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## Active case finding for tuberculosis among high-risk groups in low-incidence countries

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### SUMMARY

In low-incidence countries, tuberculosis (TB) is now largely concentrated in high-risk groups such as migrants, homeless people, illicit drug users, alcoholics and prisoners. This has led to increased efforts to implement targeted active case finding for TB among specific populations. This review examines the evidence supporting active case finding in migrants and social risk groups, as well as the cost-effectiveness of interventions. While data from observational studies support active case finding

in defined high-risk groups, further research to determine the effectiveness of specific tools and the cost-effectiveness of screening strategies is needed to inform evidence-based control methods in low-incidence countries. Inevitably, addressing TB in low-incidence countries will depend on effective disease control in high-burden countries.

**KEY WORDS:** low-incidence countries; tuberculosis; active case finding; migrants; homelessness

GLOBAL TUBERCULOSIS (TB) control efforts, underpinned by the World Health Organization (WHO) Stop TB strategy,<sup>1</sup> have focused on improving case detection and treatment completion, for example through the introduction of directly observed treatment (DOT), to reduce transmission and to limit the development of anti-tuberculosis drug resistance. The majority of cases are identified through passive case finding following the presentation of a symptomatic TB patient to health services.<sup>2</sup> TB control strategies in low-incidence countries have undergone considerable changes over the last 50 years. In response to declining rates, many countries reduced their investment in TB control, which was often followed by a

resurgence of TB in some population groups. This phenomenon requires renewed efforts to contain a more complex epidemic, including various forms of active case finding (ACF).<sup>3</sup>

ACF, defined as a strategy to identify and treat people with TB disease who would otherwise not have sought prompt medical care,<sup>2</sup> was initially widely implemented in the early part of the twentieth century. Probably best known are the efforts to screen whole populations for active pulmonary TB (PTB) with mass radiography,<sup>1,2</sup> which was one of the pillars of the ‘vertical approach’ of control in many Western countries.<sup>1</sup> As ACF is usually very resource intensive, not surprisingly, mass radiography was stopped in countries where the yield had declined with falling incidence. ACF that uses contact investigations around infectious cases, however, continues in most Western countries, even during periods of very low levels of TB. As the introduction of these interventions pre-dated the rise of evidence-based medicine, there have been limited opportunities to subject them to rigorous evaluation.<sup>4</sup>

**Previous articles in the series** Editorial: Borgdorff M W, Yew W-W, Marks G. Active tuberculosis case finding: why, when and how? *Int J Tuberc Lung Dis* 2013; 17(3): 285. **No. 1:** Lönnroth K, Corbett E, Golub J, Godfrey-Faussett P, Uplekar M, Weil D, Raviglione M. Systematic screening for active tuberculosis: rationale, definitions and key considerations. *Int J Tuberc Lung Dis* 2013; 17(3): 289–298. **No. 2:** Kranzer K, Afnan-Holmes H, Tomlin K, et al. The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review. *Int J Tuberc Lung Dis* 2013; 17(4): 432–446.

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In low-incidence countries, TB is concentrated in specific subpopulations, usually in major urban centres.<sup>5,6</sup> Risk factors are often linked to migration from a high-incidence area, lifestyle (e.g., homelessness, illicit drug use or alcoholism) or imprisonment, and can also be related to underlying illnesses. TB incidence rates in these groups often dramatically exceed background incidence,<sup>7–10</sup> for example as the result of within-group transmission among homeless persons or drug users.<sup>11</sup> Conversely, engagement with health services is often more difficult in some risk groups compared with that in the general population, resulting in delayed diagnosis, onward transmission, poor treatment adherence and a consequent disproportionate contribution of these population groups to the TB burden.<sup>6</sup> This situation has prompted the United Kingdom's National Institute for Health and Clinical Excellence (NICE) to issue specific guidance for 'hard-to-reach' groups.<sup>12</sup> This article reviews and summarises the published literature about ACF activities among high-risk groups in low-incidence countries and the effectiveness of these approaches to inform future TB control strategies in these settings. Tables 1 and 2 outline the methodology and definitions used in the review.

#### *Diagnostic tools for active case finding in low-incidence countries*

ACF is usually focused on the early detection of PTB and is sometimes limited to smear-positive disease, as these patients are deemed more infectious.<sup>15</sup> Common screening tools for ACF in low-incidence settings include tests such as a symptom enquiry (often as a standardised symptom questionnaire), and chest X-rays (CXR), used separately or in combination. Further diagnostic tools include sputum smears or cultures and molecular tests such as Xpert<sup>®</sup> MTB/RIF

**Table 1** Methodology

A literature search using Medline (1966–2012) was undertaken and supplemented with further studies cited in the reference lists of included papers and reviews. Papers in English and those that had at least an abstract in English were considered.
For social risk groups, the key words used included 'homeless', 'intravenous' 'drug use', 'IDU', 'high risk', 'prison', 'alcohol', 'migrant', 'new entrant', 'tuberculosis', 'Tuberculosis', 'TB'. The search was limited to active case finding papers in low-incidence countries. The search yielded 578 papers, 27 of which were included in the review.
For international migrant screening, the synthesis was based on available evidence from a major systematic review, <sup>13</sup> supplemented by papers published after data collection for that review was closed (February 2008), as well as from other recent reviews. Search terms included 'migrant' and 'new entrant', combined with the terms 'screening', 'case finding' and 'TB'. The search yielded 198 papers, of which 7 were deemed relevant (published after February 2008 and containing outcome information, e.g., yield).
In synthesising the evidence, study design issues and sources of bias were considered, although a structured assessment of study quality was not carried out.

**Table 2** Definitions

Low-incidence country: There are numerous definitions of a 'low tuberculosis (TB) incidence country'. For the purpose of this review, the European Centre for Disease Prevention and Control (ECDC) definition was adopted, which sets the cut-off at 20 TB cases per 100 000 population. <sup>14</sup> Based on this definition, most countries in Western Europe and North America, as well as Australia and New Zealand, would be categorised as having low TB incidence.
Active case finding: Active case finding (ACF) is defined as any strategy to identify and treat people with TB disease who would otherwise not have sought prompt medical care. <sup>2</sup> In practice, most strategies are aimed at identifying pulmonary disease. For the purpose of this review, ACF does not include initiatives aimed at screening for latent TB infection (LTBI). However, studies on ACF initiatives which focus mainly on TB disease but which also include an LTBI screening component (see Figure) were included in this review.

