

*IJTLDR Review: Active case finding and treatment adherence in risk groups  
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*State of the Art Review: Risk Factors for TB in Low Burden Countries*

## **Active case finding and treatment adherence in risk groups in the tuberculosis pre-elimination era**

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## **Abstract**

Vulnerable populations (including homeless persons, high-risk drug and alcohol users, prisoners, and other marginalized populations) contribute a disproportionate burden of tuberculosis (TB) cases in low-incidence settings. Drivers for this disease burden include increased risk of both TB transmission in congregate settings, and progression from infection to active disease. Late diagnosis and poor treatment completion further propagate the epidemic and fuel the acquisition of drug-resistance. These groups are therefore a major priority for TB control programmes in low-incidence settings. Targeted strategies include active case finding initiatives and interventions to improve treatment completion, and should be tailored to local populations. Active case finding most commonly deploys mobile x-ray unit screening, which allows sensitive, high throughput screening with immediate availability of results. Such initiatives have been found to be effective and cost-effective, and associated with reductions in proxy measures of transmission among hard-to-reach groups. The addition of point-of-care molecular diagnostics and automated x-ray readers may further streamline the screening pathway. There is little existing evidence to support interventions to improve adherence among these risk groups. Such approaches include enhanced case-management and directly-observed therapy, while video-observed therapy (currently under evaluation) appears to be a promising tool for the future. Integrating outreach services to include both case-detection and case-management interventions that share a resource infrastructure may allow cost-effectiveness to be maximised. Integrating screening and treatment for other diseases prevalent among targeted risk groups into TB outreach interventions may improve cost-effectiveness further. This article reviews the existing literature, and highlights priorities for further research.

## **Introduction**

The World Health Organization (WHO) End TB strategy, aiming to reduce tuberculosis (TB) incidence and TB mortality by 90% and 95% respectively by 2035, poses major challenges to TB control programmes in low TB incidence settings (defined as countries with an annual incidence of  $\leq 10 / 100,000$ )<sup>1</sup>. The goal in these settings is to achieve pre-elimination (defined as an annual incidence of  $< 1 / 100,000$ ) and to move towards elimination by 2035<sup>2</sup>. In order to achieve this, the setting-specific challenges in TB control in these low-incidence countries must be addressed. This requires special attention to specific populations at highest risk of TB disease, among whom much of the disease burden is now concentrated<sup>2-4</sup>.

Vulnerable populations (including homeless persons, high-risk drug users, prisoners, asylum seekers, and other marginalized populations) contribute a disproportionate number of TB cases in low-incidence settings<sup>1-3</sup>. Previous studies have attempted to quantify these disease burdens. Studies of homeless people have shown that the prevalence of active TB is heterogeneous, ranging from 200-7,700/100,000, with increased prevalence found in studies using chest radiography-based diagnosis, and in settings with higher general population TB prevalence<sup>5</sup>. Using systematic review and meta-analysis, Dolan et al. estimated that approximately 2,800/100,000 of incarcerated individuals globally have active TB<sup>6</sup>. Among high-risk drug users in London, UK, the prevalence of TB was estimated at 354/100,000, with a high proportion of cases being sputum smear-positive<sup>7</sup>. Alcohol-dependence is also associated with increased TB risk, estimated as a pooled relative risk of 2.94 in a systematic review and meta-analysis<sup>8,9</sup>.

Multiple drivers contribute to the elevated incidence of TB among these groups. Firstly, individuals in these groups are often at higher risk of TB exposure due to socio-environmental conditions that predispose to increased TB transmission, including in congregate settings such as homeless shelters and prisons<sup>10-12</sup>. Secondly, they are often at greater risk of progression from infection to TB disease. This may be due to several, synergistic factors, including poor nutrition<sup>13</sup>, co-infection with HIV<sup>14</sup>, alcohol misuse<sup>8</sup> or high-risk drug use<sup>15,16</sup>. These factors are propagated by TB cases within these groups often being diagnosed late (due to a lack of access to healthcare and late recognition of symptoms), and frequently receiving suboptimal therapy (due to the challenges of linkage and retention in care, and ensuring sustained adherence to treatment)<sup>15</sup>. This, in turn, increases the potential duration of their infective period, thereby increasing the risks of onward TB transmission, and the acquisition of drug-resistance. Further, when TB cases are eventually diagnosed, conventional contact investigations are often inadequate due to the difficulty of identifying contacts reliably<sup>17</sup>.

Recent global and European guidance highlights a clear need to strengthen TB control efforts among vulnerable groups in low-incidence settings<sup>1,3</sup>. Approaches addressing this may include active case finding initiatives, in order to promote early case-detection of TB disease, along with interventions that improve linkage and retention in TB care, to increase treatment completion. This narrative review will discuss active case finding and adherence interventions when targeting homeless persons, high-risk drug users, prisoners, and other marginalised populations in low-incidence settings. Other important risk-groups include recent migrants and people living with HIV; these are beyond the scope of this review, as they are included in other articles in this series<sup>14,18</sup>. A literature search was conducted to support this review (Box 1). Definitions of key terms used in this review, including active case finding and adherence, are included in Box 2.

## **Active case finding in risk groups in the TB pre-elimination era**

### *Screening tools and algorithms*

Active case finding involves the systematic identification of individuals with suspected active TB, in a pre-determined target group<sup>19</sup>. This requires the implementation of a pre-defined screening algorithm and may utilise tools including symptom questionnaires, chest radiographs (either mobile or off-site), or sputum diagnostics. Desirable qualities of a screening algorithm include high sensitivity, low cost, high throughput and rapid turnaround time. Table 1 summarises the sensitivity of available screening tools.

Symptom screening is generally thought to be of little value in risk groups in low-incidence settings due to limitations of poor sensitivity and specificity (particularly among populations with high prevalence of smoking, alcohol and drug use)<sup>19,20</sup>. Data evaluating the use of symptom screening as the sole initial screening tool are therefore scarce, though it may be used in combination with other methods.

