Prevalence of positive tuberculin skin test and associated factors among Makerere medical students, Kampala, Uganda

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Abstract:

Background: Tuberculosis infection among medical students is thought to be higher than that among comparable groups.

Objectives: To determine the prevalence of positive Tuberculin Skin Test (TST) and associated factors among medical students at Makerere University.

Methods: A-cross-sectional study among randomly selected medical students. Using intra-dermal technique, TST was performed by administering 0.1ml of purified protein derivative. Readings performed after 72 hours and positive TST based on an induration of ≥10mm.

Results: Of 302 students selected to participate, 292 received TST and 288 were analyzed. Of 288 students, 173(60%) were pre-clinical (years 1-3) and 115(40%) clinical (years 4&5). Overall 130 students [45.1%(C.I.39.3–51.1)] had positive TST, not different from one derived from mixture analysis [46.3%(95% Bayesian credibility interval 36.5%-55.8%)]. Positive TST prevalence among pre-clinical was 39.9%(67/173) compared to 53.0%(61/115) among clinical students, OR=1.70,C.I.(1.06-2.74) and increases in a linear pattern with increasing years of study (p=0.002,OR=5.04).

Conclusion: The prevalence of TB infection among medical students was twice higher than that of adults living in the suburbs and higher among those in clinical relative to pre-clinical years suggesting that exposure and infection might be related to clinical work. We recommend urgent institution of infection control measures.

Key words: Tuberculin skin testing, tuberculosis, medical students, Uganda

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Introduction

Tuberculosis (TB) is a major public health issue worldwide. Uganda currently is ranked 16th in the World Health Organization (WHO) report of the World's top 22 high TB burden countries.[1]

Tuberculosis infection prevalence among medical students is thought to be higher than that among comparable groups such as students of other specialties.[2,3] Furthermore, in other settings infection prevalence among medical students was found to be twice to three times as high among students in clinical years compared to pre-clinical students.[4,5]

This study was conducted to determine the prevalence of positive TST as an estimate of infection with M. tuberculosis among medical students enrolled at Makerere University, College of Health Sciences, Kampala, Uganda.

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Methods

Between April and June 2009, a cross-sectional study was conducted at Makerere University College of Health Sciences. Makerere University College of Health Sciences is the largest and oldest of four medical training institutions in Uganda. It is located within Mulago hospital, 1,500-bed capacity hospital in Uganda's capital

that serves as a national referral and training hospital with a large number of admissions of tuberculosis patients including patients with multi-drug resistant Tuberculosis (TB).[6] Makerere College of Health Sciences implements a problem-based learning curriculum, where clinical exposure starts from year 1 with an increasing number of student-patient contact hours over the study period. In this study students were classified into two stages of training; pre-clinical (years 1 to 3), students that have less than 4 hours per week of contact with patients and clinical (years 4 to 5), students that have at least 4 hours per week of contact with patients. The dichotomous classification used is in analogy with a comparable classification used in a similar study.[4]

Seven-hundred thirty-eight (738) medical students registered in 2009 for bachelor's degrees in Medicine and Surgery (MBChB), Dental Surgery (BDS) and Nursing (BSN) from year one to five (up to year four for BSN) and were eligible to participate in the study. Assuming a positive Tuberculin Skin Test (TST) prevalence of 23% among adults 18 years and older determined in previous study conducted in Kampala[7], an attrition rate of 10%, we estimated a sample of 302 medical students to determine the prevalence of positive TST among medical students. To determine the sample size to assess factors associated with positive TST, we considered year of study the main independent variable. Our assumption was that, students in later years of medical training (clinical years – i.e., years 4 and 5) have a prevalence approximating that found among health care workers in Kampala, i.e., 57%[8] and that students in early years of medical training (years 1 to 3) have a prevalence approximating the Kampala community prevalence of 23%[7]. We estimated that 42 medical students are required per group to detect a difference of 34% (i.e., 57% - 23%).

