

## HEALTH EVIDENCE NETWORK SYNTHESIS REPORT 56

**What constitutes an effective and efficient package of services for the prevention, diagnosis, treatment and care of tuberculosis among refugees and migrants in the WHO European Region?**

**Themed issues on migration and health, VIII**

Sally Hargreaves | Kieran Rustage | Laura B Nellums | Jaynaide Powis | James Milburn  
Santino Severoni | Masoud Dara | Soorej J Puthoopparambil | Jon S Friedland



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## Abstract

The WHO European Region has faced high rates of external and internal migration in recent years, with concerns that this is contributing to the burden of tuberculosis (TB), multidrug-resistant TB (MDR-TB) and TB/HIV coinfection in some countries. This report examines evidence of effective and efficient service packages for the prevention, diagnosis and treatment of TB to inform strategies to address the TB burden in refugee and migrant populations. Significant regional variations were identified in both migration levels and TB burden in refugees and migrants, as well as in approaches to TB control, with low quality of evidence in many cases. While it is unlikely that a single strategy/package will be effective for all situations, the evidence highlights some common approaches that could guide policy-making and service development. TB elimination targets for the Region will not be met unless inequalities in access to screening and treatment for migrants are addressed, alongside efforts to tackle TB globally.

## Keywords

TUBERCULOSIS – DIAGNOSIS, PREVENTION AND CONTROL; TUBERCULOSIS, MULTIDRUG-RESISTANT – DIAGNOSIS, PREVENTION AND CONTROL; LATENT TUBERCULOSIS; REFUGEES, TRANSIENTS AND MIGRANTS; PROGRAM EVALUATION; EUROPE

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## ABBREVIATIONS

BCG	Bacillus Calmette–Guérin
CXR	chest X-ray radiography
DOTS	directly observed treatment, short-course
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EU	European Union
IGRA	interferon-gamma release assay
IOM	International Organization for Migration
LTBI	latent tuberculosis infection
MDR-TB	multidrug-resistant tuberculosis
TB	tuberculosis
TST	tuberculin skin test

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# SUMMARY

## The issue

The WHO European Region has faced high rates of external and internal migration in recent years, with concerns that this may be contributing to an increase in the burden of tuberculosis (TB), multidrug-resistant TB (MDR-TB) and TB and HIV (TB/HIV) coinfection in certain countries of the Region. There is significant heterogeneity across the Region with regards to TB epidemiology and to migration patterns, and different approaches to management of TB among refugees and migrants. Despite multiple WHO policies and guidelines, there is a lack of evidence on the most cost-effective or efficient approaches for detection of TB and continuum of care across country borders.

## The synthesis question

The objective of this report is to address the question "What constitutes an effective and efficient package of services for the prevention, diagnosis, treatment and care of tuberculosis among refugees and migrants in the WHO European Region?"

## Types of evidence

The report identified relevant documents through an evidence review of the peer-reviewed and grey literature in English and Russian, including websites of relevant national and international organizations and ministries of health across the WHO European Region. Publications reporting data on packages of care for TB in refugees and migrants were included and relevant data extracted and synthesized using a narrative approach to identify approaches being implemented across the Region. Efforts were made to capture relevant data from eastern Europe and the Russian Federation, in addition to western Europe. Although the main focus was on active TB, consideration was also given to latent TB (LTBI), drug-resistant TB and TB/HIV in migrant populations.

## Results

There were significant variations identified across the Region in terms of levels of migration and burden of TB in refugees and migrants, as well as in approaches to the prevention, detection and treatment of TB, with low quality of evidence in most cases.

However, the data highlighted some features that might guide policy-making and service development in this area.

- Targeting screening at migrants moving from countries of moderate or high incidence was a cost-effective approach.
- Data indicated the acceptability of screening for TB among refugee and migrant populations in Europe.
- Creating targeted, culturally sensitive and accessible services, with a focus on reducing stigma, improved the effectiveness of services.
- The evidence indicated underreporting of the TB burden and service needs, unique barriers to care (e.g. associated with legal status) and significant disparities in access to care in forced migrants (e.g. those fleeing conflict, famine, natural disasters or persecution).
- The evidence indicated the effectiveness of incorporating screening for LTBI into migrant screening programmes and targeting migrants from countries of high TB incidence, but there was a lack of consensus on cost-effectiveness.
- Migrants to countries with a low incidence of TB have been shown to be at increased risk of MDR-TB compared with the host population, suggesting that testing and treatment for drug-resistant TB in all individuals diagnosed with TB should be part of a basic package of care.

## Policy considerations

Because of the diversity of settings across the WHO European Region, it is unlikely that a single harmonized approach to management of TB among migrants will be effective or efficient. However, some policy options can be derived from the analysis for consideration:

- incorporate screening and treatment for LTBI and MDR-TB into refugee and migrant screening programmes (e.g. at the first point of contact for newly arrived migrants with health services in the host country) in an accessible and culturally sensitive manner as part of a basic free package of care;
- improve cross-border collaboration for TB screening and care along the entire migration trajectory, with focus placed on implementing a minimum package of TB screening and care;
- develop a more holistic approach to migrant health across the Region, recognizing the rights of migrants to health, and work towards removing legal, social and cultural barriers to health services to facilitate better TB control among migrants;

- develop health education/health literacy around prevention, treatment and care for TB to increase knowledge, awareness and, subsequently, patient involvement;
- align TB policies with initiatives within the social programme, as poverty and destitution are well-known risk factors for TB transmission and reactivation;
- strengthen approaches to data collection to provide an intercountry evidence base on TB in refugees and migrants for monitoring and evaluation within national health systems; and
- encourage research to understand patterns of TB and to define innovative implementation approaches, in particular cost-effectiveness and how to improve screening and treatment completion.



# 1. INTRODUCTION

## 1.1 Background

TB is still the single leading cause of death from infectious disease worldwide, with more than 10.4 million incident cases and 1.3 million deaths in 2016 alone (down from 1.7 million in 2000), plus an additional 374 000 deaths among HIV-positive individuals (1,2). Within the WHO European Region, there was a 4.6% decline in TB incidence between 2015 and 2016, representing one of the fastest decreasing trends among all WHO regions (2). However, there were still over 260 000 cases notified in the Region in 2016, with an estimate 71 000 cases of rifampicin-resistant/MDR-TB. MDR-TB is difficult to treat because of its resistance to multiple first-line anti-TB medications, including the most potent ones (isoniazid and rifampicin), and presents significant challenges to the elimination of TB (3,4). Its occurrence is thought to have diverse reasons including quality of medicines, infection prevention control and the substantial driver of poor treatment completion rates, in particular in the European Region (2). There is also a substantial disparity in the burden of TB among WHO European Region Member States, with over 85% of all incident TB occurring in 18 high-priority countries, including the Russian Federation, Turkey and Ukraine as recently as 2015 (5).

In the vast majority (90–95%) of individuals infected with *Mycobacterium tuberculosis* globally the infection is latent (6), where the organism survives in the body in a dormant state but is suppressed by the immune system and so does not cause symptoms and is not infectious. Reactivation can occur as the result of a change in the host's immunological state (e.g. through stress, malnutrition or other illness), at which point infection can progress to active disease where the individual can become unwell and can be infectious. There is some evidence that individuals who have contracted LTBI within the previous two years are at the highest risk of progression to active TB (7), with an estimated lifetime risk of progression from LTBI to active TB of 5–15% (2). Current estimates suggest that around 25% of the global population, or around 1.7 billion individuals, harbour LTBI, with a hypothesized prevalence of 0–10% in western European countries and of 30–50% in south-eastern European nations (7).

### 1.1.1 Migration in the WHO European Region

Rates of migration have increased in recent years globally (8,9), with this upward trend also seen within the WHO European Region. For example, the Russian

Federation recorded almost 600 000 migrants in 2016, with a total net migration figure of around 245 000 (10). The Russian Federation has become an important hub for migration in recent years, receiving an influx of migrants from countries of the former Soviet Union from the west and of Asia from the east (11). In 2015, countries belonging to the European Union (EU) and the European Economic Area (EEA) recorded the highest net migration since records began in 1961, with 4.3 million migrants thought to have entered in 2015, and a total net migration of 1.9 million individuals (12). The recent and ongoing flow of migrants in the Mediterranean area is but one driver of increasing migration to Europe: over 387 000 arrivals to Europe were recorded in 2016 through these routes (13). This has led to the development of numerous official and unofficial transit camps across the Region (14). There were over 2.5 million asylum applications to EU countries in 2015 and 2016 (15), largely from Afghanistan, Iraq and the Syrian Arab Republic. The dominant migration trajectories into the EU follow a south–north and east–west trajectory. Additionally, there is considerable migration within the EU: in 2013, 17.7 million EU citizens were living in an EU country other than their country of birth (16–18).

As a result of these movements, as well as the vulnerabilities of many of these migrant groups, there has been increasing attention to the potential health service and public health impact of migration in first-arrival, transit and destination countries across the WHO European Region. The need to ensure strategies are in place to address the health and human rights needs of migrant populations was highlighted by the 2016 United Nations Summit for Refugees and Migrants (19). In recent years, the European Region has initiated high-level meetings to support the implementation of such strategies (20,21). However, numerous concerns have been raised that the response to increasing migrant populations in many European countries has been increasingly restricted health services and limitations on migrants' entitlement to care on arrival, with consequences for wider public health and infection control in the Region (22,23).

### 1.1.1.1 Migrant groups considered in this report

Reasons for migration are varied but can include the influence of globalization, conflict, changes in climate, and the availability of resources and work for local populations (8). Consequently, migrants in the WHO European Region are an extremely heterogeneous group and such diversity can make it difficult to generalize about the health needs and health care-seeking behaviour of these populations; yet it is clear that these migratory trends have significant implications for national and international health systems in the Region (8), as well as for specific health issues such as TB control.



This review focuses on refugees, migrants and asylum seekers. As there is a great deal of heterogeneity and disagreement as to how these groups are defined, even within the WHO European Region (24), the following definitions are utilized in this report.

**International migrant:** the broadest definition, used by the United Nations, is any individual who lives in a country temporarily or permanently apart from his or her usual place of residence for at least a year (25). In many cases, these individuals have migrated for reasons including family, work or education (24,26). However, migrants entering Europe also include forced migrants, who may include refugees, asylum seekers and some undocumented migrants (who may have initially entered countries with visas to work that have subsequently lapsed).

**Asylum seeker:** a migrant seeking asylum (e.g. under the 1951 United Nations Convention on the Status of Refugees), and who is specifically seeking protection from persecution in his or her country of origin due to factors such as race, religion or politics (26,27).

**Refugee:** an individual who has been granted asylum or has been successful in overturning a previous judgement that ruled against an asylum application (26,28).

**Political instability:** A unified, whole-of-government approach to noncommunicable disease prevention is the best way to ensure sustained and stable funding, resources and public health and research priorities (4). Therefore, political instability can threaten efforts to reduce the noncommunicable disease burden.

