Nursing and Community Rates of *Mycobacterium tuberculosis* Infection among Students in Harare, Zimbabwe

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(See the editorial commentary by Cobelens on pages 324–6)

**Background.** African hospitals have experienced major increases in admissions for tuberculosis, but they are ill-equipped to prevent institutional transmission. We compared institutional rates and community rates of tuberculin skin test (TST) conversion in Harare, Zimbabwe

**Methods.** We conducted a cohort study of TST conversion 6, 12, and 18 months into training among 159 nursing and 195 polytechnic school students in Harare. Students had negative TST results (induration diameter, ≤9 mm) with 2-step testing at the start of training.

**Results.** Nursing students experienced 19.3 TST conversions (increase in induration diameter, ≥10 mm) per 100 person-years (95% confidence interval [CI], 14.2–26.2 conversions per 100 person-years), and polytechnic school students experienced 6.0 (95% CI, 3.5–10.4) conversions per 100 person-years. The rate of difference was 13.2 conversions (95% CI, 6.5–20.0) per 100 person-years. With a more stringent definition of conversion (increase in the induration diameter of ≥10 mm to at least 15 mm), which is likely to increase specificity but decrease sensitivity, conversion rates were 12.5 and 2.8 conversions per 100 person-years in nursing and polytechnic school students, respectively (rate difference, 9.7 conversions per 100 person-years; 95% CI, 4.5–14.8 conversions per 100 person-years). Nursing students reportedly nursed 20,868 inpatients with tuberculosis during 315 person-years of training.

**Conclusions.** Both groups had high TST conversion rates, but the extremely high rates among nursing students imply high occupational exposure to *Mycobacterium tuberculosis*. Intense exposure to inpatients with tuberculosis was reported during training. Better prevention, surveillance, and management of institutional *M. tuberculosis* transmission need to be supported as part of the international response to the severe human immunodeficiency virus infection epidemic and health care worker crisis in Africa.

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Tuberculosis case notification rates have increased dramatically in Africa because of the HIV epidemic [1]. In Zimbabwe, the prevalence of HIV infection among adults has been >10% since the mid-1990s, with the most recent estimate being 20% [2], and the number of patients treated for tuberculosis each year has increased 10-fold since the 1980s [3]. Despite undertaking outpatient management where possible, tuberculosis has become one of the most common causes of hospital admission, with patients with suspected tuberculosis usually nursed on open wards [4–6]. These same factors are likely to apply throughout this region of Africa, which has, by far, the highest prevalence of HIV infection globally [7].

To our knowledge, regional rates of *Mycobacterium tuberculosis* infection among health care workers have not previously been reported. However, health care workers in Malawi, South Africa, and Ethiopia have very high incidence rates of tuberculosis [8–10], and cross-sectional tuberculin skin test (TST) surveys have demonstrated high rates of positivity in Uganda and Cote d’Ivoire [11, 12].
The aim of this study was to investigate the occupational risk of *M. tuberculosis* infection by comparing rates of TST conversion between nursing students and polytechnic school students in Harare, Zimbabwe. Polytechnic school students were included to provide nonoccupational rates of TST conversion, because community rates of *M. tuberculosis* transmission were unknown, and nonspecific TST conversions can occur in repeatedly tested individuals. Two-step testing, whereby individuals are not considered to have negative TST results until they have had 2 TSTs placed and read, was used to minimize the risk of false-positive conversions (“boosting”) associated with the immunological stimulus resulting from the first TST [13, 14].

**METHODS**

**Participant recruitment and procedures.** Student nurses were recruited at the start of training in Parirenyatwa and Harare Central Hospitals (Harare) and were asked to consent to a baseline questionnaire, an examination, TST, and anonymized HIV testing using the Determine kit (Abbott), with all positive and 10% of negative results confirmed using the Unigold kit (Trinity Biotech), both of which are rapid ELISA-based tests. Polytechnic school students who started administrative diplomas, which attract mainly women of educational attainment similar to that of nursing students, were asked to consent to the same procedures.