In order to get a representative sample of medical students across the years of study and degree programs, the sample was divided proportionate to the size of class, then within each year of study divided proportionate to the three bachelor's degree programs (MBChB, BDS, and BSN). Selected medical students were then approached and asked whether they would volunteer to participate in the study. Medical students with prior history of training as health care workers, those who did not consent to participate in the study and known TB patients were excluded.

For each study participant a questionnaire with relevant information was completed, including age, sex, year of study, prior contact with a TB case, and BCG vaccination status. A trained counselor provided pre and post-test counseling for HIV. Serological test for HIV was done only for subjects who consented and results were only disclosed to subjects willing to know their status.
Tuberculin skin test was performed using the intra-dermal technique, administering 0.1 ml of purified protein derivative [PPD RT-23, 2TU/0.1ml, Statens Serum Institute (SSI), Copenhagen, Denmark; Lot 08k11; Exp: 10-2011], applying it to the volar aspect of the left forearm. This was carried out by trained medical workers. Transverse diameter of the resulting induration perpendicular to the long axis of the forearm was determined by palpation after 72 hours. Readings were performed by an experienced trainer who works for the national TB program using a transparent ruler in a well-lit area.

The data were entered (double entry) into EpiData version 3.1 software (freely available at www.epidata.dk) and exported to SPSS (Statistical program for Social Sciences) version 17.0 for analysis, while ensuring data quality. The data on the number of reactors for each millimeter induration size were summarized in text file used as input file in mixture analysis using the scripts prepared by Neuenschwander for analysis with the basic application of 1 in R software.[9]
The analysis was done in the Bayesian way using the Markov Chain Monte Carlo approach. The Metropolis sampler was used to simulate from the posterior distribution of mixture model parameters. After a burn-in period of 5,000 iterations, the results of which were discarded, a thinned sample of 2,000 values out of 20,000 was used for summarizing the posterior distribution of model parameters. Significance of dichotomous and categorical variables tested using chi-square test; continuous variables tested using t-tests. Significant associations from univariate analyses tested in multivariable logistic regression analysis. An alpha level of <0.05 was considered significant.

Authorization to conduct the study was obtained from the Faculty of Medicine Research and Ethics Committee. Study approval protocol #REC REF 2009-058. Risks and benefits of TST were explained to all eligible students and TST performed only on students who expressed informed consent. Students found with signs

and symptoms suggestive of active TB were offered further tests and appropriate treatment free of charge.

Results

Characteristics of study participants:

Of the 302 selected students, 10 (3.3%) declined to participate. The most frequently mentioned reasons for declining included fear of developing ulcer and assumption that everyone would anyhow have a positive TST. Another 4 eligible medical students were excluded for not returning after intra-dermal placement of PPD (lost to follow-up), thus 288 (95.4%) medical students were analyzed (Figure 1).

Out of medical students analyzed, 173 (60%) were pre-clinical and 115 (40%) clinical.

