



Early View

Review

Screening for tuberculosis in migrants and visitors from high incidence settings: present and future perspectives

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Screening for tuberculosis in migrants and visitors from high incidence settings: present and future perspectives

Short title: Migrants and TB

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Take-Home Message

TB screening of migrants from high to low TB incidence settings contributes to national and global TB elimination.

Abstract

In most settings with a low incidence of tuberculosis (TB), foreign-born people make up the majority of TB cases, but the distribution of the TB risk among different migrant populations is often poorly quantified. In addition, screening practices for TB disease and latent TB infection vary widely. Addressing the risk of TB in international migrants is an essential component of TB prevention and care efforts in low incidence countries, and strategies to systematically screen for, diagnose, treat and prevent TB among this group contribute to national and global TB elimination goals.

This review provides an overview and critical assessment of TB screening practices that are focused on migrants and visitors from high to low TB incidence countries, including pre-migration screening and post-migration follow-up of those deemed to be at an increased risk of developing TB. We focus mainly on migrants who enter the destination country via application for a long-stay visa, as well as asylum seekers and refugees, but briefly consider issues related to short-term visitors and those with long duration multiple-entry visas. Issues related to the screening of children and screening for latent TB infection are also explored.

Background

In an increasingly connected world, international migration is happening on a scale never witnessed before. The number of international migrants has grown faster than the world's population, and reached 258 million in 2017, up from 173 million in 2000 [1]. The health and wellbeing of migrants, especially people displaced from their home country, has become a global public health priority [2]. The rates of communicable diseases such as tuberculosis (TB) are often significantly higher in migrants' countries of origin than in the destination countries. This has important implications for TB care and prevention strategies in low TB incidence countries [3-10].

According to the International Organization for Migration (IOM), an international migrant is “any person who is moving or has moved across an international border away from his/her habitual place of residence, regardless of (1) the person's legal status; (2) whether the movement is voluntary or involuntary; (3) what the causes for the movement are; or (4) what the length of the stay is” [11]. In this review, we will use the term migrant in line with this definition. We refer to refugees and asylum seekers as per the IOM definition [11] and use the term regular migrant for any migrant who is part of “orderly migration”, “in keeping with the laws and regulations governing exit of the country of origin and travel, transit and entry into the destination or host country” [11].

In many low-incidence settings, international migrants are the predominant population in which TB occurs; 86% in Australia in 2014 [12], 69% in the United States of America (USA) in 2016 [13], 74% in the United Kingdom (UK) in 2016 [14], and 90% in Sweden in 2016 [15]. Across all high-income Organization for Economic Co-operation and Development (OECD) countries, more than half of TB cases (median 52.0% in 2013) occur in foreign-born individuals [3]. Minimizing the risk of TB importation and addressing the needs of migrants is a priority area for countries with a low TB incidence to achieve TB elimination [16]. However, robust cost-benefit analyses and assessments of the cost-effectiveness of different migrant screening practices are, on the whole, lacking [17]. This is complicated by the fact that the effectiveness of screening programmes is likely to be dependent upon the successful implementation of several complementary programme components. Typically, this includes pre-migration screening (applying a range of screening algorithms) and post-migration follow-up.

Here, we critically review current screening practices for TB disease among regular migrants, asylum seekers and refugees to low-incidence settings. We explore the post-migration follow-up of people considered to be at an increased risk of developing TB at pre-migration screening. We also consider TB screening among shorter term visitors, and for migrants with multiple-entry visas, and explore issues related to children and the screening of latent TB infection (LTBI). Table 1 presents a summary of key findings and messages arising from this review.

Literature search strategy

To inform the content of this review we conducted a literature search of five databases, including Ovid MEDLINE Epub Ahead of Print, Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, and Ovid Cochrane Database of Systematic Reviews from database inception to December 2017. The following key words (or close variations) were used: “tuberculosis”, “latent tuberculosis” “screening”, “public health surveillance”, “follow-up”, “health undertaking”, “migrant”, “refugee”, “asylum seeker”, “overseas”, “foreign”, “arrival”, “entrant”, “visa applicant”, “transient”. Keywords were mapped to Medical Subject Headings (MeSH), allowing the search for matching content. We also searched the reference lists of relevant papers. Review authors provided content expertise to identify important articles in the topic area.

Pre-migration screening for TB disease

Regular migrants from TB endemic settings may not have an increased risk of TB disease compared to the general population in their country of origin [18], but their likelihood of developing TB often exceeds that of the population that they will be entering. For this reason, a number of low incidence countries mandate pre-migration screening for all migrants from high incidence settings [19].

Pre-migration TB screening, implemented routinely in the UK and in selected other European countries, the USA, Canada, Australia and New Zealand, involves the systematic screening of prospective regular migrants and refugees in their country of origin. This is often undertaken as part of a more comprehensive health screening (conducted during the visa application process for regular migrants). The goal of pre-migration screening is to identify individuals with TB disease [20], and,

notably in Canada and Australia, to identify migrants at high risk of subsequently developing TB after arrival [21, 22].

Figure 1 presents generic screening algorithms for TB disease and LTBI in migrants or visitors from settings with a high incidence of TB. Screening algorithms vary considerably between countries [21], but the major principles and algorithms are broadly similar.

