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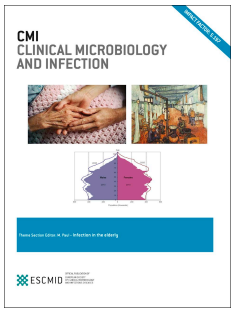

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Extrapulmonary tuberculosis among migrants in Europe, 1995 to 2017

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Abstract

Objectives

The proportion of tuberculosis (TB) cases in Europe occurring in migrants is increasing. Extrapulmonary TB poses challenges in diagnosis and treatment and causes serious morbidity and mortality, yet its extent in migrant populations is unclear. We assessed patterns of extrapulmonary TB in migrants across the European Union (EU)/European Free Trade Association (EFTA). We investigated the proportion of extrapulmonary TB cases among migrants versus non-migrants, and variations by specific site of disease, reporting European region, and migrant region of origin.

Methods

We carried out a cross-sectional secondary database analysis, utilising 23 years of data from the European Centre for Disease Prevention and Control's European Surveillance System for 32 EU/EFTA countries collected 1995-2017.

Results

1,270,896 TB cases were included, comprising 326,987 (25.7%) migrants and 943,909 (74.3%) non-migrants. 45.2% (n=147,814) of TB cases among migrants were extrapulmonary, compared to 21.7% (n=204,613) among non-migrants (p<0.001). Lymphatic, bone/joint and peritoneal/digestive TB were more common among migrant than non-migrant extrapulmonary cases. A lower proportion of extrapulmonary TB was seen in Eastern (17.4%, n=98,656 of 566,170) and Southern (29.6%, n=62,481 of 210,828) compared with Western (35.7%, n=89,498

of 250,517) and Northern (41.8%, n=101,792 of 243,381) Europe. Migrants from South-East Asia and Sub-Saharan Africa were at highest risk of extrapulmonary disease, with 62.0% (n=55,401 of 89,353) and 54.5% (n=38,327 of 70,378) of cases respectively being extrapulmonary.

Conclusions

Among TB cases in the EU/EFTA, extrapulmonary disease is significantly more common in migrants than non-migrants. There is a need to improve clinical awareness of extrapulmonary TB and integrate its detection into screening programmes.

Introduction

The proportion of tuberculosis (TB) cases in migrants has been rising across high-income countries in Europe [1] and the United States (US) [2]. In 2017, migrants comprised 33.1% of TB cases across European Union/European Economic Area (EU/EEA) countries, and over 70% in parts of Northern and Western Europe [3]. This trend is set to continue, as TB notification rates are falling faster in native-born residents than those of foreign origin in the EU/EEA [4]. In addition, migrant populations in high-income countries are growing, with 4.4 million people migrating to an EU Member State during 2017 [5].

While TB most commonly affects the lungs, it can present in almost any organ of the body, including the lymph nodes, pleura, central nervous system (CNS), bones and joints, genito-urinary tract and gastro-intestinal system [6], or disseminated as miliary TB [7]. While not usually transmissible, extrapulmonary TB can cause serious morbidity and mortality. It is more common among immunosuppressed individuals, such as those with HIV/AIDS. Extrapulmonary TB poses challenges in diagnosis and treatment, due to its wide variety of non-specific clinical presentations [8].

Globally, 15% of the 7 million incident TB cases notified in 2018 were extrapulmonary [9]. Despite this, extrapulmonary TB is rarely specifically incorporated into TB control programmes, including those targeting migrants. Current guidance from the European Centre for Disease Prevention and Control (ECDC) recommends screening for active pulmonary TB using chest X-ray and screening for latent tuberculosis infection (LTBI) using tuberculin skin test (TST) or an

interferon-gamma release assay (IGRA) soon after migrants from high TB incidence countries arrive in the EU/EEA [10], with no specific provision for detecting extrapulmonary disease.

Patterns of extrapulmonary TB in migrants are not well-understood, despite implications for morbidity and mortality. We aim to assess patterns of extrapulmonary TB in migrants in EU/European Free Trade Association (EFTA) countries through analysis of ECDC's European Surveillance System (TESSy) database. The specific objectives are to examine whether the proportion of extrapulmonary TB cases is greater in migrants compared with non-migrants, which specific sites of extrapulmonary disease are more or less common in migrants, and how the distribution of cases varies by European reporting region and migrants' region of origin.

