Pre-entry screening programmes for tuberculosis in migrants to low-incidence countries: a systematic review and meta-analysis

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Summary

Background Several high-income countries have pre-entry screening programmes for tuberculosis. We aimed to establish the yield of pre-entry screening programmes to inform evidence-based policy for migrant health screening.

Methods We searched six bibliographic databases for experimental or observational studies and systematic reviews, which reported data on migrant screening for active or latent tuberculosis by any method before migration to a low-incidence country. Primary outcomes were principal reported screening yield of active tuberculosis, yield of culture-confirmed cases, and yield of sputum smear for acid-fast bacilli cases. Where appropriate, fixed-effects models were used to summarise the yield of pre-entry screening across included studies.

Findings We identified 15 unique studies with data for 3 739 266 migrants screened pre-entry for tuberculosis between 1982 and 2010. Heterogeneity was high for all primary outcomes. After stratification by prevalence in country of origin, heterogeneity was reduced for culture-confirmed and smear-confirmed cases. Yield of culture-confirmed cases increased with prevalence in the country of origin, and summary estimates ranged from 19·7 (95% CI 10·3–31·5) cases identified per 100 000 individuals screened in countries with a prevalence of 50–149 cases per 100 000 population to 335·9 (283·0–393·2) per 100 000 in countries with a prevalence of greater than 350 per 100 000 population.

Interpretation Targeting high-prevalence countries could result in the highest yield for active disease. Pre-entry screening should be considered as part of a broad package of measures to ensure early diagnosis and effective management of migrants with active tuberculosis, and be integrated with initiatives that address the health needs of migrants.

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Introduction

Several high-income countries (Australia, Austria, Canada, France, Israel, Jordan, New Zealand, and USA) have pre-entry screening programmes for tuberculosis.[1] The UK has used a combination of upon-entry and post-entry screening for several decades, but fully transitioned to pre-entry screening on April 1, 2014.[2] Migration patterns have led to recent changes in the epidemiological profile of cases in low-incidence settings. In Europe there has been an absolute decrease in the number of tuberculosis cases reported, but only five countries report a decrease in migrant populations, ten report no change, and 11 report an increase.[3,4] The overall proportion of tuberculosis cases in individuals of foreign origin in Europe is 25·8%; however, many countries have much higher proportions, such as Sweden (89·4%), Norway (87·8%), and the UK (70·1%).[5,6] In the USA, the overall number of tuberculosis cases has been decreasing, but notifications in foreign-born individuals are 11·5 times higher than those born in the country.[7]

The number of people residing outside their country of birth is substantial. The UN Population Division estimated that globally this population consisted of 232 million people in 2013.[8,9] Between 1990 and 2013, North America accepted the largest gross inflow of migrants at 25 million, and Europe had the second largest at 23 million. A substantial number of migrants move from countries with a high incidence of tuberculosis to those with a low incidence. Reasons for migration include economics (to work in the receiving country or move away from financial crises in the country of origin), education, political instability or war, natural disasters, and reunion (joining family members in the receiving country).[10,11]

Because of the high burden of tuberculosis in migrants, many governments in low-incidence settings have implemented screening programmes. Tuberculosis screening programmes for migrants can occur at three points in time: pre-entry (before entering the country), upon entry, or post-entry. Many European countries have implemented post-entry screening and, although there are differences in the screening approach, the characteristics of such programmes are well documented.[12]

The yield of pre-entry screening programmes for tuberculosis can differ from upon-entry and post-entry programmes. With some exceptions, upon-entry and

post-entry screening tend not to be a compulsory part of visa applications; therefore, individuals undergoing screening might not be representative of the wider migrant population. Attendance for screening could be determined by patient health-seeking behaviour or the opinion of immigration staff. Conversely, pre-entry screening programmes are typically a compulsory part of the visa application process and as a result coverage is higher, if not complete, and such studies should be fully representative of the populations screened and intending to migrate.

The characteristics of post-entry and upon-entry screening programmes have been well documented, but we are not aware of any previous studies that have systematically reviewed the yield of pre-entry screening programmes.[12–14] Therefore, our aim was to establish the yield of pre-entry screening programmes for active disease and latent infection to inform future evidence-based policy for migrant health-screening initiatives.

Methods

Search strategy and selection criteria

We searched for reports published after Jan 1, 1980, in Medline, Embase, LILACS, Cochrane Infectious Diseases Group Specialized Register, Cochrane Library, Conference Proceedings Citation Index–Science, and Conference Proceedings Citation Index–Social Science & Humanities. Reference lists of included studies were hand-searched to identify further relevant work.

Detailed search terms for the bibliographic databases are presented in the appendix. In summary, terms covered the populations of interest (migrants, refugees, asylum seekers, new entrants, undocumented migrants), the intervention (pre-entry screening), and standard terms for tuberculosis.