The first stage of screening for TB disease typically involves a combination of symptom-based, physical and chest radiography assessment. Confirmatory bacteriological testing may involve sputum testing using smear microscopy, culture or polymerase chain reaction (PCR) (e.g. Xpert MTB/RIF®). Additional tests for extra pulmonary TB, such as fine needle aspiration biopsies of enlarged superficial lymph nodes, may be performed if indicated. If TB disease is identified, verification of a bacteriological response to therapy is usually required before migration is permitted (Figure 1).

Canada [23], the USA [24], Australia [25] and the UK [26] require applicants above a certain age threshold (usually 10 years, in the USA 15 years) to have a plain chest radiograph if they originate from a high TB incidence country (generally defined as an estimated TB incidence of $\geq 40/100\ 000$ population). However, most other low TB incidence countries do not have this requirement [19]. The USA, Australia, and Norway [21, 24, 25] also require all child migrants aged from 2 to 10 years (USA: 2 to 14 years) to undergo an interferon-gamma release assay (IGRA) or a tuberculin skin test (TST) for LTBI. A chest radiograph is performed only if these initial tests for infection are positive. Such testing also provides an opportunity to consider LTBI treatment in children without evidence of TB disease.

Pre-migration screening policies are underpinned by evidence from observational studies that have demonstrated high case-finding yields among screened populations, and significant reductions in the risk of TB following the implementation of pre-migration screening [27-29]. Since the yield of pre-migration screening correlates with the incidence of TB in the source country [18], pre-migration screening policies focus on regular migrants from high-incidence countries. The effectiveness of pre-migration screening to reduce TB importation is influenced by the algorithm employed and the quality

of the screening process implementation (e.g. accuracy of chest radiograph reading). Drawing upon the available observational data [29], WHO has issued a conditional recommendation that people migrating from high to low-incidence countries should be screened for TB disease before arrival [30].

A diagnosis of TB may be associated with stigma and usually results in delayed visa processing with substantial delays required to complete TB treatment, especially treatment for drug resistant TB. The detection of LTBI or minor radiographic abnormalities may also contribute to stigma and exacerbate underlying anxiety. These negative consequences of pre-migration screening, together with concern that a TB diagnosis may adversely affect the application outcome may fuel practices that undermine the validity of the screening process.

Screening for latent TB infection (LTBI)

WHO recommends that systematic LTBI screening and treatment should be considered for high-risk populations in upper middle and high income countries, using either an IGRA or a TST [31]. One of the reasons for considering LTBI screening among migrants from high to low TB incidence countries is that migrants are at their highest risk of developing TB disease within the first five years after migration. TB could be prevented if LTBI is detected and adequate preventive therapy provided [32]. Migrants may also have co-morbidities such as diabetes mellitus, chronic kidney disease or other immune compromising conditions that could increase their risk of future TB disease progression [33].

National policies for LTBI screening among migrants have different thresholds to define a high incidence TB country, prioritise different groups of migrants (i.e. asylum seekers versus regular migrants) and recommend different diagnostic tests and preventive therapy regimens [34, 35]. UK guidelines state that healthcare professionals “should maintain a coordinated programme to detect” LTBI and offer preventive treatment to new entrants aged 35 years or younger [36]. Guidelines from the USA Preventive Services Task Force recommend that asymptomatic adults with likely previous TB exposure be screened for LTBI, including “persons who were born in, or are former residents of, countries with higher TB prevalence” [37]. A review of policies from 29 OECD countries found that 25 countries (86.2%) routinely screened all migrants for TB disease; and 16 (55.2%) offered LTBI

screening, usually post-migration, of which 15 offered LTBI screening to all migrants including asylum seekers and refugees (in 8 countries this was compulsory) [19].

A study from the UK conducted in recent migrants from high TB incidence areas demonstrated that among migrants with LTBI, those who had LTBI treatment based on a positive IGRA had a significantly reduced risk of TB during the observation period compared to untreated LTBI-positive patients (incidence rate ratio, 0.17; 95% CI 0.05 to 0.60) [38].

Considerations for LTBI testing include the accuracy of the test, the risk-benefit ratio of LTBI treatment, and the impact of the test result upon clinical decision making [39, 40]. Concerns about poor effectiveness of therapy are often related to reports of low rates of LTBI treatment completion, ranging from 7-83% [41]. Uptake of LTBI testing and LTBI treatment completion rates can be improved with adequate patient support and some studies have reported that patient-centred interventions (such as pharmacist led LTBI clinics, screening offered in community colleges, free monthly drug dispensation directly through the TB clinic) improve uptake of LTBI testing (up to 75%) and LTBI treatment completion rates, among those who accepted treatment, up to 94% [42-44].

The cost effectiveness of LTBI screening among migrants is an important consideration for policy makers. Cost effectiveness studies have reported mixed results and are highly context-specific [45]. One modelling study found that cost effectiveness was optimal when a single IGRA test was offered to all migrants aged 35 years and younger from countries with an estimated TB incidence $\geq 150/100,000$ population, with the estimated ability to identify 92% of infected migrants [46]. Another modelling study found that pre-migration screening of Chinese and Indian students going to the USA would be cost effective (and prevent 157 cases of TB annually) from the destination country perspective, if the students paid for the screening themselves [47]. In a scoping review on the cost effectiveness of LTBI screening among migrants from high incidence countries, of the nine studies that met the inclusion criteria, four studies stated that IGRAs were the most cost effective test for LTBI screening generally, and two others noted that LTBI screening was cost effective only if carried out among migrants with recent close TB contact [48]. Most cost effectiveness models do not consider full programmatic scale up of LTBI screening, and the use of short-course LTBI treatment regimens have

not been considered. Therefore, more accurate estimates of the burden of migrant screening to destination countries and migrant populations are needed.

