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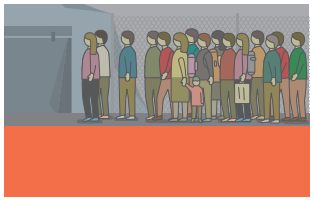

Screening for infectious diseases in newly arrived migrants in Europe: the context matters

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In the past three decades there has been a considerable increase in the number of migrants globally. In 2015, about one third of the world's migrants lived in Europe (ca 75 million, which is about 10% of the area's population), contributing to the region's economy and creating a younger demographic composition [1,2]. In recent years, an unprecedented number of forcibly displaced persons fleeing conflict, violence or disaster have come to Europe. In 2015, the peak year of this wave, more than one million asylum seekers, refugees and irregular migrants arrived in Europe [3]. For the purpose of this editorial, economic immigrants, asylum seekers and refugees are collectively referred to herein as migrants.

The *Eurosurveillance* series on screening for infectious diseases in newly arrived migrants in Europe is well timed. Seven articles are included in this series: two systematic reviews on the effectiveness and cost-effectiveness of screening for active tuberculosis (TB) and for latent TB, and five articles presenting the experiences of screening programmes—for active and latent TB, hepatitis B, hepatitis C, HIV infection, and infection with selected enteric bacteria (e.g. *Salmonella* spp., *Shigella* spp.) and helminths (e.g. *Schistosoma* spp., *Strongyloides stercoralis, Ascarislumbricoides*)—for migrants who arrived recently in several parts of Europe [4-10].

Since 2000, TB has consistently decreased in the European Union (EU) and European Economic Area (EEA). However, the current rate of decrease is insufficient to achieve the End TB Strategy targets [11-13]. In 2016, one third of all new active TB cases reported in EU/EEA countries were diagnosed in people who were born outside of the country where the case was reported or who had foreign citizenship [11]. Policies to promote timely diagnosis and treatment in migrants are, therefore, crucial [14].

The systematic review by Greenaway et al., on the effectiveness and cost-effectiveness of screening for active TB in migrants using chest X-ray as the screening test, demonstrates the heterogeneity of yield among screening programmes, which reflects the heterogeneity of disease prevalence [4]. The authors did not identify any study on the effectiveness of a screening programme as a whole and, therefore, studies on yield, sensitivity and specificity of chest X-ray to detect active TB, effectiveness of treatment and uptake of screening were reviewed. As expected, yield tends to be higher in migrant populations originating from countries with a higher incidence of endemic TB. Yield was also shown to depend on the cause for migration and the setting in which screening was carried out, a parameter that probably reflects living conditions, migration routes and migration experience. Chest X-ray was found highly sensitive but only moderately specific, and its acceptance by migrants was generally good. The authors point out that although screening for active TB would be more efficient if targeted to migrants from high TB incidence countries, many cases occur in migrants from countries with lower TB incidence and the heterogeneity between different locations in Europe limits the ability to make precise recommendations. They therefore underline that policies should be tailored to the local epidemiology of TB and emphasise the importance of addressing the issue of barriers to treatment and care for all migrants.

The latter conclusion is in line with the results of the article by Kuehne et al., who found poorer treatment outcomes in cases of pulmonary TB identified through screening in newly arrived asylum seekers in Germany from 2002–2014, compared with cases identified in other ways (diagnosis of symptomatic patients, identification of cases through contact tracing) [6]. The authors concluded that 'finding and losing' should be avoided by linking migrants with positive screening

results to treatment facilities and by investigating possible barriers to treatment completion.

The systematic review by Greenaway et al. on screening migrants for latent TB infection (LTBI) points out the importance of this issue, as the majority of TB cases in migrants in the EU/EEA are due to reactivation of LTBI [5]. Nevertheless, there is an inherent limitation in any screening policy for LTBI: currently available tests cannot distinguish the 5–15% of LTBI cases who will progress to active TB and may therefore benefit from treatment [5,15]. The review summarises evidence that groups at highest risk for progression from LTBI to active TB include people with immunosuppressive conditions (e.g. HIV infection), those who were infected recently, migrants from endemic countries with high TB incidence and those who have experienced crowded living conditions and perilous journeys. Sequential tuberculin skin testing and interferon-gamma release assay was generally found more cost-effective than single testing with either of the two tests. Barriers at patient, provider and structural levels may result in loss to follow-up and jeopardise treatment completion of eligible patients. The authors concluded that migrant-focused LTBI screening programmes may be effective and cost-effective if they are highly targeted and ensure high screening uptake, health care access and treatment completion. Further, the findings of Mueller-Hermelink et al. highlight that migrant children under the age of 6 years are at higher risk for progression from LTBI to active TB compared to older migrant children or adolescents, and effective options of prophylactic treatment are available [8,16].

Two studies in this series report findings that include stool screening for helminthic infections in Italy and in Germany [9,10]. They confirm the conclusion of previous studies that the frequency of positive screening test results depends on migrants' country of origin [17]. The Italian study found positive stool results for *Schistosoma mansoni* eggs in 7.0% of 270 migrants from sub-Saharan Africa and none in 79 screened migrants from Asia; in the German study, 0.3% of 14,511 individuals originating from a variety of countries had positive stools for *Schistosoma mansoni* eggs.

These studies also concur in another important finding: they confirm that possible enteric infections in migrants do not spill over into the local population at any appreciable degree. In particular, the German investigators addressed this issue by documenting that during the study period they did not identify any records of secondary transmission of *Salmonella* spp. or *Shigella* spp. to the host population [10]. Moreover, the studies agree that the rationale for screening migrants for enteric pathogens is mainly to prevent severe morbidity in infected individuals [9,10]. Diseases that can remain asymptomatic for a long time and lead to chronic infection with severe sequelae, like some helminthic infections, could therefore be candidates for screening [18].

The studies by Bil et al. and Buonfrate et al. support the feasibility of combined preventive programmes for newly arrived migrants in some settings, including screening for hepatitis B, hepatitis C and HIV infection, but they also show that serological evidence of infection can differ greatly between programmes and migrant groups [7,9].

A common finding of the articles in the present series corroborates a major conclusion of previous studies and reviews: migrants do not represent a significant risk for EU/EEA populations in terms of infectious disease incidence in the local population and infectious disease outbreaks [19,20]. The series adds substantial evidence to the existing body of knowledge about this in relation to TB, as well as to bacterial and helminthic enteric infections [4-10]. Despite general agreement in the scientific community, the issue continues to be debated controversially in several European countries [21]. Clear communication of existing evidence on this topic is, therefore, a priority.

A further common element in many of the articles in this series is that, despite existing limitations, potentially effective screening tools for several infectious diseases do exist, but making general recommendations for universal use is not supported by evidence. In order to formulate specific policies for screening migrants for infectious diseases, the national context needs to be taken into account—the epidemiology of diseases in each country (and in its specific migrant population), the health system framework, the priorities of health and social care for migrants—as well as the existing evidence on the effectiveness of screening, some of which is presented in this series.

Another shared theme in a number of the articles is the need to ensure migrants with a positive screening result have access to health care and treatment. Barriers to these are often present, and include structural and cultural aspects. Providing migrants with access to appropriate health care makes good public health sense, is a fundamental human right tied to the principle of non-discrimination and should be ensured by hosting countries as emphasised, for example, by the International Organization for Migration and World Health Organization [22]. Screening should never be seen as the application of 'just a test', but as a first step leading to diagnosis and treatment of those who are likely to benefit from it.

Screening for certain infectious diseases is important and, if appropriately implemented, can be cost-effective and contribute to the prevention of disease in migrants and their host communities in Europe. It is essential that the wider context affecting migrants is taken into consideration when implementing screening programmes. Optimally, screening should be part of comprehensive approaches that address all aspects

of migrants' health needs and vulnerabilities, and particular effort should be made towards this end [22].

Conflict of interest

None declared.

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The effectiveness and cost-effectiveness of screening for active tuberculosis among migrants in the EU/EEA: a systematic review

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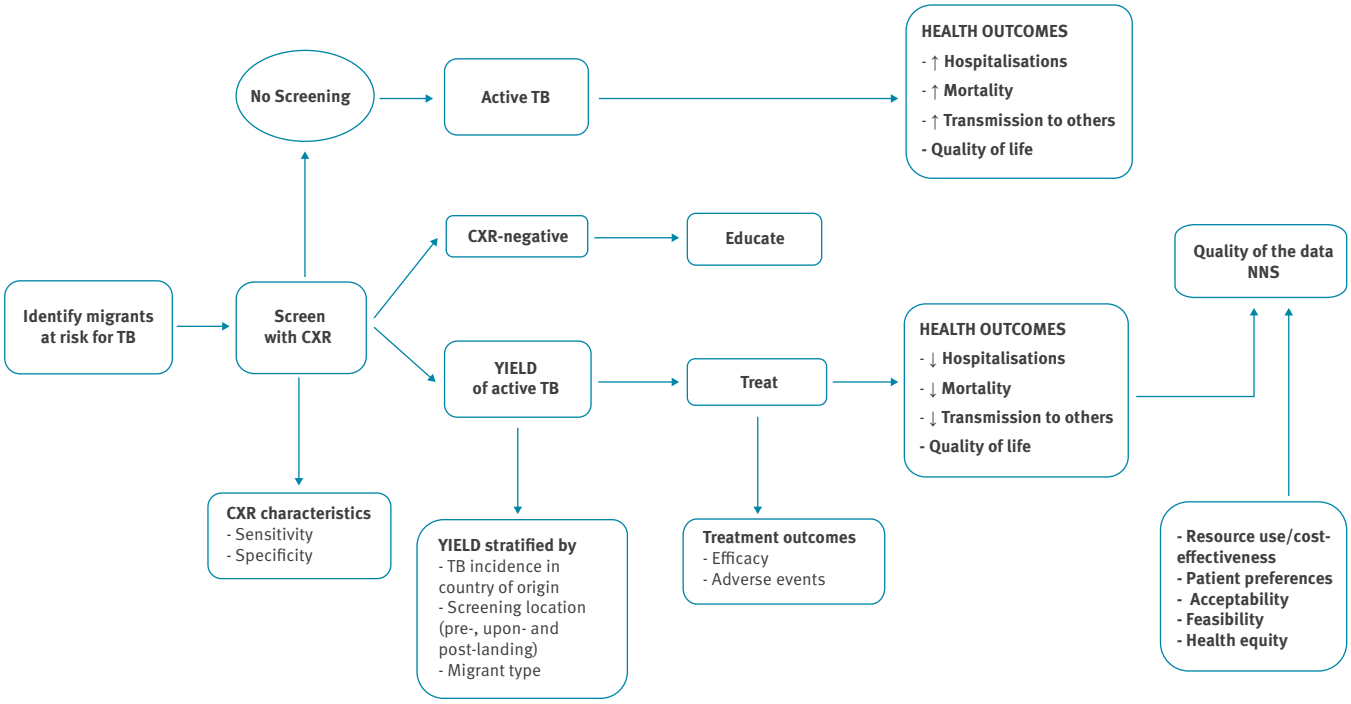
Background: The foreign-born population make up an increasing and large proportion of tuberculosis (TB) cases in European Union/European Economic Area (EU/EEA) low-incidence countries and challenge TB elimination efforts. **Methods:** We conducted a systematic review to determine effectiveness (yield and performance of chest radiography (CXR) to detect active TB, treatment outcomes and acceptance of screening) and a second systematic review on cost-effectiveness of screening for active TB among migrants living in the EU/EEA. **Results:** We identified six systematic reviews, one report and three individual studies that addressed our aims. CXR was highly sensitive (98%) but only moderately specific (75%). The yield of detecting active TB with CXR screening among migrants was 350 per 100,000 population overall but ranged widely by host country (110–2,340), migrant type (170–1,192), TB incidence in source country (19–336) and screening setting (220–1,720). The CXR yield was lower (19.6 vs 336/100,000) and the numbers needed to screen were higher (5,076 vs 298) among migrants from source countries with lower TB incidence (≤50 compared with ≥350/100,000). Cost-effectiveness was highest among migrants originating from high (>120/100,000) TB incidence countries. The foreign-born had similar or better TB treatment outcomes than those born in the EU/EEA. Acceptance of CXR screening was high (85%) among migrants. **Discussion:** Screening programmes for active TB are most efficient when targeting migrants from higher TB incidence countries. The limited number of studies identified and the heterogeneous evidence highlight the need for further data to inform screening programmes for migrants in the EU/EEA.

Introduction

Tuberculosis (TB) is a public health priority in the European Union (EU) and European Economic Area (EEA), and countries have committed themselves to the World Health Organization (WHO) *End TB Strategy* with an ambitious goal to end TB [1-4]. The foreign-born population make up an increasing and considerable number and proportion of all TB cases in countries with low TB incidence (<10 cases/100,000 population) and challenge TB elimination efforts in the EU/EEA [3,5]. More than one quarter of reported TB cases in 2015 in the EU/EEA occurred in the foreign-born population [5]. This proportion has been increasing steadily; in 2007, 13.6% of TB cases occurred in migrant populations whereas in 2013, they accounted for 21.8% [6]. In many low TB incidence countries in the EU/EEA, more than half of all TB cases occur among foreign-born individuals [5]. Between 2007 and 2012, the EU/EEA received on average 1.5 million migrants from outside of the EU/EEA, and larger numbers in 2015 and 2016 [7,8]. As a result, the foreign-born population now makes

Figure 1

Analytic framework of the evidence chain for active tuberculosis screening in migrants



CXR: chest radiography; NNS: number needed to screen; TB: tuberculosis.

up 11.4% of the population in the EU/EEA and exceeds 15% in many low TB incidence countries [7,8]. A considerable proportion of these migrants were born in countries with a high TB burden [9,10].

Given the disproportionate TB case notifications in migrant populations and the faster decline of TB rates in host populations, enhanced TB control strategies among migrants will be necessary to achieve TB elimination in the EU/EEA (defined as achieving a rate of less than one case of TB per 1,000,000 population) [1-4,11,12]. Countries have generally focused on two targeted control strategies among migrants: (i) identification of active TB with chest radiography (CXR) before or soon after arrival in the host country to detect prevalent TB cases and limit onward transmission and (ii) more recently, identifying and treating latent TB in migrants from high TB burden countries to prevent TB reactivation [13]. Many EU/EEA countries with low TB incidence screen migrants for active TB on or soon after arrival. The migrant groups targeted for screening and the location of screening are different for each country because screening guidelines for active TB in migrants are lacking at the EU/EEA level [13-15]. We conducted a systematic review on the effectiveness and a second systematic review on the cost-effectiveness of screening for active TB among migrants in the EU/EEA region with the aim of informing migrant screening guidelines.

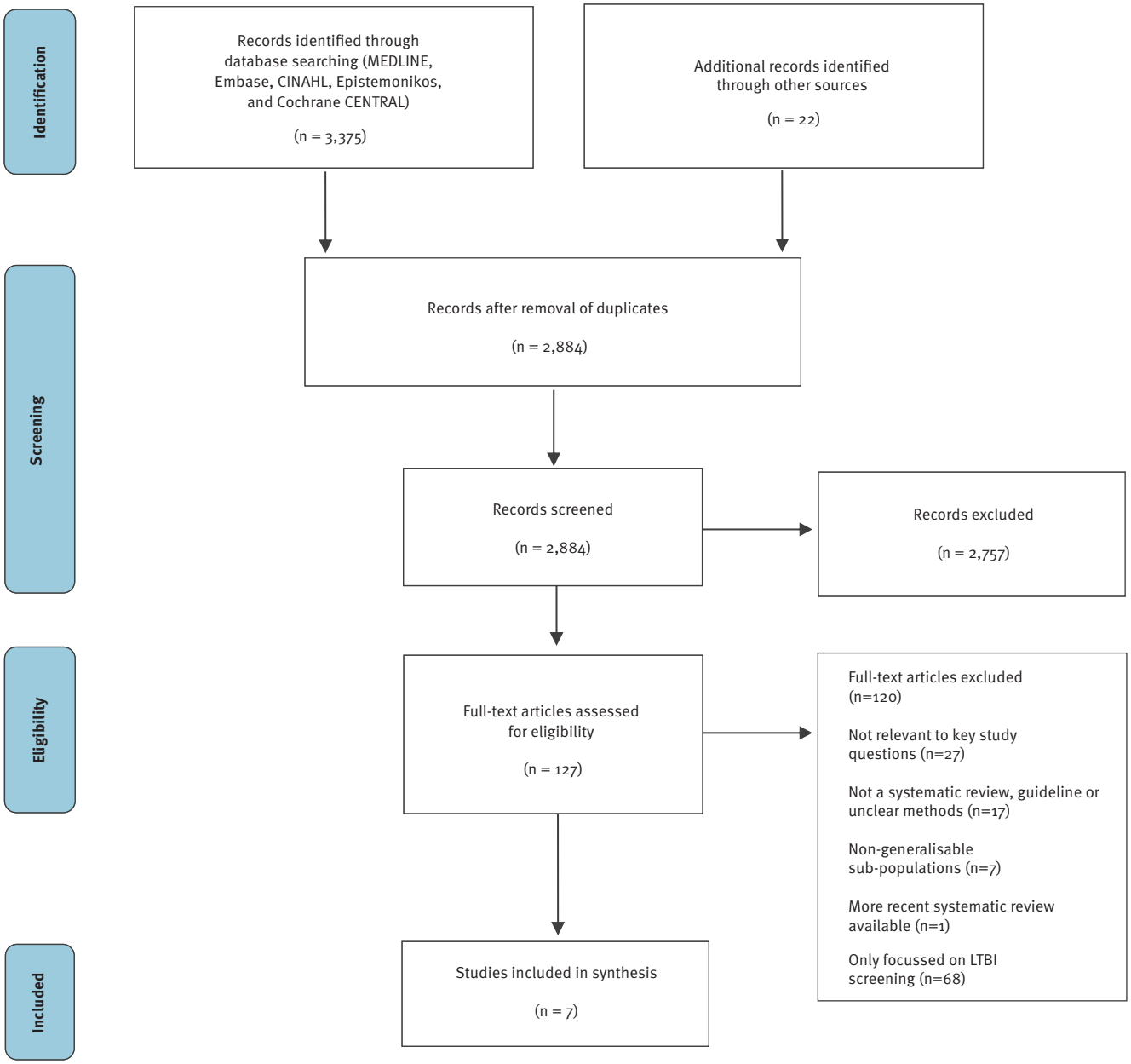
Methods

Overall approach and key questions

This review supports a project of the European Centre for Disease Prevention and Control (ECDC) to develop guidance on screening for six infectious diseases (chronic hepatitis C, hepatitis B, HIV, TB (active and latent) and intestinal parasites) in newly arrived migrants to the EU/EEA. The project followed the new Grading of Recommendations Assessment, Development and Evaluation (GRADE)-ADOLOPMENT approach to conduct systematic reviews on screening migrant populations for these six infectious diseases [16]. The review protocol and the methods of GRADE-ADOLOPMENT guideline development have been published [16,17]. All reviews followed a Cochrane methodological approach and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methods for reporting systematic reviews [18]. For each review, we developed two research questions (using a population, intervention, comparison and outcome (PICO) framework), an analytic framework to illustrate the screening evidence pathway, and identified and prioritised clinically important outcomes, following the evidence-based review methods described by the United States (US) Preventative Task Force [19,20]. We sought to answer two research questions: (i) what is the effectiveness of screening migrants arriving and living in the EU/EEA for active TB and (ii) what is the resource use, cost and cost-effectiveness of screening migrants for active TB?

Figure 2

PRISMA flow diagram, literature search for the effectiveness and cost-effectiveness of active tuberculosis screening, 1 January 2005–12 May 2016



CINAHL: Cumulative Index to Nursing and Allied Health Literature; LTBI: latent tuberculosis infection.

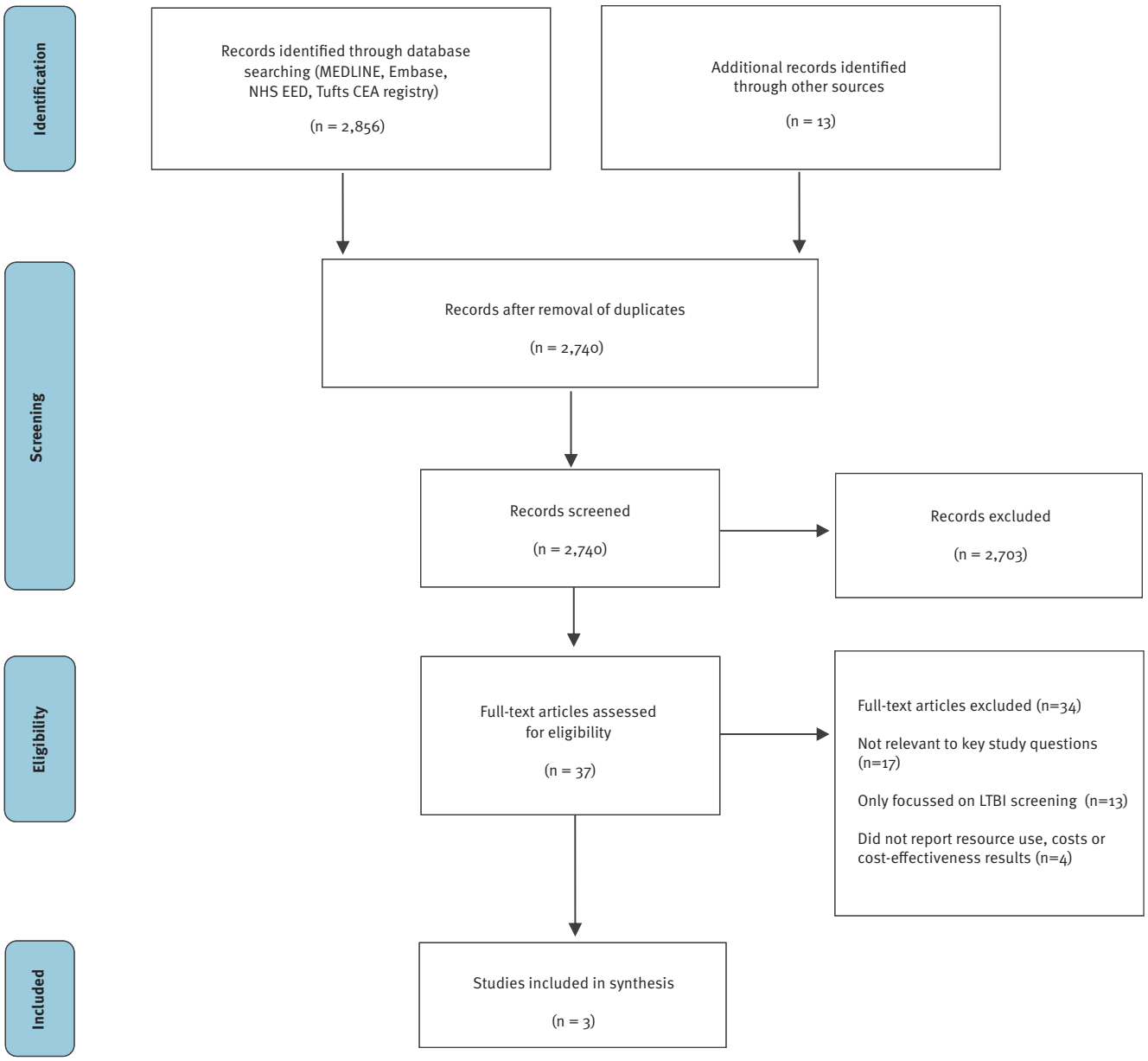
We developed an analytic framework that identified the evidence chain to address the effectiveness and cost-effectiveness of active TB screening among migrants (Figure 1) [17]. We developed the following key questions along this evidence chain: (i) what is the yield of active TB screening with CXR in migrants, (ii) what are the test performance characteristics of CXR to detect active TB, (iii) how effective is active TB therapy and what are the associated harms, (iv) what is the uptake of active TB screening by migrants, and (v) how cost-effective is screening for active TB in migrants [17]?

Search strategy and selection criteria

Following the GRADE-ADOLOPMENT process, we identified an evidence review that assessed the effectiveness of latent TB infection (LTBI) screening among migrants, published in 2011 by the Canadian Collaboration on Immigrant and Refugee Health (CCIRH), and used this as a starting point for our literature search (anchoring review) [16,21]. The CCIRH review included systematic reviews on the effectiveness of LTBI screening in migrants up to 2008 but did not review cost-effectiveness. We therefore conducted two separate searches to address our research questions. The first search

Figure 3

PRISMA flow diagram, literature search for the resource use, costs and cost-effectiveness of active tuberculosis screening, 1 January 2000–31 May 2016



LTBI: latent tuberculosis infection; NHS EED: National Health Service Economic Evaluation Database; Tufts CEA: Tufts Medical Center Cost-Effectiveness Analysis Registry.

updated the CCIRH evidence review and identified systematic reviews and guidelines on the effectiveness and cost-effectiveness of TB screening programmes in migrant populations from 2005 to 2016. The second search identified individual studies on the resource use, costs and cost-effectiveness of TB screening programmes for migrants over a longer period, 2000 to 2016, given these topics were not covered in the CCIRH evidence review. For the first search, MEDLINE via Ovid, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Epistemonikos and Cochrane CENTRAL between 1 January 2005 and 12 May 2016 were searched. We used a combination of key terms including: 'tuberculosis', 'screening', 'chest-radiograph', 'tuberculin skin test', 'interferon-gamma release assays', 'costs', 'cost-effectiveness' AND 'guidelines' and 'reviews'. The search terms and strategy in Ovid MEDLINE are included in Supplement 1. We also searched grey literature websites for published guidelines and reports from the US Centres for Disease Control and Prevention (CDC), ECDC, WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD). We did not apply language restrictions to the search. Additional guidelines and

Table 1a

Characteristics of included studies for effectiveness of active tuberculosis screening

Study	Certainty of evidence	Design	Population	Intervention/ outcomes	Results
Klinkenberg et al. 2009 [29]	Quality of systematic review (AMSTAR): 3/11. Quality of data of included individual studies (GRADE): low.	Systematic review 1998–2008. Observational studies: EU/ EEA (n = 36), non-EU (n = 14). EU countries included: Belgium, Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Norway, Spain, Switzerland, UK.	New entrants to the EU/EEA: migrant, asylum seeker, foreign-born citizen, illegal foreigner/ migrant. Non-EU were performed in the US, Canada, Australia and Japan. Type of screening: mandatory (n = 24,156), voluntary: (n = 2,855). Type of migrant: asylum seekers: (n = 17,824), other migrants: (n = 5,925), migrants/asylum seekers (n = 218,565).	Intervention: screening by CXR (at port of arrival, reception/holding/ transit centre, community post-arrival, occasional screening, follow-up screening). Outcomes: yield of active TB/100,000, 95% CI, median and IQR.	Median active TB yield/100,000, (IQR): EU countries: 350 (110–710), non-EU countries: 510 (170–1,230). Screening type: mandatory (EU): 280 (100–420); voluntary (EU): 400 (160–980). Migrant type (EU): asylum seeker: 350 (250–410), other migrant: 170 (100–630), migrant/asylum seeker: 300 (9–500). Screening setting (EU): port of arrival: 360 (100–520), port of arrival and community post arrival: 650 (0–0), reception/ holding centre: 290 (100–380), community post arrival: 220 (100–380), follow-up: 120 (90–170), occasional: 1,720 (730–2,740), port of arrival and occasional: 720 (710–1,000).
Arshad et al. 2010 [28]	Quality of systematic review (AMSTAR): 7/11. Quality of data of included individual studies (GRADE): low–very low.	Systematic review up to July 2008. Observational studies (n = 22). EU countries included: Belgium Denmark, Ireland, the Netherlands, Norway, Spain, Switzerland, UK.	Migrants assessed through active case finding or active screening programme irrespective of symptoms. n = 5,446 pulmonary TB, n = 2,620,739 screened migrants. Total types of migrants screened: asylum seekers (n = 135,265), regular immigrants (n = 2,466,492), refugees (n = 18,982).	Intervention: CXR and/or sputum smear and/or microbiological culture; routine screening programmes/on purpose screening. Outcome: number of cases detected per 100,000 individuals screened (95% CI). RR: pooled prevalence for pulmonary tuberculosis among screened migrants compared with general population in host country (95% CI).	Active TB yield/100,000 (95% CI): 349 (290–408); RR (95% CI): 48.2 (23.3–99.6). Immigrant class: refugees: 1,192 (668–1,717); RR 130.6 (58.8–290.2), migrants: 284 (204–364); RR 29.4 (9.7- 88.9), asylum seekers: 270 (198–342); RR 30.1 (19.3–47.1). European countries/immigrant class: refugees: 577 (206–949), migrants: 225 (129–322), asylum seekers: 267 (194–341). Region of origin: Europe: 236 (131–340), Africa: 655 (319–990), Asia: 1,117 (625–1,608).

AMSTAR: A MeaSurement Tool to Assess systematic Reviews [22]; CI: confidence interval; CXR: chest radiography; EEA: European Economic Area; EU: European Union; GRADE: The Grading of Recommendations Assessment, Development and Evaluation; HCW: healthcare workers; HIV: human immunodeficiency virus; IQR: interquartile range; LTBI: latent tuberculosis infection; N/A: not applicable; OR: odds ratio; PTB: pulmonary TB; QUADAS: Quality Assessment of Diagnostic Accuracy Studies; RR: risk ratio; SSA: sub-Saharan Africa; TB: tuberculosis; UK: United Kingdom; US: United States.

Table 1B

Characteristics of included studies for effectiveness of active tuberculosis screening

Study	Certainty of evidence	Design	Population	Intervention/ outcomes	Results
Aldridge et al. 2014 [25]	Quality of systematic review (AMSTAR): 8/11. Quality of data of included individual studies (GRADE): very low.	Systematic review 1980–2014. n = 15 studies.	Migrants, asylum seekers, foreign-born citizens, undocumented foreigners or migrants. 3,739,266 migrants screened between 1982 and 2010: min 873–max 3,092,729 culture-confirmed. Types of migrants screened: migrants (n = 592,673); refugees (n = 52,991), mixed (n = 3,092,729), adoptees: n = 873).	Interventions: CXR, culture, smear for acid-fact bacilli, drug-resistant disease, LTBI (any method). Outcome: yield of culture-confirmed active TB per 100,000 by TB prevalence in country of origin.	TB incidence/100,000 person-years at 7 years post migration: Africa: 190, Asia: 80, Somalia: 520, Pakistan: 160, Vietnam: 210, Former Yugoslavia: 40/100,000.
Van't Hoog et al. 2013 [30]	Quality of systematic review (AMSTAR): 6/11. Quality of data of included individual studies (GRADE): very low.	Systematic review 1992–2012. n = 17 studies (24 publications), 11 community prevalence surveys.	Adults (> 15 years) or general population undergoing first screening (HIV-negative and unknown HIV status). Median: 8,044 participants, IQR: 98–20,566.	Intervention: symptoms, CXR, combinations. Outcomes: sensitivity and specificity (95% CI) to detect active TB.	CXR screening had greater accuracy compared with symptoms screening. CXR with any abnormality: sensitivity (95% CI): 97.8% (95.1–100.0), specificity (95% CI): 75.4% (72.0–78.8). CXR with abnormality suggestive of TB: sensitivity: 86.8% (79.2–94.5), specificity: 89.4% (86.7–92.0). Any symptom screening: High HIV/SSA: sensitivity: 84.2% (75.6–92.7), specificity: 74.0% (53.1–94.9). Low HIV/Asia: sensitivity: 69.8% (57.9–81.8), specificity: 60.6% (34.7–86.0). Low and high HIV combined: sensitivity: 77.0% (68.0–86.0), sensitivity: 67.7% (50.2–85.1).

AMSTAR: A MeaSurement Tool to Assess systematic Reviews [22]; CI: confidence interval; CXR: chest radiography; EEA: European Economic Area; EU: European Union; GRADE: The Grading of Recommendations Assessment, Development and Evaluation; HCW: healthcare workers; HIV: human immunodeficiency virus; IQR: interquartile range; LTBI: latent tuberculosis infection; N/A: not applicable; OR: odds ratio; PTB: pulmonary TB; QUADAS: Quality Assessment of Diagnostic Accuracy Studies; RR: risk ratio; SSA: sub-Saharan Africa; TB: tuberculosis; UK: United Kingdom; US: United States.

studies were identified by our co-authors and through searching bibliographies of included studies. In the second search, using the search terms 'tuberculosis', 'screening', 'costs' and 'cost-effectiveness', we searched MEDLINE, Embase, the National Health Service Economic Evaluation Database (NHS EED), the Database of Abstracts of Reviews of Effects (DARE), the Tufts Medical Center Cost-Effectiveness Analysis Registry and Google Scholar for entries between 1 January 2000 and 31 May 2016.

Study selection and quality assessment

We identified and included systematic reviews and evidence-based guidelines that directly addressed each key question along the active TB screening evidence chain and prioritised documents focusing on newly arrived (< 5 years in the host country) migrants. Migrant populations included were non-forced economic migrants, and refugees, asylum seekers and illegal migrants who may have been forced to flee conflict, natural disaster, or economic peril [17]. We only included studies published in full and in English

Table 1c

Characteristics of included studies for effectiveness of active tuberculosis screening

Study	Certainty of evidence	Design	Population	Intervention/ outcomes	Results
Pinto et al. 2013 [31]	Quality of systematic review (AMSTAR): 8/11. Quality of data of included individual studies not mentioned but all studies had verification bias (assessed by QUADAS): 54% not representative, 46% did not mention blinding.	Systematic review up to 2012. n = 12 studies with combined clinical and radiographic features, 1 with clinical prediction rules.	Adult patients (≥ 15 years) with possible PTB (excluding pneumoconiosis, malignancies, immune-mediated inflammatory disease or haemodialysis). 5,767 participants.	Intervention: CXR scoring system. Outcomes: sensitivity and specificity (95% CI) with no pooling (median, range presented), diagnostic OR: odds of patient with PTB and specific clinical or radiographic feature(s)/odds without PTB and having the same feature(s).	Significantly associated with pulmonary TB: upper lobe infiltrates: OR (95% CI): 3.57 (2.38–5.37), cavities diagnostic: OR range: 1.97–25.66. Scoring systems characteristics: sensitivity: median 96%, IQR: 93–98%, sensitivity: median 46%, IQR: 35–50%.
Ködmön et al. 2016 [6]	High quality individual study (assessed by New Castle-Ottawa): 8/8.	Public health surveillance of reported active TB cases from EU and EEA countries 2007–2013. 29 countries.	Notified TB cases. 527,467 TB cases reported, 491,652 with reported country of origin, 91,925 cases from outside EU/EEA.	Intervention: N/A. Outcomes: successful treatment: cured case or treatment completed after 12 months, death during treatment.	Number of reported TB treatment outcome: EU/EEA: 86%, non-EU/EEA: 82%. Treatment success (24 countries): EU/EEA: 74.6%, non-EU/EEA: 77.4%. Treatment failure: EU/EEA: 2.3%, non-EU/EEA: 0.2%. Lost to follow-up: EU/EEA: 6.6%, non-EU/EEA: 5.4%. Death during treatment: EU/EEA: 8.2%, non-EU/EEA: 3.2%.
Mitchell et al. 2013 [32]	Quality of systematic review (AMSTAR): 3/11. Quality of studies judged to have significant degree of heterogeneity and reporting and publication bias. The tool used to measure bias was not mentioned.	Qualitative and quantitative systematic review and meta-synthesis. n = 218 studies.	(i) Risk groups found in health services (adolescents, drug-dependent, HIV-positive etc.). (ii) Congregate/occupational/ environmental (elderly, HCWs, prisoners etc.). (iii) Behavioural/marginalised risk groups (homeless, migrants, sex workers etc). 33 possible risk groups.	Intervention: N/A. Outcome: proportion of eligible persons who consented to undergo TB screening, per risk-group (equivalent of recruitment rate).	TB screening acceptability: overall: > 80%, migrants: 85% (range: 55–96%). Simple TB screening (at point-of-care) more acceptable than referral on multiple visits. Inclusion of HIV testing may be a deterrent in some risk groups. TB screening and treatment are low priority for groups facing housing insecurity, addiction, threat of violence, deportation. Screening in hard-to-reach populations is more acceptable if benefits are immediate and tangible. Acceptability of TB screening is dependent on quality of human interaction as well as perceived negative consequences.

AMSTAR: A MeaSurement Tool to Assess systematic Reviews [22]; CI: confidence interval; CXR: chest radiography; EEA: European Economic Area; EU: European Union; GRADE: The Grading of Recommendations Assessment, Development and Evaluation; HCW: healthcare workers; HIV: human immunodeficiency virus; IQR: interquartile range; LTBI: latent tuberculosis infection; N/A: not applicable; OR: odds ratio; PTB: pulmonary TB; QUADAS: Quality Assessment of Diagnostic Accuracy Studies; RR: risk ratio; SSA: sub-Saharan Africa; TB: tuberculosis; UK: United Kingdom; US: United States.

