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Risk factors for latent tuberculosis infection (LTBI) in health profession's students of the University of Parma

Silvia Bonini, Maria Grazia Riccelli, Matteo Goldoni, Luisella Selis, Massimo Corradi
Department of Medicine and Surgery, University of Parma, Parma Italy

Abstract. *Background and aim of the work:* Nowadays Tuberculosis (TB) is one of the major Public Health problems for several professional categories. According to Italian law, University students are compared to workers: the main risk for them is represented by biological risk, in particular by blood-transmitted or by air-transmitted agents. As for TB, many scientific studies demonstrated that prevalence of latent tuberculosis infection (LTBI) in Medicine and Surgery students was lower than those in health workers and in general population. The main aim of this study is the evaluation both of reliability and predictive value of a specific anamnestic questionnaire for previous exposure to Mycobacterium tuberculosis, in order to identify individuals at risk for TB. The Mantoux Tuberculin Skin Test (TST) would be executed to compare results of questionnaire. *Methods:* The study included Health Profession's Degrees who were examinated during health surveillance in the period between June 2014 and March 2016. A questionnaire including 10 closed questions was presented to every student. The questionnaire was considerated positive with at least one positive answer. *Results:* The questionnaire was presented to 580 students, 500 of which completed TST; 466 students were Italian (93.2%). Questionnaire resulted positive in 89 students (17.8%); 15 of them presented positive TST: 14 of them was strangers (93.3%). Sensibility and specificity of questionnaire resulted 100% and 84% respectively. *Conclusions:* Our data suggested that anamnestic questionnaire could be considerated an efficient mean for identifying candidates for tuberculin screening in a TB- low prevalence population.

Key words: biological risk, latent tuberculosis infection, health profession, student, anamnestic questionnaire

Introduction

Nowadays tuberculosis (TB) is one of the most important public health problems worldwide for several professional categories (1-3), and cases of drug resistance are increasing (4). This risk is increasing even in low-incidence Countries because it's related to increase immigration.

After exposure contacts can acquire infection, which will evolve in overt disease (5%) or into a latent tuberculosis infection (LTBI, 95%) and, only in 5% of cases, in reactivation of infection (5, 6).

People affected by LTBI have a 5-10% risk to develop active disease during their life: in half of case this occurs after 2-5 years from infection; this risk is significantly higher for immunocompromised subjects (5-7).

Screening for LTBI is aimed at people at high risk of contracting the disease and of progression to active disease (8).

TST is the most common test used to identify tubercular infection. This test is based on a delayed-type hypersensitivity reaction, which develops when infected subjects are exposed to filtered cellular antigens, called purified protein derivate (PPD).

A lot of studies showed that Health Workers (HW) have a high risk of exposure to MB (9-11): because of this situation, periodic screening is an important part of the health program of tuberculosis control

for this working population. This program could identify recent infections and select subjects with latent infection to stand for the therapy.

There are no reliable data about LTBI prevalence in general population to compare with the population of HW. However, the WHO estimates the prevalence of LTBI in Italy is expected to approach 12% (12).

In Italy, according to Ministry of Health's guidelines, LTBI surveillance should be based on TST, which remains the first choice test, expecially for populations in which you do not expect high adhesion, low incidence of Bacillus Calmette-Guérin (BCG) vaccination and high TB-incidence. This procedure can be integrated with IGRA to confirm TST positivity. The only use of IGRA can be considered if the examined group has high BCG vaccination rates or if high TST positivity rates are expected.

Health surveillance of HW is very important in monitoring and evaluation of each world TB-infection control program, but, nevertheless, LTBI screening in HW is not uniformly well-structured on the national territory.

Health surveillance of HW includes:

1. Baseline test for TB infection (for every newly recruited HW);
2. Periodical testing;
3. Periodical screening of signs and symptoms;
4. Training and information about TB risk.