Screening and diagnostic tools for TB and LTBI

Chest radiography and microbiologic tests for the detection of *M. tuberculosis* are widely used as screening and diagnostic tools to assess migrants for TB disease, whereas TST and IGRAs are used for LTBI screening or as the initial step in TB disease assessment (e.g. in children).

Chest radiography is a key TB screening test. Due to its high sensitivity and moderate specificity for TB, the primary role of chest radiography in TB screening is to identify individuals who should undergo microbiologic testing to rule out pulmonary TB [49]. The use of digital radiography has a number of advantages, including less radiation exposure, better image quality, reduced costs, less image variability, and the convenience and efficiency of electronic transmission of images, which facilitates off-site reading and quality control by specialist radiologists [49]. It is thus no surprise that digital chest radiography is preferred by many immigration authorities [49-51]. The accuracy of chest radiography is also critically dependent on the skills of the individual interpreting the image, which can contribute to poor inter-reader reliability. To address this, some countries have stringent requirements for the type of physicians allowed to read immigration screening radiographs, as well as for the method of reporting and categorising abnormalities [21, 51, 52]. Recent advances in machine-learning and computing power have led to the development of computer aided programs that can analyse digital chest radiographs for the presence of TB-compatible abnormalities [53, 54]. This could eliminate the problem of inter-reader variability. However, the accuracy and cost-effectiveness of this nascent technology remains unclear due to limited evidence [55, 56]. Computer aided programs may be useful in quality control and in aiding radiologists with their reading.

Microbiologic tests for detecting *Mycobacterium tuberculosis* are typically only required if TB disease is suspected—either due to the presence of symptoms, clinical findings, or radiographic abnormalities. Smear microscopy to identify acid-fast bacilli has been used to diagnose TB disease for well over a century, and remains a valuable test—as it is rapid, cheap, and provides information on the degree of infectiousness. However, it has poor sensitivity which limits its value as a stand-alone

test to rule-out active disease. In one study of 1179 Vietnamese individuals applying for an immigration visa to the USA, smear-microscopy missed 76% of culture-confirmed cases [57]. The addition of routine sputum culture in visa applicants with presumptive TB has been associated with a substantial decline in post-migration case detection in the USA since 2007 [58, 59], although temporal factors may have contributed to this decline. Between 2007 and 2012 approximately 1.5 million migrants and refugees to the USA were screened using a culture-based algorithm. About the same number of migrants and refugees were screened by a smear-based algorithm [59]. Among the 4,032 TB cases diagnosed by culture, 2,195 (54.4%) were sputum smear-negative. The annual number of reported TB cases among migrants screened with the culture-based algorithm, within one year after arrival, decreased from 1,511 to 940 from 2007 to 2012) [59]. A UK study showed that migrants screened at sites where sputum culture testing was performed on all samples, had increased odds of being diagnosed with bacteriologically confirmed TB at pre-migration screening (OR 2.4; 95% CI 1. to 3.0; $p < 0.0001$), compared with those being screened at sites with smear-based testing alone [60].

While culture is widely accepted as the reference standard for diagnosing active TB [52, 61, 62], its limitations include high cost and delayed diagnosis due to slow bacterial growth [63]. PCR-based tests, such as the fully-automated Xpert MTB/RIF® assay, are increasingly used, since they offer higher sensitivity than smear microscopy and provide results much faster than culture. However, Xpert is substantially less sensitive than culture in patients with pauci-bacillary disease, missing almost one-third of sputum smear-negative TB cases [64]. Recent guidelines from WHO [65] and other major professional organisations [61] recommend Xpert as the first microbiologic test to perform in someone with presumptive TB; a growing number of countries have introduced this within their local screening algorithms.

TST and IGRAs detect T-cell responses to *M. tuberculosis* antigens. They are primarily used in the assessment of LTBI. IGRAs are more specific than TST in individuals with previous exposure to non-tuberculous mycobacteria (NTM) or previous vaccination with Bacille Calmette- Guérin (BCG) [66]. Amongst commercially available IGRAs, the T-SPOT.TB® appears to be the more sensitive test, but the QuantiFERON Gold® assay is broadly equivalent and simpler to perform and standardise [37].

Post-migration follow-up

While pre-migration screening primarily focuses on the detection of TB disease, it also identifies migrants who have no microbiologic evidence of TB disease at the time of migration, but who are at an increased risk of developing TB disease in the future. Indicators of future TB risk include chest radiograph abnormalities consistent with previous TB infection or disease or recent contact with an infectious TB patient [67, 68]. The post-migration incidence of TB in high risk migrants identified in this way is estimated to be more than 100 times higher (relative risk (RR) 102-416) than in the general population in the destination country [69]. This risk is substantially higher than the RR of TB in other high risk groups, such as close contacts of patients with TB (RR 47) [70], patients using tumour necrosis factor (TNF)-alpha inhibitors (RR 2-29) [71], patients undergoing solid organ transplantation (RR 27) [72] or patients with chronic renal failure requiring renal replacement therapy (RR 8) [73]. Offering these high-risk migrants LTBI treatment should therefore be a priority for receiving countries with a low incidence of TB.

