Performance of QuantiFERON-TB Gold and Tuberculin Skin Test Relative to Subjects' Risk of Exposure to Tuberculosis

Sharon E. McMullen,[1] David A. Pegues,[2] Frances S. Shofer,[3] Alexandra C. Sheller,[4] and Evelyn B. Wiener[1]

[1]Student Health Service, University of Pennsylvania, Philadelphia; [2]Healthcare Epidemiology, Infection Prevention and Control, and [3]Department of Emergency Medicine, University of Pennsylvania Health System, Philadelphia; and [4]The Health Federation of Philadelphia, Pennsylvania

Background. Performance of QuantiFERON-TB Gold In-Tube (QFT-GIT) and tuberculin skin test (TST) has not been compared in a US college population with varying risk of tuberculosis exposure.

Methods. We performed a retrospective chart review of students tested for tuberculosis at the University of Pennsylvania Student Health Service between 2009 and 2011. We stratified students into high-, low-, and no-risk categories for exposure to tuberculosis and compared QFT-GIT and TST performance in risk groups adjusting demographic characteristics.

Results. During the study period, 15 936 tuberculosis tests were performed in 9483 college students. Coming from a tuberculosis-endemic country was the only risk factor significantly associated with having a positive result (odds ratio [OR] 12.9; 95% confidence interval [CI], 10.2–16.5). Test specificity was higher for TST than QFT-GIT (99.7% vs 91.4%; *P* < .0001). Application of a higher threshold for positivity improved comparability of QFT-GIT with TST in the low-risk group (adjusted OR [AOR] 1.2; 95% CI, .4–3.3) but not in the high-risk group (AOR .4; 95% CI, .3–.5).

Conclusions. QFT-GIT was less specific than TST. Our findings support the use of TST for US college students who need tuberculosis testing and the use of risk-stratified interpretation for students who are tested with QFT-GIT.

Keywords. latent tuberculosis; diagnostic techniques and procedures; sensitivity and specificity; interferon-gamma release tests.

Of the 20 million college students currently studying in the United States, 750 000 were born outside of the country [1, 2]. Many come from countries that have high incidence of *Mycobacterium tuberculosis* (tuberculosis) infection, have received bacille Calmette-Guérin (BCG) following birth, and are candidates for testing for tuberculosis infection [3]. The 2 commercially available testing methods for diagnosis of tuberculosis infection, tuberculin skin test (TST) and interferon gamma release assay (IGRA), differ in ease of administration and test interpretation, cost, sensitivity, and specificity depending on the population screened [4–11] and have not been widely evaluated in a US college-aged population [12, 13]. The Centers for Disease Control and Prevention (CDC) guidelines suggest that while TST and IGRA may be used interchangeably, IGRA is preferred in people who have been vaccinated with BCG because of the lack of cross-reactivity [3]. To explore whether these 2 test modalities performed equally regardless of risk factors, we compared the test performance of TST and QuantiFERON-TB Gold In-Tube (QFT-GIT) for detection of tuberculosis infection among a large group of US college students who varied in their risk profiles for tuberculosis infection or progression to tuberculosis disease.

METHODS

This study was a retrospective chart review of all students who underwent tuberculosis testing at the University of Pennsylvania Student Health Service (SHS)

between 1 January 2009 and 31 December 2011. The university student population consists of approximately 21 000 full-time graduate and undergraduate students, approximately 20% of whom do not come from the United States.

Tuberculosis risk factor screening is required of all full-time incoming students and is accomplished using an Internet-based screening tool that students complete once upon matriculation. The tool is based on American College Health Association (ACHA) tuberculosis screening guidelines [1] and includes questions designed to elicit risk factors related to exposure to tuberculosis (ie, coming from a country of high tuberculosis burden [defined by ACHA as tuberculosis incidence of ≥20 cases/100 000 population]; having had contact with someone with active tuberculosis; volunteering or working with high-risk populations such as hospital patients, prisoners, the homeless, or refugees). For students who report having come to the United States from a country with a high tuberculosis burden, measurement of time since immigration (<5 years vs ≥5 years) has not been recommended by ACHA since 2012 and is not assessed by the SHS tuberculosis screening tool. To identify students at increased risk of progression to active tuberculosis disease, the SHS screening tool also includes questions related to immunosuppression, including human immunodeficiency virus, cancer, diabetes, and use of immunosuppressive therapy.