Chest radiography, previously deployed for mass radiography screening for TB<sup>21</sup>, has re-emerged as a valuable initial screening tool among risk groups in recent years due to a number of strengths. These include:- the development of mobile digital radiography; relatively low cost; high throughput; high diagnostic accuracy; and immediate availability of results<sup>22-25</sup>. Chest radiography, regardless of symptoms, has therefore been the initial screening test of choice in the majority of recent studies evaluating active case finding interventions among risk groups in low-incidence settings. It should be noted, however, that sensitivity is reduced in populations with a high prevalence of advanced HIV infection - which may be relevant to some high-risk groups (e.g. injecting drug users) targeted by

interventions<sup>26</sup>. An example screening algorithm using a mobile x-ray unit (MXU) is demonstrated in Figure 1.

Sputum diagnostic tools for TB include smear microscopy, culture and molecular tests. Smear microscopy, while cheap and relatively fast to perform, is limited by poor sensitivity so is of little value as a screening tool<sup>19</sup>. Mycobacterial culture remains the gold-standard for the microbiological diagnosis of TB. It has generally been thought to have a limited role in active case finding among hard-to-reach groups in low-incidence settings due to the limitations of being dependent upon individuals' ability to produce good quality sputum samples, and slow turnaround time (up to 6 weeks) – which raises the challenge of locating positive cases after their initial screening<sup>23</sup>. However, a recent study in Copenhagen, Denmark, has shown that it may be of value in some settings<sup>27</sup>. Current molecular diagnostic tests, such as the Xpert MTB/RIF assay (Cepheid, Sunnyvale, USA), are relatively sensitive, very specific and allow fast turnaround time (<2 hours)<sup>28</sup>. They also have the potential for implementation at the point-of-care, though high cost and limited throughput mean that they are not currently viable as an initial screening tool, but may be reserved as diagnostic tools for individuals identified as high-risk of TB from the initial stage of the screening algorithm. Novel point-of-care molecular diagnostics are in the pipeline, and offer the hope of implementation as first-line screening tests in the future<sup>29</sup>.

Another approach to active case finding among risk groups is the combination of a symptom screen and tuberculin skin-test (TST) as the initial screening tools, with chest radiography performed if either is positive<sup>30-33</sup>. While both methods have low sensitivity for active TB when used in isolation, this approach relies on a high negative predictive value when both are negative. However, drawbacks include low specificity, and the requirement for at least two visits to read results. Interferon-gamma release assays (IGRA) also continue to be evaluated as tests for active TB<sup>34</sup>, but are also impaired by limited sensitivity, high cost and the requirement of a specialist laboratory<sup>35</sup>. Both TST and IGRA are therefore more commonly applied when the primary goal is screening for LTBI rather than TB disease.

Table 2 summarises published studies evaluating active case finding interventions among high-risk groups in low-incidence settings.

#### *Mobile x-ray unit screening*

Multiple studies have evaluated MXU screening approaches. The Find & Treat service in London, UK, involves a MXU screening intervention, targeting a mixed hard-to-reach population that includes homeless persons, prisoners, high-risk drug users and asylum seekers<sup>36-38</sup>. The service was initiated

after previous UK studies demonstrated the potential utility of active case finding using MXUs among these risk groups in UK cities<sup>39-43</sup>. The service has been evaluated in a number of studies. Story et al. linked individuals screened by the service to the national electronic surveillance system and demonstrated that the MXU diagnosed active TB with a sensitivity of 81.8% and specificity of 99.2%<sup>36</sup>. This study also found that cases identified by the MXU were less likely to be smear-positive than matched, passively-diagnosed controls, thereby implying that the intervention may be effective in diagnosing active TB cases earlier, and suggesting a potential impact of earlier diagnosis on reducing risk of onward transmission<sup>36</sup>. Jit et al. conducted a cost-effectiveness evaluation of the intervention. Case-detection by the service was found to be cost-effective (£18,000 - £26,000 / QALY gained)<sup>38</sup>. Further, 35.4% of cases diagnosed by the service were asymptomatic, while 22.9% had been symptomatic for >131 days, suggesting that these individuals were unlikely to be diagnosed without the intervention<sup>38</sup>.

Mobile x-ray unit screening targeting homeless people across 28 shelters in Paris over a 14-year period found 179 TB cases (from an estimated 22,000 screened), and was associated with a reduction in the proportion of cases that were clustered over time, using restriction fragment length polymorphisms (RFLP), as a proxy measure of recent transmission<sup>44</sup>. De Vries et al. evaluated a similar intervention, targeting homeless people and high-risk drug users, in Rotterdam, The Netherlands. Over a 4-year period, 28 active TB cases were diagnosed by the intervention (prevalence 327/100,000); the authors also reported a reduction in RFLP-clustering over a time, suggesting a decline in recent transmission<sup>45</sup>. Implementation of the intervention as part of a wider comprehensive social rehabilitation programme for homeless people and drug users was associated with a marked reduction in TB incidence among these risk groups in Rotterdam over time. This resulted in a subsequent reduction in efficiency and yield of the intervention, which was therefore deemed no longer necessary and withdrawn at the end of 2014<sup>46</sup>.

In a systematic review and meta-analysis of 16 studies from Western Europe, Japan, USA and Australia, the pooled prevalence of active TB from chest radiography screening of homeless people was estimated as 931/100,000 (range 434 – 3,015)<sup>22</sup>.

#### *Other active case finding approaches*

Jensen et al. implemented spot sputum screening (using microscopy and culture) among a mixed hard-to-reach population in Copenhagen in Denmark<sup>27</sup>. They demonstrated an initial TB prevalence of 2,233/100,000. Only 7/36 (19.4%) of cases were sputum smear-positive, and only 83.3% had chest radiographic changes suggestive of TB, suggesting that the remaining 17% may not have been diagnosed by an MXU intervention. While the median time to treatment was 32 days, it is

encouraging that all cases diagnosed started TB therapy, of whom 83% completed. This study demonstrates that spot sputum screening may be feasible, particularly in settings where MXUs are not available, though further data are clearly required as locating individuals with positive culture results days or weeks after screening may yet prove to be challenging in practice.

