Research article

Tuberculosis treatment outcome in the European Union and European Economic Area: an analysis of surveillance data from 2002–2011

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Monitoring the treatment outcome (TO) of tuberculosis (TB) is essential to evaluate the effectiveness of the intervention and to identify potential barriers for TB control. The global target is to reach a treatment success rate (TSR) of at least 85%. We aimed to assess the TB TO in the European Union and European Economic Area (EU/EEA) between 2002 and 2011, and to identify factors associated with unsuccessful treatment. Only 18 countries reported information on TO for the whole observation period accounting for 250,854 new culture-confirmed pulmonary TB cases. The 85% target of TSR was not reached in any year between 2002 and 2011 and was on average 78%. The TSR for multidrug-resistant (MDR)-TB cases at 24-month follow-up was 49%. In the multivariable regression model, unsuccessful treatment was significantly associated with increasing age (odds ratio (OR) = 1.02 per a one-year increase, 95% confidence interval (CI): 1.02–1.02), MDR-TB (OR = 8.7, 95% CI: 5.09–14.97), male sex (OR = 1.40, 95% CI: 1.28–1.52), and foreign origin (OR = 1.32, 95% CI: 1.03–1.70). The data highlight that special efforts are required for patients with MDR-TB and the elderly aged ≥65 years, who have particularly low TSR. To allow for valid monitoring at EU level all countries should aim to report TO for all TB cases.

Introduction

In 1991, the 44th World Health Assembly set targets to detect at least 70% of new tuberculosis (TB) cases and to cure at least 85% of those detected [1]. The Stop TB Partnership developed the *Global Plan to Stop TB 2006–2015* to achieve these targets set for 2015 within the context of the Millennium Development Goals [2]. Monitoring the outcome of TB treatment is essential to evaluate the effectiveness of the intervention and to identify the potential barriers for TB control.

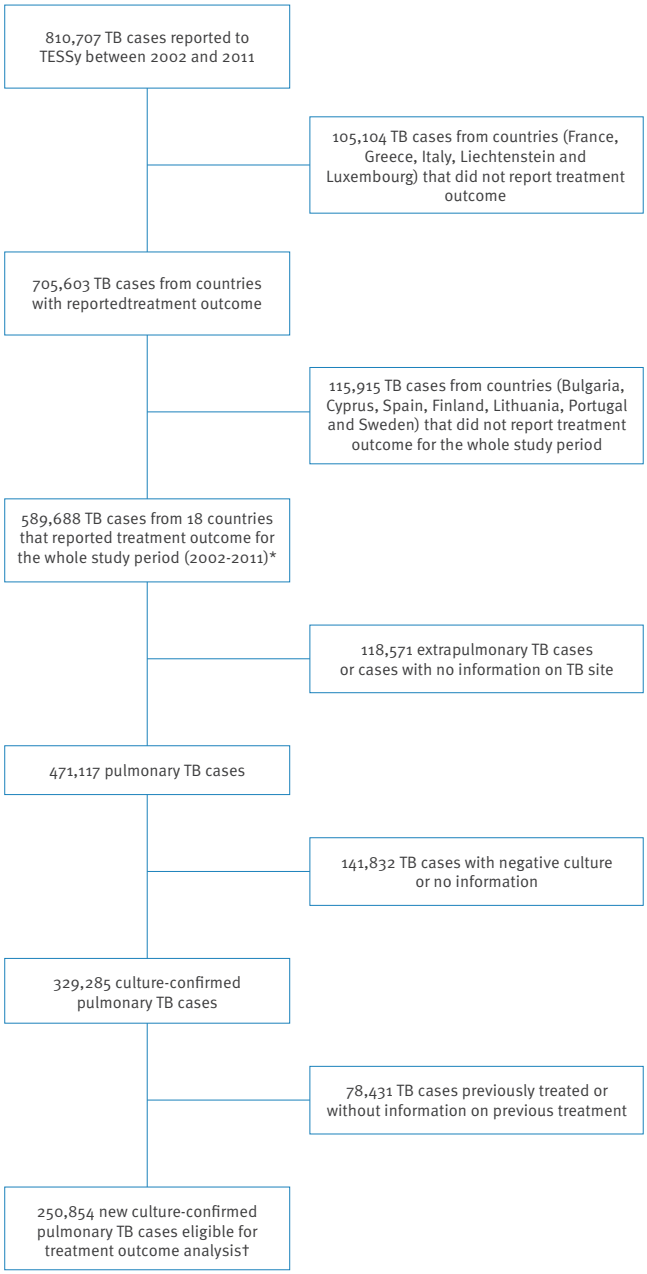
In Europe, a Working Group of the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Disease (IUATLD) published recommendations for uniform reporting by TB surveillance and cohort analysis of treatment outcome (TO) across Europe [3,4]. A minimal set of six exclusive categories of TO was recommended as standard: cured, completed, failed, died, interrupted (defaulted) and transferred out. Furthermore, analysis of TO should be separate for new and retreatment cases [4]. In 2008, the European Centre for Disease Prevention and Control (ECDC) published the *Framework Action Plan to fight Tuberculosis in the European Union* following the WHO/IUATLD recommendations; including a core indicator of 85% treatment success rate for new pulmonary culture-confirmed TB cases and 70% for new pulmonary culture-confirmed multidrug-resistant (MDR) TB cases [5].

In 2013, in the European Union and European Economic Area (EU/EEA), the TB notification rate was 12.7 per 100,000 population [6]. Notification rates were heterogeneous: five countries had incidence rates ≥ 20 and 24 countries had incidence rates < 20 cases per 100,000 population in 2013) [6]. In the majority of countries the trend in case notification rate showed a sustained decline during the period 2009-2013. In 2013, the overall treatment success rate was 73.5%.

In this study, we aimed to assess the TB TO in the EU/EEA and to identify factors associated with unsuccessful treatment applying the WHO/IUATLD recommendations for the EU/EEA for cohort analysis over a 10-year observation period.

Figure 1

Algorithm for inclusion of cases in the analysis on treatment outcome of new culture-confirmed pulmonary tuberculosis, EU/EEA, 2002–2011 (n=589,688) Algorithm for inclusion of cases in the analysis on treatment outcome of new culture-confirmed pulmonary tuberculosis, EU/EEA, 2002–2011 (n=589,688)



EEA: European Economic Area; EU: European Union

a Including Austria, Belgium, Czech Republic, Denmark, Estonia, Germany, Hungary, Ireland, Iceland, Latvia, Malta, the Netherlands, Norway, Poland, Romania, Slovenia, Slovakia and the United Kingdom.

b Denmark did not report information on previous treatment in 2005. These cases were coded as missing in the cohort (n=428).