Initial search results were imported into EPPI-Reviewer 4 where duplicates were identified and removed. An updated search was done on April 1, 2014, with Zotero.[15,16] RWA, TAY, and DZ screened titles, abstracts, and full-text reports. Disagreements were resolved by discussion, and remaining issues were assessed in conjunction with a fourth reviewer (ACH). Data from included studies were extracted in duplicate to an Excel spreadsheet (Microsoft Office for Mac 2011).

We prespecified several study types as eligible for inclusion: experimental studies (randomised controlled trials and quasi-randomised controlled trials, including before and after studies), observational studies (including retrospective and prospective cohort studies, case-control studies, cross-sectional and case series), and systematic reviews. Additional inclusion criteria were that a study needed to be published with an abstract in English, it needed to report the total number of individuals screened who plan to migrate and the number of cases of tuberculosis infection or disease identified, and screening needed to have taken place before the migrant entered a low-incidence country. Eligible studies could screen for tuberculosis by any method including radiographic,

microbiological, and a clinician's recommendation to treat an individual on the basis of clinical or radiological signs or symptoms compatible with tuberculosis. We followed the PRISMA reporting guidelines.

Definitions

We used the definition of migrants developed by Hans Rieder and colleagues[17] and used in a recent systematic review of screening in the European Union.[12] It classifies migrants into the four groups: migrant (a foreigner legally admitted and expected to settle in a host country), asylum seeker (a person wishing to be admitted to a country as a refugee and awaiting decision on their application for refugee status under relevant international instruments), foreign-born citizen (a person who is a national of the state in which they are present but who was born in another country), and undocumented foreigner or migrant (formerly classified as illegal, describing an individual who enters, stays, or works in a host country without an appropriate residence permit or visa).

There is no universally accepted definition of a low-incidence tuberculosis country. For the purpose of our analysis, we used the European Centre for Disease Prevention and Control definition of a low-incidence country as one with a notification rate below 20 cases per 100 000 in the general population.[18]

Outcomes

We considered three primary outcomes: the principal yield of pre-entry screening for active tuberculosis reported for each study (detected by any method), yield of active tuberculosis cases confirmed by culture, and yield of active tuberculosis cases confirmed by smear for

See **Online** for appendix


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┌─────────────────────────────────────┐   ┌─────────────────────────────────────┐
│ 1887 records identified through      │   │ 15 additional records identified     │
│ database searching from Jan 1, 1980  │   │ through other sources on April 1,    │
│ to April 1, 2014                     │   │ 2014                                 │
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            │ 1902 records screened     │
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                        ├─────────────────────▶│ 1745 records excluded as not     │
                        │                      │ relevant or duplicates           │
            ┌───────────────────────────┐      └──────────────────────────────────┘
            │ 157 full-text articles    │
            │ assessed for eligibility  │
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            │ 19 studies meeting        │
            │ inclusion criteria        │
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                        ├─────────────────────▶│ 4 studies excluded because of    │
                        │                      │ overlapping data with other      │
                        │                      │ studies                          │
            ┌───────────────────────────┐      └──────────────────────────────────┘
            │ 15 studies included in    │
            │ quantitative synthesis    │
            └───────────────────────────┘
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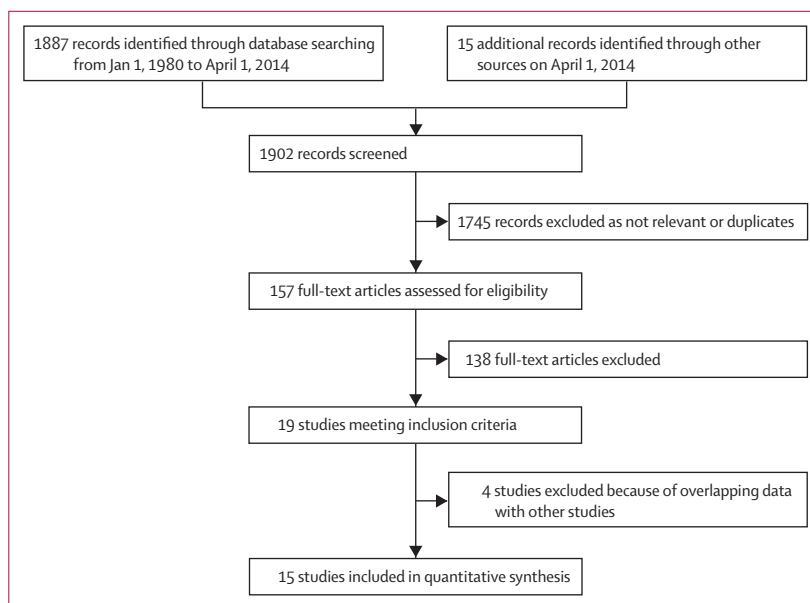
Figure 1: Study profile

acid-fast bacilli. Secondary outcomes were yield of active cases detected by radiography, yield of drug-resistant active disease, yield of latent tuberculosis (diagnosed by any method), costs associated with screening individual migrants, and costs of treatment for individuals screened and found to have tuberculosis.[19]

