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Determinants of patient and health system delay among Italian and foreign-born pulmonary tuberculosis patients

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Determinants of patient and health system delay among Italian and foreign-born pulmonary tuberculosis patients

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To the memory of Professor Caterina Mammina, University of Palermo, Coordinator of the project

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ABSTRACT

Objectives

The aim of this survey was to identify factors associated with patient delay (PD), health system delay (HSD) and total delay (TOTD) in tuberculosis (TB) patients to inform TB control programs.

Setting

The study was approved by the Italian Ministry of Health and carried out in hospitals of four Italian regions (Calabria, Apulia, Sardinia, and Sicily) from October 2014 to July 2016. Data were obtained using a questionnaire including several domains: socio-demographic data; integration index in Italy; TB risk factors; patient knowledge of TB-associated symptoms and attitudes towards TB; TB related stigma; access to TB diagnosis and treatment and health seeking behaviours; and satisfaction with care.

Participants

Patients' inclusion criteria were: i) being permanent or temporary resident in one of the above-mentioned Italian regions, and ii) being diagnosed as a new case of pulmonary TB. A total of 344 patients from 30 healthcare centres were invited to participate and 253 patients were included in the analysis. More than one-half (63.6%) were males and 55.7% were non-Italian born.

Outcome measures

Risk factors for PD, HSD and TOTD in pulmonary TB patients were assessed.

Results

Median PD, HSD and TOTD were 30, 11 and 45 days, respectively. Factors associated with longer PD were: TB-related stigma, paying for transportation, distance to the health centre, unintentional weight loss, and chest pain; being foreign-born, female and seeking care for the first time at hospital were associated with shorter HSD; on the contrary, prior unspecific treatment was associated with longer HSD.

Conclusions

Early diagnosis and prompt therapy are key areas in TB control programme. Tackling TB effectively requires addressing all the risk factors that make individuals more vulnerable by the means of public health policy, cooperation and advocacy to ensure that all patients have easy access to care and services and receive high quality healthcare.

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Strengths and limitations of this study

- The study evaluated all factors associated with patient delay, health system delay and total delay in tuberculosis patients in four Italian regions from 2014 to 2016.
- The association of health system delay and total delay with previous unspecific treatment is of concern in the current global epidemiological scenario when antimicrobial resistance is rapidly developing and spreading and a more prudent use of antimicrobials is urgently needed, by limiting the use of empirical antibiotics in patients with respiratory symptoms. Training general practitioners for the early identification of signs and symptoms and prompt referral of suspected cases to tuberculosis diagnosis and treatment health centres is essential.
- The prospective collection of data, the relevant sample size and the adjustment for confounding factors with logistic regression analysis are among the strengths of the present study.
- A selection bias should be considered, especially for foreign-born patients who may have experienced difficulties during the interview, resulting in refusal or in missing data. Also, the low education level of the overall population may have contributed to an information bias. Last, as the onset date of symptoms was self-reported, it may have been affected by recall bias.

Keywords

Surveillance; public health policy; social epidemiology.

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What is already known on this subject?

Early diagnosis and prompt treatment of tuberculosis represent key components of any national control programmes, thus the understanding of the determinants of delay are important.

Although tuberculosis has been a low-prevalence disease in Italy, most of the cases occur in vulnerable groups, such as foreign-born individuals, who represents about 50% of total cases.

What this study adds?

The study evaluated those factors associated with patient delay, health system delay and total delay in tuberculosis patients in four Italian regions from 2014 to 2016.

The association of health system delay and total delay with previous unspecific treatment is of a particular concern in the current global epidemiological scenario where antimicrobial resistance is rapidly developing and spreading and a more prudent use of antimicrobials is urgently needed, by limiting the use of empirical antibiotics in patients with respiratory symptoms. Training general practitioners for the early identification of signs and symptoms and prompt referral of suspected cases to tuberculosis diagnosis and treatment health centres is essential.

The relevant sample size and the adjustment for confounding factors with logistic regression analysis are among the strengths of the present study

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INTRODUCTION

Early diagnosis and prompt treatment of tuberculosis (TB) disease represent key components of any effective national TB control programme.[1, 2] If adequately implemented and scaled-up, they can contribute to the reduction of *Mycobacterium tuberculosis* transmission and TB elimination by 2050.[3]

In 2015 in Italy, 3.5 thousands TB cases were notified (5.8 cases per 100,000) and the mortality rate was 0.59 deaths per 100,000 residents.[4]

However, delays in diagnosis and treatment of TB frequently occur.[5] Delay in TB diagnosis leads to a more advanced disease, and, thus, poor response to therapies, undesirable clinical *sequelae*, and higher mortality risk. In addition, delay contributes to *M. tuberculosis* transmission within the community.[6, 7] It has been shown that an untreated smear-positive patient can infect, on average, 10 healthy contacts annually.[8] Finally, TB diagnosis delay is associated with higher direct and indirect costs.[9]

Delay may occur at patient or at health system level. Factors contributing to patient delay (PD) can be: socio-demographic, physical, and financial, health literacy, religious-cultural and stigma.[10] Health system delay (HSD)-related factors can be: poor TB knowledge by health providers and poor availability of effective diagnostic tools, number and types of providers encountered before TB diagnosis, patient satisfaction with TB services and waiting time.[10, 11] Thus, understanding and identifying the causes of delay in diagnosis and treatment initiation are critical to strengthen TB control programs. Particularly, the importance of social variables as drivers of epidemics and disease risk has been long recognised. Incorporating the perspectives and methods of social epidemiology into studies of infectious disease, many opportunities arise to control the disease. However, few studies have prioritised social factors as essential to understanding the epidemiology of diseases and for a basis for intervention.[12]

The aim of the present study was to identify all factors associated with PD, HSD and total delay (TOTD) in pulmonary TB (PTB) patients, in four Italian Southern regions, with a focus on social determinants.

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METHODS

Study design

The present study was conducted in the framework of an Italian project, carried out in hospitals of four Italian regions (Calabria, Apulia, Sardinia, and Sicily) from October 2014 to July 2016, and was approved by the Italian Ministry of Health. Patients' inclusion criteria were: i) being permanent or temporary resident in one of the above-mentioned Italian regions, and ii) being diagnosed as a new case of pulmonary TB.

The project was performed according to the Declaration of Helsinki, participants were fully informed of the purpose of the study, and signed a written informed consent. All data collected were treated confidentially and analysed in aggregated and anonymous form.

Data collection and definitions

Data were collected by healthcare workers of each participating centre, during a face-to-face interview at the time when patients were diagnosed and/or initiated treatment. A standardised questionnaire available in Italian, English, and French was used, and, if possible, a cultural and linguistic mediator assisted the interview with the task to facilitating communication and understanding, both on linguistic and cultural level. The questionnaire contained several domains: i) socio-demographic data; ii) integration index (II) in Italy (only for foreign-born patients), computed as described in a previous study;[13] iii) TB risk factors; iv) patient knowledge of TB-associated symptoms and attitudes towards TB; v) TB related stigma, measured according to the WHO questionnaire;[14] vi) access to TB diagnosis and treatment and health seeking behaviours; vii) dates of onset of symptoms, first contact with healthcare service, TB diagnosis confirmation and treatment initiation; viii) satisfaction with care, assessed by adopting and modifying the USAID questionnaire.[15] Definitions of delay were those adopted by USAID.[10]

Statistical analysis

Statistical analyses were performed using the SPSS software (IBM SPSS Statistics for Windows, version 22.0).

The response rate and descriptive statistics were used to characterise the sample using frequencies, means, medians and interquartile ranges (IQRs). The Shapiro-Wilk test was performed to determine whether continuous variables were normally distributed.

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Variables related to stigma and satisfaction with care domains were recorded on a 5-point Likert scale.[14, 15] Scores were converted as mean percentage score, calculated as follows: (sum of score obtained/maximum score that could be obtained) × 100.

For TB cases born abroad, the II was calculated based on the score sum of 11 selected variables from the study questionnaire [13] and then standardised to range from 0 to 10.

The two-tailed Chi-squared test was used for the statistical comparison of categorical variables, whereas quantitative variables were compared using Student's *t* test or the Mann-Whitney U test. The crude odds ratios (ORs) and the corresponding 95% confidence intervals (95%CIs) were computed. Correlation between continuous variables was also evaluated using Pearson correlation coefficient.

Median values were used as cut-off points to dichotomise quantitative variables. Thus, "longer" delays were defined if above the median value. The characteristics of patients with longer delays were compared to those of patients without, using a backward-step selection procedure by multivariable logistic regression analysis. The variables included in the model were those with P <0.1 on univariate analysis. The adjusted ORs (aOR) with the respective 95% CIs were reported. A p-value < 0.05 was considered statistically significant.

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RESULTS

A total of 344 patients from 30 healthcare centres were invited to participate. Overall, 91 (26.5%) refused the interview, and 253 patients were included in the analysis. Patients who refused the interview were older than patients who agreed (46.0 *vs*. 40.7 years, P < 0.023). However, no statistical differences resulted for country of birth and gender. Completion rate for all questions included in the analysis was ≥80%.

Overall, 55.3% of patients were temporary or permanently living in Sicily, 22.1% in Calabria, 17.4% in Apulia, and 5.2% in Sardinia.

Table 1 shows the main characteristics of the study population and comparisons for country of birth and gender. Mean age was 40.7 years (median: 38; IQR 27-53) and 63.6% were males. One hundred forty-one (55.7%) patients were born abroad and they were younger than Italians (mean age: 34.3 years and 48.7 years, respectively; P <0.001).

Stratifying by country of origin, 47.9% of patients came from European countries, and mostly from Romania (82.1%), 28.6% from the African countries, 11.4% from Eastern Mediterranean countries, 9.3% from South-East Asia, 2.1% from Western Pacific countries, and 0.7% from American countries. Foreign-born patients reported higher degree of poverty and literacy: they lived in nursing homes or did not have permanent residency (47.8%), 64.7% were unemployed or occasional workers, and 79.4% were illiterate or had less than 8 years of educational activities (P <0.05).

About one-third suffered of chronic diseases (i.e., diabetes, chronic obstructive pulmonary disease), particularly those born in Italy (39.1%). Current smokers and alcohol users were 27.2% and 6.9%, respectively. Higher percentages of smokers and alcohol users were found among male patients (32.5% and 10.1%). However, no significant differences were observed between Italian and foreign-born patients (Table 1).

Table 1. Patients' characteristics

	All % (N)	**Italian-born % (N)**	**Foreign-born % (N)**	**p***	**Males % (N)**	**Females % (N)**	**p***
Age (mean)	40.7 (246)	48.7 (109)	34.3(137)	**<0.001**	41.0 (157)	40.1 (89)	0.941
Country of birth							
Italy	44.3 (112)	-	-	-	42.2 (68)	47.8 (44)	0.389
Abroad	55.7 (141)	-	-		57.8 (93)	52.2 (48)	
Gender							

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Males	63.6 (161)	-	-	-	-	-	-
Females	36.4 (92)	-	-		-	-	
Education level							
< 8 school years	72.5 (182)	63.6 (70)	79.4 (112)	**0.005**	70.8 (114)	75.6 (68)	0.419
> 8 school years	27.5 (69)	36.4 (40)	20.6 (29)		29.2 (47)	24.4 (22)	
Residence							
Homeless/prison/ Nursing homes	20.8 (50)	3.7 (4)	34.8 (46)	**<0.001**	26.6 (41)	10.5 (9)	**0.003**
Apartment (own or rented)	79.2 (190)	96.3 (104)	65.2 (86)		73.4 (113)	89.5 (77)	
Employment							
Unemployed or occasional work	42.7 (103)	14.3 (15)	64.7 (88)	**<0.001**	47.1 (73)	34.9 (30)	**0.019**
Permanent job	26.6 (64)	33.3 (35)	21.3 (29)		28.4 (44)	23.3 (20)	
Housewife/retired/student	30.7 (74)	52.4 (55)	14.0 (19)		24.5 (38)	41.9 (36)	
Smoking habits							
Current	27.2 (67)	29.9 (32)	25.2 (35)	0.409	32.5 (51)	18.0 (16)	**0.014**
Never/former	72.8 (179)	70.1 (75)	74.8 (104)		67.5 (106)	82.0 (73)	
Alcohol abuse^							
Yes	6.9 (17)	6.3 (7)	7.3 (10)	0.758	10.1 (16)	1.1 (1)	**0.007**
No	93.1 (231)	93.7 (104)	92.7 (127)		89.9 (142)	98.9 (89)	
Chronic disease							
Yes	28.3 (71)	39.1 (43)	19.9 (28)	**0.001**	31.2 (50)	23.1 (21)	0.167
No	71.7 (180)	60.9 (67)	80.1 (113)		68.8 (110)	76.9 (70)	
Stigma (mean)	59.5 (252)	57.4 (111)	61.1 (141)	**0.038**	60.4 (161)	57.8 (91)	0.185
Integration index (mean)°	4.4 (141)	-	-	-	4.1 (93)	5.1 (48)	**0.014**
Years in Italy (mean)°	7.1 (127)	-	-	-	6.6 (85)	8.2 (42)	0.057
Patient Delay (mean)	60.5 (231)	58.6 (103)	62.0 (128)	**0.029**	53.8 (83)	64.2 (148)	0.574
Health system delay (mean)	44.2 (231)	68.1 (104)	24.7 (127)	**<0.001**	41.3 (83)	45.9 (148)	**0.004**
- **Diagnostic delay (mean)**	41.1 (225)	64.5 (102)	21.7 (123)	**<0.001**	39.8 (80)	41.8 (145)	**0.012**
- **Treatment delay**	4.5 (219)	5.1 (99)	3.9 (120)	0.691	3.0 (82)	5.3 (137)	0.397
Total delay	97.5 (248)	119.2 (110)	80.2 (138)	0.296	86.8 (91)	103.7 (157)	0.768

*p-values <0.05 are indicated in bold

^ ≥4 times a week

° only in foreign-born patients

Mean PD, HSD and TOTD were 60.5, 44.2, and 97.5 days, respectively (Table 1). Females reported lower mean HSD and Diagnostic Delay (DD) in comparison with men (41.3 *vs.* 45.9 days; P=0.004 and 39.8 *vs.* 41.8 days; P=0.012, respectively). Cases born abroad reported higher mean PD (58.6 *vs.* 62.0 days; P= 0.029), but lower mean HSD and DD (68.1 *vs.* 24.7 days and 64.5 *vs.* 21.7 days; both P <0.001).

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Patient knowledge and symptoms recognition

Foreign-born patients reported lack of knowledge on the disease more often compared with Italian-born (data reported in Supplementary Table S1). Foreign-born patients were less aware that TB is an infectious disease and transmitted by airborne bacteria. They did not know the symptoms most frequently associated with the disease, how TB is diagnosed and cured, and that multi-drug resistant TB may require a longer treatment time to achieve a cure (P <0.05).

Only 3.6% of TB patients reported no symptoms, while 49% of patients reported three or more symptoms. Overall, 65.6% had cough for more than 3 weeks. Sputum with blood was reported by only 13.4% of patients. The main reason for not seeking care was that they perceived the TB symptoms to be mild (58.9%). Foreign-born patients reported more frequently the following symptoms: cough, sputum with blood, weakness, weight loss, and chest pain. Furthermore, women reported tiredness/weakness, weight loss, chest pain, and night sweating less frequently compared with men. Being irregular migrants was the only reason for delayed seeking care in women, while in men other motivations were reported (Table S1).

Attitude towards TB and stigma

A higher percentage of men (38.6%) and foreign-born patients (44.9%) did not inform their families and friends on the disease, compared with women (12.2%) and Italian-born (9.1%) (P <0.001). Detailed results are reported in Supplementary Table S2.

A moderate level of stigma was found (mean: 59.5%; median and IQR: 58.7%, 22.7%-94.7%) in all patients. Compared with Italians, foreign-born patients reported higher overall stigma (61.1% *vs*. 57.4%, P= 0.038). Females reported a higher degree of stigma, in comparison with males, answering to the following questions: "Do you think there is less chances of marriage due to TB diagnosis?" (57% vs. 48.9%; P= 0.018) and "Is a girl unable to decide for getting TB treatment?" (44.4% vs. 36.9%; P= 0.010).

Positive correlations were detected between degree of stigma and PD (r= 0.23; P <0.001) and between degree of stigma and TOTD (r= 0.211; P= 0.003).

Access to TB care centres

Healthcare-seeking behavior of patients was as follows: General Practitioners (GP) were chosen by 30% of patients, mostly by Italians (46.8%). On the contrary, foreign-born cases were shown to seek more frequently

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the hospital care (70.3%). Around 41% of the cases were visited by more than one healthcare provider, particularly for the Italian group (53.2% *vs*. 31.7%; P= 0.001). Overall, 59% of the cases received an unspecific treatment (mainly antibiotics) before TB diagnosis; this occurred more frequently among cases born in Italy (75.7% *vs*. 51.6%; P= 0.005).

Risk analysis of delay

On univariate analysis, factors associated with long PD (≥ 30 days) were TB-related stigma, paying for transportation and distance to get to the healthcare centre, presence of unintentional weight loss, fatigue and chest pain. All these factors, except fatigue remained associated with PD on multivariate analysis (Table 2).

Table 2. Risk analysis for patient delay (Univariate and logistic regression analysis)

	PD >30 days %	OR 95%CI	p*	aOR 95%CI	p*
Foreign-born patients					
No^	29.1	1.00	0.069	-	-
Yes	40.6	1.67 (0.96 - 2.89)			
Do you know what TB is?			0.091	-	-
No^	27.8	1.00			
Yes	39.1	1.66 (0.92 – 3.00)			
Do you know how TB is diagnosed?			0.051	-	-
No^	28.7	1.00			
Yes	41.3	1.75 (0.99 – 3.07)			
Stigma			**0.001**		**0.034**
< median^	24.8	**1.00**		**1.00**	
> median	46.5	**2.64 (1.51 – 4.61)**		**2.30 (1.06 – 4.98)**	
Pay for transportation to reach the health centre			**<0.001**		**0.012**
No^	23.5	**1.00**		**1.00**	
Yes	49.4	**3.18 (1.77 – 5.73)**		**2.66 (1.24 – 5.74)**	
Did you think you had TB?			0.090	-	-
No^	33.8	1.00			
Yes	52.4	2.15 (0.87 – 5.31)			
Was the health centre where you sought care near your living place?			**0.018**		**0.037**
Yes^	21.9	1.00		**1.00**	
No	39.2	2.30 (1.15 – 4.62)		**2.46 (1.05 – 5.74)**	
Weight loss			**<0.001**		**<0.001**
No^	22.5	**1.00**		**1.00**	
Yes	56.2	**4.41 (2.48 – 7.83)**		**4.66 (2.16 – 10.05)**	
Tiredness/weakness			**0.001**	-	-
No^	25.8	**1.00**			
Yes	45.9	**2.44 (1.40 – 4.25)**			
Chest pain			**0.026**		**0.031**
No^	31.4	**1.00**		**1.00**	
Yes	47.5	**1.97 (1.08 – 3.61)**		**2.67 (1.24 – 6.49)**	
Do you suffer of chronic diseases?			**0.009**	-	-

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No^ Yes	29.6 47.8	**1.00** **2.17 (1.21 – 3.90)**			

*p-values <0.05 are indicated in bold

^ reference category

TB: tuberculosis, PD: patient delay; OR: odd ratio: a: adjusted: CI: confidence interval

Prior unspecific treatment, patients referring to a GP at the first visit, and those visited by multiple providers of different facilities were more likely to report long HSD (≥ 11 days), while females, foreign-born patients, seeking care at hospital level, presence of cough for more than 3 weeks and dizziness were associated with shorter HSD. On multivariate analysis, being foreign-born and female, seeking care at hospital and the presence of dizziness were associated with shorter HSD. Instead, prior unspecific treatment was associated with longer HSD (Table 3).

Table 3. Risk analysis for health system delay (Univariate and logistic regression analysis)

	HSD ≥11 days %	**OR 95%CI**	**p***	**aOR 95%CI**	**p***
Foreign-born patients			**<0.001**		**0.024**
No^	61.5	**1.00**		**1.00**	
Yes	37.0	**0.37 (0.22 - 0.63)**		**0.50 (0.27 - 0.91)**	
Age			0.1	-	-
> median	43.7	1.00			
≤median	54.6	1.55 (0.92 - 2.62)			
Gender			**0.003**		**<0.001**
Male^	55.4	**1.00**		**1.00**	
Female	34.9	**0.43 (0.25 - 0.75)**		**0.28 (0.15 - 0.53)**	
First visit with GP			**<0.001**	-	
No^	39.9	**1.00**			
Yes	68.7	**3.30 (1.80 - 6.06)**			
First visit at hospital			**<0.001**		**0.001**
No^	64.6	**1.00**		**1.00**	
Yes	35.7	**0.30 (0.17 - 0. 53)**		**0.35 (0.18 - 0.66)**	
After first visit, did you seek treatment from somewhere else?			**<0.001**	-	-
No^	35.1	**1.00**			
Yes	66.7	**3.70 (2.12 - 6.44)**			
Cough > 3 weeks			**0.036**	-	-
No^	57.7	**1.00**			
Yes	43.1	**0.56 (0.32 - 0.97)**			
Dizziness			**0.040**		**0.023**
No^	49.8	**1.00**		**1.00**	
Yes	21.4	**0.28 (0.75 - 1.01)**		**0.18 (0.04 - 0.78)**	
Prior unspecific treatment			**<0.001**		**0.012**

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No^ Yes	34.1 57.1	**1.00** **2.58 (1.49 - 4.46)**		**1.00** **2.25 (1.19 - 4.25)**	
Did you have repeated visits with different providers in a different facility? No^ Yes	 37.3 62.8	 **1.00** **2.84 (1.61 - 5.01)**	**<0.001**	-	-

*p-values <0.05 are indicated in bold
^ reference category

GP: general practitioner, HSD: health system delay; OR: odd ratio: a: adjusted: CI: confidence interval

Factors associated with long DD (≥7 days), were identical to those associated with HSD, and in addition, having cough for more than 3 weeks was significantly associated with shorter DD (Table S3). No variables were associated with long TD (≥2 days).

Good knowledge of TB, paying for transportations, distance to reach the health centre, prior unspecific treatment, and weight loss were associated with long TOTD (≥ 45 days), while patients reporting cough and sputum with blood and who had repeated visits with the same provider showed shorter TOTD. In the logistic regression analysis, all variables except presenting cough and knowledge of the disease were confirmed (Table 4).

