Delay in diagnosis of pulmonary tuberculosis: a survey in the Lazio region, Italy

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ABSTRACT

BACKGROUND: To estimate patient and health care delays in the ,diagnosis of pulmonary tuberculosis (PTB) and evaluate associated factors.

METHODS: PTB incident cases ≥18 years diagnosed between September 2010 and September 2011 in the Lazio region; information on symptoms,date of onset, health professional contacts, diagnostic exams performed and drugs prescribed before diagnosis were collected through a standardized questionnaire. The total delay (TD) was divided into patient delay (PD: from onset of symptoms to first contact with healthcare services) and health system delay (HSD: from first contact to diagnosis).

RESULTS: Two hundred seventy-eight cases were evaluated. Median PD,HSD and TD were 31, 15 and 77.5 days, respectively. The median PD, HSD and TD were significantly lower in foreign-born patients (26, 10.5 and 63.5 vs. 45, 36 and 100 days, respectively). Other factors independently associated with longer delay were: absence of fever and presence of weight loss for PD; prior unspecific treatment, absence of cough, consultation with a general practitioner, visit atan outpatient clinic and a PD <30 days for HSD.

CONCLUSIONS: In Italy, the delay ofTB diagnosis is similar to that estimated in other European countries. Results indicate that actions aimed to reduce diagnostic delay should be primarily addressed to Italian patients.

Key words: Pulmonary TB; immigration; Italy; patient delay; health service delay

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DOI: ***10.2427/10214***
Accepted on October 2, 2014

INTRODUCTION

An effective tuberculosis (TB) control program requires both early diagnosis and immediate initiation of treatment, also in low endemic areas [1]. This is essential to stop transmission within the community with benefits both at the individual level, improving

the patient's prognosis, and at a public health level, reducing the risk of secondary TB cases. Notably, patients become more contagious as the delay in diagnosis of TB progresses, and the longest delays are associated with the highest mycobacterial load on sputum smears [2].

Since 1950, a dramatic decline in the incidence of TB has been observed in Italy as well as in most industrialized countries; however, TB incidence has been quite stable in the last twenty years and an increase in the proportion of cases in people born abroad has been recorded [3]. A similar trend has been observed in the Lazio region, central Italy, where in 2003, the incidence was 11/100,000, higher than the cut-off level of 10/100,000 considered for defining a low-incidence country [4]. Thus, this disease remains an important challenge to healthcare services in this country.

Ideally, TB should be diagnosed within one month ofonset of symptoms. International standards state that TB should be suspected in any person with an unexplained cough for 2-3 weeks [5].

However, there is evidence that also in resource-rich countries, the time from symptoms onset of symptoms to diagnosis of TB is often much longer [1, 6] and it has been suggested that as TB declines as a major health threat, the awareness of both the physicians and the general population maydecrease, leading to prolonged delays in diagnosis and treatment [7].

A study performed in northern Italy [8] suggested that diagnostic delay may also be a significant problem in our country. In particular, diagnostic delay appears to have contributed to cause outbreaks in schools and in hospitals [9-11].

Our objective was to further contribute to evaluating the magnitude of this problem and its possible determinants, thus we studied the pulmonary TB cases diagnosed in the Lazio region.

METHODS

Lazio region (central Italy) had around 5,680,000 inhabitants in 2010 (www.demo.istat.it), with more than three million people living in the metropolitan area of Rome. Similarly to all Italian regions, it provides its citizens with a universal coverage of costs for health care.

We performed a cross-sectional survey including all incident pulmonary TB (PTB) cases diagnosed in the health services of the Lazio region (central Italy) in the period from September 2010 – September 2011. Before the study started, preliminary meetings with all hospital infectious diseases departments and the infectious diseases departments of the local health units (LHU) wereheld. In these meetings, clinicians and LHU operators were invited to collect the supplementary data required together with the case report forms usually filled in for surveillance reporting. Data were collected by patient interviews and consulting clinical records. Information was collected on: 1) presence and dates of onset of symptoms that could be associated with the suspicion of tuberculosis (i.e. cough, haemoptysis, fever, night sweats, chest pain, unintentional weight loss, loss of appetite, fatigue), date of first contact with health service structures (i.e. general practitioner, emergency departments, outpatient clinics, hospitals), presence of some comorbidities (i.e. diabetes, cancer, HIV), diagnostic exams performed (i.e. x-ray, CT scan, bronchoscopy, standard haematologic tests, echography, sputum microscopic examinations) and drugs prescribed (e.g. antibiotics) in the period between the onset of symptoms and diagnosis. Information was also retrieved from clinical notes and case notification forms. Only extra-PTB cases and relapses were excluded from the survey.

