Tuberculosis infection notification in Swiss medical students during their clinical electives

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Abstract

OBJECTIVE: The aim of this study was to assess the tuberculin skin test conversion incidence in Swiss medical students. Methods: This was a prospective cohort study of medical students at the University of Zurich, using a standardized tuberculin skin test before and after clinical electives. RESULTS: Two hundred and sixty-two students accepted the invitation to the pre-clerkship test, and 155 (59.2%) subjects were retested after an average period of 2.25 years. An increase of more than 10 mm in the transverse diameter of the induration in the retest compared to the baseline test was observed in 12 (7.7%) students. The annual conversion rate was 3.4% (95% CI 1.8-6.0%). CONCLUSIONS: Even in an industrialized country, the risk of tuberculosis infection--as estimated by the tuberculin skin test--is substantial for health care professionals. Possible explanations for the high incidence and possible bias are discussed.
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Alexander Turk,(1) Felix Angst(l) and Robert Steffen(l)

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Results: Two hundred and sixty-two students accepted the invitation to the pre-clerkship test, and 155 (59.2%) subjects were retested after an average period of 2.25 years. An increase of more than 10 mm in the transverse diameter of the induration in the retest compared to the baseline test was observed in 12 (7.7%) students. The annual conversion rate was 3.4% (95% CI 1.6-6.0%).

Conclusions: Even in an industrialized country, the risk of tuberculosis infection—as estimated by the tuberculin skin test—is substantial for health care professionals. Possible explanations for the high incidence and possible bias are discussed.


INTRODUCTION
Tuberculosis is a major concern, not only in developing countries but also in industrial nations, where elderly persons, immigrants and health care workers are at greatest risk.

The current overall notification rate of tuberculosis in Switzerland is low. In 1995, the annual rate was 11.5/100,000, with a substantial difference between the native Swiss population (6.9/100,000) and the foreign-born population (30.1/100,000). In 1993, there was concern that the reason for a renewed increase of the tuberculosis incidence, especially among young native Swiss, was HIV infection, since it was estimated that one in four tuberculosis patients were HIV positive. Similarly, an increase was observed in other countries, particularly in some areas of the USA.

These fears may also have led to the conclusion that medical employees are subject to a higher risk of infection than the general public. Various studies have shown that the tuberculin skin test (TST) conversion rate among medical employees is higher than among the rest of the population. Annual employee screening conversion rates in US health care facilities from 1963 to 1991 varied between 0.01% and 11%. Schoch et al found 37 workers with TST conversions in a larger Swiss hospital among 180 health care workers who had contact with sputum smear-positive patients. In 20 converters, the increase could be attributed to causes other than a recent infection with Mycobacterium tuberculosis.

Fagan et al examined the annual conversion rate in US medical schools, where an annual skin test is routinely conducted. They sent each school a questionnaire requesting an estimate of the yearly skin test conversion rate in their medical students. The mean estimated annual conversion rate reported by 75 schools was 1.8%. Medical students may be at increased risk, being among the first to contact patients on admission before diagnosis is made and before therapy is administered.

In Switzerland, there are guidelines for the prevention of occupational tuberculosis, but these precautions are seldom followed during the first examination of an undiagnosed patient. We conducted a prospective cohort study tracking two annual courses of medical students undertaking their basic practical training at the Medical School of the University of Zurich. The aim was to assess tuberculosis infection incidence by the conversion rate of TSTs.

METHODS
Sample
Medical education in Switzerland consists of a 6-year degree. In their 5th year, as a practical component of their studies, students are required to rotate among different hospitals and different specialties for at least 10 months. Before commencing this clinical component of the degree, the students are vaccinated against hepatitis B and receive a TST. The base test records of two annual courses (1994 and 1995) were collected. After they had
completed their clinical year, invitations for the retest were sent to all candidates, and the students were also informed through the use of overhead transparencies in the lecture theaters. The students who opted not to take the retest were phoned at home or contacted through their parents.

