scientifically justified; rather, we conducted a qualitative analysis. Main results For short- term treatments, four of ten interventions reported in nine RCTs showed an effect on both adherence and at least one clinical outcome, while one intervention reported in one RCT significantly improved patient adherence, but did not enhance the clinical outcome. For long- term treatments, 36 of 81 interventions reported in 69 RCTs were associated with improvements in adherence, but only 25 interventions led to improvement in at least one treatment outcome. Almost all of the interventions that were effective for long-term care were complex, including combinations of more convenient care, information, reminders, self- monitoring, reinforcement, counseling, family therapy, psychological therapy, crisis intervention, manual telephone follow- up, and supportive care. Even the most effective interventions did not lead to large improvements in adherence and treatment outcomes. Authors' conclusions For short- term treatments several quite simple interventions increased adherence and improved patient outcomes, but the effects were inconsistent from study to study with less than half of studies showing benefits. Current methods of improving adherence for chronic health problems are mostly complex and not very effective, so that the full benefits of treatment cannot be realized. High priority should be given to fundamental and applied research concerning innovations to assist patients to follow medication prescriptions for long-term medical disorders.	
Horsburgh, C., R., et al. (2010). Latent TB infection treatment acceptance and completion in the United States and Canada. *Chest*, *137*(2), 401-409.	BACKGROUND: Treatment of latent TB infection (LTBI) is essential for preventing TB in North America, but acceptance and completion of this treatment have not been systematically assessed. METHODS: We performed a retrospective, randomized two-stage cross-sectional survey of treatment and completion of LTBI at public and private clinics in 19 regions of the United States and Canada in 2002. RESULTS: At 32 clinics that both performed tuberculin skin testing and offered treatment, 123 (17.1%; 95% CI, 14.5%-20.0%) of 720 subjects tested and offered treatment declined. Employees at health-care facilities were more likely to decline (odds ratio [OR], 4.74; 95% CI, 1.75-12.9; P = .003), whereas those in contact with a patient with TB were less likely to decline (OR, 0.19; 95% CI, 0.07-0.50; P = .001). At 68 clinics starting treatment regardless of where skin testing was performed, 1,045 (52.7%; 95% CI, 48.5%-56.8%) of 1,994 people starting treatment failed to complete the recommended course. Risk factors for failure to complete included starting the 9-month isoniazid regimen (OR, 2.08; 95% CI, 1.23-3.57), residence in a congregate setting (nursing home, shelter, or jail; OR, 2.94; 95% CI, 1.58-5.56), injection drug use (OR, 2.13; 95% CI, 1.04-4.35), age >or= 15 years (OR, 1.49; 95% CI, 1.14-1.94), and employment at a health-care facility (1.37; 95% CI, 1.00-1.85). CONCLUSIONS: Fewer than half of the people starting treatment of LTBI completed therapy. Shorter regimens and interventions targeting residents of congregate settings, injection drug users, and employees of health-care facilities are needed to increase completion.	7_EX.TOPIC
Jasmer, R., M., et al. (2004). Tuberculosis treatment outcomes: directly observed therapy compared with self-administered therapy.	Effective treatment of tuberculosis requires adherence to a minimum of 6 months treatment with multiple drugs. To improve adherence and cure rates, directly observed therapy is recommended for the treatment of pulmonary tuberculosis. We compared treatment outcomes among all culture-positive patients treated for active pulmonary tuberculosis (n = 372) in San Francisco County, California	5_EX.POP

American Journal of Respiratory & Critical Care Medicine, *170*(5), 561-566.	from 1998 through 2000. Patients treated by directly observed therapy at the start of therapy (n = 149) had a significantly higher cure rate compared with patients treated by self-administered therapy (n = 223) (the sum of bacteriologic cure and completion of treatment, 97.8% versus 88.6%, p < 0.002), and decreased tuberculosis-related mortality (0% vs. 5.5%, p = 0.002). Rates of treatment failure, relapse, and acquired drug resistance were similar between the two groups. Forty-four percent of patients who received self-administered therapy had risk factors for nonadherence and should have been assigned to directly observed therapy. We conclude that treatment plans that emphasize directly observed therapy from the start of therapy have the greatest success in improving tuberculosis treatment outcomes.	
Kimerling, M.,E., et al. (1999). Spot sputum screening: evaluation of an intervention in two homeless shelters. *The International Journal of Tuberculosis and Lung Disease*, *3*(7), 613–619.	SETTING: Two homeless shelters in Birmingham, Alabama. OBJECTIVE: To interrupt tuberculosis transmission and evaluate the utility of spot sputum screening. DESIGN: Two shelters participated in the study between May 1996 and February 1997. A spot sputum specimen was collected on a given evening from each overnight client. Information was obtained regarding symptoms and tuberculin skin test (TST) status. There were four screenings during two rounds, with TST in round one only. RESULTS: Of 127 persons involved in the study, 120 (95%) provided specimens, and four tuberculosis cases were identified (4/127, 3.1%). Symptoms were infrequently reported. RFLP analysis (IS6110) confirmed a two-band cluster in three of the four cases; another matching two-band strain was found in a drug rehabilitation client staying in one shelter. Secondary RFLP typing (pTBN12) confirmed the homeless cluster. Costs were $1311 per case identified. Among 92 clients with a prior TST, 40% reported a positive result (37/92). Of 21 PPD tests read, 11 were > or =10 mm (52%). CONCLUSION: Spot sputum screening is effective in identifying unsuspected tuberculosis cases in shelters. It has acceptable costs, is logistically simple and efficient. Symptom screening was not useful in this general homeless population. RFLP analysis showed cloning of the two-band strain. Given the evidence for ongoing transmission, sputum screening should be considered in shelter settings.	9_IN.OTHER
Kong, P., M., et al. (2002). Skin-test screening and tuberculosis transmission among the homeless. *Emerging Infectious Diseases*, *8*(11), 1280-1284.	We describe the implementation of a mandatory tuberculosis (TB) screening program that uses symptom screening and tuberculin skin testing in homeless shelters. We used the results of DNA fingerprinting of Mycobacterium tuberculosis isolates to evaluate the effect of the program on TB incidence and transmission. After the program was implemented, the proportion of cases among homeless persons detected by screening activities increased, and the estimated TB incidence decreased from 510 to 121 cases per 100000 population per year. Recent transmission, defined by DNA fingerprinting analysis as clustered patterns occurring within 2 years, decreased from 49% to 14% (p=0.03). Our results suggest that the shelter-based screening program decreased the incidence of TB by decreasing its transmission among the homeless.	9_IN.OTHER
Kranzer, K., et al. (2010). Yield of HIV-associated tuberculosis during intensified case finding in resource-limited settings: a systematic review and meta-analysis. *The Lancet Infectious Diseases*, *10*(2), 93-102.	Intensified case finding is the regular screening for evidence of tuberculosis in people infected with HIV, at high risk of HIV, or living in congregate settings. We systematically reviewed studies of intensified case finding published between January, 1994, and April, 2009. In 78 eligible studies, the number of people with tuberculosis detected during intensified case finding varied substantially between countries and target groups of patients. Median prevalence of newly diagnosed tuberculosis was 0.7% in population-based surveys, 2.2% in contact-tracing studies, 2.3% in mines, 2.3% in programmes preventing mother-to-child transmission of HIV, 2.5% in prisons,	4_EX.OECD

	8.2% in medical and antiretroviral treatment clinics, and 8.5% in voluntary counselling and testing services. Metaregression analysis of studies that included only people with HIV showed that for each increment in national prevalence of tuberculosis of 100 cases per 100 000 population, intensified case finding identified an additional one case per 100 screened individuals (p=0.03). Microbiological sputum examination of all individuals without prior selection by symptom screening yielded an additional four cases per 100 individuals screened (p=0.05). Data on the use of serial screening, treatment outcomes in actively identified cases of tuberculosis, and cost-effectiveness, however, were lacking. Concerted action is needed to develop intensified case finding as an important method for control of tuberculosis. [References: 117]	
Long, R., et al. (2002). The emergency department is a determinant point of contact of tuberculosis patients prior to diagnosis. *International Journal of Tuberculosis and Lung Disease*, *6*(4), 332-339.	SETTING: Metropolitan Edmonton, Canada. OBJECTIVES: To determine 1) the pre-diagnosis emergency department utilization history of urban tuberculosis patients, and 2) the resource and outcome implications of emergency department utilization by tuberculosis patients pre-diagnosis. DESIGN: Nested case (emergency department attendee) control (non-emergency department attendee) study of a retrospective cohort of tuberculosis patients. PATIENTS: All tuberculosis notifications, 1994 through 1998. MAIN OUTCOME MEASURES: Emergency department utilization during the 6 months antedating the diagnosis and emergency department attendee characteristics; for those notified in 1997 and 1998, hospitalizations, nosocomial infectiousness time, and health care costs. RESULTS: Of 250 cases of tuberculosis, 117 (47%) made a total of 258 pre-diagnosis emergency department visits. Emergency department use increased the nearer the patient was to diagnosis. Emergency department attendees were more likely to be older, to have smear and/or culture positive respiratory disease, to have a risk factor for progression of infection to disease, and to have a fatal outcome. In 1997 and 1998, emergency department throughput accounted for 70% of all hospitalization days, 95% of all source case nosocomial infectiousness time, and most health care costs of tuberculosis patients pre-diagnosis. CONCLUSIONS: The emergency department is heavily utilized by urban tuberculosis patients pre-diagnosis. Emergency department throughput of tuberculosis patients pre-diagnosis has major resource and outcome implications. The emergency department may present an opportunity for earlier diagnosis.	1_EX.TB
Lorvick, J., et al. (1999). Incentives and accessibility: a pilot study to promote adherence to TB prophylaxis in a high-risk community. *Journal of Urban Health*, *76*(4), 461–467.	SETTING: A community-based directly observed preventive therapy (DOPT) program for treatment of latent tuberculosis infection among injection drug users (IDUs) in an inner-city neighborhood. OBJECTIVE: To test adherence to a 6-month course of DOPT using cash incentives and an easily accessible neighborhood location. DESIGN: Street-recruited IDUs (N = 205) were screened for Mycobacterium tuberculosis (TB) infection using the Mantoux test and two controls. Subjects who had a purified protein derivative (PPD) reaction of > or =5 mm, were anergic, or had a history of a positive PPD received clinical evaluation at a community field site, provided in collaboration with the San Francisco Department of Public Health Tuberculosis Clinic. Twenty-eight subjects were considered appropriate candidates for prophylaxis with isoniazid, and 27 enrolled in the pilot study. Participants received twice-weekly DOPT at a community satellite office, with a $10 cash incentive at each visit. RESULTS: The 6-month (26-week) regimen was completed by 24/27 (89%) participants. The median time to treatment completion was 27 weeks (range 26 to 34 weeks). The median proportion of dosing days attended in 6 months was 96%.	9_IN.OTHER

