Original Article

Risk for *Mycobacterium tuberculosis* infection among medical students at the Universidade Federal do Rio de Janeiro Faculdade de Medicina

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Introduction: There have been few Latin American studies investigating the fact that the rate of tuberculosis (TB) infection among medical students is higher than the 1.3% rate seen in the population at large.

Objective: To describe the cumulative incidence and the relative risk for TB infection among medical students.

Method: In 1998, a prospective cohort study was conducted involving medical students at the Universidade Federal do Rio de Janeiro Faculdade de Medicina who tested negative (induration <10 mm) on the tuberculin skin test (TST). Students were tested using the two-step TST method and were retested one year later. The students tested were at two different stages in their training: pre-clinical (no contact with patients) and final year (contact with patients). Information about demographic characteristics, BCG vaccination history, and instances of potential exposure to *Mycobacterium tuberculosis* were obtained using a standardized questionnaire. Of the 575 students initially enrolled, 72% (414) completed the study.

Results: The TSTs of 16 (3.9%) of the 414 students converted, representing a cumulative incidence of 3.9% (95% confidence interval = 1.06 to 12.1). Senior medical students were at an almost fourfold higher risk for *M. tuberculosis* infection than were those in pre-clinical training.

Conclusion: The risk for TST conversion is very high in this population.

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Key words: PPD. Tuberculosis-infection. Tuberculin conversion. Medical students

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INTRODUCTION

In the pre-chemotherapy era, Myers et al.[1] showed that 60% of the students at the University of Minnesota Medical School (Minneapolis, MN, USA) who initially tested negative on the tuberculin skin test (TST) tested positive by the time they graduated. By 1966, this situation had changed dramatically, and only 2 of 138 graduating students presented TST conversion[2].

In the 1990s, with the ruthless resurgence of tuberculosis (TB) in developed countries, Fagan & Poland[3], using a questionnaire aimed at medical schools in the USA, reported a 2% annual conversion rate among medical students (MS). However, some medical schools reported 10% conversion rates. In the same year, Nolan[4] stated that a 5% conversion rate was unacceptable for this special population.

The *Hospital Universitário Clementino Fraga Filho* (HUCFF, Clementino Fraga Filho University Hospital) at the *Universidade Federal do Rio de Janeiro* (Rio de Janeiro Federal University) is one of several general reference hospitals for TB and acquired immunodeficiency syndrome (AIDS) in the city of Rio de Janeiro (RJ). The MS at the *Faculdade de Medicina of the Universidade Federal do Rio de Janeiro* (FMUFRJ, Rio de Janeiro Federal University School of Medicine) engage in clinical practice in this hospital from the third through the twelfth semester.

In 1997, a transversal study among MS of the FMUFRJ was carried out and showed the prevalence of *Mycobacterium tuberculosis* infection among basic students, intermediate students and interns to be 3%, 7% and 16%, respectively[5]. In addition to advancing the hypothesis that TST conversion may occur over the course of medical school, the authors found that 92% of the MS were nonreactors or weakly positive reactors on TSTs. The present study – a one-year follow-up study of MS who were nonreactors or weakly positive reactors – was designed in order to confirm the TST conversion hypothesis.

Abbreviations used in this paper:
AIDS – Acquired immunodeficiency syndrome
FMUFRJ – Faculdade de Medicina da Universidade Federal do Rio de Janeiro
MS – Medical students
TB – Tuberculosis
HUCFF – Hospital Universitário Clementino Fraga Filho
TST – Tuberculin skin test
CDC – Centers for Disease Control and Prevention

METHODS

A prospective cohort study, involving MS who were nonreactors or weakly positive reactors on two-step TSTs in the preceding year, was conducted from January 1998 to December 1999. It was assumed that students who had entered the professional stages at the HUCFF had been exposed to TB (exposure based on the number of weekly hours of patient contact according to the curriculum). Basic students attending classes at the *Centro de Ciências da Saúde* (Health Sciences Center) – where students have no contact with patients – one year prior to the second TST were not considered to have been exposed to TB.