Table 2

Numbers needed to screen to detect one case of active tuberculosis

TB prevalence in country of origin/100,000	Yield of culture-confirmed active TB/100,000[a]	95% CI	NNS[b]	95% CI
50–149	19.7	10.3–31.6	5,076	3,175–9,709
150–249	166.2	140–194	602	514–714
250–349	133.5	111–158	749	631–903
›350	335.9	283–393	298	254–353

CI: confidence interval; CXR: chest radiography; NNS: numbers needed to screen; TB: tuberculosis.

[a] The yield of active TB detection in pre-arrival CXR screening programmes for migrants by TB incidence in country of origin from Aldrige et al. [25].

[b] NNS = 1/mean prevalence of active TB found through CXR screening stratified by TB incidence in the country of origin.

or French. If more than one version of a systematic review was identified, the most recent was considered. Studies were excluded if they were not relevant to the key questions, if they were not a systematic review or guideline, if the study methodology was unclear, and if they focussed only on non-generalisable subgroups (such as healthcare workers or HIV-positive people) or addressed only latent TB screening. Two authors screened the titles and abstracts, assessed selected full-text articles for eligibility and extracted data from included articles. Disagreements were resolved by consensus or by a third author. The methodological quality of systematic reviews was assessed using the AMSTAR tool (A Measurement Tool to Assess Systematic Reviews) and the quality of individual studies was assessed with the Newcastle-Ottawa scale [22,23]. The GRADE criteria were applied to assess the quality and certainty of the evidence for the individual studies included in the systematic reviews [24].

Data extraction and synthesis

The following information was extracted from each study: study design, objectives, analyses, quality assessment of the individual studies included in the systematic review, population examined, number of included studies, total number of participants included, intervention, outcome and results. We created GRADE evidence profiles and summary of findings tables for each outcome where appropriate. Numbers needed to screen (NNS) were estimated by calculating 1/mean prevalence of active TB found through CXR screening stratified by TB incidence in the country of origin as reported in the study by Aldridge et al. [25].

For each of the cost-effectiveness studies, we extracted the following data: economic methods used (e.g. micro-costing study, within-trial cost-utility analysis, Markov model), description of the case base population, the intervention and comparator, the absolute size and relative difference in resource use and cost-effectiveness (e.g. incremental net benefit (INB) or incremental cost-effectiveness ratio (ICER)) [26]. The certainty of economic evidence in each study was assessed using the relevant items from the 1997 Drummond checklist [27]. All currencies were converted to 2015 Euros using the Cochrane web-based currency conversion tool: https://eppi.ioe.ac.uk/costconversion/default.aspx.

Results

In the first search, we retrieved 3,375 studies through database searching and 22 additional studies identified through other sources on the effectiveness of TB screening in migrant populations (Figure 2). After removal of duplicates, 2,884 studies were screened by title and abstract. A total of 127 studies underwent full text assessment. We did not identify any single study on the effectiveness of active TB screening in migrants. We therefore included seven studies that addressed the active TB screening evidence chain: the yield of detecting active TB among migrants in CXR screening programmes (n = 3) [25,28,29], the performance characteristics of CXR to detect active TB (n = 2) [30,31], the effectiveness of TB therapy in those born in the EU/EEA and the foreign-born population (n = 1) [6], and the uptake of active TB screening by migrants (n = 1) [32]. In the second search, 2,856 articles were retrieved through database searching and an additional 13 articles identified through other resources (Figure 3). After removal of duplicates, 2,740 studies were screened by title and abstract. A total of 37 studies underwent full text assessment and three individual studies were included for analysis [33-35].

Effectiveness of active tuberculosis screening

Yield of chest radiography to detect active tuberculosis

Three systematic reviews assessed the yield of detecting active TB among migrant populations in CXR screening programmes performed before and after arrival in the EU/EEA and low TB incidence countries outside the EU/EEA [25,28,29]. The yield of active TB was heterogeneous across studies, varied by migrant type and the setting in which the screening was done and was consistently higher with higher TB incidence in the country of origin (Table 1).

Klinkenberg et al. found that the overall yield of active TB screening programmes in migrants upon and after arrival in 26 studies done in EU/EEA countries was 350 per 100,000 population [29]. The yield differed by

Table 3a

Characteristics of included studies for resource use, costs, and cost-effectiveness of active tuberculosis screening

Study	Certainty of economic evidence based on the Drummond criteria[a] [27]	Methodological approach/population	Intervention(s)	Cost-effectiveness (ICER or INB) per case prevented	Resource Requirements
Schwartzman et al. 2000 [33]	Certainty of evidence: moderate. Allowance was made for uncertainty in the estimates of costs and consequences, and ranges were provided. No PSA were performed. Justification was provided for a range of values estimated in one-way sensitivity analyses. The cost-effectiveness results were sensitive to model inputs including the probability of INH prescribed; probability of INH treatment completed; cost of inpatient treatment; TB infection rate and HIV seropositivity.	Methods: decision-analytic Markov model; 20 year time horizon; 3% discount rate, perspective of the third-party payer (central and provincial governments); scenario analysis based on INH completion conducted. Population: 20-year-old immigrants to Canada originating from Sub-Saharan Africa, South-east Asia, Western Europe. Cohort 1: 50% TB-positive, 10% HIV-positive. Cohort 2: 50% TB-positive, 1% HIV-positive. Cohort 3: 5% TB-positive, 1% HIV-positive.	Three strategies: (i) No screening (ii) CXR (iii) TST	Cohort 1: TST vs CXR: CAD 2,601(EUR 29,990); CXR vs no screening: CAD 3,934 (EUR 3,618). Cohort 2: TST vs CXR: CAD 66,759 (EUR 61,413); CXR vs no screening: CAD 10,627 (EUR 9,776). Cohort 3: TST vs CXR: CAD 68,799 (EUR 63,289); CXR vs no screening: CAD 236,496 (EUR 217,557).	Resource requirements are high in cohorts 1 and 2, and moderate in cohort 3. Costs/1,000 patients: Cohort 1 (high risk): TST: CAD 436,390 (EUR 401,444); CXR: CAD 338,310 (EUR 311,218); No screening: CAD 332,020 (EUR 305,432). Cohort 2 (intermediate risk): TST: CAD 342,730 (EUR 315,284); CXR: CAD 231,430 (EUR 212,897); No screening: CAD 218,250 (EUR 200,773). Cohort 3 (low risk): TST: CAD 62,640 (EUR 57,623); CXR: CAD 51,170 (EUR 47,072); No screening: CAD 21,820 (EUR 20,072).

CAD : Canadian dollar; CXR: chest radiography; EUR: Euro; HIV: human immunodeficiency virus; ICER: incremental cost-effectiveness ratio; INB: incremental net benefit; INH: isoniazid; PSA: probabilistic sensitivity analysis; QFT: quantiferon; TB: tuberculosis; TST: tuberculin skin test; USD: United States dollar.

[a] The Drummond Criteria [27]: (i) Was a well-defined question posed in answerable form? (ii) Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where and how often)? (iii) Was the effectiveness of the programme or services established? (iv) Were all the important and relevant costs and consequences for each alternative identified? (v) Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost working days, gained life years)? (vi) Were the cost and consequences valued credibly? (vii) Were costs and consequences adjusted for differential timing? (viii) Was an incremental analysis of costs and consequences of alternatives performed? (ix) Was allowance made for uncertainty in the estimates of costs and consequences? (x) Did the presentation and discussion of study results include all issues of concern to users?

All currencies were converted to 2015 Euros using the Cochrane web-based currency conversion tool: https://eppi.ioe.ac.uk/costconversion/default.aspx. Resource use was expressed in cost per person and classified as low (savings or ≤ USD 1,000/person (EUR 808)), moderate (USD 1,000–100,000/person (EUR 808–80,845)) or high (USD ≥ 100,000/person (EUR > 80,845)).

Table 3b

Characteristics of included studies for resource use, costs, and cost-effectiveness of active tuberculosis screening

Study	Certainty of economic evidence based on the Drummond criteria[a] [27]	Methodological approach/population	Intervention(s)	Cost-effectiveness (ICER or INB) per case prevented	Resource Requirements
Dasgupta et al. 2000 [34]	Certainty of evidence: low. Limited allowance was made for uncertainty in the estimates of costs and consequences; ranges were provided. No PSA was performed No one-way or two-way sensitivity analyses using higher or lower costs, other discount rates or comparisons were performed. Scenario analyses undertaken. The cost-effectiveness results were sensitive to costs for passive diagnosis of TB, INH prescription rate, screening referral criteria and future risk of active TB.	Methods: cost-effectiveness analysis based on prospective non-randomised cohorts; results reported in Canadian dollars; prospective cohort study over 1 year of costs. Population: immigration applicants undergoing CXR screening, already arrived immigrants requiring screening for latent TB, close contacts of active cases resident in Montreal, Quebec, Canada.	Three strategies: (i) CXR in migrants applying for a permanent residence (ii) Surveillance CXR +/−TST (iii) Close contacts CXR +/−TST	Over 1 year, the three programmes detected 27 cases of active TB and prevented 14 future cases. Close-contact screening resulted in net savings of CAD 815 (EUR 758) for each active case detected and treated and of CAD 2,186 (EUR 2,033) for each future active case prevented, compared with passive case detection.	Resource requirements were moderate in applicants and close contacts and higher on those on surveillance. Costs of TB detected and treated: Close contacts CXR +/−TST: CAD 10,275 (EUR 9,560); Applicants CXR: CAD 31,418 (EUR 29,232); Those on surveillance CXR +/−TST: 55,728 (EUR 51,850).
Oxlade et al. 2007 [35]	Certainty of evidence: moderate. Allowance was made for uncertainty in the estimates of costs and consequences; ranges were provided. No PSA was performed One-way or two-way sensitivity analyses using higher or lower costs, other discount rates and test performance characteristics were undertaken. The cost-effectiveness results were sensitive to TST and QFT sensitivity, costs of TST and QFT, close contacts investigation, the passive TB case detection rate and risk of re-activation.	Methods: decision-analytic Markov model; 20 year time horizon; 3% discount rate; Canadian health system perspective; Costs reported in 2004 Canadian dollars. Population: foreign-born entrants to Canada; close contacts of active TB cases.	Five strategies: (i) CXR (ii) No screening (iii) TST (iv) QFT (v) TST followed by QFT if TST-positive	ICER (CAD/case prevented): CXR vs no screening: CAD 875 (EUR 690); TST vs CXR: CAD 9,800 (EUR 7,738), assuming that prescription and completion rates in indicated patients were 100% (relative to the baseline assumption of 73% prescription and 50% completion).	Resource requirement were: low to moderate for CXR and moderate for QFT in immigrants from medium and high incidence countries; high for CXR and QFT in immigrants from low-incidence countries. Costs of CXR screening ranged from: low TB incidence source (2/100,000), CAD 52,553 (EUR 41,499); high TB incidence (120/100,000), CAD 328,190 (EUR 259,160).

CAD : Canadian dollar; CXR: chest radiography; EUR: Euro; HIV: human immunodeficiency virus; ICER: incremental cost-effectiveness ratio; INB: incremental net benefit; INH: isoniazid; PSA: probabilistic sensitivity analysis; QFT: quantiferon; TB: tuberculosis; TST: tuberculin skin test; USD: United States dollar.

[a] The Drummond Criteria [27]: (i) Was a well-defined question posed in answerable form? (ii) Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where and how often)? (iii) Was the effectiveness of the programme or services established? (iv) Were all the important and relevant costs and consequences for each alternative identified? (v) Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost working days, gained life years)? (vi) Were the cost and consequences valued credibly? (vii) Were costs and consequences adjusted for differential timing? (viii) Was an incremental analysis of costs and consequences of alternatives performed? (ix) Was allowance made for uncertainty in the estimates of costs and consequences? (x) Did the presentation and discussion of study results include all issues of concern to users?

All currencies were converted to 2015 Euros using the Cochrane web-based currency conversion tool: https://eppi.ioe.ac.uk/costconversion/default.aspx. Resource use was expressed in cost per person and classified as low (savings or ≤ USD 1,000/person (EUR 808)), moderate (USD 1,000–100,000/person (EUR 808–80,845)) or high (USD ≥ 100,000/person (EUR > 80,845)).

migrant type (asylum seekers: median: 350/100,000; interquartile range (IQR): 250–410, and other migrants: median: 170; IQR: 100–630) and by setting where the screening was conducted (port of arrival: median: 360; IQR: 100–5,200, reception/holding centres: median: 290; IQR: 100–380, community post arrival: median: 220; IQR: 100–380, and occasional screening: median: 1,720; IQR: 730–2,740). The yield varied widely also between host countries, from as low as 110 per 100,000 in the Netherlands to as high as 2,340 per 100,000 in Italy, probably reflecting differences in migrant type, country of origin and circumstances of travel in the migrants screened [36]. Arshad et al. assessed the yield of active TB screening among migrants originating from intermediate or high TB incidence countries upon and after entry to low TB incidence countries and found a similar overall yield of active TB case detection of 349 per 100,00 population [28]. The yield also varied by migrant type (refugees: 1,192; 95% confidence interval (CI): 668–1,717, regular migrants: 284; 95% CI: 204–364 and asylum seekers: 270; 95% CI: 198–342) and TB incidence in the country of origin (Europe: 236; 95% CI: 131–340, Africa: 655; 95% CI: 319–990 and Asia: 1,117; 95% CI: 625–1,608) [28]. Finally, Aldridge et al. assessed the yield of CXR screening for active TB among migrants in the pre-arrival TB screening programmes. No overall estimates were presented but the yield increased steadily with the TB incidence in migrant source countries. The yield was 19.6 per 100,000 in migrants originating from countries with a TB incidence lower than 50 per 100,000 and 336 per 100,000 in migrants originating from countries with a TB incidence greater than 350 per 100,000 [25]. The quality of the data in studies included in these three systematic reviews was very low to low (GRADE).

Accuracy of chest radiography to detect active tuberculosis

We identified two systematic reviews that assessed the performance of CXR to detect active TB [30,31]. Van't Hoog et al. showed that CXR (presence of any abnormality) was highly sensitive (98%) and moderately specific (75%) to detect active TB [30]. Screening for active TB with symptoms alone had lower sensitivity (78%) and specificity (68%) [30]. Pinto et al. also found that CXR to detect active TB was highly sensitive 95% (range: 81–100%) but less specific 42% (range: 22–72%) [31]. Focussing on the presence of upper lobe infiltrates and cavities increased the predictive value for diagnosing active TB. The certainty of the evidence of these two studies was judged to be very low (Table 1).

Numbers needed to screen

Using inputs of the yield of CXR reported by Aldridge in the pre-arrival programmes we estimated the NNS to detect one case of active TB in migrants stratified by TB incidence in source countries (Table 2) [25]. We found that the NNS decreased dramatically with increasing TB incidence in source countries and ranged from 5,076 in countries with a TB incidence between 50 and 149 per 100,000 to 298 in countries with a TB incidence greater than 350 per 100,000.

Effectiveness of active tuberculosis treatment

In an ECDC report on TB surveillance from 2007 to 2013, TB treatment outcomes were similar or better in those born outside the EU/EEA than in those born in the EU/EEA [6]. Treatment success was as high in the foreign-born (for all regions of origin) compared with those born in the EU/EEA (77.4% vs 74.6%); however, their failure rates (0.2% vs 2.4%) and default rates (5.4% to 6.6%) were lower. This European surveillance data was judged to be high-quality evidence (Table 1).

Acceptability of screening

Mitchell et al. conducted a review to determine the acceptability of targeted TB screening and active case finding among vulnerable and at-risk groups and found that TB screening was well accepted by the majority of risk groups, including migrants (85%; range: 55–96%). Lower acceptability was found among persons living with HIV/AIDS and individuals in refugee camps and internally displaced persons [32]. Overall, the study found that simple TB screening (at point of care) was more acceptable than referral requiring multiple visits. The evidence in this study was judged to have considerable bias (Table 1).

Cost-effectiveness of active tuberculosis screening programmes

There was very little information on the cost-effectiveness of active TB screening in migrant populations as only three studies were identified. These studies demonstrated that the most cost-effective CXR screening strategies were among high-prevalence groups, close contacts of those with known TB, and migrants at entry if they originated from intermediate (60/100,000) and high (›120/100,000) TB incidence countries [33-35] (Table 3).

Two studies demonstrated that CXR screening of migrants was cost-effective compared with no screening: Oxlade et al. determined that the ICER of CXR relative to no screening was CAD 30,000 (Canadian dollars in 2004; EUR 23,690) per case averted in migrants from intermediate TB incidence source countries, and less than CAD 1,000 (EUR 789) per case averted in the high-incidence group [35]. Similarly, CXR compared with no screening in immigrants with a risk of reactivation of more than 5% was cost-effective. Dasgupta et al. reported that close-contact screening resulted in net savings of CAD 815 (EUR 758) for each active case detected and treated and of CAD 2,186 (EUR 2,033) for each future active case prevented, compared with passive case detection [34]. The certainty of the evidence in these studies ranged from low to moderate (Table 1).

Discussion

There were no single studies that directly addressed the overall effectiveness of active TB screening programmes on the health outcomes of migrant

populations. We therefore evaluated the screening chain of evidence. The yield of detecting active TB through CXR screening of migrants was heterogeneous across studies and varied by migrant type and the setting in which the screening was done, but consistently increased with higher TB incidence in the country of origin [25,28,29]. The NNS to detect one case of active TB decreased and cost-effectiveness increased with increasing TB incidence in source countries [25,34,35]. CXR is a highly sensitive and moderately specific screening tool to detect active TB [30,31]. CXR screening is highly acceptable to most foreign-born populations [32].

The yield of CXR to detect active TB varied widely among migrant sub-groups in the three systematic reviews (120 to 2,340/100,000) however the overall yield (350 cases/100,000) in the post-arrival setting was consistent between studies [28,29]. There was also consistency in the increase in yield with increasing TB incidence in source countries in both pre- and post-arrival setting [25,28,29]. The majority of studies in the post-arrival setting were carried out in various EU/EEA countries whereas pre-arrival screening was done in migrants arriving in the United Kingdom. The wide range in yield of post-arrival screening programmes reflects the heterogeneity of the programmes and the composition of migrants screened. Post-arrival programmes differed widely between countries with respect to timing of screening (port of arrival, in reception areas, in the community or ad hoc), countries of origin of migrants received, the type of migrants targeted (all migrants, asylum seekers only or undocumented migrants), and the threshold of TB incidence in the countries of origin at which screening was performed. Although 31 EU/EEA countries have an active TB screening programme for migrants, the absolute and attributable impact on active TB rates in those countries is unknown [37,38]. Extrapolating from the impact of the well-established pre-migration TB programme in the US, there may be benefit of active TB screening in migrants on TB control in the host country. An evaluation of this programme demonstrated that detecting prevalent active TB before arrival in the US reduced TB notification rates among migrants in the first years after arrival [39].

Higher NNS and lower cost-effectiveness with higher TB incidence in countries of origin suggests that active TB screening programmes will be most efficient when targeting migrant populations from high TB incidence countries. This is consistent with WHO recommendations to focus active screening on the highest risk groups [40]. The heterogeneity of the estimates from these studies, however, limits the ability to provide more precise guidance on which type of migrants to target, the best timing to screen or the optimal threshold of TB incidence in countries of origin. Although screening migrants from the highest TB incidence countries is most efficient, the impact on TB incidence in the host country might be limited since many cases occur in migrants from countries with lower TB incidence and in migrants who entered the country many years before TB diagnosis [41,42].

Although the CXR is a good screening test for active TB and is highly sensitive (78%), confirmatory sputum culture for TB is essential to improve specificity and is the gold standard for diagnosing active TB [30,31,43]. Screening for symptoms of active TB may be a reasonable first screening tool in certain situations such as in an emergency setting with no on-site CXR facilities. These situations include the reception centres in Italy and Greece and/or when the receipt of a large number of migrants overwhelm health systems (as occurred in Europe in 2015) [8]. Those with symptoms would need referral for CXR. The choice of the screening algorithm will need to be determined by the availability, feasibility and cost of the tests.

Active TB case finding in at-risk populations is an important TB control strategy as it allows for early detection and treatment, reduces individual morbidity and prevents TB spread to others. Active screening programmes are, however, limited by the fact that the yield is low (0.31–1.21%) and that they do not capture or prevent the majority of incident TB cases occurring in the EU/EEA that are primarily due to reactivation of latent TB or new acquisition during travel [13]. Furthermore, the epidemiology of TB in the EU/EEA is heterogeneous. While migrants make up the majority of TB cases in low TB incidence EU/EEA countries, they make up a minority of cases in member states with higher TB incidence (Supplement 2). Screening for active TB in migrants will therefore need to be tailored to the local TB epidemiology in host countries, and the healthcare capacity in each setting [2,3]. Finally, many migrant sub-groups are vulnerable and face barriers in accessing heath care and treatment in the EU/EEA [44]. Addressing barriers in accessing care and treatment for all migrants, including the right to healthcare access for all and programmes tailored to address unique needs, will be essential to ensuring the most effective active TB screening and treatment programmes.

Study limitations

Our study was limited by the fact that we did not retrieve any studies that directly estimated the effectiveness of active TB screening and by the very limited data on the cost-effectiveness of active TB screening. The search was limited by the fact that it was conducted up until May 2016 and that we only included studies published in English or French. A recent narrative review of the effectiveness and cost-effectiveness, however, reports similar literature and findings as our study [45]. Our findings are further limited by the quality of the original studies that were included in the systematic reviews. Study quality was low or very low, as almost all included studies were observational studies.

Evidence gaps and future directions

Robust studies on the yield of active TB screening among migrants by age group, migration type, timing of

screening, threshold of TB incidence in source countries and the associated cost-effectiveness will be required to design the most effective active TB screening programmes. Additional studies are needed that determine the absolute and attributable impact of active TB programmes on TB control in low-incidence countries in the EU/EEA and the optimal threshold of incidence in source countries at which to screen. Finally, evidence on the comparative effectiveness and cost-effectiveness of different TB control strategies (active vs latent TB screening) for migrants will be required to prioritise TB control efforts for this population.

Conclusions

Active TB screening programmes that target migrants from high TB incidence countries will provide the highest yield and will be the most cost-effective. The heterogeneity of the estimates from the studies identified and the small number of studies addressing both the effectiveness and cost-effective of active TB screening in migrants limits the ability to provide precise guidance on which type of migrants to target, the best timing to screen or the optimal threshold of TB incidence in countries of origin. This highlights the need for further data to inform active TB screening programmes for migrants in the EU/EEA.

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Conflict of interest

KP led and CG was an author on the Canadian Migrant Guidelines including TB. AM co-led the work on the WHO LTBI screening guidelines. MP holds a Gilead Sciences grant for a project outside of the submitted work.

Authors' contributions

CG, DZ, MP, AM, RLM, TN and KP contributed to the design and research questions. KP, RC were part of the core methods team members for the ECDC Guidelines project developing the methods. DZ, MP, MvW and AM provided substantial content on the research question and design. CG, IM, BA and MW wrote the manuscript. CNAC, MW, BS, TM, CH and AM reviewed and selected the literature, and extracted and synthesised the data. RLM, AT, and NR conducted the review and synthesised the data for cost-effectiveness analysis. All authors read and approved the manuscript.

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The effectiveness and cost-effectiveness of screening for latent tuberculosis among migrants in the EU/EEA: a systematic review

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Background: Migrants account for a large and growing proportion of tuberculosis (TB) cases in low-incidence countries in the European Union/European Economic Area (EU/EEA) which are primarily due to reactivation of latent TB infection (LTBI). Addressing LTBI among migrants will be critical to achieve TB elimination. **Methods:** We conducted a systematic review to determine effectiveness (performance of diagnostic tests, efficacy of treatment, uptake and completion of screening and treatment) and a second systematic review on cost-effectiveness of LTBI screening programmes for migrants living in the EU/EEA. **Results:** We identified seven systematic reviews and 16 individual studies that addressed our aims. Tuberculin skin tests and interferon gamma release assays had high sensitivity (79%) but when positive, both tests poorly predicted the development of active TB (incidence rate ratio: 2.07 and 2.40, respectively). Different LTBI treatment regimens had low to moderate efficacy but were equivalent in preventing active TB. Rifampicin-based regimens may be preferred because of lower hepatotoxicity (risk ratio = 0.15) and higher completion rates (82% vs 69%) compared with isoniazid. Only 14.3% of migrants eligible for screening completed treatment because of losses along all steps of the LTBI care cascade. Limited economic analyses suggest that the most cost-effective approach may be targeting young migrants from high TB incidence countries. **Discussion:** The effectiveness of LTBI programmes is limited by the large pool of migrants with LTBI, poorly predictive tests, long treatments and a weak care cascade. Targeted LTBI programmes that ensure high screening uptake and treatment completion will have greatest individual and public health benefit.

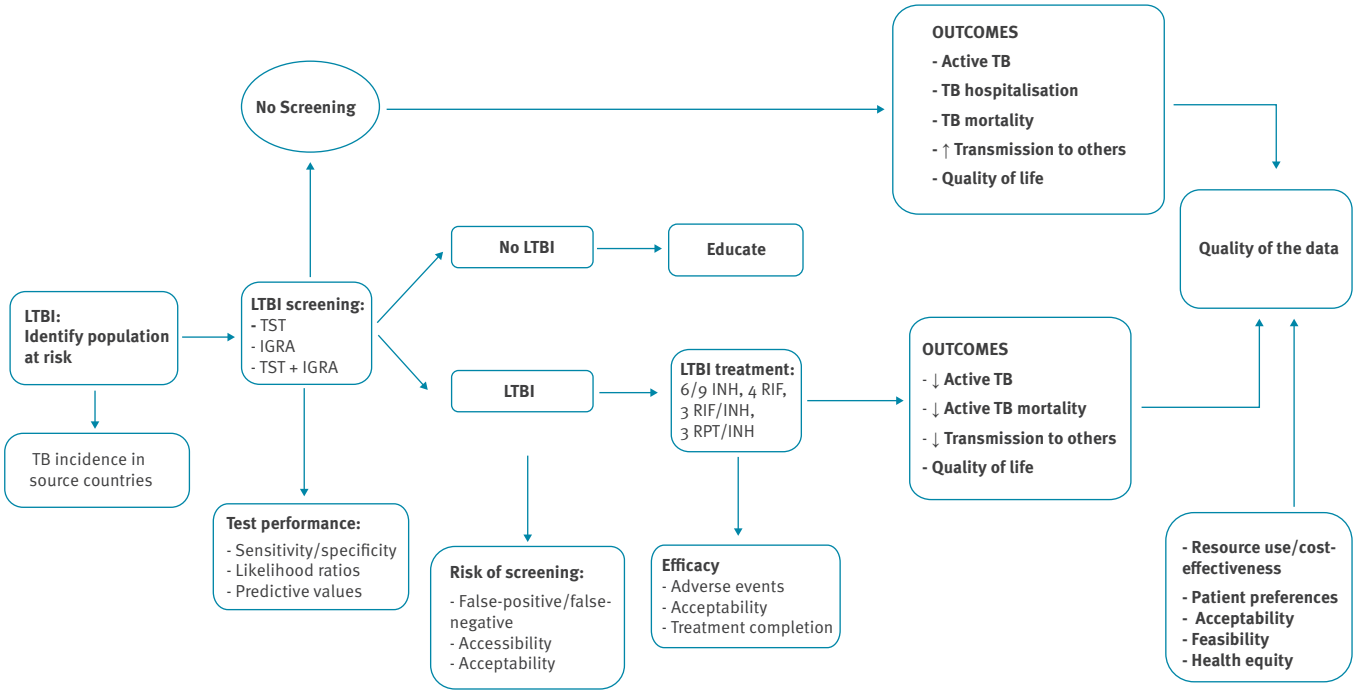
Introduction

Tuberculosis (TB) control programmes in the European Union/European Economic area (EU/EEA) have successfully managed to reduce TB rates by 50% over the past 20 years [1-4]. Although EU/EEA countries are committed to the ambitious World Health Organisation (WHO) goal of TB elimination, the rate of TB decline of 4.3% per year over the past decade (2007–2016) in the region is insufficient to achieve this goal [1-5]. It is projected that a mean decline of 18% per year will be necessary to meet the WHO goal and that TB control strategies must be scaled up, including addressing the burden of latent TB infection (LTBI) [3,5,6].

The foreign-born population makes up an increasing and considerable number and proportion of all TB cases in EU/EEA countries with a low TB incidence (< 10 cases/100,000 population) [7]. The majority of these

Figure 1

Analytic framework for latent tuberculosis screening in migrants



IGRA: interferon gamma release assay; INH: isoniazid; LTBI: latent tuberculosis infection; RIF: rifampicin; RPT: rifapentine; TB: tuberculosis; TST: tuberculin skin test.

cases are due to reactivation of LTBI acquired in the patients' countries of origin. Although foreign-born people make up 11.4% of the population in the EU/EEA, they represented more than one quarter of reported TB cases in 2015 [4,8,9]. This burden is even greater in EU/EEA countries with low TB incidence where often more than half of all reported TB cases occur in migrants [4]. This is because a considerable proportion of migrants were born in high TB burden countries where 26–46% of the population are latently infected with TB [4,10-13]. The WHO has only conditionally recommended LTBI screening among migrants living in low TB burden countries (<100 cases/100,000 population) owing to reservations about implementation and the low quality of evidence of the effectiveness and cost-effectiveness of LTBI programmes in these settings [6]. Screening the potentially large pool of latently infected migrants and treating those found to be positive poses an enormous challenge in the EU/EEA, especially since less than half of these countries have such programmes [11,14,15]. The aim of this study was to conduct a systematic review on the effectiveness and cost-effectiveness of screening for latent TB among migrants to the EU/EEA to inform migrant screening guidelines.

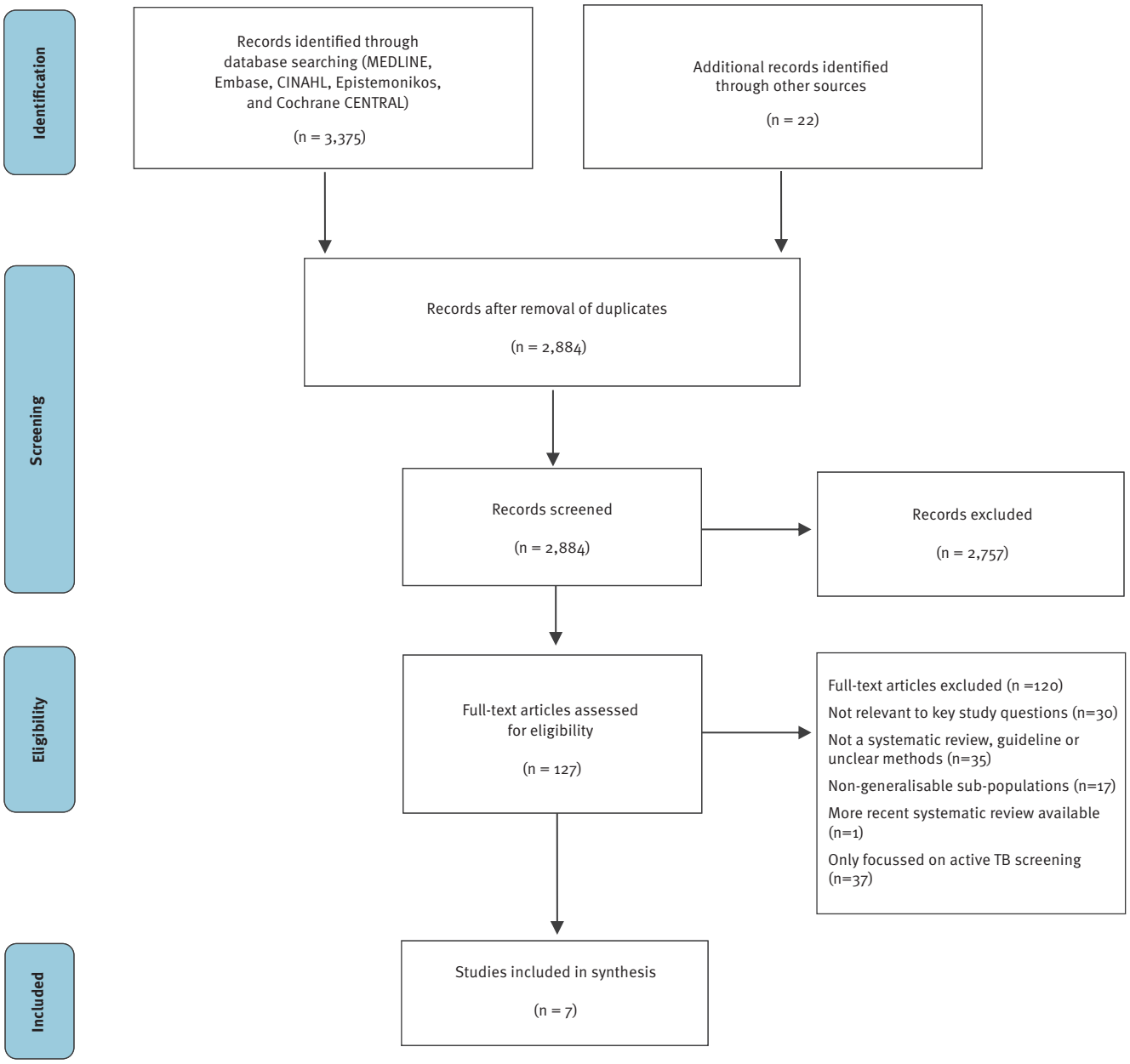
Methods

Overall approach and key questions

This review supports a project of the European Centre for Disease Prevention and Control (ECDC) to develop guidance on screening for six infectious diseases (chronic hepatitis C, hepatitis B, HIV, TB (active and latent), and intestinal parasites) in newly arrived migrants to the EU/EEA. The project followed the new Grading of Recommendations Assessment, Development and Evaluation (GRADE)-ADOLOPMENT approach to conduct systematic reviews on screening migrant populations for these six infectious diseases [16]. The review protocol and the methods of ADOLOPMENT guideline development have been published [16,17]. All reviews followed a Cochrane methodological approach and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methods for reporting systematic reviews [18]. For this review, we developed research questions (PICO), an analytic framework to illustrate the screening evidence pathway, and identified and prioritised clinically-important outcomes [19]. These evidence-based review methods were first described by the United States (US) Preventative Task Force [19,20]. We sought to answer two research questions: (i) what is the effectiveness of screening migrants arriving or living in the EU/EEA for LTBI and (ii) what is the resource use, costs and cost-effectiveness of screening migrants for LTBI? To address these questions, we developed an analytic framework (Figure 1) and the following key questions along the LTBI screening evidence pathway: (i) what are the test properties of LTBI screening tests: tuberculin skin test (TST), interferon gamma release assay (IGRA) or sequential TST/IGRA, (ii) what are the efficacy and harms of LTBI therapies, (iii) what is the uptake of screening and treatment and completion of treatment,

Figure 2

PRISMA flow diagram, literature search for the effectiveness and cost-effectiveness of latent tuberculosis screening, 1 January 2005–12 May 2016



CINAHL: Cumulative Index to Nursing and Allied Health Literature; TB: tuberculosis.