Active referral to TB services for screening is another intervention that has been evaluated in European studies among drug users, homeless persons and migrants, finding a TB prevalence of 300-1,217/100,000 among those screened<sup>47,48</sup>. Other studies from the USA using a symptom screen and TST as the initial screening test, with further evaluation including chest radiograph performed only if positive, have demonstrated a TB prevalence ranging from 0-1,217/100,000 among homeless people<sup>30-33</sup>. Two of these studies reported a reduction in TB incidence in US cities over the duration of the intervention, though other biomedical and socioeconomic factors may have contributed to these trends<sup>32,33</sup>. Screening of inmates on entry to prisons has been evaluated in Spanish and USA studies. Algorithms used on entry in these studies have generally included an initial symptom screen and TST, followed by chest radiograph if either is positive, and have shown a prevalence of active TB of 68 – 2,706/100,000<sup>49-55</sup>. However, performing a chest radiograph (rather than an initial symptom questionnaire and TST) as the initial screening test on prison entry has been associated with a reduction of exposure time to infectious TB cases (by expediting isolation)<sup>53,54</sup>, and a reduction in cost per case diagnosed<sup>56</sup>.

#### *Coverage & uptake of screening*

Ensuring adequate screening coverage and uptake must also be a priority for any active case finding intervention. Few studies have attempted to report coverage of screening programmes, which remains challenging to quantify in hard-to-reach groups due to the frequently mobile nature of these populations<sup>48,57</sup>. Acceptance and uptake of screening are also rarely reported, with uptake ranging from 14-87% in the absence of specific incentives<sup>40,41,43,58-61</sup>. Uptake is likely to be better with mobile (rather than off-site) screening programmes, though evidence for specific strategies to improve uptake is currently limited.

Aldridge et al. conducted a cluster randomised-controlled trial to examine whether volunteer peer educators (with direct experience of TB and/or homelessness) improved uptake of MXU screening at hostels in London. No difference in uptake was observed (40% in the intervention group; 45% in the control group), though the study was limited by the intervention having previously been in place at 'standard care' sites prior to the study being commenced, and therefore may have resulted in residual confounding and a reduction in the difference seen between the intervention and control arms<sup>59</sup>. Other studies from the USA have shown an increase in attendance to off-site chest radiograph referral with a

monetary incentive<sup>60</sup> and at an initial follow-up appointment following a positive TST with either a monetary incentive, or a peer health advisor, when compared to standard care<sup>61</sup>.

### *Yield of screening*

The weighted mean estimated number needed to screen has been estimated as 133 (range 22–1778), 1180 (4–2945) and 158 (108–252) when targeting homeless persons, prisoners and drug users respectively in low-incidence settings<sup>19</sup>. However, these estimates are heterogeneous, reflecting differences in TB incidence between different risk groups, and between different settings. Active case finding interventions therefore require a targeted, setting-specific approach. This should be based on local epidemiological data that can identify those populations with sufficient disease burden to justify the provision of resources to enable focused interventions. Policymakers may use surveillance data, or even targeted prevalence surveys, to identify high-risk populations on a local level, and determine the potential yield and thus cost-effectiveness of proposed active case finding interventions.

### *Future directions and research priorities for active case finding interventions*

Following a ‘positive’ initial screening test (e.g. a mobile chest radiograph in most recent studies), the most widely utilised screening algorithm involves referral to a TB service for further investigation as the next step [Figure 1]. Sputum may be sent for microbiological testing in parallel to this referral. A problem with this approach is the risk that they may not attend the TB service for further assessment. This initial loss-to-follow-up (which occurs prior to TB diagnosis) has been estimated as being as high as 31% in London<sup>37</sup> and 50% in Sydney, Australia<sup>62</sup>. Implementation of ‘point-of-care’ molecular technology to enable a microbiological diagnosis on the day of initial screening following a suggestive chest radiograph is therefore attractive. Xpert MTB/RIF offers the potential to provide this in approximately two hours, using an automated platform<sup>28</sup>. This assay also allows the prompt identification of possible multidrug-resistance, through the detection of rifampicin-resistance conferring mutations. However, there are currently no studies published that evaluate the implementation of molecular diagnostics in a mobile outreach setting in a low-incidence country; data addressing this, including newer generations of the Xpert MTB/RIF assay or similar rapid molecular diagnostics, are therefore needed.

Technology may also be applied to MXU screening algorithms through the implementation of automated x-ray readers (e.g. CAD4TB), which may reduce reliance on trained human readers while addressing issues with inter-reader reproducibility<sup>63</sup> [Figure 1]. However, data validating the software for use in low-incidence settings and in a mobile screening unit are required prior to widespread roll-out of the technology.



As discussed above, the variable prevalence of TB among high-risk groups in low-incidence settings means that active case finding interventions require a tailored approach based on local epidemiological data, followed by monitoring and evaluation of cost-effectiveness and impact at a local level. The roll-out of universal whole genome sequencing (WGS) in some low-incidence settings may allow this to be done with greater resolution in future. When used in combination with conventional epidemiological methods, WGS may enable surveillance systems to identify sites and individuals that carry a high-risk of onward transmission earlier and more precisely than epidemiological methods alone have allowed, particularly in the context of outbreaks<sup>64-66</sup>. Prospective studies that evaluate the potential impact of real-time genomic data on local TB control policies are awaited.

Qualitative studies have suggested that further increases in TB awareness, reduction in stigmatisation and improvements in perceived access to healthcare are all required to improve usage of TB services by risk groups<sup>67</sup>; further research is clearly needed to inform and evaluate strategies to address these needs. Engaging key partners, such as staff in prisons and shelters, is also integral to maximise uptake of screening programme targeting these groups.

In addition to identifying active TB cases, consideration of testing and treating for LTBI among high-risk groups is recommended (after exclusion of TB disease) in international and some national guidance in low-incidence settings<sup>68,69</sup>. Studies evaluating the yield of LTBI screening when implemented among risk groups in parallel to active TB case finding, along with acceptance and completion of LTBI treatment, and impact on incident TB risk are needed. Furthermore, risk groups for TB overlap with those for other diseases - including HIV, hepatitis B and hepatitis C<sup>70</sup>. Combining active case finding and linkage to care for these services for individuals in hard-to-reach groups may therefore be cost-effective by capitalising upon a shared resource infrastructure, though data to support this are currently lacking.

