Prevalence of tuberculin skin testing among medical students in Campos School of Medicine, Rio de Janeiro*

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Background: The Hospital Ferreira Machado, utilized, in part, as a clinical training center for graduate students from the Faculdade de Medicina de Campos, admitted 65 tuberculosis (TB) patients in 2001.

Objective: To estimate the prevalence of positive tuberculin skin tests (TST) among medical students during distinct periods of their training and to identify and analyze correlated factors. To compare positivity rates, taking into account the booster effect, and estimate incidence of positive TST by class year.

Methods: A cross-sectional study was conducted among 500 students registered in the first semester of 2002. Using a structured and validated questionnaire, data regarding demographics, BCG vaccination and potential exposure to TB patients were obtained. A professional licensed by the Health Department administered the TSTs, and the two-step Mantoux method (PPD Rt23) was used.

Results: Of the 500 eligible subjects, 316 (63.2%) were excluded. Analysis showed increasing two-step TST positivity rates corresponding to extent of clinical experience (4%, 6.4% and 13.1%) and a tendency toward correlation with professional level. The highest percentage of positive TSTs was found during the period of clinical training, which corresponded to the time of greatest exposure to patients (1000 hours).

Conclusions: a) the TST positivity rate was high (7.9%) among students; b) TST was correlated with in-hospital training stage; c) evaluation of the booster effect lead us to highly recommended boosters in order to reduce the number of false-negative TST results.

Key words: Tuberculin. Tuberculin test. Tuberculosis. Students/Medical. Cross-sectional studies.

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INTRODUCTION

In theory, the medical students attending the *Faculdade de Medicina de Campos* (FMC, Campos School of Medicine) come from families whose incomes are well above the national average. Therefore, it is assumed that the prevalence of latent tuberculosis (TB) or active TB would be lower among these students than in the general population[1]. The risk of *Mycobacterium tuberculosis* (Mtb) infection in the hospital in which these students are trained is unknown. Implementation of measures to control TB infection among medical students is considered unnecessary by those who formulate public policies[2]. However, a study was conducted at the *Universidade Federal do Rio de Janeiro* (UFRJ, Rio de Janeiro Federal University), where 93.5% of medical students come from families whose monthly incomes are, on average, ten times the minimum wage[3]. The authors showed that the prevalence of latent TB among students in clinical training was seven times higher than that estimated for the general population.

Medical students at the FMC received their clinical training at the *Hospital Ferreira Machado* (HFM, Ferreira Machado Hospital). Annually, this hospital admits more than 60 patients diagnosed with pulmonary TB in accordance with established protocols and criteria. The HFM can be classified as a moderate-risk environment regarding outbreaks of nosocomial TB[5] and is a reference center for acquired immunodeficiency syndrome (AIDS) patients from the northern and northeastern regions, as well as from the *Região dos Lagos* (Lakes Region), of the state of Rio de Janeiro.

At the FMC, medical students in the basic phase (BP) of their training do not participate in patient examinations or treatment. Contact with patients increases progressively from the intermediate clinical phase (ICP) onward into the professional-phase (PP). The incidence of positive tuberculin skin tests (TSTs) among medical students who may have been infected with Mtb has never been assessed. Therefore, a cross-sectional study, using TSTs, was conducted in order to estimate the prevalence of Mtb infection among medical students during distinct periods of their training. Comparisons were made among the BP, ICP and PP groups of students.

Abbreviations used in this paper:

AIDS– Acquired immunodeficiency syndrome
BCG – Bacillus Calmette-Guérin
FMC – *Faculdade de Medicina de Campos* (Campos School of Medicine)
HFM – *Hospital Ferreira Machado* (Ferreira Machado Hospital)
Mtb – *Mycobacterium tuberculosis*
PPD – Purified protein derivative
OR – Odds Ratio
TB – Tuberculosis
TST – Tuberculin Skin Test
URFJ– *Universidade Federal do Rio de Janeiro* (Rio de Janeiro Federal University)

METHOD

In 2002, a cross-sectional study was carried out in order to estimate the prevalence of positive TSTs among PB, PCI and PP medical students at the FMC, as well as to identify and analyze correlated factors. All students enrolled in that year were eligible for the study. We found no students either with active TB, with a clinical history of TB or undergoing immunosuppressive therapy, any of which would justify exclusion from the program. The study was approved by the Research Ethics Committee of the UFRJ *Hospital Universitário Clementino Fraga Filho* (Clementino Fraga Filho University Hospital) and ratified by the Research Ethics Committee of the FMC.