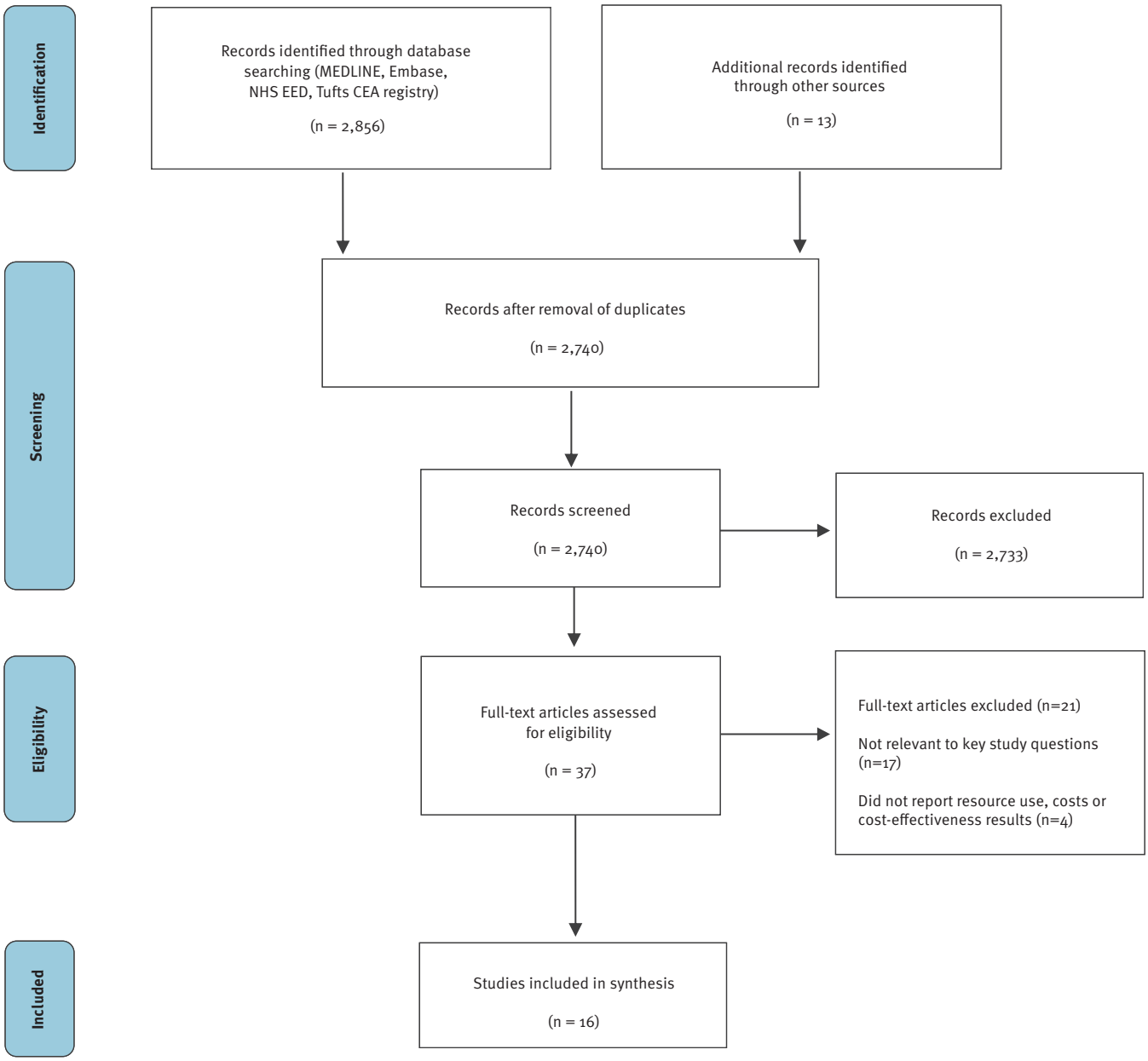
and (iv) what is the cost-effectiveness of LTBI screening and treatment for migrants [17].

Search strategy and selection criteria

Following the GRADE-ADOLOPMENT process, we identified an evidence review that assessed the effectiveness of latent TB infection (LTBI) screening among migrants, published in 2011 by the Canadian Collaboration on Immigrant and Refugee Health (CCIRH), and used this as a starting point for our literature search (anchoring review) [16,21]. The CCIRH review included systematic reviews on the effectiveness of LTBI screening in migrants up to 2008 but did not review cost-effectiveness. We therefore conducted two separate searches to address our research questions. The first search updated the CCIRH evidence review and identified systematic reviews and guidelines on the effectiveness and cost-effectiveness of TB screening programmes in migrant populations from 2005 to 2016. The second search identified individual studies on the resource use, costs and cost-effectiveness of TB screening programmes for migrants over a longer time, 2000 to 2016, given these topics were not covered in the CCIRH evidence review. For the first search, MEDLINE via Ovid, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL),

Figure 3

PRISMA flow diagram, literature search for the resource use, costs and cost-effectiveness of latent tuberculosis, 1 January 2000–31 May 2016



NHS EED: National Health Service Economic Evaluation Database (NHS EED), Tufts CEA: Tufts Medical Centre Cost-Effectiveness Analysis Registry.

Epistemonikis, and Cochrane CENTRAL between 1 January 2005 and 12 May 2016 were searched for evidence on the effectiveness and cost-effectiveness of LTBI screening programmes in migrants. We used a combination of key terms including: 'tuberculosis', 'screening', 'chest-radiograph', 'tuberculin skin test', 'interferon-gamma release assays', 'costs', 'cost-effectiveness' AND 'guidelines', 'reviews'. The search terms and strategy in Ovid MEDLINE are included in Supplement 1. We also searched grey literature and published guidelines and reports at the US Centres for Disease Control and Prevention (CDC), ECDC, WHO, and the International Union Against Tuberculosis and Lung Disease (IUATLD). We did not apply language restrictions to the search. Additional guidelines and studies were identified by our co-authors and through searching bibliographies of included studies. In the second search, using the search terms on 'tuberculosis', 'screening', 'costs' and 'cost-effectiveness', we searched MEDLINE, Embase, the National Health Service Economic Evaluation Database (NHS EED), the Database of Abstracts of Reviews of Effects (DARE) and the Tufts Medical Center Cost Effectiveness Analysis Registry and Google scholar databases between 1 January 2000 and 31 May 2016.

Table 1a

Characteristics of included studies for the effectiveness of latent tuberculosis screening, 2005–2016

Study	Quality/certainty of evidence	Design	Population	Intervention/outcomes	Results
Kahwati et al. 2016 [20]	Quality of systematic review AMSTAR: 6/11. Quality of data of included individual studies: fair to good as assessed by predefined criteria developed by USPSTF.	Systematic review up to 2016. Number of studies: n = 50 on sensitivity, n = 18 on specificity.	Asymptomatic adults at increased risk for active TB: Sensitivity n = 4,167 Specificity n = 10,693	Intervention: TST (5 mm, 10 mm, 15 mm), IGRA (T-SPOT.TB, QFT-2G, QFT-3G). Outcomes: Sensitivity, specificity (95% CI).	Sensitivity, specificity (95% CI) of LTBI screening tests: TST (5 mm): sensitivity: 79% (69–89), specificity 30–97%; TST (10 mm): sensitivity: 79% (71–87), specificity: 97% (96–99); TST (15 mm): sensitivity: 52% (35–68), specificity: 99% (98–99); IGRA (T-SPOT.TB): sensitivity: 90% (87–93), specificity: 95% (92–98); IGRA (QFT-2G): sensitivity: 77% (74–81), specificity: 98% (90–1.0); IGRA (QFT-3G): sensitivity: 80% (77–84), specificity 97% (94–99).
Pai et al. 2008 [27]	Quality of systematic review AMSTAR: 5/11. Quality of data of included individual studies: very low as assessed by GRADE.	Systematic review up to 31 March 2008, English language restriction: n = 38 studies, 3 studies QFT in high TB incidence countries.	BCG-vaccinated; Not BCG-vaccinated; n = 1,879	Intervention: TST, IGRA (QFT-2G, QFT-3G, T-SPOT.TB). Outcomes: Sensitivity, specificity (95% CI).	Sensitivity, specificity (95% CI) of LTBI screening tests: TST overall: sensitivity: 77% (71–82). TST in BCG-vaccinated: specificity: 59% (46–73). TST in non-BCG-vaccinated: specificity: 97% (95–99). IGRA (QFT): sensitivity: 76% (72–80), specificity: 98% (96–99). IGRA (QFT-2G): sensitivity: 78% (73–82). IGRA (QFT-3G): sensitivity: 70% (63–78). IGRA in BCG-vaccinated: specificity: 96% (94–98). IGRA in non-BCG-vaccinated: specificity: 99% (98–100). IGRA (T-SPOT.TB/ ELISpot): sensitivity: 90% (86–93), specificity: 93% (86–100). IGRA (T-SPOT.TB): specificity: 87% (80–92).
Kik et al. 2014 [28]	Quality of systematic review AMSTAR: 7/11. Quality of data of included individual studies: low as assessed by GRADE.	Systematic review 1999 to February 2014: n = 29 studies, 19 prospective cohorts, only 8/29 studies compared TST/ IGRA head to head.	Persons at high risk of LTBI, not on tuberculosis preventive therapy: Low TB incidence[a] ‹100/100,000 High TB incidence[a] ›100/100,000; High/intermediate incidence[a] ›40/100,000; n = 54,833	Intervention: IGRA, TST. Outcomes: PPV, NPV, RR (number of cases in those with positive test vs those with negative test), IRR (rate of disease in those with positive test vs those with negative test).	Screening tests characteristics: The pooled RR estimate: TST: 2.64 (95%CI: 2.04–3.43), IGRA: 8.45 (95% CI: 4.13–17.3). The PPV: TST: 1–7%, IGRA: 0–13%. The NPV: TST: 92–100%, IGRA: 88–100%. The pooled IRR: TST: 2.07 (95% CI: 1.38–3.11), IGRA: 2.40 (95% CI: 1.26–4.60).

AMSTAR: A MeaSurement Tool to Assess systematic Reviews [22]; BCG: Bacillus Calmette–Guérin; CI: confidence interval; CrI: credible interval; ELISpot: Enzyme-Linked ImmunoSpot; EMB: ethambutol; GRADE: The Grading of Recommendations Assessment, Development and Evaluation; HIV: human immunodeficiency virus; IGRA: interferon gamma release assay; INH: isoniazid; IRR: incidence rate ratio; LTBI: latent tuberculosis infection; NPV: negative predictive value; OR: odds ratio; PPV: positive predictive value; PZA: pyrazinamide; QFT: QuantiFERON; QFT-2G: QuantiFERON-TB Gold; QFT-3G/ QFT-GIT: QuantiFERON-TB, Gold In-Tube; RFB: rifabutin; RFP: rifampicin; RPT: rifapentine; RMP: rifampicin; RR: risk ratio; TB: tuberculosis; T-SPOT.TB: ELISPOT assay for tuberculosis; TST: tuberculin skin test; USPSTF: United States Preventive Services Task Force.

[a] Low, intermediate and high TB incidence as defined by [28].

Table 1B

Characteristics of included studies for the effectiveness of latent tuberculosis screening, 2005–2016

Study	Quality/certainty of evidence	Design	Population	Intervention/outcomes	Results
Stagg et al. 2014 [29]	Quality of systematic review AMSTAR: 8/11. Quality of data of included individual studies: unclear or high risk of bias for efficacy; evidence sparse for hepatotoxicity as assessed by Cochrane risk of bias tool.	Systematic review up to January 2014: n = 53 studies	Patients with LTBI: n patients by regimen: range: 14 (RFB-INH)–47,489 (placebo).	Interventions: INH 3–4, 6, 9, 12–74 months, RFB-INH, RPT-INH, RMP, RMP-INH 1 month, RMP-INH 3–4 months, RMP-INH-PZA, RMP-PZA, INH-EMB. Outcome: prevention of active TB; OR (95% CrI); risk of hepatotoxicity.	Various therapies containing RMP for ≥ 3 months were efficacious at preventing active TB. Regimens containing RMP may be effective alternatives to INH monotherapy. Compared with placebo, OR (95% CrI): INH 6 months: 0.64 (0.48–0.83), INH 12–72 months: 0.52 (0.41–0.66), RMP: 0.41 (0.18–0.86), RMP-INH 3–4 months: 0.52 (0.34–0.79).
Sharma et al. 2014 [30]	Quality of systematic review AMSTAR:11/11. Quality of data of included individual studies: very low to moderate as assessed by GRADE.	Systematic review up to December 2012: n = 10 studies	HIV-negative with LTBI: 10,717 patients, 2–5 years follow-up.	Interventions: RMP 3–4 months, RMP + INH 3 months vs INH 6–9 months, RMP + PZA 2 months vs INH 6 months, RFP 900 mg weekly for 3 months + INH 900 mg for 9 months. Outcome: rates of active TB/1,000, 5 years follow-up, treatment limiting adverse events, hepatotoxicity/1,000.	Effectiveness in preventing active TB, rate/1,000, RR (95% CI): RMP: 121 vs 150/1,000, RR = 0.81 (0.47–1.4); RMP + INH: 162 vs 150/1,000, RR = 1.08 (0.65–1.79); RMP + PZA vs INH: 61 vs 47/1,000, RR = 1.32 (0.42–4.13); RFP + INH: 2 vs 4/1,000, RR = 0.44 (0.18–1.07). The directly observed, shorter regimen had higher treatment completion: 82% vs 69%, RR = 1.19 (1.16 to 1.22). Hepatotoxicity: RMP vs INH, RR = 0.15 0.07–0.4).
Alsdurf et al. 2016 [31]	Quality of systematic review AMSTAR: 3/11. Quality of data of included individual studies: not reported but several gaps and limitations highlighted.	Systematic review 1946 to April 2015: Total: n = 58 studies described, 70 distinct studies: 34 prospective 36 retrospective. TST: 60 cohorts IGRA (+/– TST), 6 cohorts, testing not reported in 4 cohorts.	Patients with LTBI: 748,572 patients.	Intervention: TST, IGRA. Outcomes: number of people eligible for screening tested; number who initiated and completed screening with IGRA or TST; number with positive tests who had chest radiographic and medical evaluation; number who were prescribed, started, and, completed treatment.	Steps in the TB cascade of care associated with greater losses included: Completion of testing: 71.9%, 95% CI: 71.8–72.0; Completion of medical evaluation: 43.7%, 95% CI: 42.5–44.9; Recommendation for treatment: 35.0%, 95% CI: 33.8–36.4; Completion of treatment if started: 18.8%, 95% CI: 16.3–19.7. Steps with fewer losses included: receiving test results, referral for evaluation if test positive and accepting to start therapy if recommended. Factors associated with fewer losses included: having immunocompromising medical indications, being part of contact investigations, use of rifamycin-based regimens.

AMSTAR: A MeaSurement Tool to Assess systematic Reviews [22]; BCG: Bacillus Calmette–Guérin; CI: confidence interval; CrI: credible interval; ELISpot: Enzyme-Linked ImmunoSpot; EMB: ethambutol; GRADE: The Grading of Recommendations Assessment, Development and Evaluation; HIV: human immunodeficiency virus; IGRA: interferon gamma release assay; INH: isoniazid; IRR: incidence rate ratio; LTBI: latent tuberculosis infection; NPV: negative predictive value; OR: odds ratio; PPV: positive predictive value; PZA: pyrazinamide; QFT: QuantiFERON; QFT-2G: QuantiFERON-TB Gold; QFT-3G/ QFT-GIT: QuantiFERON-TB, Gold In-Tube; RFB: rifabutin; RFP: rifampicin; RPT: rifapentine; RMP: rifampicin; RR: risk ratio; TB: tuberculosis; T-SPOT.TB: ELISPOT assay for tuberculosis; TST: tuberculin skin test; USPSTF: United States Preventive Services Task Force.

[a] Low, intermediate and high TB incidence as defined by [28].

Table 1C

Characteristics of included studies for the effectiveness of latent tuberculosis screening, 2005–2016

Study	Quality/certainty of evidence	Design	Population	Intervention/outcomes	Results
Sandgren et al. 2016 [32]	Quality of systematic review AMSTAR: 7/11. Quality of data of included individual studies: low to moderate as assessed by Cochrane risk of bias tool.	Systematic review up to February 2014, English, French, Spanish, German, and Dutch: n = 95 studies, 43 prospective, 52 retrospective. 45 studies on initiation rates, 20 were prospective. 83 studies on completion rates, 39 were prospective.	General population, case contacts, health workers, homeless, drug users, HIV-positive, inmates, immigrants, and patients with comorbidities n = not reported.	Intervention: short intervention: ≤ 4 months RMP or 2 months RMP + PZA; long intervention: (≥ 4 months) 6–9 months INH; combined intervention. Outcomes: treatment initiation rate, treatment completion rate.	Range of initiation rate and completion rate: General population: 26–99%, 39–96%; Case contacts: 40–95%, 48–82%; Healthcare workers: 47–98%, 17–79%; Homeless: 34–90%, 23–71%; Intravenous drug users: 52–91%; 38–89%; HIV-infected: 67–92%, 55–95%; Inmates: 7–90%, 4–100%; Immigrants: 23–97%, 86%; Patients with comorbidities: 82–93%, 75–92%.

AMSTAR: A MeaSurement Tool to Assess systematic Reviews [22]; BCG: Bacillus Calmette–Guérin; CI: confidence interval; CrI: credible interval; ELISpot: Enzyme-Linked ImmunoSpot; EMB: ethambutol; GRADE: The Grading of Recommendations Assessment, Development and Evaluation; HIV: human immunodeficiency virus; IGRA: interferon gamma release assay; INH: isoniazid; IRR: incidence rate ratio; LTBI: latent tuberculosis infection; NPV: negative predictive value; OR: odds ratio; PPV: positive predictive value; PZA: pyrazinamide; QFT: QuantiFERON; QFT-2G: QuantiFERON-TB Gold; QFT-3G/ QFT-GIT: QuantiFERON-TB, Gold In-Tube; RFB: rifabutin; RFP: rifampicin; RPT: rifapentine; RMP: rifampicin; RR: risk ratio; TB: tuberculosis; T-SPOT.TB: ELISPOT assay for tuberculosis; TST: tuberculin skin test; USPSTF: United States Preventive Services Task Force.

[a] Low, intermediate and high TB incidence as defined by [28].

Study selection and quality assessment

We identified and included systematic reviews and evidence-based guidelines that directly addressed each key question along the LTBI screening evidence chain (Figure 1) and prioritised those focusing on newly arrived (< 5 years in the host country) migrants. Migrant populations included non-forced economic migrants, refugees and asylum seekers, and illegal migrants who may have been forced to flee conflict, natural disaster, or economic peril [17]. We only included studies published in full and in English or French. If more than one version of a systematic review was identified, the most recent was considered. Studies were excluded if there were not relevant to the key questions, if they were not a systematic review or guideline, if the study methodology was unclear, and if they focussed only on non-generalisable subgroups (such as healthcare workers or HIV-positive people) or addressed only active TB screening. Two authors screened the titles and abstracts, assessed selected full-text articles for eligibility and extracted data from included articles. Disagreements were resolved by consensus or by a third author. The methodological quality of systematic reviews was assessed using the AMSTAR tool (A Measurement Tool To Assess Systematic Reviews) and the quality of individual studies was assessed with the Newcastle-Ottawa scale [22,23]. The GRADE criteria were applied to assess the quality and certainty of the evidence of the individual studies included in the systematic reviews [24].

Data extraction and synthesis

The following information was extracted from each study; study design, objectives, analyses, quality of the individual studies included in the systematic review, population examined, number of included studies, total number of participants included, intervention, outcome and results. We created GRADE evidence profiles and summary of findings tables for each outcome where appropriate.

For each of the cost-effectiveness studies we extracted the following data: economic methods used (e.g. micro-costing study, within-trial cost-utility analysis, Markov model), description of the case base population, the intervention and the comparator, absolute size and relative difference in resource use, and cost-effectiveness results (e.g. incremental net benefits (INB) or incremental cost-effectiveness ratio (ICER)) [25]. The certainty of economic evidence in each study was assessed using the relevant items from the 1997 Drummond checklist [26]. All currencies were converted to 2015 Euros using the Cochrane web-based currency conversion tool: https://eppi.ioe.ac.uk/costconversion/default.aspx.

Results

Search results

In the first search on the effectiveness and cost-effectiveness of TB screening programmes in migrants, we retrieved 3,375 studies and identified 22 additional records through other sources on the effectiveness of

Table 2a

Characteristics of included studies for the resource use, costs and cost-effectiveness of latent tuberculosis screening, 2000–2016

Study	Certainty of economic evidence based on the Drummond criteria [26]	Methods /population	Intervention(s)	Cost-effectiveness (ICER or INB) per case prevented	How large are the resource requirements (costs)
Schwartzman et al. 2000 [47]	Certainty of evidence: moderate allowance was made for uncertainty in the estimates of costs and consequences and ranges were provided. No PSA were performed. Justification was provided for the range of values varied in one-way sensitivity analyses. The cost-effectiveness results were sensitive to model inputs including the probability of INH prescribed: probability of INH treatment completed, cost of inpatient treatment, TB infection rate and HIV seropositivity.	Method: decision-analytic Markov model, 20-year time horizon, 3% discount rate, perspective of the third-party payer (central and provincial governments), scenario analysis based on INH completion conducted. Population: 20-year-old immigrants to Canada originating from sub-Saharan Africa, South-east Asia, western Europe.	Three strategies: (i) No screening (ii) CXR (iii) TST	ICER (CAD/case prevented): Population 1 (50% TB-infected, 10% HIV-positive): TST vs CXR: CAD 32,601 (EUR 29,990; CXR vs no screening: CAD 3,943 (EUR 3,627). Population 2 (50% TB-infected, 1% HIV-positive): TST vs CXR: CAD 66,759 (EUR 61,413); CXR vs no screening: CAD 10,627 (EUR 9,776). Population 3 (5% TB-infected, 1% HIV-positive): TST vs CXR: CAD 68,799 (EUR 63,290); CXR vs no screening: CAD 236,496 (EUR 217,558)	Costs were large in populations 1 and 2, moderate in population 3. Costs per 1,000 patients: Population 1 (50% TB-infected, 10% HIV-positive): TST: CAD 436,390 (EUR 401,445); CXR: CAD 338,310 (EUR 311,219); No screening: CAD 332,020 (EUR 305,432). Population 2 (50% TB-infected, 1% HIV-positive): TST: CAD 342,730 (EUR 315,284); CXR: CAD 231,430 (EUR 212,897; No screening: CAD 218,250 (EU 200,773). Population 3 (5% TB-infected, 1% HIV-positive): TST: CAD 62,640 (EUR 57,623); CXR: CAD 51,170 (EUR 47,072); No screening: CAD 21,820 (EUR 20,072).

BCG: Bacillus Calmette–Guérin; CAD: Canadian dollar; CEA: cost effective analysis; CXR: chest radiography; ELISpot: Enzyme-Linked ImmunoSpot; GBP: British pound; EUR: Euro; HIV: human immunodeficiency virus; ICER: incremental cost-effectiveness ratio; IGRA: Interferon Gamma Release Assay; INB: incremental net benefit; INH: isoniazid; LTBI: latent tuberculosis infection; NHS: National Health Service; NICE: The National Institute for Health and Care Excellence; PSA: probabilistic sensitivity analysis; PZA: pyrazinamide; QALY: quality-adjusted life years; Gold In-Tube; QFT: QuantiFERON; QFT-GIT: QuantiFERON-TB, Gold In-Tube; RIF: rifampicin; RMP: rifampicin; SC; South Carolina; TB: tuberculosis; TST: tuberculin skin test; T-SPOT.TB: ELISPOT assay for tuberculosis; UK: United Kingdom; US: United States; USD: US dollar; YLG: years of life gained.

The Drummond Criteria include [26]: (i) Was a well-defined question posed in answerable form? (ii) Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)? (iii) Was the effectiveness of the programme or services established? (iv) Were all the important and relevant costs and consequences for each alternative identified? (v) Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost working days, gained life years)? (vi) Were the cost and consequences valued credibly? (vii) Were costs and consequences adjusted for differential timing? (viii) Was an incremental analysis of costs and consequences of alternatives performed? (ix) Was allowance made for uncertainty in the estimates of costs and consequences? (x) Did the presentation and discussion of study results include all issues of concern to users?

All currencies were converted to 2015 Euros using the Cochrane web-based currency conversion tool: https://eppi.ioe.ac.uk/costconversion/default.aspx. Resource use was expressed in cost per person and classified as low (savings or ≤ USD 1,000/person or EUR 808), moderate (USD 1,000–100,000/person or EUR 808–80,845) or high (USD ≥ 100,000/person or EUR > 80,845).

Table 2b

Characteristics of included studies for the resource use, costs and cost-effectiveness of latent tuberculosis screening, 2000–2016

Study	Certainty of economic evidence based on the Drummond criteria [26]	Methods /population	Intervention(s)	Cost-effectiveness (ICER or INB) per case prevented	How large are the resource requirements (costs)
Oxlade et al. 2007 [41]	Certainty of evidence: moderate allowance was made for uncertainty in the estimates of costs and consequences; ranges were provided. No PSA was performed. One-way or two-way sensitivity analyses using higher or lower costs, other discount rates, test performance characteristics were undertaken. The cost-effectiveness results were sensitive to TST sensitivity; and risk of re-activation.	Method: decision-analytic Markov model, 20-year time horizon, 3% discount rate Canadian health system perspective, costs reported in 2004 Canadian dollars. Population: foreign-born entrants to Canada, close contacts of active TB cases.	Five strategies: (i) CXR (ii) No screening (iii) TST (iv) QFT (v) TST followed by QFT if TST-positive	CXR vs no screening: more cost-effective for screening immigrants; ICER: CAD 875/case prevented (EUR 690); QFT vs TST: cost-effective in BCG-vaccinated close-contacts and casual contacts; Sequential TST/QFT vs QFT alone is cost-effective in all scenarios; Sequential screening vs TST or QFT alone: cost-saving in screening migrants from low-incidence countries.	Low to moderate costs in immigrants from medium- and high-incidence countries. High costs in immigrants from low-incidence countries. QFT. Low incidence: CAD 64,920 (EUR 51,265); High incidence: CAD 459,040 (EUR 362,488). TST: varied based on specificity and BCG-status (and age at BCG vaccination): Non-vaccinated: CAD 30,320 (EUR 23,942); Low incidence, vaccinated older age: CAD 465,260 (EUR 367,400); Sequential TST then QFT: range from CAD 27,369 (EUR 21,612) to CAD 458,475 (EUR 362,042).
Dasgupta et al. 2000 [46]	Certainty of evidence: Low Limited allowance was made for uncertainty in the estimates of costs and consequences; ranges were provided. No PSA was performed No one-way or two-way sensitivity analyses using higher or lower costs, other discount rates, or comparisons with no screening were performed. Scenario analyses undertaken. The cost-effectiveness results were sensitive to costs for passive diagnosis of TB; Isonazid prescription rate; screening referral criteria; future risk of active TB.	Method: Cost-effectiveness analysis based on prospective non-randomised cohorts; results reported in Canadian dollars. Prospective cohort study over 1 year of costs and outcomes in 3 groups (all applicants, inactive TB requiring surveillance, and close contacts) Population: Immigration applicants undergoing CXR screening; and already arrived immigrants requiring screening for LTBI, and close contacts of active cases resident in Montreal, Quebec, Canada.	Three strategies: (i) CXR in migrants applying for a permanent residence (ii) Surveillance CXR +/−TST (iii) Close contacts CXR +/−TST	CAD/per disease prevented: Applicants: costs CAD 39,409 (EUR 36,667); Surveillance: costs CAD 65,126 (EUR 60,594); Close contacts: savings CAD 2,186 (EUR 2,033).	Applicants: moderate costs; Surveillance: large costs; Close contacts: moderate savings. Total programme costs for TB disease prevented: Applicants: CAD 73,125 (EUR 68,037); Post-landing surveillance: CAD 155,729 (EUR 144,894); Close contacts: CAD 29,668 (EUR 27,603).

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The Drummond Criteria include [26]: (i) Was a well-defined question posed in answerable form? (ii) Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)? (iii) Was the effectiveness of the programme or services established? (iv) Were all the important and relevant costs and consequences for each alternative identified? (v) Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost working days, gained life years)? (vi) Were the cost and consequences valued credibly? (vii) Were costs and consequences adjusted for differential timing? (viii) Was an incremental analysis of costs and consequences of alternatives performed? (ix) Was allowance made for uncertainty in the estimates of costs and consequences? (x) Did the presentation and discussion of study results include all issues of concern to users?

All currencies were converted to 2015 Euros using the Cochrane web-based currency conversion tool: https://eppi.ioe.ac.uk/costconversion/default.aspx. Resource use was expressed in cost per person and classified as low (savings or ≤ USD 1,000/person or EUR 808), moderate (USD 1,000–100,000/person or EUR 808–80,845) or high (USD ≥ 100,000/person or EUR > 80,845).

Table 2c

Characteristics of included studies for the resource use, costs and cost-effectiveness of latent tuberculosis screening, 2000–2016

Study	Certainty of economic evidence based on the Drummond criteria [26]	Methods /population	Intervention(s)	Cost-effectiveness (ICER or INB) per case prevented	How large are the resource requirements (costs)
Iqbal et al. 2014 [33]	Certainty of evidence: low. No allowance for uncertainty. No PSA performed. No justifications provided for ranges in cohort estimates. No sensitivity analyses for cost-effectiveness estimates.	Method: costing comparison study. Population: US- and foreign-born populations, ≥18-years-old with positive TST and normal CXR without TB-related symptoms.	Two strategies: (i) TST (ii) QFT	TST: less expensive in US-born patients; QFT-G: less expensive relative to TST in foreign-born individuals. No ICER or INB reported.	Moderate to large costs in US-born individuals, and large costs in foreign-born individuals. Total costs per 1,000 patients: In US-born individuals: QFT: USD 88,420 (EUR 78,200); TST: US 63,388 (EUR 56,061). In foreign-born individuals: TST: USD 313,806 (EUR 277,535); QFT: USD 177,860 (EUR 157,302).

BCG: Bacillus Calmette–Guérin; CAD: Canadian dollar; CEA: cost effective analysis; CXR: chest radiography; ELISpot: Enzyme-Linked ImmunoSpot; GBP: British pound; EUR: Euro; HIV: human immunodeficiency virus; ICER: incremental cost-effectiveness ratio; IGRA: Interferon Gamma Release Assay; INB: incremental net benefit; INH: isoniazid; LTBI: latent tuberculosis infection; NHS: National Health Service; NICE: The National Institute for Health and Care Excellence; PSA: probabilistic sensitivity analysis; PZA: pyrazinamide; QALY: quality-adjusted life years; Gold In-Tube; QFT: QuantiFERON; QFT-GIT: QuantiFERON-TB, Gold In-Tube; RIF: rifampicin; RMP: rifampicin; SC; South Carolina; TB: tuberculosis; TST: tuberculin skin test; T-SPOT.TB: ELISPOT assay for tuberculosis; UK: United Kingdom; US: United States; USD: US dollar; YLG: years of life gained.

The Drummond Criteria include [26]: (i) Was a well-defined question posed in answerable form? (ii) Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)? (iii) Was the effectiveness of the programme or services established? (iv) Were all the important and relevant costs and consequences for each alternative identified? (v) Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost working days, gained life years)? (vi) Were the cost and consequences valued credibly? (vii) Were costs and consequences adjusted for differential timing? (viii) Was an incremental analysis of costs and consequences of alternatives performed? (ix) Was allowance made for uncertainty in the estimates of costs and consequences? (x) Did the presentation and discussion of study results include all issues of concern to users?

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Table 2D

Characteristics of included studies for the resource use, costs and cost-effectiveness of latent tuberculosis screening, 2000–2016

Study	Certainty of economic evidence based on the Drummond criteria [26]	Methods /population	Intervention(s)	Cost-effectiveness (ICER or INB) per case prevented	How large are the resource requirements (costs)
Linas et al. 2011 [36]	Certainty of evidence: moderate allowance was made for uncertainty in the estimates of costs and consequences; ranges were provided. No PSA was performed. Limited justification for ranges used in one and two-way sensitivity analyses were provided. The cost-effectiveness results were sensitive to patient age and rates of TB reactivation, sensitivity of IGRA, IGRA test cost, adherence to INH therapy and quality of life (utility) post active TB.	Method: decision-analytic Markov model, US healthcare perspective, costs in 2011 US dollars, 3% discount rate. Population: recent immigrants (adults and children), foreign-born residents living in the US for more than 5 years, close contact adults and children, individuals with HIV, homeless, injection drug users, former prisoners, gastrectomy patients, underweight patients, individuals with silicosis, diabetes or end-stage renal disease.	Four strategies: (i) No Screening (ii) TST (iii) IGRA (iv) Screening high-risk groups	ICER (USD/QALY): Child close contacts: TST vs no screening: USD 6,200 (EUR 5,166); IGRA vs TST: USD 21,100 (EUR 17,582). Adult close contacts: TST vs no screening: USD 8,900 (EUR 7,416); IGRA vs TST: USD 21,500 (EUR 17,915). Foreign-born individuals: IGRA dominated TST; IGRA vs no screening: < USD 70,000 (EUR 58,329). Recent immigrant children and adults: IGRA dominated TST; IGRA vs no screening: Adult immigrants: US 35,200 (EUR 29,331); Children: USD 74,800 (EUR 62,328).	Total costs and resource requirements not reported.

BCG: Bacillus Calmette–Guérin; CAD: Canadian dollar; CEA: cost effective analysis; CXR: chest radiography; ELISpot: Enzyme-Linked ImmunoSpot; GBP: British pound; EUR: Euro; HIV: human immunodeficiency virus; ICER: incremental cost-effectiveness ratio; IGRA: Interferon Gamma Release Assay; INB: incremental net benefit; INH: isoniazid; LTBI: latent tuberculosis infection; NHS: National Health Service; NICE: The National Institute for Health and Care Excellence; PSA: probabilistic sensitivity analysis; PZA: pyrazinamide; QALY: quality-adjusted life years; Gold In-Tube; QFT: QuantiFERON; QFT-GIT: QuantiFERON-TB, Gold In-Tube; RIF: rifampicin; RMP: rifampicin; SC; South Carolina; TB: tuberculosis; TST: tuberculin skin test; T-SPOT.TB: ELISPOT assay for tuberculosis; UK: United Kingdom; US: United States; USD: US dollar; YLG: years of life gained.

The Drummond Criteria include [26]: (i) Was a well-defined question posed in answerable form? (ii) Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)? (iii) Was the effectiveness of the programme or services established? (iv) Were all the important and relevant costs and consequences for each alternative identified? (v) Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost working days, gained life years)? (vi) Were the cost and consequences valued credibly? (vii) Were costs and consequences adjusted for differential timing? (viii) Was an incremental analysis of costs and consequences of alternatives performed? (ix) Was allowance made for uncertainty in the estimates of costs and consequences? (x) Did the presentation and discussion of study results include all issues of concern to users?

All currencies were converted to 2015 Euros using the Cochrane web-based currency conversion tool: https://eppi.ioe.ac.uk/costconversion/default.aspx. Resource use was expressed in cost per person and classified as low (savings or ≤ USD 1,000/person or EUR 808), moderate (USD 1,000–100,000/person or EUR 808–80,845) or high (USD ≥ 100,000/person or EUR > 80,845).

Table 2e

Characteristics of included studies for the resource use, costs and cost-effectiveness of latent tuberculosis screening, 2000–2016

Study	Certainty of economic evidence based on the Drummond criteria [26]	Methods /population	Intervention(s)	Cost-effectiveness (ICER or INB) per case prevented	How large are the resource requirements (costs)
Pareek et al. 2012 [48]	Certainty of evidence: moderate allowance was made for uncertainty in the estimates of costs and consequences; ranges were provided. No PSA was performed. Justification for ranges used in one and two-way sensitivity analyses were provided. The cost-effectiveness results were sensitive to diagnostic specificity of screening tests; proportion of immigrants commencing and completing treatment; costs of screening for LTBI.	Method: decision-analytic model, inputs derived from cohort study of immigrants in London, 20-year time horizon, costs in 2010 GB pounds. Population: migrants registered with one of four participating primary care practices in London, England between October 2008 and June 2010	Four strategies: (i) No port-of-entry CXR (ii) Port-of-entry CXR (iii) QFT (iv) T-SPOT.TB	The two most cost-effective screening strategies: No port-of-entry CXR+single-step QFT-GIT at incidence of 250/100,000: ICER of GBP 21,565/case averted (EUR 26,105); No port-of-entry CXR+single-step QFT-GIT at 150/100,000 incidence: ICER: GBP 31,867/case averted (EUR 38,576).	Moderate to large costs for the two listed (cost-effective) single-step QFT strategies. At the incidence threshold, total costs: 250/100,000: GBP 839,713 (EUR 1,016,518); 150/100,000: GBP 1,089,177 (EUR 1,318,508). Total costs per 10,000 screened: No screening: GBP 659,609 (EUR 798,493) T-SPOT.TB (+CXR at port of arrival): GBP 2,189,912 (EUR 2,651,009)
Pareek et al. 2011 [35]	Certainty of evidence: moderate allowance was made for uncertainty in the estimates of costs and consequences; ranges were provided. No PSA was performed. Justification for ranges used in one-way sensitivity analyses was provided. The cost-effectiveness results were robust to all ranges tested.	Method: decision-analytic Markov model, UK NHS perspective, model inputs derived from multi-centre cohort study of immigrants in the UK, 20-year time horizon, costs in 2010 GB pounds. Population: immigrants arriving to UK from countries with varying TB incidence.	Two strategies: (i) NICE guidelines 2006 (ii) QFT testing for newly arrived migrants <35 years	The two most cost-effective strategies were: Screen individuals from countries with incidence >250/100,000: ICER of GBP 17,956 per case averted (EUR 21,736); Screen at incidence >150/100,000: ICER of GBP 20,819 per case averted (EUR 25,202).	Moderate to large costs compared with no screening. Total costs: No screening: GBP 608,370 (EUR 736,465); IGRA (up to age 35): GBP 1,532,257 (EUR 1,854,881).

