Effectiveness and cost-effectiveness of screening migrants for active and latent tuberculosis

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Effectiveness and cost-effectiveness of screening migrants for active tuberculosis and latent tuberculosis infection: a narrative review of the evidence)

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Abstract

With the advent of the WHO End-TB strategy there has been a renewed interest in screening for active tuberculosis (TB) and particularly latent TB infection (LTBI). In low incidence countries a high proportion of TB cases are notified amongst migrants, which often occurs due to LTBI reactivation. We aimed to review the effectiveness and cost-effectiveness of active and latent TB screening of migrants to inform and support the TB elimination strategy in low incidence countries. We carried out a narrative review of English language papers, published between 1 January 2000 and 31 June 2016 using PubMed. All studies which described effectiveness or cost-effectiveness of active or latent TB screening amongst migrants were included. We identified 55 studies and included 40 for the effectiveness of screening, 11 for cost effectiveness and 4, which reported both. Screening for active TB can be effective and cost effective depending on the setting, target group, and screening approach. Pre-entry screening programmes have some impact on receiving countries' epidemiology. The effectiveness and cost-effectiveness of LTBI screening as predicted in mathematical models is also highly setting specific with best potential results achieved if screening is restricted to high risk groups and/ or to migrants from high-burden countries.

Introduction

Tuberculosis (TB) is a significant contributor to the global burden of disease(1). In 2015 the World Health Organization (WHO) estimated about 10.4 million new cases of TB and 1.4 million TB deaths (2). Despite an incidence decline of 1.5% between 2014-2015, TB remains an important cause of death globally(2). The End TB Strategy, ratified in 2014, sets out ambitious targets for global TB control including a 90% reduction in TB incidence and a 95% reduction in TB deaths globally by 2035(3). The strategy is based on three pillars: the first (integrated patient-centred care and prevention) outlines the importance of active case finding as a way to increase early TB diagnosis, and introduces for the first time screening for latent TB infection (LTBI) and preventative therapy among high-risk population groups as a key intervention.

The shift in migration patterns over the past 100 years has resulted in movement predominantly from countries with a high-burden of TB to low-burden countries, thus significantly impacting the TB epidemiology in low burden countries. Within these low burden, high migration countries a high proportion of new TB cases are now notified amongst the non-native population, and many of these cases arise after arrival in the host country, predominantly as a result of reactivation of LTBI(4,5). Screening for TB can be divided into active case-finding of active disease or testing for LTBI, both of which are distinct from routine passive case-finding of active disease. Screening programmes for active TB have been used throughout most of this century and the last, although their focus and target populations have changed(6). In addition, and in keeping with the ambitious aim of TB elimination in low incidence countries, there has been an increasing interest in LTBI screening which has been included in national strategies(7,8).

The aim of this paper is to provide a review of the effectiveness and cost-effectiveness of screening for active TB and LTBI of migrants. The findings will inform public health policy going forward: improving TB control and working towards TB elimination in low incidence countries.

Methodology

We reviewed the literature for studies on the effectiveness and cost-effectiveness of screening for active TB and LTBI. The search terms are included in the appendix. Studies on effectiveness included those looking at yield, coverage and impact (e.g. incidence prevented)(9) as well as uptake and treatment completion. Cost effectiveness studies included cost benefit, cost utility and cost effectiveness studies. English language papers indexed on PubMed and published between 1 January 2000 and 31 June 2016 were included in the search. In addition we hand-searched important review articles, guidelines and conference proceedings and added papers identified by experts in the field.

We pre-specified the following study types for inclusion: experimental studies (randomised controlled trials and quasi-randomised controlled trials); observational studies (retrospective and prospective cohort studies, case-control studies cross-sectional and case series); economic modelling studies and meta-analyses. Articles were included if they contained information on effectiveness or cost effectiveness of LTBI or active TB screening in migrants, defined as anyone who resides outside their country of birth, including refugees, asylum seekers and undocumented migrants.

Initial search results were imported into Zotero, then extracted into Excel (Microsoft Office for Mac 2011) and duplicates identified. The titles of the remaining articles were screened by HH for

eligibility. The full text of those that fit the inclusion criteria were read and a final list of articles was identified by HH and reviewed by DZ. A total of 55 studies were identified with 40 appropriate for the effectiveness of LTBI and active TB screening, 11 appropriate for cost effectiveness of LTBI and active TB screening and 4 which reported both cost effectiveness and effectiveness of LTBI and active TB screening (figure 1).

A limited assessment of study quality and risk of bias was made using SIGN methodology(10). Data was extracted from papers on effectiveness of screening using the format detailed in table 1 and on cost-effectiveness of screening as detailed in table 2. Data were summarised as simple proportions and ranges – the variability of studies and study heterogeneity precluded meta-analysis of our data.

Active TB

Screening for active TB has been common practice since the early and mid part of the 20th century. Most of these activities have been aimed at detecting pulmonary TB, often across whole populations and mostly using Chest X-Rays (CXRs), supplemented by a symptom check (6). As early as in 1974, the WHO's Expert Committee on Tuberculosis recommended that indiscriminate TB case-finding by mobile mass radiography should be abandoned (11) due to reduced effectiveness and cost effectiveness, a consequence of changing TB incidence and altering epidemiology (12) (6). However, new guidelines on screening for active TB were developed in 2013 based on the evidence that screening, if done in the right way and targeting the right people, may reduce suffering and death(9). Although in the context of low and middle income countries the guidelines did not issue recommendations on screening migrants, it suggested that countries with a low burden of TB and an epidemic that is concentrated among specific risk groups – such as certain ethnic groups, prisoners, or homeless people – should focus their care and prevention efforts on these groups, and specifically mentioned migrants from high incidence countries as a priority group(13). This is supported by data from national experience for identified high risk groups, such as homeless persons (14) or migrants from high incidence countries (15).

Screening practices of migrants are highly variable in respect of policy, target population, the setting for screening and the type of tests used (16)(17). A number of factors influence the effectiveness and cost effectiveness of screening programmes including screening individuals from higher burden countries (18), use of screening methods with higher sensitivity and specificity (19) and the setting of screening (20).

Effectiveness of active TB screening

Most active TB screening programmes are primarily aimed at the detection of pulmonary TB, often with CXRs as the initial screening tool, sometimes augmented with or preceded by a symptom screen (16). A diagnostic test with high specificity, such as sputum culture should be used as follow-up to reduce the number of false positive results (21). Sputum smear has a low sensitivity and should not be the confirmatory test, although it is sometimes used(20). Clinically based diagnosis should only apply after all bacteriological testing has been exhausted.

