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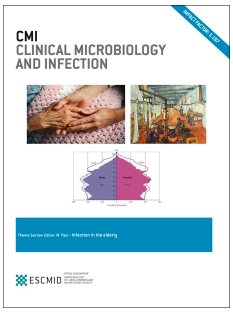

Multidrug-resistant tuberculosis and migration to Europe

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CMI Themed Review: Multidrug and extensively drug-resistant tuberculosis

Multidrug-resistant tuberculosis and migration to Europe

Running title: MDR-TB in migrants

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Abstract

Multidrug-resistant tuberculosis (MDR-TB) in low-incidence countries in Europe is more prevalent among migrants than the native population. The impact of the recent increase in migration to EU and EEA countries with a low incidence of TB (fewer than 20 cases per 100,000 [1]) on MDR-TB epidemiology is unclear. This narrative review synthesises evidence on MDR-TB and migration identified through an expert panel and database search. A significant proportion of MDR-TB cases in migrants result from reactivation of latent infection. Refugees and asylum seekers may have a heightened risk of MDR-TB infection and worse outcomes. Although concerns have been raised around 'health tourists' migrating for MDR-TB treatment, numbers are probably small and data are lacking. Migrants experience significant barriers to testing and treatment for MDR-TB, exacerbated by increasingly restrictive health systems. Screening for latent MDR-TB is highly problematic since current tests cannot distinguish drug-resistant latent infection, and evidence-based guidance for treatment of latent infection in contacts of MDR patients lacking. While there is evidence that transmission of TB from migrants to the general population is low – it predominantly occurs within migrant communities – there is a human rights obligation to improve the diagnosis, treatment, and prevention of MDR-TB in migrants. Further research is needed into MDR-TB and migration, the impact of screening on detection or prevention, and the potential consequences of failing to treat and prevent MDR-TB among migrants in Europe. An evidence-base is urgently needed to inform guidelines for effective approaches for MDR-TB management in migrant populations in Europe.

Key words

Tuberculosis; drug resistance; migration; Europe; screening; health service delivery; latent tuberculosis; MDR-TB

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is an urgent public health priority in Europe, with significant health and cost implications associated with the expensive and prolonged treatment often required [2]. Migration to and within Europe has increased dramatically in recent years [3, 4], and in many EU and EEA countries with a low incidence of TB (e.g. fewer than 20 cases per 100,000 [1]), rates of MDR-TB have been shown to be higher among migrants ('foreign-born') than the general population [5-7]. There is evidence both for MDR-TB being imported to Europe by migrants [8] and for MDR-TB being acquired or transmitted within Europe [9, 10]. Although surveillance data demonstrate that rates of drug resistance in most Western European countries remain low (<3% in new cases) [11], this may increase with migration from high MDR-TB burden countries, particularly those in Eastern Europe with the highest risk of MDR-TB among TB cases [12].

The diverse migrant population in Europe, including forced migrants (asylum seekers and refugees), undocumented migrants residing in Europe without legal status, or those migrating for family, work, or study, is estimated to include over 30 million individuals born outside the European Union (EU), and more than 17 million migrants from other EU Member States [13]. In 2015 alone, more than 1 million migrants entered Europe during the migrant crisis [14]. A cohesive evidence-base on the impact of migration on MDR-TB in Europe is essential to guide policy and practice around the identification and treatment of MDR-TB.

This narrative review examines the relationship between MDR-TB and migration in low- incidence EU countries. We consider the implications of MDR-TB for individual migrants and their communities, and for public health policy and practice.

Methods

In this paper, we systematically identified evidence on MDR-TB and migration through a database search including Embase, Medline, Global Health, and Google Scholar, as well as an expert panel which contributed to the identification of relevant research, integrating diverse views to reduce bias.

Epidemiology of migration and MDR-TB

MDR-TB is widespread globally, with an estimated 480 000 cases in 2014 [15] and significant disparities between countries and regions. In Russia, Bangladesh, and China, the proportion of previously treated TB cases that are multidrug-resistant is 49%, 29%, and 26% respectively [15]. In Eastern Europe, the proportion of previously treated TB cases that are multidrug-resistant is 69.0% in Belarus, 62.0% in Moldova and Estonia, 56.0% in Ukraine, 49.0% in Lithuania, 30% in Latvia, and 23.0% in Bulgaria [16, 17]. Many of these countries also have high rates of MDR-TB in new cases, for example Belarus (34%), Moldova (24%), Ukraine (22%), and Estonia (19%) [15]. The high rates of MDR-TB in these countries are in part due to disparities in the availability of high-quality treatment [17].