BCG: Bacillus Calmette–Guérin; CAD: Canadian dollar; CEA: cost effective analysis; CXR: chest radiography; ELISpot: Enzyme-Linked ImmunoSpot; GBP: British pound; EUR: Euro; HIV: human immunodeficiency virus; ICER: incremental cost-effectiveness ratio; IGRA: Interferon Gamma Release Assay; INB: incremental net benefit; INH: isoniazid; LTBI: latent tuberculosis infection; NHS: National Health Service; NICE: The National Institute for Health and Care Excellence; PSA: probabilistic sensitivity analysis; PZA: pyrazinamide; QALY: quality-adjusted life years; Gold In-Tube; QFT: QuantiFERON; QFT-GIT: QuantiFERON-TB, Gold In-Tube; RIF: rifampicin; RMP: rifampicin; SC; South Carolina; TB: tuberculosis; TST: tuberculin skin test; T-SPOT.TB: ELISPOT assay for tuberculosis; UK: United Kingdom; US: United States; USD: US dollar; YLG: years of life gained.

The Drummond Criteria include [26]: (i) Was a well-defined question posed in answerable form? (ii) Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)? (iii) Was the effectiveness of the programme or services established? (iv) Were all the important and relevant costs and consequences for each alternative identified? (v) Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost working days, gained life years)? (vi) Were the cost and consequences valued credibly? (vii) Were costs and consequences adjusted for differential timing? (viii) Was an incremental analysis of costs and consequences of alternatives performed? (ix) Was allowance made for uncertainty in the estimates of costs and consequences? (x) Did the presentation and discussion of study results include all issues of concern to users?

All currencies were converted to 2015 Euros using the Cochrane web-based currency conversion tool: https://eppi.ioe.ac.uk/costconversion/default.aspx. Resource use was expressed in cost per person and classified as low (savings or ≤USD 1,000/person or EUR 808), moderate (USD 1,000–100,000/person or EUR 808–80,845) or high (USD ≥100,000/person or EUR > 80,845).

Table 2f

Characteristics of included studies for the resource use, costs and cost-effectiveness of latent tuberculosis screening, 2000–2016

Study	Certainty of economic evidence based on the Drummond criteria [26]	Methods /population	Intervention(s)	Cost-effectiveness (ICER or INB) per case prevented	How large are the resource requirements (costs)
Hardy et al. 2010 [40]	Certainty of evidence: low. No allowance was made for uncertainty in the estimates of costs and consequences. No PSA was performed. Not applicable – no sensitivity analyses undertaken. No cost-effectiveness results presented.	Method: cost analysis based on a cohort study at the Leeds TB screening service for immigrants from high-incidence countries. Population: immigrants from high-incidence countries (TB incidence›200/100,000) to Leeds, England.	Two strategies: (i) QFT first; CXR if QFT-positive (Leeds protocol) (ii) CXR first; TST if pregnant, ‹16-years-old, or from sub-Saharan Africa; QFT if positive TST (NICE protocol)	Overall, the Leeds protocol was cheaper and identified more cases of LTBI (n = 105) than the NICE protocol (n = 83).	Moderate to large costs compared with no screening. Total cost of Leeds protocol in 280 patients: GBP 9,782 (EUR 12,815); Total cost of NICE protocol in 280 patients: GBP 13,347 (EUR 17,487). All individuals from countries with incidence›200/100,000
Brassard et al. 2006 [42]	Certainty of evidence: low. Limited allowance was made for uncertainty in the estimates of costs and consequences. No PSA was performed. Limited sensitivity analyses undertaken, no justification for ranges used. Net savings were sensitive to rates of hospitalisation test performance characteristics.	Method: cost–benefit analysis of school-based screening programme, 20-year time horizon, 3% discount rate; results in Canadian dollars. Population: newly arrived immigrant children to Canada (aged 14–18 years).	Two strategies: (i) LTBI school screening (ii) Passive case finding and active TB treatment	Net savings from both school-based screening and associate investigations. Total net savings from conducting both programmes of CAD 363,923 (EUR 296,803)	Moderate to large costs: Total cost of school-based screening: CAD 126,871 (EUR 103,471); Total cost of associated investigations: CAD 66,590 (EUR 54,308).
Porco et al. 2006 [43]	Certainty of evidence: low. Allowance was made for uncertainty in the estimates of costs and consequences; ranges provided. No PSA was performed. Limited justification for ranges used in sensitivity analyses. Cost-effectiveness results were mostly robust but sensitive to changes in hospitalisation rates for actively found and passively found cases; INH hepatitis rates; proportion of active cases identified.	Method: decision-analytic model, 20-year time horizon, US domestic health payer perspective, 3% discount rate; results presented in US dollars. Population: immigrants to the US.	Two strategies: (i) Follow-up programme and LTBI treatment of contacts (ii) No follow-up of notifications	Costs per QALY range: USD 7,000 (EUR –6,761) to USD 72,000 (EUR 69,549): Population of 40% TB patients (range dependent on proportion of active cases; range 0–2%). The treatment intervention was cost-saving if the fraction of active cases was 2.5% or above.	Total costs not provided. Resource requirements unclear.

BCG: Bacillus Calmette–Guérin; CAD: Canadian dollar; CEA: cost effective analysis; CXR: chest radiography; ELISpot: Enzyme-Linked ImmunoSpot; GBP: British pound; EUR: Euro; HIV: human immunodeficiency virus; ICER: incremental cost-effectiveness ratio; IGRA: Interferon Gamma Release Assay; INB: incremental net benefit; INH: isoniazid; LTBI: latent tuberculosis infection; NHS: National Health Service; NICE: The National Institute for Health and Care Excellence; PSA: probabilistic sensitivity analysis; PZA: pyrazinamide; QALY: quality-adjusted life years; Gold In-Tube; QFT: QuantiFERON; QFT-GIT: QuantiFERON-TB, Gold In-Tube; RIF: rifampicin; RMP: rifampicin; SC; South Carolina; TB: tuberculosis; TST: tuberculin skin test; T-SPOT.TB: ELISPOT assay for tuberculosis; UK: United Kingdom; US: United States; USD: US dollar; YLG: years of life gained.

The Drummond Criteria include [26]: (i) Was a well-defined question posed in answerable form? (ii) Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)? (iii) Was the effectiveness of the programme or services established? (iv) Were all the important and relevant costs and consequences for each alternative identified? (v) Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost working days, gained life years)? (vi) Were the cost and consequences valued credibly? (vii) Were costs and consequences adjusted for differential timing? (viii) Was an incremental analysis of costs and consequences of alternatives performed? (ix) Was allowance made for uncertainty in the estimates of costs and consequences? (x) Did the presentation and discussion of study results include all issues of concern to users?

All currencies were converted to 2015 Euros using the Cochrane web-based currency conversion tool: https://eppi.ioe.ac.uk/costconversion/default.aspx. Resource use was expressed in cost per person and classified as low (savings or ≤ USD 1,000/person or EUR 808), moderate (USD 1,000–100,000/person or EUR 808–80,845) or high (USD ≥ 100,000/person or EUR › 80,845).

Table 2G

Characteristics of included studies for the resource use, costs and cost-effectiveness of latent tuberculosis screening, 2000–2016

Study	Certainty of economic evidence based on the Drummond criteria [26]	Methods /population	Intervention(s)	Cost-effectiveness (ICER or INB) per case prevented	How large are the resource requirements (costs)
Khan et al. 2002 [44]	Certainty of evidence: moderate allowance was made for uncertainty in the estimates of costs and consequences; ranges provided. Monte Carlo simulation was performed. Justification for ranges used in sensitivity analyses was provided. Cost-effectiveness results were mostly robust, however sensitive to changes in INH or RMP resistance; cost of RMP.	Method: decision-analytic model, region-specific resistance profiles constructed from a cross-sectional dataset. Time horizon was average life expectancy of foreign-born persons in the US minus median age of migrants. 3% discount rate; results reported in US dollars. Population: newly arrived immigrants to the US.	Four strategies: (i) No intervention (ii) TST followed by treatment with INH (iii) Treatment with RMP, (iv) Treatment with RIF plus PZA for those with a positive test result	A strategy of detecting and treating LTBI among immigrants would result in both health benefits and economic savings. RIF may only be superior to INH in migrants of certain national origins; this analysis includes a comparison of INH with a hybrid RIF/PZA regime.	Costs varied considerably by country of origin and prevalence. Costs for INH treatment: South Korea: USD 6.2 million (EUR 6,517,956); Mexico: USD 60.9 million (EUR 64,023,151). Costs for RIF treatment: South Korea: USD 6.9 million (EUR 7,253,854); Mexico: USD 69.7 million (EUR 73,274,443). Note: costs varied with size of immigrant population and prevalence.
Chang et al. 2002 [45]	Certainty of evidence: low. No allowance was made for uncertainty in the estimates of costs and consequences. No PSA was performed. No sensitivity analyses undertaken. Net savings were not tested for plausible changes in costs or benefits.	Method: cost-benefit study of 706 foreign-born students in a Maryland school; results presented in US dollars. Population: foreign-born school students in the US.	Two strategies: (i) No screening (ii) TST screening	Net benefit of USD 65,733 (EUR 70,675) of the TST screening and treatment intervention.	Moderate costs. Total cost of USD 32,617 (EUR 35,069) for TST screening and follow up treatment in 706 foreign-born school students.

BCG: Bacillus Calmette–Guérin; CAD: Canadian dollar; CEA: cost effective analysis; CXR: chest radiography; ELISpot: Enzyme-Linked ImmunoSpot; GBP: British pound; EUR: Euro; HIV: human immunodeficiency virus; ICER: incremental cost-effectiveness ratio; IGRA: Interferon Gamma Release Assay; INB: incremental net benefit; INH: isoniazid; LTBI: latent tuberculosis infection; NHS: National Health Service; NICE: The National Institute for Health and Care Excellence; PSA: probabilistic sensitivity analysis; PZA: pyrazinamide; QALY: quality-adjusted life years; Gold In-Tube; QFT: QuantiFERON; QFT-GIT: QuantiFERON-TB, Gold In-Tube; RIF: rifampicin; RMP: rifampicin; SC; South Carolina; TB: tuberculosis; TST: tuberculin skin test; T-SPOT.TB: ELISPOT assay for tuberculosis; UK: United Kingdom; US: United States; USD: US dollar; YLG: years of life gained.

The Drummond Criteria include [26]: (i) Was a well-defined question posed in answerable form? (ii) Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)? (iii) Was the effectiveness of the programme or services established? (iv) Were all the important and relevant costs and consequences for each alternative identified? (v) Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost working days, gained life years)? (vi) Were the cost and consequences valued credibly? (vii) Were costs and consequences adjusted for differential timing? (viii) Was an incremental analysis of costs and consequences of alternatives performed? (ix) Was allowance made for uncertainty in the estimates of costs and consequences? (x) Did the presentation and discussion of study results include all issues of concern to users?

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Table 2h

Characteristics of included studies for the resource use, costs and cost-effectiveness of latent tuberculosis screening, 2000–2016

Study	Certainty of economic evidence based on the Drummond criteria [26]	Methods /population	Intervention(s)	Cost-effectiveness (ICER or INB) per case prevented	How large are the resource requirements (costs)
Shah et al. 2012 [34]	Certainty of evidence: high. Allowance was made for uncertainty in the estimates of costs and consequences. PSA was performed. Sensitivity analyses undertaken and justification for ranges of model estimates provided. Cost-effectiveness results were robust to all changes in key model parameters.	Method: decision-analytic model. CEA undertaken from a US health system perspective, over a 1- and 5-year time horizon. Costs presented in 2012 US dollars, discounted at 3% per annum. Population: individuals referred to public health clinics with suspected LTBI on the basis of a positive TST.	Two strategies: (i) Treat all TST-positive referrals (ii) Treat those with positive results on adjunctive QFT-GIT testing	USD 1,202 (EUR 983) per QALY gained with TST+QFT vs TST alone.	Negligible costs and savings. Resource use, TST alone: symptom screen, CXR, liver chemistries, +LTBI treatment. TST+QFT-GIT resource use: QFT, symptom screen, CXR, liver chemistries, +LTBI treatment only if QFT positive. Total costs per individual at 1 year USD 360 (EUR 294); per person for TST alone: USD 370 (EUR 302); per person for TST+QFT: USD 10 (EUR 8) difference.
Mancuso et al. 2011 [37]	Certainty of evidence: moderate Allowance was made for uncertainty in the estimates of costs and consequences. PSA was not performed. Justification for ranges in sensitivity analyses was provided. Cost-effectiveness results were sensitive to changes in prevalence of LTBI; test performance characteristics; cost of tests.	Method: decision-analytic Markov model. CEA undertaken from a US societal perspective, over a 20-year time horizon. Costs presented in 2009 US dollars, discounted at 3% per annum. Population: recruits entering the US military at Fort Jackson, SC, US.	Four strategies: (i) Targeted screening (ii) Universal screening with IGRA +/– TST in low prevalence US military recruits (iii) Sequential testing strategies (iv) No screening	Targeted testing the most cost-effective vs no screening: ICER: USD 285,777 (EUR 246,015)/case prevented Sequential strategies and universal QFT testing are dominated.	Large costs compared with no screening. Screening per 200,000 recruits: No screening: USD 1,540,000 (EUR 1,325,731); Targeted screening: USD 6,580,000 (EUR 5,664,487); Targeted TST+QFT: USD 13,620,000 (EUR 11,724,972); Targeted TST+T-SPOT: USD 13,760 (EUR 11,845); Universal TST: USD 14,720 (EUR 12,671).
Deuffic-Burban et al. 2010 [39]	Certainty of evidence: moderate. Allowance was made for uncertainty in the estimates of costs and consequences. PSA was not performed. Justification for ranges in sensitivity analyses was provided. Cost-effectiveness results were sensitive to changes in TST specificity; costs of treatment.	Method: decision-analytic Markov model. CEA undertaken from a French healthcare payer's perspective, over a patient's lifetime, ca 48 years time horizon. Costs presented in 2007 Euros, discounted at 3% per annum. Population: adults in close contacts with BCG vaccinated.	Four strategies: (i) No testing (ii) TST (iii) TST+QFT for close contacts who have been BCG vaccinated (iv) QFT	TST had higher costs and lower efficacy than QFT (i.e. dominated). TST+QFT: ICER of EUR 560 (EUR 581[a]) /YLG compared with no testing; QFT=ICER of EUR 730 (EUR 757[a]) YLG compared with TST+QFT.	Negligible costs and savings. The discounted direct medical lifetime costs of care per patient were: No testing EUR 417 (EUR 432[a]); TST EUR 476 (EUR 493[a]); QFT EUR 443 (EUR 459[a]); TST+QFT EUR 435 (EUR 451[a]).

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The Drummond Criteria include [26]: (i) Was a well-defined question posed in answerable form? (ii) Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)? (iii) Was the effectiveness of the programme or services established? (iv) Were all the important and relevant costs and consequences for each alternative identified? (v) Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost working days, gained life years)? (vi) Were the cost and consequences valued credibly? (vii) Were costs and consequences adjusted for differential timing? (viii) Was an incremental analysis of costs and consequences of alternatives performed? (ix) Was allowance made for uncertainty in the estimates of costs and consequences? (x) Did the presentation and discussion of study results include all issues of concern to users?

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[a] 2007 Euros were converted to 2015 Euros for comparability.

Table 21

Characteristics of included studies for the resource use, costs and cost-effectiveness of latent tuberculosis screening, 2000–2016

Study	Certainty of economic evidence based on the Drummond criteria [26]	Methods /population	Intervention(s)	Cost-effectiveness (ICER or INB) per case prevented	How large are the resource requirements (costs)
Pooran et al. 2010 [38]	Certainty of evidence: moderate. Allowance was made for uncertainty in the estimates of costs and consequences. PSA was not performed. Justification for ranges in sensitivity analyses was provided. Cost-effectiveness results were sensitive to changes in LTBI prevalence; test sensitivity and specificity; LTBI treatment costs.	Method: decision analytic model. CEA undertaken from a UK healthcare perspective, over a 2-year time horizon. Costs presented in 2008 GB pounds, no discounting. Population: close contacts of individuals with TB in the UK.	Five strategies: (i) TST alone (ii) T-SPOT.TB assay alone (iii) TST followed by T-SPOT.TB assay when TST was positive (TST/T-SPOT.TB) (iv) Quantiferon-TB-Gold-In-Tube (QFT-GIT) alone (v) TST followed by QFT-GIT when TST was positive	Incremental cost per active case prevented (compared with no screening): TST: GBP 47,840 (EUR 60,938); QFT-GIT: GBP 42,051(EUR 53,564); T-SPOT.TB: GBP 39,712 (EUR 50,584); TST/QFT-GIT: GBP 37,699 (EUR 48,020); TST/T-SPOT.TB: GBP 37,206 (EUR 47,392). In most cases T-SPOT.TB dual screening was the most cost-effective strategy, TST alone the least cost-effective.	Large costs compared with no screening. Total costs including treatment, follow-up and test costs per 1,000 contacts: T-SPOT.TB: GBP 203,983 (EUR 259,832); QFT-GIT: GBP 202,921 (EUR 258,479); TST: GBP 199,589 (EUR 254,235); TST/T-SPOT.TB: GBP 162,387 (EUR 206,847); TST/QFT-GIT: GBP 157,048 (EUR 200,047); No screening: GBP 57,148 (EUR 72,794).

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latent TB screening in migrant populations (Figure 2). After removal of duplicates, 2,884 studies were screened by title and abstract. A total of 127 studies were selected for full text assessment. We did not identify any single study on the effectiveness of LTBI screening in migrants or the general population. We therefore included seven systematic reviews that addressed the LTBI screening chain of evidence; the test properties of LTBI screening tests (n = 3) [20,27,28], the efficacy and harms of LTBI therapies (n = 2) [29,30], and the LTBI care cascade including uptake of screening and treatment initiation and completion (n = 2) [31,32]. In the economic search 2,869 articles were identified. After duplicate removal 2,740 articles were screened by title and abstract (Figure 3). A total of 37 studies underwent full text assessment and 16 individual studies were included [33-48].

Performance of diagnostic tests for latent tuberculosis infection

Three systematic reviews assessed the properties of the diagnostic tests used in LTBI screening (Table 1). The systematic reviews by Pai et al. and Kahwati et al. evaluated the performance of TST and IGRA in populations not vaccinated with bacillus Calmette–Guérin (BCG) and found that the TST, at a 10 mm cut-off, and IGRA had similar and good sensitivity (79%) and high specificity (> 97%) to detect LTBI [20,27]. In addition, Pai et al. showed that the TST was limited by lower specificity (59%) in BCG-vaccinated populations [27]. The third systematic review by Kik et al. estimated the ability of TST or IGRA to predict the risk of developing active TB among those with LTBI [28]. We included and present the data from eight of the 29 studies in the Kik review as they were the only ones that performed both TST and IGRA in the same study subjects and compared the results to those with a negative test [28]. The positive predictive value (PPV) and the pooled incidence rate ratios (IRR) estimated by comparing test-positive and -negative cohorts were similar for TST and IGRA. Both predicted the development of active TB poorly [28]. The PPV (range) and the IRR (95% CI) were, respectively, 1–7% and 2.07 (1.38–3.11) for the TST and 0–13% and 2.40 (1.26–4.60) for the IGRA [28].

Efficacy and harms of therapy for latent tuberculosis infection

Two systematic reviews examined the efficacy and associated harms of latent TB therapies to prevent the development of active TB [29,30]. Both reviews found that the efficacy of several different regimens of rifampicin (RIF) (monotherapy and combinations) was low to moderate and equivalent to isoniazid (INH) treatment for 6–12 months. Stagg et al. published a network meta-analysis of 53 randomised controlled trials on the efficacy and harms of different latent TB regimens in which 42 were directly compared [29]. In the meta-analysis of the nine placebo-controlled trials, the odds of developing active TB among those who took INH for 6 months compared with placebo were 0.64 (95% CI: 0.48–0.83). In the network meta-analysis of all 53 studies, the odds of developing active TB in the 3–4 months of RIF regimen compared with placebo were 0.41 (0.18–0.86) [29]. The Cochrane review by Sharma et al. found similar efficacy for the following three comparisons: (i) RIF monotherapy for 3–4 months vs INH for 6–9 months, (ii) RIF + INH for 3 months vs INH for 6–9 months and (iii) weekly rifapentine (RFP) + INH for 3 months vs INH for 9 months. The comparative relative risks (RR) with 95% CI for these rifamycin combinations vs INH were 0.81 (0.47 to 1.4), 1.08 (0.65 to 1.79) and 0.44 (0.18 to 1.07), respectively [30]. In that review, the RIF-based regimens were better tolerated, with lower RR of hepatotoxicity (0.15; 95% CI: 0.07–0.4), and had better adherence (82% vs 69%, RR = 1.19 (95% CI: 1.16–1.22)) [30].

Latent tuberculosis infection care cascade: screening uptake and completion of therapy

Two systematic reviews reported on the LTBI care cascade including the uptake of screening and treatment as well as initiation and completion of therapy [31,32]. Alsdurf et al found that only 18.8% of all those eligible for screening completed LTBI therapy and that the rate was low for all sub-groups, including migrants (14.3%) [31]. This was due to progressive losses at all stages of the care cascade: 71.9% (95% CI: 71.8–72.0) completed testing, 43.7% (95% CI: 42.5–44.9) completed medical evaluation, 35.0% (95% CI: 33.8–36.4) were recommended for treatment and 18.8% (95% CI: 16.3-19.7) completed treatment if started [31]. Sandgren et al. found that treatment initiation (23–97%) and treatment completion (7–86%) varied widely among migrants [32].

Resource use, cost and cost-effectiveness of screening for latent tuberculosis infection

The cost-effectiveness analysis of studies summarised in our review focused primarily on comparisons between LTBI screening strategies (e.g. TST, IGRA or sequential TST/IGRA), comparisons with other screening techniques such as chest radiography (CXR) for active TB, a combination of CXR/TST, or no screening, among different risk groups (Table 2). The strategies compared were heterogeneous across most studies. Eleven of the 16 included studies addressed an LTBI screening strategy and included a migrant group; however, only three studies were specifically about migrants in EU/EEA countries [35,40,48]. The cost-effectiveness of screening strategies was dependant on test characteristics, which tests were being compared, the cost of tests and whether or not the population was BCG-vaccinated.

Four studies reported that screening with a single-step IGRA was less costly or more cost-effective relative to TST screening in migrants to prevent incident TB [33,35,36,48]. In one study in the US by Linas et al., a single IGRA dominated TST in all comparisons. However, IGRA was only cost-effective at a willingness-to-pay threshold of less than USD 75,000 per QALY (EUR 62,496/QALY) compared with no screening among

migrants younger than 25 years of age, with an incremental cost-effectiveness ratio (ICER) ranging from USD 52,900–74,800 per QALY (EUR 44,080–62,329/QALY). For migrants older than 45 years, the intervention was unlikely to be cost-effective, with an ICER for IGRA vs no screening between USD 103,000–283,000 per QALY gained (EUR 85,827–235,817/QALY) [36]. Two studies conducted in the United Kingdom (UK) by Pareek et al. found that performing an IGRA in migrants aged 16–35 years and originating from countries with a TB incidence of >150 per 100,000 was the most cost-effective LTBI strategy, with an ICER of ca GBP 20,000 (EUR 24,211) to GBP 30,000 (EUR 36,317) per active TB case prevented [35,48].

Other studies investigated the optimal LTBI testing strategy in different high-risk populations such as contacts of active cases or migrants from TB-endemic countries [38,39,41]. Sequential TST/IGRA testing was preferred over single TST or IGRA, especially in those who had a high likelihood of a true positive TST (LTBI prevalence >5%) and were BCG-vaccinated after infancy [39,41]. Oxlade et al. found that sequential TST-IGRA screening was cost-effective compared with single-step IGRA screening. That study suggested that it was most cost-effective to use an IGRA to screen TST-positive cases, and that IGRA screening was favoured only among those who had received BCG vaccination after infancy [41]. In a French study by Deuffic-Burban, sequential TST-IGRA screening was a more cost-effective strategy for BCG-vaccinated close contacts of active TB patients than IGRA alone [39]. For TST-IGRA compared with no testing, the ICER was EUR 560 (EUR 581, as per 2015) per year of life gained (YLG), and for IGRA compared with TST-IGRA, the ICER was EUR 730 (EUR 757) per YLG in the scenario when LTBI prevalence was more than 5%. This was robust across a wide range of LTBI prevalence. In the study by Pooran et al., sequential TST-IGRA testing was more cost-effective compared with no screening or single-step TST, with an incremental cost per active case prevented of GBP 37,699 (EUR 48,020) to GBP 37,206 (EUR 47,392) among contacts of active TB [38].

Discussion

There were no single studies that directly addressed the effectiveness of latent TB screening programmes on the health outcomes of migrants. Therefore, we evaluated the LTBI screening chain of evidence. The majority of TB cases in low TB incidence countries in the EU/EEA occur in migrants born in countries with higher TB incidence and occur primarily due to reactivation of latent infection. The tools to detect and treat LTBI, however, have many limitations. IGRA and TST have high sensitivity to detect LTBI but they both predicted the development of active TB poorly [20,27,28]. All latent TB therapies were equivalent but their effectiveness in preventing the development of active TB was only low to moderate [29,30]. RIF regimens may be preferable because they have considerably lower hepatotoxicity and higher treatment completion rates than INH [30]. The LTBI care cascade is weak as only a minority of patients (both general population and migrants) eligible for LTBI screening actually complete LTBI treatment [31]. Limited economic analyses of LTBI screening among migrants suggest that targeted screening for young migrants from high TB incidence countries (>150/100,000) is the most cost-effective strategy [35]. The WHO *End TB Strategy*, with a goal to eliminate TB by 2050, highlights the need to decrease the substantial reservoir of individuals with latent TB infection at risk of progression to active TB [49,50]. A substantial proportion of migrants were born in high TB burden countries and many have latent TB infection (26–46%) [4,13]. A major challenge is identifying those at highest risk for progression to active disease so that targeted programmes can be developed that will promote the health of migrants and have the highest public health impact.

Ca 5–15% of individuals with latent infection will develop active TB during their lifetime [51,52]. The groups at highest risk of progression to active TB disease are those with immunosuppressive conditions (i.e. HIV infection, immunosuppressive therapies with anti-tumour necrosis factor treatment, organ transplantation or dialysis) and those infected recently [6]. The risk of disease progression is greatest close to the time of infection, with almost half of disease progression cases occurring within the first 2–3 years after exposure [53]. Migrants arriving from endemic areas have the highest rates of active TB soon after arrival in host countries, which is probably due to recent exposure in their countries of origin. Fifty per cent of cases, however, occur 5 or more years after arrival and the risk remains elevated throughout their lifetime [54-57]. Being an asylum seeker or refugee, TB exposure during crowded conditions or perilous journeys to host countries, or recent travel back to TB-endemic countries of origin may also increase the risk of active TB in the migrant population [58-60]. The complex epidemiology of TB among migrants needs to be taken into consideration when developing LTBI programmes for this population to ensure the highest individual and public health benefit. The lack of robust population-based data is, however, a major obstacle in developing targeted LTBI programmes for migrants. Estimates on the individual, combined and attributable population contribution of each of these risk factors to developing TB among migrants will be required. There are also few studies on cost-effectiveness to inform latent TB programmes concerning migrants. Only two studies conducted in the UK specifically addressed which migrant groups should be targeted for LTBI screening and treatment [35,48]. These results however, may not be generalisable to all EU/EEA countries as willingness to pay thresholds, per capita health care expenditures, and health priorities vary between countries.

In addition to these data gaps, the tools to diagnose and treat latent TB have limitations. The LTBI care cascade is weak, lowering the effectiveness and

impact of screening programmes. Both TST and IGRA poorly predict the small proportion (‹15%) of those infected with TB who will progress to active disease. As a consequence, a large number of people need to be screened and treated to prevent one case of active TB [6]. Operational issues related to TST and IGRA may decrease screening uptake: The TST requires a second visit 48–72 h after the first visit to read the skin test induration (test result) and IGRA testing is generally costlier than TST and may not be as widely available in EU/EEA countries [61]. Patients with latent TB are asymptomatic and thus long treatment regimens ranging from 3 to 9 months lead to poor treatment completion [32]. The latent TB care cascade involves several steps including identifying patients in need of screening, offering screening and treatment by providers, and uptake and completion of screening and treatment by patients. This process requires the understanding and engagement of patients and providers. The low proportion of those eligible for screening who complete LTBI treatment is a result of losses at every point of the care cascade because of barriers at patient, provider and structural level [31].

Migrants encounter several barriers in accessing healthcare and consequently, treatment initiation (23–97%) and completion rates (7–86%) are variable [21,32,62,63]. In addition, practitioners may lack adequate knowledge of which migrants should be screened and treated [21,64]. Addressing barriers at both the patient and provider level will therefore be required to strengthen the LTBI care cascade and to ensure individual and public health benefits of LTBI programmes. With the adoption of the WHO *End TB Strategy* there is recognition of the importance of scaling up preventive therapy. Less than half of EU/EEA countries, however, have LTBI programmes for migrants and there are numerous challenges to developing and implementing new programmes [11,14,15]. These include the heterogeneity of populations and migrant subgroups affected by TB in individual EU/EAA countries as well as economic and operational considerations. LTBI screening programmes will therefore need to be tailored to the local TB epidemiology in host countries, the TB risk in migrant sub-groups, and implementation based on the health priorities and economic and healthcare capacity in each setting [2,3].

Study limitations

Our study was limited by the fact that we did not retrieve any studies that directly estimated the effectiveness of LTBI screening programmes among migrants or the general population. There are limited data on the cost-effectiveness of LTBI screening in these populations. The search was limited by the fact that it was conducted only up until May 2016 and that we only included studies published in English or French. A recent narrative review of the effectiveness and cost-effectiveness, however, found similar literature and findings as our study [65]. Our findings are further limited by the low or very low quality of most of the original studies that were included in the systematic reviews.

Evidence gaps and future directions

Better evidence is urgently needed on the individual, combined and attributable population contribution of risk factors leading to progression from LTBI to active TB in migrants. Intervention studies that determine how to improve the identification of target populations and retain them in care along with cost-effectiveness studies that use this intervention and the epidemiological data will be needed to develop programmes with the highest impact. Ultimately, better diagnostic tests that accurately predict those individuals who will develop active TB as well as shorter, well-tolerated and more effective treatment to promote adherence, will be needed to achieve TB elimination.

Conclusions

The latent TB burden among migrants needs to be addressed in order to promote the health of this population and to achieve TB elimination in the EU/EEA. At present, broad implementation of LTBI screening and treatment programmes is hindered by the large pool of migrants with LTBI (a small proportion of whom will develop active TB), diagnostic tests that poorly predict which individuals will develop active TB, long LTBI treatment regimens, as well as several patient, provider and institutional barriers that lead to poor uptake of screening and treatment completion. Despite these limitations, migrant-focused latent TB screening programmes may be effective and cost-effective if they are highly targeted and well implemented.

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Conflict of interest

KP led and CG was an author on the Canadian Migrant Guidelines including TB. AM co-led the work on the WHO LTBI screening guidelines. MP holds a Gilead Sciences grant for a project outside of the submitted work.

Authors' contributions

CG, DZ, MP, AM, RLM, TN and KP contributed to the design and research questions. KP and RC were part of the core methods team members for the ECDC Guidelines project

developing the methods. DZ, MP, MvW and AM provided substantial content on the research question and design. CG, IM, BA and MW wrote the manuscript. CNAC, MW, BS, TM and CH reviewed and selected the literature, and extracted and synthesised the data. RM, AT and NR conducted the review and synthesised the data for cost-effectiveness analysis. All authors read and approved the manuscript.

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Research article

Negligible import of enteric pathogens by newly arrived asylum seekers and no impact on incidence of notified *Salmonella* and *Shigella* infections and outbreaks in Rhineland-Palatinate, Germany, January 2015 to May 2016

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Introduction: The 2015 refugee crisis raised concerns about an import of infectious diseases affecting the German population. **Aims:** To evaluate public and individual health benefits of stool screening, and explore whether importation of enteric pathogens by newly arrived asylum seekers impacts on the host population. **Methods:** We used data from mandatory stool screening to determine the overall, age, sex, and country-specific prevalence of enteric bacteria and helminths. We used surveillance data to assess whether the number of incoming asylum seekers influenced notifications of salmonellosis and shigellosis in Rhineland-Palatinate. **Results:** *Salmonella* were found in 0.2% (95% confidence interval (CI) 0.2–0.3%) of 23,410 samples collected from January 2015 to May 2016. Prevalence was highest in children under 5 years (0.8%; 95% CI: 0.5–1.3%). No *Shigella* or invasive *Salmonella* spp. were detected. In a subset of 14,511 samples, the prevalence of helminth infestation was 2.4% (95% CI: 2.1–2.6%), with highest proportions detected in adolescents (4.6%; 95% CI 3.8–5.4%) and among Eritreans (9.3%; 95% CI: 7.0–12.0%); in the latter particularly *Schistosoma mansoni* and *Taenia* spp. The increase in asylum applications did not increase notifications of salmonellosis and shigellosis. No transmission from asylum seekers to German residents was notified. **Conclusion:** Public health risk associated with imported enteric pathogens is very low overall. Addressing individual and public health risks, we recommend replacing stool screening of all newly arrived asylum seekers by a targeted approach, with target groups and approaches being adapted if necessary. Target groups supported by our data are children, adolescents, and Eritreans.

Introduction

Sparked primarily by the Syrian civil war but also by other conflicts in the Middle East and Southern Asia, the number of first-time asylum applications in Germany increased more than fourfold in 2 years [1]. In response, Rhineland-Palatinate, a federal state with a population of ca 4 million, established 29 asylum seeker reception centres, temporarily accommodating over 60,000 asylum seekers.

A large proportion of these asylum seekers, i.e. displaced people whose refugee status has yet to be confirmed, originate from Eastern Africa, and Western and Southern Asia (regions according to [2]). There, the standard of water, sanitation, and food hygiene is lower than in Western Europe [3], resulting in a higher incidence of gastro-intestinal infections. Besides, migration itself often entails exposure to unsafe water and food. Such reasoning underlines the hypothesis of migration fostering importation of enteric pathogens to Europe, with a potential of onward transmission as demonstrated by outbreaks in asylum seeker reception centres [4]. These fears are contrasted by expert opinion on imported infections remaining largely confined to the migrant population and thus being negligible

Table 1

Enteric bacteria in newly arrived asylum seekers detected through stool screening, by country and region of origin, Rhineland-Palatinate, Germany, January 2015–May 2016 (n = 23,410)

Region[a] and country of origin	Total samples	Culture results					
		Salmonella spp.			*Shigella* spp.		
		n	%	95% CI	n	%	97.5% CI[b]
Southern Europe							
Albania	3,196	5	0.2	0.0–0.4	0	0.0	0.0–0.1
Kosovo*	1,748	3	0.2	0.0–0.1	0	0.0	0.0–0.2
Serbia	831	0	0.0	0.0–0.0[b]	0	0.0	0.0–0.4
the former Yugoslav Republic of Macedonia	586	2	0.3	0.0–1.2	0	0.0	0.0–0.6
Bosnia-Herzegovina	284	0	0.0	0.0–1.3[b]	0	0.0	0.0–1.3
Subtotal	**6,645**	**10**	**0.2**	**0.1–0.3**	**0**	**0.0**	**0.0–0.1**
Eastern Africa							
Eritrea	596	2	0.3	0.0–1.2	0	0.0	0.0–0.6
Somalia	419	0	0.0	0.0–0.9[b]	0	0.0	0.0–0.9
Other[c]	12	0	0.0	0.0–26.5[b]	0	0.0	0.0–26.5
Subtotal	**1,027**	**2**	**0.2**	**0.0–0.7**	**0**	**0.0**	**0.0–0.4**
Western Asia							
Syria	8,128	23	0.3	0.2–0.4	0	0.0	0.0–0.1
Armenia	218	0	0.0	0.0–1.7[b]	0	0.0	0.0–1.7
Iraq	120	0	0.0	0.0–3.0[b]	0	0.0	0.0–0.0
Other[c]	151	0	0.0	0.0–2.4[b]	0	0.0	0.0–2.4
Subtotal	**8,617**	**23**	**0.3**	**0.2–0.4**	**0**	**0.0**	**0.0–0.0**
Southern Asia							
Afghanistan	3,903	11	0.3	0.1–0.5	0	0.0	0.0–0.1
Pakistan	787	1	0.1	0.0–0.7	0	0.0	0.0–0.5
Iran	530	0	0.0	0.0–0.7[b]	0	0.0	0.0–0.7
Other[c]	16	0	0.0	0.0–20.6[b]	0	0.0	0.0–20.6
Subtotal	**5,236**	**12**	**0.2**	**0.1–0.4**	**0**	**0.0**	**0.0–0.1**
Northern Africa							
Egypt	121	1	0.8	0.0–4.5	0	0.0	0.0–3.0
Other[c]	37	1[e]	2.7	0.1–14.2	0	0.0	0.0–9.5
Subtotal	**158**	**2**	**1.3**	**0.2–4.5**	**0**	**0.0**	**0.0–2.3**
Other[d]	246	1[f]	0.4	0.0–2.2	0	0.0	0.0–1.5
Unknown	1,481	2	0.1	0.0–0.1	0	0.0	0.0–0.3
Total	**23,410**	**52**	**0.2**	**0.2–0.3[g]**	**0**	**0.0**	**0.0–0.2[g]**

CI: confidence interval.

