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Impact of migration on tuberculosis epidemiology and control in the EU/EEA

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Recently, European Union (EU)/European Economic Area (EEA) countries have witnessed an unprecedented volume of migration, with 1,046,599 migrants arriving in Europe in 2015 [1]. Of these migrants, most have Syrian, Afghan or Iraqi nationality, and they mainly arrived via the eastern Mediterranean route. Before the increase in migration in 2015, the EU/EEA area was already an attractive destination, with 33.5 million people born outside of the EU living in an EU country on 1 January 2014 [2].

Two reports published in this issue of *Eurosurveillance* address the potential impact of migration on tuberculosis (TB) epidemiology in the EU/EEA [3,4]. The article by Hollo et al. [3] focuses on the influence of migratory movements within the EU/EEA of people originating from other EU/EEA countries. Within the EU, free movement of persons is a fundamental right which is guaranteed to EU citizens by the Treaties [5]. In 2013, 3.3% of all TB cases notified in the EU/EEA originated from other EU/EEA countries and more than 60% of those originated from Poland and Romania. This reflects the diversity of the epidemiological settings and migration flows within the EU/EEA, with Romania having a high TB notification rate whereas the TB notification rate in Poland is only slightly above the EU/EEA average [6]. The article addresses the possible impact of this diversity on the local incidence of disease. Ködmön et al. [4] analysed the epidemiology of TB cases in individuals originating from outside the EU/EEA. In 2013, these accounted for 22% of all notified TB cases. The difference in incidence between the migrants' country of origin and country of settlement may be greater than the differences between EU/EEA countries, and the potential impact is a matter of concern.

The latest TB surveillance data report, published by the World Health Organization Regional Office for Europe and the European Centre for Disease Prevention and Control on the occasion of World TB Day 2016, shows that in 2014, 58,008 TB cases were reported by 29 EU/EEA countries (Italy and Liechtenstein did not report), a notification rate of 12.8 TB cases per 100,000 population [6]. Since the start of EU-level TB surveillance in 1995, the annual number of reported cases has decreased by almost 50% [7], with a decrease in the TB notification rate of on average 3.8% per year in the last five years. There is significant heterogeneity in the EU/EEA, with country-specific notification rates differing more than 30-fold, ranging from 2.5 in Iceland to 79.7 per 100,000 in Romania, and with 18 countries reporting rates below 10 cases per 100,000. Likewise, the case load is unevenly distributed with three countries (Poland, Romania and the United Kingdom (UK)) accounting for ca 50% of all reported cases and Romania alone accounting for 27% of all cases.

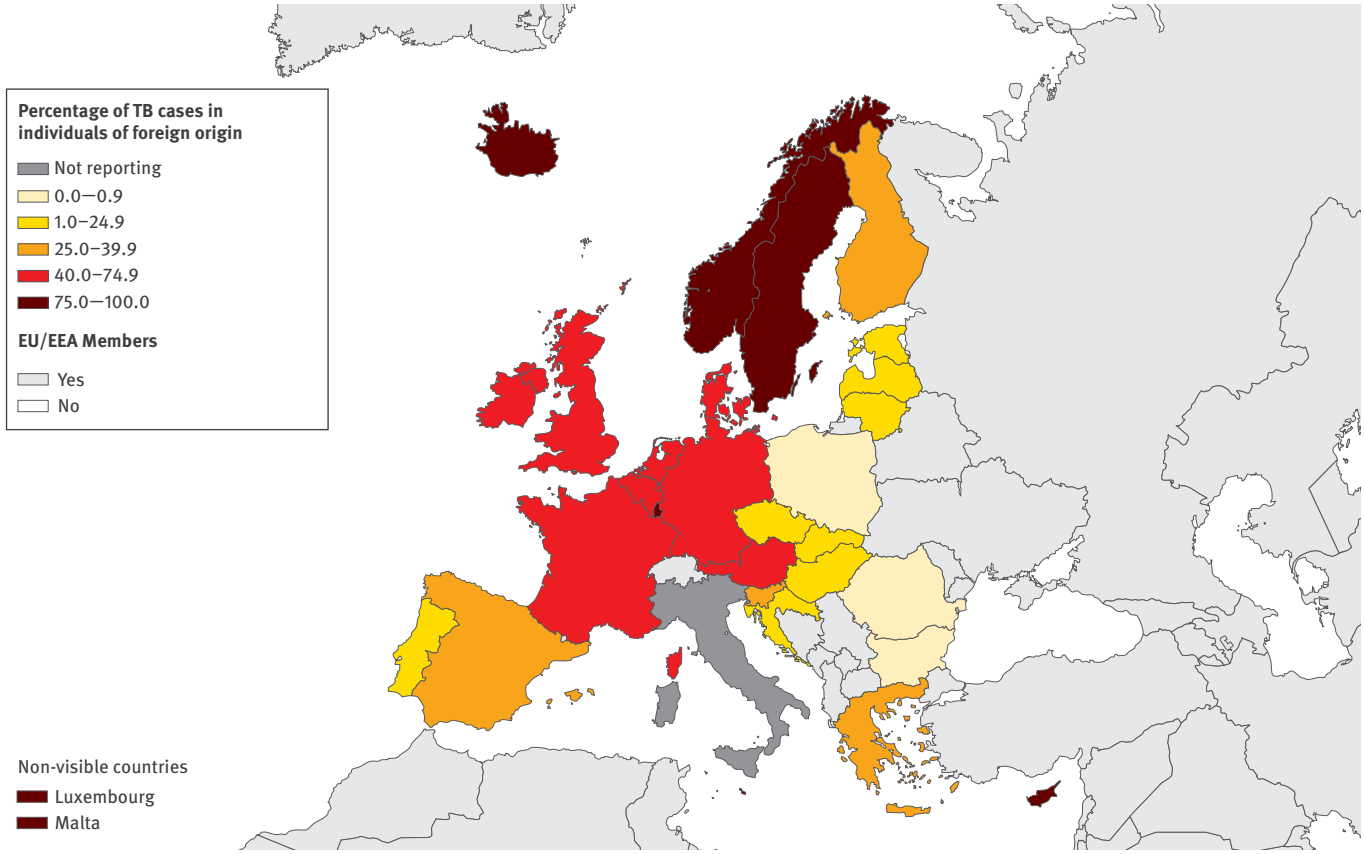
Of all TB cases notified in 2014, 15,565 (27%) were diagnosed in individuals of foreign origin, i.e. is born in a country different to the reporting country [6]. The proportion of TB cases in individuals of foreign origin increased in the last decade from 20% in 2005 to 27% in 2014. This proportional increase does not reflect an increase in numbers. Country-specific proportions of TB cases in individuals of foreign origin ranged from below 1% in Bulgaria, Poland and Romania to above 75% in Cyprus, Iceland, Luxembourg, Malta, Norway and Sweden (Figure).

Four countries (France, Germany, Spain and the UK) reported 75% of all cases in individuals of foreign origin. Thus, for the EU/EEA to progress towards TB elimination, we need to address TB in migrant population groups [8].

The TB notification data of 2015 are currently being collected by the countries and will be notified to the EU-level surveillance system later this year. EU-level TB surveillance data allow for evaluating total number of TB cases in individuals from other countries but not

Figure

Percentage of tuberculosis cases in individuals of foreign origin, European Union/European Economic Area, 2014 (n = 58,008)



EU/EEA: European Union/European Economic Area; TB: tuberculosis.

Source: [6]

for assessing the influence of recent migration on TB epidemiology since information on time since arrival in the country is not requested. This information is collected in a number of EU/EEA countries, for example in UK and the Netherlands [9,10].

Historically, migrants have frequently been regarded as potential carriers of disease that could be transmitted to the local population or generate costs to the health system. This was already the case when Europeans migrated to America in the 19th century and were submitted to stringent health controls before departure and on arrival, mainly for the identification of TB and psychiatric diseases, thus ascertaining that they would not be a financial burden for the society [11]. Hollo et al. [3] showed that only a small proportion of TB cases in individuals of foreign origin in EU/EEA countries originated from other EU/EEA countries and therefore transmission associated with migration within the EU/EEA will be limited. While the report by Ködmön et al. [4] acknowledges the important and increasing contribution of migration from high-incidence countries outside the EU/EEA to the epidemiology of TB in Europe, the risk of TB transmission to the resident population appears to be negligible based on the results of studies using genotyping information [12,13].

Screening migrants, before, at or after entry, may be considered and is an option that is implemented by some EU countries [14]. It aims at identifying active TB cases before or soon after arrival in the host country to ensure treatment and to limit onward transmission. The timing, extent and procedure of screening applied in the different EU/EEA countries are very diverse [14] and information on cost effectiveness is limited [15]. What has been shown is that TB rates often remain high in migrant populations long after entry into the host country due to reactivation of a previously acquired TB infection or, more rarely, recent infection acquired in the receiving country [16,17]. Therefore, some countries submit migrants to repeated screening [18]. In general, this implies higher costs, and the yield of repeated screening seems to decrease with time.

It is important to remember that, even in population groups where TB is considered a frequent disease, the incidence rate is seldom higher than 200 per 100,000 population, meaning that the vast majority of migrants,

even those originating from so-called high-incidence countries do not have and never will develop TB. Targeting the appropriate group and using the appropriate method for screening is therefore important and can reduce the cost of the procedure.

The estimated TB incidence in two of the three main countries of origin of the current migrants (Afghanistan, Iraq and Syria) is not substantially different from that in the EU/EEA, i.e. 189 per 100,000 population in Afghanistan, 43 in Iraq and 17 in Syria vs 13.2 per 100,000 in the EU/EEA (range: 3.3 in Iceland to 81.0 in Romania) [19]. As expected, the number of TB cases detected when screening Syrians is low [20]. Thus, screening for active TB is presumably not a good option for migrants from low TB incidence countries. Nevertheless, migrants may have an increased risk of acquiring TB infection or developing TB disease due to the challenging conditions encountered during travel to the EU/EEA or while waiting in the reception centres or temporary housing for the result of their application for refugee status. A pilot study conducted in Switzerland demonstrated that migrants who travelled by ground and sea transportation had a significantly higher risk of having latent TB infection (LTBI) than migrants travelling by air [21]. Thus travel and housing conditions should be taken into account when assessing whether screening programmes are necessary.

To reduce the pool of TB-infected cases that might give rise to active TB cases, migrants can be screened for LTBI by tuberculin skin test or interferon gamma release assay. This strategy has been implemented in some countries for all legal migrants, for selected categories of legal migrants or for asylum seekers/refugees [14]. Screening for LTBI and providing preventive treatment has been shown to be cost-effective for migrants from countries with a TB incidence of more than 200 per 100,000, especially if the strategy is focused on young migrants [22].

In conclusion, even though the majority of migrants entering the EU at the moment do not originate from high-incidence countries, TB in migrants is proportionally becoming more important in the EU/EEA. Migrants may arrive in the EU/EEA with TB or develop TB later on due to a latent infection contracted in their country of origin. Screening for active disease (by radiography or clinical examination) can diagnose prevalent TB but will not reduce incident TB after arrival. Thus, it is crucial to make the health system accessible to all, including undocumented migrants, and to provide migrants with the care that they need to ensure early TB diagnosis and treatment [23].

Conflict of interest

MvdW is among the authors of references [3] and [4] described in this editorial.

Authors' contributions

MvdW and JPZ contributed equally to the writing of the manuscript.

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Increased incidence of invasive meningococcal disease of serogroup C / clonal complex 11, Tuscany, Italy, 2015 to 2016

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We report an increase of serogroup C *Neisseria meningitidis* invasive meningococcal disease in Tuscany. From January 2015 to end February 2016, 43 cases were reported, among which 10 were fatal, compared to two cases caused by serogroup C recorded in 2014 and three in 2013. No secondary cases occurred. Thirty–five strains belonged to C:P1.5–1,10–8:F3–6:ST-11(cc11). Control measures have been adopted and immunisation campaigns implemented. Studies on risk factors and carriage are ongoing.

In this report we present an unexpected increase of invasive meningococcal disease (IMD) in Tuscany, Italy, since January 2015, leading to a total of 43 cases, of whom 10 were fatal, due to infection with serogroup C *Neisseria meningitidis*. In Italy, serogroup C is the second most common serogroup (31% of the 115 cases with a known serogroup in 2014), after serogroup B (48% of the 115 cases in 2014) [1]. In Tuscany, the total number of IMD cases was 16 in 2014 and 12 in 2013, with two and three cases caused by serogroup C, respectively [1].

Epidemiological features

From January 2015 to February 2016, 43 laboratory-confirmed cases of IMD due to serogroup C *N. meningitidis* (31 in 2015, 12 in 2016) were reported from the Regional Health Authority of Tuscany (RHAT) to the Italian National Surveillance System for Invasive Bacterial Disease (IBD). No secondary cases were detected. The incidence rate (IR) of serogroup C cases was higher compared with the previous years: 0.83 per 100,000 inhabitants in 2015 and 1.98 in the first two months of 2016 whereas the average IR for 2012–2014 was 0.08 per 100,000 inhabitants ranging from 0.05 in 2014 to 0.11 in 2012.

The National Reference Laboratory at the National Institute of Health (Istituto Superiore di Sanità, ISS) received 22 bacterial isolates and 18 clinical samples (10 from cerebrospinal fluid (CSF) and 8 from blood) from 40 patients; for three cases material was not available. Thirty-five out of the 40 samples analysed were confirmed as C:P1.5–1,10–8:F3–6:ST-11 (cc11).