	Year of publication	Screening method	Principal case definition	Number screened	Cases identified	Yield per 100 000 population screened	Population screened	Country of origin	Receiving country	Country where screening took place	Years screened
Bollini et al[25]	1998	Chest radiograph; if compatible with tuberculosis, sputum smear samples were taken on 3 consecutive days	One or more positive samples by sputum smear	131 241	729	555	Migrants	Vietnam	USA, Australia, Canada	Vietnam	1992–94
Dasgupta et al[27]	2000	Chest radiograph; if compatible with tuberculosis, sputum smear samples and tuberculin tests when judged as appropriate	Culture positive or radiographic improvement after at least 2 months therapy	12 898	17	132	Migrants	Multiple	Canada	Multiple	1996–97
Gorbacheva et al[26]	2010	Chest radiograph, clinical examination, history, and tuberculin skin test; three sputum specimens in those with findings that suggested tuberculosis	One or more positive sample by sputum smear or culture	23 459	151	644	Refugees	Bhutan	USA, Canada, Australia, New Zealand, Denmark, Norway	Nepal	2007–09
King et al[28]	2011	Chest radiograph; if compatible with tuberculosis, sputum smear and culture testing*	Clinical cases, or one or more positive samples by sputum smear or culture	378 939	519	137	Migrants	Multiple	Australia	Multiple	2009–10
Lange et al[29]	1989	5 tuberculin units of purified protein derivative	10 mm induration after purified protein derivative test	873	9	1031	Adoptees	South Korea	USA	South Korea	1985–88
Lui et al[30]	2009	Chest radiograph; if compatible with tuberculosis, sputum smear samples were taken on 3 consecutive days	Inactive tuberculosis: radiograph-positive, acid-fast bacilli sputum smear-negative tuberculosis	3 092 729	29 998	970	Mixed	Multiple	USA	Multiple	1999–2005
Malone et al[31]	1994	Chest radiograph and physical examination; if compatible with tuberculosis, sputum smear and culture testing on three consecutive samples	Presumptive active tuberculosis†	11 000	340	3091	Migrants	Haiti	USA	US naval base in Guantanamo Bay, Cuba	1991–93
Maloney et al[32]	2006	Chest radiograph; if compatible with tuberculosis, sputum smear and culture testing on three consecutive samples	Acid-fast bacilli sputum smear-positive or culture-positive cases	14 098	183	582	Migrants	Vietnam	USA	Vietnam	1998–99
Mor et al[33]	2012	Chest radiograph, clinical examination, history, and tuberculin skin test; three sputum specimens in those with findings that suggested tuberculosis	Active pulmonary tuberculosis‡	13 379	57	426	Migrants	Ethiopia	Israel	Ethiopia	2001–05
Oeltmann et al[34]	2008	Chest radiograph, clinical examination, and history; three sputum specimens in those with findings that suggested tuberculosis	Clinical and acid-fast bacilli sputum smear-positive cases	15 455	272	1760	Refugees	Laos	USA	Thailand	2004–05
Painter et al[35]	2013	Chest radiograph, clinical examination, history, and sputum testing for *Mycobacterium tuberculosis* as per CDC 2009 technical instructions	QuantiFERON—TB Gold In-Tube Assay and tuberculin skin test positive§	1475	859	Not applicable¶	Migrants	Vietnam	USA	Vietnam	2008–10

(Table 1 continues on next page)

	Year of publication	Screening method	Principal case definition	Number screened	Cases identified	Yield per 100 000 population screened	Population screened	Country of origin	Receiving country	Country where screening took place	Years screened
(Continued from previous page)											
Plant et al[36]	2004	Chest radiograph, clinical examination, and history; three sputum specimens in those with findings that suggested tuberculosis	Acid-fast bacilli sputum smear-positive or culture-positive cases	6018	36	598	Migrants	Vietnam	Australia	Vietnam	1997–2001
Wang et al[37]	1991	Chest radiograph followed by three sputum cultures in those with findings that suggested tuberculosis	Inactive tuberculosis‖	21 956	1173	5343	Migrants	Multiple	Canada	Multiple	1982–85
Watkins et al[38]	2005	Chest radiograph	Radiograph-positive cases	1669	170	10 186	Migrants	Vietnam	Australia	Vietnam	Not stated
Yanni et al[39]	2013	Chest radiograph, clinical examination, history, and sputum testing for *M tuberculosis* as per CDC 2009 technical instructions	One or more positive samples by sputum smear or culture	14 077	1	7	Refugees	Iraq	USA	Jordan	2007–09

*Limitations in sputum smear and culture methods were reported by study authors. †Full definition not provided and unable to contact corresponding author. ‡Symptomatic patient with pulmonary disease and confirmed *Mycobacterium tuberculosis* complex culture. §Following the results of chest radiograph, applicants were invited to participate in a study of the tuberculin skin test and QuantiFERON—TB Gold In-Tube Assay for which they would be provided the results, but the result of which would not affect their visa application; varying size of the tuberculin skin test induration was used as cutoff. ¶Yield for latent tuberculosis for this study is not presented since the primary aim of the study was to compare the sensitivity of QuantiFERON—TB Gold In-Tube Assay with the tuberculin skin test for culture-positive pulmonary tuberculosis; therefore, it was done on a sample of migrants with and without abnormal radiograph results, and therefore yield of latent tuberculosis will not be representative. ‖Inactive tuberculosis defined by authors as "radiograph shows evidence of tuberculosis, it is repeated at a minimum interval of 3 months to confirm stability of the lesion. In addition, three sputum cultures, incubated for 7–8 weeks, taken at least 24 h apart, are required to be negative".