### **Treatment adherence in risk groups in the TB pre-elimination era**

There have been few studies evaluating the role of interventions in improving adherence and active TB treatment completion among individuals from risk groups [Table 3]. Of these, 8 studies have evaluated enhanced case management interventions (including directly observed therapy (DOT), since this is not offered universally in low TB-incidence settings), while one has studied financial incentives.

### *Enhanced case management*

Three studies have evaluated interventions that involved an integrated approach of both active case finding and enhanced case management<sup>38,48</sup>. Jit et al. assessed the case management component of the London Find & Treat service, which supports treatment completion by maintaining contact with patients during treatment, accompanying them to clinic appointments, arranging visits in community, and involving peers<sup>38</sup>. The case management service supports hard-to-reach individuals diagnosed by the service, and referred from other local TB services. The evaluation by Jit et al. found that the case management component of the service was highly cost-effective (cost £4,100 - £6,800 per QALY gained). Treatment completion was 61.2% in the intervention cohort, compared to 51.7% with standard care after one year<sup>38</sup>.

De Vries and colleagues provided a range of enhanced case management approaches in combination with their active case finding programme in Rotterdam<sup>45</sup>. This included DOT, priority shelter accommodation, voluntary admission to TB hospitals, assistance applying for temporary residence permits, and detention as a last resort for non-compliant, infectious cases (14 patients). Incentives such as public transport tickets were also provided. They achieved treatment completion of 89.2%. In Frankfurt, Germany, Goetsch et al. provided education and enhanced case management (delivered by community health workers) for drug users and homeless people diagnosed with active TB following active referral to TB services for screening, and achieved treatment completion in 76%<sup>48</sup>.

Two studies have described enhanced cases management approaches including the provision of accommodation for homeless persons, achieving treatment completion of 80-90%<sup>71,72</sup>, along with a reduction in the mean period of hospitalisation after introduction of the intervention and a reduction in TB incidence among homeless persons in their locality over the study period<sup>71</sup>.

Three studies have evaluated the effectiveness of DOT in improving treatment completion in a mixed hard-to-reach population. These studies demonstrated improved treatment completion with DOT compared to self-administered treatment<sup>73,74</sup>, particularly when provided in a community setting<sup>73</sup> and when administered by peers<sup>75</sup>.

### *Incentives*

Data on the use of financial incentives to improve adherence to therapy for TB in risk groups are lacking. In one study, Bock et al. studied the impact of financial incentives on treatment completion among a mixed hard-to-reach population in Georgia, USA, and found that DOT attendance improved

following the introduction of a grocery voucher incentive for each DOT attendance, when compared to attendance prior to the intervention<sup>76</sup>.

#### *Future directions and research priorities for treatment adherence interventions*

Video-observed therapy (VOT) is an exciting recent development, involving patients filming themselves taking medications on a computer or mobile device, before securely transmitting these images to a remote observer<sup>77</sup>. This technology may allow enhanced case management and DOT to offer a more patient-centred approach, bridging the gap between TB patients and their healthcare providers, and reducing the need for resource-intensive face-to-face encounters. Early studies have demonstrated that VOT is both feasible and acceptable to patients receiving TB treatment in the USA and Mexico<sup>78</sup>, and in Belarus<sup>79</sup>. A randomised-controlled trial comparing adherence to TB therapy when treatment is delivered by VOT vs. standard DOT among hard-to-reach patients in London has recently been completed with extremely promising initial results, though full published results are awaited<sup>80</sup>.

While electronic reminder systems (e.g. short message service (SMS)) may also be of some benefit in improving adherence to appointments and treatment for TB services, the impact of such interventions on adherence and treatment completion in risk groups in low-incidence settings has not been evaluated<sup>81</sup>.

## **Conclusions**

Vulnerable groups - including homeless persons, prisoners, high-risk drug users and other marginalised groups – are a major priority for TB control programmes in low-incidence countries due to their disproportionate disease burden, ongoing high risk of transmission, and poor treatment outcomes. Interventions targeting these groups should aim to increase timely case-detection, and improve linkage-to-care and completion of therapy.

Interventions must be tailored to address local priorities, based on knowledge of regional epidemiology and risk groups, and must be monitored and evaluated at a local level. Mobile x-ray units appear to be effective and cost-effective<sup>38</sup> in achieving timely case-detection, and have been associated with reductions in proxy measures of transmission<sup>44,45</sup>. Implementation of new technology – including molecular diagnostics at the point-of-care (to expedite microbiological TB diagnosis), and universal whole genome sequencing (to supplement epidemiological data and identify transmission foci promptly) - may aid existing interventions to improve effectiveness in the future.

Interventions to improve treatment completion among these risk groups must also be tailored to individuals and may include enhanced case management (by both healthcare workers and peers), the provision of supervised accommodation for homeless persons, and supervised treatment (particularly when delivered in community and by peers). Incentives may also have a role, though evidence for this among risk groups are lacking. VOT is an extremely promising technology and is currently under evaluation as a tool to improve adherence in hard-to-reach groups. Integrating both active case finding and strategies to improve adherence into outreach interventions is likely to be cost-effective, by capitalising on shared resource infrastructure, while integrating testing and treatment for other diseases with overlapping risk profiles (e.g. HIV, hepatitis B and hepatitis C) into TB outreach services may improve overall cost-effectiveness further.