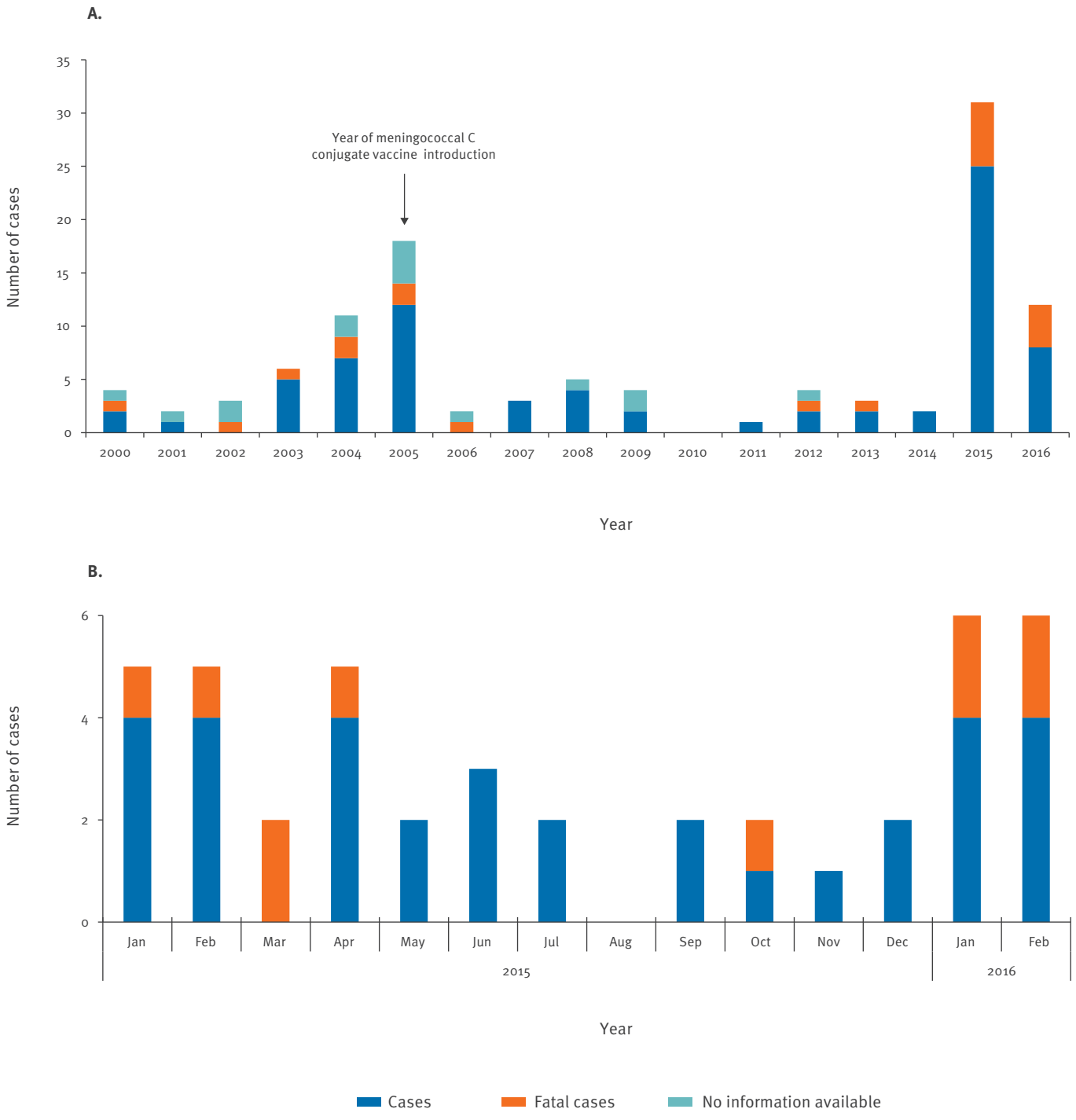
The median age of the 43 cases reported in the period was 28 years (range: 9–82), with the age group 20–29 years being the most affected (n=15; IR: 3.9/100,000), followed by the age group 9–19 years (n=10; IR: 2.6/100,000). Interestingly, 18 cases were reported among people over 30 years old (IR: 0.5/100,000), and 11 among people over 55 years old (IR: 0.6/100,000). There was no notable difference between males and females, with 21 cases registered among women and 22 among men.

The main clinical manifestations were: sepsis only (n=18), sepsis and meningitis (n=14), followed by meningitis only (n=11). Ten patients aged between 12 and 82 years died.

Information on vaccination status was available for 42 of the 43 cases detected between January 2015 and February 2016. Five patients had been vaccinated with meningococcal C conjugate (MCC) vaccine. Apart from one case in an individual aged 62 years, vaccinated on the day of the symptom onset, in the remaining four cases aged 9, 12, 17, 22 years, the vaccine was administered in 2006, 2007, 2013 and 2008, respectively. In the latter cases, the apparent vaccine failure was likely to be due to the relatively short duration of the protection induced by one vaccine dose [2]. Two of the

Figure 1

Annual distribution of serogroup C invasive meningococcal disease cases by outcome, January 2000–February 2016 (n=111 cases) (A) and monthly distribution, January 2015– February 2016 (B) (n=43 cases), Tuscany, Italy

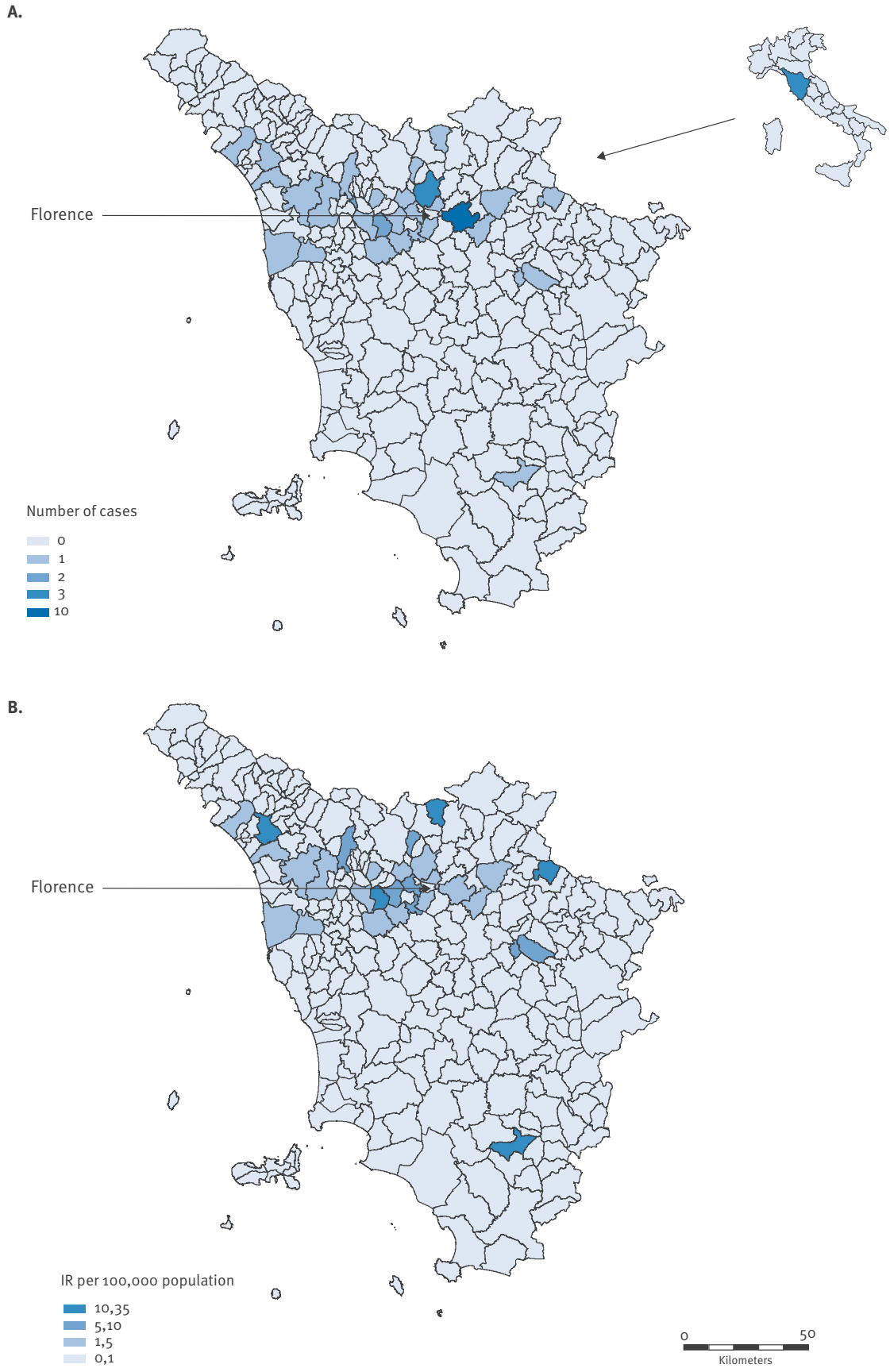


vaccinated cases developed meningitis and two sepsis (one of them died).

Figure 1 shows the case distribution by year from January 2000 to February 2016 and by month for January 2015 to February 2016, and Figure 2 presents the geographical distribution of the cases. An increase in the number of cases was observed since January 2015 in a densely populated area in the north of Tuscany, between the cities of Florence, Prato, and Empoli. Between January and April 2015, the cases were confined in this area. At the end of the spring, some cases occurred in the coastal area of Tuscany, between Pisa and Viareggio, an area frequented by young people during the summer. From the end of September 2015, the cases reappeared in the original area, where 12 cases with four deaths occurred in the first two months of 2016.

Figure 2

Number (A) and incidence rate per 100,000 inhabitants (B) of serogroup C invasive meningococcal disease cases, by municipality of symptom onset; Tuscany, Italy, January 2015 to February 2016



The incidence rate was calculated as the ratio between the number of cases in the study period (14 months) divided by the person-years of exposure (calculated as the people living in each municipality of Tuscany in 2015 (www.demo.istat.it), multiplied by the exposure time in years (i.e. 14 months/12=1.17 years)).

Background

Meningococcal serogroup C strains cc11, are known to cause invasive disease burden worldwide [3] and are responsible for high mortality rates among cases [4]. Outbreaks due to C:P1.5–1,10–8:F3–6:ST-11(cc11) of IMD were reported in Germany in 2013 [5], in France in 2014 [6], in Italy among staff members of a cruise ship at the port of Livorno, Tuscany, in 2012 [7], and in two clusters in northern Italy, in December 2007 and July 2008, respectively, showing a high rate of septicaemia and fatal outcome [8].

The RHAT introduced the MCC vaccine in the regional immunisation schedule in 2005, with three doses to all children at three, five, and 13 months of age (subsequently turning to a single dose at 13 months, in 2008), and a catch-up immunisation until six years of age with a single dose. In 2007, the RHAT also implemented a catch-up vaccination programme with a single dose of MCC targeting the age group 11 to 14 year-olds. At national level, MCC was introduced in the Italian National Immunisation Plan in 2012 [9].

Public health response

Since March 2015, the RHAT involved ISS in the microbiological characterisation (including genomic analysis) and public health response. The factors contributing to an excess of IMD cases due to such hyper-virulent meningococcal C strain remain currently unknown but investigations are ongoing. An immunisation campaign has been implemented and continuously adapted to the evolution of the epidemiological situation. Starting with 30 March 2015, a single dose of meningococcal (ACYW) polysaccharide-protein conjugate vaccine has been actively offered free-of-charge to the age group 11–19 years-old, even if already vaccinated with MCC in childhood (letters with invitations have been sent to individuals within this age group); the vaccine has been offered to individuals aged 20–44 years residing in the area of the local health units that reported at least one case of serogroup C *N. meningitidis* since 2015 (Arezzo, Empoli, Florence, Lucca, Massa, Pistoia, Pisa, Prato and Versilia). Up to 31 December 2015, 120,272 children and teenagers aged between 11 and 19 years were vaccinated, leading to a coverage of 42.5% in this age group; 109,101 individuals aged between 20 and 44 years were vaccinated (vaccine coverage 14%). On 16 February 2016, due to the increasing number of cases in age groups not previously included in the vaccination target groups, the immunisation campaign was extended to the whole Tuscany Region and to older people, using the monovalent vaccine as an alternative option to the tetravalent vaccine, maintaining the active offer only to 11–20 years age group.

Following the advice of the European Centre for Disease Prevention and Control (ECDC), standard operating procedures for public health management of IMD, including contact tracing and administration of chemoprophylaxis to close contacts, already established before 2015, were extended and included the recommendation to offer vaccination to unimmunised people [10].

Conclusion

In order to investigate the reasons of this unusual increase in the number of cases, to assess possible epidemiological links between cases, and to identify specific groups of population at risk for both meningococcal serogroup C disease and carriage status, research protocols consisting in detailed investigation of the cases and *N. meningitidis* cross sectional carriage surveys are going to be implemented in Tuscany, shortly. Molecular characterisation of meningococcal of serogroup C isolates, in particular those belonging to the finetype C:P1.5–1,10–8:F3–6:ST-11(cc11), is in progress, to define the correlation with isolates reported in other countries [5,6]. The same analysis is now performed also in IMD cases occurring in other Italian Regions, in order to verify the spread of the strain involved in the outbreak in Tuscany to other Italian areas.

These investigations will help to better understand the dynamic of the ongoing circulation of this hyper-virulent meningococcal serogroup C strain and to identify groups of population at higher risk, in order to address specific prevention strategies, develop preparedness plans for an effective response to future IMD threats, and to address the ongoing public health concern.

At present, the Italian Health Authorities have enhanced IMD surveillance activities but did not consider necessary to provide special recommendations for people travelling to Tuscany.

Acknowledgements

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Conflict of interest

None declared.

Authors' contributions

PS proposed the study and together with AM, PP and GR conceived the study design. PS drafted the manuscript. AM and PP performed the statistical analysis of IMD clinical cases and together with GR further drafted the text. FV contributed to the public health responses regarding the IMD cases at regional level. CF, AN, PV performed the microbiological analyses on samples under the supervision of PS. FPD, SI, RG contributed to the revision of the analysis of IMD cases and together with RG and MGP further revised the manuscript. GR critically revised the manuscript. All authors have read and approved the submitted manuscript.