Low incidence TB countries in Europe are receiving increasing numbers of migrants from high-incidence countries, who are over-represented among MDR-TB cases. Across EU and EEA Member States, reported surveillance data suggest 73.4% of MDR-TB cases are in migrants (born outside of the reporting country) [18], among whom, 51.7% of MDR-TB cases occur in migrants originating from the EU [19]. In Germany, migrants comprise 94.0% of MDR-TB cases, though only 58.7% of TB cases. Similarly, in the UK migrants comprise 90.4% of MDR-TB cases, but only 69.1% of TB cases, and in France migrants account for 89.2% of MDR-TB infections, though only 55.6% of TB cases (Table 1) .

The proportion of the population in a selection of European countries that is foreign born, as well as the proportion of notified cases of TB and MDR-TB that occur in migrants, is shown in Figure 1. This figure illustrates that in much of North and Western Europe, migrants are over-represented among cases of TB, and particularly MDR-TB, given their distribution in the general population. The figure also points to disparities between Western and Eastern Europe, with migrants comprising a low proportion of TB and MDR-TB cases in Lithuania and Romania, which can be attributed both to the low rates of migration and high incidence of TB (and particularly MDR-TB). Other research and surveillance data also highlight disparities in rates of TB and MDR-TB within Europe [20].

A significant proportion of cases of MDR-TB in migrants in low-incidence countries are likely to result from reactivation of latent infection acquired prior to migration [21]. Reactivation of latent TB most often occurs in the first 2-5 years following migration [22], which may be partly attributed to poor living conditions and barriers to accessing health services [6, 23]. his increased risk may persist in migrants in comparison to the general population [24].

There is some evidence that a significant proportion of TB cases (new infection or reinfection) among migrants result from re-exposure during return visits to their home countries, often to visit friends or relatives [25], yet data on MDR-TB infection acquired by this route are lacking. It is important to note that migrant communities often cluster together in host countries, and disease is therefore more likely to spread within their own communities, rather than to the surrounding host population [26, 27].

Migrants at high risk of MDR-TB

Migrants fleeing conflict or other violence (e.g. the current influx of asylum seekers entering Europe from the Middle East and Africa), may be at increased risk of TB and MDR-TB [24] due to the collapse of health service infrastructure in the context of conflict. The breakdown of health systems has been shown to contribute to an increase in TB incidence, may also be a risk factor for the development of MDR-TB [28, 29]. Some migrant groups including refugees, refused asylum seekers, victims of trafficking, and undocumented migrants may be at particularly high risk of MDR-TB due to exposure to destitution, poor social conditions (e.g. overcrowding, poor living conditions, incarceration or detention, and homelessness), exposure to other migrants from high-incidence countries during their migration trajectory, or co-infection (e.g. with HIV). These migrant groups may also be excluded from health services or be fearful of accessing services due to their legal status, preventing them from accessing free screening, diagnosis, or treatment [30]. However, empirical evidence on the risk of MDR-TB in these groups, or their general health needs, are insufficient.

There is also a relatively small group – in the context of the current mass movement of populations – of "health tourists" who migrate or travel with the specific aim of seeking treatment for MDR-TB [31]. These individuals may have previously received treatment, but failed multiple courses of therapy in their home countries, and migrate to access better treatment options [8]. Within this group, there is a small proportion of relatively affluent patients able to pay themselves for treatment. Recently concerns have been raised around the implications of health tourism for European health services and the wider public health [32, 33]. Disparities in rates of TB and MDR-TB between low-incidence countries in Europe and high-incidence countries globally, and inequalities in the distribution of resources (including in the availability and affordability of treatment) may be drivers of this, and have been particularly highlighted between Western and Eastern Europe [17]. Overall, however, data on patterns of health tourism are lacking.