Studies evaluating the properties and predictive values of different screening tests and algorithms suggest that initial screening with CXR followed by a highly specific confirmatory tests, such as the Gene Xpert or (if feasible), mycobacterial culture, have the highest predictive value and lowest numbers needed to screen (NNS) to detect active pulmonary TB (19). Clinical symptoms (such as prolonged cough) can be either used alone, in parallel with CXR or as an initial screen to identify those requiring CXR. Test properties vary with the background prevalence, sensitivities are between 65 and 90% for standardised combined symptom enquiry (ideally using scoring systems) with low specificity (30-68%)(22,23). Initial symptom screens may be cheaper but have lower positive predictive values (PPV) and higher NNS than CXR-based programmes (24).

Sputum smear microscopy, although widely available, is limited by its relatively poor sensitivity and can lead to a high proportion of false negative results(25). Van't Hoog et al, when comparing screening algorithms highlight that both the NNS and predictive values are highly dependent on the TB prevalence in the screening setting, emphasising that choice of screening method should reflect the country demographic and epidemiology (20). Despite CXRs being

used as a key method for screening, there is little clinical trial data to inform evidence based policy decisions.

Screening programmes can be administered pre-entry, on-entry or post-entry. Alvarez et al surveyed screening practices in high migration, low incident countries in 2008 and found that on-entry screening was undertaken by Norway, Switzerland and the UK (out of a total of 13) and often aimed at migrant sub-populations – for example limiting screening to migrants from countries with higher estimated TB incidence, or to high risk populations, such as refugees or asylum seekers (16). Some countries utilise post-arrival screening programmes, for example as a required component of access to specific services, in holding centres (26) or as follow up to pre-entry screening(27), and these are often limited to specific high risk target populations or settings(17). Pre-entry screening programmes are now used by a number of countries. In these programmes, screening is often mandatory, for example as part of the visa approval process(28)(29). Pre-entry screening can be carried out for recognised refugees often in neighbouring countries, but are usually not feasible for those who apply for asylum on arrival in the host country(28,30).

The coverage of active screening programmes varies, depending on the type of programme, the target group, and importantly, whether it is a voluntary or mandatory programme. Unsurprisingly, mandatory pre-entry screening programmes have the highest coverage, usually approaching 100%(15). In programmes where screening is part of a prescribed procedure such as in migration reception centres, uptake is also very high (31–33). Interestingly Klinkenberg et al, after reviewing screening practices in EU/EEA countries (on-entry and post entry only), reported that the high coverage in mandatory programmes did not necessarily correlate with

higher yields of TB identified (TB yield of 0.28% compared to 0.40% in voluntary screening) (15). Erkens et al reported on the Dutch experience of biannual screening post entry, demonstrating that coverage decreased from 59% in the second to 34% in the fifth round of successive screenings(34).

For screening programmes to be effective it is important to ensure that those who screen positive are linked into treatment, either in the national treatment programme overseas or domestically. There have been well documented difficulties with this for on-entry screening programmes(35,36). It is possible that pre-entry screening strategies have some advantages if they are well linked into national treatment programmes(28).

Due to the significant heterogeneity of TB case definitions in different papers, the yield of active TB screening is difficult to assess and varies by target group/ country, type of migrant and setting of the programme (table 1). For bacteriologically confirmed TB, yields vary between 70 and approximately 1,600 per 100,000 (table 1). There is some evidence that pre-entry programmes have higher yields than on-entry and post entry programmes, although this review only included three countries with pre-entry screening. (15). Aldridge et al in their meta analysis of pre-entry screening programmes report higher yields amongst migrants from countries with a higher incidence of TB (18). Arshad et al also found higher yields among migrants from Africa or Asia compared to European migrants (three times and two times higher respectively (37).

Migrants are a heterogeneous group of individuals and the type of migrants screened also influences the yields of TB identified in screening programmes. For example Arshad et al identified a four times higher yield of TB cases among refugees compared to other migrants(37).

The authors provided a number of potential explanations including the fact that refugees (where migration is forced) are less affected by the 'healthy migrant effect' than other groups of migrants. Other factors such as individual risk factors, such as previous contact to TB cases or a longer and more hazardous migration route or the quality of the screening programme can also influence the effectiveness of identifying TB cases through programmatic screening (38,39).

There is a scarcity of evidence evaluating the impact of active TB screening on domestic TB incidence rates. A number of studies have compared screening yields with prevalent rates in migrants in the recipient country (21,25) . Liu et al reported that following the introduction of a culture based pre-entry screening programme there was a 40% decrease in the number of TB cases among migrants in the USA within 1 year of arrival (21). The UK reported a similar trend, demonstrating decreasing numbers of prevalent pulmonary TB cases as numbers of pulmonary TB cases found overseas increase(25,38). Since these CXR-based programmes only detect pulmonary cases, their relative impact relates to the epidemiology in the recipient country. In the UK, where almost three quarters (73%) of cases occur amongst the non UK-born population and where the majority of cases are extra-pulmonary, domestically notified cases were reduced by 6% through pre-entry screening, although almost all prevalent pulmonary cases had been detected(25). Some studies modelled the number of TB cases averted following implementation of pre entry screening programmes. Dasgupta et al identified that pre-entry screening in Canada was more successful at reducing domestic TB case notifications within one year of arrival compared to post-entry surveillance of migrants with latent TB (40). Wingate et al. reported even higher numbers of TB cases averted in their model, 157 cases annually, through pre-entry screening among students from China and India studying in the USA (41). Most cross-

sectional studies analysing on-entry screening for migrant sub-populations are relatively small-scale, focus on the target population and do not analyse the impact on incidence (table 1).

Cost Effectiveness of active TB screening programmes

Evidence on cost effectiveness for active TB screening initiatives is also surprisingly limited. We have not found any studies, which calculate costs per quality adjusted life years (QALYs) for these active screening programmes. Most evidence comes from mathematical modelling studies, where active case finding is either presented as part of a more complex intervention (e.g. an LTBI screening programme with point-prevalent cases) (42) or is setting specific (e.g. to inform a potential expansion of USA pre-entry screening to Indian and Chinese students)(41). Furthermore, the generalisability of such findings may be limited. The outcome of interest is also heterogeneous – ranging from a simple cost analysis (43)to the cost per number of detected cases(41). The findings are often very context specific and cost effectiveness is estimated from a health system perspective. This is particularly relevant for programmes where part or all of the costs are borne by the screening recipient – as is common practice in pre-entry screening. Within this limited literature a number of studies found that screening for active TB was cost-effective or even cost-saving from a recipient country perspective (table 2) in a range of different settings although more research is evidently required on this topic.