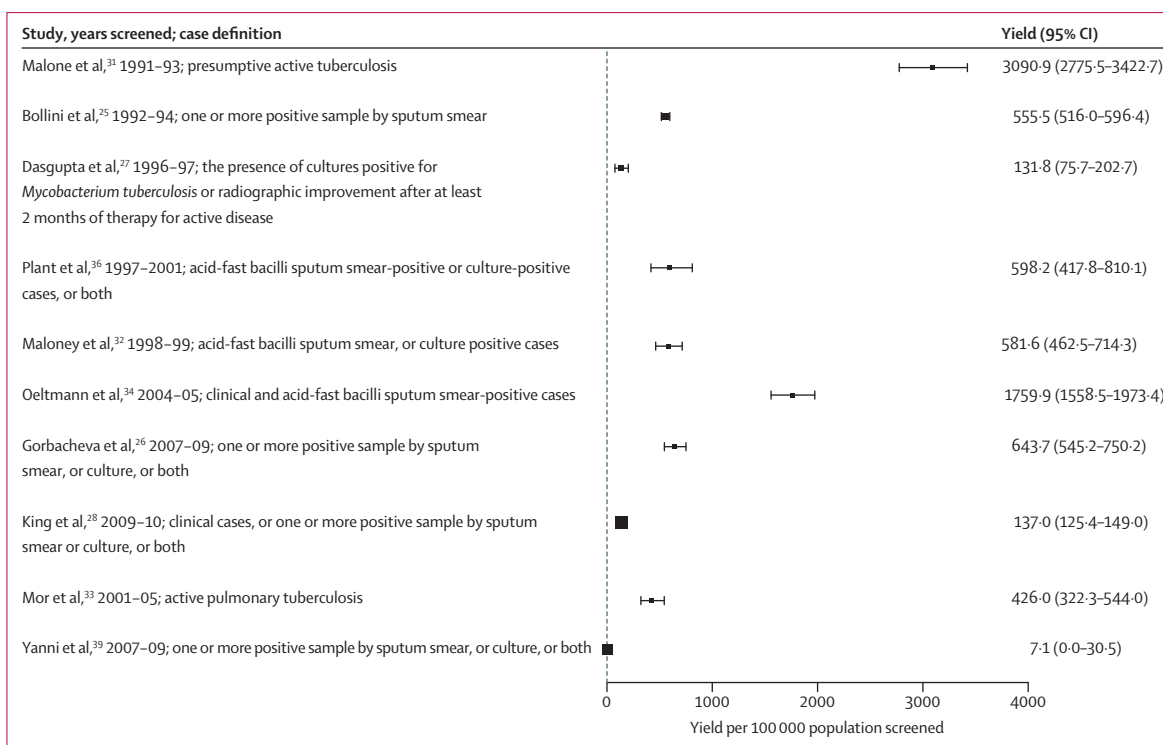*Table 1:* Studies reviewed

Figure 2: Forest plot of pre-entry screening programme yield for principal outcome of active tuberculosis cases found by each study (case definition varies between studies, sorted by year of publication)