Source: The European Surveillance System (TESSy). TESSy was operational since 2008 and for data from 2002-2007 data were transferred into TESSy from the historical database of the former EuroTB project for the TB surveillance activities in Europe.

Methods

Data source

Since January 2008, all EU countries (27; since February 2015 28 countries, after Croatia has joined) and the EEA countries Iceland and Norway (Liechtenstein has not reported data since 2007) report their available data on TB to The European Surveillance System (TESSy) hosted by ECDC [6]. For years between 1996 and 2007, data were transferred into TESSy from the historical database of the former EuroTB project for the TB surveillance activities in Europe. In this paper, we analysed data of TB TO during 2002-2011 and extracted from TESSy on 2 October 2013.

Since the reporting year 2002, case-based TO data have been provided by EU/EEA countries for cases notified one year before the year of TO reporting. Since 2005, TO data of MDR-TB cases have been reported for cases notified two years earlier [6]. Thus, for TO analysis of MDR-TB cases data reported between 2005 and 2010 were used in this study.

Definitions

In line with the WHO/IUATLD recommendation for EU/EEA countries [3,4] the cohort eligible for the TO analysis included new culture-confirmed pulmonary TB cases. Cases are observed until the first outcome up to a maximum of 12 months after the start of treatment and MDR-TB cases for 24 months. TO was categorised based on the WHO/IUATLD recommendations [4] with two additional categories 'Still on treatment' and 'Unknown' (Table 1) [6,7].

A new TB case was defined as a case that never previously received drug treatment for active TB, or received anti-TB drugs for less than one month. Five countries (Belgium, Denmark, Ireland, Norway and the United Kingdom (UK)) did not report information about previous treatment and for those previous diagnosis was used as a proxy for defining new and previously treated cases.

The term native case refers to cases born in or, if this information was unavailable, having citizenship in the reporting country. Foreign origin refers to cases born in (or citizens of) a country different from the reporting country.

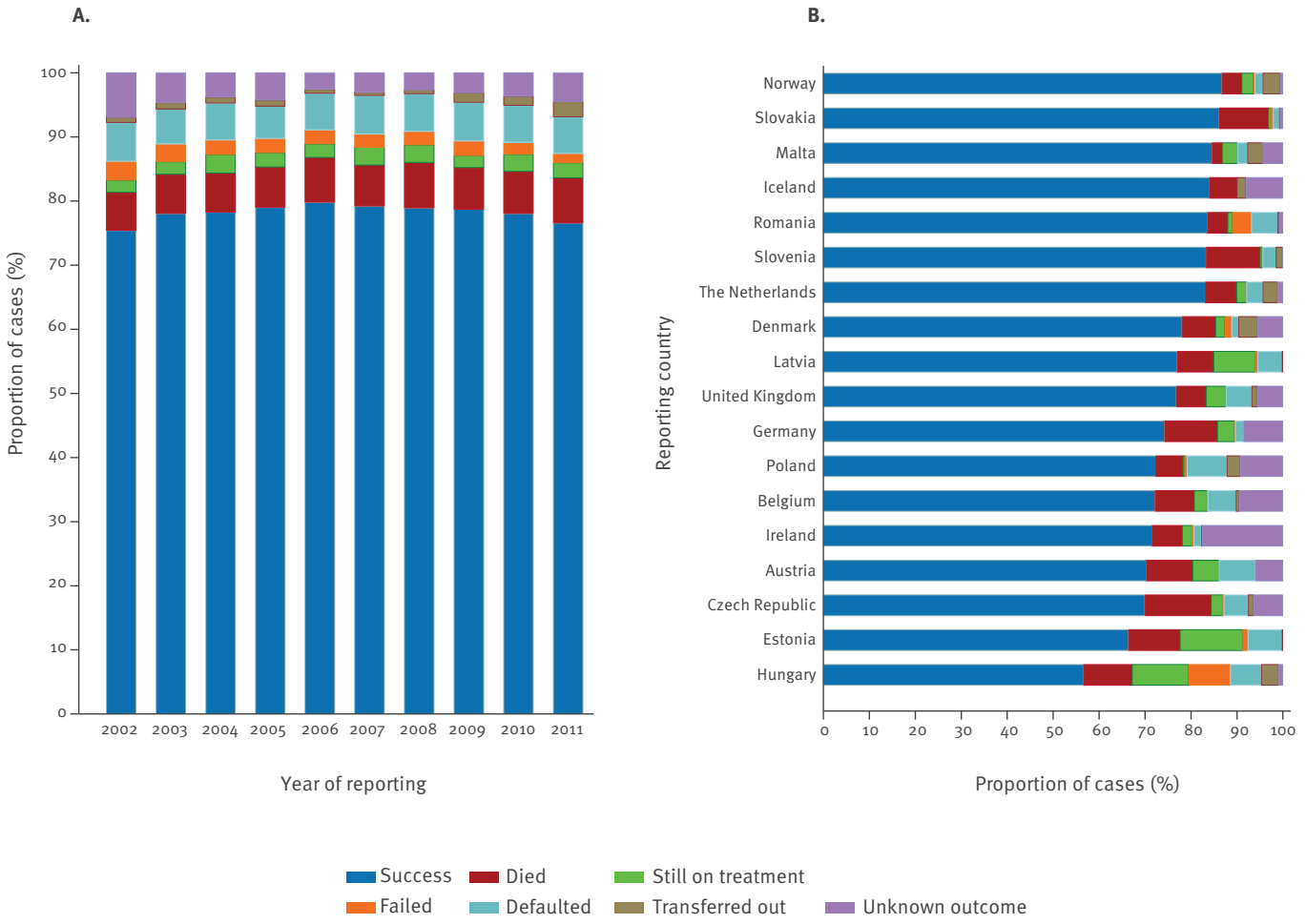
MDR-TB was defined as TB with resistance to at least rifampicin and isoniazid. A low TB incidence country was defined as country with TB incidence rate <20 cases per 100,000 population and a high TB incidence country with TB incidence rate ≥ 20 cases per 100,000 population.

Statistical analysis

Data were described by totals and percentages. The chi-squared test was used to assess differences in categorical variables. Only cases from countries

Figure 2

Treatment outcome of new culture-confirmed pulmonary tuberculosis cases in the EU/EEA by A. Reporting years B. Reporting countries, 2002–2011 (n=250,854)



Source: The European Surveillance System (TESSy). TESSy was operational since 2008 and for data from 2002-2007 data were transferred into TESSy from the historical database of the former EuroTB project for the TB surveillance activities in Europe.

that reported on TO for the whole study period were included in TO calculation and the statistical model.