Approximately 500 students per year begin their medical training at the FMC. The study subjects were divided into three levels by extent of clinical experience. As part of their regular schedules, first- and second-year (BP) students have contact with patients for less than 100 hours per year, whereas third- and fourth-year (ICP) students have between 100 and 1000 hours of contact, and fifth- and sixth-year (PP) students have more than 1000 hours.

All participating subjects gave written informed consent and completed a validated questionnaire[3], containing questions regarding demographics, BCG vaccination, and length of attendance at the FMC, as well as potential exposure to TB in the home, at the HFM, in outpatient clinics or in other hospitals. BCG vaccination was confirmed by verifying the presence of a vaccination scar over the right deltoid insertion (Table 1). Division into distinct socioeconomic classes was made according to the Critério Brasil (Brazil Criterion)[6]

All TSTs were administered using the Mantoux method[7]. Number 27 disposable needles and 1-ml syringes were used. A 0.1-ml dose (2 TU) of purified protein derivative (PPD)-Rt 23 was injected into the back of the left forearm of each student. The PPD-Rt 23 (State Serum Institute, Copenhagen, Denmark) was formulated by the *Centro Nacional de Referência para Tuberculose Professor Hélio Fraga* (Professor Hélio Fraga National Reference Center for TB) and is equivalent to the standard 5-TU PPD dose. A professional licensed by the Health Department administered the TSTs. Induration at the PPD injection site was measured by palpation at 48-72 hours after injection.

Students who had reactions of < 10 mm induration were re-tested (at least) one to (at most) three weeks later. Those who had reactions of 10mm induration after the first TST were considered to have a reactive (positive) TST and were not re-tested. Positive TST was defined as a reaction of 10 mm induration to the first TST or a positive booster effect (reaction of 10 mm induration) to the second TST[7]. The booster effect was considered positive when induration after the second TST was 10 mm and was at least 6 millimeters greater than the induration seen after the first TST. This classification was aimed at comparison with data in the international literature[8,9].

All students presenting positive TSTs were examined by a pulmonologist, who requested chest X-rays and sputum smear microscopy (for those students who presented expectoration). All of these students were advised to seek medical assistance if they experienced respiratory symptoms during the study.

There were at least 480 graduate students enrolled at the FMC in 2002. Taking into account an estimated 2.63% incidence of positive TST at the beginning of the course and a 16.18% incidence at the end of the course[3], a 95% confidence interval (95% CI), statistical power of 80% and a two-tailed ± of 0.05, the minimum number of subjects needed to conduct an investigation would be 172. A convenience sample that surpasses the minimum number was used.

Correlations between categorical variables and the outcome were determined using the chi-

TABLE 1

Caracteristics of medical students participating in the study; Campos (RJ), 2002

Caracteristic	Medical Students	
	Number/Total	(%)
Submitted to at least 1 complete TST process	345/500	(69.0)
Submitted to 2 complete TST processes	311/500	(62.2)
Included	316/500	(63.2)
Mean age (years ± SD)	21.7 ± 2.3	
Female	161/316	(50.9)
Male	155/316	(49.1)
Professed previous BCG vaccination	269/316	(85.1)
Presence of BCG vaccination scar	281/316	(88.9)
Brazil Criterion socioeconomic class:	Class A – 104/316	(32.9)
	Class B – 103/316	(35.7)
	Class C – 18/316	(5.6)
Contact with TB in the home	13/316	(4.1)
Internship in TB treatment	8/316	(2.5)
Internship in a hospital unaffiliated with the FMC	166/316	(52.5)
Basic phase of training	100/316	(31.6)
Intermediate clinical phase of training	109/316	(34.5)
Professional phase of training	107/316	(33.9)

TST: tuberculin skin test; SD: standard deviation; BCG: Bacillus Calmette-Guérin; ; TB: tuberculosis; FMC: *Faculdade de Medicina de Campos* (Campos School of Medicine)

square test or, when indicated, Fisher's exact test. Correlations between continuous variables and the outcome were determined using the Student's *t*-test or, when indicated, Kruskal-Wallis test. The level of statistical significance was set at 5%. In order to compare the incidence among groups, the ratio of the proportions (odds ratio) was described using a 95% confidence interval. During the electronic processing and analysis, data collected from the questionnaires were input into the January 2001 EPI INFO 6.04 statistical analysis application[10], which was used to carry out univariate and bivariate analysis of dichotomous and continuous variables. In order to identify independent factors correlated with positive TST in the study subjects, multivariate analysis with logistical regression was carried out. The STATA 7.0 program was used for the multivariate analysis, which included all variables attaining *p* values d•0.05 in the bivariate analysis.