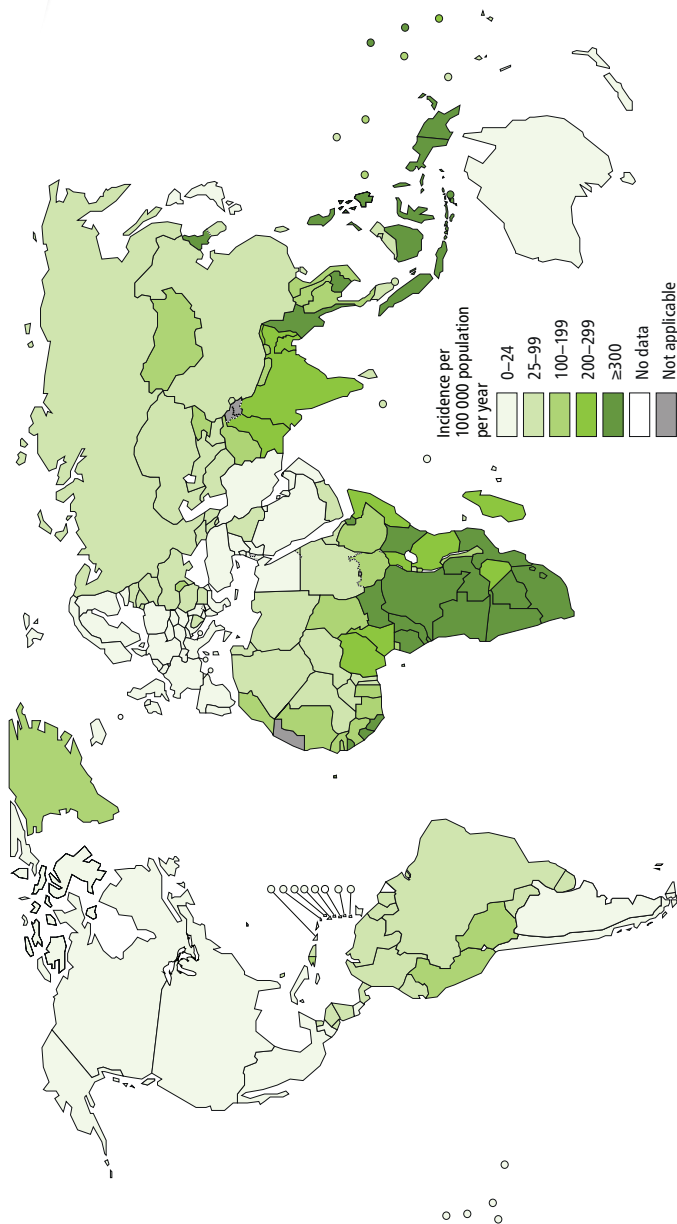
**Undocumented migrant:** an individual who is without legal status in the country to which he or she has migrated or who has overstayed after a visa/working permit has expired (29).

This report uses the term refugees and migrants to refer to all groups of migrants unless otherwise specified. Many regional datasets and literature focus on comparisons between foreign-born or non-EU-born individuals and the native/host populations, or just refer to migrants or immigrants, so where these datasets are described the authors' terms are used.

### 1.1.2 TB epidemiology among migrants in the European Region

The dominant migration routes into the Region follow a south–north and east–west trajectory, with migrants often originating from countries of high TB incidence and moving to those of low incidence (Fig. 1).

Fig. 1. Estimated incidence of TB cases per 100 000 population, 2016



Source: WHO, 2017 (2).



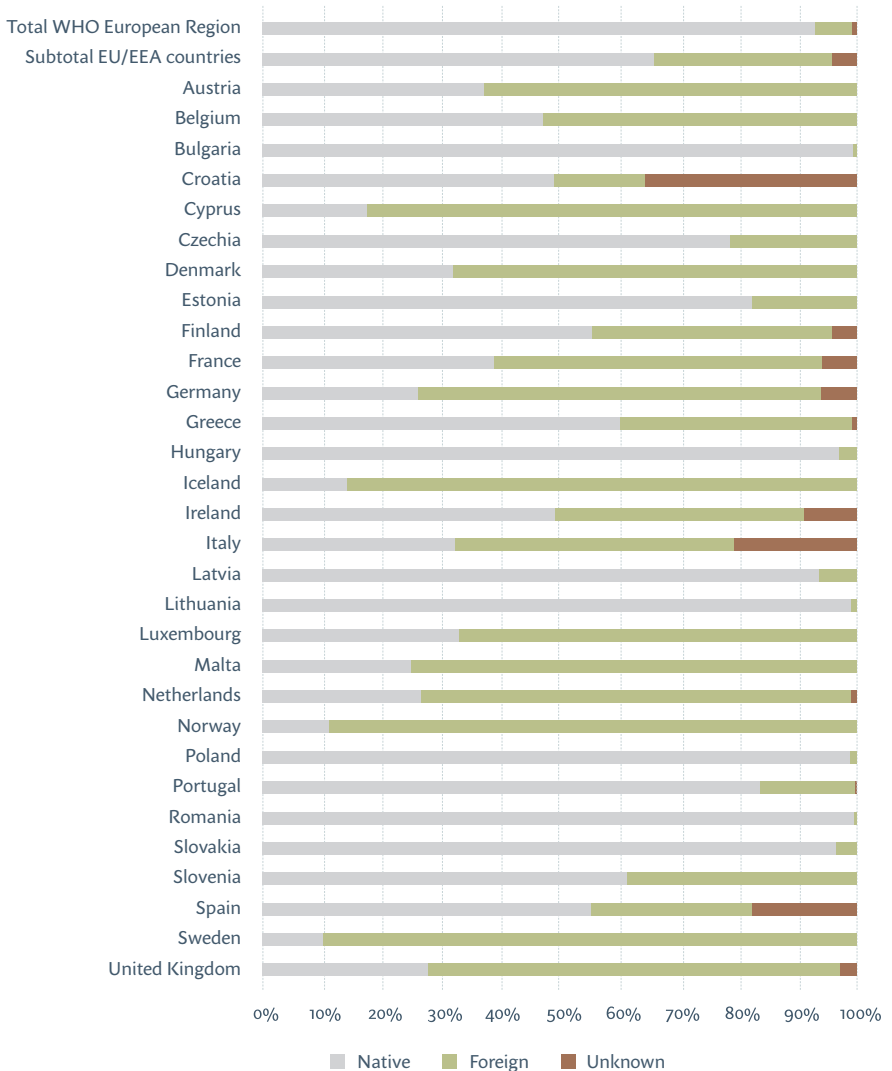


In 2015, 30% of all TB notifications within the WHO European Region, on average, were reported to be in foreign-born individuals (5), a number that has been increasing in recent years. Disproportionate rates of TB in migrants may be attributed to infection in high-incidence countries of origin (either prior to migration or during travel) or exposure to TB during or following migration (e.g. poor or overcrowded living conditions in camps or transit centres, malnutrition, poor hygiene and the presence of other neglected comorbidities such as diabetes or HIV) (3,30,31). There is significant heterogeneity in rates of TB in migrants across the WHO European Region, which includes 28 EU countries and 25 countries in eastern Europe and central Asia. In western European countries such as France, Germany, Italy and the United Kingdom, over 50% of all TB cases occur in migrants, while in countries such as Norway and Sweden, the proportion of TB cases in migrant (foreign-born) individuals is even greater, at 85–90% (3). This is in stark contrast to countries such as Hungary, Poland and Slovakia, which have a higher incidence of TB in the native population and where migrants account for less than 5% of the total proportion of TB cases (3). Despite the high burden of TB in migrants in many countries, there is evidence that TB within migrant communities does not significantly influence the levels of TB within the native population, with migrants unlikely to spread TB to the wider population in receiving countries (32). Rather, it appears the acquisition of TB among migrants is as a result of local transmission within migrant communities themselves or from reactivation of LTBI (33). While there is evidence of the importation of TB between countries of the EU or EEA (predominantly from the east to west), the overriding implication is that TB control efforts should focus largely on migrants from countries with endemic TB outside the European Region (Figs 2 and 3) (5,16). In addition, it is important to note that most cases of TB in most of the non-EU/EEA countries of the WHO European Region are in the native population and so data on migrant status may not be routinely recorded as migration may not be a key area of interest, with the exception of Switzerland and Israel (Fig. 3).

The epidemiology of TB in migrant populations in the WHO European Region is influenced by numerous factors including rates of LTBI. Activation of LTBI is thought to be the main driver of active TB (and MDR-TB) in low-incidence countries, rather than transmission in the host country (34). Migrant populations may be particularly vulnerable to reactivation through exposure to poor social conditions or malnutrition, and inability to control other comorbidities (30,31).

Although LTBI does not always progress to active TB, recent efforts have focused on the prospect of screening for and treating LTBI among migrants as a means of reducing the burden of active TB by preventing reactivation (3).

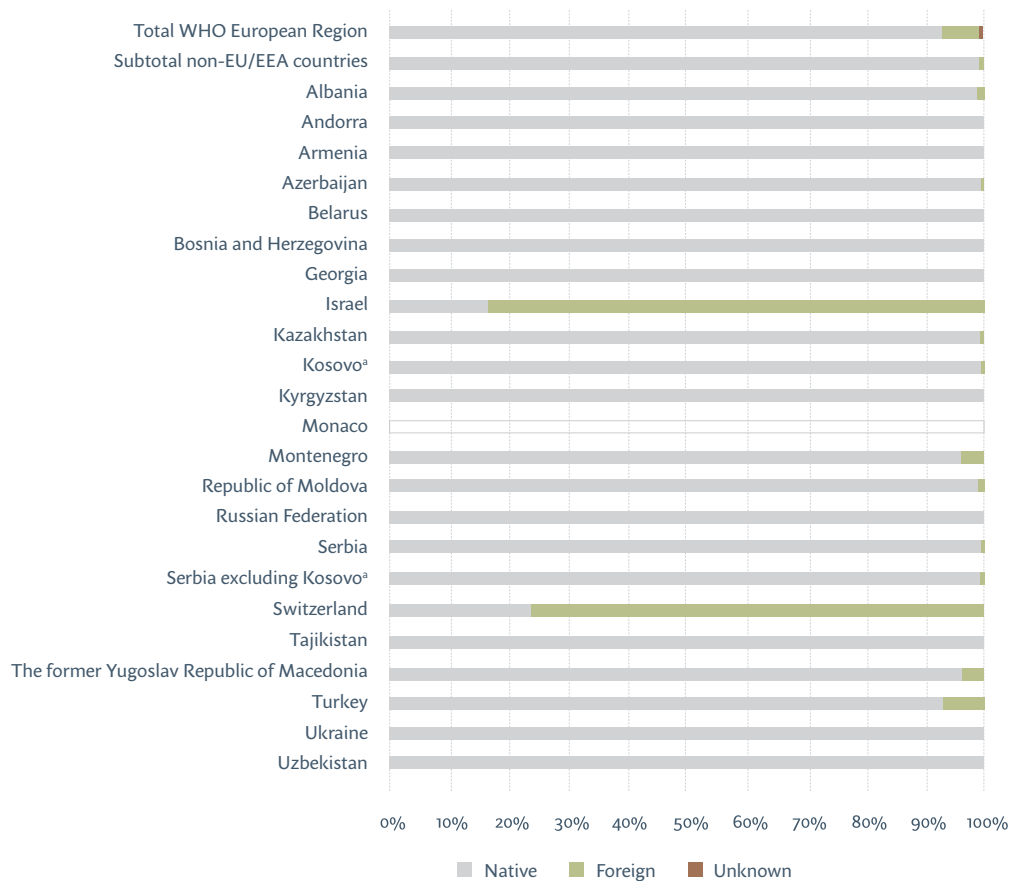
Fig. 2. Active TB cases among native and foreign-born individuals in EU/EEA countries, 2015



Source: European Centre for Disease Prevention and Control & WHO Regional Office for Europe, 2017 (5).



Fig. 3. Active TB cases among native and foreign-born individuals in non-EU/EEA countries in the WHO European Region, 2015



<sup>a</sup> In accordance with Security Council resolution 1244 (1999).

Source: European Centre for Disease Prevention and Control & WHO Regional Office for Europe, 2017 (5).

Migrants in Europe experience a disproportionate burden of MDR-TB compared with non-migrant populations, with many individuals entering the WHO European Region from countries with a high burden of MDR-TB (2). In addition, there is migration within the WHO European Region from areas with a high burden of MDR-TB (e.g. countries in eastern Europe and central Asia). It is thought that overall the proportion of MDR-TB attributable to foreign-born individuals within the EU/EEA could be around 73.4% (35), although there is significant heterogeneity in patterns of MDR-TB among migrants across the WHO European Region (Fig. 4). In countries such as France, Germany, Italy and the United Kingdom, over 80% of diagnosed MDR-TB occurs in foreign-born individuals, while this is less than 5% in countries such as Romania and Lithuania (36). Little is known about the burden of MDR-TB in specific migrant groups, including refugees.