**TSTs.** TSTs used 2 U of RT-23 PPD in Tween-80 (Statens Serum Institute). Reactions were assessed after 48–72 h. Placement and assessment followed recommended techniques [14]. Students with baseline TST reactions of ≤9 mm in diameter underwent a second TST after 7–14 days (2-step testing). The largest of these 2 TST reactions was recorded as the 2-step reaction size.

**Follow-up.** Students for whom both 2-step reaction sizes were ≤9 mm received followed-up TSTs at 6, 12, and 18 months. Skin test conversions were defined as a ≥10-mm increase in induration over the 2-step reaction size (American Thoracic Society criteria) [14]. For quality assurance, 10% of readings (systematic selection) were duplicated by a second reader, with a consensus reading if the results differed by ≥2 mm. Nursing students were asked to record all ward attachments and the number of patients with tuberculosis whom they nursed.

Follow-up continued until the first of TST conversion, the end of the students’ studies, 18 months follow-up, or July 2005, when a second anonymized specimen was requested from all participants for HIV testing.

**Ethics.** Ethics approval was given by the Ethics Committees of London School of Hygiene and Tropical Medicine, Biomedical Research and Training Institute, Harare Central Hospital, and Medical Research Council of Zimbabwe. Written informed consent was obtained from all participants. Participants with TST conversion were provided with health information and were investigated if they were symptomatic, but they were not offered isoniazid preventive therapy, consistent with local and international policy [15]. HIV tests were conducted, and the results were stored under dedicated laboratory numbers with no other personal identifiers. Voluntary counselling and testing were offered to all participants.

**Data analysis.** Data were captured using EpilInfo 2002 (Centers for Disease Control and Prevention) and were analyzed using Stata, version 9.0 (Stata Corporation). Differences between baseline categorical variables were investigated with Fisher’s exact test. For cohort analysis, individual records were split into time intervals between TSTs. Time-at-risk started and finished 6 weeks before TST placement, because of the intrinsic time lag between *M. tuberculosis* infection and TST conversion [13]. TST conversions were assumed to have occurred midway between TSTs. Poisson regression was used for univariate and multivariate analysis of survival time records.

**RESULTS**

Participation and retention rates are summarized in figure 1. There was a high rate of loss to follow-up because subjects left the polytechnic school, but otherwise, retention was high. No student left because of ill health, although 1 died of trauma, and 2 nursing students remained in the cohort after receiving a diagnosis of tuberculosis. There were no significant differences in baseline characteristics among students who left the study versus those who completed follow-up among either the nursing or the polytechnic school students.

**Baseline TST reactivity.** At their first TST, 145 (28.0%) of 518 polytechnic school students and 95 (27.1%) of 351 nursing students had a reaction size ≥10 mm, with the nonzero mode at 8 and 9 mm, respectively (figure 2) [16, 17]. Large reactions were uncommon (3.4% of nursing and 3.5% of polytechnic school students had inductions ≥17 mm), and there were no significant differences between student groups. One hundred ninety-one participants (22.4%) boosted from ≤9 mm to ≥10 mm at their second (2-step) TST.

![Figure 1](cid2007-44-318-f1.jpg) Participation and retention in a study of rates of *Mycobacterium tuberculosis* infection among students in Harare, Zimbabwe. TST, tuberculin skin test.
Significant risk factors for initial (unboosted) TST positivity (≥10 mm at the first TST) using data from all students (polytechnic and nursing) were having had a mixed urban and rural upbringing (positive TST results, 50.3% vs. 40.1%; P = .025) and reporting past household contact with ≥1 patient with tuberculosis (positive TST results, 34.7% vs. 25.7%; P = .023).

*TST cohort and conversion rates.* Baseline characteristics of 159 and 195 nursing and polytechnic school students, respectively, who had negative 2-step TST results and who were included in the TST cohort are shown in table 1. The 2 cohorts had similar characteristics, although nursing students were slightly older and more likely to be female, to be married, to have come from a crowded home, to have parents who were health care workers, to have previously worked in a hospital, and to be living in student hostels (provided as single bedrooms with shared bathroom and kitchen facilities). Bacille Calmette-Guérin (BCG) vaccination was reported by 94.3% of students, and evidence of vaccination was supported by visible scarring on 82.0% of persons who reported past vaccination.