(Cepheid, Sunnyvale, CA, USA). The test properties for some of these tools, including diagnostic accuracy and inter-reader agreement for radiography, are dependent on the background prevalence of TB in the screened population and setting.<sup>16</sup>

There are very limited published data on symptom screening in low-incidence settings. Standard items on symptom questionnaires are cough lasting more than 2–3 weeks, haemoptysis, fever, weight loss and night sweats. Considered separately, each of these symptoms has a low specificity for PTB. However, observational studies from high-burden settings suggest that where these symptoms are combined, for example by enquiring about 'any symptom', they show moderate to high sensitivity (65–90%), albeit with low to moderate specificity (30–68%) to detect microbiologically confirmed TB.<sup>17–19</sup> The sensitivity of symptom enquiry may be improved through the use of standardised questions and scoring systems,<sup>19,20</sup> but this often leads to low specificity. In addition, ACF should ideally detect TB early, before the symptoms become obvious. Among hard-to-reach groups, such as illicit drug users, symptoms may be difficult to interpret, given that the individuals may have a chronic cough or weight loss for other reasons. Symptom enquiry on its own is therefore unlikely to be helpful for ACF among some high-risk groups in low-incidence countries. In practice, symptom questionnaires are often combined with other case-finding tools.<sup>21–23</sup>

In low-incidence countries, radiological screening for TB targeting specific high-risk groups has re-emerged as a viable approach.<sup>24</sup> Digital CXR technology makes it easier to conduct ACF among risk groups with good test properties and reasonable inter-reader agreement.<sup>25</sup> Recent observational data have suggested that the sensitivity and specificity of digital CXR screening for active disease in these settings can be as high as 82% and 99%, respectively.<sup>10</sup> CXR test properties depend on the presence of typical radiological features (which may be absent or difficult to identify

in early disease and in immunocompromised individuals), the quality of the X-ray film, the skills of the reader and the background TB prevalence in the population screened. CXR screening will not identify extra-thoracic presentations of TB. Based on observational studies in low-incidence countries, reported levels of CXR sensitivity and specificity range between 59% and 82% and 52% and 99%, respectively.<sup>25–27</sup>

Patients' sputum may be obtained during ACF, usually following a positive result from either a symptom questionnaire or CXR. The sputum is examined using Ziehl-Neelsen or auramine-based stains ('sputum smear') to detect acid-fast bacilli. Population-level data on smear-based screening among high-risk groups in low-incidence countries are lacking. Although cases with a positive smear are more infectious,<sup>15</sup> outbreaks due to transmission from smear-negative PTB have occasionally been reported,<sup>28</sup> with molecular epidemiological studies estimating that 10–20% of all transmission arises from such cases.<sup>29–31</sup> The predictive value of sputum smears depends on the prevalence of TB in the screened population, the quality of the sample collection, the number of smears taken<sup>32</sup> and overall quality control.<sup>33</sup>

Mycobacterial culture (e.g., on Löwenstein-Jensen slopes or liquid media) is very sensitive and remains the diagnostic standard for TB.<sup>16</sup> However, its use for case-finding exercises is limited by the length of time needed for bacterial growth. The use of liquid media improves diagnosis by reducing the time to a positive culture, with moderate to high *Mycobacterium tuberculosis* recovery rates (74–97.8%) varying according to the study and the system used.<sup>34</sup>

Commercially available rapid nucleic acid amplification assays based on the amplification of DNA fragments from mycobacteria have a reasonably high sensitivity (86–97%) and specificity (85–99%) on smear-positive and -negative specimens.<sup>16</sup> However, their use for ACF has been limited by their relatively high cost. The WHO recently endorsed two molecular approaches to test for TB: line-probe assays (LPA) and Xpert MTB/RIF.<sup>35</sup> LPAs, based on the targeted amplification of specific parts of the *M. tuberculosis* genome, have become widely available, and the DNA amplification is automated in this diagnostic system. They are rapid, simple to use and have a high sensitivity and specificity (pooled estimates 93% and 83%, respectively) for diagnosing PTB and various drug resistances.<sup>36,37</sup> Xpert MTB/RIF, another molecular assay, has pooled sensitivities of around 98% (95% confidence interval [CI] 98–99) and 75% (95%CI 72–78) for smear-positive and smear-negative sputum samples, respectively, whereas specificities were given as 99% (95%CI 99–99%) for both smear-positive and smear-negative samples.<sup>16</sup> Globally, Xpert appears to be cost-effective for diagnosing multidrug-resistant TB.<sup>38</sup> However, if used as a screening test for ACF programmes in low-incidence countries, the high cost

of these tests would in all likelihood render them non-cost-effective.

#### *Targeting the delivery of active case finding*

In low-incidence areas, potential risk groups for ACF include contacts of (P)TB cases, migrants and asylum seekers,<sup>39</sup> indigenous populations with a high incidence of TB, drug users, homeless persons and alcoholics, as well as persons in high-risk occupational settings, such as staff in health care or elderly care, patients and staff in psychiatric facilities, and patients with co-morbidities, such as those who have tested positive for the human immunodeficiency virus (HIV; Table 3). A separate group, not discussed here, is made up of patients in advance of planned immunosuppression, such as solid organ recipients or candidates for tumour necrosis factor alpha blocking medication ('biologicals').<sup>42</sup> Apart from established public health practices, such as screening contacts of infectious index cases, and legal requirements, such as migrant screening in many low-incidence countries, the relative importance and burden of disease in other risk groups is setting-specific. Ultimately, the decision to screen specific groups should be based on a needs assessment, taking into account the disease burden, the level of transmission, access to health care, the cost-effectiveness of interventions and opportunity costs, and should be complemented by tailored opportunities for completion of the diagnostic process and treatment.