According to Italian law (Article 2, Legislative Decree number 81/2008) Universitary students are compared to workers, so they must be evaluated for specific professional risks during health surveillance.

As for LTBI screening in Medicine and Surgery students, in some Universities TST is combined with a risk questionnaire for LTBI. The only published study which validated the use of a questionnaire as an accurate means of identifying candidates for TB screening was carried out in Virginia (USA) (13).

In the USA, according to the American College Health Association (ACHA) Guidelines, all new members of Colleges or Universities must be screened through a questionnaire about risk factors for TB. If the questionnaire is positive, student will be further screened with TST, IGRA or both (14).

Two Italian studies showed a very low prevalence of LTBI among students of the Faculty of Medicine and Surgery and Health Professions. The first study, conducted at Naples University, included 3374 students and reported a TST positive prevalence of 3.9% (128 students) and a positive IGRA prevalence of 1.05% (35 students) (15).

The second study included 1302 students of the University of Genoa and showed a IGRA positive prevalence of 0.1% (2 students) and a positive TST prevalence of 0.8% (11 students) (16).

Collected data on 2694 students in Medicine and Surgery of University of Parma showed a prevalence of positive TST of 2.6% (70 students) and a prevalence of positive IGRA of 1% (27 students).

Comparing these prevalences to those of HW of the Hospital of Parma (9.6% positive TST and 2.2% positive IGRA) there was a significative difference between the two populations (O.R. 86.61, p 0.0001 for TST and O.R. 9.98, p 0.0016 for IGRA).

Considering only data on 1605 students before any training in the Hospital (first year for Health Care Professions and first and second year for Medicine and Surgery), we found a prevalence of positive TST of 2.1% (33 students) and a prevalence of positive IGRA of 0.8% (13 students).

These data didn't show a statistically significant difference in the prevalence of IGRA positive tests among students before and after their training (O.R. 1.45, p 0.2288).

However, considering prevalence of TST in the two groups, difference became statistically significant (O.R. 4.47, p 0.0366).

The main aim of this study is the evaluation both reliability and predictive value of a specific anamnestic questionnaire for previous exposure to Mycobacterium tuberculosis, in order to identify individuals at risk for TB in a low risk population.

Materials and methods

This study was carried out on a population of students enrolled in Degree Coursed of Medicine and Surgery and of Health Profession of the University of Parma.

The study included students undergone to health surveillance at Preventive Medicine Service from June

2014 to March 2016: a TST was planned for every student. An anamnestic questionnaire was administered to every student before carrying out TST.

The questionnaire is composed by 10 closed questions (yes/no) and formulated on the basis of risk factors and specific signs and symptoms for TB, as indicated by CDC (7), by the Operating Protocol for the health surveillance and the monitoring of TB in Italian Penitentiary Institutes (Ministry of Justice, 2008) and along the lines of similar medical history tests developed by the ACHA for the TB routine screening for the access of American students at the college and university campuses (14).

The questionnaire was considered positive if at least one answer was positive.

WHO data were used to identify TB high-risk Countries (Countries with incidence >20 cases for 100000 inhabitants) (17).

TST was performed regardless of this study at Preventive Medicine Service of the University Hospital of Parma by trained health care workers. A standard dose of 0.1 ml of purified protein derivate (Tubertest®, Sanofi Pasteur, Lyon, France) was slowly injected intradermally into the inner surface of the forearm and a small, blanched papule, disappearing after approximately ten minutes. The reaction was read by measuring the diameter of induration across the forearm in millimeters.

A positive TST was defined as an induration measuring ≥10 mm in healthy subjects. The skin test reaction should be read between 48 and 72 hours after administration.

Data were analyzed with PASS 14 software. The minimum sample size was set to 400 students: in fact, assuming a prevalence of positive TEST of about 5% (15), this sample size has a power (1-beta) of about 80% to detect a change in the sensitivity from 0.5 to 0.8 and a power of 100% to detect a change in specificity from 0.5 to 0.9 using a two-tailed binomial test. The level of significance is 0.05. The level of significance reached by the sensitivity is 0.0414 and the level of significance reached by specificity is 0.0453. The negative predictive value should be at least 0988.