Methods

Data and definitions

We analysed 23 years of data from ECDC's TESSy database for 32 EU/EFTA countries (henceforth 'Europe') collected from inception in 1995 to 2017. Detailed data collection methods and definitions have been described [3]. In brief, designated experts within national surveillance institutes submit case-based data to TESSy, where a TB case is defined following the World Health Organization (WHO) as a bacteriologically confirmed or clinically diagnosed case [11]. Data on all reported cases in Europe 1995-2017 were extracted.

The analysis was restricted to TB cases with known migrant status and site of TB. We define a migrant as a person born in, or having citizenship of, a country different to the reporting country. Extrapulmonary TB is classified as a case involving organs or anatomical sites other than the lungs, with or without co-existent lung disease. Specific site of extrapulmonary TB was grouped as: lymphatic, pleural, bone/joint including spine, disseminated, genito-urinary, peritoneal/digestive, CNS including meningitis, and other. Region of Europe was defined using the United Nations Geoscheme for Europe: Eastern, Northern, Southern and Western [12]. Region of origin was defined using an adaptation of World Bank regions: Eastern Europe and Central Asia, Europe, North America and Oceania, Latin America and the Caribbean, Middle East and North Africa, South-East Asia, and Sub-Saharan Africa [13]. Definitions are presented in Figure S1.

Statistical methods

We assessed how key demographic characteristics differed between migrants and non-migrants, using t tests for continuous variables and chi-square tests for categorical variables. We compared the difference in proportion of extrapulmonary TB between migrants and non-migrants using chi-square tests. We repeated this analysis in subgroups, firstly dividing the sample into drug susceptible and multi-drug resistant (MDR)-TB (defined as resistance to at least isoniazid and rifampicin), and secondly dividing the study period in two (1995-2006 and 2007-2017). In addition, we used two-sample tests of proportion to compare the difference in proportion of extrapulmonary TB at a given site between migrants and non-migrants, chi-square tests to compare the proportion of TB that is extrapulmonary between the different regions of

Europe, and one-sample tests of proportion to compare the difference in proportion of pulmonary versus extrapulmonary TB in each migrant region of origin. In sensitivity analyses, we repeated these analyses defining extrapulmonary TB as cases involving *only* organs or anatomical sites other than the lungs. A p value of $p<0.01$ was considered statistically significant. All analyses were conducted in StataSE v15.

Ethical statement

The study was based on data collected on the basis of statutory notification in each EU/EFTA country and reported anonymously to ECDC per decision No 2119/98/EC of the European Parliament and of the Council.

Results

Sample characteristics

1,611,762 TB cases were notified in the EU/EFTA between 1995-2017 and reported in TESSy, of which 1,270,896 (78.9%) had data available on migrant status and site of TB and were included in the analyses (Figure 1). The included sample comprises 326,987 (25.7%) migrants and 943,909 (74.3%) non-migrants. Migrant regions of origin and destination are shown in Figure S2, and sample characteristics by migrant status are presented in Table 1.

The mean age of included migrants with TB is 38 years compared with 48 years in non-migrants ($p<0.001$), and 59.9% (n=195,264 of 326,208) of migrants are male compared with 66.0%

(n=622,902 of 943,438) of non-migrants (p<0.001). Migrant TB cases in the EU/EFTA originate from diverse areas of the world, most commonly South-East Asia (34.2%, n=89,303 of 261,074) and Sub-Saharan Africa (26.9%, n=70,341). The most common countries of origin for migrants with TB are India (n=30,174), Pakistan (n=23,081), Somalia (n=20,453), and Romania (n=14,620). In Eastern and Southern Europe, the majority of TB cases are in non-migrants, whereas in Northern and Western Europe around half are in migrants. Migrants were reported to be less likely than non-migrants to have been previously diagnosed with TB (p<0.001).

Extrapulmonary TB in migrants

The proportion of TB that is extrapulmonary is significantly greater among migrants than non-migrants (Figure 2): 45.2% (n=147,814 of 326,987) of cases among migrants were extrapulmonary, compared to 21.7% (n=204,613 of 943,909) among non-migrants (p<0.001). This pattern is seen in both drug susceptible and MDR-TB (both p<0.001), and in the earlier (1995-2006) and later (2007-2017) parts of the study period (both p<0.001, Table S1).