[a] Grouping of regions according to [2], except for Kosovo*.

[b] Zero percent estimates are provided with a one-sided, 97.5% CI.

[c] Combines countries from given region with fewer than 100 subjects examined.

[d] Combines countries from regions not displayed in table and with fewer than 100 subjects examined.

[e] Country of origin of this sample: Morocco (1/16).

[f] Country of origin of this sample: Nigeria (1/13).

[g] Variance estimate was calculated while accounting for clustering of subjects by country.

*This designation is without prejudice to positions on status, and is in line with UNSCR 1244/1999 and the ICJ Opinion on the Kosovo declaration of independence.

for European public health [5]. To date; however, little data are available to support this view for enteric pathogens.

National and federal-state law regulates the health status assessment of newly arrived asylum seekers in Rhineland-Palatinate [6,7]. Upon first presentation at an asylum seeker reception centre, each individual undergoes a mandatory medical examination. Apart from screening for tuberculosis, this examination includes a screening of a single stool sample for *Salmonella* spp., *Shigella* spp., and helminth eggs. To date, there has been no public health evaluation of stool screening in newly arrived asylum seekers in

Table 2

Enteric bacteria and helminths in newly arrived asylum seekers detected through stool screening, by age, Rhineland-Palatinate, Germany, January 2015– May 2016 (n = 23,410 screened for enteric bacteria; n = 14,511 screened for helminth eggs)

Age group	Enteric bacteria				Helminth eggs			
	Positive		Negative		Positive		Negative	
(years)	n	%	n	%	n	%	n	%
0 to<5	20	0.8	2,391	99.2	19	0.9	2,049	99.1
5 to<10	6	0.3	2,060	99.7	36	2.7	1,306	97.3
10 to<20	7	0.1	5,178	99.9	134	4.6	2,805	95.4
20 to<30	12	0.2	7,150	99.8	105	2.4	4,309	97.6
30 to<40	4	0.1	3,897	99.9	37	1.6	2,242	98.4
40 to<50	2	0.1	1,781	99.9	9	0.9	967	99.1
≥ 50	1	0.1	901	99.9	4	0.8	489	99.2
Total	**52**	**0.2**	**23,358**	**99.8**	**344**	**2.4**	**14,167**	**97.6**

Rhineland-Palatinate, and publications regarding the results and public health benefits of similar screening programs from other federal states in Germany and European countries are limited [8].

The aim of this study was to evaluate the public and individual health benefits of stool screening, and to explore whether the import of enteric pathogens by asylum seekers impacts on the host population's health. To this end, we describe the prevalence of enteric pathogens among incoming asylum seekers and stratify by age, sex, and geographic origin as potential risk factors for pathogen carriage. Additionally, by using data from the federal state-wide mandatory notification system, we check whether the number of incoming asylum seekers influenced the number of notified cases and outbreaks of salmonellosis and shigellosis in Rhineland-Palatinate.

Methods

This study analyses data from mandatory stool screening collected from January 2015 to May 2016. Laboratory analyses were performed by the Federal State Agency for Consumer and Health Protection Rhineland Palatinate. Stool samples were tested for *Salmonella* spp. and *Shigella* spp. During the peak period of migration, microscopy for helminths was conducted in two thirds of samples only. This was achieved by rotating the subset of reception centres included in the study every 2 weeks.

Laboratory methods

Deoxycholate-Citrate (DC) and Xylose-Lysine-Deoxycholate (XLD) agar plates as well as Tetrathionat and Selenit enrichment bouillons (all Oxoid, Wesel, Germany) were inoculated with stool and incubated overnight at either 37 °C or, in case of Tetrathionat bouillon, at 42 °C. Suspicious colonies were classified as *Salmonella* spp. based on the results from decarboxylase activity, hydrogen sulphide and indole production, and mannitol fermentation. Putative *Salmonella*spp. and *Shigella* spp. were further serotyped by agglutination (Sifin, Berlin, Germany). Cellophane thick smears were prepared for stool microscopy as proposed by Kato 1954 [9]. All diagnostic parameters presented in this study are subject to a quality management system which includes regular participation in ring trials.

Data management and analysis

Date of birth, sex, country of origin, and laboratory results were extracted from the electronic laboratory information and management system (Blomesystem GmbH, Jena, Germany), and imported into Stata 14 while omitting personal identifiers. We calculated prevalences of enteric pathogens by age group (0–4, 5–9, 10–19, 20–29, 30–39, 40–49, ≥ 50 years) and country of origin. Countries were classified into geographic regions according to the M49 standard used by the United Nations Statistics Division [2]. In order to identify predictors of pathogen carriage, age group- and sex-specific prevalences were compared using Pearson's chi-squared test. When calculating prevalences of enteric pathogens in the overall study group, the variance estimate was corrected for clustering of subjects on the country level using the 'cluster' option of the 'proportion' command in Stata 14.

Detection of *Salmonella* spp. (invasive and non-invasive) and *Shigella* spp., but not of the helminths discussed in this study, is notifiable according to §7 of the German Protection against Infection Act (Infektionsschutzgesetz, IfSG) [7]. For the period from 2007 to 2016, the yearly numbers of salmonellosis and shigellosis notifications and outbreaks in Rhineland-Palatinate were extracted from the German Infectious Disease Surveillance Network Database (SurvNet) and compared with the published number of asylum applications in Rhineland-Palatinate [1]. In October 2015, the asylum status of cases was added to mandatory notifications in SurvNet. We extracted notified cases of salmonellosis and shigellosis in newly arrived asylum seekers from SurvNet for the period from October 2015 to December 2016 and checked whether these were linked to secondary cases, which would be notifiable according to §6 IfSG [7].

Ethics

Stool screening as described is mandated by the IfSG [7] and the Administrative Act number 21260 of the federal state of Rhineland-Palatinate [6]. Thus, no individual informed consent was sought for this research.

Results

In total, 23,410 stool samples were tested from January 2015 to May 2016 (Table 1). The majority of samples were from newly arrived asylum seekers from Syria (n = 8,128), followed by Afghanistan (n = 3,903), Albania (n = 3,196), and Kosovo (n = 1,748). The median age was 22 years (range: 0–90; interquartile range (IQR):

Table 3

Helminth infestation in newly arrived asylum seekers detected by stool screening, Rhineland-Palatinate, Germany, January 2015–May 2016 (n = 14,511)

Region[a] and country of origin	Sample size	Microscopy results															
		Overall positive		*Ascaris lumbricoides*		*Trichuris trichiura*		*Hymenolepis nana*		*Schistosoma mansoni*		*Enterobius vermicularis*		*Ancylostoma/Necator* spp.		*Taenia* spp.	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Southern Europe																	
Albania	2,436	36	1.5	1	0.0	20	0.8	2	0.1	0	0.0	11	0.5	0	0.0	2	0.1
Kosovo*	1,704	11	0.6	0	0.0	6	0.4	1	0.1	0	0.0	4	0.2	0	0.0	0	0.0
Serbia	604	14	2.3	2	0.3	7	1.2	2	0.3	0	0.0	3	0.5	0	0.0	0	0.0
the former Yugoslav Republic of Macedonia	436	2	0.5	0	0.0	2	0.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Bosnia-Herzegovina	180	1	0.6	0	0.0	0	0.0	1	0.6	0	0.0	0	0.0	0	0.0	0	0.0
Subtotal	**5,360**	**64**	**1.2**	**3**	**0.1**	**35**	**0.7**	**6**	**0.1**	**0**	**0.0**	**18**	**0.3**	**0**	**0.0**	**2**	**0.0**
Eastern Africa																	
Eritrea	571	53	9.3	1	0.2	1	0.2	4	0.7	40	7.0	0	0.0	2	0.4	5	0.9
Somalia	403	22	5.5	0	0.0	19	4.7	0	0.0	0	0.0	2	0.5	1	0.2	0	0.0
Other[b]	11	1	9.1	1	9.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Subtotal	**985**	**76**	**7.7**	**2**	**0.2**	**20**	**2.0**	**4**	**0.4**	**40**	**4.1**	**2**	**0.2**	**3**	**0.3**	**5**	**0.5**
Western Asia																	
Syria	2,628	15	0.6	0	0.0	1	0.0	3	0.1	0	0.0	8	0.3	1	0.0	2	0.1
Armenia	199	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other[b]	174	2	1.1	0	0.0	0	0.0	1	0.6	0	0.0	0	0.0	0	0.0	1	0.6
Subtotal	**3,001**	**17**	**0.6**	**0**	**0.0**	**1**	**0.0**	**4**	**0.1**	**0**	**0.0**	**8**	**0.3**	**1**	**0.0**	**3**	**0.1**
Southern Asia																	
Afghanistan	3,200	133[d]	4.2	80	2.5	13	0.4	24	0.8	0	0.0	7	0.2	5	0.2	1	0.0
Pakistan	651	29	4.5	6	0.9	6	0.9	5	0.8	0	0.0	0	0.0	11	1.7	1	0.2
Iran	236	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other[b]	7	2	28.6	0	0.0	1	14.3	1	14.3	0	0.0	0	0.0	0	0.0	0	0.0
Subtotal	**4,094**	**164[d]**	**4.0**	**86**	**2.1**	**20**	**0.5**	**30**	**0.7**	**0**	**0.0**	**7**	**0.2**	**16**	**0.4**	**2**	**0.0**
Other[c]	287	7	2.4	0	0.0	1	0.3	0	0.0	4	1.4	0	0.0	2	0.7	0	0.0
Unknown	784	16	2.0	3	0.4	3	0.4	5	0.6	3	0.4	1	0.1	1	0.1	0	0.0
Total	**14,511**	**344**	**2.4**	**94**	**0.7**	**80**	**0.6**	**49**	**0.3**	**47**	**0.3**	**36**	**0.2**	**23**	**0.2**	**12**	**0.1**

Positive samples in the 'other' categories: *Ascaris lumbricoides*: Ethiopia (1/9); *Trichuris trichiura*: Bangladesh (1/6), Nigeria (1/13); *Hymenolepis nana*: Bangladesh (1/6), Irak (1/56); *Schistosoma mansoni*: Central African Republic (2/29), Egypt (1/90), Equatorial Guinea (n=1/1); *Ancylostoma/Necator* spp.: Mali (1/7), Sierra Leone (1/1); *Taenia* sp: Georgia (1/75).

[a] Grouping of regions according to [2], except for Kosovo.

[b] Combines countries from given region with fewer than 100 subjects examined.

[c] Combines countries with fewer than 100 subjects examined from regions not included in this table.

[d] Includes three *Strongyloides stercoralis* positive samples not otherwise displayed in this table.

*This designation is without prejudice to positions on status, and is in line with United Nations Security Council Resolution 1244/99 and the International Court of Justice Opinion on the Kosovo declaration of independence.

0–87). Information on sex was available for 18,720 samples, 7,307 were from females (39.0%).

Enterobacteria

Fifty-two of the 23,410 samples tested positive for *Salmonella* spp. (0.2%).

The highest prevalence of *Salmonella* spp. in stools was detected in asylum seekers from Egypt (0.8%), followed by Afghanistan, Eritrea, the former Yugoslav Republic of Macedonia, and Syria (all 0.3%). No *Salmonella* were detected in samples from Armenia, Bosnia-Herzegovina, Iran, Iraq, Serbia, or Somalia. *Salmonella* spp. were more commonly identified in stools from children under 10 years of age when compared with all other age groups (0.6% vs 0.1%; chi-squared $p<0.001$) (Table 2). Females were more likely to carry *Salmonella* spp. (n=29/7,307; 0.4%; 95% CI: 0.3–0.6) than males (n=16/11,413; 0.1%; 95% CI: 0.1–0.2; chi-squared $p<0.001$).

Table 4

Number of asylum applications and salmonellosis and shigellosis notifications, incidence and outbreaks in Rhineland-Palatinate, Germany, January 2007–December 2016

Year	Asylum applications[a]	Salmonellosis notifications			Shigellosis notifications		
		Confirmed cases[b]	Incidence[c]	Number of outbreaks[d]	Confirmed cases[b]	Incidence[c]	Number of outbreaks[d]
2007	767	3,635	90.6	298	44	1.1	5
2008	883	2,607	65.0	221	29	0.7	1
2009	1,106	1,691	42.1	125	40	1.0	4
2010	1,653	1,466	36.5	84	49	1.2	4
2011	1,830	1,287	32.1	67	45	1.1	2
2012	2,582	1,142	28.5	58	28	0.7	2
2013	4,383	943	23.5	42	59	1.5	3
2014	6,922	881	22.0	46	34	0.9	4
2015	17,625	726	18.1	26	24	0.6	2
2016	36,985	729	18.2	31	31	0.8	1

[a] To the federal state of Rhineland-Palatinate [1].

[b] Notified to the responsible health authorities according to §7 of the German Protection Against Infection Act (Infektionsschutzgesetz) [7].

[c] Notified laboratory-confirmed cases per 100,000 population.

[d] Defined as at least two cases with an epidemiological link; notified according to the responsible health authorities according to §6 German Protection Against Infection Act (Infektionsschutzgesetz) [7].

Helminths

Overall, 14,511 samples were tested for helminth eggs. The predominant country of origin for those newly arrived asylum seekers tested was Afghanistan (n = 3,200), followed by Syria (n = 2,628), Albania (n = 2,436), and Kosovo (n = 1,704). The median age was 21 years (range: 0–88; IQR 0–78). Sex was available for 11,597 samples, 4,356 were from females (37.6%).

A total of 344 samples tested positive (prevalence 2.4%; 95% CI: 2.1–2.6). Males (n = 205/7,241; 2.8%; 95% CI: 2.5–3.2) had a significantly higher prevalence of helminth infestation compared with females (n = 95/4,356; 2.2%: 95% CI: 1.8–2.7; chi-squared p = 0.033). Most commonly identified helminths were *Ascaris lumbricoides* (0.7%; 95% CI: 0.5–0.8) and *Trichuris trichiura* (0.6%; 95% CI: 0.4–0.7). *Hymenolepis nana* was detected in 49 samples (0.3%; 95% CI: 0.2–0.4), *Schistosoma mansoni* in 47 (0.3%; 95% CI: 0.2–0.4), *Enterobius vermicularis* in 36 (0.2%; 95% CI: 0.2–0.3), *hookworm* in 23 (0.2%; 95% CI: 0.1–0.2), and *Taenia* spp. in 12 (0.1%; 95% CI: 0.0–0.1) (Table 3). Larvae from *Strongyloides stercoralis* were seen in three samples.

Helminth infestation was most commonly detected in asylum seekers from Eastern Africa namely Eritrea (9.3%; 95% CI: 7.0–12.0; predominantly *S. mansoni*), and Somalia (5.5%; 95% CI: 3.5–8.1; predominantly *T. trichiura*), followed by the Southern Asian countries Pakistan (4.5%; 95% CI: 3.0–6.3; predominantly hookworm) and Afghanistan (4.2%; 95% CI: 3.5–4.9; predominantly *A. lumbricoides*). The prevalence of helminth infestation was more common in those under 20 years of age, compared with older age groups (3.0% vs 1.9%; chi-squared p < 0.001) (Table 2).

Impact of asylum seekers on notified cases and outbreaks

While the number of asylum applications increased over 40-fold from 2007 to 2016, notifications and outbreaks of salmonellosis and shigellosis continuously decreased (Table 4).

Since the introduction of asylum status to mandatory notifications in SurvNet in October 2015 until the end of 2016, four confirmed cases of salmonellosis and three confirmed cases of shigellosis were reported in asylum seekers in Rhineland-Palatinate, compared with 896 salmonellosis and 41 shigellosis cases in the host population. One of the notified salmonellosis cases in asylum seekers occurred secondary to a German case. There were no records of secondary transmission of *Salmonella* spp. or *Shigella* spp. from an asylum seeker to either the host population or other asylum seekers.

Two cases of *S.* Typhi/*S.* Paratyphi were notified in the resident population in Rhineland-Palatinate during this time period, both of whom reported prior travel to endemic countries (India and Bangladesh).

Discussion

Our analysis of a large sample of screened stools and surveillance data provides evidence against the hypothesis that the import of enteric bacteria by newly-arrived asylum seekers has an impact on public health of the host population. The increase in the number of asylum applications in Rhineland-Palatinate did not lead to an increase of notified cases and outbreaks of

salmonellosis and shigellosis. Furthermore, we did not detect a single record of *Salmonella* spp. or *Shigella* spp. transmission event following a case in an asylum seeker. Only 0.2% of samples from newly arrived asylum seekers tested positive for *Salmonella* spp. and none for *Shigella* spp., corroborating the results of one report from Bavaria [8] and re-confirming that import of enteric bacteria by asylum seekers is rare.

We found helminth infestation in 2.4% of newly arrived asylums seekers. This is well above the prevalence reported in Germany, and other countries in Western and Northern Europe [10]. To adequately discuss the value of screening for helminths, these results need to be assessed in terms of (i) person-to-person transmissibility and (ii) morbidity in case of infection, with the latter being particularly important in infections with long latency periods and irreversible sequelae.

Many geohelminths require maturation in soil before they become infective (e.g. *A. lumbricoides and T. trichiura*) and, as in the case of *S. stercoralis* and hoo kworms *(Ancylostomatidae),* infect humans through penetration of healthy skin. These mechanisms put open defecation and barefoot walking at the centre of transmission, which grossly reduces the probability of transmission in Germany. Irreversible sequelae through low burden, asymptomatic infections are uncommon in the immunocompetent host, allowing for curative treatment with onset of symptoms. Hence, an increased prevalence of geohelminths in asylum seekers compared with the host population does not justify general screening.

We detected 47 cases of schistosomiasis, 40 of whom were newly arrived asylum seekers from Eritrea. Although human schistosomiasis finds most suitable ecologic conditions for its transmission in the tropics, a recent outbreak of *S. haematobium* infection in visitors to the Mediterranean island of Corsica demonstrates a low, but tangible risk of its emergence in Europe [11]. Infection with schistosomes often remains asymptomatic for years, yet the tissue damage caused during this period remains irreversible [12], rendering early diagnosis through screening of asymptomatic individuals that were exposed at high-risk destinations important.

E. vermicularis was detected in 0.2% of newly-arrived asylum seekers, predominantly in children. Enterobiasis is easily transmitted from person-to-person, common in autochthonous populations in Europe [10], and reported to cause outbreaks in childcare facilities in Germany [13]. It generally responds well to treatment and has no serious health effects. Therefore, we consider it to be unlikely that importation of *E. vermicularis* to an extent described here has a negative impact on public health in Germany or elsewhere in Europe.

We detected *H. nana* in 0.3% of samples (49/14,511), of which 34 were from children and adolescents. A study from Italy found *H. nana* in seven of 5,351 stool samples (0.1%) of hospitalised patients, six of whom were children under 15 years [14]. Hence, prevalence of hymenolepiasis in newly arrived asylum seekers appears somewhat higher when compared with the autochthonous population in Europe. Direct person-to-person transmission of *H. nana* via ingestion of eggs, including autoinfection, is common. Infestation with *H. nana* is more common among children, not associated with long-term sequelae, and responds well to treatment. Therefore, we conclude, that its importation could have some minor negative public health impact in Germany or elsewhere in Europe.

Apart from being the definitive host of *T. solium*, humans can also become infected by its eggs, which then develop into the parasitic stage that is usually seen in the intermediate host (i.e. in pigs). Cysticercosis is a rare, but disabling and potentially life-threatening disease, as the parasite can affect the central nervous system (neurocysticercosis) and lead to serious, incurable neurologic symptoms [15]. Standard microscopy does not allow differentiation between the eggs of *T. solium* and *T. saginata*. This circumstance complicates the risk assessment, as only eggs of *T. solium* infest humans. Information with regard to *T. solium* endemicity is sparse, and unavailable for Afghanistan, Albania, Eritrea, and Pakistan [16], i.e. those countries where nine of 12 *Taenia* spp. infections in our study population were imported from. Therefore, our data support a marginal chance for severe morbidity caused by secondary cysticercosis following import by newly arrived asylum seekers. This; however, will primarily affect asylum seekers themselves, through autoinfection, and must be balanced against occurrence of cysticercosis after import of *T. solium* eggs through travel and migration from countries within the European Union where *T. solium* is endemic [16,17].

This study has limitations. First, native stool samples were sent by mail to our laboratory, which may have affected the detection of pathogens. This particularly applies to *Shigella dysenteriae* and *S. boydii*, which are known to be more sensitive to environmental stress than other *Shigella* spp. Besides, the estimated meta-analytic sensitivities of stool microscopy of one vs three samples (Kato-Katz) are, for *A. lumbricoides* 63.8 vs 70.4%, *T. trichiura* 82.2 vs 90.5%, and hookworm 59.5 vs 74.3% [18]. Thus, the presented data are likely to underestimate the prevalence of enteric pathogen carriage in newly arrived asylum seekers to a certain extent. These differences, however, are not large enough to invalidate our conclusions. Second, during the peak of the refugee crisis, most reception centres were providing food through catering services. In settings where asylum seekers are involved in food handling, stool screening for enteric pathogens needs to be evaluated differently. Finally, although of interest in the given context, we were not able to report

on microscopy results of protozoa (e.g. *Giardia lamblia*, *Entamoeba histolytica*), as these are not part of the mandatory screening. However, in light of evidence on its person-to-person transmissibility from research in day care centres [19,20], we acknowledge that screening for *G. lamblia* may be a meaningful addition to the proposed screening in children.

Critically reviewing the risk assessment above and acknowledging the limitations of our study, we conclude that routine screening of newly arrived asylums seekers for enteric bacteria with the aim to prevent onward transmission in the described population and setting is obsolete. Similar reasoning applies for most helminth infections currently screened for in Rhineland-Palatinate. At the same time, our data demonstrate that surveillance of imported enteric bacteria and parasites provides an important basis to identify particular individual and public health risks. To prevent severe, long-term morbidity due to schistosomiasis and cysticercosis and the further spread of these infections in Europe, we recommend screening of Eritrean asylum seekers for helminth infestation with a focus on *Schistosoma* and *Taenia* spp., using targeted methods at specialised institutions. Further research is needed to clarify the endemicity of *T. solium* in Eritrea [16].

We recommend continuing the screening of one stool sample of asymptomatic children and adolescents for enteric pathogens. The prevalence of enteric pathogens was elevated in these groups that are also less likely to adhere to hand hygiene and other individual infection prevention measures. Besides, children are known to suffer most from the harmful consequences some of the helminth infestations may have, such as anaemia, stunting, and nutrient deficiency [21-23]. Hence, targeted screening of this risk group would allow to prevent such harm, both from an individual and public health point of view. It should also allow future identification of risk groups among children that may require intensified screening at specialised institutions. Similarly, ongoing testing for enteric pathogens in a representative subsample of all newly arrived asylum seekers will be required to adapt the targeted approach to changing patterns of migration and associated risks.

Note

*This designation is without prejudice to positions on status, and is in line with United Nations Security Council Resolution 1244/99 and the International Court of Justice Opinion on the Kosovo declaration of independence.

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Conflict of interest

None declared.

Authors' contributions

PZ initiated the study, DK and MV supervised the laboratory work, MG and FB designed the database and drafted a first version of the tables, LE and PZ drafted a first version of the manuscript and finalized the statistical analyses, DK, MV, FB, KJ, and MG revised this draft, all authors read and agreed with the final version of the manuscript.

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Research article

Extended screening for infectious diseases among newly arrived asylum seekers from Africa and Asia, Verona province, Italy, April 2014 to June 2015

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Background and aim: Management of health issues presented by newly arrived migrants is often limited to communicable diseases even though other health issues may be more prevalent. We report the results of infectious disease screening proposed to 462 recently-arrived asylum seekers over 14 years of age in Verona province between April 2014 and June 2015. **Methods:** Screening for latent tuberculosis (TB) was performed via tuberculin skin test (TST) and/or QuantiFERON-TB Gold in-tube assay and/or chest X-ray. An ELISA was used to screen for syphilis. Stool microscopy was used to screen for helminthic infections, and serology was also used for strongyloidiasis and schistosomiasis. Screening for the latter also included urine filtration and microscopy. **Results:** Most individuals came from sub-Saharan Africa (77.5%), with others coming from Asia (21.0%) and North Africa (1.5%). The prevalence of viral diseases/markers of human immunodeficiency virus (HIV) infection was 1.3%, HCV infection was 0.85% and hepatitis B virus surface antigen was 11.6%. Serological tests for syphilis were positive in 3.7% of individuals. Of 125 individuals screened for TB via the TST, 44.8% were positive and of 118 screened via the assay, 44.0% were positive. Of 458 individuals tested for strongyloidiasis, 91 (19.9%) were positive, and 76 of 358 (21.2%) individuals from sub-Saharan Africa were positive for schistosomiasis. **Conclusions:** The screening of viral diseases is questionable because of low prevalence and/or long-term, expensive treatments. For opposing reasons, helminthic infections are probably worth to be targeted by screening strategies in asylum seekers of selected countries of origin.

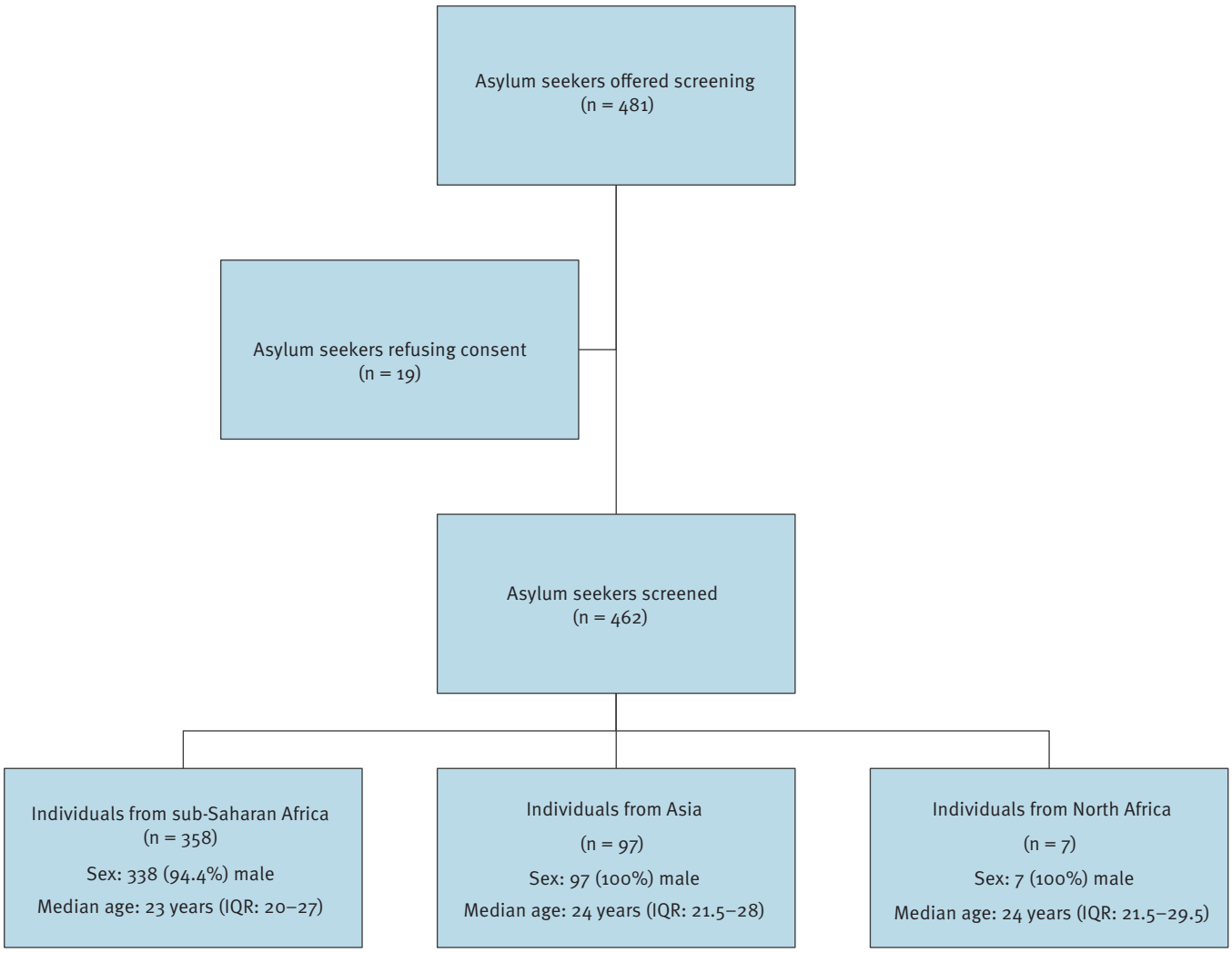
Introduction

In 2015, there were an estimated 244 million international migrants, representing 3% of the global population [1]. In recent years, the flow of migrants from Northern Africa to the coasts of southern Italy via the Central Mediterranean migration route has been constantly increasing, reaching 181,126 migrants in 2016 [2]. The term migrant encompasses a heterogeneous population that includes refugees, asylum seekers and economic migrants that come from countries with large differences in the prevalence of diseases [3]. Well-defined screening protocols specifically addressing migrants from different geographical areas are important to detecting some infectious diseases, regardless of whether or not they are causing symptoms. However, the main aim of European health authorities is avoiding the possible spreading of infectious diseases to local populations [4]. Migrants are therefore mostly screened for active [5] and latent tuberculosis (TB) [6,7], human immunodeficiency virus (HIV) infection and chronic viral hepatitis [8,9]. Almost no action aside from local initiatives is taken towards other infections such as parasitic diseases although these often have a higher prevalence than the aforementioned infections [10-14]. Moreover, their treatment is exceedingly shorter and cheaper than treatment for HIV and viral hepatitis, and can prevent severe and even fatal complications in the affected individuals [12,15-17].

In general, the inclusion of infections in a screening programme should take different issues into account. Cost-effectiveness is one of them, but other perspectives should also be considered, such as the heterogeneity of migrant populations in terms of prevalence of specific health problems. Studies have been performed on migrants attending clinics for any reason [13,18], but data from these are not reliable enough to estimate the real prevalence in the general migrant population.

Figure

Flow of extended screening for infectious diseases among asylum seekers from Africa and Asia, Verona province, Italy, April 2014–June 2015



The aim of this study is to estimate the prevalence of a series of infectious diseases, communicable and non-communicable, in a cohort of asylum seekers that recently arrived in Europe and temporarily residing in a series of refugee shelters in Verona province, northern Italy.

Methods

Study population and setting

This retrospective observational study includes reporting data from infectious disease screening activities systematically carried out from April 2014 to June 2015 in 14 refugee shelters in Verona province, northern Italy. The shelters are managed by different cooperatives that receive financial support from the Italian government. The study population included asylum seekers over 14 years of age arriving in the last 6 months. Two infectious diseases physicians were in charge of the screening activities and regularly went to the shelters to check on the health of newly arrived asylum seekers. Those requiring specific workup/treatment were referred either to the local health unit, Azienda Sanitaria Locale (ASL), or to a hospital depending on the level of diagnostic workup/treatment required. Extended screening for infectious diseases was offered to all asylum seekers referred by the physicians to the Centre for Tropical Diseases (CTD) in Negrar, Verona, for the blood sampling. Those who accepted were asked to sign an informed consent form, with parents or a legal guardian signing for individuals less than 18 years of age. Demographic data were registered according to the documents issued by the prefectures where the individuals applied for asylum.

Screening strategy

In addition to the full blood cell count (FBC), some diagnostic tests for specific infections were proposed:

Viral diseases/infections

Screening for HIV infection was performed with an ELISA (Beckman Coulter, Inc.), and a Western blot (Fujirebio

Table 1

Regions and countries of origin of asylum seekers, Verona province, Italy, April 2014–June 2015

Region	Country	Number of asylum seekers (n)	Percentage within region (%; 95% CI)
Sub-Saharan Africa	Angola	1	0.3 (0.1–1.6)
	Burkina Faso	8	2.2 (1.1–4.3)
	Cameroon	3	0.8 (0.3–2.4)
	Congo	1	0.3 (0.1–1.6)
	Côte d'Ivoire	24	6.7 (4.5–9.8)
	Eritrea	6	1.7 (0.7–3.6)
	The Gambia	40	11.2 (8.3–14.8)
	Ghana	39	10.9 (8.0–14.5)
	Guinea	4	1.1 (0.4–2.8)
	Guinea-Bissau	4	1.1 (0.4–2.8)
	Mali	103	28.8 (24.3–33.7)
	Nigeria	81	22.6 (18.6–27.2)
	Senegal	28	7.8 (5.5–11.0)
	Somalia	14	3.9 (2.3–6.5)
	Sudan	2	0.6 (0.2–2.0)
	Total	**358**	**100.0**
Asia	Afghanistan	1	1.0 (0.2–5.6)
	Bahrain	1	1.0 (0.2–5.6)
	Bangladesh	38	39.2 (30.1–49.1)
	Nepal	1	1.0 (0.2–5.6)
	Pakistan	54	55.7 (45.8–65.2)
	Palestine	1	1.0 (0.2–5.6)
	Sri Lanka	1	1.0 (0.2–5.6)
	Total	**97**	**100.0**
North Africa	Morocco	6	85.7 (48.7–97.4)
	Tunisia	1	14.3 (2.6–51.3)
	Total	**7**	**100.0**

CI: confidence interval.

Diagnostics) was used as confirmatory test. Depending on the ASL of reference, some individuals were tested for antibodies against hepatitis B virus (HBV), namely the HBV core antibody (anti-HBc) and the HBV surface antibody (anti-HBs) respectively, although most individuals were tested for HBV surface antigen (HBsAg). All assays for HBV were ELISA (Beckmann Coulter, Inc.). Antibodies against hepatitis C virus were also detected with ELISA (Beckman Coulter, Inc.).

Bacterial diseases

Screening for syphilis was conducted by screening for *Treponema pallidum* using an IgG ELISA test (Fujirebio Diagnostics) and a rapid plasma reagin, while the *Treponema pallidum* haemaglutination assay (TPHA) was used for confirmatory tests. Screening for TB was conducted with tuberculin skin test (TST), and/or QuantiFERON-TB Gold in-tube assay (QFT-GIT), and/or chest X-ray, depending on the ASL.

Helminthic infections

Helminthic infections were screened with the following methods: stool examination for ova and parasites (O and P) after formol-ether concentration with three samples being collected on different days, urine examination after micropore filtration for *Schistosoma haematobium* (only for asylum seekers from sub-Saharan Africa), serology for *Schistosoma* spp. (Schistosoma mansoni ELISA kit, Bordier Affinity Products SA, Crissier, Switzerland) and *Strongyloides stercoralis* (in-house immunofluorescence test, IFAT).

All individuals positive for any screening test were referred to the CTD for the appropriate clinical management. The results were then entered anonymously in an Excel database.

Statistical analysis

Descriptive statistics were used to describe the characteristics of the entire cohort. Categorical variables were reported as frequencies and proportions, while

Table 2

Results of screening tests for latent tuberculosis, Verona province, Italy, April 2014–June 2015

Screening test	Total[a]			Sub-Saharan Africa		Asia		North Africa	
	Tested individuals	Positive individuals		Positive/tested individuals		Positive/tested individuals		Positive/tested individuals	
	N	n	%	n/N	%	n/N	%	n/N	%
TST	125	56	44.8	37/82	45.1	16/38	42.1	3/5	60
QFT-GIT	118	52	44.0	45/94	47.9	7/24	29.2	0/0	0
Chest X-ray[b]	260	35	14.5	27/193	13.9	7/61	11.5	1/6	16.7

QFT-GIT: QuantiFERON-TB Gold in-tube assay; TST: tuberculin skin test.

