

Case Report

Tuberculosis and drug resistance in a region of Southern Italy among native and foreign-born populations: A twelve-year province-based study

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ARTICLE INFO

Keywords:

Migration
Rifampicin
MDR
TB/HIV
Epidemiology
Public health

ABSTRACT

Tuberculosis (TB) remains a significant global health challenge, with the World Health Organization (WHO) aiming for a 95% reduction in TB deaths by 2030. Disparities in TB detection persist, particularly regarding gender, immigration status, and resistance patterns. In Calabria, Italy—a key entry point for migrants from high-TB-incidence regions—TB poses a notable public health risk. This multicenter, retrospective study examines newly diagnosed TB cases in Calabria from 2012 to 2023, focusing on rifampicin-resistant TB (RR-TB).

During this period, 800 TB cases were diagnosed, with 270 (33.7 %) in native-born Italians and 530 (66.2 %) in foreign-born individuals, showing significant differences in age ($p < 0.001$) and gender ($p = 0.013$). Among 685 patients of this cohort with available HIV status, 24 (3.5 %) were people living with HIV (PLWH), primarily from Africa, and diagnosed at higher rates of RR-TB ($p < 0.001$). TB cases varied by province, correlating with specific birthplaces. A total of 27 (3.4 %) RR-TB cases were identified, with heightened resistance to multiple drugs. Among these strains, 20 (74.1 %) were isoniazid-resistant (MDR-TB).

This study underscores the need for comprehensive TB control strategies, especially regarding co-infection with HIV and the emergence of drug-resistant strains, emphasizing the importance of early detection and tailored management in Southern Italy.

1. Introduction

The global fight against tuberculosis (TB) faces significant challenges, despite the World Health Organization (WHO) aiming to reduce TB deaths by 95 % by 2030 [1]. Gender disparities in TB prevalence, detection, and reporting represent a critical aspect of this global health

issue [2]. In the recent years, global geopolitical changes, first triggered by the COVID-19 pandemic and later worsened by war in high-endemic regions, have created conditions that may allow TB to reemerge as a threat even in low-endemic areas [3–5]. In 2023, the *Mycobacterium tuberculosis* complex (MTBC) likely regained its position as the leading causes of death worldwide, after being surpassed by COVID-19 for three

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<https://doi.org/10.1016/j.jctube.2025.100512>

Available online 27 January 2025

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consecutive years [1].

An increased incidence of TB has been observed among historically marginalized racial or ethnic groups and those residing in impoverished housing conditions [6]. Immigration from regions with high TB incidence remains a key factor in the potential rise of TB cases, including concerning percentages of MTBC strains resistant to rifampicin (RR-TB) or multidrug-resistant (MDR-TB), which impose substantial burdens on healthcare systems even in low-incidence TB countries [7].

Furthermore, people living with HIV (PLWH) face heightened vulnerability to RR/MDR-TB, complicating individual health outcomes and public health efforts, particularly in migrants from South-East Asian countries, Europe, and Africa, which are important areas for MDR-TB/HIV co-infection [8].

Italy's healthcare system operates under a decentralized model, with regions managing their healthcare services while adhering to national health policies [9]. This setup allows for tailored healthcare delivery based on regional demographics and needs. However, disparities in health indicators, spending, and healthcare professional distribution highlight the complexity of Italy's healthcare landscape, with per capita health expenditure remaining below the European average [10]. Law No. 40/1998 led to the establishment of reception centers for asylum seekers across Italy, with the Saint Anna Reception Center within the Calabrian province of Crotone serving as a crucial hub for managing immigration inflows [11,12].

Italian police data from 2022 reveal a staggering 55.8 % increase in immigrant arrivals compared to the previous year [13]. In 2023, data from the Ministry of the Interior confirmed a rise in immigrant arrivals in Italy, with 157,652 arrivals compared to 105,131 the previous year [14]. Calabria continues to be the non-insular region in Italy with the highest number of migrant landings, reinforcing its role as a critical entry point for immigrants arriving from the Mediterranean [15]. Therefore, it offers an opportunity for TB screening and intervention to prevent TB spread in Italy and Southern Europe. Comprehensive surveillance and research are crucial in this region, where drug-resistant TB is a major concern [13]. This study examines TB spread in Calabria over twelve years, aiming to identify factors contributing to drug-resistant TB transmission and inform targeted healthcare strategies.