Among extrapulmonary TB cases, specific site varies by migrant status (Table 2). For migrants, 47.6% (n=37,150 of 78,077) of extrapulmonary TB is lymphatic, compared with 25.3% (n=43,933 of 173,604) in non-migrants (p<0.001). This varies by country of origin, e.g. among migrants from India, 52.4% (n=2,079 of 3,971) of extrapulmonary TB is lymphatic. Conversely, 17.6% (n=13,730 of 78,077) of extrapulmonary TB is pleural in migrants versus 42.1% (n=73,052 of 173,604) in non-migrants (p<0.001). 24,965 TB cases (4,336 migrants and 20,629 non-migrants) were reported to include both pulmonary and pleural involvement. Differences are also seen for bone/joint (p<0.001) and peritoneal/digestive TB (p<0.001), which are relatively more common

in migrants than in non-migrants, and genito-urinary TB (p<0.001), which is less common in migrants.

Extrapulmonary TB by European reporting region

A relatively low proportion of extrapulmonary TB is seen in Eastern (17.4%, n=98,656 of 566,170) and Southern (29.6%, n=62,481 of 210,828) Europe compared with Western (35.7%, n=89,498 of 250,517) and Northern (41.8%, n=101,792 of 243,381) Europe (Table 3). Migrants are reported to have a greater proportion of extrapulmonary TB than non-migrants only in Western and Northern Europe (both p<0.001). For example, in Northern Europe, 58.5% of TB (n=72,868 of 124,547) is extrapulmonary among migrant cases compared with 24.3% (n=28,924 of 118,834) among non-migrants (p<0.001). Figure 3 shows that in Northern and Western European countries, a high proportion of TB occurs in migrants, with a particularly high proportion of extrapulmonary TB being among migrants. In Southern and Eastern European countries, a lower proportion of TB is in migrants, and this pattern does not differ markedly between pulmonary and extrapulmonary TB.

Extrapulmonary TB and migrants' region of origin

Over half of TB cases are extrapulmonary among migrants from South-East Asia (62.0%, n=55,401 of 89,353, p<0.001) and Sub-Saharan Africa (54.5%, n=38,327 of 70,378, p<0.001) (Figure 4), which are the most common regions of origin for migrant TB cases in Europe. For example, of 30,174 TB cases among migrants from India, 21,303 (70.6%) were extrapulmonary.

In contrast, the proportion of reported extrapulmonary disease is particularly low among migrants from Eastern Europe and Central Asia (20.6%, n=11,576 of 56,310, p<0.001).

Sensitivity analyses

In sensitivity analyses, we established that these patterns are seen whether extrapulmonary TB is defined as *any* extrapulmonary or *only* extrapulmonary TB (Figures S3-4 and Tables S2-4).

Discussion

We found that the proportion of TB that is extrapulmonary is significantly greater among migrants than non-migrants. These data are consistent with single-country studies in the UK and Netherlands indicating that migrants are at increased risk of extrapulmonary TB [14, 15]. The reasons for this are not fully understood. At a time of rising migration to Europe and other high-income countries, with a growing proportion of TB cases occurring in migrants [2, 5], extrapulmonary TB in this group is an increasingly important issue. Indeed, the reported proportion of extrapulmonary TB increased from 16.4% in 2002 to 22.4% in 2011 in the EU/EEA [16]. Extrapulmonary TB poses challenges in diagnosis and treatment, with implications for patient outcomes. Thus, migrants' disproportionate burden of extrapulmonary TB may contribute to their worse treatment outcomes [17].

We found that specific site of extrapulmonary TB varies by migrant status. The reasons for this are unclear, but it may reflect the distribution of types of extrapulmonary TB in countries of

origin. For example, India has relatively high rates of lymphatic TB [18], a pattern mirrored among Indian migrants. Migrants were observed to have a lower proportion of pleural TB than non-migrants. However, this should be interpreted with caution, as many cases were reported to include both pulmonary and pleural involvement. Such cases may be classified as having pulmonary plus pleural disease (i.e. extrapulmonary), or as pulmonary disease only. Differences are also seen for other sites of TB (bone/joint, peritoneal/digestive, and genito-urinary). However, the absolute numbers of cases are low for these extrapulmonary sites, so a statistical difference may have relatively little clinical implication. These could also potentially be artefacts; for example, genito-urinary TB may be misdiagnosed as more common sexually transmitted infections or urinary tract infections, delaying TB diagnosis [19].