[a] In addition to the data reported in the table, an additional 42 individuals were tested with both TST and QFT-GIT: 16 were negative to both methods, 16 were positive to both, 3 were positive to TST only and 7 were positive to QFT-GIT only.

[b] Positive chest X-rays were considered those with any pulmonary abnormalities, including calcified nodules. Abnormalities of other anatomical sites, e.g. heart, vessels, were not included in this analysis.

quantitative variables were presented as medians with interquartile ranges (IQR). We also investigated associations between age, infections and eosinophilia through Student's t-test and univariate logistic models. Lastly, we fitted a multivariate logistic regression model to assess a possible association of age and of parasitic infections with the probability of eosinophilia. Statistical analyses were performed using Epi Info programme version 3.5 [19] and R version 3.3.3 [20].

Ethical clearance

The study protocol received ethical clearance from the ethics committee for clinical trials in the provinces of Verona and Rovigo (Comitato Etico per la sperimentazione Clinica delle Province di Verona e Rovigo) on 10 May 2017 (protocol number 24126).

Results

The screening was offered to 481 asylum seekers but as 19 refused, 462 individuals were screened and included in this analysis (Figure). The median age was 24 years (IQR: 20–28) and 95.7% (n = 442) were male. Most came from sub-Saharan Africa (77.5%; n = 358), with others originating from Asia (21%; n = 97) or from North Africa (1.5%; n = 7) (Table 1). Of note, 22.3% of individuals came from Mali.

In the whole cohort, the median eosinophil count was 210/µL (IQR: 120–420), and 144 individuals (31.2%) presented a eosinophil count ≥ 350/µL (i.e. had eosinophilia). In relation to the regions, eosinophilia was present in 105 of 358 (29.3%) individuals from sub-Saharan Africa (median eosinophil count: 550/µL; IQR: 450–740), 38 of 97 (39.2%) individuals from Asia (median eosinophil count: 605/µL; IQR: 465–930), and one of seven individuals from North Africa (eosinophil count: 580/µL). In the Asia subgroup, eosinophilia was present in 18 of 38 individuals from Bangladesh and 18 of 54 individuals from Pakistan.

Viral diseases/infections

Six of 455 individuals (1.3%) screened were positive for HIV infection. They were all from sub-Saharan Africa: two from Côte d'Ivoire, two from The Gambia, one from Mali and one from Guinea-Bissau. The percentage of HIV-positive individuals of all of individuals screened from sub-Saharan Africa was 1.7% (6/353). Of the 457 people screened for HBV infection by being tested for HBsAg, 53 (11.6%) tested positive. Most (n = 49) came from sub-Saharan Africa, representing 13.8% of people from that region who underwent this screening test (n = 355). The remaining four individuals came from Asia, representing 4.2% of people from that region who were screened (n = 95). In addition, 99 of 338 individuals (29.3%) screened for anti-HBs were positive while 107 of 172 individuals (62.2%) screened for anti-HBc were positive. Of the 118 individuals tested for HCV infection, only one person (0.85%) tested positive.

Bacterial diseases

In terms of screening for syphilis, 4.5% of individuals from sub-Saharan Africa were positive (16/352), and 1.0% of individuals from Asia were positive (1/95), whereas none of the seven individuals from North Africa were positive. The results of the screening tests for TB are summarised in Table 2. In addition to the data reported in the table, an additional 42 individuals were tested with both TST and QFT-GIT: 16 were negative to both methods, 16 were positive to both, three were positive to TST only and seven were positive to QFT-GIT only. Two-hundred and sixty individuals underwent a chest X-ray, which was normal in 217 (83.5%) cases. Ninety-four people were screened for latent TB exclusively with chest X-ray, and eight (8.5%) of them presented any pulmonary abnormalities. Forty-nine individuals with a positive TST underwent a chest X-ray, and nine presented abnormal pulmonary findings, whereas 30 individuals with a positive QFT-GIT underwent a chest X-ray and seven had pulmonary abnormalities.

Table 3

Results of stool examination for ova and parasites[a], Verona province, Italy, April 2014–June 2015

Region	Individuals screened by stool microscopy	Positive for *Strongyloides stercoralis* larvae		Positive for *Schistosoma mansoni* eggs		Positive for hookworm[b] eggs		Positive for Ascaris lumbricoides eggs		Positive for *Trichuris trichiura* eggs		Positive for other parasites[a]	
	n	n	%	n	%	n	%	n	%	n	%	n	%
Sub-Saharan Africa (n=358)	270	9	3.3	19	7.0	34	12.6	2	0.7	4	1.5	80	29.6
Asia (n=97)	79	6	7.6	0	0	13	16.5	2	2.5	9	11.4	17	21.5

[a] Reporting is focused on helminths determined to be clinically relevant, such as soil-transmitted helminths. Some other parasites, both helminths and protozoa, might not have a clinical relevance and are included in the other parasites group (e.g. *Hymenolepis nana* and *Endolimax nana*).

[b] Includes *Ancylostoma duodenale* and *Necator americanus*.

Helminthic infections

A stool sample was provided by 270 of 358 (75.4%) individuals coming from sub-Saharan Africa and 79 of 97 (81.4%) individuals coming from Asia; thus, no significant association was observed between region and will to provide a stool sample (chi-squared test, p value = 0.285). Among the seven individuals coming from North Africa, three did not supply a stool sample. Table 3 shows the main results of stool examination, in relation to region of origin of the asylum seekers. In addition to the data reported in the table, urine was examined for O and P in 96 of the individuals from sub-Saharan Africa, and 20 (20.8%) presented *S. haematobium* eggs. Of the four individuals from North Africa that supplied stool samples, all were negative for O and P. Screening with *S. stercoralis* serology was done for 458 individuals, 91 (19.9%) of whom were positive. Of the latter, 14 (32.6%) had positive stool microscopy for *S. stercoralis* larvae. One additional individual had positive microscopy and negative serology. Hence, 92 of 458 (20.1%) individuals tested were positive to any test for *S. stercoralis*, and 15 (3.3%) had larvae in stool. In terms of regions, 64 of 358 (17.9%) people from sub-Saharan Africa were positive to any test for *S. stercoralis*(serology and/or stool microscopy), whereas 28 of 97 (28.9%) individuals from Asia were. Of 358 individuals from sub-Saharan Africa tested, 76 (21.2%) were positive for at least one test for *Schistosoma* spp. (urine microscopy or stool microscopy or serology). Three of them had negative serology, whereas 32 individuals had positive serology and negative detection of *Schistosoma* spp. eggs.

Table 4 displays a summary of the univariate and multivariate analyses regarding the association between eosinophilia and either age or the main helminthiasis in the entire cohort of asylum seekers, as well as in the sub-Saharan African and Asian subgroups. As expected, people with eosinophilia were more likely to be infected with *S. stercoralis*, *Schistosoma* spp. and hookworm (*Ancylostoma duodenale* and *Necator americanus*). Adjusted ORs highlight a strong association between helminthic infections and the probability of presenting eosinophilia, both in the entire cohort and in individuals from sub-Saharan Africa. In contrast, the presence of *S. stercoralis* was not associated with eosinophilia in individuals from Asia (adjusted odds ratio (OR): 0.76, 95% confidence interval (CI): 0.25–2.13).

Discussion

Infectious diseases are not the main problem affecting individuals that are part of the large, current wave of migration to Italy, often through the perilous Central Mediterranean route. Those who survive the journey almost invariably have, at least in our experience with a large number of asylum seekers, a history of experiencing physical, sexual and/or psychological harassment, violence and often torture. A recently published review underlines the role of traumatic experiences during the migration process on various aspects of health and health conditions [21]. Mental and psychosocial diseases, including depression and anxiety disorder, as well as the consequences of physical traumatism, are probably the first health priority to be dealt with [22,23].

However, attention should also be paid to infectious diseases, especially because of concerns about infection spreading to the local population that are often unfounded. In Italy therefore, the only screening formally indicated so far includes a clinical assessment for scabies and one for clinical and/or latent TB (protocols for the latter are not uniform). Many individuals are also screened for HIV, although there is no formal country-wide protocol for this infection, and a number are also screened for hepatitis B and C, with different, informal protocols.

At the CTD we applied, as a pilot initiative within the Veneto Region, an extended screening in Verona province that included screening for neglected helminthic infections. These are not a cause of concern for the local population, but may place a heavy clinical burden,

Table 4

Crude and adjusted odds ratios for the association between helminthic infections[a] and eosinophilia among all migrants and stratified by region of origin, Verona province, Italy, April 2014–June 2015

Covariate	Eosinophilia present		Eosinophilia absent		Crude OR (95% CI)	Adjusted OR (95% CI)b
	n/N	%	n/N	%		
Total (n = 461)[c,d]						
Age (median, IQR)	23	(20–26)	24	(20–28)	0.96 (0.93–0.99)	0.98 (0.94–1.02)
Strongyloides stercoralis	42/144	29.2	51/316	16.1	2.14 (1.33–3.41)	1.98 (1.11–3.52)
Schistosoma spp.	46/144	31.9	36/308	11.7	3.55 (2.17–5.84)	5.13 (2.93–9.18)
Hookworm[e]	32/126	25.4	15/227	6.7	4.81 (2.53–9.53)	5.28 (2.63–11.00)
Sub-Saharan Africa (n = 357)[d]						
Age	22	(20–26)	24	(20–28)	0.96 (0.92–1.01)	0.97 (0.91–1.01)
S. stercoralis	30/105	28.6	34/251	13.6	2.55 (1.45–4.45)	2.80 (1.37–5.79)
Schistosoma spp.	46/105	43.8	36/252	14.3	4.68 (2.78–7.93)	6.38 (3.46–12.05)
Hookworm[e]	22/94	23.4	12/176	6.8	4.17 (1.99–9.14)	4.69 (2.02–11.22)
Asia (n = 97)[f]						
Age	23	(19–27)	25	(21–29)	0.96 (0.89–1.02)	1.00 (0.93–1.06)
S. stercoralis	12/38	31.6	17/59	28.8	1.14 (0.46–2.75)	0.76 (0.25–2.13)
Hookworm[e]	10/31	32.3	3/48	6.3	7.14 (1.95–34.38)	7.54 (1.95–38.10)

CI: confidence interval; IQR: interquartile range; OR: odds ratio.

[a] Infections were diagnosed using any of the following: urine microscopy or stool microscopy or serology.

[b] Adjusted for age and for the presence of other helminth infections through a multivariate logistic regression model.

[c] The total includes seven individuals coming from North Africa.

[d] The value does not include one person from the cohort (n = 462) for whom info about eosinophil count is missing.

[e] Includes Ancylostoma duodenale and Necator americanus.

[f] No Schistosoma spp. was detected in individuals from Asia so it was not possible to adjust the model for this infection.

even after many years, on infected individuals, including life-threatening complications of strongyloidiasis or schistosomiasis. The prevalence of neglected parasitic infections was high. These are most often asymptomatic, and therefore may only be detected with a specially designed screening, and they are never considered a priority as they cause no harm to the autochthonous population.

As far as HIV/AIDS is concerned, the prevalence in individuals from sub-Saharan Africa is low compared to the helminthic infections, and no individual from North Africa or Asia was found to be infected. The same is even more true for HCV infection as there was only one infected individual in the whole study population. On the contrary, prevalence of HBV infection was high and similar to that found by studies on other migrant populations [13,24]. Latent TB was high in our study population, which is similar to findings reported in recent papers from other European countries [13,24]. Is an extended screening such as the one we carried out worthwhile? A definitive answer would need to be based on a formal cost-effectiveness study, and that was well beyond the scope of this paper. However, we believe that our results certainly question the usefulness of screening for HCV infection because of its low prevalence in combination with extremely high-cost treatment that has limited its use to advanced stages of the disease. The utility of HIV screening is also debatable, as is that of HBV infection. Both imply treatments that, besides being very expensive, require a long-term management and a treatment compliance that is particularly difficult to obtain in this often very mobile population. The same problem, though to a lesser extent, concerns latent TB screening: shorter courses, i.e. 3 months, of treatment are available and some local health units in our region have been able to achieve 80% or more of treatment success (personal communication, C. Postiglione April 2018). However, others simply refrain from providing any treatment as they feel unable to ensure sufficient compliance and follow-up in this group of individuals. We argue that if treatment is not offered and adequate conditions to guarantee compliance cannot be ensured through directly observed treatment (DOT) or a similar strategy, latent TB screening is not a good use of resources and should not be proposed.

Helminthic infections can also potentially cause serious health consequences for infected individuals, however, person-to-person transmission does not represent an issue and treatment is comparatively straight forward. Like our study, other studies reported high prevalence of some helminths targeted by the screening of asymptomatic individuals [14,25]. While the implementation of screening activities for these infections sometimes faces obstacles, such as refusal to supply biological samples and test limitations (low sensitivity of stool

examination in case of *Schistosoma* spp. and *S. stercoralis* infections, and concerns about specificity of serology), treatment of these infections is short, often a stat dose, very effective, well tolerated and reasonably cheap [14]. Two studies of cost-effectiveness of the management of this group of diseases in immigrants were carried out in the United States (US) [17,26], with a particular focus on strongyloidiasis, concluding that presumptive treatment was the more cost-effective option, especially if provided in the country of origin before departure.

These studies from the US are not particularly applicable to the Italian situation for several reasons. First, schistosomiasis was highly prevalent in our study, but, reflecting a different geographical origin of immigrants, the American studies did not consider this infection in their analyses. Second, treatment before migration is obviously not possible given that many migrants are arriving in Europe without having previous contact with authorities. Third, drug availability and cost are a major concern in Italy given that ivermectin and praziquantel, which are used for strongyloidiasis and schistosomiasis, respectively, are not registered and need to be imported at a non-negligible cost. Fourth, by the Italian Constitution, every individual in Italy has the right to the best-available healthcare which means that any difference in medical approach between Italians and non-Italians would be discriminatory. Although offering screening for helminthic infections only to symptomatic people might presumably increase the compliance to diagnostic tests and treatment, this approach would considerably reduce asymptomatic infected individuals access to treatment. Also, as schistosomiasis and strongyloidiasis frequently lead to chronic indolent diseases, such a strategy would leave the largest proportion of infected individuals, asymptomatic individuals, at high risk of potentially-fatal complications. A halfway measure, which also takes difficulties in obtaining the stool samples into consideration, might be presumptive treatment for helminthic diseases based on the presence of eosinophilia. This might be a particularly valid option for population subgroups and/or helminths where the association between helminths and eosinophilia proved to be strong. In comparison with a strategy that screens symptomatic people, a smaller proportion of infected individuals would be left without treatment. Moreover, this approach would reduce the costs and the logistical constraints of universal screening. However, the negative predictive value of eosinophilia might not be sufficiently high to safely exclude strongyloidiasis and schistosomiasis, as suggested previously [14]. An in-depth cost-effectiveness analysis should be conducted.

In any case, the current strategy of not addressing neglected parasitic diseases is not acceptable.

A main limitation of this study is that the cohort of asylum seekers was almost entirely composed of males so we could not evaluate possible, sex-related differences in the distribution and proportion of the same infections. Moreover, our results may not be representative of the situation of asylum seekers in other countries in Europe/other Italian settings. The main strength is that this paper adds to the little data available in the medical literature on an extensive screening of newly-arrived asylum seekers that includes helminthic infections, regardless of whether or not clinical symptoms are present. We believe that our data on a cohort of individuals, mostly originating from sub-Saharan Africa, particularly contribute to filling a gap of knowledge in terms of relevant helminthic infections possibly presented by asylum seekers in Italy. This may prove particularly useful as the Italian Ministry of Health recently issued new screening guidelines that recommend the screening of asylum seekers and refugees for strongyloidiasis and schistosomiasis for the first time [27].

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Conflict of interest

None declared.

Authors' contributions

D Buonfrate, Z Bisoffi, and F Gobbi drafted the manuscript. V Marchese, C Postiglione, G Monteiro, F Gobbi, performed the screening activities. G Monteiro and G Napoletano supervised the screening activities. V Marchese and C Postiglione collected the data. D Buonfrate, F Gobbi and Z Bisoffi analysed the data. G Giorli performed the statistical analysis. All authors commented and agreed upon the final manuscript.

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Research article

Universal screening for latent and active tuberculosis (TB) in asylum-seeking children, Bochum and Hamburg, Germany, September 2015 to November 2016

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Background: In Germany, the incidence of tuberculosis (TB) in children has been on the rise since 2009. High numbers of foreign-born asylum seekers have contributed considerably to the disease burden. Therefore, effective screening strategies for latent TB infection (LTBI) and active TB in asylum seeking children are needed. **Aim:** Our aim was to investigate the prevalence of LTBI and active TB in asylum seeking children up to 15 years of age in two geographic regions in Germany. **Methods:** Screening for TB was performed in children in asylum seeker reception centres by tuberculin skin test (TST) or interferon gamma release assay (IGRA). Children with positive results were evaluated for active TB. Additionally, country of origin, sex, travel time, TB symptoms, TB contact and Bacille Calmette-Guérin (BCG) vaccination status were registered. **Results:** Of 968 screened children 66 (6.8%) had TB infection (58 LTBI, 8 active TB). LTBI prevalence was similar in children from high (Afghanistan) and low (Syria) incidence countries (8.7% vs 6.4%). There were no differences regarding sex, age or travel time between infected and non-infected children. Children under the age of 6 years were at higher risk of progression to active TB (19% vs 2% respectively, p=0,07). Most children (7/8) with active TB were asymptomatic at the time of diagnosis. None of the children had been knowingly exposed to TB. **Conclusions:** Asylum seeking children from high and low incidence countries are both at risk of developing LTBI or active TB. Universal TB screening for all asylum seeking children should be considered.

Introduction

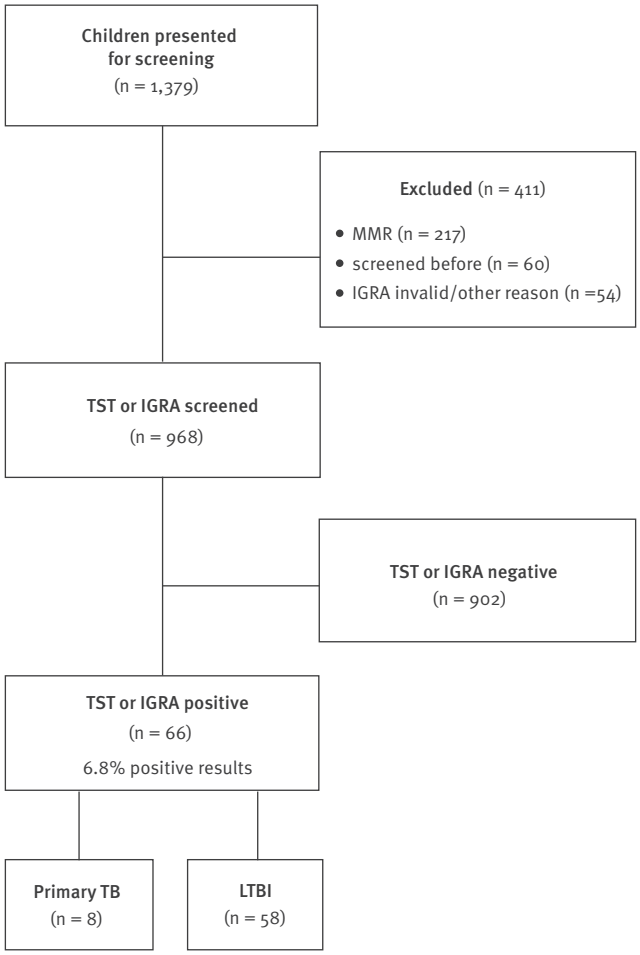
In recent years, Germany experienced a major increase in the number of migrants. Of 890,000 refugees/asylum seekers (hereafter referred to as asylum seekers) who reached Germany in 2015, more than one third were younger than 18 years. Most of them came from Syria, Iraq and Afghanistan [1].

Tuberculosis (TB) incidence rates in Germany had seen little change for several years until 2013, when numbers of TB cases started to rise. In 2015, an increase in incidence of 29.4% compared with the previous year was recorded [2]. Among the 5,865 cases notified there were 196 children up to 15 years of age. Incidence rates of TB are linked to migration with almost three quarters of TB patients in 2016 in Germany being foreign-born [3]. In foreign-born children the incidence of TB is 37 times higher than in children born in Germany (21.4 vs 0.6/100,000 children).

Asylum seekers have a higher risk of exposure to TB, both in their countries of origin and during migration. Furthermore, an increased risk for disease progression of latent tuberculosis infection (LTBI) due to physical and psychosocial stress factors has been observed [4]. In Germany, asylum seekers aged 15 years and older entering reception centres require a medical certificate stating the absence of any signs of potentially infectious pulmonary TB based on chest X-ray findings [5]. For children and adolescents up to the age of 15 years, an immunodiagnostic screening for TB, either by tuberculin skin test (TST) or interferon gamma release assay (IGRA), is recommended [6]. Immunodiagnostic tests can identify children with LTBI before they develop active TB [7]. In these children, preventive treatment significantly reduces the risk of progression and therefore further spread of the disease and further costs

Figure

Flowchart and results of screening procedures in children and adolescents at seven asylum seeker reception centres in Bochum and Hamburg, Germany, September 2015–November 2016 (n = 1,379)



IGRA: interferon gamma release assay; LTBI: latent tuberculosis infection; MMR: measles-mumps-rubella vaccination; TB: tuberculosis; TST: tuberculin skin test.

associated with severe TB, especially in young children [8,9].

The approach to screen all asylum seekers for LTBI and active TB would entail considerable pressure on healthcare resources. Responding to the European refugee crisis in 2015, many countries have therefore concentrated exclusively on screening for active TB [10] and so far, there is no uniform screening procedure for asylum seekers in Europe [10].

The aim of this study was to investigate the prevalence of TB infection in refugees up to 15 years of age in two geographic regions in Germany by immunological screening. The screening was carried out as part of the initial medical screening of asylum seekers at the reception centres ('Erstaufnahmeeinrichtung') upon arrival in Germany.

Methods

Between September 2015 and November 2016, children and adolescents aged from 3 months up to 15 years, were screened for TB infection using TST (2 IU PPD RT 23, Statens Serum Institute, Copenhagen, Denmark) and/or IGRA (QuantiFERON Gold in tube, Qiagen, Germantown, United States). Seven asylum seeker reception centres participated in two different German urban settings, three in Bochum and four in Hamburg. Asylum seekers in Germany usually stay in reception centres for 1 to 3 weeks before moving on to their secondary accommodation. Children who were immunised against measles, mumps and rubella (MMR) within the previous 4 weeks were excluded as live-attenuated MMR vaccines can lead to a temporary suppression of the cell-mediated immune response and result in false-negative TST results [11]. The excluded children were followed up 4 to 6 weeks later at the secondary accommodation.

A questionnaire assessed sociodemographic data including age, sex, country of origin, travel time as well as TB symptoms, TB contact (child of family member had contact with a known TB patient) and Bacille Calmette–Guérin (BCG) vaccination status.

In Hamburg, children were screened using TST and the test was considered positive if the transverse induration diameter was at least 10 mm as recommended by current guidelines [12]. In Bochum, children under the age of five were initially screened by TST, children and adolescents from 5 up to 15 years were screened by IGRA, due to a temporal shortage in TST. Screening and interpretation of TST results were the same as in Hamburg.

BCG vaccination status (mostly self-reported) and typical scars were recorded. Additionally, every child was assessed by a general medical examination. TST- or IGRA-positive children were referred to specialised children's hospitals for further diagnostics (e.g. chest X-ray, ultrasound, IGRA, sputum or gastric aspirates) and treatment.

Definitions

Following national guidelines, LTBI was defined as immunological evidence of infection (positive TST and/or IGRA) in absence of signs of active TB (clinical, radiological, microbiological) and active TB as evidence of TB with either microbiological and/or radiological and/or clinical signs of TB [6].

Statistical analysis

Data were analysed using SPSS 24.0 statistics software. Descriptive statistics were calculated for all variables. Comparisons between groups were made using the t-test or the Mann–Whitney U Test. For association between categorical variables chi-squared test or Fisher`s exact test was performed. A p value less than 0,05 was considered to be statistically significant.

Table

Sociodemographic data of screened children by screening results in seven asylum seeker reception centres in Bochum and Hamburg, Germany, September 2015–November 2016

	Total		LTBI		Active TB		LTBI and active TB	
	N	%	n	%	n	%	n	%
Number of children	968	100	58	6	8	0.8	66	6.8
Age (median months)	71.1	NA	99	NA	55.5	NA	80.5	NA
Male	516	53.3	32	55.2	6	75	38	57.6
Country of origin								
Syria	377	38.9	21	36.2	3	37.5	24	36.4
Iraq	289	29.9	17	29.3	3	37.5	20	30.3
Afghanistan	217	22.4	17	29.3	2	25	19	28.8
Other[a]	85	8.8	3	5.2	0	0	3	4.5
BCG vaccinated	558	57.6	34	58.6	5	62.5	39	39.1
Travel time (median, in days)	21	NA	30	NA	30	NA	30	NA
TB contact	5	99.5	0	0	0	0	0	0
TB symptoms	69	7.1	2	3	1	12.5	1	0.02

BCG: Bacille Calmette-Guérin; LTBI: latent tuberculosis infection; NA: not applicable; TB: tuberculosis.

[a] Other: Armenia (n= 1); Azerbaijan (n= 1); Georgia (n=5); Iran (n=41); Nigeria (n=11); Albania/Kosovo* and Serbia (n=14); Somalia (n=5); stateless (n=7).

*This designation is without prejudice to positions on status, and is in line with UNSCR 1244/1999 and the ICJ Opinion on the Kosovo declaration of independence.

Consent was provided by guardians in the presence of a translator. The study was approved by local ethical committees in both Bochum and Hamburg and conducted according to current guidelines for asylum seeking children and adolescent screening [12].

Results

A total of 1,379 asylum seeking children, aged from 3 months up to 15 years were included for evaluation in this study, 926 in Bochum and 453 in Hamburg.

We excluded 411 children from the screening: 217 had recently received MMR vaccine, 60 were screened previously in other reception centres, 80 had an acute febrile illness and 54 showed either indeterminate IGRA or were lost to follow-up (Figure). Recently vaccinated children, febrile children and those with indeterminate IGRA results received documentation regarding their current screening status and were (re-) screened at their long- term accommodation.

Of the 968 children who underwent screening the median age was 71.1 months (IQR 35–116). The majority (n=707; 73%) of the children were from the Middle East, mainly Syria (n=377; 38.9%) and Iraq (n=289; 29.9%). The third biggest group of asylum seeking children was from Afghanistan (n=217; 22.2%).

There were 66 children and adolescents with positive TST or IGRA results. Median age was 80.5 months (range: 6–168; IQR 42.7–141.5); 38 (57.6%) were boys. Of all infected children 24 (36.3%) were from Syria, 20 (30.3%) from Iraq and 19 (28.8%) from Afghanistan. In total, 31 children (47.7%) were under the age of 6 years at the time of screening. All 66 children and adolescents with positive TST or IGRA results were referred to a paediatric hospital for further diagnostics and therapy; 58 children (32 boys, 26 girls) were diagnosed with LTBI and treated with isoniazid and rifampicin for 3 months [13]. Eight children (6 boys, 2 girls) were diagnosed with active TB by chest X-ray and/or microbiological investigations and treated according to national recommendations [6]. Among these eight there were one sputum smear-positive adolescent and two children with PCR and microbiological cultures positive for *M. tuberculosis* complex.

Sociodemographic data and screening results are summed up in the Table.

Children with latent tuberculosis

Children with LTBI were older (median age 80.5 vs 71.1 months, p=0,057) than children without TB infection. The majority was from Syria (n=21; 36.2%), followed by Iraq (n=17; 29.3%) and Afghanistan (n=17; 29.3%). These percentages correlate well with the overall distribution of asylum seekers' countries of origin (Table).

The prevalence of LTBI differed only slightly between children from high and low incidence countries: Afghanistan (17/217; 7.8%) vs Syria (21/377; 5.6%; p= 0,27) and Iraq (17/289; 5.9%; p= 0,44) . Although asylum seeking children with LTBI were older than the ones without LTBI, those under the age of 6 years were

at higher, although not statistically significant risk of progression to active TB (19% vs 2% respectively; p=0,074). There were no significant differences regarding sex, travel time, symptoms or BCG vaccination status between children with and without TB infection.

Children with active tuberculosis

The eight children with active TB were younger than the total of the screened children and those with LTBI (median 55.5 months vs 71.1 vs 80.5 months, p= 0,1); six of them were male. Of the eight children, three were from Syria and three from Iraq. The other two were from Afghanistan. There were no significant differences in travel time and BCG vaccination in comparison to the total cohort. Seven children did not report any symptoms suggestive for TB (prolonged cough, fever, night sweats). None of them reported contact with a TB patient.

Discussion

Universal screening for TB detected 6.8 % children with LTBI and active TB in our study population of asylum seeking children up to the age of 15 years. About half of the children with LTBI were younger than 6 years and therefore at high risk of progression to active and especially disseminated TB if not treated promptly [14]. We also identified eight children in this age group who already progressed to active TB. In a large cohort study from Amsterdam, the risk of developing active TB was slightly lower for infected school age children but still reported to be up to 19.1% [15]. We identified two cases of active TB in this age group. Thus, our findings stress the importance of including children and young adolescents in national screening strategies.

Even though the overall risk of TB transmission by children is lower than by adults [14], there are reported cases in which school-aged children with active TB infected up to 39% of their contacts [16]. Considering the situation in crowded asylum seeker accommodations, the risk of transmission might be even higher [17]. The risk of developing active TB when infected has been shown to be higher in adult asylum seekers in comparison to the population in their countries of origin [18,19]. It remains unclear whether this is the case in children as well. An immunological screening of asylum seeking children of all age groups could potentially be helpful in preventing cases of infectious TB and in minimising the risk of progression to active and possibly disseminated disease in young children.

One approach to screening refugee children is to screen only children from countries with high TB incidence (above 100 cases/100,000 population). This approach does not seem ideal for different reasons [20]. Our data show that LTBI and active TB are not restricted to children from high incidence countries like Afghanistan (189 cases/100,000 population) [21]. Syrian children, the largest group of our study population, had similar percentages of TB infection as children from Afghanistan. The International Organization for Migration (IOM) and the World Health Organization (WHO) documented rising TB incidence in Syria since 2013 [4]. For 2015, the official TB incidence is reported to be 20 cases per 100.000 inhabitants by the WHO, but it is doubtful whether this figure reflects the actual numbers as precise recording in times of war and civil unrest is known to be difficult [4].

Another reason for the increased numbers of TB infection in Syrian and Iraqi asylum seeking children might be related to travel routes and travel time to Germany. Of the 44 children from Syria and Iraq who had positive screening results, 13 spent a month or more in refugee camps along the Balkan route or before crossing the Mediterranean Sea. Very often medical support and nutrition during migration are inadequate and refugees from high and low TB incidence countries live together in crowded accommodations.

Symptom-based screening of refugees has been standard practice in many countries [10]. However, sensitivity and specificity of symptom-based screening is poor [22-24] and does not represent an effective screening approach, especially in young children [24]. In our study only one child with active TB displayed suggestive symptoms, while seven were detected by immunological screening and subsequent investigations.

Responding to the enormous increase in asylum seekers in 2015, many local authorities in Germany and other Western European countries concentrated on screening direct contacts of infectious TB patients [10,12]. Our data shows that contacts to TB cases were either not remembered or not stated by the children or their guardians, maybe due to fear of stigma connected with TB.

In our experience, universal TB screening in asylum seeking children is both effective and feasible. However, documentation of screening results and assurance of treatment completion in infected and diseased children remains crucial.

In addition to recording the screening result in the national vaccination card , asylum seeking children in the two urban areas involved in this study were supposed to receive a refugee health document (North Rhine-Westphalia health card (NRW Gesundheitskarte)); Hamburger health booklet (Hamburger Gesundheitsheft) in order to collate existing data and prevent redundant examinations. Despite the large overall amount of data that are collected in the process of providing healthcare to asylum seekers, there are neither federal standards for documentation, nor is there a standard set of collected health items in Germany [25,26]. In view of national and international mobility of asylum seekers, an innovative European solution of health information management would be desirable for the future.
Preventive therapy of LTBI in children is well tolerated and prevents progression to active TB in more than

90% [13]. Therefore, reduction of cases of active TB seems feasible in asylum seeking children. In order to assure treatment completion, different challenges have to be tackled in this hard-to-reach population. The stigma of being diagnosed with TB has to be addressed and resolved. Easy access to healthcare and increased tuberculosis awareness are vital [27]. In addition, directly observed therapy (DOTS) in asylum seeker reception centres and subsequent housing facilities could improve success rates.

Cost-effectiveness of TB screening was not investigated in our study. In a recent review in adults, LTBI screening in asylum seekers was described as cost effective [28]. None of the included studies, however, evaluated the subgroup of children.

An ideal approach would be to assess the overall exposure risk and perform baseline TB screening for all asylum seekers – both children and adults – upon arrival and pursue follow-ups over the next 2 years.

The 'End TB Strategy', adopted by WHO Member States in 2014, identifies TB in hard-to-reach populations – such as asylum seekers– as an important public health challenge for low-incidence countries like Germany and other Western European countries and recommends the implementation of comprehensive social and healthcare interventions [29].

Even though we screened a comparably high number of children, there are various study limitations that need to be taken into consideration. First our cohort is likely not to be representative for the general population of asylum seekers that reached Germany during the time of our investigation. It rather presents a snapshot at the moment of data collection, when the total numbers of asylum seekers, even in single reception centres, were not reliably documented. The distribution of asylum seekers within Germany was very heterogeneous for example regarding the country of origin and therefore a nationwide study would have been desirable. Another problematic issue was the high mobility of the asylum seekers. Anecdotal evidence showed that the latter were frequently registered twice at different centres and moved freely between them. Therefore, either double or incomplete registration could have caused a bias regarding epidemiological data, follow-up investigations and treatment [25,26].

Conclusion

In conclusion, our data supports the implementation of universal screening for LTBI and active TB in asylum seeking children of all ages and from both high and low TB incidence countries using immunological tests such as TST or IGRAs in order to prevent future active TB cases and further spread of the disease. Careful documentation of screening results and completion of preventive therapy should be ensured to guarantee the success of this screening approach.

Conflict of interest

The authors declare no conflict of interest.

Authors' contributions

Maya Mueller-Hermelink, Robin Kobbe, Benedikt Methling, Cornelius Rau, Ulf Schulze-Sturm, Isa Auer, Frank Ahrens and Folke Brinkmann acquired clinical data. Maya Mueller-Hermelink, Robin Kobbe and Folke Brinkmann drafted the manuscript and Benedikt Methling, Cornelius Rau, Ulf Schulze-Sturm, Isa Auer, and Frank Ahrens reviewed the manuscript. All authors approved the final version.

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Research article

Find and treat or find and lose? Tuberculosis treatment outcomes among screened newly arrived asylum seekers in Germany, 2002 to 2014

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Background: Germany has a low tuberculosis (TB) incidence. A relevant and increasing proportion of TB cases is diagnosed among asylum seekers upon screening. **Aim:** We aimed to assess whether cases identified by screening asylum seekers had equally successful and completely reported treatment outcomes as cases diagnosed by passive case finding and contact tracing in the general population. **Methods:** We analysed characteristics and treatment outcomes of pulmonary TB cases notified in Germany between 2002 and 2014, stratified by mode of case finding. We performed three multivariable analyses with different dependent variables: Model A: successful vs all other outcomes, Model B: successful vs documented non-successful clinical outcome and Model C: known outcome vs lost to follow-up. **Results:** TB treatment success was highest among cases identified by contact tracing (87%; 3,139/3,591), followed by passive case finding (74%; 28,804/39,019) and by screening asylum seekers (60%; 884/1,474). Cases identified by screening asylum seekers had 2.4 times higher odds of not having a successful treatment outcome as opposed to all other outcomes (A), 1.4 times higher odds of not having a successful treatment outcome as opposed to known non-successful outcomes (B) and 2.3 times higher odds of loss to follow-up (C) than cases identified by passive case finding. **Conclusion:** Screened asylum seekers had poorer treatment outcomes and were more often lost to follow-up. Linking patients to treatment facilities and investigating potential barriers to treatment completion are needed to secure screening benefits for asylum seekers and communities.