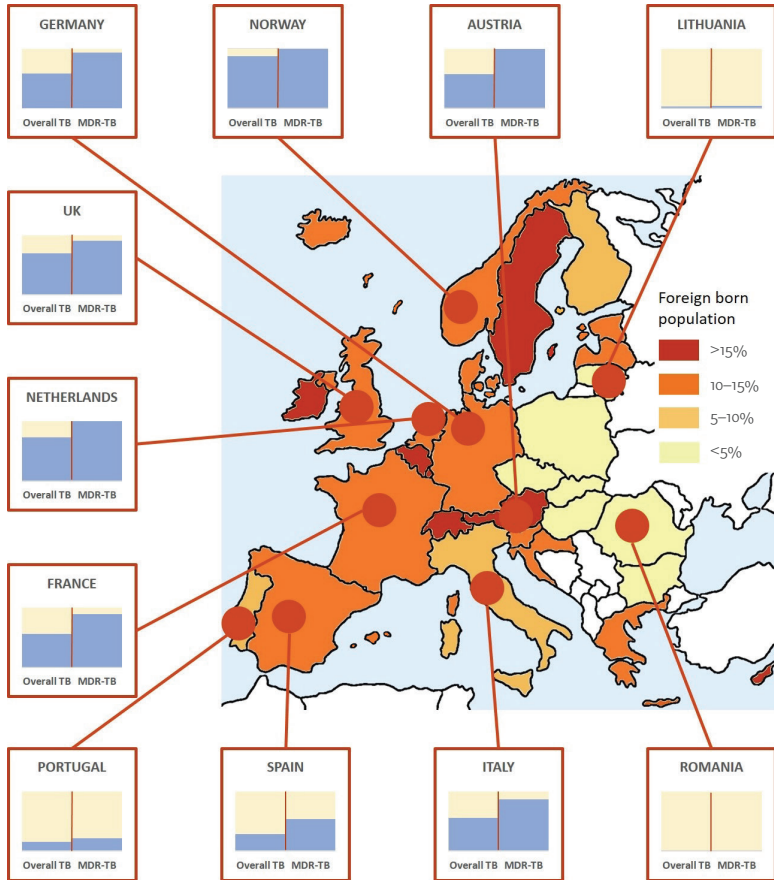
In addition, epidemiology is influenced by rates of TB/HIV coinfection, which is disproportionately experienced by migrant communities and has significant implications for treatment and individual health outcomes (3,4). European data show that the prevalence of HIV/TB coinfection differs drastically between countries and between migrant groups; however, migrants are more likely, overall, to suffer from coinfection than their non-migrant counterparts (37). The data also show that migrants with HIV/TB coinfection are at increased risk of unsuccessful treatment outcomes compared with non-migrants (37). The burden of HIV/TB coinfection in migrants also hints at another important aspect of migrant health: refugees and migrants are not just disproportionately affected by disease such as TB, which forms the focus of this report, but in fact experience a disproportionate burden of other infectious diseases, such as HIV, hepatitis B and C and malaria (38). Migrants may also be at an increased risk of poor mental health outcomes, such as depression and post-traumatic stress disorder, which can present challenges to the management of infectious diseases (39).

### 1.1.3 TB risk factors in refugee and migrant populations

While there is no systematic and causative link between being a migrant or refugee and having TB, there are a myriad of complex and interconnected factors that refugees and migrants can be exposed to that increase their risk of acquiring TB at all stages of the migratory process (40,41):

- residing pre-migration within a country with a high TB burden (41);
- residing pre-migration in an area experiencing conflict, and thus with interrupted health care systems;
- experiencing adverse condition during the migratory process;

Fig. 4. MDR-TB among foreign-born individuals in certain European countries



Source: Reprinted from Clinical Microbiology and Infection 23(3), Hargreaves S, Lönnroth K, Nellums LB, Olaru ID, Nathavitharana RR, Norredam M et al. Multidrug-resistant tuberculosis and migration to Europe, 141-6. Copyright 2017, with permission from Elsevier (36).

Notes: Blue bars represent the proportion of infections that are in foreign-born individuals.

- spending time in crowded transit camps;
- experiencing social deprivation in the destination country; and
- not having access to screening and health care, even in relatively affluent destination countries (depending on the legal system of the country and an individual's migration status), and thus not accessing early diagnosis and treatment.

Undocumented migrants may be particularly at risk for diseases such as TB because they may be more likely to experience poverty and/or destitution and they might face significant barriers to accessing treatment, even when they are theoretically entitled to free health care. Administrative decisions, monetary costs and health care practitioners' interpretation of law can prevent individuals from getting the care they need (22). What is also clear is that TB is primarily a disease of poverty, with social deprivation and substandard living conditions magnifying the risk of TB (41). Evidence from EU countries in 2017 revealed that 40.2% of non-EU-born individuals were at risk of poverty and social exclusion versus 21.7% of native-born individuals, which perhaps helps to shed some light on why migrants experience an unequal burden of TB in many countries in the WHO European Region (42). The challenge that TB in migrant and refugee populations represents needs to be tackled with increasing political and economic resources, and with more efficient allocation of resources. In addition, improvement in the accessibility of and entitlement to regional health systems and social care is required (19).

### 1.1.4 Barriers to care for refugees and migrants

Early diagnosis and treatment of LTBI and active TB in high-risk groups are essential components of TB control programmes. There is evidence that screening is acceptable to migrants, supporting the feasibility and benefit of implementing it more routinely in these communities (43–45). However, there are also significant barriers to detection and treatment that are experienced by migrant communities, and these must be addressed if programmes are to be successful. One qualitative study of migrants in the United Kingdom, exploring barriers to screening for infectious diseases, found the key factors that impacted on access to timely screening were disease-related stigma in migrant communities and services being perceived as non-migrant friendly (44). It is acknowledged that stigma reduction is an important component in TB elimination globally, yet few interventions have been rigorously evaluated in either migrant or non-migrant populations; support groups such as TB clubs, combined with a conscious focus on improving attitudes in the local community, could reduce stigma, but more research is required focusing



on specific experiences of migrant populations in the WHO European Region (46). Key barriers to TB screening identified in the literature are:

- migrant sensitivities:
  - fear of services
  - fear of disease-related stigma and discrimination, and
  - concerns about confidentiality;
- patient background and culture:
  - low perception of risk and
  - limited health literacy;
- other individual barriers:
  - financial barriers and
  - insufficient information/explanation of screening;
- poor service delivery by health care providers:
  - lack of professionalism among health care providers and
  - lack of training and support for health care providers;
- structural/service barriers:
  - poor management (referrals)
  - multiple steps for screening tests
  - lack of an appropriate confidential space
  - limited funding
  - poor communication between services and laboratories
  - lack of coordination across services, and
  - time constraints.

A number of facilitators to improving screening uptake in migrant communities have been identified:

- well-trained and dedicated screening staff:
  - culturally sensitive and appropriate services
  - trust and respect for the judgement of staff
  - interviews conducted by a health care worker in a migrant's native language (47), and
  - language support;
- migrant involvement:
  - patient involvement in service delivery and
  - increasing migrant community ownership and collaborations;

- outreach:
  - awareness-raising in migrant communities around health access and disease prior to screening and
  - testing in user-friendly outreach settings (e.g. general health check approach and promotion, anonymous testing approach);
- effective service provider management:
  - efficient testing, communication of results and referrals
  - high-quality care and support
  - clear patient pathways
  - quality assurance, and
  - strong coordination.

### 1.1.5 Overview of global and regional frameworks

The End TB strategy is ambitious in seeking to achieve a 90% reduction in TB incidence compared with 2015 (to <10 cases/100 000 population) globally by 2035, with the ultimate aim of TB elimination. This is to be achieved through the establishment and enactment of three central pillars of care, policy and research (48,49). The first pillar calls for integrated, patient-centred care and prevention, including early diagnosis of TB with universal drug-susceptibility testing, plus strategies such as collaborative TB/HIV activities and management of comorbidities. The second pillar advocates the need for bold policies and supportive systems, highlighting the need for political commitment backed by adequate resources to prevent and treat TB, while also demanding universal health coverage policies and regulatory frameworks to provide greater social protection, poverty alleviation and actions on the root causes of TB. The third pillar describes the necessity of intensified research and innovation in the face of the TB epidemic to discover and develop new tools and to optimize the implementation and impact of innovations (49). The United Nations Sustainable Development Goals call for an end to poverty in all its forms everywhere to ensure healthy lives, a commitment that aligns with strategies to reduce the burden of TB in the WHO European Region and globally (50).

The WHO European Region has already generated a roadmap to implement the Tuberculosis action plan for the WHO European Region 2016–2020 (51,52); this represents a regional adaptation of the End TB strategy, with wide-reaching policies that should aid migrant care, for example implementation of cross-border mechanisms to ensure a continuum of care for internal and external migrants, as well as for stateless individuals (51,52). This action plan, alongside the





End TB strategy and the Health 2020 policy framework (53), can only be effectively implemented to address inequity if there is improved coordination of TB services in the WHO European Region, with consensus on a minimum package for cross-border TB control and care (54,55). The End TB strategy is reflected in a framework for low-incidence countries, which includes much of the western WHO European Region. This specifically calls for nations to address the needs of migrants and establish effective cross-border initiatives, ensuring elements such as universal and culturally sensitive access to health care, alongside social support to address the social determinants of TB (56). More recent guidance from the European Centre for Disease Prevention and Control (ECDC) specifically highlights the need for greater health communication and education among vulnerable groups such as migrants (57), with the organization currently in the process of defining and publishing guidance for the management and control of LTBI, active TB and other key infections in newly arrived migrants to the EU/EEA (58).

Various elements of the End TB strategy have been adopted by most WHO European Region Member States, such as the development of migrant-friendly hospitals in Switzerland. This initiative used information campaigns targeted at health institutions and their staff to increase awareness and use of migrant-friendly resources to improve the quality of care provided to migrant patients (59).

In 2011, the European Parliament approved a resolution on reducing health inequalities in the EU and called on Member States to implement universal, equitable and affordable access to health care for all, particularly undocumented migrants (60). Many non-EU countries in the WHO European Region have vague or non-existent legal frameworks for cross-border TB control, although all have made a commitment to uphold the right to health for all and to World Health Assembly resolution 61.17 on health of migrants (61,62). The Council of Europe (including 47 Member States of the WHO European Region) in 2017 adopted recommendations on action required at a national level on migration and access to health care (62).

Outside of Europe, key frameworks have been developed, providing guidance on the prevention, detection and treatment of TB in migrant populations, which are directly relevant to the migrant population in many WHO European Region countries. These have included recommendations for post-arrival assessment of forced migrant populations (63), clinical guidelines for refugees and migrants (including for infectious diseases) (64) and guidelines on infectious disease assessment for migrants (65).

### 1.1.6 The objectives of this report

The objective of this report is to identify and synthesize evidence on effective and efficient packages of services for prevention, diagnosis, treatment and care for TB in the WHO European Region. The main focus is on active TB but consideration is also given to LTBI, drug-resistant TB and TB/HIV in migrant populations.

## 1.2 Methodology

A review of peer-reviewed and grey literature was carried between July and October 2017 to identify documents containing information relating to the prevention, diagnosis and detection, or treatment of migrants with all forms of TB and those containing information on cross-border collaborations, country capacity, operational challenges, effectiveness and efficacy. Publications in either English or Russian reporting any data, qualitative or quantitative, relevant to the synthesis question, and which were from, or related to, the 53 WHO European Region Member States were included with no date restrictions, although there was a focus on documents published from 2010 onwards.

The search of the databases yielded 19 290 citations, with 2700 additional records identified through hand searching of other sources, giving a total of 21990 documents. After removal of duplicates, 8866 individual records were screened by title and abstract and any that did not report on the areas of this review were excluded. The full text was screened for 595 documents and 140 (2,7–20,22–31,34–51,53,56–153) were included that spanned the whole WHO European Region. These were used in a narrative synthesis to summarize the evidence base for an effective and efficient package of care to manage TB in refugee and migrant populations across the Region. Annex 1 contains full details of the methodology.



