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Joint efforts needed to stop transmission of tuberculosis in Europe

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Even though the number of notified tuberculosis (TB) cases in the World Health Organization (WHO) European Region has continuously gone down, from 474,794 in 2007 to 380,366 in 2011 [1], there is no room for complacency. The number of extrapulmonary TB (EPTB) cases in the European Union (EU) and the European Economic Area (EEA) is not decreasing and a considerable number of TB patients do not finish their TB treatment successfully.

On 24 March, World Tuberculosis Day, we commemorate the day when Robert Koch announced the discovery of the cause of TB, the bacillus *Mycobacterium tuberculosis*. In 2010, the European Centre for Disease Prevention and Control (ECDC) used the occasion of World Tuberculosis Day to raise awareness on multidrug-resistant TB (MDR-TB) in the EU/EEA [2]. A year later, ECDC created attention for children that are affected by TB [3,4], and in 2012, the focus was on tuberculosis in hard to reach populations and vulnerable groups that are especially prevalent in larger cities in the EU/EEA. This year we aim to raise awareness about TB occurring outside of the lungs, i.e. EPTB. Patients with EPTB constitute a group which does not receive specific attention in international TB control strategies but contributes to the burden of disease nevertheless. EPTB can affect almost any organ in the body. The most common organs of EPTB are pleura, lymph nodes, and the genitourinary tract [5].

In this issue of *Eurosurveillance*, Sandgren et al. [5] describe the EPTB epidemiology in the EU/EEA using 10 years of surveillance data. In the period 2002 to 2011, overall TB notification rates decreased, mainly due to a decrease in pulmonary TB. The notification rates of EPTB however, did not show a downward trend. Thus the proportion of cases with EPTB increased from 16% in 2002 to 22% in 2011. Only 34% of the EPTB cases were culture-confirmed compared to 63% of the pulmonary TB cases. These figures indicate the difficulties in diagnosing EPTB. They are also highlighted in a Euroroundup where eleven EU countries describe the challenges faced in diagnosing EPTB [6]. Countries report that EPTB is often not considered in the differential diagnosis because it is a rare disease. Furthermore, most medical professionals do not have experience in diagnosing EPTB. The fact that EPTB can present with a variety of symptoms that may mimic symptoms of other pathologies poses an additional challenge for the diagnosis. Finally, obtaining an appropriate sample for confirmation of EPTB was identified as an obstacle in the diagnostic process.

Another study in this issue on extrapulmonary TB describes the burden of TB meningitis in Germany [7]. Analysis of surveillance data from 2002 to 2009 showed that 422 (0.9%) of all TB patients had TB meningitis as main or secondary form of TB. In the 2002 to 2011 surveillance data from the EU/EEA, 2.9% of all EPTB cases for which a specific site of disease was known noted as major site meninges [5]. If we assume that the proportion with TB meningitis is the same in the 60,000 EPTB cases without known specific site of disease this would result in 0.7% of all notified TB patients having TB meningitis.

Monitoring of treatment outcome is one of the pillars of TB control and assesses how many of the potentially infectious TB cases notified were declared cured at the end of treatment. France has up to now not been able to report TB treatment outcome data to the European Surveillance System (TESSy) because data were not available at the national level. Therefore, it is interesting to see the report from Antoine et al. [8] on treatment outcomes of pulmonary TB cases notified in 2009. Compared to the EU/EEA data, the treatment outcomes in France seem to be less favourable although data are not fully comparable, i.e. in France 70% of the pulmonary TB cases had a successful treatment outcome whereas this was at 79% for the newly diagnosed pulmonary culture-positive cases in the EU/EEA [1]. A paper by Mor et al. [9] from Israel showed that both non-national migrants and Israeli citizens had higher treatment success rates compared to what was reported for the EU/EEA and for France. However, the treatment success rate for Israeli citizens was significantly better (96%) compared to non-national

migrants (81%). It would be interesting to use the lessons learned in Israel to further improve TB treatment in the EU/EEA.

In 2011, TB notification rates were below 10 per 100,000 population in 19 EU/EEA countries and below 20 in 22 countries [1]. Countries with a TB notification rate of <20 per 100,000 population are considered to have entered the TB elimination phase. Since many EU/EEA countries with a low notification rate diagnose a considerable percentage of their TB cases in migrants, elimination of TB as a public health problem (i.e. TB incidence <1 case per million population) may be not feasible. However, we believe that stopping the transmission of TB is feasible by early detection of cases, adequate treatment and comprehensive contact investigation.

At European level, several complementing activities are on-going to prevent and control the spread of TB. The ECDC activities on TB are guided by the Framework Action Plan to Fight Tuberculosis in the European Union (EU) [10]. Other documents relevant for TB prevention and control in Europe are the Berlin Declaration [11] and the Consolidated Action Plan to Prevent and Combat Multidrug- and Extensively Drug-Resistant Tuberculosis (M/XDR-TB) in the World Health Organization (WHO) European Region [12].

The reported data in this issue show that TB prevention and control needs to be further improved in Europe. To coordinate and to strengthen TB control in the EU/EEA and the WHO European Region, several TB networks have been established. This year, from 28 May until 31 May, three TB networks will meet in the Hague, the Netherlands: the Joint ECDC/WHO European Tuberculosis Surveillance Network, the Wolfheze Movement [13], and the ECDC coordinated European Reference Laboratory Network for Tuberculosis (ERLN-TB) [14]. For the first time, participants of the three networks will meet and discuss progress made since the endorsement of the above mentioned Berlin Declaration, the ECDC Action Plan, and the WHO Regional Office for Europe Consolidated Action Plan. The joint meeting should identify further activities necessary to reach the targets and outputs defined in the above mentioned plans to progress towards control of TB in Europe.

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Fatal case of extensively drug-resistant *Mycobacterium tuberculosis* Beijing genotype infection in an injecting drug user, Athens, Greece, 2012

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We present the first fatal case of extensively drug-resistant tuberculosis (XDR-TB) in an injecting drug user (IDU) in Athens, Greece, co-infected with human immunodeficiency virus and hepatitis C virus and discuss the implications for public health. Despite immediate initiation of treatment, the patient's condition gradually deteriorated and he died 16 days after hospital admission because of multiple organ failure. The contact tracing investigation revealed no further infections among the patient's contacts.

We report the first fatal case of extensively drug-resistant tuberculosis (XDR-TB) in an injecting drug user (IDU) in Athens, co-infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) and discuss the implications for public health in times of austerity in Greece.

Since 2011, Greece has been facing a considerable outbreak of HIV infections among IDU in Athens. Although concerns about migration have been raised, there has been no evidence that HIV is a migrant-specific issue, except for migrants who inject drugs [1].

XDR-TB is defined as resistance to rifampicin and isoniazid (multidrug-resistant tuberculosis; MDR-TB) plus resistance to a fluoroquinolone and at least one of the three injectable second-line drugs (SLD): amikacin, kanamycin, capreomycin [2]. XDR-TB constitutes an emerging issue in Europe and a significant public health problem in countries of the former Soviet Union (FSU) [3,4]. It has been identified in 84 countries and the average proportion of MDR-TB cases with XDR-TB worldwide was 9.0% (range 6.7-11.2%) in 2012 [5]. XDR-TB has been associated with HIV in countries such as Latvia and Ukraine [4]. Treatment outcomes have been significantly worse for patients with drug-resistant TB, as therapeutic options are limited, less effective, more toxic and costly [5].

In Greece, TB incidence is underreported [6]. From 2006 to 2009, 13 XDR-TB cases were recorded at the National Reference Laboratory for Mycobacteria (NRLM) in Athens: nine cases among Greek nationals, most of them repatriated from the FSU and the remaining four cases were recorded among migrants. XDR-TB ratio among MDR-TB cases was 19% [7].

Case report

On 18 October 2012, a man in his early 40s originating from Ukraine, was admitted to the HIV Unit, 'Andreas-Sygros' University Hospital, in Athens, Greece. The patient presented with fever, weight loss, abdominal pain, diarrhoea and fatigue. He had lived for more than a decade in Greece and had a medical history of intravenous drug abuse, HIV (Centers for Disease Prevention and Control (CDC) HIV classification subcategory B3) and HCV co-infection. Due to poor compliance to antiretroviral therapy, his HIV infection remained uncontrolled and he developed resistance to multiple antiretroviral drugs. In February 2012, he had a CD4 count of 25 cells/uL and a viral load of 39,000 copies/mL. One month before his admission to hospital, the patient had returned to Greece from a six-month visit to Ukraine.

Upon admission, physical examination revealed hepatosplenomegaly and diffuse abdominal tenderness. Auscultation of thorax revealed bilateral crackles. Blood pressure was 110/60 mmHg, $SatO_2$ 97%, 82 bpm, and breaths 26 per minute. Computed tomography (CT) revealed interlobular and bronchial thickening of lower lung lobes, with a calcified granuloma of the left lower lobe and lymph nodes of the left pulmonary hilum and

in the sub-cardinal area, a small pleural effusion (left) and enlarged lymph nodes in the Haller's tripod and the hepatic hilum. Laboratory investigation showed mild anaemia, increased erythrocyte sedimentation rate (ESR), gamma-glutamyl transferases (gamma-GT), serum alkaline phosphatase (SAP), lactate dehydrogenase (LDH) and hypoalbuminemia.

Highly active antiretroviral therapy (HAART) was reinitiated immediately consisting of raltegravir, atazanavir, ritonavir and AZT/3TC/ABC (with intravenous trimethoprim-sulfamethoxazole (TMP-SMX) as prophylactic treatment for *Pneumocystis carinii*). Blood and gastric fluid specimens were sent to NRLM for acid fast bacilli (AFB) microscopy and mycobacterial culture. Smears did not reveal AFB. However, due to the advanced HIV condition, the clinical presentation, the geographic origin and recent travel history, and the severity of the patient's condition, empiric therapy was initiated against both *Mycobacterium tuberculosis* and *M. avium*. Tuberculin skin test (TST) and Quantiferon TB Gold IT testing (Cellestis, Australia) were negative, but these results were attributed to the patient's immunosuppression. The patient was administered rifabutin, isoniazid, ethambutol orally, and intravenous clarithromycin and amikacin.

Despite treatment, the patient's condition gradually deteriorated. Due to severe anaemia and leucopoenia, a bone marrow examination was performed to rule out a lymphoproliferative disorder, and histology indicated a mycobacterial infection. Bone marrow smears did not show AFB. An abdominal CT scan showed hepatomegaly, lesions in the spleen, and a considerable amount of free peritoneal fluid in the pelvis minor. Fifteen days after initiation of treatment, mycobacterial growth was detected in gastric fluid and blood by automated liquid culture (BD Bactec MGIT 960, Maryland, USA). After one more day the patient died of multiple organ failure.

Molecular analyses

M. tuberculosis complex was identified using Genotype MTBDR*plus v.2* (Hain Lifescience, Nehren, Germany). The assay revealed mutations S531L (*rpoB* gene) and S315T1 (*katG* gene), confirming resistance to rifampicin and isoniazid, respectively. Mutations D94G (*gyrA* gene) and A1401G (*rrs* gene), conferring resistance to fluoroquinolones and injectable SLD, respectively, were found by the Genotype MTBDR*sl* assay (Hain Lifescience, Germany). This profile was consistent with XDR-TB, and the HIV Unit was informed postmortem. MIRU-VNTR 24-loci genotyping was requested from the World Health Organization / Global Laboratory Initiative (WHO/GLI) Supranational Mycobacterium Reference Laboratory, Health Protection Agency, London, United Kingdom. The isolate belonged to the single 'East European' subtype of the Beijing lineage that is present in Estonia and widely in eastern Europe [8]. Phenotypic drug susceptibility testing (DST) using the modified proportion method on solid and liquid media confirmed molecular DST results (Table).

Table

Drug susceptibility testing results, fatal case of extensively drug-resistant tuberculosis in an injecting drug user, Athens, Greece, 2012

Drug	Resistant (R) / Sensitive (S)
Isoniazid 0.2 ug/mL	R[a]
Rifampicin 40ug/mL	R[a]
Ethambutol 2ug/mL	R[a]
Pyrazinamide 100ug/mL	R[b]
Streptomycin 5ug/mL	R[a]
Amikacin 1ug/mL	R[a]
Ofloxacin 2ug/mL	R[a]
Capreomycin 40ug/mL	R[a]
Cycloserine 40ug/mL	R[a]
Ethionamide 40ug/mL	R[a]

[a] Indirect proportion method on solid media (Löwenstein-Jensen).
[b] MGIT 960.

Contact tracing investigation

Investigation of the patient's contacts included four close family contacts. Family contacts and healthcare workers in the HIV unit of the hospital underwent a comprehensive individual risk assessment with chest X-ray, TST or Quantiferon TB Gold IT testing at the Clinic for Multidrug Resistant Tuberculosis, Athens, following the European guidelines [9]. All contacts were informed about the risks and symptoms, and were provided with easy access to the clinic for regular clinical observation. No evidence of infection was found as of 15 March 2013.

Discussion

TB control is facing major challenges worldwide. Co-infection with HIV (TB/HIV) and MDR/XDR TB make control activities more complex and demanding. Treatment options for XDR-TB are extremely limited because SLD are less effective, more toxic, and more costly than first-line therapies [10]. In immunocompromised patients, XDR-TB is devastating; in a study from South Africa, 52/53 patients died, with median survival of 16 days from time of diagnosis [11]. TB and HIV among IDU are converging with hepatitis C, further complicating the management of cases [12] .

To our knowledge, this is the first report of a fatal XDR-TB Beijing genotype disseminated infection in an IDU co-infected with HIV and HCV in Greece. HIV-related TB continues to increase even in countries with well-organised national TB control programmes that are implementing the directly observed treatment short-course (DOTS). The Tuberculosis Committee of the Hellenic Center for Disease Control and Prevention

(HCDCP) worked on a National Tuberculosis Control Program which was completed in 2007 and since then has been part of the National Action Plan to Prevent Communicable Diseases, 2008-2012. The Committee has made suggestions for improvement in terms of TB underreporting and synchronisation between the services controlling TB, but these have not been fully put into practice [13]. Immigration from areas with high MDR/XDR-TB incidence and the effects of the current economic crisis, in particular increased unemployment and numbers of homeless people, along with budget cuts in prevention services and in services targeted at vulnerable and hard to reach population groups, add to already existing challenges to the control of TB including MDR/XDR-TB as well as to prevention and control of HIV.

The primary strategy for controlling and preventing TB includes rapid disease diagnosis and initiation of treatment. Speed of detection is important for public health. Diagnosis of active TB by microscopy or culture can be more difficult in HIV patients, as their bacterial load is usually lower [14]. Gene Xpert MTB/RIF (Cepheid, Sunnyvale, CA), a rapid molecular assay endorsed by the WHO in December 2010 for the simultaneous detection of TB and rifampicin resistance, is recommended to be used as the initial diagnostic test in individuals suspected of MDR/XDR-TB or HIV/TB co-infection [15]. In Greece and in a number of other European countries, the Xpert MTB/RIF assay has not been introduced in clinical routine yet because of its high costs [16].

Collaborative TB/HIV activities should be applied at European level to reduce TB burden among people living with HIV and the burden of HIV among TB patients [17]. The threats to public health emerging from the spread of MDR/XDR-TB among HIV individuals should make TB case detection, treatment and prevention a priority for the national AIDS control programmes. Apart from active case finding using innovative TB diagnostic assays, other interventions such as early initiation of antiretroviral therapy, strengthening HIV and TB surveillance and implementing joint recording and reporting formats, scaling-up uptake of co-trimoxazole preventive therapy and antiretroviral therapy, and last but not least, implementing WHO/United Nations Office on Drugs and Crime (UNODC)/Joint United Nations Programme on HIV/AIDS (UNAIDS) guidelines for addressing TB/HIV in people who inject drugs [18], should save lives in the future.

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Conflict of interest

None declared.

Authors' contributions

KL and DP wrote the manuscript including conception and design, acquisition, analysis and interpretation of data. SK provided clinical care and participated in data collection. PI carried out molecular analysis and made helpful comments. SK supervised mycobacterial culture, DST and Quantiferon testing. ST performed contact tracing investigation. IM carried out liquid culture and DST. AP supervised contact tracing investigation and made useful comments. MS performed MIRU VNTR genotyping. FD, VP and EV revised the manuscript critically and gave final approval of the version to be submitted for publication. All authors read and approved the final manuscript.

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Extrapulmonary tuberculosis in the European Union and European Economic Area, 2002 to 2011

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Tuberculosis (TB) is decreasing in the European Union/ European Economic Area (EU/EEA), but remains a significant public health problem. Although pulmonary TB accounts for the majority of the cases and is the main transmissible form of the disease, extrapulmonary TB also contributes to the burden of disease and does not receive specific attention in international control strategies. We performed a descriptive analysis to assess the burden and trends of extrapulmonary TB in EU/EEA countries. During 2002–11, 167,652 cases of extrapulmonary TB were reported by the 30 Member States. Extrapulmonary TB accounted for 19.3% of all notified cases, ranging from 5.8% to 44.4% among the Member States. Overall, TB notification rates decreased in 2002–11 due to a decrease in pulmonary TB. Notification rates of extrapulmonary TB remained stable at 3.4 per 100,000 in 2002 and 3.2 per 100,000 in 2011. Thus the proportion of extrapulmonary TB increased from 16.4% in 2002 to 22.4% in 2011. Of all extrapulmonary TB cases reported during 2002–11, 37.9% were foreign-born or citizens of another country, 33.7% were culture-confirmed, and the overall treatment success was 81.4%. A significant percentage of notified TB cases are extrapulmonary, and in contrast to pulmonary TB, extrapulmonary TB rates are not decreasing.

Introduction

Tuberculosis (TB) is primarily a disease of the lungs (pulmonary TB), but can affect almost any organ in the body. The term extrapulmonary TB is used to describe the occurrence of TB at sites other than the lung. The most common sites of extrapulmonary TB are lymph nodes, genitourinary tract, pleura, bones and joints, meninges and the central nervous system, peritoneum and other abdominal organs [1-3]. Tuberculosis also exists in a disseminated (miliary) form, with a general bacteraemia spreading the infection throughout the body [4].

Of the 6.2 million cases of TB in the world notified to the World Health Organisation (WHO) in 2011, 5.8 million were new cases, and of the latter, 0.8 million (15%) cases had extrapulmonary TB [5]. In the WHO Europe region, 253,769 new cases of TB were notified, of which 42,489 (17%) had extrapulmonary TB [5].

Extrapulmonary TB is rarely addressed in the public health literature. There are however many clinical case reports and case series published, describing patients with different forms of extrapulmonary TB [6-8]. In these publications, extrapulmonary TB is often perceived more as a clinical peculiarity than a public health problem. A reason why extrapulmonary TB is not given high priority on the public health agenda is probably that it does not contribute significantly to the transmission of the disease, very much the same reasoning as used for childhood TB [9,10]. Patients with extrapulmonary TB do not receive specific attention in international TB control strategies [11,12]. However, extrapulmonary TB contributes significantly to TB-related morbidity and can cause complications, lifelong sequelae and disabilities [1,13-15]. From a public health perspective, there is therefore a need to address this group of patients, as they do contribute to the total burden of disease and they do have a significant impact on available resources of national health systems.

Trend analyses of extrapulmonary TB have been conducted, among others in the Netherlands, Serbia, Spain, the United Kingdom, and the United States (US) [16-21]. An in-depth analysis of extrapulmonary TB in the Member States of the European Union (EU) and European Economic Area (EEA) has not been undertaken. The analysis presented here aims to provide a descriptive overview of the trends in extrapulmonary TB notifications, diagnosis, and treatment outcome during the last 10 years, 2002 to 2011.

Methods

Data source and collection

We performed a descriptive analysis of surveillance data to assess the burden and trends of extrapulmonary TB in EU/EEA countries between January 2002 and December 2011. Data were extracted from The European Surveillance System (TESSy) for the years 2007 to 2011, and from the former EURO-TB network's historical databases for the years 2002 to 2006, held

at the European Centre for Disease Prevention and Control (ECDC). Data from 30 EU and EEA countries reporting to the ECDC were analysed. For the purpose of the study, country-specific data for pulmonary and extrapulmonary TB cases were extracted for the years of analysis, for both new and retreatment cases.

