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*Series: Tuberculosis in hard-to-reach populations*

**Title:**

# Effectiveness of interventions aiming at identifying and managing tuberculosis among hard-to-reach populations: A systematic review

**Authors:**
Charlotte C. Heuvelings[1], *MD*; Sophia G. de Vries[1], *MD*; Patrick F. Greve[1], *MD*; Benjamin J. Visser[1], *MD*; Sabine Bélard[1], *MD*; Saskia Janssen[1], *MD*; Anne L. Cremers[1], *MA*; René Spijker[2,3], MSc; Beth Shaw[4], *MSc*; Ruaraidh A. Hill[4,5], *PhD*; Prof. Alimuddin Zumla[6] *FRCP*; Andreas Sandgren[7], *PhD;* Marieke J. van der Werf[7*], *PhD;* Prof. Martin P. Grobusch[1], *FRCP*

**Institutional affiliations:**

1. Center of Tropical Medicine and Travel Medicine, Department of Infectious Diseases, Division of Internal Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands
2. Medical Library, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands
3. Cochrane Netherlands, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands
4. National Institute for Health and Care Excellence, Level 1A, City Tower, Piccadilly Plaza , Manchester, M1 4BT, United Kingdom
5. Health Services Research, University of Liverpool, Liverpool, UK
6. Division of Infection and Immunity, University College London, and NIHR Biomedical Research Centre at UCL Hospitals, London, United Kingdom.
7. European Centre for Disease Prevention and Control, Tomtebodavägen 11a, 171 65 Solna, Sweden

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*Corresponding author
Dr. M.J. van der Werf, European Centre for Disease Prevention and Control, Tomtebodavägen 11a, 171 65 Solna, Sweden. Email: marieke.vanderwerf@ecdc.europa.eu

**Summary**

Tuberculosis (TB) is over-represented in hard-to-reach (under-served) populations in high income, low TB incidence countries. The mainstay of TB care is reliant on early detection of active TB patients (case finding), contact tracing and treatment completion. We performed a systematic review of interventions with a scoping component of relevant studies published between 1990-2015 to update and extend previous NICE reviews on the effectiveness of interventions aimed at identifying and managing TB in hard-to-reach populations. We identified an additional 19 studies to the 26 studies included in the NICE reviews. The analyses showed that TB screening by (mobile) chest X-ray improved screening coverage and TB identification, reduced diagnostic delay and was cost-effective among several hard-to-reach populations. Sputum culture in pre-migration screening and active referral to a TB clinic improved identification rates. Monetary incentives improved TB identification and management among drug users and homeless people. Enhanced case management, good cooperation between services and directly observed therapy improved treatment outcome and compliance. Strong conclusions cannot be drawn due to heterogeneity of evidence with regard to study population, methodology, and quality.

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## Introduction

Early detection and diagnosis of tuberculosis (TB) followed by effective treatment is the cornerstone of global TB control efforts.[1,2] An estimated three million people remain undetected each year.[3] By detecting TB early and managing TB disease effectively, severe disease can be prevented[4,5] and mortality and transmission reduced.[6-8] Health services rely on people with TB to recognize their symptoms and seek treatment. To detect cases early, individuals with symptoms need to engage with health care in a timely fashion, or need to be actively identified. Health care facilities should be accessible; health care workers should be able to identify people with signs and symptoms of TB and request appropriate diagnostic tests; diagnostic tests should be available and performed using quality-assured methods; and finally, results of the diagnostic tests should be reported to the health care worker to be able to start TB treatment immediately.[9] This sequence of events needs to work optimally to minimise delays between the development of the signs and symptoms and the start of treatment. TB treatment consists of several anti-TB drugs for at least six months.[10] To adhere to this lengthy treatment regimen is challenging for TB patients, up to 20% are lost to follow-up.[3,11]

In low TB incidence countries (<10 TB cases per 100,000),[12] TB is concentrated in vulnerable and hard-to-reach (under-served) populations.[13,14] These hard-to-reach populations, such as people who are migrants, refugees, homeless, prisoners, drug users, sex workers and people living with HIV are at greater risk of TB due to an increased risk of exposure or due to an impaired host defence.[15] Addressing TB in these hard-to-reach populations is a priority area for action to achieve TB elimination.[16] This poses formidable challenges in low TB endemic regions. Firstly, health care workers practising in these areas encounter TB patients infrequently and therefore may not suspect TB initially, resulting in diagnostic delay.[17] Secondly, individuals from hard-to-reach populations commonly attribute symptoms of TB to other causes.[18,19] In addition, stigmatisation, fear of death from TB, language barriers, minimal knowledge about TB services, lengthy treatment duration and side effects are major barriers for seeking health care and treatment compliance.[20] Consequently, individuals belonging to hard-to-reach populations are often diagnosed late and frequently do not complete treatment.[21,22]

In order to collect the evidence for developing guidance on improving TB identification and management among these populations we performed a systematic review of interventions with a scoping component to ascertain: 1) 'Which interventions are effective and cost-effective at identifying and managing TB and/or raising awareness about TB among hard-to-reach populations?'; 2) 'What factors affect the effectiveness of those interventions?'; 3) 'How transferable are the findings on effectiveness across hard-to-reach populations or settings?'; and 4) 'What are the adverse or unintended effects?'.

The findings of this review series served as the evidence base for the development of guidance for controlling TB in hard-to-reach and vulnerable populations by the European Centre for Disease Prevention and Control (ECDC).[23]

## Methods

In preparing for the systematic review we identified two reviews conducted by the Matrix Knowledge Group, commissioned by the National Institute for Health and Clinical Excellence (NICE), on

interventions for TB in hard-to-reach populations.[24,25] We decided to update and extend these NICE reviews[24,25] applying the same methodology, but adjusting the focus, i.e. excluding latent TB and expanding geographical coverage. The reviews were conducted following standards described by the Cochrane Collaboration[26] and NICE.[27] Results are reported according to the PRISMA guidelines for reporting of systematic reviews.[28] The review protocol was registered in the database of prospectively registered systematic reviews in health and social care, PROSPERO (CRD42015017660 and CRD42015019449).

***Search strategy and eligibility criteria***

Medline, Medline In-Process and Embase were searched using the search strategies used previously for the NICE reviews, which covered the period 1990 to September 2010.[24,25] Searching over the period performed for the NICE reviews was not repeated; rather an updated search was conducted covering the period 2010 to 10 April 2015. The search for the expanded geographical scope and hard-to-reach populations (see population section of PICO) covered the period 1990 to 10 April 2015. Reference lists of systematic reviews covering a similar topic were reviewed for relevant publications. Studies solely focussing on the detection and management of latent TB infection were excluded. No language restrictions were applied.

Population

In addition to the hard-to-reach populations covered by the NICE reviews (migrants including refugees, asylum seekers and the Roma population, homeless people including rough sleepers and shelter users, drug users, prisoners and sex workers)[24,25] we included people living with HIV and children within vulnerable and hard-to-reach populations. Also, the previous NICE reviews only included studies conducted in Organisation for Economic Co-operation and Development (OECD) countries (see **Box 1**).[24,25] We updated this search and expanded the geographical coverage to all European Union (EU)/European Economic Area (EEA) and EU candidate countries..

Intervention

All interventions aiming to improve TB identification and management in the above listed hard-to-reach populations were included. Predefined interventions included in the protocol were the use of TB diagnostics like chest X-ray (CXR), the use of TB identification tools like symptom-based questionnaires and mobile X-ray units (MXU), the use of incentives and social support, treatment for comorbidities and directly observed therapy (DOT) to improve TB management. The use of the tuberculin skin test (TST) and interferon gamma release assay (IGRA) were included only if used as an initial step in the diagnostic pathway to identify active TB cases. The interventions pre- and post-migration screening and sputum smear and culture as part of pre-migration screening were identified during the review process and were added to the non-exclusive intervention list (Supplementary Material I).