Some countries have established post-migration follow-up programmes for migrants at increased risk of developing TB. The follow-up programmes may consist of one medical follow-up visit in the destination country (the usual approach adopted in the USA, [59]) or it can encompass multiple follow-up visits spanning two or more years (the usual approach in Australia [74, 75]). Follow-up programmes that conduct serial chest radiographs aim to identify cases of TB disease early, reducing secondary TB transmission within the community and improving the outcome of affected individuals [75]. To date, the effectiveness—in particular the cost-effectiveness—of such programmes remains unclear, since many high risk migrants do not attend routine follow-up visits [17]. It seems reasonable to consider LTBI treatment as an alternative, or as an addition to chest radiograph follow-up, as the benefit of LTBI treatment for high risk groups is well documented [76, 77].

A substantial proportion of TB cases diagnosed soon after migration are likely to have been present at the time of pre-migration screening, or occur among short-term visitors – for whom screening is not performed routinely. As elaborated above, the number of missed cases can be reduced by adding a requirement for sputum culture for patients with radiographic abnormalities or symptoms during pre-migration screening.

The considerable challenges of providing TB care to migrants from different linguistic and cultural backgrounds need to be acknowledged and addressed. Healthcare systems in receiving countries need to provide access to culturally appropriate and high-quality healthcare for migrants in order to detect and treat TB in this group. Training of clinicians is required, along with removal of any restrictions in access to healthcare such as those that only allow treatment for emergency care. Discussions about the benefits of LTBI treatment in someone who is completely asymptomatic can be particularly challenging, especially when health beliefs are not aligned with evidence-based Western medicine [78]. Those involved in migrants' care need to be aware of and address important cultural differences in health beliefs [79].

Asylum seekers and refugees

Asylum seekers and refugees, defined as persons who have fled from their country of origin for fear of persecution, and have applied for protection [80], are a particularly high-risk group for developing TB [81-83]. Many refugees originate from countries with a high incidence of TB [84] and often continue to live in conditions of deprivation in the destination country. The same is true for asylum seekers, defined as persons who seek safety from persecution or serious harm in a country other than their own and who await a decision on the application for refugee status under relevant international and national instruments [11]. For asylum seekers and refugees, limited access to healthcare, combined with economic vulnerability, may contribute to significant delays in TB diagnosis. For refugees and asylum seekers with TB, flight from persecution may interrupt their treatment, leading to poor outcomes and acquired drug resistance, as well as potential ongoing TB transmission [85, 86]. Time spent in crowded refugee camps increases the risk of TB exposure and infection. Refugees may also have other risk factors for TB disease, such as malnutrition, chronic kidney disease, diabetes mellitus and human immunodeficiency virus (HIV) co-infection.

The WHO has published detailed guidelines for establishing effective pre-migration TB care and prevention among asylum seekers and refugees [84]. These recommendations focus on strengthening the health system in countries of origin and implementing the core elements of an effective TB programme. In settings torn by war or civil unrest, strengthening poor local healthcare

infrastructure may not be possible, and screening is only feasible at or after entry to a low-incidence country.

If accepted by a receiving country, refugees usually require routine symptom-based and radiographic screening to exclude TB disease with attention to physical and psychological comorbidities. Such screening may be implemented prior to migration, at the point of entry, or after arrival depending on the receiving country [87]. Some receiving countries screen refugees for LTBI pre-migration, given their increased risk of infection and subsequent progression to disease [39]. LTBI treatment or serial screening for disease, can then be initiated for those testing positive with TST or IGRA. High treatment completion rates for LTBI therapy can be achieved with appropriate social and health care support [88].

The yield of TB cases from screening low-risk refugees within Europe has been found to be low [39]. A German study suggested that TB cases identified at entry screening were concentrated in asylum seekers from only a few countries, and that screening was most efficient in migrants from these countries (e.g. Cameroon, Eritrea, Gambia, Georgia, Pakistan, Russia and Somalia) [89]. Hence, TB control policies must be tailored to the risk profile of refugee populations and be implemented in the broader context of appropriate social, economic and health care support throughout the migration process. Europe has experienced an unprecedented influx of refugees and asylum seekers in recent years. It is essential that access to early TB diagnosis and care among refugees is ensured, and that the coordination of TB screening efforts in Europe is improved to benefit refugee populations, protect the public at large and to achieve the targets of the End TB Strategy [90, 91].

Short-term visitors and those with long-duration multi-entry visas

The risk of TB in visitors, that is those granted temporary admission to stay in a country for less than 3-6 months at a time, in particular among those who travel regularly from high- to low-incidence settings, is not well known. Unlike permanent or long-term migrants, short-term visitors are rarely screened [7, 21]. In an era where movement of people across borders is considered essential for business, trade and economic development, screening policies may be in tension with policies to decrease perceived barriers to travel. However, given the dramatic increase in people movement

between high and low TB incidence settings, consideration should be given to addressing the challenge of TB in short-term visitors, if the WHO goal of TB elimination is to be realised [92].

In recent decades, the pattern of international migration has changed in complexity, with a greater emphasis on short-term visits, frequent returns and circular migration where cumulative risk factors and exposure should be considered [93]. In OECD countries, inbound tourism contributes more than 4% of gross domestic product (GDP), 5% of employment and 20% of service exports and continues to increase year by year [94].

