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Treatment outcomes and relapses of pulmonary tuberculosis in Lazio, Italy, 1999—2001: a six-year follow-up study

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Summary
Objectives: The aim of this study was to enhance tuberculosis (TB) treatment outcome monitoring by linking diverse surveillance systems and estimating treatment outcomes including relapse.
Methods: Tuberculosis treatment was surveyed in the Lazio region (Italy) from 1999 to 2001; a six-year follow-up of notified cases was undertaken to detect relapses. The results were analyzed as a population-based case—control study comparing each unsuccessful outcome and relapse with eligible controls.
Results: Of the 974 patients who entered the survey, 805 (82.6%) had complete treatment evaluations; 398 (49.4%) had a successful outcome, 401 (49.8%) had an unsuccessful outcome, and six developed chronic TB. Death was associated with age >64 years (OR 5.9; 95% CI 3.1—11.2), male gender (OR 2.1; 95% CI 1.0—4.4), and using second-line drugs (OR 2.3; 95% CI 1.0—5.4). Treatment failure was associated with previous treatment (OR 3.0; 95% CI 1.4—6.7) and being male, being foreign born (OR 6.6; 95% CI 2.1—21.2), receiving second-line drugs (OR 7.4; 95% CI 1.8—29.5), and receiving modified therapy (OR 5.1; 95% CI 1.7—14.9). Relapses after successful outcomes were detected in 5.5%, for which the strongest predictor was having extrapulmonary lesions (OR 22.8; 95% CI 1.8—287.3).
Conclusions: Linking our survey data to other surveillance systems improved the mortality estimates and detected a high rate of relapse. Having received previous treatment and being a foreigner were independent determinants of treatment failure, suggesting that both acquired and primary drug resistance affect TB patients in Lazio.
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Introduction

Treatment surveillance is an essential tool in the evaluation of the impact of tuberculosis (TB) control programmes,[1] especially for multi-drug resistant tuberculosis (MDR-TB).[2] Early detection and adequate treatment are the most important tools to control MDR-TB. Successful treatment interrupts the transmission of infection, which prevents additional cases of acquired MDR-TB and avoids the development of chronic or recurrent TB. MDR-TB can be either the consequence of or be caused by unsuccessful treatment, which may occur by transmission of an MDR strain of *Mycobacterium tuberculosis* or following inadequate treatment.[3–6] Both situations challenge tuberculosis control, because standardized short-course chemotherapy (SSCC) is less effective in these patients, and second-line drugs are less effective and more toxic than first-line drugs.[7]

As with other surveillance systems, validity issues may affect TB treatment surveillance, made worse by the lengthy treatment required. While many studies report results of treatment surveillance, most do not use data from other sources to test the accuracy of TB treatment outcomes. Further, most surveillance systems do not include long-term outcomes such as relapses, because the follow-up period is too short. Among those with recurrent TB, relapse represents the reactivation of a latent infection.[6,8]

This study aimed to improve the accuracy of a TB treatment survey by linking the information to other surveillance systems, to estimate TB relapses in the six years after initial notification, and to analyze risk factors for unsuccessful treatment outcomes.

Methods

We surveyed TB treatment outcomes in residents of the Lazio region of Italy (5 255 028 inhabitants), reported to the TB surveillance system for pulmonary TB, who began treatment between 1 January 1999 and 31 December 2001. Only new or relapsed cases were included. Patients infected with *Mycobacterium bovis* and *Mycobacterium avium* were excluded. Active follow-up of treatment outcomes lasted for at least 12 months after treatment began, and ended on 31 December 2002. In addition, we looked for deaths of TB patients in the regional cause-mortality register (CMR). Relapses in patients who started treatment in the period 1999–2001 were detected by linking our data with the infectious diseases notification registry (IDNR) and the hospital discharge registry (HDR). This linkage was conducted between 1 January 2000 and 31 December 2005.