The HUCFF provides hospital services to an average of 300 TB patients every year. In a longitudinal study conducted from 1994 to 1997, 32 (8.7%) of the 368 health professionals assessed presented TST conversion[6]. The MS in the professional stages practice in HUCFF infirmaries, emergency rooms, and clinics in rotation.

Annually, 200 students are admitted to the FMUFRJ medical school, and the course lasts 6 years. In the present study, the MS were classified as basic (first three semesters) or professional (fourth to twelfth semesters, having 20 to 40 hours per week of professional contact with patients). The Research Ethics Committee of the HUCFF and of the FMUFRJ approved the study. The MS gave written informed consent and completed a standardized questionnaire evaluating sociodemographic characteristics. Participants were checked for BCG vaccination scar during the interview.

From January 1998 to December 1999, nonreactor and weakly positive reactor MS were contacted for resubmission to TST. A professional trained by the Ministry of Health administered the TST, using the Mantoux test. The TST was performed in accordance with the guidelines of the Ministry of Health, which provided the purified protein derivative (PPD). Conversion was defined as an increase $\geq$10 mm in induration over that of the two-step test performed the year prior[7].

The chest X-rays of all students who presented TST conversion were normal. Prior BCG vaccination

was determined by the presence of a vaccination scar on the right arm. Family income lower than 10,000 reals (exempt from income tax) was considered low for this population.

In the transversal study conducted in the preceding year, the proportional difference between infected professional students and infected basic students was 8%, with a 95% confidence interval (95% CI) of 2.5% to 11.2%. The size of the sample was calculated in order to find this proportional difference between the cumulative incidences in the two groups.

A database was created using the Epi-Info 6.0 software program. The SAS software program (SAS Institute, Cary, NC, USA) was used for all statistical analyses. Chi-square test and Fisher's exact test were used for categorical variables. Chi-square test was used for the analysis of linear tendency. Statistical significance level was set at 0.05% throughout the study[8]. Cumulative incidence and incidence rate were the frequency measures[9]. The number of hours of exposure according to the FMUFRJ curriculum was used in order to allow the use of the incidence rate. Relative risks and 95% CI were calculated[9].

RESULTS

The transversal study comprised a total number of 618 students, and 575 were eligible for a new test. Of the total, 7% were excluded because they tested positive on the TST. Another 28% fell out of contact because they graduated, did not report for the second TST or did not answer the two phone calls made in a final attempt to track down missing students for the final TST (Table 1). Three-fourths of the students who fell out of contact were 21 years of age or older and had high family incomes. These proportions are significantly different than those of the final population (Table 2).

As shown in Table 3, the final population of the study comprised 414 students (who were younger), with similar numbers of males and females, most of in the professional stages at the FMUFRJ. Three-fourths of this population presented a BCG vaccination scar and only 9% had been submitted to BCG vaccination during the year of the study. None of the students who had been vaccinated in the year preceding the study presented TST conversion according to the adopted criteria. One-third of the final study population reported annual income equal to or less than 10,000 reals. Of the 414 students tested, 190 (45%) were basic students and 224 (54%) were professional students. The latter were submitted to two TSTs in the preceding year and another for the present study. Of the 224 professional students, 55 (13.3%) received the study TST at the beginning of the sixth semester, 61 (14.7%) at the beginning of the ninth, 33 (8.0%) at the beginning of the tenth, 23 (5.6%) at the beginning of the eleventh and 52 (12.5%) at the beginning of the twelfth. The students in the basic semesters were submitted to the two tests at the beginning of the first year and to the study TST at the beginning of the third semester.

TABLE 1
Study population

	N	Description
Total students since transversal study	618	All students who ever tested in the transversal study
Excluded	43	positive TST
Eligible	575	All students who were submitted to the two-step TST
Dropouts	161	52 graduated and 109 chose not to participate in the cohort or did not report for the readings
Final study population	414	
Basic students	190	No theoretical hours of exposure/week in the CCS
Professional students	224	Maximum of 40 hours of exposure/week in the HUCFF-UFRJ

N: total number of students; TST: tuberculin skin test; CCS: Centro de Ciências da Saúde da Universidade Federal do Rio de Janeiro (UFRJ); HUCFF: Hospital Universitário Clementino Fraga Filho da UFRJ.