The limited information about the health status of visitors, and their need for and use of medical services, has hindered an objective evaluation of this area of public health policy [95]. In some countries, visitors are intentionally excluded from data collection. For example, in the USA, TB cases are not included in official case counts when a person is in the USA for less than 90 days [9]. Despite this, we know that TB is a concern in these groups and studies have shown up to 20% of notifications in the USA occur among visitors or temporary residents [96]. In Australia, the National Notifiable Disease Surveillance data from 2012-16 identified that short-term overseas visitors (where this data was captured) made up 7% of all TB notifications [97].

The case study in Box 1 shows data from a simple modelling exercise to assess the TB risk among visitors coming from China and India to Australia if long-term (10-year) multiple-entry (allowing up to 3 months stay per year) visas for these nationalities were to be introduced.

Another case study by Weinberg et al. reported cases of TB among foreign-born, temporary workers in the USA, working predominantly in the tourism industry, and highlighted delayed presentation and diagnostic delays of up to 3 months due to a lack of awareness amongst clinicians. This was further complicated by problems in TB contact-tracing due to frequent changes of location and use of bunk-style accommodation among temporary workers [9]. A study from the United Arab Emirates among migrants undergoing medical visa screening found that the TB prevalence among new applicants (first screening) was significantly higher (49.3 per 100,000) than among migrants who underwent repeat screening for visa renewal (25.2 per 100,000) [98]. Travel back to the country of origin was, however,

not captured in the study, and it is therefore not possible to determine whether the risk of TB decreased significantly despite return visits to the home country.

The economic and other benefits derived from short-term travel provide an imperative to strike a balance between promoting ease of travel and a safe environment that limits the spread of communicable diseases, in particular TB. Greater policy coherence, the development of long-term strategic approaches and engagement with a range of public and private stakeholders (e.g. employers of short-term migrants) will be essential. Given the high global rates of TB disease and infection, the identification of all short-term visitors who pose a risk of TB importation and domestic transmission is not feasible [8], but better risk stratification may guide practical steps to minimize risk. As a minimum, policy-makers must ensure that any legal, financial and social barriers to access healthcare are removed for anyone with a potentially serious infectious disease, enabling early diagnosis and treatment [99].

Paediatric perspectives

Historically, TB control programmes have focused almost exclusively on the identification and treatment of infectious adult cases, with little recognition that children suffer high disease burdens in TB endemic areas with uncontrolled transmission of *M. tuberculosis* [100]. It is estimated that ~1 million children developed TB disease in 2016 [101] with most cases occurring in TB endemic settings, where TB is likely to be a major, albeit unrecognised, contributor to child mortality [102, 103]. The rising tide of drug resistant TB also affects children, with high rates of MDR-TB reported in children from settings with evidence of MDR-TB transmission [104, 105].

Migrant children can be exposed to TB in their country of origin, as well as in neighbouring countries or refugee camps during periods of displacement. After arrival in a receiving country with a low TB incidence, children may be exposed to visitors from TB endemic countries within migrant communities or when visiting their country of origin. The risk of TB disease progression is highly dependent on the child's age at the time of infection (children <2-5yrs are particularly vulnerable), the time since infection (>90% of disease progression occurs within 12 months of primary infection) and the child's immune status (severely malnourished and HIV-infected children are most vulnerable) [106].

Given the vulnerability of young children to rapid disease progression, screening for TB infection and the provision of LTBI treatment is important. LTBI detection is complicated by the poor specificity of the TST in children routinely vaccinated with BCG at birth [107]. IGRAs are not affected by BCG vaccination. Although indeterminate results have been a concern and blood collection is challenging in young children [108], reliable IGRA results are achieved in the vast majority of refugee children [109]. There is evidence that IGRAs are accurate even in children less than 2 years of age and that indeterminate results, if adequate blood volumes have been secured, usually have other (non-age related) explanations such as an acute infection [110]. Results from the UK suggest that children with a positive TST and negative IGRA are not at risk of TB development [111].

Children with documented LTBI, especially those who are young and vulnerable, benefit from appropriate LTBI treatment. Unfortunately, with LTBI no test can determine whether the infecting organism might be drug resistant, emphasizing the importance of taking a careful TB exposure history [100]. Despite the availability of effective LTBI treatment, repeat exposure and future reinfection may occur after successful treatment, particularly if a migrant returns to their country of origin [112]. Therefore, in order to protect the most vulnerable children, it is important to vaccinate young children (<5 years) of migrant families born in low incidence settings with BCG, if a prolonged return visit to the country of origin or another TB endemic setting is planned. Table 2 provides an overview of issues to consider regarding paediatric TB in migrant populations, with a brief summary of challenges and practice recommendations.

The diagnosis of TB disease is often delayed in migrant children if this is not considered a likely diagnosis by the local clinician. It is important to ensure clinicians who manage these children consider the diagnosis of TB when they present with symptoms of the disease, which are often non-specific in nature.

Child-friendly TB drug formulations are often unavailable in low TB incidence countries, as pharmaceutical companies lack the financial incentives to support local drug registration. This limits the availability of low volume drugs that are unlikely to generate a profit, although special access

schemes may facilitate use of these “orphan drugs”. Given the availability of quality assured child-friendly water-dispersible fixed drug combination tablets via the Global Drug Facility (GDF) [113], it is hoped that children in low TB incidence settings will also have access to these drugs.