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Presentation with gastrointestinal symptoms and high case fatality associated with group W meningococcal disease (MenW) in teenagers, England, July 2015 to January 2016

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Atypical clinical presentations associated with group W meningococcal disease (MenW) are well-described and include pneumonia, septic arthritis, endocarditis and epiglottitis/supraglottitis. Following anecdotal reports of teenagers presenting with predominantly gastrointestinal symptoms, we undertook a case review of MenW cases in 15 to 19 year-olds diagnosed in England between July 2015 and January 2016. Of the 15 cases, seven presented with a short history of nausea, vomiting and diarrhoea; five of these seven cases died within 24 hours of presentation to hospital.

The United Kingdom is currently experiencing a national outbreak of group W invasive meningococcal disease (IMD) due to rapid expansion of a single endemic hyper-virulent strain belonging to sequence type (ST) 11 clonal complex (cc) [1]. Group W IMD is associated with atypical clinical presentations, including pneumonia, septic arthritis, endocarditis and epiglottitis/supraglottitis, mainly in older adults [2]. In early 2016, enhanced national surveillance conducted by Public Health England identified two fatal group W IMD cases in teenagers who presented with predominantly gastrointestinal symptoms, prompting a review of all 15 to 19 year-olds diagnosed with group W IMD in England in the current epidemiological year. Laboratory-confirmed cases were identified through national surveillance [1] and case records were rapidly reviewed on HPZone, a national web-based case management system used by health protection teams (HPTs) to record public health events and actions.

Case series

Between July 2015 and January 2016, 15 group W IMD cases were confirmed in previously-healthy 15 to 19 year-olds (9 females, 6 males), none of whom had received a meningococcal ACWY (MenACWY) conjugate vaccine. No direct epidemiological, temporal or spatial links between cases were identified. Nine cases were confirmed by culture and eight were serotyped as W:2a, a surrogate marker for the hyper-virulent ST-11 cc (Table). For each case, all available data in the public health and surveillance records were retrieved retrospectively and summarised in the Table.

Seven teenagers (6 females, 1 male) presented predominantly with an acute (24–48 hour) history of gastrointestinal symptoms (nausea, vomiting and/or abdominal pain) together with or followed by diarrhoea in the 24 hours before attending hospital. Two cases were confirmed by blood culture and subsequently characterised as W:2a, a surrogate marker for the hyper-virulent ST-11 cc; the other five were confirmed by PCR. Four of the seven patients had been reviewed either by their general practitioner (GP) or in the Accident and Emergency Department (A and E) on the first day (n=3) or second day (n=1) of illness and sent home with a diagnosis of gastroenteritis. A non-blanching rash at presentation, leading to a consideration of IMD in the differential diagnosis, was identified in only two of the seven teenagers after arrival in hospital. At least two patients were isolated in a side-room in A and E because of diarrhoea. Five of the seven teenagers died. One had collapsed at home and died in A and E despite initial successful resuscitation. Two died with a presumed diagnosis of 'gastrointestinal sepsis' and 'peritonitis' soon after presentation to A and E and before they could be transferred to intensive care unit (ICU), while two others died in the ICU within 24 hours of admission. All fatal cases had multi-organ failure. A post-mortem report in one case noted 'necrotic intestine, shocked lung and systemic sepsis'. Of the two

Table

Summary of histories of laboratory-confirmed cases of invasive meningococcal disease, as well as infecting strain and outcomes based on public health and surveillance records, England, July 2015–January 2016 (n=15)

History and clinical features	Initial assessment[a]	IMD suspected	ICU	Outcome	Confirmation[b]	Final diagnosis
2 days D and V, stomach cramps lethargy, no rash	Saw GP on Day 1 and sent home with gastroenteritis diagnosis; sudden deterioration Day 2 with rapid progression in A and E; initially diagnosed with abdominal sepsis	N	N	Died in A and E	Blood culture	Septicaemia
1 day vomiting then diarrhoea and sore limbs; no rash	Saw GP on Day 1, sent home with gastroenteritis diagnosis; came to A and E later same day	N	N	Died in A and E	PCR blood	Septicaemia
1 day with D and V, influenza-like illness, and rapid deterioration	Profoundly septic with seizures on admission on Day 1, then became comatose	N	Y	Died in ICU next day	PCR blood	Septicaemia
3 days of D and V, headache and dehydration	Went to A and E on Day 2, sent home with gastroenteritis diagnosis; returned next day with rapid deterioration and multi-organ failure.	N	Y	Died in ICU same day	Blood culture	Septicaemia
2 days with headache and vomiting followed by 1 day diarrhoea	Found collapsed at home on Day 3 and rushed to A and E; petechial rash on back observed at A and E.	Y	N	Cardiac arrest in A and E. Died.	PCR blood	Septicaemia
1 day D and V, fever[c], headache	Hospital admission on Day 1; initial blood culture and CSF meningococcal PCR negative; developed rash after hospital admission and blood sample subsequently sent for PCR analysis tested positive (reported 12 days after onset)	N	Y	Survived	PCR blood	Septicaemia
1 day D and V, abdominal pain	Saw GP on Day 1, went to A and E next day; hypotensive, tachycardic, petechiae on face	Y	Y	Survived	PCR blood	Septicaemia
Generally unwell for 1 week; fever[c], short of breath, general aches (no rash)	Presented to A and E with transient ischaemic attacks, developed pulmonary embolism	N	N	Cardiac arrest in A and E. Died.	Blood culture	Septicaemia
1 day of fever[c], mild headache, nausea (no rash)	Admitted on Day 1 for 24 hours only; diagnosis confirmed by blood culture after discharge	N	N	Survived	Blood culture	Septicaemia
2 hours fever[c], sore throat, stiff neck and headache, with purpuric rash	Presented directly to A and E, admitted to ICU but improved within 3 days	Y	N	Survived	CSF culture	Meningitis and septicaemia
Fever[c], neck pain, aches – improved, then had painful wrist joint 3 days later	Saw GP on Day 4 with painful wrist and was referred to hospital; wrist washed out	N	N	Survived	PCR joint fluid	Septic arthritis
3 days fever[c], vomiting, hip and elbow joint pain	Admitted to hospital on Day 4 and treated with IV antibiotics, no orthopaedic intervention	N	N	Survived	Blood culture	Septic arthritis
1 day of fever[c], malaise and respiratory distress	Radiologically confirmed pneumonia on Day 1	N	N	Survived	Blood culture	Pneumonia
2 days fever[c], headache, coryza followed by 1 day vomiting and coughing blood	Radiologically confirmed pneumonia on Day 3	N	N	Survived	Blood culture	Pneumonia
5 days sore throat, fatigue, lethargy, lymphadenopathy; no fever, no rash	Seen at hospital on Day 5 and blood cultures taken but was not hospitalised; received ambulatory IV antibiotics	N	N	Survived	Blood culture	Atypical

A and E: accidents and emergency department; CSF: cerebrospinal fluid; D and V: diarrhoea and vomiting; GP: general practitioner; IMD: invasive meningococcal disease; ICU: intensive care unit; IV: intravenous; N: no; NT: non typeable; PCR: polymerase chain reaction; Y: yes.

[a] Days are numbered from the day of symptom onset which is Day 1.

[b] All culture isolates were subsequently confirmed as W:2a, a surrogate marker for the hyper-virulent sequence type 11 clonal complex, apart from one patient with pneumonia (serotyped as NT/NT/NT).

[c] Temperature was not reported.

patients who survived, both had short histories of vomiting and diarrhoea for less than 24 hours, went directly to A and E and were seriously unwell at presentation, requiring aggressive resuscitation and ICU admission.

Of the remaining eight cases (3 females, 5 males), seven cases were confirmed by blood (n=6) or cerebrospinal fluid (n=1) culture and six were subsequently characterised as W:2a, a surrogate marker for the hyper-virulent ST-11 cc; a blood culture from one patient with pneumonia was serotyped as NT/NT/NT. Among these eight individuals, two had the more characteristic clinical presentations of septicaemia – fever followed by rapid clinical deterioration (neither had a non-blanching rash) – and one died soon after presenting to A and E. A third teenager presented to A and E within hours of developing symptoms consistent with bacterial meningitis, was treated quickly and recovered without complications.

Four of the remaining five patients had other recognised 'atypical' presentations, including septic arthritis and pneumonia. The final case had non-specific symptoms lasting several days and no fever. This individual was managed with intravenous antibiotics in an ambulatory setting and blood cultures subsequently confirmed the diagnosis.

Discussion

Laboratory-confirmed group W IMD cases in England have increased from 19 cases in the 2008/09 epidemiological year to 176 cases in 2014/15, and its contribution to total IMD cases increased from 1.7% to 24% of all confirmed cases, respectively [3]. This increase has resulted from rapid expansion of a single endemic hyper-virulent strain belonging to ST 11 cc, which is also responsible for the ongoing group W IMD outbreak in Chile and other South American countries [4]. In August 2015, the United Kingdom (UK) introduced an adolescent MenACWY conjugate vaccination programme targeting 14 to 18 year-olds and new undergraduate university entrants [1].

The increase in group W IMD cases was communicated to clinical and public health colleagues through national briefing notes, peer-reviewed publications and online training materials (www.gov.uk/government/collections/meningococcal-acwy-menacwy-vaccination-programme). These communications emphasised the high case fatality and intensive care admissions, and the well-described atypical clinical presentations – pneumonia, epiglottitis/supraglottitis and septic arthritis – seen in up to a quarter of cases [2].

Although nausea, vomiting and diarrhoea are well-described symptoms of meningococcal disease [5] and are included in most public awareness leaflets and websites (e.g. http://www.mrfpaediatricguide.info/diagnosis.php.html), IMD presentation with primarily gastrointestinal symptoms, whilst previously described, is rare [6,7]. An extensive review of the literature identified only one case report in 1999 in an 80 year-old woman who presented with fever, diarrhoea and abdominal pain; those authors, in turn, had only ascertained three previous cases in young adults in the literature [8]. Consequently, for the cases presented here, IMD was often not considered at first clinical assessment and public health actions, including chemoprophylaxis and vaccination, were, therefore, often delayed and by up to two weeks in one case. There were, however, no secondary cases identified among close contacts.

Interestingly, the unusual gastrointestinal presentation was also reported in the ongoing group W IMD outbreak in Chile, where 14 of 58 group W IMD cases (24%) were initially diagnosed as gastroenteritis and eight of these 14 died [9]. Overall, diarrhoea was the only symptom that was over-represented among the 19 fatal cases (56% vs 27%, $p=0.034$), most of whom died within a day of hospitalisation. Early diarrhoea and absence of fever are associated with poor prognosis in IMD, perhaps due to later recognition [10,11].

We are currently following up all confirmed group W IMD cases in England and collecting more detailed clinical data from hospital records for cases presenting with predominantly gastrointestinal symptoms. We are aware of similar presentations in at least three young adults, suggesting that these findings are not confined to teenagers.

Conclusion

While atypical presentations such as septic arthritis, pneumonia, epiglottitis/supraglottitis and endocarditis are well-described for the less common meningococcal capsular groups (W and Y), clinical presentation with predominantly gastrointestinal symptoms – and diarrhoea, in particular – appears to be rare and currently associated with the hypervirulent ST-11 group W strain which, in teenagers at least, leads to rapidly progressive, severe disease and high case fatality. It is hoped that the adolescent MenACWY vaccination programme will help to control group W disease in the UK. In the meantime, as this hypervirulent strain is still spreading in South America and has now been reported in other European countries and Australia, it is important that frontline clinicians and public health specialists are aware of this unusual but severe presentation in order to provide appropriate safety net advice) [12], ensure prompt diagnosis and early treatment of cases, and timely chemoprophylaxis with vaccination for close contacts.

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Conflict of interest

None declared.

Authors' contributions

HC and SNL reviewed and summarised the case records. HC wrote the first draft of the manuscript. All authors reviewed and commented on the manuscript. All authors read and approved the final version.

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Research article

The effect of migration within the European Union/ European Economic Area on the distribution of tuberculosis, 2007 to 2013

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Immigration from tuberculosis (TB) high-incidence countries is known to contribute notably to the TB burden in low-incidence countries. However, the effect of migration enabled by the free movement of persons within the European Union (EU)/European Economic Area (EEA) on TB notification has not been analysed. We analysed TB surveillance data from 29 EU/EEA countries submitted for the years 2007–2013 to The European Surveillance System. We used place of birth and nationality as proxy indicators for native, other EU/EEA and non-EU/EEA origin of the TB cases and analysed the characteristics of the subgroups by origin. From 2007–2013, a total of 527,467 TB cases were reported, of which 129,781 (24.6%) were of foreign origin including 12,566 (2.4%) originating from EU/EEA countries other than the reporting country. The countries reporting most TB cases originating from other EU/EEA countries were Germany and Italy, and the largest proportion of TB cases in individuals came from Poland (n=1,562) and Romania (n=6,285). At EU/EEA level only a small proportion of foreign TB cases originated from other EU/EEA countries, however, the uneven distribution of this presumed importation may pose a challenge to TB programmes in some countries.

Introduction

The epidemiology of communicable diseases can be affected by migration; between 2007 and 2011, around 40% of HIV cases in the European Union (EU) and European Economic Area (EEA) were reported among migrants [1] [2] [3]. Migration from high-incidence countries (defined as incidence as ≥20 tuberculosis (TB) cases/100,000 inhabitants/year) is known to contribute notably to TB burden in low-incidence countries (‹20 TB cases/100,000 inhabitants/year) using the thresholds previously proposed by the Wolfheze working group [4] and adopted in the EU monitoring framework [5] [6-14]. Persons with latent TB infection as well as patients with active TB and multidrug-resistant (MDR) TB can easily move from one country to another in the EU.