Data inclusion and surveillance definitions

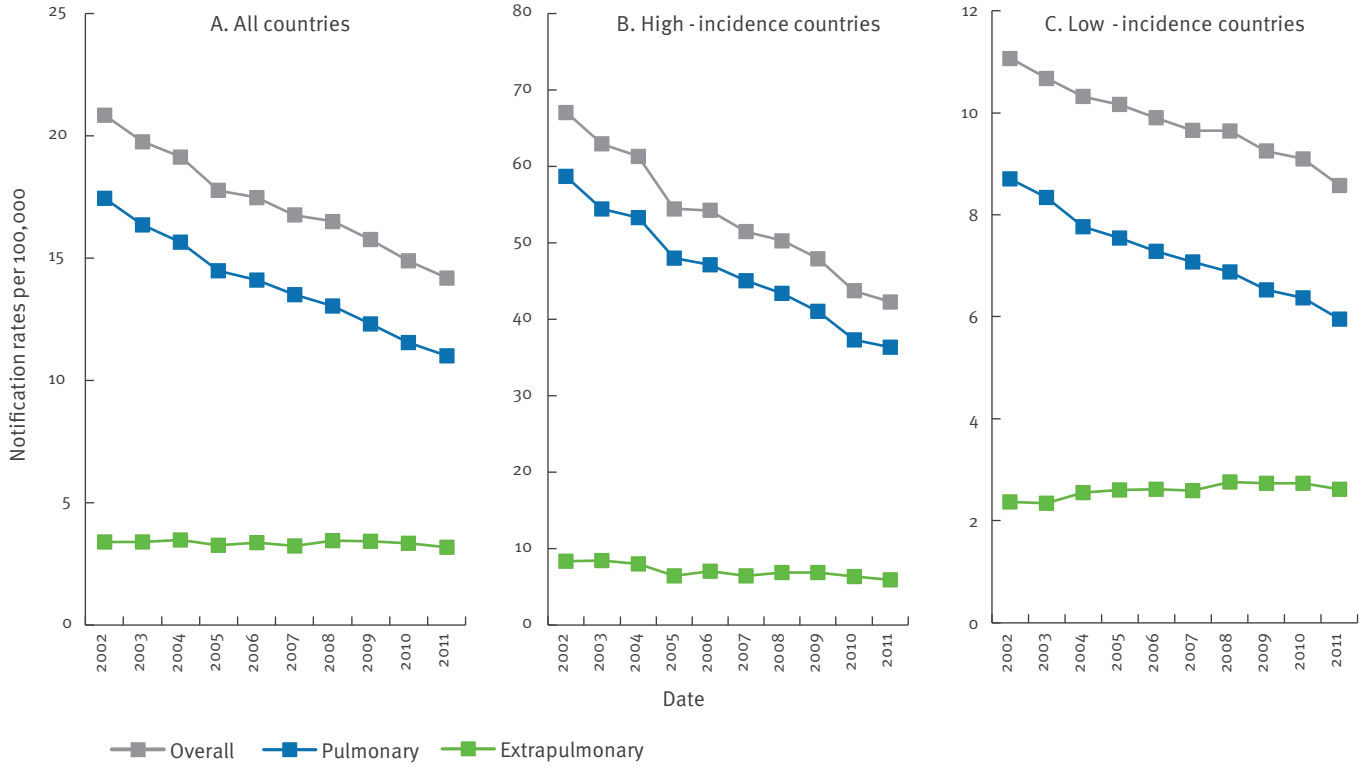
We used the definitions and categories provided in the ECDC/WHO report *Tuberculosis surveillance and monitoring in Europe 2012* [22]. Definitions of specific relevance for the analyses in this paper are given here.

All TB cases, confirmed, probable or possible, notified at country level for the year of interest were included in the dataset uploaded to TESSy. Possible cases were considered as those who only met clinical criteria. Probable cases were defined by the additional detection of acid-fast bacilli (AFB) with microscopy or of *Mycobacterium tuberculosis* in a nucleic acid amplification test or granulomata. Confirmed cases were those with a positive culture for *M. tuberculosis* or with detection of AFB with microscopy and of *M. tuberculosis* in a nucleic acid amplification test. Cases eligible for treatment, but who never started it, were also included for the purpose of this study, as well as cases diagnosed post mortem.

Site of disease was collected through two variables in TESSy: 'major site of disease' and 'minor site of disease'. For the detailed analysis, we used the variable 'major site of TB'. Pulmonary TB was defined as a case with TB affecting the lung parenchyma, the tracheobronchial tree or the larynx. Extrapulmonary TB was defined as TB with non-pulmonary presentations, and including pleural, intra-thoracic lymphatic, extrathoracic lymphatic, spine, bone/joint other than spine, meninges, central nervous system other than meninges, genitourinary, peritoneal/digestive, disseminated and other TB. Site of disease could also be recorded as unknown. Disseminated TB included TB of more than two organ systems, miliary TB and TB in which *M. tuberculosis* complex has been isolated from the blood. Cases with concurrent pulmonary and extrapulmonary TB were included in the pulmonary TB category.

Figure 1

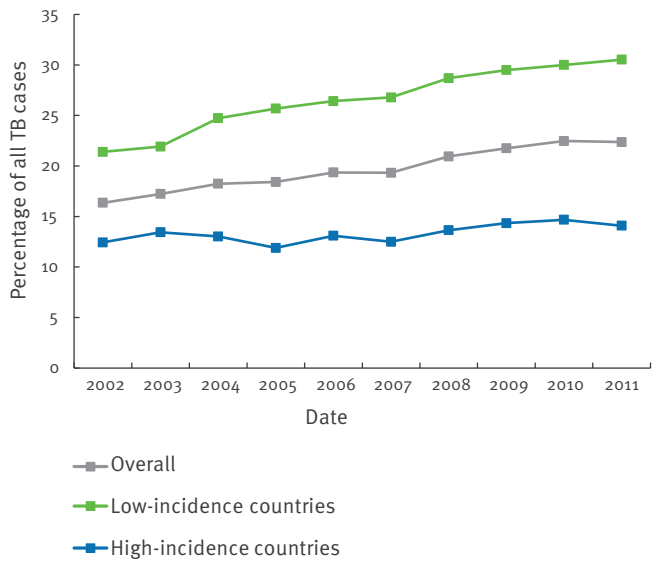
Notification rates of pulmonary, extrapulmonary and overall tuberculosis, by year and incidence level, EU/EEA Member States, 2002–11



EU/EEA: European Union/European Economic Area.

Figure 2

Proportion of extrapulmonary tuberculosis, by year and incidence level, EU/EEA Member States, 2002–11



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

The geographical origin of TB cases was classified according to place of birth (born in the country/foreign-born) or, if unavailable, citizenship (national/non-national).

Data completeness and quality

The data uploaded to TESSy went through automated checks for completeness and accuracy. In case-based data collection the probability of case duplications is minimal due to the use of unique record identifiers for reported cases. However, the main responsibility for data quality and correctness lies with the countries that provide the data. Before 2007, 26 of the 29 included EU/EEA Member States were able to report case-based data, for the year 2007 all 30 Member States reported case-based data, and thereafter 29 countries reported case-based data. Comparability of data between countries is compromised by three factors: not all Member States have reported data for the whole period 2002 to 2011, the method of reporting differs by Member State, and some definitions for reporting used by individual Member States are not consistent over time. Therefore, the analyses made in this study have different denominators depending on the variable analysed. We included a specific part in the results section on data completeness, where we specify the number of countries and the respective denominators used for each variable in the analyses.

Analysis

We used StataSE 12 (StataCorp LP, College Station, Texas, US) and Microsoft Excel 2007 for data analyses. Data collected from 2002 to 2011 were collated and tabulated in an aggregated fashion. To be transparent about completeness of data for each variable, we report the unknowns for sex, age groups, origin, previous treatment, human immunodeficiency virus (HIV) infection and TB culture result in the characteristics tables. Percentages have been calculated within the pulmonary TB or extrapulmonary TB strata separately, excluding the unknowns where applicable. Population size was obtained from the EUROSTAT database for 2002 to 2011 (http://epp.eurostat.ec.europa.eu/tgm/table.do?tab=table&language=en&pcode=tps00001&tableSelection=1&footnotes=yes&labeling=labels&plugin=1).

For some analyses, countries were grouped as high- and low-incidence TB countries based on the data reported for 2011, using the thresholds previously proposed by the Wolfheze working group [23] and adopted in the EU monitoring framework [24]. Thus, low-incidence countries were defined as those with less than 20 cases per 100,000 population in 2011 (23 countries), and high-incidence countries as those with 20 or more cases per 100,000 population in 2011 (seven countries: Bulgaria, Estonia, Latvia, Lithuania, Poland, Portugal and Romania).

Chi-square tests were used to analyse differences in proportions between groups. A p value of $p<0.05$ was considered statistically significant.

Results

Extrapulmonary tuberculosis notification and trends

During the period from 2002 to 2011, 868,726 TB cases were reported. For 3,696 of them (0.4%) the site of infection was not reported, 167,652 (19.3%) had extrapulmonary TB only, 648,225 (74.6%) had pulmonary TB only, and 49,153 (5.7%) had both and were thus classified as pulmonary TB (total 80.3%). The overall proportions of extrapulmonary TB during the study period ranged from 5.8% to 44.4% of all TB cases in the different EU/EEA Member States. As the notification rate of pulmonary TB has markedly decreased in most countries of the EU/EEA, the proportion of extrapulmonary TB increased during the period, from 16.4% of all TB cases in 2002 to 22.4% in 2011 The notification rates of extrapulmonary TB cases ranged from 0.5 per 100,000 to 13.0 per 100,000 across the EU/EEA Member States for the latest reporting year 2011. During the 10-year period, the overall extrapulmonary TB notification rates remained stable at 3.4 per 100,000 in 2002 and 3.2 per 100,000 in 2011 (Figure 1A). When stratifying the data by high- and low-incidence countries, the extrapulmonary TB notification rate seemed to be stable in both strata (Figure 1B and Figure 1C). The proportion of extrapulmonary TB was

Table 1

Characteristics of pulmonary and extrapulmonary TB cases in the EU/EEA, 2002–11

	Pulmonary TB (%)	Extrapulmonary TB (%)	Site Unknown (%)	Total (%)	p value
Total	**697,378 (80.3)**	**167,652 (19.3)**	**3,696 (0.4)**	**868,726 (100)**	
Sex	N=642,871	N=161,609	N=2,744	N=807,224	<0.01
Female	209,035 (32.5)	75,045 (46.4)	1,243 (45.3)	285,323 (35.3)	
Male	433,170 (67.4)	86,317 (53.4)	1,472 (53.6)	520,959 (64.5)	
Unknown	666 (0.1)	247 (0.2)	29 (1.1)	942 (0.1)	
Age groups	N=642,871	N=161,609	N=2,744	N=807,224	<0.01
0–14	20,017 (3.1)	12,433 (7.7)	560 (20.4)	33,010 (4.1)	
15–24	68,139 (10.6)	21,654 (13.4)	232 (8.5)	90,025 (11.1)	
25–44	231,186 (35.9)	59,234 (36.7)	721 (26.3)	291,141 (36.1)	
45–64	206,594 (32.1)	36,585 (22.6)	588 (21.4)	243,767 (30.2)	
≥65	115,656 (18.0)	31,438 (19.5)	566 (20.6)	147,660 (18.3)	
Unknown	1,279 (0.2)	265 (0.2)	77 (2.8)	1,621 (0.2)	
Origin	N=614,199	N=156,957	N=2,744	N=773,900	<0.01
Foreign	108,705 (17.7)	59,500 (37.9)	850 (31.0)	169,055 (21.8)	
Native	489,721 (79.7)	92,048 (58.6)	1,198 (43.7)	582,967 (75.3)	
Unknown	15,773 (2.6)	5,409 (3.4)	696 (25.4)	21,878 (2.8)	
Previous treatment	N=642,871	N=161,609	N=2,744	N=807,224	<0.01
No	501,136 (78.0)	136,471 (84.8)	1,498 (54.6)	639,105 (79.2)	
Yes	99,509 (15.5)	8,197 (5.1)	113 (4.1)	107,819 (13.4)	
Unknown	42,226 (6.6)	16,941 (10.5)	1,133 (41.3)	60,300 (7.5)	
HIV reported	N=80,963	N=32,799	N=15	N=113,777	<0.05
HIV tested	37,936 (46.9)	7,199 (21.9)	1 (6.7)	45,136 (39.7)	
HIV-infected b	1,586 (4.2)	468 (6.5)	0 (0.0)	2,054 (4.6)	
Unknown	43,027 (53.1)	25,600 (78.1)	14 (93.3)	68,641 (60.3)	
Culture result	N=446,449	N=149,749	N=3,696	N=599,894	<0.01
Positive	280,921 (62.9)	50,405 (33.7)	877 (23.7)	332,203 (55.4)	
Negative	96,718 (21.7)	62,873 (42.0)	643 (17.4)	160,234 (26.7)	
Unknown	68,810 (15.4)	36,471 (24.4)	2,176 (58.9)	107,457 (17.9)	
DST result					
Test performeda	175,553 (62.5)	36,217 (71.9)	520 (59.3)	212,290 (63.9)	<0.01
MDR-TB	11,554 (6.6)	466 (1.3)	15 (2.9)	12,035 (5.7)	
Treatment outcome reported	N=453,449	N=109,297	N=1,457	N=564,203	
Treatment success	333,113 (73.5)	88,980 (81.4)	769 (52.8)	422,862 (74.9)	<0.01

EU/EEA: European Union/European Economic Area; DST: drug susceptibility testing; HIV: human immunodeficiency virus; MDR-TB: multidrug-resistant tuberculosis; TB: tuberculosis.

[a] The denominator for the calculation of percentage of drug susceptibility was the number of culture-positive cases.

[b] The denominator for the calculation of percentage of HIV-infected was the number of HIV-tested cases.

higher (p<0.01) in low-incidence countries (26.4% of all TB cases) compared with high-incidence countries (13.2% of all TB cases).

Characteristics of tuberculosis cases

Extrapulmonary TB was more frequently notified in women than pulmonary TB: 46.4% of the extrapulmonary TB cases, compared with 32.5% of the pulmonary TB cases were female (Table 1). Also the age distribution was different. Extrapulmonary TB was more frequently notified in children than pulmonary TB: 7.7% of the extrapulmonary TB cases were 0 to 14 years of age, compared with 3.1% of the pulmonary TB cases (Table 1). Moreover, extrapulmonary TB was more frequently notified in individuals that were of foreign origin (37.9%) compared with pulmonary TB cases (17.7%). The proportion of extrapulmonary TB of all TB cases in individuals of foreign origin in low-incidence countries increased significantly over the period 2002 to 2011, from 48.5% in 2002 to 61.1% in 2011 (p<0.01,

Figure 3). For high-incidence countries, the time trend in the proportion of extrapulmonary TB cases of all TB cases in individuals of foreign origin was 4.1% in 2002 and 3.2% in 2011 (Figure 3).

HIV test results were available for 21.9% of the extrapulmonary TB cases compared with 46.9% of pulmonary TB cases ($p<0.01$). Extrapulmonary TB cases who had a HIV test result were more frequently ($p<0.05$) HIV-positive compared with pulmonary cases (6.5% vs. 4.2%; Table 1).

The TB diagnosis was confirmed by a positive culture in only 33.7% of the extrapulmonary TB cases. Over the same period, 62.9% of the pulmonary TB cases had a positive culture ($p<0.01$). In 24.4% of the extrapulmonary TB cases, the culture results were unknown (Table 1). The proportion of culture-positive cases increased slightly in low-incidence countries from 34.5% in 2002 to 37.5% in 2011. For high-incidence countries, the proportion of culture-positive cases was stable at 30.0% in 2002 and 30.3% in 2011.

For as many as 71.9% of the culture-positive extrapulmonary TB cases, drug susceptibility testing was performed. Multidrug-resistant TB (MDR-TB) was identified in 1.3% of the extrapulmonary TB cases compared with 6.6% of the pulmonary TB cases ($p<0.01$; Table 1).

Treatment success was achieved in 81.4% of the extrapulmonary TB cases and 73.5% of the pulmonary TB cases ($p<0.01$; Table 1).

Extrapulmonary tuberculosis sites of disease

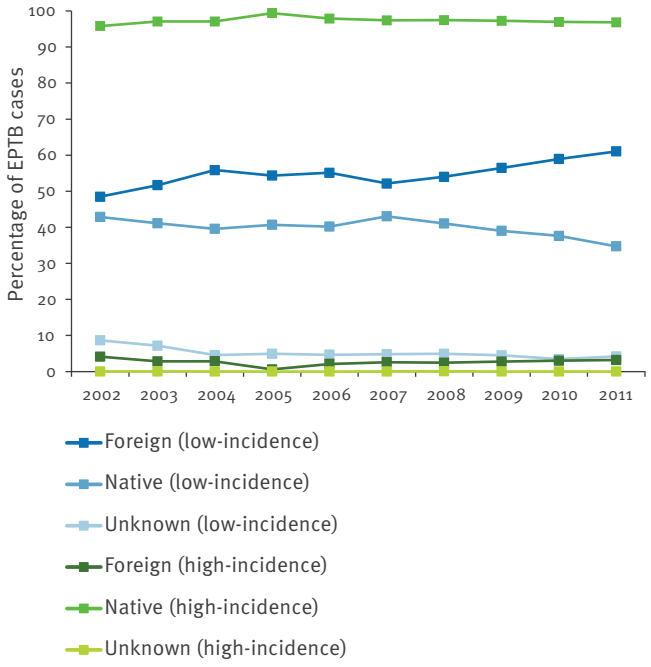
The specific site of extrapulmonary TB was reported for only 108,345 (64.6%) of the 167,652 extrapulmonary TB cases. The most frequently reported forms were pleural TB (39,749 cases, 36.7%) and extrathoracic lymphatic TB (21,812 cases, 20.1%) (Table 2).

The most frequent forms of TB among 9,735 paediatric cases (0–14 years) were lymphatic intrathoracic TB (47.2%) and pleural TB (18.5%). Meningeal TB was present in 5.8% of the paediatric cases compared with 2.9% for all the other age groups combined. The highest proportion of paediatric cases were observed in lymphatic intrathoracic TB cases (40.9%) and meningeal TB cases (17.8%). The most frequent forms of TB among 22,778 elderly cases (above 65 years) were pleural TB (29.0%) and lymphatic extrathoracic TB (21.1%) (Table 2).

Among 27,667 cases of foreign origin, 35.7% had extrathoracic lymphatic TB, 16.4% had pleural TB and 13.6% had intrathoracic lymphatic TB. In contrast, patients of native origin (n=78,477) more frequently had pleural TB (44.4%) and less frequently extrathoracic lymphatic TB (14.4%). The highest proportions of cases of native origin were observed among pleural TB cases (87.7%) and genitourinary TB cases (81.2%) (Table 2).

Figure 3

Extrapulmonary tuberculosis cases by year, origin and incidence level, EU/EEA Member States, 2002–11



EPTB: extrapulmonary tuberculosis; EU/EEA: European Union/ European Economic Area.

Overall denominator for high-incidence countries: n=51,356; overall denominator for low-incidence countries: n=104,974.

Low levels of culture confirmation were observed for several of the specific sites. Especially pleural TB cases (15.1%) meningeal TB cases (20.7%), and spinal TB cases (21.5%) were infrequently confirmed by culture. The highest proportions of culture confirmation were observed in genitourinary TB cases (40.8%) and disseminated TB cases (46.1%) (Table 2).

Overall treatment success for extrapulmonary TB cases with a known site of disease and with treatment outcome data reported was 83.2%. Only 48.9% of disseminated TB cases had a successful treatment outcome. Cases with intrathoracic lymphatic TB (82.4%) and pleural TB (86.7%) most frequently had a successful treatment outcome (Table 2).