Diagnosis of MDR-TB and screening strategies

There are significant challenges to drug susceptibility testing (DST) to diagnose MDR-TB and the accurate collection of surveillance data on MDR-TB globally. Despite the rollout of rapid molecular diagnostics including Xpert MTB/RIF and line probe assays [34, 35], diagnostic delays are common and only 123,000 cases with MDR-TB were notified globally in 2014 [36]. In many high-incidence countries, access is limited to culture-based phenotypic drug sensitivity testing (DST) for first-line and second-line drugs (which takes weeks), although the second line Hain line probe assay was recently recommended by WHO as the initial test for detection of resistance to fluoroquinolones and second-line injectable drugs [37]. Migrants from high-incidence countries may therefore have a high risk of previously undiagnosed or incorrectly diagnosed drug resistance.

Most low-incidence countries have policies to systematically screen migrants from TB-endemic countries for active TB [38], with a limited number of countries in Europe also implementing latent TB (LTBI) screening [39]. There is conflicting evidence on the most effective and cost-effective strategy for migrant TB screening, and there is significant variation in national approaches to screening [38-41], which can be explained by the weak evidence-base on the effectiveness of migrant TB screening as well as heterogeneous political environments [26]. Furthermore, though screening may be implemented, there is a lack of systematic follow-up procedures for migrants across Europe [39], which are necessary for adequate care and efforts to eliminate TB.

Yield of screening for active TB often corresponds to the epidemiology in the country of origin. However, large variations may occur due to differences in the profile of sub-populations of migrants, as well as varying risk of TB transmission and progression during the migration process [40, 42]. This is likely to be true also for the proportion of patients with MDR-TB. However, very little data have been reported specifically on yield of MDR-TB. Of 15 screening studies included in a recent systematic review on pre-entry screening programmes for TB in migrants to low-incidence countries,

only three reported data on the number of cases of MDR-TB identified within culture-confirmed cases of active TB [42]. Due to the lack of screening outcome data from surveillance systems [40, 42], as well as very limited specific research on MDR-TB in the context of migrant screening, the potential impact on early detection and interruption of MDR-TB transmission remains largely unknown. However, transmission of TB from migrants to the general population typically is low in host countries with good health-care access for migrants [26, 43-46].

Screening for latent MDR-TB is highly problematic since current tests (tuberculin skin test and interferon-gamma release assays) cannot distinguish between drug-susceptible and drug-resistant TB, and cannot predict risk of reactivation. Moreover, the best chemoprophylaxis for individuals with suspected latent MDR-TB has not yet been established. There is extremely limited data on the effectiveness of chemoprophylaxis for suspected MDR-TB [47, 48]. Furthermore, WHO did not recommend systematic prophylaxis with second-line TB drugs in contacts of patients with MDR-TB in its recent guidelines [49]. Clinical trials are needed to inform any future recommendations.

Treatment outcomes in migrants

Globally, only 50% of MDR-TB patients successfully complete treatment, with 24% lost to follow up or without outcome information [15]. For extensively drug-resistant TB (XDR-TB), only 26% of patients successfully complete treatment, with 25% lost to follow-up or without outcome information [15]. This gap is greater in countries with a higher prevalence of drug-resistance [15], and is relevant to low-incidence countries in the context of migration.

Some data suggest that migrants treated in low-incidence European countries are less likely to have successful treatment outcomes for MDR-TB than host populations. In a cohort study on treatment

outcomes for MDR-TB patients in the UK, 72.3% of migrants had a successful treatment outcome, compared with 90% of UK born (OR 0.29 [0.08-1.01]; p=0.026)[50]. This may be attributed to formal and informal barriers to testing and treatment – including fears relating to legal status or government, language and health literacy, lack of entitlement to services, and inability to pay – resulting in delays in presentation and poor treatment outcomes. Such barriers are likely to be exacerbated by increasingly restrictive health systems across Europe [3]. The intensive, complex, and lengthy treatment, and high pill burden, as well as contextual factors like alcohol or drug use, homelessness, and social stigma may further impact on treatment uptake and adherence for TB and MDR-TB. These factors undoubtedly contribute to the acquisition of drug resistance [6, 23, 24, 40, 51].

However, the migration status of patients is often not recorded, and research findings are inconsistent [52]. The limited data on treatment outcomes for MDR-TB in migrants in low-incidence countries in Europe point to the need for further research in these communities, as well as the need for strategies to improve the identification and treatment of MDR-TB in these hard-to-reach groups. This is particularly pertinent in light of the shorter MDR-TB regimen now recommended by WHO [53], which may help to improve treatment completion and cure, although further trial data are awaited.