TB treatment survey

All public and private hospitals and outpatient clinics in the region that had reported at least two TB cases per year participated in the survey. TB therapy units were asked to complete a form for each new or relapsed case of pulmonary TB at the beginning and end of treatment. Initial information included patient category according to World Health Organization (WHO) classification,[2,4,5,9] drugs prescribed, and length of therapy. New cases were defined as patients who had never been treated for tuberculosis for one month or more. Relapsed patients were those who had had previous successful treatment. Treatment failures were patients with a positive sputum smear at 5 months or later after the start of treatment. Defaulters were those who returned to treatment after an interruption of at least two months. Transfers-in had been transferred from one clinic to another and continued treatment without interruption.

The entire treatment history was reconstructed from the initial visit for TB to the treatment outcome reported from the last TB unit that treated the patient. Patient category was considered 'unknown' for transfers-in.

One treatment outcome was assigned to each TB case in the survey based on their last end-of-treatment form. Treatment outcome was considered unknown if the TB units did not complete the final treatment form.

Case definition

For the purposes of the case–control study, a case was defined as a new or relapsed patient diagnosed by sputum culture, smear examination for acid-fast bacilli, or X-rays, who was unsuccessfully treated in the survey. The unsuccessful outcomes were classified according to WHO protocol:[2,4,5,9] (1) death for any reason during treatment, (2) treatment failure or default, and (3) lost to follow-up. In our survey this group corresponded to patients transferred-out from one TB clinic to another to continue treatment. Since we reconstructed the entire treatment history of each patient, we know that this last group included patients who did not return to the same clinic or contact another clinic in the region to complete treatment. Cases reported in the CMR were included as fatal outcomes if death occurred within nine months of the start of therapy. Patients who re-presented with bacteriologically positive disease more than three months after a successful outcome,[2,6] who had not received treatment prior to the first notification,[10] and who were still alive 12 months after therapy started[6] were classified as relapses.

Control definition

Controls for each outcome (death, failure, lost) were selected from successfully treated TB patients or those who had a different unsuccessful outcome. Controls had to meet the same criteria as cases to be included, namely they had to be new or relapsed TB cases and residents of the region, who had started treatment in the period 1999–2001. Successful treatment was defined, as suggested by the WHO,[2,4,5,9] as having a microbiologically negative test at least two months after treatment began or at treatment completion.

Controls for relapses were patients who did not re-present with bacteriologically diagnosed TB by the end of follow-up, who had had a successful outcome, had received no prior treatment before the initial notification, and were still alive 12 months after treatment began.

Factors analyzed

The factors analyzed as possible predictors of unsuccessful outcomes or relapses were related to characteristics of the

infection or patient management. Characteristics of infection included: age, gender, foreign status (according to birth country and/or nationality), urban versus suburban residence, notification year, HIV status, patient category, previous treatment, site of the tuberculosis lesions, and results of the smear test. The factors related to patient management were: drugs, therapy length and modification, and transfer to another TB clinic during treatment. Educational level was used as an indicator of social class.

First-line drugs were classified according to the WHO protocol[1] and included isoniazid and/or rifampin and/or pyrazinamide and/or ethambutol with or without streptomycin.

Analyses

Univariate analyses compared each of the three types of unsuccessful outcomes (death, failure and defaulter, lost to follow-up) with all other patients who did not have that specific outcome, including those successfully treated and those with the other unsuccessful outcomes. Relapses were compared with patients at risk of relapse but who had not done so by the end of 2005. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. The role of each variable was explored using logistic regression, in terms of how it may have confounded or modified the effect of the foreign status on unsuccessful outcomes.

Multivariate models included all variables showing a univariate association and a level of statistical significance of 0.1 or less. The likelihood ratio test (LRT) was used to select the final models. STATA software (version 8, STATA Corp., TX, USA) was employed for the analysis.

Results

Treatment forms were completed for 789 of 974 TB patients included in the survey. Another 16 patients had therapy outcomes reported by other surveillance systems. We had complete information for 805 (82.6%) patients; six of them were later recognized as chronic TB patients on the basis of previous hospitalization history and were excluded from the analysis.