	CONCLUSION: Community-based DOPT using cash incentives resulted in high levels of adherence and treatment completion among drug users.	
Lucas, G., M. et al. (2007). Adherence, drug use, and treatment failure in a methadone-clinic-based program of directly administered antiretroviral therapy. *AIDS Patient Care & STDS*, *21*(8), 564-574.	Supervised dosing is a cornerstone of tuberculosis treatment. HIV treatment strategies that use directly administered antiretroviral therapy (DAART) are increasingly being assessed. In a prospective single-arm clinical trial, we enrolled methadone-maintained, HIV-infected participants to receive supervised doses of antiretroviral therapy (ART) on days when they received methadone. Other ART doses were self-administered. In this analysis we examined factors associated with retention to DAART, adherence to supervised doses, and virologic failure. Factors associated with retention to DAART were assessed with the Kaplan-Meier method and Cox proportional hazards models. Factors associated with nonadherence with supervised dosing and with virologic failure were assessed by logistic regression and techniques for longitudinal data analysis. A total of 16,453 supervised doses were administered to 88 participants over a median follow-up of 9.4 months. The median participant adherence with supervised dosing was 83%. Active drug use, determined by urine drug screens, was associated twofold increased risks of both intervention dropout and nonadherence with supervised doses. Adherence with supervised doses was strongly associated with virologic failure. Because DAART was administered only on methadone dosing days, fewer than half of the total ART doses were scheduled to be supervised in most participants. The percent of doses that was scheduled to be supervised was not associated with either adherence or with virologic failure. Given that a relatively small proportion of the total ART doses were supervised in many patients, future studies should assess how DAART affects adherence with nonsupervised doses and retention to ART.	1_EX.TB
MacIntyre, C., R., & Plant, A.,J. (1998). Preventability of incident cases of tuberculosis in recently exposed contacts. *International Journal of Tuberculosis & Lung Disease*, *2*(1), 56-61.	SETTING: Contacts of tuberculosis (TB) cases are at risk for TB. If contact screening and intervention are effective, one would expect a reduced incidence of TB in contacts who have been screened. OBJECTIVE: To measure the incidence of TB in contacts during a 2-year follow up, and to estimate the preventability of incident cases. METHODS: A retrospective cohort study of 783 contacts screened in Victoria, Australia, in 1991. Contacts were matched with the TB registry for the following 2 years. Screening records were reviewed. RESULTS: The rate of TB in contacts was 511/100,000 population/year for the first 2 years. In Poisson regression models the only significant variable predicting disease was skin test reaction size. Six of eight incident cases were potentially preventable, with a lowest achievable incidence rate of 128/100,000/year. CONCLUSION: Contacts who underwent screening for TB through a state screening programme had a high incidence of TB during the 2 year follow up. Published rates of TB of 425-670/100,000 in untreated contacts suggests that the Victorian screening programme had minimal impact on the natural history of disease progression. Intrinsic programme factors such as the appropriateness of the guidelines, adherence to guidelines and rates of preventive therapy need to be evaluated. The devolution of the TB programme in the 1980s also reduced its efficacy. Systematic assessment of screening programmes for efficacy and outcome is part of good public health practice.	5_EX.POP
MacIntyre, C.. R., & Plant, A., J. (1998). Tuberculosis in South-East Asian refugees after resettlement – can	OBJECTIVE: This study aimed to determine whether incident cases of tuberculosis (TB) in a cohort of South-East Asian refugees followed for 5 years after resettlement were potentially preventable and whether prevention of TB was optimal in a state refugee TB screening program in Victoria, Australia. DESIGN: A retrospective	9_IN.OTHER

prevention be improved by better policy and practice? *Preventive Medicine*, *27*(6), 815-820.	cohort study of 1,101 refugees from Laos, Cambodia, and Vietnam screened for TB in the 6-month period from July 1989 to January 1990 was conducted. Incident cases of TB were identified by matching each refugee with the TB notification database for 5 years from the date of initial screening. Preventability was assessed for incident cases by reviewing medical records. Screening guidelines and practice were reviewed. RESULTS: The main outcome was the preventability of cases of active tuberculosis that developed in the study population in the first 5 years after resettlement. The incidence of active TB was 363/100,000 during the first year and 109/100,000/year during the first 5 years. Five of six incident cases were assessed as potentially preventable, which if prevented would have resulted in an annual incidence of 18/100,000 over the first 5 years. Use of a more sensitive skin test definition of infection would have made an additional 245 refugees eligible for prevention and potentially prevented an additional 25 cases of TB over a lifetime. CONCLUSIONS: There is a high incidence of tuberculosis among SE Asian refugees, particularly in the first year after resettlement. A large proportion of TB may be preventable. Improvement in case prevention may be possible with updated guidelines and better implementation of screening policy.	
MacIntyre, C., R., et al. (2000). No evidence for multiple-drug prophylaxis for tuberculosis compared with isoniazid alone in Southeast Asian refugees and migrants: completion and compliance are major determinants of effectiveness. *Preventive Medicine*, *30*(5), 425-432.	BACKGROUND: The use of multiple-drug prophylaxis for tuberculosis (TB) has not been shown to be more effective than prophylaxis with isoniazid alone. The boundary between inactive pulmonary TB (class 4 TB) and culture-negative "active" pulmonary TB (class 3 TB) is often unclear, as is the intention to treat such patients as a preventive measure or as a curative measure. METHODS: We compared the effectiveness of single drug preventive therapy with isoniazid to the effectiveness of multiple drug preventive therapy for patients with asymptomatic, inactive TB, in a retrospective cohort study of 984 Southeast (SE) Asian migrants and refugees who received prophylaxis between 1978 and 1980. RESULTS: The rate of TB developing in this cohort was 122 per 100,000 person-years. There was no significant difference in development of TB between people who received isoniazid only and those who received multiple drugs. The only significant predictor of TB was noncompletion of prophylaxis [relative risk (RR) = 62, 95% confidence interval (CI) = 20-194]. Subgroup analysis on people who had completed therapy showed noncompliance as a significant predictor of TB (RR = 16, 95% CI = 1.4-179). The risk of noncompletion (RR = 4.7, 95% CI = 2.37-9.39, P < 0.0001) and noncompliance (RR = 2.2, 95% CI = 1.03-4.7, P = 0.03) was higher for patients who received multiple drugs compared with isoniazid alone. Multiple-drug therapy cost 30 times more than isoniazid alone. CONCLUSIONS: We did not find evidence in support of the empirical practice of giving multiple drugs for prevention of TB. This practice is also more costly and more likely to result in noncompliance and adverse drug reactions.	7_EX.TOPIC
MacNeil, J., R., Lobato, M., N., & Moore, M. (2005). An unanswered health disparity: tuberculosis among correctional inmates, 1993 through 2003. *American Journal of Public Health*, *95*(10), 1800-1805.	OBJECTIVES: We sought to describe disparities and trends in tuberculosis (TB) risk factors and treatment outcomes between correctional inmate and noninmate populations. METHODS: We analyzed data reported to the national TB surveillance system from 1993 through 2003. We compared characteristics between inmate and non-inmate men aged 15-64 years. RESULTS: Of the 210976 total US TB cases, 3.8% (7820) were reported from correctional systems. Federal and state prison case rates were 29.4 and 24.2 cases per 100000 inmates, respectively, which were considerably higher than those in the noninmate population (6.7 per 100000 people). Inmates with TB were more likely to have at least 1 TB risk	1_EX.TB