## 2. RESULTS

### 2.1 Prevention

There were several approaches to TB prevention reported across the reviewed literature:

- infection control strategies
- vaccination programmes
- addressing sociocultural and socioeconomic factors, including poverty
- increasing awareness and outreach.

Infection control strategies identified included administrative and environmental measures in diagnostic and treatment centres and during transfer of patients to another country. Poorly ventilated or overcrowded settings are known risk factors for TB transmission, and refugees and migrants can be exposed to these at several stages of their migration. Identification and treatment of TB (and LTBI) were considered a vital element in preventing future cases of TB through reactivation of LTBI or transmission of active TB, while adherence to TB treatment was recognized as key in the prevention of MDR-TB at an individual level.

Bacillus Calmette–Guérin (BCG) vaccination programmes for children and adolescents form part of vaccination policies in a large number of WHO European Region countries, with other countries having had such policies in place in the past (66). Use of BCG vaccination decreased in some countries because of its limited effectiveness in preventing TB (67). BCG vaccination is recommended in newly arrived migrant children and adolescents (aged <18 years) because of the protection it offers against severe forms of paediatric extrapulmonary TB, such as TB meningitis (68,69). While the protection conferred by childhood BCG vaccine decreases over time, evidence suggests it can confer some protection well into an individual's early adulthood, with a study in the United Kingdom showing 59% protection up to 15 years after vaccination (70). Current research suggests that mucosal vaccination could increase efficiency and so targeting BCG to migrants could continue to be an effective preventive measure (71).

Poor socioeconomic status and poor living conditions are implicated in the increasing incidence of TB (37). Although strategies addressing these factors could represent effective approaches to reducing the burden of TB currently seen in refugees and migrants, and are consistently highlighted in the reviewed literature, political will and cross-sector actions are essential to address these issues (33,55). Interventions could

be readily adapted to incorporate TB/HIV coinfection prevention, with integration of TB and HIV services seen as essential to tackle this dangerous subepidemic (82).

Poverty is known to create barriers to care, such as fear of missing work, transport difficulties and a lack of health insurance or ability to pay for care (81), and has a clear link to increased incidence of TB (76). Central and eastern European countries exhibited an association between lost productivity and an increase in TB cases during the changes from the Soviet Union in the 1990s (77). There is also evidence that increased social protection is associated with lower rates of TB (78). Countries such as Denmark, France and Germany, which have some of the highest levels of social spending in the WHO European Region and lowest levels of poverty, experience the lowest TB prevalence, incidence and mortality among their populations, while countries such as the Russian Federation, with lower social spending and higher rates of poverty, experience a greater TB prevalence, incidence and mortality (78). Increased social protection spending or easing of the monetary burden migrants experience could, therefore, alleviate known risk factors relating to economic circumstances such as adverse living conditions and nutritional status (33,79). There is also evidence that conditional cash transfer policies, which incentivize health education and disease prevention, may be of help for migrants experiencing social deprivation in the initial years after their migration, with a positive impact on food security and utilization of health services (80,81).

In addition to interventions targeting socioeconomic barriers to TB care, outreach that provides information about TB and health promotion campaigns (e.g. education, health literacy interventions) may help to address key barriers to adequate care such as limited health literacy or knowledge of TB, lack of knowledge of health systems or available health care, and stigma surrounding TB in migrant communities (72,73).

Guidelines from the United Kingdom's National Institute of Health and Care Excellence specifically advocate for multidisciplinary teams to raise awareness of TB in underserved populations, such as refugees and migrants, through community engagement and engagement with voluntary organizations and use of culturally appropriate and sensitive materials that can dispel myths as well as address the concerns of migrant groups (74). The guidance further extends to ensuring that health practitioners are well informed so that migrants can receive the best available care and consideration (74). In some WHO European Region countries, for example Tajikistan, provision of information has been coupled with interventions aiming to identify and lessen the stigma surrounding TB, a key barrier in tackling TB in migrant communities, along with providing support and adequate care (75).

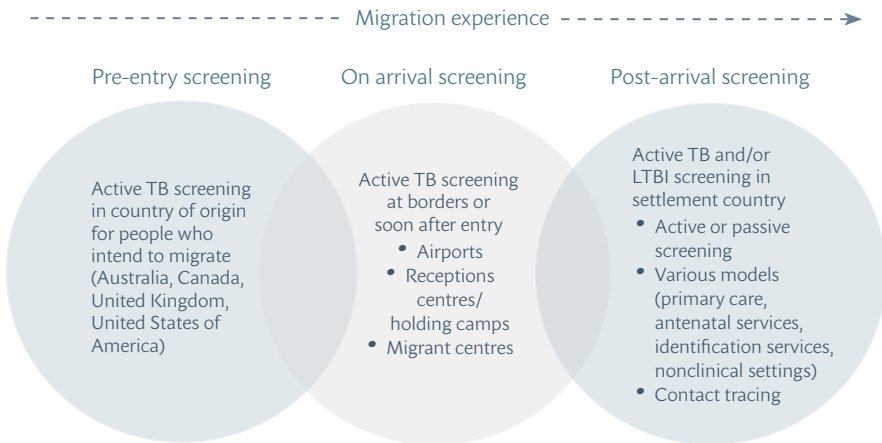
## 2.2 Diagnosis and detection

### 2.2.1 Screening refugees and migrants

There are various diagnostic tests used in screening for TB infection and disease, which may or may not be used in conjunction with clinician assessments (3,83). An effective package of care for screening refugees and migrants must use the best available diagnostic tests, along with appropriately and specifically targeting of at-risk groups.

Screening can occur at different points in the migration trajectory (Fig. 5); for example, post-entry screening can take place on arrival or after a defined amount of time spent in the destination country. However, there is limited evidence regarding when, where or how to screen diverse migrant populations entering the European Region, particularly as policies vary in terms of how screening (and subsequently treatment) is paid for, who is entitled to such care and whether screening is compulsory or voluntary (84,85). Some countries screen for LTBI as well as active TB; for example, England is pioneering a strategy to implement screening and treatment for LTBI in newly arrived migrant from high-incidence TB countries, as part of its national TB plan (Case study 1) (86,87).

Fig. 5. Multiple approaches to migrant screening



Source: Modified from Pareek et al., 2016 (3).

### Case study 1. Testing and treatment for LTBI in migrants

Over 70% of TB cases in England occur in migrant (foreign-born) individuals. Evidence suggests that the majority results from reactivation of LTBI. The United Kingdom's National Institute of Health and Care Excellence supports LTBI screening for those newly entering the country (74). In line with this, the Collaborative TB Strategy for England 2015–2020 recommends LTBI testing and treatment for recently arrive migrants in England aged 16–35 years from countries with an incidence of TB of 150 cases/100 000 population or higher (87). This is being implemented nationally in order to facilitate the detection and treatment of LTBI in recent migrants, and to ultimately reduce the burden of TB in England.

There is an increasing focus on pre-entry screening (Case study 2), particularly among low-incidence countries (3,33), which is deemed cost-effective for the host country; however, this only targets a specific subset of migrants (e.g. those with planned migration routes to receiving countries) and as a result many migrants would not be covered by these programmes (88–90). There is also a large degree of heterogeneity in the implementation of screening procedures among WHO European Region Member States (33,85). A recent review of TB in low-incidence settings concluded that the most cost-effective solution is likely to involve targeted pre-arrival screening for active TB and post-arrival screening for LTBI in migrants from settings of intermediate to high TB burden (3). However, the strength of evidence for this has been questioned as this approach is likely to be cost-effective only for the host country because the costs of screening and treatment are borne by the migrant and country of origin (91,154).

### Case study 2. Pre-entry TB screening for prospective migrants to the United Kingdom

In contrast to an earlier approach of screening migrants at the port of entry, the United Kingdom is employing a system of screening migrants prior to granting an entry visa (92); this approach is supported by evidence highlighting the role of pre-entry screening as part of a broader package of care that ensures early diagnosis and subsequent management of TB prior to migration (84).

The policy is applied to all individuals wishing to apply for a visa to the United Kingdom of greater than six months' duration and who are currently resident in a country defined by the United Kingdom as having a high incidence of TB.



### Case study 2. (contd)

Screening occurs at approved TB screening centres in the countries of origin. Individuals testing positive for TB must successfully complete a treatment regimen in their country of origin and provide a certificate of clearance validating that they are free of active pulmonary TB.

Recent estimates suggest that this type of approach could prevent 14 771 TB cases in the United Kingdom between 2016 and 2031 (90). However, the approach also raises questions about best practice to support efforts towards the elimination of TB as, although it may help to reduce the burden of TB in the receiving country, it does not necessarily contribute towards capacity-building or the reduction of LTBI or TB in the countries of origin, nor does it target high-risk migrant groups such as asylum seekers.

A recent survey of current practices in TB care among refugees in Europe found that policies for screening for active TB among migrants were heterogeneous across the 36 WHO European Region Member States that responded (54): 31 routinely screened refugees for active TB, with three reporting nonsystematic screening for symptomatic individuals; two reported no screening; 25 reported using chest X-ray radiography (CXR; 25 systematically and 21 using initial symptom-based questionnaires (systematically collected in 20 countries)); and 18 reported using bacteriological testing (with nine using sputum smear/culture collection for symptomatic individuals only). Overall, 27 of the 36 responding nations reported TB screening was carried out based on national and international guidelines, with these services being offered to both refugees and native-born individuals (54).

### 2.2.2 Diagnostic approaches for active TB

While the most appropriate diagnostic approaches for detecting TB should be informed by the specific country context, there are key examples where guidelines have been developed at a national and global level that can be used to guide the development of similar country-level diagnostic protocols in Member States. The combination of approaches to be used should be informed by the demographics of the migrant population, TB epidemiology in the Member State and available resources (63–65,93). However, all migrants should have universal access to the best methods for screening, diagnosis and drug-susceptibility testing.

A Cochrane review concluded that symptom-based screening for active TB can be highly variable in its ability to accurately detect disease, with difficulty in assessing

this approach in different epidemiological settings (83). However, combining a symptom-based approach (specifically, the presence of a prolonged cough) with CXR can result in sensitivity up to 97.8%. CXR is highlighted as an essential component in triaging and diagnosing TB by WHO and is pivotal in shortening delays to treatment in individuals (compared with an interview/symptom-based approach alone) (94,95), although it is limited in its reliability for diagnosis. Indeed, the combination of a symptom-based approach and CXR provides one of the lowest cost options to diagnose active TB, although it is important to note that a high proportion of the TB burden in migrants in Europe is extrapulmonary TB. The utilization of CXR as a large-scale screening tool in migrants also has a proven track record, with the International Organization for Migration (IOM) conducting health assessments with CXR to detect TB in 1.2 million refugees and migrants between 2011 and 2015, with 4341 confirmed cases from 63 884 individuals who had initial results indicative of TB pathology (94).

Another diagnostic test being utilized to identify TB in patients with a positive chest radiograph or symptoms of TB is a nucleic acid amplification test, Xpert MTB/RIF, which has consistently been shown to be a sensitive and time-saving diagnostic test, including among migrants in European Member States, for example in Italy and Kyrgyzstan (96,97). There is also evidence that combining it with CXR and symptom assessment (particularly, a prolonged cough) can increase the yield of true-positive results. The disadvantage is that this increases costs, which could present a barrier in resource-limited contexts (94).

### 2.2.3 Diagnostic approaches for LTBI

There is no gold standard test for LTBI, with traditional screening methods based on the tuberculin skin test (TST) and CXR (to exclude active TB) (7). Diagnostic methods vary across the Region, with eight countries using TST as the only test performed and a further 11 utilizing TST and the interferon-gamma release assay (IGRA) in combination (54). The TST can show cross-reactivity in individuals who have been vaccinated with BCG or have other nontuberculous mycobacterial infections (100). While IGRA diagnostics may represent a new standard for testing for LTBI (101), it is more expensive and still has some limitations. There is substantial variation in screening procedures among WHO European Region Member States (54), with IGRA and TST being implemented differentially depending on the setting or country-specific organization of health care. It is also important to note that tests such as the TST or IGRA are not able to assess the risk of progression to active TB.