Table 4. Risk analysis for total delay (Univariate and logistic regression analysis)

	TOTD ≥45 days %	**OR 95%CI**	**p***	**aOR 95%CI**	**p***
Foreign-born patients No^ Yes	 56.0 44.0	 1.00 0.62 (0.35 – 1.08)	0.091	-	-
Do you know what TB is? No^ Yes	 37.1 55.8	 **1.00** **2.14 (1.18 – 3.88)**	**0.012**	-	-
Pay for transportation No^ Yes	 40.5 62.3	 **1.00** **2.43 (1.32 – 4.46)**	**0.004**	 **1.00** **2.10 (1.01 – 4.35)**	**0.047**
Close distance of the first visit place Yes^ No	 32.8 56.9	 **1.00** **2.71 (1.38 – 5.31)**	**0.003**	 **1.00** **3.09 (1.38 – 6.90)**	**0.006**
Cough > 3 weeks No^ Yes	 60.3 44.5	 **1.00** **0.53 (0.29– 0.97)**	**0.038**	-	-
Sputum with blood No^ Yes	 53.5 25.0	 **1.00** **0.29 (0.12– 0.72)**	**0.005**	 **1.00** **0.12 (0.03– 0.43)**	**0.001**
Weight loss			**0.004**		**0.003**

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No^	41.9	**1.00**		**1.00**	
Yes	63.4	**2.40 (1.32– 4.36)**		**3.55 (1.56– 8.09)**	
Prior unspecific treatment			**0.003**		**0.026**
No^	37.4	**1.00**		**1.00**	
Yes	57.4	**2.26 (1.32 – 3.89)**		**2.55 (1.18– 5.82)**	
Did you have repeated visits with the same provider?			**0.029**		**0.012**
No^	53.6	**1.00**		**1.00**	
Yes	34.1	**0.45 (0.22 – 0.93)**		**0.29 (0.11 – 0.76)**	

*p-values <0.05 are indicated in bold

^ reference category

TB: tuberculosis, TOTD: total delay; OR: odd ratio: a: adjusted: CI: confidence interval

DISCUSSION

Reducing the time interval between symptoms recognition and TB treatment can decrease mycobacterial transmission, morbidity, and mortality. Although there is no general consensus on what may constitute an acceptable interval between onset of symptoms and initiation of TB treatment,[16] it has been suggested that TB delay could be used as a key indicator of programme performance.[5]

The TB notification rate in the general Italian population has been stable in the last years. However, most of the cases occur in vulnerable groups, who do not recognise the symptoms or have poor access to healthcare services. The two most affected groups are the elderly and foreign-born people. The number of TB cases in foreign-born represents about 50% of total cases in Italy.[17]

According to national estimates, in 2015, the four Italian regions involved in the project accounted for about 21% of the Italian population,[18] and 37% of migrants.[19] In our study, 55.7% patients were foreign-born, and they were younger than Italians. Younger age among foreign-born patients has also been reported in other studies.[20, 21]. Although the TB notification rate is decreasing in Europe, the reduction in individuals of foreign origin is still slower than in native residents. This represents one of the main challenges for TB elimination, especially in those European countries where individuals of foreign-born origin account for a large proportion of TB cases.[22]

The median values for PD, HSD, and TOTD in our study are similar to those reported by other studies conducted in Italy and in other European countries with low-TB incidence. A recent Italian study reported

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median PD and HSD values of 31 and 15 days, respectively.[20] European studies reported median PD ranging between 14 and 29 days,[16, 23, 24], HSD between 30 and 33 days,[17, 24] and TOTD between 62 and 63 days, respectively.[16, 25]

It is worth noting that some studies evaluated both forms of TB (pulmonary and extra-pulmonary TB), and tools for data collection and definitions of delay were widely heterogeneous among studies, thus comparisons should be made with caution. However, values for HSD and TOTD detected in our study are encouraging, probably due to a higher level of awareness of TB among involved healthcare professionals in recent years.

Similarly to our results, other studies have found that PD was longer than HSD,[20, 26] while others have found the opposite or no differences.[16, 22, 24, 25]. It is likely that patients who contact the health system lately could have more severe symptoms facilitating TB suspect and prompt diagnosis,[20] thus the higher the PD, the lower the HSD, and *vice versa*.[5, 25].

In our study, longer PD was associated with high degree of stigma, paying for transportation, distance to healthcare facility, presence of unintentional weight loss and chest pain. Aside from stigma and chest pain all others were also detected as risk factors for TOTD. Our results are consistent with the findings of the WHO Eastern Mediterranean Region study, where stigma, economic factors, and time to reach the health facility were among the main determinants of delay.[14]

TB-related stigma represents a cultural aspect which drives individuals to hide their condition from others, thus hindering them from seeking care,[27] but evidence shows that stigma barriers may be avoided through interventions addressed to improve TB-related health literacy.[9]

Chest pain and weight loss, together with cough are considered key symptoms for TB screening. Also, a study found an association between PD >90 days and chest pain.[28] Similarly, weight loss was associated with longer PD, both in Brazil and in Italy.[20, 28]

The association of HSD with birth place might be due to the low TB rate in Italy, thus TB would be less suspected and investigated in the Italian-born population, or by contrast, being a migrant may point physicians to a prompt TB diagnosis.[20] This finding is consistent with other studies.[16, 20, 21, 23]

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Female gender was associated with shorter HSD, in contrast with other studies.[5] In general, female patients are reported to encounter greater barriers (financial, physical, and health literacy) to receive appropriate medical care, which reflects longer delay. Further investigations on possible confounders should be considered.

In line with others,[24, 29] a first healthcare contact in hospital, was strongly associated with shorter HSD, while referring to GP was a risk factor for longer HSD. A combination of several factors, may explain this result: lack of TB suspicion among primary care providers in low-endemic countries; seeking assistance in hospital for patients at higher risk of TB (e.g. migrants from endemic countries) and/or with more severe TB disease who are thus investigated faster; availability and easier access to diagnostic tests and specialists within the hospital.[23]

The association of HSD and TOTD with previous unspecific treatment is in agreement with other results.[20, 23] This is of a particular concern in the current global epidemiological scenario where antimicrobial resistance is rapidly developing and spreading and a more prudent use of antimicrobials is urgently needed, by for instance, limiting the use of empirical antibiotics in patients with respiratory symptoms.[23] Training GP for the early identification of signs and symptoms and prompt referral of suspected cases to TB diagnosis and treatment health centres is essential.[27]

Finally, other factors associated with shorter TOTD were presenting sputum with blood and having visits by the same provider. Sputum with blood is usually recognised as a late sign of TB, thus patients with severe symptoms are immediately suspected for TB. Intuitively, having visits with the same provider might reduce repetition of examinations and misdiagnosis.

Our study has some limitations. A selection bias should be considered. The mediator was not often available in hospitals, thus, foreign-born patients recently arrived in Italy, may have experienced difficulties during the interview, resulting in refusal or in missing data. Also, the low education level of the overall population may have contributed to an information bias. As the onset date of symptoms was self-reported, it may have been affected by recall bias. Another limitation is that data on HIV status and other risk factors (e.g. drug use and detention status) were not available for the vast majority of patients.

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The relevant sample size and the adjustment for confounding factors with logistic regression analysis are among the strengths of the present study.

In conclusion, this study detected several modifiable factors associated with longer delay in TB patients, both attributable to patients and health system service. Interventions designed to empower the general population and stakeholders, by increasing knowledge and awareness and screening of active TB in migrants upon arrival are key actions to reduce TB delay and achieve TB control.[30] Strategies should mainly target and improve TB-related health literacy and access to care among the general population, education of GP, earlier referral of TB suspects to the hospital, where appropriate investigations for final diagnosis are readily available, and limiting the use of unspecific treatment in patients with respiratory symptoms.

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COMPETING INTERESTS

The Authors declare that they have no competing interests.

ETHICS

All procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent was obtained from all patients for being included in the study.

DATA SHARING STATEMENT

No additional data available

FUNDING SOURCE

The project entitled "*Valutazione dei determinanti di ritardo nell'accesso ai servizi sanitari, nella diagnosi e nel trattamento della tubercolosi polmonare (PTB) in popolazioni vulnerabili. Valutazione dell'impatto sull'epidemiologia locale e sulla prevalenza di resistenza/multiresistenza ai farmaci antitubercolari* - "Assessment of determinants of delay in healthcare access for the diagnosis and treatment of PTB in vulnerable populations. Assessment of the impact on the local epidemiology and on the prevalence of antituberculosis drug resistance/multiresistance" was approved and financially supported by the Italian Ministry of Health (Centro nazionale per la prevenzione e il Controllo delle Malattie, CCM 2013). The funding source had no role in any phase of the development of the current study.

CONTRIBUTORSHIP

A Agodi, C Mammina, C Nobile, R Prato and G Sotgiu conceived, designed and supervised the study and coordinated regional data collection. A Casuccio and F Vitale coordinated the project after the death of the coordinator C. Mammina. M Barchitta and A Quattrocchi designed the questionnaire and managed data collection at the central level. A Quattrocchi performed the statistical analysis and wrote the first draft of the

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manuscript. A Agodi, M Barchitta and A Quattrocchi interpreted the results and wrote the advanced version of the manuscript.

All CCM 2013 TB network co-authors supervised and coordinated at the hospital level patients' enrolment and data collection.

All Authors critically reviewed the manuscript and approved the final version.

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Supplementary material

Table S1. Correctness of patients' knowledge and symptoms recognition stratified for gender and country of birth

Characteristics	Italian-born % (N)	Foreign-born % (N)	p*	Males % (N)	Females % (N)	p*
Do you know what TB is?						
Yes	81.2 (91)	56.4 (79)	**<0.001**	65.8 (106)	70.3 (64)	0.465
No	18.8 (21)	43.6 (61)		34.2 (55)	29.7 (27)	
Do you think TB is a serious disease?						
Yes	67.9 (76)	57.2 (79)	**0.029**	63.9 (101)	58.7 (54)	0.309
No	17.9 (20)	14.5 (20)		13.3 (21)	20.7 (19)	
Don't know	14.3 (16)	28.3 (39)		22.8 (36)	20.7 (19)	
What causes TB?						
Infection	77.5 (86)	43.8 (60)	**<0.001**	61.1 (96)	54.9 (50)	0.491
Punishment	1.8 (2)	0.7 (1)		1.3 (2)	1.1 (1)	
Unavoidable	0.0 (0)	1.5 (2)		1.3 (2)	0.0 (0)	
Don't know	20.7 (23)	54.0 (74)		36.3 (57)	44.0 (40)	
What are the symptoms TB?						
Cough for more than 3 weeks	58.0 (65)	49.6 (70)	0.105	54.7 (88)	51.1 (47)	0.890
Sputum with blood	13.4 (15)	9.2 (13)		11.2 (18)	10.9 (10)	
Fever	15.2 (17)	14.2 (20)		13.7 (22)	16.3 (15)	
Weight loss	2.7 (3)	3.5 (5)		3.7 (6)	2.2 (2)	
Don't know	10.7 (12)	23.4 (33)		16.8 (27)	19.7 (18)	
How a person can get TB?						
Through germs present in air droplets expelled in the cough	69.4 (72)	37.7 (52)	**<0.001**	55.8 (87)	43.0 (37)	0.147
Sharing utensils and objects with an infected person	3.8 (4)	7.2 (10)		5.8 (9)	5.8 (5)	
Don't know	26.9 (28)	55.1 (76)		38.5 (60)	51.2 (44)	
How TB is diagnosed?						
Through sputum examination	39.0 (39)	17.1 (24)	**<0.001**	23.7 (37)	31.0 (26)	0.409
Through X-ray	32.0 (32)	25.7 (36)		28.2 (44)	28.6 (24)	
Don't know	29.0 (29)	57.1 (80)		48.1 (75)	40.4 (34)	
Can TB be cured?						
Yes	93.6 (103)	76.3 (106)	**0.001**	84.8 (134)	82.4 (75)	0.858
No	0.0 (0)	2.2 (3)		1.3 (2)	1.1 (1)	
Don't know	6.4 (7)	21.6 (30)		13.9 (22)	16.5 (15)	
Can TB require a longer treatment to be cured as for multidrug resistant forms?						
Yes	51.8 (58)	34.5 (48)	**0.016**	41.0 (66)	44.4 (40)	0.868
No	10.7 (12)	18.7 (26)		15.5 (25)	14.4 (13)	
Don't know	37.5 (42)	46.8 (65)		43.5 (70)	41.2 (37)	
Which symptoms made you seek healthcare?						
Cough for more than 3 weeks						
Yes	57.1 (64)	72.3 (102)	**0.011**	65.2 (105)	66.3 (61)	0.861
No	42.9 (48)	27.7 (39)		34.8 (56)	33.7 (31)	
Sputum with blood						

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Yes	8.0 (9)	17.7 (25)	**0.025**	14.3 (23)	12.0 (11)	0.601
No	92.0 (103)	82.3 (116)		85.7 (138)	88.0 (81)	
Fever						
Yes	50.9 (57)	50.4 (71)	0.932	50.3 (81)	51.1 (47)	0.905
No	49.1 (55)	49.6 (70)		49.7 (80)	48.9 (45)	
Weight loss						
Yes	28.6 (32)	44.7 (63)	**0.009**	44.7 (72)	25.0 (23)	**0.002**
No	71.4 (80)	55.3 (78)		55.3 (89)	75.0 (69)	
Tiredness/weakness						
Yes	38.4 (43)	52.5 (74)	**0.026**	50.9 (82)	38.0 (35)	**0.048**
No	61.1 (69)	47.5 (67)		49.1 (79)	62.0 (57)	
Dizziness						
Yes	4.5 (5)	6.4 (9)	0.507	6.8 (11)	3.3 (3)	0.232
No	95.5 (107)	93.6 (132)		93.2 (150)	96.7 (89)	
Chest pain						
Yes	17.0 (19)	30.5 (43)	**0.013**	28.6 (46)	17.4 (16)	**0.047**
No	83.0 (4393	69.5 (98)		71.4 (115)	82.6 (76)	
Night sweat						
Yes	20.5 (23)	30.5 (43)	0.073	31.1 (50)	17.4 (16)	**0.017**
No	79.5 (89)	69.5 (98)		68.9 (111)	82.6 (76)	
Did you think you had TB?						
Yes	5.4 (6)	11.4 (16)	0.090	11.8 (19)	3.3 (3)	**0.022**
No	94.6 (106)	88.6 (124)		88.2 (142)	96.7 (88)	
What factors may have made you delay seeking treatment for symptoms that led to the diagnosis of TB?						
Not aware of symptoms						
Yes	38.4 (43)	43.3 (61)	0.434	57.1 (92)	62.0 (57)	0.454
No	61.6 (69)	56.7 (80)		42.9 (69)	38.0 (35)	
Fear of rejection/ losing my job						
Yes	2.7 (3)	6.4 (9)	0.169	5.6 (9)	3.3 (3)	0.402
No	97.3 (109)	93.6 (132)		94.4 (152)	96.7 (89)	
Expensive						
Yes	0.0 (0)	9.2 (13)	**0.001**	5.6 (9)	4.3 (4)	0.667
No	100.0 (112)	90.8 (128)		94.4 (152)	95.7 (88)	
Lack of time						
Yes	5.4 (6)	7.1 (10)	0.573	5.6 (9)	7.6 (7)	0.526
No	94.6 (106)	92.9 (131)		94.4 (152)	92.4 (85)	
Distance to health centre						
Yes	0.9 (1)	2.8 (4)	0.270	2.5 (4)	1.1 (1)	0.442
No	99.1 (111)	97.2 (137)		97.5 (157)	98.9 (91)	
Lack of transportation						
Yes	0.9 (1)	0.7 (1)	0.870	0.0 (0)	2.2 (2)	0.060
No	99.1 (111)	99.3 (140)		100.0 (161)	97.8 (90)	
Previous non-satisfactory experience with the health system						
Yes	1.8 (2)	2.1 (3)	0.846	1.9 (3)	2.2 (2)	0.864
No	98.2 (110)	97.9 (138)		98.1 (158)	97.8 (90)	
Other (clandestine)						
Yes	-	-	-	9.3 (15)	1.1 (1)	**0.010**
No	-	-		90.7 (146)	98.9 (91)	

*p-values <0.05 are indicated in bold

TB: tuberculosis

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Table S2. Attitude towards TB stratified for gender and country of birth

	Italian-born % (N)	Foreign-born % (N)	p*	Males % (N)	Females % (N)	p*
Should people with TB disclose their illness to other people?						
Yes	70.5 (79)	47.1 (66)	**0.001**	53.1 (85)	65.2 (60)	**0.040**
No	8.9 (10)	19.3 (27)		18.8 (30)	7.6 (7)	
Don't know	20.5 (23)	33.6 (47)		28.1 (45)	27.2 (25)	
Who do you think is more likely to get TB, men or women?						
Men	12.5 (14)	15.0 (21)	0.305	21.2 (34)	1.1 (1)	**<0.001**
Women	5.4 (6)	10.0 (14)		4.4 (7)	14.1 (13)	
Don't know	82.1 (92)	75.0 (105)		74.9 (119)	84.8 (78)	
How did you feel when you found out that you had TB?						
Scared	37.5 (42)	45.4 (64)	0.376	36.6 (59)	51.1 (47)	0.164
Depressed	20.5 (23)	14.2 (20)		18.0 (29)	15.2 (14)	
Didn't believe (denial)	29.5 (33)	31.2 (44)		33.5 (54)	25.0 (23)	
Other	12.5 (14)	9.2 (13)		11.8 (19)	8.7 (8)	
Did you inform your friends/ family that you had TB?						
Yes	90.9 (100)	55.1 (76)	**<0.001**	61.4 (97)	87.8 (79)	**<0.001**
No	9.1 (10)	44.9 (62)		38.6 (61)	12.2 (11)	
Have your relationships with your friends/ family changed since finding out you have TB?						
Yes	22.0 (24)	14.7 (20)	0.138	15.4 (24)	22.5 (20)	0.165
No	78.0 (85)	85.3 (116)		84.6 (132)	77.5 (69)	
If yes, how?						
Improved	41.7 (10)	10.5 (2)	**0.024**	26.1 (6)	30.0 (6)	0.775
Worsened	58.3 (14)	89.5 (17)		73.9 (17)	70.0 (14)	
Are people with TB discriminated in the community?						
Yes	46.4 (51)	41.0 (57)	**0.002**	40.3 (64)	48.9 (44)	0.386
No	33.6 (37)	19.4 (27)		26.4 (42)	24.4 (22)	
Don't know	20.0 (22)	39.6 (55)		33.3 (53)	26.7 (24)	
Among TB patients, are male or female patients more discriminated?						
Male	3.7 (4)	9.3 (13)	**0.027**	10.1 (16)	1.1 (1)	**<0.001**
Female	2.85 (3)	8.6 (12)		2.5 (4)	12.1 (11)	
Don't know	93.6 (102)	82.1 (115)		87.3 (138)	86.8 (79)	

*p-values <0.05 are indicated in bold

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Table S3. Risk analysis for DD (Univariate and logistic regression analysis)

	DD ≥7 days %	DD <7 days %	OR 95%CI	p	aOR 95%CI	p
Foreign-born patients				**<0.001**		**0.024**
Yes^	40.5	68.4	**1**		**1**	
No	59.5	31.6	**0.32 (0.18 – 0.54)**		**0.48 (0.25 – 0.91)**	
Chronic disease				0.061	-	-
Yes^	32.1	21.1	1			
No	67.9	78.9	1.77 (0.97 – 3.24)			
Gender				**0.008**		**<0.001**
Female^	27.0	43.9	**1**		**1**	
Male	73.0	56.1	**0.47 (0.27 – 0.83)**		**0.30 (0.15 – 0.58)**	
First visit: General practitioner				**<0.001**	-	-
Yes^	43.1	17.3	**1**			
No	56.9	82.7	**3.63 (1.95 – 6.77)**			
First visit: Hospital				**<0.001**		**0.002**
Yes^	40.4	70.9	**1**		**1**	
No	59.6	29.1	**0.28 (0.16 – 0.49)**		**0.35 (0.18 – 0.67)**	
After first visit, did you seek treatment from somewhere else?				**<0.001**	-	-
Yes^	60.0	24.3	**1**			
No	40.0	75.7	**4.67 (2.62 – 8.31)**			
Cough more than 3 weeks				**0.035**		**0.048**
Yes^	58.6	71.9	**1**		**1**	
No	41.4	28.1	**0.55 (0.32 – 0.96)**		**0.51 (0.27 – 0.99)**	
Dizziness				**0.051**		**0.039**
Yes^	2.7	8.8	**1**		**1**	
No	97.3	91.2	**0.28 (0.08 – 1.08)**		**0.21 (0.04 – 0.92)**	
Prior unspecific treatment				**<0.001**		**0.002**
Yes^	73.0	46.5	**1**		**1**	
No	27.0	53.5	**3.11 (1.78 – 5.43)**		**2.85 (1.47 – 5.52)**	
With whom did you have repeated visits?: Different providers in a different facility				**<0.001**	-	-
Yes^	59.0	30.6	**1**			
No	41.0	69.4	**3.26 (1.82 – 5.86)**			

*p-values <0.05 are indicated in bold

^ reference category

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Determinants of patient and health system delay among Italian and foreign-born pulmonary tuberculosis patients: a multicentre cross-sectional study

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Determinants of patient and health system delay among Italian and foreign-born pulmonary tuberculosis patients: a multicentre cross-sectional study

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To the memory of Professor Caterina Mammina, University of Palermo, First Coordinator of the project

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ABSTRACT

Objectives

The aim of this cross-sectional study was to identify key factors associated with patient delay (PD), health system delay (HSD) and total delay (TOTD) in tuberculosis (TB) patients to inform TB control programs.

Setting

The study was carried out in four Italian regions (Calabria, Apulia, Sardinia, and Sicily) from October 2014 to July 2016. Data were obtained using a questionnaire including: socio-demographic data, integration index, TB risk factors; patient knowledge and attitudes towards TB, stigma, access to TB care, health seeking behaviours, and satisfaction with care.

Participants

Patients' inclusion criteria were being diagnosed as a new smear positive pulmonary TB case and living in one of the above-mentioned Italian regions. A total of 344 patients from 30 healthcare centres were invited to participate and 253 patients were included in the analysis (26.5% non-response rate). Overall, 63.6% of patients were males and 55.7% were non-Italian born.

Outcome measures

Risk factors for PD, HSD and TOTD in TB patients were assessed by multivariable analysis, adjusting for confounding.

Results

Median PD, HSD and TOTD were 30, 11 and 45 days, respectively. Factors associated with longer PD were: stigma, chest pain, weight loss, paying for transportation and distance to the health centre (the latter three also associated with TOTD). Being foreign-born, female and seeking care for the first time at hospital were associated with shorter HSD, while, prior unspecific treatment was associated with longer HSD and TOTD. Sputum with blood and repeated visits with the same provider showed shorter TOTD.

Conclusions

The study identifies several determinants of delays associated with patient's behaviours and healthcare qualities. Tackling TB effectively requires addressing key risk factors that make

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individuals more vulnerable by the means of public health policy, cooperation and advocacy to ensure that all patients have easy access to care and receive high quality healthcare.

Strengths and limitations of this study

- This is the first multiregional cross-sectional study, in Italy, investigating the association of key factors with patient delay, health system delay and total delay in pulmonary tuberculosis patients.
- Data were collected by healthcare providers and cultural mediators, using a multilingual standardised questionnaire.
- The prospective collection of data and the adjustment for confounding factors with logistic regression analysis are among the strengths of the present study.
- A selection bias should be considered, especially for foreign-born patients who may have experienced difficulties during the interview, resulting in refusal or in missing data.
- Self-reported dates for onset of symptoms and health care seeking may have been affected by recall bias.

Keywords

Surveillance; public health policy; social epidemiology; TB patients.

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INTRODUCTION

Early diagnosis and prompt treatment of tuberculosis (TB) disease represent key components of any effective national TB control programme.[1, 2] If adequately implemented and scaled-up, they can contribute to the reduction of *Mycobacterium tuberculosis* transmission and TB elimination by 2050.[3]

However, delays in diagnosis and treatment of TB frequently occur.[4] Long delays lead to a more advanced disease that may result in poor response to therapies, undesirable clinical *sequelae*, and higher mortality risk.[5] Delay also increases the risk of developing anti-TB drug resistance leading to treatment failure.[6] In addition, delay contributes to *M. tuberculosis* transmission within the community.[7,8] It has been shown that an untreated smear-positive patient can infect, on average, 10 healthy contacts annually.[9] Finally, TB diagnosis delay is associated with higher direct and indirect costs.[10]

Delay may occur at patient or at health system level. Factors contributing to patient delay (PD) can be: socio-demographic, physical, and financial, health literacy, religious-cultural and stigma.[11] Health system delay (HSD) related factors can be: poor TB knowledge by health providers and poor availability of effective diagnostic tools, number and types of providers encountered before TB diagnosis, patient satisfaction with TB services and waiting time.[11-12] Thus, understanding and identifying the causes of delay in diagnosis and treatment initiation are critical to strengthen TB control programs. Particularly, the importance of social variables as drivers of epidemics and disease risk has been long recognised. Incorporating the perspectives and methods of social epidemiology into studies of infectious disease, many opportunities arise to control the disease. [13]

However, in Europe, and especially in Italy, few studies have focused on social determinants and TB delays.