Resource implications of treating and preventing MDR-TB in migrants

Less than 25% of MDR-TB patients globally have been started on treatment, yet it is unclear how many of these patients are migrants residing in low-incidence countries in Europe [54]. A recent systematic review reported that the costs of treating MDR-TB (from the provider perspective) were between US $1218 - $83,365 (in low- to high-income countries) in comparison to US $258 - $14,659 for drug-sensitive TB [55]. The highest proportion of costs incurred is due to hospitalisation (which is

232 often extensive in some high MDR-TB burden settings such as Russia), followed by drugs and clinic
233 visits.

234 Given the potential costs for host country health systems associated with the identification and
235 treatment of TB among migrants, there may be advantages in supporting MDR-TB control efforts in
236 countries with high MDR-TB incidence. A decision analysis suggested that it may be cost saving for
237 low-incidence countries to support improved TB care and prevention in high-incidence source
238 countries for migrants [56]. Such strategies may be particularly effective for MDR-TB, given the
239 increased costs associated with MDR-TB treatment, and should be further investigated.

240

241 A cost-effectiveness analysis has shown that outpatient-based models could lower costs per
242 disability adjusted life year (DALY) by as much as 54% compared with inpatient-based models [57].
243 However, in low-incidence countries there may be an emphasis on the hospitalisation of MDR-TB
244 cases, and isolation within the hospital context to prevent spread of disease, leading to increased
245 costs. Migrants are particularly vulnerable to the social and economic consequences of TB and MDR-
246 TB and costs associated with treatment, and thus specific social and financial support may be
247 needed to facilitate screening and treatment in these communities [58]. Technology based
248 interventions including video observed therapy (VOT), mobile phone communication, or social media
249 based health literacy may be help overcome barriers to screening and treatment adherence in
250 migrants [59]. The effectiveness of existing protocol (e.g. risk assessments for low treatment
251 adherence carried out by TB services, and how this informs decisions about treatment options)
252 should also be assessed.

253

254 Further research into effective and cost-effective strategies to increase the detection and treatment
255 of MDR-TB in hard-to-reach migrant populations in low-incidence countries is needed to provide

more insight into the trade-offs between intensified screening, investment in accessible and effective clinical care, and social support for at risk migrant groups to facilitate engagement with services. Whilst these strategies may be costly, it is essential to prioritise the availability and accessibility of care. Screening cannot be meaningful without linkage to high-quality care, which ultimately is necessary to reduce migrant mortality and morbidity, as well as transmission to the wider population.

Conclusions and action points

MDR-TB is more prevalent in migrant populations in low-incidence countries in Europe than host populations. At a time when large numbers of migrants from high-incidence countries are migrating to Europe, there is insufficient data on the prevalence of MDR-TB among migrants, or the impact on incidence in receiving countries. MDR-TB may be acquired before, as well as during or following migration, due to barriers to accessing services, low treatment adherence, or increased risk of infection due to social conditions in transit or in host countries. While transmission predominantly occurs between migrants, there is a risk of transmission for both migrants and the native population. Key findings and points of action are summarised in Table 2.

There is a clear imperative to optimise the quality of diagnosis, treatment, and prevention of MDR-TB in migrants. Barriers to care include restrictions on access to health care for migrants as well as informal barriers to service uptake. In some instances, disparities in the availability of services (e.g. between Eastern and Western European countries) may lead to health tourism. Compounding these challenges is the lack of a diagnostic test to detect latent MDR-TB and to predict the risk of disease re-activation, and high-quality evidence for an effective prophylactic drug regimen.

Key research gaps include a lack of data on effective screening strategies for MDR-TB or how routine practice should be adapted across diverse health systems in Europe to improve treatment outcomes in migrants at risk of low adherence to TB treatment or with MDR-TB. There are also insufficient data on specific risk factors for MDR-TB, patterns of acquisition and transmission, and treatment outcomes in migrants in low-incidence countries in Europe. The limited evidence-base means that there are currently shortfalls in the delivery of effective and cost-effective screening and treatment strategies in migrants. Improved routine public health surveillance, as well as further research, is undoubtedly needed to better understand the relationship between MDR-TB and migration, the impact screening may have on early detection or prevention, and to quantify the consequences associated with a failure treat and prevent MDR-TB among migrants in Europe.