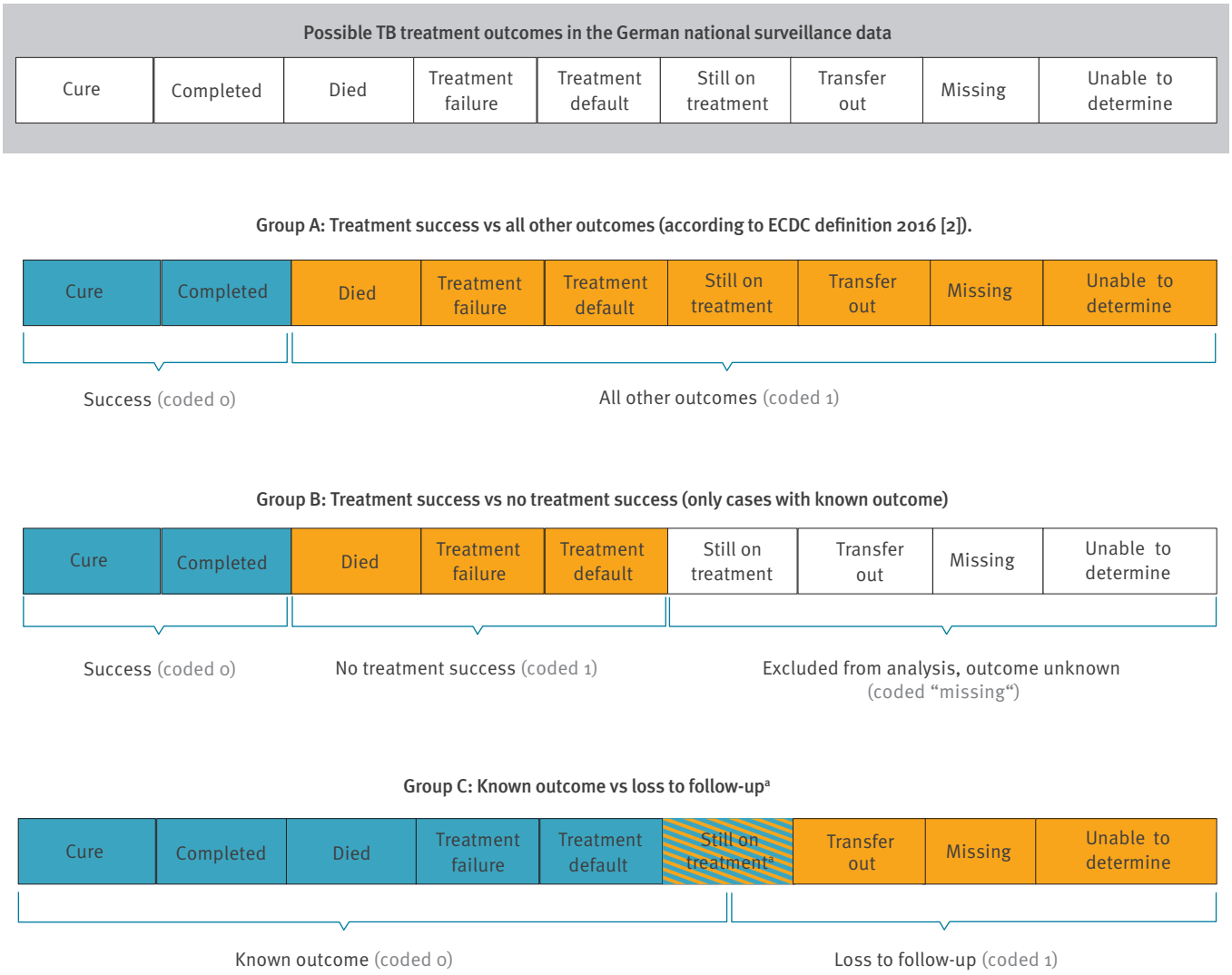
Introduction

With 10.4 million new cases of active tuberculosis (TB) in 2016, TB remains one of the world's biggest health threats [1]. Most countries in the European Union (EU) are low-incidence countries where TB predominantly affects vulnerable populations such as migrants, prisoners and people living with HIV [2]. To achieve an ongoing decrease in TB incidence in EU countries, further efforts are needed to address these often hard-to-reach groups [2]. In Germany, 5,915 cases of active TB were notified in 2016 [3]. Demographic changes and migration influence TB incidence in Germany and contributed to the end of a previously declining TB trend [3,4]. Ensuring early detection and comprehensive access of all population groups to timely and complete treatment will be essential to control TB and ultimately meet the World Health Organization's (WHO) TB elimination goals [5].

Cases found by passive case finding, i.e. TB patients diagnosed after clinical presentation with symptoms or post mortem, contributed the highest proportion of new cases in 2016 (66%) [3]. Sixteen per cent of cases had been diagnosed by active case finding among asylum seekers and refugees [3]. This proportion was on average 2.4% between 2002 and 2014 and had been increasing since 2008, when it was smallest (0.7%) [3]. Active case finding is performed among several risk groups to ensure early detection and treatment and to prevent further transmission from infectious cases. In recently exposed persons, contact tracing is performed according to German contact tracing recommendations [6]. Among asylum seekers, screening is performed to find infectious pulmonary TB cases early at admission to shared accommodations (reception centres) after entering the country. Screening for infectious pulmonary TB at entry to such shared accommodations is mandatory according to §36.4 of the Protection Against Infection Act (Infektionsschutzgesetz (IfSG)). With the increasing number of migrants seeking asylum in Germany, the mandatory screening for infectious pulmonary TB among asylum seekers has challenged

Figure 1

Grouping and coding of treatment outcomes of notified tuberculosis cases in the national notification system, Germany, 2002–2014



ECDC: European Centre for Disease Prevention and Control; TB: tuberculosis.

[a] Still on treatment is regarded as loss to follow-up when disease onset is more than 24 months ago for non-MDR-TB or more than 36 months ago for MDR-TB, the remaining cases are regarded as cases with known outcome.

For this study, 'loss to follow-up' describes cases that were 'lost' to the national TB notification system, i.e. the outcome cannot be evaluated. This should be distinguished from the newly introduced term 'lost to follow-up' that has replaced 'defaulter' in international TB reports and describes a known treatment interruption for at least two consecutive months.

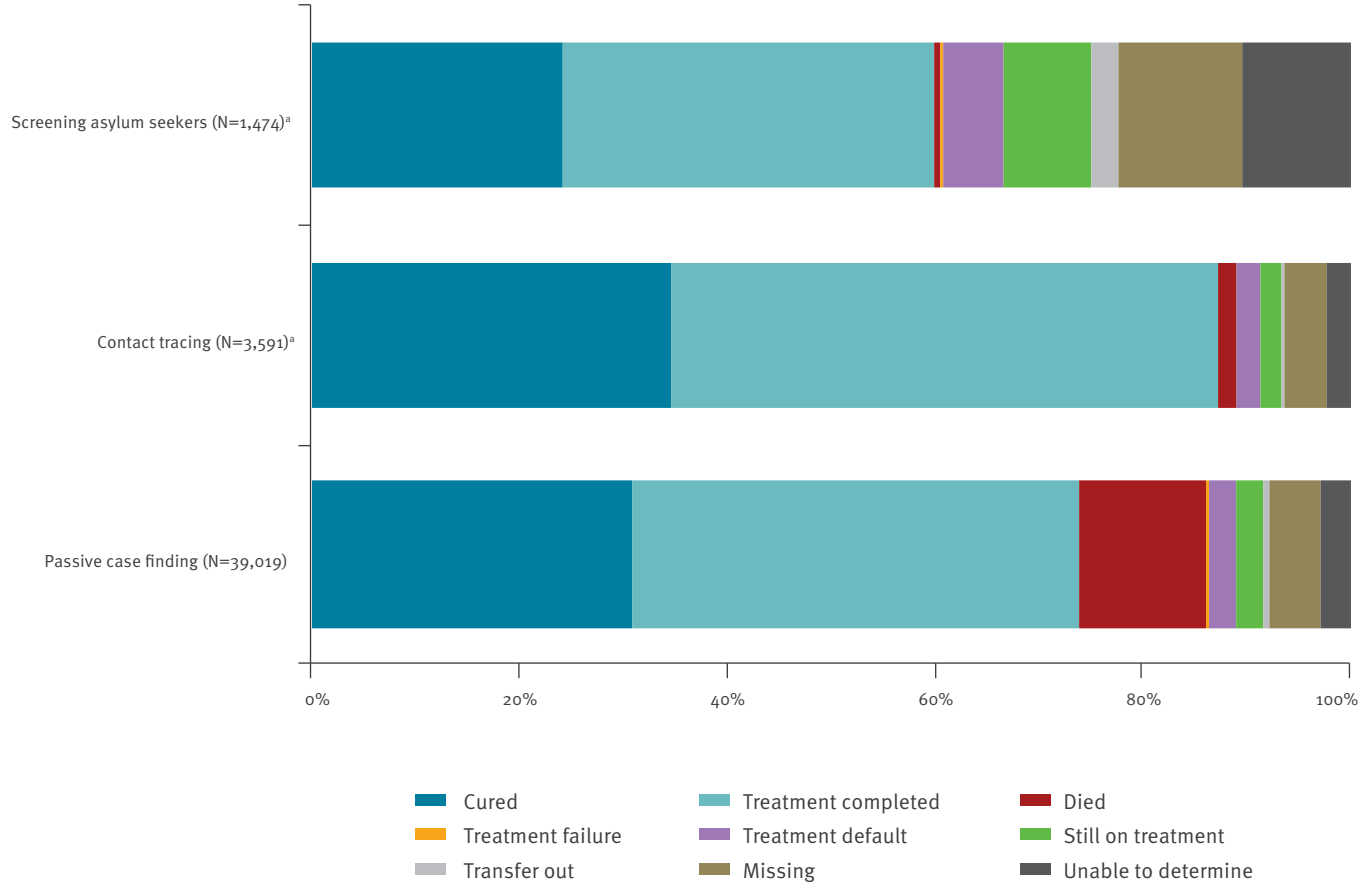
local public health authorities (LPHA) in 2014 and 2015 [7-11].

TB diagnosis – upon screening or clinical presentation – needs to be followed by rapid initiation of an effective and complete treatment to prevent further transmission, achieve cure and prevent the development of secondary drug resistance [12]. Tuberculosis treatment outcome monitoring is an essential part of TB surveillance and key for evaluating the effectiveness of TB screening and care. In line with international requirements [1,2], the German TB notification system comprises the treatment outcome categories *cured, treatment completed, died, treatment failure, treatment default, still on treatment, transfer out, missing* and *unable to determine* (Table 1). Treatment outcome is measured after 12 months follow-up and after 24 months for multidrug-resistant TB (MDR-TB) cases. The WHO and the Stop TB Partnership set the target of 90% treatment success (i.e. cured and treatment completed) for all TB cases that require treatment [1,13].

To what extent pulmonary TB found among screened asylum seekers in Germany is followed up until treatment completion, remains unclear however. We

Figure 2

Treatment outcomes of notified pulmonary tuberculosis cases by mode of case finding, Germany, 2002–2014 (n = 44,084)



[a] Active case finding.

therefore aimed to assess whether TB cases identified by screening among asylum seekers had an equally successful and completely reported treatment outcome as those diagnosed by passive case finding and by contact tracing, in order to highlight potential gaps in surveillance and case management.

Methods

Data source

We used case-based national TB notification data from Germany, reported to the Robert Koch Institute (RKI) through the electronic reporting system SurvNet@RKI [14]. Date of data extraction was 1 March 2016.

We included in our analysis pulmonary TB cases notified between 2002 and 2014 with available information on age and sex (total n = 52,995). The dataset was further restricted to cases that were identified by the following modes of case finding: (i) screening of asylum seekers, (ii) passive case finding and (iii) contact tracing (total n = 44,084). The notification system, case definitions for TB and diagnostic procedures have remained largely unchanged over the investigation period.

Definitions

For German national disease surveillance, a case of TB is defined by clinical diagnosis of TB by a physician followed by the decision to initiate a full course of anti-tuberculosis treatment, with or without bacteriological confirmation or epidemiological link [15]. Bacteriological confirmation refers to a culture of *Mycobacterium tuberculosis* complex, or a combination of a positive microscopy result for acid-fast bacilli with a positive nucleic acid amplification test (NAAT) for the same specimen type [15]. In the TB notification system, information on the patients' age, sex, country of birth and the mode of case finding is recorded, as is bacteriological testing including drug resistance, previous TB diagnosis, site of TB and treatment outcome at any time of follow-up, in this study set to at least 12 months [16].

Modes of case finding are defined by reporting guidelines [16]. Screened asylum seekers are defined as TB cases that were identified by screening asylum seekers according to §36.4 IfSG by chest X-ray (except pregnant women or children younger than 15 years) on admission to a shared accommodation [17]. In children and pregnant women, screening including clinical signs

Table 1

Tuberculosis treatment outcome categories in the national notification system, Germany, 2002–2014

Categories	Definitions
Cured	Treatment completed and culture-negative samples taken at the end of the full course treatment and on at least one previous occasion
Treatment completed	Treatment completed without evidence of failure but no tests were performed or no result was available at the end of the full course of treatment
Died	Death before cure or treatment completion, irrespective of cause
Treatment failure	Culture or sputum smear remaining positive or becoming positive again 5 months or more into the course of treatment
Treatment default[a]	Treatment interrupted for at least 2 consecutive months
Still on treatment	Patient still on treatment at 12 months (and at 24 months for multidrug-resistant (MDR) TB cases) without any other outcome during treatment
Transfer out	Patient referred to a known or unknown address and information on outcome not available
Missing	Information on treatment outcome is missing (empty field)
Unable to determine	Information on treatment outcome could not be obtained by the local public health authority

[a]'Treatment default' is the translation of the German category name 'Abbruch der Behandlung'. Internationally, the previously used term 'defaulter' has recently been replaced by 'lost to follow-up', but this is not reflected in the German TB surveillance system.

and symptoms and immunological testing with either interferon-γ release assay (IGRA) or tuberculin skin test (TST) is recommended [17,18]. Thus, the screening intended to rule out infectious pulmonary TB also leads to the detection of pulmonary TB with negative bacteriological result. Cases identified by passive case finding are defined as TB cases diagnosed after clinical presentation; TB cases diagnosed post mortem were excluded from our study. Cases identified during the follow-up of exposed persons are defined as cases identified by contact tracing. Cases identified by other active case finding were not considered in this study.

Treatment success and data completeness

To assess treatment success and data completeness, we grouped treatment outcomes in three different ways (Group A, B and C) as displayed in Figure 1.

Group A: Cases that were *cured* or had *treatment completed* were referred to as cases with *successful treatment* and compared with cases that were recorded with all other outcomes. This definition is adapted from ECDC classification 2016 [2] and is in line with WHO and the Stop TB Partnership's definitions of treatment outcomes [1,13].

Group B: Cases with successful treatment were compared with cases with known non-successful treatment outcomes (*died*, *treatment failure* or *default);* all cases with outcome categories that contained essentially no information on the result of the treatment of the case (*still on treatment, transfer out, missing* and *unable to determine)* were excluded from this comparison in order to disentangle cases with non-successful treatment outcome from cases that were *lost to follow-up*.

Group C: Cases with known treatment outcomes, both successful and unsuccessful *(successful treatment, died, treatment failure, treatment default)* were compared with cases that were *lost to follow-up* to the national tuberculosis notification system (*transfer out, missing, unable to determine* or too long *still on treatment*). The classification is based on the assumption that in all these cases, LPHA did presumably not have up-to-date information and could not ascertain the treatment outcome. 'Too long' *still on treatment* was defined as cases without MDR-TB who were notified as *still on treatment* more than 24 months after notification and MDR-TB cases who were notified as *still on treatment* more than 36 months after notification. The remaining cases notified as *still on treatment* were defined as cases with known outcome as still on treatment is valid information on the treatment status.

Data analysis and protection

We describe demographic information, i.e. age (continuous), sex (female vs male), country of birth (Germany vs WHO regions excluding Germany vs unknown), as well as clinical information, i.e. MDR (not applicable, no drug susceptibility test (DST) reported, DST reported and among those with DST: not MDR vs MDR), previous TB diagnosis (no vs yes vs unknown), infectiousness (respiratory specimen: culture-negative and smear-negative vs culture-positive and smear-negative vs smear-positive vs unknown), severity of disease (pulmonary TB with TB of the central nervous system (CNS), meningitis or disseminated TB vs pulmonary TB only or with other secondary sites vs pulmonary TB with unknown additional manifestations) and treatment outcomes (Figure 1) by mode of case finding.

We also describe the above characteristics by treatment outcome. For categorical variables, we present numbers and proportions, for continuous variables, median and interquartile range (IQR).

The associations between mode of case finding and treatment outcome or loss to follow-up were

Table 2

Demographic and clinical characteristics of pulmonary tuberculosis cases notified by mode of case finding, Germany, 2002–2014 (n = 44,084)

Characteristics of cases		Active case finding				Passive case finding	
		Screening asylum seekers		Contact tracing		Diagnosis subsequent to clinical presentation	
		N = 1,474		N = 3,591		N = 39,019	
		n	% of N	n	% of N	n	% of N
Demographic characteristics							
Median age in years (IQR)		28	(22–37)	27	(11–44)	50	(34–68)
Sex							
Female		336	23	1,628	45	14,373	37
Male		1,138	77	1,963	55	24,646	63
Place of birth							
Germany		6	0.4	2,312	64	21,420	55
Other country	WHO Region Europe without Germany	539	37	773	21	10,156	26
	WHO Region Eastern Mediterranean	377	26	104	2.9	1,682	4.3
	WHO Region Africa	320	22	84	2.3	1,722	4.4
	WHO Region South-East Asia	46	3.1	74	2.1	1,345	3.4
	WHO Region Western Pacific	82	5.6	58	1.6	997	2.6
	WHO Region Americas	4	0.3	11	0.3	266	0.7
Unknown country		100	6.8	175	4.9	1,431	3.7
Clinical characteristics							
Infectiousness							
Culture-negative, smear-negative		496	34	1,164	32	6,268	16
Culture-positive, smear-negative		498	34	1,417	39	12,737	33
Smear-positive		410	28	748	21	18,966	49
Unknown		70	4.7	262	7.3	1,048	2.7
Previous TB							
No		876	59	3,252	91	29,963	77
Yes		201	14	109	3.0	4,429	11
Unknown		397	27	230	6.4	4,627	12
Drug resistance							
Drug susceptibility test (DST reported)		838	57	2,037	57	28,950	74
Not MDR (% of DST reported)		747	89	2,004	98	28,388	98
MDR (% of DST reported)		91	11	33	1.6	562	1.9
Unknown	Not applicable; bacteriologically negative	486	33	1,129	31	6,075	16
	No drug susceptibility test reported	150	10	425	12	3,994	10
Severity of disease							
Exclusively pulmonary TB		1,173	80	3,081	86	32,620	84
Pulmonary and CNS, meningitis or disseminated TB		5	0.3	10	0.3	574	1.5
Unknown		296	20	500	15	5,825	15

CNS: central nervous system; DST: drug susceptibility test; MDR: multidrug-resistant; TB: tuberculosis; WHO: World Health Organization.

investigated with multivariable logistic regression analyses using the passive case finding group as reference group. We interpreted coefficients in terms of odds ratios (OR) and report 95% confidence intervals (CI). We designed three logistic regression models (A, B, C) with different dependent variables: one for each group (A, B, C) of treatment outcome and loss to follow-up (Figure 1). We included mode of case finding as the independent variable and the following potential confounders (as described above if not specified) in all three models: age (in groups of 15 years), sex, country of birth (simplified: Germany vs other vs unknown), drug resistance (simplified: not MDR, MDR, unknown), infectiousness, previous TB and severity of disease, as well as reporting period (2002–05 vs 2006–14) as changes in data plausibility checks and completeness checks were introduced in 2006.

Analyses were conducted with STATA version 14 (Stata corporation, Texas, United States).

Table 3

Demographic and clinical characteristics of notified pulmonary tuberculosis cases by treatment outcome, Germany, 2002–2014 (n = 44,084)

Characteristics of cases		Group A: successful outcomes (n) among all outcomes (N)			Group B: successful outcomes (n) among known outcomes (N)			Group C: known outcomes (n) among all outcomes (N)		
		n	N	% of N	n	N	% of N	n	N	% of N
Main exposure of interest										
Mode of case finding										
Passive case finding		28,804	39,019	74	28,804	34,766	83	35,214	39,019	90
Contact tracing		3,139	3,591	87	3,139	3,285	96	3,334	3,591	93
Screening asylum seekers		884	1,474	60	884	983	90	1,062	1,474	72
Demographic characteristics										
Age in years										
<15		1,611	1,782	90	1,611	1,634	99	1,654	1,782	93
15–29		6,329	7,874	80	6,329	6,645	95	6,777	7,874	86
30–44		8,256	10,322	80	8,256	8,959	92	9,105	10,322	88
45–59		7,536	9,674	78	7,536	8,652	87	8,769	9,674	91
60–74		5,649	8,070	70	5,649	7,342	77	7,432	8,070	92
≥75		3,446	6,362	54	3,446	5,802	59	5,873	6,362	92
Sex										
Female		12,699	16,337	78	12,699	14,557	87	14,761	16,337	90
Male		20,128	27,747	73	20,128	24,477	82	24,849	27,747	90
Place of birth										
Germany		17,337	23,738	73	17,337	21,653	80	21,950	23,738	92
Other country	WHO Region Europe	8,850	11,468	77	8,850	10,077	88	10,192	11,468	89
	WHO Region Eastern Mediterranean	1,701	2,163	79	1,701	1,848	92	1,892	2,163	87
	WHO Region Africa	1,675	2,126	79	1,675	1,794	93	1,819	2,126	86
	WHO Region South-East Asia	1,141	1,465	78	1,141	1,233	93	1,252	1,465	85
	WHO Region Western Pacific	886	1,137	78	886	955	93	970	1,137	85
	WHO Region Americas	232	281	83	232	244	95	248	281	88
Unknown country		1,005	1,706	59	1,005	1,230	82	1,287	1,706	75
Clinical characteristics										
Infectiousness										
Culture-negative, smear-negative		6,128	7,928	77	6,128	7,118	86	7,288	7,928	92
Culture-positive, smear-negative		11,035	14,652	75	11,035	13,089	84	13,212	14,652	90
Smear-positive		14,806	20,124	74	14,806	17,750	83	17,984	20,124	89
Unknown		858	1,380	62	858	1,077	80	1,126	1,380	82
Previous TB										
No		26,433	34,091	77	26,433	30,690	86	31,090	34,091	91
Yes		3,188	4,739	67	3,188	4,132	77	4,193	4,739	88
Unknown		3,206	5,254	61	3,206	4,212	76	4,327	5,254	82
Drug resistance										
Not MDR		24,034	31,139	77	24,034	28,066	86	28,214	31,139	91
MDR		399	686	58	399	505	79	536	686	78
Unknown	Not applicable; bacteriologically negative	5,963	7,690	77	5,963	6,930	86	7,089	7,690	92
	No drug susceptibility test reported	2,431	4,569	53	2,431	3,533	69	3,762	4,569	82
Severity of disease										
Exclusively pulmonary TB		28,163	36,874	76	28,163	33,114	85	33,583	36,874	91
Pulmonary and CNS, meningitis or disseminated TB		342	589	58	342	520	66	527	589	89
Unknown		4,322	6,621	65	4,322	5,400	80	5,500	6,621	83
Time period based on change of data plausibility and completeness checks										
2002–05		12,594	17,310	73	12,594	14,978	84	15,251	17,310	88
2006–14		20,233	26,774	76	20,233	24,056	84	24,359	26,774	91

CNS: central nervous system; DST: drug susceptibility test; MDR: multidrug-resistant; TB: tuberculosis; WHO: World Health Organization.

Table 4

Notified pulmonary tuberculosis cases - multivariable analyses for the association between the mode of case finding and treatment outcome, Germany, 2002–2014 (n = 44,084)

Characteristics of cases	Model A: success (0) vs all other outcomes (1)			Model B: success (0) vs no treatment success (1)			Model C: known outcome (0) vs loss to follow-up (1)		
	aOR	95% CI	p value	aOR	95% CI	p value	aOR	95% CI	p value
Main exposure of interest									
Mode of case finding									
Passive case finding	Ref			Ref			Ref		
Contact tracing	0.64	0.57–0.71	<0.001	0.54	0.45–0.65	<0.001	0.73	0.63–0.84	<0.001
Screening asylum seekers	2.37	2.11–2.67	<0.001	1.38	1.10–1.73	0.006	2.35	2.06–2.68	<0.001
Demographic characteristics									
Age in years									
<15	Ref			Ref			Ref		
15–29	1.84	1.54–2.20	<0.001	3.06	1.98–4.73	<0.001	1.41	1.15–1.74	<0.001
30–44	1.90	1.59–2.26	<0.001	4.79	3.13–7.34	<0.001	1.25	1.02–1.54	0.030
45–59	2.11	1.77–2.51	<0.001	7.43	4.86–11.35	<0.001	1.06	0.86–1.30	0.571
60–74	3.09	2.59–3.68	<0.001	14.53	9.52–22.19	<0.001	0.84	0.68–1.04	0.116
≥75	6.39	5.35–7.63	<0.001	34.15	22.36–52.16	<0.001	0.82	0.66–1.02	0.081
Sex									
Female	Ref			Ref			Ref		
Male	1.33	1.26–1.39	<0.001	1.52	1.42–1.62	<0.001	1.07	1.00–1.14	0.049
Place of birth									
Germany	Ref			Ref			Ref		
Other country	0.90	0.85–0.94	<0.001	0.70	0.65–0.75	<0.001	1.34	1.25–1.45	<0.001
Unknown country	1.81	1.61–2.03	<0.001	0.94	0.80–1.12	0.494	3.10	2.72–3.53	<0.001
Clinical characteristics									
Infectiousness									
Culture-negative, smear-negative	Ref			Ref			Ref		
Culture-positive, smear-negative	2.58	2.35–2.84	<0.001	2.35	2.08–2.65	<0.001	2.19	1.91–2.50	<0.001
Smear-positive	2.79	2.55–3.05	<0.001	2.54	2.27–2.85	<0.001	2.31	2.04–2.62	<0.001
Unknown	2.12	1.86–2.41	<0.001	1.64	1.37–1.97	<0.001	2.43	2.06–2.87	<0.001
Previous TB treatment									
No	Ref			Ref			Ref		
Yes	1.20	1.12–1.29	<0.001	1.18	1.08–1.28	<0.001	1.23	1.11–1.36	0.003
Unknown	1.90	1.78–2.03	<0.001	1.84	1.69–1.97	<0.001	1.73	1.59–1.88	<0.001
Drug resistance									
No MDR	Ref			Ref			Ref		
MDR	2.83	2.40–3.32	<0.001	3.03	2.40–3.83	<0.001	1.89	1.56–2.30	<0.001
Unknown	2.76	2.56–2.98	<0.001	2.56	2.33–2.81	<0.001	1.83	1.65–2.02	<0.001
Severity of disease									
Exclusively pulmonary TB	Ref			Ref			Ref		
Pulmonary and CNS, meningitis or disseminated TB	2.51	2.10–2.99	<0.001	3.25	2.63–4.00	<0.001	1.23	0.94–1.62	0.125
Unknown	1.48	1.40–1.58	<0.001	1.24	1.15–1.35	<0.001	1.83	1.70–1.98	<0.001
Time period based on change of data plausibility and completeness checks									
2002–05	Ref			Ref			Ref		
2006–14	0.91	0.86–0.95	<0.001	1.04	0.98–1.10	0.228	0.75	0.70–0.80	<0.001

aOR: adjusted odds ratio; CI: confidence interval; CNS: central nervous system; MDR: multidrug-resistant; TB: tuberculosis.

All investigated data were anonymous and collected within the legal framework of the IfSG.

Results

The cases' demographic and clinical characteristics stratified by mode of case finding are presented in Table 2.

Cases identified by screening asylum seekers (n = 1,474) were of similar median age with a smaller IQR compared with cases identified by contact tracing (n = 3,591) (28 vs 27 years) and were less often female (23% vs 45%). They had a similar proportion of culture- and smear-negative cases (34% vs 32%), more often unknown information about previous TB (27% vs 6.4%) and more often MDR-TB (11% vs 1.6%) (Table 2). Compared with cases identified by passive case finding (n = 39,019), the cases identified by screening asylum seekers had a lower median age (28 vs 50 years), a lower proportion of females (23% vs 37%) and a higher proportion of culture- and smear-negative cases (34% vs 16%), of unknown information about previous TB (27% vs 12%) and of MDR-TB (11% vs 1.9%) (Table 2).

Treatment success was highest among pulmonary TB cases identified by contact tracing (87%; 3,139/3,591), followed by cases identified by passive case finding (74%; 28,804/39,019) and by screening asylum seekers (60%; 884/1,474) (Figure 2).

The largest proportion of missing and indeterminate data on treatment outcome was among cases identified by screening asylum seekers (22%; 329/1,474), followed by patients identified by passive case finding (7.9%; 3,076/39,019) and contact tracing (6.3%; 225/3,591) (Figure 2).

Detailed analyses showed that the proportion of successful outcomes among all outcomes (Group A, Figure 1) varied not only by the mode of case finding but also by age, sex, place of birth, infectiousness, previous TB diagnosis treatment, drug resistance, severity of disease and changes in data plausibility and completeness checks (Table 3).

Treatment success (Group A) was particularly low among TB cases who had no DST reported (53%; 2,431/4,569), were 75 years or older (54%; 3,446/6,362), had MDR-TB (58%; 399/686), a severe TB manifestation (CNS, meningitis or disseminated) in addition to pulmonary TB (58%; 342/589), unknown place of birth (59%; 1,005/1,706) or were identified by screening asylum seekers (60%; 884/1,474) (Table 3).

Analysis adjusted for demographic and clinical characteristics showed that mode of case finding was independently associated with treatment success (Model A, Figure 1, Table 4). It indicated 2.4 times higher odds of non-successful treatment for cases identified by screening asylum seekers compared with cases identified by passive case finding; cases identified by contact tracing showed 0.64 times lower odds of non-successful treatment outcomes compared with passive case finding (Table 4).

Restricting analysis of treatment outcomes to cases with known outcomes (Group B, Figure 1) and comparing successful and non-successful treatment among them, treatment success was particularly low for cases aged 75 years or older (59%; 3,446/5,802), with severe manifestation in addition to pulmonary TB (66%; 342/520) and cases that had no DST reported (69%; 2,431/3,533) (Table 3). While cases identified by screening asylum seekers had higher treatment success (90%; 884/983) than cases identified by passive case finding (83%; 28,804/34,766) in the descriptive analysis of Group B, adjusted analysis indicated 1.4 times higher odds for a non-successful treatment outcome for cases identified by screening asylum seekers compared with cases identified by passive case finding (Model B, Table 4). In addition, older age, MDR-TB, severe manifestations and infectiousness were associated with particularly high odds of unsuccessful treatment outcome in Model B (Table 4).

Analysis of loss to follow-up (Group C) showed that the proportion of known outcomes among all possible treatment outcomes was lowest among cases identified by screening asylum seekers (72%; 1,062/1,474), followed by cases with unknown place of birth (75%; 1,287/1,706) and cases with MDR (78%; 536/686) (Table 3). Adjusted analysis indicated 2.3 times higher odds for loss to follow-up among cases identified by screening asylum seekers compared with cases identified by passive case finding; cases identified by contact tracing showed 27% lower odds of loss to follow-up compared with passive case finding (Model C, Table 4). Apart from identification by screening asylum seekers, cases with unknown place of birth and unknown drug resistance showed particularly high odds of getting lost to follow-up (Table 4).

Discussion

With our study, we aimed to assess treatment outcomes of pulmonary TB cases identified by screening asylum seekers. We found that cases identified by screening asylum seekers – unlike cases identified by contact tracing – had significantly poorer treatment outcomes and higher odds of loss to follow-up compared with cases identified by passive case finding after adjustment for demographic and clinical characteristics.

Cases identified by screening asylum seekers were similar to those identified by contact tracing in terms of age, infectiousness and severity of disease but were more likely to have MDR-TB or a history of previous TB diagnosis. Compared with cases identified by passive case finding, those among screened asylum seekers were younger, more often male and less infectious.

Our study results corroborate previous findings that TB screening by chest X-ray, as used for asylum seekers,

allowed early detection of cases that were still smear-negative [19-22]. Thus screening has the potential to prevent transmission and facilitate early treatment initiation. The high proportion of bacteriologically negative pulmonary TB cases (34%) raises the issue of potential overdiagnosis of TB by chest X-ray screening. However, TB cases identified by contact tracing were equally often bacteriologically negative, and the detection of bacteriologically negative TB is considered beneficial given the high risk of developing infectious TB if untreated [23]. In addition, screened asylum seekers were more likely to have had a diagnosis of MDR-TB or a positive or unknown history of previous TB compared with cases identified by passive case finding. Contributing factors may include higher rates of TB and MDR-TB in their country of birth [1] and fragmented healthcare services in countries of origin leading to treatment interruptions [24]. Of note, DST results, which are strongly warranted for treatment decisions, were frequently unavailable.

With 60% treatment success (Group A) among pulmonary TB cases identified by screening asylum seekers, 74% among those identified by passive case finding and 87% among those identified by contact tracing, none of the groups met the target of 90% treatment success [1,13]. However, the odds for non-successful treatment were substantially higher for cases identified by screening asylum seekers and markedly lower for cases identified by contact tracing compared to the cases identified by passive case finding (adjusted for other known confounders).

While asylum seeker status was independently associated with an unsuccessful treatment outcome, this was not true for reporting a foreign country of birth, which had lower odds of non-successful treatment outcomes (Model A). Other studies also found poorer treatment adherence for migrants with insecure legal status [25] and those that had arrived recently [26], but did not find an independent negative impact of foreign country of origin. Our findings contrast with a recent analysis of European data that found poorer treatment outcomes for foreign-born cases; however, that study could not distinguish between legal status and country of birth [27].

The magnitude of association between known clinical risk factors and non-successful treatment outcomes was greater when unknown outcomes were excluded from the analysis (Model B). In accordance with previous knowledge [20,27,28], increasing age, a proxy for co-morbidities and risk of dying, strongly increased the odds of non-successful treatment in model B. In addition, the odds for MDR-TB and severe disease manifestations were greater among those with negative treatment outcomes in model B compared with model A, in coherence with previous studies [20,29-32].

In our study, being identified by screening asylum seekers was also independently associated with being lost to follow-up after adjustment for potential confounders. Reasons for loss to follow-up can include the patient's decision to stop treatment without informing treatment facilities [33]. A potential explanation for this may be the lack of perceived illness [34] that might be more pronounced in cases identified by screening who had no symptoms. That patients identified by contact tracing were 27% less likely to be lost to follow-up than patients identified by passive case finding, however, indicates that even asymptomatic patients can be successfully followed up. Geographical distance to TB-treatment facilities, a trusting and supportive provider–patient relationship as well as security of legal status have been found to be predictors for treatment adherence [25,34-36]. The reduction of structural barriers to TB diagnosis and treatment including availability of free, accessible and culturally appropriate health services for vulnerable groups such as migrants has been shown to be a key element in increasing treatment success [36]. Potential structural barriers to TB treatment completion and reasons for loss to follow-up in Germany include limited access to care and interpreters [7], (forced) relocations of asylum seekers within Germany or to other countries during treatment [7,11,33] and changing administrative authorities handling the case [10].

Limitations

Our investigation was based on national notification data, and under- or overestimation of the true case number owing to under-diagnosis and under-reporting or to double-reporting cannot be entirely excluded. In addition, incomplete information for notified cases at the national level may reflect unavailable data at the treatment facility or at the LPHA level. Non-reported treatment outcome cannot entirely be disentangled from non-completed treatment in our data. The TB patient may have completed treatment within the remit of a different health authority than the one that received the initial notification, or under the supervision of a doctor or hospital that has missed to report the treatment outcome to the local health authority.

Based on the available variables in the notification data, our analysis could only compare 'asylum seekers identified by screening' with cases identified by other modes of case finding. However, cases identified by other modes of case finding may also be asylum seekers. Furthermore, incorrect classification of the mode of case finding cannot be excluded.

Full information on tuberculosis treatment outcome becomes available only 1 year after the reporting year and our study therefore includes cases notified up to and including 2014. Whether characteristics and treatment outcomes of cases notified from 2002 to 2014 can be extrapolated to cases notified later is unknown and will require evaluation. Increasing workload at LPHA level caused by increasing case numbers (by nearly 30% in 2015 [3]) may affect the follow-up of cases and completion of information.

Conclusion

The low proportion of smear-positive TB suggests that asylum seekers were found early by screening; a good starting point for successful treatment. However, they were often lost to follow-up and had poorer treatment outcomes than cases identified by passive case finding or contact tracing.