Tuberculosis notification and data completeness

Data completeness varied by country and year for several of the variables for which case-based data were reported (Table 3). There was a marked increase in the number of countries reporting case-based data during the study period for several variables. In particular, data completeness improved greatly for specific site

Table 2

Characteristics of extrapulmonary tuberculosis cases for which specific site of disease is known, EU/EEA Member States, 2002–11

	Total EPTB (%)		Pleural (%)		Lymphatic extrathorax (%)		Lymphatic intrathorax (%)		Genito-urinary (%)		Spine (%)		Bone other (%)		Meningeal (%)		CNS other (%)		Disseminated (%)		Gastro-intestinal (%)		Other (%)	
Total	**108,345**	**(100)**	**39,749**	**(36.7)**	**21,812**	**(20.1)**	**11,232**	**(10.4)**	**7,459**	**(6.9)**	**4,207**	**(3.9)**	**5,568**	**(5.1)**	**3,179**	**(2.9)**	**491**	**(0.5)**	**1,623**	**(1.5)**	**2,870**	**(2.7)**	**10,155**	**(9.4)**
Sex																								
Female	49,651	(45.8)	14,316	(36.0)	12,952	(59.4)	5,703	(50.8)	3,540	(47.5)	1,821	(43.3)	2,445	(43.9)	1,379	(43.4)	245	(49.9)	624	(38.5)	1,446	(50.4)	5,180	(51.0)
Male	58,607	(54.1)	25,417	(63.9)	8,831	(40.5)	5,519	(49.1)	3,917	(52.5)	2,385	(56.7)	3,115	(55.9)	1,799	(56.6)	246	(50.1)	999	(61.6)	1,422	(49.6)	4,957	(48.8)
Unknown	87	(0.1)	16	(0.0)	29	(0.1)	10	(0.1)	2	(0.0)	1	(0.0)	8	(0.1)	1	(0.0)	-	(0.0)	-	(0.0)	2	(0.1)	18	(0.2)
Age groups																								
0 –14	9,735	(9.0)	1,797	(4.5)	1,281	(5.9)	4,598	(40.9)	45	(0.6)	116	(2.8)	295	(5.3)	566	(17.8)	35	(7.1)	69	(4.3)	105	(3.7)	828	(8.2)
15 – 24	14,942	(13.8)	8,473	(21.3)	2,507	(11.5)	1,172	(10.4)	286	(3.8)	247	(5.9)	415	(7.5)	350	(11.0)	59	(12.0)	115	(7.1)	435	(15.2)	883	(8.7)
25 – 44	34,922	(32.2)	13,730	(34.5)	8,462	(38.8)	2,525	(22.5)	1,676	(22.5)	1,118	(26.6)	1,514	(27.2)	969	(30.5)	180	(36.7)	686	(42.3)	1,092	(38.0)	2,970	(29.3)
45 – 64	25,756	(23.8)	9,069	(22.8)	4,706	(21.6)	1,552	(13.8)	2,762	(37.0)	1,478	(35.1)	1,489	(26.7)	759	(23.9)	133	(27.1)	351	(21.6)	706	(24.6)	2,751	(27.1)
≥65	22,778	(21.0)	6,612	(16.6)	4,833	(22.2)	1,369	(12.2)	2,661	(35.7)	1,241	(29.5)	1,846	(33.2)	525	(16.5)	83	(16.9)	394	(24.3)	530	(18.5)	2,684	(26.4)
Unknown	212	(0.2)	68	(0.2)	23	(0.1)	16	(0.1)	29	(0.4)	7	(0.2)	9	(0.2)	10	(0.3)	1	(0.2)	8	(0.5)	2	(0.1)	39	(0.4)
Origin																								
Foreign	27,667	(25.5)	4,543	(11.4)	9,885	(45.3)	3,756	(33.4)	1,257	(16.9)	973	(23.1)	1,751	(31.5)	662	(20.8)	201	(40.9)	633	(39.0)	1,138	(39.7)	2,868	(28.2)
Native	78,477	(72.4)	34,867	(87.7)	11,327	(51.9)	7,149	(63.7)	6,058	(81.2)	3,171	(75.4)	3,675	(66.0)	2,430	(76.4)	287	(58.5)	960	(59.2)	1,688	(58.8)	6,865	(67.6)
Unknown	2,201	(2.0)	339	(0.9)	600	(2.8)	327	(2.9)	144	(1.9)	63	(1.5)	142	(2.6)	87	(2.7)	3	(0.6)	30	(1.9)	44	(1.5)	422	(4.2)
Previous treatment																								
No	93,311	(86.1)	36,867	(92.7)	17,955	(82.3)	9,448	(84.1)	6,103	(81.8)	3,590	(85.3)	4,427	(79.5)	2,687	(84.5)	396	(80.7)	1,279	(78.8)	2,435	(84.8)	8,124	(80.0)
Yes	5,397	(5.0)	1,222	(3.1)	1,332	(6.1)	308	(2.7)	551	(7.4)	320	(7.6)	515	(9.3)	185	(5.8)	39	(7.9)	99	(6.1)	163	(5.7)	663	(6.5)
Unknown	9,637	(8.9)	1,660	(4.2)	2,525	(11.6)	1,476	(13.1)	805	(10.8)	297	(7.1)	626	(11.2)	307	(9.7)	56	(11.4)	245	(15.1)	272	(9.5)	1,368	(13.5)
Culture results																								
Positive	26,273	(24.3)	6,003	(15.1)	7,316	(33.5)	2,453	(21.8)	3,043	(40.8)	903	(21.5)	1,927	(34.6)	658	(20.7)	148	(30.1)	749	(46.2)	870	(30.3)	2,203	(21.7)
Negative	19,196	(17.7)	5,900	(14.8)	3,769	(17.3)	3,328	(29.6)	1,309	(17.6)	818	(19.4)	950	(17.1)	451	(14.2)	131	(26.7)	315	(19.4)	468	(16.3)	1,757	(17.3)
Unknown	62,876	(58.0)	27,846	(70.1)	10,727	(49.2)	5,451	(48.5)	3,107	(41.7)	2,486	(59.1)	2,691	(48.3)	2,070	(65.1)	212	(43.2)	559	(34.4)	1,532	(53.4)	6,195	(61.0)
DST results																								
Test performed[a]	17,033	(64.8)	3,674	(61.2)	5,500	(75.2)	1,234	(50.3)	2,037	(66.9)	757	(83.8)	1,151	(59.7)	364	(55.3)	116	(78.4)	458	(61.2)	745	(85.6)	997	(45.3)
MDR-TB	250	(1.5)	71	(1.9)	55	(1.0)	21	(1.7)	18	(0.9)	23	(3.0)	24	(2.1)	10	(2.8)	-	(0.0)	7	(1.5)	9	(1.2)	12	(1.2)
Treatment outcome reported[b]	71,861	(66.3)	31,021	(78.0)	13,155	(60.3)	6,353	(56.6)	4,958	(66.5)	3,064	(72.8)	3,218	(57.8)	2,147	(67.5)	317	(64.6)	924	(56.9)	2,085	(72.7)	4,619	(45.5)
Treatment success	59,792	(83.2)	26,908	(86.7)	10,846	(82.5)	5,604	(88.2)	4,117	(83.0)	2,353	(76.8)	2,485	(77.2)	1,457	(67.9)	207	(65.3)	452	(48.9)	1,601	(76.8)	3,762	(81.5)

EU/EEA: European Union/European Economic Area; DST: drug susceptibility testing; HIV: human immunodeficiency virus; MDR-TB: multidrug-resistant tuberculosis; TB: tuberculosis.

[a] The denominator for the calculation of percentage of drug susceptibility was the number of culture-positive cases.

[b] The denominator for the calculation of percentage of HIV-infected was the number of HIV-tested cases.

Table 3

Number of EU/EEA Member States reporting data on pulmonary and extrapulmonary tuberculosis and specific site of infection, and total number of cases analysed, 2002–11

Variable	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total cases
All notified TB cases	29	29	29	29	29	30	28	29	29	29	868,726
Sex	26	27	27	26	27	30	28	29	29	29	816,077
Age	26	27	27	26	27	30	28	29	29	29	816,077
Origin of cases	23	23	23	25	25	29	28	29	29	29	736,594
Previous treatment	26	27	27	26	27	30	28	29	29	29	816,077
HIV status[a]	-	-	-	-	-	29	28	29	29	29	113,777
Culture confirmation	25	26	27	25	26	28	26	28	27	27	599,894
Drug susceptibility testing	21	22	23	22	23	25	23	25	25	25	212,290
Treatment outcome (12 months)b	19	20	20	19	21	21	22	23	24	-	564,203
Extrapulmonary TB site specified	18	19	20	22	23	26	24	26	26	26	108,345
Sex	18	19	21	23	23	26	24	26	26	26	108,345
Age	18	19	21	23	23	26	24	26	26	26	108,345
Origin of cases	17	18	18	21	22	25	24	26	26	26	108,345
Previous treatment	18	19	21	23	23	26	24	26	26	26	108,345
HIV status[a]	-	-	-	-	-	3	3	5	11	13	4,796
Culture confirmation	17	18	19	21	22	25	23	25	25	25	108,345
Drug susceptibility testing	14	15	16	17	19	21	20	23	23	23	17,033
Treatment outcome (12 months)[b]	14	15	15	17	19	19	20	22	22	-	71,861

European Union/European Economic Area; HIV: human immunodeficiency virus; TB: tuberculosis.

[a] Data on HIV status have been collected in TESSy since 2007.

[b] 12 month outcome data for a specific treatment cohort are collected in the following calendar year, therefore no data is yet available for the 2011 treatment cohort.

of disease, origin of cases, HIV status, culture confirmation, drug susceptibility testing and treatment outcome.

Discussion

This is the first descriptive analysis of trends in extrapulmonary TB notifications, diagnosis, and treatment outcome using surveillance data reported by the EU/EEA Member States to ECDC. The overall findings of our study are consistent with other studies performed in geographical regions in and outside of Europe [16-19,21]. Similar to what has been observed elsewhere, our study shows that the absolute number of notified extrapulmonary TB cases remained stable over the period from 2002 to 2011, but since notification of pulmonary TB cases has decreased, this has led to an increase in the proportion of extrapulmonary TB cases among all TB cases in the EU/EEA.

The partial incompleteness of the data and inconsistencies in reporting over time are limitations when analysing trends and comparing Member States. Overall, the completeness of data has improved over the period of analysis and the efforts to harmonise surveillance data reporting have continuously strengthened the quality and consistency of the data. As data completeness and consistency differ between variables, the pattern of missing data per country and year is very complex. Apart from incompleteness of the data as a result of different data collection and reporting practices across the Member States, there is also a significant risk for under-diagnosis and under-reporting of extrapulmonary cases [25-27]. On the other hand, it can also be argued that there is over-diagnosis of extrapulmonary TB, since only 33.7% of the cases had their diagnosis confirmed by culture.

Extrapulmonary TB can affect any part of the body, and due to the heterogeneity in clinical manifestations, the diagnosis is especially challenging. Symptoms may be diffuse and mimic other pathologies. Patients present to different specialists who may have little experience in diagnosing tuberculosis and therefore delay reaching the correct diagnosis. This leads to diagnostic delays

or even missed diagnoses [28]. For these reasons, the analysis of vital registration data and autopsy studies could be helpful when assessing the true burden of extrapulmonary TB.

The notification rates were higher in high-incidence countries of the EU/EEA compared with low-incidence countries, but the proportion of extrapulmonary TB cases was higher in low-incidence countries. One possible cause for this difference is the diagnostic capacity in the different settings. In both settings, the proportion of extrapulmonary TB cases increased as result of the decrease in pulmonary TB over the last decade [29]. Overall, low-incidence countries have a higher proportion of TB cases of foreign origin compared with high-incidence countries [22]. Our study showed that foreign origin is more common among extrapulmonary TB cases. This has also been reported by others [14,15,17,19]. We have shown that the proportion of extrapulmonary cases of foreign origin over time remained at a stable low level in high-incidence countries, while it was at a higher level and increasing in low-incidence countries. Thus, a possible factor contributing to the higher proportion of extrapulmonary TB cases in low-incidence countries is the higher overall proportion of individuals of foreign origin. Given the overrepresentation of extrapulmonary TB disease among foreign-born and the increasing presence of foreign-born individuals in several low-incidence countries, it is expected that the proportion of extrapulmonary TB in the EU will increase further. Previous studies that discussed the causes of an increased proportion of extrapulmonary TB acknowledge the association with foreign origin, but also identify other shifts in national population and TB patient demographics [19]. In our study we could not perform further in-depth analyses due to the lack of data on specific risk groups and risk factors.

We observed a higher proportion of TB/HIV co-infection among extrapulmonary cases, with 7.0% of the tested extrapulmonary TB cases reported to be HIV-seropositive compared with 4.2% of pulmonary TB cases. Due to major lack and inconsistency of data, information on HIV test results stratified by specific site was available for less than 5% of the HIV-infected patients with extrapulmonary TB. Therefore, we could not confirm the results from a previous study according to which HIV is a risk factor for disseminated TB and concurrent extrapulmonary-pulmonary TB [19].

Our study confirms that MDR-TB is less frequent among extrapulmonary TB cases than among pulmonary TB cases [17]. Given the challenges in diagnosis and obtaining an adequate sample for culture in extrapulmonary TB, the treatment regimen is often not based on the drug susceptibility pattern of the infecting strain. Nevertheless, a high treatment success of 81.4% was achieved.

The proportion of extrapulmonary TB cases that had received previous treatment was very low (5.1%), as was the proportion of extrapulmonary TB cases with drug resistance. These findings support the hypothesis of Peto et al. [19] that the proportion of extrapulmonary TB cases with previous treatment is very low and therefore the risk of drug resistance is smaller than for pulmonary TB cases.

While the primary aim of further reducing TB transmission by timely diagnosis and adequate treatment of pulmonary TB is paramount for the elimination of TB, due attention should be paid to the group of patients with extrapulmonary TB, who are often neglected in international TB control strategies. In particular, there is a need to raise clinical awareness around the diagnostic challenges posed by extrapulmonary TB. An overview of challenges in diagnosing extrapulmonary TB in the EU is presented in a paper by Solovic et al. in this issue of Eurosurveillance [30]. The proportion of extrapulmonary TB increased during the period from 2002 to 2011, mainly because the notification rate of pulmonary TB decreased. National studies drawing on risk factor data that are not available at EU/EEA level should look further into the specific challenges in each Member State.

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Conflict of interest

None declared.

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The burden of extrapulmonary and meningitis tuberculosis: an investigation of national surveillance data, Germany, 2002 to 2009

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Tuberculosis (TB) surveillance commonly focuses on pulmonary (PTB) where the main organ affected is the lung. This might lead to underestimate extrapulmonary TB (EPTB) forms, where in addition to the lung other sites are affected by TB. In Germany, TB notification data provide the main site and the secondary site of disease. To gain an overview of all the different EPTB forms, we analysed German TB notification data between 2002 and 2009 using information on both main and secondary disease site to describe all individual EPTB forms. Further, we assessed factors associated with meningitis using multivariable logistic regression. Solely analysing the main site of disease, lead to one third of EPTB manifestations being overlooked. Case characteristics varied substantially across individual extrapulmonary forms. Of 46,349 TB patients, 422 (0.9%) had meningitis as main or secondary site. Of those, 105 (25%) of the 415 with available information had died. Multivariable analysis showed that meningitis was more likely in children younger than five years and between five and nine years-old (odds ratio (OR): 4.90; 95% confidence interval (CI): 3.40–7.07 and OR: 2.65; 95% CI: 1.40–5.00), in females (OR: 1.42; 95% CI: 1.17–1.73), and in those born in the World Health Organization (WHO) regions of south-east Asia (OR: 2.38; 95% CI: 1.66–3.43) and eastern Mediterranean (OR: 1.51; 95% CI: 1.02–2.23). Overall, EPTB manifestations, including meningitis, which is often fatal, were underestimated by routine analysis. We thus recommend using all information on disease manifestation generated by surveillance to monitor severe forms and to transfer the gained knowledge to TB case management where awareness of EPTB is most important.

Introduction

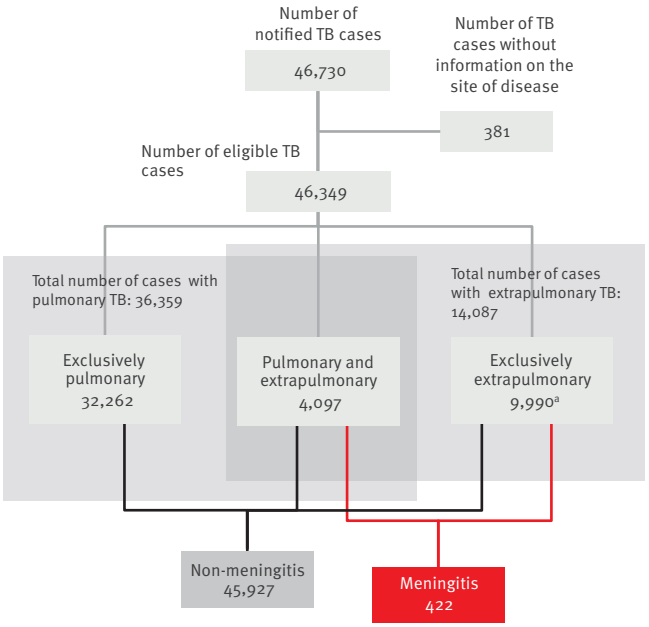
Global tuberculosis (TB) control focuses on pulmonary tuberculosis (PTB) to prevent transmission and reduce the number of new cases. Thus, in surveillance, TB cases are classified as pulmonary TB whenever lungs are involved, irrespective of any additional involvement of other organs [1]. However, extrapulmonary TB (EPTB), a collective term for diverse manifestations affecting any other anatomic site than the lung parenchyma and the tracheobronchial tree, substantially contributes to the TB burden. In the European Union and European Economic Area (EU/EEA), 22% of TB patients notified in 2010 only had extrapulmonary manifestations [2]. EPTB is more common in immunocompromised individuals, especially people living with human immunodeficiency virus (HIV) [3-7], but also females and different ethnic groups [3,5-10]; for example, in the United Kingdom (UK) all non-white ethnic groups were associated with EPTB [8]. Socio-behavioural factors including smoking and alcohol abuse, in contrast, were associated with pulmonary manifestation [6,7,11-13].

Some EPTB forms, such as meningitis cause severe disease. Reported case fatality ranges from 20 to 69% [14] in different settings worldwide with up to half of surviving patients presenting with irreversible sequelae, including paraplegia, blindness, motor and cognitive deficits [15-19]. Prognosis is largely influenced by early diagnosis and adequate treatment [4,17-19].

Meningitis TB most commonly occurs in infants and toddlers, mainly within three months after infection [3,20]. Its development may be influenced by genetic factors, differing across ethnic groups and certain strains of *Mycobacterium tuberculosis* complex [7,21]. Further, vitamin D deficiencies [22] and underlying conditions influencing immunocompetency, including HIV infection [13,19,21,23] diabetes mellitus, malignancy and recent corticosteroid treatment, as well as alcohol abuse (in adults), have been described as risk factors for meningitis TB. Bacillus Calmette–Guérin (BCG) vaccines were reported to have a preventive effect in young children (30–82%) [24].

Figure 1

Overview of the notified tuberculosis patients and investigated groups, Germany, 2002–2009 (n=46,730)



TB: tuberculosis.

[a] 28 cases with no information on the main site of disease but available information on the secondary site are included in the exclusively extrapulmonary TB cases (n=9,990) presented in this flow chart.

In 2010, Germany, a low incidence country for TB (5.3 cases per 100,000 population in 2010), reported that 21% of patients had exclusively EPTB [25]. National TB surveillance captures disease manifestations as main and secondary site of disease (whereby only up to two sites can be recorded) and classifies extrapulmonary forms into 11 sites as recommended by the World Health Organization (WHO): intrathoracic lymph nodes (LN), extrathoracic LN, pleura, genitourinary tract, abdomen, spine, bone and joints, meninges, other central nervous system (CNS), disseminated TB and any other organ [1]. Lungs, when affected by TB, can only be recorded as the main site of disease. If two different extrapulmonary sites are affected, physicians are asked to classify the more severely affected one as main site of disease. In line with other countries, surveillance data analyses and reporting focus on the main site of disease (privileging PTB). This may lead to underestimate EPTB manifestations overall, as well as EPTB forms causing severe disease such as meningitis TB.

We conducted a study to (i) estimate the frequency of all individual EPTB forms, irrespective of the classification as main or secondary site, (ii) describe demographic and clinical characteristics of patients affected by specific extrapulmonary sites of disease and (iii) identify factors associated with meningitis TB.

Methods

Data source

We used case-based TB surveillance data from Germany between 2002 and 2009, electronically reported to the Robert Koch Institute (RKI) until 1 August 2010, and population data from the Federal Statistical Office to calculate incidences [26]. Surveillance defines active TB cases based on clinical diagnosis and the indication of a full-course of anti-TB treatment regimen with or without bacteriological confirmation or known epidemiological link to another confirmed case [27]. The notification system, case definitions and diagnostic procedures have remained largely the same over the investigation period. This is as well reflected by the stable proportion of bacteriologically-confirmed cases (72% to 75%) from 2002 to 2009.

Data analysis

We grouped cases into three categories: PTB only, both PTB and EPTB, and EPTB only (Figure 1), and calculated mean annual incidences (cases/100,000 populations). Further, we compared the proportions of these three groups in 2002 to those in 2009.

We calculated the frequency of all 11 EPTB sites (i) using information regarding the main site of disease only and (ii) combining information from main and secondary sites of disease and compared the number of EPTB affected sites detected using either classifications. As up to two different disease sites per patient can be recorded, the same patient may belong to two different disease manifestation groups.

To identify characteristics of patients affected by specific extrapulmonary manifestations, we tabulated demographic (i.e. age, sex, country of birth (foreign vs. German)) and clinical information (i.e. hospitalisation, duration of hospitalisation (in days) and case fatality ratio (CFR)) by site of disease. We presented proportions for categorical variables and median and interquartile-ranges (IQRs) for continuous variables. We excluded implausible values (e.g. negative values) in the duration of hospitalisation from the analysis.

To identify factors associated with meningitis TB, we compared meningitis (both as main and as secondary site) with non-meningitis TB cases in terms of possible exposures using the chi-squared test, odds ratios (OR), 95% confidence intervals (CI) and two-sided p-values. Exposures examined included age, sex, country of birth, as well as being a new case, i.e. not previously treated. We grouped countries of birth into Germany,

Table 1

Effect of taking in account the main and secondary sites of tuberculosis in identifying extrapulmonary tuberculosis, Germany, 2002–2009 (n=46,389 patients)

TB forms or TB sites	Total TB sites according to the main site of disease notified[a] (N=46,321)[b]	Total TB sites resulting from the main and secondary sites of disease notified (N=51,232)[c]	Increase of EPTB sites resulting from taking secondary sites into account (%)
Pulmonary	36,359	36,359	NA
Extrapulmonary	9,962	14,873	50
Extrathoracic lymph nodes	3,330	4,129	24
Pleura	1,579	2,806	78
Intrathoracic lymph nodes	1,130	1,812	60
Genitourinary	1,243	1,590	28
Bone and joints	610	835	37
Abdominal	455	750	65
Spine	373	544	46
Disseminated	192	521	171
Meninges	**288**	**422**	**47**
Central nervous system	64	116	81
Other forms	698	1,348	93

EPTB: extrapulmonary tuberculosis; NA: not applicable; TB: tuberculosis.