Rates of TST conversion (an increase in TST induration of ≥10 mm in diameter) were high in both groups, but they were 3 times higher (incidence rate ratio [IRR], 3.2; 95% CI, 1.7–6.5) among nursing students (conversion rate, 19.3 conversions per 100 person-years of follow-up; 95% CI, 14.2–26.2 conversions per 100 person-years of follow-up) than among polytechnic school students (6.0 conversions per 100 person-years of follow-up; 95% CI, 3.5–10.4 conversions per 100 person-years of follow-up). The difference in the conversion rate was 13.2 conversions per 100 person-years of follow-up (95% CI, 6.5–20.0 conversions per 100 person-years of follow-up), as shown in table 2.

A more stringent definition of TST conversion (increase of ≥10 mm to a final induration of ≥15 mm in diameter) reduced the conversion rate, although rates were still high in both groups (12.5 and 2.8 conversions per 100 person-years of follow-up among nursing and polytechnic school students, respectively), as shown in table 2.

**Other potential risk factors for TST conversion.** Having parents who were health care workers was a significant risk factor for TST conversion for polytechnic school students (IRR, 6.9; 95% CI, 1.5–31.3). However, TST conversion rates did not vary significantly by HIV infection status (IRR adjusted for differences between student groups, 0.86; 95% CI, 0.27–2.8), self-reported BCG vaccination (adjusted IRR, 1.7; 95% CI, 0.41–6.8), or presence of a scar (adjusted IRR, 1.2; 95% CI, 0.63–2.2). Also, the number of previous TSTs, type of accommodation (data not shown), and incident HIV infection (3 seroconversions in each group) had no significant effect. Multivariable models including other potential explanatory variables, such as age, sex, crowding in the family home, type of student accommodation, and community contact with patients with tuberculosis during studies, did not reveal any further significant predictors of TST conversion.

Student nurses reported contact with 20,868 patients with tuberculosis during 315 person-years of training (table 3). There was no significant relationship between high-exposure attachments and TST conversions, but the power to resolve risks was limited: students rotated through a mean of 5 different ward attachments between skin tests, and at least 1 high exposure attachment preceded 92.2% of TSTs.

**DISCUSSION**

We have demonstrated high rates of contact with patients with tuberculosis and high TST conversion rates among student nurses training in an African city with a high prevalence of HIV infection. The TST conversion rate in nurses was 19.3 conversions per 100 person-years—13.2 conversions per 100 person-years higher than the rate for polytechnic school students. This contrasts with rates of ≤1 conversion per 100 person-years among some hospital workers in the United States [18] and is considerably higher than rates of 12.8 and 9.3 conversions per 100 person-years in Brazil [19] and Thailand [20], respectively, among studies that used similar methodology. Qualified staff in high-exposure wards may face even higher risks, because student nurses were away from wards for almost 40% of their training and were in low-exposure wards for one-third of their training.