	factor compared with noninmates (60.1% vs 42.0%, respectively) and to receive directly observed therapy (65.0% vs 41.0%, respectively); however, they were less likely to complete treatment (76.8% vs 89.4%, respectively). Among inmates, 58.9% completed treatment within 12 months compared with 73.2% of noninmates. CONCLUSIONS: Tuberculosis case rates in prison systems remain higher than in the general population. Inmates with TB are less likely than noninmates to complete treatment.	
Malmborg, R., et al. (2006). Can public-private collaboration promote tuberculosis case detection among the poor and vulnerable? *Bulletin of the World Health Organization*, *84*(9), 752-758.	Private-public mix (PPM) DOTS is widely advocated as a DOTS adaptation for promoting progress towards the international tuberculosis (TB) control targets of detecting 70% of TB cases and successfully treating 85% of these. Private health care plays a central role in health-care provision in many developing countries that have a high burden of TB. It is therefore encouraging that PPM projects are being set up in various countries around the world to explore possible interaction between the national TB programmes and other partners in the fight against TB. The objective of this review was to use the published literature to assess the range of providers included in PPMs for their ability to provide case-detection services for the vulnerable. From a case-detection perspective, we identify the essential elements of a pro-poor PPM model, namely, cost-effectiveness from a patient perspective, accessibility, acceptability and quality. The review revealed that a very large part of the total spectrum of potential PPM-participating partners has not yet been explored; current models focus on private-for-profit health-care providers and non-governmental organizations. We conclude that it is important to think critically about the type of private providers who are best suited to meeting the needs of the poor, and that more should be done to document the socioeconomic status of patients accessing services through PPM pilots. [References: 49]	7_EX.TOPIC
McNabb, S., J., et al. (2004). Applying a new conceptual framework to evaluate tuberculosis surveillance and action performance and measure the costs, Hillsborough County, Florida, 2002. *Annals of Epidemiology*, *14*(9), 640-645.	PURPOSE: Tuberculosis (TB) elimination is an important US public health goal and improving the performance of TB surveillance and action and reducing the costs will help achieve it. But, there exists the need to better evaluate the performance and measure the costs. METHODS: We pilot tested an evaluation strategy in Hillsborough County, Florida using a conceptual framework of TB surveillance and action with eight core and four support activities. To evaluate performance, we developed indicators and validated their accuracy, usefulness, and measurability. To measure the costs, we obtained financial information. RESULTS: In 2001, Hillsborough County reported 78 (7%) of the 1145 Florida TB cases. Nineteen (24%) were previously arrested. While 13 (68%) of the 19 were incarcerated during the 2 years prior to being reported, only 1 (5%) of 19 was reported from the jail. From 111 TB suspects, 219 (25%) of 894 sputum specimens were inadequately collected. Of the $1.08 million annual budget, 22% went for surveillance, 29% for support, and 49% for action. CONCLUSIONS: This conceptual framework allowed measurement of TB surveillance and action performance and cost. The evaluation performed using it revealed missed opportunities for detection of TB cases and wasted resources. This conceptual framework could serve as a model for evaluation of TB surveillance and action.	7_EX.TOPIC
Menendez, E., White, M., C., & Tulsky, J., P. (2001). Locating study subjects: predictors and successful search strategies with inmates released from a US	Minimizing loss to follow-up in longitudinal studies is critical. The purpose of this study was to examine the ability to locate subjects recently released from jail, identify predictors of being able to find a subject, and describe effective search strategies for this unique population. The sample for this cohort study included study subjects who were sought for interview after release from jail. Inmates in the San Francisco City and County Jail were enrolled in a randomized	1_EX.TB

county jail. *Controlled Clinical Trials*, *22*(3), 238-247.	trial of incentives to improve follow-up for tuberculosis therapy after release from jail. Sociodemographic, health-related, and extensive locating information was collected during baseline interviews in jail. The main outcome was successful location of the subject. Study personnel recorded data on the number and nature of attempts made to find subjects in order to describe successful search strategies. Of 254 persons sought for the postrelease interview, 188 (74.0%) were found. Primary English speakers were more likely than Spanish speakers to be found (relative risk: 3.2, 95% confidence interval: 1.5-6.7, p = 0.002). Nearly one quarter of subjects (24%) were found back in jail, and the remainder were found in the community. Phone calls and letters to the subjects, and personal contacts to family and friends were successful strategies for 53% of the subjects. Seeking persons in programs, such as shelters and drug and alcohol programs, was successful in finding 18% of English-speaking subjects. Outreach efforts in sections of the city where Latinos spent time, including popular restaurants and community gathering places, were successful in finding 13% of Spanish-speaking subjects. We conclude that study subjects released from jails can be successfully located using well-defined search protocols tailored to the ethnicity of the sample and including a variety of strategies. Employment of bilingual personnel is important when a large proportion of subjects is monolingual and non-English speaking.	
Mohle-Boetani, J., C., et al. (2002). Tuberculosis outbreak in a housing unit for human immunodeficiency virus-infected patients in a correctional facility: transmission risk factors and effective outbreak control. *Clinical Infectious Diseases*, *34*(5), 668-676.	In 1995, an outbreak of tuberculosis (TB) occurred among residents of a correctional-facility housing unit for inmates infected with human immunodeficiency virus (HIV). We isolated and treated patients who were suspected to have TB. To determine risk factors for in-prison transmission of TB, we conducted a case-control study to compare inmate case patients infected with a distinct outbreak strain of TB with control subjects who resided in the HIV unit. We identified 15 case patients during a 4-month period. Among inmates with a CD4 count of /=20 hours per week in a communal day room (odds ratio, 42; P=.002) and were less likely to have a television in their single-person room (odds ratio, 0.10; P=.003). The communal day room was a likely site of transmission. Successful collaboration between the correctional system and public health departments halted the outbreak.	1_EX.TB
Moore, R., D., et al. (1996). Cost-effectiveness of directly observed versus self-administered therapy for tuberculosis. *American Journal of Respiratory and Critical Care Medicine*, *154*(4), 1013.	Decision analysis was used to compare three alternative strategies for a 6-mo course of treatment for tuberculosis: directly observed drug therapy (DOT), self-administered fixed-dose combination drug therapy, and self-administered conventional individual drug therapy. Estimates of effectiveness were obtained from the published literature. Estimates of costs were obtained from the literature and the Baltimore City Health Department. Both DOT and fixed-dose combination therapy were less costly and more effective than conventional therapy, although DOT was most cost-effective. In total, the average cost per patient treated was $13,925 for DOT, $13,959 for fixed-dose combination therapy, and $15,003 for conventional therapy. Per 1,000 patients treated, 31 relapses and three deaths could be expected for DOT, 96 relapses and eight deaths for fixed-dose combination therapy, and 133 relapses and 13 deaths for conventional therapy. The marginal cost-effectiveness of DOT relative to fixed-dose combination therapy was most sensitive to variability in the direct cost of DOT and less sensitive to relapse rates for DOT and fixed-dose combination therapy. The inferior cost-effectiveness of conventional therapy was not sensitive to plausible variability in cost or effectiveness. Both DOT and fixed-dose combination therapy were cost-effective relative to conventional therapy, although DOT is probably most cost-effective.	5_EX.POP

Morisky, D., E., et al. (1990). A patient education program to improve adherence rates with antituberculosis drug regimens. *Health Education & Behavior*, *17*(3), 253.	An incentive scheme to reward positive health behaviours plus targeted educational counselling sessions was implemented in a randomised clinical controlled trial. Patients with active tuberculosis or preventive patients were randomly assigned to a special intervention (SI) group or a usual care (UC) control group. Results demonstrate the positive effects of a structured health education programme. (Abstract amended)	5_EX.POP
NoY, J., & Popay, J. (2007). Directly observed therapy and tuberculosis: how can a systematic review of qualitative research contribute to improving services? A qualitative meta-synthesis. *Journal of Advanced Nursing*, *57*(3), 227-243.	AIM: This paper reports the findings from a qualitative meta-synthesis concerning people with, or at risk of, tuberculosis, service providers and policymakers and their experiences and perceptions of tuberculosis and treatment. BACKGROUND: Directly observed therapy is part of a package of interventions to improve tuberculosis treatment and adherence. A Cochrane systematic review of trials showed an absence of evidence for or against directly observed therapy compared with people treating themselves. METHOD: Qualitative systematic review methods were used to search, screen, appraise and extract data thematic analysis was used to synthesize data from 1990 to 2002, and an update of literature to December 2005. Two questions were addressed: 'What does qualitative research tell us about the facilitators and barriers to accessing and complying with tuberculosis treatment?' and 'What does qualitative research tell us about the diverse results and effect sizes of the randomized controlled trials included in the Cochrane review?' Findings help explain the diverse trial results in a Cochrane systematic review of directly observed therapy and tuberculosis and consider implications for research, policy and practice. FINDINGS: Five themes emerged from the 1990 to 2002 synthesis: socio-economic circumstances, material resources and individual agency; explanatory models and knowledge systems in relation to tuberculosis and its treatment; the experience of stigma and public discourses around tuberculosis; sanctions, incentives and support, and the social organization and social relationships of care. Two additional themes emerged from the 2005 update. CONCLUSION: The qualitative meta-synthesis improved the relevance and scope of the Cochrane review of trials. The findings make a major contribution to the development of theory concerning global WHO-branded disease control and the practicality of local delivery to people. [References: 86]	6_EX.NON-EMP
Orlando, G., et al. (2010). Interferon-gamma releasing assay versus tuberculin skin testing for latent tuberculosis infection in targeted screening programs for high risk immigrants. *Infection*, *38*(3), 195-204.	BACKGROUND: Recent immigrants from developing countries (20 mM (k = 0.47), in subjects aged 40-50 years (k = 0.41) and in unvaccinated persons (k = 0.40). In a multiple logistic regression model continent of origin, class of TB prevalence in the country of origin and contacts with TB patients were found to be significantly associated with the probability of TST and QFT-IT positive result. Low education levels were associated only to an increased risk of TST positive results. CONCLUSIONS: The drawback of the TST screening strategy in recent immigrants from highly endemic countries is due to low sensitivity/specificity of the test and to high drop-out rate with an overall significant lowering in strategy efficacy/efficiency. The higher QFT-IT specificity prevents unnecessary overload of the health care system and, although more expensive, might represent a cost-effective alternative to TST in targeted screening programs directed to high risk populations.	7_EX.TOPIC
Oxlade, O., Schwartzman, K., & Menzies, D. (2007). Interferon-gamma release assays and TB	OBJECTIVE: Interferon-gamma release assays (IGRA) are now available alternatives to tuberculin skin testing (TST) for detection of latent tuberculosis infection (LTBI). We compared the cost-effectiveness of TST and IGRA in different populations and clinical situations, and with variation of a number of parameters. METHODS:	7_EX.TOPIC