RESULTS

Of the 500 students enrolled at the FMC in 2002, 259 (51.8%) were males and 258 (51.6%) were above the age of 21 (Table 1). Every effort was made to involve all 500. We visited locations where classes or practical activities were in progress, gave lectures on our study, and invited voluntary participation.

A total of 400 (80%) of the students filled out the questionnaire and gave written informed consent. The first TST was administered to 350 students (70%), analyzed in 345 (69%), and found to be positive in 5 (2 from the ICP and 3 from the PP), for a prevalence of 1.4%. A total of 320 students (64%) underwent a second TST, which was analyzed in 311 (62.2%) and found to be positive in 20 (6.4% of the 311). The incidence of positive booster effect was 5.8% (18/311). The rate of positivity for the first and second TSTs combined was 7.9% (25/316) (Tables 1 and 2).

TABLE 2
Results of bivariate analysis of extra-curricular factors correlated with positive TST among medical students; Campos (RJ), 2002

Extra-curricular factor	+TST		–TST		OR	95% CI	*p*
	n	(%)	*n*	(%)			
	25	(7.9)	291	(92.1)		(95%CI)	
Age							
> 21	18	(11.0)	146	(95.4)			
≤21	7	(4.6)	145	(89.0)	2.57	(0.98 – 7.02)	0.03**
Gender							
Male	10	(6.5)	145	(93.5)			
Female	15	(9.3)	146	(90.7)	0.67	(0.27 – 1.65)	0.35**
Presence of BCG scar	25	(8.9)	256	(90.1)			
Absence of BCG scar	0	(0.0)	40	(100.0)	N/A	N/A	0.04*
Socioeconomic Status							
Class A	12	(6.5)	172	(93.5)	1	-	-
Class B	10	(8.8)	103	(91.2)	1.39	(0.58 - 3.33)	0.46
Class C	3	(15.0)	16	(85.0)	2.69	(0.69 – 10.52)	0.16
Contact with TB in the home±							
Yes	0	(0.0)	12	(100.0)			
No	25	(8.7)	264	(91.3)	0.00	(0.00 – 4.07)	0.34*
Time since BCG vaccinationβ							
≤ 2 years	3	(30.0)	7	(70.0)			
> 2 years	10	(7.8)	120	(92.2)	5.14	(0.89– 27.73)	0.05*
Time since BCG vaccinationβ							
≤ 4 years	4	(26.7)	11	(73.3)			
> 4 years	9	(7.2)	116	(92.8)	4.69	(1.01 – 20.84)	0.03*

TST: tuberculin skin test; BCG: Bacillus Calmette-Guérin; TB: tuberculosis; OR: odds ratio; 95% CI: 95% confidence interval

*Fisher's exact test **Chi-square test ±15 students did not respond β 176 students did not respond

Of the 500 students enrolled, 184 (36.8%) were not included in the study. Of those, 84 completed the questionnaire but either did not return to undergo testing or began and did not complete the TST process. An additional 100 students did not fill out the questionnaire.

Among the 316 students (63.2%) included in the study, 31.6% (100/316) were BP students, 34.5% (109/316) were ICP students, and 33.9% (107/316) were PP students (Table 1). The minimum length of attendance was 1 month and the maximum was 84 months (mean, 36 months). Among the 184 students who were not included in the study, 36.4% (67/184) were BP students, 29.3% (54/184) were ICP students, and 34.3% (63/184) were PP students.

The rate of positivity for the first and second TSTs combined was 7.9% (25/316), representing 4% (4/100) in the PB, 6.4% (7/109) in the ICP and 13.1% (14/93) in the PP (Table 3).

No significant correlation was found between positive TST and socioeconomic status, contact with a pulmonary TB patient in the family, gender, internship prior to that established in the curriculum, treating pulmonary TB patients, or internship in a TB clinic (Tables 2 and 3).