Improving the detection and treatment of infectious diseases in migrants is essential in order to improve the health status of migrants, and host countries must acknowledge their obligation to migrants' human right to health. Specifically, there should be an emphasis on targeting migrants from high TB incidence countries to improve the detection of MDR-TB (e.g. routinely testing all migrants with TB for drug resistance), and facilitating access to treatment (e.g. free MDR-TB diagnosis and treatment in any EU country, and culturally competent care [60]). The development of coherent guidelines is also a crucial next step to ensure the roll out of effective and cost-effective approaches to the management and prevention of MDR-TB in migrant populations in low-incidence countries in Europe.

Transparency declaration

KL is a staff member of the World Health Organization (WHO). The author alone is responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of WHO. SH, LBN, IDO, RRN, MN, and JSF have no conflicts of interest to declare.

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Figure legend:

Figure 1 MDR-TB and migration in Europe*

The boxes in this figure illustrate the proportion of TB cases and MDR-TB cases that occur in migrants (blue stacks) in each country. Columns in the boxes represent the percentage of foreign born overall, among the total tuberculosis (TB) and multi-drug resistant TB (MDR-TB) cases reported in that country. On the map, the different shadings of the countries represent the proportions of foreign-born individuals living in that country that are comprised by migrants.

*Data [12, 15-21, 23, 24, 61]

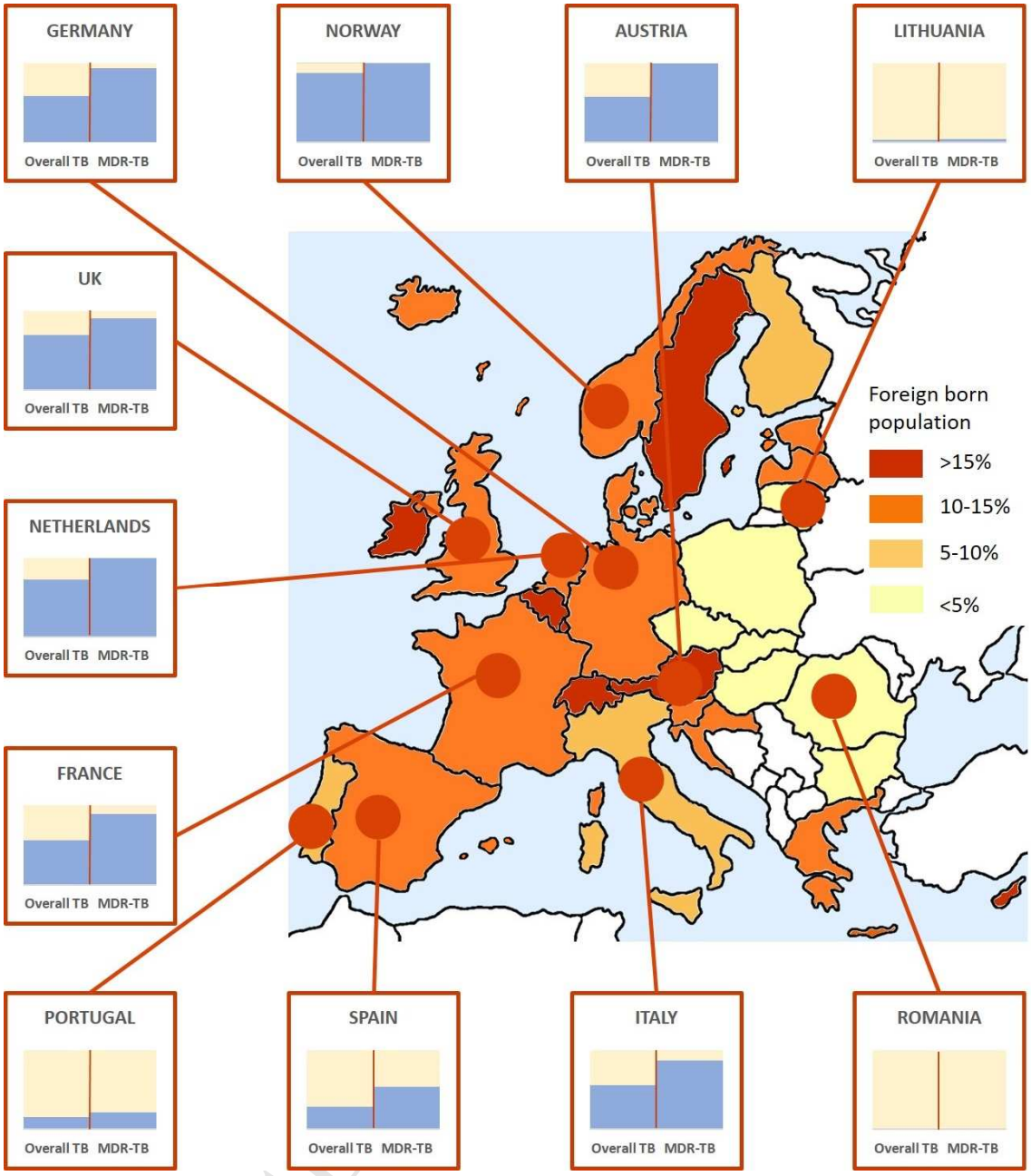
Table 1 TB and MDR-TB in migrants in Europe