The chi square test and the Fisher exact test were used for the comparison of the questionnaire variables; a difference having of p value <0.05 was considered significant.

O.R. values with the respective 95% confidence interval were reported.

Specificity, sensitivity, negative and positive predictive value, with the respective confidence intervals at 95%, were calculated to test the ability of our pre-screening questionnaire to select and, in second instance, to submit individuals at risk of tuberculosis infection to TST, and, on the other hand, to exclude subjects not at risk for TB infection.

Furthermore, subgroup analysis on the study population was performed, considering provenance and vaccination status as variables.

According to the Italian legislation concerning the guidelines on observational studies, ethical approval for conducting this survey was unnecessary, and on this basis, cross-sectional studies do not require a formal approval by local Institutional Review Boards (18).

Personal information regarding the subjects included in the study was protected according to Italian law (19).

Results

The questionnaire was administrated to a total of 600 students: 513 subsequently completed TST and were included in the analysis (Table 1); 87 students were not included in the study because they did not complete TST execution in time.

Considering 513 students, 475 of them were Italian (93%) and 38 came from other Countries (7%): 37 of them were born in countries with high TB incidence (>20 cases per 100000 inhabitants like Albania, Bosnia, Cameroon, Ecuador, Eritrea, Ghana, Morocco, Moldova, Macedonia, Nigeria, Iran, Paraguay, Peru, Romania) and one of them was born in a Country with low TB incidence (<20 cases per 100000 inhabitants: Germany).

Considering students undergone to TST, 496 (96.7%) had a negative outcome and 17 (3.3%) a positive outcome.

Overall, the prevalence of positive TST among Italian students was 0.21%, and among foreign student of 42%.

Table 1. Demographic characteristics of students with positive and negative TST

	Numbers (%) of students		Total
	positive TST	negative TST	
Sex			
Males	6	161	167
Females	11	335	346
Provenance			
Born in Italy	1	474	475
Born abroad*	16	22	38
Degree course			
Medicine and Surgery	8	270	278
Health professions**	9	226	235

* Albania, Bosnia, Camerun, Ecuador, Eritrea, Germany, Ghana, Morocco, Moldova, Macedonia, Nigeria, Iran, Paraguay, Peru, Romania.
** Nursing, Physiotherapy, Logopedia, Orthoptics, Obstetrics, Hearing Aid Techniques, Radiology Techniques, Laboratory Techniques.

Among positive TST (1 Italian student and 16 foreign students), in 7 cases IGRA confirmed positivity and in 10 cases IGRA resulted as negative. Three students completed the prophylaxis, two refused it and one of them had to stop for adverse effects. A female student is awaiting the pneumological evaluation (Figure 1).

Prevalence of LTBI in our population was 1.36%.

As for the questionnaire, it resulted as positive in 85 cases out of 513 (16.6%): 17 of them (20%) also showed a positive TST, while 68 (80%) showed a negative TST. Questionnaire resulted negative in other 428 cases and negativity was confirmed in all cases by TST (Table 2).

Sensitivity of the questionnaire in the overall study population (capacity of correct identification of TST positive individuals) was found to be 100%, while specificity (capacity of correct identification of TST negative individuals) was 86%.