Students who answer yes to any of the screening questions must be tested for tuberculosis infection. They can choose either TST or, since mid-2011, QFT-GIT. All healthcare professional students (ie, medical, nursing, and dental students) are tested at matriculation regardless of risk factors in order to create a baseline for future occupational testing; those who choose TST as their baseline test must complete a 2-step TST. All students with positive TST or QFT-GIT results must follow up with a chest radiograph and clinical evaluation in order to rule out tuberculosis disease. During the study period, 4 cases of active tuberculosis disease were diagnosed among students. None were identified through the prematriculation screening process.

We queried the SHS electronic medical record, Point and Click Solutions (version 11.0, Burlington, MA), and extracted the following demographic and clinical information: sex, date of birth, "international" designation by the university registrar, academic program, year in school, type of degree being pursued, ethnicity, country of origin, BCG history, and self-reported risk factors for tuberculosis infection and progression to tuberculosis disease. In addition, we extracted the following tuberculosis test information: type of tuberculosis test, date of test, qualitative result (ie, positive or negative), and quantitative result (ie, measurement of skin induration in millimeters for TST and tuberculosis-nil values for QFT-GIT).

All students who had a TST or QFT-GIT performed at SHS during the study period, who were aged ≥18 years, and who had completed a prematriculation tuberculosis risk screening questionnaire were eligible for inclusion in this study. All TSTs were administered and interpreted by SHS registered nurses using CDC-approved methods [14], including best practices such as enhancing interrater reliability with nurse-to-nurse consultations for borderline results and establishing proficiency by the performance of a high volume of TSTs. QFT-GITs were collected by SHS phlebotomists who were trained in specimen collection and handling, including proper tube-shaking technique. All specimens were analyzed at a single reference laboratory according to manufacturer guidelines [15]. Students' test results were excluded if a TST was not interpreted, QFT-GIT vendor did not report quantitative results, or QFT-GIT results had indeterminate values. Additionally, for students who were tested multiple times, only the initial tuberculosis test result was included in this analysis in order to avoid multiple observations on the same student.

Students were stratified into 3 risk categories for exposure to tuberculosis: high risk (those who reported having come from a country of high tuberculosis burden, defined as at least 20 incident cases of active tuberculosis disease per 100 000 population), low risk (those who did not come from a country of high tuberculosis burden but who reported any risk factor for exposure to tuberculosis, including having had an active tuberculosis contact or occupational exposure), and no risk (those who reported no risk factors for exposure to tuberculosis). The no-risk group included healthcare professional students' baseline testing and students who only reported risk factors for progression to tuberculosis disease such as an immunosuppressive condition.

We compared the frequencies of selected demographic characteristics and self-reported risk factors for tuberculosis infection and progression among students receiving TST or QFT-GIT and the probability of positive tuberculosis tests by risk group using χ^2 or Fisher's exact test. We compared the test performance of QFT-GIT to TST in tuberculosis exposure risk groups using logistic regression, adjusting for sex, age, academic level (undergraduate vs graduate), and Asian ethnicity. Tuberculosis test specificity was calculated as the proportion of negative test results among students in the no-risk group. We calculated QFT-GIT specificity using 2 cut-points: the manufacturer's recommended value of tuberculosis-nil ≥0.35 IU/mL and tuberculosis-nil ≥1.0 IU/mL. All data analyses were performed using SAS statistical software (version 9.3, SAS Institute, Cary, NC). This study protocol, including waiver of consent and Health Insurance Portability and Accountability Act waiver of authorization, was approved by the institutional review board of the University of Pennsylvania on 30 April 2012 (approval number 815 645).

RESULTS

Between 1 January 2009 and 31 December 2011, 15 936 tests for tuberculosis infection were performed at SHS, including 14 468
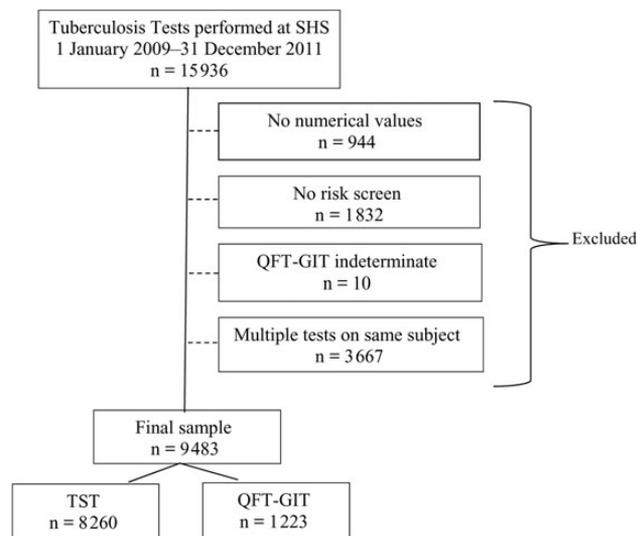
Figure 1. Study participant flow. Abbreviations: QFT-GIT, QuantiFERON-TB Gold In-Tube; SHS, Student Health Service; TST, tuberculin skin test.