Trend analysis of treatment success rate was conducted using the nonparametric test for trend across ordered groups i.e. the reporting years. A logistic regression model was used to examine the association between the TO, successful vs unsuccessful, and potential predictor variables age, sex, geographical origin, MDR-TB and reporting year. In the regression model, TB TO was categorised as treatment success vs unsuccessful treatment. Independent variables were systematically investigated in the univariate analysis and in the multivariable model for adjusting to possible confounders. To correct for the clustering within countries, we specified that the standard errors allow for intragroup correlation, assuming that the observations are independent across groups (clusters) but not necessarily within groups. Based on the regression coefficient of the model, odds ratios (OR) with their 95% confidence interval (CI) were also calculated to assess the strength of association.

All tests were two-sided and considered significant if $p < 0.05$. All analyses were performed using STATA (version12, StataCorp, LP, TX, US) software.

Ethical statement

This study was based on national surveillance data submitted to ECDC. Therefore, written informed consent from the patients was not required due to the anonymous nature of the data.

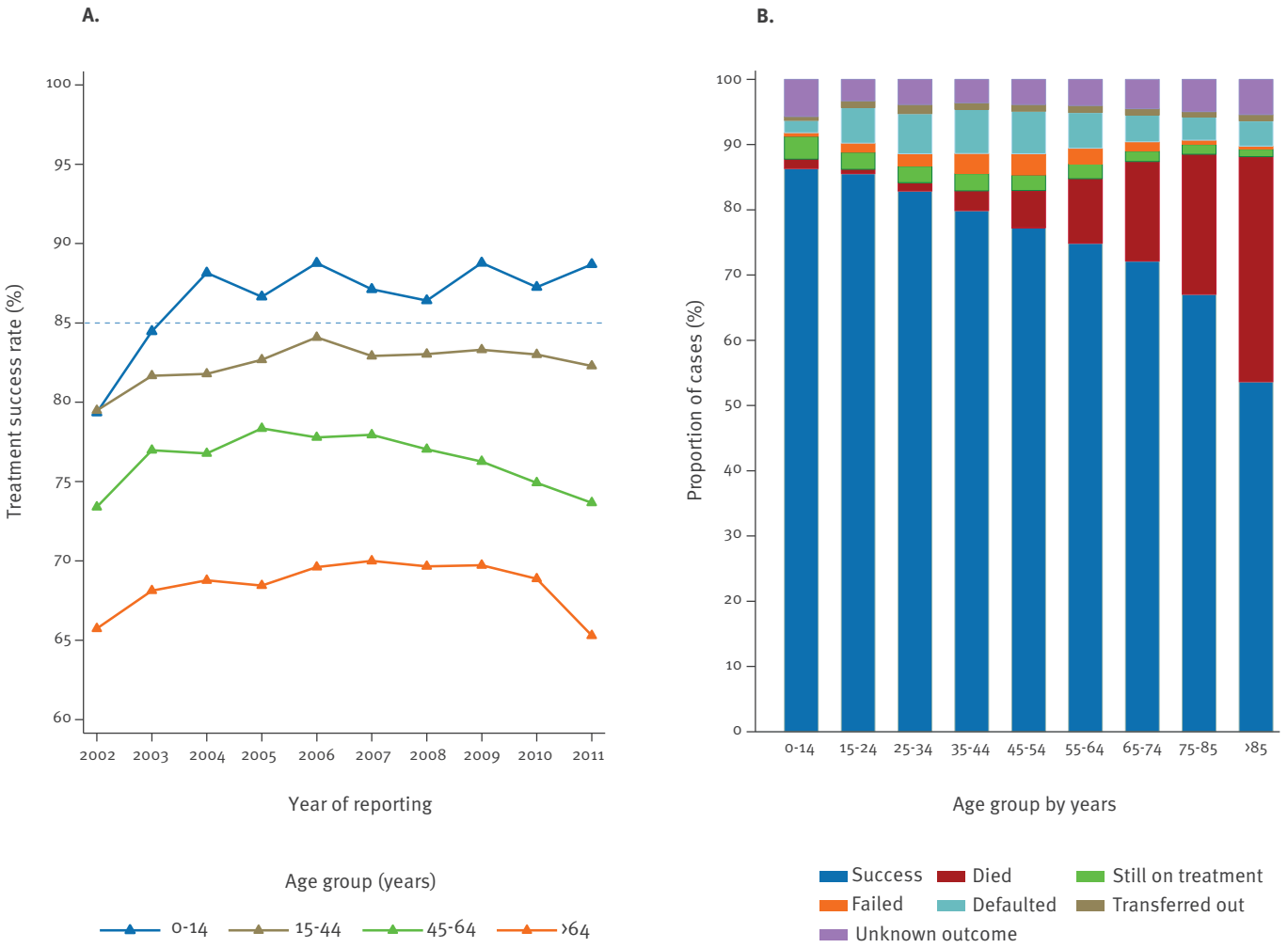
Results

Treatment outcome reporting

Between 2002 and 2011, a total of 810,707 TB cases were notified. Of these, 83.3% (n = 675,627) had information on TO. The number of countries, that reported information on TO, increased from 21 countries in 2002 to 25 countries in 2011. Five countries (France, Greece,

Figure 3

Treatment success rate of new culture-confirmed pulmonary tuberculosis in the EU/EEA. 3A. Age group 3B. Treatment outcome by reporting year, 2002–2011 (n=250,810)



EU: European Union; EEA: European Economic Area

Source: The European Surveillance System (TESSy). TESSy was operational since 2008 and for data from 2002-2007 data were transferred into TESSy from the historical database of the former EuroTB project for the TB surveillance activities in Europe.

Italy, Liechtenstein and Luxembourg) did not report on TO in any year between 2002 and 2011. Eighteen countries (Austria, Belgium, Czech Republic, Denmark, Estonia, Germany, Hungary, Ireland, Iceland, Latvia, Malta, the Netherlands, Norway, Poland, Romania, Slovenia, Slovakia and the UK) provided information on TO for the whole 10-year study period (2002–2011), corresponding to 589,688 TB cases (72.7% of all reported cases). Of these 589,688 TB cases, 42.5% (n=250,854) were new culture-confirmed pulmonary TB cases eligible for our analysis (Figure 1).