Contact investigation usually aims to detect individuals with latent TB infection (LTBI), especially in people at high risk of progressing to active disease or early TB disease (Figure). While contact investigation is a recognised approach for ACF, previous reviews and guidelines have comprehensively addressed its role.<sup>43,44</sup> More evidence is needed to support this well-established strategy.<sup>4,45</sup>

The concentration of TB in particular high-risk groups inevitably means that coordinated efforts to

**Table 3** Risk groups for active case finding

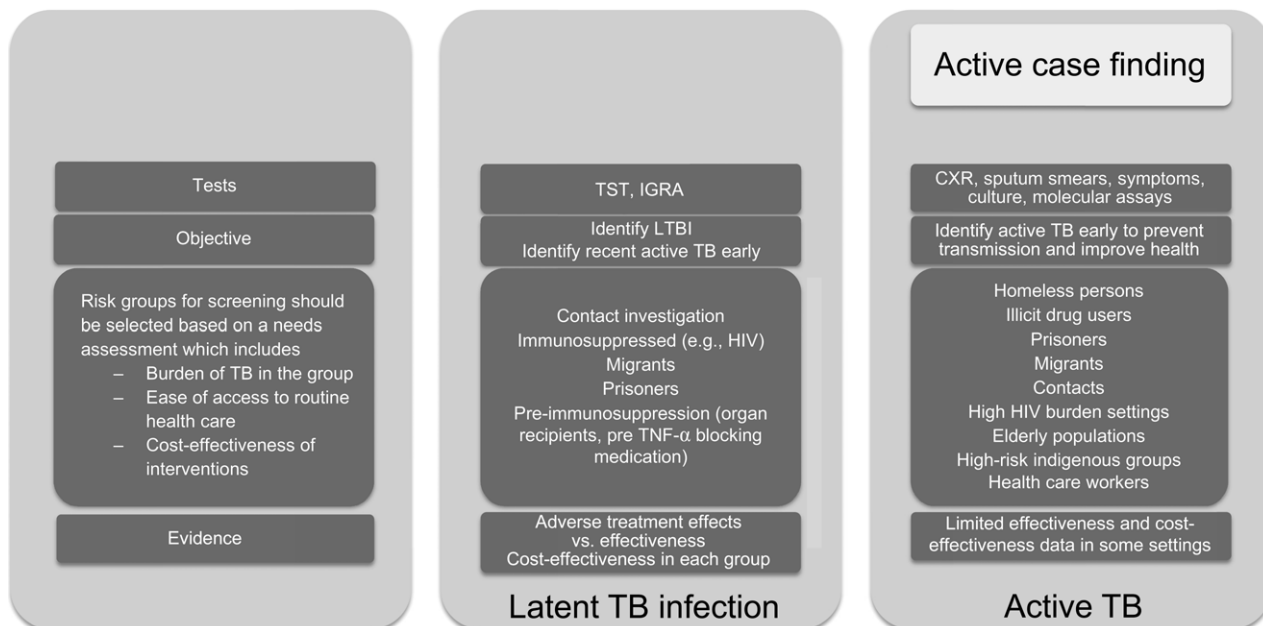
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Active case finding (ACF) strategies in low-incidence countries often target defined groups with a higher relative incidence of tuberculosis (TB) compared to that of the general population. By implication, this also includes patients with higher susceptibility because of an underlying condition (e.g., human immunodeficiency virus infection), but case finding and screening strategies among these groups are usually part of a medical work-up, informed by professional guidance documents.<sup>40,41</sup> These groups will not therefore be addressed in this review.

Furthermore, occupational groups that work with susceptible populations (e.g., health care workers) are screened for active and latent TB infection due to increased risk and the consequences of transmission. However, guidance and practices of occupational health clearance for TB is regulated through national guidelines in many low-incidence countries.

For the purposes of this paper, TB risk is defined by relative incidence in groups such as migrants (including asylum seekers and refugees) and other 'social' risk groups (including homeless persons, prisoners and drug users).

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**Figure** Conceptual model based on the natural history of TB illustrating opportunities for active case finding. TB = tuberculosis; TST = tuberculin skin test; IGRA = interferon gamma release assay; LTBI = latent tuberculosis infection; HIV = human immunodeficiency virus; TNF = tumour necrosis factor; CXR = chest X-ray.

implement ACF in low-incidence areas are focused on migrants from high-incidence areas and other risk groups, such as homeless people, prisoners and drug users.<sup>13</sup> This article therefore focuses on these risk groups in particular.

#### Migrants

The screening of migrants from countries with a high incidence of TB is well established in many low-incidence areas.<sup>46,47</sup> The screening tools used, the screening sites and the subgroups of migrants targeted differ substantially between countries. For example, a recent survey by Pareek et al., showed considerable variations in the approaches used by member states of the Organisation for Economic Co-operation and Development.<sup>48</sup> Several other large surveys have been conducted to review the type and efficacy of case finding initiatives, both globally<sup>13,49</sup> and in Europe.<sup>50,51</sup> Migrant screening can take place before entry (pre-departure screening), at entry (on-arrival or port-of-entry screening) or after arrival (post-entry screening).

The effectiveness of migrant screening, usually assessed through screening yield and sometimes coverage,<sup>13</sup> is influenced by the rates of TB in the country of origin of the new entrants, the conditions of migration (infection acquired pre-entry) and the migrants' subsequent travel back to those countries (infection acquired post-entry on return to country of origin).<sup>52–54</sup> Furthermore, living conditions among migrants in low-incidence countries, in particular those living in deprived, overcrowded settings, may lead to post-entry transmission of infection between migrants.

In line with the objective to find and treat the most infectious cases, CXR screening is used most frequently and, if positive, is usually followed by further investigations, such as sputum smears and culture confirmation.<sup>49–51</sup> Occasionally, CXR screening is preceded by a symptom enquiry.<sup>13</sup> Some countries, such as the United States<sup>55</sup> and Australia,<sup>56</sup> use CXRs to follow up inactive forms of TB, usually organised as post-entry screening within the host country. Migrant ACF is also combined with LTBI screening in some countries.<sup>50</sup>

Almost all current new migrant ACF programmes are centrally organised, but implementation is often decentralised. In some countries, the requirement to comply with TB screening is linked to migrants' rights and responsibilities, such as when there is an obligation for TB health clearance screening as a condition for obtaining a residence visa, as is the case for Australia,<sup>50</sup> the Netherlands,<sup>50,57</sup> Switzerland,<sup>50,58</sup> Norway<sup>50,59</sup> and the USA.<sup>50</sup> Asylum seekers and refugees, who are recognised as having a high risk of TB even among migrants, are often targeted as a high priority group for screening.<sup>50,59,60</sup> In some countries, all those who apply for an extended stay visa (e.g., more than 3–6 months) or for residency are screened.<sup>49–51</sup>

The overall median yield of any migrant screening in the European Union (EU) was estimated at 0.35% (interquartile range [IQR] 0.11–0.71), but the yield was lower when only studies from large, national programmes were included (0.18% [IQR 0.11–0.35]).<sup>13</sup> Non-EU studies had a slightly higher, but comparable yield (0.51%, IQR 0.17–1.23).<sup>13</sup> In studies published after 2008, we also found a comparable

yield (median 0.31%, IQR 0.26–0.61, Appendix Table A.1\*).<sup>49,55,56,59,61–63</sup> In their recent international survey, Alvarez et al. found a lower overall yield (0.11%, IQR 0.08–0.15).<sup>49</sup> However, coverage is highly variable by setting, with Klinkenberg et al. reporting a range of between <20% and 100%, although most national programmes had higher coverage (>90%).<sup>13</sup> Mandatory programmes had a higher median coverage than voluntary programmes (90.6% vs. 48.5%).<sup>13</sup>