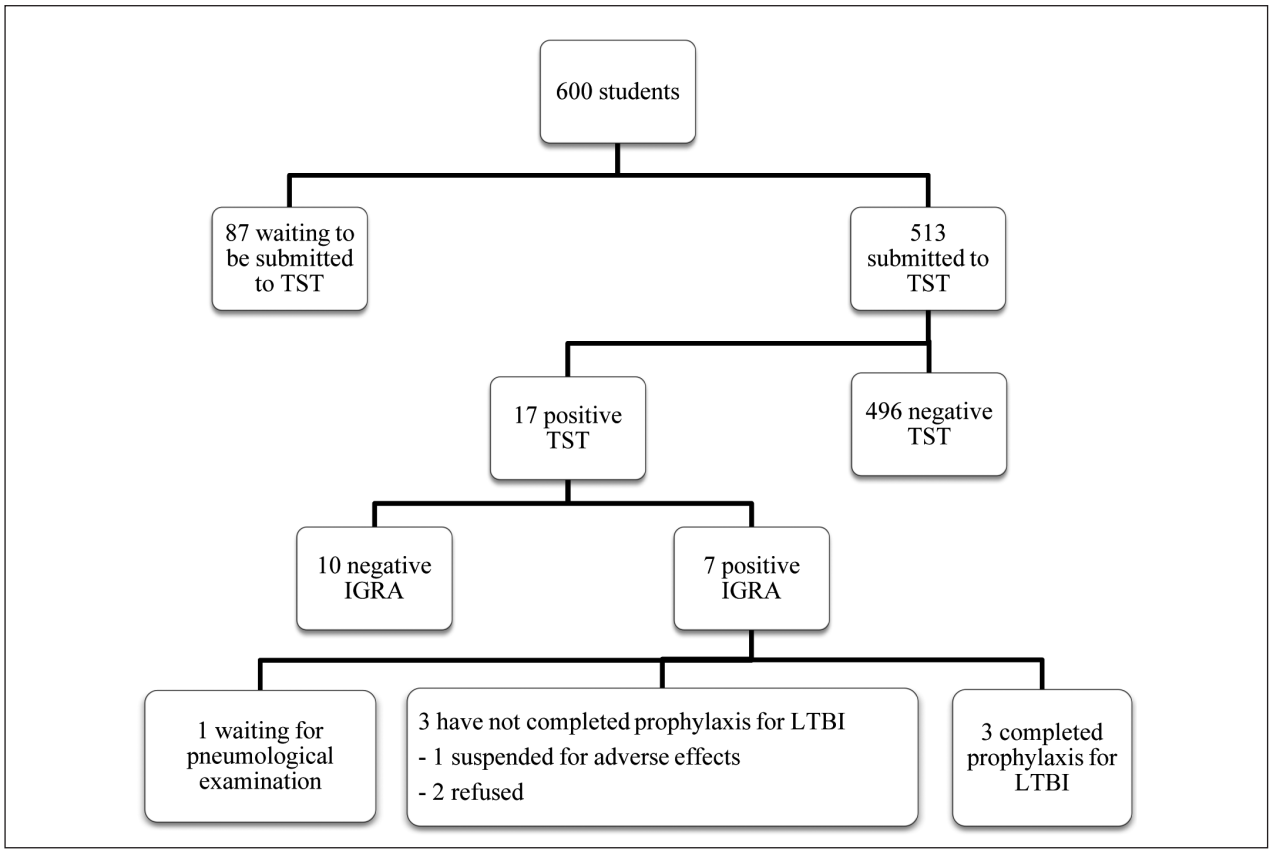

Figure 1. Descriptive analysis of the recruited subjects

Table 2. Correlation between the outcome of the questionnaire and the TST

	Positive TST	Negative TST	Total
Positive questionnaire	17	68	85
Negative questionnaire	0	428	428
Total	17	496	513

Positive predictive value of the questionnaire (TST proportion of positives among those with positive questionnaire) was found to be 20%, while negative predictive value (TST proportion of negatives among those with negative questionnaire) was 100%.

Considering single variables, previous BCG vaccination and origin in high-risk Countries showed a positive predictive value, independently of the positive TST outcome, with OR=344 (C.I. 43.72-2718.41), p<0.00001 and OR=401.68 (C.I. 50.60-3188.69), p<0.00001 respectively.