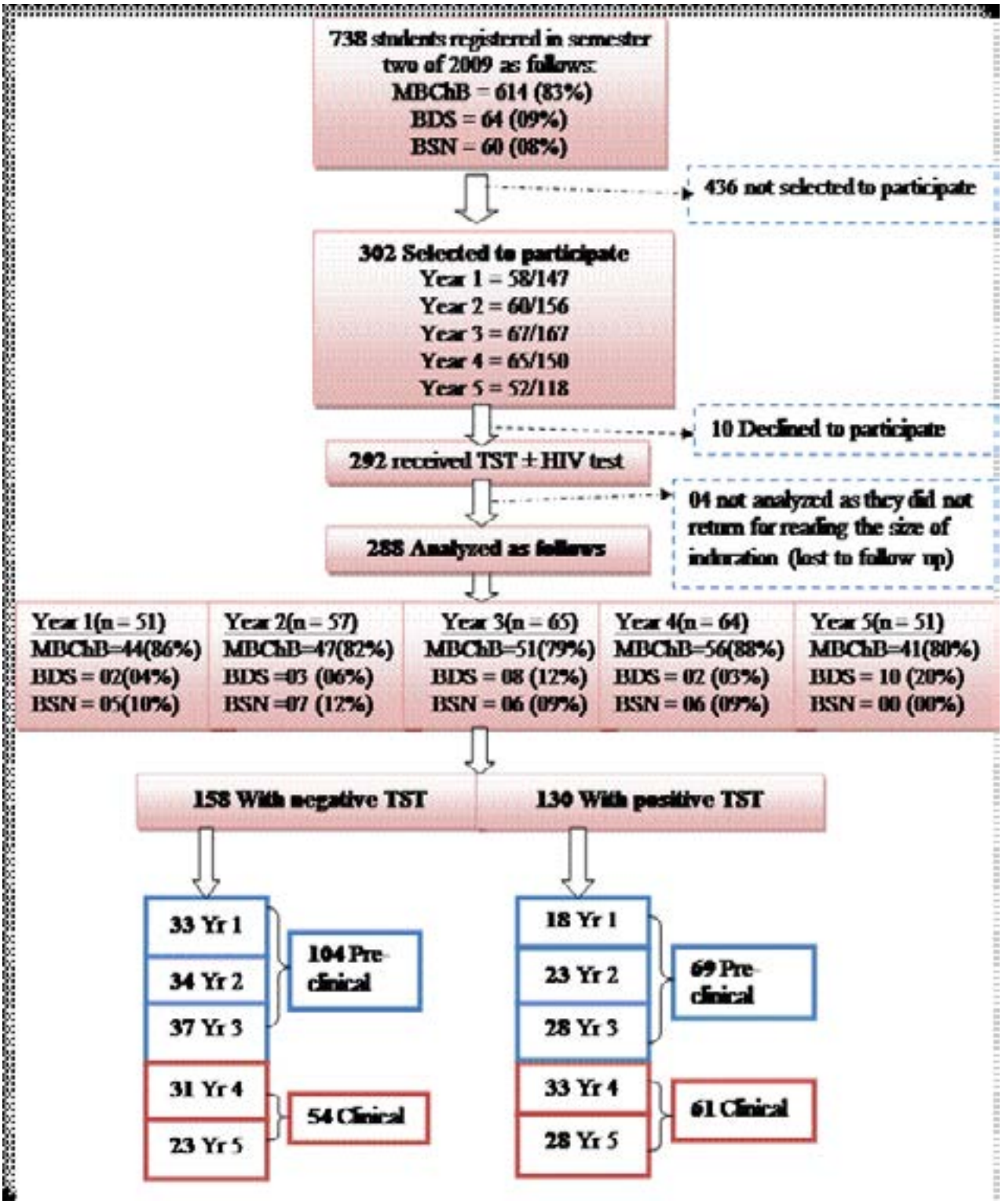

Figure 1:Study flow diagram of undergraduate Makerere University medical students, Mulago hospital, 2009

The two groups were essentially comparable except that clinical students were older, more knowledgeable about tuberculosis (TB) transmission and acknowledged positive history of contact, Table 1. Male students were 173 (62%) and female 115 (38%). This was comparable to the general student population (65% male and 35% female).

Table 1: Comparison of social, demographic and medical characteristics between pre-clinical and clinical undergraduate Makerere University medical students, Mulago hospital, 2009

Characteristic	Pre-clinical (years 1, 2 & 3) students (N=173) n(%)	Clinical (years 4 & 5) Students (N=115) n(%)	*p-value*
Mean age ± SD (yrs)	22.4 ± 2.6	25.0 ± 2.8	≤0.001
Male sex:	108(62.4)	71(61.7)	0.828
Residence: Resides at University halls of residence	29(74.6)	82(71.3)	0.4□7
Nationality- Ugandan	14(94.8)	105(91.3)	□.□47
Region of origin:			
- Western	36(22.0)	21(18.3)	
- Central	78(45.0)	44(38.3)	
- Eastern	21(12.1)	24(20.9)	
- Northern	29(16.7)	17(14.7)	
- None-Ugandan	09(□5.2)	09(07.8)	0.259
Course of student:			
- MB.ChB	141(81.5)	97(84.3)	
- BDS	14(08.1)	12(10.4)	
- BSN	18(10.4)	06(05.2)	0.257
No history of smoking	169(97.7)	113(98.3)	0.739
Positive history of alcohol intake	57(33.1)	50(43.9)	0.067
Has history of TB contact	48(27.7)	68(60.7)	≤0.001
Has co-curricular clinical practice	28(16.6)	28(24.3)	0.106
HIV Status:			
- HIV negative	105(60.7)	71(61.7)	
- HIV positive	00(0.00)	00(0.00)	
- Declined HIV test	68(39.3)	44(38.3)	0.859
BCG vaccination scar present	125(72.7)	80(69.6)	0.568
No Knowledge of TB transmission	39(22.8)	12(10.4)	0.007