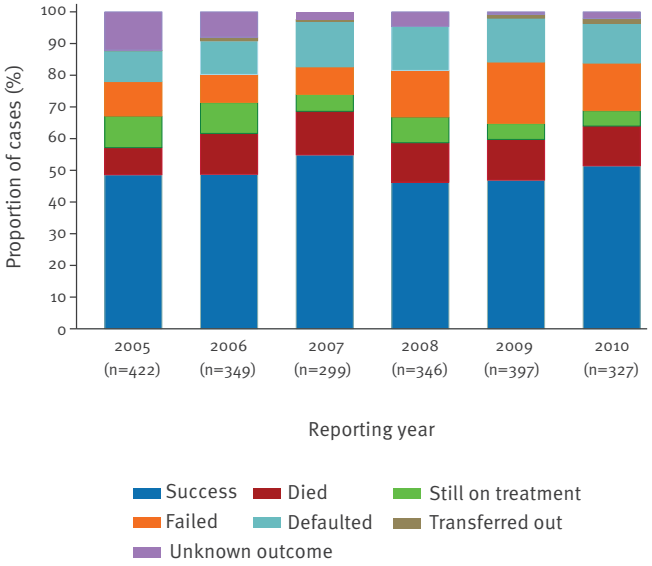
Significant differences were observed in the demographic characteristics between included and excluded cases. Compared with the excluded cases, the included new culture-confirmed pulmonary TB cases were more likely to be men (67.2% vs 63.7%; p<0.001), of native origin (84.4% vs 78.7%; p<0.001) and non-MDR-TB (98.6% vs 97.9%, p<0.001) respectively. Also, the treatment success rate was higher in included cases compared with excluded ones (78.2% vs 71.1%; p<0.001).

Cohort characteristics

The majority of cohort cases were reported by Romania, Poland, Germany and the UK (45.1%, 17.8%, 9.7% and 9.5% respectively). The median age of cases was 45 years (interquartile range (IQR) 31–57). Of cohort cases 67.2% were male and 14.9% were of foreign origin. MDR-TB was reported in 1.4% (n=3,597) of the cohort cases, mainly from Romania (n=1,219), Latvia (n=802) and Estonia (n=460). Information of drug susceptibility

Figure 4

Treatment outcome at 24-month follow-up for new culture-confirmed pulmonary MDR-TB cases in the EU/EEA, 2005–2010 (n=2,140)



EU: European Union; EEA: European Economic Area; MDR: multidrug-resistant; TB: tuberculosis.

Source: The European Surveillance System (TESSy). TESSy was operational since 2008 and for data from 2002-2007 data were transferred into TESSy from the historical database of the former EuroTB project for the TB surveillance activities in Europe.

testing results for isoniazid and rifampicin was missing in almost half of the cases (48.4%) (Table 2).

Twelve-month treatment outcome

The overall proportion of cases with reported treatment success was 78.2% (country range 56.6% in Hungary to 86.8% in Norway). Treatment success rate was higher among female cases compared with male cases (81.6% vs 76.5% respectively; p<0.01) overall and in each respective reporting year, age group and geographical origin (data not shown). About 6.5% of TB cases died (country range 2.2% in Malta to 14.4% in Czech Republic). On average, 2.4% of cases were still on treatment at the end of the 12-month follow-up period (country range 0% in Iceland to 13.7% in Estonia); 32.7% of these cases were MDR-TB. The proportion of cases with unsatisfactory outcome 12 months after start of treatment was 8.9% (country range 2.0% in Iceland and Germany to 19.6% in Hungary). Of them 2.2% were reported as treatment failure, 5.7% as defaulted and 1.0% as transferred out. Cases with unknown TO accounted for 4.0% (country range 0% in Latvia and Estonia to 17.6% in Ireland) (Figure 2).

The treatment success rate decreased with increasing age (85.3% treatment success in cases aged<15 years vs 68.4% in cases aged>64 years; p<0.001) (Figure 3a,b). The death rate rose substantially with increasing age of cases (1.8% death rate in cases aged<15 years vs 19.4% in cases aged>64 years; p<0.001) (Figure 3b).

A higher proportion of cases with unknown outcome was noticed among cases aged<15 years compared with other age groups.

The treatment success rate was slightly higher among native cases than among cases of foreign origin (78.7% vs 77.3% respectively; p=0.05). In native cases, a higher proportion of deaths (6.9% in native cases vs 4.3% in cases of foreign origin; p<0.001) and treatment failure (2.7% in native cases vs 0.2% in cases of foreign origin; p<0.001) was observed. Also the proportion of cases with advanced age was higher in native cases than cases of foreign origin (cases aged>64 years accounted for 17.2% in native cases vs 10.8% in cases of foreign origin; p<0.001). The proportion of cases with unknown outcome was markedly higher in cases of foreign origin than in native cases (3.0 vs 6.5% respectively; p<0.001).

Adjusting for age and country of origin revealed no significant differences in treatment success rate between countries with low or high incidence (OR 0.7; p=0.1). Noticeably, the proportion of elderly aged >64 years was higher in low incidence countries compared with high incidence countries (cases aged>64 years accounted for 20.9% vs 14.6% respectively; p<0.001). Similarly, cases of foreign origin were more presented in low incidence countries (44.7% vs 0.8% respectively; p<0.001).

Twenty-four-month treatment outcome of multidrug-resistant tuberculosis

Between 2005 and 2010, 2,140 MDR-TB cases were reported from the 18 EU/EEA countries included in the analysed cohort. The overall treatment success rate for MDR-TB cases at 24-month follow-up was 49.2% and did not reach the 70% target of treatment success rate for MDR-TB cases in any year of the observation period. About 12.0% of MDR-TB cases died and 7.3% were still on treatment at the end of 24-month follow-up. The proportion of cases with unsatisfactory outcome was 26.3% (including 13.1% failed, 12.4% defaulted and 0.8% transferred out). About 5.2% of the MDR-TB cases were reported with unknown TO (Figure 4).

Trend analysis

The 85% target of overall treatment success rate was not reached in any year between 2002 and 2011. Analysis of trends shows that the treatment success rate increased from 75.4% in 2002 to 79.8% in 2006 (p=0.04), then subsequently decreased to 76.6% in 2011 (p=0.07). No change in the cohort profile regarding proportions of age groups, sex and MDR-TB was observed over time. The proportion of cases of foreign origin increased from (N=3672; 14.5%) in 2006 to (N=4081; 18.5%) in 2011 (p<0.001). Some countries (Belgium, Germany, Hungary, Romania and the UK) showed a continuous increase in the treatment success rate throughout the observation period, while for other countries (Austria, Denmark, Estonia, Netherlands and Poland) a decline was observed (data not shown).