Latent TB infection

LTBI screening is aimed at detecting individuals who are asymptomatic but have a risk of progression to active TB in the near or remote future. Although there is a wide variation of settings and policies around LTBI screening and treatment for migrants, usually programmes are voluntary for participants whilst complex ethical considerations of mandatory screening are of

concern(44). The observed effectiveness and estimated cost-effectiveness of LTBI screening not only depends on test and treatment specific variables, model assumptions and economic perspective but also behaviour-specific variables, such as test and treatment uptake and treatment completion (figure 2)(45).

Most authors recognise the importance of tackling LTBI in order to improve TB control. In a number of low incidence countries, including in Europe, a large proportion of TB occurs among migrant populations, often a considerable time after entry to the country(4). This observation together with the fact that molecular clustering among migrants is relatively low(46)is often seen as evidence of the importance of LTBI reactivation to explain these foreign born cases.

Effectiveness of LTBI screening

Diagnostic accuracy of LTBI tests

It is not possible to directly measure latent TB infection. The three currently commercially available tests - tuberculin skin test (TST) and two interferon gamma release assays (IGRA), QunatiFERON and T-SPOT.TB - test a human immune response to Mycobacterial antigens. The TST is applied through an intradermal injection of 0.1ml purified protein derivative tuberculin and the size of the potential induration is read 48-72 hours later. Both IGRA tests are based on detecting the release of the cytokine Interferon Gamma (IFN-γ), which is produced in response to *M. tuberculosis* complex specific antigens, the early secretory antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10). QantiFERON is an enzyme-linked immunosorbent assay (ELISA) test, T-SPOT.TB an immunospot assay. A number of studies have explored the test

properties, usually against the gold standard of active TB and the test agreement (kappa). The sensitivity of these three tests is comparable (76-90%), but the specificity of IGRA tests tends to be higher than TST (93-95% vs. 57%), due to the absence of cross-reactivity with environmental mycobacteria and BCG(47).

Whilst there is an abundant literature on sensitivity and specificity, the more important test property is the progression rate– the likelihood that a person with a positive test will go on to develop active TB, from the individual perspective, and the number need to treat to prevent one TB case (NNT) from the public health system perspective. Large cohort studies with sufficient follow up time are needed to answer this question. A number of systematic reviews have estimated progression rates: Rangaka et al found progression rates between 0.4-4.8 per 100 person years in IGRA positive individuals(48); Diel et al estimated a pooled progression rate of 2.7% (95% CI, 2.3%–3.2%) and 1.5% (95% CI, 1.2%–1.7%) for IGRAs and TST respectively(49). In another meta-analysis Diel et al found progression rates between 8-15% and 2-3% over 19-24 months for IGRAs and TST respectively(50). However, all of these reviews are based on a mixture of studies in different groups, often largely contacts of active cases. They also report on a mixture of settings, such as high and low incidence countries, which may partly explain differing results.

Review-level evidence examining LTBI progression rates in migrant populations is scarce. A systematic review of Campbell et al(51) included three studies on progression rates in migrants from high to low incidence countries: MacIntyre et al(52) reports five incident cases in a cohort of 437 TST positive, treatment naïve, Australia-bound refugees (1.1%) over 5 years; Truong et al (53)found 9 cases in a cohort of 191 US-bound Tibetans (4.7%) followed up over a mean of 19

months; and Harstad(54) reported 8 cases amongst 236 Quantiferon positive, treatment naïve asylum seekers in Norway (3.4%) followed up over 23-32 months. A cohort study reported up to 15.6% reactivation rate over 15 years(55) in a TST positive treatment naïve South Asian population in England.

Robust evidence on reactivation rates, based on well-designed and large cohort studies, is required. However, it is fair to conclude that the PPV for all commercially available tests for LBTI is relatively low (about 1-15%) in any at-risk population, including migrants, demonstrating the need to target programmes in order to optimise effectiveness and cost-effectiveness. Whilst efforts to limit screening to migrants from high incidence countries are common(56), a recent large cohort study identified other important risk factors of becoming an incident case, alongside increasing incidence in the country of origin, such as chest-X-Ray abnormalities (without active TB) and visa type(57). Operationalising these findings may help to improve the relatively low predictive value of LTBI tests and reduce the numbers needed to screen.

Treatment regimens

There have been a number of systematic reviews on the effectiveness of LTBI treatment. Currently used regimens include a 6-9 months monotherapy of isoniazid, a 3 months combination therapy of isoniazid and rifampicin and a 3-4 months monotherapy of rifampicin. All of these have good efficacy in trials. Smieja et al estimated a reduction of the relative risk (RR) for developing active TB in non-HIV infected persons treated with 6 months isoniazid as RR 0.40, (95% CI 0.31 to 0.52)(58). More recently this has been confirmed by Stagg et al (OR 0.64, CI 0.48-0.83)(59). Two further systematic reviews have recently emphasised the benefits of

rifamycin-containing regimens. Sharma et al found an equivalent efficacy to prevent TB events between a 3-4 months rifampicin (3-4R), either as monotherapy or in combination with isoniazid, compared with 6 months isoniazid monotherapy. Sharma et al also identified significantly fewer hepatotoxicity events (RR 0.12, 95% CI 0.05 to 0.30) and better treatment adherence for 3-4R monotherapy(60). Stagg et al confirmed these findings both in conventional and Bayesian network meta-analysis. The authors reported rifamycin containing regimes ranked amongst the most efficacious and least toxic of all (TB prevention for 3-4R compared with placebo had an OR of 0.41, CI 0.18 to 0.86)(59). Superior treatment adherence, inferior hepatotoxicity risk, and equivalent efficacy have been reported using once-weekly rifapentine regimens(61), and this regimen is recommended by the WHO. However, it is not licensed in Europe and in most other countries outside the US yet, a very relevant current barrier to more widespread use. It can be concluded that highly efficacious LTBI treatment regimens are available, although barriers to completion include the length and pill burden of treatments, adverse drug reactions, and the high mobility of migrants that correlates with a higher risk of defaulting from treatment.

The screening care cascade

For LTBI screening to be effective and cost-effective high rates of screening uptake and then subsequent completion of treatment are essential. A number of systematic reviews have recently explored behavioural, structural and programmatic aspects in detail. A systematic review by Alsdurf et al identified significant losses to follow up on every step of the care cascade – from screening uptake to treatment completion(62). In their meta-analysis the researchers analysed 70 independent cohorts, of which 12 were constituted by migrants, and found a testing uptake of 71.9% (95% CI 71.8–72.0) and a treatment completion rate of 18.8% (CI 16·3–

19·7). However, it is worth noting that this review contained a highly diverse range of contexts in low, middle and high-income countries, addressing different target populations, type of programmes and even tests used. Nevertheless, the main message is clear –getting persons with LTBI tested and treated remains a challenge. In their recent systematic review, Sandgren et al reported LTBI initiation rates among migrant populations ranging between 23-97% (n=4 studies) and a range of 7-86% LTBI treatment completion rate (n=5 studies)(63). The authors considered the data too heterogeneous to present a pooled analysis but found higher completion rates associated with shorter regimens, a finding which is corroborated elsewhere in the literature (61,64). A systematic review by Stuurman et al (n=23 studies) showed that shorter treatment regimens and directly observed therapy correlated with treatment completion. Amongst migrant sub-populations (n=3 studies) there was a generally positive effect of social interventions (such as education, adherence coaching, peer counselling, or cultural interventions), particularly if combined with the use of shorter regimens(65).