The free movement of persons within the EU is a fundamental right guaranteed to EU citizens by the Treaties [15]. Before 2010, the migration flows within the EU/EEA were mainly from eastern European Member States to Member States in the south and west [16] [17]. Driven by the economic crisis, from 2007 onwards, an increase was seen in numbers of people migrating from the countries most heavily affected by the depression (Greece, Spain, Italy, Ireland and Portugal) to western and northern EU countries [16]. In 2013, 17.7 million EU citizens were living in an EU country other than their country of birth, corresponding to 3.5% of the total population [18]. The highest number of migrants from other EU countries resided in Germany (3,635,265; 4.4% of the total population) and the lowest in Estonia (13,238; 1.0% of the total population). Possible cross-border transmission of communicable diseases as a consequence of free movement of persons across the borders has raised concerns in some countries [19,20].

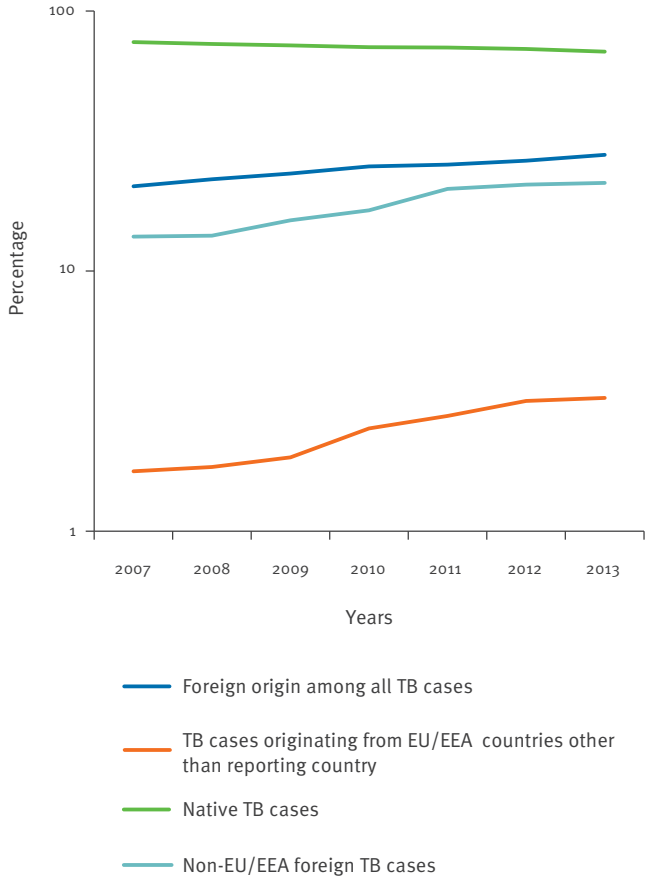
To our knowledge, the effect of migration within the EU/EEA on the epidemiology of TB has not been analysed previously. The objective of this study was therefore to estimate the extent of cross-border movement of TB cases within the EU/EEA. In addition, we aimed to characterise the ‘foreign’ TB cases originating from other EU/EEA countries, and to identify possible major patterns with respect to countries from which cases originate and which countries report such cases. Our quantitative descriptive analysis of the EU/EEA-wide TB surveillance data by geographical origin of cases may support decisions to implement targeted TB prevention and control measures where needed.

Methods

We carried out a descriptive analysis of all TB cases reported to The European Surveillance System (TESSy)

Figure 1

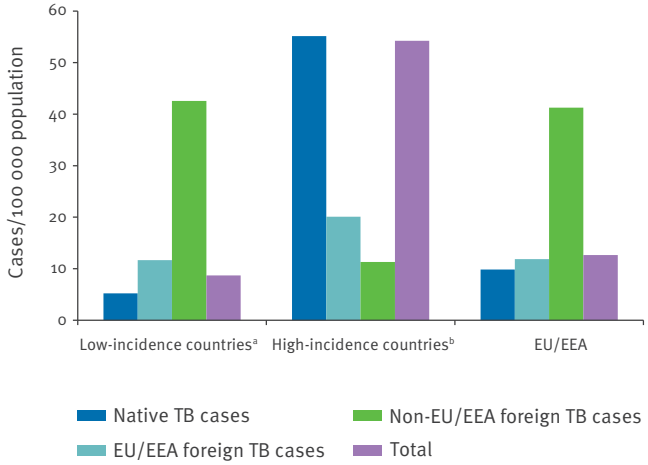
Proportions of tuberculosis cases by origin in the EU/EEA, 2007–2013



EEA: European Economic Area; EU: European Union; TB: tuberculosis.

Figure 2

Tuberculosis notification rates in low[a]- and high-incidence[b] EU/EEA countries by subgroup of origin, 2013



EEA: European Economic Area; EU: European Union; TB: tuberculosis.

Low-incidence countries are defined as having an incidence <20 TB cases per 100,000 inhabitants per year, and high-incidence countries as having an incidence ≥20 TB cases per 100,000 inhabitants per year, using the thresholds previously proposed by the Wolfheze working group [4] and adopted in the EU monitoring framework [5].

a Low TB incidence countries: Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Luxembourg, Malta, the Netherlands, Norway, Poland, Slovakia, Slovenia, Spain, Sweden and United Kingdom.

b High TB incidence countries: Bulgaria, Estonia, Latvia, Lithuania, Portugal and Romania.

by national surveillance institutes in 27 EU and two EEA countries from 2007 to 2013. Data collection methods and definitions are described elsewhere [21]. Liechtenstein reported TB surveillance data to TESSy only in 2007 and Croatia joined the EU in July 2013, so both countries were excluded from the analysis.

After submission to TESSy, data are subjected to automated checks for completeness and accuracy followed by expert-driven manual data validation. For the calculation of notification rates, country population denominators were obtained from Eurostat (www.epp.eurostat.ec.europa.eu) [18]. Notification rates for 'foreign TB cases' of EU/EEA origin and non-EU/EEA origin, and for the native population were calculated only for 2013 due to incomplete historical population data stratified by area of origin from Eurostat [18].

Definition of native and foreign tuberculosis cases

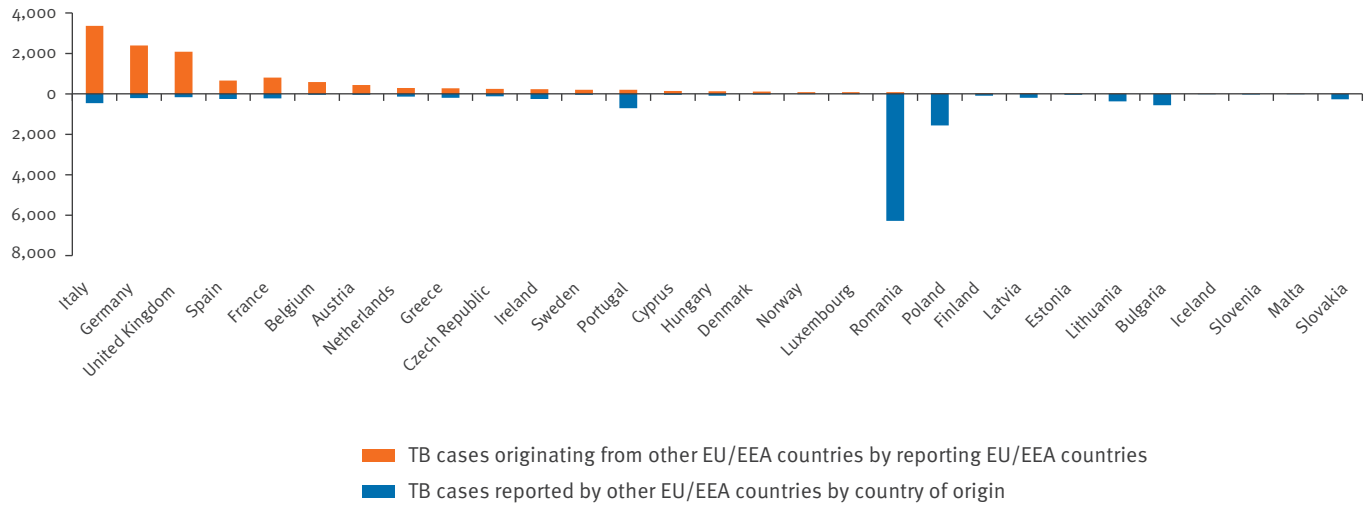
For Austria, Belgium, Greece, Hungary and Poland, we used citizenship to assign geographic origin, for the remaining 24 countries place of birth was used as a proxy indicator for the geographic origin of a TB case. A 'native TB case' was defined as a TB case reported by the patient's country of birth or citizenship, and a 'foreign TB case' as a case reported by a country different from the patient's country of birth or citizenship. The foreign cases were further divided into cases originating from outside of the EU/EEA and cases from other EU/EEA countries. Cases defined as 'foreign' but with missing country of origin, were excluded from the analysis. Cases originating from countries that do not exist any longer i.e. 'Soviet Union', 'Yugoslavia', 'Czechoslovakia' were recoded as 'foreign, country not specified'. TB cases originating from Greenland and Faroe Islands were considered as native Danish cases, and the cases originating from Jersey and Gibraltar were classified as native cases of the United Kingdom (UK).

Data analysis

We analysed the data by age and sex, site of disease, previous treatment, laboratory confirmation, and drug susceptibility testing results for the two main first-line anti-TB drugs (isoniazid and rifampicin), HIV co-infection and treatment success 12 months after start of treatment. The distribution of these variables was stratified by origin, excluding the unknowns where

Figure 3

Tuberculosis cases originating from other EU/EEA countries by reporting EU/EEA country and tuberculosis cases reported by other EU/EEA countries by country of origin, 2007–2013



EEA: European Economic Area; EU: European Union.

applicable. In a sensitivity analysis, we excluded all native cases reported by Romania and Poland. Both countries accounted for large shares of native cases and foreign cases reported by other EU/EEA countries while hardly reporting any cases of other EU/EEA origin themselves. The exclusion of Romanian and Polish native cases was thus meant to identify and avoid any potential bias resulting from largely comparing foreign and native cases from these two countries.

To compare incidence levels, countries were grouped as high- and low-incidence TB countries based on the data reported for 2013. Thus, high-incidence countries were six countries: Bulgaria, Estonia, Latvia, Lithuania, Portugal and Romania, and low-incidence countries all other EU/EEA countries.

For data analysis, we used Stata 13 (StataCorp LP, College Station, Texas, US) and Microsoft Excel 2010. Chi-squared tests were used to analyse differences between percentages. A p value of less than 0.01 was considered as statistically significant.

Results

During the period 2007 to 2013, a total of 527,467 TB cases (notification rate 14.9/ 100,000) were reported of which 11,788 cases (2.2%) were reported as 'origin unknown'. Of these cases with unknown origin, 11,595 (98.4%) were reported from countries defining origin by country of birth and 193 (1.6%) from countries defining origin by citizenship. Of the remaining 515,679 cases, 385,898 (74.8%) were reported as native and 129,781 (25.2%) as foreign. Among foreign cases, 121,994 (94.0%) were defined by country of birth and 7,787 (6.0%) by citizenship. Country of origin was reported for 104,491 (80.5%) of all foreign cases whereas 25,290 (19.5%) foreign cases were reported without country of birth/citizenship. Country-specific proportions of foreign TB cases with country of origin reported ranged from 0.1% (213/147,843) in Romania to 85.7% (2,090/2,438) in Norway. The vast majority, 91,925 (88.0%) of foreign TB cases with known origin came from outside the EU/EEA. In total, 12,566 cases (2.4% of all TB cases and 9.7% of foreign TB cases) were reported to originate from another EU/EEA country. Country-specific proportions of foreign TB cases of EU/EEA origin varied between 0.05% (9/18,365) in Bulgaria and 36.6% (136/372) in Cyprus (Table 1). Most of the foreign TB cases of EU/EEA origin were diagnosed in Italy 3,368 (12.2% of all cases reported in Italy), Germany (2,388; 7.7%) and the UK (2,089; 3.5%). The proportion of TB cases originating from another EU/EEA country was reported to be below 1% in seven countries (Bulgaria, Latvia, Lithuania, Poland, Romania, Slovakia and Slovenia); 1 up to 10% in 18 countries (Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Malta, the Netherlands, Norway, Portugal, Spain, Sweden and UK) and more than 10% in Cyprus, Iceland, Italy and Luxembourg.

Even though the overall TB notification rate declined by 5% annually from 2007 to 2013, the number of foreign TB cases from other EU/EEA countries increased from 1,428 (1.7% of all TB cases) in 2007 to 2,093 (3.3%) in 2013 ($p<0.01$), while the overall number of foreign TB cases increased from 17,809 (21.2%) in 2007 to 18 011 (28.0%) in 2013 (Figure 1). In the same period, the number of cases with unknown origin decreased from 2,384 (2.8%) to 1,407 (2.2%).