Limited positive cases for the other individual variables did not allow independent analysis for each one in our series (Table 3).

Considering the origin of the subjects, there were 37 positive questionnaires among foreigners (97%), 16 of which were also TST positive. Among Italian subjects there were 48 positive questionnaires (10%), one of which was TST positive.

In the subgroup of foreign students, which included both subjects from TB high-risk countries and subjects from low-risk countries, sensitivity of the questionnaire was high (100%), but specificity was very low (9%); positive predictive value was 44%, while negative predictive value was 100%.

On the other side, considering Italian subjects, specificity and sensitivity of the questionnaire were respectively 90% and 100%, positive predictive value was lower (2%) and negative predictive value was 100%.

Discussion

On the base of data obtained with this observational study, the questionnaire showed good results, especially considering that it was used as a pre-screening test. Sensitivity and specificity were comparable to those reported by the only similar study published in literature, carried out on American students (13).

Positive predictive value, amounting to 20%, is quite limited but completely acceptable for using the questionnaire in a pre-screening phase which provides an additional diagnostic investigation.

Table 3. Validity of positive TST predictors in the studied population

Variable	N. students with positive risk factors	N. students with positive TST	Sensitivity %	Specificity %	Positive predictive value (V+)	Negative predictive value (V-)
Positive questionnaire	85	17	100 (80.5-100.0)	86.3 (82.9-89.2)	20 (12.1-30.1)	100 (99.1 -100.0)
BCG vaccination	38	16	94.1 (82.9-100.0)	95.6 (93.8-97.4)	42.1 (26.4-56.8)	99.8 (99.4-100.0)
Countries with high TB incidence	35	16	94.1 (82.9-100.0)	96.2 (94.5-97.9)	45.7 (29.2-62.2)	99.8 (99.4-100.0)
Close contacts with TB patients	28	1				
Stays in high incidence countries	21	2				
Symptomatology	4	1				
Immuno-depression	7	0				

The most significant parameter we set out to test was the negative predictive value, which amounted to 100%: this result satisfied the objectives of our study, because it defined the questionnaire as a safe method for selecting only students to be subjected to investigation, minimizing the risk of false negatives.

Using the questionnaire in the study population, probability to neglect LTBI cases is close to zero.

Negative predictive value reported by Koppaka et al. (13) was 99.5%, confirming the reliability of a risk determination anamnestic system in specific populations with low expected LTBI risk.

Our study focused the analysis on students placed in the healthcare environment and confirmed these data also for the population of our interest.

In this study, LTBI prevalence among students was 1.36% (positive IGRA).

The limited size of the sample did not allow to establish a statistically significant independent correlation for each proposed questionnaire variables: among them, BCG vaccination and coming from high-risk countries were strongly associated with a positive TST, confirming already known data and their importance as risk factors (16, 20-21).

Given the high positivity of TST among foreign students with positive questionnaire, directly perform IGRA (without TST) could be a possible alternative strategy for this subgroup of students.

Conclusion

The recent introduction of an efficient monitoring system and adequate preventive measures against TB transmission, together with the availability of an effective treatment of LTBI and TB, have substantially reduced the TB occupational risk in high and middle income Countries (22).

These factors, together with the results obtained from this study, suggested that the questionnaire could be a reliable, practical and economical means of selecting candidates in a population with a low prevalence of tuberculosis, such as those constituted by the students of the Faculty of Medicine and Surgery.

Moreover, the selective application of the TST to a population with a higher prevalence of positive results, in this case foreign students, could improve the reliability of the results obtained.

Data could make us assume a new approach to TB contact investigation based on a better investigation of the epidemiology of LTBI in the population.

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Correspondence:
Professor Massimo Corradi
Parma University Hospital,
Via Gramsci 14 - 43126 Parma (Italy)
Tel. +390521033098
Fax +390521033076
E-mail: massimo.corradi@unipr.it