Impact on host country epidemiology

How effective LTBI screening will be and the magnitude of impact on the respective country epidemiology will depend on how well LTBI screening and treatment can be targeted and how well the programme can be operationalized, including ensuring high uptake and completion of treatment. There are no empiric studies which directly compare the effectiveness of an LTBI screening and treatment intervention with no screening, any estimation of impact must therefore be indirect. A number of mathematical modelling studies have looked at this question(66), however it is worth noting that parameterisation of these models is often based on observational studies of differing quality.

A number of modelling studies have explored the effect of LTBI screening on the respective country incidence and often report a large impact compared with other interventions. Hill et al modelled the effect of different TB control interventions on TB incidence in the USA projecting over the next 50 years and concluded that “targeted testing and treatment of LTBI will be necessary (…) to achieve levels close to elimination in an acceptable timeframe”(66). In the context of achieving the WHO End TB strategy goals, Houben et al have modelled a number of different interventions in South Africa, China and India and demonstrated that in countries such as China with a good TB programme performance and a relatively small epidemiological contribution of transmission to TB incidence, addressing LTBI systematically is key to further significant incidence reductions and achieving interim targets by 2025(67). Dye et al analysed the prospects of TB elimination by 2050 in four country scenarios – South Africa, China, India and the United States. Notwithstanding the importance and transmission reduction in high incidence settings, the authors also conclude that in HIV low prevalence settings “preventive therapy for infected people” will have to supplement efforts, outlining the practical challenges, and potential solutions in better biomarkers and shorter therapy regimens(68) .

There are only few country-specific studies, which directly quantify the expected impact of LTBI screening. Varughese et al estimate an 18.5% TB incidence reduction in Canada, if new migrants from countries of an incidence above 50 per 100,000 were screened and treated for LTBI(69). For Australia, Denholm et al estimated that an effective combination of LTBI screening and treatment would reduce incidence by about one third to half by 2050 with higher sensitivity tests and shorter treatment regimens leading to greater benefits. The numbers needed to screen varied by target population, screening test and treatment regimen between 136 and 427 per TB case prevented(70).

Cost Effectiveness of LTBI screening

A number of studies have explored the cost effectiveness of LTBI screening, although none included the programmatic aspects (such as uptake) to a full extent. Whilst costs and gains of the programmes are context specific and dependent on the test used, the economic perspective, the target population, programme and treatment costs, most modelling studies have demonstrated cost effectiveness for example amongst migrant children in Canada(71) or among adults in the USA(63,64). Cost-effectiveness is most commonly expressed as cost per case prevented, not cost per QALY. What is acceptable for a healthcare system varies – in the USA less than $100,000 per QALY is acceptable, whereas in the UK the threshold is £30,000. These preferences will also determine whether an intervention is deemed cost-effective or not.

A number of modelling studies outline the importance of a targeted approach for screening migrants. Oxlade et al found that TST-based screening is only cost-effective in high-risk populations, with high reactivation rates (1.2-5%) (74). Pareek and colleagues modelled cost-effectiveness of screening in migrants for different incidence threshold and found that screening to an incidence threshold of 150 per 100,000 in the country of origin would allow detection of 92% of LTBI positives at a cost of £20,818 per case prevented (cost effective in the UK). Wingate et al examine the cost-effectiveness of pre-entry screening for LTBI and found this highly cost effective when targeting US-bound migrants from moderate to high incidence countries(41).

A few systematic reviews have summarised the cost-effectiveness evidence. Auguste et al included 10 cost-effectiveness studies in total (2 amongst migrants) in their review and found that among recent migrants TST alone was the most cost-effective strategy (incremental cost

effectiveness ratio, ICER £1,524 per QALY)(75). The key finding of the cost-effectiveness of TST-based migrant screening has been corroborated elsewhere (76). This has to be balanced against potential overdiagnosis/overtreatment (due to the reduced specificity) and feasibility in programmatic screening and the practicalities including the need to return for reading. Nienhaus and colleagues reviewed 5 cost studies and 8 cost effectiveness studies and concluded that whilst the unit price of IGRA may be higher, this is offset by the reduced costs for investigation (including CXRs) and treatment in positive individuals (77). In another scoping review of economic evaluations on LTBI screening strategies for migrants, Zammarchi and colleagues identified nine studies, and concluded that LTBI screening was cost-effective according to seven of them. Two studies found that LTBI screening is cost-effective only if carried out in immigrants who are contacts of active TB cases. Findings of four studies support interferon gamma release assay as the most cost-effective test for LTBI screening in migrants(78). A recent systematic review of methods used for economic modelling concluded that methodological limitations and heterogeneity make comparisons and generalizations difficult(45).

Strengths and limitations

We present a narrative review. Differing from systematic reviews, our objectives and eligibility criteria were kept necessarily wide in order to provide a broad and informed overview of a complex area(79). We therefore included a range of populations, interventions, comparisons, outcomes and study designs allowing us to identify gaps for future research and inform the design of subsequent, more targeted systematic reviews on this topic. Our review was carried out systematically, but was limited to Medline-indexed English language papers, published in

the past 15 years. We also provided a limited assessment about study quality and risk of bias, using an appropriate tool(10).

A key limitation to this paper is that rather than comprehensively describing which interventions provide the most effective and cost-effective methods of screening migrants for active and latent TB, we highlight key areas, which require further exploration using well-described systematic review methodology. Another key limitation is the quality of the underlying studies. There is significant variation in the type and size of study, the setting and their methodology, ranging from systematic reviews to small single setting observational studies. The overall poor quality of many underlying studies, as well as the limitations of the narrative nature of this review means that conclusions should be drawn with caution.

Conclusions

In conclusion, despite the above limitations it is likely that both screening for active and latent TB can be effective and cost effective if highly targeted and well implemented. There are a number of trade-offs and policy choices for all types of screening. Particularly in LTBI screening the behavioural factors may influence effectiveness and cost-effectiveness to a great extent and should be considered. An important example is the consideration of IGRAs for LTBI testing which, despite higher unit costs, could be more effective and cost-effective operationally and therefore lead to higher impact on the host countries' epidemiology. More evidence is needed, and improved monitoring and evaluation systems for LTBI may help to obtain appropriate data. There is an urgent need for high quality, operational research to use such data to evaluate

effectiveness and cost effectiveness of the existing programmes in a more standardised way and inform future direction of screening and treatment approaches and there is also a need for systematic reviews to explore specific questions outlined here in further detail.