Up to two different TB disease sites per patient can be recorded. Lungs, when affected by TB, can only be recorded as the main site of disease. If two different EPTB sites are affected, the more severely affected is classified as main site of disease. If three or more sites are affected, the case is to classify as 'disseminated'.

[a] As there is one main site of disease per patient the total number of TB sites according to the main site notified, equals the number of patients.

[b] 28 of 46,349 patients included in the study did not have information on main site of disease. According to the rules of the notification system, these patients had only EPTB forms recorded as secondary sites.

[c] As up to two sites per patient can be recorded (main and secondary site) the number of total TB sites resulting from considering the main and secondary sites of disease is greater than the number of patients. The 28 patients with information on secondary sites were included in the analysis.

Turkey, Newly Independent States of the former Soviet Union (NIS), other countries of the WHO European region, as well as other WHO regions. We considered four age groups (individuals younger than 5 years, 5 to 9 years, 10 to 14 years and 15 years or older). We included variables associated at p=0.2 in the univariable analysis in a multivariable logistic regression analysis using forward selection. We tested pairwise interactions of independent variables at each step and only included them when the likelihood ratio test pointed to an improvement of the model with a p-value less than 0.05.

We analysed data using Excel (version 11, Microsoft Corporation Redmond, Washington, USA) and Stata (version 12.1, StataCorp LP, TX, USA) software.

Results

Study population

From 2002 to 2009, a total of 46,730 TB patients were reported in Germany (mean annual incidence of 6.3 cases per 100,000 population). Of the 46,349 patients with information on the anatomic site of disease, 32,262 (70%) had exclusively PTB, 4,097 (8.8%) had both PTB and EPTB and 9,990 (22%) had EPTB only (Figure 1). The TB incidence decreased from 9.3 to 5.4 cases per 100,000 populations in the study period. However, the proportions of disease manifestations remained relatively stable: There was a 1.1% decrease in exclusively PTB, a 0.5% increase in both PTB and EPTB and a 0.6% increase in exclusively EPTB between 2002 and 2009.

Frequency of extrapulmonary tuberculosis forms

When we used combined information on the main and secondary sites of disease rather than the main site only, overall EPTB affected sites increased by a factor of 1.5 (Table 1). The increases ranged from a factor of 1.2 for extrathoracic LN (3,330 vs 4,129) to a factor of 2.7 (192 vs 521) for disseminated TB.

Characteristics of extrapulmonary tuberculosis patients

Overall, EPTB patients were similar to PTB patients in terms of median age and CFR (Table 2). However, they were more frequently female (49% (6,956/14,072) vs

Table 2

Demographic and clinical characteristics of tuberculosis patients by site of disease, reported as main or secondary site, Germany, 2002–2009 (n=46,349 patients)

TB site or form	Patients n (%)[a]	Demographic factors					Clinical factors			
		Median age in years (IQR)	Sex		Country of birth		Fatal outcome n/N (%)[b]	Hospitalisation		
			Male n/N (%)[b]	Female n/N (%)[b]	Germany n/N (%)[b]	Abroad n/N (%)[b]		Hospitalised n/N (%)[b]	Observations of duration n	Median duration in days
Pulmonary	36,359 (78)	48 (33–67)	23,159/36,324 (64)	13,165/36,324 (36)	20,430/35,039 (58)	14,609/35,039 (42)	1,665/35,798 (5)	(IQR)	16,797	28 (13–51)
Extrapulmonary	14,087 (30)	48 (31–68)	7,116/14,07 (51)	6,956/14,072 (49)	6,652/13,650 (49)	6,998/13,650 (51)	599/13,905 (4)	9,378/13,944 (67)	6,838	19 (9–35)
Extrathoracic LN	4,129 (9)	43 (30–64)	1,524/4,123 (37)	2,599/4,123 (63)	1,340/4,010 (33)	2,670/4,010 (67)	45/4,076 (1)	2,525/4,094 (62)	1,871	14 (7–25)
Pleura	2,806 (6)	48 (32–69)	1,866/2,805 (67)	939/2,805 (33)	1,645/2,713 (61)	1,068/2,713 (39)	112/2,774 (4)	2,006/2,790 (72)	1,493	23 (13–38)
Intrathoracic LN	1,812 (4)	41 (24–63)	848/1,808 (47)	960/1,808 (53)	699/1,742 (40)	1,043/1,742 (60)	33/1,792 (2)	1,235/1,785 (69)	950	16 (8–32)
Genitourinary	1,590 (3)	61 (46–72)	905/1,589 (57)	684/1,589 (43)	1,046/1,542 (68)	496/1,542 (32)	51/1,564 (3)	970/1,562 (62)	690	14 (8–29)
Bone and joints	835 (2)	53 (32–73)	440/834 (53)	394/834 (47)	398/813 (49)	415/813 (51)	22/824 (3)	586/829 (71)	391	24 (13–43)
Abdomen	750 (2)	41 (29–62)	390/750 (52)	360/750 (48)	294/735 (40)	441/735 (60)	49/740 (7)	560/747 (75)	399	24 (12–39)
Spine	544 (1)	54 (33–71)	295/544 (54)	249/544 (46)	237/529 (45)	292/529 (55)	22/536 (4)	398/540 (74)	277	29 (14–53)
Disseminated	521 (1)	54 (33–75)	273/520 (53)	247/520 (48)	265/507 (52)	242/507 (48)	138/516 (27)	392/510 (77)	293	29 (11–57)
Meninges	**422 (1)**	**48 (30–67)**	**215/422 (51)**	**207/422 (49)**	**227/408 (56)**	**181/408 (44)**	**105/415 (25)**	**303/418 (72)**	**199**	**36 (15–60)**
Central nervous system other than meninges	116 (0)	46 (30–64)	70/115 (61)	45/115 (39)	56/114 (49)	58/114 (51)	15/115 (13)	82/115 (71)	52	36 (19–52)
Other extrapulmonary organ	1,348 (3)	54 (35–72)	697/1,347 (52)	650/1,347 (48)	738/1,310 (56)	572/1,310 (44)	55/1,330 (4)	890/1,332 (67)	640	18 (9–34)

LN: lymph nodes; TB: tuberculosis.

[a] Up to two sites of TB per patient could be notified. The percentage of patients with TB at a given site, or with a particular form of TB, is calculated based on a total of 46,349 patients.

[b] For patients for whom the information was available.

Table 3

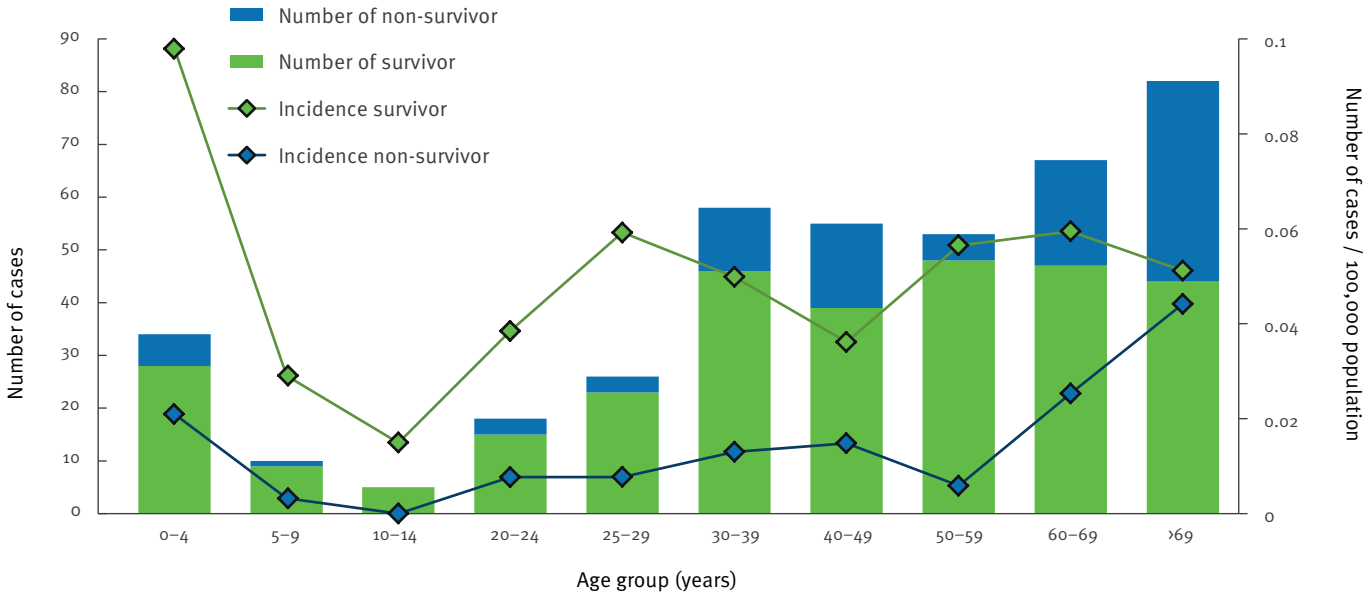
Univariable and multivariable analysis for the association between demographic characteristics of patients with meningitis tuberculosis and patients with non-meningitis tuberculosis, Germany, 2002–2009 (n=46,349)

Characteristics of cases	Meningitis tuberculosis	Non-meningitis tuberculosis	Univariable analysis		Multivariable analysis	
	n (%)	n (%)	OR (95% CI)	P value	OR (95% CI)	P value
Number of cases	422 (0.9)	45,927 (99.1)	NA	NA	NA	NA
Age group						
≥15 years	373 (0.8)	44,239 (99.2)	Reference	NA	Reference	NA
10–14 years	5 (1.3)	383 (98.7)	1.55 (0.64–3.76)	0.335	1.48 (0.61–3.60)	0.390
5–9 years	10 (2.2)	450 (97.8)	2.64 (1.40–4.97)	0.003	2.65 (1.40–5.00)	0.003
0–4 years	34 (3.9)	848 (96.2)	4.76 (3.33–6.80)	<0.001	4.90 (3.40–7.07)	<0.001
Sex						
Male	215 (0.8)	27,681 (99.2)	Reference	NA	Reference	NA
Female	207 (1.1)	18,201 (98.9)	1.46 (1.21–1.77)	<0.001	1.42 (1.17–1.73)	<0.001
Place of birth						
Germany	227 (0.9)	24,824 (99.1)	Reference	NA	Reference	NA
Newly Independent States of the former Soviet Union	20 (0.5)	4,466 (99.6)	0.49 (0.31–0.77)	0.002	0.54 (0.34–0.85)	0.008
Turkey	17 (0.6)	2,909 (99.4)	0.64 (0.39–1.05)	0.076	0.69 (0.42–1.13)	0.140
WHO western Pacific region	10 (0.8)	1,245 (99.2)	0.88 (0.47–1.66)	0.689	0.91 (0.48–1.73)	0.780
WHO European region	42 (1.0)	4,392 (99.1)	1.05 (0.75–1.46)	0.791	1.12 (0.80–1.56)	0.510
WHO African region	26 (1.2)	2,231 (98.9)	1.27 (0.85–1.92)	0.244	1.33 (0.88–2.01)	0.171
WHO region of the Americas	2 (0.7)	274 (99.3)	0.80 (0.20–3.23)	0.752	0.80 (0.20–3.25)	0.757
WHO south–east Asian Region	35 (2.0)	1,752 (98.0)	2.18 (1.53–3.13)	<0.001	2.38 (1.66–3.43)	<0.001
WHO eastern Mediterranean region	29 (1.3)	2,196 (98.7)	1.44 (0.98–2.13)	0.064	1.51 (1.02–2.23)	0.038
Type of case						
Previous TB treatment	21 (0.5)	3,973 (99.5)	Reference	NA	NA	NA
New	320 (0.9)	34,840 (99.1)	1.74 (1.12–2.71)	0.014	Not included in the final model	Not included in the final model

NA: not applicable; TB: tuberculosis; WHO: World Health Organization.

Figure 2

Number and incidence of meningitis tuberculosis patients by age group according to surviving outcome, Germany, 2002–2009



36% (13,165/36,324)) and more often foreign-born (51% (6,998/13,650) vs 42% (14,609/35,039)).

Across the individual extrapulmonary forms there were large differences in case characteristics. Genitourinary TB patients, for instance, were characterised by a high median age (61 years, IQR: 46–72) and only 32% (496/1,542) of foreign-born.

The CFR was only 1% (45/4,076) in extrathoracic LN, but 27% (138/516) in disseminated TB. The median duration of hospitalisation was longest in meningitis and other CNS TB (36 days, IQR: 15–60 and 36 days, IQR: 19–52, respectively).

Meningitis tuberculosis

Meningitis TB was reported in 0.9% (422/46,349) of patients as main or secondary site, and in 0.6% (288/46,349) as the main site only. This manifestation was most frequent in children, affecting 3.9% (34/882) of those younger than five years old, 2.2% (10/460) of the five to nine year-olds, and 1.3% (5/388) of the 10 to 14 year-olds. Though, only 0.8% (373/44,612) patients aged 15 years and above had meningitis, this age group accounted for 88% (373/422) of all meningitis patients. These proportions were stable from 2002 to 2009 in all age groups. Meningitis was more frequent among female than among male patients (1.1% (207/18,408) and 0.8% (215/27,896), respectively).

The proportion of patients with meningitis varied by the region of origin, ranging from 0.5% (20/4,486) among patients born in the NIS, and 0.9% (227/25,051) among those born in Germany, to 2.0 % (35/1,787) among those born in the south-east Asia WHO region (Table 3).

In multivariable analysis, compared with non-meningitis TB cases, patients with meningitis TB were more likely to be children younger than 5 years (OR: 4.90; 95% CI: 3.40–7.07) and children between five and nine years-old (OR: 2.65; 95% CI: 1.40–5.00) (Table 3). Female patients were more affected than males (OR: 1.42; 95% CI: 1.17–1.73). Meningitis TB patients were less likely to be born in the NIS (OR: 0.54; 95% CI: 0.34–0.85) than in Germany. There were no significant differences for patients born in Turkey or in the Americas, the western Pacific, the remaining European and the African WHO regions. An origin of the south-east Asia and the eastern Mediterranean region was significantly associated with meningitis (OR: 2.38; 95% CI: 1.66–3.43; and OR: 1.51; 95% CI: 1.02–2.23, respectively).

Being a new case as well as the examined pairwise interaction terms was not statistically significant in the multivariable model, nor did they contribute to improve the model fit. They were therefore excluded from the final model.

The CFR of meningitis TB patients was 25% (105/415) overall, but higher in adults than in patients younger than 15 years (27% (98/366) vs. 14% (7/49); Figure 2). In children, meningitis accounted for about half (7/13) of all illness-related deaths.

Discussion

Our investigation of national TB surveillance data for EPTB between 2002 and 2009 indicated that in Germany analysing solely the main site of disease, as commonly done in surveillance, leads to overlooking one third of extrapulmonary manifestations reported as the secondary site. This applied to all individual EPTB manifestations including severe forms. European Centre for Disease Prevention and Control (ECDC) data indicate that, on average, about 6% of all TB patients in EU/EEA countries are reported with both PTB and EPTB [2]. This suggests that there could be similar increases in proportions of extrapulmonary forms, such as meningitis, in other countries if both main and secondary site of diseases were considered.

Patients with any extrapulmonary manifestations were more often female and born abroad. This supports earlier findings [5,6,8,10,28,29] and may reflect differences in TB pathogenesis related to sex [30] and ethnicity [8], as well as risk factor patterns varying by sex and region of origin [6-8,10]. Exceptions, such as the high proportion of genitourinary TB patients being born in Germany, are partly explained by the advanced patients' age, in which the proportion of foreign-born individuals is small in Germany [31]. Such interactions across case characteristics underline the need for stratified and multivariable analyses, as we illustrated for meningitis TB.

Overall 0.9% TB patients had meningitis, whereas only 0.6% had been reported as main site of disease. Hence, re-classification increased the number of reported cases by a factor of 1.5. A similar proportion (0.5%) of meningitis TB was found in Germany from 1996 to 2000, based on main site of disease only [28]. This stable proportion over time, in a context of a decrease in overall TB case numbers, suggests that there was neither a rise nor a particular progress in reducing this severe form.

Children younger than five years were most affected by meningitis; representing 8% of all meningitis cases, though accounting for less than 2% of TB patients in Germany. This is in line with a 1970 to 2000 cohort study of CNS TB patients in Canada, reporting that 10% of CNS cases were younger than five years of age [32].

While meningitis was rare (0.8%) among TB patients who were 15 years and older, this age group accounted for 88% of all meningitis patients. A similar age distribution of meningitis cases was observed in a cohort study in Canada, whereby the age group older than 15 years contributed to 82% of all meningitis patients [32]. A similar value of 76% was found for this age group in a retrospective analysis of notified meningitis cases in Denmark [19]. These countries have age structures comparable to Germany. Meningitis TB cases in adults may be an expression of age-specific risk factors including diabetes mellitus and immune compromising conditions [19,21].

In multivariable analysis, meningitis TB remained independently associated with young age and being female, similar to findings from Canada [32], as well as specific regions of origin. The association of meningitis with south-east Asia and eastern Mediterranean regions of origin is consistent with high proportions of all EPTB in patients born in these regions, and a low proportion in patients born in the NIS (data not shown). As to meningitis in particular, differences by region of origin might be shaped by the regions' HIV prevalence, which is relatively high in the south-east Asia region [33], and different levels of BCG vaccination and different BCG strains in use. BCG has been withdrawn based on risk-benefit assessments from the immunisation schedule since 1998 in Germany, in line with other low incidence countries [34,35], but remains endorsed and widely used elsewhere [36]. These findings need to be interpreted with care given that meningitis case numbers were small for some regions of origin, and that risk factor patterns may differ across countries within one WHO region.

Meningitis was a severe EPTB form in terms of longest median hospital stay and case fatality. One quarter of patients with meningitis died and the CFR was almost twice as high in adults as in children. Similarly, a long term mortality study on meningitis TB patients in Denmark, from 1972 to 2008, reported that patients aged between 16 and 60 years had a 2.68 times increased risk of death compared to children [14]. The observed 14% CFR in children is higher than those described by hospital-based studies in Spain (11%; N=28) and Argentina (7%; N=40) [17,18]. However, case inclusion criteria in those studies might have differed from surveillance data and case numbers were small.

Our investigation was solely based on national routine TB surveillance data consisting of a legally defined variable set.

The data source did not contain information on comorbidities associated with EPTB such as HIV/ acquired immunodeficiency syndrome (AIDS) or diabetes mellitus, on BCG vaccination status, on socio-behavioral factors including smoking and alcohol consumption, or treatment, precluding comprehensive risk factor analyses for EPTB forms.

Our study was subject to several limitations. First, data on hospitalisation were not complete as they do not belong to the surveillance key variables demanded and validated with high priority. A reporting bias, for instance, if longer hospitalisations were more frequently known and documented, may exist. Second,

misclassification between meningitis and other CNS TB or differences in case ascertainment among physicians cannot be entirely ruled out. For this reason, we ran the multivariable analysis twice, first only with meningitis TB (as presented), and second merging meningitis with non-meningitis CNS TB cases as the outcome of interest. The findings of both models did not vary markedly. Only the association with the WHO African region had additionally become significant.

Conclusion

National TB surveillance data provide both, information on occurrence of disease and its severity in terms of CFR and hospital stay. This information is needed to refine estimates of the *Mycobacterium tuberculosis* complex-related disease burden, currently restricted to pulmonary or pooled TB data [37], and to prioritise across different pathogen-related diseases within a country [38]. Site-specific analyses of EPTB forms, as shown for meningitis, help to target future research on risk factors, clinical outcome, diagnostic tools, and preventive and therapeutic options adapted to the individual manifestations.

As to TB case management, knowledge of population groups most affected by extrapulmonary sites helps physicians to timely consider EPTB as differential diagnosis. This is important in low incidence countries with small patient numbers and risk of waning expertise. Given the frequent co-occurrence of pulmonary and extrapulmonary sites, routine screening for PTB among EPTB patients, and vice versa, is essential.

Averting meningitis and other severe TB forms through timely contact tracing and preventive chemotherapy, in agreement with national recommendations [39], needs to be of high priority.

Altogether, EPTB manifestations, including often fatal meningitis, are more widespread in Germany than so far reflected by routine analyses. We thus recommend to monitor severe disease more closely using all information on disease manifestation and severity generated by surveillance, and to transfer the gained knowledge to TB case management where awareness of EPTB is most important.