	Number screened	Total cases of active disease identified	Smear-positive cases	Culture-positive cases	Multidrug-resistant cases	Radiograph-positive cases	Latent tuberculosis cases	Population screened	Country of origin	Receiving country
Bollini et al[25]	131 241	729 (0·6%)	729 (0·6%)	..	..	..	..	Migrants	Vietnam	US, Australia, Canada
Dasgupta et al[27]	12 898	17 (0·1%)	..	..	..	722 (5·6%)	353 (2·7%)	Migrants	Multiple	Canada
Gorbacheva et al[26]	23 459	151 (0·6%)	54 (0·2%)	..	..	..	..	Refugees	Bhutan	USA, Canada, Australia, New Zealand, Denmark, Norway
King et al[28]*	12 795	113 (0·9%)	4 (0·0%)	43 (0·3%)	..	..	..	Migrants	Philippines	Australia
King et al[28]*	59 666	87 (0·1%)	2 (0·0%)	24 (0·0%)	..	..	..	Migrants	India	Australia
King et al[28]*	13 621	84 (0·6%)	6 (0·0%)	43 (0·3%)	..	..	..	Migrants	Vietnam	Australia
King et al[28]*	71 600	43 (0·1%)	1 (0·0%)	14 (0·0%)	..	..	..	Migrants	China	Australia
King et al[28]*	42 503	24 (0·1%)	2 (0·0%)	8 (0·0%)	..	..	..	Migrants	South Korea	Australia
King et al[28]*	12 859	20 (0·2%)	0	8 (0·1%)	..	..	..	Migrants	Malaysia	Australia
King et al[28]*	9192	15 (0·2%)	1 (0·0%)	0	..	..	..	Migrants	Indonesia	Australia
King et al[28]*	1512	14 (0·9%)	1 (0·1%)	10 (0·7%)	..	..	..	Migrants	Cambodia	Australia
King et al[28]*	10 608	13 (0·1%)	0	2 (0·0%)	..	..	..	Migrants	Thailand	Australia
King et al[28]*	2861	12 (0·4%)	0	5 (0·2%)	..	..	..	Migrants	Nepal	Australia
Lange et al[29]	873	9 (1·0%)	..	..	..	..	9 (1·0%)	Adoptees	South Korea	USA
Lui et al[30]	2 714 223	26 075 (1·0%)	..	..	..	26 075 (1·0%)	..	Migrants	Multiple	USA
Lui et al[30]	378 506	3923 (1·0%)	..	..	..	3923 (1·0%)	..	Refugees	Multiple	USA
Malone et al[31]	11 000	340 (3·1%)	..	37 (0·3%)	..	..	..	Migrants	Haiti	USA
Maloney et al[32]	14 098	82 (0·6%)	82 (0·6%)	183 (1·3%)	5 (0·0)	1331 (9·4%)	..	Migrants	Vietnam	USA
Mor et al[33]	13 379	57 (0·4%)	..	37 (0·3%)	..	150 (1·1%)	..	Migrants	Ethiopia	Israel
Oeltmann et al[34]	15 455	272 (1·8%)	34 (0·2%)	57 (0·4%)	24 (0·2%)	..	..	Refugees	Laos	USA
Oeltmann et al[34]	5637	1624 (28·8%)	..	..	..	..	1624 (28·8%)	Refugees	Laos	USA
Painter et al[35]	20 100	211 (1·0%)	..	211 (1·0%)	..	2087 (10·4%)	..	Migrants	Vietnam	USA
Plant et al[36]	5108	25 (0·5%)	15 (0·3%)	..	..	..	..	Migrants	Vietnam	Australia
Plant et al[36]	910	11 (1·2%)	6 (0·7%)	..	..	..	..	Migrants	Cambodia	Australia
Wang et al[37]	21 956	1173 (5·3%)	..	..	..	..	..	Migrants	Multiple	Canada
Watkins et al[38]	1669	170 (10·2%)	..	..	..	170 (10·2%)	..	Migrants	Vietnam	Australia
Yanni et al[39]	14 077	1 (0·0%)	..	..	..	..	251 (1·8%)	Refugees	Iraq	USA

*Study reports that overall 230 cases were culture confirmed and 67 were smear positive, but not all of these data are included as the data on number of migrants screened was not presented for all countries.

Table 2: Studies included within the quantitative review

Statistical analysis

We used fixed-effects models with Freeman-Tukey transformation of data to estimate summary yield of pre-entry screening across studies and subgroups where appropriate.[20,21] We used the I^2 transformation to describe the proportion of total variation in study estimates that is due to heterogeneity.[22] Where we identified overlapping data on an individual screening programme, we included the publication with the largest amount of data (by time period or number of individuals screened). Where appropriate, we presented economic components of the studies in a narrative format.

We did a subgroup analysis for the primary outcomes to assess the effect of prevalence in the country of origin, the screening method used (eg, radiographic, microbiological, clinical), the receiving country, and the type of migrants screened. Because there are no universally accepted categories to classify prevalence of tuberculosis at the country level, we chose to use the

following groups: 20–49, 50–149, 150–249, 250–349, and 350 or more cases per 100 000 population. We used WHO prevalence estimates for the middle year in which screening was done.[23] Where possible, we extracted data for primary outcomes for each of the subgroups (eg, different countries of origin) and then included them in the subgroup analysis.

RWA and TAY independently assessed the risk of bias for included studies with the Grading of Recommendations Assesssment, Development, and Evaluation (GRADE) approach.[24] Any disagreements were discussed and resolved with the help of a third reviewer (ACH) where necessary.