Approval for the study was obtained from the Ethics Committees of the participating institutions. All included patients provided written informed consent.

Statistical analysis

In accordance with previous studies [8, 12-14], we evaluated: "patient delay" (PD), i.e. the time from onset of the first symptom(s), possibly related to PTB, to the first contact with any type of healthcare service (formal or informal); "health system delay" (HSD), i.e. the time from patient's first contact with healthcare services to the date of diagnosis or the date of the start of treatment, whichever date came first. The total delay (TD) was defined as the sum of the PD and of HSD.

According to Gagliotti et al. [8], a long PD was defined as >1 month, while a long HSD was defined as a period exceeding the median HSD observed in the study population (i.e. 15 days).

The association of long PD and long HSD was initially evaluated using descriptive statistics such as median and interquartile range (IQR) for continuous variables, and contingency tables for categorical variables. To evaluate the characteristics independently associated with long PD and long HSD, multiple logistic models were applied. The final model was based on the selection of those variables that were associated with a p-value <0.20 at the univariate analysis; among these variables, a further selection was madeusing a backward selection based on the log-likelihood ratio test [15].

Data were analysed using Stata software (Stata Corp, College Station, TX, USA), release 11.0.

RESULTS

Table 1 shows some characteristics of the 278 cases included stratified by place of birth. One hundred eighty-two (65.5%) of them were born abroad in highly endemic countries, particularly in Romania (94, 33.8%) Overall, the median age was 36.1 years. Foreign-born patients were younger than those born in Italy (median age 33.9 vs. 51.6 years). More than half of the patients were males (58.6%); however, females were prevalent among the cases born in Italy (54.2%). Only a low percentage of cases also had an extra-pulmonary form (overall 5.0%). Around 20% of cases received an unspecific treatment (mainly antibiotics) before diagnosis; this happened more frequently among cases born in Italy. Regarding the healthcare provider consulted before diagnosis, the general practitioner was seen by around 45% of cases with a slightly higher percentage for patients born in Italy; foreign-born cases went more frequently to the emergency departments, while those born in Italy consulted the outpatient service more frequently. Around 65% of cases consulted only one healthcare provider and around 6% consulted three or more of those (data not shown).

The median PD was 31 days in the whole population, beinglonger among Italian patients compared to foreign-born patients (45 vs. 26 days) (Table 1). Overall, a PD>30 days was observed in 50.4% of the patients; when stratifying by birthplace, this percentage was 59.4% among cases born in Italy and 45.6% among those born abroad.

Overall, the median HSD was 15 days: 36 and 10.5 days in the Italians and foreign-born patients, respectively. A HSD>15 days was observed in 49.6% of the whole population, with a higher percentage among Italians (64,6%) than foreign-born people (41.8%).

The median TD was 77.5 days in the whole population, 100 and 63.5 days in patients born in Italy and foreign-born patients, respectively. A TD ≥100 days was reported in 38.1% of the study population (50.0% and 32.4% in patients born in Italy and foreign-born patients, respectively).

It is worthy of note that 148 (53%) smear-positive TB patients had a median TD of 77.5 days, similar to that observed in smear-negative patients (data not shown).

Table 2 shows the frequency and percentage of patients with a long PD, stratified by several patient characteristics. The estimated adjusted odds ratios (AOR) calculated with a multiple logistic regression model are also reported in the table. Overall, a long PD was observed in 50.4% of the study population, with a higher percentage among Italians (59.4% vs. 45.6%, P=0.03). The percentage of a long PD increased in patients aged >35 years, particularly among those aged >50 years; however, the association was not statistically significant. Neither sex, nor the localization site of TB resulted significantly associated with long PD. Among symptoms, absence of fever and presence of unintentional weight loss, loss of appetite and fatigue were associated with along PD at the univariate analysis. When performing the multiple logistic model, only three variables were included in the final model: being born in Italy (AOR=2.28, 95%CI: 1.33-3.91), absence of fever (AOR=1.88, 95%CI: 1.13-3.14) and presence of unintentional weight loss (AOR=3.39, 95% CI: 1.93-5.94), which independently increased the odds of having a long PD. Age, loss of appetite and fatigue, which were no longer associated with a long PD when simultaneously adjusting for the other characteristics of the patients, were then excluded from the final model.