2. Methods

In this multicenter, retrospective study, newly diagnosed TB cases in Calabria were included, focusing on RR-TB. We analyzed a population-based dataset of individuals diagnosed with TB and hospitalized in Calabria from January 1st, 2012, to December 31st, 2023. Data were retrieved from electronic health records. Only patients with MTBC isolated through culture and tested for antibiotic susceptibility were included in the study. Therefore, patients diagnosed using molecular identification methods, such as MTBC-specific nucleic acid amplification tests, were excluded from this analysis unless the TB diagnosis was confirmed by culture. Regions were defined according to the WHO classification [1]. Patient data were anonymized per Italian privacy laws (Legislative Decrees 101/2018 and 196/2003). Each patient received a unique numerical identifier, and results were presented in aggregate form to ensure privacy.

Cultures were conducted using liquid and Lowenstein-Jensen solid media. Antibigrams were conducted using the BD BACTEC™ MGIT™ 960 SIRE kit (Becton Dickinson and Co., Sparks, MD, USA) for rifampicin, isoniazid, and ethambutol, following the manufacturers' instructions. The BD BACTEC™ MGIT™ 960 PZA kit (Becton Dickinson and Co., Sparks, MD, USA) was employed to assess susceptibility to pyrazinamide, according to the manufacturer's guidelines. Once acid-fast bacilli growth was confirmed, all strains were tested using an immunochromatographic assay to identify MTBC and differentiate it from non-tuberculous mycobacteria (BD MGIT™ Tbc Identification Test, Becton Dickinson and Co., Sparks, MD, USA), following the manufacturer's instructions. Species identification, when performed, was

accomplished using the GenoType MTBC assay (Hain Lifesciences, Nehren, Germany), according to the manufacturer's guidelines.

Statistical analysis was performed using STATA software (Release 16), with a significance level set at $\alpha = 0.05$. Continuous variables were described by median and interquartile range (IQR), and categorical variables by absolute frequencies and percentages. The Student–Welch *t*-test or Mann–Whitney *U* test was used for continuous variables, while Pearson's chi-squared test assessed categorical variables. Additionally, a chi-squared test for trend was conducted to analyze the temporal dynamics in the cases of TB among foreigners versus native-born across the years.

3. Results

During the study period, a total of 800 TB cases (for which MTBC isolated through culture and tests for antibiotic susceptibility were available) were diagnosed in Calabria. The characteristics of patients are summarized in Table 1.

Males represented the majority at 583 (72.9 %) and the median age was 36 years (IQR: 25–54). A total of 270 (33.7 %) were native-born, with a median age of 57 years (IQR: 39–71), while 530 (66.2 %) were foreign-born, exhibiting a significantly lower median age of 31 years (IQR: 23–42) compared to native-born Italians ($p < 0.001$). A trend of progressive increase in the number of foreign-born patients was observed over the years compared to native-born cases ($p = 0.02$) as reported in Fig. 1.

We identified 24/685 (3.5 %) PLWH (for 115 patients HIV status was not available). Their median age was 33 years (IQR: 25–39) and 6/24 (25 %) were females. PLWH were more likely to be infected with RR ($p < 0.001$) and isoniazid-resistant ($p < 0.001$) MTBC strains. Of these patients, a significantly higher rate was from the African Region ($p = 0.015$).

The distribution of TB cases varied across different provinces as shown in Fig. 2. TB diagnosis was significantly more frequent in native-born in the province of Cosenza ($p = 0.006$), whereas it was more frequent in foreign born in the provinces of Crotone ($p < 0.001$) and Vibo Valentia ($p = 0.013$). By contrast, no significant correlation was found between birthplace and TB cases in the remaining provinces.

The species of MTBC was identified in 353/800 (44.1 %) cases. Of these strains, *Mycobacterium tuberculosis* represented the main etiological agent. *Mycobacterium africanum* was isolated only from samples of foreign-born patients, all of whom originated from the African Region.

The study identified 27 (3.4 %) patients infected with RR strains, with a median age of 34 years (IQR: 28–51). Females constituted a minority of cases (10/27, 34.6 %). Among these cases, 4/27 (14.8 %) were native-born Italians. Foreign-born patients represented the significant majority of RR-TB cases ($p = 0.03$), in particular those from Eastern Europe compared to those from other countries ($p < 0.001$).

