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# Tuberculin skin tests among medical students at risk for nosocomial transmission of *Mycobacterium tuberculosis* in Yazd, Iran

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## Abstract

Tuberculosis is an important public health issue throughout the world. Medical students, like other health care workers, are exposed to tuberculosis during their clinical rotations. The objective of this study was to evaluate latent tuberculosis infection in preclinical medical students and new infections during clinical rotations. A prospective study was performed between 2008 and 2011 in Yazd by serial Tuberculin Skin Test in medical students. Medical students who have passed their 3.5 year preclinical stage were invited to participate in a 3-step PPD study before starting their clinical rotations. They were examined initially for BCG scar. In the first skin test, induration ≥10 mm was taken as positive. Students with initial negative test were retested 14 days later to identify boosting effect. Third test was done between 1 to 3 years after the second step.

Seventy medical students were invited and 54 of them participated in the study (77.1% response rate). In the first test, 39.6% (95% CI 26-53.2%) had positive skin test ≥10mm. In the second step 10 mm increase in induration was observed in one student without BCG scar and 7 mm increase in induration was seen in another student. In the third step eight students (20.5%, 95% CI: 7.83% to 33.17%) converted from negative to positive (TST≥10mm) during the period of study.

Tuberculosis is an occupational infection among medical students. As a result, implementation of an effective tuberculosis infection control program is mandatory for prevention of tuberculosis among medical students.

**Keywords:** Cross infection and transmission; Tuberculin test; *Mycobacterium tuberculosis* and isolation and purification; Students, medical

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## Introduction

Tuberculosis (TB) is still an important public health issue throughout the world. There is more risk for the health care workers than for the general population.[1]Several studies considered tuberculosis as occupational hazard in health care workers throughout the world.[1,2,3] Medical students are exposed to tuberculosis during their clinical rotations as well. Several studies have been done in some countries with and without routine administration of Bacillus Calmette–Guérin (BCG) vaccine at birth.[3,4] To our knowledge, no other study regarding rate of infection of medical students has been done in Iran yet. BCG vaccine was administered for TB prevention at birth in Iran. The periodic tuberculin skin testing (TST) in health care workers (HCWs) is useful for detection of new infections.[5,6] We designed a study to evaluate latent tuberculosis infection in preclinical medical students and new infection during clinical rotations.

## Subjects and methods

This is a prospective study performed to evaluate latent tuberculosis infection in preclinical medical students and to find incidence of new infection during their clinical rotations by serial TSTs. The study was performed in a teaching hospital between 2008 and 2011 in Yazd city with 566152 inhabitants in central Iran. Medical students who have passed their 3.5 year preclinical stage were invited to participate in the study. A questionnaire was completed by participating medical students to obtain information about age, gender, previous history of tuberculosis, previous exposure to known pulmonary tuberculosis patient, household contact, chemoprophylaxis history and BCG vaccination history. Students signed an informed consent. The study received ethical approval from the research deputy of the medical faculty of Shahid Sadoughi University of Medical sciences, Yazd, Iran.

## Study design

TST is an important tool for detection of latent tuberculosis infection (LTBI). All students were invited to participate in a 3-step PPD study after their 3.5 year preclinical stage and before starting their clinical rotations. They were examined initially for BCG scar, because BCG vaccine is administered at birth in Iran. Then a 5 Unit TST (5-U TST) was performed by a trained health care worker over the volar surface of left arm. 0.1 ml of 5-U tuberculin solution was injected intradermal, then maximal transverse diameter of the induration was measured in millimeters by ruler after 48-72 hours by a single investigator. The results were entered into each student's questionnaire; in the first skin test induration ≥10 mm was taken as positive. As Thana Khawcharoenporn *et al.* stated, findings suggest that chest radiographs may be restricted to medical students with reactive initial and second-step TSTs; chest x ray was taken for few students.[5] Students with a positive TST without signs and symptoms of tuberculosis and with normal chest X ray were considered to have LTBI. In resource-limited settings where testing for LTBI is not mandatory, the World Health Organization (WHO) recommends Isoniazid (INH) preventive treatment only for HIV infected persons[7] and children < 5 years who are household contacts of persons with sputum smear-positive pulmonary TB.[8] National program of control of tuberculosis in Iran is the same as the WHO recommendations mentioned above, so none of the participants received chemoprophylaxis. Students with induration >15 mm were evaluated for active tuberculosis by taking history, chest X ray and sputum for AFB staining in case they had cough. Students with initial negative 5-U TST were retested 14 days later to identify boosting effect. Boosting phenomenon was defined as ≥6mm increase in induration observed when compared to the first skin test. Students who did not develop boosting effect were identified as true negative TST and were invited to do the third step TST. Third step TST was done between 1 to 3 years after the second step. Tuberculin conversion was defined as a newly positive TST after a documented negative-baseline TST. An increase of 10 mm over the baseline was defined as conversion.[9]

Statistical analysis was performed using the SPSS version 13.0 software. All probabilities were two-tailed and p values < 0.05 were regarded as significant. Data were described as mean with standard deviation. The Chi-square test or the Fisher exact test was used to compare categorical variables whenever appropriate.