Pre-entry screening is currently used by the USA,<sup>61</sup> Australia, Canada, New Zealand and the United Kingdom, with migrants required to obtain a TB health clearance certificate from a designated centre in their country of origin; in the event of positive findings, treatment completion may be required. The costs for obtaining this are usually borne by the individual.<sup>49</sup> Pre-entry programmes are therefore attractive to the host countries and, where they are supported by an effective quality assurance programme, can improve the early detection of cases.<sup>61</sup> A retrospective observational study from the USA suggested that pre-entry screening with CXR, combined with smears and culture, was associated with a reduction in TB occurring among migrants within 6 months of arrival.<sup>61</sup> In another observational study, the Israeli screening programme in Ethiopia was also shown to reduce the risk of TB among migrants screened overseas compared to those screened after arrival.<sup>62</sup> A Canadian descriptive study identified limitations of the pre-entry screening programme and suggested strengthening LTBI detection among high-risk migrants after arrival.<sup>64</sup> The median yield of pre-entry screening programmes was estimated to be higher than other forms of migrant screening (1.21%, IQR 0.85–1.25),<sup>13</sup> an observation also shared by Mor et al. in their analysis before and after the introduction of their pre-entry screening programme in Israel.<sup>62</sup> Pre-entry screening has a theoretical coverage of 100%.

Several countries have an on-arrival screening system using CXR and symptom enquiry,<sup>51</sup> usually at ports of entry, with subsequent follow-up within the country administered and funded by the host country itself. This system has inherent problems, including its cost, relatively low case yield, estimated at 0.18% (IQR 0.09–0.35),<sup>13</sup> and difficulties with seamless integration into national health services for further follow-up.<sup>65,66</sup> Coverage was estimated at 92.4%.<sup>13</sup>

A number of countries have centrally organised ACF systems for new migrants after arrival. Service models vary, and include screening in transit centres<sup>50,67</sup> or referral to Municipal Health Services (the Netherlands).<sup>50</sup> In some countries, such as Australia, post-entry systems are used to follow up individuals who have been found to be at a higher risk of TB (e.g.,

with non-specific CXR changes pre-entry) or to organise LTBI screening.<sup>56</sup> National post-entry screening programmes inside and outside the EU achieved a yield of 0.3%.<sup>13</sup> We found a slightly higher yield of post-entry screening in more recent studies (0.42%, IQR 0.31–0.62, Appendix Table A.2).<sup>7,9,21–23,68–90</sup>

Several authors have examined the costs and cost-effectiveness of various migrant screening models. Migrant screening at entry was not found to be cost-effective and had little impact on overall TB trends.<sup>91</sup> Targeting post-entry LTBI screening at migrants from countries with an incidence of TB exceeding 150 per 100 000 population was found to be cost-effective.<sup>92</sup> The cost-effectiveness of pre-entry schemes from the perspective of the receiving country has been demonstrated, largely because only a minority of costs are borne by the host country,<sup>62</sup> but it will depend on the setting and incidence thresholds.

Further research into the potential impact of integrating LTBI screening into ACF activities on the epidemiology of low-incidence countries and into its cost-effectiveness would be beneficial. In addition, questions about the impact of migrant screening on host-country epidemiology remain, and few studies present data other than yield and coverage. Several studies have reported numbers of ‘missed cases’ (e.g., TB cases arising from the screened ‘TB-free’ cohort).<sup>62</sup> One study presented ecological evidence that the incidence of TB in countries with migrant screening programmes was lower than in those without such a programme, but these findings are difficult to interpret, as the direction of association is unclear, and there is considerable potential for inter- and intra-country confounding.<sup>49</sup> There is therefore a need for robustly designed studies to estimate the impact of migrant screening on the host country’s epidemiology. Any screening should ideally be delivered as part of a package of care to migrants that includes support for other health needs.<sup>93</sup>

#### *Social risk groups*

The incidence of TB among homeless persons, illicit drug users, alcohol misusers or prisoners substantially exceeds the background rates in many low-incidence countries.<sup>6,8,94</sup> To administer and evaluate ACF initiatives among these groups, it is necessary to define those who are eligible and implement an effective outreach strategy—a process that can be complex and challenging.<sup>12</sup> ACF can be initiated by local public health services.<sup>7,9,10,22,71,73</sup> Organisations with experience of working with these groups, often from the voluntary sector or civil society, are well placed to facilitate such initiatives. Compared with large, centrally organised migrant screening programmes, many ACF activities in these risk groups are small-scale and more local.

Despite the large number of initiatives, few have been evaluated and published. Appendix Table A.2

\*The Appendix is available in the online version of this article at <http://www.ingentaconnect.com/content/ijatld/ijatld/2013/00000017/00000005/art00004>

(A and B) shows those ACF initiatives among homeless persons, illicit drug users, alcohol misusers and prisoners in low-incidence countries, where clear outcome information was available. The majority (17/27) of these studies describe ACF among homeless populations. CXR-based case finding is the most common approach, often supported by symptom enquiry and further investigations as required (e.g., sputum smears).<sup>7,9,71,74,76</sup> Common settings for voluntary screening are shelters.<sup>78</sup> Although voluntary screening dominates the method of delivery, some programmes tried to link ACF or TB screening to shelter admission and associated benefits.<sup>78,95</sup> Most ACFs specifically target PTB, but some programmes screen for LTBI, either alone<sup>96,97</sup> or in conjunction with PTB.<sup>72,78</sup> A mobile X-ray unit has been used successfully to facilitate ACF in Rotterdam,<sup>7</sup> Paris<sup>9</sup> and London<sup>73</sup> among homeless persons, prisoners, illicit drug users and asylum seekers.

The size and yield of the programmes aimed at homeless persons was highly variable (Appendix Table A.2A). Programmes screened between 120 and 22 000 homeless people (median 726), and detected 0–313 cases of active TB (median 9.5). For programmes where information on the screened population and yield was available ( $n = 14$ ), the case yield ranged between 0% and 6%, highlighting the importance of targeting the intervention appropriately. The most robust evidence of effectiveness was shown by assessing secular trends in recognised molecular clusters in Rotterdam, with evidence of decline of a proxy indicator of recent transmission after introduction of systematic mobile digital CXR screening among illicit drug users and homeless persons.<sup>7</sup> This study demonstrated the potential for population-level benefit by reducing transmission, in addition to the expected individual patient health gain through earlier diagnosis.