However, high quality data evaluating the impact of active case finding initiatives and (in particular) interventions to improve treatment adherence among risk groups in low-incidence settings are generally lacking. More high-quality studies are required that examine the impact of such interventions on timely case-detection, treatment outcomes, risk of onward transmission, and maximising uptake of the interventions themselves. If the End TB strategy goals of achieving pre-elimination and moving towards elimination in low-incidence settings by 2035 are to be reached, a concerted and prolonged effort will be required to reach these vulnerable groups, engage and retain them in care to the point of treatment completion. If we are serious about elimination, these efforts must be maintained even in light of falling cost-effectiveness, as TB incidence (and thus screening yield) declines. Finally, while this review has focused on biomedical interventions that aim to reduce the burden of TB disease among risk groups, we should not forget the imperative need to address the issue at its true core. We must continue to strive to improve access to healthcare among risk groups, while also reducing the size of risk group populations themselves, by implementing policies that seek to reduce health inequity and social exclusion directly.

### **Box 1: Search Strategy**

A literature search was performed using Medline (1946 - September 2017) to supplement this narrative, state of the art review. In short, two search sets were created and then combined using 'and', using comprehensive search terms for (1) 'tuberculosis' and (2) 'homeless' or 'drug users' or 'prisoners' or 'vulnerable populations'. This yielded 2,317 articles. Additional articles were identified by reviewing references of included studies and review articles, and by consulting experts in the field. Original research articles investigating active case finding initiatives or interventions to promote adherence among the aforementioned risk groups in low TB-incidence settings (defined as incidence <10/100,000) were identified. Studies that focused on contact tracing or specific outbreak investigations, or identifying and treating latent TB infection (LTBI) only, were excluded. After review of titles, abstracts and full-texts as appropriate, 45 relevant articles were identified (Tables 2 & 3), with a narrative approach to synthesis.

### **Box 2: Definitions (adapted from<sup>19,82</sup>)**

Active case finding - systematic identification of people with suspected active TB in a predetermined target group.

Adherence - extent to which a patient's history of therapeutic drug-taking coincides with the prescribed treatment.

Low TB incidence country – country with annual TB incidence  $\leq 10 / 100,000$  persons.

Passive case finding - a patient-initiated pathway to TB diagnosis that starts with a person presenting spontaneously to healthcare services.

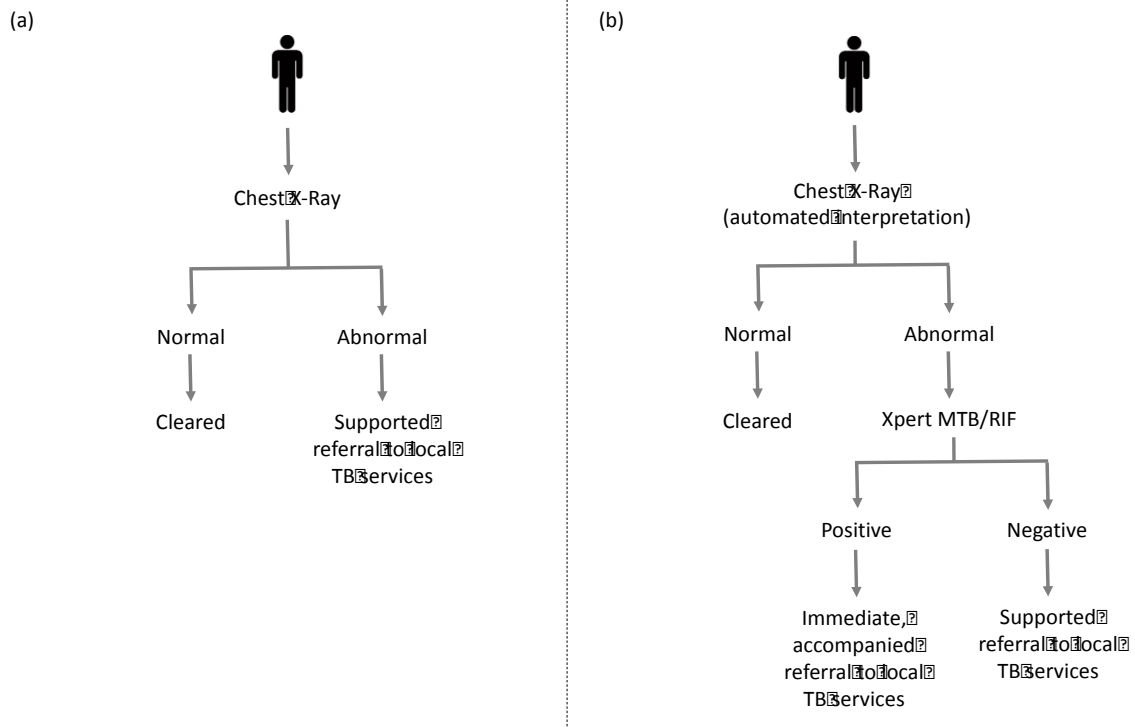
Risk group - any group of people in which the prevalence or incidence of TB is significantly higher than in the general population.

Screening coverage - proportion of total eligible target population who complete screening.

Screening test - a test that distinguishes people with a high likelihood of having active TB from people who are highly unlikely to have active TB.

Screening uptake - proportion of those offered screening who complete it.

**Figure 1:** Flowcharts demonstrating example screening algorithms for mobile X-ray unit service screening high-risk populations for active tuberculosis in low-incidence settings using (a) historic approach; and (b) new approach incorporating a molecular diagnostic test and automated chest radiograph reader. ‘Immediate’ refers to same day referral. Following referral, routine TB investigations (including microbiological confirmation) and treatment should occur via local TB services in both algorithms.



**Table 1:** Table summarising estimated sensitivity and specificity of currently available screening tools for active tuberculosis. Adapted from World Health Organization Systematic screening for active tuberculosis: Principles and recommendations<sup>19</sup>

<b>Screening tool</b>	<b>Sensitivity (%)</b>	<b>Specificity (%)</b>
Symptom screen (any symptom)	77 (68–86)	68 (50–85)
Chest x-ray (any abnormality compatible with TB)	98 (95–100)	75 (72–79)
Sputum-smear microscopy	61 (31–89)	98 (93–100)
Xpert MTB/RIF	92 (70–100)	99 (91–100)
Liquid culture (gold standard)	100	100

**Table 2:** Summary of included studies of active case finding (ACF) among selected risk groups from low tuberculosis (TB) incidence countries. Studies categorised according to initial screening step as (a) mobile x-ray unit (MXU) screening; (b) studies using symptom-, TST- or sputum-screening; (c) screening on entry to institution; (d) active referral to TB services for screening; (e) one-off prevalence surveys; (f) interventions to encourage screening uptake; and (g) systematic review & meta-analysis / modelling. Studies listed by year of publication (reverse chronological order).