Comparator

Studies were included if they reported on the effectiveness and/or cost-effectiveness of interventions in hard-to-reach populations. Effectiveness was defined as improving any measure of screening uptake or treatment outcome, like increased number (or proportion) of people screened, increased treatment compliance rate, reduced TB related mortality, or reduced TB incidence. During the review process we re-defined the comparator, every intervention group was compared to a relevant comparison group. These included for example, no intervention or usual care, another intervention, or historical comparison. For the cost-effectiveness of interventions we followed the conclusion of the individual study.

Outcome

For this systematic review we did not exclude studies on the basis of outcomes. Thus, studies providing a quantitative outcome or a qualitative description of the outcome were included.

See **Supplementary Material I** for PICOS (Population-Intervention-Comparator-Outcome-Study design) questions and **Supplementary Material II** for the complete search strategy and results.
Information on service models and organisational structures, including different types of healthcare workers and settings, supporting TB identification and management is not the focus of this systematic review and is reported in another systematic review by this group.

***Study selection and data management***

All citations identified were uploaded into an EndNote database, and duplicates were removed (EndNote X7·1, Thomson Reuters 2014). The first 25 citations were used for pilot testing and refining the inclusion criteria. Three authors screened titles and abstracts independently. One author screened 100% of the citations; the other two authors screened both 50% of the citations. Disagreement was resolved by discussion; the full text was assessed in case of disagreement. Full texts of the included citations were retrieved; irretrievable articles were excluded, i.e. articles not available online, from the university library or through contacting authors. Two authors assessed the full text records for inclusion by using a full text assessment inclusion checklist. Disagreement was resolved by discussion. Agreement after screening on title and abstract was 99·5% with an inter-rater reliability (Cohen's kappa) of $\kappa = 0{\cdot}985$.

***Data collection and data items***

Data was extracted by using the data extraction forms used in the previous NICE reviews.[24,25] Information on characteristics of participants, setting, type of intervention, type of outcome measure, method of analysis and results was extracted from each included study. Data extraction was performed independently by two authors on a random 10% of studies included. On the remaining studies, one author conducted the data extraction, which was checked by a second author. Any disagreement was resolved by discussion. Where necessary, authors were contacted by email to verify data and to obtain additional data.

***Risk of bias in individual studies and overall strength of evidence***

Studies were assessed for quality and risk of bias by using the modified NICE Quality Assessment Tool (based on the Graphical appraisal tool for epidemiological studies)[24,25] which includes assessment of selection of study sample, minimisation of selection bias and contamination, controlling of confounding, outcome measurements, analytical methods and risk of bias. Two authors independently assessed 10% of the studies. The remaining 90% were assessed by one author and checked by a second author. Any disagreement was resolved by discussion. Each study was given a quality rating based on the quality assessment: high quality [++], medium quality [+], or low quality [-]. Strength of conclusions was assessed and reported as described before[24,25] (**Supplementary Material III**).

***Synthesis of results***

To maximise comparability of the results with those of the NICE reviews,[24,25] data synthesis was structured similarly by hard-to-reach population. Data synthesis was performed using a narrative synthesis approach and we assessed whether meta-analysis was possible taking into consideration the heterogeneity of the studies (study design, participants, setting, intervention and outcome). Only the results of this review are presented in the results. To provide the complete body of evidence the combined results of this review and the NICE reviews[24,25] are presented in **Tables 1 and 2**.

***Role of the funding source***

The funder of the study was involved in study design, data interpretation, and reporting.

**Results**

***Study selection***

Of the 13,783 unique citations screened on title and abstract, 146 citations were selected for full text assessment, seven were irretrievable. Sixteen studies were included in this review, with a further three identified through citation searching (see **Figure 1** for details).[29-47]

***Study characteristics***

Characteristics for all nineteen included studies are described in **Table 1**, evidence tables are in **Supplementary Material IV**. Twelve of the included studies focussed on migrants,[29-36,38,41,43,45] of which one focussed on children.[41] Three studies focussed on mixed hard-to-reach populations;[39,42,46] two on drug users;[40,44] one on people living with HIV[47] and one on homeless people.[37] None of the included studies focussed on sex workers. Eight studies were conducted in the EU, two in the United Kingdom (UK),[39,42] one in Estonia,[44] one in France,[37] one in Germany,[46] one in Italy,[47] one in Norway[32] and one in Portugal.[40] The remaining eleven studies were conducted outside the EU, eight in the United States (US),[29,31,33-36,41,43] two in Israel[30,38] and one in Switzerland.[45]

The interventions to improve identification of TB applied active case finding by using (mobile) CXR,[30,37-39,42] symptom-based questionnaire,[45] TST or IGRA[31,36,41]; adding sputum smear[34,39] or sputum culture[29,33,43] to a screening algorithm; and active referral to a TB clinic.[32,35,40,44] The interventions to

manage TB were enhanced case management, i.e. a package of supportive care tailored to patients' needs,[40,42,46] and concomitant TB and HIV treatment.[47]

***Risk of bias within studies***

The results of quality assessment are presented in **Supplementary Material V**. The heterogeneity in type of hard-to-reach population, interventions, reported outcomes and study designs between the included studies made it inappropriate to perform a meta-analysis.

***Results by hard-to-reach group***

The interventions and outcomes per hard-to-reach population are summarised in **Table 2**; for detailed evidence statements, combined with the findings of the NICE reviews[24,25] see **Supplementary Material III.**

Interventions aiming to improve TB identification

***Migrants***

The 12 studies focussing on TB identification in migrants are divided into pre- and post-migration screening studies.

*Effectiveness and cost-effectiveness of pre-migration screening by CXR*

Mor et al. concluded that pre-migration screening by CXR of migrants from Ethiopia to Israel was effective, and cost-effective.[38] The sensitivity of using CXR as a screening tool for the detection of active pulmonary TB and sputum-confirmed TB was 80·1% (95% confidence interval [95% CI] 68·1 to 89·9%) and 86·1% (95% CI 72·1 to 94·7%), respectively; with a specificity of 99·2% (95% CI: 99·1-99·4%) and 99·1% (95% CI: 99·0-99·3%), respectively. The costs of diagnosing one patient with pulmonary TB were calculated to be US$5,820. The authors concluded that this was cost-effective, as treating one migrant with TB in Israel in 2012 was US$7,619. No further investigations for TB were undertaken for migrants with a negative CXR.[38]

*Effectiveness of including sputum culture as part of pre-entry TB screening*

Every legal migrant applying for a permanent visa to the United States (US) undergoes pre-entry TB screening; in 2007, the Centers for Disease Control and Prevention (CDC) added sputum culture to the pre-migration screening programme.[48] Three studies[29,33,34] reported that 54·4% to 80·0% of culture positive cases were smear negative; all three studies concluded that these cases would have been missed if sputum culture was not part of the TB screening algorithm. Two studies found that the number of active TB cases diagnosed within the first 6-12 months after arrival decreased, compared to the preceding years, after adding sputum culture to the screening algorithm.[29,43] It was estimated that the improved TB screening protocol including sputum culture, combined with DOT, could save the US US$15 million a year.[33] All four studies were retrospective studies using two interventions at the same time (sputum culture and DOT). Therefore, the precise contribution of each intervention to the reduction of newly diagnosed active TB cases within one year of arrival in the US is unknown.