We also found a higher proportion of extrapulmonary TB in Northern and Western Europe compared with Southern and especially Eastern Europe, with the disproportionate burden of extrapulmonary TB among migrants seen only in Northern and Western Europe. The reasons for this are unclear. Extrapulmonary TB is thought to usually follow reactivation of latent infection rather than occurring at initial infection, with the exception of TB meningitis [20]. Most migrant TB cases are infected before arrival in host countries, with subsequent reactivation of LTBI [21]. This is especially true in final destination, high-income countries of Northern and Western Europe, which may contribute to the higher prevalence of extrapulmonary TB in migrants in these regions. Transit countries in Southern and Eastern Europe may see a slightly higher proportion of migrants arriving with active TB or transmission, for example in refugee camps [22]. In addition, healthcare access for migrants varies significantly across Europe [23], and once migrants settle in final destination countries, they may become better integrated into health

systems, and more likely to seek care for symptoms of extrapulmonary TB. By contrast, public health initiatives targeting migrants in transit countries tend to focus on preventing the spread of pulmonary TB. However, even in final destination countries migrants often face significant barriers to healthcare access [24]; therefore this is unlikely to account fully for the observed differences across Europe.

The proportion of extrapulmonary TB is highest among migrants from South-East Asia and Sub-Saharan Africa. This is consistent with data from Germany and across the EU/EEA showing that migrant TB cases from Asia and Africa were more likely than non-migrant patients to present with extrapulmonary disease [25, 26]. Migrants from certain regions may be genetically predisposed to extrapulmonary manifestations of TB [14]. Some countries in Northern and Western Europe host large migrant populations from the Indian subcontinent, where extrapulmonary TB is relatively common [18]. Extrapulmonary TB is also more common in the immunosuppressed, including HIV/AIDS patients [27], and the high burden of TB-HIV co-morbidity in Sub-Saharan Africa may contribute to increased risk of extrapulmonary TB [28]. However, TB-HIV co-morbidity accounts for a small proportion of TB cases in Europe, and therefore is unlikely to be a major driver of the observed patterns.

Strengths and limitations

By using surveillance data reported by EU/EFTA Member States to ECDC between 1995-2017, this study utilises data from over 1 million TB cases, enabling a comprehensive analysis of patterns of extrapulmonary TB in migrants across Europe. In all EU/EFTA countries, TB is a notifiable disease; however, data quality varies significantly between national surveillance

systems, and there are gaps in reporting. 340,866 TB cases were excluded from our analyses because they lacked data on either migrant status or site of TB. The proportion of all notified TB cases that have this data available, and are therefore included, increases over time, from below 50% until 2001 to over 80% from 2002 and over 90% since 2004 (Table S5).

Most co-variates have good completeness in our dataset (Table S6). Age, gender, and reporting country are over 99% complete, country of origin is 90% complete, previous TB diagnosis is ~85% complete, and site of TB among extrapulmonary cases is ~70% complete. However, HIV status was only collected from 2000 onwards, meaning that in our sample only 17% of cases had data on HIV status. This potentially important variable was therefore excluded from analyses. The limited nature of the data available prevented us from unpicking the relative impact of host and environmental factors and *M.tb* lineage. This, and the pattern of drug resistance in relation to migration status and site of TB, warrants further investigation. Furthermore, migrant status is defined by country of birth in some countries and country of citizenship in others, which may influence the findings.