Table 1

Summary of tuberculosis treatment outcome categories according to the WHO/IUATLD recommendations and the ECDC surveillance report 2015

Categories	Definitions
Cured	Treatment completion and culture-negative samples taken at the end of treatment and on at least one previous occasion.
Completed	Treatment completed, but case does not meet the criteria to be classified as cured or treatment failure.
Failed	Culture or sputum smear remaining positive or becoming positive again five months or later into the course of treatment.
Died	Death before cured or treatment completion, irrespective of cause.
Defaulted	Treatment interrupted for two months or more, not resulting from a decision of the care provider.
Transferred out	Patient referred to another clinical unit for treatment and information on outcome not available.
Still on treatment	Patient still on treatment at 12 months and at 24 months for MDR-TB cases without any other outcome during treatment.
Unknown outcome	Information on outcome not available, for cases not known to have been transferred.
Groups created for the purpose of this study	
Unsatisfactory outcome	The percentage of cases that interrupted treatment, were transferred or failed treatment out of all notified.
Successful outcome/treatment success	The percentage of cases that were cured or completed treatment out of all notified.
Unsuccessful treatment	The percentage of cases that were not cured or completed treatment out of all notified (i.e. unsatisfactory outcome, death, still on treatment and unknown outcome).

ECDC: European Centre for Disease Prevention and Control; IUATLD: International Union against Tuberculosis and Lung Disease; WHO: World Health Organization.

Factors associated with unsuccessful treatment

In the multivariable logistic regression model, unsuccessful treatment was significantly associated with increasing age of the case (adjusted OR (aOR) = 1.02 per a one-year increase, 95%CI: 1.02–1.02), male sex (aOR = 1.40, 95%CI: 1.28–1.52) and foreign origin (aOR = 1.32, 95%CI: 1.03–1.70). The strongest association with unsuccessful treatment was observed with MDR-TB (aOR = 8.7, 95%CI: 5.09–14.97). No association was found between unsuccessful treatment and reporting period (aOR = 0.96, 95%CI: 0.71–1.30) (Table 3). In a separate analysis using a multivariable multinomial model, we did not find any difference in factors associated with death and those associated with the other unsuccessful treatment outcomes i.e. unsatisfactory outcome, still on treatment and unknown outcome (data not shown).

Discussion

This study investigated TB TO and factors associated with unsuccessful treatment in the EU/EEA over 10 years following the WHO/IUATLD recommendations for cohort analysis. It shows that the overall treatment success rate of new culture-confirmed pulmonary TB cases in the EU/EEA was 78.2% and failed to reach the 85% target in any year between 2002 and 2011. The study also indicates that main factors associated with unsuccessful treatment were increasing age, male sex, foreign origin and MDR-TB.

Still some countries do not provide information on TO to TESSy and for those who reported on TO, the proportion of cases with unknown outcome remained high at 4.0% overall. It is true that an unknown TO does not necessarily represent a negative one, yet from a programmatic perspective, lack of knowledge about TO deprives the programme from important information to guide TB control. Moreover, no significant improvement in treatment success rate was observed over the 10-year study period. These findings demonstrate a programmatic weakness within TB control in the EU/EEA and highlight the urgent need for strengthening the monitoring and evaluation process at country level [8].

Another analysis of data in TESSy reported by 22 EU/EEA countries in 2007, showed a treatment success rate of 79.5% for new culture-confirmed pulmonary cases [8]. A meta-analysis of published reports of TB TO in Europe found that 74.4% of outcomes were successful [9]. Another study conducted in 18 EU/EEA countries in 2005, showed a mean success rate of only 69% [10]. These results need to be compared with caution due to the different definition of cohort used and the different study periods [11]. Higher treatment success rates were reported in low incidence countries in North America, with 89% in the United States (US) in 2013, and with 86% in 2012 in Canada [12,13].

In the multivariable regression model, male sex was independently associated with unsuccessful treatment. The lower treatment success rate in men compared

Table 2 A*

Characteristics of new pulmonary culture-positive tuberculosis cases in the EU/EEA[a], 2002–2011 (n=250,854)

Demographic and clinical features of TB cases	Number of cases (n = 250,854 cases)	Percent
Sex		
Female	82,336	32.8
Male	168,442	67.2
Unknown	76	0.03
Age group		
<15	3,477	1.4
15–44	125,800	50.2
45–64	79,815	31.8
>64	41,718	16.6
Unknown	44	0.02
Geographical origin		
Native cases	202,129	80.6
Cases of foreign origin	37,471	14.9
Unknown	11,254	4.5
HIV status		
Positive	623	0.3
Negative	14,889	5.9
Unknown	235,342	93.8
Multidrug-resistance		
No	125,880	50.2
Yes	3,597	1.4
Unknown	121,377	48.4
EU/EEA countries		
Countries with low TB incidence rate[b]	82,711	33.0
Countries with high TB incidence rate[c]	168,143	67.0
Countries reporting treatment outcome for the whole study period		
Austria	4,030	1.6
Belgium	4,922	2.0
Czech Republic	4,911	2.0
Denmark	1,928	0.8
Estonia	2,771	1.1
Germany	24,195	9.7
Hungary	6,347	2.5
Ireland	1,704	0.7
Iceland	50	0.02
Latvia	7,727	3.1
Malta	91	0.1
The Netherlands	5,205	2.1

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

[a] Including 18 countries that reported treatment outcome for the whole study period: Austria, Belgium, Czech Republic, Denmark, Estonia, Germany, Hungary, Ireland, Iceland, Latvia, Malta, the Netherlands, Norway, Poland, Romania, Slovenia, Slovakia and the United Kingdom.

[b] Countries with low TB incidence rate (<20,000/100,000 population) included Austria, Belgium, Czech Republic, Denmark, Germany, Hungary, Ireland, Iceland, Malta, the Netherlands, Norway, Slovenia, Slovakia and UK.

[c] Countries with high TB incidence rate (≥20,000/100,000 population) included Estonia, Latvia, Poland and Romania.

Source: The European Surveillance System (TESSy). TESSy was operational since 2008 and for data from 2002-2007 data were transferred into TESSy from the historical database of the former EuroTB project for the TB surveillance activities in Europe.