Role of the funding source

The study sponsors had no role in study design, the collection, analysis, and interpretation of data. The corresponding author confirms that he had full access to all the data in the study and had final responsibility for the decision to submit for publication.
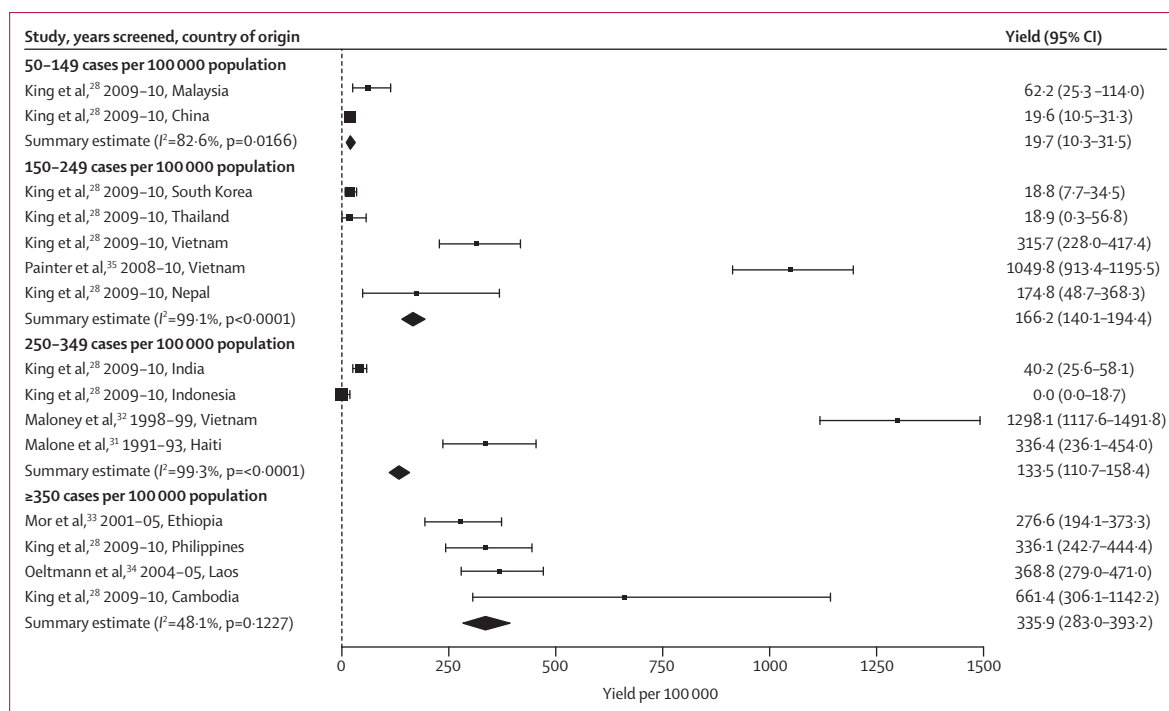
Figure 3: Forest plot of pre-entry screening programme yield of culture-positive cases of tuberculosis, stratified by WHO prevalence of tuberculosis in country of origin (sorted by prevalence in country of origin)

Results

A search of six bibliographic databases was done on April 5, 2013, and updated on April 1, 2014. 1887 studies were identified (figure 1). 15 more reports were identified through other sources, including the review of references of included studies. 157 full-text articles were retrieved and assessed for eligibility, and 19 manuscripts met the inclusion criteria after double screening and review.[25–43] After further review and extraction of data, four studies were excluded from the final analysis because they contained overlapping data for the primary outcomes.[40–43]

The 15 studies included in the final analysis reported data on 3 739 266 individual migrants screened between 1982 and 2010 (table 1).[25–39] The smallest study had data on 873 migrants and the largest 3 092 729 migrants. Screening protocols varied between studies, but many included an initial chest radiograph, clinical examination, and testing for smear and culture. The principal outcome for ten studies reporting data on active tuberculosis included a combination of smear, culture, or intention to treat on the basis of clinical findings as part of their case definition (figure 2). Meta-analyses of yield for all three primary outcomes showed high levels of heterogeneity (I^2>90%) and therefore we did not calculate summary effect estimates across studies.

No studies reported the number of individuals tested by sputum culture or smear and therefore it was only possible to calculate yield based on the total number of individuals screened, and not by total number of microbiological tests done (table 2). Six studies presented data on 755 cases that

were culture confirmed among 452 971 individuals initially screened.[27,28,31–35] Six studies had data on smear-positive cases of tuberculosis, with 987 cases identified in the 569 210 individuals initially screened.[25,26,28,32,34,36] Most studies reported sputum smear testing on three samples for those individuals with radiograph or clinical symptoms that suggested tuberculosis (appendix). Some variation existed in the number of positive samples needed to classify individuals with smear-positive disease.

After stratifying results by prevalence of tuberculosis in the country of origin, heterogeneity was reduced for culture-positive and smear-positive confirmed cases, but not the principal outcome—active tuberculosis cases (figure 3, appendix). There was an increasing yield of culture-positive and smear-positive cases with increasing prevalence in the country of origin. Summary estimates of yield of culture-positive cases ranged from 19·7 (95% CI 10·3–31·5) cases identified per 100 000 individuals screened in countries with a prevalence of 50–149 cases per 100 000 population to 335·9 (283·0–393·2) per 100 000 in countries with a prevalence of greater than 350 per 100 000 population (figure 3). The results of the meta-analyses were dominated by one large study, which acknowledged some limitations with data for smear and culture testing because this was not uniformly done across all sites and for all cases.[28] Across all included studies, prevalence of culture-confirmed cases was highest in migrants to the USA from Vietnam with 1298 cases per 100 000 individuals screened (95% CI 1118–1499; appendix).