*Effectiveness of post-migration screening by CXR*

Mor et al. concluded that post-migration screening by CXR in detained migrants from the Horn of Africa was effective with a sensitivity of 100%, a specificity of 96·1% and a positive predictive value of 17·7% for identifying cases with a final diagnosis of TB (sputum confirmed cases and cases started on TB treatment without sputum confirmation) as no additional TB cases were reported during the detention period.[30] To diagnose one migrant with active TB, 98 people needed to be screened by CXR. Sputum testing, performed on all migrants with suspected CXRs, was undertaken in a TB clinic; 5·6 people needed to be tested to diagnose one TB case. Total costs of post-migration screening by CXR were US$4,519 per TB case diagnosed; this was concluded to be cost-effective as the costs to treat one migrant with TB in Israel in 2015 were US$ 7,335.[30]

*Effectiveness of post-migration screening by TST or IGRA as an initial step to identify active TB cases*

Migrants applying for a temporary US visa undergo a TST or an IGRA (QuantiFERON TB Gold in Tube assay (QFT-G)); if the test is positive, a CXR is performed.[49] Results from Chuke et al. suggested that neither the QuantiFERON-TB Gold (QFT-G) nor the TST were effective tools to identify migrants with CXRs consistent with TB from high incidence countries with a high Bacillus Calmette-Guérin (BCG) vaccination coverage. The overall test agreement between CXR and TST was 50·1% and between CXR and QFT-G 63·5%. Of all culture or smear confirmed TB cases, 100% had a positive TST test and only 43·8% had a positive QFT-G test; the number of sputum confirmed TB cases was too low to draw valid conclusions.[31]

A 2013 study[36] showed no significant difference between the sensitivity of QFT-G and TST with a cut-off point of 10 mm (TST-10) (QFT-G 86·4%, 95% CI: 79·3%-91·7%; TST-10 81·1%, 95% CI: 73·3%-87·5%, $p$=0·12) for identifying culture-confirmed cases when used for TB screening in migrants from high-incidence countries with a high BCG vaccination coverage. However, there was a statistically significant difference between the sensitivity of QFT-G and TST with a cut-off point of 15 mm (TST-15) (86·4% and 52·3%, respectively; TST-15 95% CI: 43·4%-61·0%, $p$<0·001).

The use of TST as a screening tool for internationally adopted children was compared to screening by CXR in a study with a small sample size[41]. Using a cut-off point of 10 mm induration for the TST was shown to be likely better than 5 mm. No participants were identified with active TB, and not all children had undergone the comparator intervention CXR.

*Effectiveness of post-migration screening by symptoms-based questionnaire*

A Swiss study retrospectively evaluated the effectiveness of TB screening using a symptom-based questionnaire.[45] Screening asylum seekers by symptom-based questionnaire had a sensitivity of 55·2% and a specificity of 96·0%, compared to the gold standard, i.e. microbiologically confirmed TB cases starting TB treatment within 90 days of screening. It was also compared with the previously used screening method, CXR screening. TB screening by CXR yielded a 100% sensitivity. The time between screening and start of treatment was 19 days longer for people screened using the symptom-based questionnaire compared to those screened using CXR.[45]

*Effectiveness of post-migration active referral*

Bell and colleagues examined the effect of different support activities for referral to post-arrival follow-up appointments for migrants with suspected non-infectious TB entering the US.[35] These migrants were informed to attend a follow-up appointment in the US within 30 days of arrival. Providing migrants with any kind of support at the port of entry (scheduled appointment, direct phone number or indirect phone number) significantly improved follow-up attendance (adjusted hazard ratio [aHR] 4·0, 95% CI 3·0-5·2, $p<0·0001$) and shortened the time between arrival and attending the follow-up appointment (16 versus 69 days) compared to no support. The highest impact was seen in the group receiving a direct phone number (aHR=7·5, 95% CI 4·8–11·6, $p<0·0001$); 67% were seen within 30 days of arrival. There was no significant difference in follow-up attendance between the scheduled appointment and the direct phone number groups (aHR=1·1, 95% CI 0·8-1·3, $p=0·69$).

Reaching out to migrants improved TB clinic attendance rates and reduced patient delay in Norway in a comparative study with a small sample size.[32] Patients referred to the TB clinic were repeatedly contacted through various means, such as in person, by telephone or by letter. Among asylum seekers, attendance at the first TB clinic appointment increased from 60·9% (95% CI 47-75) before the intervention (no active referral system) to 93·2% (95% CI 87-100) after. Among other migrants, attendance rate increased from 72·4% (95% CI 65-80) to 88·6% (95% CI 83-94). Median time between screening and TB clinic attendance decreased among both asylum seekers (15 weeks before intervention to 8 weeks after, $p=0·04$) and other migrants (30 weeks before intervention to 10 weeks after, $p<0·001$).

***Homeless people, drug users and prisoners***

*Effectiveness of screening by Mobile X-ray Unit (MXU)*

Three studies focussed on the use of MXU in TB screening.[37,39,42] Using MXU to screen homeless people at a Parisian shelter increased the number of identified TB cases over the first three years compared to the time before the use of MXU.[37] TB transmission was evaluated by examining related *Mycobacterium tuberculosis* strains among newly diagnosed TB cases. Within 10 years the number of related cases decreased among shelter users from 14·3 to 2·7 related cases/year ($p<0·01$); a decrease in the proportion of related cases was also found in non-shelter users (decrease from 75% to 25%, $p<0·01$).

MXU screening was also evaluated in homeless people, drug users, prisoners and asylum seekers in London.[39] If the CXR was suggestive of TB, people were referred for further investigations. Screening results were matched to TB culture confirmed cases among the mentioned hard-to-reach populations, notified in the national TB register. MXU had a sensitivity of 81·8% (95%CI 64·5–93·0) and a specificity of 99·2% (95%CI 99·1–99·3); cases diagnosed by MXU were less likely to be smear positive than the passively identified cases (odds ratio [OR] 0·34, 95% CI: 0·14-0·85, $p=0·022$).

Jit et al. examined the effectiveness and cost-effectiveness of the "Find and Treat" service for homeless people and drug users in London compared to normal care without this service.[42] The "Find and Treat" service screened homeless people and drug users by MXU, provided support during treatment and supported people that had been previously lost to follow-up. The service identified 16 TB cases per year.

Thirty-five percent of the cases were asymptomatic and 23% were late presenters (with a delay between first symptoms and treatment). The authors concluded that, without the service, these TB cases were unlikely to be identified. The "Find and Treat" service was effective and cost-effective as the incremental cost ratio for the MXU was £18,000 per QALY gained; the threshold used by NICE is £20,000-£30,000/QALY gained.

*Effectiveness of active referral*

A study conducted in Estonia evaluated the effectiveness of active referral to a TB clinic organised by the methadone drug treatment programme versus passive referral.[44] Reminding the drug users about their appointment improved TB clinic attendance and was more effective than passive referral, where the drug users made the appointment themselves (OR 3·9, 95% CI 1·4-10·4, $p$=0·007). The authors calculated that active referral to the TB clinic would cost €18 per drug user. None of the drug users in this small study were diagnosed with TB; therefore, the cost made per identified case could not be calculated.

Duarte and colleagues evaluated the effectiveness of early identification of active TB in drug users through improving co-operation between key partners (street teams, TB clinic, drug users support centres, local public health department and local hospital).[40] Key partners were trained to identify people using drugs in their services and settings; increasing TB screening rate by promoting health-seeking behaviour; handing out notification cards for screening at the TB clinic; offering free transport to the TB clinic and free care at the TB clinic; combined with improved screening procedures at the TB clinic, where a symptom-based questionnaire, a TST, and a CXR were undertaken. Screening was offered annually for people having had TB contact or exhibiting TB symptoms. TB screening uptake improved from 125 drug users screened before to 465 drug users screened after implementation. Before implementation, 82 drug users were identified with active TB, of which 13·4% ($n$=11) were identified by screening. Over a similar period following the implementation, 59 cases of active TB were detected, of which 61·0% ($n$=36) were identified by screening.

<u>Interventions aiming to improve TB management</u>

***Homeless people, drug users and prisoners***

The improved co-operation between key partners in the study by Duarte and colleagues also led to improved qualitative outcomes of case management (including improved feelings of self-esteem, communication skills and health seeking behaviour), extra health care services and provision of TB treatment under supervision for drug users with active TB.[40] Poor treatment compliance decreased from 47·6% to 23·7% (odds ratio [OR] 0·34; 95% CI 0·16 to 0·72) and default rates dropped from 35·4% to 10·2% (OR 0·21, 95% CI 0·08 to 0·54) compared to the time before improved co-operation. Mortality decreased from 18·3% to 13·6% (OR 0·7, 95% CI 0·28 to 1·78).