The overall cumulative incidence of TST conversion in the study population was 3.9%. The cumulative incidence of TST conversion among the professional students was 5.8%, compared to 1.6% among the basic students (Table 4). Therefore, there was a significant difference of 4% between the two groups (p = 0.0260). The proportion of students who presented TST conversion showed a tendency proportional to class year, according to the chi-square test for linear tendency (Table 4). However, TST conversion among students in the initial professional stages was not significantly different than among those nearing graduation (p = 0.7373).

The TST conversion rate per 1000 students/year was four times higher for the professional students than for basic students (Table 4). The relative risk for TST conversion among students nearing graduation was 6 times higher than that for those basic students. The TST conversion rate

TABLE 2
Profile of the group of subjects not completing the study

	Students not monitored throughout n = 161	Final study population n = 414
Professional students	78/161 (48%)	224/414 (54%)
Basic students	83/161 (52%)	190/414 (46%)
Females	83/161 (51%)	197/414 (47%)
BCG vaccination	107/154 (70%)	309/413 (75%)
No vaccination scar	47/154 (30%)	104/ 413 (25%)
Age ≥ 21*	119/161 (74%)	269/414 (65%)
Income** > R$10,000/year	132/157 (84%)	267/412 (64%)
Income ≤ R$10,000/year	25/157 (16%)	145/412 (36%)

*p = 0.040 (chi-square test)

**$p \leq 0.001$ (chi-square test)

TABLE 3
Characteristics of the final study population

	Number/total	(%)
Population completing the study	414/575	72.0
Median age	21	
Females	217/414	52.4
Males	197/414	47.6
BCG revaccination in the year prior	38/414	9.1
Vaccination scar	309/413	74.8
Low family income	143/412	35.0
Basic students	190/414	45.9
Professional students	224/414	54.1
Sixth semester	55/414	13.3
Ninth semester	61/414	14.7
Tenth semester	33/414	8.0
Eleventh semester	23/414	5.6
Twelfth semester	52/414	12.5

per 1000 students/hour in each semester is shown in Table 4. Likewise, there was no significant difference between students in the sixth semester and those in the twelfth semester.

DISCUSSION

This study did not reject the hypothesis of TST conversion proposed in the transversal study[5], that is, the students who had not been infected with the TB bacillus were retested and TST conversion had occurred. In our study, the cumulative incidence among professional students was 5.8%, and that among basic students was only 1.6%, a difference of 4.2%, which is within the expected range for TST conversion.

Among the favorable points of the present study are the large number of participants and the fact that students had actually been tested. Therefore, it is not like a database, which avoids the memory bias. This study, unlike other studies in the literature[10,11], had an appropriate control group with similar nonoccupational exposure and was carried out on the condition that students had been submitted to two previous TSTs. In addition, this study was planned in order to confirm TST conversion among students, because individuals in this age bracket are more vulnerable to TB[12]. One health professional administered the tests and another was responsible for the readings. Through analysis of the FMUFRJ curriculum, we were able to estimate the TST conversion rate per student hour of exposure, a desirable measure in a study on incidence.

