Risk factors for death among tuberculosis cases: analysis of European surveillance data

N. Lefebvre*,# and D. Falzon*

ABSTRACT: **The proportion of tuberculosis (TB) patients in the European Union (EU) who die remains high (8% overall). The aim of the present study was to quantify the risk of dying associated with demographic and clinical factors.**

Case-based data on 39,566 TB patients notified by 15 EU countries during 2002–2004 were analysed using logistic regression.

It was observed that advancing age and resistance to isoniazid and rifampicin were the strongest determinants of death, while male sex, European origin, pulmonary site of disease and previous anti-TB treatment were weaker predictors. Risk varied between reporting countries, presumably reflecting differences in patient profiles, reporting practices and programme effectiveness.

In conclusion, earlier suspicion, diagnosis and treatment may reduce deaths, particularly among the elderly. Special attention is needed to avert the development and transmission of multidrug-resistant tuberculosis.

KEYWORDS: Death, epidemiology, European Union, risk factors, tuberculosis

AFFILIATIONS
*EuroTB, Dept of Infectious Diseases, Institut de Veille Sanitaire, Saint-Maurice, and
#Dept of Infectious Diseases and Tropical Medicine, University Hospital, Strasbourg, France.

CORRESPONDENCE
D. Falzon
EuroTB
Dept of Infectious Diseases
Institut de Veille Sanitaire
12 rue du Val d'Osne
94415 Saint-Maurice Cedex
France
Fax: 33 141796802
E-mail: d.falzon@invs.sante.fr

Although tuberculosis (TB) mortality has reached very low levels in the developed world, the proportion of pulmonary TB cases who die in most countries of the European Union (EU) is one of the highest in the world [1]. The burden of TB deaths in Europe is higher than that of other key infectious diseases [2]. In certain classes of TB patients, the risk of dying could be reduced through improved care [3, 4]. Studying the determinants of death in TB patients could help both the public health worker and the clinician alike to identify vulnerable individuals and important factors warranting more targeted action. The present authors used surveillance data on recent TB notifications from 15 EU countries to quantify the risk of dying.

MATERIALS AND METHODS

European countries annually report national TB surveillance data to EuroTB, a network funded by the European Commission [5]. Of 27 EU countries, 20 countries now report outcomes, including death, as part of an anonymised individual dataset. Submission of data is based on consensus recommendations and the methodology used has been described elsewhere [6]. A case was classified as ''died'' if the first outcome observed within 12 months of case detection was death from any cause. In the present study, a previous history of TB was defined as a past episode of curative combination therapy with anti-TB drugs for $\geqslant 1$ month. Geographical origin was determined by the patient's place of birth or citizenship in three countries (Austria, Belgium and the Netherlands). Cases with both pulmonary and extrapulmonary TB were included under ''pulmonary''. Multidrug resistance (MDR) was defined as resistance to both isoniazid and rifampicin at initial drug susceptibility testing.

Deaths observed among TB patients were compared with those expected from national mortality statistics. Data for total deaths were obtained from Eurostat [7] and population statistics from the United Nations Populations Division [8].

Bivariate and multivariable analyses were restricted to culture-positive patients with complete data for plausible determinants of death available on the European dataset (sex, age, geographical origin, site of disease, previous history of TB, and drug susceptibility testing results). To enhance comparability, countries were only included if $\geqslant 50\%$ of their reported cases had been confirmed by culture and if initial drug susceptibility testing results were available for $\geqslant 80\%$ of culture-positive cases. Countries reporting <30 deaths·yr^{-1} were excluded. As the present study was carried out using routinely collected, anonymous surveillance data, ethical clearance was not deemed necessary.

The ''null hypothesis'' of no association between death and putative explanatory variables was

tested using data pooled from all countries for all 3 yrs. Bivariate analysis was employed to assess the association between death and year of report, sex, age group, region of origin, site of disease, previous history of TB, MDR and country of report, using the Chi-squared test to assess statistical significance (a p-value <0.05 was considered significant). Logistic regression was used to identify variables independently associated with risk of death. MDR was stratified by previous history of TB with a term of interaction to adjust for effect modification (no MDR; primary MDR, *i.e.* MDR without previous history of TB; and secondary MDR, *i.e.* with previous history). Results of bivariate analysis and logistic regression were reported as crude and adjusted odds ratio (OR), respectively, with 95% confidence intervals (CI).