Patients with RR-TB exhibited higher resistance rates to isoniazid ($p < 0.001$), ethambutol ($p < 0.001$), and pyrazinamide ($p < 0.001$) compared to those without RR-TB. Among RR-TB strains, 20 (74.1 %) were isoniazid-resistant (MDR-TB). Interestingly, patients referred to Crotone were more likely to have RR-TB ($p = 0.02$). Demographical, clinical and microbiological characteristics of patients included in this study, according to rifampicin-resistance, are summarized in Table 2.

4. Discussion

In the present study, we included 800 TB cases diagnosed in the Calabria Region (Southern Italy) over twelve years. Of these cases, 33.7 % were native-born and 66.2 % were foreign-born, with men accounting the 72.9 % of cases. RR-TB was observed in 3.4 % of MTBC isolates and it was significantly linked to resistance to isoniazid (8.7 %), ethambutol (3.2 %), and pyrazinamide (8.2 %), with an overall rate of MDR strains of 2.5 %. Notably, RR-TB was more common among PLWH and foreign-born individuals, especially from Eastern Europe.

Table 1

Demographical, clinical and microbiological characteristics of patients included in this study, according to geographic area of birth.

Demographical and clinical features				
Variable	Overall	Native-born	Foreign-born	p-value
N. of individuals, (%)	800 (100)	270 (33.7)	530 (66.2)	
Age, median (IQR)	36 (25–54)	57 (39–71)	31 (23–42)	<0.001
Gender female, n. (%)	217 (27.1)	88 (32.6)	129 (24.3)	0.013
Birthplace (WHO region)				
African, n. (%)	148 (18.5)	0 (0)	148 (27.9)	–
Americas, n. (%)	3 (0.4)	0 (0)	3 (0.6)	–
South-East Asian, n. (%)	19 (2.4)	0 (0)	19 (3.6)	–
European Region, n. (%)	530 (66.2)	270 (100)	219 (41.3)	–
Eastern Europe, n. (%)	214 (26.7)	0 (0)	214 (40.4)	–
Eastern Mediterranean, n. (%)	115 (14.4)	0 (0)	115 (21.7)	–
Western Pacific, n. (%)	8 (1)	0 (0)	8 (1.5)	–
Unknown, n. (%)	17 (2.1)	0 (0)	17 (3.2)	–
Pulmonary involvement, n. (%)	725 (90.6)	241 (89.3)	482 (90.9)	0.675
HIV status				
PLWH ^a	24 (3.5)	5 (2.1)	19 (4.2)	0.145
unknown	115 (14.4)	32 (11.8)	83 (15.7)	0.146
<i>Mycobacterium tuberculosis</i> complex species				
tuberculosis, n. (%)	333 (41.6)	104 (38.5)	229 (43.2)	–
africanum, n. (%)	12 (1.5)	0 (0)	12 (2.3)	–
bovis, n. (%)	8 (1)	5 (1.8)	3 (0.6)	–
unknown, n. (%)	447 (55.9)	161 (60)	286 (54)	–
Drug-resistance				
rifampicin, n. (%)	27 (3.4)	4 (1.5)	23 (4.3)	0.034
isoniazid, n. (%)	70 (8.7)	20 (7.4)	50 (9.4)	0.337
ethambutol, n. (%)	26 (3.2)	6 (2.2)	20 (3.8)	0.242
pyrazinamide, n. (%)	66 (8.2)	19 (7)	47 (8.9)	0.373
Province of diagnosis				
Catanzaro, n. (%)	233 (29.1)	81 (30)	152 (28.7)	0.697
Cosenza, n. (%)	201 (25.1)	84 (31.1)	117 (22.1)	0.005
Crotone, n. (%)	111 (13.9)	19 (7)	92 (17.3)	<0.001
Reggio Calabria, n. (%)	190 (23.7)	73 (27)	117 (22.1)	0.119
Vibo Valentia, n. (%)	65 (8.1)	13 (4.8)	52 (9.8)	0.014

Continuous variables are expressed as median and interquartile range (IQR), while categorical variables are presented as number (n.) and percentage (%). WHO: World Health Organization; HIV: human immunodeficiency viruses; PLWH: people living with HIV.

^a Data calculated on a total of 685 patients for whom HIV status was available.

The study's findings on gender disparities in TB cases align with previous observations, confirming that men are disproportionately affected. Possible explanations include behavioral and occupational factors, such as smoking [16], alcohol consumption [17], and exposure to occupational risks like silica dust [18]. Biological differences, including hormonal and genetic factors, may contribute to the higher rates of diagnoses in men [19]. Conversely, social and cultural barriers often result in underreporting among women, highlighting the need for targeted interventions to address these disparities [2].