Patients included in the study ($N = 799$) were more likely to be male and to have been reported in the first year of the study. They were more likely to have positive smear tests or lesions exclusively in the respiratory tract. There were more patients with higher education included than excluded (18.0% and 9.5%), but this was not analyzed further due to the large amount of missing information (Table 1). Treatment profiles show that patients included in the study were less seriously ill. Those included were more likely to have been given first-line drugs (90.9% vs. 82.3%), been treated for six months (63.0% vs. 52.7%), and to have been transferred to outpatient clinics (9.9% vs. 4.1%).

Among the 799 patients with complete outcome information, there were 401 unsuccessfully treated cases: 55 deaths (6.9%), 16 treatment failures (2.0%), 20 defaulters (2.5%), and 310 (38.8%) transferred-out from a single unit/lost to follow-up. Twenty-three deaths (41.8%) were reported in the CMR. These patients had received different outcome classifications in the TB treatment surveillance: three had been reported as successful outcome, four as transferred-out, six as lost to follow-up, and 10 as unknown outcome. There were 398 successfully treated patients (49.8%), 179 were cured and 219 completed treatment.

Pulmonary TB cases were categorized at the beginning of treatment as new (81%), relapses (7%), or previously treated who had failed or interrupted treatment (4%); 8% of cases were transferred-in to a study clinic and their initial category could not be assessed. Treatment lasted longer than six months for 25% of patients and 9% were given second-line drugs. The majority of patients (87%) started and completed treatment at the same clinic, 10% were transferred to an outpatient clinic, and 3% to another hospital.

Twenty relapses (5.5%) occurred after successful treatment among those successfully treated for the first TB episode ($n = 360$). A mean interval of 32 months elapsed between starting therapy and the relapse (range 12—74 months).

The risk of dying during TB treatment was higher for patients aged over 64 years, males and those treated with second line drugs; foreigners had lower risk (Table 2). Failures/defaulters were more likely to have been previously treated. Males whose treatment failed were more likely to be foreigners, to have been given second-line drugs, or to have had their therapy modified, as shown in the final model (Table 3). Those lost to follow-up were more likely to be foreign-born, whereas modified treatment or being transferred to an outpatient clinic showed a protective effect for this outcome, as shown in the final model (Table 4).

Nationality was reported for 257 (95.9%) out of the 285 patients classified as foreign. Among all foreigners, patients from Southeast Asia (OR 13.62; 95% CI 1.12—94.52) and Eastern Europe (OR 7.57; 95% CI 1.75—29-56) had the highest risk of having a negative outcome.

TB relapses were more frequent among patients aged 35—64 years (50%) and males (70%). After adjusting for other variables, the risk of relapse was even higher for patients who had extrapulmonary lesions. Those who had been treated for more than six months and those who had modified the treatment were at higher risk of relapse, though the results were not statistically significant (Table 5).

Discussion

Links with other surveillance systems

The use of record-linkage to the cause-mortality register allowed us to detect 23 more deaths than reported to the TB treatment surveillance. Among these, 10 were excluded because TB treatment forms were not completed and the outcome was unknown; another ten were classified in the surveillance as transfer-out or lost to follow-up. The record-linkage to the hospital discharge register identified six chronic TB cases that had to be excluded from the TB treatment surveillance. These results give an estimate of the possible misclassification of incident TB cases and suggest that incomplete treatment surveillance may be due to patient death.

Routinely linking different systems is an unlikely solution to improve TB treatment surveillance, but these procedures

Table 1 Cases of pulmonary TB included and not included in the case–control study by demographic and clinical factors; Lazio, 1999–2001

