Latent tuberculosis infection in healthcare trainees: The need for structured occupational health surveillance in low-incidence countries

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Abstract. *Background and aim:* Latent tuberculosis infection (LTBI) remains a significant occupational health concern, even in low-incidence countries. Healthcare students and medical residents are exposed to Mycobacterium tuberculosis (MT) during clinical training, emphasizing the need for structured health surveillance. This study analyzes data from a health surveillance program for tuberculosis-related biological risk among healthcare trainees at a university hospital in Northern Italy (2018–2022), aiming to demonstrate the necessity of implementing systematic TB surveillance protocols. *Methods:* A total of 2,087 healthcare students and medical residents underwent routine tuberculin skin test (TST) screening; interferon-gamma release assays (IGRA) were performed to confirm positive TST results. Demographic characteristics, professional role, and vaccination history were analyzed. A multiple logistic regression model was used to assess factors associated with TST positivity. *Results:* Among the participants, 710 (34%) were male and 1,377 (66%) were female, with a mean age of 23.6 ± 4.5 years. TST was performed in 2,053 individuals (98.4%), and 52 (2.5%) tested positive. IGRA confirmed LTBI in 6 cases (11.5%). Foreign nationality and older age were significantly associated with TST positivity, while no association was found for sex or professional role. *Conclusions:* LTBI surveillance is essential for healthcare trainees, ensuring early detection, risk mitigation, and infection control. These findings emphasize the importance of maintaining targeted LTBI surveillance among healthcare trainees, even in low-incidence settings. Systematic screening programs contribute to early detection and infection control, reinforcing the role of occupational health services in safeguarding both trainees and patients. (www.actabiomedica.it)

Key words: Health surveillance, healthcare students, latent tuberculosis infection (LTBI) tuberculosis, tuberculin skin test (TST), Interferon-gamma release assay (IGRA)

Introduction

Tuberculosis (TB) is a contagious infectious disease caused by *Mycobacterium tuberculosis* (MT). To this day, it remains one of the leading causes of death worldwide. According to data from the "Global Tuberculosis Report 2024", 8.2 million people were diagnosed with tuberculosis in 2023. TB has once again become the leading cause of death from a single infectious agent globally, overtaking COVID-19 after three years: during the same year, an estimated 1.25 million people globally succumbed to TB (1,2).

The incidence and distribution of the disease vary across different regions, with developing countries

being the most affected: incidence rates in these areas range from 150 to 400 cases per 100,000 inhabitants. Globally, it is estimated that over two billion people have been infected with MT, yet only 5-10% of them develop active disease during their lifetime. However, dormant bacilli can reactivate even years after the initial infection (3).

In Italy, 2,600 cases were diagnosed in 2023, equating to a rate of 4.4 cases per 100,000 inhabitants: this figure falls below the threshold of 10 cases per 100,000 inhabitants, classifying Italy as a low-incidence country, according to WHO guidelines (1). Cases are predominantly concentrated in Central-Northern regions, whereas fewer cases are reported in the South.

Among workers at higher risk of contracting TB are healthcare professionals: transmission in healthcare settings typically occurs through direct contact with patients with active TB or exposure to materials potentially contaminated with MT, such as during the handling of MT samples in microbiology laboratories (4,5). Many occupationally-acquired TB cases stem from underestimating the infectious risk, thus highlighting the need to enhance knowledge about TB transmission and adopt effective measures to reduce nosocomial infections (6,7). The employer, assisted by the occupational physician (OP), must take all necessary actions to limit the spread of the infection by isolating and testing all contacts of individuals with active TB (6).

The Italian legislation and guidelines on occupational safety highlights a key role of OPs in early identification of individuals with LTBI in order to contain and prevent the spread of epidemic outbreaks. According to the guidelines of the Italian Society of Occupational Medicine (SIML) (4), the health surveillance for biological risk from TB is recommended according to a consequential approach consisting of the tuberculin skin test (TST) as the first-level test and the interferon-gamma release assay (IGRA) as the second-level test. If the IGRA test is positive, the individual must undergo assessment by a specialist in pulmonology/infectious diseases and, if necessary, a chest X-ray. The specialist will then provide recommendations regarding the need for antitubercular chemoprophylaxis.

Similarly, the Lombardy Region guidelines focus on health surveillance for LTBI risk in healthcare

workers, recommending a gold-standard approach consisting of TST followed by IGRA in case of a positive TST result (8). Workers undergoing treatment for LTBI will have periodic clinical check-ups with the pulmonologist/infectious disease specialist, while those unwilling or unable to undergo treatment will follow specialist recommendations in collaboration with the OP, who will decide their fitness for work.

Healthcare students and residents, like healthcare workers, are exposed to biological risk from MT during hospital internships. Therefore, health surveillance for LTBI remains crucial, even in low-incidence countries like Italy, for early diagnosis and active disease prevention (9,10-15). Thus, a baseline test for LTBI diagnosis is strongly recommended for healthcare students and residents before starting clinical activities, as outlined in the guidelines (4,6).