RESULTS

In total, 15 countries (Austria, Belgium, the Czech Republic, Denmark, Estonia, Germany, Ireland, Latvia, Lithuania, the Netherlands, Portugal, Slovakia, Slovenia, Sweden and the UK) satisfied the selection criteria for the study. Deaths among TB cases reported in 2003 were compared with those expected in 13 countries with available national mortality data (table 1). While the proportion of subjects dying increased progressively with age among TB cases, the ratio of observed to expected deaths was highest in young adults.

In the period 2002–2004, 82,314 TB cases in total were notified by the 15 countries, of whom 52,479 (64%) were culture-positive and 46,151 (56%) had drug susceptibility testing results available. A total of 39,566 (48%) cases with complete data for the variables of interest were retained for the rest of the analysis (table 2). Three countries reported half of the cases: Germany (24%), the UK (15%) and Portugal (11%). One-fifth of cases were reported by the three Baltic States (Estonia, Latvia and Lithuania).

TB cases were predominantly male (65%) and the median age was 43 yrs, with 2% aged <15 yrs and 24% aged ⩾60 yrs. Most cases were European (68%), 12% were African and 6% originated from the Indian subcontinent (definitions are given in table 2). Most cases had pulmonary disease (84%) and no previous history of TB (86%). Only 5% of patients had MDR, but this proportion was higher in the Baltic States than in the other 12 countries (19.6 *versus* 1.6%, respectively; p<.001). Patients with a previous history of TB were more likely to have MDR (20.2 *versus* 2.8%; p<0.001). Overall, 3,085 (7.8%) cases

died (ranging 5–12% between countries), 29,184 (73.8%) cases completed treatment (country range 56–86%) and 7,297 (18.5%; country range 2–37%) were either lost to follow-up or failed to resolve illness.

At bivariate analysis, death was significantly associated with the following factors: male sex, age >19 yrs, pulmonary TB and a previous history of TB (table 2). MDR was associated with death and this association was nearly twice as great in cases with a previous history of TB (secondary MDR, OR 3.1) than in cases without (primary MDR, OR 1.6). The year of notification had no influence on death. The risk of death was significantly higher in nine countries compared with the Netherlands (which was used as the reference). The risk of dying was between two and five times higher in European subjects compared with cases from elsewhere. The association with smear-positive pulmonary TB was not statistically different than for smear-negative cases (data not shown). In multivariate analysis, death remained significantly associated with male sex, increasing age, European origin, pulmonary localisation and MDR, with a risk of death greater for secondary MDR (OR 3.6, 95% CI 3.0–4.3) than for primary MDR (OR 2.5, 95% CI 2.0–3.1). Two countries had ORs significantly lower than the reference country, *i.e.* Portugal and the Czech Republic.

DISCUSSION

The present analysis was based on TB surveillance data reported by 15 industrialised or fairly well-developed European countries. The data were case-based and pooled over 3 yrs. A number of demographic and clinical factors related to the risk of dying among notified TB cases were identified. The strongest independent risk factors of death were advancing age and MDR, although male sex, European ethnicity, pulmonary TB and country of report also showed significant association. Clinicians and other health professionals should be aware of these findings, which may be relevant to their practice.

A number of limitations are highlighted. When generalising findings, it should be taken into consideration that this analysis was limited to culture-positive patients with available results for drug susceptibility testing. Countries included have had drug-resistance surveillance for a number of years and their laboratories perform well on quality assurance [6]. No outcome data were available for a number of large European countries,

TABLE 1	Observed and expected deaths among tuberculosis (TB) patients in 13 European Union countries[#] in 2003				
Age group yrs	Total mortality rate[¶] ·1000^{-1}	TB cases n	Observed deaths n (%)	Expected deaths n	Observed deaths/ expected deaths
0–19	0.44	2234	17 (0.8)	0.97	17.46
20–39	0.80	10591	255 (2.4)	8.47	30.11
40–59	3.88	8819	639 (7.2)	34.25	18.66
60+	40.20	7549	1796 (23.8)	303.46	5.92
Total	10.20	29193	2707 (9.3)	347.15	7.80

[#]: Austria, the Czech Republic, Estonia, Germany, Ireland, Latvia, Lithuania, the Netherlands, Portugal, Slovakia, Slovenia, Sweden and the UK; [¶]: from Eurostat [7] and the United Nations Populations Division [8].