Factors	Cases						
	Entered survey (*N* = 968)		With known outcome (*N* = 799)		With unknown outcome (*N* = 169)		
	n	%	*n*	%	*n*	%	*p*-Value[a]
Age (years)							0.43
<14	31	3.2	22	2.8	9	5.3	
15–34	356	36.8	296	37.0	60	35.5	
35–64	402	41.5	331	41.4	71	42.0	
65+	176	18.2	148	18.5	28	16.6	
MI[b]	3	0.3	2	0.3	1	0.6	
Gender							**0.002**
M	614	63.4	516	64.6	98	58.0	
F	315	32.5	259	32.4	56	33.1	
MI[b]	39	4.0	24	3.0	15	8.9	
Foreign status							0.03
No	608	62.8	514	64.3	94	55.6	
Yes	360	37.2	285	35.7	75	44.4	
MI[b]	0						
Residence							0.02
Rome	562	58.1	480	60.1	82	48.5	
Other cities/towns	375	38.7	295	36.9	80	47.3	
MI[b]	31	3.2	24	3.0	7	4.1	
Notification year							**0.001**
1999	378	39.0	336	42.1	42	24.9	
2000	307	31.7	220	27.5	87	51.5	
2001	283	29.2	243	30.4	40	23.7	
Previous treatment							0.74
No	785	81.1	645	80.7	140	82.8	
Yes	100	10.3	83	10.4	17	10.1	
MI[b]	83	8.6	71	8.9	12	7.1	
HIV status							0.33
Positive	21	2.2	19	2.4	2	1.2	
Negative[c]	947	97.8	780	97.6	167	98.8	
TB site							**0.001**
Pulmonary	724	74.8	630	78.8	94	55.6	
Pulm.+ extrapulm.	47	4.9	37	4.6	10	5.9	
MI[b]	197	20.4	132	16.5	65	38.5	
Smear							**0.001**
Positive	580	59.9	508	63.6	72	42.6	
Negative[c]	189	19.5	157	19.6	32	18.9	
MI[b]	199	20.6	134	16.8	65	38.5	
Education (years)							**0.001**
1–8	349	36.1	312	39.0	37	21.9	
9–17	160	16.5	144	18.0	16	9.5	
MI[b]	459	47.4	343	42.9	116	68.6	

[a] *p*-Value has been tested by comparing the distribution of not included cases who did not start therapy and who did not finish the survey to that of included cases separately.
[b] Missing information.
[c] Including 'not known' results.

Table 2 Risk of dying during treatment of TB pulmonary; Lazio, 1999–2001

Factors	Death		Crude		Adjusted	
	Yes (*N* = 55)	No (*N* = 744)	OR	95% CI	OR	95% CI
Age (years)						
<65	21	606	1			
65+	34	114	**8.61**	**4.82–15.37**	**5.92**	**3.14–11.19**
MI[a]	0	24				
Gender						
F	12	247	1			
M	43	473	1.87	0.97–3.61	2.06	0.98–4.36
MI[a]	0	24				
Foreign status						
No	52	462	1			
Yes	3	282	**0.09**	**0.03–0.31**	**0.16**	**0.04–0.72**
MI[a]	0	0				
Residence						
Rome	30	450	1			
Other towns	24	271	1.33	0.76–2.32		
MI[a]	1	23				
Previous treatment						
No	43	602	1			
Yes	10	73	1.92	0.92–3.98	1.28	0.55–2.98
MI[a]	2	69				
HIV status						
No[b]	55	725	1			
Yes	0	19	NC			
Smear						
Negative[c]	7	150	1			
Positive	37	471	1.68	0.74–3.85		
MI[a]	11	123				
Prescribed drugs						
First line	44	682	1			
Second line	11	62	**2.75**	**1.32–5.59**	**2.34**	**1.02–5.37**
MI[a]	0	0				
Length of therapy						
6 months	32	471	1			
≥7 months	13	183	1.04	0.54–2.04		
MI[a]	10	90				
Modified therapy						
No	19	333	1			
Yes	5	137	0.64	0.23–1.75		
MI[a]	31	274				
Transferred to:						
No other clinic	54	642	1			
Out-patient clinic	0	79	NC			
Another hospital	1	20	0.59	0.08–4.51		
MI[a]	0	3				

NC = not computable.
[a] Missing information.
[b] Including 'not known' results.
[c] Case confirmed only by X-ray test or by tuberculin test or with 'not known' smear result.