Two studies focused on improving TB management in mixed hard-to-reach populations. A small German study showed that community health workers (CHW) reaching out to homeless people and drug users to provide TB education and enhanced case management (CHW based), achieved low treatment dropout rates (10·5%), while routine practice (no CHW) resulted in a 33 to 50% dropout rate.[46]

The previously discussed "Find and Treat" service in London also assessed TB education, case holding (activities to keep patients in care), and treatment support among drug users and homeless people.[42] Complex cases referred to the service showed an increased compliance rate (61·2% vs. 51·7% after 1 year) and a decreased loss to follow-up rate (2·6% vs. 34·7% after 1 year) compared to patients presenting themselves passively via other services. Furthermore, the authors concluded that this part of the "Find and Treat" service appears to be cost-effective as well, as the incremental cost ratio for the case management aspect of the service was £4,100/QALY gained. This estimation is based on a number of assumptions and in the most unfavourable conditions would be £6,800/QALY gained. Both estimates are below the threshold used by NICE. The possible prevention of secondary infections caused by a patient with active pulmonary TB or the prevention of drug resistant TB were not taken into account.

***People living with HIV***

We identified one study focussing on TB management in people living with HIV. An Italian group found that simultaneous administration of combined antiretroviral therapy (cART) and TB treatment significantly reduced the mortality rate (incidence rate ratio [IRR] 0·14, 95% CI 0·06 to 0·30, $p<0·001$) compared to TB treatment without cART.[47]

No studies were identified on the effectiveness or cost-effectiveness of interventions identifying or managing TB among sex workers. None of the included studies evaluated the effectiveness of improving TB awareness among hard-to-reach populations.

*Secondary review questions*

As the majority of the studies focused on migrants, the transferability of results to other hard-to-reach populations is likely to be limited. None of the studies focused on factors that impacted on effectiveness of the interventions.

*Grading and summary of evidence*

The majority of the studies included in this review provided weak to moderate quality evidence. The grading of evidence and a complete overview of the combined evidence of this review and the previous reviews[24,25] can be found in the evidence statements (**Supplementary Material III**).

## Discussion

This systematic review identified 19 new studies[29-47] published between 2010 and 2015, on top of the 26 studies,[50-75] published between 1990 and 2010, identified for the NICE reviews.[24,25]

*Effective interventions*

Screening migrants by CXR is effective in identifying active TB cases and reducing TB importation, it is cost-effective and less costly than screening by TST.[30,38,53,54,61,62,64]

A systematic review and meta-analysis by Paquette et al. reported similar findings in the homeless population.[76] In hard-to-reach populations it is important to provide results instantly as follow-up attendance might be low. CXRs can be read instantly. This is a massive advantage over other diagnostic tests like TST, QFT-G and sputum smear/culture.

Using MXUs makes access to TB screening easier. We found that TB identification improved among several hard-to-reach populations when MXU was used, it was also a cost-effective tool.[37,39,42,58] All people living in the targeted hard-to-reach population should be screened as screening only symptomatic people would miss a substantial number of TB cases.[66]

A systematic review by Aldridge et al. found high yields for pre-migration screening especially if programmes focus on migrants from high-incidence countries.[77] The addition of sputum culture to the US pre-migration screening programme, initially targeting migrants from high-incidence countries, improves TB identification in the home country and reduces TB importation into the host country.[29,33,34,43] It takes around four weeks for the culture results to come back, this imposes a small risk of getting infected during the time waiting for the results. Xpert MTB/RIF could be useful as a pre-migration screening tool in migrants from high-incidence countries, it is more sensitive than sputum smear, provides results within two hours and is cheaper than sputum culture in many settings.[78] Studies exploring this intervention should be conducted.

Another effective intervention is active referral to a TB clinic, either by appointment or by providing a phone number. It improves TB screening uptake among migrants[32,35] and drug users[40,44] for minimal extra costs. The barrier of finding an appropriate TB clinic and organising an appointment is negated by this intervention.

Enhanced case management results in high treatment completion rates,[42,46,60] decreases loss to follow-up, reduces TB related mortality and TB incidence[71] and is cost-effective[42] in homeless people and drug users. Guiding and supporting these vulnerable populations in adhering to the long treatment helps improving treatment completion.

Although the World Health Organization (WHO) advices integration of HIV and TB services,[79] we only found one study reporting on simultaneous HIV and TB treatment, showing a reduction in TB related mortality.[47] A systematic review by Uyie et al. found that the WHO recommendation to integrate HIV and TB services was effective in African countries.[80] Integrated HIV and TB care in low-incidence countries needs evaluation.

The NICE review[25] found that DOT increases successful treatment outcomes[69] and improves treatment adherence among several hard-to-reach populations,[67,75] even more when combined with incentives.[68,72] Partial DOT, only given during the first two months of treatment, can be as effective as full DOT.[70] Providing DOT in a TB clinic or via social outreach did not show a significant difference in treatment

outcome.[70] This is in contrast with other systematic reviews focussing on middle and high incidence countries, showing that community DOT was more effective than clinic DOT[81] or self administration.[82] No significant difference was found in treatment compliance between DOT administered by a family member and receiving regular treatment consisting of monthly check-ups.[73] A systematic review by Tian et al. found that community DOT given by a non-family member was most effective.[83] As with enhanced case management, DOT helps vulnerable people living in hard-to-reach populations adhering to their lengthy treatment regimen.

The NICE reviews[24,25] found that the use of incentives improves TB screening uptake, screening completion and adherence to treatment among homeless people[50,56] and drug users,[57] and is cost-effective when used to identify TB cases among drug users.[58] People living in those hard-to-reach populations belong to the most disadvantaged sections in society; incentives can help to get their daily needs and providing incentives is therefore a valuable intervention.

*Ineffective interventions*

Post-migration screening by symptom-based questionnaire does not seem to be effective,[45] and incarceration negatively affects treatment completion in mixed hard-to-reach populations (80% drug users).[74] No clear conclusions can be drawn about the effectiveness of QFT-G and TST for the identification of active TB in migrants[31,36] and children adopted from high-incidence areas.[41]

*Strengths*

An important strength of this systematic review of interventions is that it was conducted following the PRISMA and Cochrane Collaboration guidelines for reporting systematic reviews. We followed established screening protocols, including double screening of search results and the search was highly sensitive. The methodology followed that of the NICE reviews[24,25] closely in order to extend the body of evidence.

*Limitations*

The main limitation of this review is that we were unable to perform a meta-analysis due to a substantial heterogeneity across the included studies. The included studies focussed on different hard-to-reach populations, different interventions, had different designs and different outcomes. Furthermore, the populations defined as “hard-to-reach populations” might be debatable as not every individual in the discussed hard-to-reach populations are hard-to-reach, this may differ per setting and person. To be inclusive we included migrants and people living with HIV as they normally have a higher TB incidence rate compared to other populations. We used broad and sensitive search terms to include all types of interventions aiming to improve TB identification and management; this search strategy can affect reproducibility.

The majority of evidence was assessed as being weak-to-moderate; therefore, few strong conclusions could be drawn. Main areas in which the included studies were lacking are: identification of and control for confounding factors and use of appropriate analytical methods.

Most of the studies focused on migrants. No studies were found focussing on sex workers, and few studies included children within vulnerable and hard-to-reach populations, prisoners, homeless people, drug users and people living with HIV. As a result evidence for these hard-to-reach populations is limited. Since our review included studies conducted in EU, EU candidate countries, EEA and OECD countries, we did not assess studies on combined HIV and TB care done in high-incidence countries, therefore the evidence on people living with HIV is limited.

The secondary research questions could not be addressed as no studies were found examining the factors impacting the effectiveness of the interventions, nor any adverse or unintended effects of the interventions were reported.

Only three studies included in this update of the review[30,38,42] and seven studies[51,52,58,61,62,65] identified by the NICE reviews[24,25] focused on economic data. The majority of these studies focussed on the use of CXR in migrants,[30,38,51,61,62] prisoners,[52] and MXU in mixed populations.[42,65]

*Recommendations*

Given the target populations and the setting, it is often challenging to perform 'clean', unbiased and un-confounded trials. However, efforts should be made to improve the quality of future studies. Future studies may assess Xpert MTB/RIF as a pre-migration screening tool for migrants from high-incidence countries.