Little information was available on cost-effectiveness. One study using spot sputum screening calculated that ACF cost about US\$1311 (£820) per case identified.<sup>75</sup> A recent economic evaluation of the UK Find and Treat Service, which performs mobile X-ray screening in London, concluded that the ACF component was cost-effective at approximately US\$28 766–35 156 (£18 000–22 000) per quality adjusted life year (QALY) gained.<sup>73</sup>

The follow-up and treatment of homeless patients with TB can be difficult. Significant loss to follow-up has been shown in some programmes, usually between the point of referral for further investigation and subsequent diagnosis.<sup>22</sup> An integrated service, bringing both comprehensive testing and treatment to the 'street', appeared to be more successful.<sup>73</sup>

When screening was embedded within a TB clinic follow-up and the administration of care and DOT was optimised, a treatment completion rate of 89% was achieved among a population of illicit drug users

and homeless people.<sup>7</sup> Peer educators and community health workers, usually those who have had TB or the social risk factor, may also be able to play a role in improving success rates.<sup>98,99</sup>

Nine studies described systematic ACF programmes in prisons. These initiatives were usually centrally organised case-finding exercises based on CXR or symptom questionnaires; most (8/9) had an LTBI screening component as well, predominantly in the USA.<sup>19,82,84,85,87,89,90</sup> Seven of the studies describe screening as part of the medical assessment process on admission to prison; the other two were cross-sectional studies.<sup>84,87</sup> Some countries have published guidance for screening in prisons, and there have been two audits of the effectiveness of implementing Centers for Disease Control and Prevention guidelines.<sup>82,85</sup>

Where known ( $n = 5$ ), the size of the screened population ranged between 702 and 209 076 prisoners (median 11 576), and between 1 and 218 TB cases (median 19) were detected (Appendix Table A.2B). For programmes where information was given or could be calculated ( $n = 5$ ), the case yield ranged between 0.01% and 2.7%. An extensive European survey found that about 91% of the 22 responding countries performed TB screening on entry to prisons, mostly using CXR or sputum screening, with a yield of 0.39% (range 42–2362 cases).<sup>83</sup> None of the studies contained information on cost-effectiveness.

Few studies describe ACF exclusively aimed at people with drug or alcohol problems, but there is a sizeable overlap with ACF in prisoners and homeless persons. A substantial proportion of those screened by the mobile X-ray initiatives described previously (Rotterdam, Paris and London) belong to these risk groups.<sup>7,70,73,81</sup> One of the cross-sectional studies describing ACF focused on an opioid detoxification unit in an urban prison, and found 73 cases among the 1314 screened (5.6% yield). Another study described the successful use of financial incentives to improve the referral rate for CXR after LTBI screening.<sup>77</sup>

#### *Improving target group identification*

The evidence reviewed in this article suggests that the case yield of ACF programmes is highly variable, not only between different risk groups, but also within similar risk groups and across roughly comparable outreach initiatives. This may be driven by differences in underlying risks (e.g., homelessness is a complex term that includes a wide variety of subgroups) and in the incidence of TB between the same risk groups in different countries. Consequently, any ACF programme in a low-incidence country should be informed by a needs assessment and robust surveillance.

It has been shown that clustering is higher among certain risk groups compared to other TB patients.<sup>100</sup>

The evaluation of such evidence should form part of any needs assessment to determine which groups should be targeted. This is important because it is likely that transmission will vary according to the setting, the risk group and the virulence of certain *Mycobacterium tuberculosis* strain types.<sup>101</sup> Molecular strain typing information of the TB isolate, using restriction fragment length polymorphism or mycobacterial interspersed repetitive units-variable number of tandem repeats, is now systematically collected in a number of low-incidence countries. It has been used to epidemiologically describe and investigate molecular clusters and, in some countries, produce national guidance documents for cluster investigation.<sup>102</sup> While recent transmission cannot always be assumed within molecular clusters, these techniques have assisted outbreak investigations<sup>11</sup> and the detection of transmission chains;<sup>103</sup> where contact tracing procedures were good, however, this did not lead to the detection of many more additional cases.<sup>104</sup> Given that the aim of ACF is to find PTB and hence prevent further transmission, knowledge about molecular clustering and transmission patterns may be useful to target interventions more effectively, and should be used to inform ACF among high-risk groups.<sup>105</sup>

A further approach to targeting ACF activities is the use of geographic information systems (GIS). GIS mapping tools have been used to identify particular communities at higher risk of TB,<sup>106,107</sup> and may be combined with other sources of information, such as qualitative research tools and traditional epidemiology, to describe meeting places for some high-risk groups more accurately and target them more effectively.<sup>96</sup>

## CONCLUSION

There have been numerous successful ACF activities in countries with a low incidence of TB. Ideally, ACF should lead to both an impact on transmission and direct benefits for the individual patient through early detection. The effectiveness and, in some cases, cost-effectiveness of ACF among social risk groups, particularly the homeless, have been demonstrated, including evidence of transmission interruption. The evidence for screening of migrants depends on many factors, such as the screening setting and population, but overall it is less compelling, and further research is needed.

With low-incidence countries striving towards TB elimination, it may be necessary to improve the targeting of ACF campaigns. Collaboration with the voluntary sector and civil society is essential for case-finding interventions among hard-to-reach groups. New technologies, including molecular strain typing and/or GIS, may provide useful information for targeting. In addition, tools for the detection and treatment of LTBI need to be improved. Inevitably, as successful

TB control in low-incidence settings depends upon the global control effort, investment in international programmes in high-burden countries should remain a significant focus of low-incidence countries.

*Conflict of interest:* none declared.