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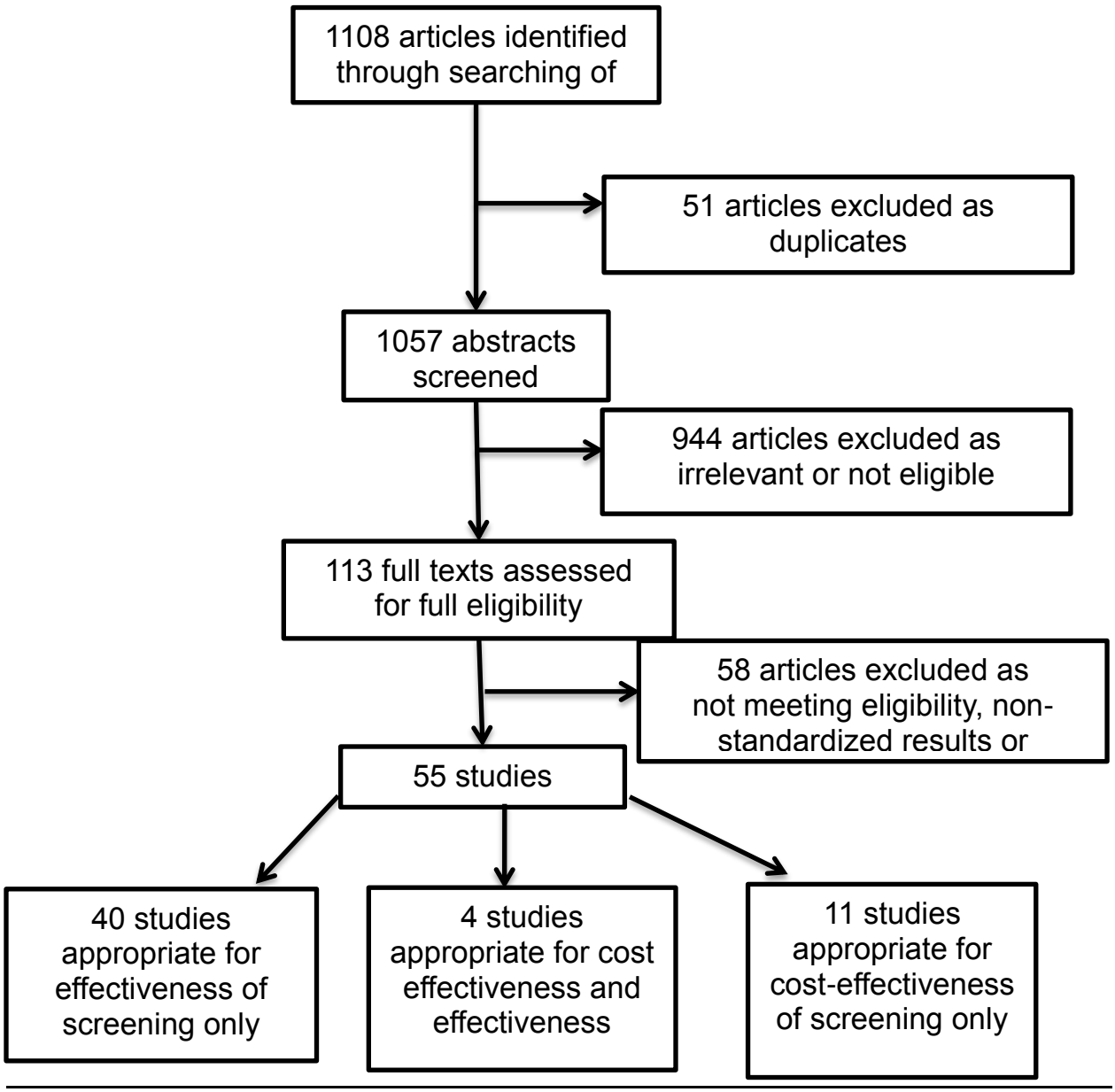

Figure 1 – inclusion of studies

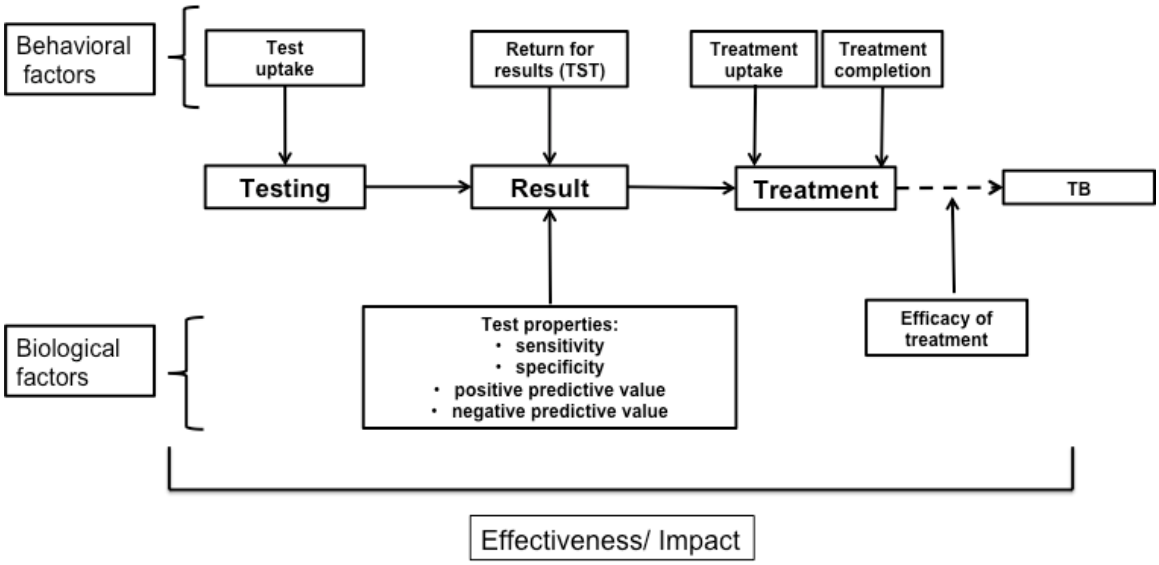

Figure 2 – conceptual model for LTBI screening

appendix – search terms

The database was searched using the following search phrases:

" Tuberculosis AND (screening OR mass screening OR prevalence OR yield OR incidence) AND (migrants OR new arrivals OR refugees OR asylum seekers OR immigrants) "

and

" Tuberculosis AND (screening OR mass screening OR prevalence OR yield OR incidence) AND (cost-effect* OR cost-bene* OR "Cost- Benefit Analysis) AND (migrants OR new arrivals OR refugees OR asylum seekers OR immigrants)"

Author	Year	Study design	Screening setting	Host country of new migrants	Type of migrant	Active (pulmonary unless stated otherwise) or Latent	Primary screening method	*Yield*	Total population size/sample size (Coverage)	SIGN score (+/++)
Campbell et al (51)	2015	Meta-Analysis	Post entry	Multiple	All migrants	Latent	TST *or* IGRA	40.7% (1232/3028) 32.2% (974/3028)	Unknown	+
Arshad et al (37)	2010	Meta-Analysis	On entry	Multiple	All migrants	Active	CXR and sputum smear and culture	0.035 per 100,000	Unknown	++
Trauer and Krause (80)	2011	Prospective cohort study	Post entry	Australia	All refugees	Latent	TST	31.9% (146/458)	465 (98.5%)	+
Mulder et al (81)	2013	Prospective cohort study	Post entry	Netherlands	All migrants	Latent	TST	TST > 10mm: 42.6% (273/643) TST >15mm : 23.0% (145/643)	2569 (25.1%)	+
Pareek et al (82)	2013	Prospective cohort study	Post entry	UK	All symptomatic migrants. Asymptomatic migrants from countries with TB incidence >40 per 100,000	Latent	QFT-GIT *and* T-spot *and* TST	6.6% (38/229) 22.5% (36/160) 30.3% (53/175)	306 (75.5%)	++
Carvalho et al (83)	2005	Prospective cohort study	Post entry	Italy	Migrants from countries with TB incidence >50 per 100,000	Latent	TST	58.2% (124/213)	(1613) 13.2%	++
Meier et al (33)	2016	Prospective cohort study	Post entry	Germany	Asylum seekers	Active	Sputum culture	93 per 100,000 (11/11773)	11773 (100%)	+
Pareek et al (84)	2011	Prospective cohort study	Post entry	UK	All Migrants referred from on entry screening	Latent	IGRA	19.9% (245/1229)	1633 (75.3%)	++
Bodenmann et al (85)	2009	Prospective cohort study	Post entry	Switzerland	Undocumented migrants	Active and latent	*Active*: sputum smear and culture	1600 per 100,000 (2/125)	161 (77.6%)	+

						Latent: IGRA	19.2% (24/125)	161 (77.6%)	
Bua et al (86)	2006	Prospective cohort study	Post entry	Italy	Migrants from Sub Saharan Africa, Bangladesh or Pakistan	Latent	TST *and*	36.9% (40/149)	Unknown	+
							QFT-GIT	14.7% (16/109)	Unknown	
Lucas et al (87)	2010	Prospective cohort study	Post entry	USA	Refugee children from Africa or Burma	Latent	TST *or*	17.8% (54/304)	Unknown	+
							QFT-GIT *or*	9.8% (45/460)		
							T-spot	9.0% (38/420)		
Flynn et al (88)	2012	Retrospective cohort study	Post entry	Australia	All migrants	Active	CXR	420 per 100,000 (79/18801)	Unknown	+
Johnsen et al (89)	2005	Retrospective cohort study	On entry	Norway	Asylum seekers	Active including extra pulmonary	MMR scan	110 per 100,000 (22/19912)	23644 (84%)	+
Khan et al (90)	2015	Retrospective cohort study	Pre entry	Canada	All migrants	Active	Sputum culture	106 per 100,000 (380 /357085)	357085 (100%)	+
Liu et al (91)	2009	Retrospective cohort study	Pre entry	USA	All migrants	Active	*Active*: CXR and sputum smear	961 per 100,000 (26075/2714223)**	26075 (100%)	+
Mathez et al (92)	2007	Retrospective cohort study	Pre entry	Switzerland	All adult migrants	Active	Sputum smear and culture	556 per 100,000 (50/8995)	8995 (100%)	+

Brassard et al (71)	2006	Retrospective cohort study	Post entry	Canada	Migrant children	Latent	TST	21% (542/2525)	3710 (68%)	+
Chang et al (93)	2002	Retrospective cohort study	Post entry	USA	All migrant students	Latent	TST	16.4% (116/706)	(706)100%	+
Baussanno et al (94)	2013	Retrospective cohort study	Post entry	Italy	Socially marginalised migrants (at social care centres)	Active and latent	Sputum smear and culture	2719 per 100,000 (744/27,358)	Unknown	+
							TST	34.6% (9183/26554)	Unknown	
Minodier et al (95)	2010	Retrospective cohort study	Post entry	Canada	Migrant children	Latent	TST and CXR	22.7% (777/3401)	4375 (82.3%)	+
Levesque et al (96)	2004	Retrospective cohort study	Post entry	Canada	Asylum seekers	Latent	TST	21.6% (49/227)	582 (55.5%)	+
Li et al (97)	2010	Retrospective cohort study	Post entry	USA	All migrants	Latent	TST	39.5% (crude numbers not reported)	51637 (90.1%)	+
Mulder et al (98)	2012	Retrospective cohort study	Post entry	Australia	All migrants	Latent	QFT-GIT	24% (128/541)	Unknown	+
Harling et al (31)	2007	Retrospective cohort study	On-entry	UK	Asylum seekers	Active	Bacteriologically confirmed	70 per 100,000 (3/4275)	4563 (94%)	+
Lifson et al (99)	2002	Retrospective cohort study	Post entry	USA	All refugees	Active and Latent	*Latent*: TST	48.6% (1145/2545)	(3914) 65%	
							Active: CXR and sputum culture	0 per 100,000 (0/2545)		+
Desale et al (100)	2013	Retrospective cross sectional study	Post entry	USA	Hispanic migrants	Latent	TST	41.9% (164/391)	81.80%	+
Mor et al (101)	2008	Retrospective cohort study	Pre and post entry	Israel	Ethiopian migrants	Active	Sputum smear and culture	*Pre entry:* 324 per 100,000 person years	24051 (61%)	+