TB cases among migrants are diagnosed up to many years post-migration also in settings where screening is performed.[84] Easy access to health care and TB awareness are important to identify this group and other hard-to-reach populations. Future studies should focus on access to health care for hard-to-reach populations and on raising TB awareness, e.g. the effect of health education days at shelters, needle exchange programmes and refugee camps, or providing TB education leaflets at pre-migration screening clinics, ports-of-entry and HIV clinics on identification of TB cases.

## Conclusions

This systematic review of interventions developed the evidence base for the ECDC guidance document for controlling TB in European hard-to-reach populations.[23] Our findings can also be used by policy makers to set out guidelines and recommendations to improve identification and management of active TB among hard-to-reach populations.

The results from the previous NICE reviews and this review provide evidence that pre-migration screening by CXR, including sputum cultures in the screening algorithm, screening by MXU, active referral for TB screening, enhanced case management and combined HIV/TB treatment improves TB identification and management in hard-to-reach populations.

## Conflict of interest

The authors have no conflict of interest to disclose.

## Authors' contribution

CCH, SGdV, BJV and MPG conceived the protocol. RS conducted the literature search. CCH, SGdV and BJV performed the study selection. CCH, SGdV, PFG, BJV, SB and SJ collected the data and performed quality/risk assessment. CCH and PGF synthesised the data and created the tables and figures. CCH prepared the manuscript and supplementary files. MPG and MvdW supervised the whole process. All authors were involved in interpretation of the data and revising the manuscript.

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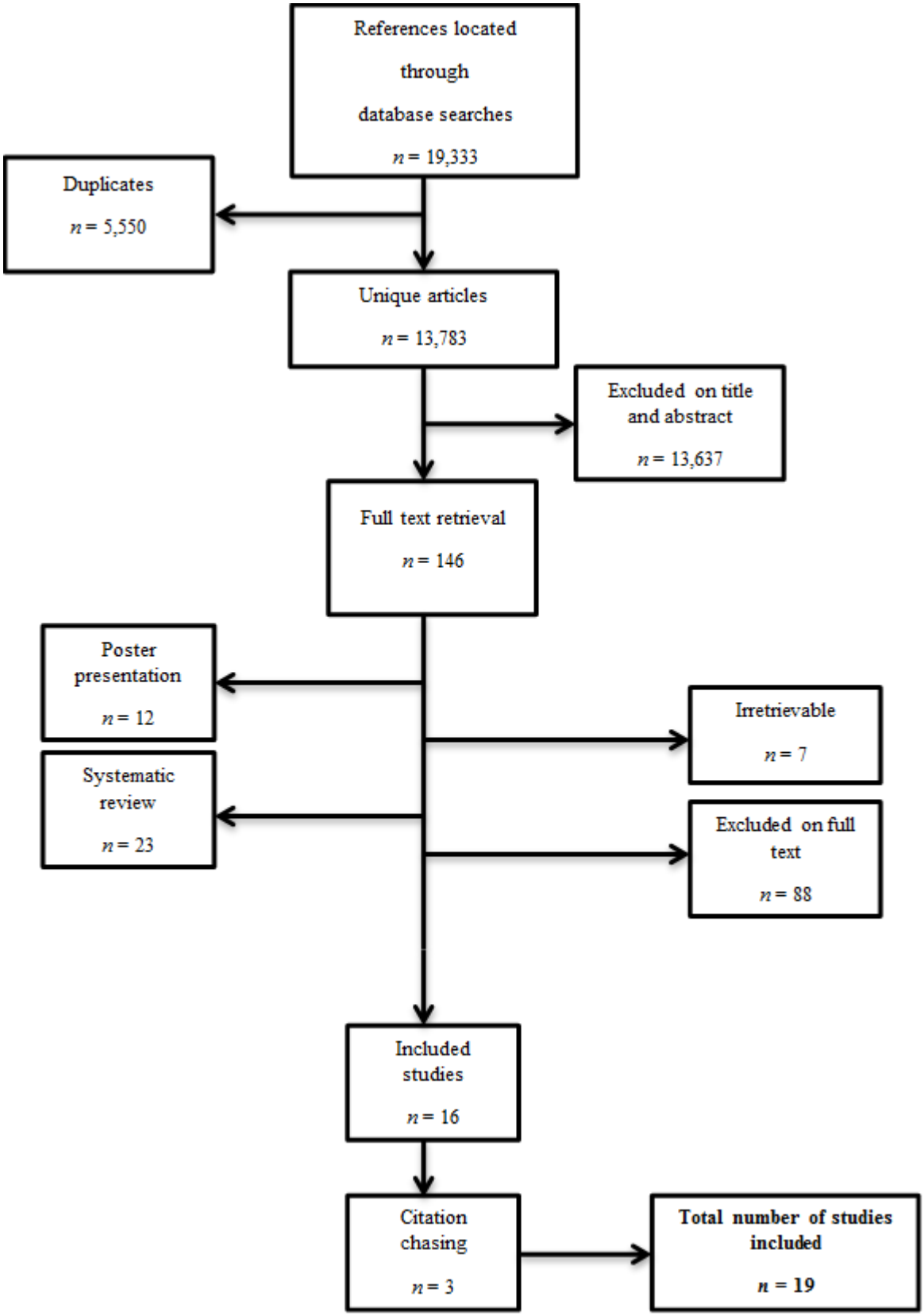
**Figure 1. Study selection process**




For the Organisation for Economic Co-operation and Development countries and hard-to-reach populations discussed in the previous NICE reviews,[24,25] the study period covers 2010 to 10 April 2015
For the newly included European Union (EU)/European Economic Area/EU candidate countries and the newly included hard-to-reach populations, people living with Human Immunodeficiency Virus (HIV) and children within vulnerable and hard-to-reach populations, the study period covers 1990-2015