Table 1

Total numbers and notification rates of tuberculosis cases per 100,000 population and percentage of cases of foreign origin and foreign EU/EEA origin, 2007–2013

Country	Total number of notified TB cases	TB notification rate per 100,000	Number of TB cases originating from outside the reporting country[a]	Percentage of foreign origin	Number of notified TB cases in persons originating from other EU/EEA countries[a]	Percentage of foreigners originating from other EU/EEA countries	Percentage of EU/EEA foreign cases among all cases
Austria	5,058	8.6	2,119	41.9	440	20.8	8.7
Belgium	7,065	9.3	3,595	50.9	581	16.2	8.2
Bulgaria	18,365	35.3	44	0.2	9	20.5	0.05
Cyprus	372	6.5	301	80.9	136	45.2	36.6
Czech Republic	4,771	6.5	884	18.5	242	27.4	5.1
Denmark	2,597	6.7	1,560	60.1	108	6.9	4.2
Estonia	2,592	27.7	441	17.0	27	6.1	1.0
Finland	2,289	6.1	574	25.1	33	5.7	1.4
France	36,632	8.1	17,547	47.9	799	4.6	2.2
Germany	31,197	5.4	14,360	46.0	2,388	16.6	7.7
Greece	3,966	5.1	1,601	40.4	269	16.8	6.8
Hungary	10,165	14.7	228	2.2	133	58.3	1.3
Iceland	82	3.7	55	67.1	9	16.4	11.0
Ireland	3,003	9.5	1,295	43.1	225	17.4	7.5
Italy	27,695	6.6	13,684	49.4	3,368	24.6	12.2
Latvia	7,019	47.3	385	5.5	33	8.6	0.5
Lithuania	14,067	64.5	360	2.6	24	6.7	0.2
Luxembourg	232	6.6	144	62.1	78	54.2	33.6
Malta	292	10.1	233	79.8	6	2.6	2.1
The Netherlands	7,048	6.1	5,005	71.0	295	5.9	4.2
Norway	2,438	7.2	2,090	85.7	85	4.1	3.5
Poland	55,709	20.8	345	0.6	36	10.4	0.1
Portugal	19,336	26.6	2,709	14	201	7.4	1.0
Romania	147,843	104.4	213	0.1	78	36.6	0.1
Slovakia	3,405	9.0	48	1.4	8	16.7	0.2
Slovenia	1,261	8.8	341	27	9	2.6	0.7
Spain	49,222	15.2	15,058	30.6	662	4.4	1.3
Sweden	4,163	6.4	3,518	84.5	195	5.5	4.7
UK	59,583	13.7	41,044	68.9	2,089	5.1	3.5
Total	**527,467**	**14.9**	**129,781**	**24.6**	**12,566**	**9.7**	**2.4**

EEA: European Economic Area; EU: European Union; TB: tuberculosis; UK: United Kingdom.

[a]Data on country of origin not reported from years 2007 to 2010 by France, and from 2008 and 2009 by Portugal.

Compared with native TB cases, cases from other EU/EEA countries were more frequently female, 15 to 44 years old and affected by pulmonary TB. Their previous treatment, culture result and treatment outcome were less commonly known, and they were less frequently successfully treated. In contrast, they were more frequently tested for susceptibility to TB drugs than native cases, but found to have 38% less MDR TB. Finally, compared with native TB cases, cases from other EU/EEA countries were 60% less frequently tested for HIV co-infection; those tested, however, were not significantly more often HIV-positive than native cases (Table 2).

A statistically significant difference ($p<0.01$) between the native cases and TB cases originating from other EU/EEA countries was seen for all the clinical and microbiological characteristics except for the proportions of cases with unknown site of disease and the proportions of HIV-positive cases.

Excluding Romanian and Polish native cases from this analysis made no difference to these findings.

Notification rates by geographical origin of tuberculosis cases

Of the 64,327 TB cases notified in 2013, 44,909 (69.8%) were native TB cases, providing a notification rate of 9.8 per 100,000 for the native population. Of the total number of foreign cases, 14,050 (21.8%) were reported among foreigners originating from outside of the EU/EEA (notification rate 41.3/100,000 population), and 2,093 (3.3%) among foreigners originating from the EU/EEA outside of the reporting country (notification rate 11.9/100,000 population).

The vast majority, 2,015 (96.3% of all foreign cases from EU/EEA countries), of foreign TB cases originating from the EU/EEA, were reported in low-incidence countries and only 78 (3.7%) were registered in high-incidence EU countries in 2013. As illustrated in Figure 2, in 2013 the notification rate per 100,000 migrant population with EU/EEA origin was 20.1 for high-incidence countries, which is about one third of the notification rate among the native population (55.2), and almost two times higher than the notification rate among foreigners coming from outside the EU/EEA (11.3). The notification rate of 11.7 per 100,000 population observed in low-incidence countries among foreigners originating from the EU/EEA is twice as high as among the national population (5.2), and less than one third of the notification rate of TB cases coming from outside of EU/EEA (42.6) (Figure 2).

Country of origin of tuberculosis cases with foreign EU/EEA origin

TB cases originating from other EU/EEA countries, originated from 29 different countries: 6,285 cases (50.0%) from Romania, 1,562 (12.4%) from Poland, 704 (5.6%) from Portugal, 563 (4.5%) from Bulgaria, and 458 (3.6%) from Italy (Figure 3).

At the EU/EEA level, the seven-year average proportion of cases originating from other EU/EEA countries was 2.4%, but in some countries the share was much higher, reaching up to 36.6% of all TB cases reported in Cyprus during 2007 to2013, 33.6% in Luxembourg, 11.0% in Iceland and 12.2% in Italy (Table 1). A vast majority (92.5%) of TB cases from other EU/EEA countries reported by Italy originated from Romania, the country with the highest burden of TB in the EU/EEA.

Discussion

Our results show that only 3.3% (2,093/64,327) of TB cases notified in the EU/EEA in 2013 originated from other EU/EEA countries. This roughly matches the 3.5% of all persons residing in the EU that originated from other EU countries in 2013 [18]. Therefore, free movement between countries within the EU/EEA does not seem overall to cause disproportionate challenges for TB prevention and control in the EU/EEA.

Throughout the study period, the proportion of foreign TB cases originating from other EU/EEA countries slowly increased from 1.7 to 3.3% of all TB cases, while the percentage of native TB cases declined from 76.0% to 69.8%. There were notable differences between the numbers of TB cases originating from the respective countries and 'foreign TB cases' from EU/EEA reported by them. The migration flow of TB cases was mainly from TB high-incidence countries to low-incidence countries. This is expected since the TB burden is divided unevenly across the EU [22]. In 2007 to 2013, Germany, Italy and the UK reported most foreign TB cases from other EU/EEA countries and Bulgaria, Poland and Romania were the countries from which most TB cases from EU/EEA countries reported by other EU/EEA countries originated. In 2013, the EU countries with the largest population of EU immigrants were France, Germany and the UK [18] and the EU countries with the highest numbers of emigrants were Poland, Romania and Spain [23]. We do not see a clear pattern in the size of the migrant population from other EU/EEA countries and the number of foreign TB cases from other EU/EEA countries. This is expected as TB in migrants does not only depend on the size of the migrant population but also on the TB incidence in the country of origin and other factors such as living conditions of migrant populations and mixing patterns [14]. In general, the level of TB transmission is not high between groups of different ethnic origin in the EU/EEA [24], however, it is not known whether this applies to the migrants originating from the other EU/EEA countries.

Our study design entails some limitations. In the absence of data indicating in which country the infection was contracted, we used the country of birth and citizenship as proxy indicators for origin of the TB cases. This might have led to under- or overestimation of the case numbers in the subgroups by geographical origin, for example if native cases actually got infected abroad, or if foreign cases were infected in their current country of residence. In addition, the comparability of data between countries is compromised by three factors: not all countries have reported all data for the whole period 2007 to 2013; the method of reporting differs between countries; and some reporting practices applied by individual countries, e.g. relating to origin, previous treatment, drug susceptibility testing and treatment outcome are not consistent over time. For the descriptive analysis presented here, possible interactions between parameters like sex ratio and age distribution of migrants have not been taken into account. Finally, under-reporting of TB may have led to an underestimation of TB burden. Recent studies from England [25], Greece [26] and regions within Italy [27], the Netherlands [28], Romania [29] and Spain [30] have estimated under-reporting to range between 15% and 80%. One of these studies, however, found that under-reporting applied less to migrants than the native population (18% vs 68%) [27].

Our results show that drug susceptibility testing results were available more frequently for foreign TB cases of EU/EEA origin than native cases. This is supported by the fact that the main countries reporting TB cases in

Table 2

Comparison of native and foreign tuberculosis cases originating from within or outside of the EU/EEA, 2007–2013[a]

	Native cases		p-value[b]	Foreign cases			
				EU/EEA origin		non-EU/EEA origin	
	N	%		N	%	N	%
Total	385,898	73.2	<0.01	12,566	2.4	91 925	17.4
Sex							
Female	130,124	33.7	<0.01	4.638	36.9	38,580	42.0
Male	255,523	66.2	<0.01	7,891	62.8	53,122	57.8
Unknown	251	0.1	<0.01	37	0.3	223	0.2
Age groups							
0–14	17,499	4.5	<0.01	506	4.0	2,601	2.8
15–24	37,285	9.7	<0.01	1 880	15.0	14,741	16.0
25–44	116,386	30.2	<0.01	6 040	48.1	48,683	53.0
45–64	132,046	34.2	<0.01	2 748	21.9	17,611	19.2
≥65	82,331	21.3	<0.01	1 349	10.7	8,157	8.9
Unknown	351	0.1	<0.01	43	0.3	132	0.1
Site of disease							
Pulmonary	322 277	83.5	<0.01	10 850	86.3	53 111	57.8
Extrapulmonary	63 025	16.3	<0.01	1 686	13.4	38 463	41.8
Unknown	596	0.2[c]	p=0.02	30	0.2[c]	351	0.4
Previous treatment[d]							
No	308,126	79.8	<0.01	8,371	66.6	70,386	76.6
Yes	57,822	15.0	<0.01	891	7.1	5,721	6.2
Unknown	19,950	5.2	<0.01	3,304	26.3	15,818	17.2
HIV infection[e]							
HIV tested	81,518	21.1	<0.01	1,060	8.4	5,876	6.4
HIV infected[f]	3,634	4.5	p=0.03	62	5.8	567	9.6
Culture result							
Positive	238,373	61.8	<0.01	8,099	64.5	56,766	61.8
Negative	80,066	20.7	<0.01	1,261	10.0	8,321	9.1
Unknown	67,459	17.5	<0.01	3,206	25.5	26,838	29.2
DST result total	325,278	NA	NA	7,737	NA	71,386	NA
Test performed[g]	141,097	43.4	<0.01	5,419	70	46,393	65.0
MDR-TB	8,450	6.0	<0.01	200	3.7	1,356	2.9
Cohort 2007–2012 total	340,989	NA	NA	10,417	NA	77,845	NA
Treatment outcome reported	298,464	87.5	<0.01	6,618	63.5	63,600	81.7
Treatment success[h]	223,323	74.8	<0.01	4,449	67.2	49,256	77.4

DST: drug susceptibility testing; EEA: European Economic Area; EU: European Union; HIV: human immunodeficiency virus, MDR: multidrug-resistant; NA: not applicable; TB: tuberculosis; UK: United Kingdom.

[a] Origin (native/foreign) was not reported for 11,788 (2.2% from all reported) cases and country of origin was not specified for 25,290 (4.8% from all reported) cases.

[b] Comparing EU/EEA foreigners and native TB cases.

[c] Real percentage of unknown site information for foreign cases of EU/EEA origin is 0.24 and for native cases 0.15.

[d] Equals previous treatment history (reported as 'previous diagnosis' by Belgium, Denmark, Ireland, Norway, Sweden (2007) and the UK).

[e] TB cases reported by countries that reported only HIV-positive cases are excluded from the nominator.

[f] Percentages based on HIV-tested cases.

[g] Percentage of cases tested for drug susceptibility to isoniazid and rifampicin among all culture-positive cases, excluding countries who did not report case-based DST data.

[h] Calculated outcome after 12 months of treatment for all cases reported 2007 to 2012. France, Greece and Italy did not report treatment outcome results and are excluded from the treatment outcome analysis.

migrants of EU/EEA origin report higher proportions of drug susceptibility testing than the main countries reporting native cases, Romania and Poland. In 2007 to 2013, the proportion of MDR-TB was lower among foreign cases originating from other EU/EEA countries than in native cases. Also, of all MDR-TB cases reported by low-incidence countries of the EU/EEA, less than 10% originated from other EU/EEA countries. This implies that migration within the EU/EEA is not the main driver of MDR-TB incidence in low-incidence EU/EEA countries.

The mean age of foreign TB cases of EU/EEA origin was lower than among the native TB cases. It is not surprising that most of the foreign TB cases of EU/EEA origin occur within the population at working age considering that the most frequent factor influencing the decision to migrate in the EU is employment [16], followed by family reunion, study and retirement. The proportion of culture-positive and of pulmonary cases was higher among migrants from EU/EEA countries than among natives. This could possibly be explained by migrants having a higher threshold for seeking healthcare in a foreign country and the challenge of accessing healthcare in a foreign country, leading to a delayed diagnosis and more advanced disease.

We noted that the completeness of data on TB treatment history was exceptionally low and the treatment outcome 12 months after start of treatment was less frequently reported for foreign cases originating from other EU/EEA countries compared with native cases and cases from non-EU/EEA countries. Persons diagnosed with TB in another EU/EEA country may decide to return to their country of origin for treatment. In this case the treatment outcome may not be made available to the country that diagnosed the case. The issues in cross-border exchange of TB case information have been identified before [31,32], and the need for facilitated referral and exchange of information between EU/EEA countries is evident.

In conclusion, the uneven distribution of TB diagnosed in persons originating from other EU/EEA countries within the EU/EEA may pose an incentive for coordinated EU action to improve TB programmes in individual countries. Awareness of the number of cases deriving from specific EU high-incidence countries can facilitate targeted TB prevention and control efforts in receiving countries, optimally in collaboration with the TB cases' countries of origin. In all EU/EEA countries, however, the number of TB cases from non-EU/EEA countries was higher than the number of foreign TB cases originating from other EU/EEA countries [33], implying that TB control efforts addressing migrant populations should primarily focus on migrants coming from TB-endemic regions outside of the EU/EEA.

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Conflict of interest

None declared.

Authors' contributions

Vahur Hollo coordinated the data analysis, wrote the manuscript and contributed to the study design. Saara Magdalena Kotila drafted parts of the manuscript, contributed to the revision of the manuscript and data analysis. Csaba Ködmön contributed to the data analysis and study design. Phillip Zucs contributed to the study design, data analysis and the manuscript writing. Marieke Johanna van der Werf contributed to the design of the study, interpreted the results and revised the manuscript.