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## APPENDIX

**Table A.1** Published active case-finding initiatives among migrants in low-incidence countries since 2008

Study	Title	Country	Target group	Study type	Intervention	Tools	Yield	Coverage	Comments
Harstad et al., 2010 <sup>59</sup>	The role of entry screening in TB case finding among asylum seekers in Norway	Norway	Asylum seekers	Retrospective cohort analysis	On arrival screening	TST for all and CXR for all aged >15 years	0.67% (15/2237)	Not given	13 additional cases (46%) found in cohort. (Study only included adults) FU for 2237/5112 asylum seekers (44%). LFU = 525
Liu et al., 2009 <sup>55</sup>	Overseas screening for tuberculosis in US-bound immigrants and refugees	USA	All refugees and immigrants	Retrospective cohort analysis	Pre-entry screening	CXR and symptoms	0.24% 6504/2714223)	100%	The study reports 26075 diagnosed smear-negative PTB cases (961/100000) plus 47 smear-positive, but only a small minority was confirmed by obligatory follow-up in the USA
Lowenthal et al., 2011 <sup>61</sup>	Reduced importation of TB after the implementation of an enhanced pre-immigration screening protocol	USA	Migrants from Mexico, the Philippines and Viet Nam before and after 2007 (implementation of new policy)	Retrospective cohort analysis comparing a more sensitive screening policy in pre-entry with the previous policy	Pre-entry screening	Symptoms and CXR for those aged >15 years	Not given	Not given	After implementation of new policy, the proportion of cases detected in the USA decreased from 86/2049 (4.2%) to 22/1430 (1.5%; $P < 0.001$ ). The new policy included sputum culture for applicants with an abnormal CXR consistent with TB, signs or symptoms of TB or HIV infection.
Mor et al., 2008 <sup>62</sup>	Pre-immigration screening process and pulmonary TB among Ethiopian migrants in Israel	Israel	Migrants from Ethiopia	Retrospective cohort analysis, comparing pre-entry screening (since 2001) with post-entry screening (pre-2001)	Comparison of pre-entry and post-entry screening	TST for all and CXR for all aged >6 months	46/14768 (0.31%) pre-entry and 19/9283 (0.2%) post-entry	Not given	267 and 324 cases/100000 py were detected pre-entry and post-entry, respectively (rate ratio 0.82, $P < 0.01$ )
Flynn et al., 2012 <sup>56</sup>	Post-migration screening for active TB in Victoria, Australia	Australia	Immigrants with inactive TB who signed a 'health undertaking'	Retrospective cohort analysis	Post-entry screening	CXR, symptom screening and TST, as appropriate	0.42% (79/18801)	Not given	The study reports on people with some evidence of past TB in pre-entry screening, i.e., a high-risk population. The 79 cases detected represent 83% of cases in the cohort (16 cases not detected).
Tafari et al., 2011 <sup>63</sup>	TB screening in migrant reception centers: results of a 2009 Italian survey	Italy	Asylum seekers in one reception centre (Bari Palese)	Cross-sectional (survey)	Post-entry screening	TST and CXR	0.81% (8/982)	97.50%	A one-off post-entry TB screening initiative
Alvarez et al., 2011 <sup>49</sup>	A comparative examination of TB immigration medical screening programmes from selected countries with high immigration and low TB incidence rates	Canada, France, Jordan, the Netherlands, Australia, New Zealand, Sweden, Germany, Switzerland, USA, UK, Spain, Japan, Italy, UAE, Israel	Asylum seekers, refugees, long-term migrants	Survey of immigration practices in 16 low-incidence, high-migration, countries	Three countries had no national immigration screening, the majority (8/13) applied mixed strategies (e.g., pre- and post-entry, such as Australia). Three screened only after arrival, one on arrival and one pre-entry only	Variable combinations, TST and CXR dominate	0.05% (Canada) to 0.15% (Jordan). Cases ranged from 11 to 400 of 8995–50000 screenees	Unclear	

TST = tuberculin skin test; CXR = chest X-ray; FU = follow-up; LFU = loss to follow-up; USA = United States of America; TB = tuberculosis; HIV = human immunodeficiency virus; py = person-years; UK = United Kingdom; UAE = United Arab Emirates.

**Table A.2A** Published and evaluated active case-finding initiatives among homeless persons and drug users in low-incidence countries

Study	Year	Title	Setting	Intervention	Tools	Study design and organisation	Effectiveness
Badiaga et al. <sup>68</sup>	2009	Contribution of a shelter-based survey for screening respiratory diseases in the homeless	Two homeless shelters in Marseille, France	Voluntary ACF in homeless shelters	SQ, sputum, CXR	Cross-sectional study	2/221 PTB
Barry et al. <sup>69</sup>	1986	TB screening in Boston's homeless shelters	Homeless shelters in Boston, USA	Voluntary ACF in homeless shelters	CXR, TST, sputum	A 4-night screening programme in the shelter and retrospective case review	26 TB cases/year. 15/26 resistant cases and 5/15 in persons previously TST-negative. Denominator unclear—shelter has 350 beds.
Bernard et al. <sup>9</sup>	2012	Impact of a 14-year screening programme on TB transmission among the homeless in Paris	28 homeless shelters in Paris, France	Mobile X-ray unit-based ACF (1994–2007) in homeless shelters using a mobile radiological screening unit	CXR	Centrally organised CXR-based programme by la Direction de l'Action sociale, de l'Enfance et de la Santé (DASES), a health institution supervised by the Paris city council	313 TB cases/ 22 000 CXR in 514 sessions. Clustering among cases decreased from 75% to 30% among all TB cases in shelters ( $P < 0.01$ ) between 1994 and 2007.
de Vries and van Hest <sup>70</sup>	2006	From contact investigation to TB screening of drug addicts and homeless persons in Rotterdam	Homeless population and illicit drug users in Rotterdam, the Netherlands	Contact tracing around a homeless person and a drug user led to wider screening amongst homeless persons	TST, CXR	Contact tracing exercise, screening homeless persons, drug users and hostel staff	6/507 had intrathoracic TB. LTBI in 29%. RFLP analysis found significant clustering.
de Vries et al. <sup>7</sup>	2007	Impact of mobile radiographic screening on TB among drug users and homeless persons	Homeless population in Rotterdam and illicit drug users, the Netherlands	Voluntary CXR screening with mobile unit	CXR	CXR screening via mobile X-ray unit amongst Rotterdam homeless and drug users.	28 PTB (327/100 000 CXRs, 12 smear-positive. Clustering decreased from 80% to 45% in 2005 (after introduction of screening programme).
Goetsch et al. <sup>71</sup>	2012	TB among drug users and homeless persons: impact of voluntary X-ray investigation on ACF	Homeless and IDU population in Frankfurt, Germany	Voluntary CXR-based screening programme of IDU and homeless population	CXR	Voluntary outreach-based programme, supported by key worker and awareness-raising activities	39 PTB in 3477 persons (14 drug users and 25 homeless). Case-finding rate 1.122/100 000. Overall 76% treatment completion rate.
Griffin and Hoff <sup>72</sup>	1999	TB screening in Kansas City homeless shelters	Five homeless shelters in Kansas City, USA	Voluntary LTBI testing and ACF in homeless shelters	TST, CXR	Voluntary TST followed by CXR	No active cases. 89/856 TST-positive.
Jit et al. <sup>73</sup>	2011	Dedicated outreach service for hard to reach patients with TB in London: observational study and economic evaluation	Hard-to-reach groups, including homeless persons and persons with drug and alcohol problems, London, UK	Find and Treat service—dedicated service for hard-to-reach groups in London. Two components—follow-up of existing cases and ACF, of which latter analysed here	CXR	Voluntary screening through mobile unit	Mobile CXR screening estimated to identify 16 active TB cases each year. It is estimated that 22.9% of symptomatic cases would probably not have presented for treatment without the service. An additional 35.4% were asymptomatic on screening and might have presented much later (or not at all).
Karpińska-Jazdon et al. <sup>74</sup>	2006	Epidemiology of TB of the respiratory tract in the homeless in Poznań	Homeless shelters in Poznań, Poland	Centrally-organised (health department) programme for case finding	CXR	CXR screening organised for registered homeless individuals and shelter users. 403 homeless and 57 staff screened.	43/460 referred for further investigation (403 homeless and 57 staff). 83 had abnormal CXR and 2 had active PTB.
Kimerling et al. <sup>75</sup>	1999	Spot sputum screening: evaluation of an intervention in two homeless shelters	Two homeless shelters in Birmingham, AL, USA	Spot sputum specimen from each overnight client, plus symptom screen and TST status in initial round	TST, sputum, SQ	Systematic study to evaluate utility of spot sputum screen	4/120 had PTB (3 of RFLP clustered). A high proportion had LTBI (40% with prior TST and 51% with TST during study).