Although the study's findings could be impacted by the possible underestimation of HIV-positive patients, with 115/800 (14.4 %) patients having an HIV status that was not available, HIV infection was identified as significantly associated with RR-TB, consistently with WHO report indicating high rates of MDR-TB/HIV co-infection, especially in countries like China, Democratic Republic of the Congo and India [1]. The study observed a unique trend in Calabria, where PLWH from Africa

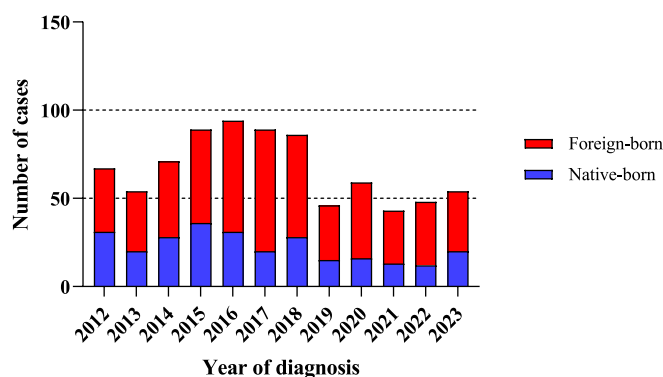


Fig. 1. Number of tuberculosis diagnoses by year in Calabria, Italy. Overall cases are represented by a single bar divided into two sections representing foreign-born (red) and native-born patients (blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

were at higher risk compared to other WHO regions, likely reflecting local migratory patterns. This contrasts with global trends, which identify South-East Asia as a high-risk region, underscoring the importance of considering regional demographics in risk assessment [1,20–22]. RR/MDR-TB is also a pressing concern in Eastern Europe, given that 8/12 (66.7 %) countries (Azerbaijan, Belarus, Kazakhstan, Republic of Moldova, Russian Federation, Tajikistan, Ukraine and Uzbekistan) reported by WHO as with a worrying prevalence of MDR-TB are located in this geographic area of Europe [1]. Accordingly, in the present study a RR-TB was significantly higher among individuals coming from Eastern Europe, particularly from Romania. The COVID-19 pandemic may have exacerbated these challenges, potentially disrupting healthcare services and delaying TB diagnoses, which could have contributed to a resurgence of RR/MDR-TB in this region [13,23,24]. This is consistent with findings from northern Italy, which previously highlighted how the pandemic led to a reduction in TB notifications in 2020, likely driven by reduced mobility, disruptions in screening programs, and delays in diagnosis [25].

In 2022 and 2023, immigrant arrivals increased in Italy, with the Calabria Region confirming the main non-insular destination on the Mediterranean Route [13–15]. As a result, we have observed a trend of progressive reduction in cases diagnosed in Italians with an increase in cases foreign-born patients during the study period ($p = 0.02$). This shift suggests that Calabria is becoming a more prominent destination for migrants. This surge is likely attributable, at least in part, to the ripple effects of geopolitical changes due to the COVID-19 pandemic and the ongoing conflict between Russia and Ukraine. The unprecedented disruptions to health services resulting from these crises have strained the healthcare system and interrupted essential services. These factors have collectively heightened vulnerability to TB transmission and exacerbated pre-existing health disparities [23,24,26]. Of note, in our study, a significant number of migrants originated from the Russian Federation, Ukraine, and nearby countries such as Romania, Bulgaria, and Moldova, accounting for 214/530 (40.4 %) TB cases among foreign-born people in this study.

In the Calabria Region, patients with TB attending the provincial hospitals in Crotone ($p < 0.001$) and Vibo Valentia ($p = 0.014$), the two provinces with the highest percentages of RR-TB cases (7.2 % and 4.6 %, respectively), were significantly more likely to be foreign-born individuals, frequently originating from high-TB-endemic countries. Interestingly, we found that people diagnosed in Crotone province demonstrated a significantly increased risk of RR-TB compared with those referred to the hospitals in the other provinces of the Calabria Region. The reason of this finding should be further investigated; however, we can hypothesize that it could be influenced by the presence in this province of the main hub for the reception and management of