This study also had some limitations. Of the eligible students, 28% fell out of contact. Most older students fell out of contact because they

TABLE 4
Cumulative incidence, incidence rate and relative risk of TST conversion among students at the UFRJ School of Medicine

	Cumulative incidence* (%)	Incidence rate	Relative risk
	95% CI	95% CI	95% CI
Professional students	5.8	58.04/1,000	3.68
n = 224	(3.4 to 9.7)	students/year	(2.55 to 4.68)
Basic students	1.57	15.78/1,000	1
n = 190	(0.50 to 4.50)	students/year	
Sixth semester	7.27	$7.57/10^5$	4.61
20 h exposure/week	(2.90 to 17.30)	students/year	(1.15 to 5.68)
n = 55		(2.06 to 19.4)	
Ninth semester	3.27	$2.27/10^5$	2.08
30 h exposure/week	(0.90 to 11.20)	students/year	(1.52 to 5.68)
n = 61		(0.28 to 8.23)	
Tenth semester	6.06	$4.20/10^5$	3.84
30 h exposure/week	(1.70 to 19.6)	students/year	(0.26 to 7.72)
n = 33		(0.51 to 15.21)	
Eleventh semester	0/23	-	
40 h exposure/week			
n = 23			
Twelfth semester	9.61	$5.08/10^5$	6.08
40 h exposure/week	(4.2 to 20.6)	students/year	(2,66 to 9.50)
n = 52		(1.62 to 11.70)	

*$p = 0.0419$
UFRJ: Universidade Federal do Rio de Janeiro; 95% CI: 95% confidence interval

graduated. Therefore, the results of this study might represent an underestimation in the case of professional students.

The analysis of the TST conversion rate was impaired since not all students attending the various semesters were represented in the study. Among those represented, the number of students per stratum was small, making it difficult to make statistically significant comparisons among the semesters. Since the study cohort consisted of voluntary participants, self-selection bias certainly played a role in any underestimation in the results. Students fearing TST conversion might have chosen to remain anonymous and not participate in the following year due to the potential discomfort of preventive treatment being prescribed and later denied.

Finally, results may show bias in relation to the null hypothesis due to the fact that the study had been underway since 1997 (transversal study) and therefore might have raised the awareness level among the population involved. Students who were aware of the risks might have used special masks (respirators) or avoided respiratory examination rooms or isolation areas. This is a participation bias, which is more frequently seen in intervention studies[13].

Since students were submitted to a two-step TST in the preceding year, the present results do not refer to the booster phenomenon[14,15].

Ruffino Netto et al.[16], in a unique pioneering study, reported that 64.8% of BCG-vaccinated students were still nonreactors on TSTs administered two years after the vaccination. The students in the present study who had been vaccinated with BCG tested negative on TSTs. However, studies involving other types of vaccines, populations, and age groups have shown that 90% of BCG-vaccinated subjects present an induration of $\geq$10 mm in diameter within 8 to 12 weeks after vaccination[17]. In addition, confirming our results and those of Ruffino Netto et al.[16], a study among Danish students showed that the children vaccinated with one of the 10 BCG strains did not present significant TST reactions within 8 weeks after vaccination[18]. Nevertheless, we consider the possibility that an error occurred in the reading of the TSTs of this group of students. The present study reinforces the use of TST in the population under study, in which most individuals were vaccinated during childhood.

The TST conversion rate was high among the FMUFRJ students. Our results show higher conversion rates than those reported in the majority of TST conversion studies conducted on health professions in the USA. For 20 years, these studies have been performed in areas with low TB prevalence (TST conversion rate of 0.11%[19]) and with high TB prevalence (TST conversion rate from 1.9% to 2.3%)[20]. The difference between our results and those in high-prevalence areas in the USA is likely due to the difference of TB incidence between the two countries. In addition, the HUCFF did not, at the time of the study, comply with the guidelines for biosafety measures or treatment of latent TB infection established by the Centers for Disease Control and Prevention (CDC)[21] and the American Thoracic Society[22].

In Latin America, there have been few prospective studies demonstrating TST conversion rates among students or health professionals. In the present study, TST conversion rates among interns (twelfth semester students) were very similar to those reported in other studies. For example, in a prospective study, Muzy de Souza[6] found a conversion rate of 8% among health professionals, which was identical to the 8% found among interns at the *Faculdade de Medicina da Universidade Federal Fluminense* (Fluminense Federal University School of Medicine) in a study conducted by Costa[24]. However, the latter study did not include a control group. In a study carried out at the *Hospital Universitário Gaffreé e Guinle* (Gaffreé and Guinle University Hospital), Ferreira[24] reported a 4.2% TST conversion rate, despite having assessed basic and professional students prospectively. Unfortunately, 70% of the students fell out of contact, which compromised the validity of the results.