Table 2 B*

Characteristics of new pulmonary culture-positive tuberculosis cases in the EU/EEA[a], 2002–2011 (n=250,854)

Demographic and clinical features of TB cases	Number of cases (n = 250,854 cases)	Percent
Countries reporting treatment outcome for the whole study period		
Norway	1,216	0.5
Poland	44,577	17.8
Romania	113,068	45.1
Slovenia	1,679	0.7
Slovakia	2.553	1.0
UK	23,880	9.5
Treatment outcome		
Success (cured or treatment completed)	196,105	78.2
Died	16,222	6.5
Still on treatment (12 months follow-up)	5,914	2.4
Failed	5,583	2.2
Defaulted	14,392	5.7
Transferred out	2,653	1.0
Unknown outcome	9,985	4.0

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

[a] Including 18 countries that reported treatment outcome for the whole study period: Austria, Belgium, Czech Republic, Denmark, Estonia, Germany, Hungary, Ireland, Iceland, Latvia, Malta, the Netherlands, Norway, Poland, Romania, Slovenia, Slovakia and the United Kingdom.

[b] Countries with low TB incidence rate (<20,000/100,000 population) included Austria, Belgium, Czech Republic, Denmark, Germany, Hungary, Ireland, Iceland, Malta, the Netherlands, Norway, Slovenia, Slovakia and UK.

[c] Countries with high TB incidence rate (≥20,000/100,000 population) included Estonia, Latvia, Poland and Romania.

Source: The European Surveillance System (TESSy). TESSy was operational since 2008 and for data from 2002-2007 data were transferred into TESSy from the historical database of the former EuroTB project for the TB surveillance activities in Europe.

with women was mostly attributed to a higher proportion of died, failed and defaulted in men compared with women, which persisted when stratifying by reporting year, country of origin and age group (with exception among cases aged <15 years). Another study done in the EU reported also that the success rate was higher in women and this was due to a greater occurrence of defaulted and treatment failure in men [10]. A study from South Africa found that men were less likely to adhere to their treatment than women and male sex was associated with the risk of treatment interruption [14]. The poorer TO in men can be attributed to some behavioural components such as alcohol and drug abuse, which are still predominant among men. Studies done in Paris [15] and Hamburg [16] indicated that unsuccessful TB treatment was associated with alcohol and injecting drug use. A Spanish study showed that injecting drug use was associated with treatment default; while alcoholism was associated with death during TB treatment [17]. According to the European

Table 3

Factors associated with treatment outcome among new culture-confirmed pulmonary tuberculosis cases, 2002–2011 (n=250,854)

Predicting factors	Treatment success (totals)		Univariable analysis[a]		Multivariable analysis[a,b]	
	Yes	No	OR (95% CI)	p value	AOR (95% CI)	p value
Increase in age per year (continues variable)	196,895	53,959	1.02 (1.01–1.02)	<0.001	1.02 (1.02–1.02)	<0.001
Sex						
Female	67,512	14,824	1	<0.001	1	<0.001
Male	129,323	39,119	1.38 (1.27–1.49)		1.40 (1.28–1.52)	
Country of origin						
Native cases	159,617	42,512	1	0.72	1	0.03
Cases of foreign origin	29,151	8,320	1.07 (0.74–1.56)		1.32 (1.03–1.70)	
Multidrug-resistance						
No	99,666	26,214	1	<0.001	1	<0.001
Yes	1,252	2,345	7.12 (4.07–12.44)		8.7 (5.09–14.97)	
Unknown	95,977	25,400	1.00 (0.77–1.32)	0.96	1.08 (0.86–1.36)	0.51
Reporting year						
2002 to 2006	105,566	29,445	1	0.73	1	0.81
2007 to 2011	91,329	24,514	0.96 (0.77–1.19)		0.96 (0.71–1.30)	

EU: European Union; EEA: European Economic Area; MDR: multidrug-resistant; TB: tuberculosis.

[a]Univariable and multivariable analysis were performed using logistic regression models specifying that standard errors allow for intra-country correlation (controlling for clustering within countries).

[b]Tuberculosis cases with available information for all predicting factors were included in the multivariable analysis (n = 239,485/250,854).

The logistic regression models were based on 12-month outcomes for non-MDR TB cases and on 24-month outcomes for MDR-TB cases.

Source: The European Surveillance System (TESSy). TESSy was operational since 2008 and for data from 2002-2007 data were transferred into TESSy from the historical database of the former EuroTB project for the TB surveillance activities in Europe.

Monitoring Centre for Drugs and Drug Addiction, drug use and alcohol consumption are considerably more common among men than women in EU countries [18]. Biological factors may also contribute to the different TB TO between males and females. Animal models showed that male mice developed more severe TB disease, while females were more resistant and exhibit more robust immune responses to infection [19].

In our study, the proportion of cases with unsatisfactory outcomes was 8.9%; thus below the maximum proportion of 10% in the WHO/IUATLD recommendations. This threshold aims to serve National TB Programmes as an orientation to direct their efforts in improving TO [4]. Three countries: Hungary, Poland and Romania, exceeded the 10% proportion of unsatisfactory outcomes. The proportion of deaths (any cause) was on average 6.5%. A high proportion of deaths among pulmonary TB cases (10%) was also reported by Canada in 2012 [13].

An inverse relationship between treatment success rate and increasing age was observed in this study. This can be partially explained by the increasing death rate with advancing age; as a result of demographic changes with an ageing population. However, studies from high- and low-incidence countries reported that older age also increases the risk of unsuccessful TB treatment [20-22]. The elderly are at increased risk for missed diagnosis [23] due to the fact that a diagnosis of TB among the elderly is often difficult due to atypical, non-specific clinical manifestation and may be confused with other concomitant age-related diseases [24,25]. This can lead to a delayed diagnosis and more advanced disease at presentation which in turn leads to increased mortality among the elderly [24,25]. A study in Norway demonstrated that deaths occurred mainly because TB diagnosis was established too late and half of the cases were only detected at autopsy [26]. Also a study from the US found that advanced age was strongly associated with unrecognised pulmonary TB leading to premature death [27]. Therefore, a high index of suspicion for TB in the elderly is undoubtedly justifiable [23]. Most recently, the *WHO Framework towards TB elimination in low-incidence countries* highlighted the particular challenges in treating active TB in the elderly and the importance of early diagnoses among them [28]. Furthermore, screening for active TB among the elderly has been suggested by WHO depending on the local TB epidemiology and risk-benefit assessments [28]. At present in Japan, early case detection and treatment are considered as the most effective TB control measures among the elderly in order to protect them from TB death [29].

In our analysis, MDR-TB was the strongest risk factor for unsuccessful treatment and treatment success rate of MDR-TB cases at 24-month follow-up was 49.2%, far

below the 70% target, a sign of the seriousness of the MDR-TB epidemic in the EU/EEA. It is well documented that treatment failure and mortality are higher among MDR-TB cases than among susceptible cases [30,31].