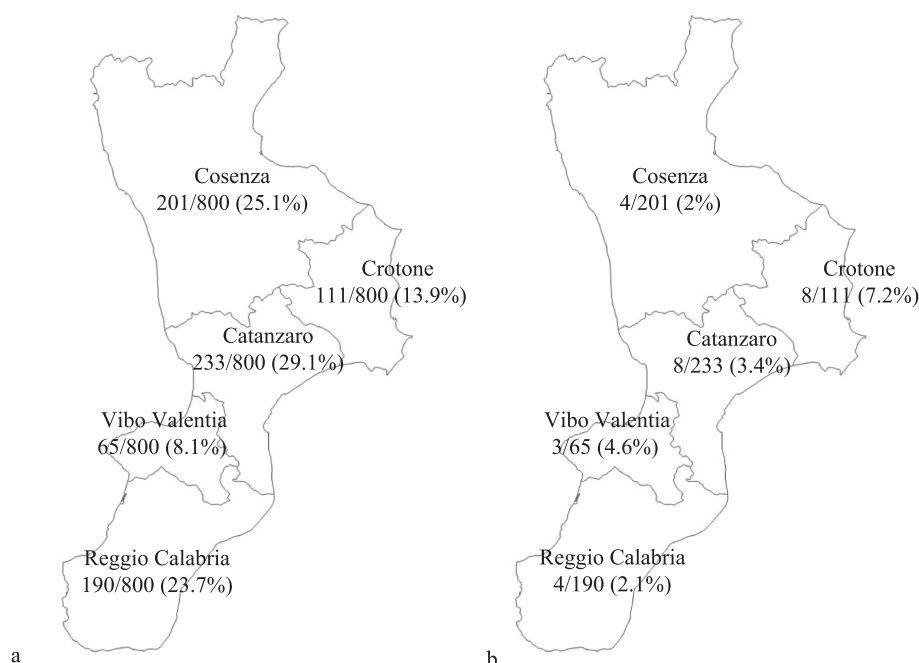


Fig. 2. Overall (a) and rifampicin-resistant (b) cases diagnosed in the Calabria region per province in the study period. Data are presented as number and percentage.

immigrants from Mediterranean Sea (*i.e.*, coming from African and Eastern Mediterranean Regions) in Calabria. A previous study in Barcelona identified a district in the city that is the most socio-economically disadvantaged, where a large proportion of the population from high-TB-endemic countries of Southeast Asia had settled [27]. On one hand, factors such as the prevalence of TB in migrants' countries of origin, the presence of drug-resistant strains, and the high rates of undiagnosed infections in those regions may contribute to this phenomenon. On the other hand, it has been suggested that travel history, including factors such as duration and conditions of the journey, can independently increase the risk of developing active TB [12]. Moreover, the trend of increasing foreign-born individuals in the Calabria Region could further exacerbate this situation. This analysis, supported by similar findings from other European settings [25,27], highlights that certain groups and geographic areas within regions generally considered to have low TB endemicity may actually bear a disproportionate TB burden. In these contexts, targeted efforts should be prioritized.

In conclusion, our findings support the need to implement comprehensive screening programs in principal migrants' reception hubs all over the country in order to mitigate TB transmission. The regional implementation of targeted TB control policies and programs—such as screening for TB infection among migrants, proactive contact tracing, symptoms-based testing, improving access to healthcare, and ensuring treatment adherence—can be particularly effective in areas with high TB incidence and socio-economic challenges. These measures could significantly enhance the fight against TB and help reduce its transmission in vulnerable populations.

5. Conclusion

Overall, the study highlights the different demographic and resistance patterns of TB across the Calabria Region, underscoring the need for tailored strategies in disease management. The findings emphasize the importance of localized surveillance and targeted public health interventions to curb TB transmission, particularly in relation to migration patterns and RR-TB among vulnerable populations such as PLWH. Addressing gender disparities in TB detection is crucial. The ongoing humanitarian crises in the Mediterranean further stress the need for coordinated efforts, comprehensive screening, timely diagnosis, and

access to quality healthcare. The Calabria's strategic position can significantly contribute to broader health security initiatives in response to evolving migration and public health challenges.