(continued)

**Table A.2A** *Continued*

Study	Year	Title	Setting	Intervention	Tools	Study design and organisation	Effectiveness
Kumar et al. <sup>22</sup>	1995	TB among the homeless at a temporary shelter in London: report of a CXR screening programme	One homeless shelter in London, UK	Voluntary CXR and symptom screening	SQ and CXR	Voluntary CXR at one shelter during two Christmas periods 1992 and 1993. Total transient population 3600, of whom 595 were screened.	30/595 (5%) suggestive CXR changes. 9 (1.5%) had active TB, 8 not active TB, 13 no diagnosis (4 declined investigation and 9 did not attend).
Lau and Ferson <sup>76</sup>	1997	Surveillance for TB among residents of hostels for homeless men	Five homeless hostels in Eastern Sydney, NSW, Australia	Centrally-organised CXR-screening programme in NSW	CXR	Mobile CXR screening	506/3555 residents abnormal CXR, but only 2 with active PTB found through screening. There were 7 self-presenters in the same period. Approximately 50% of abnormal CXR persons lost to follow-up.
McAdam et al. <sup>23</sup>	1990	The spectrum of TB in a New York City men's shelter clinic (1982–1988)	On-site clinic at a men's shelter in New York City, NY, USA	Prospective cross-sectional survey	TST, SQ, CXR, sputum	Voluntary enrolment into study if attending clinic for any reason.	6% of 1853 with active TB over 73 months. LTBI 42.8%. 36% treatment completion rate.
Perlman et al. <sup>77</sup>	2003	Impact of monetary incentives on adherence to referral for screening CXRs after syringe exchange-based TST	Syringe exchange programme for IDUs in New York, NY, USA	Comparing successful CXR referral before and after monetary incentives	TST: if positive followed by CXR	Voluntary enrolment in research study	119 and 58 IDUs enrolled for control and intervention time, respectively. Successful referral for 46/58 (79%) in intervention group and 17/119 (14%) in control group ( $P < 0.0001$ ; OR 23, 95%CI 9.5–57). Median time to CXR was shorter in intervention group (2 vs. 11 days, $P < 0.0001$ ).
Solsona et al. <sup>78</sup>	2001	Screening for TB upon admission to shelters and free-meal services	Homeless persons who wanted to enter shelters in Barcelona, Spain	Prevalence study of LTBI and PTB in the homeless community	CXR, TST, sputum	ACF and LTBI screening on admission to homeless shelters	5/447 (1.11%) had PTB, 335 (75%) had LTBI, 62 (13.8%) had radiographic evidence of inactive PTB
Southern et al. <sup>79</sup>	1999	TB among homeless people in London: an effective model of screening and treatment	Homeless persons hostels and day centres in South London, UK	Voluntary screening for LTBI and PTB on site, observational study to assess acceptability, yield and treatment completion	TST, CXR, SQ	Screening on site, research study	10 PTB cases (0.5%) among clients. SQ not found to be helpful, 80% completed treatment, 5 started on chemoprophylaxis.
Stevens et al. <sup>80</sup>	1992	Public health management of TB among the single homeless: is mass miniature X-ray screening effective?	Eight hostels for homeless people in South London, UK	Voluntary CXR screening of homeless persons	CXR	Screening with mobile X-ray unit on site, follow-up if abnormal CXRs	No PTB cases among the 547 screened
van Hest et al. <sup>81</sup>	2008	Estimating the coverage of a targeted mobile TB screening programme among illicit drug users and homeless persons with truncated models	Homeless population, Rotterdam, the Netherlands	Voluntary CXR screening using mobile X-ray unit	CXR	Mobile X-ray unit	The programme reached about two thirds of the target population annually; 23% had reached the target of two CXRs per year. No information on yield.
White et al. <sup>82</sup>	2001	TB prevalence in an urban jail: 1994 and 1998	San Francisco City and County Jail, CA, USA	Followed CDC guidelines on new reception screening with SQ, TST and CXR as appropriate	SQ, TST, CXR	Centrally organised new reception screening following CDC guidelines. Here comparison of two cohorts 1994 and 1998	Active TB 72.1/100 000—no difference between cohorts. In 1998, a third of active cases were found through TB screening vs. passive presentation.

ACF = active case finding; SQ = symptom questionnaire; CXR = chest X-ray; PTB = pulmonary tuberculosis; TB = tuberculosis; USA = United States of America; TST = tuberculin skin test; LTBI = latent tuberculosis infection; RFLP = restriction fragment length polymorphism; IDU = illicit drug user; UK = United Kingdom; NSW = New South Wales; CDC = Centers for Disease Control and Prevention.