The available evidence highlights an increasing emphasis on screening for LTBI across Europe, with a particular focus on at-risk communities, including forced





migrants and migrants from countries of moderate to high TB incidence (56,98). Multiple international guidelines recommend consideration of LTBI screening, although there is limited evidence regarding the effectiveness or cost-effectiveness of this approach (99).

#### 2.2.4 Targeting high-risk refugees and migrants

Regardless of how a country is implementing screening for LTBI or active TB, there is growing evidence that this must take a targeted and considered approach to be effective or cost-effective, and that the impact of screening programmes can vary considerably based on the approaches used and who is screened. One study examining screening at or shortly after arrival found that asylum seekers had a greater incidence of TB compared with other migrants (350 cases/100 000 population versus 170 cases/100 000 in other migrants) (102). A similar study reported 192, 270 and 284 cases/100 000 population in refugees, asylum seekers and regular migrants, respectively (103). The heterogeneity in the burden of TB across groups migrating into Europe indicates the need for screening to be targeted based on migrant type/reason for migration, TB incidence in countries of origin and factors such as age or migration trajectory. A 2016 study with a cohort of more than 500 000 migrants in a pre-entry screening programme utilizing sputum smear and culture testing plus CXR showed that the yield of screening increased with an increasing incidence of TB in the country of origin (104). Although there can be a large degree of heterogeneity in the yield of diagnostic techniques, the number of individuals that had to be screened to detect one case of active TB consistently fell when using CXR and with an increasing incidence of TB in the country of origin, suggesting that screening should be targeted at high-risk groups (e.g. from high-incidence countries) to increase the effectiveness and cost-effectiveness (100,105,154).

The evidence for screening for LTBI among refugees and migrants is similar, with yield and cost-effectiveness increasing with increasing incidence in the country of origin (98). However, LTBI screening gives no indication as to the risk of reactivation, which is thought to account for the majority of TB in migrants (154), and which pre-entry and on-arrival screening for active TB do not necessarily target. Evidence suggests that reactivation may peak around four years after migration, suggesting that follow-up screening for active TB among high-risk groups such as migrants could be beneficial, in addition to providing access to meaningful primary care services on or soon after arrival (104). A recent review of TB in low-incidence settings concluded that the most cost-effective solution is likely to involve targeted pre-arrival screening of migrants for active TB and post-arrival screening for LTBI in migrants from settings of intermediate-high TB burden (3); however,

the evidence base on the cost-effectiveness of different screening approaches is limited. Case study 3 outlines a national TB control programme implemented in the light of increased migration rates from countries of high TB incidence and incorporating the five elements of the DOTS (directly observed treatment, short-course) strategy recommended by WHO (106).

### Case study 3. The new National Tuberculosis Control Programme in Israel, a country of high immigration

In light of increasing rates of migration, in 1997 Israel implemented a new National Tuberculosis Programme (106) incorporating the five elements of the DOTS strategy in addition to four unique features:

- DOTS is universally applied with no exceptions and for the full duration of treatment;
- DOTS is administered using a community-based strategy;
- unique screening procedures are routinely performed, plus case investigation and treatment of LTBI, with a focus on the new immigrant population; and
- original research was conducted into the cultural–anthropological needs of immigrants from Ethiopia and health professionals working with these communities and applied to the National Tuberculosis Programme.

The research results were applied to the National Tuberculosis Programme and Ethiopian health workers were trained to assist the district health offices and TB clinics in bridging the culture gap with migrants from these communities. This approach may benefit other low-prevalence countries where TB is influenced by migration.

## 2.3 Treatment and care

Treatment completion is a critical component of efforts to control the global TB epidemic, with well-defined guidelines from WHO on the best treatment approaches (107). The dominant approach since the mid-1990s is DOTS, which still forms the basic standard of care in 2018 (49,107). Management of drug-resistant TB will include additional components. The comprehensive, patient-centred approaches of the End TB strategy, and elements such as psychosocial and material support reflected in TB treatment guidelines from WHO, should be incorporated into TB services for migrant populations.

However, the evidence base required to inform guidance and approaches for successful treatment outcomes is often inadequate. A 2016 survey of 36 WHO



European Region Member States revealed that 31 (86%) reported screening for active TB and 19 (52.7%) for LTBI, with nine reporting no LTBI screening policies (54). Only 19 (53%) countries collected data on treatment success rates for active TB, with 10 reporting they had no procedures; 11 (30%) collected data on LTBI treatment outcomes, with completion rate data available from eight (22%); 22 (61%) collected information on active TB; and 20 (56%) reported having no procedures (54). The limited evidence that does exist regarding completion of treatment for LTBI suggests rates may range anywhere from 22% to 60% (112), with significant loss to follow-up across the LTBI care cascade; this loss is unlikely to be noticed with suboptimal monitoring procedures (113). However, there are examples of interventions in which a high level of treatment completion has been achieved; for example, treatment completion for LTBI was 80% in a well-monitored population provided with stable housing conditions in a Swiss canton (114).

Although there are standardized recommendations for treatment regimens, variation in access to treatment and treatment adherence impact on the effectiveness of care, and there is evidence in migrant populations of loss to follow-up at every stage of the screening and treatment pathway, plus challenges in linking screening with secondary care (43,108).

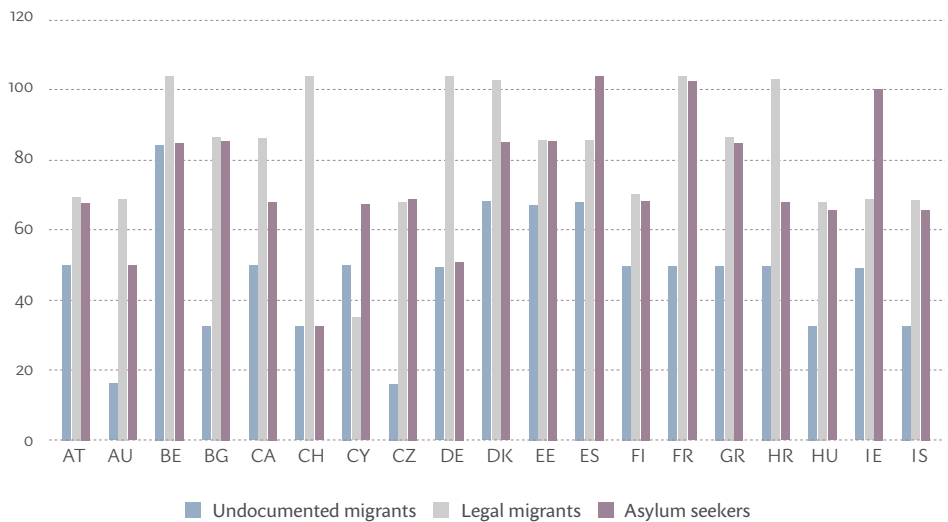
There are also issues with the structure of services, with a lack of consistency among health professionals and legislative bodies with regard to how migrant-centred health care is delivered or prioritized in practice (109). In addition to contributing to poorer and more costly individual health outcomes and the risk of MDR-TB, barriers to accessing and adhering to treatment may be particularly significant for individuals with TB/HIV coinfection or MDR-TB (91,110). For example, in 29 EU/EEA countries surveyed, TB treatment completion among TB/HIV-coinfected individuals was reported to be just 57.9%, compared with 83.5% for those without coinfection (111). Consequently, specific guidance may be needed to facilitate screening and treatment completion in migrant populations (57,107).

Providing affordable and equitable access to health care among migrants affected by TB is also an essential component in ensuring that treatment is completed (55,56). Despite this, some countries within the Region still fail to provide access to health care for migrants or have failed to remove other obstacles to uptake of such health care (115–118). While some countries provide free TB diagnosis and treatment to migrants, others either have no legal framework to ensure access to health care services free of charge or do not apply the framework in practice (55). Fig. 6 shows scores for entitlement to health care for receiving countries by migrant type, highlighting that across Europe undocumented migrants consistently

face limited entitlements compared with legal migrants and asylum seekers. Undocumented migration status, coupled with a fear of deportation, is consistently associated with non-adherence and non-completion of TB treatment among migrant populations (110,119). The removal of barriers such as legal consequences (e.g. deportation) is a pertinent step for ensuring that migrants engage more fully with treatment and would also allow researchers and health care professionals to engage with those at risk in order to assess what treatments and interventions will be optimal in eliminating TB.

Even for migrants who do not experience political or legal barriers, substantial social and economic obstacles could be identified, including language issues, limited health literacy or stigma, as well as the direct and indirect costs of missing work or having to pay for care (73,81,110,120). Evidence indicated that strategies to reduce the burden of poverty (e.g. social spending) may also contribute to efforts

Fig. 6. Scores for entitlement to health care for receiving countries by migrant type, 2014



Notes: Legal migrants are migrants who have a documented/legal status to reside in the host country (i.e. have been granted political asylum or a visa); two-letter country codes are used.

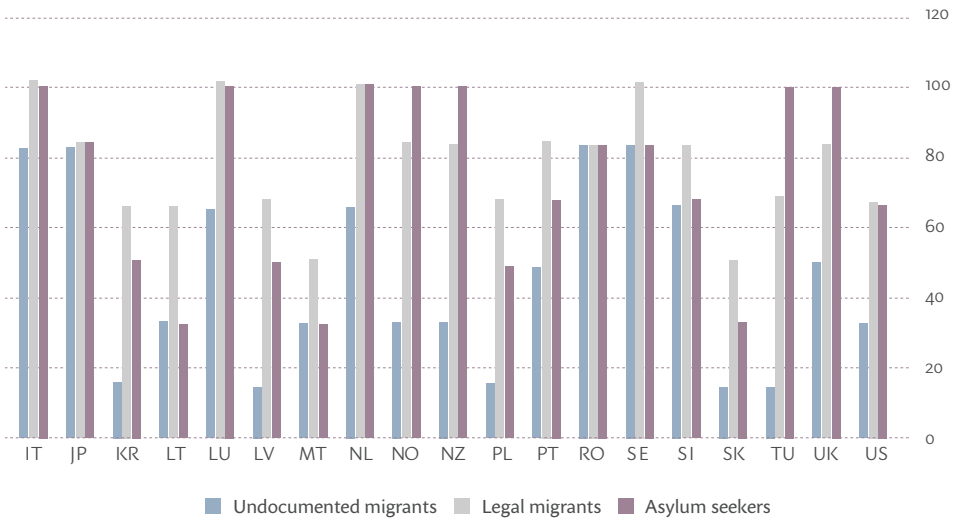
Source: Migrant Integration Policy Index, 2015 (155).



to reduce the burden of TB, including by supporting the uptake and completion of treatment (76). A further barrier for treatment of LTBI may be reluctance to engage in treatment for a condition that is currently inert and asymptomatic, especially given that the treatment can be lengthy and is associated with side-effects (121). Indeed, the absence of any overt disease means that LTBI may not be perceived by some individuals as an illness warranting treatment, particularly in light of other significant health, social, economic or legal needs (119).

In some cases, effective interventions are relatively simple and cost-effective to implement. A study from Uzbekistan on MDR-TB treatment in migrants showed that high-quality information and patient involvement in treatment decisions resulted in improved treatment outcomes (122). The inclusion of nonclinical professionals such as social care workers in outreach work is likely to be a highly acceptable intervention for migrants and can aid in coordinating treatment services

Fig. 6. (contd)



for migrants and potentially provide a route to improving migrant knowledge of TB (57). Mobile medical outreach teams have operated in Paris since 2000: loss to follow-up rates for TB treatment among homeless and undocumented migrants have fallen from over 50% in 2000 to less than 10% in 2016 (57); similar successes have been reported in other countries. Educational aids providing medical information about TB may also support patient adherence to treatment. ExplainTB targets smartphone users and utilizes 26 languages to provide video and audio information for children and individuals with limited literacy (123).