Country	Year of report	Total number of TB cases [n]	Total number of migrants with TB [n (%)]	Total number of MDR-TB cases [n]	Total number of migrants with MDR-TB [n (%)]
Austria	2014	582	374 (64.3%)	20	20 (100.0%)
Denmark	2010	359	216 (60.2%)	2	1 (50.0%)
France	2014	4845	2692 (55.6%)	111	99 (89.2%)
Germany	2014	4488	2635 (58.7%)	89	79 (94.0%)
Italy	2010	3249	1809 (5.6%)	87	76 (87.4%)
Lithuania	2010	1938	47 (2.4%)	506	11 (2.2%)
The Netherlands	2014	823	602 (73.1%)	6	6 (100.0%)
Norway	2014	325	302 (92.9%)	10	10 (100.0%)
Portugal	2014	2264	360 (15.9%)	23	5 (21.7%)
Romania	2010	21078	38 (0.2%)	502	0 (0.0%)
Spain	2014	5018	1446 (28.8%)	35	19 (54.3%)
United Kingdom	2014	7077	4890 (69.1%)	52	47 (90.4%)

Data: [26, 32, 40, 41, 61-67]

Table 1 Key findings and points of action

Key Findings	Points of action
Problem • MDR-TB widespread globally: 480,000 cases of MDR-TB or XDR-TB in 2014 • Migration from high MDR-TB burden countries may contribute to increase in MDR-TB case notification rates in low-incidence countries • Risk of MDR-TB higher among migrants in low-incidence countries in Europe than general population • No screening test for latent MDR-TB • MDR-TB infection may be acquired through return travel to country of origin visiting friends and family • New infection or re-infection of MDR-TB due to poor social conditions and barriers to health care on arrival • Barriers to health services prevent the effective detection and treatment of MDR-TB in migrants, both in country of origin and in the host country	**Access to services** • Facilitate access to diagnosis and effective follow-up and treatment for migrants • Policies restricting free access to statutory health services in European host countries need addressing: they present barriers to diagnosis and treatment, which may increase risk of transmission and acquisition of MDR-TB • Develop social and financial support mechanisms for migrant patients **Screening and treatment guidelines** • Significant variations in screening strategies for migrants in Europe due to weak evidence base and heterogeneous political environments • Need for consistency in policy and practice across Europe, as well as development of evidence based guidelines for the prevention and treatment of MDR-TB in migrants **Research** • Need for further research on MDR-TB in migrants to provide robust evidence base for policy and practice


GERMANY
Overall TB MDR-TB
NORWAY
Overall TB MDR-TB
AUSTRIA
Overall TB MDR-TB
LITHUANIA
Overall TB MDR-TB
UK
Overall TB MDR-TB
NETHERLANDS
Overall TB MDR-TB
FRANCE
Overall TB MDR-TB
PORTUGAL
Overall TB MDR-TB
SPAIN
Overall TB MDR-TB
ITALY
Overall TB MDR-TB
ROMANIA
Overall TB MDR-TB
Foreign born population
>15%
10-15%
5-10%
<5%