The aim of the present study was to identify the duration and the key factors related to PD, HSD and total delay (TOTD) in pulmonary TB patients, in four Italian Southern regions, with a focus on social determinants.

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METHODS

Study design

The present cross-sectional study was conducted in four Italian regions (Calabria, Apulia, Sardinia, and Sicily) from October 2014 to July 2016, and was approved and financed by the Italian Ministry of Health.

Patients' inclusion criteria were being diagnosed as a new smear positive pulmonary TB case and living in one of the above-mentioned Italian regions. Foreign-born patients were enrolled regardless of their legal migrant status (e.g. refugees, asylum seeker, and illegal migrants). Negative smear, relapse, retreatment and extrapulmonary TB cases were excluded.

The project was performed according to the Declaration of Helsinki, participants were fully informed of the purpose of the study, and signed a written informed consent. All data collected were treated confidentially and analysed in aggregated and anonymous form.

Sample Size calculation and Sampling Procedure

A sample size of 261 was estimated by using single population proportion estimation formula with an assumption of 95% confidence interval, 6% margin of error, and 50.4% proportion of PD (> 30 days).[14] Furthermore, considering 20% of nonresponse rate, the final sample size was 321. All patients meeting the inclusion criterion, attending the healthcare facility during the study period, were prospectively invited to participate in the study.

Data collection and definitions

Data were collected by healthcare workers of each participating centre, during a face-to-face interview at the time when patients were diagnosed and/or initiated treatment. A standardised questionnaire available in Italian, English, and French was used, and if possible, a cultural and linguistic mediator assisted the interview with the task to facilitate communication and understanding, both on linguistic and cultural level. Operators with adequate background of the health topic, within the specific cultures/languages, supported and assisted patients and healthcare professionals during clinical examinations.

The questionnaire contained several domains: i) socio-demographic data; ii) integration index (II) in Italy (only for foreign-born patients), computed as described in a previous study;[15] iii) TB risk factors; iv) patient knowledge of TB-associated symptoms and attitudes towards TB; v) TB related stigma, measured according

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to the WHO questionnaire;[16] vi) access to TB diagnosis and treatment and health seeking behaviours; vii) dates of onset of symptoms, first contact with healthcare service, TB diagnosis confirmation and treatment initiation; viii) satisfaction with care, assessed by adopting and modifying the USAID questionnaire.[17]

PD was defined as the time interval between the onset of symptoms and patient's first contact with any type of health care service (including hospital and primary health care).[16,17] HSD was defined as the time interval between the first consultation with a health care provider and the initiation of treatment. [16,17] This can be subdivided into: diagnostic delay (DD) as the time interval between the presentation to a health care provider and the date of diagnosis and treatment delay (TD) as the time interval between TB diagnosis and initiation of anti-TB treatment. Thus, TOTD was defined as the time interval from the onset of symptoms until the treatment initiation.[17,18]

Statistical analysis

Statistical analyses were performed using the SPSS software (IBM SPSS Statistics for Windows, version 22.0).

The response rate and descriptive statistics were used to characterise the sample using frequencies, means, medians and interquartile ranges (IQRs).

Poverty was defined in relation to housing circumstances as living in community centres, first aid centres or prisons. Education level was dichotomised into two categories (high and low), using a cut-off of 8 school years.

Variables related to stigma and satisfaction with care domains were recorded on a 5-point Likert scale.[16,17] Scores were converted as mean percentage score, calculated as follows: (sum of score obtained/maximum score that could be obtained) × 100.

For TB cases born abroad, the II was calculated based on the score sum of 11 selected variables from the study questionnaire and then standardised to range from 0 to 10.[15]

Longer delays (outcome) were defined according to previous Italian studies. Particularly, long PD was defined as >30 days, while long HSD and TOTD were defined as > the median value observed in the study population, for HSD and TOTD, respectively.[14,19]

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Median values were also used as cut-off points to dichotomise quantitative variables (e.g. age and stigma). The two-tailed Chi-squared test was used for the statistical comparison of categorical variables, whereas quantitative variables were compared using Student's *t* test, as the sample was big enough. The Levene's test was performed to verify the homogeneity of variance across groups.

The characteristics of patients with longer delays (all forms) were compared to those of patients without (comparators) and the crude odds ratios (ORs) and the corresponding 95% confidence intervals (95%CIs) were computed.

All variables with P <0.1 on univariate analysis were included in the multivariable logistic regression analysis, using a backward-stepwise selection procedure. The breakpoint for variable removal was set at 0.10. The adjusted ORs (aOR) with the respective 95% CIs were reported. A P-value < 0.05 was considered statistically significant.

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RESULTS

A total of 344 patients from 30 healthcare centres were invited to participate. Overall, 91 (26.5%) refused the interview, and 253 patients were included in the analysis. Patients who refused the interview were older than patients who agreed (46.0 *vs*. 40.7 years, P = 0.023). However, no statistical differences resulted for country of birth and gender. Completion rate for all questions included in the analysis was ≥80%.

Overall, 55.3% of patients were temporary or permanently living in Sicily, 22.1% in Calabria, 17.4% in Apulia, and 5.2% in Sardinia.

Table 1 shows the main characteristics of the study population and comparisons for country of birth and gender. Mean age was 40.7 years (median: 38; IQR 27-53) and 63.6% were males. One hundred forty-one (55.7%) patients were born abroad and they were younger than Italians (mean age: 34.3 years and 48.7 years, respectively; P <0.001).

Stratifying by country of origin, 47.9% of patients came from European countries, and mostly from Romania (82.1%), 28.6% from the African countries, 11.4% from Eastern Mediterranean countries, 9.3% from South-East Asia, 2.1% from Western Pacific countries, and 0.7% from American countries. Foreign-born patients reported higher degree of poverty and literacy: they lived in nursing homes or did not have permanent residency (47.8%), 64.7% were unemployed or occasional workers, and 79.4% were illiterate or had less than 8 years of educational activities (P <0.05).

About one-third suffered of chronic diseases (i.e. HIV/AIDS, diabetes, chronic obstructive pulmonary disease, disability, renal failure and cardiovascular disease), particularly those born in Italy (39.1%). Current smokers and alcohol users were 27.2% and 6.9%, respectively. Higher percentages of smokers and alcohol users were found among male patients (32.5% and 10.1%). However, no significant differences were observed between Italian and foreign-born patients (Table 1).

Patient knowledge and symptoms recognition

Foreign-born patients reported lack of knowledge on the disease more often compared with Italian-born (data reported in Supplementary Table S1). Foreign-born patients were less aware that TB is an infectious disease and transmitted by airborne bacteria. They did not know the symptoms most frequently associated with the

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disease, how TB is diagnosed and cured, and that multi-drug resistant TB may require a longer treatment time to achieve a cure (P <0.05).

Only 3.6% of TB patients reported no symptoms, while 49% of patients reported three or more symptoms. Overall, 65.6% had cough for more than 3 weeks. Sputum with blood was reported by only 13.4% of patients. The main reason for not seeking care was that they perceived the TB symptoms to be mild (58.9%). Foreign-born patients reported more frequently the following symptoms: cough, sputum with blood, weakness, weight loss, and chest pain. Furthermore, women reported tiredness/weakness, weight loss, chest pain, and night sweating less frequently compared with men. Being irregular migrants was the only reason for delayed seeking care in women, while in men other motivations were reported (Table S1).

Attitude towards TB and stigma

A higher percentage of men (38.6%) and foreign-born patients (44.9%) did not inform their families and friends on the disease, compared with women (12.2%) and Italian-born (9.1%) (P <0.001). Detailed results are reported in Supplementary Table S2.

A moderate level of stigma was found (mean: 59.5%; median and IQR: 58.7%, 22.7%-94.7%) in all patients. Compared with Italians, foreign-born patients reported higher degree of stigma (53.9% *vs*. 41.4%, P= 0.049).

Access to TB care centres

Healthcare-seeking behavior of patients was as follows: General Practitioners (GP) were chosen by 30% of patients, mostly by Italians (46.8%). On the contrary, foreign-born cases were shown to seek more frequently the hospital care (70.3%). Around 41% of the cases were visited by more than one healthcare provider, particularly for the Italian group (53.2% *vs*. 31.7%; P= 0.001). Overall, 59% of the cases received an unspecific treatment (mainly antibiotics) before TB diagnosis; this occurred more frequently among cases born in Italy (75.7% *vs*. 51.6%; P= 0.005).

Risk analysis of delay

Median PD, HSD and TOTD were 30, 11, and 45 days, respectively (Table 1). On univariate analysis, factors associated with long PD (≥ 30 days) were TB-related stigma, paying for transportation and distance to get to the healthcare centre, presence of unintentional weight loss, fatigue and chest pain. All these factors, except fatigue remained associated with PD on multivariate analysis (Table 2).

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Prior unspecific treatment, patients referring to a GP at the first visit, and those visited by multiple providers of different facilities were more likely to report long HSD (≥ 11 days), while females, foreign-born patients, seeking care at hospital level, presence of cough for more than 3 weeks and dizziness were associated with shorter HSD. On multivariate analysis, being foreign-born and female, seeking care at hospital and the presence of dizziness were associated with shorter HSD. Instead, prior unspecific treatment was associated with longer HSD (Table 3).

Factors associated with long DD (≥7 days), were identical to those associated with HSD, and in addition, having cough for more than 3 weeks was significantly associated with shorter DD (Table S3). No variables were associated with long TD (≥2 days).

Good knowledge of TB, paying for transportations, distance to reach the health centre, prior unspecific treatment, and weight loss were associated with long TOTD (≥ 45 days), while patients reporting cough and sputum with blood and who had repeated visits with the same provider showed shorter TOTD. In the logistic regression analysis, all variables except presenting cough and knowledge of the disease were confirmed (Table 4).

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DISCUSSION

Reducing the time interval between symptoms recognition and TB treatment can decrease mycobacterial transmission, morbidity, and mortality. Although there is no general consensus on what may constitute an acceptable interval between onset of symptoms and initiation of TB treatment,[20] it has been suggested that TB delay could be used as a key indicator of programme performance.[4]

The TB notification rate in the general Italian population has been stable in the last years.[21]

However, most of the cases occur in vulnerable groups, who do not recognise the symptoms or have poor access to healthcare services. The two most affected groups are the elderly and foreign-born people. The number of TB cases in foreign-born represents about 50% of total cases in Italy.[22]

According to national estimates, in 2015, the four Italian regions involved in the project accounted for about 21% of the Italian population.[23] In our study, 55.7% patients were foreign-born, and they were younger than Italians. Younger age among foreign-born patients has also been reported in other studies.[14,24] Although the TB notification rate is decreasing in Europe, the reduction in individuals of foreign origin is still slower than in native residents. This represents one of the main challenges for TB elimination, especially in those European countries where individuals of foreign-born origin account for a large proportion of TB cases.[25]

In our study, the median values for PD (30 days), HSD (11 days, of which 7 days for DD and 2 days for TD, respectively), and TOTD (45 days) are similar to those reported by other studies conducted in Italy and in other European countries with a low-TB incidence. Particularly, a recent Italian study reported median PD and HSD values of 31 and 15 days, respectively.[14] European studies reported median PDs of 14 days (France),[26] 28 days (Norway),[27] and 29 days (UK).[20] Considering HSD (and its two components), studies reported median values of 15 days (Croatia),[28] 25 days (for DD in France),[26] 30 days (UK),[20] and 33 days (Norway).[27] Median values for TOTD ranged between 62 days (UK),[20] and 63 days (Norway).[27]

However, it is worth noting that some studies evaluated both forms of TB (pulmonary and extra-pulmonary), and tools for data collection and definitions of delay were widely heterogeneous among studies, thus comparisons should be made with caution.

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Nevertheless, median values detected in our study are encouraging. Indeed, for PD a median value of 30 days has been considered an acceptable value by many authors,[19, 29] although others have suggested values less than 3 weeks.[30]

Regarding HSD, our median value is below the accepted value, which is considered to be 15 days.[29] Low values of HSD and TOTD might probably due to a higher level of awareness of TB among involved healthcare professionals in Italy, in recent years.

Similarly to our results, other studies have found that PD was longer than HSD,[14, 31] while others have found the opposite,[26, 27] or no differences.[20]. It is likely that patients who contact the health system lately could have more severe symptoms facilitating TB suspect and prompt diagnosis,[14] thus the higher the PD, the lower the HSD, and *vice versa*.[4, 27].

In our study, longer PD was associated with high degree of stigma, paying for transportation, distance to healthcare facility, presence of unintentional weight loss and chest pain. Aside from stigma and chest pain all others were also detected as risk factors for TOTD. Our results are consistent with findings of the WHO Eastern Mediterranean Region study, where stigma, economic factors, and time to reach the health facility were among the main determinants of delay.[16]

TB-related stigma represents a cultural aspect which drives individuals to hide their condition from others, thus hindering them from seeking care,[32] but evidence shows that stigma barriers may be avoided through interventions addressed to improve TB-related health literacy.[11]

The reason that chest pain and weight loss were associated with PD is not clear. Although, these symptoms together with cough are considered key TB symptoms. Other studies retrieved similar results. Chest pain was found positively associated with longer PD (> 90 days) in a Brazilian study,[33] and with TOTD (>60 days) in Ethiopia.[29] Similarly, weight loss was associated with longer PD, both in Brazil (>30 days)[33] and in Italy (>15 days),[14] with PD (>27 days) and TOTD (>50 days) in Uzbekistan,[34] and with HSD (>18 days) in another Brazilian study.[35] These results could be explained by the fact that patients considered these as transient symptoms from a general illness, hence, maybe, initiating self-treatment lasting until deterioration and manifestation of other specific symptoms. Furthermore, timely referral to healthcare facilities for disabling symptoms may be challenging for migrants due to financial constraints, poor health literacy, and

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stigma. In addition, a long delay, favours disease progression and therefore symptom appearance. Also, non-specific symptoms could lead to longer suspicion delays by the clinician.

The association of HSD with birth place might be due to the low TB rate in Italy, thus TB would be less suspected and investigated in the Italian-born population, or by contrast, being a migrant may point physicians to a prompt TB diagnosis.[14] This finding is consistent with other studies.[14,20]

Female gender was associated with shorter HSD, in contrast with other studies.[4] In general, female patients are reported to encounter greater barriers (financial, physical, and health literacy) to receive appropriate medical care, which reflects longer delay. Further investigations on possible confounders should be considered.

In line with others,[4, 32, 36, 37] a first healthcare contact in hospital, was strongly associated with shorter HSD, while referring to GP was a risk factor for longer HSD. A combination of several factors, may explain this result: lack of TB suspicion among primary care providers in low-endemic countries; seeking assistance in hospital for patients at higher risk of TB (e.g. migrants from endemic countries) and/or with more severe TB disease who are thus investigated faster; availability and easier access to diagnostic tests and specialists within the hospital.[26]

The association of HSD and TOTD with previous unspecific treatment is in agreement with other results.[14, 26] This is of a particular concern in the current global epidemiological scenario where antimicrobial resistance is rapidly developing and spreading and a more prudent use of antimicrobials is urgently needed, by for instance, limiting the use of empirical antibiotics in patients with respiratory symptoms.[26] Training GP for the early identification of signs and symptoms and prompt referral of suspected cases to TB diagnosis and treatment health centres is essential.

Finally, other factors associated with shorter TOTD were presenting sputum with blood and having visits by the same provider. Sputum with blood is usually recognised as a late sign of TB, thus patients with severe symptoms are immediately suspected for TB. Intuitively, having visits with the same provider might reduce repetition of examinations and misdiagnosis.

Our study has some limitations, some of them specific to the cross-sectional study design. A selection bias should be considered. In fact, the mediator was not often available in hospitals, thus, foreign-born patients

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recently arrived in Italy, may have experienced difficulties during the interview, resulting in refusal or in missing data. Also, the low education level of the overall population may have contributed to an information bias. Furthermore, as the onset date of symptoms was self-reported, it may have been affected by recall bias. Another limitation is that data on HIV status and other risk factors (e.g. alcohol and drug use and detention status) were not available for the vast majority of patients.

In the present study, several aspects have been investigating as key factors contributing to delay in TB patients. However, further studies addressing other components of delay[7, 32, 38] and other stakeholders may be necessary to understand all factors that are closely associated with delay. Furthermore, in our regression model we did not take into account for the potential collinearity of explanatory variables, which could explain complex relationship involving several risk factors at the same time. A possible approach to combine the relevant variables into summary scores or indexes and assesses the relationship of these with the outcome of interest have to explored.

This is the first multiregional cross-sectional study, conducted in Italy, which investigated the association of several factors with PD, HSD and TOTD delay in pulmonary TB patients. It provides new evidence which can be addressed through tailored actions, in order to reduce the burden of TB in Italy. Furthermore, the prospective collection of data in four Italian regions, using a multilingual standardised questionnaire and the adjustment for confounding factors with logistic regression analysis are among the strengths of the present study.

In conclusion, this study detected several modifiable factors associated with longer delay in TB patients, both attributable to patients and health system service. Interventions designed to empower the general population and stakeholders, by increasing knowledge and awareness and screening of active TB in migrants upon arrival are key actions to reduce TB delay and achieve TB control.[39] Strategies should mainly target and improve TB-related health literacy and access to care among the general population, education of GP, earlier referral of TB suspects to the hospital, where appropriate investigations for final diagnosis are readily available, and limiting the use of unspecific treatment in patients with respiratory symptoms.

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All CCM 2013 TB network collaborators supervised and coordinated at the hospital level patients' enrolment and data collection.

COMPETING INTERESTS

The Authors declare that they have no competing interests.

ETHICS

All procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent was obtained from all patients for being included in the study.

DATA SHARING STATEMENT

No additional data available

FUNDING SOURCE

The project entitled "*Valutazione dei determinanti di ritardo nell'accesso ai servizi sanitari, nella diagnosi e nel trattamento della tubercolosi polmonare (PTB) in popolazioni vulnerabili. Valutazione dell'impatto sull'epidemiologia locale e sulla prevalenza di resistenza/multiresistenza ai farmaci antitubercolari* - "Assessment of determinants of delay in healthcare access for the diagnosis and treatment of PTB in

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vulnerable populations. Assessment of the impact on the local epidemiology and on the prevalence of antituberculosis drug resistance/multiresistance" was approved and financially supported by the Italian Ministry of Health (Centro nazionale per la prevenzione e il Controllo delle Malattie, CCM 2013). The funding source had no role in any phase of the development of the current study.

CONTRIBUTORSHIP

A Agodi, C Nobile, R Prato and G Sotgiu conceived, designed and supervised the study and coordinated regional data collection. A Casuccio and F Vitale coordinated the project. M Barchitta and A Quattrocchi designed the questionnaire and managed data collection at the central level. A Quattrocchi performed the statistical analysis and wrote the first draft of the manuscript. A Agodi, M Barchitta and A Quattrocchi interpreted the results and wrote the advanced version of the manuscript.

All Authors critically reviewed the manuscript and approved the final version.

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Tables

Table 1. Patients' characteristics

		All % (N)	Italian-born % (N)	Foreign-born % (N)	p*	Males % (N)	Females % (N)	p*
Age (mean)		40.7 (246)	48.7 (109)	34.3(137)	**<0.001**	41.0 (157)	40.1 (89)	0.941
Country of birth	Italy	44.3 (112)	-	-	-	42.2 (68)	47.8 (44)	0.389
	Abroad	55.7 (141)	-	-		57.8 (93)	52.2 (48)	
Gender	Males	63.6 (161)	-	-	-	-	-	-
	Females	36.4 (92)	-	-		-	-	
Education level	Low	72.5 (182)	63.6 (70)	79.4 (112)	**0.005**	70.8 (114)	75.6 (68)	0.419
	High	27.5 (69)	36.4 (40)	20.6 (29)		29.2 (47)	24.4 (22)	
Residence	Homeless/prison/ Nursing homes	20.8 (50)	3.7 (4)	34.8 (46)	**<0.001**	26.6 (41)	10.5 (9)	**0.003**
	Apartment (own or rented)	79.2 (190)	96.3 (104)	65.2 (86)		73.4 (113)	89.5 (77)	
Employment	Unemployed or occasional work	42.7 (103)	14.3 (15)	64.7 (88)	**<0.001**	47.1 (73)	34.9 (30)	**0.019**
	Permanent job	26.6 (64)	33.3 (35)	21.3 (29)		28.4 (44)	23.3 (20)	
	Housewife/retired/student	30.7 (74)	52.4 (55)	14.0 (19)		24.5 (38)	41.9 (36)	
Smoking habits	Current	27.2 (67)	29.9 (32)	25.2 (35)	0.409	32.5 (51)	18.0 (16)	**0.014**
	Never/former	72.8 (179)	70.1 (75)	74.8 (104)		67.5 (106)	82.0 (73)	
Alcohol abuse^	Yes	6.9 (17)	6.3 (7)	7.3 (10)	0.758	10.1 (16)	1.1 (1)	**0.007**
	No	93.1 (231)	93.7 (104)	92.7 (127)		89.9 (142)	98.9 (89)	
Chronic diseases[†]	Yes	28.3 (71)	39.1 (43)	19.9 (28)	**0.001**	31.2 (50)	23.1 (21)	0.167
	No	71.7 (180)	60.9 (67)	80.1 (113)		68.8 (110)	76.9 (70)	
Stigma	>median	48.4 (122)	41.4 (46)	53.9 (76)	**0.049**	51.6 (83)	42.9 (39)	0.185
	≤median	51.6 (130)	58.6 (65)	46.1 (65)		48.4 (78)	57.1 (52)	
Integration index (mean)°		4.4 (141)	-	-	-	4.1 (93)	5.1 (48)	**0.008**
Years in Italy (mean)°		7.1 (127)	-	-	-	6.6 (85)	8.2 (42)	0.242
Patient Delay	Median (IQR)	30 (8-60)	15 (7-60)	30 (14-60)	-	30 (10-60)	28 (7-60)	-
	(>30 days)	64.5 (149)	29.1 (30)	40.6 (52)	0.069	37.2 (55)	32.5 (27)	0.480
Health system delay	Median (IQR)	11 (5-33)	21 (7.25-61)	8 (4-22)	-	14.5 (6-37)	8 (4-31)	-
	(>11 days)	48.1 (111)	61.5 (64)	37.0 (47)	**<0.001**	55.4 (82)	34.9 (29)	**0.008**
Diagnostic delay	Median (IQR)	7 (3-30)	15 (4.75-60)	7 (3-15)	-	14 (4-30)	6 (3-28)	-
	(>7 days)	49.3 (111)	64.7 (66)	36.6 (45)	**<0.001**	55.9 (81)	37.5 (30)	**0.008**

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Treatment delay	Median (IQR)	2 (1-4)	2 (1-4)	2 (1-4)	-	2 (1-5)	2 (1-4)	-
	(>2 days)	38.4 (84)	38.4 (38)	38.3 (46)	0.994	40.9 (56)	34.1 (28)	0.322
Total delay	Median (IQR)	45 (25-121)	53 (25-123)	40 (25-97)	-	47 (26-99)	41 (16-120)	-
	(>45 days)	49.5 (97)	56.0 (50)	44.0 (47)	0.091	66.0 (64)	34.0 (33)	0.525

*p-values <0.05 are indicated in bold

^ ≥4 times a week

° only in foreign-born patients

† HIV/AIDS, diabetes, chronic obstructive pulmonary disease, disability, renal failure, cardiovascular disease