TABLE 2 Profile of tuberculosis (TB) cases according to vital status, and results of bivariate and multivariable analysis in the European Union (EU) during 2002–2004

Variable	Patients who died	Patients who did not die	Total subjects n	Bivariate crude OR (95% CI)	Multivariable adjusted OR (95% CI)
Total[#]	3085 (7.8)	36481 (92.2)	39566		
Year of notification					
2002	845 (8.0)	9684 (92.0)	10529	1	1
2003	1159 (8.1)	13216 (91.9)	14375	1.01 (0.92–1.10)[##]	1.02 (0.92–1.13)[##]
2004	1081 (7.4)	13581 (92.6)	14662	0.91 (0.83–1.00)[##]	0.93 (0.84–1.03)[##]
Sex					
Female	835 (6.0)	13007 (94.0)	13842	1	1
Male	2250 (8.7)	23474 (91.3)	25724	1.49 (1.38–1.62)***	1.48 (1.35–1.61)***
Age group yrs					
0–19	23 (1.1)	2133 (98.9)	2156	1	1
20–39	327 (2.2)	14864 (97.8)	15191	2.04 (1.33–3.12)***	1.88 (1.23–2.88)***
40–59	891 (7.1)	11714 (92.9)	12,605	7.05 (4.64–10.72)***	5.18 (3.40–7.88)***
60+	1844 (19.2)	7770 (80.8)	9614	22.01 (14.43–33.56)***	18.40 (12.12–27.92)***
Geographical origin					
Europe[¶]	2650 (9.9)	24086 (90.1)	26736	1	1
Balkans[+]	71 (3.9)	1772 (96.1)	1843	0.36 (0.29–0.46)***	0.46 (0.36–0.59)***
FSU	118 (5.9)	1878 (94.1)	1996	0.57 (0.47–0.69)***	0.50 (0.41–0.61)***
Indian subcontinent[§]	93 (3.8)	2332 (96.2)	2425	0.36 (0.29–0.45)***	0.61 (0.48–0.77)***
Rest of Asia[f]	34 (2.2)	1538 (97.8)	1572	0.20 (0.14–0.28)***	0.43 (0.30–0.61)***
Africa	99 (2.2)	4460 (97.8)	4559	0.20 (0.16–0.25)***	0.55 (0.44–0.68)***
America and Oceania	20 (4.6)	415 (95.4)	435	0.44 (0.28–0.69)***	0.77 (0.48–1.24)[##]
Site of disease					
Extrapulmonary alone	332 (5.3)	5940 (94.7)	6272	1	1
Pulmonary	2753 (8.3)	30541 (91.7)	33294	1.61 (1.43–1.81)***	1.42 (1.25–1.61)***
Previous history of TB[¶¶]					
No	2400 (7.0)	31697 (93.0)	34097	1	Not included[¶¶]
Yes	685 (12.5)	4784 (87.5)	5469	1.89 (1.73–2.07)***	
MDR testing results[¶¶]					
Not MDR	2759 (7.4)	34753 (92.6)	37512	1	1
Primary MDR	106 (11.2)	842 (88.8)	948	1.59 (1.29–1.95)***	2.49 (1.98–3.12)***
Secondary MDR	220 (19.9)	886 (80.1)	1106	3.13 (2.68–3.65)***	3.61 (3.02–4.32)***
Country of notification					
Austria	180 (9.4)	1725 (90.6)	1905	2.00 (1.54–2.59)***	1.25 (0.95–1.64)[##]
Belgium	137 (7.0)	1808 (93.0)	1945	1.45 (1.10–1.90)***	0.92 (0.70–1.23)[##]
Czech Republic	93 (5.7)	1536 (94.3)	1629	1.16 (0.86–1.56)[##]	0.47 (0.35–0.64)***
Denmark	58 (6.6)	827 (93.4)	885	1.34 (0.96–1.88)[##]	1.31 (0.92–1.88)[##]
Estonia	145 (10.0)	1301 (90.0)	1446	2.13 (1.63–2.80)***	1.12 (0.84–1.50)[##]
Germany	912 (9.6)	8626 (90.4)	9538	2.02 (1.62–2.52)***	1.19 (0.95–1.51)[##]
Ireland	38 (6.1)	580 (93.9)	618	1.25 (0.85–1.85)[##]	0.83 (0.55–1.24)[##]
Latvia	256 (7.2)	3277 (92.8)	3533	1.49 (1.17–1.91)***	0.85 (0.66–1.11)[##]
Lithuania	341 (11.4)	2649 (88.6)	2990	2.46 (1.94–3.13)***	1.11 (0.85–1.44)[##]
The Netherlands	93 (5.0)	1779 (95.0)	1872	1	1
Portugal	208 (4.7)	4,215 (95.3)	4423	0.94 (0.73–1.21)[##]	0.66 (0.51–0.86)***
Slovakia	151 (12.1)	1095 (87.9)	1246	2.64 (2.01–3.46)***	1.08 (0.81–1.43)[##]
Slovenia	90 (11.6)	689 (88.4)	779	2.50 (1.84–3.39)***	1.22 (0.89–1.68)[##]
Sweden	51 (7.3)	648 (92.7)	699	1.51 (1.06–2.14)*	1.18 (0.81–1.71)[##]
UK	332 (5.5)	5726 (94.5)	6058	1.11 (0.88–1.40)[##]	1.22 (0.95–1.58)[##]