screening in high-income countries: a cost-effectiveness analysis. *The International Journal of Tuberculosis and Lung Disease*, *11*(1), 16–26.	Markov modelling was used to compare expected TB cases and costs over 20 years following screening for TB with different strategies among hypothetical cohorts of foreign-born entrants to Canada, or contacts of TB cases. The less expensive commercial IGRA, Quanti-FERON-TB Gold (QFT), was examined. Model inputs were derived from published literature. RESULTS: For entering immigrants, screening with chest radiograph (CXR) would be the most and QFT the least cost-effective. Sequential screening with TST then QFT was more cost-effective than QFT alone in all scenarios, and more cost-effective than TST alone in selected subgroups. Among close and casual contacts, screening with TST or QFT would be cost saving; savings with TST would be greater than with QFT, except in contacts who were bacille Calmette-Guerin (BCG) vaccinated after infancy. CONCLUSIONS: Screening for LTBI, with TST or QFT, is cost-effective only if the risk of disease is high. The most cost-effective use of QFT is to test TST-positive persons.	
Pillaye, J., & Clarke, A. (2003). An evaluation of completeness of tuberculosis notification in the United Kingdom. *BMC Public Health*, 3, 31.	BACKGROUND: There has been a resurgence of tuberculosis worldwide, mainly in developing countries but also affecting the United Kingdom (UK), and other Western countries. The control of tuberculosis is dependent on early identification of cases and timely notification to public health departments to ensure appropriate treatment of cases and screening of contacts. Tuberculosis is compulsorily notifiable in the UK, and the doctor making or suspecting the diagnosis is legally responsible for notification. There is evidence of under-reporting of tuberculosis. This has implications for the control of tuberculosis as a disproportionate number of people who become infected are the most vulnerable in society, and are less likely to be identified and notified to the public health system. These include the poor, the homeless, refugees and ethnic minorities. METHOD: This study was a critical literature review on completeness of tuberculosis notification within the UK National Health Service (NHS) context. The review also identified data sources associated with reporting completeness and assessed whether studies corrected for undercount using capture-recapture (CR) methodology. Studies were included if they assessed completeness of tuberculosis notification quantitatively. The outcome measure used was notification completeness expressed between 0% and 100% of a defined denominator, or in numbers not notified where the denominator was unknown. RESULTS: Seven studies that met the inclusion and exclusion criteria were identified through electronic and manual search of published and unpublished literature. One study used CR methodology. Analysis of the seven studies showed that undernotification varied from 7% to 27% in studies that had a denominator; and 38%-49% extra cases were identified in studies which examined specific data sources like pathology reports or prescriptions for anti-tuberculosis drugs. Cases notified were more likely to have positive microbiology than cases not notified which were more likely to have positive histopathology or be surgical in-patients. Collation of prescription data of two or more anti-tuberculosis drugs increases case ascertainment of tuberculosis. CONCLUSION: The reporting of tuberculosis is incomplete in the UK, although notification is a statutory requirement. Undernotification leads to an underestimation of the disease burden and hinders implementation of appropriate prevention and control strategies. The notification system needs to be strengthened to include education and training of all sub-specialities involved in diagnosis and treatment of tuberculosis. [References: 35]	7_EX.TOPIC
Porco, T., C., et al. (2006). Cost-	BACKGROUND: Immigrants to the U.S. are required to undergo overseas screening for tuberculosis (TB), but the value of evaluation	9_IN.OTHER

effectiveness of tuberculosis evaluation and treatment of newly-arrived immigrants. *BMC Public Health*, *6*(1), 157.	and treatment following entry to the U.S. is not well understood. We determined the cost-effectiveness of domestic follow-up of immigrants identified as tuberculosis suspects through overseas screening. METHODS: Using a stochastic simulation for tuberculosis reactivation, transmission, and follow-up for a hypothetical cohort of 1000 individuals, we calculated the incremental cost-effectiveness of follow-up and evaluation interventions. We utilized published literature, California Reports of Verified Cases of Tuberculosis (RVCTs), demographic estimates from the California Department of Finance, Medicare reimbursement, and Medi-Cal reimbursement rates. Our target population was legal immigrants to the United States, our time horizon is twenty years, and our perspective was that of all domestic health-care payers. We examined the intervention to offer latent tuberculosis therapy to infected individuals, to increase the yield of domestic evaluation, and to increase the starting and completion rates of LTBI therapy with INH (isoniazid). Our outcome measures were the number of cases averted, the number of deaths averted, the incremental dollar cost (year 2004), and the number of quality-adjusted life-years saved. RESULTS: Domestic follow-up of B-notification patients, including LTBI treatment for latently infected individuals, is highly cost-effective, and at times, cost-saving. B-notification follow-up in California would reduce the number of new tuberculosis cases by about 6-26 per year (out of a total of approximately 3000). Sensitivity analysis revealed that domestic follow-up remains cost-effective when the hepatitis rates due to INH therapy are over fifteen times our best estimates, when at least 0.4 percent of patients have active disease and when hospitalization of cases detected through domestic follow-up is no less likely than hospitalization of passively detected cases. CONCLUSION: While the current immigration screening program is unlikely to result in a large change in case rates, domestic follow-up of B-notification patients, including LTBI treatment, is highly cost-effective. If as many as three percent of screened individuals have active TB, and early detection reduces the rate of hospitalization, net savings may be expected.	
Rendleman, N., J. (1999). Mandated tuberculosis screening in a community of homeless people. *American Journal of Preventive Medicine*, *17*(2), 108–113.	BACKGROUND: To examine the effects of a community program on tuberculosis incidence, prevalence, and transmission requiring users of public facilities to carry cards certifying their compliance with a tuberculosis screening, prophylaxis, and treatment program. Community knowledge of tuberculosis and costs and benefits of the program are described. SETTING: A West Coast "skid row" community with historically high rates of tuberculosis, homelessness, poverty, and use of drugs and alcohol. DESIGN: Analysis of tuberculosis activity in communities in Oregon using Oregon Health Division Tuberculosis Data Bank data. Description of community response and cost considerations. MAIN OUTCOME MEASURES: Rates of active disease, mortality, and skin-test response. Compliance with card use and understanding of tuberculosis control measures. Program expenditures. RESULTS: An 89% drop in active disease in the highest-risk community in Oregon occurred over the first 10 years of the program. Compliance with the program permitting the use of public facilities, based on cooperation with skin testing, radiology, sputum collection, and therapy has been between 33% of converters completing prophylaxis in the worst year to 100% of active cases completing 4-drug therapy in the best. Facilities that provide services have been almost universal in requiring cooperation for participants. Costs have been reduced. CONCLUSION: A program of mandated compliance with tuberculosis skin testing, radiologic and sputum examination and treatment, coupled with education and outreach, succeeded in drastically reducing active	9_IN.OTHER