Table 3 Risk of failure or defaulter therapy for TB pulmonary cases; Lazio, 1999–2001

Factors	Failure or defaulter				Females		Males	
	Yes (*N* = 36)	No (*N* = 763)	OR	95% CI	Adj. OR	95% CI	Adj. OR	95% CI
Age[a] (years)								
35–64	31	596	1					
65+	5	143	0.67	0.24–1.76				
MI[b]	0	24						
Gender								
F	9	250	1					
M	27	489	1.53	0.71–3.31				
MI[b]	0	24						
Foreign status								
No	19	495	1					
Yes	17	268	1.65	0.31–1.19	0.69	0.06–7.55	**6.63**	**2.08–21.16**
MI[b]	0	0						
Residence								
Rome	25	455	1					
Other towns	10	285	0.64	0.30–1.35				
MI[b]	1	23						
Previous treatment								
No	25	620	1					
Yes	9	74	**3.01**	**1.36–6.71**	2.43	0.19–30.84	1.09	0.27–4.34
MI[b]	2	69						
HIV status								
No[c]	36	750	1					
Yes	0	19	NC					
Smear								
Negative[d]	4	153	1					
Positive	27	481	2.15	0.74–6.23				
MI[b]	5	129						
Prescribed drugs								
First line	25	701	1					
Second line	11	62	**4.97**	**2.34–10.59**	4.05	0.29–55.92	**7.37**	**1.84–29.45**
MI[b]	0	0						
Length of therapy								
6 months	26	477	1					
≥7 months	7	189	0.68	0.29–1.59				
MI[b]	3	97						
Modified therapy								
No	9	343	1					
Yes	14	128	4.17	1.76–9.87	1.46	0.16–13.37	**5.07**	**1.72–14.94**
MI[b]	13	292						
Transferred to:								
No other clinic	30	666	1					
Out-patient clinic	4	75	1.18	0.41–3.45				
Another hospital	2	19	2.34	0.52–10.50				
MI[b]	0	3						

NC = not computable.

[a] Odds ratios of dying were calculated for cases aged 65+ years vs. those aged 35–64 years because there were no TB cases younger than 35 years.

[b] Missing information.

[c] Including 'not known' results.

[d] Case confirmed only by X-ray test or by tuberculin test or with 'not known' smear result.

Table 4 Risk of being lost to therapy follow-up for TB pulmonary cases; Lazio, 1999–2001

Factors	Lost to follow-up		Crude OR	95% CI	Adj. OR	95% CI
	Yes (*N* = 310)	No (*N* = 489)				
Age[a] (years)						
0–14	4	18	1			
15–34	132	164	**3.62**	**1.20–10.96**		
35–64	134	197	**3.06**	**1.01–9.25**		
65+	39	109	1.61	0.51–5.05	0.85	0.46–1.59
MI[b]	1	1				
Gender						
F	94	165	1			
M	200	316	1.11	0.82–1.51	1.46	0.89–2.38
MI[b]	16	8				
Foreign status						
No	160	354	1			
Yes	150	135	**2.45**	**1.82–3.31**	**3.48**	**2.11–5.74**
MI[b]	0	0				
Residence						
Rome	198	282	1			
Other towns	101	194	0.74	0.55–1.00		
MI[b]	11	13				
Previous treatment						
No	260	385	1			
Yes	28	55	0.75	0.47–1.22		
MI[b]	22	49				
HIV status						
No[c]	301	479	1			
Yes	9	10	1.43	0.58–3.57		
Smear						
Negative[d]	63	94	1			
Positive	198	310	0.95	0.66–1.37		
MI[b]	49	85				
Prescribed drugs						
First line	286	440	1			
Second line	24	49	0.75	0.45–1.26		
MI[b]	0	0				
Length of therapy						
6 months	189	314	1			
≥7 months	61	135	0.75	0.53–1.07		
MI[b]	60	40				
Modified therapy						
No	140	212	1			
Yes	14	128	**0.17**	**0.09–0.30**	**0.17**	**0.09–0.32**
MI[b]	156	155				
Transferred to:						
No other clinic	299	397	1			
Out-patient clinic	1	78	**0.02**	**0.002–0.12**	**0.02**	**0.003–0.1**
Another hospital	8	13	0.82	0.33–2.00	1.06	0.32–3.57
MI[b]	2	1				

[a] Adjusted odds ratios were calculated for cases aged 65+ years vs. those aged 0–64 years.
[b] Missing information.
[c] Including 'not known' results.
[d] Case confirmed only by X-ray test or by tuberculin test or with 'not known' smear result.