Although we found only a slight difference in treatment success rate in native and foreign cases, being of foreign origin was a significant risk factor for unsuccessful TO in our analysis. Markedly, a high proportion of cases of foreign origin had unknown outcome. It is unclear to which extent this might be due to migration for medical reasons. Overall, this result suggests that programmatic issues may play a role including access to healthcare in the context of mobility e.g. patients returning to their country of origin before the treatment is completed, as was observed in a study from London [32], and challenges in cross-border collaboration. Thus, the 61st World Health Assembly in 2008 called on countries to address migrant health issues in a more integrated, harmonised approach [33]. Foreign origin may be a proxy for other unmeasured indicators related to migration. In the EU, migrants have been reported to be at risk of not receiving the same level of healthcare in the preventive, diagnostic and treatment services as the native communities [34]. This might be due to a combination of factors including legal and working status, social exclusion, substandard economic condition and barriers in accessing healthcare services [34].

Limitations

This study has a number of limitations. A considerable proportion of reported cases was without information on TO and was therefore excluded from the analysis. Following the WHO/IUATLD recommendation for TO monitoring in the EU/EEA, only new culture-confirmed pulmonary TB cases were eligible for the analysis cohort, accounting for 42% of reported cases. Furthermore, a higher treatment success rate was found among included cases compared to excluded ones. Our results thus reflect the situation of the defined cohort and might overestimate the overall treatment success rate in the EU/EEA. A possible selection bias related to reporting countries can be noticed; some countries were overrepresented in our cohort e.g. Romania accounted for 45% of the cases included. Information on drug susceptibility testing results was missing for almost half of cases, some of whom may have been MDR-TB. Due to the unavailability of cause of death information in the database, we could not distinguish between cases who died from TB or due to other causes during TB treatment. This would be of particular importance for analysing TO among the elderly. With the data currently reported to TESSy, it is not possible to investigate some factors known to be associated with TB TO such as comorbidity (like HIV infection), drug or alcohol abuse, homelessness and other socioeconomic factors. These underlying factors are important for mapping risk groups in order to improve TB prevention and access to TB services, since TB is concentrated in certain at-risk groups in most low-incidence countries [28]. Poor implementation of TB programme guidelines in some EU/EEA countries might partially account for suboptimal TO, especially among MDR-TB cases. However, the degree of implementation of guidelines within countries and the appropriateness of the guidelines are beyond the scope of this paper.

Conclusion

In conclusion, shortcomings in TO reporting remain a challenge in monitoring TB control in the EU/EEA. The treatment success rate was 78%, below the global target of 85% for the decade after 2002. Special efforts are required for patients with MDR-TB, who have particularly low treatment success rates. For elderly patients, a high index of clinical suspicion for TB is required to ensure early diagnosis and treatment of TB [24], and improve TO among them. Finally, to allow for valid monitoring at EU/EEA level, all countries should aim to report TO for all TB cases. Collecting additional variables on social determinants, alcohol and drug abuse, and co-morbidities could increase our understanding of the factors related to TB TO and support the design of appropriate interventions.

*Erratum

Table 2 had to be replaced due to technical issues on 11 December 2015.

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Conflict of interest

The authors declare that they have no competing interests.

Authors' contributions

Concept and design (BK, WH, BH, MvdW), statistical analysis (BK), interpretation of the data (BK, VH), drafting the manuscript (BK) and critical revision of the manuscript for important intellectual content (BK, WH, BH, MvdW, VH, LF). All authors read and approve the final manuscript.