Table 3 shows the frequency and percentage of HSD>15 days stratified by several patient characteristics and the estimated AOR of factors which were independently associated with this outcome. As for PD, patients with HSD>15 days were significantly more prevalent among those cases born in Italy than in those born abroad. Regarding sex, HSD >15 days was significantly more frequent among females. Patients who

TABLE 1

CHARACTERISTICS OF THE PULMONARY TB CASES INCLUDED IN THE STUDY FROM SEPTEMBER 2010 - SEPTEMBER 2011; LAZIO REGION, ITALY

	BIRTHPLACE					
	ITALY		ABROAD		TOTAL	
MEDIAN AGE (IQR)	51.6	(34-69)	33.9	(26-42)	36.1	(28-51)
SEX, N (COLUMN %)						
MALE	44	(45.8%)	119	(65.8%)	163	(58.6%)
FEMALE	52	(54.2%)	62	(34.1%)	114	(41.0%)
NOT INDICATED	0	(0.0%)	1	(0.1%)	1	(0.4%)
SITE OF THE DISEASE, N (COLUMN %)						
ONLY PULMONARY	89	(92.7%)	175	(96.2%)	264	(95.0%)
PULMONARY & EXTRA-PULMONARY	7	(7.3%)	7	(3.8%)	14	(5.0%)
PRIOR TREATMENT BEFORE DIAGNOSIS						
ANTIBIOTICS	22	(22.9%)	28	(15.4%)	50	(18.0%)
NONE	71	(74.0%)	151	(83.0%)	222	(79.9%)
OTHER	3	(3.1%)	3	(1.6%)	6	(2.2%)
HEALTH PROVIDER CONSULTED BEFORE DIAGNOSIS						
GENERAL PRACTITIONER	46	(47.9%)	78	(42.9%)	124	(44.6%)
OUTPATIENT CLINIC	40	(41.7%)	36	(19.8%)	76	(27.3%)
EMERGENCY SERVICE	23	(24.0%)	101	(55.5%)	124	(44.6%)
NON-CONVENTIONAL HEALTH SERVICE	1	(1.0%)	7	(3.8%)	8	(2.9%)
HOSPITAL	23	(24.6%)	38	(20.9%)	61	(21.9%)
PATIENT DELAY						
MEDIAN DAYS (IQR)	45	(15-88)	26	(14-75)	31	(15-78)
LONG PATIENT DELAY (>30 DAYS)						
YES	57	(59.4%)	83	(45.6%)	140	(50.4%)
NO	39	(39.6%)	99	(54.4%)	138	(49.6%)
HEALTH SYSTEM DELAY						
MEDIAN DAYS (IQR)	36	(9-82.5)	10.5	(3-38)	15	(4-58)
LONG HEALTH SYSTEM DELAY (>15 DAYS)						
YES	62	(64.6%)	76	(41.8%)	138	(49.6%)
NO	34	(35.4%)	106	(58.2%)	140	(50.4%)
TOTAL DELAY						
MEDIAN DAYS (IQR)	100	(55.5-152)	63.5	(32-117)	77.5	(40-123)
TOTAL, N (ROW %)	96	(34.5%)	182	(65.5%)	278	

received prior non-specific treatments reported more frequently a HSD significantly longer than 15 days. Regarding symptoms, in general their presence (except for chest pain) occurred more frequently in patients reporting shorter HSDs; however, none of them were significantly (i.e. with $p<0.05$) associated with the outcome. Patients consulting a general practitioner and those visiting an outpatient clinic presented a significantly higher percentage of HSD>15