**Tuberculin skin testing**

Testing was performed by skilled staff of the Institute of Social and Preventive Medicine of the University of Zurich, according to the guidelines of the Swiss Union against Tuberculosis and Lung Diseases (Schweizerische Vereinigung gegen Tuberkulose und Lungenkrankheiten, SVTL):²⁰ 0.1 mL containing the 2-TU tuberculin PPD RT23 (from Berna, Berne, Switzerland) was administered intradermally (Mantoux technique) on the volar aspect of the forearm. Members of staff were annually instructed in administering and reading the test by a senior member of the institute. They were blinded to the results of the first skin test of the students and to the history of exposure to tuberculosis.

After an interval of 72 h, the maximal transverse diameter of the induration in millimeters was measured with a flexible plastic ruler using the ballpoint method. After an average observation period of 2.25 years, changes in the transverse diameter of the induration were reassessed by a retest. The results were entered into each student’s personal vaccination document, where information about their vaccination with Bacille Calmette-Guérin (BCG) was also recorded.

**Questionnaire**

After taking the second test, every subject was requested to complete a questionnaire. Information was gathered about age, sex, type and duration of clinical clerkship, and possible contact with cases of infectious tuberculosis. Furthermore, there were questions regarding possible tuberculosis infection and therapy, other TSTs during that period, contact with tuberculosis outside of the clerkship, contacts with at-risk populations (HIV-positive people, residents in old people’s home, intravenous drug users) and immunodeficiency.

**Case definition and analysis**

The size of the transverse diameter of the induration of the TST is currently the best method to ascertain the probability of the occurrence of tuberculosis infection. A change from baseline examination to retest of more than 10 mm defined a conversion according to the guidelines of the Schweizerische Vereinigung gegen Tuberkulose und Lungenkrankheiten (SVTL) for preventive chemotherapy. The absolute value greater than 10 mm at retest and previous BCG vaccination are relevant for other interpretation strategies.³⁵ Contact with sputum smear-positive tuberculosis was examined as a predictor for conversion.

**RESULTS**

**Subjects**

Among 491 students enrolled in 1994 and 1995 at the Medical School of the University of Zurich, 262 (53.4%) responded to the invitation for the baseline test and 155 presented themselves for a retest, representing 59.2% of all candidates who had a baseline test (Table 1). Only three questionnaires were not returned, and attempts to trace them remained unsuccessful, leaving a sample of 152 subjects with complete data. In the whole study population, 35 (23%) did a part of their clinical rotations in foreign countries: 14 in western Europe, one in eastern Europe, eight in North America, Australia and the Pacific region, and 12 in developing countries. According to the study coordinator, 25% of all the students enrolled in these two classes went abroad for 1–3 months. The mean age was 27 years at the second testing (Table 1). All students were Caucasians and had lived for at least 4 years in Switzerland before the first testing.

**Tuberculin test results**

Figures 1 and 2 show the overall distribution of the results for the baseline test and for the retest for the subjects with complete sets of baseline tests and retests (n=155). The distribution of the pairwise differences between the baseline test and the retest per subject is

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Number of conversions of both classes in relation to the observation time and the annual conversion rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1994</td>
<td>95% CI</td>
</tr>
<tr>
<td>No. of results at first testing</td>
<td>130</td>
</tr>
<tr>
<td>No. of results at second testing</td>
<td>73</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>56.2</td>
</tr>
<tr>
<td>Mean age at second testing</td>
<td>27 years</td>
</tr>
<tr>
<td>Conversions</td>
<td>5</td>
</tr>
<tr>
<td>% conversions</td>
<td>6.8</td>
</tr>
<tr>
<td>Observation time in person years</td>
<td>177.26</td>
</tr>
<tr>
<td>% conversions/year</td>
<td>2.8</td>
</tr>
</tbody>
</table>
shown in Figure 3. A positive difference indicates an increase, and a negative difference a decrease, in the subject’s tuberculin reaction at retest compared to the baseline test.