Distribution of TST reactivity and determination of the prevalence of infection:

The data was analyzed with mixture analysis. The distribution of observed, mixture and component distributions among the 288 students is shown in Figure 2.

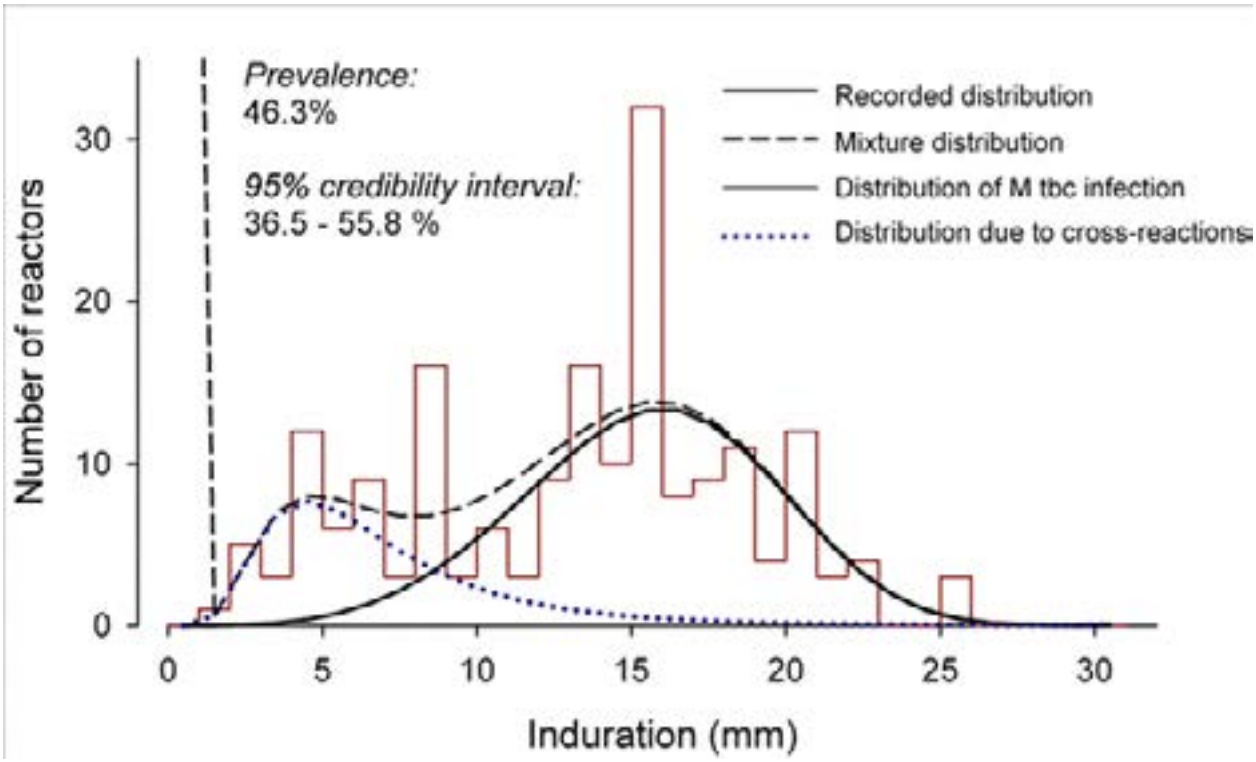

Figure 2: Tuberculosis skin test reaction sizes, observed, mixture, cross reaction and tuberculosis infection distribution, undergraduate Makerere University medical students, Kampala, Uganda, 2009, N=288.