Implications

The findings have important clinical implications for migrant-receiving countries, particularly in Northern and Western Europe. Although there are many reports and guidelines relating to managing TB and migrant health, none adequately address the key issues arising from extrapulmonary TB in this group. There is a need to improve diagnostic facilities and awareness of extrapulmonary TB among healthcare staff, particularly when assessing patients from South-East Asia and Sub-Saharan Africa. In addition, detection of extrapulmonary TB should be

integrated into screening programmes, with a focus on migrants. Extrapulmonary TB must be considered when screening for latent as well as active disease, when it is essential to ascertain that patients do not have active extrapulmonary disease before initiating preventative chemoprophylaxis for LTBI. Programmes that target migrants for LTBI screening and treatment could therefore have an indirect benefit of detecting and preventing extrapulmonary TB.

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Conflict of interest: None

Authors' contributions: SH, JSF, LBN, and SEH were involved in concept and study design. MvdW and TN facilitated data access and retrieval. SEH carried out the analyses, with input from SH, JSF, LBN and KR. All authors contributed to manuscript writing.

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328 **Figure 1.** Sample flow chart

329 EU/EFTA: European Union/European Free Trade Association, TB: tuberculosis

330

331 **Figure 2**. Site of TB among migrant and non-migrant TB cases in the EU/EFTA, 1995-2017

332 (n=1,270,896)

333 EU/EFTA: European Union/European Free Trade Association, TB: tuberculosis

334 Extrapulmonary TB defined as any case of TB involving organs or anatomical sites other than the lungs,

335 with or without co-existent lung disease

336 p value calculated using χ^2 test (χ^2=6.7x10^4, p<0.001)

337 **Figure 3.** Proportion of pulmonary and extrapulmonary TB among migrant and non-migrant TB

338 cases in selected countries of the EU/EFTA, 1995-2017

339 EU/EFTA: European Union/European Free Trade Association, TB: tuberculosis

340 Extrapulmonary TB defined as any case of TB involving organs or anatomical sites other than the lungs,

341 with or without co-existent lung disease

342 The boxes in the figure illustrate the proportion of pulmonary and extrapulmonary TB cases that occur in

343 migrants in each country. On the map, the different shadings of the countries represent the proportions

344 of individuals with foreign citizenship living in that country on 1st January 2016 (source: Eurostat, online

345 data code: migr_pop1ctz).

346 **Figure 4**. Site of TB among migrant TB cases in the EU/EFTA by region of origin, 1995-2017

347 (n=261,074)

348 EU/EFTA: European Union/European Free Trade Association, TB: tuberculosis

Extrapulmonary TB defined as any case of TB involving organs or anatomical sites other than the lungs, with or without co-existent lung disease

*p<0.001, a greater proportion of TB is pulmonary

†<0.001, a greater proportion of TB is extrapulmonary

p values are two-sided, calculated using one-sample test of proportion (H_0 = the proportions of pulmonary and extrapulmonary TB are equal)

356 **Table 1**. Characteristics of migrant and non-migrant TB cases in the EU/EFTA, 1995-2017

357 (n=1,270,896)

	Migrants		Non-migrants		Total	
	n	%	n	%	n	%
Total	**326,987**	**25.7**	**943,909**	**74.3**	**1,270,896**	
Age						
Mean, SD	37.9	16.8	47.8	20.3	45.3	19.9
Gender						
Female	130,944	40.1	320,536	34.0	451,480	35.6
Male	195,264	59.9	622,902	66.0	818,166	64.4
Region of origin						
Eastern Europe and Central Asia	56,310	21.6	558,595	63.1	614,905	53.6
Europe, North America and Oceania	24,392	9.3	326,970	36.9	351,362	30.6
Latin America and the Caribbean	11,329	4.3	-		11,330	1.0
Middle East and North Africa	9,399	3.6	-		9,405	0.8
South-East Asia	89,303	34.2	-		89,353	7.8
Sub-Saharan Africa	70,341	26.9	-		70,378	6.1
Reporting region						
Eastern Europe	4,921	1.5	561,249	59.5	566,170	44.6
Southern Europe	69,159	21.2	141,669	15.0	210,828	16.6
Western Europe	128,360	39.3	122,157	12.9	250,517	19.7
Northern Europe	124,547	38.1	118,834	12.6	243,381	19.2
Previous TB diagnosis						
Yes	24,864	10.4	143,771	17.0	168,635	15.5
No	213,423	89.6	703,879	83.0	917,302	84.5
Site of TB						
Pulmonary	179,173	54.8	739,296	78.3	918,469	72.3
Extrapulmonary	147,814	45.2	204,613	21.7	352,427	27.7