(RFLP = restriction fragment length polymorphism; CXR = chest X-ray; QALY = quality-adjusted life-year; CDC = Centres for Disease Control and Prevention)

Study	Year	Setting	Target population	Design, Intervention & Comparator	Key Findings
<b>(a) Mobile x-ray unit screening</b>					
Bernard et al. <sup>44</sup>	2012	Paris, France	Homeless people	Observational evaluation of 14-year MXU ACF programme in 28 shelters. No comparator arm.	179 TB cases / approx. 22,000 screened; reduction in case-clustering using RFLP from 75% to 30% (p<0.01)
Story et al. <sup>83</sup>	2012	London, UK	Mixed (homeless, drug users, prisoners, asylum-seekers)	Observational evaluation of MXU screening programme. Compared to passively-detected cases identified through routine surveillance.	Sensitivity of CXR 81.8%; specificity 99.2%. Cases identified through screening less likely to be smear-positive than passively identified cases (p = 0.022). 33/47,510 CXRs had culture-confirmed TB (0.069%)
Jit et al. <sup>38</sup>	2011	London, UK	Mixed (homeless, drug users, prisoners, asylum-seekers)	Observational cost-effectiveness analysis of ACF using MXU intervention. Compared to passively-detected cases identified through routine surveillance.	Case-detection intervention was cost-effective (£18,000-£26,000/QALY gained)
de Vries et al. <sup>45</sup>	2007	Rotterdam, Netherlands	Homeless people and drug users	Observational evaluation of voluntary MXU ACF. No comparator arm.	28 TB cases identified (prevalence 327/100,000 CXRs), 12 smear-positive; reduction in clustered cases over time using RFLP (80% to 45%)
Watson et al. <sup>37</sup>	2007	London, UK	Mixed (homeless, drug users, prisoners, asylum-seekers)	Observational evaluation of voluntary MXU screening, Compared to passively-detected cases identified through routine surveillance.	222/20,357 individuals screened referred; 154 (69%) seen by TB services; 43 commenced on TB treatment. Passively-detected cases had almost 3 x delay to diagnosis and risk of smear-positivity than ACF cases.
Southern et al. <sup>42</sup>	1999	London, UK	Homeless people	Observational evaluation of screening with symptom questionnaire, TST and CXR on-site. Lunch voucher to encourage uptake. No comparator arm.	10/2,000 (0.5%) had active TB; symptom questionnaire 'not useful'; 80% treatment completion
Lau & Ferson <sup>62</sup>	1997	Sydney, Australia	Homeless people	Observational evaluation of voluntary MXU ACF in 5 hostels; referral to TB service if TB suspected. No comparator arm.	506/3555 screened (14.2%) had abnormal CXR. Only 2 cases of active TB (0.05%). Approx. 50% of those with abnormal chest x-ray lost to follow-up.



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Stevens et al. <sup>43</sup>	1992	London, UK	Homeless people	Observational evaluation of voluntary MXU screening. No comparator arm.	547 screened; screening uptake 44%; 42% attendance at follow-up for abnormal CXRs; 0 new cases of TB identified
Capewell et al. <sup>39</sup>	1986	Edinburgh, UK	Homeless	Observational evaluation of voluntary MXU screening. Compared to passively-detected cases identified through routine surveillance.	42/4687 (0.9%) of CXRs had TB (65% of all TB cases in hostel-dwellers). Fewer ACF cases were sputum smear positive (26% vs. 58% in passively-detected)
Patel <sup>40</sup>	1985	Glasgow, UK	Homeless	Observational evaluation of voluntary MXU screening with food voucher incentive. No comparator arm.	Uptake 47%; 133/9,132 screened had TB (1.5%)
<b>(b) Studies using symptom-, TST- or sputum-screening</b>					
Janssens et al. <sup>58</sup>	2017	Geneva, Switzerland	Homeless people	Observational evaluation of screening with questionnaire (symptoms, epidemiological risk). Chest x-ray screening performed if score >10. No comparator arm.	Uptake 87.3%; 30/726 (4.1%) positive questionnaire; 0/24 referred for testing had active TB
Jensen et al. <sup>27</sup>	2015	Copenhagen, Denmark	Mixed (homeless persons; persons with alcohol and/or substance abuse; and other socially marginalised persons)	Observational evaluation of screening using sputum microscopy & culture at 11 locations, on 7 occasions. No comparator arm.	36 / 1075 had TB. 24 cases identified at first screening of each participant (prevalence 2233/100 000). 35/36 (97.2%) TB cases culture-positive; 7/36 (19.4%) smear-positive; 28/36 (77.8%) had chest X-ray suggestive of TB. 30/36 (83.3%) had a successful outcome.
McAdam et al. <sup>32</sup>	2009	New York City, USA	As McAdam et al., 2009	Observational evaluation of screening with symptom questionnaire & TST. Sputum smear & culture, and CXR if TST-positive (or previous TST or active TB). No comparator arm.	Coverage 3-13.9% of homeless population. 63/28,835 active TB (0.24%). Incidence fell from 1,502/100,000 (1992) to 171/100,000 (2004)
Miller et al. <sup>31</sup>	2006	Texas, USA	Homeless people and prisoners (parallel interventions compared)	Observational evaluation of screening with symptom questionnaire & TST. Further investigations if TST positive. Selection for homeless screening unclear. Cases treated under DOT. Incentives for treatment provided for homeless (dietary supplements or fast-food coupons). No comparator arm.	Homeless - 10 /822 active TB (1.2%); prisoners 7/22,920 active TB (0.03). Estimated that LTBI treatment of homeless persons and jail inmates will avert 11.9 and 7.9 TB cases at a cost of \$14,350 and \$34,761 per TB case, respectively
Kong et al. <sup>33</sup>	2002	Denver, USA	Homeless people and drug users	Observational evaluation of screening with symptom screen & TST at 4 shelters and 6 drug recovery programmes. If either positive, referral to TB service. Screening required to stay at shelter / drug programme. No comparator arm.	Estimated TB incidence among all homeless decreased from 510 to 121 cases / 100,000 / year during intervention years. Recent transmission (DNA fingerprinting definition) decreased from 49% to 14% (p=0.03).