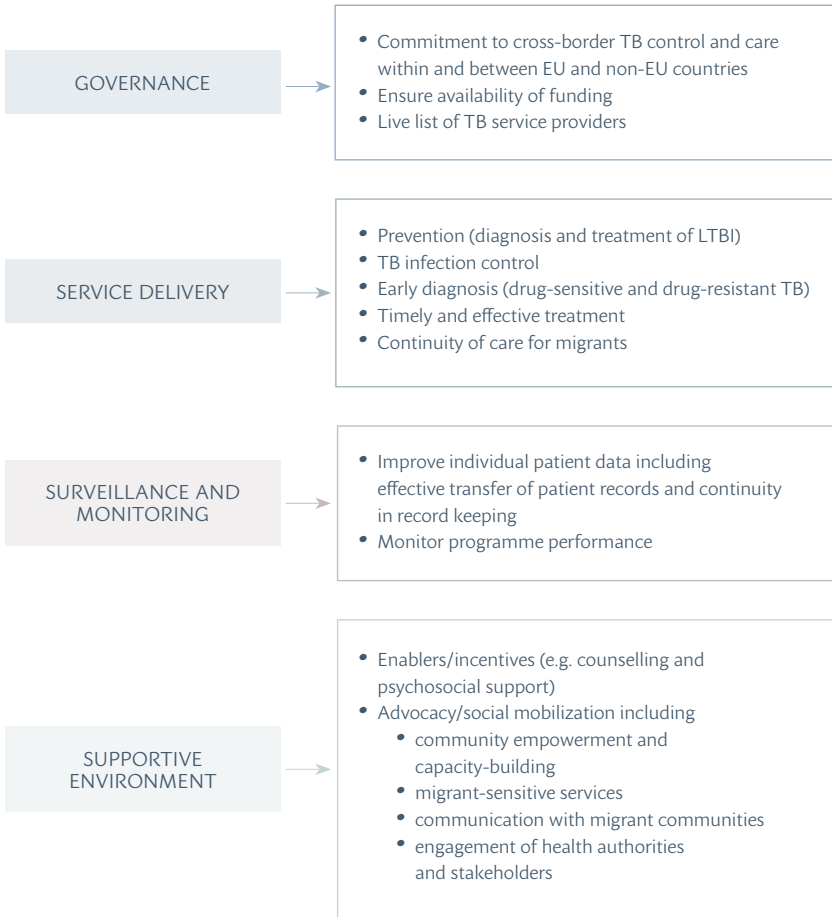
## 2.4 Cross-border collaboration: what works?

Given the dynamic epidemiology of TB along the migration trajectory, cross-border collaboration is essential for the successful prevention, identification and treatment of TB in destination countries, as well for reducing the risk of infection in countries of origin or transit, where the incidence of TB may be higher and infection prevention and control resources more limited (33,124). The global TB crisis cannot be tackled by countries acting alone (125), particularly when migrants with TB or LTBI and are likely to continue to cross borders on their journey (126). A minimum package for cross-border TB control and care in the WHO European Region has already been developed (Fig. 7) in which all people crossing a border would have access to preventive measures and treatment free of charge, including for LTBI, in transit, host and return countries. The guidelines champion legal frameworks and political engagement, effective and timely diagnosis and treatment, and effective continuity of care (55). Similar frameworks and targets have also been adopted as recently as 2016 in the form of the strategy and action plan for refugee and migrant health in the WHO European Region (21), and there have been calls for a more human rights-based approach to addressing TB and migration (127). This strategy further reiterates the need for establishing frameworks for intercountry collaboration and legal rights for migrant health care, as well as for expanding ethical screening and assessment and acting upon social determinants of poor health.

Case study 4 highlights lessons learned from a cross-border investigation of a cluster of patients with MDR-TB (128,129); Case study 5 highlights a cross-border collaboration to improve screening and treatment for TB among labour migrants in central Asia (130).



Fig. 7. The minimum package of cross-border care for TB in migrants



Source: Dara et al., 2012 (55).

#### Case study 4. A joint cross-border investigation of a cluster of MDR-TB in Austria, Germany and Romania

Recent research has shown that cross-border collaboration could be an effective tool in mapping TB outbreaks and may be particularly relevant in tracking MDR-TB outbreaks and their associated strains. In March 2014, the Austrian National Reference Laboratory detected a molecular MDR-TB cluster of five isolates, prompting an unprecedented investigation as to whether transmission of these isolates had occurred within Austria or whether it was international. Links to German and Romanian national TB contact points for WHO and ECDC allowed the international epidemiological outbreak investigation to take place.

Through a collaborative effort employing self-designed questionnaires, along with drug-susceptibility testing and whole genome sequencing, the cross-border team was able to ascertain that transmission had occurred among several patients in the same city of provenance in Romania, prior to its importation and domestic transmission in Austria, showing the link between TB and migration in these cases (128).


The study overall highlighted that collaboration is capable of providing a much better insight into transmission of TB among migrants within the WHO European Region, with identification of a single MDR-TB cluster found to be present in at least four countries and among just 10 individuals. The study may provide a framework for countries to share and compare information in the future, which could aid in enhanced detection of TB and MDR-TB strains and perhaps allow the mapping of their transnational migratory routes. While the scalability of such methods may be in question, they could be essential in tackling the MDR-TB subepidemic in the WHO European Region (19).

#### Case study 5. Reducing TB among central Asian labour migrants

The Central Tuberculosis Research Institute of the Russian Academy of Medical Science reported in 2017 that the incidence of TB and MDR-TB was 2.5 times higher among labour migrants than in the general population (130); this was attributed to overcrowded, poorly ventilated living conditions and lack of access to TB diagnostic and treatment services.

To address these risks, Project HOPE implemented a cross-border TB control programme among labour migrants, in partnership with WHO, IOM,





### Case study 5. (contd)

the joint United Nations Programme on HIV/AIDS, the International Federation of Red Cross and Red Crescent Societies and six local nongovernmental organizations. The programme, supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria, focused on improving TB case notification and initiation of treatment among labour migrants regardless of their documentation status in seven sites in Kazakhstan with the highest concentration of labour migrants. In addition to TB education and diagnostic and treatment services, the programme included an advocacy component to improve policies on TB control and care.

Since July 2015, over 80 000 migrants have received TB education and 23 000 have been screened for TB, 944 of whom were diagnosed with TB and started treatment. In addition, a working group on migration and TB was established in Kazakhstan and, in coordination with the government, the programme held two annual high-level meetings to establish a new regional working group, which has drafted agreements between Kazakhstan and both Kyrgyzstan and Tajikistan on cross-border TB control among labour migrants. These achievements serve as a model for international cross-border collaboration to tackle the burden of TB.

## 2.5 Operational issues

### 2.5.1 Challenges to implementation of interventions

The mobility of migrants and the fact that the country in which they are diagnosed may not be their final destination can make linking diagnosis and further care difficult. Administrative factors (e.g. poor linking of patient records across countries) (131) and legal concerns (e.g. for undocumented migrants) (132) can further increase the risk of loss to follow-up. These operational challenges highlight the need for an interconnected multinational approach to caring for refugees and migrants with TB (133,134). Case study 6 outlines a research consortium looking at early detection methods and integrated management of TB in Europe (135).

A further issue is that local health systems can become overwhelmed in many European countries dealing with a significant influx of refugees and migrants. Countries on the borders of the Region, such as Greece, Italy and Turkey, that act as major thoroughfares for migrant traffic have seen surge-capacity issues (136).

Even countries in the interior of the Region, such as Austria, Belgium, the Netherlands and Norway, have seen challenges in adequately addressing the health needs of arriving refugees and migrants or in complying with national and international guidance (54).

#### Case study 6. E-Detect TB: a research consortium for the early detection and integrated management of TB in Europe

The E-Detect consortium aims to contribute to the ultimate elimination of TB within the EU, bringing together six partnered Member States (Bulgaria, Italy, Netherlands, Romania, Sweden and the United Kingdom) to jointly evaluate evidence-based interventions and develop a framework in collaboration with ECDC to support best practice approaches (135). The consortium is focused on utilizing evidence-based interventions to ensure early detection and diagnosis and on improving the integration of care and support in both low- and high-incidence countries. Part of the group's mission statement is to prioritize migrants along with other vulnerable groups, including those with MDR-TB, and a multipronged approach is used. While largely geared towards diagnosis and detection, the plan alludes to the importance of linking patients into care once they have been diagnosed; it also attempts to encourage intercountry collaborations and data gathering to support the implementation of future policies and frameworks.

There are four main approaches encapsulated within the E-Detect plan:

- outreach for early diagnosis and treatment utilizing mobile units equipped with X-ray units, computer-aided detection software and modern molecular testing;
- screening new and settled asylum seekers as well as refugees for both active TB and LTBI, to support optimal care and generate evidence for future regional policies;
- establishment of a database for LTBI and active TB screening of migrants in Europe;
- utilization of data from participating Member States to create a unified and standardized system for reporting, thus enabling epidemiological analysis for tailoring future interventions; and
- analysis of best practice from countries where national strategic plans have been most effective in order to create tool- and country-specific plans, which can act as an aid in developing frameworks within other countries in the Region.



## 2.5.2 Country capacity

A country's capacity to deal with TB is influenced by the resources of its health system and also by the political will and motivation to provide adequate care, particularly for migrant populations. There are examples of political engagement with the problem of TB control. One example is the Tuberculosis Europe Coalition, an informal network of 340 members, including 17 EU Member States and 30 WHO European Region Member States (138), which has the capacity for rapid communication in both English and Russian, ensuring that the Russian-speaking Member States can be involved.

Sufficient funding is essential for any programmes for TB prevention and control, and reports from 2016 have indicated a significant global shortfall in the level of funding needed for elimination of TB (139,140). It has been estimated that US\$ 9.84 billion was required in 2011–2015 to combat global TB but only a third of that was actually spent, with funding for research and development declining and funding levels in 2015 approaching those in 2011 (139). More striking and concerning than this global shortfall are the trends observed among WHO European Region Member States, where funding has also declined in recent years. The higher-income countries that might be considered best placed to lead the efforts for TB control, including Denmark, France, Germany, the Netherlands, Norway, Sweden and the United Kingdom, all record declines in funding (139). Case study 7 describes the Immigration and Refugee Health Working Group, which facilitates the exchange of information and ideas on how best to optimize international practices for the screening and treatment of prospective migrants (143).

### Case study 7. Capacity strengthening through pre-migration TB screening programmes

The Immigration and Refugee Health Working Group facilitates the exchange of information and ideas on how best to optimize international practices for the screening and treatment of prospective migrants (143). The large-scale pre-entry screening programmes that may prove effective in tackling TB require building additional clinics, radiology facilities and laboratories; this has to be accomplished through developing existing country infrastructure, delivering new infrastructure or building in-country partnerships and strengthening domestic national TB programmes.

Under the stewardship of the Working Group, new culture laboratories have been established in many countries with a high incidence of TB, such as

### Case study 7. (contd)

China and India, allowing the implementation of first- and second-line drug-sensitivity testing, as well as facilitating access to molecular testing equipment. The participating countries also help to train panel physicians in origin countries, who are then responsible for examining and aiding in the screening of prospective migrants, and provide educational aids for staff and patients. The capacity-building endeavours of the participating countries ensures that the public health standards of recipient countries are more adequately adhered to, while countries contributing to international migration are provided with the facilities to improve control of domestic TB, as well as TB in prospective migrants. Researchers have suggested that these international arrangements could be replicated between high-income, low-burden WHO European Region countries and the less wealthy, high-priority countries in the east of the Region, allowing a greater synergy and efficiency in tackling TB across the Region.