Barret-Connor[25] and Randa & Rabinovich[11] reported that professional students (theoretically exposed to *M. tuberculosis* for a greater number of hours) had a higher risk of TST conversion. In the present study, students in their sixth semester had a higher TST conversion rate than did those in semesters during which, in theory, students were exposed to TB for more hours. This could have been a random finding or could be due to the fact that the theoretical 20 hours of hospital practice during the fifth semester may actually translate to a greater number of hours. Students have intense

practice in infirmaries and other services in which they perform semiology, anamnesis, and diagnosis. These students are motivated to be present in health care areas during extracurricular time. Consequently, the use of the curriculum might have created a mistaken classification system, since students could have been exposed for longer periods than what was theoretically believed for that specific semester.

We used a criterion to consider TST conversion: induration should be ≥10 mm. This criterion is higher than what is usually recommended when evaluating individuals at risk for infection with *M. tuberculosis*[23]. Although this caused decreased sensitivity in the evaluation of TST conversion, it represented a more specific infection estimate. This criterion was particularly important if we consider the fact that Brazil has higher BCG vaccination incidence, and that the Ministry of Health has recommended re-vaccination for those subjects designated at risk for infection because they tested negative on TST[26]. There might be an unknown percentage of students infected by atypical mycobacteria. It has been suggested that nonspecific reactions are more prevalent in tropical and subtropical climates[27]. In a study comprising 226 students in Rio de Janeiro, Madeira and Gontijo[28] reported that 12% of the students presented a skin reaction, ranging from 5 to 9 mm, to PPD-G210. In the same study, only 3% of the students presented reactions ≥10 mm. Consequently, it seems that the selected cutoff value reduced the risk of administering anti-TB prophylaxis and causing a TST cross reaction in students that might have been infected with atypical mycobacteria. In a recent study conducted in the USA, a review was suggested in relation to this cutoff value in areas where there is high prevalence of atypical mycobacteria[28]. The authors of that study suggested the use of 15 mm of induration because they attributed induration from 5 to 14 mm to infection with atypical mycobacteria. A new study involving this special population, similar to the studies carried out among students in the 1970s by Madeira & Gontijo[28], would help elucidate questions related to the best cutoff point.

The annual TST conversion rate of 3.9% found in the present study is within the range reported by Fagan & Poland[3]. Despite the epidemiological differences between Brazil and the USA, the findings of the present study are similar to those of some American hospitals prior to the adoption of biosafety measures.

In the past decade, American studies have shown a decrease in the TST conversion rate with the adoption of control measures against the nosocomial transmission of TB[30]. These guidelines were established by the CDC in 1994[21] and involve three levels: administrative, engineering, and personal respiratory protection using filter respirators approved by the National Institute for Occupational Safety and Health (NIOSH N-95 or higher). In the USA, the results have shown that the adoption of at least the administrative guidelines has proven an efficacious measure, and TST conversion rates have decreased[30].

Among the administrative guidelines, the TB questionnaire has been reintroduced in the USA, not only for health professionals but for MS as well, since the early 1990s. The HUCFF students, theoretically, suffered less exposure to other general hospitals. Therefore, they may, in the analysis of the impact of administrative measures adopted in order to control infection with *M. tuberculosis*, serve as an even more efficacious marker of nosocomial TB infection than do the health professionals themselves. Annual follow-up exams of students would suffice.

This study has shown the necessity for controlling nosocomial transmission of TB. This is not surprising and, above all, the present study reflects the reality of a country in which TB is endemic, with an estimated annual incidence of 54.7 per 100,000 inhabitants[32].

We believe that, due to the principal technological advances and increased interest in the TB research, strategies for controlling TB infection, which extrapolates to controlling the disease itself, may be much closer than a decade ago.

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