CRediT authorship contribution statement

Salvatore Rotundo: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Salvatore Nisticò:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Helen Linda Morrone:** Writing – original draft, Visualization, Investigation, Data curation, Conceptualization. **Luigia Gallo:** Visualization, Data curation. **Saveria Dodaro:** Visualization, Data curation. **Carmelo Papola:** Visualization, Data curation. **Pasquale Minchella:** Visualization, Validation, Supervision. **Giovanni Matera:** Visualization, Validation, Supervision. **Francesca Greco:** Visualization, Validation, Supervision. **Luigi Principe:** Visualization, Validation, Supervision. **Lorenzo Antonio Surace:** Visualization, Validation, Supervision. **Francesco Lucia:** Visualization, Validation, Supervision. **Francesca Serapide:** Visualization, Validation, Supervision. **Alessandro Russo:** Visualization, Validation, Supervision, Methodology. **Carlo Torti:** Visualization, Validation, Supervision, Conceptualization. **Enrico Maria Trecarichi:** Writing – review & editing, Validation, Methodology, Formal analysis, Data curation, Conceptualization.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Ethical statement

The study was approved by the ethics committee of the Calabria Region (n. 118 – June 13th, 2024) and was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Written informed consent was waived.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

Table 2
Demographical, clinical and microbiological characteristics of patients included in this study, according to rifampicin-resistance.

Demographical and clinical features				
Variable	Overall	Rifampicin-resistant	Rifampicin-sensitive	p-value
N. of individuals, (%)	800 (100)	27 (3.4)	773 (96.6)	
Age, median (IQR)	36 (25–54)	34 (28–51)	37 (25–54)	0.864
Gender male, n. (%)	583 (72.9)	17 (63)	566 (73.2)	0.239
Birthplace (WHO region)				
African, n. (%)	148 (18.5)	2 (7.4)	146 (18.9)	0.131
Americas, n. (%)	3 (0.4)	2 (7.4)	1 (0.1)	<0.001
South-East Asian, n. (%)	19 (2.4)	0 (0)	19 (2.4)	–
European Region, n. (%)	530 (66.2)	20 (74.1)	469 (60.7)	0.16
Eastern Europe, n. (%)	214 (26.7)	16 (59.2)	198 (25.6)	<0.001
Eastern Mediterranean, n. (%)	115 (14.4)	3 (11.1)	112 (14.5)	0.623
Western Pacific, n. (%)	8 (1)	0 (0)	8 (1)	–
Unknown, n. (%)	17 (2.1)	0 (0)	17 (2.2)	–
Pulmonary involvement, n. (%)	725 (90.6)	27 (100)	698 (90.3)	0.1
HIV status				
PLWH ^a	24 (3.5)	4 (17.4)	20 (3.2)	<0.001
unknown	115 (14.4)	4 (14.8)	111 (14.4)	0.947
<i>Mycobacterium tuberculosis</i> complex species				
tuberculosis, n. (%)	333 (41.6)	16 (59.3)	317 (41)	–
africanum, n. (%)	12 (1.5)	0 (0)	12 (1.5)	–
bovis, n. (%)	8 (1)	0 (0)	8 (1)	–
unknown, n. (%)	447 (55.9)	11 (40.7)	436 (56.4)	–
Drug resistance				
isoniazid, n. (%)	70 (8.7)	20 (74.1)	50 (6.5)	<0.001
ethambutol, n. (%)	26 (3.2)	12 (44.4)	14 (1.8)	<0.001
pyrazinamide, n. (%)	66 (8.2)	10 (37)	56 (7.2)	<0.001
Province of diagnosis				
Catanzaro, n. (%)	233 (29.1)	8 (29.6)	225 (29.1)	0.953
Cosenza, n. (%)	201 (25.1)	4 (14.8)	197 (25.5)	0.209
Crotone, n. (%)	111 (13.9)	8 (29.6)	103 (13.3)	0.016
Reggio Calabria, n. (%)	190 (23.7)	4 (14.8)	186 (24.1)	0.267
Vibo Valentia, n. (%)	65 (8.1)	3 (11.1)	62 (8)	0.563

Continuous variables are expressed as median and interquartile range (IQR), while categorical variables are presented as number (n.) and percentage (%). WHO: World Health Organization; HIV: human immunodeficiency viruses; PLWH: people living with HIV.

^a Data calculated on a total of 685 patients for whom HIV status was available.

the work reported in this paper.

Acknowledgement

The Calabria TB group, besides the main authors of this paper, includes the following clinicians: Chiara Costa, Lucio Cosco, Antonio Mastroianni, Giuseppe Foti, Carmelo Battaglia, Nicola Serrao, Maurizio Pino, Tommasina Nicoletta, Michele Brogna, Alfredo Vallone, Caterina Filia, Domenico Calabrò, Giorgio Carlo Cotrona, Giuseppina Berardelli,

Francesco D'Aleo, Helenia Mastrangelo.

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