Conclusions and outlook

A substantial proportion of TB cases in many countries with a low incidence of TB occur in migrants originating from high-incidence settings. Therefore, strategies to prevent and manage TB in international migrants are important to meet TB elimination targets in low-incidence countries. Existing national TB screening programmes that aim to reduce the risk of TB after arrival, while minimising the burden of screening to migrants, vary considerably. Table 3 outlines current evidence gaps and/or future research needs to inform optimal screening practices for TB in migrant populations. It is hoped that quality improvements and refinements in approaches will lead to expanded TB prevention efforts among migrants at highest risk of developing disease.

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Box and Tables

Box 1. Case example – Modelling of TB risk among visitors coming from China and India to Australia if long-term multiple-entry visas are introduced

In 2016 the Australian government granted 7.7 million temporary visas with only 8% of temporary visa-holders having been screened for TB pre-migration. The numbers of tourists in Australia are expected to double, reaching more than 15 million in the next decade, with particularly substantial rises in tourists from China and India. From 2006/07 to 2015/16 the number of Chinese tourists has risen by nearly 400% to 890,000 per year, and the number of Indian tourists has grown by 280% over the same period. To meet this demand, the Australian government has looked at different products to facilitate travel to Australia, for instance 10 year multi-entry visas for Chinese nationals with a stay period of up to 3 months.

To consider the risk of TB in visitors to Australia with long-term multi-entry visas from high TB burden countries, the Australian Department of Immigration and Border Protection commissioned modelling of predicted TB cases and cost of treatment. The model was based on an estimated 100,000 visitors from China and India, staying in Australia for 3 months per year and returning to their home country for the remaining 9 months a year over a period of 10 years. This modelling estimated 730 and 1358 additional TB cases from China and India respectively over ten years. The number could be substantially reduced to an estimated 393 and 487 extra TB cases respectively through initial and/or periodic screening.

Details about the modelling study can be found in the online supplement.

Table 1: Summary of key findings and messages

<p>Pre-migration screening</p> <ul style="list-style-type: none"> ▪ The goal of pre-migration screening is to identify individuals with TB disease and, notably in Canada and Australia, to identify migrants at high risk of subsequently developing TB after arrival in the destination country. ▪ The screening involves a physical assessment and chest radiograph evaluation of adult and adolescent migrants from high-incidence settings and LTBI testing (IGRA and TST) in children, with chest x-rays conducted only in case of a positive test for LTBI. ▪ Chest radiographs identify individuals with presumptive TB who should undergo microbiologic testing to rule out pulmonary TB. ▪ Performing a sputum culture (or Xpert MTB/RIF®) in all presumptive TB cases increases the diagnostic yield of pre-migration screening and reduces the risk of post-migration TB. ▪ Findings from observational studies indicate that pre-migration screening is successful in reducing the post-migration incidence of TB in people from high-incidence settings.
<p>Screening for LTBI</p> <ul style="list-style-type: none"> ▪ Migrants experience the highest risk of TB disease development during the first 2-5 years after migration to a low TB incidence setting; which supports the potential value of LTBI treatment. ▪ LTBI screening practices vary significantly between countries. ▪ Low uptake and completion of LTBI treatment is a concern, but can be improved with adequate patient support and provision of patient-centred services. ▪ The cost-effectiveness of LTBI screening strategies requires further evaluation.
<p>Post migration follow-up</p> <ul style="list-style-type: none"> ▪ Migrants who have chest radiograph abnormalities consistent with old TB infection or disease at pre-migration screening, have a high post-migration incidence of TB ▪ The (cost-) effectiveness of follow-up programmes conducting serial chest radiographs for early TB disease identification is unclear. ▪ LTBI treatment as an alternative to serial chest radiography should be considered ▪ The challenges of providing unrestricted health care access and effective communication across cultural and linguistic barriers require careful consideration.
<p>Asylum seekers and refugees</p> <ul style="list-style-type: none"> ▪ Asylum seekers and refugees have a higher risk of TB than other migrants from settings with a similar TB incidence ▪ TB control policies must be tailored to the risk profile of refugee and asylum seeker populations and be implemented in the broader context of appropriate social, economic and health care support throughout the migration process
<p>Short-term visitors and those with long-duration multi-entry visas</p> <ul style="list-style-type: none"> ▪ Multiple short-term visits and circular migration are becoming increasingly important for international business and economic development ▪ There are only limited data available on the TB risk posed by short-term visitors and better monitoring systems need to be implemented ▪ Removing financial and social barriers to access healthcare services are key to enable early diagnosis and treatment in this group.
<p>Paediatric perspectives</p> <ul style="list-style-type: none"> ▪ Given the vulnerability of young children to develop rapid disease progression, screening for TB infection and the provision of LTBI treatment has added relevance in this group ▪ It is important to vaccinate young children of migrant families born in low incidence settings with BCG, if a return visit to the country of origin or another TB endemic setting is planned.