**Table 1. Characteristics of studies aiming to improve TB identification and TB management**

| Year | First Author | Hard-to-reach group | Aim | Intervention | Comparator | Study design | Outcome measure | Sample size | Country | Quality score |
|---|---|---|---|---|---|---|---|---|---|---|
| **TB identification (studies identified by this review)** | | | | | | | | | | |
| 2010 | Schneeberger Geisler et al.[45] | Migrants | To compare the detection of pulmonary TB by TB screening based on a symptom-based questionnaire (2007-2008) versus TB screening by chest radiography (2004-2005). | Symptom-based questionnaire | CXR | Retrospective cross-sectional comparison | | *n* = 53,306 | Switzerland | + |
| 2011 | Duarte et al.[40] | IVDU | To evaluate the effect of the intervention (key partners promoting health-seeking behaviour, eliminating potential barriers, TB screening at chest clinic and DOT for TB treatment) on diagnosis of TB and treatment compliance. | Active screening / referral | Passive screening / referral | Retrospective review of records; effectiveness comparison | Reported TB cases | *n* = 590<br>I: 465<br>C: 125 | Portugal | - |
| 2011 | George et al.[41] | Migrants/ children | To examine the clinical utility of tuberculin skin testing (TST) and subsequent chest radiograph screening for TB disease in recently immigrated, asymptomatic internationally adopted children. | TST | CXR | Prospective cross-sectional | CXR suggestive of TB | *n* = 566 | US | - |
| 2011 | Jit et al.[42] | Homeless, drug users | To assess the cost-effectiveness of the Find and Treat service for diagnosing and managing hard to reach individuals with active tuberculosis in London. | MXU - screening | Self presentation | Observational and cost-effectiveness | Incremental costs from healthcare taxpayer perspective | *n* = 668 (of roughly 11,000 screened individuals) | UK | + |
| 2011 | Lowenthal et al.[43] | Migrants | To determine whether TB disease importation decreased following the addition of sputum cultures to the pre-migration screening protocol for people with abnormal CXR, symptoms of TB or HIV+ and if the intervention reduced transmission (e.g., smear-positive and culture-positive) of TB. | Expanding screening protocol with sputum culture (and DOTS) | Sputum smear | Retrospective observational effectiveness | Reported TB cases within 6 months of arrival | *n* = 3,479 | US | + |
| 2011 | Ruutel et al.[44] | Drug users | To evaluate case management interventions (active referral to TB centre made by the methadone programme) aimed at increasing tuberculosis screening & treatment entry. | Active referral to TB clinic (appointment | Passive referral (appointment organised by participant) | Pilot - RCT | TB clinic attendance | *n* = 112 | Estonia | + |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | organised by study) | | | | | | |
| 2012 | Bernard et al.[37] | Homeless | To measure the impact of an active TB case finding programme on the transmission of TB among the homeless in Paris. | MXU | No MXU | Effectiveness | Screening uptake, active TB cases, related TB cases (same strain) | *n* = 22,000 | France | + |
| 2012 | Mor et al.[38] | Migrants | To determine the validity of pre-migration TB screening by CXR in migrants from Ethiopia wanting to migrate to Israel. | CXR | Sputum smear/culture | Retrospective records review / cost-effectiveness | Accuracy of CXR as pre-migration screening tool | *n* = 13,379 | Israel | + |
| 2012 | Story et al.[39] | Mixed | 1. To calculate the sensitivity and specificity of mobile digital CXR for identifying pulmonary TB among high risk groups in an urban setting (London)<br>2. To determine whether cases of active pulmonary TB identified by MXU were less likely to be sputum smear positive on diagnosis than passively identified cases from the same populations. | 1. MXU – screening<br>2. Sputum smear | 1. Sputum culture confirmation<br>2. Passive presenters | Observational | Sensitivity and specificity of mobile digital CXR screening | *n* = 38,717 | UK | + |
| 2013 | Assael et al.[34] | Migrants | To analyse the proportion of positive sputum smears in Mexican migrants with culture confirmed TB. | Sputum smear | Sputum culture | Retrospective effectiveness | Culture confirmed TB cases with a positive sputum smear | *n* = 122 | US | - |
| 2013 | Bell et al.[35] | Migrants | To examine the efficacy of the referral processes at US Port-of-Entry. | Active referral (direct appointment, direct phone number or indirect phone number) | No referral | Effectiveness | TB follow up attendance and time to follow-up visit | *n* = 1,218 | US | + |
| 2013 | Painter et al.[36] | Migrants | To measure the sensitivity of TST and QFT-G in detecting culture-confirmed pulmonary tuberculosis among migrants. | Two-stage screening by TST or QFT-G and CXR | Sputum culture confirmation | Effectiveness | Sensitivity of TST and QFT-G in culture confirmed pulmonary TB cases | *n* = 1,475 from a population of 20,100 | US | + |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 2014 | Chuke et al.[31] | Migrants | To evaluate the effectiveness of TST versus QFT-G as part of screening for active TB in US migrants from a country with a high BCG vaccination coverage. | TST and QFT-G | CXR, sputum culture | Effectiveness comparison of different tests | Test agreement QFT-G, TST and CXR | *n* = 1,246 | US | - |
| 2014 | Harstad et al.[32] | Migrants | To improve the follow-up of patients with positive TB screening results by increasing the collaboration between healthcare services and new routines for summoning patients. | 1. Active referral follow-up (letters, contact by phone)<br>2. Reduce number of tests | No active referral / follow-up, no adjusted programme | Effectiveness comparison | TB clinic attendance and time from screening to examination | *n* = 257<br><br>I: 123<br>C: 134 | Norway | - |
| 2014 | Posey et al.[33] | Migrants | To report on the implementation of the new pre-migration TB screening programme introduced by the CDC in 2007 (sputum culture and DOT). | Expanding screening protocol with sputum culture | Sputum smear | Report | Smear-ve/ culture+ve TB cases | *n* = 1,100 | US | - |
| 2015 | Liu et al.[29] | Migrants | To evaluate the effect of pre-migration screening with a culture-based algorithm on preventing the importation of TB to the United States by migrants and refugees from foreign countries. | Expanding screening protocol with sputum culture (and DOTS) | Sputum smear | Population-based, cross-sectional | Smear-ve/ culture+ve TB cases and annual reported TB cases | *n* = 3,212,421 | US | + |
| 2015 | Mor et al.[30] | Migrants | To evaluate the validity of TB screening by CXR and the related costs in detained undocumented migrants from the Horn of Africa (post-migration, during detention in prison). | CXR | Sputum smear/culture | Cross-sectional (cost-) effectiveness | Positive CXRs and cost per active TB cases detected | *n* = 1,087 | Israel | - |
| **TB identification (studies identified by the previous NICE review)** | | | | | | | | | | |
| 1995 | Citron et al.[50] | Homeless | To assess the feasibility and effectiveness of incentives and education on uptake of TB screening. | Incentives and education | No incentives/ education | Historical effectiveness comparison | Screening uptake | *n* = 4,682<br><br>I: 1,082<br>C: 3,600 | UK | + |
| 1996 | Pilote et al. [56] | Homeless | To assess the effectiveness of providing monetary incentives or peers to improve adherence to screening compared with usual care. | Incentives or peers | Usual care (no incentives nor peers) | RCT | Screening completion | *n* =244<br><br>I: 165<br>C: 79 | US | ++ |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 1996 | Puisis et al. [59] | Prisoners | To evaluate the effectiveness of high-speed CXR screening compared with TST screening. | Miniature CXR | TST | Historical effectiveness comparison | Active TB cases, costs per active case | *n* = 173,319<br><br>I: 126,608<br>C: 46,711 | US | - |
| 1999 | Sciortino et al.[63] | Migrants | To assess the effectiveness of active referral to TB clinic in host country after pre-entry screening showed latent TB, to detect active TB among recent migrants. | Active referral | No referral | Retrospective cohort | Active TB cases | *n* = 2,547 | US | + |
| 2000 | Dasgupta et al.[51] | Migrants | To model the cost-effectiveness of active case detection by CXR screening compared to passive case-detection. | CXR | Passive case detection | Cost-effectiveness model | Incremental cost per active case prevented | *n* = 0 | Canada | + |
| 2000 | Schwartzman and Menzies [62] | Migrants | To model the cost-effectiveness of screening for active TB by using CXR or TST versus passive case detection. | Screening by CXR or TST | Passive case detection | Cost-effectiveness model | Incremental cost per active case prevented | *n* = 0 | Canada | ++ |
| 2001 | Jones and Schaffner[52] | Prisoners | To model the cost-effectiveness of miniature CXR screening compared to symptom-based and TST-based screening. | Miniature CXR | Symptom-based and TST | Cost-effectiveness analysis | Active TB cases identified per 1,000 tested and costs per case | *n* = 0 | US | + |
| 2001 | Perlman et al. [58] | Drug users | To examine the cost-effectiveness of TB screening at a syringe exchange programme versus the costs of identifying active TB cases without the intervention. The cost-effectiveness of using a monetary incentive to improve adherence to TB screening by CXR. | TB screening at a syringe exchange programme plus monetary incentives | Passive case detection | Cost-effectiveness | Cost per active TB case averted | Not applicable | US | ++ |
| 2001 | Verver et al. [64] | Migrants | To evaluate the impact of TB screening, by CXR or TST, at a TB clinic, on the severity of the disease at diagnosis and on the length of the infectious period compared to passive case detection. | Screening by CXR or TST | Passive case detection | Retrospective cohort | Severity of TB disease and length of infectious period | *n* = 822<br><br>I: 454<br>C: 368 | The Netherlands | + |
| 2003 | Perlman et al. [57] | Drug users | To compare the effectiveness and cost-effectiveness of the use of monetary incentives to complete TB screening by CXR. | Monetary incentives | No incentives | Historical comparison | Screening completion, time between referral and CXR, cost per case prevented | *n* = 177<br><br>I: 58<br>C: 119 | US | ++ |