Table 5 Risk of relapsing for TB pulmonary cases in treatment surveillance; Lazio, 1999–2001

Factors	Relapse		Crude OR	95% CI	Adj. OR	95% CI
	Yes (*N* = 20)	No (*N* = 340)				
Age[a] (years)						
0–14	1	17	1			
15–34	7	132	0.90	0.10–7.78		
35–64	10	132	1.29	0.16–10.69		
65+	2	58	0.59	0.05–6.87		
MI[b]	0	1				
Gender						
F	6	126	1			
M	14	206	1.43	0.53–3.81	1.98	0.30–12.83
MI[b]	0	8				
Foreign status						
No	15	241	1			
Yes	5	99	0.81	0.29–2.29	0.14	0.01–1.83
MI[b]	0	0				
Residence						
Rome	14	195	1			
Other towns	5	137	0.51	0.18–1.44	0.16	0.02–1.60
MI[b]	1	8				
HIV status						
No[c]	20	330	1			
Yes	0	10	NC			
TB site						
Pulmonary	14	271	1			
Pulm. + extrapulm.	3	12	4.84	1.22–19.13	**22.84**	**1.82–287.3**
MI[b]	3	57				
Smear						
Negative[d]	4	76	1			
Positive	13	205	1.20	0.38–3.81		
MI[b]	3	59				
Prescribed drugs						
First line	20	319	1			
Second line	0	21	NC			
MI[b]	0	0				
Length of therapy						
6 months	11	228	1			
≥7 months	6	89	1.49	0.57–3.92	**5.46**	**0.71–41.74**
MI[b]	3	23				
Modified therapy						
No	5	168	1			
Yes	7	85	2.77	0.85–8.98	**4.54**	**0.61–33.61**
MI[b]	8	87				
Transferred to:						
No other clinic	16	268	1			
Out-patient clinic	3	63	0.80	0.23–2.82		
Another hospital	0	9	NC			
MI[b]	1	0				

NC = not computable.
[a] Adjusted odds ratios were calculated for cases aged 65+ years vs. those aged 0–64 years.
[b] Missing information.
[c] Including 'not known' results.
[d] Case confirmed only by X-ray test or by tuberculin test or with 'not known' smear result.

could be carried out from time to time for patients with no information on treatment outcome.

The unknown TB treatment outcomes

Up until 2000, patients lost to follow-up and transferred-out were not usually included in analyses of unsuccessful treatment.[11–14] However, other authors classify these outcomes as treatment interruption.[15–17] There is a large range in the estimates of patients lost to follow-up in the literature: in some countries values of 20–24% have been reported,[18–20] while in others the estimates are 4–8%,[13,21] suggesting possible differences in interpreting the WHO definitions. Modifications were introduced in 2001 in the WHO European region to overcome this problem, and countries were requested to monitor cases with unknown treatment history.[5,22]

We included both transfer-out and lost to follow-up in our survey and analyzed them together because our hypothesis was that both groups were less likely to complete therapy. A recent paper that tracked the modifications introduced in Europe in 2001 strengthens this belief, showing that 'defaulted and transferred' were applied interchangeably with 'unknown' outcomes.[22]

On the other hand, monitoring unknown outcomes is not easy due to a lack of treatment information. We decided to exclude from the analysis those patients for whom only the first form was completed when there was no more information from other sources, but to include patients who had later information reported by the TB unit with outcomes such as transferred or lost to follow-up. Although these outcomes do not allow a final judgment on the entire course of treatment, they do provide more information about the first months of treatment.

Factors associated with unsuccessful treatment outcomes

Death

Age was the strongest factor associated with death during treatment. More fatal outcomes were reported in Europe (5.8%) than in other parts of the world in 2000.[23] In our study, patients born in Italy made up 94% of the fatalities, possibly explained by their older age (mean 64.6 years vs. 45.4 years among foreigners who died). None of the patients who died were known to be HIV positive.