Among the 155 students, there were 12 cases (7.7%, 95% CI 4.0–13.5%) who had an increase of more than 10 mm of their TST (beyond the bold line at the cutoff point in Figure 3). With an overall observation time of 349.35 person-years and an individual average observation period of 2.25 years, 3.4% conversions per year (95% CI 1.8–6.0%) were found (Table 1). Of the 12 subjects who demonstrated a TST conversion, one did a part of the clinical electives in New York City, while the other 11 subjects did all clinical rotations in Switzerland.

Contact with infectious tuberculosis patients and BCG vaccination

Of the 155 students, 55 (35.5%) recalled having had contact with infectious tuberculosis patients during their clinical work, 62 indicated having no contact, 35 could not recall such exposure, and three students did not return the questionnaires. This results in a relative risk (RR) of 1.26 ((5/55)/(7/97)) for remembered contact with infectious tuberculosis patients, with a 95% CI of 0.38–4.16. Among the 12 students with conversions who all returned their questionnaires, five remembered contact, whereas three reported no contact and four could not remember if they had any.
One hundred and thirty (83.9%) students had received BCG vaccination, usually during childhood. Eleven of the 12 people with conversions had received a previous BCG vaccination. In one case, the vaccination status was unknown.

DISCUSSION

Incidence of the tuberculin skin test conversion

In our data, a conversion rate of 7.7% (95% CI 4.0–13.5%) was observed after an average observation period of 2.25 years, corresponding to 3.4% conversions per year (95% CI 1.8–6.0%). All these test subjects with conversions were sent to their family physicians to confirm a possible tuberculosis infection—in particular with a chest X-ray—and to receive secondary prophylaxis with isoniazid as recommended by the guidelines for management of tuberculosis.12,14

Our annual conversion rate falls among median values in similar studies conducted elsewhere. The conversion rate can be considered as remarkably high for Switzerland. A study of TSTs among hospital employees in Switzerland showed that, among 180 workers who had contact with sputum smear-positive tuberculosis patients, 37 (20.6%) had increases compared to their initial tuberculin tests (at the time of employment). Of those 37 increases, 20 (11.1%) were retrospectively attributed to causes other than a recent infection with Mycobacterium tuberculosis.10 Over the past three decades, the reported annual incidence rates among American health care workers varied between 0.01% and 11.0%,9 medical students accounting for 1.8%.11

There are four possible explanations for the comparatively high conversion rate of 7.7%:

1. false administration and reading technique
2. boosting resulting from repeated skin testing, BCG vaccination or infection with environmental mycobacteria
3. selection bias
4. true conversions.

Administering and reading technique

Although only well-instructed and blinded (to previous test and history of exposure) staff members administered the test, it is nevertheless possible that false readings could have occurred. In Figures 1 and 2, digit-preferences for 5 mm and 8 mm might be suspected, but no preference for even numbers or for the numbers 10 and 15 is observed.17 We therefore tried to maximize valid and reliable test results.

Boosting resulting from repeated skin testing, BCG vaccination or infection with environmental mycobacteria

When repeating a tuberculin skin test within less than 1.5 years, one may trigger false-positive reactions due to boosting.12,18-19 In our sample, only two subjects were retested within 1.5 years of the base test, and both were positive. The question arises whether we have to consider boosting after a longer interval than 1.5 years. This phenomenon is more likely to occur in older people; for example, the rate is 20% among 50-year-olds.12 Therefore, in our young population, the number of false-positive results may be considered small.

In our sample, 83.9% of the 155 students had received a previous BCG vaccination approximately 20 years earlier. It is very likely that, after such a long
interval, the first reaction to tuberculin wanes and that the second reaction could be ‘boosted’. It is therefore known that the extent of waning differs for different vaccines and ages at vaccination.\textsuperscript{20,21} It is also known that different BCG strains induce tuberculin reactivity to different degrees, which makes clear interpretation more difficult.\textsuperscript{22} In the recent literature, it is recommended to administer two-step initial skin testing to eliminate up to 80\% of false-positive ‘boosted’ conversions due to BCG vaccinations.\textsuperscript{23} On the other hand, the guidelines of the SVTL for prevention of occupational tuberculosis\textsuperscript{24} recommend the administration of two-step tuberculin testing only in employees older than 35 years; however, no one exceeded this limit in our sample.