TABLE 2

ASSOCIATION OF SEVERAL CHARACTERISTICS WITH A PATIENT DELAY (PD) >30 DAYS

		PD >30 DAYS		TOTAL	P-VALUE	AOR*	95% CI		P-VALUE
		N	%						
BIRTHPLACE	Italy	57	59.4	96	0.03	2.28	1.33	3.91	<0.01
	Abroad	83	45.6	182		1.00			
AGE	≤25	24	43.6	55	0.06	NI			
	26-35	30	40.5	74					
	36-50	43	55.8	77					
	>50	42	60.0	70					
SEX	Male	86	52.8	163	0.41	NI			
	Female	54	47.4	114					
	Not indicated	0	0.0	1					
SITE OF TB	Only pulmonary (PTB)	134	50.8	264	0.56	NI			
	PTB + extra PTB	6	42.9	14					
COUGH	No	36	46.2	78	0.38	NI			
	Yes	104	52.0	200					
HAEMOPTYSIS	No	112	51.4	218	0.52	NI			
	Yes	28	46.7	60					
FEVER	No	79	55.2	143	0.09	1.88	1.13	3.14	0.02
	Yes	61	45.2	135		1.00			
NIGHT SWEATS	No	105	49.8	211	0.72	NI			
	Yes	35	52.2	67					
CHEST PAIN	No	103	48.8	211	0.36	NI			
	Yes	37	55.2	67					
UNINTENTIONAL WEIGHT LOSS	No	79	43.2	183	0.01	1.00			
	Yes	61	64.2	95		3.39	1.93	5.94	<0.01
LOSS OF APPETITE	No	101	47.0	215	0.04	NI			
	Yes	39	61.9	63					
FATIGUE	No	93	46.5	200	0.04	NI			
	Yes	47	60.3	78					
DISPNEA	No	131	50.6	259	0.79	NI			
	Yes	9	47.4	19					
RESPIRATORY SYMPTOMS	No	24	49.0	49	0.83	NI			
	Yes	116	50.7	229					
NON-RESPIRATORY SYMPTOMS	No	36	45.0	80	0.26	NI			
	Yes	104	52.5	198					

*From a multiple logistic model; variables included in the final model were initially selected among those with a p-value <0.20 at the univariate analysis; further selections were madeat each step bybackward selection excluding those with the highest p-value>0.20; NI: not included in the final model.

TABLE 3

ASSOCIATION OF SEVERAL CHARACTERISTICS WITH A HEALTH SYSTEM DELAY (HSD) >15 DAYS

		HSD >15 DAYS		TOTAL	P-VALUE	AOR*	95% CI		P-VALUE
		N	%						
BIRTHPLACE	Italy	62	64.6	96	<0.01	2.03	1.04	3.95	0.04
	Abroad	76	41.8	182		1.00			
SEX	Male	70	42.9	163	0.01	NI			
	Female	68	59.6	114					
	Not indicated	0	0.0	1					
AGE	≤25	29	52.7	55	0.53	NI			
	26-35	34	45.9	74					
	36-50	35	45.5	77					
	>50	39	55.7	70					
SITE OF TB	Only pulmonary (PTB)	130	49.2	264	0.56	NI			
	PTB + extraPTB	8	57.1	14					
PREVIOUS UNSPECIFIC	No	92	41.4	222	<0.01	1.00			
TREATMENT	Yes, antibiotics	41	82.0	50		3.45	1.37	8.67	0.01
	Yes, other	5	83.3	6		5.40	0.56	52.16	0.15
COUGH	No	44	56.4	78	0.16	2.84	1.40	5.74	<0.01
	Yes	94	47.0	200		1.00			
HAEMOPTYSIS	No	112	51.4	218	0.27	NI			
	Yes	26	43.3	60					
FEVER	No	75	52.4	143	0.33	NI			
	Yes	63	46.7	135					
NIGHT SWEATS	No	108	51.2	211	0.36	NI			
	Yes	30	44.8	67					
CHEST PAIN	No	101	47.9	211	0.29	NI			
	Yes	37	55.2	67					
UNINTENTIONAL	No	93	50.8	183	0.59	NI			
WEIGHT LOSS	Yes	45	47.4	95					
LOSS OF APPETITE	No	110	51.2	215	0.35	NI			
	Yes	28	44.4	63					
FATIGUE	No	103	51.5	200	0.32	NI			
	Yes	35	44.9	78					
DISPNEA	No	132	51.0	259	0.10	NI			
	Yes	6	31.6	19					
RESPIRATORY	No	30	61.2	49	0.07	NI			
SYMPTOMS	Yes	108	47.2	229					