The higher risk of death for patients treated with second-line drugs (20% of those who died vs. 9% of those who survived) is coherent with the known higher toxicity these drugs have compared with first-line drugs,[7] and suggests the patients were drug resistant.

Failures and defaulters

We included in this group those patients still in treatment at the end of the six or nine months of standard course. The surveillance system changed in 2001 and these patients were defined with an independent outcome, but previously they had been classified as 'not evaluated by the end of the follow-up' and the outcomes were considered unknown.[22] Our study was inspired by the 1998 European WHO recommendations that suggested reporting the outcome as failure when the patient was still in treatment after six/nine months of treatment, and attributing the category already treated to continue his/her treatment surveillance in this case.

The strength of the association between treatment failure and second-line drugs in both female and male patients suggests that MDR-TB is the cause. Previous treatment is a clear predictor of an unsuccessful outcome.[11,24] However, we observed that previous treatment was weakly associated with failure, and was observed only in female patients, while being a foreigner and receiving second-line drugs were the most important predictors of treatment failure in males. One possible interpretation of these results is that males born abroad have primary multi-drug resistance. The highest risk of failure was observed in patients from Eastern Europe and Southeast Asia, which is consistent with this hypothesis. Although no differences were found between drugs prescribed to non-Italians and Italians, other aspects of treatment that were not analyzed here[3,12,16,25,26] could have made treatment inadequate in foreign-born patients.

A misclassification of previous treatment could also have contributed to these results. Illegal immigrants are more likely to deny previous treatment,[27] and we observed a higher risk of failure for foreign-born males, who more frequently than females are illegal immigrants.

Loss to follow-up and transfer-out

The similar risk profiles observed in our study for both those lost to follow-up and transfer-outs support the hypothesis that the problems they faced were linked to patient management.

The protective effect of outpatient clinic transfer and modification of therapy suggests treatment retention, although the conclusion should be made with caution because the result may be due to reverse causation, i.e., patients who are less seriously ill are more likely to complete treatment.

Relapse

Recurrent TB was considered relapse because information on DNA fingerprints of the *M. tuberculosis* isolates was not available. The absence of HIV-positive patients in this group supports the relapse hypothesis. The percentages of relapses observed in the study population (7%) and observed in the follow-up period amongst new TB cases (5.5%) are higher than those reported by WHO for Europe in 2003 (4%),[23] but consistent with the results of other trials.[10] Higher estimates of relapses (12% and 36%) have been reported in areas with high drug resistance.[28,29] The high risk of relapse for patients with extrapulmonary lesions has not been previously reported,[30] and we are not able to explain this result. The period of 3–6 months after treatment ended that we used as the shortest interval to define a relapse is usually adopted in successfully treated patients.[6,10,29] Follow-ups of six years have been increasingly adopted,[31] probably because of data availability.

Limitations of the study

The most important limitation of this study is a possible selection bias due to the exclusion of those patients who did not have any outcome information, which could have prevented comparisons of important patient and treatment

characteristics. Patients included did not differ for being a foreigner, the factor in which we were most interested, or for previous treatment. However, the generalizability of the results may be affected by gender and severity of illness.

A second important limitation is the absence of data on drug resistance that prevents us directly estimating its impact on failure and relapse.

A national study project on TB treatment outcome in HIV positive patients began in 2000, which may have reduced compliance with the regional survey for these patients in the second year of our study. The decrease over time in information reported also suggests other reasons for poor compliance, including difficulties in sustaining reporting over a long time.

Conclusions

Linking TB outcomes with data from other surveillance systems markedly improved the mortality estimates and allowed us to detect recurrent cases of the disease. The ability to accurately detect recurrent disease is a valuable addition to current surveillance systems as an evaluation tool for TB control programs.

Previous treatment and foreign status were independent determinants of failure and default, and suggest the coexistence of both acquired and primary drug resistance in our region. Some factors linked to patient management emerged as risk factors for being lost to follow-up, suggesting difficulties in access to health services for foreign-born patients.

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