TB – tuberculosis; LTBI – Latent TB infection; IGRA – interferon gamma release assay; TST – tuberculin skin test; BCG – Bacille Calmette-Guerin

Table 2: Paediatric issues to consider regarding TB in migrant populations

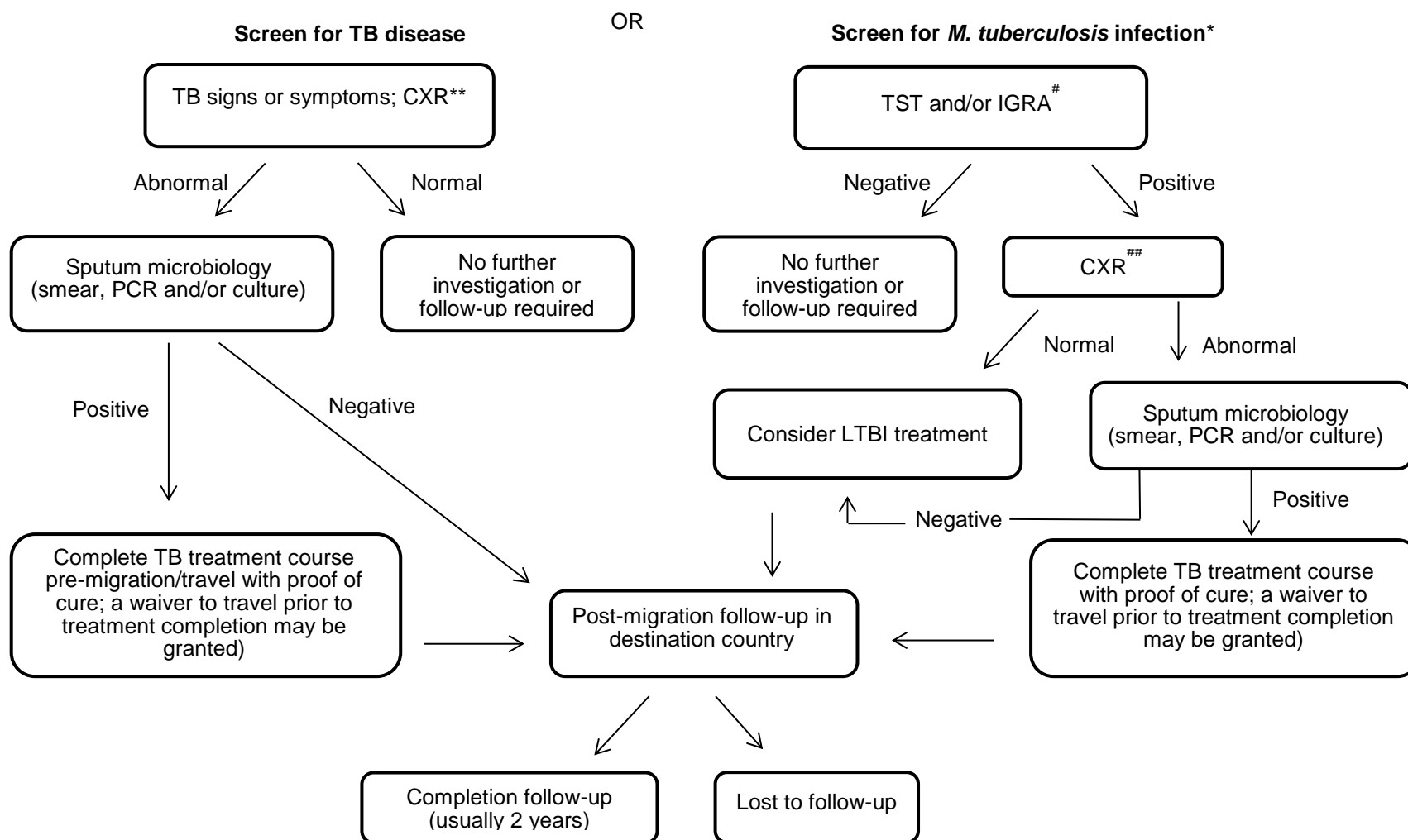
Priority areas	Challenges	Practice considerations
Exposure/ Infection & Prevention	Screening for LTBI - Poor specificity of TST in young BCG vaccinated children - no test to detect LTBI with drug resistant strains	It is important to always take a careful TB exposure history, specifically asking about known drug resistance or poor treatment response in possible source cases. IGRA is not influenced by BCG and is preferred, although blood collection and indeterminate results may be problematic in young children, especially those aged <2 years
	Risk of re-exposure - Risk of future re-exposure to TB during return visit to country of origin - no marker of reinfection - preventive therapy does not protect against future re-infection	The risk of re-infection following future visits to TB endemic countries (e.g. during return visits to the country of origin) is poorly quantified in the absence of a reinfection test, however, it should be considered even in children who completed a course of preventive therapy
	Providing BCG vaccination - BCG vaccination is not routinely provided to children born to immigrant families	BCG vaccination provides valuable protection against disseminated forms of TB in vulnerable young children and should be made available to all (HIV-uninfected) children <5 years of age, if future TB exposure is thought to be likely (e.g. if visiting country of origin)
Diagnosis & Treatment	Identifying children with TB disease - TB often not considered by clinicians in low burden settings	It is important to raise awareness that childhood TB is common in settings with uncontrolled TB transmission. It should be included in the differential diagnosis of immigrant children with likely TB exposure.
	Ruling out drug resistant TB - difficult without bacteriological confirmation	A history of close contact with someone who died from a chronic disease, had known drug resistant TB or poor treatment response provides a critical clue to possible drug resistant TB. The only way to confirm the diagnosis is through bacteriological confirmation, with phenotypic or genotypic DST. However, treatment according to the DST profile of the most likely source case is warranted in young children in whom bacteriological confirmation cannot be achieved.
	Providing child-friendly treatment - often not available in countries with strict (profit driven) sponsorship requirements, without avenues for "orphan drugs"	Child-friendly water-dispersible FDC tablets are available through the GDF, but they are not routinely available in low incidence countries (unless special access schemes are used). There are no child friendly options for second line TB drugs.