Data are presented as n (%), unless otherwise indicated. OR: odds ratio; CI: confidence interval; FSU, Former Soviet Union countries (Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova Republic, Russian Federation, Tajikistan, Turkmenistan, Ukraine, Uzbekistan); MDR: multidrug resistance (resistance to at least isoniazid and rifampicin). [#]: including all culture-positive cases with results on initial susceptibility testing to isoniazid and rifampicin, and excluding cases with missing data on age, sex, country of origin and site of disease. [¶]: EU and other non-EU countries including Baltic States (Estonia, Latvia, Lithuania); [+]: Albania, Bosnia and Herzegovina, Croatia, Macedonia FYR, Montenegro, Serbia, Turkey; [§]: Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, Sri Lanka; [f]: excluding Turkey and Asian FSU countries; [##]: nonsignificant; [¶¶]: interaction between previous history of TB and MDR was taken into account by recoding MDR status in not MDR, primary MDR (without previous history of TB) and secondary MDR (with previous history). *: $p<0.05$; ***: $p<0.001$.

such as France, Italy and Spain. The immediate cause of death of TB patients was not available. Other studies have shown that this is frequently not directly related to TB [9] and may explain the differences in the likelihood of dying between countries. While 7.8% of patients died, a substantial proportion of the patients lost to follow-up or still on treatment at 12 months may also have died. Moreover, inclusion of cases detected at *post mortem* and classification of all cases dying in the outcome category ''died'', as is recommended, may vary between countries. Intercountry differences may reflect the heterogeneity of patient profiles, as well as different practices in patient recruitment, diagnostic delays, reporting complete-ness, extent of disease [10] and the specialisation of carers [3]. Nonetheless, the adjusted risk of dying was comparable between most countries, attesting, to a degree, to the validity of pooled analyses of European surveillance data.

Efforts should be made to ensure the completeness of reporting of treatment outcome among TB patients, using information from vital registration to complete reporting of deaths where possible. Information not currently available in the European dataset but which may be relevant to this type of study and to public health action could be collected in future. The contribution of HIV is important [11]. Factors, such as chronic obstructive pulmonary disease, alcohol abuse, drug use, malignancy, diabetes and tobacco smoking, which have also been described, may be relevant [9, 11–13]. The relationships observed in the present study may partly be explained by the effect of such confounders, the frequency of which is expected to vary according to age and sex. The higher risk in the elderly is partly due to increased comorbidity [4]. The association with male sex could be a consequence of repeated short treatment interruptions among males, as has been documented in different settings; better case-holding may improve outcomes [14].