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Table 2. Risk analysis for patient delay (Univariate and logistic regression analysis)

	PD >30 days %	OR 95%CI	p*	aOR 95%CI	p*
Foreign-born patients					
No^	29.1	1.00	0.069	-	-
Yes	40.6	1.67 (0.96 - 2.89)			
Do you know what TB is?			0.091	-	-
No^	27.8	1.00			
Yes	39.1	1.66 (0.92 – 3.00)			
Do you know how TB is diagnosed?			0.051	-	-
No^	28.7	1.00			
Yes	41.3	1.75 (0.99 – 3.07)			
Stigma			**0.001**		**0.034**
< median^	24.8	**1.00**		**1.00**	
> median	46.5	**2.64 (1.51 – 4.61)**		**2.30 (1.06 – 4.98)**	
Pay for transportation to reach the health centre			**<0.001**		**0.012**
No^	23.5	**1.00**		**1.00**	
Yes	49.4	**3.18 (1.77 – 5.73)**		**2.66 (1.24 – 5.74)**	
Did you think you had TB?			0.090	-	-
No^	33.8	1.00			
Yes	52.4	2.15 (0.87 – 5.31)			
Was the health centre where you sought care near your living place?			**0.018**		**0.037**
Yes^	21.9	1.00		**1.00**	
No	39.2	2.30 (1.15 – 4.62)		**2.46 (1.05 – 5.74)**	
Weight loss			**<0.001**		**<0.001**
No^	22.5	**1.00**		**1.00**	
Yes	56.2	**4.41 (2.48 – 7.83)**		**4.66 (2.16 – 10.05)**	
Tiredness/weakness			**0.001**	-	-
No^	25.8	**1.00**			
Yes	45.9	**2.44 (1.40 – 4.25)**			
Chest pain			**0.026**		**0.031**
No^	31.4	**1.00**		**1.00**	
Yes	47.5	**1.97 (1.08 – 3.61)**		**2.67 (1.24 – 6.49)**	
Chronic diseases			**0.009**	-	-
No^	29.6	**1.00**			
Yes	47.8	**2.17 (1.21 – 3.90)**			

*p-values <0.05 are indicated in bold

^ reference category

PD: patient delay; OR: odd ratio; a: adjusted: CI: confidence interval; TB: tuberculosis

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Table 3. Risk analysis for health system delay (Univariate and logistic regression analysis)

	HSD >11 days %	OR 95%CI	p*	aOR 95%CI	p*
Foreign-born patients			**<0.001**		**0.024**
No^	61.5	**1.00**		**1.00**	
Yes	37.0	**0.37 (0.22 - 0.63)**		**0.50 (0.27 - 0.91)**	
Age			0.1	-	-
> median	43.7	1.00			
≤median	54.6	1.55 (0.92 - 2.62)			
Gender			**0.003**		**<0.001**
Male^	55.4	**1.00**		**1.00**	
Female	34.9	**0.43 (0.25 - 0.75)**		**0.28 (0.15 - 0.53)**	
First visit with GP			**<0.001**	-	
No^	39.9	**1.00**			
Yes	68.7	**3.30 (1.80 - 6.06)**			
First visit at hospital			**<0.001**		**0.001**
No^	64.6	**1.00**		**1.00**	
Yes	35.7	**0.30 (0.17 - 0. 53)**		**0.35 (0.18 - 0.66)**	
After first visit, did you seek treatment from somewhere else?			**<0.001**	-	-
No^	35.1	**1.00**			
Yes	66.7	**3.70 (2.12 - 6.44)**			
Cough > 3 weeks			**0.036**	-	-
No^	57.7	**1.00**			
Yes	43.1	**0.56 (0.32 - 0.97)**			
Dizziness			**0.040**		**0.023**
No^	49.8	**1.00**		**1.00**	
Yes	21.4	**0.28 (0.75 - 1.01)**		**0.18 (0.04 - 0.78)**	
Prior unspecific treatment			**<0.001**		**0.012**
No^	34.1	**1.00**		**1.00**	
Yes	57.1	**2.58 (1.49 - 4.46)**		**2.25 (1.19 - 4.25)**	
Did you have repeated visits with different providers in a different facility?			**<0.001**	-	-
No^	37.3	**1.00**			
Yes	62.8	**2.84 (1.61 - 5.01)**			

*p-values <0.05 are indicated in bold

^ reference category

HSD: health system delay; OR: odd ratio: a: adjusted; CI: confidence interval; GP: general practitioner;

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Table 4. Risk analysis for total delay (Univariate and logistic regression analysis)

	TOTD >45 days %	OR 95%CI	p*	aOR 95%CI	p*
Foreign-born patients			0.091	-	-
No^	56.0	1.00			
Yes	44.0	0.62 (0.35 – 1.08)			
Do you know what TB is?			**0.012**	-	-
No^	37.1	**1.00**			
Yes	55.8	**2.14 (1.18 – 3.88)**			
Pay for transportation			**0.004**		**0.047**
No^	40.5	**1.00**		**1.00**	
Yes	62.3	**2.43 (1.32 – 4.46)**		**2.10 (1.01 – 4.35)**	
Close distance of the first visit place			**0.003**		**0.006**
Yes^	32.8	**1.00**		**1.00**	
No	56.9	**2.71 (1.38 – 5.31)**		**3.09 (1.38 – 6.90)**	
Cough > 3 weeks			**0.038**	-	-
No^	60.3	**1.00**			
Yes	44.5	**0.53 (0.29– 0.97)**			
Sputum with blood			**0.005**		**0.001**
No^	53.5	**1.00**		**1.00**	
Yes	25.0	**0.29 (0.12– 0.72)**		**0.12 (0.03– 0.43)**	
Weight loss			**0.004**		**0.003**
No^	41.9	**1.00**		**1.00**	
Yes	63.4	**2.40 (1.32– 4.36)**		**3.55 (1.56– 8.09)**	
Prior unspecific treatment			**0.003**		**0.026**
No^	37.4	**1.00**		**1.00**	
Yes	57.4	**2.26 (1.32 – 3.89)**		**2.55 (1.18– 5.82)**	
Did you have repeated visits with the same provider?			**0.029**		**0.012**
No^	53.6	**1.00**		**1.00**	
Yes	34.1	**0.45 (0.22 – 0.93)**		**0.29 (0.11 – 0.76)**	

*p-values <0.05 are indicated in bold

^ reference category

TOTD: total delay; OR: odd ratio: a: adjusted; CI: confidence interval; TB: tuberculosis

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Supplementary material

Table S1. Correctness of patients' knowledge and symptoms recognition stratified for gender and country of birth

Characteristics	Italian-born % (N)	Foreign-born % (N)	p*	Males % (N)	Females % (N)	p*
Do you know what TB is?						
Yes	81.2 (91)	56.4 (79)	**<0.001**	65.8 (106)	70.3 (64)	0.465
No	18.8 (21)	43.6 (61)		34.2 (55)	29.7 (27)	
Do you think TB is a serious disease?						
Yes	67.9 (76)	57.2 (79)	**0.029**	63.9 (101)	58.7 (54)	0.309
No	17.9 (20)	14.5 (20)		13.3 (21)	20.7 (19)	
Don't know	14.3 (16)	28.3 (39)		22.8 (36)	20.7 (19)	
What causes TB?						
Infection	77.5 (86)	43.8 (60)	**<0.001**	61.1 (96)	54.9 (50)	0.491
Punishment	1.8 (2)	0.7 (1)		1.3 (2)	1.1 (1)	
Unavoidable	0.0 (0)	1.5 (2)		1.3 (2)	0.0 (0)	
Don't know	20.7 (23)	54.0 (74)		36.3 (57)	44.0 (40)	
What are the symptoms TB?						
Cough for more than 3 weeks	58.0 (65)	49.6 (70)	0.105	54.7 (88)	51.1 (47)	0.890
Sputum with blood	13.4 (15)	9.2 (13)		11.2 (18)	10.9 (10)	
Fever	15.2 (17)	14.2 (20)		13.7 (22)	16.3 (15)	
Weight loss	2.7 (3)	3.5 (5)		3.7 (6)	2.2 (2)	
Don't know	10.7 (12)	23.4 (33)		16.8 (27)	19.7 (18)	
How a person can get TB?						
Through germs present in air droplets expelled in the cough	69.4 (72)	37.7 (52)	**<0.001**	55.8 (87)	43.0 (37)	0.147
Sharing utensils and objects with an infected person	3.8 (4)	7.2 (10)		5.8 (9)	5.8 (5)	
Don't know	26.9 (28)	55.1 (76)		38.5 (60)	51.2 (44)	
How TB is diagnosed?						
Through sputum examination	39.0 (39)	17.1 (24)	**<0.001**	23.7 (37)	31.0 (26)	0.409
Through X-ray	32.0 (32)	25.7 (36)		28.2 (44)	28.6 (24)	
Don't know	29.0 (29)	57.1 (80)		48.1 (75)	40.4 (34)	
Can TB be cured?						
Yes	93.6 (103)	76.3 (106)	**0.001**	84.8 (134)	82.4 (75)	0.858

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No	0.0 (0)	2.2 (3)		1.3 (2)	1.1 (1)	
Don't know	6.4 (7)	21.6 (30)		13.9 (22)	16.5 (15)	
Can TB require a longer treatment to be cured as for multidrug resistant forms?						
Yes	51.8 (58)	34.5 (48)	**0.016**	41.0 (66)	44.4 (40)	0.868
No	10.7 (12)	18.7 (26)		15.5 (25)	14.4 (13)	
Don't know	37.5 (42)	46.8 (65)		43.5 (70)	41.2 (37)	
Which symptoms made you seek healthcare?						
Cough for more than 3 weeks						
Yes	57.1 (64)	72.3 (102)	**0.011**	65.2 (105)	66.3 (61)	0.861
No	42.9 (48)	27.7 (39)		34.8 (56)	33.7 (31)	
Sputum with blood						
Yes	8.0 (9)	17.7 (25)	**0.025**	14.3 (23)	12.0 (11)	0.601
No	92.0 (103)	82.3 (116)		85.7 (138)	88.0 (81)	
Fever						
Yes	50.9 (57)	50.4 (71)	0.932	50.3 (81)	51.1 (47)	0.905
No	49.1 (55)	49.6 (70)		49.7 (80)	48.9 (45)	
Weight loss						
Yes	28.6 (32)	44.7 (63)	**0.009**	44.7 (72)	25.0 (23)	**0.002**
No	71.4 (80)	55.3 (78)		55.3 (89)	75.0 (69)	
Tiredness/weakness						
Yes	38.4 (43)	52.5 (74)	**0.026**	50.9 (82)	38.0 (35)	**0.048**
No	61.1 (69)	47.5 (67)		49.1 (79)	62.0 (57)	
Dizziness						
Yes	4.5 (5)	6.4 (9)	0.507	6.8 (11)	3.3 (3)	0.232
No	95.5 (107)	93.6 (132)		93.2 (150)	96.7 (89)	
Chest pain						
Yes	17.0 (19)	30.5 (43)	**0.013**	28.6 (46)	17.4 (16)	**0.047**
No	83.0 (4393	69.5 (98)		71.4 (115)	82.6 (76)	
Night sweat						
Yes	20.5 (23)	30.5 (43)	0.073	31.1 (50)	17.4 (16)	**0.017**
No	79.5 (89)	69.5 (98)		68.9 (111)	82.6 (76)	
Did you think you had TB?						
Yes	5.4 (6)	11.4 (16)	0.090	11.8	3.3 (3)	**0.022**

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				(19)		
No	94.6 (106)	88.6 (124)		88.2 (142)	96.7 (88)	
What factors may have made you delay seeking treatment for symptoms that led to the diagnosis of TB?						
Not aware of symptoms						
Yes	38.4 (43)	43.3 (61)	0.434	57.1 (92)	62.0 (57)	0.454
No	61.6 (69)	56.7 (80)		42.9 (69)	38.0 (35)	
Fear of rejection/ losing my job						
Yes	2.7 (3)	6.4 (9)	0.169	5.6 (9)	3.3 (3)	0.402
No	97.3 (109)	93.6 (132)		94.4 (152)	96.7 (89)	
Expensive						
Yes	0.0 (0)	9.2 (13)	**0.001**	5.6 (9)	4.3 (4)	0.667
No	100.0 (112)	90.8 (128)		94.4 (152)	95.7 (88)	
Lack of time						
Yes	5.4 (6)	7.1 (10)	0.573	5.6 (9)	7.6 (7)	0.526
No	94.6 (106)	92.9 (131)		94.4 (152)	92.4 (85)	
Distance to health centre						
Yes	0.9 (1)	2.8 (4)	0.270	2.5 (4)	1.1 (1)	0.442
No	99.1 (111)	97.2 (137)		97.5 (157)	98.9 (91)	
Lack of transportation						
Yes	0.9 (1)	0.7 (1)	0.870	0.0 (0)	2.2 (2)	0.060
No	99.1 (111)	99.3 (140)		100.0 (161)	97.8 (90)	
Previous non-satisfactory experience with the health system						
Yes	1.8 (2)	2.1 (3)	0.846	1.9 (3)	2.2 (2)	0.864
No	98.2 (110)	97.9 (138)		98.1 (158)	97.8 (90)	
Other (clandestine)						
Yes	-	-	-	9.3 (15)	1.1 (1)	**0.010**
No	-	-		90.7 (146)	98.9 (91)	

*p-values <0.05 are indicated in bold

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Table S2. Attitude towards TB stratified for gender and country of birth

	Italian-born % (N)	Foreign-born % (N)	p*	Males % (N)	Females % (N)	p*
Should people with TB disclose their illness to other people?						
Yes	70.5 (79)	47.1 (66)	**0.001**	53.1 (85)	65.2 (60)	**0.040**
No	8.9 (10)	19.3 (27)		18.8 (30)	7.6 (7)	
Don't know	20.5 (23)	33.6 (47)		28.1 (45)	27.2 (25)	
Who do you think is more likely to get TB, men or women?						
Men	12.5 (14)	15.0 (21)	0.305	21.2 (34)	1.1 (1)	**<0.001**
Women	5.4 (6)	10.0 (14)		4.4 (7)	14.1 (13)	
Don't know	82.1 (92)	75.0 (105)		74.9 (119)	84.8 (78)	
How did you feel when you found out that you had TB?						
Scared	37.5 (42)	45.4 (64)	0.376	36.6 (59)	51.1 (47)	0.164
Depressed	20.5 (23)	14.2 (20)		18.0 (29)	15.2 (14)	
Didn't believe (denial)	29.5 (33)	31.2 (44)		33.5 (54)	25.0 (23)	
Other	12.5 (14)	9.2 (13)		11.8 (19)	8.7 (8)	
Did you inform your friends/ family that you had TB?						
Yes	90.9 (100)	55.1 (76)	**<0.001**	61.4 (97)	87.8 (79)	**<0.001**
No	9.1 (10)	44.9 (62)		38.6 (61)	12.2 (11)	
Have your relationships with your friends/ family changed since finding out you have TB?						
Yes	22.0 (24)	14.7 (20)	0.138	15.4 (24)	22.5 (20)	0.165
No	78.0 (85)	85.3 (116)		84.6 (132)	77.5 (69)	
If yes, how?						
Improved	41.7 (10)	10.5 (2)	**0.024**	26.1 (6)	30.0 (6)	0.775
Worsened	58.3 (14)	89.5 (17)		73.9 (17)	70.0 (14)	
Are people with TB discriminated in the community?						
Yes	46.4 (51)	41.0 (57)	**0.002**	40.3 (64)	48.9 (44)	0.386
No	33.6 (37)	19.4 (27)		26.4 (42)	24.4 (22)	
Don't know	20.0 (22)	39.6 (55)		33.3 (53)	26.7 (24)	
Among TB patients, are male or female patients more discriminated?						
Male	3.7 (4)	9.3 (13)	**0.027**	10.1 (16)	1.1 (1)	**<0.001**
Female	2.85 (3)	8.6 (12)		2.5 (4)	12.1 (11)	
Don't know	93.6 (102)	82.1 (115)		87.3 (138)	86.8 (79)	

*p-values <0.05 are indicated in bold

TB: tuberculosis

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Table S3. Risk analysis for DD (Univariate and logistic regression analysis)

	DD >7 days %	OR 95%CI	p	aOR 95%CI	p
Foreign-born patients			**<0.001**		**0.024**
Yes^	36.6	**1**		**1**	
No	64.7	**0.32 (0.18 – 0.54)**		**0.48 (0.25 – 0.91)**	
Chronic disease			0.061	-	-
Yes^	59.3	1			
No	45.1	1.77 (0.97 – 3.24)			
Gender			**0.008**		**<0.001**
Female^	37.5	**1**		**1**	
Male	55.9	**0.47 (0.27 – 0.83)**		**0.30 (0.15 – 0.58)**	
First visit: General practitioner			**<0.001**	-	-
Yes^	71.2	**1**			
No	40.5	**3.63 (1.95 – 6.77)**			
First visit: Hospital			**<0.001**		**0.002**
Yes^	36.1	**1**		**1**	
No	67.0	**0.28 (0.16 – 0.49)**		**0.35 (0.18 – 0.67)**	
After first visit, did you seek treatment from somewhere else?			**<0.001**	-	-
Yes^	71.0	**1**			
No	34.4	**4.67 (2.62 – 8.31)**			
Cough more than 3 weeks			**0.035**		**0.048**
Yes^	44.2	**1**		**1**	
No	59.0	**0.55 (0.32 – 0.96)**		**0.51 (0.27 – 0.99)**	
Dizziness			**0.051**		**0.039**
Yes^	23.1	**1**		**1**	
No	50.9	**0.28 (0.08 – 1.08)**		**0.21 (0.04 – 0.92)**	
Prior unspecific treatment			**<0.001**		**0.002**
Yes^	60.4	**1**		**1**	
No	33.0	**3.11 (1.78 – 5.43)**		**2.85 (1.47 – 5.52)**	
With whom did you have repeated visits?: Different providers in a different facility			**<0.001**	-	-
Yes^	66.3	**1**			
No	37.6	**3.26 (1.82 – 5.86)**			

*p-values <0.05 are indicated in bold

^ reference category

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Determinants of patient and health system delay among Italian and foreign-born pulmonary tuberculosis patients: a multicentre cross-sectional study

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To the memory of Professor Caterina Mammina, University of Palermo, First Coordinator of the project

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ABSTRACT

Objectives

The aim of this cross-sectional study was to identify key factors associated with patient delay (PD), health system delay (HSD) and total delay (TOTD) in tuberculosis (TB) patients to inform TB control programs.

Setting

The study was carried out in four Italian regions (Calabria, Apulia, Sardinia, and Sicily) from October 2014 to July 2016. Data were obtained using a questionnaire including: socio-demographic and lifestyle data, integration index, comorbidities, patient knowledge and attitudes towards TB, stigma, access to TB care, health seeking behaviours, and satisfaction with care.

Participants

Patients' inclusion criteria were being diagnosed as a new smear positive pulmonary TB case and living in one of the above-mentioned Italian regions. A total of 344 patients from 30 healthcare centres were invited to participate and 253 patients were included in the analysis (26.5% non-response rate). Overall, 63.6% of patients were males and 55.7% were non-Italian born.

Outcome measures

Risk factors for PD, HSD and TOTD in TB patients were assessed by multivariable analysis, adjusting for confounding.

Results

Median PD, HSD and TOTD were 30, 11 and 45 days, respectively. Factors associated with longer PD were: stigma, chest pain, weight loss, paying for transportation and distance to the health centre (the latter three also associated with TOTD). Being foreign-born, female and seeking care for the first time at hospital were associated with shorter HSD, while, prior unspecific treatment was associated with longer HSD and TOTD. Sputum with blood and repeated visits with the same provider showed shorter TOTD.

Conclusions

The study identifies several determinants of delays associated with patient's behaviours and healthcare qualities. Tackling TB effectively requires addressing key risk factors that make individuals more vulnerable

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by the means of public health policy, cooperation and advocacy to ensure that all patients have easy access to care and receive high quality healthcare.

Strengths and limitations of this study

- This is the first multiregional cross-sectional study, in Italy, investigating the association of key factors with patient delay, health system delay and total delay in pulmonary tuberculosis patients.
- Data were collected by healthcare providers and cultural mediators, using a multilingual standardised questionnaire.
- The prospective collection of data and the adjustment for confounding factors with logistic regression analysis are among the strengths of the present study.
- A selection bias should be considered, especially for foreign-born patients who may have experienced difficulties during the interview, resulting in refusal or in missing data.
- Self-reported dates for onset of symptoms and health care seeking may have been affected by recall bias.

Keywords

Surveillance; public health policy; social epidemiology; TB patients.

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INTRODUCTION

Early diagnosis and prompt treatment of tuberculosis (TB) disease represent key components of any effective national TB control programme.[1 2] If adequately implemented and scaled-up, they can contribute to the reduction of *Mycobacterium tuberculosis* transmission and TB elimination by 2050.[3]

However, delays in diagnosis and treatment of TB frequently occur.[4] Long delays lead to a more advanced disease that may result in poor response to therapies, undesirable clinical *sequelae*, and higher mortality risk.[5] In addition, delay contributes to *M. tuberculosis* transmission within the community.[6 7] It has been shown that an untreated smear-positive patient can infect, on average, 10 healthy contacts annually.[8] Finally, TB diagnosis delay is associated with higher direct and indirect costs.[9]

Delay may occur at patient or at health system level. Factors contributing to patient delay (PD) can be: socio-demographic, physical, financial, health literacy, religious-cultural and stigma.[10] Health system delay (HSD) related factors can be: poor TB knowledge by healthcare providers and poor availability of effective diagnostic tools, number and types of providers encountered before TB diagnosis, patient satisfaction with TB services and waiting time.[10 11] Thus, understanding and identifying the causes of delay in diagnosis and treatment initiation are critical to strengthen TB control programs. Particularly, the importance of social variables as drivers of epidemics and disease risk has been long recognised. Incorporating the perspectives and methods of social epidemiology into studies of infectious disease, many opportunities arise to control the disease.[12]

However, in Europe, and especially in Italy, few studies have focused on social determinants and TB delays.

The aim of the present study was to identify the duration and the key factors related to PD, HSD and total delay (TOTD) in pulmonary TB patients, in four Italian Southern regions, with a focus on social determinants.

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METHODS

Study design

The present cross-sectional study was conducted in four Italian regions (Calabria, Apulia, Sardinia, and Sicily) from October 2014 to July 2016, and was approved and financed by the Italian Ministry of Health.

Patients' inclusion criteria were being diagnosed as a new smear positive pulmonary TB case (with or without extra-pulmonary TB) and living in one of the above-mentioned Italian regions. Foreign-born patients were enrolled regardless of their legal migrant status (e.g. refugees, asylum seeker, and illegal migrants). Negative smear, relapse, retreatment cases and those with only extra-pulmonary TB were excluded.

The project was performed according to the Declaration of Helsinki, participants were fully informed of the purpose of the study and signed a written informed consent. All data collected were treated confidentially and analysed in aggregated and anonymous form.

Patient and Public Involvement

The present study was conducted without patient and public involvement. Results of the research will be available on request to any study participant to disseminate key study findings providing feedback on the research outcome towards which they have contributed.

Sample Size calculation and Sampling Procedure

A sample size of 261 was estimated by using single population proportion estimation formula with an assumption of 95% confidence interval, 6% margin of error, and 50.4% proportion of PD (> 30 days).[13] Furthermore, considering 20% of nonresponse rate, the final sample size was 321. All patients meeting the inclusion criteria, attending the healthcare facility during the study period, were prospectively invited to participate in the study.