The amount of boosting due to infection by ubiquitous environmental mycobacteria is usually considered to be underestimated, particularly in warmer climates. In colder climates, such as in Switzerland, the rate of conversion due to nontuberculosis mycobacteria is considered to be low.\textsuperscript{25,26}

Selection bias

Only 59.2\% of the students tested pre-clerkship could be retested after the period of their clinical rotation, which is less than expected, even though several attempts were made to reach and motivate the students. The low response rate could be accounted for by the fact that testing was done on a voluntary basis and that tuberculosis is probably not perceived as an important health risk among young health professionals. Testing on a voluntary basis may increase the conversion rate, due to selection of subjects with increased risk. It is possible that students presented themselves who knew that they had been subjected to a higher risk of infection. Among our subjects, 23\% spent part of their time in clinical rotations in foreign countries, but only 13 students (8\%) stayed in non-Western countries. Therefore, comparing this figure with the total of 24\% of all students in the two studied age classes who went abroad for a few months (1–3 months), there is no overrepresentation of students who have been abroad in the sample. Although we made inquiries concerning the countries and the medical specialties (surgery, internal medicine, etc.) in which the students worked, it is impossible to assess the individual risk of each student and the distribution of tuberculosis risk. However, on the basis of the above-mentioned figures, we think that the majority of the students were at low risk.

Furthermore, there is remarkable variability in the predictive value of a positive tuberculin test, depending on the sample selection: based on TSTs of more than 500 000 Navy recruits,\textsuperscript{27} the positive predictive value for persons having had contact with tuberculosis could be as high as 70\%, whereas, for those without contact, the positive predictive value was only 10\%.\textsuperscript{28} On the other hand, Geiseler et al have found in the USA that tuberculin-negative graduates from one medical school from 1938 to 1981, 63\% of whom subsequently had active tuberculosis, converted their tuberculin reaction during medical school or clinical training.\textsuperscript{29}

True conversions

Finally, the most important reason for an increase in positive Mantoux skin tests is infection with \textit{M. tuberculosis}. The annual conversion rate of 3.4\% is higher than expected, and there are not only true conversions, although this is comparable with 1.8\% conversions per year among medical students in the USA.\textsuperscript{11} However, it is undeniable that students are often unprotected when seeing a patient before a diagnosis is made and therapy is administered.

Whether one can determine a true tuberculosis infection by skin testing is a question of the positive predictive value of the test, which depends on the prevalence. Some authors report high sensitivity (94\%)\textsuperscript{28} and a positive predictive value of 88\% at a prevalence of 10\%, but a positive predictive value of only 16\% at a prevalence of 0.28\%.\textsuperscript{30} This has led to a broad discussion regarding the appropriateness and practicality of the TST to diagnose tuberculosis infection, especially when there is a clinically manifest course.\textsuperscript{30–32}

CONCLUSION

Even in an industrialized country such as Switzerland, the risk of tuberculosis infection may persist for certain risk groups, such as health care workers, if one is considering only tuberculin skin testing. However, the conclusion that a positive skin test result implies a true tuberculosis infection is dependent on the positive predictive value of the test, which is problematically low in populations with low disease prevalence. Because nearly every medical student has had a BCG vaccination, obtaining a clear interpretation of tuberculin conversions is a challenge. Therefore, the conclusion that every converted person has true tuberculosis is problematic, due to the various problems of testing, interpretation, and manifestation, leading to difficulties in the guidelines and management of the disease.

Initial two-step tuberculin skin testing is recommended,\textsuperscript{19} but it is obvious that this is insufficient to eliminate all false-positive (e.g. ‘boosted’) results. Based upon our results, we consider compulsory tuberculin skin testing after the clinical rotations for medical (and nursing) students to be desirable. Exposure to sputum smear-positive tuberculosis cannot lead to a valid risk assessment. However, there is a lack of valid and reliable new data on risk assessment, incidence rates and prevalence of tuberculosis among medical personnel. Given this current situation, the actual guidelines for preventive chemotherapy and strategies of primary prevention of tuberculosis need to be discussed and further improved.
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