## Results

Seventy medical students were invited and 54 of them participated in this study (77.1% response rate). Students mean age was 21.7 years (range, 21-26 years) and 45 medical students (83.3%) were

**Table I. Number of conversions in first and third step of Tuberculin Skin Test (TST) in study subjects**

| | First test | Third test |
|---|---|---|
| Age mean, year (range) | 21.7 (21-26) | 23.2 (22-25) |
| Gender male: female | 9:45 | 5:34 |
| BCG scar (%) | 48/54 (88.9) | 35/39 (89.7) |
| Response rate (%) | 54/70 (77.1) | 39/54 (72.2) |
| Conversion rate (%) | | 8/39 (20.5) |
| Positive TST rate (%) | 21/53 (39.6) | 23/39 (59) |

female. Forty eight (88.9%) of participants had BCG scar. Two students reported household contact with tuberculosis patients. None of the students had history of tuberculosis neither developed tuberculosis during 3-year period of the study (Table I).

Figures 1 and 2 show the overall distribution of the results in the first and third step TST in subjects who participated in both steps. In the first step of TST, 21 students (39.6%, 95% CI: 26-53.2%) had positive skin test ≥10mm, all of them had BCG scar, 4 (7.4%) of them had induration ≥20mm. All of them had LTBI.

In the second step 10 mm increase in induration was observed in one student without scar of BCG and 7 mm increase in induration was seen in another student.

In the third (late) step performed 1-3 years later only 39 (72.2%) participated in the study from whom 23 students (59%, 95% CI: 42.8-75.1%) had positive TST. Eight students (20.5%, 95% CI: 7.83% to 33.17%) converted from negative to positive (TST≥10mm) during the period of study, two of them did not have BCG scar, 14 students had an increase of >10mm in their TST and 17 students had >6mm increase in their TST. Six students had decrease in TST induration between 1-10mm. Figure 3 demonstrates the distribution of the pairwise differences between the first and the third step TST. A positive difference indicates an increase, and a negative difference a decrease, in the subject's tuberculin reaction at the third step compared to the first step test.

## Discussion

In the present study in the first step of TST, 38.9% had reactive skin test. They had neither previous history of tuberculosis nor signs or symptoms compatible with tuberculosis during the study period. Chest x rays were taken for few students which all of them were normal; so they probably had LTBI. All of students with positive skin test had BCG scar because of BCG vaccination at birth. A positive TST reaction as a result of BCG wanes in the great majority of vaccinated neonates after 5 years.[10] Because HCWs with a history of BCG are