	tuberculosis, transmission, deaths, and cost in a homeless community.	
Rose, D., N. (2000). Benefits of screening for latent Mycobacterium tuberculosis infection. *Archives of Internal Medicine*, *160*(10), 1513-1521.	BACKGROUND: The benefits of screening for latent Mycobacterium tuberculosis infection are unknown for most people, because screening has not been studied in clinical trials and preventive therapy has not been tested in all risk groups for whom it is recommended. METHOD: A MEDLINE search was performed to determine tuberculosis risk. A Markov model was used to analyze tuberculin skin test screening and preventive therapy for 3-year-old and 30-year-old persons with positive test results. Outcome measures were lifetime and 10-year tuberculosis risk, including spread to others, life expectancy extension, and number needed to screen and number needed to treat to prevent 1 case and 1 death during 10 years. RESULTS: The benefits of screening and preventive therapy outweigh the risks for all groups tested, although the benefits range from large to small. The number needed to screen to prevent 1 case is 10 to 6888, and the number needed to treat is 2 to 179. Persons with human immunodeficiency virus infection, intravenous drug abuse, or end-stage renal disease treated with transplantation and children exposed to high-risk adults have the highest tuberculosis rates and the lowest number needed to screen and number needed to treat to prevent cases and deaths. The range of risks found in the literature for some risk groups, such as persons with silicosis, leukemia or lymphoma, end-stage renal disease treated with dialysis, or prolonged corticosteroid therapy, is wide and, as a result, the benefits of screening are uncertain. CONCLUSIONS: The benefits of screening and preventive therapy vary widely, although the benefits outweigh the risks for all risk groups. The benefits are large for some risk groups and uncertain for others.	6_EX.NON-EMP
Rozovsky-Weinberger, J., et al. (2005). Delays in suspicion and isolation among hospitalized persons with pulmonary tuberculosis at public and private US hospitals during 1996 to 1999. *Chest*, *127*(1), 205-212.	BACKGROUND: While prior studies have shown that public and private hospitals differ in their rates of suspicion and isolation of patients who are at risk for tuberculosis (TB), no study has investigated whether this variation is due to differences in the impact of patient case-mix on hospitals or to variations attributable to specific hospital practice patterns. OBJECTIVE: To investigate patient-level and hospital-level factors associated with delays in TB suspicion and isolation among inpatients with pulmonary TB disease. DESIGN: Retrospective cohort study of patients hospitalized with culture-positive pulmonary TB during 1996 to 1999. SETTING: Patients with culture-proven pulmonary TB treated at three public hospitals (765 patients) and seven not-for-profit private hospitals (172 patients) in Chicago, Los Angeles, and southern Florida that provided care for five or more patients with TB per year during the study period. MEASUREMENTS: Two-day rates (within 48 h from admission) of acid-fast bacilli (AFB) smear orders and 1-day rates (within 24 h from admission) of TB isolation. RESULTS: Two-day rates of ordering AFB smears were > 80% at three public and two private hospitals vs 65 to 75% at five private hospitals. One-day rates of TB isolation at the three public hospitals were 64%, 79%, and 86%, respectively, vs 39 to 58% at the seven private hospitals. Delays of > 2 days in ordering AFB smears were associated with patient-level factors: absence of cough (adjusted odds ratio [AOR], 6.02; 95% confidence interval [CI], 3.82 to 9.52), cavitary lung lesion (AOR, 5.17; 95% CI, 1.98 to 13.50), night sweats (AOR, 3.38; 95% CI, 1.90 to 5.99), chills (AOR, 1.70; 95% CI, 1.01 to 2.88), and female gender (AOR, 1.66; 95% CI, 1.06 to 2.60). Delays of > 1 day in ordering pulmonary isolation were associated with patient-level factors: absence of cough (AOR, 3.40; 95% CI, 2.31 to 5.03), cavitary lung lesion (AOR, 2.66; 95% CI, 1.57 to 4.50), night sweats	5_EX.POP

	(AOR, 1.98; 95% CI, 1.35 to 2.92), and history of noninjecting drug use (AOR, 1.86; 95% CI, 1.16 to 2.99) and one hospital-level factor: receiving care at a nonpublic hospital. Even after adjustment for patient-level factors, TB patients at private hospitals were half as likely as those at public hospitals to be placed in pulmonary isolation (AOR, 0.47; 95% CI, 0.30 to 0.72), while odds of suspecting TB in these same patients were similar at both hospitals. CONCLUSION: Private hospitals should order TB isolation for all patients for whom AFB smears are ordered, a policy that has been instituted previously at public hospitals in our study.	
Schumann, A., Nyamathi, A., & Stein, J., A. (2007). HIV risk reduction in a nurse case-managed TB and HIV intervention among homeless adults. *Journal of Health Psychology*, *12*(5), 833-843.	This study evaluated a six-month nurse case-managed intervention against a standard care control program among 295 sheltered homeless adults from Los Angeles, USA. The primary aim of the intervention was encouraging latent tuberculosis infection treatment completion. The secondary aim was reducing HIV risk, the focus of this report. A longitudinal path model revealed that the intervention impacted cognitive factors of AIDS Knowledge, Perceived AIDS Risk and Self-efficacy for Condom Use, but did not impact substance use and risky sexual behaviors. The dual intervention program for HIV and TB provided promising synergistic effects by targeting risk factors common to both infections.	7_EX.TOPIC
Selwyn, P., A., et al. (1993). Utilization of on-site primary care services by HIV-seropositive and seronegative drug users in a methadone maintenance program. *Public Health Reports*, *108(*4),.492-500.	The feasibility of on-site primary care services and their use by human immunodeficiency virus HIV-seropositive and seronegative injecting drug users within an outpatient methadone maintenance program are examined. A 16-month prospective study was conducted within an ongoing cohort study of HIV infection at a New York City methadone program with on-site primary care services. The study group consisted of 212 seropositive and 264 seronegative drug injectors. A computerized medical encounter data base, with frequencies of primary care visits and with diagnoses for each visit, was linked to the cohort study data base that contained information on patients' demographic characteristics, serologic status, and CD4+ T-lymphocyte counts. Eighty-one percent of the drug injectors in the study voluntarily used on-site primary care services in the methadone program. Those who were HIV-seropositive made more frequent visits than those who were seronegative (mean annual visits 8.6 versus 4.1, P < .001), which increased with declining CD4+ T-lymphocyte counts; 79 percent of those who were seropositive with CD4 counts of less than 200 cells per cubic millimeter received on-site zidovudine therapy or prophylaxis against Pneumocystis carinii pneumonia, or both. Common primary care diagnoses for patients seropositive for HIV included not only conditions specific to the human immunodeficiency virus but also bacterial pneumonia, tuberculosis, genitourinary infections, asthma, dermatologic disease, psychiatric illness, and complications of substance abuse; those who were seronegative were most frequently seen for upper respiratory infection, psychiatric illness, complications of substance abuse, musculoskeletal disease, hypertension, asthma, and diabetes mellitus. Vaginitis and cervicitis, other gynecologic diseases, and pregnancy were frequent primary care diagnoses among both seropositive and seronegative women.	7_EX.TOPIC
Smieja, M., J., et al. (2000). Isoniazid for preventing tuberculosis in non-HIV infected persons. *Cochrane Database of Systematic Reviews*, (2), p.001363.	BACKGROUND: Although isoniazid (INH) is commonly used for treating tuberculosis (TB), it is also effective as preventive therapy. OBJECTIVES: The objective of this review was to estimate the effect of 6 and 12 month courses of INH for preventing TB in HIV-negative people at increased risk of developing active TB. SEARCH STRATEGY: We searched the Cochrane Infectious Diseases Group trials register, the Cochrane Controlled Trials Register, Medline, Embase and reference lists of articles. We hand-searched Science	5_EX.POP

	Citation Index and Index Medicus. SELECTION CRITERIA: Randomised trials of INH preventive therapy for 6 months or more compared with placebo. Follow-up for a minimum of 2 years. Trials enrolling patients with current or previously treated active TB, or with known HIV infection, were excluded. Criteria were applied by two reviewers independently. DATA COLLECTION AND ANALYSIS: Trial quality was assessed by two reviewers independently, and data extracted by one reviewer using a standardized extraction form. MAIN RESULTS: Eleven trials involving 73,375 patients were included. Trials were generally of high quality. Treatment with INH resulted in a relative risk (RR) of developing active TB of 0.40, (95% confidence interval (CI) 0.31 to 0.52), over two years or longer. There was no significant difference between 6 and 12 month courses (RR of 0.44, 95% CI 0.27 to 0.73 for six months, and 0.38, 95% CI 0.28 to 0.50 for 12 months). Preventive therapy reduced deaths from TB, but this effect was not seen for all cause mortality. INH was associated with hepatotoxicity in 0.36% of people on 6 months treatment and in 0.52% of people treated for 12 months. REVIEWER'S CONCLUSIONS: Isoniazid is effective for the prevention of active TB in diverse at-risk patients, and six and 12 month regimens have a similar effect. [References: 15]	
Snyder, D., C., et al. (1999). Tuberculosis prevention in methadone maintenance clinics. Effectiveness and cost-effectiveness. *American Journal of Respiratory & Critical Care Medicine*, *160*(1), 178-185.	To determine the effectiveness and cost-effectiveness of a program to provide screening for tuberculosis infection and directly observed preventive therapy (DOPT) in methadone maintenance clinics, we determined completion rates of screening for tuberculosis infection, medical evaluation, and preventive therapy, as well as the number of active tuberculosis cases and tuberculosis-related deaths prevented, in five clinics in San Francisco, California. Between 1990 and 1995, a total of 2,689 clients (of whom 18% were HIV-seropositive) were screened at least once. Of eligible clients, 99% received tuberculin skin tests, 96% received a medical examination, 91% began isoniazid preventive therapy, and 82% completed preventive therapy. Program effectiveness was enhanced by close collaboration between public health and methadone maintenance programs and the use of incentives and enablers. Over a 3-yr follow-up period, only one verified case of tuberculosis was reported among clients with a positive tuberculin skin test, thereby preventing as much as 95% of expected tuberculosis cases. Over 10 yr, we estimate the program would prevent 30.0 (52%) of 57.7 expected cases of tuberculosis, and 7.6 (57%) of 13.4 expected tuberculosis-related deaths. The program cost $771,569, but averted an estimated $876,229, for a net savings of $104,660 (average of $3, 724 per case prevented). Our study demonstrates that when effectively implemented, screening for tuberculosis infection and DOPT in methadone maintenance clinics is a highly cost-effective approach to prevent tuberculosis.	7_EX.TOPIC
Solsona, J., et al., et al. (2001). Screening for tuberculosis upon admission to shelters and free-meal services. *European journal of epidemiology*, *17*(2), 123–128.	BACKGROUND: The homeless are at very high risk of suffering tuberculosis (TB). The aims of this study were to determine the prevalence and risk factors for tuberculosis infection and disease among the homeless in Barcelona and to evaluate the roles of case finding and contact investigation. METHODS: Observational prevalence study carried out between 1997 and 1998. PARTICIPANTS: 447 homeless patients (394 men and 53 women) were evaluated before admission to shelters and free-meal services. At the same time, 48 co-residents with smear-positive TB patients in 2 long-term shelters were evaluated too. A chest X-ray and Tuberculin Skin Test were performed on all subjects. Sputum smears were processed by the Ziehl-Neelsen and Lowenstein-Jensen procedures in patients with radiographic findings consistent with pulmonary TB. RESULTS: Of the 447 homeless examined, 335	9_IN.OTHER