Positive TST was found to correlate significantly with age, presence of BCG scar, length of time since BCG vaccination (equal to or less than two years; equal to or less than four years), internship in another hospital and PP (Tables 2 and 3).

The booster effect was not correlated with gender ($p = 0.37$), age ($p = 0.16$), BCG vaccination ($p = 0.10$) or class year ($p = 0.11$).

In the initial multivariate analysis, variables found to be statistically significant in the bivariate analyses were evaluated, based on data collected from only 140 students (those who provided such data). However, after verifying the presence of colinearity, only three variables were taken into account: internship in hospitals unaffiliated with the medical school, time since BCG vaccination equal to or less than four years, and being a PP student. Among these variables, time since BCG vaccination equal to or less than four years ($p = 0.05$; 95% CI = 0.99 – 15.99) and being a PP

TABLE 3
Results of bivariate analysis of curricular activities correlated with positive TST among medical students; Campos (RJ), 2002

Curricular activity	+TST		–TST		OR	95% CI	*p*
	n	(%)	*n*	(%)			
	25	(7.9)	291	(92.1)			
Class year							
BP	4	(4.0)	96	(96.0)	1		
ICP	7	(6.4)	102	(93.6)	1.65	(0.47 – 5.08)	0.44
PP	14	(13.1)	93	(86.9)	3.61	(1.15 – 11.38)	0.03
Previous internship							
Yes	11	(9.6)	103	(90.4)			
No	14	(6.9)	204	(93.1)	1.43	(0.58 – 3.51)	0.39**
Treated a TB patient[α]							
Yes	12	(11.0)	97	(89.0)			
No	11	(6.3)	164	(93.7)	1,84	(0.73 – 4.69)	0.15**
Clinical training in a TB clinic[β]							
Yes	0	(0.0)	8	(100.0)			
No	25	(8.2)	280	(91.8)	0.00	(0.00-6.97)	0.50*
Clinical training in another hospital[ϕ]							
Yes	16	(10.9)	131	(89.1)			
No	8	(4.9)	155	(95.1)	2.37	(0.92 – 6.25)	0.05

TST: tuberculin skin test; TB: tuberculosis; OR: odds ratio; 95% CI: 95% confidence interval; BP: basic phase; ICP: intermediate clinical phase; PP: professional phase; *Fisher's exact test ;** chi-square test; [±]32 students did not respond; [?]3 students did not respond; [ϕ]6 students did not respond

student (p= 0.06; 95% CI = 0.96 – 28.07) showed a tendency toward significant correlation with positive TST (Table 4).

DISCUSSION

Cross-sectional studies have a limited capacity to determine causal relationships. A longitudinal study would be more suitable for analyzing the risk of infection and correlated factors, and the conversion rate. Within our milieu, Muzy de Souza[13] conducted a study that involved both cross-sectional and longitudinal analysis. The author reported that, in the cross-sectional analysis, the prevalence of Mtb infection among health professionals was 51% and, in the longitudinal analysis, the rate of TST conversion was 8.7%. There is little such data regarding medical students in developing countries. In a study conducted in Mexico, Muñoz-Barret et al.[14] described a 41% prevalence Mtb infection among fifth-year medical students and a 14% prevalence among first-year students. Based on the results of our study, which show rates of TST positivity increasing in parallel with class year, we formulated the hypothesis that TST conversion occurs in the period of more frequent clinical practice, as has been previously reported[3,11,12]. In university hospitals in the cities of Rio de Janeiro and Niterói (both located in the state of Rio de Janeiro), Ferreira[11], Silva[3] and Costa[12] conducted studies involving medical students in the same age bracket as those evaluated in the present study. The authors reported the prevalence of Mtb infection to be 20.4%, 9.2% and 3.6%, respectively. Ferreira[11] and Silva[3] demonstrated a significant difference between PP and PB students in TST positivity rates. Costa[12] described a 7.5% rate of TST conversion among interns (sixth-year PP students).

TABELA 4
Resultados da análise multivariada (regressão logística) de 140 alunos de Medicina; Campos (RJ), 2002

PT +	RC	p valor	IC 95%
EFF	1,00	0,61	0,99 – 1,02
BCG ≤ 4 anos	3,99	0,05	0,99 – 15,99
PP	5,20	0,06	0,96 – 28,07

PT: prova tuberculínica; EFF: estágio fora da faculdade; RC: razão de chances IC: intervalo de confiança; PP: período profissional; BCG: bacilo de Calmette-Guérin.