## 2.5.3 Effectiveness and efficiency of TB programmes

Determining what is considered to be most effective for an intervention/programme has long been identified as pivotal for intercountry/interregional comparisons and for harmonizing policies and practices (55,146,147). Yet there is no clear method of assessing the effectiveness and efficiency of migrant TB programmes within the literature, with some publications assessing the cost-effectiveness of care/screening, but perhaps not programme effectiveness against TB elimination goals nor in terms of whether treatment is timely, accessible, has adequate capacity and is deemed appropriate and acceptable by those in receipt of such treatment (58,156). This reflects the difficulty in how effectiveness is defined or prioritized by different stakeholders (144). Models are often limited by key assumptions for which empirical data are weak and programme feasibility scenarios optimistic. Consequently, a more robust evidence base is needed in order to improve estimates around cost-effectiveness.

Cost-effectiveness analyses for screening (section 2.2.4) indicate that indiscriminate mass screening of migrants is the least preferred and cost-effective option, while screening that targets high-risk groups is most cost-effective (91,148), with evidence that post-migration follow-up screening may be particularly cost-effective (88,157). In countries in the Region with a low incidence of TB, the most cost-effective solution may involve a mix of targeted pre-arrival screening of migrants for active TB and post-arrival screening for LTBI in migrants from countries of intermediate/high



TB burdens (3). However, models may only consider costs for the host country, and not costs to patients or origin countries (e.g. for pre-migration screening).

There are also suggestions that shifting the cost of screening to countries of origin may be optimal because costs are often much greater in receiving countries (149). However, this ignores other important components of an effective regional approach, such as equity, ethics and financial burden (149) and the fact that areas of conflict or natural disasters may not have an effective health care system. When seeking to evaluate cost–effectiveness, it may be useful to consider the recent report on the cost of health care provision for irregular migrants published by the EU Agency for Fundamental Rights, which stated that "regular preventive care, as opposed to providing only emergency care, is cost-saving for health care systems" (150), which also aligns with commitments made as part of the United Nations Sustainable Development Goals (50).

The literature suggests that effective approaches should integrate multiple elements as part of a complex intervention/package of care (33,52,151–153); examples of models or frameworks that facilitate these complex interventions include the Tuberculosis action plan for the WHO European Region 2016–2020 (51), the Wolfheze consensus statement (55), the ERS (European Respiratory Society)–WHO TB Consilium (153,158) and TBnet (153,159).

Complex interventions that can have an effective impact across the whole of the Region require harmonizing and facilitating cross-border responses to TB (55,152,153). In 2012, guidelines were established for a minimum package of cross-border TB control and care in the WHO European Region (55). The package calls for action at all levels including governance, with recommendations for legal guidelines to ensure cooperation and care, and adequate funding. Diagnosis and treatment of LTBI is recommended, without any threat of deportation while individuals are undergoing treatment. The guidelines also cover supporting counselling for individuals with TB, and for advocacy and social mobilization (55,160). Despite these guidelines being in place for five years, the same points are being reiterated in recent publications, with questions as to whether TB elimination is now at substantial risk because of the relative lack of progress in generating effective and cohesive cross-border care (152,153).

## 3. DISCUSSION

### 3.1 Strengths and limitations of this review

While the review used a robust and comprehensive search strategy, it was not a formal systematic review. Although searches identified evidence in Russian as well as English, with the capacity to translate and incorporate these works where needed, data from some Member States were lacking, particularly from the Russian Federation and countries in eastern Europe and central Asia. This may reflect the fact that in many of these countries TB is largely confined to the native population and so research and dialogue would have less focus on migrant populations. Furthermore, some data and interventions could be missed if these were not reported in English or Russian. There were issues with the quality of evidence within many areas of TB management and care across the Region, with significant heterogeneity in the data identified, variations in how data were recorded and variation in how migrant groups were defined.

This report has attempted to highlight and synthesize key areas of policy and change for TB control in refugees and migrants that would be likely to have an impact at all levels and across the heterogeneous scenario of the WHO European Region. Searches included multiple databases and websites, as well as government websites for all 53 Member States. The analysis has focused on the most relevant and recent evidence because this field is relatively fast moving and policy-makers need to be able to access the most relevant research if they are to make evidence-informed decisions.

### 3.2 Key considerations for the WHO European Region

While this report highlights the significant diversity and heterogeneity of approaches being implemented across Europe, and the challenges in harmonizing the response across the Region, it must also be recognized that TB is a global issue and the European context should be considered in conjunction with TB control globally.

The review has highlighted the heterogeneity of TB in refugees and migrants across the WHO European Region, with significant regional differences in the prevalence of the various forms of TB in refugees across the Region and also variations in prevalence of the various forms relative to that of the host country. Evidence



suggests that TB transmission from refugees and migrants to the host population is likely to be low and that TB is predominantly circulating in refugee and migrant communities in countries with a low incidence of TB. This is likely to reflect both limited interaction between migrants and host populations in such settings and the availability of good health services. In the context of increasingly restrictive health services in Europe, rates of transmission may increase considerably. It is unsurprising, therefore, that approaches to addressing TB in refugees and migrants across the Region are also very varied. In several countries, it is not addressed at all through specific programmes and/or there is limited capacity to tackle LTBI or MDR-TB in either the host or the migrant population.

The evidence base to inform guidelines for effective approaches for managing TB in refugees and migrants is variable and there is often a lack of high-quality or easily comparable data. Cross-country collaborations and dialogue in the field of migrant health require data that are comparable across the Region, both with regard to TB and to how different groups of migrant are defined.

Overall, there was still a lack of clarity in the evidence regarding cost-effective strategies in terms of when, where and how migrants should be screened for TB; whether to focus on active TB, LTBI or both; and how to support successful treatment outcomes. The findings suggest that refugee and migrant communities perceive relevant TB screening to be acceptable, with high uptake where such services are accessible (43–45). Education targeting both service providers and migrants is needed to ensure that TB services are delivered to diverse refugee and migrant communities in a way that is culturally sensitive and people centred (46). European guidelines that specifically focus on migrant populations and infectious diseases are currently lacking but are being prepared (58).

Even where optimal interventions can be identified, there may be challenges to their implementation, which could be related to training, availability of health care practitioners at the right location or to more migrant-specific challenges, such as cultural disparities and the transient nature of many migrant communities. Identifying and addressing these operational challenges is of huge importance in ensuring theoretically effective interventions reach their full potential.

There is general consensus that tackling LTBI in at-risk refugee and migrants is now critical in order to meet regional TB elimination targets; this will require the development of improved LTBI diagnostic techniques and algorithms to allow scaling up. The limited evidence available also makes it clear that programmes should

seek to improve measures for drug-sensitive TB, as well as TB/HIV coinfection and MDR-TB, the last being a growing concern in migrants across the Region.

The impact on MDR-TB epidemiology of the recent high levels of migration to western Europe is unclear, although currently migrants (particularly refugees and asylum seekers) face a greater burden of MDR-TB and worse outcomes than the host population in countries of low TB incidence. In countries with a higher incidence of TB, there is evidence that treatment programmes for MDR-TB may not be easily accessible for either the host or the migrant population.

The recommended minimum package aims to break down the key barriers to diagnosis and treatment, and to data exchange for migrants and other cross-border travellers with TB.


The major finding from this report is that it is unlikely that "one size will fit all" when it comes to a package of services targeting TB in all its forms in migrant populations in the WHO European Region. However, the data highlight some common approaches that could guide policy-making and service development in this area. The Wolfheze consensus statement defines a minimum package to ensure cross-border TB control and care in the WHO European Region (55). It states that service delivery provision in general should be:

- free of charge for the patient;
- culturally competent;
- respectful of patient rights;
- provided without interruption; and
- designed through participatory consultative approaches involving patient organizations, cross-border and migrant communities and staff and professionals.

Specific features of an effective package include:

- **prevention:** diagnosis and treatment of LTBI;
- **infection control:** administrative and environmental measures and personal protection;
- **diagnosis:** early diagnosis, including of drug-resistant TB;
- **contact management:** for all relevant family members and contacts;
- **treatment:** prompt and effective, including for coinfections, irrespective of patient's legal status;
- **continuity of care:** no deportation while being treated, quality treatment and anti-TB drugs for continuation of treatment should be verified before any patient transfers occur; and



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- **confidentiality:** health workers should maintain confidentiality, and be protected in doing so, and not report patients with TB, including undocumented migrants, to regulatory authorities.

What is clear from this evidence synthesis is that TB elimination targets for the WHO European Region will not be met if inequalities in access to diagnosis and treatment in migrant populations are not tackled. Better international and regional legal frameworks would ensure that refugees and migrants are able to access a basic acceptable level of statutory health care on arrival. Tackling TB in the Region will also ultimately require fundamental societal issues to be addressed, such as poverty, overcrowding and homelessness, which face refugees, migrants and other vulnerable groups. Greater coordination and political commitment are needed to ensure adequate resources for countries hardest hit by the epidemic in both the WHO European Region itself and countries with major emigration.

### 3.3 The constituents of an effective and efficient package of services

Evidence suggests that a package of services should target screening for LTBI and active TB in children and adults in line with the TB incidence in their countries of origin; this is likely to be cost-effective although data are inconclusive (56,98,99). Although multiple guidelines support screening for active TB and for LTBI, the effective and efficient delivery of such screening across countries of the WHO European Region is inconsistent (see section 2.3).

Early detection and diagnosis is key, and so it is critical to ensure TB screening and treatment through statutory health services and/or free and easily accessible migrant screening programmes. Educational measures should target both migrants and health care providers to provide culturally appropriate information on TB risk; signs and symptoms of disease; screening, diagnosis and treatment options; and how to access follow-up care and treatment where appropriate (46). Any package of care for migrant populations in the Region will crucially need to recognize the rights of migrants to health, and work towards removing legal, social and cultural barriers to statutory health services.

A more restrictive approach is evolving across the Region with regard to access to mainstream health services by refugees and migrants; the impact that this will have on TB control is not known. All countries in the Region should be encouraged to work towards implementation of the minimum package of cross-border

TB control and care defined in the Wolfheze consensus statement, which advocates for access to screening and treatment for all migrants regardless of legal status (55).

Incorporation of testing for LTBI in migrant screening programmes across the Region is currently ad hoc, and countries will need to be encouraged and resourced to generate robust evidence on whether and how to implement such screening programmes. It is not clear how feasible and appropriate screening for LTBI is in more resource-stretched countries in the Region, and it is important to ensure programmes to address active TB are in place as a priority. It is also unclear how best to implement screening programmes for LTBI in migrant populations, and robust research is needed to define where to do this and how to engage migrants so that they complete the screening and treatment pathway. Any package of care should also give specific consideration to facilitating universal drug-sensitivity testing and treatment for MDR-TB in refugee and migrant populations, which are disproportionately affected by MDR-TB.

The shortfall in good country-specific data has an adverse effect on information sharing and continuity of care for people moving between countries in the Region. Increased data sharing coupled with a rigorous assessment of effectiveness and cost-effectiveness may allow for more rational use of resources, including avoiding unnecessary repeating of diagnostic tests.

The data analysed in the report suggest that multiple approaches are likely to be needed to improve migrant screening for TB across the Region. As active TB often develops several years after infection, the optimum approach is to ensure access to statutory primary medical services for refugees and migrants, and effective education on the warning signs and symptoms. Consideration too needs to be given to the fact that thousands of migrants circulating in the Region will largely bypass statutory screening programmes (particularly if lacking documentation), and special approaches to TB screening and treatment will need to be defined and implemented for these hard-to-reach groups to facilitate early detection. Evidence points to the benefit of pre-departure screening on TB epidemiology in European countries, but this inevitably targets a narrow subset of migrants migrating for largely economic reasons, and it does not take into consideration the wider cost implications for these individuals or countries of origin. The United Kingdom is the main country initiating pre-departure screening currently, but it could be considered as a policy option for other European countries seeing consistently high rates of migration from countries of high TB incidence. Such programmes should take into consideration factors relating to human rights, ethics and costs (to health systems as well as migrants). Community-based approaches and ensuring



access to meaningful primary care services on or soon after arrival is the optimum approach, with TB care integrated with other health services to encourage timely and meaningful access to screening and treatment. Consideration should also be given to rolling out screening for LTBI and active TB in the transit camps emerging across the Region, where some migrants are increasingly staying for long periods of time.