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Conflict of interest

The authors declare that they have no competing interests.

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Treatment outcome monitoring of pulmonary tuberculosis cases notified in France in 2009

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The proportion of patients considered to be cured is a key indicator to assess national tuberculosis (TB) control. In France, TB treatment outcome monitoring was implemented in 2007. This article presents national results on treatment outcome among patients with pulmonary TB reported in France in 2009 and explores determinants of potentially unfavourable outcome. Information on treatment outcome was reported for 63% of eligible pulmonary cases of whom 70% had a successful outcome. In a multivariate analysis, potentially unfavourable outcome (17%), compared to treatment success, was significantly associated with being male, born abroad and having lived in France for less than 10 years, being in congregate settings when treatment was initiated, or having a previous history of anti-TB treatment. Enhanced awareness of treatment outcome monitoring is essential to improve the coverage and the quality of information. Earlier diagnosis and improved management of the disease in the elderly may reduce death due to TB. The high proportion of potentially unfavourable outcomes should be further investigated as they may require additional vigilance and/or actions in term of efforts of TB control in some population groups.

Introduction

France is considered to be a low tuberculosis (TB) incidence country with 8.1 TB cases notified per 100,000 population in 2010 (n=5,187), but the disease tends to be concentrated in urban settings and in certain population groups [1]. Early detection and prompt management of patients by adequate and complete treatment remain the main tools of TB control and form the main objectives of the French national TB control programme launched in 2007 [2]. Appropriate treatment can cure the patient, limit the spread of the disease in the community by reducing the infectious period of the patient, and avoid the development of drug resistance. The proportion of cases considered to be cured is therefore a key indicator in the evaluation of national TB programmes. In 1995, the World Health Organization (WHO) set a target of 85% treatment success among new sputum smear-positive cases [3]. Following recommendations for the standardisation of TB treatment outcome in Europe published in 1998 [4], national systems for routine treatment outcome monitoring was gradually developed in all European countries. In France, following a pilot study in 2005 and some local initiatives, especially in Paris and its suburbs in the mid-1990s [5], a national system for treatment outcome monitoring in TB patients was implemented in 2007 as part of the mandatory TB notification system. This article presents the national results of treatment outcome monitoring among patients with pulmonary TB reported in France in 2009 and explores determinants of potentially unfavourable outcome.

Methods

Data sources

In France, TB is a mandatorily notifiable disease. Each physician or microbiologist diagnosing TB should report the case to their corresponding Regional Health Agency (Agence Régionale de Santé, ARS) using a standardised paper notification form. Twelve months after the start of treatment or after the date of diagnosis, the ARS requests information from the notifying physician on treatment outcome of the patient, through a paper form sent directly or via the district TB control centre (Centre de lutte antituberculeuse, CLAT). This form contains the originally collected patient data, i.e. date of notification, date of birth, first name, initial of last name and postcode of residence, and allows the physician to add the outcome. Data are anonymised and transmitted electronically to the French Institute for Public Health Surveillance (Institut de Veille Sanitaire; InVS) every year.

The cohort eligible for our analysis included patients with pulmonary TB, with or without extra-pulmonary localisation, notified in 2009 in France (including overseas districts). Overseas districts are always included in national surveillance results. Among hundred French districts, four are overseas. Cases notified in these overseas districts represent annually around 2–3% of all cases notified in France. We excluded patients who after notification were found not to have TB (atypical

Table 1

Treatment outcome categories used for surveillance, France, 2009

Treatment outcome category	Definitions
1. Treatment success (treatment completed)	Patient is declared cured by a clinician, with or without documented bacteriological conversion, and has taken at least 80% of the standard anti-TB treatment
2. Death	Death of the patient during treatment, including
	death from TB
	death from another cause
	unknown link between death and TB
3. Treatment stopped	Treatment has been stopped because of
	other diagnosis
	other reason
4. Still on treatment at 12 months	Patient is still on treatment at 12 months, for reasons including
	initially planned treatment for more than 12 months (e.g. because of drug resistance)
	treatment interruption for more than two months
	treatment change for (one or several situations) • initial or acquired drug resistance • adverse reactions to treatment • failure of the initial treatment (insufficient clinicalresponse or non-negativity of bacteriological results)
5. Transfer out	Patient has been transferred to another hospital or to another physician than the notifying person
6. Lost to follow-up	Patient was lost to follow-up during treatment and is still lost to follow-up 12 months after starting treatment
7. Information unknown	

TB: tuberculosis.

mycobacteria, cancer etc.) and patients with a post-mortem diagnosis of TB.

Tuberculosis case definition

TB cases to be notified include patients with clinical and/or radiological signs compatible with TB and with a clinician decision to treat the patient with a standard anti-TB treatment, whether cases are confirmed by a positive culture for *Mycobacterium tuberculosis* complex or not.

Following the European definition for surveillance [6], pulmonary TB includes TB affecting lung parenchyma, tracheobronchial tree or larynx.

Treatment outcome monitoring

The principles and methods of TB surveillance implemented in France are based on European recommendations [4] adapted to the French context. In the 1998 European recommendations, successful outcomes included two categories: 'treatment completed' (documented treatment completion but no documented bacteriological conversion) and 'cured' (documented bacteriological conversion during the continuation phase) [4]. In France, as in some other European countries [7,8] the category 'treatment completion', indicating a treatment success, was defined as 'documented treatment completion with or without documented bacteriological conversion' and included patients classified as 'cured'.

Information collected on outcome (Table 1) is about the situation of the patients whose TB was notified within 12 months following the start of treatment or the date of diagnosis.

Patients classified as 'defaulter' in the WHO definitions [3] (i.e. patients lost to follow-up, still on treatment at 12 months due to treatment interruption of more than two months, and treatment stop), and patients transferred out to another clinician and service, were considered, in this study, as having a potentially unfavourable outcome [9]. These outcomes may indicate a higher risk of relapse or anti-TB drug resistance.

Initial TB notification and treatment outcome monitoring forms are available on the InVS website at the following link: https://www.formulaires.modernisation.gouv.fr/gf/cerfa_13351.do

Statistical analysis

Data analysis was performed on eligible cases for whom information on treatment outcome was available. Unless otherwise indicated in the text, the denominator for calculated percentages was the number of cases with known information. Data analysis was performed with Epi Info software (version 3.3.2 TM, Centers for Disease Control, United States) and Stata 11 (Stata Corporation Texas, United States). Data comparisons were made using the chi-square test or Fisher's exact test, with a p value of less than 0.05 (5%) considered statistically significant.

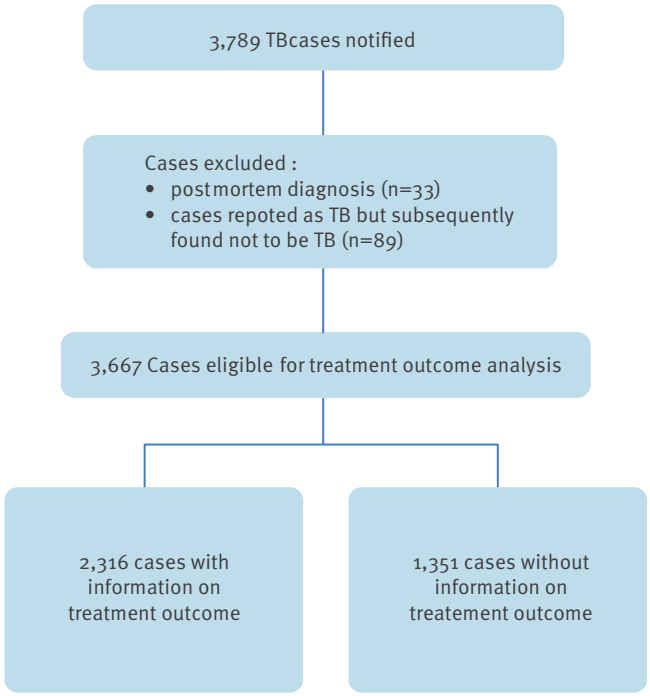
Characteristics of patients with potentially unfavourable outcome were compared with patients with treatment success, using multivariable logistic regression. The variables sex and age group were systematically included in the multivariable analysis as well as variables with a p value of less than 0.2 in the bivariate analysis. Possible interactions in the model were investigated. Goodness of fit was assessed by the Hosmer and Lemeshow test.

Results

Files transmitted by ARS included reports of 3,789 pulmonary TB cases notified in 2009, accounting for around 70% of all notified TB cases.

Figure 1

Algorithm for inclusion of cases in the analysis on treatment outcome of pulmonary tuberculosis cases notified in France, 2009 (n=3,789)



TB: tuberculosis.

Of these 3,789 pulmonary cases, 122 cases were excluded from the analysis: 33 cases because they were diagnosed post-mortem, and 89 cases because they were initially reported as TB disease but subsequently found not to have TB. The remaining 3,667 pulmonary cases reported in 2009 were therefore eligible for the analysis of treatment outcomes (Figure 1).

Information on outcomes of treatment was completed for 2,316 patients with pulmonary TB reported in 2009 (63% of eligible cases: 2,316/3,667) of whom 96.5% lived in metropolitan France and 3.5% in overseas territories. Information on treatment outcome was lacking for 37% of the patients (1,351/3,667) either because the notifying person did not receive the form (insufficient contact details, career change, treatment outcome monitoring not implemented by the district) or because the clinician did not retrieve information on the patient.

Case characteristics

Among the 2,316 cases notified in 2009 with reported information on treatment outcome, 61% were male. The median age was 43 years (interquartile range: 29–64 years). Information on country of birth was completed for 2,169 (94%) cases, of whom 51% (1,106/2,169) were born in France and 49% (1,063/2,169) were born abroad.

Patients living in congregate settings at the time of treatment start represented 14% (315/2,316) of the cases. Two thirds (66%)of these patients were living in sheltered housing or in residential centres, 21% in nursing homes for the elderly, 11% were in prison, and for 3% the type of congregate setting was not reported.

Information on previous history of anti-TB treatment was available for 65% (1,503/2,316) of the pulmonary cases included in the study. Of these cases, 14% (204/1,503) had a previous history of treatment and 86% (1,299/1,503) were new cases.

Among pulmonary cases with known information, 53% (1,145/2,179) were sputum smear-positive. Culture result was reported for 61% (1,419/2,316) of cases, of whom 98% (1,417/1,419) were positive. The proportion of multidrug-resistant cases (resistant to at least isoniazid and rifampicin) was 2.3% among cases with a drug susceptibility testing result reported in the notification form (n=812).

Distribution of cases according to sex, age, birthplace, history of TB and multidrug resistance were similar for cases with and cases without information on treatment outcome.

The situation of the patients regarding treatment outcome

The proportion of treatment success was 70% (1,623/2,316) among patients with pulmonary TB reported in 2009 for whom information of treatment outcome was available (Table 2). The proportion of treatment success was significantly higher in cases with a negative sputum smear result than in those with a positive sputum smear result (73% versus 67%; $p<0.001$) and was 71.2% (467/652) in the cohort of new sputum smear-positive cases.

Thirty per cent of eligible pulmonary TB cases notified in France in 2009 and with available information on treatment outcome (693/2,316) did not complete the treatment at 12 months. Of these:

- 222 (32%) patients died during the treatment; 28% of the deaths were due to TB, 44% were not due to TB, and for 28% the link between death and TB was unknown;
- 220 (32%) patients were lost to follow-up during the treatment and remained so 12 months after treatment start;
- 119 (17%) patients were transferred out to another service or physician;
- 100 (14%) patients were still on treatment at 12 months; this was due to initially planned treatment of more than 12 months for 43 patients, to treatment modification (anti TB drug resistance, adverse reactions and treatment failure) for 34 patients, and to

treatment interruption of more than two months for 23 cases.
- 32 (5%) patients had stopped their treatment.

Being lost to follow-up or still on treatment at 12 months due to treatment interruption of more than two months, and treatment stop and being transferred out were considered as a potentially unfavourable treatment outcome and were reported for a total of 394 patients (17%).

The proportion of patients with successful treatment decreased with age, while the proportion of deaths increased (Figure 2). Thus, in persons younger than 25 years, the proportion of pulmonary cases with treatment success was 76% (273/357) and the proportion of deaths was 1.1% (4/357), while they were respectively 57% (324/567) and 28% (159/567) among those aged 65 years and older ($p<0.001$). The proportion of patients with potentially unfavourable outcome of treatment was more than 10% in all age groups and peaked at 22% in young adults aged 15 to 24 years (57/264).

Determinants of potentially unfavourable treatment outcome

The multivariable analysis (Table 3) identified the following factors as significantly associated with potentially unfavourable outcome compared to treatment success:
being male (odds ratio (OR): 1.6; 95% confidence interval (CI): 1.1 to 2.1);
being born abroad and having lived in France less than 10 years before the start of treatment (OR: 1.6; 95% CI: 1.1 to 2.4 for entry less than five years, and OR: 1.8; 95% CI: 1.1 to 3.0 for entry five to nine years before TB diagnosis);
living in congregate settings, including sheltered housing, residential centres, prison, or nursing homes for elderly persons, at the time of the start of treatment (OR: 2.5; 95% CI: 1.7 to 3.7);
having a previous history of anti-TB treatment (OR: 2.0; 95% CI: 1.2 to 3.1).

No significant interaction was found in the final model.

Discussion

Treatment outcome monitoring in France among pulmonary cases reported in 2009 resulted in information provided for 63% of the cases. Of those, 70% had completed treatment (with or without bacteriological conversion) within one year.

Some limitations should be taken into account when interpreting the results presented. A large proportion of reported cases were missing information on treatment outcome (37%), although this proportion has been decreasing since the implementation of treatment outcome monitoring (45% in 2007, 40% in 2008) [10]. Information is difficult to obtain, especially when, as in France, data are collected through surveys rather than registered, and when several different professionals and institutions may be involved in the management

Table 2

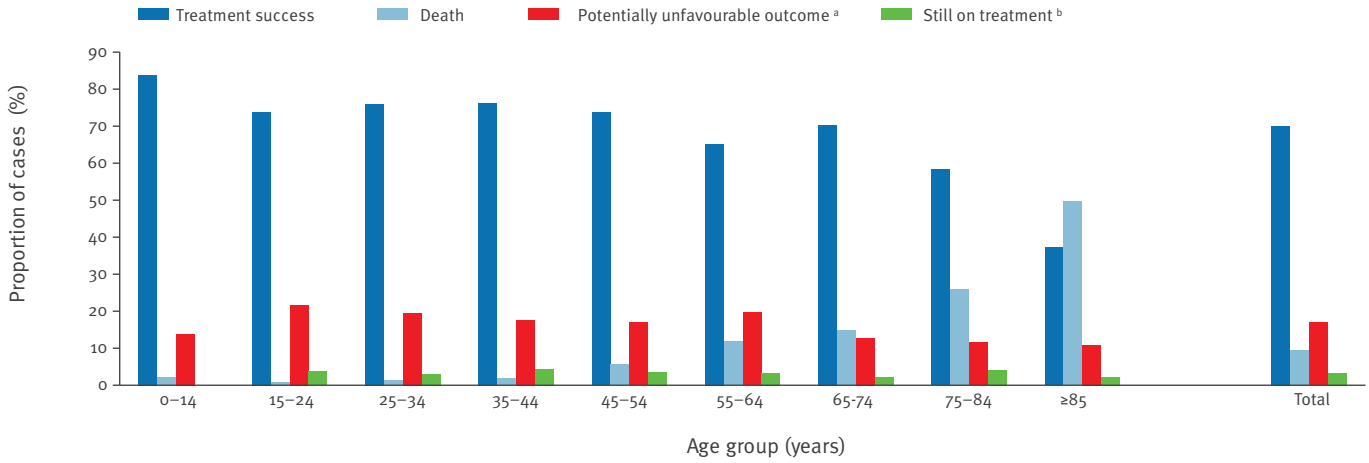
Pulmonary tuberculosis cases, by treatment outcome, France, 2009 (n=2,316)

Situation at 12 months after starting treatment or being notified	Pulmonary cases	
	Number of cases	Proportion
Treatment success (with or without bacteriological conversion)	1,623	70.1
Death	222	9.6
• due to TB	62	2.7
• not due to TB	97	4.2
• link TB and death not known	63	2.7
Treatment stopped	32	1.4
Still on treatment due to	100	4.3
• initially planned treatment >12 months,	43	1.8
• treatment modification (adverse reaction, anti-TB drug resistance, treatment failure)	30	1.3
• treatment interruption	23	1.0
• reasons not provided	4	0.2
Transfer out	119	5.1
Lost to follow-up	220	9.5
Total	2,316	100.0

TB: tuberculosis.

Figure 2

Pulmonary tuberculosis cases, by treatment outcome situation at 12 months and by age group, France, 2009 (n=2,316)



[a] Potentially unfavourable outcomes: treatment stopped, still on treatment due to treatment interruption (for more than two months), lost to follow up, transfer out.

[b] Still on treatment including initially planned treatment for >12 months, treatment modification (adverse reaction, anti-tuberculosis drug resistance, treatment failure).

and the follow-up of one TB patient. The form used to complete information on treatment outcome is sent to the notifying physician who may not be the one following the patient during the treatment. In addition, national regulations on confidentiality and data protection limit the information available to retrieve the patient data. Efforts are therefore needed to facilitate the collection of information and to improve awareness of health professionals in order to increase the proportion of cases with information on the outcome of treatment.

Most socio-demographic and clinical data for cases with information on treatment outcome were similar to those for cases without information. However, other factors that are not collected as part of the notification, such as co-morbidities, drug or alcohol consumption, but probably also living and housing conditions, could have an impact on the outcome of treatment [11-14]. From the available information, it is not possible to determine whether cases without information on treatment outcome would be more, equally or less likely to complete their treatment than those for whom the outcome of treatment is known. In addition the high proportion of missing information for previous history of anti TB treatment (35%) and culture results (39%) should be taken into account. Therefore caution is needed when extrapolating the results presented in this article to all TB patients.

Among the patients with pulmonary TB reported in 2009 for whom the outcome of treatment was provided, 70% (1,623/2,316) had a successful outcome within 12 months after its start. The proportion of treatment success was significantly higher in patients with sputum smear-negative TB compared to those with sputum smear-positive TB (73% versus 67%; p<0.001). The lower proportion of treatment success in patients who are more likely to transmit the disease should be further investigated.

The proportion patients with successful treatment was 71% (467/652) in the cohort of new sputum smear-positive cases and was well below the WHO target of 85% favourable treatment outcomes. The European recommendations indicated that it may be difficult to reach a death rate lower than 5% and that the rate of unsatisfactory outcome should not exceed 10% [4].

In France, the proportion of deaths (due or not due to TB) was higher than 5% with 9.6% among pulmonary TB cases. This was mainly due to the impact of TB in the elderly (65 years and older) who represented 26% (974/3,789) of patients with pulmonary TB initially reported in 2009 and 25% of patients with information on treatment outcome (567/2,316). Among those who died within the 12 months following initiation of treatment, 72% were 65 years and older (159/222). This proportion is comparable with other low-incidence countries [15].

Table 3

Determinants of potentially unfavourable outcome versus treatment success among pulmonary tuberculosis cases reported in France, 2009 (n=2,017[a])

Case characteristic (at the time of TB notification)	Number of cases		Univariable analysis for potentially unfavourable outcome vs. treatment success			Multivariable analysis for potentially unfavourable outcome vs. treatment success		
	Potentially unfavourable outcome[b]	Treatment success	OR	[95% CI]	p Value	OR	[95% CI]	p Value
Total	**394**	**1,623**	-	-	-	-	-	-
Sex (n=2,010)								
Female	117	661	Ref			Ref		
Male	277	955	1.6	[1.3–2.1]	p<0.001	1.6	[1.1–2.1]	0.005
Age (n=2,016)					p=0.573			p=0.537
0–24 years	70	273	Ref			Ref		
25–44 years	158	645	0.9	[0.7–1.3]	0.776	0.9	[0.6–1.4]	0.790
45–64 years	99	380	1.0	[0.7–1.4]	0.928	0.9	[0.6–1.5]	0.853
≥65 years	67	324	0.8	[0.6–1.2]	0.257	0.7	[0.4–1.2]	0.190
Place of birth and time since arriving in France (n=1,598)					p<0.001			p=0.029
Born in France	138	780	Ref			Ref		
Born abroad and arrived in France <5 years before diagnosis	84	236	2.0	[1.5–2.7]	<0.001	1.6	[1.1–2.4]	0.014
Born abroad and arrived in France 5–9 years before diagnosis	32	104	1.7	[1.1–2.7]	0.012	1.8	[1.1–3.0]	0.020
Born abroad and arrived in France >9 years before diagnosis	37	187	1.1	[0.8–1.7]	0.580	1.1	[0.7–1.7]	0.763
Homeless (n=1,771)								
No	316	1,372	Ref			Ref		
Yes	29	54	2.3	[1.4–3.8]	p<0.001	1.2	[0.6–2.3]	0.558
Being in congregate settings (n=1,809)								
No	266	1,284	Ref			Ref		
Yes	91	168	2.6	[1.9–3.5]	p<0.001	2.5	[1.7–3.7]	p<0.001
Previous anti-TB treatment (n=2,017)					p=0.005			p=0.015
No	206	960	Ref			Ref		
Yes	47	122	1.8	[1.2–2.6]	0.002	2.0	[1.2–3.1]	0.004
Unknown history of previous anti-TB treatment	141	541	1.2	[0.9–1.5]	0.110	1.0	[0,7–1,7]	0.823
Sputum smear result (n=1,988)								
Negative	178	840	Ref			Ref		
Positive	206	764	1.3	[1.1–1.6]	0.008	1.3	[0.9–1.7]	0.103
Drug susceptibility results for INH and RMP (n=2,017)					p=0.476			
TB sensitive to INH and RMP (not multidrug-resistant)	142	560	Ref			-		
Multidrug-resistant	3	6	1.9	[0.5–7.9]	0.333	-	-	-
Drug susceptibility result not known	249	1,057	0.9	[0.7–1.2]	0.531	-	-	-

Differences between totals (394 and 1,623) and totals by case characteristic are due to missing information.