Table 1. Characteristics of Subjects Undergoing Tuberculin Skin Test and QuantiFERON-TB Gold In-Tube Testing

Characteristic	Tuberculin Skin Test, n = 8260 (%)	QuantiFERON-TB Gold In-Tube, n = 1223 (%)	P Value
Sex			
Female	4806 (58.2)	658 (53.8)	.004
Male	3454 (41.8)	565 (46.2)	
Age (years)			
18–22	3498 (42.4)	430 (35.2)	<.001
23–29	4017 (48.6)	703 (57.5)	
≥30	745 (9.0)	90 (7.4)	
Ethnicity			
Asian	2850 (36.5)	653 (59.9)	<.001
Black, African American	507 (6.5)	50 (4.6)	
Caucasian, White	3454 (44.2)	292 (26.8)	
Hispanic	414 (5.3)	41 (3.8)	
Multiethnic/racial	518 (6.6)	53 (4.9)	
Other	73 (0.9)	2 (0.2)	
Academic level			
Graduate	5377 (65.1)	946 (77.4)	<.001
Undergraduate	2883 (34.9)	277 (22.7)	
Academic program			
Healthcare	2424 (29.4)	358 (29.3)	.99
Non-healthcare	5836 (70.7)	865 (70.7)	

(90.8%) TST and 1468 (9.2%) QFT-GIT tests (Figure 1). We excluded 6453 (40.5%) tuberculosis tests, including 72 QFT-GIT results that lacked quantitative results and were performed by a reference laboratory different from the laboratory that performed all of the other QFT-GITs included in the study. We also excluded 872 TSTs that were administered at SHS but not interpreted. Because most TSTs at SHS are performed to meet students' matriculation requirements and because this requirement is enforced by registration hold (which does not allow students to register for subsequent classes), it is likely that most of these 872 students were eventually retested.

Of the 9483 unique students included in the analysis (Table 1), there were 8260 (87.1%) TST results and 1223 (12.9%) QFT-GIT results. Of study students, 46.0% (n = 4361) reported having come from a country of high tuberculosis burden, 41.7% (n = 3957) reported at least 1 risk factor for exposure to tuberculosis other than having come from a country of high tuberculosis burden, and 12.3% (n = 1165) reported no risk factors for exposure to tuberculosis (Table 2). Students who chose to be tested with QFT-GIT were significantly more likely to be male graduate students of Asian ethnicity than students who were tested with TST (Table 1).

There were 807 positive tuberculosis test results, including 16.7% of tests in the high-risk group, 1.6% in the low-risk group, and 1.2% in the no-risk group (Table 3). Students who came from a country of high tuberculosis burden were significantly more likely to have a positive tuberculosis test result than those from other countries (odds ratio 12.9; 95% confidence interval [CI], 10.2–16.5; Table 2). Other exposure risk factors, including having had contact with a person with active

tuberculosis or occupational risk factors, were not associated with increased odds of positive tuberculosis test. Having more than 1 risk factor for tuberculosis exposure did not increase the odds of a positive tuberculosis test result. Risk factors relating to immune compromise were not associated with increased odds of positive tuberculosis test. Because information about students' BCG history was missing for 75% of students, we did not include BCG as a variable for analysis.

Of the 4361 students in the high-risk group, a similar proportion had positive QFT-GIT (16.5%) compared with TST (16.8%; $P = .8$). In contrast, among the 3957 students in the low-risk group, a substantially higher proportion had a positive QFT-GIT (6.4%) than TST result (1.3%; $P < .0001$). The difference between the proportion of positive QFT-GIT and positive TST results was even greater among the 1165 students in the no-risk group (QFT-GIT 8.6% vs TST 0.3%; $P < .0001$; Figure 2). Tuberculosis test specificity was higher for TST than QFT-GIT (99.7% vs 91.4%; $P < .0001$). Applying a QFT-GIT cut-point of tuberculosis-nil ≥1.0 IU/mL increased QFT-GIT specificity from 91.4% to 96.1% ($P < .0001$).