In Italy BCG vaccination in the current epidemiological and risk context, can be considered as an individual protective measure, though its indication is limited to specific situations. It is recommended for healthcare personnel, medical students, and nursing students, as well as for individuals with a negative tuberculin test, working in high-risk healthcare environments or with multidrug-resistant TB exposure and who are unable to undergo chemoprophylaxis due to clinical contraindications (4).

This study analyzes data related to health surveillance for biological risk from TB in a sample of healthcare students and residents at a University Hospital in Northern Italy from 2018 to 2022, aiming to demonstrate the necessity of implementing health surveillance for tuberculosis-related biological risks.

Patients and Methods

The study included a total sample of 2,087 individuals, including undergraduate healthcare students and residents who completed internships between January 2018 and December 2022. Before starting their internships, these individuals underwent preventive health surveillance through administration of the TST, followed by an IGRA test if the TST was positive. This study was conducted as part of a public health surveillance initiative and, in accordance with

applicable ethical guidelines, did not require institutional review board approval (16).

The study considered the following characteristics: sex, age, nationality, degree program or postgraduated training occupation (student or resident), previous BCG vaccination, previous TB diagnosis, or LTBI already under prophylaxis.

Categorical variables were reported as absolute and relative frequencies, whereas the continuous variable (age) was expressed as mean ± standard deviation. A multiple logistic regression model was used to assess the association between the dependent variable (TST result) and independent variables (sex, age, nationality, occupation). Data were analyzed using SAS (SAS Institute, Cary, NC, USA) statistical software.

Results

The study included 2,087 individuals. The number of TST screenings performed per year was as follows: 438 in 2018 (21%), 417 in 2019 (20%), 229 in 2020 (11%), 501 in 2021 (24%), and 502 in 2022 (24%). The characteristics of participants are summarized in Table 1. The sample consisted of 710 males (34%) and 1,377 females (66%), with a mean age of 23.6 ± 4.5 years old. In terms of occupation, 1,398 (67%) were undergraduate healthcare students, while 689 (33%) were medical residents. Regarding the country of origin, 1,985 were of Italian nationality (95.1%) and 102 were foreign nationals (4.9%); the foreign nationals were divided into two subgroups based on TB endemicity: 33 individuals came from low-incidence countries (32% of foreigners), while 69 came from medium- and high-incidence countries (68% of foreigners).

Among the 2,087 individuals examined, 2,053 (98.4%) underwent the TST, and 34 individuals were directly tested with IGRA because they had previously performed IGRA during previous health surveillance (1.6%). Of those who underwent the TST, 52 tested positive (2.5%) and 2,001 tested negative (97.5%). All 34 individuals who underwent the IGRA test directly were negative.

The 52 TST-positive individuals underwent the IGRA test as per guidelines; of these, 46 were negative (88.5%) and 6 were positive (11.5%). The vaccination

history was also investigated: 46 individuals had no prior BCG vaccination, while 6 had been vaccinated and therefore were not subjected to chest X-ray.

The 46 individuals who underwent chest X-ray all tested negative, excluding any cases of active TB. In total, 6 cases of LTBI were recorded in this study. Of these 6 cases, only one individual was born abroad, and none had been vaccinated with the BCG vaccine.

All individuals with LTBI began prophylactic treatment, but only 5 completed it. The one individual who did not complete the prophylaxis was re-evaluated quarterly by the pulmonologist for two years, with chest X-rays as needed.

The multiple logistic regression analysis revealed that a positive TST result was significantly

Table 1. Characteristics of the study population.

	N	*%*
Sex		
Male	710	34.0
Female	1377	66.0
Age		
Mean ± SD	23.6 ± 4.5	
Occupation		
Student	1398	67.0
Resident	689	33.0
Nationality		
Italian	1985	95.1
Other	102	4.9
TB low-incidence country	33	32.0
TB medium- or high-incidence country	69	68.0
Diagnostic tests		
Tuberculin skin test (TST)		
Negative	2001	97.5
Positive	52	2.5
Interferon-gamma release assay (IGRA)		
Negative	46	88.5
Positive	6	11.5
Chest X-ray		
Negative	6	100.0
Positive	0	0.0

associated with foreign nationality (OR 21.06, 95% CI 11.40–38.90; p < 0.001) and older age (OR 1.10, 95% CI 1.05–1.15; p < 0.001), whereas no significant association was observed with sex and occupation.

Discussion

The aim of this study was to analyze the incidence of LTBI in a population of healthcare students and medical residents during a 5-year period (2018-2022), treating both groups equally in terms of health surveillance and related biological risk from MT.