							Post entry: 267 per 100,000 person years	24051 (39%)	
Varkey et al (102)	2007	Retrospective cohort study	Post entry	USA	All refugees	Active (including extra pulmonary) and latent	*Active*: Drug records	800 per 100,000 (116/13,866)	13866 (100%)	+
							Latent: TST	50.7% (4990/9842)	13866 (70.9%)	
Harstad et al (54)	2010	Retrospective cohort study	On and post entry	Norway	Asylum seekers	Active including extra pulmonary	Abnormal CXR or TST	On entry: 671 per 100,000 (15/2237)	4643 (49%)	+
								Post entry: 581 per 100,000 (13/2237)	4643 (49%)	
Tafuri et al (103)	2011	Cross sectional study	Post entry	Italy	Asylum seekers	Active	TST	814 per 100,000 (8/982)	1007 (97.5%)	+
King et al (104)	2011	Cross sectional study	Pre entry	Australia	All migrants	Active	Sputum smear and culture	137 per 100,000 (519/378939)	378939 (100%)	++
Maloney et al (105)	2006	Cross sectional study	Pre entry	USA	Vietnamese migrants	Active	Sputum smear and culture	582 per 100,000 (183/14098)	14098 (100%)	++
Mor et al (103)	2012	Cross sectional study	Pre entry	Israel	Ethiopian migrants	Active	Sputum culture	305 per 100,000 (43/13379)	13379 (100%)	++
Plant et al (107)	2005	Cross sectional study	Pre entry	Australia	Vietnamese and Cambodian migrants	Active	Sputum smear and culture	598 per 100,000 (36/6018)	Unknown	+
Aldridge et al (108)	2016	Cross sectional study	Pre entry	UK	Migrants from countries with incidence >40 per 100,000	Active	Sputum smear and culture	92 per 100,000 (439/476455	692362 (68.6%)	++
Liu et al (21)	2015	Cross sectional study	Pre entry	USA	All migrants	Active	Sputum smear and culture	258 per 100,000 (4032/1561460)	1561406 (100%)	++

Alvarez et al (109)	2011	Cross-Sectional study*	Post, on and pre entry screening	Multiple	Varied	Active	Varied	(per 100,000) Canada:53.6 France 70; Jordan: 153 ; Netherlands 105; Switzerland 122	Unknown	++
Losi et al (110)	2011	Cross sectional study	Post entry	Italy	Migrant children	Active and latent	*Active*: Sputum smear and culture	600 per 100,000(4/621)	Unknown	+
							Latent: QFT-GIT and TST	*QFT-GIT:* 34.5% (80/232) *of which*		
								TST >10mm: 82.5% (50/80)		
								QFT-GIT negative and TST >10mm: 35.5% (54/152)		
Padovese et al (111)	2013	Cross sectional study	Post entry	Malta	All Migrants	Active and Latent	*Active:* IGRA	7661 per 100,000 (19/214)	500 (Estimated coverage:16.6%)	+
							Latent: TST	45.0% (225/500)		
Yanni et al (112)	2013	Cross sectional study	Pre entry	USA	Iraqi refugees	Active and latent	Any from: medical history, physical examination, CXR sputum smear and culture	*Active:* 7 per 100,000 (1/14077)	18990 (74.1%)	++
								Latent: 1.8% (251/13669)	18990 (72%)	
Winje et al (113)	2008	Cross sectional study	Post entry	Norway	Asylum seekers	Latent	TST *and*	50.4% (460/912)	2813 (33.7%)	+
							QFT-GIT	28.9% (264/912)		

Hladun et al (114)	2014	Cross sectional study	Post entry	Spain	Migrants from low and middle income countries	Active and latent	*Active*: CXR *Latent*: TST	5782 per 100,000 (17/294) 28.1% (87/309)	Unknown	+
Erkens et al (34)	2008	Retrospective cohort study	On entry and post entry follow up	The Netherlands	Migrants from non-western countries staying for >3 months. Excluding asylum seekers	Active	Active: CXR followed by bacteriology	On entry: 119 per 100,000 (81/ 68122) on entry Post entry 9, 37 and 97 per 100,000 for migrants from countries with incidence of <100, 100–200 and >200 per 100,000 respectively	On entry: not reported Post entry: 59% to 34% (2nd to 5th round)	++

Note: All sputum smear and culture tests were performed following an abnormal chest X-ray.
*Survey of immigration practices in 16 low incident high migration countries.
Notes for methodology: SIGN methodology indicates: ++ High quality/low bias, + Acceptable/low bias.
SIGN methodology states that retrospective cohort studies and single centre studies can receive no higher than + (acceptable/low bias) which explains the large number of acceptable retrospective cohort studies.
SIGN methodology does not provide a checklist for cross-sectional studies. Therefore the SIGN study was adapted for cross sectional studies using the cohort study checklist. Cross sectional studies could not score higher than + (acceptable/low bias).

Author	Year	Country	Active/Latent (pulmonary unless specified)	Type of Economic Evaluation	Data source	Perspective	Model Horizon Discount rate	Cost description	Population screened/ Screening method	Differential costs	ICER	TB cases averted or identified	SIGN score (++/+)
Brassard et al (71)	2006	Canada	Latent	CBA	Clinical trial	Health care payer	No	All labour costs (nurses, doctors) and material costs (e.g. swabs, educational booklets)	TST: Migrant children TST: Migrant children and if positive, contacts	Total savings: $242,432 Total savings: $328,722		25.6 36.1	++

Dasgupta et al (40)	2000	Canada	Active and Latent	CEA	Administrative databases	Health care payer	Markov 20 years	CXR, clinic visits, investigations, administration fees, doctor and pharmacist fees, drugs, hospitalisation		Incremental costs (cost if no programme-cost of programme) 1)Incremental costs (savings) for prevalent TB cases treated 2)Incremental costs (savings) for future TB disease prevented		++
									Pre entry, CXR	1) 21,091 2) $25,129	7.85	
									Post entry surveillance, TST	1) $40,879 2) $25,128	1.58	
									Close contact screening, TST:	1) ($-845) 2) ($-2,267)	3.21	
Hardy et al (115)	2010	UK	Latent	CEA	Clinical trial	Health care payer	No	Cost per case LTBI identified	Leeds protocol: QFT followed by CXR for migrants from countries >200 per 100,000	Cost per case identified: $116 Cost to screen one migrant: $43	Not reported	++
									NICE guidelines 2006*	Cost per case identified:$200 Cost to screen one migrant: $59		