	(75%) were infected with Mycobacterium tuberculosis. Active pulmonary TB was diagnosed in five persons (1.11%), and 62 (13.8%) had radiographic evidence of inactive pulmonary TB. Tuberculosis infection was associated with age and smoking, but not with sex or alcohol abuse. No significant differences in infection rates were found between the main group and 48 homeless co-residents of smear-positive subjects. Only 16.9% of the homeless with active TB in Barcelona in the same period were diagnosed through active case-finding, the remainder being mainly detected in hospitals (69.8%) and other several centres (13.3%). CONCLUSIONS: Homeless individuals have a very high risk of TB infection and disease and contact investigation requires specific methods for them. Programmes of screening and supervised treatment should be ensured in this group.	
Spyridis, P., et al. 2003. The impact of Greece's childhood tuberculosis screening programme on the epidemiological indexes in the greater Athens area. *International Journal of Tuberculosis & Lung Disease*, *7*(3), 248-253.	SETTING: A hospital referral centre for childhood tuberculosis in Athens. OBJECTIVE: To evaluate the effectiveness of the screening programme implemented for childhood tuberculosis, through its impact on the epidemiological index. DESIGN: In Greece, tuberculosis has been systematically screened for in children since 1991 using the tuberculin skin test. The epidemiological and clinical profiles of all tuberculous children who attended the TB clinic were compared. The children were divided into those who attended in 1982-1990 and those who did so in 1991-1999. RESULTS: A total of 1122 TB patients were screened. In the second period there was an increase in numbers of immigrant children (3% vs. 28%, P = 0.0001), the rate of extra-pulmonary TB decreased (16% vs. 7.6%, P = 0.0001), patients identified by the screening programme increased (19% vs. 57%, P = 0.0001) and the number of symptomatic children fell (51% vs. 16%, P = 0.0001). The proportion of children who failed to attend for regular follow-up was lower during the second period (20% vs. 7%, P = 0.0001). CONCLUSIONS: Our study suggests that the screening programme applied in Greece during the last decade has contributed to the early identification of tuberculosis, and the limitation of symptomatic patients and extrapulmonary TB cases.	5_EX.POP
Sreeramareddy, C., T., et al. (2009). Time delays in diagnosis of pulmonary tuberculosis: a systematic review of literature. *BMC Infectious Diseases*, 9, 91.	BACKGROUND: Delay in diagnosis of pulmonary tuberculosis results in increasing severity, mortality and transmission. Various investigators have reported about delays in diagnosis of tuberculosis. We aimed at summarizing the data on these delays in diagnosis of tuberculosis. METHODS: A systematic review of literature was carried out. Literature search was done in Medline and EMBASE from 1990 to 2008. We used the following search terms: delay, tuberculosis, diagnosis, and help-seeking/health-seeking behavior without language restrictions. In addition, indices of four major tuberculosis journals were hand-searched. Subject experts in tuberculosis and authors of primary studies were contacted. Reference lists, review articles and text book chapters were also searched. All the studies were assessed for methodological quality. Only studies carried out on smear/culture-positive tuberculosis patients and reporting about total, patient and health-care system delays were included. RESULTS: A total of 419 potential studies were identified by the search. Fifty two studies qualified for the review. The reported ranges of average (median or mean) total delay, patient delay, health system delay were 25-185 days, 4.9-162 days and 2-87 days respectively for both low and high income countries. Average patient delay was similar to health system delay (28.7 versus 25 days). Both patient delay and health system delay in low income countries (31.7 days and 28.5 days) were similar to those reported in high income countries (25.8 days and 21.5 days). CONCLUSION: The results of this review suggest that there is a	7_EX.TOPIC

	need for revising case-finding strategies. The reported high treatment success rate of directly observed treatment may be supplemented by measures to shorten the delay in diagnosis. This may result in reduction of infectious cases and better tuberculosis control. [References: 68]	
Stevens, A., et al. (1992). The public health management of tuberculosis among the single homeless: is mass miniature X-ray screening effective? *British Medical Journal*, *46*(2), 141.	STUDY OBJECTIVE – The aim was to test the assumption that mass miniature x ray screening of the single homeless (hostel residents) is a cost-effective means of controlling pulmonary tuberculosis. DESIGN – The study was a prospective experimental screening exercise to identify new cases of active tuberculosis completing treatment. SETTING – The setting was eight hostels in south London. A mobile x ray screening facility was set up outside the hostels. SUBJECTS – Subjects were 547 single homeless residents in the hostels. They were encouraged to attend for chest x ray, and for active follow up of abnormal x rays. MAIN RESULTS – No new cases of active tuberculosis were found. CONCLUSIONS – Mass miniature x ray is ineffective in controlling tuberculosis because of its unacceptability and increasing inaccessibility to this population.	9_IN.OTHER
Storla, D., G., Yimer, S., & Bjune, G., A. (2008). A systematic review of delay in the diagnosis and treatment of tuberculosis. *BMC Public Health*, 8, 15.	BACKGROUND: Early diagnosis and immediate initiation of treatment are essential for an effective tuberculosis (TB) control program. Delay in diagnosis is significant to both disease prognosis at the individual level and transmission within the community. Most transmissions occur between the onset of cough and initiation of treatment. METHODS: A systematic review of 58 studies addressing delay in diagnosis and treatment of TB was performed. We found different definitions of, for example, debut of symptoms, first appropriate health care provider, time to diagnosis, and start of treatment. Rather than excluding studies that failed to meet strict scientific criteria (like in a meta-analysis), we tried to extract the "solid findings" from all of them to arrive on a more global understanding of diagnostic delay in TB. RESULTS: The main factors associated with diagnostic delay included human immunodeficiency virus; coexistence of chronic cough and/or other lung diseases; negative sputum smear; extrapulmonary TB; rural residence; low access (geographical or sociopsychological barriers); initial visitation of a government low-level healthcare facility, private practitioner, or traditional healer; old age; poverty; female sex; alcoholism and substance abuse; history of immigration; low educational level; low awareness of TB; incomprehensive beliefs; self-treatment; and stigma. CONCLUSION: The core problem in delay of diagnosis and treatment seemed to be a vicious cycle of repeated visits at the same healthcare level, resulting in nonspecific antibiotic treatment and failure to access specialized TB services. Once generation of a specific diagnosis was in reach, TB treatment was initiated within a reasonable period of time. [References: 57]	7_EX.TOPIC
Tanke, E., D., & Leirer, V., O. (1994). Automated telephone reminders in tuberculosis care. *Med Care*, (4), 380-389.	This study assessed the impact of automated telephone reminders in a population of 2,008 patients scheduled for appointments in a public health tuberculosis clinic. Overall, remainders increased appointment attendance from 52% to 62%. Reminders were more effective for some applications than others, but the effectiveness of reminders did not differ significantly across patient age, sex, or ethnicity. Counter to theoretical predictions, neither attribution of the reminder message to an authority nor a statement stressing the importance of the appointment significantly increased the effectiveness of the reminder above the level obtained without these enhancements.	5_EX.POP
Taylor, Z., et al. (2000). Causes and costs of hospitalization of	OBJECTIVE: To examine the costs, lengths of stay and patient characteristics associated with tuberculosis (TB) hospitalizations. METHODS: A prospective cohort study of 1493 TB patients followed	7_EX.TOPIC