Such high rates of nosocomial *M. tuberculosis* transmission will inevitably carry considerable risk [8, 10, 21–23]. The risk of disease following *M. tuberculosis* infection is higher than generally appreciated when infection occurs for the first time in adulthood. In a European study of young adult household...
Table 1. Baseline characteristics of the nursing and polytechnic school cohort participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nursing students</th>
<th>Polytechnic school students</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median TST reaction size (25th–75th percentile), mm</td>
<td>4 (0–8)</td>
<td>5 (0–8)</td>
<td>.10</td>
</tr>
<tr>
<td>Age, mean years ± SD</td>
<td>21.8 ± 3.4</td>
<td>21.4 ± 2.6</td>
<td>.03</td>
</tr>
<tr>
<td>Male sex</td>
<td>36 (22.6)</td>
<td>64 (32.8)</td>
<td>.04</td>
</tr>
<tr>
<td>Married status</td>
<td>36 (22.6)</td>
<td>19 (9.7)</td>
<td>.002</td>
</tr>
<tr>
<td>HIV infection a</td>
<td>12 (7.8)</td>
<td>7 (3.6)</td>
<td>.10</td>
</tr>
<tr>
<td>Childhood environment</td>
<td></td>
<td></td>
<td>.08</td>
</tr>
<tr>
<td>Rural</td>
<td>48 (30.2)</td>
<td>39 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>49 (30.8)</td>
<td>65 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>62 (39.0)</td>
<td>91 (46.7)</td>
<td></td>
</tr>
<tr>
<td>≥1 parent is a health care worker</td>
<td>18 (11.3)</td>
<td>6 (3.1)</td>
<td>.001</td>
</tr>
<tr>
<td>Parental occupation, if not nursing c</td>
<td></td>
<td></td>
<td>.27</td>
</tr>
<tr>
<td>Professional</td>
<td>40 (28.4)</td>
<td>39 (20.6)</td>
<td></td>
</tr>
<tr>
<td>Self-employed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formal sector</td>
<td>25 (17.7)</td>
<td>40 (21.2)</td>
<td></td>
</tr>
<tr>
<td>Informal sector</td>
<td>42 (30.0)</td>
<td>69 (36.5)</td>
<td></td>
</tr>
<tr>
<td>Manual worker</td>
<td>34 (24.1)</td>
<td>41 (21.7)</td>
<td></td>
</tr>
<tr>
<td>Self-rated family wealth</td>
<td></td>
<td></td>
<td>.16</td>
</tr>
<tr>
<td>Above average</td>
<td>9 (5.7)</td>
<td>11 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>130 (81.8)</td>
<td>171 (87.7)</td>
<td></td>
</tr>
<tr>
<td>Below average</td>
<td>20 (12.6)</td>
<td>13 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Crowding in childhood home, persons per room</td>
<td></td>
<td></td>
<td>.03</td>
</tr>
<tr>
<td>≤1</td>
<td>40 (25.5)</td>
<td>59 (30.6)</td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>86 (54.8)</td>
<td>115 (59.6)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>31 (19.8)</td>
<td>19 (9.8)</td>
<td></td>
</tr>
<tr>
<td>Reported receipt of BCG vaccine</td>
<td>151 (95.0)</td>
<td>183 (93.9)</td>
<td>.65</td>
</tr>
<tr>
<td>Previous hospital work</td>
<td>24 (15.1)</td>
<td>7 (3.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Accommodation while a student</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hostel, single bedroom d</td>
<td>109 (68.6)</td>
<td>32 (16.4)</td>
<td></td>
</tr>
<tr>
<td>Shared flat/house</td>
<td>26 (16.4)</td>
<td>39 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Family flat/house</td>
<td>24 (15.1)</td>
<td>124 (63.6)</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of subjects, unless otherwise indicated. BCG, bacille Calmette-Guérin; TST, tuberculin skin test.

* Maximum of baseline and boost reaction size.
* Not available for 5 nursing students.
* Highest of maternal and paternal occupations, not including children of health care workers.
* Provided by educational institution.

contacts, 14.5% of subjects developed tuberculosis within 3 years of TST conversion [24], and estimates from the United Kingdom and The Netherlands place the 5-year risk of disease after the first infection in adulthood at 13.8% and 24.5%, respectively [25, 26]. The baseline TST profile, with a low prevalence of large reaction sizes, suggests that most students in the current study had not previously been infected with *M. tuberculosis*, as is likely for students in much of Africa [16,17]. HIV-infected adults, including most inpatients and some health care workers in Zimbabwe, will be at even higher risk of disease following infection [27].

Nosocomial *M. tuberculosis* transmission can be greatly reduced through infection-control measures [18–20]. Guidelines for resource-poor settings have been successfully applied in Brazil and Thailand [19, 20]. These guidelines emphasize administrative interventions, including outpatient management and separation of persons with suspected tuberculosis in dedicated wards as much as possible [15]. Isolating persons with suspected tuberculosis becomes difficult when tuberculosis is on the differential diagnosis of many admission forms, however, and patients may themselves be endangered through investigation on tuberculosis wards [28]. Simple environmental interventions, including engineering to maximize natural ventilation, may be of particular importance in resource-poor
Table 2. Rates of conversion of tuberculin skin test (TST) results and incidence rate ratios for nursing versus polytechnic school students, using 2 different definitions of a TST conversion.