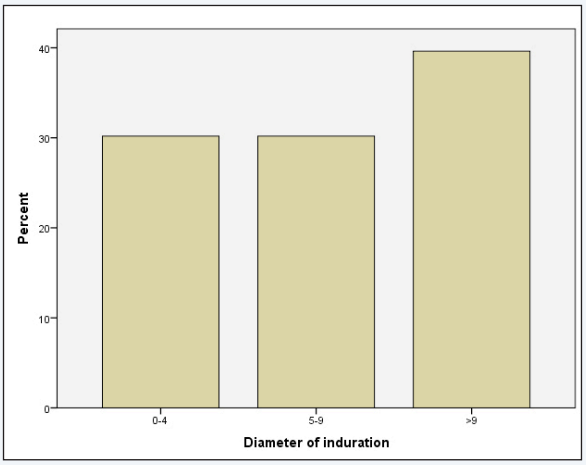


**Figure 1. Distribution of the results of PPD in the first step. n=54**

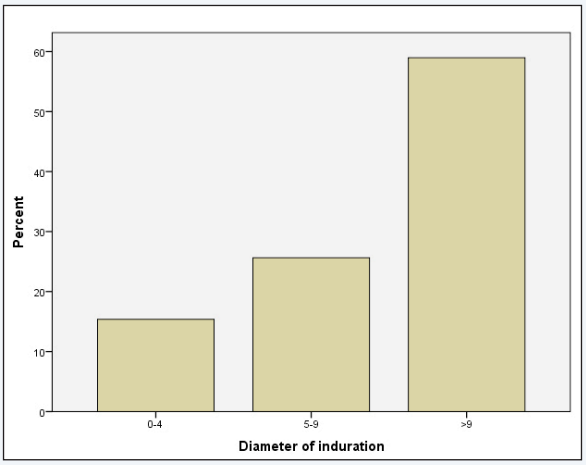


**Figure 2. Distribution of the results of PPD in the third step. n=39**

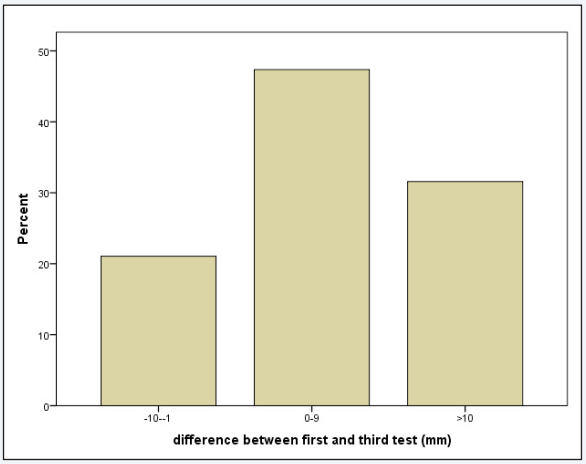


**Figure 3. Pair wise differences between first and third TST (mm)**

frequently from high TB-prevalence countries, positive test results for *M. tuberculosis* infection in HCWs with previous BCG vaccination should be interpreted as representing infection with *M. tuberculosis*. Test results for *M. tuberculosis* infection for HCWs with a history of BCG should be interpreted by using the same diagnostic cut off points used for HCWs without a history of BCG vaccination.[11] In a similar study in Thailand where BCG is administered at birth, rate of LTBI in medical students was reported as high as in our study. Based on two studies which evaluated the use of the TST and QFT-GIT assays in the diagnosis of LTBI in countries with high burden of TB and routine BCG vaccination at birth, strong agreement between TST (at a cut-off of ≥10mm) and the QFT-GIT assay was observed.[12,13] We assume that high rate of reactive skin test in our study subjects could probably be due to infection with *M. tuberculosis*, although a recent study performed by Legesse *et al.* in Ethiopia, did not show a strong agreement between TST and QFT-GIT assay.[14] The small sample size in the present study made us unable to find other factors that may have been associated with TST reactions among medical students with and without BCG vaccine scars.

In contrast to the study done by Dagnew *et al.*, in which all of the study participants were males, in the present study most of the participants were females.[11] Dagnew *et al.*, found a higher rate of TST positivity (46.7%) than what we report here (38.9%). In another study Legesse *et al.*, reported a higher prevalence of LTBI in males than females using TST, but they did not find any difference between gender using the QFT assay.[14]

Forty eight (88.9%) of participants in the present study had BCG scar, although BCG scar waning is uncommon; presence of BCG scar may be lower than BCG coverage. In a study Padungchan *et al.* reported 97% BCG scar in vaccine recipients after a long time, so BCG scar is more objective and reliable than recall.[15]

To identify students with boosting effect, second-step TST was done but only in two students 10 mm increase in induration was observed, which probably suggest that regression of TST is uncommon. We conclude that frequent exposure to tuberculosis may prevent regression of TST. However two-step TST could not exclude all false positive and false negative results.

Eight students (20.5%) converted from negative to positive (i.e. TST≥10mm) during the follow up period.

All of these students were examined and none of them had tuberculosis. One explanation for high proportion of conversion might be the high rate of those lost to follow up, because only 39 (72.2%) of students tested in the pre-clinical stage participated in the third step. We tried repeatedly to make remaining students interested in the study but we were not successful; this can happen in every study were participation is voluntary. Pain experienced in the first and second TST decreased their compliance. Less painful skin tests such as multiple tuberculin skin tests (puncture technique) may improve compliance in similar studies. High rate of conversion highlights nosocomial transmission during clinical rotations in medical students in our hospital. No specific TB infection-control program for medical students was being used in the hospital where the study was carried out. A high risk of nosocomial infection among medical students and young physicians during training in hospitals, even in countries with a low prevalence of TB, has been reported.[3,16,17]Another explanation for high rate observed in the present study may be the use of low cutoff value (at least 10mm) in countries where BCG vaccination is routine at birth.

Limitations of this study were the small sample size, non-participation of male students and the voluntary nature of it, which could have selected subjects with increased risk, so overestimating the rate of infection.

## Conclusions

In summary, our study demonstrates that TB is a significant occupational problem among medical students in Yazd. Transmission of TB can have serious consequences. This is particularly true with MDR-TB strains. Hospitals have been shown to be important place for MDR-TB transmission. So implementation of effective TB infection control program is necessary for prevention of tuberculosis among health care workers and medical students.

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