358 EU/EFTA: European Union/European Free Trade Association, SD: standard deviation, TB: tuberculosis

359 Extrapulmonary TB defined as any case of TB involving organs or anatomical sites other than the lungs,

360 with or without co-existent lung disease

361 Data reported as: n, % unless otherwise stated

362 Sample sizes: Age, n=1,268,544; Gender, n=1,269,646; Region of origin, n=1,146,733; Reporting region,

363 n=1,270,896; Previous TB diagnosis, n=1,085,937; Site of TB, n=1,270,896

364 The difference between migrants and non-migrants for each characteristic is statistically significant at
365 p<0.001 calculated using t test for continuous variables or χ^2 for categorical variables: Age, t=251.9;
366 Gender, χ^2=4.0x10^3; Reporting region, χ^2=3.6x10^5; Previous TB diagnosis, χ^2=6.0x10^3; Site of TB,
367 χ^2=6.7x10^4

368

369

370 **Table 2**. Site of TB among migrant and non-migrant extrapulmonary TB cases in the EU/EFTA,
371 1995-2017 (n=251,681)

	Migrants		Non-migrants	
	n	%	n	%
Lymphatic	37,150	47.6*	43,933	25.3
Pleural	13,730	17.6†	73,052	42.1
Bone/joint incl. spine	6,417	8.2*	12,513	7.2
Disseminated	3,947	5.1*	8,245	4.8
Genito-urinary	3,174	4.1†	11,547	6.7
Peritoneal/digestive	3,091	4.0*	3,879	2.2
CNS incl. meningitis	2,775	3.6*	5,835	3.4
Other	7,793	10.0*	14,600	8.4
Total	78,077		173,604	

372 CNS: central nervous system, EU/EFTA: European Union/European Free Trade Association, TB:
373 tuberculosis
374 Extrapulmonary TB defined as any case of TB involving organs or anatomical sites other than the lungs,
375 with or without co-existent lung disease
376 'Other' refers to TB infection in any organ or anatomical sites of the body that falls outside the categories
377 above
378 There are an additional 100,746 cases not reported here for which site of TB is known to be
379 extrapulmonary, but exact site of TB is unknown
380 * Proportion is higher in migrants
381 † Proportion is higher in non-migrants

382 **Table 3**. Site of TB among cases reported by countries in the Eastern, Southern, Western and

383 Northern regions of the EU/EFTA, 1995-2017 (n=1,270,896)

	Pulmonary TB		Extrapulmonary TB		Total
	n	%	n	%	n
Eastern Europe	**467,514**	**82.6**	**98,656**	**17.4***	**566,170**
Migrant	*3,994*	*81.2*	*927*	*18.8*	*4,921*
Non-migrant	*463,520*	*82.6*	*97,729*	*17.4*	*561,249*
Southern Europe	**148,347**	**70.4**	**62,481**	**29.6***	**210,828**
Migrant	*47,908*	*69.3*	*21,251*	*30.7*	*69,159*
Non-migrant	*100,439*	*70.9*	*41,230*	*29.1*	*141,669*
Western Europe	**161,019**	**64.3**	**89,498**	**35.7***	**250,517**
Migrant	*75,592*	*58.9*	*52,768*	*41.1*	*128,360*
Non-migrant	*85,427*	*69.9*	*36,730*	*30.1*	*122,157*
Northern Europe	**141,589**	**58.2**	**101,792**	**41.8***	**243,381**
Migrant	*51,679*	*41.5*	*72,868*	*58.5*	*124,547*
Non-migrant	*89,910*	*75.7*	*28,924*	*24.3*	*118,834*
Total	**918,469**	**72.3**	**352,427**	**27.7**	**1,270,896**

384 EU/EFTA: European Union/European Free Trade Association, TB: tuberculosis

385 Extrapulmonary TB defined as any case of TB involving organs or anatomical sites other than the lungs,

386 with or without co-existent lung disease

387 *The difference in proportion of TB that is extrapulmonary between each region and each other region is

388 significant at p<0.001, p values calculated using χ^2, e.g. Eastern vs. Northern Europe $\chi^2=5.4\times10^4$, p<0.001