There was a high proportion of uninfected students in our sample (320/345), as well as in those of Ferreira (355/446)[11] and Silva (413/455)[3]. This indicates that, among students practicing in university hospitals and AIDS reference centers in the state of Rio de Janeiro, there are many who have never been exposed to Mtb. Therefore, these students are at high risk for infection by the TB bacillus if the rate of TB transmission increases in these institutions, especially in those which have not adopted appropriate biosafety measures[2].

The prevalence observed in our study is lower than that observed by Ferreira[11] or Silva[3]. This is due in part to the fact that our sample is comprised of younger students and that their socioeconomic status is higher than that of the general population. It is also necessary to take into account the fact that our study was conducted in a city with a lower population density and lower incidence of TB than the cities where the above-mentioned studies were conduced. It is also notable that some biosafety measures, such as the implementation of norms and protocols for preventing TB transmission among health-care workers[7], have been used at the study site (HFM) since 1999. Such measures may have contributed to reducing TB transmission.

This study showed a clear correlation between positive TST and BCG vaccination (Table 2), as reported by other authors[14,15]. Nevertheless, based on the presence of BCG vaccination scar, there is still a tendency toward correlation between being a PP student and positive TST.

The booster effect was not correlated with BCG vaccination and further research is needed in order to investigate the aforementioned phenomenon, especially within populations who live in regions where there is a high prevalence of nontuberculous mycobacteria.

This study has its limitations. Even though we exceeded the number of students estimated in the initial sample calculation, there was a selection bias in the study due to the fact that student participation was optional. Nevertheless, there are no mechanisms for making student participation in this kind of study compulsory. It is possible that students who knew that they were TST reactive avoided participating in the study and that those who had been previously exposed to TB patients were more interested in participating. Silva[3],

Ferreira[11] and Costa[12] also observed the aforementioned bias in a nonrandomized evaluation of the prevalence of latent TB among medical students in teaching hospitals.

In studies conducted in the USA, Malasky et al.[16] and Wurtz et al.[17] collected information about TSTs in medical schools by means of questionnaires that were mailed to the schools. The authors do not mention whether any verbal orientation was given to the students involved. In the current study, we were afforded the opportunity to explain the questionnaire and its objectives to the medical students at the FMC. We gave these lectures to as many students as possible.

The estimated prevalence of Mtb infection among the general population in the Americas (excluding the USA and Canada) is 25%[1]. The result of the current study (TST positivity rate of 7.9%) may be due to the fact that the subjects were young and of higher socioeconomic status than the general population.

Due to the magnitude of the TB epidemic in Brazil, public health policies prioritize the identification and appropriate treatment of TB patients. Little or no emphasis is placed on the prevention of TB transmission among medical or nursing students in health centers that are used for their training. Consequently, TST administration is not standard practice in medical or nursing schools.

Similar studies should be conducted in other public and private medical schools in Brazil. It is relevant to point out that longitudinal studies provide information regarding the risk of nosocomial infection among medical and nursing students. The results of the present study, as well as those from other recent studies conducted in Brazil[3,11,13], strongly suggest that medical students should undergo at least one TST upon entry into university and another after beginning their clinical training, and that chemoprophylaxis is indicated in cases of tuberculin conversion, with or without active TB. This recommendation is in compliance with the guidelines established by the Centers for Disease Control and Prevention[7], the International Union Against Tuberculosis and Lung Diseases[18] and the World Health Organization[19].

The high percentage of negative TSTs among medical students at the beginning of the course compels us to recommend TB control procedure orientation programs at clinical training locales. Discussions should be opened regarding the implementation of nosocomial TB control programs in hospitals that are used, officially or unofficially, in the clinical training of medical students in Brazil. It is essential that the Health Department be committed to promoting studies that would either validate or invalidate the recommendation for BCG re-vaccination of health professionals (working in any type of health care facility) who test negative on their first and second TSTs. In addition, operational studies that could optimize the treatment of latent TB in these individuals should be promoted.

Furthermore, we suggest that analysis of TST positivity rates among graduate students in clinical training at university hospitals may be a useful indicator in monitoring the impact of the diverse biosafety measures adopted during the various training periods.

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