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| 2005 | Monney and Zellweger[54] | Migrants | To compare the effects of active screening, by CXR ± TST, at the POA with passive case detection on bacteriological and clinical presentation of TB. | CXR ± TST screening at POA | Passive case detection | Retrospective cohort | Positive sputum smear/culture | *n* = 179<br>I: 71<br>C: 108 | Switzerland | + |
| 2005 | Schwartzman et al. [61] | Migrants | To model the cost-effectiveness of adding TST to the standard CXR screening at port-of-arrival (POA). | CXR plus TST | CXR only | Cost-effectiveness model | Cost-savings | *n* = 0 | US | ++ |
| 2007 | Laifer et al. [53] | Migrants | To compare active screening, by CXR, at POA with passive case detection of foreign-born residents. | CXR screening at POA | Passive case detection | Retrospective cohort | Active TB cases, positive sputum smear, mortality | *n* = 102<br>I: 43<br>C: 59 | Switzerland | + |
| 2007 | Watson et al. [65] | Homeless; prisoners; Drug users | To evaluate the effectiveness and cost-effectiveness of a digital MXU compared with passive case-identification. | Active screening by CXR at POA | Passive case-detection | Retrospective case-control | Active TB cases, time to diagnosis, positive sputum smear, costs to prevent one active case | *n* = 20,357 | UK | ++ |
| 2008 | Mor et al.[55] | Migrants | To examine the effectiveness and cost-effectiveness of pre-migration screening and post-migration screening at POA. | Pre-migration screening | Post-migration screening | Retrospective cohort analysis | Active TB cases, time between migration and diagnosis, cost-savings | *n* = 24,051<br>I: 14,768<br>C: 9,283 | Israel | - |
| 2008 | Ricks[60] | Drug users | To compare the effectiveness of using peers versus 'standard' public health workers to coordinate contact tracing. | Peers | Nurse care worker | RCT | Contacts traced | *n* = 102<br>I: 53<br>C: 49 | US | ++ |
| 2009 | Yates et al. [66] | Prisoners | To assess the impact on case-detection of limiting CXR to individuals with symptoms of TB. | Symptom-based screening by CXR | Universal screening | Retrospective cohort | Active TB cases missed | *n* = 13,546<br>I: 5,616<br>C: 7,930 | UK | - |

**TB management (studies identified by this review)**

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| 2011 | Duarte et al.[40] | Drug users | To evaluate the effect of the intervention (key partners promoting health-seeking behaviour, eliminating potential barriers, TB screening at | Period 2003-2005: implemen- | Period 2001-2003: before the | Retrospective review of records; | Adherence to treatment | I: 465<br>C: 125 | Portugal | - |

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| | | | chest clinic and DOT for TB treatment) on diagnosis of TB and treatment compliance. | tation of DOT, follow-up of non-compliance and providing medical or drug abuse treatment | implemen-tation of DOT | effectiveness comparison | | | | |
| 2011 | Jit et al.[42] | Homeless people and drug users | To assess the cost-effectiveness of the "Find and Treat" service for diagnosing and managing hard-to-reach individuals with active tuberculosis in London. | Period 2007-2010: Find and Treat service: Case holding & treatment support by peers | No case holding and peer support | Observational and cost-effectiveness | Incremental costs from healthcare taxpayer perspective | I: 494<br>C: 315 | United Kingdom | + |
| 2012 | Girardi et al.[47] | People living with HIV | To estimate the impact of cART on TB outcome. | Concurrent cART and TB treatment | Administratio n of cART before TB treatment | Multicentre, prospective, observational | Treatment outcome | I: 151<br>C: 95 | Italy | + |
| 2012 | Goetsch et al.[46] | Homeless people and drug users | To establish a sustainable low-threshold CXR screening programme for pulmonary TB among drug users and homeless people and to integrate this into the existing public health programme for active case finding.<br>To estimate the coverage of the programme, assess other risk factors and determine TB rates and treatment outcome in these two groups. | Enhanced case management, hospital admission for initiation of treatment for active TB | Comparing the beginning of the 5 year intervention period with the end | Retrospective effectiveness | Treatment outcome | *n* = 39 | Germany | - |
| **TB management (studies identified by the previous NICE review)** | | | | | | | | | | |
| 1994 | Alwood et al.[67] | People living with HIV and drug users | To evaluate the effectiveness of supervised therapy for tuberculosis (TB) in patients with HIV infection. | DOT | Partial supervision and self-administratio n | Retrospective chart review | Adherence to treatment, mortality | *n* = 78<br>I: 48<br>C: 30 | US | - |
| 1996 | Diez et al.[71] | Homeless people | To evaluate a social care and health follow-up programme providing directly observed treatment, primary health care and, if necessary, accommodation. | Social care support (DOT, primary health care + | Normal care | Retrospective cohort | Annual TB incidence rate | I: 210<br>C: NR | Spain | - |

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| | | | | accommodation) | | | | | | |
| 1997 | Oscherwitz et al. [74] | Drug and alcohol users | To determine which patients TB controllers attempt to detain, how often and where patients are detained, and how many of these patients complete TB treatment. | Legal detention | No legal detention | Retrospective cross-sectional cohort | Adherence to treatment | *n* = 4,325<br><br>I: 67<br>C; 4,258 | US | - |
| 2001 | Bock et al.[68] | Drug users | To determine whether incentives increase adherence to directly observed therapy (DOT) for tuberculosis (TB) treatment. | DOT plus incentives | DOT only | Historical comparison | Adherence to treatment | *n* = 112<br><br>I: 55<br>C: 57 | US | + |
| 2002 | Rodrigo et al.[75] | Prisoners | To evaluate the TB prevention and control programmes in Barcelona prisons and obtaining conclusions that would allow any necessary modifications to be introduced to improve their effectiveness. | DOT | Treatment as usual (no DOT) | Historical comparison | Adherence to treatment | *n* = NR | Spain | - |
| 2003 | Chemtob et al. [69] | Migrants | To describe the new programme, using directly observed treatment (DOT), and compare the outcome of treatment prior and after its realisation. | DOT | Treatment as usual (no DOT) | Historical comparison | Adherence to treatment and outcome | *n* = 877<br><br>I: 671<br>C: 206 | Israel | - |
| 2003 | MacIntyre et al.[73] | Migrants | To describe the effectiveness of a family-based programme of directly observed treatment (DOT) for tuberculosis. | DOT delivered by a family member | Self-administration and monthly clinic visits | RCT | Adherence to treatment | *n* = 173<br><br>I: 87<br>C: 86 | Australia | + |
| 2004 | Deruaz & Zellweger[70] | Migrants, alcohol or drug users, homeless people and prisoners | Evaluation of first experience of the directly observed therapy (DOT) programme for tuberculosis introduced in the Canton of Vaud in 1997. | Full DOT<br><br>DOT delivered at TB clinic | Partial DOT (DOT only first 2 months of treatment)<br><br>DOT delivered at social outreach site | Historical comparison | Adherence to treatment and outcome | *n* = 54<br><br>I: 36<br>C: 18 | Switzerland | - |
| 2005 | Schwartzman et al.[61] | Migrants | To model the effectiveness and cost-effectiveness of a pre-migration DOTS programme. | DOTS | No DOTS | Cost-effectiveness model | Cost, TB related morbidity and mortality among Mexican migrants in the US | *n* = 0 | US | ++ |

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| 2006 | Juan et al.[72] | Migrants, homeless people, drug or alcohol users, people living with HIV | To compare directly observed treatment (DOT) of tuberculosis through pharmacy offices with self-administered treatment in patients at risk for non-adherence. | DOT plus incentives | Self-administration | Historical comparison | Adherence to treatment | *n* = 213<br><br>I: 101<br>C: 112 | Spain | + |
| 2008 | Ricks[60] | Drug users | To compare the effectiveness of using peers versus 'standard' public health workers to coordinate TB treatment . | Enhanced case management by peers | Limited case management by heath care professionals | RCT | Adherence to treatment | *n* = 94<br><br>I: 48<br>C: 46 | US | ++ |