CI: confidence interval; INH: isoniazid; OR: odds ratio; RMP: rifampicin; TB: tuberculosis.

[a] Including patients with potentially unfavourable outcome or with treatment success. Excluding deaths (n=222), patients still on treatment due to initially planned treatment of >12 months (n=43), treatment modification (n=30) or unavailability of reasons for being still on treatment (n=4).

[b] Including treatment stop, still on treatment due to treatment interruption, lost to follow-up and transfer out.

Deaths unrelated to TB should not be considered as unfavourable treatment outcome in terms of TB control. Similarly, a patient still on treatment at 12 months because the initial treatment was planned to be longer than one year or changed due to side effects or an insufficient clinical response to the treatment, will not always have an unfavourable final outcome. This would be especially true in countries with low TB incidence such as France, where financial, technical and medical resources make it likely that the final outcome of most patients still in treatment at 12 months will be favourable [16].

However, the proportion of potentially unfavourable outcomes was 17% in patients with pulmonary TB notified in 2009. This included those lost to follow-up, those still on treatment at 12 months due to treatment interruption of more than two months, treatment stop or transfer out to another clinician and service.

Patients lost to follow-up represented 9.5% of the cases with information on treatment outcome. According to information provided by some clinicians, the category 'lost to follow-up' may not only be used to qualify the status of the patient, but also to indicate that the records of the patients were lost. However, both situations are unfavourable in terms of TB control.

The proportion of 5.1% of patients transferred out may be due in part to the organisation of healthcare in France, where several health professionals or services may be involved in the diagnosis and follow-up of the patients until the end of the treatment [17]. In addition, population mobility within France but also internationally may impact on the proportion of patients transferred out. Therefore, improving international collaboration to ensure adequate follow-up of patients moving abroad as well as measures to ensure continuity of the treatment and improve the exchange of information between services in France are essential [18]. The situation of the patient may not be unfavourable, but missing information can make it impossible to draw any conclusions about whether or not the treatment was successful.

Male patients who were born abroad and had lived in France for less than 10 years before the start of treatment, who were living in congregate settings at the time of the start of treatment or who had a previous history of anti-TB treatment, were at risk for an unfavourable treatment outcome. Despite some differences in methods and cohort definition, these results are consistent with other studies performed in western European countries [11,14].

It was impossible, due to small numbers of the study population, to include the precise type of congregate setting in the model. The results should therefore be interpreted with caution. However, a large proportion of the part of the study population living in congregate settings was housed in shelters, residential centres or prisons, where the mobility is usually high. Possible discontinuation of treatment for released prisoners has been described in other studies in Europe [19-21]. Disruption of treatment may also occur when a patient is leaving a sheltered housing or residential house before the end of the treatment. Therefore strengthening communication and coordination between the healthcare systems in and outside these institutions seems essential.

Despite the limitations owing to the large proportion of cases without information, the fact that 67% of sputum smear-positive cases and 70% of all pulmonary cases had completed treatment, will be a basis for trends analyses in the coming years.

In some other European countries with a similar epidemiological situation such as Germany and the United Kingdom, the proportion of treatment completion was lower than 75% in the first years of national treatment outcome monitoring and has increased after that [6,22].

In France, TB incidence has been decreasing for a few decades, especially in persons born in France, and the number and proportion of paediatric TB cases as well as the proportion of resistance among new cases have been stable and low [1]. This situation is encouraging in terms of TB control, but contrasts with the results of treatment outcome monitoring. The results presented here demonstrate the need to improve the proportion of patients with reported information and the quality of collected information. Enhanced awareness of the value of treatment outcome monitoring is therefore essential. Earlier diagnosis and improved management of the disease in the elderly may reduce death due to TB [23]. The high proportion of potentially unfavourable outcomes should be closely monitored as they may indicate particular population groups in which vigilance and/or TB control measures need to be improved, including persons born abroad and recently arrived in France, persons living in congregate settings at the start of treatment and patients with a previous history of anti-TB treatment.

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Challenges in diagnosing extrapulmonary tuberculosis in the European Union, 2011

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In the European Union (EU) 72,334 tuberculosis (TB) cases were notified in 2011, of which 16,116 (22%) had extrapulmonary tuberculosis (EPTB). The percentage of TB cases with EPTB ranged from 4% to 48% in the reporting countries. This difference might be explained by differences in risk factors for EPTB or challenges in diagnosis. To assess the practices in diagnosis of EPTB we asked European Union/European Economic Area (EU/EEA) countries to participate in a report describing the diagnostic procedures and challenges in diagnosing EPTB. Eleven EU Member States participated and reports showed that in the majority EPTB is diagnosed by a pulmonologist, sometimes in collaboration with the doctor who is specialised in the organ where the symptoms presented. In most countries a medical history and examination is followed by invasive procedures, puncture or biopsy, to collect material for confirmation of the disease (by culture/histology/cytology). Some countries also use the tuberculin skin test or an interferon-gamma-release-assay. A wide variety of radiological tests may be used. Countries that reported challenges in the diagnosis of EPTB reported that EPTB is often not considered because it is a rare disease and most medical professionals will not have experience in diagnosing EPTB. The fact that EPTB can present with a variety of symptoms that may mimic symptoms of other pathologies does pose a further challenge in diagnosis. In addition, obtaining an appropriate sample for confirmation of EPTB was frequently mentioned as a challenge. In summary, diagnosis of EPTB poses challenges due to the diversity of symptoms with which EPTB may present, the low level of suspicion of clinicians, and due to the difficulty in obtaining an adequate sample for confirmation.

Introduction

Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium tuberculosis*. It most commonly affects the lungs, but it can affect virtually any organ. A case with TB in any site other than pulmonary is considered an extrapulmonary TB (EPTB) case. In 2011, globally 6.2 million TB cases were notified and 0.8 million cases with EPTB [1]. The most common site of EPTB is lymph nodes [2]. Other sites include pleura, urogenital tract, bones and joints, meninges, central nervous system (CNS), bowel and/or peritoneum, pericardium, and skin. Some types of EPTB, e.g. tuberculosis meningitis, cause substantial mortality and morbidity in children and adults [3].

Studies from the Netherlands and United States showed that EPTB is more often diagnosed in women and is associated with ethnic minorities and those born in other countries [2,4-6]. Also, studies from different geographical areas have shown that human immunodeficiency virus (HIV)-infected individuals have a higher frequency of EPTB [2,5-7]. In general, EPTB affects people with a weak immune system caused by diabetes, HIV, or malnourishment, very young children and elderly, or those undergoing prolonged treatment with chemotherapy or cortisone [5].

Since EPTB can affect virtually all organs, it has a wide variety of clinical manifestations, which may cause difficulty and delay in diagnosis. This is illustrated by the many published case reports [8,9]. It is also illustrated

by the longer health system delays in diagnosis of EPTB compared to pulmonary TB [10-12].

In the European Union (EU) 16,116 EPTB cases were notified in 2011, i.e. 22% of all TB cases [13]. The percentage of TB cases with EPTB differed widely from 4% of all notified TB cases in Hungary up to 48% in the United Kingdom (UK). This difference might be explained by differences in risk factors for EPTB. However, it could also result from challenges in diagnosis. In this study we assessed the challenges in diagnosing EPTB in EU/European Economic Area (EEA) countries.

Methods

We approached the officially nominated EU/EEA national TB surveillance contacts points for the European Centre for Prevention and Control (ECDC) in Stockholm, Sweden, by email in August 2012 and asked whether they were interested in participating in a study on diagnosing EPTB. Those who indicated interest were requested to provide a description of practices leading to EPTB diagnosis in their country. They were specifically asked to answer the following questions: (i) what are the procedures for diagnosing EPTB in your country?; (ii) who is in charge of diagnosing and treating EPTB in your country?; and (iii) what are specific challenges in the diagnosis of EPTB in your country? In addition, we asked whether the country had guidelines available for diagnosis of EPTB.

Contact points were asked to submit a report by 1 October 2012. The reports were reviewed and edited and the edited versions were shared between the participating countries, which were particularly asked to answer follow-up questions and provide corrections and additional clarifications to their own report.

In addition to the country reports we retrieved data on pulmonary and EPTB from the 'Tuberculosis surveillance and monitoring in Europe, 2013 (situation in 2011) report', for the 11 countries that participated in the study [14].

Country reports

The countries that participated in the study consisted of 11 EU Member States. In Table 1 and 2, we provide the main epidemiological information about pulmonary and EPTB in the 11 countries. All countries provided a description of the procedures to diagnose EPTB. Nine Member States additionally referred to guidelines available in their country for EPTB diagnosis (Table 3). Below we provide the country descriptions in alphabetical order. For all countries, the initial diagnosis relied on a medical examination, but in this study more

Table 1

Tuberculosis and extrapulmonary tuberculosis notification numbers, rates, and percentages in 11 European Union Member States, 2011

Country	All TB cases		TB cases with extrapulmonary TB		Extrapulmonary TB %
	N	Notification rate per 100,000 population	N	Notification rate per 100,000 population	
Austria[a]	687	8.2	136	1.6	20
Czech Republic	600	5.7	78	0.7	13
Germany[a]	4,316	5.3	926	1.1	21
Malta	33	7.9	11	2.6	33
Netherlands	1,007	6.0	441	2.6	44
Poland	8,478	22.2	599	1.6	7
Romania	19,212	89.7	2,781	13.0	14
Slovakia	399	7.3	62	1.1	16
Slovenia	192	9.4	27	1.3	14
Sweden	586	6.2	228	2.4	39
United Kingdom[a]	8,963	14.3	4,313	6.9	48

TB: tuberculosis.

[a] It was not reported whether TB was pulmonary or extrapulmonary for 11 TB cases in Austria, 44 TB cases in Germany and 47 TB cases in the United Kingdom.

Source: [14].

Table 2

Major sites of extrapulmonary tuberculosis in 11 European Union Member States, 2011

Country	Site of extrapulmonary tuberculosis									
	Lymphatic N (%)	Pleural N (%)	Urogenital N (%)	Bone N (%)	Spinal N (%)	Gastro-intestinal N (%)	Meningal N (%)	Disseminated N (%)	CNS other N (%)	Other extra-pulmonary N (%)
Austria	65 (48)	20 (15)	16 (12)	8 (6)	3 (2)	8 (6)	1 (1)	2 (1)	2 (1)	11 (8)
Czech Republic	34 (44)	16 (21)	6 (8)	2 (3)	6 (8)	0 (0)	0(0)	0(0)	2 (3)	12 (15)
Germany	431 (47)	147 (16)	90 (10)	67 (7)	34 (4)	43 (5)	22 (2)	13 (1)	9 (1)	70 (8)
Malta	6 (55)	1 (9)	1 (9)	0 (0)	1 (9)	0 (0)	1 (9)	0 (0)	0 (0)	1 (9)
Netherlands	225 (51)	64 (15)	19 (4)	11 (2)	26 (6)	33 (7)	3 (1)	0 (0)	7 (2)	53 (12)
Poland	149 (25)	214 (36)	68 (11)	40 (7)	35 (6)	12 (2)	10 (2)	16 (3)	2 (0)	53 (9)
Romania	535 (19)	1,606 (58)	117 (4)	89 (3)	129 (5)	65 (2)	129 (5)	0 (0)	3 (0)	108 (4)
Slovakia	20 (32)	18 (29)	7 (11)	0 (0)	13 (21)	1 (2)	0 (0)	0 (0)	0 (0)	3 (5)
Slovenia	10 (37)	11 (41)	1 (4)	1 (4)	1 (4)	3 (11)	0 (0)	0 (0)	0 (0)	0 (0)
Sweden	139 (61)	15 (7)	2 (1)	11 (5)	19 (8)	20 (9)	5 (2)	0 (0)	3 (1)	14 (6)
United Kingdom[a]	2,360 (49)	492 (10)	130 (3)	181 (4)	320 (7)	349 (7)	150 (3)	89 (2)	61 (1)	647 (14)

CNS: central nervous system.

[a] United Kingdom data were provided by the Health Protection Agency and data were provided for all sites of extrapulmonary tuberculosis for a case. The 4,313 extrapulmonary tuberculosis cases had 4,779 sites of disease.

Source: [14].

Table 3

Availability of guidelines for the diagnosis of extrapulmonary tuberculosis in 11 European Union Member States, 2012

Country	Guidelines for diagnosis of extrapulmonary TB available (yes/no)	If guidelines available, name of document	References
Austria	No	NA	NA
Czech Republic	Yes	TBC dospělých. Standard léčebného plánu; Standard léčebného plánu - tuberkulóza dětí a mladistvých	[23,24]
Germany	Yes[a]	Empfehlungen zur Therapie, Chemoprävention und Chemoprophylaxe der Tuberkulose im Erwachsenen- und Kindesalter	[25]
Malta	Yes	Prevention, Control and Management of Tuberculosis - A National Strategy for Malta	[26]
Netherlands	Yes[b]	Handboek TBC-bestrijding Nederland; NVMM-richtlijn Mycobacteriële laboratoriumdiagnostiek	[21,27]
Poland	Yes	Podręcznik gruźlicy-zalecenia NPZG	[17]
Slovakia	Yes	Professional guidance of the Ministry of Health for the management of tuberculosis and other mycobacteriosis and for screening and follow up in the field of phthisiology	[28]
Slovenia	Yes	National Tuberculosis Programme Slovenia – Clinical diagnosis and treatment of TB	[29]
Sweden	Yes	Tuberkulos – Vägledning för sjukvårdspersonal	[30]
Romania	No[c]	NA	NA
United Kingdom	Yes	Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control	[20]

NA: not applicable; TB: tuberculosis.

[a] Guidelines for diagnosis of extrapulmonary TB are partially available.
[b] The guidelines for diagnosis of extrapulmonary TB are focused on laboratory diagnostics.
[c] Although some recommendations are included in the norms for the implementation of the Romanian TB programme.

emphasis is given to the tests to confirm the clinical diagnosis.

Austria

Between 2008 and 2011, 120 to 140 cases of EPTB were diagnosed, which accounted for 16% to 20% of all TB patients. The TB incidence was about 8/100,000 population. The most common forms of EPTB were lymphatic TB (65 cases, 48% of all EPTB), pleural TB (20 cases, 15% of all EPTB), and urogenital TB (16 cases, 12% of all EPTB) (Table 2).

The majority of the EPTB patients are diagnosed at pulmonary in-patient clinics. When patients are diagnosed outside of pulmonary clinics, e.g. internal medicine wards, infection control and hygienic representatives are usually involved. Patients diagnosed outside pulmonary clinics are normally referred to a pulmonary clinic for initiation of TB treatment. The continuation-phase of the treatment is under observation and is organised between out-patient pulmonary physicians and public health services. In paediatric cases, treatment is initiated and managed in paediatric units.

One of the main challenges is the fact that EPTB is often not considered as a potential differential diagnosis. Due to the fact that there is no suspicion of TB, diagnostic specimens, such as biopsies or surgical specimens, are fixed and immersed in formalin or other preserving agents and are therefore not suitable for microbiological culture testing. Those specimens can still be used for polymerase chain reaction (PCR) analysis.

In Austria, anecdotal evidence suggests that TB treatment is often initiated late in EPTB patients. Collection of data on the duration of diagnostic delay and correct diagnosis of TB might be useful to confirm this and if the case to sensitise physicians.

Czech Republic

In 2011, there were 600 cases of TB reported to the TB register of the Czech Republic (notification rate 5.7/100,000 population) of which 78 (13%) cases were diagnosed with EPTB (Table 1).

The procedures used in the Czech Republic to diagnose EPTB are radiology, microbiology, histology and clinical evaluation. Of the 78 cases with EPTB, 31 (40%) were bacteriologically confirmed.

The most common forms of EPTB were lymphatic TB (34 cases, 44% of all EPTB cases), pleural TB (16 cases, 21% of all EPTB cases), spinal TB (6 cases, 8% of all EPTB cases), and urogenital TB (6 cases, 8% of all EPTB cases) (Table 2).

Diagnosis of EPTB is normally performed by pulmonologists/phthisiologists in cooperation with the relevant specialist. EPTB is a rare diagnosis and therefore it is often not taken into consideration. Treatment is conducted by pulmonologists/phthisiologists.

Germany

In 2011, 926 EPTB cases accounted for 21% of all notified TB cases in Germany (Table 1). The proportion of EPTB has remained stable since 2001, when EPTB accounted for 20% of all TB. The most common forms of EPTB were lymphatic TB (431 cases, 47% of all EPTB cases), pleural TB (147 cases, 16% of all EPTB cases) and urogenital TB (90 cases, 10% of all EPTB cases) (Table 2). The majority of EPTB patients in Germany were foreign born (57% in 2011).

The most common procedure for diagnosing extrathoracic lymph nodes is direct puncture of the node or extirpation. Intrathoracic lymph nodes are punctured by endobronchial ultrasound or surgically by mediastinoscopy. For pleural disease, surgical or medical thoracoscopy and/or needle biopsy are the most common procedures. All procedures include direct microscopy and culture of the pleural fluid. Urogenital TB is diagnosed either in urine or the affected organ itself. Direct staining of the liquor and culture of the liquor are the most common confirmative diagnostic methods for CNS TB, but computed tomography (CT) and magnetic resonance imaging (MRI) together with the clinical evaluation remain tools for diagnosis.

Culture confirmation was positive in 59% of reported EPTB cases, the lowest culture confirmation rate was for CNS TB.

EPTB, especially TB of the lymph nodes, is treated by pulmonary or infectious diseases specialists. CNS and urogenital TB is usually also treated by neurologists and urologists.

Malta

Between 2001 and 2011, a total of 94 cases of EPTB were reported and the notification rates increased from 0.26/100,000 to 2.6/100,000 ($P < 0.001$). The proportion of EPTB increased from 6% (1/16) to 33% (11/33) ($P=0.04$). In 2011, the most common forms of EPTB were lymphatic TB (6 cases, 54% of all EPTB cases) (Table 2). Sixty-two percent (58/94) of EPTB cases over the whole 2001 to 2011 period were among undocumented African migrants. The notification rate of EPTB in undocumented African migrants was 106/100,000 compared to 0.54/100,000 in people born in Malta (chi-squared test, $P=0.001$).

Diagnosis includes a medical history and examination, a tuberculin skin test (TST) and an interferon-gamma-release-assay (IGRA) test. A chest X-ray is also done to exclude or confirm co-existing pulmonary TB. Other radiological tests may be indicated. Appropriate specimens are sent for histology and microbiology. Microbiological specimens are tested for acid-fast bacilli (AFB) and then cultured for *Mycobacterium tuberculosis* complex, including those that are AFB negative.

According to national TB guidelines, all patients suspected of EPTB are referred to infectious disease/TB specialists at the main hospital who are responsible for the diagnosis and treatment. However, since EPTB may occur in any organ, diagnosis may be initiated by the relevant specialist of the affected site. Between 2006 and 2011, 84% (61/73) of the EPTB cases had specimens sent for culture. Treatment is started without waiting for culture results if the test for acid-fast bacilli (direct Ziehl-Neelsen test) and the clinical picture are consistent with a diagnosis of TB. Treatment is continued even if subsequent culture results are negative.

A particular challenge regarding EPTB in Malta is detection of these cases in undocumented African migrants. EPTB (except thoracic EPTB) is detected by passive surveillance. National studies have noted that passive surveillance may not be very effective in detecting TB cases in migrants [15]. Even though migrants have free access to TB healthcare in Malta, they may have difficulties in approaching the healthcare system due to lack of information, language or cultural barriers [16]. This may cause diagnostic delays.

Netherlands

In 2011, 441 (44%) of the 1,007 notified TB cases in the Netherlands were diagnosed with EPTB (Table 1). The most common forms of EPTB were lymphatic TB (225 cases, 51% of all EPTB cases), pleural TB (64 cases, 51% of all EPTB cases) and urogenital TB (19 cases, 4% of all EPTB cases) (Table 2). The majority of TB patients in the Netherlands were foreign born (710 foreign born cases, 71 of all cases) and the percentage of EPTB cases was highest in this group.