	Study design	Quality assessment						Quality	Importance
		Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Principal outcome	Observational*	15	Serious†‡	Very serious§	Serious¶‖	No serious imprecision	Reporting bias** dose response gradient††	Very low	Important
Sputum culture	Observational*	6	Serious†‡‡	Serious§§	Serious¶¶¶	No serious imprecision	Reporting bias** dose response gradient††	Very low	Important
Sputum smear	Observational*	6	Serious†‡‡	Serious§§	Serious¶¶¶	No serious imprecision	Reporting bias**	Very low	Important
Chest radiograph	Observational*	5	Serious†	Very serious§	Very serious¶‖	No serious imprecision	Reporting bias**	Very low	Important
Latent tuberculosis	Observational*	3	Serious†	Very serious§	Very serious¶	No serious imprecision	Reporting bias**	Very low	Not important
Multidrug-resistant tuberculosis	Observational*	3	Serious†‡‡	Serious§§	Serious¶¶¶	No serious imprecision	Reporting bias**	Very low	Important

*Case series. †Most studies were at some risk of bias for failure to develop and apply appropriate eligibility criteria and measurements of outcome that had limitations. ‡Largest study for analysis by subgroup[28] stated that "smear and culture testing may be offered but of variable quality". Several studies only look back at results of individuals who arrived in the low-incidence country—a potential bias if there was a difference in the proportion who travelled by test result, which is likely to be the case. §Substantial heterogeneity existed among studies with CIs that minimally overlapped. The proportion of the variation in point estimates due to among-study differences was large and exploration of a-priori subgroup analyses did not substantially explain this. ¶Populations across studies varied; however, the evidence summaries are highly relevant to policy makers and those interpreting the studies, and outcomes (such as active tuberculosis) are likely to be of interest and important to migrants. ‖Interventions and outcomes varied greatly, particularly as smear and culture testing was offered but of variable quality in the largest included study for analysis by subgroup[28] and as many studies included radiographic diagnoses with substantial variation in the radiographic case definition used. Additionally, studies with high detection rates (Watkins et al[38]) seem likely to have included inactive and old tuberculosis scars in addition to active disease. **Data for all years from countries conducting pre-entry screening were not available in the published literature. ††Some evidence to suggest that higher tuberculosis prevalence in country conducting pre-entry screening was associated with a higher yield of cases. ‡‡There was the potential for outbreak bias in one study[34] because it was initiated as a result of an unusually high number of cases. §§Substantial heterogeneity among studies with CIs that showed minimal or no overlap. The proportion of the variation in point estimates due to between-study differences was large. Exploration of a-priori subgroups reduced heterogeneity. ¶¶Interventions and outcomes for multidrug-resistant cases are likely to be less variable due to procedures involved in laboratory testing being somewhat uniform across sites, although the consistency with which these were applied across studies might cause some issues in relation to indirectness.

Table 3: GRADE summary of findings and quality of evidence for the primary and secondary outcomes

With the exception of culture-confirmed cases in refugees (I^2=0%, p=0·85), heterogeneity remained high for all three primary outcomes (I^2>90%) after stratifying by population, screening method, and receiving country (full results are presented in the appendix).

In the studies that reported data on culture-confirmed cases, three described yield of multidrug-resistant tuberculosis. 33 cases in 183 individuals with culture-confirmed disease were found in these three studies.[28,32,34] Although most studies had radiographic screening as a first-line test, numerator and denominator data for this specific outcome were only presented in five studies.[27,30,32,33,38] 34495 chest radiograph-positive cases were reported among the 3154873 individuals screened, and probably included both active and inactive (or old) tuberculosis. Not all studies provided details as to how radiographs were analysed and classified, which might result in a great deal of variation between studies.

Three studies reported data on latent tuberculosis infection, with 1884 latent infections identified in 20587 individuals screened (varying tests and cutoffs were used—see appendix).[29,34,39] One study reported tests for latent tuberculosis on a sample of migrants on the basis of radiograph results (testing 1000 applicants with radiographic findings consistent with active tuberculosis and 500 applicants with a normal radiograph). Therefore, the yield of latent tuberculosis from this study does not represent population prevalence of latent tuberculosis infection and the results were not included in this secondary analysis.[35]

Cost-effectiveness was examined in one study with data from the Canadian pre-entry migrant screening programme from June, 1996, to June, 1997. Compared with passive detection of cases after arrival in Canada, this study estimated the incremental cost (savings) to treat each case of prevalent active tuberculosis detected pre-entry as CAN$39409.[27] A further study, using data presented in this systematic review,[33] estimated the cost of running a health station for an active tuberculosis screening programme in Ethiopia at US$60100 for about 3500 individuals screened per annum.[44] No data were found on costs of treatment for individuals screened and identified as having tuberculosis.

We used GRADE criteria to assess the risk of bias of included studies (table 3). All included studies were observational in nature and therefore the evidence for each outcome was initially determined as low (as per the GRADE methodology). This systematic review focuses on describing yield of existing screening programmes in operational settings and therefore observational studies are an appropriate study design. Most studies were at risk of bias because of the eligibility criteria applied, and the reporting and measurement of exposure and outcome data. Substantial heterogeneity existed for primary outcomes, with CIs across studies showing minimal or no overlap with the exception of culture-confirmed and smear-confirmed disease when stratified by prevalence in country of origin. Because of these limitations, the quality of evidence for all outcomes was downgraded to very low.