tuberculosis patients in the United States. *International Journal of Tuberculosis & Lung Disease*, *4*(10), 931-939.	from diagnosis to completion of therapy at 10 public health programs and area hospitals in the US. The main outcome measures were the following: 1) occurrence, 2) cost, and 3) length of stay of TB-related hospitalizations. RESULTS: There were 821 TB-related hospitalizations among the study participants; 678 (83%) were initial hospitalizations and 143 (17%) were hospitalizations during the treatment of TB. Patients infected with human immunodeficiency virus (HIV) (OR 1.8, 95% CI 1.2-2.6), and homeless patients (OR, 1.7 95% CI 1.1-2.8) were at increased risk of being hospitalized at diagnosis. Homeless patients (RR 2.5, 95%CI 1.5-4.3), patients who used alcohol excessively (RR 1.9, 95% CI 1.2-3.0), and patients with multidrug-resistant TB (RR 5.7, 95% CI 2.7-11.8) were at increased risk of hospitalization during treatment. The median length of stay varied from 9 to 17 days, and median costs per hospitalization varied from $6441 to $12968 among the sites. CONCLUSION: Important social factors, HIV infection, and local hospitalization practice patterns contribute significantly to the high cost of TB-related hospitalizations. Efforts to address these specific factors are needed to reduce the cost of preventable hospitalizations.	
Thomas, R., E. (1997). Mantoux (tuberculosis) testing. Evaluation of guidelines for testing in Canadian institutions. *Canadian Family Physician*, 43, 933-938.	OBJECTIVE: To evaluate the guidelines for Mantoux testing and isoniazid (INH) prophylaxis in various institutions and shelters for the homeless in Canada in light of research in Canada and other industrialized countries. DATA SOURCES: MEDLINE searches from January 1980 to June 1996 yielded 219 articles, some of which were case reports. The bibliographies of these articles were searched for relevant titles. A further search adding the words randomized, controlled trial and controlled clinical trial yielded two citations, neither of which was a randomized, controlled trial. DATA EXTRACTION: Studies were included if they described the incidence, screening, diagnosis, or prophylaxis of tuberculosis (TB), in institutions in Canada. DATA SYNTHESIS: Studies of staff patients in institutions tend to be incomplete in reporting exposure to TB, extent of Mantoux testing, and whether INH prophylaxis was completed. CONCLUSIONS: Institutions admitting patients with TB should follow the 1996 recommendations of the Canadian Thoracic Society (CTS). The best way to implement the recommendations is to have a TB control officer who administers protocols to identify staff and patients at risk for TB and a committee that regularly monitors implementation of CTS guidelines. [References: 40]	7_EX.TOPIC
Umbricht-Schneiter, A., et al. (1994). Providing medical care to methadone clinic patients: referral vs on-site care. *American Journal of Public Health*, *84*(2), 207-210.	OBJECTIVES: Intravenous drug users are at high risk for medical illness, yet many are medically underserved. Most methadone treatment programs have insufficient resources to provide medical care. The purpose of this study was to test the efficacy of providing medical care at a methadone clinic site vs referral to another site. METHODS: Patients with any of four target medical conditions were randomized into an on-site group offered medical care at the methadone treatment clinic and a referred group offered medical care at a nearby clinic. Entry to treatment and use of medical services were analyzed. RESULTS: Of 161 intravenous drug users evaluated, 75 (47%) had one or more of the target medical conditions. Fifty-one were randomized. In the on-site group (n = 25), 92% received medical treatment; in the referred group (n = 26), only 35% received treatment. CONCLUSIONS: Providing medical care at a methadone treatment program site is more effective than the usual referral procedure and is a valuable public health intervention.	1_EX.TB
Underwood, B., R., et al. (2003). Contact tracing and population screening for tuberculosis--who	BACKGROUND: The aim of the study was to investigate the relative effectiveness of four strategies in detecting and preventing tuberculosis: contact tracing of smear-positive pulmonary disease, of smear-negative pulmonary disease and of non-pulmonary disease,	9_IN.OTHER

should be assessed?. *Journal of Public Health Medicine*, *25*(1), 59-61.	and screening new entrants. METHODS: An analysis of patient records and a TB database was carried out for an NHS Trust-based tuberculosis service in a socio-economically deprived area. Subjects were contacts of all patients treated for TB between 1997 and 1999. New entrants were screened in 1999. Outcomes measured were numbers of cases of active tuberculosis detected and numbers of those screened given chemoprophylaxis. RESULTS: A total of 643 contacts of 227 cases of active TB were seen, and 322 new entrants to the United Kingdom. The highest proportion of contacts requiring full treatment or chemoprophylaxis were contacts of smear-positive index cases (33 out of 263 contacts; 12.5 per cent). Tracing contacts of those with smear-negative pulmonary tuberculosis (12 out of 156; 7.7 per cent) and non-pulmonary disease (14 out of 277; 6.2 per cent) was significantly more effective in identifying individuals requiring intervention (full treatment or chemoprophylaxis) than routine screening of new entrants (10 out of 322; 3.1 per cent). CONCLUSIONS: Screening for TB of new entrants to the United Kingdom is part of the national programme for control and prevention of TB, whereas tracing contacts of those with smear-negative and non-pulmonary disease is not. This study demonstrates that, in our population, the contact-tracing strategy is more effective than new entrant screening. It is not likely that the contacts have caught their disease from the index case, but rather that in high-incidence areas such as ours such tracing selects extended families or communities at particularly high risk.	
Walker D, M., R. (2000). An incremental cost-effectiveness analysis of the first, second and third sputum examination in the diagnosis of pulmonary tuberculosis. *International Journal of Tuberculosis and Lung Disease*, *4(*3), 246-251.	This record was compiled by CRD commissioned reviewers according to a set of guidelines developed in collaboration with a group of leading health economists.	4_EX.OECD
Weis, S., E., et al. (1994). The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. *New England Journal of Medicine*, *330*(17), 1179-1184.	BACKGROUND: Tuberculosis has re-emerged as an important public health problem, and the frequency of drug resistance is increasing. A major reason for the development of resistant infections and relapse is poor compliance with medical regimens. In Tarrant County, Texas, we initiated a program of universal directly observed treatment for tuberculosis. We report the effect of the program on the rates of primary and acquired drug resistance and relapse among patients with tuberculosis. METHODS: We collected information on all patients with positive cultures for Mycobacterium tuberculosis in Tarrant County from January 1, 1980, through December 31, 1992. Through October 1986, patients received a traditional, unsupervised drug regimen. Beginning in November 1986, nearly all patients received therapy under direct observation by health care personnel. RESULTS: A total of 407 episodes in which patients received traditional treatment for tuberculosis (January 1980 through October 1986) were compared with 581 episodes in which therapy was directly observed (November 1986 through December 1992). Despite higher rates of intravenous drug use and homelessness and an increasing rate of tuberculosis during this 13-year period, the frequency of primary drug resistance decreased from 13.0 percent to 6.7 percent ($P < 0.001$) after the institution of direct observation of therapy, and the frequency of acquired resistance declined from 14.0 percent to 2.1 percent ($P < 0.001$). The relapse rate decreased from 20.9 percent to 5.5 percent ($P < 0.001$), and the number of relapses	5_EX.POP

	with multidrug-resistant organisms decreased from 25 to 5 (P < 0.001). CONCLUSIONS: The administration of therapy for M. tuberculosis infection under direct observation leads to significant reductions in the frequency of primary drug resistance, acquired drug resistance, and relapse.	
White, M., C., et al. (2003). Strategies for effective education in a jail setting: the Tuberculosis Prevention Project. *Health Promotion Practice*, *4*(4),.422-429.	Jails are a unique setting for health education. The Tuberculosis (TB) Prevention Project was designed to improve completion of care for latent TB infection in released inmates. As part of an ongoing clinical trial to improve rates of completion, educators provided TB-focused educational sessions to 1,027 inmates. This article describes the educational sessions and illustrates some of the barriers to working in a jail setting and strategies to overcome them. The nature of the jail itself, inmate characteristics, the characteristics of educators, and the educational sessions themselves interacted in different ways to enhance or impair the interaction. Jail is a setting in which the population is at high risk for a number of health problems and health education is increasingly important.	7_EX.TOPIC
White, M., C., et al. (2005). Incidence of TB in inmates with latent TB infection: 5-year follow-up. *American Journal of Preventive Medicine*, *29*(4), 295-301.	BACKGROUND: Inmates are a high-risk population for tuberculosis (TB) control efforts, including treatment for latent tuberculosis infection (LTBI). Completion of therapy after release has been poor. The goal of this study was to evaluate therapy completion and active disease over 5 years in a cohort of inmates. METHODS: The sample was from a completed randomized trial in 1998-1999 of education or incentive versus usual care to improve therapy completion after release from the San Francisco County Jail. Records from the jail, the County Tuberculosis Clinic, and the California TB Registry were used to measure therapy completion and development of active TB. Analyses were conducted in 2005. RESULTS: Of a total 527 inmates, 31.6% (n=176) completed therapy, of whom 59.7% (n=105) completed it in jail. Compared with the U.S.-born, foreign-born inmates residing in the United States for < or =5 years were less likely to complete the therapy (adjusted odds ratio [AOR]= 0.49, 95% confidence interval [CI]=0.28-0.85), and those with more education were more likely to complete the therapy (AOR=1.06, 95% CI=1.01-1.12). Three subjects developed active TB in the 5 years of follow-up, resulting in an annual rate of 108 per 100,000. Compared with California rates, subjects were 59 times as likely to develop active TB (standardized morbidity ratio of 59.2, 95% CI=11.2-145.1). None had completed therapy, none were new immigrants, and two were known to be HIV-positive at diagnosis. CONCLUSIONS: Completion of therapy for LTBI is a challenge, but the active TB seen in this jail cohort emphasizes the importance of continued efforts to address TB risk in this population.	9_IN.OTHER
White, M., C., Cuttler, S., & Zhao, X. (2007). Linking released inmates to TB clinic for treatment of latent tuberculosis infection: Why is it so difficult? *Journal of Correctional Health Care*, *13*(3), 206-215.	Released inmates who are infected with Mycobacterium tuberculosis are at high risk for not completing therapy. This study describes reasons for postrelease behavior in a cohort of participants from a randomized trial. We interviewed 230 participants after the primary trial endpoint (visit to the tuberculosis [TB] clinic within 30 days of release) had occurred. Those participants who, in jail, thought they would have social support for continuing therapy but after jail indicated they did not have such support were half as likely to have gone to the TB clinic (odds ratio 0.5, 95% confidence interval 0.2 to 0.9), controlling for drug/alcohol problems and factors significant in the original randomized trial (study group and recent immigrant status). The disruption of incarceration alters postrelease life, and inmates who find social support has changed after release may be nonadherent. Information gathered from incarcerated persons may not predict postrelease reality. (PsycINFO Database Record (c) 2010 APA, all rights reserved) (journal abstract)	6_EX.NON-EMP