The point estimate of the prevalence of infection thus calculated was 46.3% with a 95% Bayesian credibility interval of 36.5% to 55.8%. This mixture analysis-derived point estimate of 46.3% did not differ importantly from a prevalence of 45.1% using a cut-off point of 10 or more millimetres to denote infection. For all subsequent analyses, a "positive" reaction was thus defined as a reaction of 10 or more (Table 2).

Table 2: Prevalence of Positive TST among undergraduate Makerere University Medical students in respective years of study using a cut-off of 10mm and above to determine a positive test, Mulago hospital, 2009

Year of study	Number Tested	Number with Positive TST	Prevalence of Positive TST (C.I.)
1	51	18	35.3(22.4-50.0)
2	57	23	40.4(27.6-54.2)
3	65	28	43.1(30.8-56.0)
4	64	33	51.6(38.7-64.2)
5	51	28	54.9(40.3-68.9)
Total	288	130	45.1(39.3-51.1)

Positive TST prevalence increased in a linear pattern with increasing years of study (p=0.002, OR=5.04); that is, year one 35.3%; year two 40.4%; year three 43.1%; year four 51.6% and year five 54.9% although, the confidence intervals were overlapping across the years of study. Positive TST prevalence among pre-clinical students was 67/173 (39.9%) compared to 61/115 (53.0%) among clinical students, OR = 1.70, C.I. (1.06-2.74).

Factors associated with positive TST:

We found age, male sex, history of contact with a case of TB, the course dental surgery and being a clinical student predictive of a positive skin test at univariable analysis, Table 3.

Table 3: Univariate analysis of social, demographic and medical characteristics of undergraduate Makerere University medical students (n=288), Mulago hospital, 2009

Characteristic	Negative TST (N=158)	Positive TST (N=130)	OR (C.I.)	*p-value*
Mean age ± SD (Yrs)	23.0 ± 2.8	24.0 ± 3.1		0.004
Sex:				
- Female	70	38	1.00	
- Male	88	92	1.93 (0.17-3.14)	0.009
Course:				
- MB.ChB	139	99	1.00	
- BDS	09	17	2.65 (1.13-6.19)	0.024
- BSN	10	14	1.21 (0.48-3.01)	0.687
Student categorization:				
- Pre-clinical	104	69	1.00	
- Clinical	54	61	1.70 (1.06-2.74)	0.028
History of smoking:				
- No	157	125	1.00	
- Yes	01	05	6.28 (0.72-54.4)	0.095
History of alcohol intake:				
- No	96	83	1.00	
- Yes & irregular	56	41	0.85 (0.51-1.39)	0.513
- Yes and regular	05	05	1.26 (0.36-4.45)	0.723
Contact with a case of TB				
- No	105	64	1.00	
- Yes	52	65	2.09 (1.29-3.38)	0.003
HIV Status:				
- HIV negative	97	79	1.00	
- Declined test	61	51	1.03 (0.64-1.65)	0.914
BCG Vaccination Scar:				
- Absent	64	36	1.00	
- Present	111	94	1.08 (0.65-1.81)	0.764
Knowledge of TB transmission:				
- Yes	130	105	1.00	
- No	27	24	1.10 (0.60-2.02)	0.757

At multivariable logistic analysis, only male sex, the course dental surgery and contact with a case of TB were predictive of a positive test, Table 4.

Table 4: Univariate and multivariable logistic analysis of factors associated with positive TST among undergraduate Makerere University medical students (n=288), Mulago hospital, 2009

	Univariate Analysis		Multivariable logistic Analysis	
Characteristic	**OR**	**P-value**	**aOR**	**p-value**
Mean age (Yrs)		**0.004**	1.05	0.284
Male sex	1.93	**0.009**	2.23	**0.004**
Course:				
- MBChB	1.00			
- BDS	2.65	**0.024**	3.17	**0.014**
- BSN	1.21	0.687	1.56	0.481
Clinical students	1.70	0.028	1.35	0.306
BCG Scar present	1.08	0.764	1.36	0.284
Reported history of contact with a case of TB	2.09	**0.003**	1.86	**0.022**

A graphic representation of age, contact with a case of TB and prevalence of positive TST shows that all three parameters increase with increasing years of study. However, the increase in positive history of contact from the third to the fourth year was dramatic and this coincides with the time students start longer clinical sessions, Figure 3.