*From a multiple logistic model; variables included in the final model were initially selected among those with a p-value <0.20 at the univariate analysis; further selections were made at each step by backward selection excluding thosewith the highest p-value>0.20; NI: not included in the final model

TABLE 3 (CONTINUED)

ASSOCIATION OF SEVERAL CHARACTERISTICS WITH A HEALTH SYSTEM DELAY (HSD) >15 DAYS

		HSD >15 DAYS		TOTAL	P-VALUE	AOR*	95% CI		P-VALUE
		N	%						
RESPIRATORY SYMPTOMS	No	30	61.2	49	0.07	NI			
	Yes	108	47.2	229					
NON-RESPIRATORY SYMPTOMS	No	46	57.5	80	0.10	NI			
	Yes	92	46.5	198					
GENERAL PRACTITIONER	No	50	32.5	154	<0.01	1.00			
	Yes	88	71.0	124		7.16	3.54	14.52	<0.01
OUTPATIENT CLINIC	No	80	39.6	202	<0.01	1.00			
	Yes	58	76.3	76		8.85	4.08	19.22	<0.01
EMERGENCY DEPARTMENT	No	91	56.5	161	0.07	NI			
	Yes	47	40.2	117					
HOSPITAL	No	120	55.3	217	<0.01	NI			
	Yes	18	29.5	61					
PD>30 DAYS	No	85	61.6	138	<0.01	2.71	1.45	5.05	<0.01
	Yes	53	37.9	140		1.00			

*From a multiple logistic model; variables included in the final model were initially selected among those with a p-value <0.20 at the univariate analysis; further selections were made at each step by backward selection excluding thosewith the highest p-value>0.20; NI: not included in the final model

days; on the contrary, those referring to an emergency department, those hospitalized and those reporting a PD longer than 30 days had a significantly, or quite significantly, lower percentage of HD>15 days. In the final multiple logistic analysis we found that being born in Italy (AOR=2.03, 95% CI: 1.04-3.95), receiving previous non-specific treatment (AOR=3.45, 95% CI: 1.37-8.67 for antibiotics, AOR=5.40, 95% CI: 0.56-52.16 for other treatments), reporting no cough (AOR=2.84, 95% CI: 1.40-5.74), seeking the advice of a general practitioner (AOR=7.16, 95% CI: 3.54-14.52), being seen at an outpatient clinic (AOR=8.85, 95% CI: 4.08-19.22) and having a PD>30 days were all independently associated with HSD >15 days.

DISCUSSION

The time between onset of symptoms and TB diagnosis is a key parameter in the transmission dynamics of TB [16]. Our study found a median TD of 77.5 days in line with those estimated in 58 studies, reported by Storla et al. in a review, varying between 21 and 136 days [1]. It is remarkable that a recent study carried out in France estimated a median delay time of 68 days [14]. Our estimated median TD also resulted slightly longer than that estimated in another Italian region (i.e. 65 days in Emilia-Romagna, northern Italy) [8]; besides, greaterdifferences were found when dividing the delay in PD and in HSD. In our study, the median PD was four-fold longer (31 days) and the median HSD was clearly shorter (15 days), compared to those estimated (36 and 7 days, respectively) in the previous Italian study conducted in Emilia-Romagna region [8]. The difference between the median PD values could be partly due to differently organized health systems in the two regions. To this regard, it is noteworthy that in our study only 45% of patients had a GP consultation. However, as in many other studies, it is confirmed that when the median PD was short, this was often counterbalanced by a long median HSD [1]. In fact, it is likely that patients who immediately contact the health system could have less severe symptoms which could facilitate TB misdiagnosis, with a subsequent increase of the HSD.