Winje, B., A., et al. (2008). Screening for tuberculosis infection among newly arrived asylum seekers: comparison of QuantiFERONTB Gold with tuberculin skin test. *BMC Infectious Diseases*, *8*, 65.	BACKGROUND: QuantiFERONTB Gold (QFT) is a promising blood test for tuberculosis infection but with few data so far from immigrant screening. The aim of this study was to compare results of QFT and tuberculin skin test (TST) among newly arrived asylum seekers in Norway and to assess the role of QFT in routine diagnostic screening for latent tuberculosis infection. METHODS: The 1000 asylum seekers (age > or = 18 years) enrolled in the study were voluntarily recruited from 2813 consecutive asylum seekers arriving at the national reception centre from September 2005 to June 2006. Participation included a QFT test and a questionnaire in addition to the mandatory TST and chest X-ray. RESULTS: Among 912 asylum seekers with valid test results, 29% (264) had a positive QFT test whereas 50% (460) tested positive with TST (indurations > or = 6 mm), indicating a high proportion of latent infection within this group. Among the TST positive participants 50% were QFT negative, whereas 7% of the TST negative participants were QFT positive. There was a significant association between increase in size of TST result and the likelihood of being QFT positive. Agreement between the tests was 71-79% depending on the chosen TST cut-off and it was higher for non-vaccinated individuals. CONCLUSION: By using QFT in routine screening, further follow-up could be avoided in 43% of the asylum seekers who would have been referred if based only on a positive TST (> or = 6 mm). The proportion of individuals referred will be the same whether QFT replaces TST or is used as a supplement to confirm a positive TST, but the number tested will vary greatly. All three screening approaches would identify the same proportion (88-89%) of asylum seekers with a positive QFT and/or a TST > or = 15 mm, but different groups will be missed.	1_EX.TB

13.0 Appendix E. Example quality assessment forms

13.1 Quantitative study

Malotte et al. (2001)	
1. Is the source population or source area well described?	**Comments**
++	Demographics of participants are thoroughly reported (Table 1); country is indicated; study setting well described.
2. Is the eligible population or area representative of the source population or area?	**Comments**
+	The place and time of recruitment (recruited from an initial study on TB skin test adherence, April 1994-September 1997) was identified. The study describes eligibility clearly and provides the criteria by which this was assessed, as well as the population number that was subsequently ineligible for participation. The eligible group however may not be representative of all drug users in California, USA.
3. Do the selected participants or areas represent the eligible population?	**Comments**
+	Inclusion/exclusion criteria were explicitly stated. Since the selected population was a volunteer sample of the eligible population it may not be fully representative.
4. How was confounding minimised?	**Comments**
+	Allocation to exposure and comparison was randomised.
5. Were interventions (and comparisons) well described and appropriate?	**Comments**
++	Described in detail/replicable.
6. Was the allocation concealed?	**Comments**
++	Numbered, opaque, sealed envelopes containing the assigned treatment condition were administered to study nurses to ensure

	concealment
7. Were participants and/or investigators blind to exposure and comparison?	**Comments**
NA	
8. Was the exposure to the intervention and comparison adequate?	**Comments**
++	Exposure level does not impact on outcomes. The exposure is adequate in both groups.
9. Was contamination acceptably low?	**Comments**
++	No participant from either group was exposed to the other.
10. Were other interventions similar in both groups?	**Comments**
NR	
11. Were all participants accounted for at study conclusion?	**Comments**
++	Treatment completion rates was the outcome being measured and drop-out rates have been described with reasons for drop-out.
12. Did the setting reflect usual UK practice?	**Comments**
+	Drug users in the UK have similar access to 'storefront' clinics. However, since this is a US study, it is not certain whether provision of services and research conducted at these clinics appropriately reflects UK practice.
13. Did the intervention or control comparison reflect usual UK practice?	**Comments**
+	Directly-observed treatment, the use of an outreach worker and the provision of incentives (treatments provided in this study) for TB adherence for a drug using population is common in the UK.
14. Were the outcome measures	**Comments**

reliable?	
++	The primary outcome measure was the percentage of medication taken as prescribed; and completion of medication regimen. This was objectively verified by observation (participants were observed swallowing all medications).
15. Were all outcome measurements complete?	**Comments**
++	All were accounted for.
16. Were all important outcomes assessed?	**Comments**
++	All important outcomes assessed, including reasons for drop-out/default.
17. Were outcomes relevant?	**Comments**
++	The outcomes assessed are all relevant in order to find the independent and combined effects of monetary incentives and outreach worker provision of DOT.
18. Were there similar follow-up times in exposure and comparison groups?	**Comments**
++	Equal time.
19. Was follow-up time meaningful?	**Comments**
++	8-12 month follow up, depending on prescribed duration of treatment (based on HIV status).
20. Were exposure and comparison groups similar at baseline? If not, were these adjusted?	**Comments**
++	No demographic or drug use variable was significantly related to intervention groups.
21. Was intention to treat (ITT) analysis conducted?	**Comments**
++	Intervention effects were also tested in both univariate and multivariate logistic regression analyses, on an intention-to-treat basis.
22. Was the study sufficiently powered to detect an intervention effect (if one exists)?	**Comments**
NR	Not reported.
23. Were the estimates of effect size	**Comments**

given or calculable?	
++	Reported thoroughly.
24. Were the analytical methods appropriate?	**Comments**
++	Appropriate.
25. Was the precision of intervention effects given or calculable? Were they meaningful?	**Comments**
++	P value, and CI and AOR are all reported.
26. Are the study results internally valid? (i.e., unbiased)	**Comments**
++	The baseline characteristics were not significantly different between groups. There were no significant flaws in the study design.
27. Are the study results generalisable to the source population? (i.e. externally valid)	**Comments**
+	Not statistically.

13.2 Economic evaluation

Kominski et al. (2010)	
1. Is the study population appropriate for the topic being evaluated?	**Comments**
Partly	Only 80% of the participants in the study are foreign-born and thus not completely appropriate for an understanding of this hard-to-reach group (new entrants).
2. Are the interventions appropriate for the topic being evaluated?	**Comments**
Yes	
3. Is the system in which the study was conducted sufficiently similar to the UK context?	**Comments**
Partly	US study.
4. Were the perspectives clearly stated?	**Comments**
Yes	Societal perspective.
5. Are all direct health effects on individuals included, and are all other effects included where they are material?	**Comments**
Yes.	
6. Are all future costs and outcomes discounted appropriately?	**Comments**
Partly.	3% discounting rate is used in this study rather than the best accepted annual rate of 3.5%.
7. Is the value of health effects expressed in terms of quality adjusted life years (QALYs)?	**Comments**
Yes.	
8. Are costs and outcomes from other sectors fully and appropriately measured and valued?	**Comments**
Yes	Costs occurring in other sectors have been reported. One example is the cost of letters sent to adolescents.
9. Overall judgement (no need to	**Comments**

continue if not applicable)	
Partly applicable	Although relevant to NHS context & NICE guidelines, the study is conducted in the USA and not all selected participants are considered hard to reach for the purposes of developing this particular guideline.
10. Does the model structure adequately reflect the nature of the topic under evaluation?	**Comments**
Yes	The model design and its structural elements appropriately reflect the nature of the topic: the study identified treatment pathways; used quality-adjusted life year; provided incremental analysis; and reported predicators of compliance. The assumptions underlying the method were also sufficiently informed: obtained from an actual study conducted, published literature or Medicare records.
11. Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	**Comments**
Yes.	Lifetime TB-related costs.
12. Are all important and relevant outcomes included?	**Comments**
Yes.	Relevant outcomes reported: adherence to isoniazid preventive therapy; total cost of LTBI treatment; average lifetime TB-related costs; ICER/QALYs.
13. Are the estimates of baseline outcomes from the best available source?	**Comments**
Partly.	Baseline outcomes have not been identified from a recent well-conducted systematic review of the literature. However, the estimates of baseline outcomes do appear from a natural sample from a previous study, published literature and Medicare records, that are likely to reflect outcomes relevant for the purposes of this review.
14. Are the estimates of relative 'treatment' effects from the best available source?	**Comments**
Partly	The study did not use treatment effects from a published systematic review. Instead, they used

	outcomes from a cohort of people in their own trial, which is considered a good available estimate.
15. Are all important and relevant costs included?	**Comments**
Yes.	
16. Are the estimates of resource use from the best available source?	**Comments**
Partly.	Not derived from a systematic review but are considered the best available estimates.
17. Are the unit costs of resources from the best available source?	**Comments**
Partly.	Unit costs of resources included charges made to Medicare (USA), which may differ from current UK NHS/PSS unit costs.
18. Is an appropriate incremental analysis presented or can it be calculated from the data?	**Comments**
Yes.	
19. Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	**Comments**
Yes.	
20. Is there any potential conflict of interest?	**Comments**
Unclear.	The article does not indicate whether or not there are financial conflicts of interest.
21. Overall assessment	**Comments**
Minor limitations	The study only fails to meet a few of the quality criteria presented here, but this is unlikely to change the conclusions about cost-effectiveness.