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Research article

Migration-related tuberculosis: epidemiology and characteristics of tuberculosis cases originating outside the European Union and European Economic Area, 2007 to 2013

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Migrants arriving from high tuberculosis (TB)-incidence countries may pose a significant challenge to TB control programmes in the host country. TB surveillance data for 2007–2013 submitted to the European Surveillance System were analysed. Notified TB cases were stratified by origin and reporting country. The contribution of migrant TB cases to the TB epidemiology in EU/EEA countries was analysed. Migrant TB cases accounted for 17.4% (n = 92,039) of all TB cases reported in the EU/EEA in 2007–2013, continuously increasing from 13.6% in 2007 to 21.8% in 2013. Of 91,925 migrant cases with known country of origin, 29.3% were from the Eastern Mediterranean, 23.0% from south-east Asia, 21.4% from Africa, 13.4% from the World Health Organization European Region (excluding EU/EEA), and 12.9% from other regions. Of 46,499 migrant cases with known drug-susceptibility test results, 2.9% had multidrug-resistant TB, mainly (51.7%) originating from the European Region. The increasing contribution of TB in migrants from outside the EU/EEA to the TB burden in the EU/EEA is mainly due to a decrease in native TB cases. Especially in countries with a high proportion of TB cases in non-EU/EEA migrants, targeted prevention and control initiatives may be needed to progress towards TB elimination.

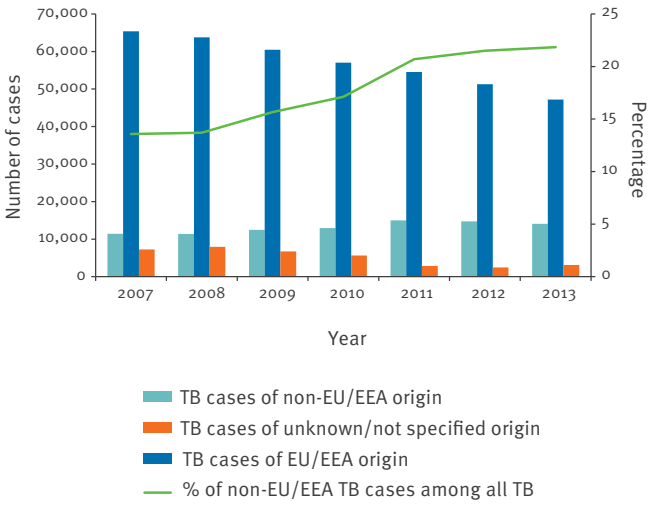
Introduction

The tuberculosis (TB) notification rate in the European Union and European Economic Area (EU/EEA) declined from 16.8 per 100,000 population in 2007 to 12.7 per 100,000 in 2013 [1]. However, in some low-incidence countries, the decline in TB notification rate has slowed down, especially in countries reporting a high proportion of TB cases in individuals of foreign origin, i.e. migrants. In general, migration is influenced by socioeconomic and political factors [2]. Economic, social and political stability is relatively high in the EU/EEA which thus attracts immigrants from many low-income countries around the world [3]. On average (years 2007–2012), 1.5 million migrants from outside the EU/EEA were registered annually in EU and EEA countries [4]. A considerable proportion of these migrants are coming from countries with a high TB burden such as Bangladesh, Brazil, China, India, Morocco, Pakistan, Russian Federation, Somalia and Ukraine [5]. They may arrive in the EU/EEA with active TB disease, or with latent TB infection (LTBI). To detect TB disease in migrants, several EU/EEA countries have introduced (pre-)entry screening programmes [6-8]. Screening of migrants for LTBI is also being explored by some countries, such as the Netherlands [9]. However, screening programmes will not identify all TB or LTBI cases among migrants, due to the limited sensitivity of the current screening tests (mainly chest x-ray and tuberculin skin test or interferon gamma release assay). Also, not all migrant groups are covered by the screening programme, e.g. undocumented migrants are often not included. In addition, migrants frequently travel back to their country of origin where they may be (re-) infected with TB [10].

Migrants developing TB may pose a challenge to TB programmes in the EU/EEA due to language and cultural differences [11]. Also, undocumented migrants may not access the healthcare system due to fear of deportation, and migrants whose stay is legal may be unfamiliar with the healthcare system and therefore encounter problems in seeking healthcare [12]. Since countries with low TB notification rates report high numbers of TB cases in migrants in particular, it is important to study this phenomenon because addressing TB in migrants will be essential to achieving the goal of TB programmes, i.e. TB elimination [13]. Therefore, the aim of this study is to quantify and to geographically

Figure 1

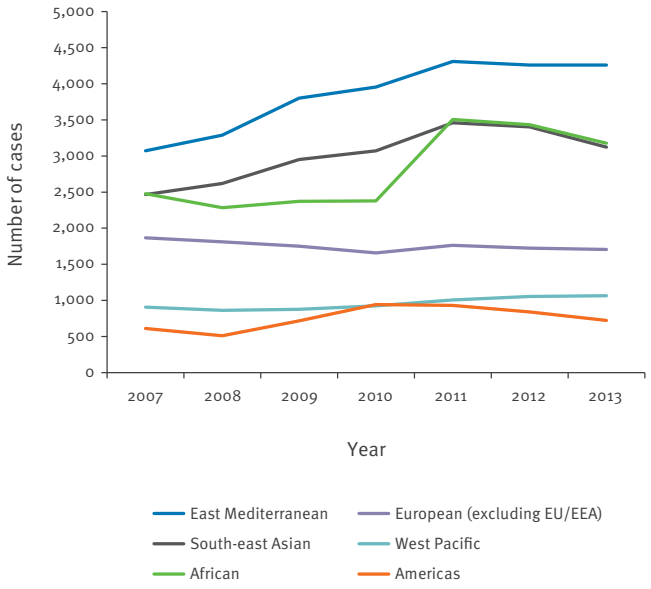
Number of tuberculosis cases by year and origin, and percentage of non-European Union/European Economic Area cases among all tuberculosis cases, European Union/European Economic Area, 2007–2013



EEA: European Economic Area; EU: European Union; TB: tuberculosis.

Figure 2

Number of tuberculosis cases of non- European Union/European Economic Area origin by year and World Health Organization Region, 2007–2013 (n=91,925)



EEA: European Economic Area; EU: European Union.

and epidemiologically characterise migration-related importation of TB to EU/EEA countries.

Methods

The European Centre for Disease Prevention and Control (ECDC) has collected case-based TB surveillance data from EU and EEA countries since 2007 and stored them in a common database (The European Surveillance System, TESSy) hosted by ECDC. Designated national surveillance institutions are responsible for data reporting to TESSy and for data validation.

The detailed data collection methods and definitions are described elsewhere [1]. TB cases were defined according to agreed case definitions published by the European Commission [14] and confirmed, probable and possible cases were included in the analysis. Surveillance data reported by 29 EU/EEA countries and covering the period from 2007 to 2013 were extracted from the database on 3 October 2014. Place of birth was used as a proxy indicator for the geographic origin of a TB case in most countries; except for Austria, Belgium, Greece, Poland, Hungary (from 2010 onwards) and for Malta (only in 2010) where citizenship was used. Place of birth outside EU/EEA borders was used as proxy for migrant TB in most countries. Non-EU/EEA citizenship was used for Austria, Belgium, Greece, Poland, Hungary (from 2010 onwards) and for Malta (only in 2010).

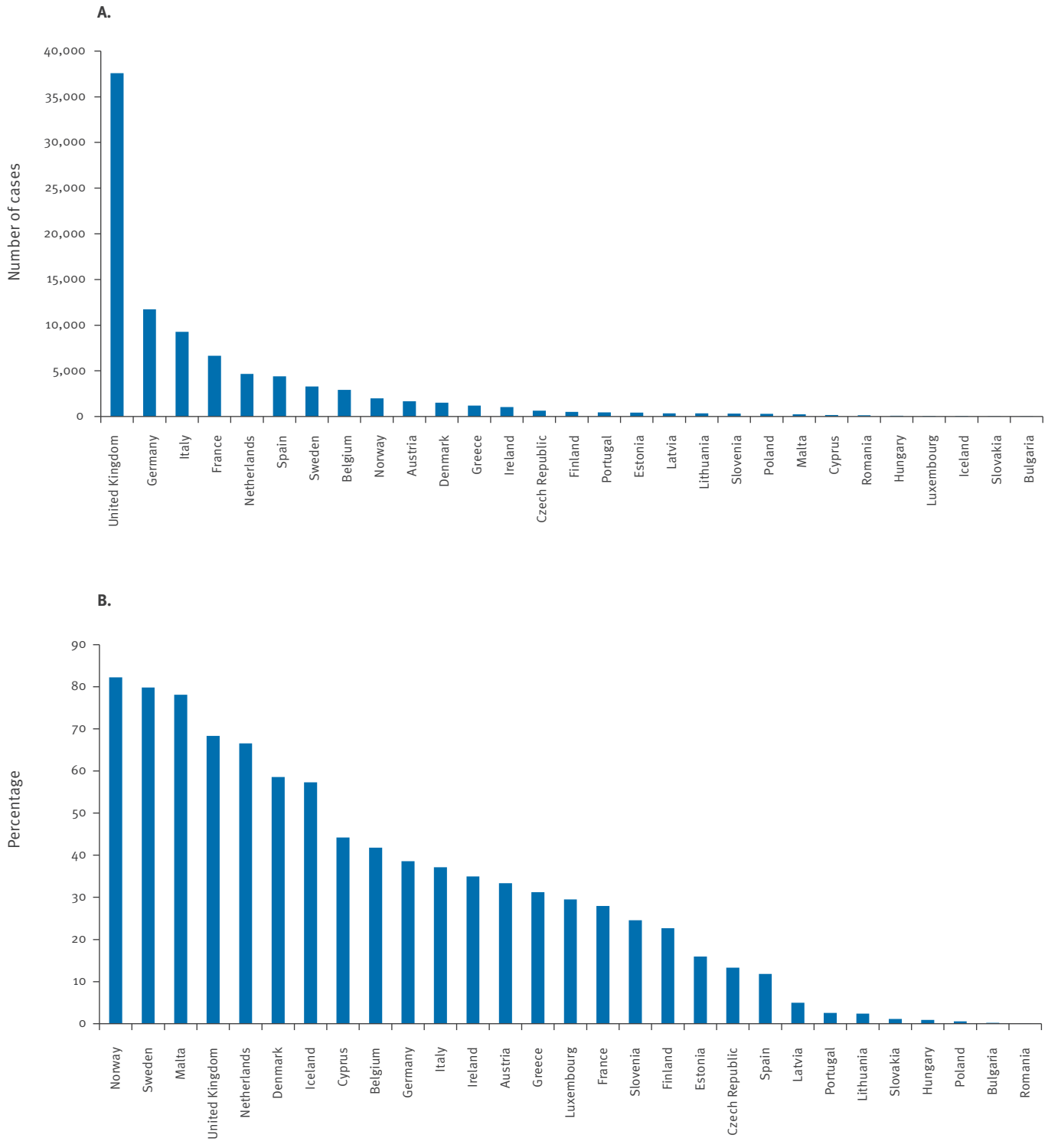
The analysis was restricted to TB cases with known origin. The areas of origin were defined according to the World Health Organization (WHO) regions described in the *Global Tuberculosis Report, 2013* [15].

The European Region refers to the WHO European Region excluding the EU and EEA (Iceland, Liechtenstein and Norway) countries. To assign country of origin (based on place of birth), we used the ISO 3166–1 codes for countries, dependent territories, and special areas of geographical interest which are published by the International Organization for Standardization [16]. The origin of cases reported by or from populated Overseas Countries and Territories of EU countries was assigned according to their geographic location and such cases counted as cases in individuals of non-EU/EEA origin. Cases reported/coded in the system as originating (based on place of birth) either from 'Soviet Union' (Former Soviet Union (FSU) countries: Armenia, Azerbaijan, Belarus, Estonia (EU), Georgia, Kazakhstan, Kyrgyzstan, Latvia (EU), Lithuania (EU), Moldova, Russian Federation, Tajikistan, Turkmenistan, Ukraine and Uzbekistan) or 'Yugoslavia' (Bosnia and Herzegovina, Croatia (EU), Kosovo*, Montenegro, Serbia, Slovenia (EU) and the former Yugoslav Republic of Macedonia) were classified as cases of unspecified origin (n = 114), because some parts of those two historical countries belong to the EU today as indicated in brackets.