**List of Abbreviations**

C=Control group; cART= combined Antiretroviral Therapy; CXR = Chest X-ray; CDC = Centers for Disease Control and Prevention; DOT = Direct Observed Treatment; DOTS = Direct Observed Treatment Short-course; HIV = Human Immunodeficiency Virus; HTRG = Hard-To-Reach Group; I= Intervention group; MXU = Mobile X-ray Unit; *n* = number; NICE = National Institute for Health and Clinical Excellence; NR = Not Recorded; POA = Port-Of-Arrival; QFT-G = QuantiFERON-TB Gold Test; RCT = Randomised Controlled Trial; TB = Tuberculosis; T-SPOT = T-SPOT.TB; TST = Tuberculin Skin Test; UK = United Kingdom; US = United States

**Table 2. Main interventions and outcomes aiming to improve TB identification and management**

| Hard to reach group | Intervention | Outcomes |
|---|---|---|
| **TB identification** | | |
| **Migrants** | TB screening by CXR +/- TST | - Pre- and post-migration screening by CXR is effective and cost-effective.[30,38]<br>- Sensitivity and specificity of CXR screening for sputum confirmed TB (culture or smear) was respectively 86·1%-100% and 96.1%-99·1%.[30,38]<br>- Active screening by CXR and/or TST improved the identification of active TB cases; resulted in earlier diagnosis, reduced TB transmission and TB importation.[53,54,61,64]<br>- Screening migrants by CXR seems to be cost-effective, and less costly than screening by TST.[30,38,61,62] |
| | Sputum culture included in pre-migration screening | - 54·4%-80·0% of the culture confirmed TB cases were smear negative [29,33,34]<br>- The number of active TB cases diagnosed within 6-12 months of arrival in the host country decreased when screening included sputum culture.[29,43]<br>- Including sputum culture as part of pre-migration screening could save the US $15 million a year.[33] |
| | Active referral | - Active referral by letter, scheduled clinic appointment, providing a direct phone number for the TB clinic or indirect phone number improved clinic attendance and shortened the time between arrival and clinic attendance compared to no referral. The highest impact was seen when a direct phone number or a scheduled clinic appointment was provided.[32,35]<br>- Active referral did not identify all active TB cases among new entrants.[63] |
| | TB screening by IGRA / TST | - Neither QFT-G nor TST are good screening tools for TB screening in migrants from high incidence countries with a high BCG vaccination coverage.[31]<br>- There is no difference in sensitivity between QFT-G and TST-10 for culture confirmed TB cases in migrants from high incidence countries with high BCG vaccination coverage. However, QFT-G had a higher sensitivity than TST-15 (86·4% versus 52·3%, $p<0·001$).[36]<br>- TST-10 is a better cut-off point for the screening active TB than TST-5 in migrant children.[41,51] |
| | TB screening by symptom-based questionnaire | - Symptom-based questionnaire is not an effective TB screening tool for migrants,[30] the sensitivity was 55·2% with a specificity of 96·0%.[45] |
| **Homeless people** | TB screening by MXU | - TB screening by MXU improved TB detection among homeless people and decreased TB transmission among homeless people.[37] |
| | Incentives | - The use of incentives increased screening uptake and completion.[50,56] |
| **Drug users** | Active referral | - Active referral to the TB clinic, organised by methadone programme, improved TB clinic attendance among drug users for minimal extra costs.[44] |
| | Incentives | - The use of monetary incentives improved screening completion[57] and was cost-effective.[58] |
| **Prisoners** | TB screening by CXR | - TB screening by TST had a comparable yield as screening by CXR.[59]<br>- Screening by CXR is more cost-effective than screening by TST.[52]<br>- All prisoners, not just symptomatic prisoners, should be screened otherwise a substantial number of TB cases might be missed.[66] |
| **Mixed populations** | TB screening by MXU | - TB screening by MXU among homeless people, drug users, prisoners and asylum seekers had a sensitivity of 81·8% and a specificity of 99·2%. Cases diagnosed by MXU were less likely to be smear-positive therefore reducing TB transmission.[39]<br>- TB screening by MXU among homeless people, drug users and prisoners improved TB identification especially among asymptomatic people and late presenters.[42]<br>- TB screening by MXU seemed to be cost-effective.[42] |

| **TB management** | | |
|---|---|---|
| **Migrants** | Directly Observed Treatment | - DOT increased successful treatment outcomes.[69]<br>- DOT administered by a family member did not improve adherence to treatment.[73]<br>- Pre-migration DOT programmes reduced TB related morbidity and mortality in the host country and was cost-effective.[61] |
| **Homeless** | Enhanced case management | - Enhanced case management reduced treatment dropout rates.[42,46]<br>- Enhanced case management plus extra health care services and/or social support improved treatment adherence, decreased annual TB incidence and TB related deaths.[46,71] |
| | Incentives | - The use of incentives improved adherence to treatment.[50,56] |
| **Drug users** | Enhanced case management | - Enhanced case management improved treatment compliance and reduced TB related mortality.[46]<br>- Enhanced case management by peers and community health workers improved treatment completion rates.[60] |
| **Prisoners** | Directly Observed Treatment | - DOT improved adherence to treatment.[75] |
| **People living with HIV** | Simultaneous TB and HIV treatment | - Simultaneous TB and HIV treatment reduced TB related mortality rate.[47] |
| | Directly Observed Treatment | - DOT improved treatment adherence.[67] |
| **Mixed populations** | Case holding and treatment support by peers | - Improved treatment compliance and reduced lost to follow-up.[42]<br>- This was a cost-effective intervention.[42] |
| | Directly Observed Treatment | - Partial DOT, only given during the first 2 months of treatment, can be as effective as full DOT, given during the whole treatment period.[70]<br>- DOT plus incentives improved treatment completion.[68,72]<br>- DOT in TB clinic or via social outreach did not differ in treatment outcome.[70] |
| | Detention for treatment | - Legal detention did not improve adherence to treatment in mixed-hard-to-reach populations (80% drug users).[74] |

## List of Abbreviations

ART = Antiretroviral Therapy; BCG = Bacillus Calmette–Guérin; CXR = Chest X-Ray; DOT = Directly Observed Treatment; HIV = Human Immunodeficiency Virus; IGRA = Interferon Gamma Release Assay; MXU = Mobile X-ray Unit; QFT-G = QuantiFERON-TB Gold Test; TB = tuberculosis; TST = Tuberculin Skin Test

**Box 1. Inclusion/exclusion criteria for this review**

- Discussing an intervention relating to identifying and managing TB cases;
- Having been conducted in any of the EU/EEA countries, the candidate countries* and the other OECD countries**;
- Having been published in 2010 or later for the OECD countries**;
- Having been published in 1990 or later for the EU/EEA countries and the EU candidate countries* not being one of the OECD countries;
- Including data from any hard-to-reach population:
    - homeless people, including rough sleepers and shelter users
    - people who abuse drugs or alcohol
    - sex workers
    - prisoners or people with a history of imprisonment
    - migrants, including vulnerable migrant populations such as asylum seekers, refugees and the Roma population
    - children within vulnerable and hard-to-reach populations
    - people living with HIV
- Present qualitative and/or quantitative empirical data;
- Being a (cost)-effectiveness study, or any other type of quantitative primary research discussing (cost-)effectiveness.

Exclusion criteria:

- Latent TB;
- Studies solely discussing service models and organisational structures, including different types of healthcare workers and settings ;
- Systematic review (only used for reference searching).

*EU/EEA = European Union, European Economic Area; OECD = Organisation for Economic Co-operation and Development; TB = Tuberculosis.*

** EU candidate countries = Albania, Montenegro, Serbia, the former Yugoslav Republic of Macedonia and Turkey*

*** OECD countries = Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Luxembourg, Mexico, the Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States*

**Supplementary Materials**

**Supplementary Material I.** PICOS (Population-Intervention-Comparator-Outcome-Study design)

**Supplementary Material II.** Search strategy

**Supplementary Material III.** Evidence statements

**Supplementary Material IV.** Evidence tables

**Supplementary Material V.** Quality Assessment