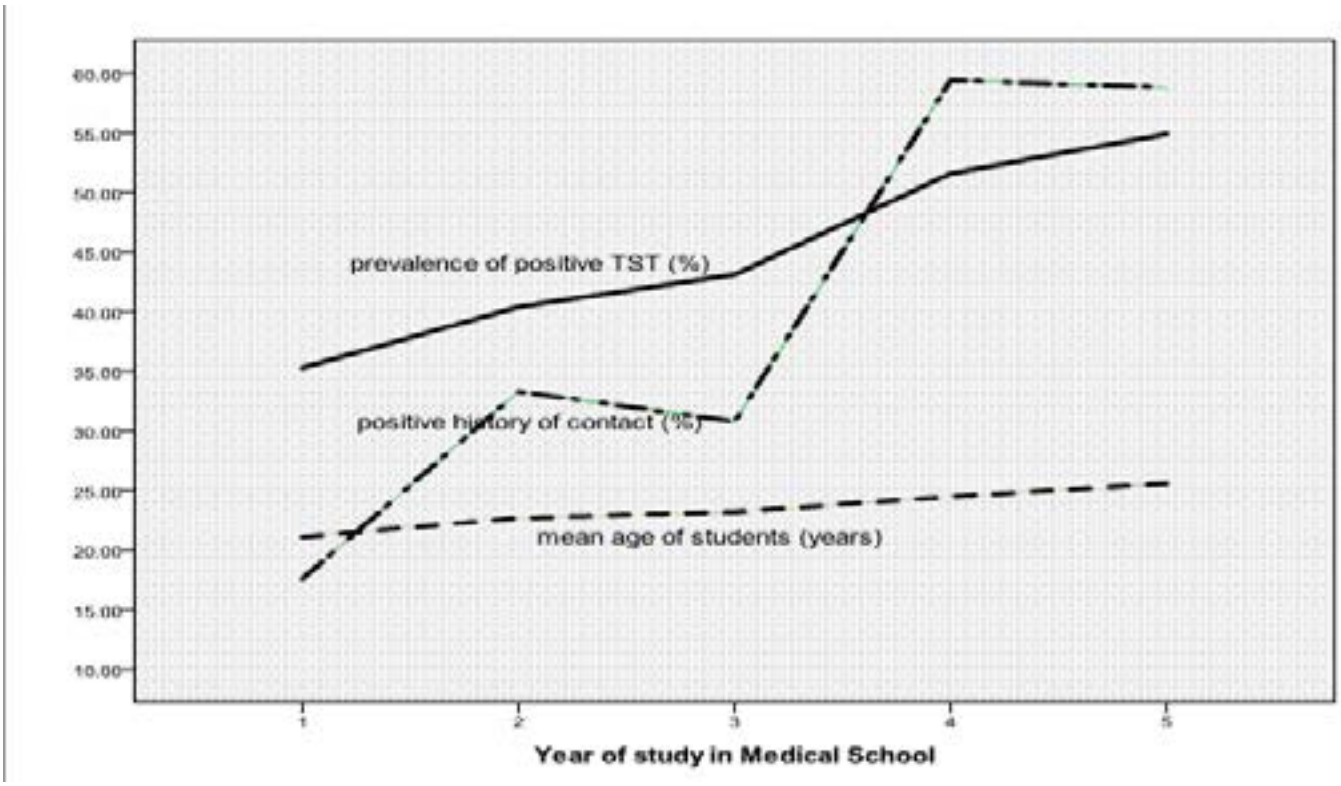

Figure 3: Correlation between prevalence of positive TST, percentage of positive history of contact and mean age of medical students in successive years of study, undergraduate Makerere University medical students, Kampala, Uganda, 2009, N=288.