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Griffin & Hoff <sup>30</sup>	1999	Kansas, USA	Homeless people	Observational evaluation of screening with TST screening; CXR in TST positive cases. No comparator arm.	0 cases of active TB; 89/856 TST positive
Kimerling et al. <sup>84</sup>	1999	Birmingham, USA	Homeless people	Observational evaluation of screening with sputum culture, symptom screen (and TST in round 1/4) for overnight clients. No comparator arm.	4/127 screened (3.1%) had TB. 3/4 clustered using RFLP. Costs estimated to be \$1311/case identified. Only 1/4 cases reported productive cough on symptoms screen
McAdam et al. <sup>85</sup>	1990	New York City, USA	Homeless people attending shelter clinic (for work programme clearance or for evaluation of any medical problem)	Observational evaluation of screening with symptom questionnaire & TST. Sputum smear & culture, and CXR if TST-positive (or previous TST or active TB). No comparator arm.	100/1,853 (6%) had active TB. Treatment completion 36%
<b>(c) Screening on entry to institution</b>					
Rutz et al. <sup>51</sup>	2008	Baltimore, USA	Prisoners	Cross-sectional evaluation of adherence to CDC TB control policy. Symptom screen and TST on arrival (as per CDC guidance); if either positive, referral for CXR and clinical evaluation. No comparator arm.	28/97 of intake health interviews conducted correctly. Delays noted in diagnostic testing of 51 detainees isolated for suspected TB.
Saunders et al. <sup>86</sup>	2001	San Diego, USA	Prisoners	Observational evaluation of screening with symptom review, TST, and CXR for all new entrants. Compared to previous policy of only symptoms review and TST.	8/1,830 screened with universal CXR had TB (no change in incidence from previous practice). CXR screening of all inmates reduced exposure time to active TB cases by 75%
Solsona et al. <sup>87</sup>	2001	Barcelona, Spain	Homeless people	Observational evaluation of screening with TST, CXR and sputum (if CXR suggestive) in people entering shelters. No comparator arm.	5/447 (1.1%) had active TB; 335 (75%) had LTBI
White et al. <sup>55</sup>	2001	San Francisco, USA	Prisoners	Observational evaluation of screening with symptom screen and TST on arrival (as per CDC guidance); if either positive, referral for CXR and clinical evaluation. No comparator arm.	In 1994, 25 active TB cases booked into the jail (prevalence 78.5/100,000); only 3/25 were new diagnoses. In 1998, 21 active TB cases booked in (prevalence 72.1/100 000); only 7/21 new diagnoses.
Brock et al. <sup>52</sup>	1998	Georgia, USA	Prisoners	Observational evaluation of screening with symptom screen and TST on arrival (as per CDC guidance); if either positive, referral for CXR and clinical evaluation. No comparator arm.	142 TB cases identified; 74% detected through screening. 38% lost-to-follow-up
Puisis et al. <sup>54</sup>	1996	Chicago, USA	Prisoners	Observational evaluation of screening with miniature CXR on arrival. Compared to previous approach using TST screening.	86/126,608 (0.07%) screened had TB; 67 diagnosed by X-ray and 19 by diagnostic work-up. Mean time from entry to isolation reduced from 17.6 days with TST screening to 2.3 days with CXR screening.

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Martin-Sanchez et al. <sup>49</sup>	1995	Northwest Spain	Prisoners	Observational evaluation of screening with TST. CXR if TST-positive or HIV-positive. Sputum microscopy/culture if CXR abnormal. No comparator arm.	TB diagnosed in 12/944 (1.26%); only 4/12 cases were new diagnoses via screening
Martin et al. <sup>50</sup>	1994	Barcelona, Spain	Prisoners	Observational evaluation of screening with TST. CXR if TST or HIV-positive. Sputum microscopy/culture if CXR abnormal. No comparator arm.	19/702 (2.7%) who completed screening had TB
Bellin et al. <sup>88</sup>	1993	New York City, USA	Persons admitted to an opiate detoxification unit in an urban jail	Observational evaluation of screening with TST & CXR screening. No comparator arm.	73/1,314 had CXR changes consistent with active TB
<b>(d) Active referral to TB services for screening</b>					
Jimenez-Fuentes et al. <sup>47</sup>	2014	Barcelona, Spain	Drug users, 'economically disadvantaged' & recent migrants from hyperendemic countries	Observational evaluation of referral to TB service for clinical evaluation and chest X-ray screening (from various referral sources). No comparator arm.	30/5,982 screened had TB (0.5%). Prevalence 1.77% in recent migrants; 0.30% in economically disadvantaged; 0.62% in drug users
Goetsch et al. <sup>48</sup>	2012	Frankfurt, Germany	Drug users and homeless persons	Observational evaluation of referral for departmental CXR screening by community health workers. No comparator arm.	Screening coverage 18-26%; 39/3477 screened had TB (1.1%)
<b>(e) One-off prevalence surveys</b>					
Badiaga et al. <sup>89</sup>	2009	Marseilles, France	Homeless people	Observational evaluation of comprehensive, multidisciplinary screening of participants including symptom screen, sputum microscopy & culture, chest radiograph. No comparator arm.	2/221 (1%) had TB
Kumar et al. <sup>41</sup>	1995	London, UK	Homeless people	Observational evaluation of symptom & CXR screening for two years. In year one, CXR only if symptomatic. In year two, chest x-ray universal. No comparator arm.	595/3600 (16.5%) accepted screening; 30/595 (5%) had changes suggestive of active tuberculosis. 9/595 (1.5%) had confirmed TB; 13 did not attend follow-up
Barry et al. <sup>90</sup>	1986	Boston, USA	Homeless people	Observational evaluation of one-off active case finding with TST, CXR, sputum culture over 4-night period. No comparator arm.	3/586 (0.5%) had confirmed TB
<b>(f) Interventions to encourage screening uptake</b>					
Aldridge et al. <sup>59</sup>	2015	London, UK	Homeless people	Cluster RCT (46 hostels; 2,342 participants) of volunteer peer educators to encourage MXU screening uptake. Compared to standard care.	No difference in uptake between peer educator (median 40%) and control (median 45%) hostels
Perlman et al. <sup>60</sup>	2003	New York City, USA	Drug users attending needle-exchange programme	Observational evaluation of monetary incentive to attend external chest x-ray screening (if TST positive). Compared to historical approach with no monetary incentive.	Adherence to CXR referral within 7 days 79% with monetary incentive vs. 14% without (p<.0001). Median time to CXR shorter among those given incentive (2 vs. 11 days; p < .0001)