Liechtenstein reported TB surveillance data to TESSy only for 2007 and was therefore excluded from the analysis. Croatia joined the EU in July 2013 and was considered a non-EU/EEA country in the analysis. France, Italy, and Spain are not reporting drug resistance data to TESSy and were excluded from the analysis of laboratory data and drug resistance. Treatment outcome data were not reported by France, Greece, and Italy in

Figure 3

Number of tuberculosis cases (A) and percentage of tuberculosis cases (B) of non- European Union/European Economic Area origin among tuberculosis cases with known country of origin (B), by reporting country, European Union/European Economic Area, 2007–2013 (n=91,925)

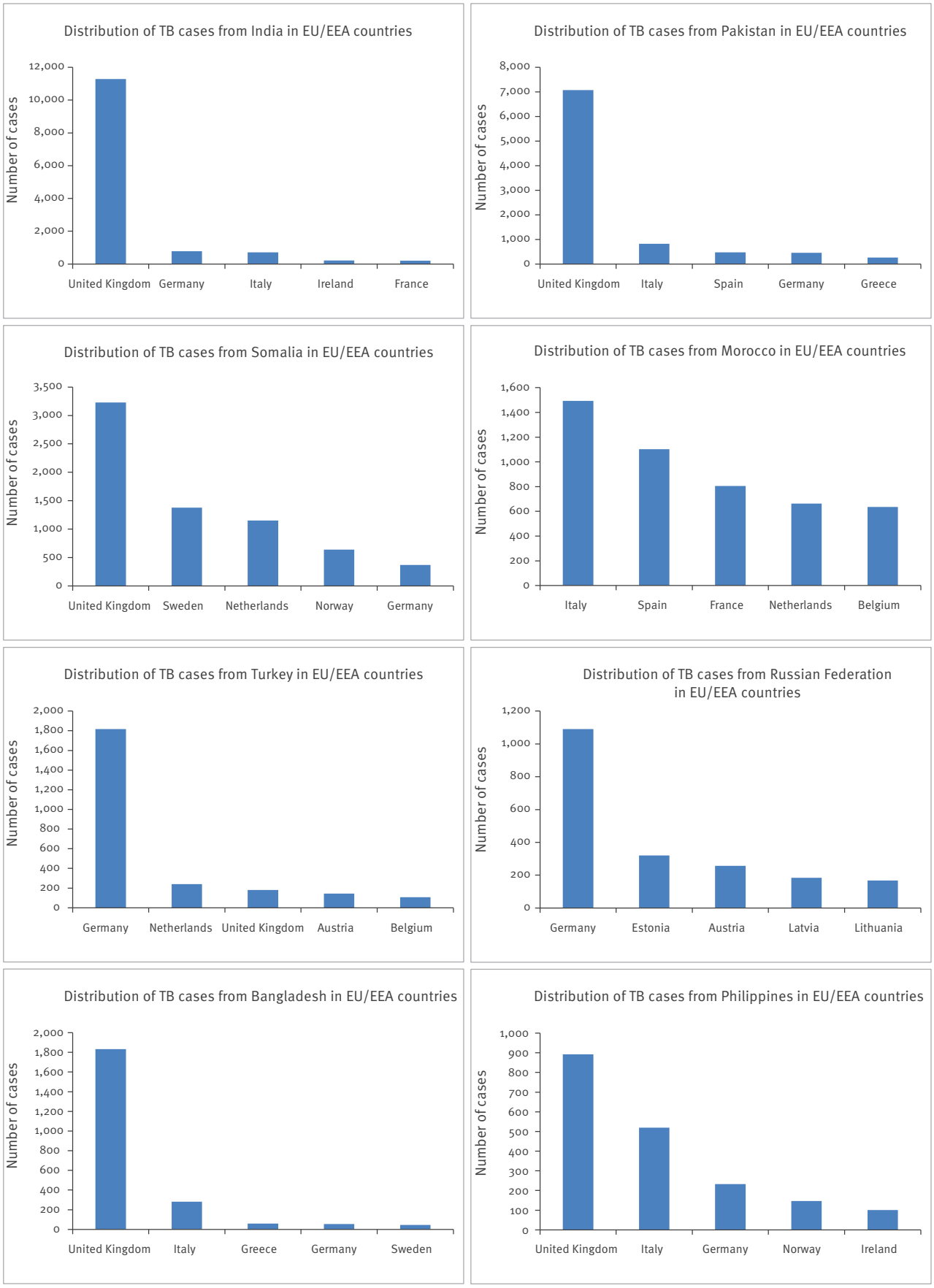


2007–2012, and by Spain in 2007–2009. Therefore, these countries were excluded from the treatment outcome analysis. TB treatment was considered successful if a case was cured or their treatment completed 12 months after start of treatment.

TB cases were described by year of reporting, origin and country of reporting. Native cases (EU/EEA origin) and cases from outside the EU/EEA were compared by sex, age, previous treatment history, TB site, laboratory confirmation status, drug resistance, HIV status and treatment outcome. Differences were considered statistically significant, if $p<0.01$ as determined by

Figure 4

Distribution of tuberculosis cases originating from India, Pakistan, Somalia, Morocco, Turkey, Russian Federation, Bangladesh and the Philippines across the five European Union/European Economic Area countries with the highest reported numbers, 2007–2013 (n=47,440)



EEA: European Economic Area; EU: European Union; TB: tuberculosis.

Table A

Characteristics of tuberculosis cases with reported country of origin by region of origin, European Union/European Economic Area, 2007–2013 (n=491,538)

	WHO Region																Total	
	EU/EEA		Total non-EU/EEA		Eastern Mediterranean		South-East Asian		African		European (excluding EU/EEA)		Western Pacific		Americas			
	N	%	N	%	N	%[a]	N	%[a]	N	%[a]	N	%[a]	N	%[a]	N	%[a]	N	%
Total	**399,613**	**81.3**	**91,925**	**18.7**	**26,945**	**29.3**	**21,097**	**23.0**	**19,629**	**21.4**	**12,280**	**13.4**	**6,697**	**7.3**	**5,277**	**5.7**	**491,538**	**100**
Sex																		
Male	264,068	66.1	53,122	57.8	16,348	60.7	12,022	57.0	11,667	59.4	7,381	60.1	3,112	46.5	2,592	49.1	317,190	64.5
Female	135,220	33.8	38,580	42.0	10,545	39.1	9,016	42.7	7,918	40.3	4,868	39.6	3,561	53.2	2,672	50.6	173,800	35.4
Unknown	325	0.1	223	0.2	52	0.2	59	0.3	44	0.2	31	0.3	24	0.4	13	0.2	548	0.1
Age groups (years)																		
0–14	18,034	4.5	2,601	2.8	1,052	3.9	276	1.3	612	3.1	368	3.0	138	2.1	155	2.9	20,635	4.2
15–24	39,266	9.8	14,741	16.0	5,538	20.6	3,007	14.3	3,338	17.0	1,071	8.7	1,049	15.7	738	14.0	54,007	11.0
25–44	122,780	30.7	48,683	53.0	13,012	48.3	12,439	59.0	11,584	59.0	4,910	40.0	3,740	55.8	2,998	56.8	171,463	34.9
45–64	135,147	33.8	17,611	19.2	4,786	17.8	3,499	16.6	3,210	16.4	3,680	30.0	1,379	20.6	1,057	20.0	152,758	31.1
65+	83,946	21.0	8,157	8.9	2,504	9.3	1,864	8.8	856	4.4	2,236	18.2	379	5.7	318	6.0	92,103	18.7
Unknown	440	0.1	132	0.1	53	0.2	12	0.1	29	0.1	15	0.1	12	0.2	11	0.2	572	0.1
Previous TB history																		
No	317,268	79.4	70,386	76.6	21,080	78.2	17,409	82.5	14,728	75.0	7,838	63.8	5,105	76.2	4,226	80.1	387,654	78.9
Yes	58,781	14.7	5,721	6.2	1,627	6.0	1,137	5.4	996	5.1	1,411	11.5	337	5.0	213	4.0	64,502	13.1
Unknown	23,564	5.9	15,818	17.2	4,238	15.7	2,551	12.1	3,905	19.9	3,031	24.7	1,255	18.7	838	15.9	39,382	8.0
Site of disease																		
Pulmonary	333,989	83.6	53,111	57.8	13,737	51.0	9,215	43.7	11,961	60.9	10,168	82.8	4,287	64.0	3,743	70.9	387,100	78.8
Extra-pulmonary	64,968	16.3	38,463	41.8	13,109	48.7	11,818	56.0	7,592	38.7	2,032	16.5	2,384	35.6	1,528	29.0	103,431	21.0
Unknown	656	0.2	351	0.4	99	0.4	64	0.3	76	0.4	80	0.7	26	0.4	6	0.1	1,007	0.2
Laboratory confirmation																		
Confirmed	214,612	53.7	47,925	52.1	13,920	51.7	12,278	58.2	9,202	46.9	7,748	63.1	3,577	53.4	1,200	22.7	262,537	53.4
Not confirmed	119,397	29.9	23,693	25.8	7,457	27.7	7,013	33.2	4,103	20.9	3,105	25.3	1,484	22.2	531	10.1	143,090	29.1
Laboratory data not reported	65,604	16.4	20,307	22.1	5,568	20.7	1,806	8.6	6,324	32.2	1,427	11.6	1,636	24.4	3,546	67.2	85,911	17.5
Drug resistance among DST done																		
DST done among laboratory confirmed	147,090	68.5	46,499	97.0	13,580	97.6	12,030	98.0	8,945	97.2	7,322	94.5	3,443	96.3	1,179	98.3	193,589	73.7
Susceptible	126,945	86.3	40,538	87.2	12,044	88.7	10,794	89.7	8,046	89.9	5,679	77.6	2,912	84.6	1,063	90.2	167,483	86.5
Mono-resistant	8,664	5.9	3,492	7.5	1,069	7.9	813	6.8	614	6.9	552	7.5	358	10.4	86	7.3	12,156	6.3
Poly-resistant	2,821	1.9	1,107	2.4	270	2.0	199	1.7	145	1.6	387	5.3	92	2.7	14	1.2	3,928	2.0
MDR among DST done	8,660	5.9	1,362	2.9	197	1.5	224	1.9	140	1.6	704	9.6	81	2.4	16	1.4	10,022	5.2
XDR among MDR	691	8.0	80	5.9	6	3.0	2	0.9	2	1.4	68	9.7	2	2.5	0	0.0	771	7.7
HIV status																		
Tested for HIV	83,062	20.8	5,876	6.4	1,626	6.0	372	1.8	1,189	6.1	1,206	9.8	422	6.3	1,061	20.1	88,938	18.1
HIV-positive among tested	3,999	4.8	567	9.6	32	2.0	18	4.8	289	24.3	114	9.5	14	3.3	100	9.4	4,566	5.1

DST: drug susceptibility testing; MDR: multidrug resistant; EEA: European Economic Area; EU: European Union; N: number; WHO: World Health Organization; XDR: extensively drug resistant.

[a] Percentage among TB cases in individuals of non-EU/EEA origin.

Table B

Characteristics of tuberculosis cases with reported country of origin by region of origin, European Union/European Economic Area, 2007–2013 (n=491,538)

	WHO Region																Total	
	EU/EEA		Total non-EU/EEA		Eastern Mediterranean		South-East Asian		African		European (excluding EU/EEA)		Western Pacific		Americas			
	N	%	N	%	N	%[a]	N	%[a]	N	%[a]	N	%[a]	N	%[a]	N	%[a]	N	%
Treatment outcome[b]																		
Number of reported cases 2007–2012	352,428		77,875		22,687		17,975		16,452		10,574		5,632		4,555		430,303	
Treatment outcome reported	305,945	86.8	63,600	81.7	18,841	83.0	16,492	91.7	11,994	72.9	9,148	86.5	4,443	78.9	2,656	58.3	369,545	85.9
Success	228,351	74.6	49,256	77.4	15,141	80.4	12,839	77.8	9,328	77.8	6,444	70.4	3,349	75.4	2,155	81.1	277,607	75.1
Failed	6,900	2.3	109	0.2	29	0.2	9	0.1	10	0.1	48	0.5	10	0.2	3	0.1	7,009	1.9
Defaulted	20,176	6.6	3,436	5.4	848	4.5	1,083	6.6	615	5.1	538	5.9	271	6.1	81	3.0	23,612	6.4
Died	25,123	8.2	2,052	3.2	503	2.7	475	2.9	303	2.5	595	6.5	101	2.3	75	2.8	27,175	7.4
Still on treatment	9,427	3.1	4,312	6.8	1,202	6.4	1,309	7.9	829	6.9	606	6.6	275	6.2	91	3.4	13,739	3.7
Not evaluated	15,968	5.2	4,435	7.0	1,118	5.9	777	4.7	909	7.6	917	10.0	437	9.8	251	9.5	20,403	5.5

DST: drug susceptibility testing; MDR: multidrug resistant; EEA: European Economic Area; EU: European Union; N: number; WHO: World Health Organization; XDR: extensively drug resistant.

[a] Percentage among TB cases in individuals of non-EU/EEA origin.

[b] Treatment outcome 12 months after starting treatment for cases notified in 2007–2012.

chi-squared test. Statistical analysis was performed using Stata 13 software (StataCorp, Texas, US).

Results

Of 527,467 TB cases notified in the EU/EEA from 2007 to 2013, 399,613 (75.8%) were reported as originating from EU/EEA countries, 92,039 (17.4%) as originating from non-EU/EEA countries, and for 35,815 (6.8%), country of origin was not reported. Among 491,652 TB cases with reported country of origin, 122,627 (24.9%) originated from outside the reporting country. Of these, 91,925 (75%) originated from outside the EU/EEA, 30,588 (24.9%) were of EU/EEA origin, and 114 (0.1%) originated from 'Soviet Union' or 'Yugoslavia'. The proportion of TB cases with reported non-EU/EEA origin increased from 13.6% (n=11,403) in 2007 to 21.8% (n=14,050) in 2013, the proportion of TB cases with reported EU/EEA origin decreased from 77.8% (n=65,390) in 2007 to 73.4% (n=47,185) in 2013, while the proportion of TB cases with unknown or unspecified origin decreased from 8.6% (n=7,221) to 4.8% (n=3,092) in the same period (p<0.001) (Figure 1).

Of 92,039 cases with non-EU/EEA origin, the country of origin was reported for 91,925 (99.9%) cases, with the majority coming from the Eastern Mediterranean Region (29.3%, n=26,945), the South-East Asian Region (23.0 %, n=21.097) and the African Region (21.4%, n=19,629) (Table).