**Table A.2B** Published and evaluated active case finding initiatives among prisoners in low-incidence countries

Author	Year	Title	Setting	Intervention	Tools	Study design and organisation	Effectiveness
Aerts et al. <sup>83</sup>	2006	TB and TB control in European prisons	Survey of TB screening in prisons of 52 countries in WHO European Region	On-reception screening in prison	Variable, CXR and sputum most common	91% of the responding countries (n = 22) performed ACF for TB on entry into prison	Median yield was 395/100000 (range 42–2362 cases)
Bellin et al. <sup>84</sup>	1993	Abnormal CXRs in intravenous drug users: implications for TB screening programmes	Urban jail, USA	1314 persons admitted to an opiate detoxification unit in an urban jail were screened	CXR, TST	Cross-sectional study	73 (5.6%) had TB-related abnormalities on CXR
Brock et al. <sup>85</sup>	1998	TB case detection in a state prison system	Reception screening in Georgia prisons, USA	ACF and LTBI screening in federal prisons and jails in Georgia, USA	TST, CXR, SQ	Application of CDC guidance to reception screening in prison; retrospective case review to assess compliance	142 TB cases between 1993 and 1998. 74% of cases detected through prison reception screening; 38% lost to follow-up among those released while on treatment.
Martin et al. <sup>86</sup>	1994	Case finding of PTB on admission to a penitentiary centre	One prison in Barcelona, Spain	TB screening was offered to all admissions to the penitentiary (N = 804) between October 1989 and June 1990	TST, CXR, sputum	On-reception screening	PTB was found in 19/702 prisoners who completed screening.
Martin-Sanchez et al. <sup>87</sup>	1995	Predictive factors of <i>Mycobacterium tuberculosis</i> infection and PTB in prisoners	Leon Penitentiary Centre, Spain	Organised TB screening (LTBI and ACF) programme for inmate population as prevalence study	TST, CXR, sputum	One-off research study	PTB prevalence 1.26%; LTBI 55.5% (95%CI 52.5–58.5); HIV-TB co-infection rate 9.2%
Puisis et al. <sup>88</sup>	1996	CXR screening for TB in a large urban county jail	Cook County Jail, Chicago, IL, USA	On-reception CXR screening, evaluation of this new intervention (previously TST with diagnostics)	CXR	Centrally organised screening on reception	PTB in 86/126 608 inmates (67 through CXR screening and 19 from diagnostic work-up). CXR screening (compared to previous TST follow-up) reduced mean time from prison admission to isolation from 17.6 to 2.3 days.
Rutz et al. <sup>89</sup>	2008	TB control in a large urban jail: discordance between policy and reality	Large prison in Baltimore, MD, USA	Audit of CDC guidelines to perform SQ and proceed to TST and CXR as appropriate	SQ, TST, CXR	Centrally organised, systematically applied symptom screening at prison reception	1 PTB case in 11 576 detainees; 344 had (3%) LTBI
Saunders et al. <sup>21</sup>	2001	TB screening in the federal prison system: an opportunity to treat and prevent TB in foreign-born populations	A federal prison in San Diego, CA, USA	Offering CXR, TST and SQ to all new receptions in San Diego prisons between July and December 1998	CXR, TST, SQ	Centrally organised on-reception screening (LTBI and ACF) in prison	8/1830 treated for PTB (when CXR universal), 8 others in 6 months before this (CXR follows TST/SQ). CXR screening reduced exposure time to active TB cases by 75%, but TB incidence remained the same.
Schneider et al. <sup>90</sup>	2007	TB control among people in US Immigration and Customs Enforcement custody	US Immigration and Customs Enforcement Centres, USA	Retrospective review of reception screening/ case finding	TST and CXR, four facilities have designated X-ray screening facilities	TB screening on reception	76 TB cases in 2004, 142 TB cases in 2005, incidence rates 83 and 122/100000 for these years. 58% were sputum-positive, 32% were smear-positive, 17% had symptoms on diagnosis. Most patients were deported before completion of treatment.

TB = tuberculosis; WHO = World Health Organization; CXR = chest X-ray; ACF = active case finding; USA = United States of America; TST = tuberculin skin test; SQ = symptom questionnaire; LTBI = latent tuberculosis infection; PTB = pulmonary tuberculosis; HIV = human immunodeficiency virus; CDC = Centers for Disease Control and Prevention.

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**R É S U M É**

Dans les pays à faible incidence, la tuberculose (TB) est largement concentrée dans des groupes de population à risque, tels que les migrants, les personnes sans domicile fixe, les usagers de drogues illicites, et les personnes alcool-dépendantes ou en prison. Cette situation a conduit à des efforts accrus pour mettre en place des dépistages actifs de cas de TB ciblés dans des populations spécifiques. Cette étude analyse les arguments scientifiques justifiant le dépistage actif chez les migrants et dans les groupes de population socialement à risque, ainsi que le rapport coût-efficacité des interventions.

Bien que les données provenant d'études d'observations soient en faveur de la recherche active de cas dans des groupes définis comme à haut risque, des études complémentaires sont nécessaires pour déterminer l'efficacité des outils spécifiques et le rapport coût-efficacité des stratégies de dépistage afin que les mesures de maîtrise de la TB des pays à faible incidence s'appuient sur des preuves scientifiques. La TB dans les pays à faible incidence dépendra inévitablement d'une maîtrise efficace de la maladie dans les pays à forte incidence.

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**R E S U M E N**

Hoy en día, en los países con baja incidencia, la tuberculosis (TB) se concentra en los grupos con alto riesgo de contraer la enfermedad como son los inmigrantes, las personas sin domicilio, los consumidores de drogas, los alcohólicos y la población de las prisiones. Esta situación ha dado lugar a una intensificación en la ejecución de las medidas de búsqueda activa de casos en poblaciones específicas. En el presente estudio se examinan los datos sobre la búsqueda activa de casos en las personas inmigrantes y en los grupos sociales de riesgo, además de la rentabilidad de las intervenciones. Los datos de los estudios observacionales respaldan la búsqueda de casos

en los grupos específicos con alto riesgo de contraer la TB, pero se precisan nuevas investigaciones que determinen la eficacia de los instrumentos específicos de esta búsqueda y la rentabilidad de las estrategias de detección sistemática, con el propósito de documentar la elaboración de métodos de control basados en datos científicos y destinados a los países con baja incidencia. Es inevitable que la respuesta al problema de la TB en los países con baja incidencia dependerá de un control eficaz de la enfermedad en los países que presentan una alta carga de morbilidad.

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