The documentation of mode of case finding in German TB notification data proved useful for the evaluation of group-specific treatment outcomes, namely screened asylum seekers. We recommend a standardised approach to reporting of case finding information across Europe to allow evaluation of treatment success and comparison across countries by modes of case finding. Regarding treatment outcome data, we need to better disentangle non-reported treatment outcomes from reporting incomplete course of treatment and to address both issues individually to obtain high treatment success.

Increased case detection by screening can only unfold its health benefits when detected tuberculosis is effectively treated and reliably cured. Tuberculosis screening activities among asylum seekers can be a door to access general medical care. TB screening at admission to reception centres may also reduce TB exposure and reduce the need for resource-intensive contact investigations in these settings.

While specific reasons for the higher odds of non-successful treatment among asylum seekers in Germany need to be studied further, available research suggests that patients need to be better linked to treatment facilities and structural barriers to treatment completion need to be addressed to secure screening benefits for asylum seekers and the communities.

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Conflict of interest

None declared.

Authors' contributions

AK and LF designed the study and developed the multivariable analyses models. AK conducted the review of available literature, performed the analysis and prepared all tables and figures. AK and LF wrote the manuscript. WH, BH and BB provided input to outcome categorisation, model conceptualisation and the manuscript. All authors reviewed and approved the final manuscript.

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Integrating hepatitis B, hepatitis C and HIV screening into tuberculosis entry screening for migrants in the Netherlands, 2013 to 2015

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We evaluated uptake and diagnostic outcomes of voluntary hepatitis B (HBV) and C virus (HCV) screening offered during routine tuberculosis entry screening to migrants in Gelderland and Amsterdam, the Netherlands, between 2013 and 2015. In Amsterdam, HIV screening was also offered. Overall, 54% (461/859) accepted screening. Prevalence of chronic HBV infection (HBsAg-positive) and HCV exposure (anti-HCV-positive) in Gelderland was 4.48% (9/201; 95% confidence interval (CI): 2.37–8.29) and 0.99% (2/203; 95% CI: 0.27–3.52), respectively, all infections were newly diagnosed. Prevalence of chronic HBV infection, HCV exposure and chronic HCV infection (HCV RNA-positive) in Amsterdam was 0.39% (1/256; 95% CI: 0.07–2.18), 1.17% (3/256; 95% CI: 0.40–3.39) and 0.39% (1/256; 95% CI: 0.07–2.18), respectively, with all chronic HBV/HCV infections previously diagnosed. No HIV infections were found. In univariate analyses, newly diagnosed chronic HBV infection was more likely in participants migrating for reasons other than work or study (4.35% vs 0.83%; odds ratio (OR) = 5.45; 95% CI: 1.12–26.60) and was less likely in participants in Amsterdam than Gelderland (0.00% vs 4.48%; OR = 0.04; 95% CI: 0.00–0.69). Regional differences in HBV prevalence might be explained by differences in the populations entering compulsory tuberculosis screening. Prescreening selection of migrants based on risk factors merits further exploration.

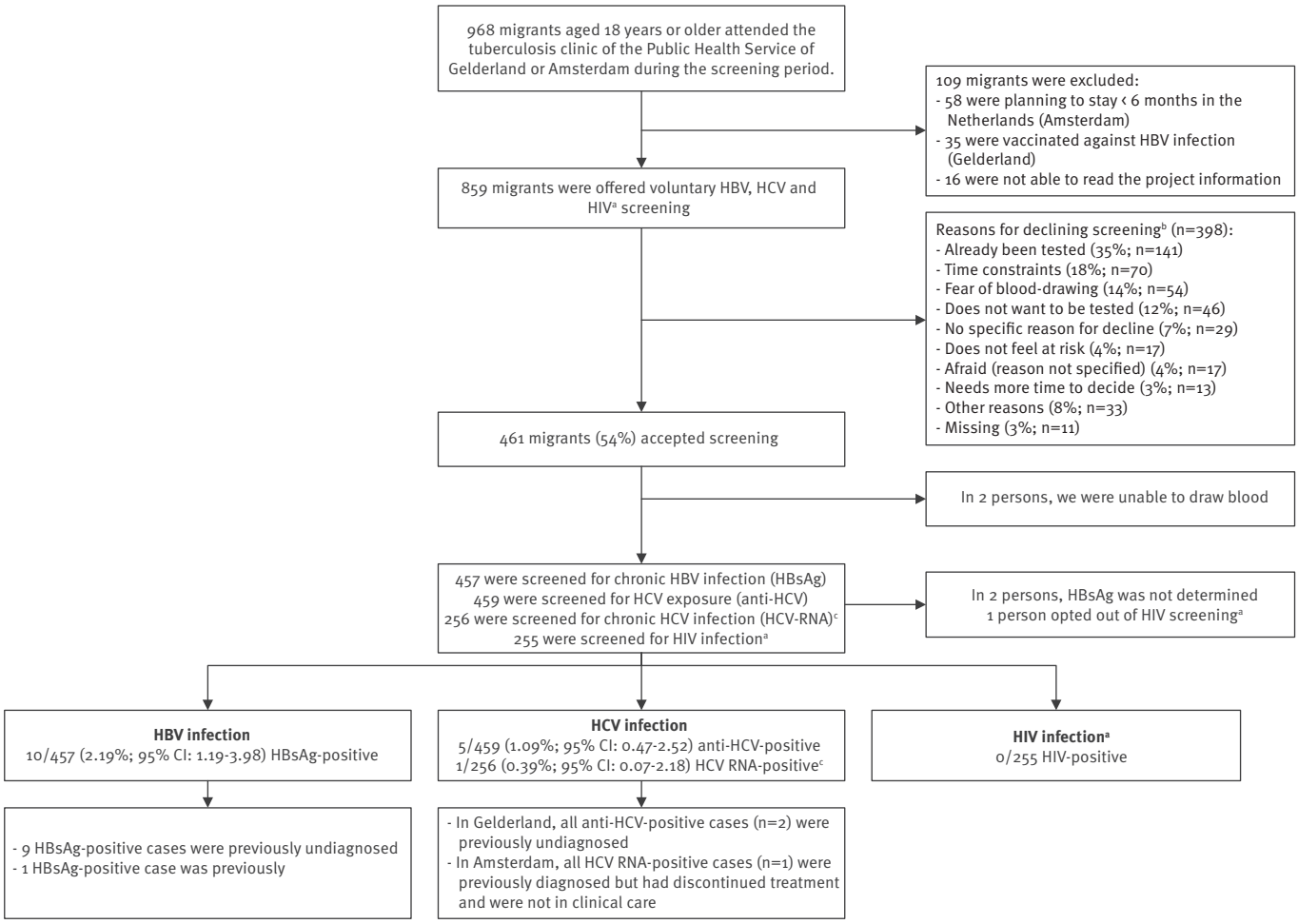
Introduction

In the Netherlands, it is estimated that 39,000 individuals have a chronic hepatitis B virus (HBV) infection (HBsAg-positive) [1], 19,000 have a chronic hepatitis C virus (HCV) infection (HCV RNA-positive) [2] and 23,000 have a human immunodeficiency virus (HIV) infection [3]. A large proportion of chronic HBV infections (ca 50%) and past/chronic HCV infections (ca 40%; anti-HCV positive) are estimated to be found among migrants coming from countries endemic for HBV or HCV, respectively, and ca 40% of HIV patients in clinical care are migrants [1,3,4].

Currently, effective treatment options are available for HBV, HCV and HIV infections. However, the often asymptomatic onset of these infections and disease development of HBV and HCV infections may delay diagnosis and therefore treatment. Screening for HBV, HCV and HIV can identify undiagnosed infections, improving the prognosis and limiting transmission to others by linking infected persons to treatment and care at an early stage [5-8]. To find undiagnosed cases, several HBV and HCV screening programmes, mostly community-based, have targeted specific groups of migrants in the Netherlands in recent years [9]. The prevalence found in those programmes ranged from 0% to 9.5% for chronic HBV infection (HBsAg-positive) and from 0% to 6.5% for HCV exposure (anti-HCV positive), depending on the target group and the recruitment strategy [9,10-18]. However, these programmes

Figure

Recruitment strategy and clinical outcomes of hepatitis B, hepatitis C and HIV screening offered to migrants attending compulsory tuberculosis entry screening at the public health services, the Netherlands, 2013–2015 (n = 859)



HBV: hepatitis B virus, HCV: hepatitis C virus, HIV: human immunodeficiency virus.

[a] HIV screening was only offered at the Public Health Service of Amsterdam.

[b] The percentages add up to >100% as participants could have mentioned more than one reason for declining screening.

[c] HCV RNA was only tested in Amsterdam.

were not sustainable, because they were done only once, highly labour-intensive and tailored to particular migrant groups and residential areas [9]. The integration of screening into existing healthcare services could increase long-term sustainability and continuity in reaching and screening key populations. In addition, integration would most probably make such screening programmes more cost-effective because fewer additional resources would be required. As countries with high endemicity for tuberculosis (TB) largely overlap with countries with a high HBV, HCV or HIV prevalence, screening for these viruses could be integrated into the existing TB entry screening performed by TB departments of the public health services in the Netherlands. TB entry screening is compulsory for migrants from outside the European Union (EU) who intend to stay in the Netherlands for more than three months [19]. Since January 2015, the compulsory screening has been further restricted to non-EU migrants originating from countries with TB incidence of more than 50 per 100,000 inhabitants per year.

To evaluate whether integrated TB, HBV, HCV and HIV screening is effective and acceptable among migrants, we initiated a screening project offering additional voluntary HBV, HCV and HIV screening to migrants undergoing compulsory TB screening. We studied the uptake of screening and the prevalence and determinants of newly diagnosed HBV, HCV and HIV infections. The resulting data can be used to support policy-makers in the decision on integrating screening for these infections into the existing TB entry screening for migrants.

Table 1

Characteristics of migrants who accepted hepatitis B, hepatitis C and HIV[a] screening during compulsory tuberculosis screening at public health services, the Netherlands 2013–2015 (n = 459)

	Total (n = 459)		Gelderland (n = 203)		Amsterdam (n = 256)		p value
	median	IQR	median	IQR	Median	IQR	
Age (years)	29	26-35	28	25-34	30	27-36	<0.001
	n	%	n	%	N	%	
Sex							
Male	211	45.97	92	45.32	119	46.48	0.804
Female	248	54.03	111	54.68	137	53.52	
Reason for migration							
Work or study	244	53.16	93	45.81	151	58.98	<0.001
Other (e.g. family reunification)	162	35.29	110	54.19	52	20.31	
Missing	53	11.55	0	0.00	53	20.70	
Intended length of stay in the Netherlands[b]							
<1 year	NA		19	9.36	NA		NA
1–2 years			28	13.79			
>2 years			116	57.14			
Missing			40	19.70			
Region of origin (categorised according to WHO regions)							
South-East Asia	154	33.55	47	23.15	107	41.80	<0.001
Europe (southern/eastern)	95	20.70	42	20.69	53	20.70	
Western Pacific	86	18.74	42	20.69	44	17.19	
Africa	61	13.29	32	15.76	29	11.33	
Eastern Mediterranean	39	8.50	22	10.84	17	6.64	
Americas (Latin America/Caribbean)	23	5.01	18	8.87	5	1.95	
Missing	1	0.22	0	0.00	1	0.39	
Estimated HBV prevalence (HBsAg-positive) in the country of origin[c]							
<2%	204	44.44	66	32.51	138	53.91	<0.001
≥2%	252	54.90	136	67.00	116	45.31	
Missing	3	0.65	1	0.49	2	0.78	
Estimated HCV prevalence (HCV-RNA positive) in the country of origin[c]							
<2.5%	398	86.71	179	88.18	219	85.55	0.470
≥2.5%	60	13.07	24	11.82	36	14.06	
Missing	1	0.22	0	0.00	1	0.39	
Estimated HIV prevalence in the country of origin[c]							
<2.12%	403	87.80	173	85.22	230	89.84	0.104
≥2.12%	55	11.98	30	14.78	25	9.77	
Missing	1	0.22	0	0.00	1	0.39	
Registered at a general practitioner in the Netherlands[d]							
No	NA		NA		174	67.97	NA
Yes					78	30.47	
Missing					4	1.56	
Registered for health insurance coverage in the Netherlands[d]							
No	NA		NA		72	28.13	NA
Yes, Dutch health insurance					122	47.66	
Yes, foreign health insurance					27	10.55	
Yes, student health insurance					10	3.91	
Yes, but unknown which one					21	8.20	
Missing					4	1.56	

HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IQR: interquartile range; NA: not applicable (not measured); WHO: World Health Organization.

[a] HIV screening was included only in Amsterdam.

[b] Measured only among participants from Gelderland.

[c] Participants were grouped and categorised according to the estimated HBV, HCV and HIV prevalence reported by Schweitzer et al. [21], Gower et al. [22] and the Global Burden of Disease Study [23], respectively.

[d] Measured only among participants from Amsterdam.

This table excludes migrants who accepted screening but in whom blood-drawing failed (n = 2).

Table 2

Univariate analysis of potential determinants of newly diagnosed chronic hepatitis B infection among migrants who accepted hepatitis B, hepatitis C and HIV[a] screening during compulsory tuberculosis entry screening at public health services, the Netherlands, 2013–2015 (n = 456)

	Newly diagnosed chronic HBV infection		Univariate analyses		p value
	n/N	%	OR	95% CI	
Sex					
Male	3/210	1.43	1	Ref	0.433
Female	6/246	2.44	1.72	0.43–6.98	
Age					
18–26 years	2/125	1.60	1	Ref	0.165
27–32 years	6/175	3.43	2.18	0.43–11.00	
>32 years	1/156	0.64	0.40	0.04–4.43	
Reason for migration					
Work or study	2/242	0.83	1	Ref	0.019
Other (e.g. family reunification)	7/161	4.35	5.45	1.12–26.60	
Missing	0/53	0.00	[b]	[b]	
Intended length of stay in the Netherlands[c]					
<1 year	0/19	0.00	1	Ref	0.399
1–2 years	2/28	7.14	3.68	0.17–81.03	
>2 years	3/114	2.63	1.22	0.06–24.64	
Missing	4/40	10.00	[b]	[b]	
Region of origin (categorised according to WHO regions)					
South-East Asia	3/154	1.95	1	Ref	0.976
Europe (southern/eastern)	3/95	3.16	1.64	0.36–7.37	
Western Pacific	2/84	2.38	1.31	0.25–6.80	
Africa	1/60	1.67	1.09	0.16–7.56	
Eastern Mediterranean	0/39	0.00	0.55	0.28–10.83	
Americas (Latin America/ Caribbean)	0/23	0.00	0.92	0.05–18.40	
Missing	0/1	0.00	[b]	[b]	
Estimated HBV prevalence (HBsAg-positive) in the country of origin[d]					
<2%	3/204	1.47	1	Ref	0.664
≥2%	5/249	2.01	1.37	0.32–5.82	
Missing	1/3	33.33	[b]	[b]	
Location of screening					
Gelderland	9/201	4.48	1	Ref	0.026
Amsterdam	0/255	0.00	0.04	0.00-0.69	

CI: confidence interval; HBV: hepatitis B virus; Ref: reference value, OR: odds ratio; WHO: World Health Organization.

[a] HIV screening was included only in Amsterdam.

[b] Missing categories were excluded from the analysis.

[c] Measured only among participants from Gelderland.

[d] Participants were grouped and categorised according to the estimated HBV prevalence reported by Schweitzer [21].

This table excludes migrants who accepted screening but in whom blood drawing failed (n = 2), participants in which HBsAg was not determined (n = 2), and the previously diagnosed HBV-infected participant (n = 1).

Methods

Study population

This screening project was performed at five TB departments of the public health services in the Netherlands (a convenience sample: four in the province of Gelderland, one in the city of Amsterdam). In Gelderland, recruitment continued until at least 352 TB department visitors had been asked to participate (October 2013 to February 2015). The sample size was based on an expected prevalence of 4.5% HBsAg-positive samples, with a 2.5% margin of error at an alpha of 0.05 in order to detect a minimum HBsAg positivity rate of at least 2%. In Amsterdam, we used

a convenience sample of 250 participants, and recruitment took place from July 2015 through August 2015. Migrants visiting these TB departments have migrated primarily for work, study or family reunification. Asylum seekers are usually screened at TB departments in refugee centres and were therefore not included in this project. HBV and HCV screening was offered to all migrants attending the five TB departments for their compulsory TB entry screening. In Amsterdam, HIV screening was also offered.

Recruitment

Migrants 18 years or older who were able to read the project information were eligible for HBV, HCV and HIV screening. In Gelderland, migrants were excluded if they had been vaccinated against HBV, whereas in Amsterdam, HBV vaccination history was not recorded. In Amsterdam, migrants were excluded if they intended to stay less than 6 months in the Netherlands, in order to ensure that those testing positive could be linked to care in the Netherlands.

All participants provided written informed consent. The project was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki. The local medical ethics committee of the region Arnhem-Nijmegen (Radboud University Medical Center) approved the screening project (2013/172).

Screening procedure

In Gelderland, migrants received information about HBV, HCV and HIV screening before their appointment for TB screening by post. In Amsterdam, where only walk-in TB consultations are provided, migrants received information about HBV, HCV and HIV screening on arrival for TB screening. Project information was available in Dutch and English and, in Amsterdam, also in Arabic, Chinese, French, Portuguese, Russian and Spanish. After eligible migrants had completed their routine TB screening, they were asked to participate in this screening project and the informed consent form was signed. Blood was drawn from those who accepted HBV, HCV and HIV screening. In Amsterdam, participants could opt out of testing for any of the three infections individually.

From all eligible migrants, the following data were collected during their TB screening visit: age, sex, country of origin and intended length of stay in the Netherlands. In Gelderland, reason for migration was included as an open-ended question. In Amsterdam, data on the reason for migration were derived from migration forms that categorised answers as work/study or other (e.g. partner or family reunification, but not further specified). In Amsterdam, participants were also asked whether they were currently registered with a general practitioner (GP) in the Netherlands and whether they had health insurance. In both regions, all persons who declined HBV, HCV and HIV screening were asked for the reason for non-participation, using an open-ended question.

Laboratory testing

In Gelderland, blood samples were tested for anti-HBc and anti-HCV at the laboratory of the Gelre Hospital in Apeldoorn (ADVIA Centaur, Siemens, Germany), Meander Medical Center in Amersfoort (ARCHITECT, Abbott, United States) or Slingeland Hospital in Doetinchem (Cobas 6000, Roche, Switzerland). Samples positive for anti-HBc were further tested for HBsAg, anti-HBs, anti-HBe and HBeAg.

In Amsterdam, blood samples were first tested for HBsAg, anti-HCV, and HIV antigen or antibodies (LIAISON XL MUREX, DiaSorin, Italy) at the laboratory of the public health service of Amsterdam. Samples positive for HBsAg were further tested for anti-HBc, anti-HBs, anti-HBe and HBeAg. Samples positive for anti-HCV were further tested for HCV RNA (HCV Quantitative test, version 2.0, Cobas AmpliPrep/Cobas TaqMan, Roche, Switzerland). Samples positive for HIV antigen or antibodies were confirmed with Western blot (INNO-LIA HIV I/II Score, Innogenetics, Belgium), HIV-1 p24 antigen test (Vidas HIV P24, Bio Merieux) and HIV viral-load testing (HI2CAP, Roche, Switzerland).

Persons found HBsAg-positive were considered to have a chronic HBV infection. As the incidence of acute HBV infection in the Netherlands is very low, also among migrants, we assumed all HBsAg-positive persons to be chronically infected. Persons found positive for anti-HCV were considered exposed to HCV, persons positive for HCV RNA were considered to have a chronic HCV infection, and persons with confirmed HIV antigen- or antibody-positive tests were considered HIV-positive.

Follow-up procedure

Participants who did not have a chronic HBV infection, an HCV infection or HIV infection received a letter with their test results. Participants with an infection were verbally informed of their test results by a nurse or doctor at the public health service and referred to their GP, the first point of care in the Netherlands. At the TB clinics in Gelderland, HCV RNA testing for those who tested anti-HCV positive was not included. These participants were referred to their GP for further testing. In accordance with the Dutch Public Health Act, chronic HBV infections were reported to the department of infectious diseases of the public health service in each patient's hometown, to enable contact tracing.

In Amsterdam, participants with a chronic HBV, chronic HCV or HIV infection were contacted 3 and 6 months after they had received their results to ask if they had received follow-up care. We collected data on whether they had started treatment and whether they had visited their GP or a specialist.

Statistical analyses

We described the following characteristics for all eligible migrants: age, sex, reason for migration, intended length of stay, region of origin, registration at GP, health insurance coverage, and HBV, HCV and HCV

prevalence in the country of origin. Countries of origin were grouped into regions of origin according to the World Health Organization classification [20]. We also created three dichotomous variables (low-endemic vs intermediate/high-endemic) related to the HBV, HCV and HIV prevalence in the country of origin, using estimates by Schweitzer et al. [21], Gower et al. [22] and the Global Burden of Disease Study [23], respectively. Based on the categorisation of the reported estimates in the literature cut-off points of 2.0%, 2.5% and 2.12% were used to dichotomise HBV, HCV and HIV prevalence, respectively.

We compared the characteristics between those who refused and those who accepted the additional HBV, HCV and HIV screening, and also between participants recruited in Gelderland and those recruited in Amsterdam, using chi-squared tests for categorical variables and Mann–Whitney U test for continuous variables. We calculated the screening uptake (defined as the number of migrants who accepted screening among all the eligible persons) and described reasons for declining screening. In all analyses, the four sites in Gelderland were treated as one, as all used the same recruitment strategy and served comparable populations.

HBsAg, anti-HCV, HCV RNA and HIV prevalence and corresponding 95% confidence intervals (CI) were calculated using Wilson intervals. Using univariate logistic regression analyses, we examined determinants of a newly diagnosed chronic HBV infection, excluding persons with a previously diagnosed HBV infection. Penalised logistic regression was used to calculate odds ratios (OR) and 95% CI in a table with a zero cell count.

In all analyses, cases with unknown or missing data were excluded. Analyses were performed using STATA Intercooled 13.1 (STATA Corporation, College Station, United States). Statistical significance was set at $p < 0.05$.

Results

Characteristics of participants

A total of 968 migrants, aged 18 years or older, attended the five TB departments for their TB entry screening (Figure).

In Gelderland, 35 migrants were excluded because of prior HBV vaccination. In Amsterdam, 58 migrants were excluded because they intended to stay less than 6 months in the Netherlands. Furthermore, 16 migrants were excluded because they were unable to read the project information. Of 859 eligible migrants who were asked to participate, 461 (54%) accepted HBV or HCV (and in Amsterdam, HIV) screening. There was no significant difference between response rates in Gelderland vs Amsterdam (57% vs 51%; $p = 0.113$). Sex, age, region of origin, reason for migration, intended length of stay in the Netherlands and HBV and HCV prevalence in the country of origin did not significantly differ between those who refused and those who accepted screening. Participants who originated from a country with an estimated HIV prevalence of ≥ 2.12% were more likely to accept screening compared with participants from a country with an estimated HIV prevalence of < 2.12% (65% vs 52%; $p = 0.022$). The most commonly mentioned reasons for declining screening were: already been tested (35%; 141/398), time constraints (18%; 70/398) and fear of blood-drawing (14%; 54/398). Already been tested as a reason for declining was more likely to be reported by migrants from South-East Asia compared with other regions (50% vs 10–36%; $p < 0.001$) and by migrants visiting the TB clinic in Amsterdam compared with Gelderland (42% vs 25%; $p < 0.001$).

Two of the 461 migrants who accepted screening were ultimately not screened because blood-drawing failed. For 459 screened participants (203 in Gelderland and 256 in Amsterdam), median age was 29 years (interquartile range (IQR): 26–35 years) and 46% were male (Table 1). About half of the participants migrated for work/study (53%), and a third (34%) of all participants originated from South-East Asia. Only one person (1/256; 0.39%) in Amsterdam opted out of HIV testing, citing a low risk perception.

Participants in Gelderland were younger and more often had migrated for reasons other than work/study (e.g. family reunification) compared with Amsterdam, where most participants had migrated because of work/study. The region of origin also differed significantly between the participants from Gelderland and Amsterdam ($p < 0.001$). Furthermore, participants in Gelderland more often originated from a country with an HBV prevalence of ≥ 2% compared with Amsterdam participants.

Prevalence and determinants of newly diagnosed HBV, HCV and HIV infections

In Gelderland, 29 of the 203 participants were anti-HBc-positive (14.3%; 95% CI: 10.1–19.8%) and the prevalence of chronic HBV infections was 4.48% (9/201; 95% CI: 2.37–8.29%). In two cases, HBsAg was not determined. Two of the 203 participants were anti-HCV-positive (0.99%; 95% CI: 0.27–3.52%). All HBV and HCV infections in Gelderland were newly diagnosed.

In Amsterdam, one of the 256 participants had a chronic HBV infection (0.39% (1/256; 95% CI: 0.07–2.18%). Three of 256 participants were anti-HCV-positive (1.17%; 95% CI: 0.40–3.39%) of whom one had a chronic HCV infection (0.39% (1/256; 95% CI: 0.07–2.18%). Both participants in Amsterdam with a chronic HBV and HCV infection were previously diagnosed. The participant with chronic HBV infection reported that they had been successfully treated and were being monitored in their country of origin. The participant with chronic HCV infection had started treatment in the country of origin, but discontinued it there because of

side effects. This patient was referred to a Dutch hepatitis treatment centre and successfully completed HCV treatment approximately 6 months after screening. No HIV infections were found in Amsterdam.

Characteristics of all participants with a newly diagnosed chronic HBV infection (9/457; 1.97%; 95% CI: 1.04–3.70%) are shown in Table 2. In univariate analyses, participants who migrated to the Netherlands for reasons other than work/study were more likely to have a newly diagnosed chronic HBV infection than those who migrated for work/study (4.3% vs 0.8%; OR = 5.45; 95% CI: 1.12–26.60). Participants in Amsterdam were less likely to have a newly diagnosed chronic HBV infection than those in Gelderland (0% vs 4.5%; OR = 0.04; 95% CI: 0.00–0.69). No other variables were statistically significantly associated with having a newly diagnosed chronic HBV infection.

Discussion

In this project, about half (54%) of the migrants attending the existing compulsory TB entry screening at public health services accepted additional HBV, HCV and HIV screening. The prevalence of chronic HBV infection (HBsAg-positive) and HCV exposure (anti-HCV-positive) in Gelderland was 4.48% and 0.99%, respectively, and all were newly diagnosed. The prevalence of chronic HBV infection in Amsterdam was 0.39%. The prevalence of HCV exposure (anti-HCV-positive) and chronic HCV infection (HCV RNA-positive) in Amsterdam was 1.17% and 0.39%, respectively. All chronic HBV and HCV infections in Amsterdam were previously diagnosed. No HIV infections were found.

Surprisingly, we found a significant difference in the prevalence of newly diagnosed chronic HBV infections between Gelderland (4.48%) and Amsterdam (0%). There are several potential explanations. The background HBV prevalence in the countries of origin of Gelderland participants was higher compared with Amsterdam participants. However, in univariate analyses, background HBV prevalence was not associated with newly diagnosed chronic HBV infection. In addition, those who migrated to the Netherlands for reasons other than work/study were more likely to have a newly diagnosed HBV infection, perhaps reflecting an increased risk among those with a lower socioeconomic status. The fact that more Gelderland participants migrated to the Netherlands for reasons other than work/study might therefore help explain the higher prevalence found among Gelderland participants. The differences in country of origin and reason for migration between participants in Gelderland and Amsterdam indicate that different areas in the Netherlands attract different groups of migrants, which is most probably due to work, study or housing opportunities in a given area or due to the migration history of family members. Another explanation for the varying prevalence of newly diagnosed chronic HBV infections might be differences in unmeasured HBV risk factors between participants from Gelderland and Amsterdam. Prior HBV vaccination was not among the exclusion criteria in Amsterdam, but it was in Gelderland.

In a comparable study from Scotland, where an integrated TB, HBV, HCV and HIV screening was only offered to international students, the prevalence of newly diagnosed HBV infections was also low (HBsAg prevalence: 2.6%, prevalence of newly diagnosed HBV infections: 1.3%, no HCV or HIV infections were found) [24]. The screening uptake found in both regions of our project was higher compared with the project in Scotland (35%) and compared with previous non-integrated HBV and HCV screening projects targeting migrants in the Netherlands (range: 7–42%) [9,10-18,24]. Uptake was lower compared with response rates for antenatal HBV and HIV screening of migrants in the Netherlands (HBV: 99.99%, HIV: 99.8%) [25], however, pregnant women could be generally more interested in screening if its primary aim is to prevent transmission to the unborn child. Furthermore, antenatal HBV and HIV testing in the Netherlands are offered according to the opt-out principle (everyone gets tested unless they explicitly refuse). The opt-out approach substantially improves HIV testing rates not only among pregnant women but also among clients of outpatient clinics focussed on sexually transmitted infections [26,27]. Similarly, an opt-out testing strategy might improve response rates to integrated HBV, HCV and HIV screening at the TB departments.

We found that the most common reason for declining screening was having already been tested. This might be indicative of a group with adequate access to care in their country of origin, in which HBV, HCV and HIV screening might therefore yield fewer newly diagnosed infections. Our results suggest that adding HIV screening is acceptable to migrants, as we saw no statistically significant difference in uptake between Amsterdam, where HIV screening was included, and Gelderland, where it was not. Only one person opted out of the HIV testing.

Unfortunately, the resources needed to add HBV, HCV and HIV screening to the compulsory TB-entry screening were not measured. Whether adding HBV, HCV and HIV screening to the compulsory TB entry screening in the Netherlands will be cost-effective needs to be further explored. A previous study from the Netherlands estimated that one-time-only, non-integrated HBV screening of all migrants from HBV-endemic countries (estimated background HBsAg prevalence: 3.35%), with a participation rate of 35%, was most probably cost-effective [28]. Although the overall HBV prevalence in our project was lower than 3.35%, overall HCV prevalence was low and no HIV infections were found, integrating HBV, HCV and HIV screening into the TB entry screening might also be cost-effective, as the programme costs of integrated screening programmes are expected to be lower compared with non-integrated screening. To further increase effectiveness, a pre-screening selection of migrants based on risk factors

deserves exploration, e.g. reason for migration, country of origin, or HBV, HCV and HIV risk factors such as blood transfusion history and injecting drug use [29].

If HBV, HCV and HIV screening were to be integrated into the TB entry screening, it should be taken into account that not all migrants are registered with a GP or have a Dutch health insurance at the time of screening. Although registering with a GP is easy and all Dutch citizens (including legal migrants and regardless of health status) are entitled to Dutch health insurance, extra guidance is needed to make sure that HBV, HCV and HIV-diagnosed migrants register with a GP and get a Dutch health insurance, and that they will be successfully referred and linked to specialised care [30,31]. Also, additional screening for migrants is needed to reach HBV, HCV and HIV risk groups who are not required to have TB entry screening (e.g. migrants from countries with high endemicity for HBV, HCV or HIV but with low endemicity for TB). Alternatives such as case finding through GPs should be explored for effectiveness and acceptability.

Our project has several limitations. Firstly, as our objective was to study the acceptability and effectiveness of HBV, HCV and HIV screening within the normal TB screening procedures, we decided not to measure HBV, HCV and HIV risk factors. Measuring HBV, HCV and HIV risk factors would have provided more insight into the usefulness of risk-based screening and could potentially have provided more insight into the differences between the prevalence of newly diagnosed chronic HBV infections between Gelderland and Amsterdam. Also, due to a low number of HBV infections, the analyses of demographic and migration characteristics as potential determinants of HBV were limited. Secondly, results of this project may not be generalisable to all migrants attending TB screening in the Netherlands, especially as we found regional differences in the characteristics and HBV prevalence of our populations and as migration flow changes over time. Finally, the inclusion criteria, recruitment procedures (the available translations and the timing of receipt of the project information) and screening procedure (in- or exclusion of HIV testing) differed slightly between the two regions. However, despite these small differences, uptake of screening between Gelderland and Amsterdam was similar.

Conclusion

About half of the migrants visiting the five TB departments accepted HBV, HCV and HIV screening. The prevalence of newly diagnosed HBV infections was lower intermediate (2–4.99% [21]) in migrants screened in Gelderland, but no newly diagnosed HBV infections were found in Amsterdam. This regional difference probably reflects the differences in countries of origin and reasons for migration (which may be related to differences in social economic status) between participants in Gelderland and Amsterdam. The prevalence of newly diagnosed HCV infections was low in both regions, and no HIV infections were found. A more effective strategy might be targeted, integrated TB, HBV, HCV and HIV screening for migrants, which includes prescreening selection based on risk factors and an opt-out testing approach. Data and cost-effectiveness studies are needed for decision-making regarding the implementation of HBV, HCV and HIV screening that is integrated into entry screening at TB departments.

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Conflict of interest

MP and FRZ report that their institute received grants from Gilead Sciences, Inc., Roche, MSD and AbbVie and non-financial support from OraSure Technologies, all not related to this project.

Authors' contributions

Janneke Bil wrote the draft manuscript. Peter Schrooders, Judith Klomp, Lutje Huijbregts, Toos Weagemaekers and Alma Tostmann designed and coordinated the project in Gelderland. Janneke Bil, Maria Prins, and Freke Zuure designed and coordinated the project in Amsterdam. Peter Kouw, Gerard Sonder, Henry de Vries, Maarten Scholing and Wieneke Meijer contributed to project design and logistics in Amsterdam. All authors provided substantial contributions to the interpretation of the data and to subsequent drafts, and all approved the final version of the manuscript.

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Epidemiologijos žinios
Užkreciamuju ligu profilaktikos ir kontroles centras
Center for Communicable Disease Prevention and Control, Vilnius
Online. In Lithuanian.
http://www.ulac.lt/index.php?pl=26

Netherlands

Infectieziekten Bulletin
Rijksinstituut voor Volksgezondheid en Milieu
National Institute of Public Health and the Environment, Bilthoven
Monthly, print and online. In Dutch.
http://www.rivm.nl/infectieziektenbulletin

Norway

MSIS-rapport
Folkehelseinstituttet, Oslo
Weekly, print and online. In Norwegian.
http://www.folkehelsa.no/nyhetsbrev/msis

Poland

Meldunki o zachorowaniach na choroby zakazne i zatruciach w Polsce
Panstwowy Zaklad Higieny,
National Institute of Hygiene, Warsaw
Fortnightly, online. In Polish and English.
http://www.pzh.gov.pl

Portugal

Saúde em Números
Ministério da Saúde,
Direcção-Geral da Saúde, Lisbon
Sporadic, print only. In Portuguese.
http://www.dgs.pt

Romania

Info Epidemiologia
Centrul pentru Prevenirea si Controlul Bolilor Transmisibile, National Centre of Communicable Diseases Prevention and Control, Institute of Public Health, Bucharest
Sporadic, print only. In Romanian.
Sporadic, print only. In Romanian.
http://www.insp.gov.ro/cnscbt/index.php?option=com_docman&Itemid=12

Slovenia

CNB Novice
Inštitut za varovanje zdravja, Center za nalezljive bolezni, Institute of Public Health, Center for Infectious Diseases, Ljubljana
Monthly, online. In Slovene.
http://www.ivz.si

Spain

Boletín Epidemiológico Semanal
Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Madrid
Fortnightly, print and online. In Spanish.
http://revista.isciii.es

Sweden

Folkhälsomyndighetens nyhetsbrev
Folkhälsomyndigheten, Stockholm
Weekly, online. In Swedish.
http://www.folkhalsomyndigheten.se

United Kingdom

England and Wales

Health Protection Report
Public Health England, London
Weekly, online only. In English.
https://www.gov.uk/government/collections/health-protection-report-latest-infection-reports

Northern Ireland

Communicable Diseases Monthly Report
Communicable Disease Surveillance Centre, Northern Ireland, Belfast
Monthly, print and online. In English.
http://www.cdscni.org.uk/publications

Scotland

Health Protection Scotland Weekly Report
Health Protection Scotland, Glasgow
Weekly, print and online. In English.
http://www.hps.scot.nhs.uk/ewr

European Union

"Europa" is the official portal of the European Union. It provides up-to-date coverage of main events and information on activities and institutions of the European Union.
http://europa.eu

European Commission - Public Health

The website of European Commission Directorate General for Health and Consumer Protection (DG SANCO).
http://ec.europa.eu/health

Health-EU Portal

The Health-EU Portal (the official public health portal of the European Union) includes a wide range of information and data on health-related issues and activities at both European and international levels.
http://ec.europa.eu/health-eu

European Centre for Disease Prevention and Control

The European Centre for Disease Prevention and Control (ECDC) was established in 2005. It is an EU agency aimed at strengthening Europe's defences against infectious diseases. It is located in Stockholm, Sweden.
http://www.ecdc.europa.eu

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