Regarding factors associated with TB diagnostic delay, we found that in general, and for any kind of delays examined (TD, PD, and HSD), patients born in Italy had a longer median time of delay (100, 45 and 36 vs. 63.5, 26 and 10.5 days in patients borninItaly and in

those bornabroad, respectively). Conversely, previous studies found a longer HSD for patients born abroad [8, 14, 17]. One possible explanation for the longer HSD in patients born in Italy is that physicians do not suspect TB in this group since the incidence of TB is low in Italy. Furthermore, the median age at TB diagnosis in this group was >50 years old; misdiagnosis can also occur because TB is often confused with other diseases that are more prevalent among older people. On the other hand, being a migrant from an endemic country may point physicians to a TB diagnosis [1, 8, 14]. Surprisingly and in contrast with previous studies [8, 14, 17], people born abroad also had a shorter median PD. In fact, factors such as stigma, fear of deportation, language problems and cultural differences could delay the decision of these patients to seek help. However, in contrast with these factors favouring delay, many of these patients were probably capable of recognizing TB symptoms because of past experiences with relatives and/or friends and consequently having specific knowledge of TB symptoms. The suspect of having been previously infected could have made them seek help early. Another possible explanation can be a different recall of when the onset of symptoms occurred.

Other factors independently associated with a PD>30 days were the absence of fever and the presence of unintentional weight loss. Also Tattevin et al. [14] found a similar association with fever, although the outcome they considered was a PD >15 days. This does not seem surprising because fever is usually considered a key symptom for patients to seek help. Conversely, unintentional weight loss was found associated with a longer delay in diagnosis in Quebec, Canada [18]. It is not surprising that this symptom was associated with a PD >30 days because it cannot be immediately identified and it is difficult to determinethe exact time of occurrence.

Regarding a HSD >15 days, the other factors, namely a previous unspecific treatment (both antibiotics and other treatments), the absence of cough, consultation with a general practitioner, the visit at an outpatient clinic and a PD >30 days resulted independently associated. The association with previous unspecific treatment is in accordance with what was found by a French study [14], while the association with the absence of cough and with the different healthcare provider consulted (i.e. general practitioner and outpatient clinic visit) is in agreement with the study performed in northern Italy [8]. Noteworthy is that no older age, neither female sex were independently associated with this outcome, in contrast with many studies as reported by Storla et al. [1]. No previous studies showed the inverse association of HSD with PD. However, this can be indirectly confirmed by the evaluation of the median PD and HSD reported in Table 2 of the article by Storla et al. [1]; in fact, overall, the two medians had a significant inverse correlation of -0.31, meaning that on the average, higher values of PD corresponded to lower medians of HSD, and vice versa.

Several limitations should be taken into account when interpreting our results. In line with previous retrospective studies, reporting symptoms and their dates of onset is affected by recall bias and we cannot exclude that differential recall bias was also present in our study, particularly between patients born in Italy and those born abroad. Another limitation is that data on HIV status were not provided for the vast majority of patients. Also, the study covered around 63% of cases reported to the surveillance system in that period. However, no selection bias is expected, given that the large majority of cases were not included due to delays in the participation of centres in the study which dependedon longer waiting times for ethics committee approval.

CONCLUSION

TB delay in the Lazio region is considerably high, with 38.1% of cases exceeding 100 days from onset of symptoms. This percentage is 50% for patients born in Italy, highlighting that this issue is particularly commonamong people at low risk for TB. Strategies to increase awareness to TB in healthcare providers, such as general practitioners, should be considered.

CONFLICT OF INTEREST: *All authors deny any potential conflicts of interest, including relevant financial interests, activities, relationships and affiliations (other than those affiliations listed on the title page) relevant to the subject of this manuscript.*

ACKNOWLEDGEMENTS: *The study was supported in part by an unrestricted grant from the Italian Ministry of Health "Progetto di ricerca finalizzata 2007, n. 102: Delayed diagnosis and presentation to care for tuberculosis and HIV infection: analysis of determinants and evaluation of strategies to improve timely access to care".*

Preliminary results of this study were presented in part at the residency program dissertations of Valentina Mazzocato (at the Catholic University, Infectious Diseases residency program, Rome;,Italy) and Silvia Pozzato (at Tor Vergata University, Hygiene and Predictive Medicine residency program, Rome, Italy).

We thank Dr. Maria Fenicia Vescio for his suggestions after having read a preliminary version of the manuscript and Dr. Anna Maria Carinci and Ms. Andrea Baker for text revision.

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