Data collection and definitions

Data were collected by healthcare workers of each participating centre, during a face-to-face interview at the time when patients were diagnosed and/or initiated treatment. A standardised questionnaire available in Italian, English, and French was used, and if possible, a cultural and linguistic mediator assisted the interview with the task to facilitate communication and understanding, both on linguistic and cultural level.

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Operators with adequate background of the health topic, within the specific cultures/languages, supported and assisted patients and healthcare professionals during clinical examinations.

The questionnaire contained several domains: i) socio-demographic and lifestyle data; ii) integration index (II) in Italy (only for foreign-born patients), computed as described in a previous study;[14] iii) TB comorbidities; iv) patient knowledge of TB-associated symptoms and attitudes towards TB; v) TB related stigma, measured according to the WHO questionnaire;[15] vi) access to TB diagnosis and treatment and health seeking behaviours; vii) dates of onset of symptoms, first contact with healthcare service, TB diagnosis confirmation and treatment initiation; viii) satisfaction with care, assessed by adopting and modifying the USAID questionnaire.[16]

PD was defined as the time interval between the onset of symptoms and patient's first contact with any type of health care service (including hospital and primary health care).[15 16] HSD was defined as the time interval between the first consultation with a healthcare provider and the initiation of treatment.[15 16] This can be subdivided into: diagnostic delay (DD) as the time interval between the presentation to a healthcare provider and the date of diagnosis and treatment delay (TD) as the time interval between TB diagnosis and initiation of anti-TB treatment. Thus, TOTD was defined as the time interval from onset of symptoms until treatment initiation.[16 17]

Statistical analysis

Statistical analyses were performed using the SPSS software (IBM SPSS Statistics for Windows, version 22.0).

The response rate and descriptive statistics were used to characterise the sample using frequencies, means, medians and interquartile ranges (IQRs). Valid percentage was reported when missing data were excluded.

Poverty was defined in relation to housing circumstances as living in community centres, first aid centres or prisons. Education level was dichotomised into two categories (high and low), using a cut-off of 8 school years.

Variables related to stigma and satisfaction with care were recorded on a 5-point Likert scale.[15 16] Scores were converted as mean percentage score, calculated as follows: (sum of score obtained/maximum score that could be obtained) × 100.

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For TB cases born abroad, the II was calculated based on the score sum of 11 selected variables from the study questionnaire and then standardised to range from 0 to 10.[14]

Longer delays (outcome) were defined according to previous Italian studies. Particularly, long PD was defined as >30 days, while long HSD and TOTD were defined as > the median value observed in the study population, for HSD and TOTD, respectively.[13 18]

Prevalence estimates of longer delay, using cut-off values reported from other studies, were reported in Supplementary Table S1.

Median values were also used as cut-off points to dichotomise quantitative variables (e.g. age and stigma). The two-tailed Chi-squared test was used for the statistical comparison of categorical variables, whereas quantitative variables were compared using Student's *t* test, as the sample was big enough. The Levene's test was performed to verify the homogeneity of variance across groups.

The characteristics of patients with longer delays (all forms) were compared to those of patients without (comparators) and the crude odds ratios (ORs) and the corresponding 95% confidence intervals (95%CIs) were computed.

All variables with P <0.1 on univariate analysis were included in the multivariable logistic regression analysis, using a backward-stepwise selection procedure. The breakpoint for variable removal was set at P= 0.10. The adjusted ORs (aOR) with the respective 95% CIs were reported. A P-value < 0.05 was considered statistically significant.

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RESULTS

A total of 344 patients from 30 healthcare centres were invited to participate. Overall, 91 (26.5%) refused the interview, and 253 patients were included in the analysis. Patients who refused the interview were older than patients who agreed (mean age: 46.0 and. 40.7 years, respectively; P = 0.023). However, no statistical differences resulted for Country of birth and gender. Completion rate for all questions included in the analysis was ≥80%.

Overall, 55.3% of patients were temporary or permanently living in Sicily, 22.1% in Calabria, 17.4% in Apulia, and 5.2% in Sardinia.

Table 1 shows the main characteristics of the study population and comparisons for Country of birth and gender. Mean age was 40.7 years (median: 38; IQR 27-53) and 63.6% were males. One hundred forty-one (55.7%) patients were born abroad and they were younger than Italians (mean age: 34.3 years and 48.7 years, respectively; P <0.001).

Stratifying by Country of origin, 47.9% of patients came from European Countries, and mostly from Romania (82.1%), 28.6% from the African Countries, 11.4% from Eastern Mediterranean Countries, 9.3% from South-East Asia, 2.1% from Western Pacific Countries, and 0.7% from American Countries. Foreign-born patients reported higher degree of poverty and literacy: they lived in nursing homes or did not have permanent residency (47.8%), 64.7% were unemployed or occasional workers, and 79.4% were illiterate or had less than 8 years of educational activities (P <0.05).

About one-third suffered of chronic diseases (i.e. HIV/AIDS, diabetes, chronic obstructive pulmonary disease, disability, renal failure and cardiovascular disease), particularly those born in Italy (39.1%). Current smokers and alcohol users were 27.2% and 6.9%, respectively. Higher percentages of smokers and alcohol users were found among male patients (32.5% and 10.1%). However, no significant differences were observed between Italian and foreign-born patients (Table 1).

Patient knowledge and symptoms recognition

Foreign-born patients reported lack of knowledge on the disease more often compared with Italian-born (Supplementary Table S2). Foreign-born patients were less aware that TB is an infectious disease and is transmitted by airborne bacteria. They did not know the symptoms most frequently associated with the

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disease, how TB is diagnosed and cured, and that multi-drug resistant TB may require a longer treatment time to achieve a cure (P <0.05).

Only 3.6% of TB patients reported no symptoms, while 49% of patients reported three or more symptoms. Overall, 65.6% had cough for more than 3 weeks. Sputum with blood was reported by only 13.4% of patients. The main reason for not seeking care was that they perceived the TB symptoms to be mild (58.9%).

Foreign-born patients reported more frequently the following symptoms: cough, sputum with blood, weakness, weight loss, and chest pain, compared with Italian-born patients. Furthermore, women reported tiredness/weakness, weight loss, chest pain, and night sweating less frequently compared with men. Being irregular migrants was the only reason for delayed seeking care in women, while in men other motivations were reported (Table S2).

Attitude towards TB and stigma

A higher percentage of men (38.6%) and foreign-born patients (44.9%) did not inform their families and friends on the disease, compared with women (12.2%) and Italian-born (9.1%) (P< 0.001). Detailed results are reported in Supplementary Table S3.

A moderate level of stigma was found (mean: 59.5%; median and IQR: 58.7%, 22.7%-94.7%) in all patients. Overall, 53.9% of foreign-born patients reported TB related stigma above the median value, compared with 41.4% of Italian born (P= 0.049) (Table 1).

Healthcare-seeking behaviour and access to TB care centres

General Practitioners (GP) were consulted, as first choice, by 30% of patients, mostly Italians (46.8%). On the contrary, foreign-born cases were shown to seek more frequently the hospital care (70.3%). Around 41% of the cases were visited by more than one healthcare provider, and this was mainly reported by the Italian group (53.2% *vs*. 31.7%; P= 0.001). Overall, 59% of the cases received unspecific treatment (mainly antibiotics) before TB diagnosis; this occurred more frequently among cases born in Italy (75.7% *vs*. 51.6%; P= 0.005).

Risk analysis of delay

Median PD, HSD and TOTD were 30, 11, and 45 days, respectively (Table 1). On univariate analysis, factors associated with long PD (> 30 days) were TB-related stigma, paying for transportation and distance

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to get to the healthcare centre, presence of unintentional weight loss, fatigue and chest pain. All these factors, but fatigue remained associated with PD on multivariate analysis (Table 2).

Prior unspecific treatment, patients referring to a GP at the first visit, and those visited by multiple providers in different facilities were more likely to report long HSD (> 11 days), while female gender, non-Italian origin, seeking care at hospital level, presence of cough for more than 3 weeks and dizziness were associated with shorter HSD. On multivariate analysis, being foreign-born and female, seeking care at hospital and presence of dizziness remained associated with shorter HSD. Instead, prior unspecific treatment was associated with longer HSD (Table 3).

Factors associated with long DD (>7 days), were identical to those associated with HSD, and in addition, having cough for more than 3 weeks was significantly associated with shorter DD (Table S4). No variables were associated with long TD (>2 days).

Finally, good knowledge of TB, paying for transportations, distance to reach the health centre, prior unspecific treatment, and weight loss were associated with long TOTD (> 45 days), while patients reporting cough and hemophthisis and who had repeated visits with the same provider showed shorter TOTD. In the logistic regression analysis, all variables except cough and knowledge of the disease were confirmed (Table 4).

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DISCUSSION

Reducing the time interval between symptoms recognition and TB treatment can decrease mycobacterial transmission, morbidity, and mortality. Although there is no general consensus on what may constitute an acceptable interval between onset of symptoms and initiation of TB treatment,[19] it has been suggested that overall TB delay could be used as a key indicator of programme performance.[4]

The TB notification rate in the general Italian population has been stable in the last years.[20] However, most of the cases occur in vulnerable groups, who do not recognise the symptoms or have poor access to healthcare services. The two most affected groups are the elderly and foreign-born people. The latter group accounts for about 50% of all TB cases in Italy (data until 2008).[21]

In our study, 55.7% patients were foreign-born, and they were younger than Italians. Younger age among foreign-born patients has also been reported in other studies.[13 22] Although, the TB notification rate is decreasing in Europe, the reduction in individuals of foreign origin is still slower than in native residents. This represents one of the main challenges for TB elimination, especially in those European countries where individuals of foreign-born origin represent a large proportion of TB cases.[23]

In our study, the median values for PD (30 days) and HSD (11 days, of which 7 days for DD and 2 days for TD, respectively) are similar to those reported by other studies conducted in Italy and in other European countries with a low-TB incidence. Particularly, a recent Italian study reported median PD and HSD values of 31 and 15 days, respectively.[13] European studies reported median PDs of 14 days (France),[24] 28 days (Norway),[25] and 29 days (UK).[19] Considering HSD (and its two components), studies reported median values of 15 days (Croatia),[26] 25 days (for DD in France),[24] 30 days (UK),[19] and 33 days (Norway).[25] However, in our study, median TOTD (45 days) was lower than values reported elsewhere, which ranged between 62 days (UK),[19] and 63 days (Norway).[25]

Table S1 shows median values reported by other studies,[13 19 24-26] and the prevalence of delay that would have been detected in our study, by using them.

It is worth noting that some studies evaluated both forms of TB (pulmonary and extra-pulmonary), and tools for data collection and definitions of delays were widely heterogeneous among studies, thus comparisons should be made with caution.

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Nevertheless, median values detected in our study are encouraging. Indeed, for PD a median value of 30 days has been considered an acceptable value by many authors,[18 27] although others have suggested values less than 3 weeks.[28]

Regarding HSD, our median value is below the accepted value, which is considered to be 15 days.[27] Low values of HSD and TOTD might probably due to a higher level of awareness of TB among involved healthcare professionals in Italy, in recent years. Similarly to our results, other studies have found that PD was longer than HSD,[13 29] while others have found the opposite,[24 25] or no differences.[19] It is likely that patients who contact the health system later could have more severe symptoms facilitating TB suspicion and prompt diagnosis,[13] thus the higher the PD, the lower the HSD, and *vice versa.*[4 25]

In our study, longer PD was associated with high degree of stigma, paying for transportation, distance to healthcare facility, presence of unintentional weight loss and chest pain. Aside from stigma and chest pain all others were also detected as risk factors for TOTD. Our results are consistent with findings of the WHO Eastern Mediterranean Region study, where stigma, economic factors, and time to reach the health facility were among the main determinants for delayed access to healthcare system.[15]

TB-related stigma represents a cultural aspect which drives individuals to hide their condition from others, and refusing seeking care,[30] but evidence shows that stigma barriers may be avoided through interventions addressed improving TB-related health literacy.[10]

The reason why chest pain and weight loss were associated with long PD is not clear, because these symptoms, together with persistent cough, are considered key TB signs. Other studies retrieved similar results. Chest pain was found positively associated with longer PD (> 90 days) in a Brazilian study,[31] and with TOTD (>60 days) in Ethiopia.[27] Similarly, weight loss was associated with longer PD, both in Brazil (>30 days)[31] and in Italy (>15 days),[13] with PD (>27 days) and TOTD (>50 days) in Uzbekistan,[32] and with HSD (>18 days) in another Brazilian study.[33] These results could be explained by the assumption that patients consider these as transient symptoms from a general illness, hence, maybe, initiating self-treatment lasting until deterioration and manifestation of other specific symptoms. Furthermore, timely referral to healthcare facilities for disabling symptoms may be challenging due to financial constraints, poor health

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literacy, and stigma. In addition, a long delay until diagnosis favours disease progression and therefore symptom appearance. Also, non-specific symptoms could lead to longer suspicion delays by the clinician.

Especially for foreign-born patients, language barriers, poor knowledge of symptoms, fear of immigration authorities and long wait for appointment have been associated with delay in seeking care,[34 35] raising concerns about the equity of access to care among TB patient. Thus, understanding immigrants' views of TB and the obstacles that they face when accessing the health system, taking into consideration the social, economic and legislative context of the new Country where they live, has an important role and should be considered in TB control programmes.

The association of HSD with birth place might be due to the low TB rate in Italy, thus TB would be less suspected and investigated in the Italian-born population, or by contrast, being a migrant may point physicians to a prompt TB diagnosis.[13] This finding is consistent with other studies.[13 19]

Female gender was associated with shorter HSD, in contrast with other studies.[4] In general, female patients are reported to encounter greater barriers (financial, physical, and health literacy) for appropriate medical care and treatment. Further investigations on possible confounders should be considered.

In line with others,[4 30 36 37] a first healthcare contact in hospital, was strongly associated with shorter HSD, while referring to GP was a risk factor for longer HSD. A combination of several factors, may explain this result: lack of TB suspicion among primary care providers in low-endemic countries; seeking assistance in hospital for patients at higher risk of TB (e.g. migrants from endemic countries) and/or with more severe TB disease who are thus investigated faster; availability and easier access to diagnostic tests and specialists within the hospital.[24]

Furthermore, repeated visits, especially with different healthcare workers in different health facilities, has been retrieved as predictor of HSD in other studies,[15 17 38-40] however we did not find this association in the final model. It has been reported that generally, patients see different healthcare providers in case of poor clinical suspicions of signs and symptoms, failure to request for proper investigations, refer patients to specialised TB centre for further investigations,[41] or when they receive inappropriate treatment that can modify the clinical picture of the disease.[40]

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The association of HSD and TOTD with previous unspecific treatment is in agreement with other results.[13 24] This is of a particular concern in the current global epidemiological scenario where antimicrobial resistance is rapidly developing and spreading and a more prudent use of antimicrobials is urgently needed, by for instance, limiting the use of empirical antibiotics in patients with respiratory symptoms.[24] Training GP for the early identification of signs and symptoms and prompt referral of suspected cases to TB diagnosis and treatment health centres is essential.

Finally, other factors associated with shorter TOTD were presenting sputum with blood and having visits by the same provider. Sputum with blood is usually recognised as a late sign of TB, thus patients with severe symptoms are immediately suspected for TB. Intuitively, having visits with the same provider might reduce repetition of examinations and misdiagnosis.

Our study has some limitations, some of them specific to the cross-sectional study design. A selection bias should be considered. In fact, the mediator was not often available in hospitals, thus, foreign-born patients recently arrived in Italy, may have experienced difficulties during the interview, resulting in refusal or in missing data. In any case, no difference has been detected for country of birth among responders and non-responders and the completion rate for the questions included in the analyses was at least 80%. Also, the low education level of the overall population may have contributed to an information bias. However, since a higher frequency of low educational level was shown in foreign-born patients than in patients born in Italy, a differential misclassification could be supposed and thus the direction of the bias is unpredictable. Furthermore, as the onset date of symptoms was self-reported, it may have been affected by recall bias that could have occurred heterogeneously in the whole sample. Another limitation is that data on HIV status and other risk factors (e.g. alcohol and drug use and detention status) were not available for the vast majority of patients.

In the present study, several aspects have been investigating as key factors contributing to PD and HSD in TB patients. However, further studies addressing other components of delays[6 30 42] may be necessary to understand all factors that are closely associated with delay in the diagnosis and treatment of TB. Furthermore, in our regression model we did not take into account for the potential collinearity of

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explanatory variables, which could explain complex relationship involving several risk factors at the same time, for example the use of unspecific antibiotics and multiple visits with healthcare providers

A possible approach to combine the relevant variables into summary scores or indexes and assesses the relationship of these with the outcome of interest should be explored.

This is the first multiregional cross-sectional study, conducted in Italy, which investigated the association of several factors with PD, HSD and TOTD delay in pulmonary TB patients. It provides new evidence which can be addressed through tailored actions, in order to reduce the burden of TB in Italy. Furthermore, the prospective collection of data in four Italian regions, using a multilingual standardised questionnaire and the adjustment for confounding factors with logistic regression analysis are among the strengths of the present study.

In conclusion, this study detected several modifiable factors associated with longer delay in TB patients, both attributable to patients and health system service. Interventions designed to empower the general population and stakeholders, by increasing knowledge and awareness and screening of active TB in migrants upon arrival are key actions to reduce PD and HSD and achieve TB control.[43] Strategies should mainly target alleviating stigma around TB, improving TB-related health literacy and access to care among the general population, education of GP, earlier referral of TB suspects to the hospital, where appropriate investigations for final diagnosis are readily available, and limiting the use of unspecific treatment in patients with respiratory symptoms.

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All CCM 2013 TB network collaborators supervised and coordinated at the hospital level patients' enrolment and data collection.

COMPETING INTERESTS

The Authors declare that they have no competing interests.

ETHICS

All procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent was obtained from all patients for being included in the study.

DATA SHARING STATEMENT

No additional data available

FUNDING SOURCE

The project entitled "*Valutazione dei determinanti di ritardo nell'accesso ai servizi sanitari, nella diagnosi e nel trattamento della tubercolosi polmonare (PTB) in popolazioni vulnerabili. Valutazione dell'impatto sull'epidemiologia locale e sulla prevalenza di resistenza/multiresistenza ai farmaci antitubercolari* - "Assessment of determinants of delay in healthcare access for the diagnosis and treatment of PTB in

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vulnerable populations. Assessment of the impact on the local epidemiology and on the prevalence of antituberculosis drug resistance/multiresistance" was approved and financially supported by the Italian Ministry of Health (Centro nazionale per la prevenzione e il Controllo delle Malattie, CCM 2013). The funding source had no role in any phase of the development of the current study.

CONTRIBUTORSHIP

A Agodi, C Nobile, R Prato and G Sotgiu conceived, designed and supervised the study and coordinated regional data collection. A Casuccio and F Vitale coordinated the project. M Barchitta and A Quattrocchi designed the questionnaire and managed data collection at the central level. A Quattrocchi performed the statistical analysis and wrote the first draft of the manuscript. A Agodi, M Barchitta and A Quattrocchi interpreted the results and wrote the advanced version of the manuscript.

All Authors critically reviewed the manuscript and approved the final version.

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Tables

Table 1. Patients' characteristics

		All % (N)	Italian-born % (N)	Foreign-born % (N)	p*	Males % (N)	Females % (N)	p*
Age (mean)		40.7 (246)	48.7 (109)	34.3(137)	**<0.001**	41.0 (157)	40.1 (89)	0.941
Country of birth (n=253)	Italy	44.3 (112)	-	-	-	42.2 (68)	47.8 (44)	0.389
	Abroad	55.7 (141)	-	-		57.8 (93)	52.2 (48)	
Gender (n=253)	Males	63.6 (161)	60.7 (68)	66.0 (93)	0.389-	-	-	-
	Females	36.4 (92)	39.3 (44)-	34.0 (48)-		-	-	
Education level (n=251)	Low	72.5 (182)	63.6 (70)	79.4 (112)	**0.005**	70.8 (114)	75.6 (68)	0.419
	High	27.5 (69)	36.4 (40)	20.6 (29)		29.2 (47)	24.4 (22)	
Residence (n=240)	Homeless/prison/ Nursing homes	20.8 (50)	3.7 (4)	34.8 (46)	**<0.001**	26.6 (41)	10.5 (9)	**0.003**
	Apartment (own or rented)	79.2 (190)	96.3 (104)	65.2 (86)		73.4 (113)	89.5 (77)	
Employment (n=241)	Unemployed or occasional work	42.7 (103)	14.3 (15)	64.7 (88)	**<0.001**	47.1 (73)	34.9 (30)	**0.019**
	Permanent job	26.6 (64)	33.3 (35)	21.3 (29)		28.4 (44)	23.3 (20)	
	Housewife/retired/student	30.7 (74)	52.4 (55)	14.0 (19)		24.5 (38)	41.9 (36)	
Smoking habits (n=236)	Current	27.2 (67)	29.9 (32)	25.2 (35)	0.409	32.5 (51)	18.0 (16)	**0.014**
	Never/former	72.8 (179)	70.1 (75)	74.8 (104)		67.5 (106)	82.0 (73)	
Alcohol abuse^ (n=248)	Yes	6.9 (17)	6.3 (7)	7.3 (10)	0.758	10.1 (16)	1.1 (1)	**0.007**
	No	93.1 (231)	93.7 (104)	92.7 (127)		89.9 (142)	98.9 (89)	
Chronic diseases† (n=251)	Yes	28.3 (71)	39.1 (43)	19.9 (28)	**0.001**	31.2 (50)	23.1 (21)	0.167
	No	71.7 (180)	60.9 (67)	80.1 (113)		68.8 (110)	76.9 (70)	
Stigma (n=252)	>median	48.4 (122)	41.4 (46)	53.9 (76)	**0.049**	51.6 (83)	42.9 (39)	0.185
	≤median	51.6 (130)	58.6 (65)	46.1 (65)		48.4 (78)	57.1 (52)	
Integration index (mean)°		4.4 (141)	-	-	-	4.1 (93)	5.1 (48)	**0.008**
Years in Italy (mean)°		7.1 (127)	-	-	-	6.6 (85)	8.2 (42)	0.242
Patient Delay (n=231)	Median (IQR)	30 (8-60)	15 (7-60)	30 (14-60)	-	30 (10-60)	28 (7-60)	-
	(>30 days)	64.5 (149)	29.1 (30)	40.6 (52)	0.069	37.2 (55)	32.5 (27)	0.480
Health system delay (n=225)	Median (IQR)	11 (5-33)	21 (7.25-61)	8 (4-22)	-	14.5 (6-37)	8 (4-31)	-
	(>11 days)	48.1 (111)	61.5 (64)	37.0 (47)	**<0.001**	55.4 (82)	34.9 (29)	**0.008**
Diagnostic delay (n=225)	Median (IQR)	7 (3-30)	15 (4.75-60)	7 (3-15)	-	14 (4-30)	6 (3-28)	-
	(>7 days)	49.3 (111)	64.7 (66)	36.6 (45)	**<0.001**	55.9 (81)	37.5 (30)	**0.008**

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Treatment delay (n=219)	Median (IQR)	2 (1-4)	2 (1-4)	2 (1-4)	-	2 (1-5)	2 (1-4)	-
	(>2 days)	38.4 (84)	38.4 (38)	38.3 (46)	0.994	40.9 (56)	34.1 (28)	0.322
Total delay (n=208)	Median (IQR)	45 (25-121)	53 (25-123)	40 (25-97)	-	47 (26-99)	41 (16-120)	-
	(>45 days)	49.5 (97)	56.0 (50)	44.0 (47)	0.091	66.0 (64)	34.0 (33)	0.525

*p-values <0.05 are indicated in bold

^ ≥4 times a week

° only in foreign-born patients

† HIV/AIDS, diabetes, chronic obstructive pulmonary disease, disability, renal failure, cardiovascular disease