EPTB is diagnosed based on clinical symptoms, a matching medical history, risk factors indicating likelihood of infection with *M. tuberculosis*, such as exposure to an infectious TB patient and origin from or travel to an high endemic area, as well as results of histological or bacteriological tests of body material. TST and IGRA are not recommended for the diagnosis of EPTB. However, in some cases they may provide supportive evidence.

The majority of patients with symptomatic EPTB were diagnosed by lung physicians (194 cases, 44% of all EPTB cases) and other clinical specialists (185 cases, 42% of all EPTB cases). In most cases, when TB is suspected or diagnosed in a clinical setting, a lung physician takes charge of further diagnosis and treatment. Ten to 15% of the patients with EPTB were diagnosed by Municipal Health Services through screening of risk groups and contact investigation.

Since the absolute number of patients diagnosed with EPTB is low, most medical professionals will only rarely be involved in diagnosis and treatment of EPTB. It is therefore a challenge to maintain sufficient knowledge among clinicians to avoid diagnostic delays.

Another challenge is the confirmation of the diagnosis of EPTB because it can be difficult to obtain a sample and to confirm the diagnosis with a positive culture. In the group detected through active case finding in 2011, 17% (8/47) of the cases were confirmed by culture and 2.1% (1/47) through PCR or histology. Over the years in the period from 2005 to 2011, 64% (1,698/2,659) of the EPTB cases found through passive case finding were confirmed by culture and an additional 10% (262/2,659) were confirmed by PCR or histology.

Poland

In 2011, 599 EPTB cases without coexisting pulmonary TB were notified, 7% of all TB cases (notification rate 1.6/100.000) (Table 1). For several years the percentage of EPTB has been low. The reason may be insufficient awareness, difficulties in diagnosis or low prevalence of factors which are considered risk factors for EPTB. The most common forms of EPTB were pleural TB (214 cases, 36% of all EPTB cases), lymphatic TB (149 cases, 25% of all EPTB cases), and urogenital TB (68 cases, 11% of all EPTB cases).

Guidelines for the diagnosis of EPTB in Poland are included in the TB manual that was issued in 2001 (Table 3) [17]. Diagnosis is done either by pulmonologists or by others specialists, depending on the site of EPTB. The most common situation is that doctors are supported by pulmonologists in the diagnosis of EPTB. Pulmonologists are responsible for the treatment of EPTB cases. If hospitalisation is required, patients are usually treated in TB wards, under the responsibility of pulmonologists. Cases of TB/HIV co-infection are most often diagnosed by infectious diseases specialists and often also treatment is provided by infectious diseases specialists.

The doctor performing the diagnosis decides whether and which invasive procedures are used for obtaining clinical material for microbiological diagnosis. Pulmonologists believe that TB is too often diagnosed without microbiological confirmation (only 35% of the EPTB cases were bacteriologically confirmed between 2007 and 2011) and for this reason there may be substantial over-diagnosis. For example, pleural TB was bacteriologically confirmed in 56% of the cases in 2011; pericardial TB was confirmed in 50% of the reported cases; and intrathoracic lymphatic TB in children was confirmed in only 13% of the cases.

In Poland, data on delay in diagnosis of EPTB are not collected. However, pulmonologists consider based on anecdotal evidence that other specialists are not aware of TB.

Romania

In 2011, 2,781 EPTB cases were notified, accounting for 14% of all TB cases (Table 1). The proportion of EPTB increased from 11% in 2002 to 14% in 2011. The most common forms of EPTB were pleural TB (1,606 cases,

58% of all EPTB cases), lymphatic TB (535 cases, 19% of all EPTB cases), and spinal TB and TB meningitis (both 129 cases, 5% of all EPTB cases). Between 8% and 10% of the EPTB cases were bacteriologically confirmed by smear and culture according to the national electronic TB data base.

Diagnosis of EPTB is done by organ specific specialists together with the pulmonologist, while treatment of EPTB cases is managed by pulmonologists.

Often patients with EPTB will need several diagnostic procedures by different medical units to establish the diagnosis. For example, lymph node TB will be investigated by the pulmonologist, who will also assess epidemiological links with known TB patients, and might perform a TST and/or IGRA, chest X-ray, bronchoscopy, smear and culture, and histopathological examination of the specimen obtained by puncture or biopsy. Furthermore, ultrasound imaging might be performed at the Excellence Centre for Endoscopy. A radiologist might be involved to evaluate the lymph node using CT or MRI. Finally a surgeon might do a biopsy or remove the lymph node.

The involvement of different persons in the diagnosis may cause diagnostic delays.

Slovakia

In Slovakia, 399 TB cases were notified in 2011 (7.3/100,000 population). Of those 62 (16%) were diagnosed with EPTB. The most common forms of EPTB were lymphatic TB (20 cases, 32% of all EPTB cases), pleural TB (18 cases, 29% of all EPTB cases), and spinal TB (13 cases, 21% of all EPTB cases).

The standard procedure for diagnosing EPTB is puncture or biopsy for culture and histology or/and cytology. Eighteen percent of the EPTB cases were bacteriologically confirmed. Histological and cytological confirmation was obtained in 28%.EPTB is also diagnosed based on clinical symptoms, medical history, risk factors, such as close contact with TB patients, presence of TB in the family, patients who have immigrated from high incidence settings, and results of histological or bacteriological tests of body material. TST and IGRA tests are also used. Diagnostic tests are performed after a specialist refers the suspected EPTB case to the National Institute for TB, Lung Diseases and Thoracic Surgery for further investigation. In 2011, in 33 (54%) EPTB cases the decision of the clinician to start TB treatment was based on clinical symptoms, history and non-specific examinations' results.

Thirty-seven (60%) patients with symptomatic EPTB were diagnosed by pulmonologists and other clinical specialists. In most cases, when TB is suspected or diagnosed, a lung physician is involved and is responsible for further diagnosis and treatment. If hospitalisation is required, usually patients are treated in the specialised EPTB wards of the National TB Institute, under the care of a pulmonologist in collaboration with other specialists.

The main challenge is to maintain sufficient knowledge on TB among clinicians to avoid long diagnostic delays in those with symptomatic EPTB. EPTB is too often diagnosed empirically without microbiological confirmation and for this reason often over-diagnosed.

Slovenia

In 2011, 192 cases of TB were notified in Slovenia, 133 (69%) with pulmonary TB, 27 (14%) with EPTB and 32 patients (17%) with pulmonary TB and EPTB. The most common forms of EPTB were pleural TB (11 cases, 41% of all EPTB cases) lymphatic TB (10 cases, 37% of all EPTB cases) and gastrointestinal TB (3 cases, 11% of all EPTB cases). In 23 (85% of all EPTB cases) cases, diagnosis was based on typical histological images, and confirmed by culture from biopsy material. In four (15% of all EPTB cases) patients, the disease was not culture confirmed. EPTB was diagnosed post mortem based on histology in three patients. In the past five years the proportion of patients with EPTB varied between 14 and 18%.

According to the recommendations of the National TB programme and the guidelines for diagnosis and treatment of TB, all patients suspected of EPTB should be confirmed by culture before starting treatment. Often pulmonologist cooperate with specialists from other specialties, such as orthopaedic surgeons, thoracic surgeons, urologists and others to diagnose EPTB.

Pulmonologists are responsible for the treatment of both pulmonary TB and EPTB. Pulmonary TB should be excluded using relevant samples in patients suspected or diagnosed with EPTB.

Sweden

In 2011, 586 TB cases were notified in Sweden of which 228 (39%) had EPTB. During the last five years (2007 to 2011) the percentage of EPTB of all TB cases reported has been quite stable with an average of 40%. The high percentage of EPTB might be due to good coverage of reporting. The most common forms of EPTB were lymphatic TB (139 cases, 61% of all EPTB cases), gastrointestinal TB (20 cases, 9% of all EPTB cases), and spinal TB (19 cases, 8% of all EPTB cases).

The standard procedure for diagnosing EPTB is puncture or biopsy for culture and histology/cytology. Puncture and/or biopsy are most frequently performed to diagnose lymph node TB. However, it is also performed if TB is suspected at other sites, including skeletal and gastrointestinal TB. To diagnose TB in intrathoracical lymph nodes, endobronchial puncture or biopsy through mediastinoscopy is considered. TB of the CNS (meningitis, tuberculoma) is also confirmed by culture. The only type of EPTB that is never confirmed by culture is retinal TB. The diagnosis is always on suspicion of an ophthalmologist who refers to a clinic of infectious

diseases for further investigation; i.e. chest X-ray and immunological tests like IGRA. Often an ex-juvantibus treatment will be initiated and the ophthalmologist will follow the clinical course. Of the EPTB cases an average of 70% is bacteriologically confirmed. An additional five to10% is diagnosed by histology showing necrotising granuloma and the remaining on clinical grounds.

Infectious disease clinics are in charge of diagnosing and treating all cases of EPTB (and in most regions also pulmonary TB), but diagnosis might happen in another speciality, depending on the presenting symptoms. Paediatricians usually care for EPTB cases in children <18 years of age, often in co-operation with the infectious disease clinic.

United Kingdom

In the UK the proportion of cases with TB in extra pulmonary sites has steadily increased over the last decade [18]. In 2011, 48% (4,313 EPTB cases/8,963 TB cases) of EPTB cases were diagnosed with exclusive EPTB with a further 828 cases having disease affecting both pulmonary and extrapulmonary sites. In the UK all sites of EPTB are registered. In total 4,779 different sites were registered for the 4,313 EPTB cases. The most common forms of EPTB were lymphatic TB, 2,390/4,779 (49%), pleural TB, 492/4,779 (10%), and gastrointestinal TB, 349/4,779 (7%).

The diagnosis of patients often requires specific procedures to obtain samples such as lumbar puncture and a brain scan (MRI or CT) in those with CNS TB. The UK National Institute for Health and Clinical Excellence has outlined recommendations for the diagnosis of EPTB [19,20].

As EPTB can affect several organs, its clinical presentation may mimic symptoms and signs of other pathologies. Inevitably, patients present to the clinical speciality that usually treats the commonest differential diagnoses for each site of disease. For example, renal TB may be diagnosed by nephrologists, CNS TB may present to neurologists and skin TB to dermatologists. In general, patients with EPTB are managed with support from experts with knowledge of TB.

Discussion

In 2011, 72,334 TB cases were notified by 29 EU/EEA countries. Of these 16,116 (22%) were EPTB cases [13]. In the EU/EEA countries, extrapulmonary TB was more frequent in females, in children, and in individuals who were foreign born or had citizenship from another country [13]. The percentage of TB cases with EPTB notified by the different EU/EEA countries ranged from 4 to 48% (and 67% in Iceland with 6 EPTB cases). In the countries presented in this study the percentage EPTB ranged from 7% in Poland to 48% in the UK.

Several countries have recommendations for the diagnosis of EPTB (Table 3). The UK recommendations specify what imaging technique should be used for each site, what type of biopsy should be performed and which material should be cultured [20]. The guidelines in the Netherlands are focused on laboratory diagnostics [21]. In most other countries a medical history and examination is followed by invasive procedures, puncture or biopsy, to collect material for confirmation (culture/histology/cytology/PCR) of the disease. Some countries (Malta, Slovakia and Romania) also use TST or IGRA. A wide variety of imaging tests may be used: ultrasound, CT or MRI.

Not all countries reported challenges in the diagnosis of EPTB, but those that did, reported that EPTB is often not considered because it is a rare disease and therefore not included in the differential diagnosis. If TB is not considered body material will not be sent for bacteriological confirmation or will be processed in such a way that it will not be subsequently usable for bacteriological confirmation if EPTB is suspected at a later stage. In cases where TB is considered, it is often difficult to obtain body material to confirm the diagnosis. Diagnosis of EPTB might require several diagnostic procedures by different medical units. The involvement in the diagnosis of different persons/units may cause a delay in diagnosis. The fact that EPTB can present with a variety of symptoms that may mimic symptoms of other pathologies poses a further challenges in diagnosis.

Since by definition EPTB does not affect the lung parenchyma, the tracheobronchial tree, EPTB patients will normally not present to pulmonologists. They will seek care from a general practitioner, a paediatrician or from an organ specific specialist who will infrequently encounter an EPTB case and do therefore not include EPTB in their differential diagnosis. The countries reported that in the majority of cases, EPTB is diagnosed by a pulmonologist, sometimes in collaboration with the organ specific specialist. Alternatively, e.g. in Malta, patients suspected of EPTB are referred to infectious disease or TB specialists. Thus, patients with EPTB need be referred from a more generalist doctor, or organ specific specialist, to a pulmonologist. This may increase the diagnostic delay.

Longer health system delays in diagnosis of EPTB compared to pulmonary TB have been reported [10-12]. The countries participating in this study did not have data available on delays in diagnosis, but anecdotal evidence suggests that delays in diagnosis of EPTB might be long. Systematic collection of information on diagnostic delay might be useful to understand the extent of the problem and to sensitise physicians.

In most countries, the treatment of EPTB is the responsibility of the pulmonologist. In some countries, such as Sweden and the UK, infectious disease specialists are involved or responsible for treatment of EPTB cases. Paediatricians are involved in the treatment of EPTB in children. Since TB and EPTB is a rare disease in most EU/EEA countries not all clinicians have

experience with the treatment. To guarantee adequate treatment and treatment support, TB treatment should be provided by clinicians with ample experience in treating and supporting EPTB patients.

Countries reported large differences in the percentage of confirmed EPTB cases, from 10% in Romania to 80% in Sweden. Confirmation of EPTB was frequently mentioned as a challenge. Confirmation of EPTB is challenging for a number of reasons: the difficulty to obtain an adequate sample; the apportioning of the sample for various diagnostic tests resulting in non-uniform distribution of microorganisms; the pauci-bacillary nature of the specimens; the presence of inhibitors that undermine the performance of nucleic acid amplification-based techniques; and the lack of an efficient sample processing technique universally applicable on all types of extrapulmonary samples [22]. Diagnoses of EPTB without microbiological confirmation may result in over-diagnosis.

Conclusion

Diagnosis of EPTB poses challenges due to the diversity of symptoms with which EPTB may present, the low level of suspicion among clinicians, and the difficulty in obtaining an adequate sample for confirmation. Raising awareness among non-pulmonary physicians about EPTB and guidelines for diagnosis and treatment of EPTB may result in more timely and adequate diagnosis.

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Tuberculosis diagnostic delay and therapy outcomes of non-national migrants in Tel Aviv, 1998-2008

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Non-national migrants have limited access to medical therapy. This study compares diagnostic delay and treatment outcomes of non-insured non-national migrants (NINNM) with insured Israeli citizens (IC) in the Tel Aviv tuberculosis (TB) clinic between 1998 and 2008. Patient delay was the time from symptoms onset to doctor's visit, while system delay was measured from doctor visit to anti-TB therapy administration. We randomly sampled 222 NINNM and 265 IC. NINNM were younger than IC, had lower male to female ratio and fewer smoked. They had less drug/alcohol abuse, more cavitations on chest radiography, longer patient and shorter system delay. Mean patient and system delays of all patients were 25±14 and 79±42 days, respectively. In multivariate analysis, being NINNM, asymptomatic or smoking predicted longer patient delay, while being asymptomatic or having additional co-morbidity predicted longer system delay. Treatment success in sputum smear-positive pulmonary TB NINNM was 81% and 95.7% in IC (p=0.01). Treatment success was not associated with patient or system delay. In multivariate analysis, work security and treatment adherence predicted treatment success. NINNM had longer patient delay and worse therapy outcome, while IC had longer system delay. Both delays should be reduced. NINNM should be informed that TB therapy is free and unlinked with deportation.

Introduction

The global movement of people from less-resourced countries to more affluent and industrialised countries seeking work and improved living conditions has increased during the last decades [1]. Health authorities in many countries of destination are concerned with the potential importation of tuberculosis (TB) by migrants who originate in high TB prevalence areas [2], as it is estimated that about one third of them are infected with *Mycobacterium tuberculosis*, and approximately 5 to 10% of those infected will eventually develop active TB [3].

Undocumented migrants in the United States (US) and Europe are usually not medically insured and are most likely excluded from health services [4, 5]. Nevertheless, most industrialised countries cover TB treatment costs for all non-national migrants (NNM), mainly to protect the citizens in the hosting countries from infection [6]. This approach is also being practiced in Israel, which has become a selected destination for labor migration since the early 1990ies.

Israel is a country of around eight million inhabitants, and it is estimated that 226,000 NNM presently stay in the country. The majority originate from low-resourced countries, characterised by a high TB burden [7]. Of all 6.2 million Jews living in Israel in 2011, 1.9 (30.1%) were born outside Israel. Unlike NNM, Jewish homecomers to Israel are naturalised upon arrival and are never refused nor delayed, regardless of their health status, age, education or sex. They are also entitled to a comprehensive package of social, educational and financial benefits, including medical insurance from day one of their arrival, in order to accelerate their absorption into society. The policy of encouraging the migration of individuals of Jewish decent is one of the core values of the Israeli society, who is keen to assimilate the newcomers [8].

Most NNM live in Tel Aviv, which is the largest metropolis of Israel (1.3 million inhabitants), and functions as the commercial, cultural and social center for all NNM communities in Israel.

Documented NNM who hold a valid working visa are medically insured by their employer in private medical insurances as long as they are employed. Regretfully, in many instances when a NNM is diagnosed with TB, they lose their jobs, and the medical insurance companies tend to refrain from covering medical expenses, claiming that TB is an exacerbation of a prevailing medical condition. Undocumented NNM, who account for around half of all migrant workers in Israel, are not

medically insured. The Israeli Ministry of Health reimburses TB clinics for treating both documented and undocumented NNM. In order to reduce barriers to medical treatment, therapy at the TB clinics is free and confidential, and patients are not reported to the immigration authorities or to their employers.

Diagnostic delay, comprised of patient and system delays, is an important determinant in TB control. Long diagnostic delay was found in Italy and Spain to result in more severe presentation and extensive disease, as well as an increased likelihood of TB transmission and elevated reproductive rate of TB in the community [9,10]. The aim of our study was to assess factors associated with diagnostic delay, and to compare diagnostic delay and treatment success between non-insured NNM (NINNM) and that of Israeli citizens (IC) in the Tel Aviv lung clinic. Our hypotheses was that NINNM will have longer diagnostic delays and worse treatment outcomes than IC, as they may not have access to most of the ambulatory services, and in addition they may (wrongly) perceive that their illness might be used by their employer to discharge them or lead to deportation.

Methods

In our retrospective study we compared a random sample of NINNM and IC who were older than 18 years of age and were treated in the Tel Aviv TB outpatient clinic for active TB between 1998 and 2008. The catchment area of the TB clinic includes Tel Aviv and central Israel, with a population of about two million people.

IC were either Israeli-born or born elsewhere and naturalised. Patients were excluded from the study if they were naturalised during the TB-treatment, and if they started or completed their treatment in another TB clinic.

Definitions used

A TB case was defined as a patient with pulmonary or extrapulmonary TB diagnosed by a pulmonologist specialised in TB, on the basis of clinical symptoms, and who additionally (i) had either direct sputum smear microscopy or culture positive for *M. tuberculosis*, and/or (ii) was prescribed a full course of anti-TB drugs for a period longer than three months due to TB-related symptoms, or due to chest radiography findings.

Outcome variables were diagnostic delay, namely patient and system delay, as well as treatment success. Patient delay was defined as the time elapsed from the estimated date of onset of symptoms, as reported by the patients, to the first time they attended medical care with regard to those symptoms. System delay was defined as the time elapsed from the first medical visit with regard to the TB symptoms until initiation of anti-TB therapy. Patient or system delays were categorised as 'long' if they were greater than the mean delay of all patients sampled. Treatment success was defined as patients who were cured or completed therapy, as classified by the World Health Organization (WHO) guidelines [11].

Independent variables for diagnostic delay and treatment success included sex, country of birth, citizenship, length of stay in Israel, TB site, smoking, drug or alcohol use, employment status, human immunodeficiency virus (HIV) infection, any underlying chronic disease, and sputum smear, culture and drug susceptibility results.

Continuous variables were presented by means and standard deviations (SD). Comparisons between groups were made using the chi-square or Fisher's exact test for categorical variables and Student's *t*-test for continuous attributes distributed normally or the Mann-Whitney test for variables whose distribution was not normal. All p-values reported are based on two-tailed comparisons with statistical significance set at $p<0.05$. Variables which were found significant in the bivariate analysis, and after assessing for collinearity, were entered the multivariate analysis performed by the logistic regression model. The statistical package SPSS (17.0 version for Windows, Chicago, IL, USA) was used for the analyses.

Ethical approval was granted from the Institutional Review Board of E. Wolfson hospital, Holon, Israel.

Results

Between January 1998 and December 2008, 355 NINNM (23.7%) and 1,139 (76.3%) IC TB patients were treated in the Tel Aviv TB clinic, while 222 and 265 of these respectively, were included in the study. The male to female ratio and rate of NINNM to IC in the total sample was not significantly different than that of those who were not selected ($p=0.06$ and $p=0.17$, respectively), yet the average age of the sample was 2.3 years younger that of the patients who were not selected ($p=0.03$).