<table>
<thead>
<tr>
<th>TST result conversion criteria</th>
<th>Nursing students</th>
<th></th>
<th>Polytechnic school students</th>
<th></th>
<th>Rate difference per 100 PYFU (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of conversions/PYFU</td>
<td>Conversion rate per 100 PYFU</td>
<td>No. of conversions/PYFU</td>
<td>Conversion rate per 100 PYFU</td>
<td></td>
</tr>
<tr>
<td>American Thoracic Society criteria*</td>
<td>41/213</td>
<td>19.3</td>
<td>13/216</td>
<td>6.0</td>
<td>13.2 (6.5–20.0)</td>
</tr>
<tr>
<td>Induration size ≥15 mm and increase of ≥10 mm</td>
<td>28/225</td>
<td>12.5</td>
<td>6/218</td>
<td>2.8</td>
<td>9.7 (4.6–14.8)</td>
</tr>
</tbody>
</table>

**NOTE.** For each group, the number of person-years of follow-up (PYFU) varies slightly between analyses, because follow-up was stopped at the time of conversion.

* Increase in the induration size of ≥10 mm.

settings [15]. Preventive therapy after TST conversion is highly effective [29] but requires dedicated programs, supplies, and willing staff [23, 30]. TST surveillance of health care workers is obligatory in the United States but not recommended for resource-poor settings [14, 18]. More active occupational health programs are urgently needed, in any case, to maximize access to post–HIV exposure prophylaxis and long-term HIV care. Inclusion of routine TST surveillance and preventive therapy that is not solely targeted to known HIV-positive individuals may add considerably to the confidentiality and acceptability of long-term care programs for health care workers, as well as having the major benefit of reducing the incidence of tuberculosis [27, 31].

Our estimates of community rates of *M. tuberculosis* transmission are surprisingly high. Nonspecific conversions will have contributed [13], but even with stringent definitions, the conversion rate was 2.8 conversions per 100 person-years for polytechnic school students. Most parts of Africa are thought to have *M. tuberculosis* transmission rates of 0.5%–1.5% per year [16], although recent data are scarce. Higher rates of 2.9% and 3.3% per year have been reported for Nairobi, Kenya [32], and Cape Town, South Africa [33], respectively. The baseline TST profile argues against long-term exposure to high rates of *M. tuberculosis* transmission in participants of this study. It is plausible that students are at unusually high risk of infection, because student life tends to be sociable and communal, and in settings of endemicity, persons of this age group have high rates of tuberculosis [1]. It is also plausible that *M. tuberculosis* transmission rates are increasing as a result of the HIV epidemic. Data from Africa do not consistently suggest this [27], but there are few recent estimates from Southern Africa—the worst-affected region.

The study has a number of limitations, including high loss to follow-up in the polytechnic cohort, although the rate of participation by students who continued their studies was high; this reduced study power but is unlikely to have biased our results, because reasons for leaving were unrelated to health. The TST is low cost, well standardized, and predictive of future tuberculosis and has minimal infrastructure requirements. Great expertise has accumulated in its use and in the interpretation of results [17]. The main disadvantage is suboptimal specificity, which varies by BCG coverage and climate [16, 17]. In warm climates, nonspecific tuberculin sensitivity can be marked, as in our participants [34]. This may have led to a high rate of nonspecific TST conversions, although our rate difference estimates should be robust to nonspecific events.
Specificity can be increased by more-stringent definitions of conversion, but this happens at the cost of reducing sensitivity [13]. Newer immunological assays have better specificity. However, whole-blood cytokine assays may be less sensitive for detection of latent tuberculosis infection than the TST [35]. The Elispot is both sensitive and highly specific [36, 37], but it is expensive and requires rapid laboratory processing.

We have demonstrated a high risk of TST conversion among nursing students in Harare that is likely to be accompanied by considerable risk to patients and health care workers. Institutionally acquired tuberculosis may become an increasing problem as HIV care services are scaled up in Africa, and better recognition, surveillance, and management of the risks and consequences are needed. Strengthening these aspects could make an essential contribution towards current efforts to reverse the health care worker crisis and improve care of HIV infection in Africa [27].

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