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Table 2. Risk analysis for patient delay (Univariate and logistic regression analysis)

	PD >30 days %	OR 95%CI	p*	aOR 95%CI	p*
Foreign-born patients					
No^	29.1	1.00	0.069	-	-
Yes	40.6	1.67 (0.96 - 2.89)			
Do you know what TB is?			0.091	-	-
No^	27.8	1.00			
Yes	39.1	1.66 (0.92 – 3.00)			
Do you know how TB is diagnosed?			0.051	-	-
No^	28.7	1.00			
Yes	41.3	1.75 (0.99 – 3.07)			
Stigma			**0.001**		**0.034**
< median^	24.8	**1.00**		**1.00**	
> median	46.5	**2.64 (1.51 – 4.61)**		**2.30 (1.06 – 4.98)**	
Pay for transportation to reach the health centre			**<0.001**		**0.012**
No^	23.5	**1.00**		**1.00**	
Yes	49.4	**3.18 (1.77 – 5.73)**		**2.66 (1.24 – 5.74)**	
Did you think you had TB?			0.090	-	-
No^	33.8	1.00			
Yes	52.4	2.15 (0.87 – 5.31)			
Was the health centre where you sought care near your living place?			**0.018**		**0.037**
Yes^	21.9	1.00		**1.00**	
No	39.2	2.30 (1.15 – 4.62)		**2.46 (1.05 – 5.74)**	
Weight loss			**<0.001**		**<0.001**
No^	22.5	**1.00**		**1.00**	
Yes	56.2	**4.41 (2.48 – 7.83)**		**4.66 (2.16 – 10.05)**	
Tiredness/weakness			**0.001**	-	-
No^	25.8	**1.00**			
Yes	45.9	**2.44 (1.40 – 4.25)**			
Chest pain			**0.026**		**0.031**
No^	31.4	**1.00**		**1.00**	
Yes	47.5	**1.97 (1.08 – 3.61)**		**2.67 (1.24 – 6.49)**	
Chronic diseases			**0.009**	-	-
No^	29.6	**1.00**			
Yes	47.8	**2.17 (1.21 – 3.90)**			

*p-values <0.05 are indicated in bold

^ reference category

PD: patient delay; OR: odd ratio; a: adjusted: CI: confidence interval; TB: tuberculosis

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Table 3. Risk analysis for health system delay (Univariate and logistic regression analysis)

	HSD >11 days %	OR 95%CI	p*	aOR 95%CI	p*
Foreign-born patients			**<0.001**		**0.024**
No^	61.5	**1.00**		**1.00**	
Yes	37.0	**0.37 (0.22 - 0.63)**		**0.50 (0.27 - 0.91)**	
Age			0.1	-	-
> median	43.7	1.00			
≤median	54.6	1.55 (0.92 - 2.62)			
Gender			**0.003**		**<0.001**
Male^	55.4	**1.00**		**1.00**	
Female	34.9	**0.43 (0.25 - 0.75)**		**0.28 (0.15 - 0.53)**	
First visit with GP			**<0.001**	-	
No^	39.9	**1.00**			
Yes	68.7	**3.30 (1.80 - 6.06)**			
First visit at hospital			**<0.001**		**0.001**
No^	64.6	**1.00**		**1.00**	
Yes	35.7	**0.30 (0.17 - 0. 53)**		**0.35 (0.18 - 0.66)**	
After first visit, did you seek treatment from somewhere else?			**<0.001**	-	-
No^	35.1	**1.00**			
Yes	66.7	**3.70 (2.12 - 6.44)**			
Cough > 3 weeks			**0.036**	-	-
No^	57.7	**1.00**			
Yes	43.1	**0.56 (0.32 - 0.97)**			
Dizziness			**0.040**		**0.023**
No^	49.8	**1.00**		**1.00**	
Yes	21.4	**0.28 (0.75 - 1.01)**		**0.18 (0.04 - 0.78)**	
Prior unspecific treatment			**<0.001**		**0.012**
No^	34.1	**1.00**		**1.00**	
Yes	57.1	**2.58 (1.49 - 4.46)**		**2.25 (1.19 - 4.25)**	
Did you have repeated visits with different providers in a different facility?			**<0.001**	-	-
No^	37.3	**1.00**			
Yes	62.8	**2.84 (1.61 - 5.01)**			

*p-values <0.05 are indicated in bold

^ reference category

HSD: health system delay; OR: odd ratio: a: adjusted; CI: confidence interval; GP: general practitioner;

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Table 4. Risk analysis for total delay (Univariate and logistic regression analysis)

	TOTD >45 days %	OR 95%CI	p*	aOR 95%CI	p*
Foreign-born patients			0.091	-	-
No^	56.0	1.00			
Yes	44.0	0.62 (0.35 – 1.08)			
Do you know what TB is?			**0.012**	-	-
No^	37.1	**1.00**			
Yes	55.8	**2.14 (1.18 – 3.88)**			
Pay for transportation			**0.004**		**0.047**
No^	40.5	**1.00**		**1.00**	
Yes	62.3	**2.43 (1.32 – 4.46)**		**2.10 (1.01 – 4.35)**	
Close distance of the first visit place			**0.003**		**0.006**
Yes^	32.8	**1.00**		**1.00**	
No	56.9	**2.71 (1.38 – 5.31)**		**3.09 (1.38 – 6.90)**	
Cough > 3 weeks			**0.038**	-	-
No^	60.3	**1.00**			
Yes	44.5	**0.53 (0.29– 0.97)**			
Sputum with blood			**0.005**		**0.001**
No^	53.5	**1.00**		**1.00**	
Yes	25.0	**0.29 (0.12– 0.72)**		**0.12 (0.03– 0.43)**	
Weight loss			**0.004**		**0.003**
No^	41.9	**1.00**		**1.00**	
Yes	63.4	**2.40 (1.32– 4.36)**		**3.55 (1.56– 8.09)**	
Prior unspecific treatment			**0.003**		**0.026**
No^	37.4	**1.00**		**1.00**	
Yes	57.4	**2.26 (1.32 – 3.89)**		**2.55 (1.18– 5.82)**	
Did you have repeated visits with the same provider?			**0.029**		**0.012**
No^	53.6	**1.00**		**1.00**	
Yes	34.1	**0.45 (0.22 – 0.93)**		**0.29 (0.11 – 0.76)**	

*p-values <0.05 are indicated in bold

^ reference category

TOTD: total delay; OR: odd ratio: a: adjusted; CI: confidence interval; TB: tuberculosis

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Supplementary material

Table S1. Median delays from literature and prevalence of delay in the present study

Delay/ Prevalence of delay	Pezzotti et al. 2015 (Italy)[13]	Saldana et al., 2013 (UK) [19]	Tattevin et al., 2012 (France)[24]	Farah et al., 2006 (Norway)[25]	Jurcev-Savicevic et al. 2013 (Croatia)[276]
Median PD (days)	31	29	14	28	
Prevalence of PD*	64.5	50.2	59.7	50.2	
Median HSD (days)	15	30	-	33	15
Prevalence of HSD*	40.9	29.3	-	25.3	40.9
Median TOTD (days)	-	62	-	63	-
Prevalence of TOTD*	-	42.3	-	40.9	-

*Prevalence of delay that would have been retrieved in our study, by applying median values from other studies

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Table S2. Correctness of patients' knowledge and symptoms recognition stratified for gender and country of birth

Characteristics	Italian-born % (N)	Foreign-born % (N)	p*	Males % (N)	Females % (N)	p*
Do you know what TB is? (n=252)						
Yes	81.2 (91)	56.4 (79)	**<0.001**	65.8 (106)	70.3 (64)	0.465
No	18.8 (21)	43.6 (61)		34.2 (55)	29.7 (27)	
Do you think TB is a serious disease? (n=250)						
Yes	67.9 (76)	57.2 (79)	**0.029**	63.9 (101)	58.7 (54)	0.309
No	17.9 (20)	14.5 (20)		13.3 (21)	20.7 (19)	
Don't know	14.3 (16)	28.3 (39)		22.8 (36)	20.7 (19)	
What causes TB? (n=248)						
Infection	77.5 (86)	43.8 (60)	**<0.001**	61.1 (96)	54.9 (50)	0.491
Punishment	1.8 (2)	0.7 (1)		1.3 (2)	1.1 (1)	
Unavoidable	0.0 (0)	1.5 (2)		1.3 (2)	0.0 (0)	
Don't know	20.7 (23)	54.0 (74)		36.3 (57)	44.0 (40)	
What are the symptoms TB? (n=253)						
Cough for more than 3 weeks	58.0 (65)	49.6 (70)	0.105	54.7 (88)	51.1 (47)	0.890
Sputum with blood	13.4 (15)	9.2 (13)		11.2 (18)	10.9 (10)	
Fever	15.2 (17)	14.2 (20)		13.7 (22)	16.3 (15)	
Weight loss	2.7 (3)	3.5 (5)		3.7 (6)	2.2 (2)	
Don't know	10.7 (12)	23.4 (33)		16.8 (27)	19.7 (18)	
How a person can get TB? (n=242)						
Through germs present in air droplets expelled in the cough	69.4 (72)	37.7 (52)	**<0.001**	55.8 (87)	43.0 (37)	0.147
Sharing utensils and objects with an infected person	3.8 (4)	7.2 (10)		5.8 (9)	5.8 (5)	
Don't know	26.9 (28)	55.1 (76)		38.5 (60)	51.2 (44)	
How TB is diagnosed? (n=240)						
Through sputum examination	39.0 (39)	17.1 (24)	**<0.001**	23.7 (37)	31.0 (26)	0.409
Through X-ray	32.0 (32)	25.7 (36)		28.2 (44)	28.6 (24)	
Don't know	29.0 (29)	57.1 (80)		48.1 (75)	40.4 (34)	
Can TB be cured? (n=249)						
Yes	93.6 (103)	76.3 (106)	**0.001**	84.8 (134)	82.4 (75)	0.858
No	0.0 (0)	2.2 (3)		1.3 (2)	1.1 (1)	
Don't know	6.4 (7)	21.6 (30)		13.9 (22)	16.5 (15)	
Can TB require a longer treatment to be cured as for multidrug resistant forms? (n=251)						

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Yes	51.8 (58)	34.5 (48)	**0.016**	41.0 (66)	44.4 (40)	0.868
No	10.7 (12)	18.7 (26)		15.5 (25)	14.4 (13)	
Don't know	37.5 (42)	46.8 (65)		43.5 (70)	41.2 (37)	
Which symptoms made you seek healthcare?						
Cough for more than 3 weeks (n=253)						
Yes	57.1 (64)	72.3 (102)	**0.011**	65.2 (105)	66.3 (61)	0.861
No	42.9 (48)	27.7 (39)		34.8 (56)	33.7 (31)	
Sputum with blood (n=253)						
Yes	8.0 (9)	17.7 (25)	**0.025**	14.3 (23)	12.0 (11)	0.601
No	92.0 (103)	82.3 (116)		85.7 (138)	88.0 (81)	
Fever (n=253)						
Yes	50.9 (57)	50.4 (71)	0.932	50.3 (81)	51.1 (47)	0.905
No	49.1 (55)	49.6 (70)		49.7 (80)	48.9 (45)	
Weight loss (n=253)						
Yes	28.6 (32)	44.7 (63)	**0.009**	44.7 (72)	25.0 (23)	**0.002**
No	71.4 (80)	55.3 (78)		55.3 (89)	75.0 (69)	
Tiredness/weakness (n=253)						
Yes	38.4 (43)	52.5 (74)	**0.026**	50.9 (82)	38.0 (35)	**0.048**
No	61.1 (69)	47.5 (67)		49.1 (79)	62.0 (57)	
Dizziness (n=253)						
Yes	4.5 (5)	6.4 (9)	0.507	6.8 (11)	3.3 (3)	0.232
No	95.5 (107)	93.6 (132)		93.2 (150)	96.7 (89)	
Chest pain (n=253)						
Yes	17.0 (19)	30.5 (43)	**0.013**	28.6 (46)	17.4 (16)	**0.047**
No	83.0 (93)	69.5 (98)		71.4 (115)	82.6 (76)	
Night sweat (n=253)						
Yes	20.5 (23)	30.5 (43)	0.073	31.1 (50)	17.4 (16)	**0.017**
No	79.5 (89)	69.5 (98)		68.9 (111)	82.6 (76)	
Did you think you had TB? (n=252)						
Yes	5.4 (6)	11.4 (16)	0.090	11.8 (19)	3.3 (3)	**0.022**
No	94.6 (106)	88.6 (124)		88.2 (142)	96.7 (88)	
Factors for delay in seeking care						
Not aware of symptoms (n=253)						
Yes	38.4 (43)	43.3 (61)	0.434	57.1 (92)	62.0 (57)	0.454

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No	61.6 (69)	56.7 (80)		42.9 (69)	38.0 (35)	
Fear of rejection/losing job (n=253)						
Yes	2.7 (3)	6.4 (9)	0.169	5.6 (9)	3.3 (3)	0.402
No	97.3 (109)	93.6 (132)		94.4 (152)	96.7 (89)	
Costs (n=253)						
Yes	0.0 (0)	9.2 (13)	**0.001**	5.6 (9)	4.3 (4)	0.667
No	100.0 (112)	90.8 (128)		94.4 (152)	95.7 (88)	
Lack of time (n=253)						
Yes	5.4 (6)	7.1 (10)	0.573	5.6 (9)	7.6 (7)	0.526
No	94.6 (106)	92.9 (131)		94.4 (152)	92.4 (85)	
Distance to health centre (n=253)						
Yes	0.9 (1)	2.8 (4)	0.270	2.5 (4)	1.1 (1)	0.442
No	99.1 (111)	97.2 (137)		97.5 (157)	98.9 (91)	
Lack of transportation (n=253)						
Yes	0.9 (1)	0.7 (1)	0.870	0.0 (0)	2.2 (2)	0.060
No	99.1 (111)	99.3 (140)		100.0 (161)	97.8 (90)	
Previous non-satisfactory experience with the health system (n=253)						
Yes	1.8 (2)	2.1 (3)	0.846	1.9 (3)	2.2 (2)	0.864
No	98.2 (110)	97.9 (138)		98.1 (158)	97.8 (90)	

*p-values <0.05 are indicated in bold

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Table S3. Attitude towards TB stratified for gender and country of birth

	Italian-born % (N)	Foreign-born % (N)	p*	Males % (N)	Females % (N)	p*
Should people with TB disclose their illness to other people? (n=252)						
Yes	70.5 (79)	47.1 (66)	**0.001**	53.1 (85)	65.2 (60)	**0.040**
No	8.9 (10)	19.3 (27)		18.8 (30)	7.6 (7)	
Don't know	20.5 (23)	33.6 (47)		28.1 (45)	27.2 (25)	
Who do you think is more likely to get TB, men or women? (n=252)						
Men	12.5 (14)	15.0 (21)	0.305	21.2 (34)	1.1 (1)	**<0.001**
Women	5.4 (6)	10.0 (14)		4.4 (7)	14.1 (13)	
Don't know	82.1 (92)	75.0 (105)		74.9 (119)	84.8 (78)	
How did you feel when you found out that you had TB? (n=253)						
Scared	37.5 (42)	45.4 (64)	0.376	36.6 (59)	51.1 (47)	0.164
Depressed	20.5 (23)	14.2 (20)		18.0 (29)	15.2 (14)	
Didn't believe (denial)	29.5 (33)	31.2 (44)		33.5 (54)	25.0 (23)	
Other	12.5 (14)	9.2 (13)		11.8 (19)	8.7 (8)	
Did you inform your friends/ family that you had TB? (n=248)						
Yes	90.9 (100)	55.1 (76)	**<0.001**	61.4 (97)	87.8 (79)	**<0.001**
No	9.1 (10)	44.9 (62)		38.6 (61)	12.2 (11)	
Have your relationships with your friends/ family changed since finding out you have TB? (n=245)						
Yes	22.0 (24)	14.7 (20)	0.138	15.4 (24)	22.5 (20)	0.165
No	78.0 (85)	85.3 (116)		84.6 (132)	77.5 (69)	
If yes, how? (n=43)						
Improved	41.7 (10)	10.5 (2)	**0.024**	26.1 (6)	30.0 (6)	0.775
Worsened	58.3 (14)	89.5 (17)		73.9 (17)	70.0 (14)	
Are people with TB discriminated in the community? (n=249)						
Yes	46.4 (51)	41.0 (57)	**0.002**	40.3 (64)	48.9 (44)	0.386
No	33.6 (37)	19.4 (27)		26.4 (42)	24.4 (22)	
Don't know	20.0 (22)	39.6 (55)		33.3 (53)	26.7 (24)	
Among TB patients, are male or female patients more discriminated? (n=249)						
Male	3.7 (4)	9.3 (13)	**0.027**	10.1 (16)	1.1 (1)	**<0.001**
Female	2.85 (3)	8.6 (12)		2.5 (4)	12.1 (11)	
Don't know	93.6 (102)	82.1 (115)		87.3 (138)	86.8 (79)	

*p-values <0.05 are indicated in bold

TB: tuberculosis

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Table S4. Risk analysis for DD (Univariate and logistic regression analysis)

	DD >7 days %	OR 95%CI	p	aOR 95%CI	p
Foreign-born patients			**<0.001**		**0.024**
Yes^	36.6	**1**		**1**	
No	64.7	**0.32 (0.18 – 0.54)**		**0.48 (0.25 – 0.91)**	
Chronic disease			0.061	-	-
Yes^	59.3	1			
No	45.1	1.77 (0.97 – 3.24)			
Gender			**0.008**		**<0.001**
Female^	37.5	**1**		**1**	
Male	55.9	**0.47 (0.27 – 0.83)**		**0.30 (0.15 – 0.58)**	
First visit: General practitioner			**<0.001**	-	-
Yes^	71.2	**1**			
No	40.5	**3.63 (1.95 – 6.77)**			
First visit: Hospital			**<0.001**		**0.002**
Yes^	36.1	**1**		**1**	
No	67.0	**0.28 (0.16 – 0.49)**		**0.35 (0.18 – 0.67)**	
After first visit, did you seek treatment from somewhere else?			**<0.001**	-	-
Yes^	71.0	**1**			
No	34.4	**4.67 (2.62 – 8.31)**			
Cough more than 3 weeks			**0.035**		**0.048**
Yes^	44.2	**1**		**1**	
No	59.0	**0.55 (0.32 – 0.96)**		**0.51 (0.27 – 0.99)**	
Dizziness			**0.051**		**0.039**
Yes^	23.1	**1**		**1**	
No	50.9	**0.28 (0.08 – 1.08)**		**0.21 (0.04 – 0.92)**	
Prior unspecific treatment			**<0.001**		**0.002**
Yes^	60.4	**1**		**1**	
No	33.0	**3.11 (1.78 – 5.43)**		**2.85 (1.47 – 5.52)**	
With whom did you have repeated visits? Different providers in a different facility			**<0.001**	-	-
Yes^	66.3	**1**			
No	37.6	**3.26 (1.82 – 5.86)**			

*p-values <0.05 are indicated in bold

^ reference category

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Determinants of patient and health system delay among Italian and foreign-born pulmonary tuberculosis patients: a multicentre cross-sectional study

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To the memory of Professor Caterina Mammina, University of Palermo, First Coordinator of the project

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ABSTRACT

Objectives

The aim of this cross-sectional study was to identify key factors associated with patient delay (PD), health system delay (HSD) and total delay (TOTD) in tuberculosis (TB) patients to inform control programs.

Setting

The study was conducted in four Italian regions in 2014-2016. Data were obtained using a questionnaire including: socio-demographic and lifestyle data, TB comorbidities, patient knowledge and attitudes towards TB, stigma, access to TB care, and health seeking behaviours.

Participants

Patients' inclusion criteria were being diagnosed as a new smear positive pulmonary TB case and living in one of the above-mentioned Italian regions. Overall, 344 patients from 30 healthcare centres were invited to participate and 253 patients were included in the analysis (26.5% non-response rate); 63.6% were males and 55.7% were non-Italian born.

Outcome measures

Risk factors for PD, HSD and TOTD in TB patients were assessed by multivariable analysis. Adjusted odds ratios (aOR) and 95% confidence intervals (95%CI) were calculated.

Results

Median PD, HSD and TOTD were 30, 11 and 45 days, respectively. Factors associated with longer PD were: stigma (aOR:2.30;95%CI:1.06-4.98), chest pain (aOR:2.67;95%CI:1.24-6.49), weight loss (aOR:4.66;95%CI:2.16-10.05), paying for transportation (aOR:2.66;95%CI:1.24-5.74) and distance to the health centre (aOR:2.46;95%CI:1.05-5.74) (the latter three were also associated with TOTD). Shorter HSD was associated with foreign-born and female status (aOR:0.50;95%CI:0.27-0.91; aOR:0.28;95%CI:0.15-0.53, respectively), dizziness (aOR:0.18,95%CI:0.04–0.78) and seeking care at hospital (aOR:0.35;95%CI:0.18-0.66). Prior unspecific treatment was associated with longer HSD (aOR:2.25;95%CI:1.19-4.25) and TOTD (aOR:2.55;95%CI:1.18-5.82). Haemoptysis (aOR:0.12;95%CI:0.03-0.43) and repeated visits with the same provider (aOR:0.29;95%CI:0.11-0.76) showed shorter TOTD.

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Conclusions

This study identifies several determinants of delays associated with patient's behaviours and healthcare qualities. Tackling TB effectively requires addressing key risk factors that make individuals more vulnerable by the means of public health policy, cooperation and advocacy to ensure that all patients have easy access to care and receive high quality healthcare.

Strengths and limitations of this study

- This is the first multiregional cross-sectional study, in Italy, investigating the association of key factors with patient delay, health system delay and total delay in pulmonary tuberculosis patients.
- Data were collected by healthcare providers and cultural mediators, using a multilingual standardised questionnaire.
- The prospective collection of data and the adjustment for confounding factors with logistic regression analysis are among the strengths of the present study.
- A selection bias should be considered, especially for foreign-born patients who may have experienced difficulties during the interview, resulting in refusal or in missing data.
- Self-reported dates for onset of symptoms and health care seeking may have been affected by recall bias.

Keywords

Surveillance; public health policy; social epidemiology; TB patients.

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INTRODUCTION

Early diagnosis and prompt treatment of tuberculosis (TB) disease represent key components of any effective national TB control programme.[1 2] If adequately implemented and scaled-up, they can contribute to the reduction of *Mycobacterium tuberculosis* transmission and TB elimination by 2050.[3]

However, delays in diagnosis and treatment of TB frequently occur.[4] Long delays lead to a more advanced disease that may result in poor response to therapies, undesirable clinical *sequelae*, and higher mortality risk.[5] In addition, delay contributes to *M. tuberculosis* transmission within the community.[6 7] It has been shown that an untreated smear-positive patient can infect, on average, 10 healthy contacts annually.[8] Finally, TB diagnosis delay is associated with higher direct and indirect costs.[9]

Delay may occur at patient or at health system level. Factors contributing to patient delay (PD) can be: socio-demographic, physical, financial, health literacy, religious-cultural and stigma.[10] Health system delay (HSD) related factors can be: poor TB knowledge by healthcare providers and poor availability of effective diagnostic tools, number and types of providers encountered before TB diagnosis, patient satisfaction with TB services and waiting time.[10 11] Thus, understanding and identifying the causes of delay in diagnosis and treatment initiation are critical to strengthen TB control programs. Particularly, the importance of social variables as drivers of epidemics and disease risk has been long recognised. Incorporating the perspectives and methods of social epidemiology into studies of infectious disease, many opportunities arise to control the disease.[12]

However, in Europe, and especially in Italy, few studies have focused on social determinants and TB delays.