The association between pulmonary TB and death is amplified by the rarity of severe forms of extrapulmonary TB in the EU. In 2005, meningitis and disseminated forms of TB represented <2% of all TB cases reported [6]. TB patients in the EU originating from high-prevalence countries were less likely to die than European patients. This ''healthy migrant effect'' has been reported elsewhere [15] and has been attributed to the better physical condition of the average foreign patient when compared with the native. However, it may also be more likely for a migrant worker with TB to be detected earlier in the course of disease as a result of active screening programmes, with consequent benefits from more timely care [16].

Finally, given the strong risk of dying with multidrug resistance, strict adherence to prescribed treatment regimens, early drug susceptibility testing and the use of adequate medication are crucial to avert the emergence and propagation of drug resistance. This is particularly relevant in the Baltic States and other countries of the former Soviet Union, where multidrug resistance is highly prevalent.

REFERENCES

1 World Health Organization. Global tuberculosis control: surveillance, planning, financing. WHO report 2007. (WHO/HTM/TB/2007.376). Geneva, WHO, 2007.

2 van Lier E, Havelaar A, Nanda A. The burden of infectious diseases in Europe: a pilot study. *Euro Surveill* 2007; 12: E3–E4.

3 Vasankari T, Holmstrom P, Ollgren J, Liippo K, Kokki M, Ruutu P. Risk factors for poor tuberculosis treatment outcome in Finland: a cohort study. *BMC Public Health* 2007; 7: 291.

4 Zevallos M, Justman JE. Tuberculosis in the elderly. *Clin Geriatr Med* 2003; 19: 121–138.

5 EuroTB. Surveillance of tuberculosis in Europe. WHO Collaborating Centre. www.eurotb.org Date last updated: February 14, 2008. Date last accessed: December 1, 2007.

6 EuroTB and the national coordinators for tuberculosis surveillance in the WHO European Region. Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2005. Saint-Maurice, Institut de Veille Sanitaire, 2007.

7 European Commission Eurostat, www.epp.eurostat.ec.europa.eu Date last accessed: December 17, 2007.

8   United Nations Population Division. Annual Population 1950–2050 (The 2006 revision). New York, United Nations, 2007.

9   Sterling TR, Zhao Z, Khan A, *et al.* Mortality in a large tuberculosis treatment trial: modifiable and non-modifiable risk factors. *Int J Tuberc Lung Dis* 2006; 10: 542–549.

10 Walpola HC, Siskind V, Patel AM, Konstantinos A, Derhy P. Tuberculosis-related deaths in Queensland, Australia, 1989–1998: characteristics and risk factors. *Int J Tuberc Lung Dis* 2003; 7: 742–750.

11 Zumla A, Malon P, Henderson J, Grange JM. Impact of HIV infection on tuberculosis. *Postgrad Med J* 2000; 76: 259–268.

12 Alisjahbana B, Sahiratmadja E, Nelwan EJ, *et al.* The effect of type 2 diabetes mellitus on the presentation and treatment response of pulmonary tuberculosis. *Clin Infect Dis* 2007; 45: 428–435.

13 Bates MN, Khalakdina A, Pai M, Chang L, Lessa F, Smith KR. Risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis. *Arch Intern Med* 2007; 167: 335–342.

14 Balasubramanian R, Garg R, Santha T, *et al.* Gender disparities in tuberculosis: report from a rural DOTS programme in south India. *Int J Tuberc Lung Dis* 2004; 8: 323–332.

15 Borgdorff MW, Veen J, Kalisvaart NA, Nagelkerke N. Mortality among tuberculosis patients in The Netherlands in the period 1993–1995. *Eur Respir J* 1998; 11: 816–820.

16 Laifer G, Widmer AF, Simcock M, *et al.* TB in a low-incidence country: differences between new immigrants, foreign-born residents and native residents. *Am J Med* 2007; 120: 350–356.