The protocol adopted involves a sequential approach with an initial TST followed by a confirmatory IGRA test. This approach has proven to be more cost-effective than using IGRA as the first-line test for the entire sample, considering that the study population consists mainly of young, unvaccinated individuals from low TB prevalence areas (4,8).

The TST positivity rate was 2.5%, lower than that observed among healthcare workers in other low-incidence areas. This low positivity rate can be attributed to limited exposure and a reduced risk of contact with infectious TB cases. Unlike healthcare workers, students and residents have a shorter cumulative exposure time due to their younger age and fewer years of hospital experience. Furthermore, in low-incidence settings, like Lombardy, the likelihood of encountering infectious TB patients is significantly lower than in high-incidence regions.

Compared to other Italian studies conducted over the past decade, our findings align with the range of TST positivity rates reported, varying from 0.8% to 6% (7, 10-15). Such variability can be explained by differences in sample size, the inclusion of students from different degree programs and training levels, and regional TB incidence.

In our study, characteristics associated with TST positivity included foreign nationality and older age, in line with national and international literature, which identifies these factors as statistically significant predictors of a positive TST (10-13). Conversely, sex and occupation (student vs. resident) were not statistically significant factors in our analysis.

The 52 subjects who tested positive for TST underwent confirmatory IGRA testing, which yielded positive results in only six individuals (11.5%), confirming LTBI. The remaining 46 individuals tested negative, including those with a prior BCG vaccination, suggesting that the positive TST results in vaccinated individuals were likely due to a booster effect rather than true infection. The low BCG vaccination rate in our sample reflects the declining use of this vaccine in low-prevalence countries, where it is recommended only in specific cases, such as children living with TB-positive adults or healthcare workers at high risk who cannot take chemoprophylaxis.

All 6 IGRA-confirmed LTBI cases underwent chest X-rays and pulmonology evaluations following a multidisciplinary approach. In some cases, additional consultations with infectious disease specialists or bronchoscopists were required. Pulmonology consultations were scheduled for all individuals with IGRA-confirmed positivity and, in certain cases, for individuals with highly reactive TST despite a negative IGRA result, which could be due to immunosuppression. The specialist evaluation was essential for a comprehensive assessment of clinical, laboratory, and radiological data to confirm or exclude LTBI. In some cases, additional investigations such as CT scans or bronchoalveolar lavage (BAL) were requested when clinical suspicion remained despite a normal chest X-ray.

The six subjects with LTBI represented 0.3% of the sample, a slightly lower percentage compared to other Italian studies analyzing the same categories of healthcare students and medical residents (11-15). Of these six subjects with LTBI, five adhered to the recommended chemoprophylactic therapy, a higher adherence rate compared to the study by Lamberti et al. (2014), in which only 8 out of 27 individuals underwent prophylaxis (13). The high adherence rate to chemoprophylaxis is attributed to the adoption of a three-month pharmacological therapy (rifampin/isoniazid) and monthly and laboratory monitoring, which minimized adverse effects and improved compliance. In particular, at baseline, a comprehensive laboratory panel was performed to assess general health, liver function, and immunosuppression (e.g., HIV screening). In cases with abnormal findings, treatment

decisions were individualized based on a risk-benefit assessment. During therapy, liver function tests were conducted monthly or more frequently if abnormalities were detected, continuing for one month after treatment completion. This close monitoring helped mitigate the risk of adverse effects and reinforced adherence.

Although LTBI cases in our study were limited, untreated infections can progress to active TB, posing a risk to hospital colleagues, patients, and personal contacts. Therefore, implementing a structured preventive health surveillance protocol for biological risk from MT remains essential in this population.

During the COVID-19 pandemic (particularly in 2020), there was a temporary reduction in TST screenings, likely due to healthcare system reorganization. However, surveillance activities resumed promptly, and LTBI cases were identified both before and after the pandemic, suggesting a limited overall impact on LTBI detection.

Conclusions

TB remains one of the leading causes of death worldwide, constituting a major public health challenge. Although Italy is classified as a low-incidence country, continuous preventive measures remain essential to control TB transmission, especially in healthcare settings. The biological risk posed by MT is insidious and often underestimated

One of the most significant findings of this study is that none of the six individuals diagnosed with LTBI reported known contact with active TB cases. This finding highlights the value of proactive health surveillance, especially among healthcare students and medical residents. Even in low-incidence countries, where TB is often perceived as a negligible risk, early identification and management of TB-related biological risk are essential. These measures not only protect the individuals themselves but also prevent potential transmission to patients and colleagues throughout their future careers.

In conclusion, this study confirms the need for structured and systematic health surveillance protocols to enable early detection of TB infection, following national and regional guidelines. Occupational physicians are central to the effective implementation of these measures, helping to prevent nosocomial TB transmission. Through early detection, treatment, and monitoring of LTBI, these protocols contribute to the broader goal of TB elimination in low-incidence countries like Italy.

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