### 3.4 Policy considerations

Political engagement and will is paramount to successfully tackling TB within the WHO European Region, particularly in regards to improving TB care and prevention for refugees and migrants. Political and legislative changes need to encompass both equitable and universal access to TB diagnosis and care and reduce the social risk factors surrounding TB for both refugees/migrants and the host population. Effective decision-making in this area is complex and requires the provision of evidence and data around the key issues. However, some policy options can be derived from the current analysis for consideration:

- incorporate screening and treatment for LTBI and MDR-TB into refugee and migrant screening programmes (e.g. at the first point of contact for newly arrived migrants with health services in the host country) in an accessible and culturally sensitive manner as part of a basic free package of care;
- improve cross-border collaboration for TB screening and care along the entire migration trajectory, with focus placed on implementing a minimum package of TB screening and care;
- develop a more holistic approach to migrant health across the Region, recognizing the rights of migrants to health, and work towards removing legal, social and cultural barriers to health services to facilitate better TB control among migrants;
- develop health education/health literacy around prevention, treatment and care for TB to increase knowledge, awareness and, subsequently, patient involvement;
- align TB policies with initiatives within the social programme, as poverty and destitution are well-known risk factors for TB transmission and reactivation;
- strengthen approaches to data collection to provide an intercountry evidence base on TB in refugees and migrants for monitoring and evaluation within national health systems; and
- encourage research to understand patterns of TB and to define innovative implementation approaches, in particular cost-effectiveness and how to improve screening and treatment completion.

## 4. CONCLUSIONS


This report has explored options for an efficient and effective package of prevention, detection and treatment for LTBI, active TB, drug-resistant TB and TB/HIV in refugees and migrants in the WHO European Region. The analysis has clearly highlighted that a single package of services is unlikely to be effective when targeting the diverse migrant populations in the Region within countries with widely different contexts, resource constraints and TB incidence. However, the data highlight some common approaches that could guide policy-making and service development in this area. These include developing targeted migrant-sensitive services; expanding the focus from active TB to include LTBI and MDR-TB in particular at-risk migrant groups, which could be a cost-effective approach impacting TB epidemiology in the Region; and full implementation of the minimum package of cross-border TB control and care defined for the WHO European Region in the Wolfheze consensus statement and the European Tuberculosis action plan. Evidence on TB in the Region is generally of low quality and would benefit from more targeted and robust research, with a view to developing effective services. Underpinning all of these issues in TB control is the need to develop a more holistic and people-centred approach to migrant health across the Region, involving migrants themselves in order to better understand their views, priorities and perspectives. Member States should recognize the rights of migrants to health and should work towards removing legal, social and cultural barriers to statutory health services. TB elimination targets for the Region will not be met unless inequalities in access to screening, diagnosis and treatment in refugee and migrant populations are tackled, thus ensuring the future resilience of the health systems responsible for tackling the global TB epidemic.



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## ANNEX 1. SEARCH STRATEGY

### Databases and websites

Searches of all databases and websites were conducted between July and October 2017 by two researchers. The following databases were examined (inception to October 2017) for peer-reviewed academic literature using defined search terms: CABI (Centre for Agriculture and Biosciences International), CINAHL (Cumulative Index to Nursing and Allied Health Literature), Cochrane, Embase, European Journal of Public Health, Global Health, HMIC (Health Management Information Consortium), Ingenta, MEDLINE, OpenGrey, ProQuest Dissertations, PubMed, Russian Science Citation Index, Scopus, Web of Science and WHO Global Index Medicus.

Websites of the following were searched for grey literature sources: Consortium for Applied Research on International Migration, ECDC, Eurostat, IOM, Journal of the American Medical Association, Migrant Integration Policy Index, the Office of the United Nations High Commissioner for Refugees, OpenSIGLE, SOPHIA (Society of Practitioners of Health Impact Assessment), TB Coalition, United Nations and WHO. Russian literature was searched using BASE (Bielefeld Academic Search Engine) and eLibrary.RU. Additionally, the ministry of health website for each WHO European Region Member State was examined.

### Study selection

The title and abstracts of all citations yielded in the search of the databases and websites were screened by four reviewers to identify papers addressing the study aims. The full text of each relevant publication was then also screened by four reviewers to identify papers for final inclusion. All published primary research studies, viewpoints/editorials and grey literature (including national and international reports and case studies) were considered that fulfilled the following inclusion criteria:

- written in either English or Russian;
- reporting qualitative or quantitative data with no date restriction (although with a focus on papers published from 2010 onwards);
- migrants, refugees or asylum seekers as the population of interest;
- conducted in, or related to, the 53 WHO European Region Member States;
- TB in terms of evidence of prevention, diagnosis and detection, and treatment; and
- cross-border collaborations, country capacity, operational challenges, effectiveness and efficacy related to TB control.



The only exclusion criterion was that migrants, refugees or asylum seekers were not mentioned anywhere within the body of work.

## Data extraction

Data on effective and efficient packages of care for the prevention, diagnosis and treatment of TB in migrants across the WHO European Region were extracted and synthesized to identify approaches being implemented across Europe and key strategies for effectively addressing TB in migrant communities.

The search of the databases and websites yielded 19 290 citations, with 2700 additional records identified through hand searching or other sources, giving a total of 21 990. After removing duplicates, 8866 individual records were included in the title and abstract screening, during which 8271 were excluded. The full texts of 595 records were screened, and 140 documents were included in the synthesis in the final report.

## Search terms

The following is a representative search strategy (PubMed):

migrant\*[tw] OR migration[tw] OR immigra\*[tw] OR refugee\*[tw] OR asylum[tw] OR foreign born[tw] OR foreign-born[tw] OR displaced[tw] OR Emigration and Immigration [MeSH] OR Refugees[MeSH] OR Emigrants and Immigrants[MeSH] OR Human Migration[MeSH] OR Transients and Migrants[MeSH] AND Tuberculosis[tw] OR TB[tw] OR LTBI[tw] OR latent tuberculosis OR MDR-TB[tw] or MDRTB[tw] OR XDRTB[tw] OR XDR-TB[tw] OR Extensively Drug-resistant tuberculosis[MeSH] OR Tuberculosis[MeSH] OR Tuberculosis, Multidrug-resistant[MeSH] AND Prevention[tw] OR diagnosis[tw] OR detection[tw] OR treatment[tw] OR care[tw] OR effectiveness[tw] OR policy[tw] OR screening[tw] OR transmission[tw] AND WHO European Region[tw] OR Albania OR Andorra OR Armenia OR Austria OR Azerbaijan OR Belarus OR Belgium OR Bosnia OR Herzegovina OR Bulgaria OR Croatia OR Cyprus OR Czech Republic OR Denmark OR Estonia OR Finland OR France OR Georgia OR Germany OR Greece OR Hungary OR Iceland OR Ireland OR Israel OR Italy OR Kazakhstan OR Kyrgyzstan OR Latvia OR Lithuania OR Luxembourg OR Malta OR Monaco OR Montenegro OR Netherlands OR Norway OR Poland OR Portugal OR Moldova OR Romania OR Russia OR Russian Federation OR San Marino OR Serbia OR Slovakia OR Slovenia OR Spain OR Sweden OR Switzerland OR Tajikistan OR Macedonia OR Yugoslavia OR Yugoslav OR Turkey OR Turkmenistan OR Ukraine OR United Kingdom OR UK OR England OR

Ireland OR Scotland OR Wales OR Great Britain OR Uzbekistan OR EEA OR EU OR European Union OR Europe OR European Economic Area.

The number of results for each database and website are as follows.

### Bibliographic databases and journals:

BASE [31]  
CABI [215]  
CINAHL [160]  
Cochrane [615]  
eLibrary.RU [326]  
Embase [5489]  
European Journal of Public Health [43]  
Global Health [1426]  
HMIC [65]  
Ingenta [339]  
Journal of the American Medical Association [41]  
MEDLINE [3307]  
OpenGrey [42]  
ProQuest Dissertations [23]  
PubMed [4903]  
Russian Science Citation Index [7]  
Scopus [64]  
Web of Science [1066]  
WHO Global Index Medicus [536].

### European databases:

ECDC [19]  
Eurostat [45]  
IOM [64]  
TB Coalition [23]  
United Nations [2]  
WHO [439].

No results were obtained for Consortium for Applied Research on International Migration, Migrant Integration Policy Index, the Office of the United Nations High Commissioner for Refugees, OpenSIGLE or SOPHIA.



### Ministries of health and government websites:

Bulgaria, <https://www.mh.government.bg/bg/> [4]

Israel, <https://www.health.gov.il/English/Pages/HomePage.aspx> [18]

Italy, [http://www.salute.gov.it/portale/p5\\_11.jsp](http://www.salute.gov.it/portale/p5_11.jsp) [9]

Lithuania, <https://sam.lrv.lt/en/> [15]

Malta, <https://deputyprimeminister.gov.mt/en/Pages/health.aspx> [11]

Monaco, <http://en.gouv.mc/Government-Institutions/The-Government/Ministry-of-Health-and-Social-Affairs> [22]

Netherlands, <https://www.government.nl/ministries/ministry-of-health-welfare-and-sport> [1]

Norway, <https://www.regjeringen.no/en/dep/hod/id421/> [18]

Serbia, <http://www.zdravlje.gov.rs/> [1]

Spain, <http://www.msc.es/> [22]

Switzerland, <https://www.bag.admin.ch/bag/en/home.html#> [12]

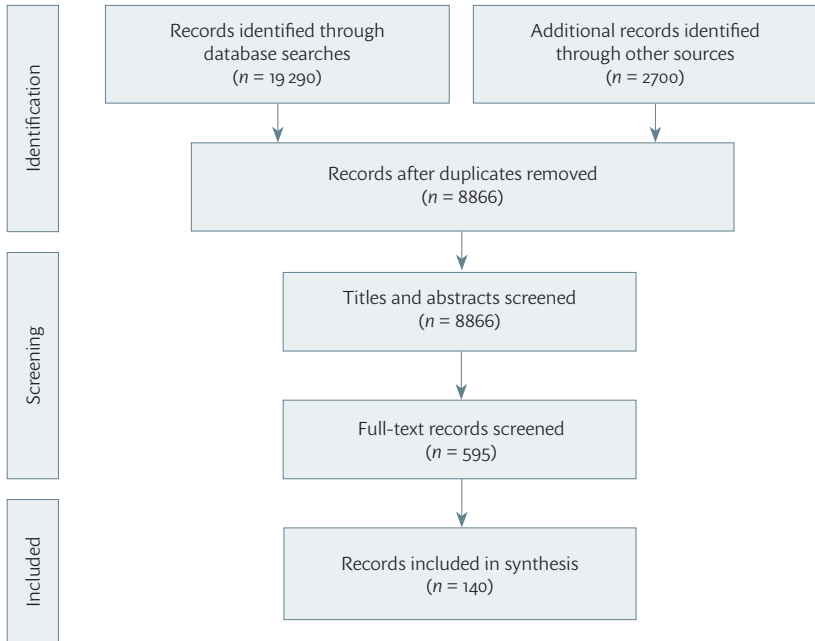
United Kingdom, <https://www.gov.uk/government/organisations/department-of-health> [2566]

Uzbekistan, <http://www.minzdrav.uz/en/> [1]

No data were found for Albania, Andorra, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bosnia and Herzegovina, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Kazakhstan, Kyrgyzstan, Latvia, Montenegro, Poland, Portugal, Republic of Moldova, Romania, Russian Federation, San Marino, Slovakia, Slovenia, Sweden, Tajikistan, the former Yugoslav Republic of Macedonia, Turkey, Turkmenistan and Ukraine.

Fig. A1.1 outlines the search flow to give the final 140 documents.

Fig. A1.1. Flow chart for included studies











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