Khan et al (72)	2002	USA	Latent	CEA & CUA	Databases	Societal	Markov lifetime 3%	Transportation, ambulatory care, interpreters, laboratory tests, medications, adverse drug reactions, hospitalisation and patient's time	Hypothetical cohort of adult migrants[†]: TST followed by Isoniazid TST followed by rifampin TST followed by rifampin and pyrazinamide	Total savings of $83-124 million per year.	Incremental cost per QALY gained: Savings of $1258-8189 or dominated depending on migrant country of origin. Dominated (all country of origin) Savings of $1756-73455 depending on migrant country of origin.	Total of 9000-10,000 cases averted	++
Linas et al (113)	2011	USA	Latent	CEA & CUA	Published literature	Health care payer	Markov lifetime 3%	Diagnostic, laboratory costs, CXR, labour costs, medication, direct observed therapy, hospitalisation, contact tracing	Recent adult migrant TST IGRA		Dominated $39,040	Not reported	++
Haukaas et al (117)	2016	Norway	Latent	CEA	Published literature, expert opinion,	Health care payer	Markov 10 years 4%	Hospitalisation, medication, pre-discharge meeting, laboratory	Hypothetical cohort of migrants from countries where incidence >35 per 100,000		Compared to no screening:	TB cases averted per 1,000 screens over 10 years:	+

					hospital accounts			tests	TST +IGRA	Dominated	2.7	
									IGRA only	$29,907	3.9	
									IGRA for migrants with risk factors (e.g. HIV)	$3,215	0.8	
Oxlade et al (118)	2007	Canada	Active and Latent	CEA	Published literature	Societal	Markov 20 years 3%	All government, health system costs and patients' out of pocket expenses. Does not include non TB-related deaths or disabilities	Hypothetical cohort of migrants	per case averted compared to no screening	Number of cases averted:	+
									CXR	$772-1.9million	0.5-4.3	
									TST	$120268-413,729	1.2-27.0	
									TST+QFT	Dominated	Not reported	
									QFT	$55,291-990,502	1.3-27.0	
Pareek et al (84)	2011	UK	Latent	CEA	Data from prospective	Health care payer	No	UK NICE guidelines	Migrants <35 years residing in the UK for <5 years	Per case averted	% of cases identified:	++

					cohort analysis				Questionnaire + QFT >150 cases of TB per 100,000	$27,777	92%	
									Questionnaire + QFT >250 cases of TB per 100,000	$24,939	24.4%	
Pareek et al (94)	2013	UK	Latent	CEA	Data from prospective cohort analysis	Health care payer	UK treasury and NICE guidelines : 3.5%	Treatment, diagnostic, contact tracing, out-patient care, hospitalisation	Variety of screening algorithms used at varying screening incidence thresholds	Most cost effective screening migrants from countries with incidence ≥ 150 per 100,000 with QFN-GIT and no on entry CXR: $39712/case avoided	7.8 cases of averted when screening migrants with QFT from countries with 150 per 100,000.	++
Porco et al (119)	2006	USA	Latent	CEA and CUA	Published literature and administrative	Health care payer	Markov 20 years 3%	Treatment, Direct observed therapy, hospitalisation, home	Hypothetical cohort of new migrants with smear negative TB		Number of cases averted	

					data bases			visits, diagnostics	Follow up of smear negative migrants	7.7 QALYs gained	US$ 5435 per QALY and $ 5805 per case averted	4	
La Marcus et al (120)	2015	USA	Latent	CEA	Published literature	Health care payer and government	Markov 20 years 3%	Overseas cost: direct observed therapy, treatment, diagnostics Domestic cost:	Refugees from countries categorized into low, moderate and high TB	Net cost (costs) of overseas screening over 20 years when refugees screening 1) frequently or 2) infrequently		Cases averted with overseas screening 1) frequent screening 2) infrequent screening	+
									TST, low incidence	1) ($570,000) 2) $5.6 million		1) 48 2)509	
									TST, moderate incidence	1) $1.7 million 2) $2.0 million		1) 185 2) 255	
									TST, high incidence	1) $5.0 million 2) ($922,000)		1) 48 2) 66	
Auguste et al (121)	2016	UK	Latent	CEA	Published literatu	Health care payer	Markov 100 years, 3.5%	Diagnostic tests, CXR, gastric	Recently arrived migrants:		ICER (per QALY gained)	Not reported	++

					re			lavage, sputum examination, treatment and side effects	TST (>5mm)		$1519 (vs QFN-GIT)	
									QFT-GIT		N/A	
									T-spot.TB		Dominated	
									TST (>5mm)+ QFN-GIT		$59,483 (vs TST >5mm only)	
Schwartzman and Menzies (122)	2000	Canada	Active	CBA	Hospital annual reports and health insurance	Government	Markov 20 year, 3%	Physician and personnel costs, diagnostics, treatment, hospitalisation	Hypothetical cohort of migrants		ICER (per case averted compared to no screening)	+
									CXR		High TB/HIV population: $4078	
											Low TB/HIB population: $244,612	
									TST		Compared to CXR:	
											High TB/HIV population: $33,723	
											Low TB/HIV population: Dominant	
Chang et al (93)	2002	USA	Latent	CBA	Data from retrospective	Not defined	No	Screening and medical follow up	Foreign born children:			+
									TST+ CXR	Net cost saving : $90 439.92	11 cases	

					cohort analysis							averted	
Wingate et al (41)	2015	USA	Active	CEA	Online databases	Societal	N/A (costs calculated for first year only)	Student opportunity costs, hospitalisation, treatment, diagnostics, lost tuition fees for universities, burden to insurers	Students from China, Germany or India. CXR followed by sputum smear and culture		ICER per case averted (USD) China $ 23,098 India: $**15,681**	Total: 157 cases averted	++

*NICE guidelines 2006 : CXR in all immigrants from countries with TB incidence>40 per 100,000 and >16 years, TST if <16 years or <35 years from Sub Saharan Africa or from countries >500 per 100,000. QTF –GIT in TST positive to confirm LTBI.
† _Hypothetical cohort >18 years old entering USA from China, Philippines, S. Korean Vietnam, Asia and Pacific India, S.Asia, Mexico, Haiti, Latin America and Caribbean
‡ _Risk groups include recent immigrant adults and children, foreign-born residents living in the U.S. for more than five years (stratified by age), close contact adults and children, HIV-infected individuals, the homeless, injection drug users, former prisoners, gastrectomy patients, underweight patients, and persons with silicosis, diabetes, and end-stage renal disease.

Abbreviations: CBA- Cost Benefit Analysis; CUA- Cost Utility Analysis; CEA-Cost Effectiveness Analysis, CXR- Chest X-Ray

Notes for methodology: SIGN methodology indicates: ++ High quality/low bias, + Acceptable/low bias.
All costings were first converted to 2017 prices taking into account inflation using http://fxtop.com/. Costings were then converted into US Dollar on 21/03/2017 using http://www.ukforex.co.uk/currency-converter.

Table 3

Number of studies and TB case yield ranges for different types of screening and settings.

	Active		**Latent**	
	Number of studies identified	Range (per 100,000)	Number of studies identified	Range (%)
Post entry	13	0-7661	23	9-82.5
Pre entry	11	7-961	1	1.8
On entry	5	0.035-671	0	0

*It was not possible to further stratify by migrant type due to the heterogeneity of the screening criteria