The aim of the present study was to identify the duration and the key factors related to PD, HSD and total delay (TOTD) in pulmonary TB patients, in four Italian Southern regions, with a focus on social determinants.

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METHODS

Study design

The present cross-sectional study was conducted in four Italian regions (Calabria, Apulia, Sardinia, and Sicily) from October 2014 to July 2016, and was approved and financed by the Italian Ministry of Health.

Patients' inclusion criteria were being diagnosed as a new smear positive pulmonary TB case (with or without extra-pulmonary TB) and living in one of the above-mentioned Italian regions. Foreign-born patients were enrolled regardless of their legal migrant status (e.g. refugees, asylum seeker, and illegal migrants). Negative smear, relapse, retreatment cases and those with only extra-pulmonary TB were excluded.

The project was performed according to the Declaration of Helsinki, participants were fully informed of the purpose of the study and signed a written informed consent. All data collected were treated confidentially and analysed in aggregated and anonymous form.

Patient and Public Involvement

The present study was conducted without patient and public involvement. Results of the research will be available on request to any study participant to disseminate key study findings providing feedback on the research outcome towards which they have contributed.

Sample Size calculation and Sampling Procedure

A sample size of 261 was estimated by using single population proportion estimation formula with an assumption of 95% confidence interval, 6% margin of error, and 50.4% proportion of PD (> 30 days).[13] Furthermore, considering 20% of nonresponse rate, the final sample size was 321. All patients meeting the inclusion criteria, attending the healthcare facility during the study period, were prospectively invited to participate in the study.

Data collection and definitions

Data were collected by healthcare workers of each participating centre, during a face-to-face interview at the time when patients were diagnosed and/or initiated treatment. A standardised questionnaire available in Italian, English, and French was used, and if possible, a cultural and linguistic mediator assisted the interview with the task to facilitate communication and understanding, both on linguistic and cultural level.

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Operators with adequate background of the health topic, within the specific cultures/languages, supported and assisted patients and healthcare professionals during clinical examinations.

The questionnaire contained several domains: i) socio-demographic and lifestyle data; ii) integration index (II) in Italy (only for foreign-born patients), computed as described in a previous study;[14] iii) TB comorbidities; iv) patient knowledge of TB-associated symptoms and attitudes towards TB; v) TB related stigma, measured according to the WHO questionnaire;[15] vi) access to TB diagnosis and treatment and health seeking behaviours; vii) dates of onset of symptoms, first contact with healthcare service, TB diagnosis confirmation and treatment initiation; viii) satisfaction with care, assessed by adopting and modifying the USAID questionnaire.[16]

PD was defined as the time interval between the onset of symptoms and patient's first contact with any type of health care service (including hospital and primary health care).[15 16] HSD was defined as the time interval between the first consultation with a healthcare provider and the initiation of treatment.[15 16] This can be subdivided into: diagnostic delay (DD) as the time interval between the presentation to a healthcare provider and the date of diagnosis and treatment delay (TD) as the time interval between TB diagnosis and initiation of anti-TB treatment. Thus, TOTD was defined as the time interval from onset of symptoms until treatment initiation.[16 17]

Statistical analysis

Statistical analyses were performed using the SPSS software (IBM SPSS Statistics for Windows, version 22.0).

The response rate and descriptive statistics were used to characterise the sample using frequencies, means, medians and interquartile ranges (IQRs). Valid percentage was reported when data was missing (pairwise deletion method). Furthermore, the magnitude (proportion) of missing data was quantified and reported in Supplementary Table S1.

Poverty was defined in relation to housing circumstances as living in community centres, first aid centres or prisons. Education level was dichotomised into two categories (high and low), using a cut-off of 8 school years.

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Variables related to stigma and satisfaction with care were recorded on a 5-point Likert scale.[15 16] Scores were converted as mean percentage score, calculated as follows: (sum of score obtained/maximum score that could be obtained) × 100.

For TB cases born abroad, the II was calculated based on the score sum of 11 selected variables from the study questionnaire and then standardised to range from 0 to 10.[14]

Longer delays (outcome) were defined according to previous Italian studies. Particularly, long PD was defined as >30 days, while long HSD and TOTD were defined as > the median value observed in the study population, for HSD and TOTD, respectively.[13 18]

Prevalence estimates of longer delay, using cut-off values reported from other studies, were reported in Supplementary Table S2.

Median values were also used as cut-off points to dichotomise quantitative variables (e.g. age and stigma). The two-tailed Chi-squared test was used for the statistical comparison of categorical variables, whereas quantitative variables were compared using Student's *t* test, as the sample was big enough. The Levene's test was performed to verify the homogeneity of variance across groups.

The characteristics of patients with longer delays (all forms) were compared to those of patients without (comparators) and the crude odds ratios (ORs) and the corresponding 95% confidence intervals (95%CIs) were computed.

All variables with P <0.1 on univariate analysis were included in the multivariable logistic regression analysis, using a backward-stepwise selection procedure. The analysis was only run on cases which have a complete set of data. The breakpoint for variable removal was set at P= 0.10. The adjusted ORs (aOR) with the respective 95% CIs were reported. A P-value < 0.05 was considered statistically significant.

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RESULTS

A total of 344 patients from 30 healthcare centres were invited to participate. Overall, 91 (26.5%) refused the interview, and 253 patients were included in the analysis. Patients who refused the interview were older than patients who agreed (mean age: 46.0 and. 40.7 years, respectively; P = 0.023). However, no statistical differences resulted for Country of birth and gender. Completion rate for all questions included in the analysis was ≥80%. Missing data ranged from 0.4% to 21.7% (Table S1).

Overall, 55.3% of patients were temporary or permanently living in Sicily, 22.1% in Calabria, 17.4% in Apulia, and 5.2% in Sardinia.

Table 1 shows the main characteristics of the study population and comparisons for Country of birth and gender. Mean age was 40.7 years (median: 38; IQR 27-53) and 63.6% were males. One hundred forty-one (55.7%) patients were born abroad and they were younger than Italians (mean age: 34.3 years and 48.7 years, respectively; P <0.001).

Stratifying by Country of origin, 47.9% of patients came from European Countries, and mostly from Romania (82.1%), 28.6% from the African Countries, 11.4% from Eastern Mediterranean Countries, 9.3% from South-East Asia, 2.1% from Western Pacific Countries, and 0.7% from American Countries. Foreign-born patients reported higher degree of poverty and literacy: they lived in nursing homes or did not have permanent residency (47.8%), 64.7% were unemployed or occasional workers, and 79.4% were illiterate or had less than 8 years of educational activities (P <0.05).

About one-third suffered of chronic diseases (i.e. HIV/AIDS, diabetes, chronic obstructive pulmonary disease, disability, renal failure and cardiovascular disease), particularly those born in Italy (39.1%). Current smokers and alcohol users were 27.2% and 6.9%, respectively. Higher percentages of smokers and alcohol users were found among male patients (32.5% and 10.1%). However, no significant differences were observed between Italian and foreign-born patients (Table 1).

Patient knowledge and symptoms recognition

Foreign-born patients reported lack of knowledge on the disease more often compared with Italian-born (Supplementary Table S3). Foreign-born patients were less aware that TB is an infectious disease and is transmitted by airborne bacteria. They did not know the symptoms most frequently associated with the

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disease, how TB is diagnosed and cured, and that multi-drug resistant TB may require a longer treatment time to achieve a cure (P <0.05).

Only 3.6% of TB patients reported no symptoms, while 49% of patients reported three or more symptoms. Overall, 65.6% had cough for more than 3 weeks. Sputum with blood was reported by only 13.4% of patients. The main reason for not seeking care was that they perceived the TB symptoms to be mild (58.9%).

Foreign-born patients reported more frequently the following symptoms: cough, sputum with blood, weakness, weight loss, and chest pain, compared with Italian-born patients. Furthermore, women reported tiredness/weakness, weight loss, chest pain, and night sweating less frequently compared with men. Being irregular migrants was the only reason for delayed seeking care in women, while in men other motivations were reported (Table S3).

Attitude towards TB and stigma

A higher percentage of men (38.6%) and foreign-born patients (44.9%) did not inform their families and friends on the disease, compared with women (12.2%) and Italian-born (9.1%) (P <0.001). Detailed results are reported in Supplementary Table S4.

A moderate level of stigma was found (mean: 59.5%; median and IQR: 58.7%, 22.7%-94.7%) in all patients. Overall, 53.9% of foreign-born patients reported TB related stigma above the median value, compared with 41.4% of Italian born (P= 0.049) (Table 1).

Healthcare-seeking behaviour and access to TB care centres

General Practitioners (GP) were consulted, as first choice, by 30% of patients, mostly Italians (46.8%). On the contrary, foreign-born cases were shown to seek more frequently the hospital care (70.3%). Around 41% of the cases were visited by more than one healthcare provider, and this was mainly reported by the Italian group (53.2% *vs*. 31.7%; P= 0.001). Overall, 59% of the cases received unspecific treatment (mainly antibiotics) before TB diagnosis; this occurred more frequently among cases born in Italy (75.7% *vs*. 51.6%; P= 0.005).

Risk analysis of delay

Median PD, HSD and TOTD were 30, 11, and 45 days, respectively (Table 1). On univariate analysis, factors associated with long PD (> 30 days) were TB-related stigma, paying for transportation, distance to

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get to the healthcare centre, presence of unintentional weight loss, fatigue, chest pain and suffering of chronic diseases. In the final model of the multivariable analysis, stigma (aOR: 2.30, 95%CI: 1.06 – 4.98), paying for transportation (aOR: 2.66, 95%CI: 1.24 – 5.74), distance to the healthcare centre (aOR: 2.30, 95%CI: 1.06 – 4.98), weight loss (aOR: 4.66, 95%CI: 2.16 – 10.05) and chest pain (aOR: 2.67, 95%CI: 1.24 – 6.49) remained associated with PD (Table 2).

Prior unspecific treatment, patients referring to a GP at the first visit, and those visited by multiple providers in different facilities were more likely to report long HSD (> 11 days), while female gender, non-Italian origin, seeking care at hospital level, presence of cough for more than 3 weeks and dizziness were associated with shorter HSD. On multivariable analysis, being foreign-born (aOR: 0.50, 95%CI: 0.27 – 0.91) and female (aOR: 0.28, 95%CI: 0.15 – 0.53), seeking care at hospital (aOR: 0.35, 95%CI: 0.18 – 0.66) and presence of dizziness (aOR: 0.18, 95%CI: 0.04 – 0.78) remained associated with shorter HSD. While, prior unspecific treatment was associated with longer HSD (aOR: 2.25, 95%CI: 1.19 – 4.25) (Table 3).

Factors associated with long DD (>7 days), were identical to those associated with HSD, and in addition, having cough for more than 3 weeks was significantly associated with shorter DD (Table S5). No variables were associated with long TD (>2 days).

Finally, good knowledge of TB, paying for transportation, distance to reach the health centre, prior unspecific treatment, and weight loss were associated with long TOTD (> 45 days), while patients reporting cough and hemophthisis and who had repeated visits with the same provider showed shorter TOTD. In the logistic regression analysis, paying for transportation (aOR: 2.10, 95%CI: 1.01 – 4.35), distance to reach the centre (aOR: 3.09, 95%CI: 1.38 – 6.90), prior unspecific treatment (aOR: 2.55, 95%CI: 1.18 – 5.82), and weight loss (aOR: 3.55, 95%CI: 1.56 – 8.09), repeated visits with the same provider (aOR: 0.29, 95%CI: 0.11– 0.76) and haemoptysis (aOR: 0.12, 95%CI: 0.03– 0.43), were independently associated with TOTD (Table 4).

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DISCUSSION

Reducing the time interval between symptoms recognition and TB treatment can decrease mycobacterial transmission, morbidity, and mortality. Although there is no general consensus on what may constitute an acceptable interval between onset of symptoms and initiation of TB treatment,[19] it has been suggested that overall TB delay could be used as a key indicator of programme performance.[4]

The TB notification rate in the general Italian population has been stable in the last years.[20] However, most of the cases occur in vulnerable groups, who do not recognise the symptoms or have poor access to healthcare services. The two most affected groups are the elderly and foreign-born people. The latter group accounts for about 50% of all TB cases in Italy (data until 2008).[21]

In our study, 55.7% patients were foreign-born, and they were younger than Italians. Younger age among foreign-born patients has also been reported in other studies.[13 22] Although, the TB notification rate is decreasing in Europe, the reduction in individuals of foreign origin is still slower than in native residents. This represents one of the main challenges for TB elimination, especially in those European countries where individuals of foreign-born origin represent a large proportion of TB cases.[23]

In our study, the median values for PD (30 days) and HSD (11 days, of which 7 days for DD and 2 days for TD, respectively) are similar to those reported by other studies conducted in Italy and in other European countries with a low-TB incidence. Particularly, a recent Italian study reported median PD and HSD values of 31 and 15 days, respectively.[13] European studies reported median PDs of 14 days (France),[24] 28 days (Norway),[25] and 29 days (UK).[19] Considering HSD (and its two components), studies reported median values of 15 days (Croatia),[26] 25 days (for DD in France),[24] 30 days (UK),[19] and 33 days (Norway).[25] However, in our study, median TOTD (45 days) was lower than values reported elsewhere, which ranged between 62 days (UK),[19] and 63 days (Norway).[25]

Table S2 shows median values reported by other studies,[13 19 24-26] and the prevalence of delay that would have been detected in our study, by using them.

It is worth noting that some studies evaluated both forms of TB (pulmonary and extra-pulmonary), and tools for data collection and definitions of delays were widely heterogeneous among studies, thus comparisons should be made with caution.

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Nevertheless, median values detected in our study are encouraging. Indeed, for PD a median value of 30 days has been considered an acceptable value by many authors,[18 27] although others have suggested values less than 3 weeks.[28]

Regarding HSD, our median value is below the accepted value, which is considered to be 15 days.[27] Low values of HSD and TOTD might probably due to a higher level of awareness of TB among involved healthcare professionals in Italy, in recent years. Similarly to our results, other studies have found that PD was longer than HSD,[13 29] while others have found the opposite,[24 25] or no differences.[19] It is likely that patients who contact the health system later could have more severe symptoms facilitating TB suspicion and prompt diagnosis,[13] thus the higher the PD, the lower the HSD, and *vice versa.*[4 25]

In our study, longer PD was associated with high degree of stigma, paying for transportation, distance to healthcare facility, presence of unintentional weight loss and chest pain. Aside from stigma and chest pain all others were also detected as risk factors for TOTD. Our results are consistent with findings of the WHO Eastern Mediterranean Region study, where stigma, economic factors, and time to reach the health facility were among the main determinants for delayed access to healthcare system.[15]

TB-related stigma represents a cultural aspect which drives individuals to hide their condition from others, and refusing seeking care,[30] but evidence shows that stigma barriers may be avoided through interventions addressed improving TB-related health literacy.[10]

The reason why chest pain and weight loss were associated with long PD is not clear, because these symptoms, together with persistent cough, are considered key TB signs. Other studies retrieved similar results. Chest pain was found positively associated with longer PD (> 90 days) in a Brazilian study,[31] and with TOTD (>60 days) in Ethiopia.[27] Similarly, weight loss was associated with longer PD, both in Brazil (>30 days)[31] and in Italy (>15 days),[13] with PD (>27 days) and TOTD (>50 days) in Uzbekistan,[32] and with HSD (>18 days) in another Brazilian study.[33] These results could be explained by the assumption that patients consider these as transient symptoms from a general illness, hence, maybe, initiating self-treatment lasting until deterioration and manifestation of other specific symptoms. Furthermore, timely referral to healthcare facilities for disabling symptoms may be challenging due to financial constraints, poor health

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literacy, and stigma. In addition, a long delay until diagnosis favours disease progression and therefore symptom appearance. Also, non-specific symptoms could lead to longer suspicion delays by the clinician.

Especially for foreign-born patients, language barriers, poor knowledge of symptoms, fear of immigration authorities and long wait for appointment have been associated with delay in seeking care,[34 35] raising concerns about the equity of access to care among TB patient. Thus, understanding immigrants' views of TB and the obstacles that they face when accessing the health system, taking into consideration the social, economic and legislative context of the new Country where they live, has an important role and should be considered in TB control programmes.

The association of HSD with birth place might be due to the low TB rate in Italy, thus TB would be less suspected and investigated in the Italian-born population, or by contrast, being a migrant may point physicians to a prompt TB diagnosis.[13] This finding is consistent with other studies.[13 19]

Female gender was associated with shorter HSD, in contrast with other studies.[4] In general, female patients are reported to encounter greater barriers (financial, physical, and health literacy) for appropriate medical care and treatment. Further investigations on possible confounders should be considered.

In line with others,[4 30 36 37] a first healthcare contact in hospital, was strongly associated with shorter HSD, while referring to GP was a risk factor for longer HSD. A combination of several factors, may explain this result: lack of TB suspicion among primary care providers in low-endemic countries; seeking assistance in hospital for patients at higher risk of TB (e.g. migrants from endemic countries) and/or with more severe TB disease who are thus investigated faster; availability and easier access to diagnostic tests and specialists within the hospital.[24]

Furthermore, repeated visits, especially with different healthcare workers in different health facilities, has been retrieved as predictor of HSD in other studies,[15 17 38-40] however we did not find this association in the final model. It has been reported that generally, patients see different healthcare providers in case of poor clinical suspicions of signs and symptoms, failure to request for proper investigations, refer patients to specialised TB centre for further investigations,[41] or when they receive inappropriate treatment that can modify the clinical picture of the disease.[40]

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The association of HSD and TOTD with previous unspecific treatment is in agreement with other results.[13 24] This is of a particular concern in the current global epidemiological scenario where antimicrobial resistance is rapidly developing and spreading and a more prudent use of antimicrobials is urgently needed, by for instance, limiting the use of empirical antibiotics in patients with respiratory symptoms.[24] Training GP for the early identification of signs and symptoms and prompt referral of suspected cases to TB diagnosis and treatment health centres is essential.

Finally, other factors associated with shorter TOTD were presenting sputum with blood and having visits by the same provider. Sputum with blood is usually recognised as a late sign of TB, thus patients with severe symptoms are immediately suspected for TB. Intuitively, having visits with the same provider might reduce repetition of examinations and misdiagnosis.

Our study has some limitations, some of them specific to the cross-sectional study design. A selection bias should be considered. In fact, the mediator was not often available in hospitals, thus, foreign-born patients recently arrived in Italy, may have experienced difficulties during the interview, resulting in refusal or in missing data. In any case, no difference has been detected for country of birth among responders and non-responders and the completion rate for the questions included in the analyses was at least 80%.

Missing data are a challenge which could affect the quality of the evidence, limit power, and reduce generalizability, causing a distortion from the truth.[42 43] There is no general consensus from the literature regarding an acceptable percentage of missing data in a data set for valid statistical inferences, yet. Cut-off values have been proposed ranging from 5% to 20%.[44 45] In our study we retrieved a certain amount of missing data, up to 21%, and observations with missing data have been excluded in the multivariable analysis, hence reducing the final sample size. In addition, the pattern of missingness was not explored. Thus missing data may represent potential bias in our findings. The questionnaire used for data collection could have been a plausible cause for missing data in our study, because of the length of the survey, and the unavailability of translation in languages other than English and French. Thus, to prevent missing data in further studies, the data collection tool should be designed and adapted to the needs of the target population, piloted and monitored during the study.

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Also, the low education level of the overall population may have contributed to an information bias. However, since a higher frequency of low educational level was shown in foreign-born patients than in patients born in Italy, a differential misclassification could be supposed and thus the direction of the bias is unpredictable. Furthermore, as the onset date of symptoms was self-reported, it may have been affected by recall bias that could have occurred heterogeneously in the whole sample. Another limitation is that data on HIV status and other risk factors (e.g. alcohol and drug use and detention status) were not available for the vast majority of patients.

In the present study, several aspects have been investigating as key factors contributing to PD and HSD in TB patients. However, further studies addressing other components of delays[6 30 46] may be necessary to understand all factors that are closely associated with delay in the diagnosis and treatment of TB. Furthermore, in our regression model we did not take into account for the potential collinearity of explanatory variables, which could explain complex relationship involving several risk factors at the same time, for example the use of unspecific antibiotics and multiple visits with healthcare providers

A possible approach to combine the relevant variables into summary scores or indexes and assesses the relationship of these with the outcome of interest should be explored.

This is the first multiregional cross-sectional study, conducted in Italy, which investigated the association of several factors with PD, HSD and TOTD delay in pulmonary TB patients. It provides new evidence which can be addressed through tailored actions, in order to reduce the burden of TB in Italy. Furthermore, the prospective collection of data in four Italian regions, using a multilingual standardised questionnaire and the adjustment for confounding factors with logistic regression analysis are among the strengths of the present study.

In conclusion, this study detected several modifiable factors associated with longer delay in TB patients, both attributable to patients and health system service. Interventions designed to empower the general population and stakeholders, by increasing knowledge and awareness and screening of active TB in migrants upon arrival are key actions to reduce PD and HSD and achieve TB control.[47] Strategies should mainly target alleviating stigma around TB, improving TB-related health literacy and access to care among the general population, education of GP, earlier referral of TB suspects to the hospital, where appropriate investigations

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for final diagnosis are readily available, and limiting the use of unspecific treatment in patients with respiratory symptoms.

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All CCM 2013 TB network collaborators supervised and coordinated at the hospital level patients' enrolment and data collection.

COMPETING INTERESTS

The Authors declare that they have no competing interests.

ETHICS

All procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent was obtained from all patients for being included in the study.

DATA SHARING STATEMENT

No additional data available

FUNDING SOURCE

The project entitled "*Valutazione dei determinanti di ritardo nell'accesso ai servizi sanitari, nella diagnosi e nel trattamento della tubercolosi polmonare (PTB) in popolazioni vulnerabili. Valutazione dell'impatto sull'epidemiologia locale e sulla prevalenza di resistenza/multiresistenza ai farmaci antitubercolari* - "Assessment of determinants of delay in healthcare access for the diagnosis and treatment of PTB in

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vulnerable populations. Assessment of the impact on the local epidemiology and on the prevalence of antituberculosis drug resistance/multiresistance" was approved and financially supported by the Italian Ministry of Health (Centro nazionale per la prevenzione e il Controllo delle Malattie, CCM 2013). The funding source had no role in any phase of the development of the current study.

CONTRIBUTORSHIP

A Agodi, C Nobile, R Prato and G Sotgiu conceived, designed and supervised the study and coordinated regional data collection. A Casuccio and F Vitale coordinated the project. M Barchitta and A Quattrocchi designed the questionnaire and managed data collection at the central level. A Quattrocchi performed the statistical analysis and wrote the first draft of the manuscript. A Agodi, M Barchitta and A Quattrocchi interpreted the results and wrote the advanced version of the manuscript.

All Authors critically reviewed the manuscript and approved the final version.