Compared with native TB cases, TB cases in individuals of non-EU/EEA origin were more frequently female (42.0% vs 33.8%, p<0.001) and under 45 years of age (71.8% vs 45.1%, p<0.001) (Table). Cases of non-EU/EEA origin had a previous TB history less frequently (6.2% vs 14.7%, p<0.001), but a proportion of cases with unknown previous history three times higher than native cases. Extrapulmonary TB was much more commonly diagnosed in cases of non-EU/EEA origin (41.8% vs 16.3%, p<0.001). Very similar proportions, just over 50% of cases were laboratory-confirmed in both native and migrant cases, but the latter were much more extensively tested for drug susceptibility (97.0% vs 68.5%, p<0.001), and were found to be mono-resistant and poly-resistant slightly more frequently, but not multidrug-resistant (9.9% vs 2.9%, p<0.001). The majority of multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB cases in individuals of non-EU/EEA origin were from the European Region, where the highest percentage of MDR-TB cases among the cases with available drug susceptibility testing (DST) results (9.6%, n=704) was observed, as well as the highest percentage of XDR-TB cases among MDR-TB (9.7%, n=68). Of 704 MDR-TB cases originating from the European Region, 678 (96.3%) were notified in cases coming from 13 non-EU/EEA 'Soviet Union' countries (data not shown). The highest percentage of mono-resistance to a first-line anti-TB drug was observed in cases originating from the Western Pacific Region (10.4%, n=358). Most cases with mono-resistance originated from the Philippines, Vietnam and China (145, 117 and 48 respectively). Among the mono-resistant TB cases from the Philippines, 83.4% (n=121) were resistant to isoniazid, while in cases originating from Vietnam and China, 55.6% (n=65) and 60.4% (n=29) were resistant to isoniazid (data not shown). In the period 2007–2013 the trend in MDR-TB prevalence among cases of non-EU/EEA origin did

not change significantly (p=0.94, data not shown). Cases of non-EU/EEA origin were tested for HIV much less frequently than native cases (6.4% vs 20.8%, p<0.001), but tested HIV-positive twice as often (9.6% vs 4.8%, p<0.001). Among cases of non-EU/EEA origin, the majority and highest prevalence of HIV co-infection was found in cases originating from the African Region. A higher proportion of treatment success was reported in migrant cases (77.4% vs 74.6%, p<0.001), while the proportion that died during treatment was lower (3.2% vs 8.2%, p<0.001). The percentage of TB cases where the treatment outcome was 'lost to follow-up' was lower in the cases of non-EU/EEA origin (5.4% vs 6.6%), but the percentage of non-evaluated cases was higher (7.0% vs 5.2%). The lowest treatment success rate, 70.4%, was observed among cases from the European Region.

From 2007 to 2011, the number of notified TB cases in individuals of non-EU/EEA origin increased for all WHO Regions except for the European region (Figure 2). Thereafter, the number remained the same or decreased slightly. In the same period, the number of TB cases with unknown country of origin decreased from 8.6% in 2007 to 4.8% in 2013. The mean annual increase in the period 2007–2011 was highest for cases originating from Americas (13.5%; standard deviation (SD): 18.4), followed by the African Region (10.9%; SD: 20.4), the South-East Asian Region (8.9%; SD: 8.1), the Eastern Mediterranean Region (8.9%; SD: 5.3) and the Western Pacific Region (2.8%; SD: 4.2), while for cases originating from the European Region a mean annual decrease of 1.3% (SD: 3.7) was observed. The mean increase in the number of notified cases was the highest for cases originating from the Eastern Mediterranean Region (n=309; SD: 183.1), followed by the African Region (n=256; SD: 411.3), the South-East Asian Region (n=248; SD: 238.2), the Americas (n=75; SD: 145.1) and the Western Pacific Region (n=25; SD: 52.7). The notification of cases originating from the European Region showed the mean decrease of 26 cases annually (SD: 63.2).

Of all TB cases in individuals of non-EU/EEA origin, 40.9% (n=37,573) were reported by the United Kingdom (UK), 12.8% (n=11,728) by Germany and 10.1% (n=9,264) by Italy (Figure 3A. The highest contribution of TB cases in individuals of non-EU/EEA origin to the national TB burden was observed in Norway with 82.4% (n = 1,997), Sweden with 79.9% (n = 3,274) and Malta with 78.1% (n = 228) (Figure 3B).

The reported non-EU/EEA TB cases originated from 186 countries, dependent territories, and special areas of geographical interest with 51.6% coming from India (15.3%), Pakistan (10.9%), Somalia (8.5%), Morocco (5.7%), Turkey (3.0%), Russian Federation (2.9%), Bangladesh (2.7%), and the Philippines (2.6%). Their distribution mirrors the typical migration flows and destination country preferences (Figure 4). Between 2007 and 2013, increasing numbers of TB cases from India, Pakistan and Morocco were notified (p<0.001, data not shown).

Most cases from India (80.3%, n=11,293) were reported by the UK (Figure 4). The UK also reported a large percentage of the cases originating from Pakistan (70.5%, n=7,073), from Somalia (41.2%, n=3,228), from Bangladesh (74.7%, n=1,833), and from Philippines (36.7%, n=892). Germany reported 66.8% (n=1,818) of all reported cases from Turkey and 40.6% (n=1,091) of all reported cases from Russian Federation. While, Italy reported the largest percentage of cases from Morocco (28.7%, n=1,493).

Discussion

Almost one in five TB cases notified in the EU/EEA between 2007 and 2013 originated from a country outside the EU/EEA, but this varied from<1% to>80% between the 29 countries included in this study. The percentage of migrant TB cases increased from 13.6% to 21.8% between 2007 and 2013, while the overall number of cases of non-EU/EEA origin increased from 11,403 in 2007 to 14,975 in 2011 and slightly decreased thereafter to 14,050 in 2013. The increasing percentage of migrant TB among all notified TB cases is largely attributable to the decreasing numbers of native TB cases and cases with unknown origin. The highest mean annual increase in notifications was observed in TB cases originating from the Eastern Mediterranean and African Regions. The only decreasing trend was seen in cases originating from the European Region. Increasing trends in notified TB cases in migrants have also been observed in other high-income countries such as Australia, Canada, and the United States (US) [17-19].

TB cases originating from eight countries accounted for 51.6% of all TB cases in individuals of non-EU/EEA origin. This can be explained by the burden of TB in these countries [15] and the relatively high number of migrants from these countries to the EU/EEA [5,6]. Data from Australia, Canada and the US showed that the TB notification rate among migrants is strongly associated with the TB burden in the country of origin [18]. Among foreign-born and US-born cases in the US, the level of education, living conditions, low income and unemployment were associated with higher TB rates; this association was stronger in the foreign-born cases. According to the authors, these results support the hypothesis that the TB rates among foreign-born cases are more strongly influenced by experiences in their country of origin than by the environments in the host country [19]. Similarly to the situation in the EU/EEA, the 25 to 44 years-old age group was most represented in the US among foreign-born TB cases [20]. In the EU/EEA, the high proportions of males seen among cases originating from the Eastern Mediterranean and European Regions suggest that the majority of TB cases from these regions are migrant workers. This is supported by Eurostat data according to which, on average

29% of residence permits were issued in 2008–2012 due to employment and 28% due to family reasons [5].

Exposure to TB before immigration to the EU/EEA and when travelling back to the country of origin for family visits may result in relatively high latent TB infection rates in migrant populations [21-23]. Several studies suggest that the majority of cases among migrants occur due to TB infection or reinfection when travelling to their home country [20,24,25] or due to reactivation of latent TB [20,26,27]. However, TB in migrants might also be due to recent infection or reinfection in the host country after local exposure [27-30].

According to the Eurostat data, there are remarkable differences in the number of migrants received by different EU/EEA countries. The UK, Italy, Germany, France, the Netherlands and Spain received the highest number of non-EU/EEA migrants during the period 2007–2012 [4]. In most EU/EEA Member States, this migration peaked in 2010, which was probably largely attributable to the global financial crisis [4,31]. Both the geographical distribution of reported TB cases in individuals of non-EU/EEA origin and their overall trend over time appears to follow the general migration patterns described [5,20]. As the biggest reporting country of TB cases in individuals of non-EU/EEA origin, the UK saw the majority of these cases originating from India, Pakistan and Bangladesh. The same three countries were also among the top five countries contributing to the TB burden in the US [20].

The highest prevalence of MDR-TB and XDR-TB was observed among cases of non-EU/EEA European origin. In the US in 2007–2009, 1.5% of foreign-born cases with available DST results were reported with MDR-TB, and the highest percentage (9.3%) was also observed among cases of European origin [32]. Equally, in Canada, the highest percentage of MDR-TB cases (2.9%) among foreign-born TB cases originated from the European Region [33]. This reflects the high prevalence of drug resistance among TB cases in the non-EU/EEA European Region [15].

Extrapulmonary TB was more frequently reported in TB cases in individuals of non-EU/EEA origin. Since extrapulmonary TB (excluding laryngeal TB) is rarely infectious, these cases will not contribute to transmission in the host country but do have an impact on health service costs. Further, extrapulmonary TB can result in significant suffering [34] and the diagnosis is often challenging [35]. Therefore, healthcare workers need to have a relatively high level of suspicion when persons of non-EU/EEA origin present with unexplained signs and symptoms that might be caused by extrapulmonary TB.

As expected, given the global HIV situation [36], most HIV co-infections were observed among cases of African and Western Pacific origin.

In Japan, 63.4% foreign-born smear-positive TB cases had a successful treatment outcome in the period 2007–2010 [37]. The situation in the EU/EEA is much better with 77.4% of TB cases in individuals of non-EU/EEA origin having a successful treatment outcome 12 months after starting treatment. Among TB cases in individuals of non-EU/EEA origin notified in EU/EEA, 17.9% percent did not have treatment outcome data reported, while in Japan, treatment outcome was not available for 16.6% of foreign-born smear-positive cases [37]. In the EU/EEA, the lowest treatment success rate (70.4%) was observed in cases from the European Region. This is probably attributable to the high percentage of MDR TB and XDR TB cases which require more than 12 months of treatment and would therefore be reported as 'still on treatment' 12 months after starting treatment. Another reason may be the high percentage of non-evaluated cases (10.0%) which might mask the real number of cases lost to follow-up. The non-uniform use of treatment outcome categories such as 'lost to follow-up', 'transferred out', 'still on treatment' and 'unknown' across the EU/EEA Member States might contribute to the high number of cases with non-evaluated treatment outcome [38]. In contrast to an earlier publication from the year 2000 that covers the period 1993-1997, where origin from 'Eastern Europe' and 'Yugoslavia' were identified as risk factors for loss to follow-up [39], the percentage of this treatment outcome in our study was smaller in TB cases in individuals of non-EU/EEA origin than in cases of EU/EEA origin. The percentage was especially low in cases originating from the European Region outside the EU/EEA. The treatment success rate in TB cases in individuals of non-EU/EEA origin was higher compared with native TB cases (77.4% vs 74.6%), and the fatality rate was lower (3.2% vs 8.2%). The percentage of TB cases over 64 years of age was lower in migrants compared with native TB cases (8.9% vs 21.0%) which explains the treatment outcome results.

Limitations

This study is based on TB surveillance data submitted to ECDC by the EU/EEA countries. In the EU/EEA TB surveillance system, only a limited number of variables are collected. Also, not all reported information is complete, and data quality is primarily the responsibility of the individual country. The origin of 6.8% of TB cases notified between 2007 and 2013 was not reported. In addition, three countries did not report case-based drug resistance data, and four countries did not report case-based treatment outcome data for the whole period. Due to this missing information, our results might not provide the complete picture of TB epidemiology among cases of non-EU/EEA origin. Furthermore, TB rates among immigrants could not be calculated due to the unavailability of migrant population data.

The differences in reporting of country of origin (country of birth vs nationality) might affect the comparability of data between some countries. The burden of non-EU/EEA migrant TB cases might be underestimated

in countries reporting nationality, as the migrants might have obtained the citizenship of the host country before TB was diagnosed.

Italy, France and Spain are not reporting TB drug resistance data to TESSy. The exclusion of TB cases reported by these countries compromises the representativeness of laboratory results in this study as these three countries received a relatively high number of non-EU/EEA immigrants.

The laboratory confirmation rate has been shown to be below 50% in some major reporting countries EU/EEA MSs [1] which might lead to the underestimation of resistant TB cases.

The HIV testing coverage among TB cases is suboptimal and does therefore not allow for an in-depth analysis of the data. The low testing coverage might lead to under- or over estimation of TB/HIV co-infection in EU/EEA.

Conclusions

Migration from outside the EU/EEA contributes markedly to the TB burden in the EU/EEA. Targeted prevention and control efforts (e.g. access to healthcare for all migrants including undocumented migrants, avoiding interruption of treatment) and implementation of active case finding approaches (e.g. screening at entry point, screening for latent TB infection) focussed on non-EU/EEA migrants may be needed in order to diagnose cases early, provide adequate treatment and support and reduce the burden of TB among migrants.

*This designation is without prejudice to positions on status, and is in line with United Nations Security Council resolution 1244/99 and the International Court of Justice Opinion on the Kosovo declaration of independence.

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Conflict of interest

None declared.

Authors' contributions

CK contributed to the study design, performed the data analysis, and wrote the first draft of the manuscript, PZ contributed to the study design, and contributed to further versions of the manuscript and approved the final version before submission, MvdW contributed to the study design and data analysis, and contributed to further versions of the manuscript and approved the final version before submission.

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WHO publishes an implementation framework on active tuberculosis drug-safety monitoring and management (ADSM)

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In February 2016, the Global TB Programme of the World Health Organization (WHO) released its framework for the implementation of active tuberculosis (TB) drug-safety monitoring and management (aDSM), adapted to the specific needs and context of national TB programmes [1].

Active drug-safety monitoring and management, or aDSM, is defined as '*the active and systematic clinical and laboratory assessment of patients on treatment for extensive drug-resistant TB, or with new TB drugs or novel multidrug-resistant TB (MDR-TB) regimens to detect, manage and report suspected or confirmed drug toxicities*'. The recording and reporting activities of aDSM primarily target the serious adverse events (SAEs) as a basic requirement. The appropriate and timely management of drug-related harms is an integral component of aDSM.

Health programmes that systematically monitor patient safety are in a better position to prevent and manage adverse drug reactions, relieve patient suffering and improve treatment outcomes. This is particularly relevant to national TB programmes at this point, as new TB medicines and novel regimens for MDR-TB come on the market and become widely used. Programme staff and technical agencies are currently putting in place systems to monitor the effectiveness and safety of these regimens.

More information is available on the WHO dedicated website (www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/pharmacovigilance) and the WHO MDR-TB treatment handbook [2].

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