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Pilote et al. <sup>61</sup>	1996	San Francisco, USA	Homeless people	RCT of monetary incentives vs peer health advisor vs standard care to encourage TST positive people to attend TB clinic for further screening.	69 (84%) with monetary incentive completed first follow-up appointment, vs. 62 (75%) with peer health adviser vs 42 (53%) with usual care. 3/173 (1.7%) screened had active TB
<b>(g) Systematic review &amp; meta-analysis / modelling</b>					
Paquette et al. <sup>22</sup>	2014	N/A	Homeless people	Systematic review and meta-analysis of CXR screening	Pooled prevalence of active TB in 16 study cohorts 931/100,000 population screened. 6/7 longitudinal screening programs reported reduction in regional TB incidence after implementation
van Hest et al. <sup>57</sup>	2008	Rotterdam, Netherlands	Homeless people and drug users	Modelling study using truncated models to estimate coverage of MXU ACF	Screening programme reached approx. 2/3 of estimated target population at least annually
Brewer et al. <sup>91</sup>	2001	USA	Homeless people	Modelling study in US homeless populations using computer-based simulation model to examine impact of TB-control strategies on projected TB cases and deaths.	10% increase in access to treatment among homeless persons with active TB produced largest declines in predicted TB cases and deaths after 10 years
Jones & Schaffner <sup>56</sup>	2001	USA	Prisoners	Cost-effectiveness analysis using primary data from literature review of miniature CXR screening.	Cost of screening with miniature chest radiography estimated as \$9,600/case identified

**Table 3:** Summary of included studies of interventions to improve adherence and treatment completion among selected risk groups from low tuberculosis (TB) incidence countries. Studies categorised as (a) Studies using enhanced case management; (b) studies using DOT; (c) studies using incentives. Studies listed by year of publication (reverse chronological order).

(ACF = active case finding; DOT = directly observed therapy).

Study	Year	Setting	Target population	Design, Intervention & Comparator	Key findings
<b>(a) Studies using enhanced case management</b>					
Goetsch et al. <sup>48</sup>	2012	Frankfurt, Germany	Drug users and homeless persons	Observational evaluation of enhanced case management, hospital admission for initiation of treatment. No comparator arm.	Treatment completion 76%
Jit et al. <sup>38</sup>	2011	London, UK	Mixed (including homeless people, prisoners, drug users, asylum seekers)	Observational evaluation of enhanced case management with treatment support by peers. Compared to passively detected cases (from routine surveillance).	Case-management highly cost-effective (£4100-£6800/QALY gained). Treatment completion 61.2% (vs. 51.7%) in case management cohort.
de Vries et al. <sup>45</sup>	2007	Rotterdam, Netherlands	Homeless people and drug users	Observational evaluation of DOT, and a range of other enhanced case management approaches including priority shelter accommodation, voluntary admission to TB hospitals, assistance applying for temporary residence permits. Detention as a last resort (14 patients). Incentives such as public transport tickets also provided. No comparator arm.	Treatment completion 89.2%
LoBue et al. <sup>72</sup>	1999	San Diego, USA	Homeless persons	Observational evaluation of DOT and supervised accommodation provided. No comparator arm.	Treatment completion achieved in 18/20 cases. Cost savings for infectious patients estimated as \$27,034 per patient.
Diez et al. <sup>71</sup>	1996	Barcelona, Spain	Homeless people	Observational evaluation of DOT, primary health care & accommodation. Compared with historical trends.	Decrease in local TB incidence among homeless (from 32.4 to 19.8 per 100,000 from 1987-1992; p = 0.03). 19.6% of patients failed to complete treatment, and decrease in mean period of hospitalization from 27.1 to 15.7 days from 1986-1992
<b>(b) Studies using DOT</b>					
Ricks et al. <sup>75</sup>	2015	Chicago, USA	Drug users	RCT. Substance users randomized to DOT administered by either 1) public health personnel (standard arm) or 2) previous substance-using or HIV/AIDS outreach workers (enhanced arm)	Standard arm had a significantly higher risk of non-completion of treatment (39% vs. 15%)
Kim et al. <sup>73</sup>	2007	Chicago, USA	Prisoners	Observational comparison of those who received DOT vs those	DOT associated with higher treatment completion (59% vs

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				who did not.	29.1%); higher if DOT in community (70.8% field DOT vs 43.5% clinic DOT)
Juan et al. <sup>74</sup>	2006	Valencia, Spain	Mixed population at risk for non-adherence (HIV, alcoholism, drug use, immigrant or homeless and/or previous failure to complete)	Observational evaluation of pharmacy-delivered DOT compared to historic self-administration cohort	Treatment completion 75.2% in DOT group, vs. 26.7% self-administration group (P < 0.001). DOT increased cost of treatment by 400 Euros.
<b>(c) Studies using incentives</b>					
Bock et al. <sup>76</sup>	2001	Georgia, USA	Mixed, non-adherent TB cases (inc homeless, alcohol/drug-dependence, HIV)	Observational evaluation of \$5 grocery voucher for each kept DOT attendance. Compared to historical cohort.	Improved adherence to DOT in intervention cohort (60 vs 19%)

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