Discussion

We identified data on nearly 4 million migrants screened pre-entry and found that yield for culture-confirmed and

smear-confirmed cases was highest when screening was done in high-prevalence countries. Only two studies presented data on the associated costs or cost effectiveness of their pre-entry screening programme. To our knowledge, this is the first systematic review and meta-analysis of pre-entry screening programme data for tuberculosis, which identified 15 studies with unique data on this topic. We used established systematic review procedures including double screening review, and PRISMA reporting guidelines for systematic reviews and meta-analyses.[19] We attempted to reduce bias in the review process by following empirically based review guidelines.[24]

There was substantial heterogeneity between studies, limiting our ability to synthesise results across settings and outcomes. With the exception of yield of culture-confirmed and smear-confirmed cases, when stratified by prevalence of tuberculosis in country of origin, and culture-confirmed cases in refugees, heterogeneity in the primary and secondary outcomes remained high after exploring potential a-priori explanatory variables. Data on the age of those screened was not provided consistently, which might be particularly important for latent tuberculosis and studies that included old tuberculosis detected by chest radiograph. The top five countries of origin for migrants from developing to developed countries in 2010 were Mexico, India, China, Philippines, and Turkey.[11] Although data are presented for India, China, and the Philippines, the migrants are not entirely representative of migrant flow between developing and developed countries. It was not clear from most studies whether there was uniform drug susceptibility testing or whether only retreatment cases were tested. There was a risk of misclassification in the principal outcomes reported by many studies, particularly for those that included clinically identified cases (with an intention to treat) as part of the case definition.

A previously published systematic review focused on all types of migrant screening programmes for tuberculosis in the European Union and European Economic Area, independent of where the screening took place.[12] The review by Klinkenberg and colleagues[12] did not identify any studies of pre-entry screening by European countries; however, data were separately reported from three pre-entry screening programmes performed by countries outside the European Union and European Economic Area. All studies of non-European Union studies were identified and included in our systematic review. A total of 14 studies reported data from upon-entry screening programmes in the European Union and European Economic Area with a median active tuberculosis yield of 360 (IQR 100–520) cases per 100 000 people screened. Five studies reported data on community post-entry screening with a summary median active tuberculosis yield of 220 (IQR 100–380) cases per 100 000 people invited to screening. Direct comparisons with upon-entry and

post-entry screening programmes are difficult to make because of the lack of comparability between study designs, secular trends, and the populations considered. Pre-entry screening, when done in countries with a prevalence of tuberculosis greater than 350 per 100 000 population seems to be within a similar range as these upon-entry and post-entry programmes.

Pre-entry screening programmes aim to identify cases of active tuberculosis before arrival of the migrant in the host country. Our review provides evidence that pre-entry screening programmes have varying yield that increases with prevalence in the country of origin. Screening in countries with prevalence of less than 150 per 100 000 will probably result in low yield of culture-confirmed and smear-confirmed cases.

Pre-entry screening programmes might need the migrant to cover the bulk of costs of testing and treatment; however, the programmes still might not be entirely cost-neutral for the receiving country because of the governance and oversight needed for appropriate operation. The paucity of cost-effectiveness data on these schemes should therefore be addressed because there is uncertainty of the value of pre-entry screening compared with other tuberculosis control activities.

Data from surveillance programmes around the world suggest that rates of disease in migrants from high-incidence countries remain high for many years after entry, so tuberculosis control programmes in low-incidence countries should not rely entirely on pre-entry screening for active tuberculosis in migrants.[7,45–47] For example, in the UK, 50% of tuberculosis in migrant groups occurs more than 5 years after entry.[6] Additionally, these schemes could miss tuberculosis following unplanned migration and in undocumented migrants who might have higher risk. Health care provision for migrants after arrival to a host country and other tuberculosis control measures should therefore remain a priority, because screening migrants will not prevent a high proportion of future cases of disease.

Emerging evidence suggests that domestic returns for investment in tuberculosis control programmes overseas might make them cost effective, and policy makers might wish to consider implementation alongside pre-entry screening programmes.[48,49] Such an enlightened self-interest approach to global tuberculosis control might be not only more cost effective, but also could overcome screening-induced inequalities, so that a greater number of individuals in need benefit from treatment, not just those in a position to leave their country of origin. This broader view would enhance global collaboration in efforts to eliminate tuberculosis.

In many low-incidence countries, risk of tuberculosis is greatest in migrant populations. Some of this disease can be identified by pre-entry screening with the highest yield achieved when programmes focus on high-prevalence countries. Pre-entry screening might therefore make a

contribution to control within the receiving country, but the cost-effectiveness remains unclear and where the cost of screening is borne by the migrant or their country of origin this might increase inequalities. When used, pre-entry screening should therefore be considered as part of a broader package of measures to ensure early diagnosis and effective management of migrants with active tuberculosis, and be integrated with other initiatives addressing the health needs of migrants.

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