Other findings:
Of the 176/288 (61%) students who consented for HIV serological test, none was positive.
Five students had signs and symptoms suggestive of active TB, although CXRs done did not reveal evidence of active disease.
Two students (0.7%) developed large ulcers, 5/288(1.7%) developed significant blistering, 74/288 (25.7%) reported intense itching and no significant side effects occurred in 200 (69.4%) students. Data was missing for 7(2.4%) students.

Discussion

Prevalence of positive TST:
In this cross sectional survey, approximately 1 in every 2 medical students has a positive TST. This prevalence is in the range of the 1958 and 1970 national TST surveys in Uganda[10] that found a prevalence of 46.0% and 48.7% respectively in the age range 20-24 years (the age range of most medical students). We found this prevalence however, higher than what was observed in a Kampala community survey , where about 1 in every 5 adults had a positive TST.[7] Also higher than that of medical students from a tuberculosis (TB) endemic area of Rio de Jenerio State – Brazil (8%),[4] but lower than what was observed among practicing health care workers in Kampala city (57%).[8]

The high prevalence might be related to the fact that, Mulago hospital complex has high TB case notification; as a result students operate in an M. tuberculosis high risk environment. This and the observation of a steep increase in prevalence over the relatively short study period suggests that infection due to community exposure alone may not fully account for the high prevalence, but that exposure and infection might be related to the clinical work during study years, suggesting nosocomial exposure to TB. In addition, the dramatic increase in positive history of contact especially from the time students start longer clinical rotations might represent the turning point when these students acquire M. tuberculosis infection, (Figure 3).

Other factors associated with positive TST:
Male students were two times likely to have a positive TST compared to their female counterparts, consistent with previous studies in Uganda[8] and Brazil,[4,11] which we think is related to behavior patterns. Male are more likely to undertake risky behavior such as ignore recommendations for preventive measures.

Dental students were more than twice likely to have a positive TST compared to MBChB students. This is probably related to the fact that, the dental clerkship focuses on dental procedures thus, subjecting the students to operate within a vicinity of high aerosol production. However, a systematic review on TB among health workers found nursing as the most high risk occupation[2].

We found evidence of BCG vaccination not associated with TST positivity as was the case in a previous Ugandan survey[10]. This we think is in line with the findings, which showed that, the effect of BCG vaccination on TST positivity would have waned after 12 years following vaccination (vaccination in Uganda is at birth).

Prevalence of HIV infection was 0% (61% acceptance). We think this is representative of the true situation. One of the possible reasons is the very low regular alcohol consumption 3.5% (a risk factor for HIV infection in a Ugandan study) among these students. We also found tobacco smoking very low among these students (2.0%).
However, a high proportion of these students are not knowledgeable of TB transmission compared to counterparts from Brazil,[4] (17% versus 10%). This could impact on ability to protect themselves during clerkships.

Limitations
We did not use two steps testing for non-reactors; we also did not have a comparison group; differentiation between household and hospital contact was not done during data collection and the fact that TST unlike interferon gamma based assays does not detect specific antigens for M. tuberculosis like ESAT-6 and CFP-10.

Conclusion

Makerere medical students have a higher prevalence of positive TST compared to adults living in the suburbs of the city where the medical school is located. This and the observation of a steep increase over the relatively short study period suggest that infection from community exposure alone may not fully account for the high prevalence at the end of the study. It is likely that exposure and infection might be related to the clinical work during the study years, suggesting nosocomial exposure to Tuberculosis. Other predictive factors were being a male student and the course Dental Surgery.

List of abbreviations

TB – Tuberculosis
TST – Tuberculin Skin Testing
PPD RT – Purified Protein Derivative
SSI – Statens Serum Institute

Competing interests

Other than the normal scholarly gains, there are no other gains authors might receive from taking part in this study. The authors declare that they have no competing interests.

Authors' contribution

Lou Joseph Kenyi (LJK) – Study development, developed data collection tools, data collection, analysis of data and Manuscript development. Okot-Nwang Martin (OM) –study development, supervision of data collection, manuscript development. Achilles Katamba (AK) – study conception and design, development of data collection tools, analysis of data and heavily contributed to manuscript writing

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