NINNM were diagnosed with TB 3.1±2.7 years following their arrival in Israel, and the IC (n=165, 62.5% of all IC) who were born outside Israel were diagnosed 23±17 years after their arrival ($p<0.01$). Of all NINNM, 109 (49.1%) were born in south-east Asia, 49 (22.1%) in Africa, 39 (17.6%) in eastern Europe, 13 (5.9%) in south America and 12 (5.3%) in the middle east.

NINNM were younger than IC, were more often females, were more likely to originate in high TB burden countries, and to be employed while diagnosed. They were less likely to smoke or be drug/alcohol dependent and had less chronic diseases (Table 1). The proportion of extrapulmonary TB cases among all TB cases in NINNM did not differ from that in IC. NINNM were more likely to have cavitations on chest radiography than IC and had more sputum smear positive, were hospitalised for longer periods and had longer patient delay and shorter system delay. No differences were found in the

Table 1

Characteristics of patients included in study, Tel Aviv tuberculosis clinic, 1998-2008 (n=487)

Characteristic		Non-insured non-national migrant N=222 n (%)[a]	Israeli citizen N=265 n (%)[a]	p value
Age at diagnosis (years, SD)		35.0±9.8	53.7±19.7	<0.01
Male sex		101 (45.5)	161 (60.8)	0.01
Originating in high TB prevalence area[b]		213 (95.9)	155 (58.5)	<0.01
Employed while diagnosed		175 (78.8)	75 (28.3)	<0.01
Substance abuse[c]		4 (1.8)	22 (8.3)	0.02
Previous TB diagnosis		13 (5.9)	50 (18.9)	<0.01
Any underling chronic disease		23 (10.4)	103 (38.9)	<0.01
Smoking[c]		22 (9.9)	92 (34.7)	<0.01
HIV infection		11 (5.0)	5 (1.9)	0.07
Mean time from arrival in Israel to TB diagnosis (years, SD)		3.1±2.7	23±17	<0.01
Any symptom related to TB[d]		161 (72.5)	193 (72.8)	1
Pulmonary TB		158 (71.2)	191 (72.1)	0.8
Pulmonary TB in patients residing in Israel < 5 years		128 (57.6)	47 (17.7)	0.02
Extrapulmonary TB site	Pleura[e]	14 (24.4)	21 (29.5)	0.3
	Lymph nodes[e,f]	36 (58.5)	12 (21.6)	<0.01
	Urogenital[e]	3 (3.7)	19 (21.6)	<0.01
	Musculoskeletal[e]	2 (2.4)	6 (6.8)	0.1
	Other sites[e]	9 (11.1)	18 (20.5)	0.07
Cavitations in chest radiography[g]		67 (42.4)	46 (24.1)	<0.01
Sputum smear-positive[g]		79 (50.0)	70 (36.6)	0.04
Culture-positive[g]		106 (67.1)	109 (57.1)	0.05
Resistant to any first-line anti-TB drug[h]		34 (21.5)	30 (15.7)	0.1
Multidrug resistance		4 (2.5)	8 (4.2)	0.3
Hospitalised due to TB		94 (42.3)	114 (43.0)	0.9
Length of hospitalisation (weeks)		9.9±5.9	7.6±7.5	0.04
DOT adherence >80% for six months of treatment		192 (86.5)	229 (86.4)	0.5
Treatment success[i]		185 (83.3)	241 (90.9)	0.01
Mean patient delay (days, SD)		33.1±3.6	18.6±2.8	0.01
Mean system delay (days, SD)		48.9±5.3	105.3±11.1	<0.01

Percentages were calculated on the basis of the number of cases for which information was available.

DOT: directly observed treatment; HIV: human immunodeficiency virus; SD: standard deviation; TB: tuberculosis.

[a] Unless otherwise specified.
[b] Above 20 cases per 100,000 population.
[c] Present or past.
[d] Cough longer than three weeks, haemopthysis, chest pain, sub-febrile teperature, weight loss, night sweats.
[e] In extrapulmonary tuberculosis patients.
[f] If there were multiple sites, the site other than the peripheral lymph node was considered the principle site.
[g] In pulmonary tuberculosis patients.
[h] Isoniazid, rifampicin, ethambutol, pyrazinamide.
[i] Patients who were cured or whose treatment was completed.

Table 2

System and patient delay of patients included in study, Tel Aviv tuberculosis clinic, 1998-2008 (n=487)

Characteristic		Patient delay (mean 25±14 days)			System delay (mean 79±42 days)		
		Below the mean N=316 n (%)[a]	Above the mean N=171 n (%)[a]	p value	Below the mean N=282 n (%)[a]	Above the mean N=205 n (%)[a]	p value
Age at diagnosis (years, SD)		43.5±17.7	48.1±13.2	0.02	47.5±19.3	41.6±16.5	0.01
Male sex		171 (54.1)	80 (46.7)	0.2	156 (55.3)	108 (52.7)	0.6
Non-insured non-national migrant		114 (36.1)	96 (56.1)	<0.01	139 (49.3)	74 (36.1)	<0.01
Originating in high TB prevalence area[b]		218 (70.0)	145 (84.8)	<0.01	212 (75.2)	154 (75.1)	0.2
Years from arrival to Israel[c]		15.6±19.1	9.1±15.1	0.01	12.1±17.5	14.5±18.8	0.2
Employed while diagnosed		148 (46.8)	92 (53.8)	0.01	146 (51.8)	93 (45.3)	0.07
Substance abuse[d]		14 (4.6)	11 (6.4)	0.39	14 (4.9)	11 (5.4)	1
Previous TB diagnosis		45 (14.2)	18 (10.5)	0.4	39 (13.8)	24 (11.7)	0.5
Any underlying chronic disease		87 (27.5)	37 (21.6)	0.3	60 (21.3)	66 (32.5)	<0.01
Smoking[d]		86 (27.2)	23 (13.4)	<0.01	52 (18.4)	56 (27.3)	0.05
HIV infection		10 (3.1)	6 (3.5)	0.8	8 (1.8)	8 (3.9)	0.6
Any symptom related to TB[e]		208 (65.8)	26 (15.2)	<0.01	182 (64.5)	39 (19.1)	<0.01
Referral to TB clinic by	Self referral/	N/A	N/A	N/A	5 (2.0)	0 (0.0)	<0.01
	Screening	N/A	N/A	N/A	188 (72.3)	109 (53.7)	N/A
	General practitioner	N/A	N/A	N/A	67 (25)	94 (45.8)	N/A
Extrapulmonary TB		83 (26.2)	50 (29.2)	0.39	74 (26.2)	57 (27.8)	1
Cavitations in chest radiography		24 (7.2)	17 (9.9)	0.01	28 (9.9)	13 (6.4)	0.26
Sputum smear-positive[f]		96 (30.4)	82 (47.9)	0.04	89 (31.5)	78 (38.0)	0.2
Culture-positive[f]		168 (53.2)	94 (55.0)	0.14	133 (47.2)	130 (63.4)	<0.01
Resistant to any first line anti-TB drug[g]		38 (12.0)	25 (14.6)	0.7	30 (10.6)	33 (16.1)	0.6
Multidrug resistance		7 (2.2)	5 (2.9)	0.7	4 (1.4)	8 (3.9)	0.29
Hospitalised due to TB		116 (36.7)	87 (50.9)	0.01	101 (35.8)	103 (50.2)	0.01

HIV: human immunodeficiency virus; SD: standard deviation; TB: tuberculosis.

[a] Unless otherwise specified
[b] Above 20 cases per 100,000 population.
[c] For patients not born in Israel.
[d] Present or past.
[e] Cough longer than three weeks, haemopthysis, chest pain, sub-febrile teperature, weight loss, night sweats.
[f] In pulmonary tuberculosis patients.
[g] Isoniazid, rifampicin, ethambutol, pyrazinamide.

rate of multidrug resistance or any single drug resistance between the two groups.

The mean patient delay for all patients in our study was 25±14 days and mean system delay was 79±42 days (p<0.01). Longer than average patient delay was more common in older patients, NINNM, those originating from high TB burden countries or who spent fewer years in Israel, those who did not smoke, and patients who were less symptomatic (Table 2). Additionally, those who had longer patient delay also had more cavitations on chest radiography and were more often sputum smear positive or hospitalised for a longer period than those who had shorter than average patient delay. Patients with longer than average system delay were younger, more often IC, had more underlying chronic disease, were more often smokers and had less TB symptoms.

Multivariate analysis suggested that being a NINNM, asymptomatic or a smoker are factors predicting longer patient delay; while being asymptomatic or having an underlying chronic disease are predicting factors for longer system delay (Table 3).

The rate of treatment success of the entire study population was 87.5% (426/487). Among patients with sputum smear-positive pulmonary TB, 81% (64/79) of the NINNM and 95.7% (67/70) of the IC achieved treatment success, p=0.01. Patients whose treatment outcome

Table 3

Multiple logistic regression analysis of the factors associated with patient and system delay for patients included in study, Tel Aviv tuberculosis clinic, 1998-2008 (n=487)

Characteristic	Patient delay		System delay	
	p value	OR (95% CI)	p value	OR (95% CI)
Age at diagnosis	0.9	1.0 (0.9-1.1)	0.4	1.0 (0.9-1.1)
Non-insured non-national migrants	0.01	3.5 (1.3-9.5)	0.8	0.5 (0.2-1.1)
Asymptomatic	0.01	1.3 (1.2-1.8)	0.02	1.6 (2.3-3.5)
Originating from a high TB prevalence area[a]	0.7	0.9 (0.3-3.3)	N/A	N/A
Employed while diagnosed	0.5	0.7 (0.3-1.9)	N/A	N/A
Smoking[b]	0.01	2.5 (1.2-5.0)	N/A	N/A
Cavitations on chest radiography	0.8	0.9 (0.9-1.1)	N/A	N/A
Any underlying chronic disease	N/A	N/A	0.03	2.4 (1.1-5.2)
Culture-positive	N/A	N/A	0.1	1.7 (0.9-3.3)
Hospitalisation due to TB	N/A	N/A	0.1	0.6 (0.3-1.2)

CI: confidence interval; N/A: nNot applicable; OR: odds ratio, TB: tuberculosis.

[a] Above 20 cases per 100,000 population.
[b] Present or past.

Table 4

Treatment success for patients included in study, Tel Aviv tuberculosis clinic, 1998-2008 (n=487)

Characteristic	Success N=426 n (%)[a]	No success N=61 n (%)[a]	p value
Age at diagnosis (years, SD)	45±18.01	46.63±21.5	0.52
Male sex	230 (54.0)	32 (52.5)	0.89
Israeli citizen	241 (56.6)	24 (39.3)	0.01
Originating in a high TB prevalence area[b]	97 (22.8)	12 (19.7)	0.74
Employed while diagnosed	217 (50.9)	33 (54.1)	0.63
Substance abuse[c]	21 (4.9)	5 (8.2)	0.35
Any underling chronic disease	107 (25.1)	19 (31.1)	0.43
Smoking[c]	99 (23.2)	15 (24.6)	0.87
HIV infection	9 (2.1)	7 (11.5)	0.02
Any symptom related to TB[d]	310 (72.8)	44 (72.1)	1
Pulmonary TB	312 (73.2)	37 (60.7)	0.04
Resistant to any first line anti-TB drug[e]	53 (24.4)	11 (18.0)	0.11
Multidrug resistance	10 (2.3)	2 (3.2)	0.646
Lost job due to TB diagnosis[f]	28 (12.9)	16 (48.5)	<0.01
DOT adherence >80% for six months of treatment	398 (93.4)	23 (37.7)	<0.01
Patient delay (days±SD)	25.6±2.5	20.7±5.0	0.48
System delay (days±SD)	80.4±7.3	73.7±12.6	0.75

DOT: directly observed treatment; HIV: human immunodeficiency virus; SD: standard deviation; TB: tuberculosis.

[a] Unless otherwise specified
[b] Above 20 cases per 100,000 population.
[c] Present or past.
[d] Cough longer than three weeks, haemopthysis, chest pain, sub-febrile teperature, weight loss, night sweats.
[e] Isoniazid, rifampicin, ethambutol, pyrazinamide.
[f] Of all patients employed while diagnosed with tuberculosis.

Treatment success was defined as patients who were cured or completed therapy, as classified by the WHO guidelines [12].

Table 5

Multiple logistic regression analysis of the factors associated with treatment success, for patients included in study, Tel Aviv tuberculosis clinic, 1998-2008 (n=487)

	p value	OR (95% CI)
Israeli citizenship	0.8	1.08 (0.4-2.9)
HIV infection	0.4	0.4 (0.05-3.0)
Pulmonary TB	0.1	0.49 (0.2-1.3)
Employment sustained (was not discharged)	<0.01	7.65 (2.6-22.7)
DOT adherence >80% for six months of treatment	<0.01	11.2 (3.6-36.6)

CI: confidence interval; DOT: directly observed treatment; HIV: human immunodeficiency virus; OR: odds ratio; TB: tuberculosis.

Treatment success was defined as patients who were cured or completed therapy, as classified by the WHO guidelines [12].

was successful were more commonly IC, HIV-free, had pulmonary TB, kept their jobs during their illness and adhered to the regimen of directly observed therapy (DOT) (Table 4).

Multivariate analysis suggested that having work secured during illness and adherence to DOT are predictors for treatment success (Table 5).

Discussion

Patient delay in this study was longer in NINNM and system delay was longer in IC. The rates of TB treatment success after six months of therapy were inferior in NINNM compared to IC.

NINNM in our study were younger and had better health determinants than IC, similar to findings published earlier in Canada and the US [12,13]. This phenomenon is labeled as the 'healthy migrant effect', and points to the self-selection of healthier and better prepared individuals to overcome the difficulties pertaining to migration [11]. The majority of the IC in our study were born in high TB burden areas and they were older and had stayed in Israel for a longer time than NINNM. Given that Israel is a low TB prevalence country, those IC diagnosed with TB who were born outside Israel were probably infected in their countries of origin before they immigrated to Israel. It is assumed that they developed active TB due to weakening of their immune system, older age, or other concomitant underlying medical conditions.

Although there is no consensus to what length a diagnostic delay is accepted [14], the patient delay in our study and the system delay in NINNM were within the limits of timeframes published from Italy and Spain [10,14,15], yet system delay among IC was much longer, corresponding to findings in a study from Taiwan reporting on system delay in Taiwanese nationals [16]. The majority of IC in our study were older than NINNM and had underlying chronic diseases that might have masked TB symptoms. In our own experience, IC patients usually consult their family physician during the initial stage of their disease, however, the low TB incidence among IC might lead physicians to reduce their index of suspicion regarding the possibility of TB diagnosis. The physicians probably order other tests rather than TB-diagnostic procedures. Cough was found to be a significant complaint associated with system delay among citizens in Brazil, reducing healthcare providers' sensitivity to the possibility of TB, as cough is a symptom for many other respiratory diseases as well [17]. NINNM often consult one of the two general free outpatient clinics in Tel Aviv designated for non-insured patients. Healthcare providers in these clinics are familiar with the specific medical conditions of migrants and are more sensitive to the possibility of TB diagnosis than general physicians in clinics serving IC, and thus generally refer patients to the free TB clinic in a relatively timely manner.

NINNM had longer patient delay than IC, as also found in Italy [14], possibly due to a combination of reasons: lack of medical insurance, non-acquaintance with availability of free TB services, or the efforts necessary to commute to the clinic. Additionally, fear of deportation or discontinuation of their employment and other or social barriers may hinder the migrants of using the available TB services [18]. The outcome of presenting late at a physician was demonstrated in our study. It resulted in a more extensive disease, greater rates of positive smear results and the presence of cavitations on chest radiographs among the NINNM. It may also explain the need for longer hospitalisation for NINNM, possibly because their disease was more progressive and their living conditions did not allow for domestic isolation in the community.

Extrapulmonary TB patients had longer system delay. A possible explanation for this is that the symptoms are often diffuse and non-specific which renders the medical process of differential diagnosis more difficult, and probably leads the physician to search for other causes. Although extra pulmonary TB is seldom infectious, delay in diagnosis may increase morbidity and mortality [10,19].

Treatment success rate in the Tel Aviv TB clinic for the study period was higher than the WHO goal of 85% [20]. Although citizenship was not found to be a variable predicting treatment success by the regression model, IC had better treatment outcome than NINNM in the univariate analysis. Most NINNM who did not reach

treatment success were 'transferred out' or 'defaulted from therapy' (data not presented), as they either left Israel at their own discretion or that treatment demands of more than six months of therapy made it impossible for them to combine their work duties with clinic visits. It is noteworthy that employment security was a significant predictive determinant for treatment success in our study. Nevertheless, longer patient or system delays were not found to be associated with treatment success, and it may be that the clinics' outreach efforts for the patients and supporting them in completing treatment, regardless of the severity of the disease, had a positive impact on adherence.

This study is subject to limitations on recall bias, due to the retrospective approach of data collection with resulting uncertainty of the actual onset of symptoms, as well as linguistic and cultural gaps which might limit the effectiveness of the medical interview performed by the physician. However, data were collected in a similar fashion for IC and NINNM alike, and the bias, if it exists, is non-differential and conservative. Additionally, due to the retrospective nature of the study, other determinants such as homelessness, income, education and other health perception attributes could not be ascertained. We also were not able to define whether patients were infected in Israel or acquired the infection in their country of origin, and reactivated in Israel. Finally, the generalisation of the study results to all NNM in Israel may be questionable. Yet, most of the migrant workers, especially those non-insured, reside in Tel Aviv.

Conclusions

NINNM in our study had longer patient delay, while IC had longer system delay. Both delays should be reduced. As many industrialised countries in Europe host migrants, our finding may be valid for organisations providing healthcare for migrants. Health professionals should use the opportunity of TB screenings where performed, to inform migrants about the possibility that TB may develop in later stages, and discuss with them about typical TB symptoms. NINNM in Israel should also be advised about possibilities of free TB treatment, and that care is independent of deportation regulations. Additionally, it would be desirable to establish a system of employment security to counteract the economic instability and to loss of income of NINNM infected with TB. In order to ensure treatment completion, NINNM who return to work at the final stages of their treatment should be provided DOT in a flexible approach, by costumising the time and place to make it convenient for the patients, and possibly with financial incentives for them to complete treatment and adhere to follow-up. Finally, primary care physicians should be informed that TB diagnosis in IC is possible, to increase their index of suspicion.

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ECDC and WHO/Europe joint report on tuberculosis surveillance and monitoring in Europe

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The European Centre for Disease Prevention and Control (ECDC) and the World Health Organization (WHO) Regional Office for Europe launched jointly the fifth report on surveillance and monitoring of tuberculosis (TB) in Europe [1]. Since 2008, ECDC and WHO/Europe have coordinated the collection and analysis of TB surveillance data across the countries of the WHO European Region (except Liechtenstein, Monaco and San Marino).

This year's report highlights two subsets of TB cases that tend to be neglected by routine surveillance: extrapulmonary TB cases (based on data from The European Surveillance System (TESSy) and prisoners with TB (based on Tuberculosis Monitoring and Evaluation (TME) data).

In the European Union/European Economic Area (EU/EEA) 72,334 cases of TB were reported in 2011 in 29 countries, which was 4% less than in 2010. The EU/EEA notification rate was 14.2 per 100,000 population, continuing the long-term decreasing trend. Multidrug-resistant TB (MDR-TB) was reported in 5% of cases with available drug susceptibility testing results (2% of new TB cases and 17% of previously treated cases) and continues to be most prevalent in the three Baltic countries. Extensively drug-resistant TB was reported for 13% of 1,017 MDR-TB cases tested for second-line drug susceptibility. Of all TB cases with known human immunodeficiency virus (HIV) status, 5% were co-infected with the virus. In 2011, 22% of all TB cases were notified with exclusively extrapulmonary TB (mostly lymphatic and pleural TB); 35% of them were confirmed by culture, 1% was multidrug-resistant and 82% were labelled as treatment successes. Seventy-four percent of all TB cases notified in 2010 and 32% of MDR-TB cases notified in 2009 had successfully completed their treatment.

In 2011 in the WHO European Region, the 2015 Millennium Development Goal (MDG) target of halting the prevalence and death associated with TB and reversing its incidence has been partially achieved with TB incidence falling in the Region at a rate of about 5% per year between 2000 and 2011. Nevertheless, the prevalence of TB was estimated at 56 cases per 100,000 population in the Region and TB mortality was 4.9 deaths per 100,000 population (around 44,000 in total). According to the report, it will therefore not be possible to reach the target of 50% reduction by 2015. As for the TB cases in prisons, given that only few countries report TB from correctional institutions, it was difficult to calculate the extent to which prisons contribute to the regional TB burden. However, there were some countries in eastern Europe where TB cases in prisons exceeded 10% of the countrywide total of new TB cases, and in others the notification rate was close to or exceeded 1,000 cases per 100,000 prison population. In some low-incidence countries however, there was a higher risk of TB in prisons than in the general population.

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