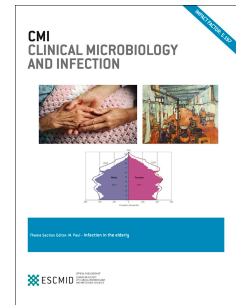


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Multidrug-resistant tuberculosis and migration to Europe

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1 **CMI Themed Review: Multidrug and extensively drug-resistant**
2 **tuberculosis**

3
4 **Multidrug-resistant tuberculosis and migration to Europe**

5
6 **Running title: MDR-TB in migrants**

7
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29

30 Abstract

31

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

50 Key words

51 Tuberculosis; drug resistance; migration; Europe; screening; health service delivery; latent

52 tuberculosis; MDR-TB

53 Introduction

54

55 Multidrug-resistant tuberculosis (MDR-TB) is an urgent public health priority in Europe, with
56 significant health and cost implications associated with the expensive and prolonged treatment
57 often required [2]. Migration to and within Europe has increased dramatically in recent years [3, 4],
58 and in many EU and EEA countries with a low incidence of TB (e.g. fewer than 20 cases per 100,000
59 [1]), rates of MDR-TB have been shown to be higher among migrants ('foreign-born') than the
60 general population [5-7]. There is evidence both for MDR-TB being imported to Europe by migrants
61 [8] and for MDR-TB being acquired or transmitted within Europe [9, 10]. Although surveillance data
62 demonstrate that rates of drug resistance in most Western European countries remain low (<3% in
63 new cases) [11], this may increase with migration from high MDR-TB burden countries, particularly
64 those in Eastern Europe with the highest risk of MDR-TB among TB cases [12].

65

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

73

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

77

78 Methods

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

83

84 **Epidemiology of migration and MDR-TB**

85

86 MDR-TB is widespread globally, with an estimated 480 000 cases in 2014 [15] and significant
87 disparities between countries and regions. In Russia, Bangladesh, and China, the proportion of
88 previously treated TB cases that are multidrug-resistant is 49%, 29%, and 26% respectively [15]. In
89 Eastern Europe, the proportion of previously treated TB cases that are multidrug-resistant is 69.0%
90 in Belarus, 62.0% in Moldova and Estonia, 56.0% in Ukraine, 49.0% in Lithuania, 30% in Latvia, and
91 23.0% in Bulgaria [16, 17]. Many of these countries also have high rates of MDR-TB in new cases, for
92 example Belarus (34%), Moldova (24%), Ukraine (22%), and Estonia (19%) [15]. The high rates of
93 MDR-TB in these countries are in part due to disparities in the availability of high-quality treatment
94 [17].

95

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

104

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

113

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

119

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

126

127 **Migrants at high risk of MDR-TB**

128

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

141
142 There is also a relatively small group – in the context of the current mass movement of populations
143 – of “health tourists” who migrate or travel with the specific aim of seeking treatment for MDR-TB
144 [31]. These individuals may have previously received treatment, but failed multiple courses of
145 therapy in their home countries, and migrate to access better treatment options [8]. Within this
146 group, there is a small proportion of relatively affluent patients able to pay themselves for
147 treatment. Recently concerns have been raised around the implications of health tourism for
148 European health services and the wider public health [32, 33]. Disparities in rates of TB and MDR-TB
149 between low-incidence countries in Europe and high-incidence countries globally, and inequalities in
150 the distribution of resources (including in the availability and affordability of treatment) may be
151 drivers of this, and have been particularly highlighted between Western and Eastern Europe [17].
152 Overall, however, data on patterns of health tourism are lacking.

153

154 **Diagnosis of MDR-TB and screening strategies**

155

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

165

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

174

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

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

187
188 Screening for latent MDR-TB is highly problematic since current tests (tuberculin skin test and
189 interferon-gamma release assays) cannot distinguish between drug-susceptible and drug-resistant
190 TB, and cannot predict risk of reactivation. Moreover, the best chemoprophylaxis for individuals with
191 suspected latent MDR-TB has not yet been established. There is extremely limited data on the
192 effectiveness of chemoprophylaxis for suspected MDR-TB [47, 48]. Furthermore, WHO did not
193 recommend systematic prophylaxis with second-line TB drugs in contacts of patients with MDR-TB in
194 its recent guidelines [49]. Clinical trials are needed to inform any future recommendations.

195

196 **Treatment outcomes in migrants**

197

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

203

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

206 outcomes for MDR-TB patients in the UK, 72.3% of migrants had a successful treatment outcome,
207 compared with 90% of UK born (OR 0.29 [0.08-1.01]; $p=0.026$)[50]. This may be attributed to formal
208 and informal barriers to testing and treatment – including fears relating to legal status or
209 government, language and health literacy, lack of entitlement to services, and inability to pay –
210 resulting in delays in presentation and poor treatment outcomes. Such barriers are likely to be
211 exacerbated by increasingly restrictive health systems across Europe [3]. The intensive, complex, and
212 lengthy treatment, and high pill burden, as well as contextual factors like alcohol or drug use,
213 homelessness, and social stigma may further impact on treatment uptake and adherence for TB and
214 MDR-TB. These factors undoubtedly contribute to the acquisition of drug resistance [6, 23, 24, 40,
215 51].

216

217 However, the migration status of patients is often not recorded, and research findings are
218 inconsistent [52]. The limited data on treatment outcomes for MDR-TB in migrants in low-incidence
219 countries in Europe point to the need for further research in these communities, as well as the need
220 for strategies to improve the identification and treatment of MDR-TB in these hard-to-reach groups.
221 This is particularly pertinent in light of the shorter MDR-TB regimen now recommended by WHO
222 [53], which may help to improve treatment completion and cure, although further trial data are
223 awaited.

224

225 **Resource implications of treating and preventing MDR-TB in migrants**

226

227 Less than 25% of MDR-TB patients globally have been started on treatment, yet it is unclear how
228 many of these patients are migrants residing in low-incidence countries in Europe [54]. A recent
229 systematic review reported that the costs of treating MDR-TB (from the provider perspective) were
230 between US \$1218 - \$83,365 (in low- to high-income countries) in comparison to US \$258 - \$14,659
231 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

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

262

263 **Conclusions and action points**

264

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

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

279

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

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

299

300 **Transparency declaration**

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

304

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452

453 **Figure legend:**

454 **Figure 1 MDR-TB and migration in Europe***

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

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

461

462

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
<p>Problem</p> <ul style="list-style-type: none"> • 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 	<p>Access to services</p> <ul style="list-style-type: none"> • 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 <p>Screening and treatment guidelines</p> <ul style="list-style-type: none"> • 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 <p>Research</p> <ul style="list-style-type: none"> • Need for further research on MDR-TB in migrants to provide robust evidence base for policy and practice