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Tables

Table 1. Patients' characteristics

		All % (N)	Italian-born % (N)	Foreign-born % (N)	p*	Males % (N)	Females % (N)	p*
Age (mean)		40.7 (246)	48.7 (109)	34.3(137)	**<0.001**	41.0 (157)	40.1 (89)	0.941
Country of birth (n=253)	Italy	44.3 (112)	-	-	-	42.2 (68)	47.8 (44)	0.389
	Abroad	55.7 (141)	-	-		57.8 (93)	52.2 (48)	
Gender (n=253)	Males	63.6 (161)	60.7 (68)	66.0 (93)	0.389-	-	-	-
	Females	36.4 (92)	39.3 (44)	34.0 (48)		-	-	
Education level (n=251)	Low	72.5 (182)	63.6 (70)	79.4 (112)	**0.005**	70.8 (114)	75.6 (68)	0.419
	High	27.5 (69)	36.4 (40)	20.6 (29)		29.2 (47)	24.4 (22)	
Residence (n=240)	Homeless/prison/ Nursing homes	20.8 (50)	3.7 (4)	34.8 (46)	**<0.001**	26.6 (41)	10.5 (9)	**0.003**
	Apartment (own or rented)	79.2 (190)	96.3 (104)	65.2 (86)		73.4 (113)	89.5 (77)	
Employment (n=241)	Unemployed or occasional work	42.7 (103)	14.3 (15)	64.7 (88)	**<0.001**	47.1 (73)	34.9 (30)	**0.019**
	Permanent job	26.6 (64)	33.3 (35)	21.3 (29)		28.4 (44)	23.3 (20)	
	Housewife/retired/student	30.7 (74)	52.4 (55)	14.0 (19)		24.5 (38)	41.9 (36)	
Smoking habits (n=236)	Current	27.2 (67)	29.9 (32)	25.2 (35)	0.409	32.5 (51)	18.0 (16)	**0.014**
	Never/former	72.8 (179)	70.1 (75)	74.8 (104)		67.5 (106)	82.0 (73)	
Alcohol abuse^ (n=248)	Yes	6.9 (17)	6.3 (7)	7.3 (10)	0.758	10.1 (16)	1.1 (1)	**0.007**
	No	93.1 (231)	93.7 (104)	92.7 (127)		89.9 (142)	98.9 (89)	
Chronic diseases† (n=251)	Yes	28.3 (71)	39.1 (43)	19.9 (28)	**0.001**	31.2 (50)	23.1 (21)	0.167
	No	71.7 (180)	60.9 (67)	80.1 (113)		68.8 (110)	76.9 (70)	
Stigma (n=252)	>median	48.4 (122)	41.4 (46)	53.9 (76)	**0.049**	51.6 (83)	42.9 (39)	0.185
	≤median	51.6 (130)	58.6 (65)	46.1 (65)		48.4 (78)	57.1 (52)	
Integration index (mean)°		4.4 (141)	-	-	-	4.1 (93)	5.1 (48)	**0.008**
Years in Italy (mean)°		7.1 (127)	-	-	-	6.6 (85)	8.2 (42)	0.242
Patient Delay (n=231)	Median (IQR)	30 (8-60)	15 (7-60)	30 (14-60)	-	30 (10-60)	28 (7-60)	-
	(>30 days)	64.5 (149)	29.1 (30)	40.6 (52)	0.069	37.2 (55)	32.5 (27)	0.480
Health system delay (n=225)	Median (IQR)	11 (5-33)	21 (7.25-61)	8 (4-22)	-	14.5 (6-37)	8 (4-31)	-
	(>11 days)	48.1 (111)	61.5 (64)	37.0 (47)	**<0.001**	55.4 (82)	34.9 (29)	**0.008**
Diagnostic delay (n=225)	Median (IQR)	7 (3-30)	15 (4.75-60)	7 (3-15)	-	14 (4-30)	6 (3-28)	-
	(>7 days)	49.3 (111)	64.7 (66)	36.6 (45)	**<0.001**	55.9 (81)	37.5 (30)	**0.008**

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Treatment delay (n=219)	Median (IQR)	2 (1-4)	2 (1-4)	2 (1-4)	-	2 (1-5)	2 (1-4)	-
	(>2 days)	38.4 (84)	38.4 (38)	38.3 (46)	0.994	40.9 (56)	34.1 (28)	0.322
Total delay (n=208)	Median (IQR)	45 (25-121)	53 (25-123)	40 (25-97)	-	47 (26-99)	41 (16-120)	-
	(>45 days)	49.5 (97)	56.0 (50)	44.0 (47)	0.091	66.0 (64)	34.0 (33)	0.525

*p-values <0.05 are indicated in bold

^ ≥4 times a week

° only in foreign-born patients

† HIV/AIDS, diabetes, chronic obstructive pulmonary disease, disability, renal failure, cardiovascular disease

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Table 2. Risk analysis for patient delay (Univariate and logistic regression analysis)

	PD >30 days %	OR 95%CI	p*	aOR 95%CI	p*
Foreign-born patients					
No^	29.1	1.00	0.069	-	-
Yes	40.6	1.67 (0.96 - 2.89)			
Knowledge of what TB is			0.091	-	-
No^	27.8	1.00			
Yes	39.1	1.66 (0.92 – 3.00)			
Knowledge of how TB is diagnosed			0.051	-	-
No^	28.7	1.00			
Yes	41.3	1.75 (0.99 – 3.07)			
Stigma			**0.001**		**0.034**
< median^	24.8	**1.00**		**1.00**	
> median	46.5	**2.64 (1.51 – 4.61)**		**2.30 (1.06 – 4.98)**	
Pay for transportation to reach the health centre			**<0.001**		**0.012**
No^	23.5	**1.00**		**1.00**	
Yes	49.4	**3.18 (1.77 – 5.73)**		**2.66 (1.24 – 5.74)**	
Did you think you had TB?			0.090	-	-
No^	33.8	1.00			
Yes	52.4	2.15 (0.87 – 5.31)			
Close distance of the first visit place			**0.018**		**0.037**
Yes^					
No	21.9	1.00		**1.00**	
	39.2	2.30 (1.15 – 4.62)		**2.46 (1.05 – 5.74)**	
Weight loss			**<0.001**		**<0.001**
No^	22.5	**1.00**		**1.00**	
Yes	56.2	**4.41 (2.48 – 7.83)**		**4.66 (2.16 – 10.05)**	
Tiredness/weakness			**0.001**	-	-
No^	25.8	**1.00**			
Yes	45.9	**2.44 (1.40 – 4.25)**			
Chest pain			**0.026**		**0.031**
No^	31.4	**1.00**		**1.00**	
Yes	47.5	**1.97 (1.08 – 3.61)**		**2.67 (1.24 – 6.49)**	
Chronic diseases			**0.009**	-	-
No^	29.6	**1.00**			
Yes	47.8	**2.17 (1.21 – 3.90)**			

*p-values <0.05 are indicated in bold

^ reference category

PD: patient delay; OR: odd ratio; a: adjusted: CI: confidence interval; TB: tuberculosis

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Table 3. Risk analysis for health system delay (Univariate and logistic regression analysis)

	HSD >11 days %	OR 95%CI	p*	aOR 95%CI	p*
Foreign-born patients			**<0.001**		**0.024**
No^	61.5	**1.00**		**1.00**	
Yes	37.0	**0.37 (0.22 - 0.63)**		**0.50 (0.27 - 0.91)**	
Age			0.1	-	-
> median	43.7	1.00			
≤median	54.6	1.55 (0.92 - 2.62)			
Gender			**0.003**		**<0.001**
Male^	55.4	**1.00**		**1.00**	
Female	34.9	**0.43 (0.25 - 0.75)**		**0.28 (0.15 - 0.53)**	
First visit with GP			**<0.001**	-	
No^	39.9	**1.00**			
Yes	68.7	**3.30 (1.80 - 6.06)**			
First visit at hospital			**<0.001**		**0.001**
No^	64.6	**1.00**		**1.00**	
Yes	35.7	**0.30 (0.17 - 0. 53)**		**0.35 (0.18 - 0.66)**	
Seeking treatment somewhere else, after first visit			**<0.001**	-	-
No^	35.1	**1.00**			
Yes	66.7	**3.70 (2.12 - 6.44)**			
Cough > 3 weeks			**0.036**	-	-
No^	57.7	**1.00**			
Yes	43.1	**0.56 (0.32 - 0.97)**			
Dizziness			**0.040**		**0.023**
No^	49.8	**1.00**		**1.00**	
Yes	21.4	**0.28 (0.75 - 1.01)**		**0.18 (0.04 - 0.78)**	
Prior unspecific treatment			**<0.001**		**0.012**
No^	34.1	**1.00**		**1.00**	
Yes	57.1	**2.58 (1.49 - 4.46)**		**2.25 (1.19 - 4.25)**	
Repeated visits with different providers in a different facility			**<0.001**	-	-
No^					
Yes	37.3	**1.00**			
	62.8	**2.84 (1.61 - 5.01)**			

*p-values <0.05 are indicated in bold

^ reference category

HSD: health system delay; OR: odd ratio: a: adjusted; CI: confidence interval; GP: general practitioner;

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Table 4. Risk analysis for total delay (Univariate and logistic regression analysis)

	TOTD >45 days %	OR 95%CI	p*	aOR 95%CI	p*
Foreign-born patients			0.091	-	-
No^	56.0	1.00			
Yes	44.0	0.62 (0.35 – 1.08)			
Do you know what TB is?			**0.012**	-	-
No^	37.1	**1.00**			
Yes	55.8	**2.14 (1.18 – 3.88)**			
Pay for transportation			**0.004**		**0.047**
No^	40.5	**1.00**		**1.00**	
Yes	62.3	**2.43 (1.32 – 4.46)**		**2.10 (1.01 – 4.35)**	
Close distance of the first visit place			**0.003**		**0.006**
Yes^	32.8	**1.00**		**1.00**	
No	56.9	**2.71 (1.38 – 5.31)**		**3.09 (1.38 – 6.90)**	
Cough > 3 weeks			**0.038**	-	-
No^	60.3	**1.00**			
Yes	44.5	**0.53 (0.29– 0.97)**			
Sputum with blood			**0.005**		**0.001**
No^	53.5	**1.00**		**1.00**	
Yes	25.0	**0.29 (0.12– 0.72)**		**0.12 (0.03– 0.43)**	
Weight loss			**0.004**		**0.003**
No^	41.9	**1.00**		**1.00**	
Yes	63.4	**2.40 (1.32– 4.36)**		**3.55 (1.56– 8.09)**	
Prior unspecific treatment			**0.003**		**0.026**
No^	37.4	**1.00**		**1.00**	
Yes	57.4	**2.26 (1.32 – 3.89)**		**2.55 (1.18– 5.82)**	
Repeated visits with the same provider			**0.029**		**0.012**
No^					
Yes	53.6	**1.00**		**1.00**	
	34.1	**0.45 (0.22 – 0.93)**		**0.29 (0.11 – 0.76)**	

*p-values <0.05 are indicated in bold

^ reference category

TOTD: total delay; OR: odd ratio: a: adjusted; CI: confidence interval; TB: tuberculosis

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Supplementary material

Table S1. Proportion of missing data, for the variables included in the multivariable analyses

Variable	N	%
Stigma	1	0.4
Prior unspecific treatment	1	0.4
Did you think you had TB?	1	0.4
Do you know what TB is?	1	0.4
Chronic diseases	2	0.8
After first visit, did you seek treatment from somewhere else?	5	2.0
First visit with GP	6	2.4
First visit at hospital	6	2.4
Age	7	2.8
Do you know how TB is diagnosed?	13	5.1
Pay for transportation to reach the health centre	21	8.3
Patient Delay	22	8.7
Health system delay	22	8.7
Diagnostic delay	28	11.1
Treatment delay	34	13.4
Did you have repeated visits with different providers in a different facility?	35	13.8
Did you have repeated visits with the same provider?	35	13.8
Total delay	45	17.8
Close distance of the first visit place	55	21.7

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Table S2. Median delays from literature and prevalence of delay in the present study

Delay/ Prevalence of delay	Pezzotti et al. 2015 (Italy)[13]	Saldana et al., 2013 (UK) [19]	Tattevin et al., 2012 (France)[24]	Farah et al., 2006 (Norway)[25]	Jurcev-Savicevic et al. 2013 (Croatia)[276]
Median PD (days)	31	29	14	28	
Prevalence of PD*	64.5	50.2	59.7	50.2	
Median HSD (days)	15	30	-	33	15
Prevalence of HSD*	40.9	29.3	-	25.3	40.9
Median TOTD (days)	-	62	-	63	-
Prevalence of TOTD*	-	42.3	-	40.9	-

*Prevalence of delay that would have been retrieved in our study, by applying median values from other studies

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Table S3. Correctness of patients' knowledge and symptoms recognition stratified for gender and country of birth

Characteristics	Italian-born % (N)	Foreign-born % (N)	p*	Males % (N)	Females % (N)	p*
Do you know what TB is? (n=252)						
Yes	81.2 (91)	56.4 (79)	**<0.001**	65.8 (106)	70.3 (64)	0.465
No	18.8 (21)	43.6 (61)		34.2 (55)	29.7 (27)	
Do you think TB is a serious disease? (n=250)						
Yes	67.9 (76)	57.2 (79)	**0.029**	63.9 (101)	58.7 (54)	0.309
No	17.9 (20)	14.5 (20)		13.3 (21)	20.7 (19)	
Don't know	14.3 (16)	28.3 (39)		22.8 (36)	20.7 (19)	
What causes TB? (n=248)						
Infection	77.5 (86)	43.8 (60)	**<0.001**	61.1 (96)	54.9 (50)	0.491
Punishment	1.8 (2)	0.7 (1)		1.3 (2)	1.1 (1)	
Unavoidable	0.0 (0)	1.5 (2)		1.3 (2)	0.0 (0)	
Don't know	20.7 (23)	54.0 (74)		36.3 (57)	44.0 (40)	
What are the symptoms TB? (n=253)						
Cough for more than 3 weeks	58.0 (65)	49.6 (70)	0.105	54.7 (88)	51.1 (47)	0.890
Sputum with blood	13.4 (15)	9.2 (13)		11.2 (18)	10.9 (10)	
Fever	15.2 (17)	14.2 (20)		13.7 (22)	16.3 (15)	
Weight loss	2.7 (3)	3.5 (5)		3.7 (6)	2.2 (2)	
Don't know	10.7 (12)	23.4 (33)		16.8 (27)	19.7 (18)	
How a person can get TB? (n=242)						
Through germs present in air droplets expelled in the cough	69.4 (72)	37.7 (52)	**<0.001**	55.8 (87)	43.0 (37)	0.147
Sharing utensils and objects with an infected person	3.8 (4)	7.2 (10)		5.8 (9)	5.8 (5)	
Don't know	26.9 (28)	55.1 (76)		38.5 (60)	51.2 (44)	
How TB is diagnosed? (n=240)						
Through sputum examination	39.0 (39)	17.1 (24)	**<0.001**	23.7 (37)	31.0 (26)	0.409
Through X-ray	32.0 (32)	25.7 (36)		28.2 (44)	28.6 (24)	
Don't know	29.0 (29)	57.1 (80)		48.1 (75)	40.4 (34)	
Can TB be cured? (n=249)						
Yes	93.6 (103)	76.3 (106)	**0.001**	84.8 (134)	82.4 (75)	0.858
No	0.0 (0)	2.2 (3)		1.3 (2)	1.1 (1)	
Don't know	6.4 (7)	21.6 (30)		13.9 (22)	16.5 (15)	
Can TB require a longer treatment to be cured as for multidrug resistant forms? (n=251)						

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Yes	51.8 (58)	34.5 (48)	**0.016**	41.0 (66)	44.4 (40)	0.868
No	10.7 (12)	18.7 (26)		15.5 (25)	14.4 (13)	
Don't know	37.5 (42)	46.8 (65)		43.5 (70)	41.2 (37)	
Which symptoms made you seek healthcare?						
Cough for more than 3 weeks (n=253)						
Yes	57.1 (64)	72.3 (102)	**0.011**	65.2 (105)	66.3 (61)	0.861
No	42.9 (48)	27.7 (39)		34.8 (56)	33.7 (31)	
Sputum with blood (n=253)						
Yes	8.0 (9)	17.7 (25)	**0.025**	14.3 (23)	12.0 (11)	0.601
No	92.0 (103)	82.3 (116)		85.7 (138)	88.0 (81)	
Fever (n=253)						
Yes	50.9 (57)	50.4 (71)	0.932	50.3 (81)	51.1 (47)	0.905
No	49.1 (55)	49.6 (70)		49.7 (80)	48.9 (45)	
Weight loss (n=253)						
Yes	28.6 (32)	44.7 (63)	**0.009**	44.7 (72)	25.0 (23)	**0.002**
No	71.4 (80)	55.3 (78)		55.3 (89)	75.0 (69)	
Tiredness/weakness (n=253)						
Yes	38.4 (43)	52.5 (74)	**0.026**	50.9 (82)	38.0 (35)	**0.048**
No	61.1 (69)	47.5 (67)		49.1 (79)	62.0 (57)	
Dizziness (n=253)						
Yes	4.5 (5)	6.4 (9)	0.507	6.8 (11)	3.3 (3)	0.232
No	95.5 (107)	93.6 (132)		93.2 (150)	96.7 (89)	
Chest pain (n=253)						
Yes	17.0 (19)	30.5 (43)	**0.013**	28.6 (46)	17.4 (16)	**0.047**
No	83.0 (93)	69.5 (98)		71.4 (115)	82.6 (76)	
Night sweat (n=253)						
Yes	20.5 (23)	30.5 (43)	0.073	31.1 (50)	17.4 (16)	**0.017**
No	79.5 (89)	69.5 (98)		68.9 (111)	82.6 (76)	
Did you think you had TB? (n=252)						
Yes	5.4 (6)	11.4 (16)	0.090	11.8 (19)	3.3 (3)	**0.022**
No	94.6 (106)	88.6 (124)		88.2 (142)	96.7 (88)	
Factors for delay in seeking care						
Not aware of symptoms (n=253)						
Yes	38.4 (43)	43.3 (61)	0.434	57.1 (92)	62.0 (57)	0.454

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No	61.6 (69)	56.7 (80)		42.9 (69)	38.0 (35)	
Fear of rejection/losing job (n=253)						
Yes	2.7 (3)	6.4 (9)	0.169	5.6 (9)	3.3 (3)	0.402
No	97.3 (109)	93.6 (132)		94.4 (152)	96.7 (89)	
Costs (n=253)						
Yes	0.0 (0)	9.2 (13)	**0.001**	5.6 (9)	4.3 (4)	0.667
No	100.0 (112)	90.8 (128)		94.4 (152)	95.7 (88)	
Lack of time (n=253)						
Yes	5.4 (6)	7.1 (10)	0.573	5.6 (9)	7.6 (7)	0.526
No	94.6 (106)	92.9 (131)		94.4 (152)	92.4 (85)	
Distance to health centre (n=253)						
Yes	0.9 (1)	2.8 (4)	0.270	2.5 (4)	1.1 (1)	0.442
No	99.1 (111)	97.2 (137)		97.5 (157)	98.9 (91)	
Lack of transportation (n=253)						
Yes	0.9 (1)	0.7 (1)	0.870	0.0 (0)	2.2 (2)	0.060
No	99.1 (111)	99.3 (140)		100.0 (161)	97.8 (90)	
Previous non-satisfactory experience with the health system (n=253)						
Yes	1.8 (2)	2.1 (3)	0.846	1.9 (3)	2.2 (2)	0.864
No	98.2 (110)	97.9 (138)		98.1 (158)	97.8 (90)	

*p-values <0.05 are indicated in bold

TB: tuberculosis

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Table S4. Attitude towards TB stratified for gender and country of birth

	Italian-born % (N)	Foreign-born % (N)	p*	Males % (N)	Females % (N)	p*
Should people with TB disclose their illness to other people? (n=252)						
Yes	70.5 (79)	47.1 (66)	**0.001**	53.1 (85)	65.2 (60)	**0.040**
No	8.9 (10)	19.3 (27)		18.8 (30)	7.6 (7)	
Don't know	20.5 (23)	33.6 (47)		28.1 (45)	27.2 (25)	
Who do you think is more likely to get TB, men or women? (n=252)						
Men	12.5 (14)	15.0 (21)	0.305	21.2 (34)	1.1 (1)	**<0.001**
Women	5.4 (6)	10.0 (14)		4.4 (7)	14.1 (13)	
Don't know	82.1 (92)	75.0 (105)		74.9 (119)	84.8 (78)	
How did you feel when you found out that you had TB? (n=253)						
Scared	37.5 (42)	45.4 (64)	0.376	36.6 (59)	51.1 (47)	0.164
Depressed	20.5 (23)	14.2 (20)		18.0 (29)	15.2 (14)	
Didn't believe (denial)	29.5 (33)	31.2 (44)		33.5 (54)	25.0 (23)	
Other	12.5 (14)	9.2 (13)		11.8 (19)	8.7 (8)	
Did you inform your friends/ family that you had TB? (n=248)						
Yes	90.9 (100)	55.1 (76)	**<0.001**	61.4 (97)	87.8 (79)	**<0.001**
No	9.1 (10)	44.9 (62)		38.6 (61)	12.2 (11)	
Have your relationships with your friends/ family changed since finding out you have TB? (n=245)						
Yes	22.0 (24)	14.7 (20)	0.138	15.4 (24)	22.5 (20)	0.165
No	78.0 (85)	85.3 (116)		84.6 (132)	77.5 (69)	
If yes, how? (n=43)						
Improved	41.7 (10)	10.5 (2)	**0.024**	26.1 (6)	30.0 (6)	0.775
Worsened	58.3 (14)	89.5 (17)		73.9 (17)	70.0 (14)	
Are people with TB discriminated in the community? (n=249)						
Yes	46.4 (51)	41.0 (57)	**0.002**	40.3 (64)	48.9 (44)	0.386
No	33.6 (37)	19.4 (27)		26.4 (42)	24.4 (22)	
Don't know	20.0 (22)	39.6 (55)		33.3 (53)	26.7 (24)	
Among TB patients, are male or female patients more discriminated? (n=249)						
Male	3.7 (4)	9.3 (13)	**0.027**	10.1 (16)	1.1 (1)	**<0.001**
Female	2.85 (3)	8.6 (12)		2.5 (4)	12.1 (11)	
Don't know	93.6 (102)	82.1 (115)		87.3 (138)	86.8 (79)	

*p-values <0.05 are indicated in bold

TB: tuberculosis

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Table S5. Risk analysis for DD (Univariate and logistic regression analysis)

	DD >7 days %	OR 95%CI	p	aOR 95%CI	p
Foreign-born patients			**<0.001**		**0.024**
Yes^	36.6	**1**		**1**	
No	64.7	**0.32 (0.18 – 0.54)**		**0.48 (0.25 – 0.91)**	
Chronic disease			0.061	-	-
Yes^	59.3	1			
No	45.1	1.77 (0.97 – 3.24)			
Gender			**0.008**		**<0.001**
Female^	37.5	**1**		**1**	
Male	55.9	**0.47 (0.27 – 0.83)**		**0.30 (0.15 – 0.58)**	
First visit with GP			**<0.001**	-	-
Yes^					
No	71.2	**1**			
	40.5	**3.63 (1.95 – 6.77)**			
First visit athospital			**<0.001**		**0.002**
Yes^	36.1	**1**		**1**	
No	67.0	**0.28 (0.16 – 0.49)**		**0.35 (0.18 – 0.67)**	
After first visit, did you seek treatment from somewhere else?			**<0.001**	-	-
Yes^	71.0	**1**			
No	34.4	**4.67 (2.62 – 8.31)**			
Cough more than 3 weeks			**0.035**		**0.048**
Yes^	44.2	**1**		**1**	
No	59.0	**0.55 (0.32 – 0.96)**		**0.51 (0.27 – 0.99)**	
Dizziness			**0.051**		**0.039**
Yes^	23.1	**1**		**1**	
No	50.9	**0.28 (0.08 – 1.08)**		**0.21 (0.04 – 0.92)**	
Prior unspecific treatment			**<0.001**		**0.002**
Yes^	60.4	**1**		**1**	
No	33.0	**3.11 (1.78 – 5.43)**		**2.85 (1.47 – 5.52)**	
Did you have repeated visits with different providers in a different facility?Yes^			**<0.001**	-	-
No	66.3	**1**			
	37.6	**3.26 (1.82 – 5.86)**			

*p-values <0.05 are indicated in bold

^ reference category

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