References

1. World Health Organization (WHO). 44th World Health Assembly, Resolutions and Decisions. Resolution WHA44.8. Geneva: WHO; 1991. Available from: http://www.who.int/tb/publications/tbresolution_wha44_8_1991.pdf?ua=1
2. Stop TB Partnership and World Health Organization. Global Plan to Stop TB 2006-2015: Actions for Life – Towards a world free of tuberculosis. WHO/HTM/STB/2006.35. Geneva: WHO; 2006. http://www.stoptb.org/assets/documents/global/plan/globalplanfinal.pdf
3. Rieder HL, Watson JM, Raviglione MC, Forssbohm M, Migliori GB, Schwoebel V, et al. Surveillance of tuberculosis in Europe. Working Group of the World Health Organization (WHO) and the European Region of the International Union Against Tuberculosis and Lung Disease (IUATLD) for uniform reporting on tuberculosis cases. Eur Respir J. 1996;9(5):1097-104. Available from: DOI: 10.1183/09031936.96.09051097 PMID: 8793477
4. Veen J, Raviglione M, Rieder HL, Migliori GB, Graf P, Grzemska M, et al. Standardized tuberculosis treatment outcome monitoring in Europe. Recommendations of a Working Group of the World Health Organization (WHO) and the European Region of the International Union Against Tuberculosis and Lung Disease (IUATLD) for uniform reporting by cohort analysis of treatment outcome in tuberculosis patients. Eur Respir J. 1998;12(2):505-10. Available from: DOI: 10.1183/09031936.98.12020505 PMID: 9727811
5. European Centre for Disease Prevention and Control (ECDC). A Framework Action Plan to fight Tuberculosis in the EU. Stockholm: ECDC; 2008. Available from: http://ecdc.europa.eu/en/publications/Publications/0803_SPR_TB_Action_plan.pdf
6. European Centre for Disease Prevention and Control/WHO Regional Office for Europe (ECDC/WHO EURO). Tuberculosis surveillance and monitoring in Europe 2015. Stockholm: ECDC; 2015. Available from: http://ecdc.europa.eu/en/publications/Publications/tuberculosis-surveillance-monitoring-Europe-2015.pdf
7. Falzon D, Scholten J, Infuso A. Tuberculosis outcome monitoring--is it time to update European recommendations?Euro Surveill. 2006;11(3):20-5.PMID: 16567878
8. Manissero D, Hollo V, Huitric E, Kodmon C, Amato-Gauci A. Analysis of tuberculosis treatment outcomes in the European Union and European Economic Area: efforts needed towards optimal case management and control.Euro Surveill. 2010;15(11).PMID: 20338143
9. Faustini A, Hall AJ, Perucci CA. Tuberculosis treatment outcomes in Europe: a systematic review. Eur Respir J. 2005;26(3):503-10. Available from: DOI: 10.1183/09031936.05.00103504 PMID: 16135735
10. Falzon D, Le Strat Y, Belghiti F, Infuso A, Euro TB. Correspondents. Exploring the determinants of treatment success for tuberculosis cases in Europe.Int J Tuberc Lung Dis. 2005;9(11):1224-9.PMID: 16333929
11. van Hest R, Ködmön C, Verver S, Erkens CG, Straetemans M, Manissero D, et al. Tuberculosis treatment outcome monitoring in European Union countries: systematic review. Eur Respir J. 2013;41(3):635-43. Available from: DOI: 10.1183/09031936.00030612 PMID: 22790913
12. Centers for Disease Control and Prevention (CDC). Reported Tuberculosis in the United States, 2013. Atlanta: CDC; October 2014. Available from: http://www.cdc.gov/tb/statistics/reports/2013/pdf/report2013.pdf
13. Public Health Agency of Canada. Tuberculosis in Canada 2012 - Pre-Release. Ottawa (Canada): Minister of Public Works and Government Services Canada; 2014. Available from: http://www.phac-aspc.gc.ca/tbpc-latb/pubs/tbcan13pre/assets/pdf/tbcan13pre-eng.pdf
14. Connolly C, Davies GR, Wilkinson D. Who fails to complete tuberculosis treatment? Temporal trends and risk factors for treatment interruption in a community-based directly observed therapy programme in a rural district of South Africa.Int J Tuberc Lung Dis. 1999;3(12):1081-7.PMID: 10599011
15. Valin N, Hejblum G, Borget I, Mallet HP, Antoun F, Che D, et al. Management and treatment outcomes of tuberculous patients, eastern Paris, France, 2004. Int J Tuberc Lung Dis. 2009;13(7):881-7.PMID: 19555539
16. Diel R, Niemann S. Outcome of tuberculosis treatment in Hamburg: a survey, 1997-2001.Int J Tuberc Lung Dis. 2003;7(2):124-31.PMID: 12588012
17. Working Group on Completion of Tuberculosis Treatment in Spain,Caylà JA, Caminero JA, Rey R, Lara N, Vallés X, Galdós-Tangüis H. Current status of treatment completion and fatality among tuberculosis patients in Spain.Int J Tuberc Lung Dis. 2004;8(4):458-64.PMID: 15141739
18. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Selected Issue 2: A gender perspective on drug use and responding to drug problems. ISBN 92-9168-250-0. Lisbon: EMCDDA; 2006. Available from: http://www.drugs.ie/resourcesfiles/ResearchDocs/Europe/Research/2006/sel2006_2-en.pdf
19. Nhamoyebonde S, Leslie A. Biological differences between the sexes and susceptibility to tuberculosis.J Infect Dis. 2014;209(3) Suppl 3;S100-6. Available from: DOI: 10.1093/infdis/jiu147 PMID: 24966189
20. Lefebvre N, Falzon D. Risk factors for death among tuberculosis cases: analysis of European surveillance data. Eur Respir J. 2008;31(6):1256-60. Available from: DOI: 10.1183/09031936.00131107 PMID: 18515556
21. Bustamante-Montes LP, Escobar-Mesa A, Borja-Aburto VH, Gómez-Muñoz A, Becerra-Posada F. Predictors of death from pulmonary tuberculosis: the case of Veracruz, Mexico.Int J Tuberc Lung Dis. 2000;4(3):208-15.PMID: 10751065
22. Hauer B, Brodhun B, Altmann D, Fiebig L, Loddenkemper R, Haas W. Tuberculosis in the elderly in Germany. Eur Respir J. 2011;38(2):467-70. Available from: DOI: 10.1183/09031936.00199910 PMID: 21804163
23. Rajagopalan S. Tuberculosis and aging: a global health problem.Clin Infect Dis. 2001;33(7):1034-9. Available from: DOI: 10.1086/322671 PMID: 11528577
24. Packham S. Tuberculosis in the elderly.Gerontology. 2001;47(4):175-9. Available from: DOI: 10.1159/000052794 PMID: 11408720
25. Zevallos M, Justman JE. Tuberculosis in the elderly.Clin Geriatr Med. 2003;19(1):121-38. Available from: DOI: 10.1016/S0749-0690(02)00057-5 PMID: 12735118
26. Naalsund A, Heldal E, Johansen B, Kongerud J, Boe J. Deaths from pulmonary tuberculosis in a low-incidence country.J Intern Med. 1994;236(2):137-42. Available from: DOI: 10.1111/j.1365-2796.1994.tb01275.x PMID: 8046312
27. Rieder HL, Kelly GD, Bloch AB, Cauthen GM, Snider DE. Tuberculosis diagnosed at death in the United States. Chest. 1991;100(3):678-81. Available from: DOI: 10.1378/chest.100.3.678 PMID: 1889256
28. World Health Organization (WHO). Framework towards tuberculosis elimination in low-incidence countries. WHO/HTM/TB/2014.13. Geneva: WHO; 2014. Available from: http://apps.who.int/iris/bitstream/10665/132231/1/9789241507707_eng.pdf?ua=1
29. Ohmori M, Wada M, Yoshiyama T, Uchimura K. (Factors related to early case detection of tuberculosis in health service facilities for the elderly).Kekkaku. 2003;78(6):435-42.PMID: 12872702
30. Espinal MA, Kim SJ, Suarez PG, Kam KM, Khomenko AG, Migliori GB, et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. JAMA. 2000;283(19):2537-45. Available from: DOI: 10.1001/jama.283.19.2537 PMID: 10815117
31. Noeske J, Nguenko PN. Impact of resistance to anti-tuberculosis drugs on treatment outcome using World Health Organization standard regimens.Trans R Soc Trop Med Hyg. 2002;96(4):429-33. Available from: DOI: 10.1016/S0035-9203(02)90383-4 PMID: 12497982
32. Conaty SJ, Dart S, Hayward AC, Lipman MC. Reasons for low reported treatment success in notified tuberculosis patients from a London hospital according to new outcome reporting. Commun Dis Public Health. 2004;7(1):73-6.PMID: 15137286
33. World Health Organization (WHO). Resolution WHA 61.17. Health of migrants. In: Sixty-first World Health Assembly, Geneva, 19-24 May 2008. Resolutions and decisions, annexes. Geneva: WHO; 2008:2 (document WHA61/2008/REC/1). Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA61-REC1/A61_REC1-en.pdf
34. Fernandes A, Miguel JP. Health and migration in European Union: better health for all in an inclusive society. 291173/09. Lisboa. Instituto Nacional de Saúde Doutor Ricardo Jorge 2009. Available from: http://www.insa.pt/sites/INSA/Portugues/Publicacoes/Outros/Documents/Epidemiologia/HealthMigrationEU2.pdf