TB – tuberculosis; LTBI – Latent TB infection; TST – tuberculin skin test; BCG – Bacille Calmette-Guerin; MDR – multidrug resistant (i.e. resistance to isoniazid and rifampicin); DST- drug susceptibility testing; FDC – fixed drug combination; GDF – Global Drug Facility; HIV – human immunodeficiency virus

Table 3: Evidence gaps and/or future research needs to inform optimal screening practices for TB in migrants

Category	Evidence gap/ research question
Pre-migration TB screening	Can computer aided analysis of digital chest radiographs improve diagnostic accuracy (reduce false positive and false negative reports)?
	Does the use of Xpert MTB/RIF instead of sputum smear in migrants with abnormal chest radiography improve diagnostic accuracy?
	Does the routine use of Xpert MTB/RIF Ultra increase active case finding and diagnostic yield?
LTBI screening	Which migrants (e.g. age, immune status, co-morbidities) stand to benefit most from LTBI screening and treatment?
	Is LTBI screening and treatment of specific migrant groups (e.g. TB incidence in country of origin) cost-effective?
Post migration surveillance	Are post-migration follow-up programmes using serial chest x-rays for early case detection (cost-) effective?
	Should all migrants with abnormal chest radiography suggestive of previous TB disease, but no current evidence of active TB disease, be offered LTBI treatment (or full TB treatment)?
Asylum seekers and refugees	How can TB and LTBI screening be tailored to the risk profile of refugee and asylum seekers to optimize the screening yield/programme effectiveness?
	How can TB care be best integrated with other health care services for asylum seekers and refugees?
	How can the risk of perceived or real victimization resulting from selective TB screening policies be minimised?
Short-term visitors, multi-entry visas	Should short-term visitors and people on multi-entry visas coming from countries with a high incidence of TB to low incidence countries be screened for TB? If so, how should an optimal screening algorithm look (e.g. including risk stratification)?

Figure 1: Example of generic screening algorithms used in migrants or visitors from high incidence settings



*If no signs or symptoms suggestive of TB disease (and CXR negative in case of recent TB contact)

**History of previous TB and HIV status also assessed

some countries perform IGRA in TST positive children (to increase test specificity in BCG vaccinated individuals)

Sometimes done irrespective of TST/IGRA result eg. young children in recent close contact with an infectious TB case (US) to avoid a CXR if TST/IGRA is negative

LTBI – latent TB infection; TST – tuberculin skin test; IGRA – Interferon- γ release assay; CXR – Chest radiograph; PCR - polymerase chain reaction test (eg. Xpert MTB/RIF®); LTBI – latent TB infection

Online Supplement

Modelling the effect of alternative pre-migration screening strategies: A decision-analysis model (prepared by Greg J Fox, Jessica Bestrashniy)

The primary objective was to compare the effect of pre-migration screening, versus no screening, on the incidence of TB in Australia among visitors and migrants receiving selected classes of visas from selected high-prevalence countries (Strategy A). Secondary objectives were:

- To evaluate the effect of a repeat screening algorithm (baseline, 2, 4, 6 and 8 years) versus single screening only (Strategy B)
- To evaluate the effect of pre-migration screening, if this was restricted to 'high risk' populations only (Strategy A2)
- To evaluate the cost to the Australian healthcare system of screening strategies A and B

Model summary:

- Decision analysis model (TreeAge Pro 2017)
- Health costs (\$AUD) from Australian health system perspective
- **Excludes:**
 - Cost of associated contact investigations
 - Cost of off-shore screening
 - Hypothetical cohort of 100,000 migrants entering Australia
- Assumes visitors/migrants spend 3 months per year in Australia, 9 months in country of origin, each year over the 10 year period
- 10 year time horizon (10 year visa)
- Outcomes:
 - TB cases diagnosed and treated in Australia
 - Health costs from an Australian health systems perspective
 - MDR-TB cases in Australia
 - Total TB cases diagnosed in any country
 - All-cause mortality

Model parameters:

Parameter	Value
Cost Variables	
Cost of treating MDR TB (AUD)	AUD \$258,089 / case
Cost of treating TB (AUD)	AUD \$11,538 / case
Incidence and Prevalence of TB	
Annual incidence China	67 per 100,000 population / year
Annual incidence India	217 per 100,000 population / year
Prevalence of LTBI China	28%
Prevalence of LTBI India	40%
Proportion of MDR-TB China	6.6% of newly diagnosed TB
Proportion of MDR-TB India	3% of newly diagnosed TB
Proportion of prevalent TB in China	108 per 100,000 population
Proportion of prevalent TB in India	500 per 100,000 population
Screening variables	
Case detection rate of screening	100%
Treatment Outcomes	
Probability of relapse	2.5% / year in first 2 years, then 1% / year following
Probability of cure Australia	95%
Probability of cure in China	90%
Probability of cure in India	74%
Mortality rate per 1000 (non-TB)	0.7% / year