Application of the higher QFT-GIT cut-point improved the comparability of QFT-GIT with TST in the low-risk group (AOR 1.2; 95% CI, .4–3.5) but not in the high-risk group (AOR 0.4; 95% CI, .3–.5; Figure 3). An increase in the

Table 2. Unadjusted Analysis of Risk Factors for Positive Tuberculosis Test

Risk Factor	Positive Tuberculosis Test (N = 807)		Negative Tuberculosis Test (N = 8676)		Odds Ratio	95% Confidence Interval
	n	(%)	n	(%)		
High risk country	729	(16.7)	3632	(83.3)	12.9	10.2–16.5
Active tuberculosis contact	13	(5.8)	211	(94.2)	0.7	.4–1.2
Hospital work	105	(2.7)	3733	(97.3)	0.2	.2–.2
Prison work	10	(4.1)	234	(95.9)	0.5	.2–.9
Homeless work	51	(2.9)	1693	(97.1)	0.3	.2–.4
Refugee work	10	(3.0)	329	(97.0)	0.3	.2–.6
No risk factor	14	(1.2)	1151	(98.8)	0.1	.1–.2

QFT-GIT cut-point to tuberculosis-nil ≥1.0 IU/mL in the no-risk group decreased the adjusted odds of a positive QFT-GIT test result compared with TST 2-fold, although results may be unreliable due to too few events in the model.

DISCUSSION

Among a large group of college students who underwent tuberculosis testing, the odds of a positive result varied substantially. In students who reported risk factors for exposure to tuberculosis, the rate of test positivity was highest in those who reported having come from a tuberculosis-endemic country and lowest in those with professional or volunteer experience in hospitals. While TST and QFT-GIT performances were comparable in the high-risk group, QFT-GIT was less specific than TST.

The only risk factor associated with significant odds for a positive tuberculosis test result in our college-aged population was that of having come from a country of high tuberculosis burden. Although the proportion of positive tuberculosis test results was slightly higher in students reporting 1 or more risk factor for tuberculosis exposure (range, 2.7%–5.8%) compared with those reporting no risk factors (1.2%), overall >90% (729/807) of positive tuberculosis tests were among

students from a high-risk country. Additionally, we found no benefit in identifying immunocompromised students in a population overall with very low prevalence of risk factors for progression to tuberculosis disease. College healthcare professionals could consider streamlining tuberculosis screening questionnaires in order to identify students at highest risk for exposure to tuberculosis (ie, those who come from a tuberculosis-endemic country), especially in situations where resources and capacity for tuberculosis testing services are limited.

There is no gold standard reference test for detection of tuberculosis infection [3, 16–19]. Specificity is estimated using populations that are considered to be at no risk for tuberculosis infection, with negative results assumed to be accurate [3, 4, 6, 10, 13, 20, 21]. Because TST shares some of the same antigens found in BCG [6, 22], positive TST results in people who have been vaccinated with BCG often have been characterized as being falsely positive [7, 23, 24]. Studies comparing tuberculosis

Table 3. Test Results by Risk Category

Test	High Risk	Low Risk	No Risk	All
Tuberculosis test, positive	729	64	14	807
Tuberculosis test, negative	3632	3893	1151	8676
Tuberculosis test, all	4361	3957	1165	9483
TST, positive	594	47	3	644
TST, negative	2938	3644	1034	7616
TST, all	3532	3691	1037	8260
QFT-GIT, positive	135	17	11	163
QFT-GIT, negative	694	249	117	1060
QFT-GIT, all	829	266	128	1223

Abbreviations: QFT-GIT, QuantiFERON-TB Gold In-Tube; TST, tuberculin skin test.
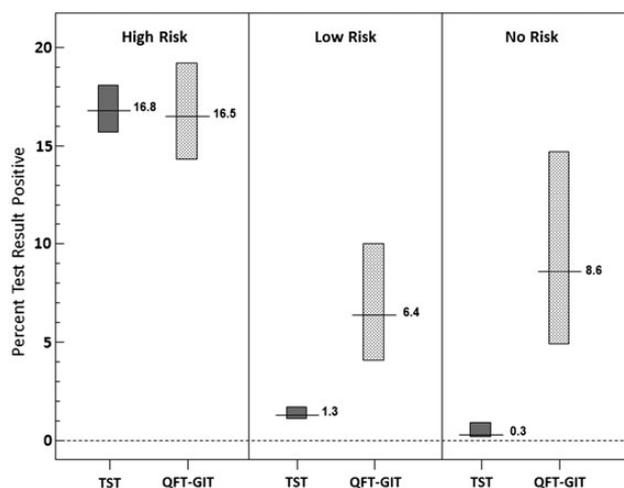
Figure 2. Results of tuberculin skin test and QuantiFERON-TB Gold In-Tube test by student risk of tuberculosis exposure. Abbreviations: QFT-GIT, QuantiFERON-TB Gold In-Tube; TST, tuberculin skin test.
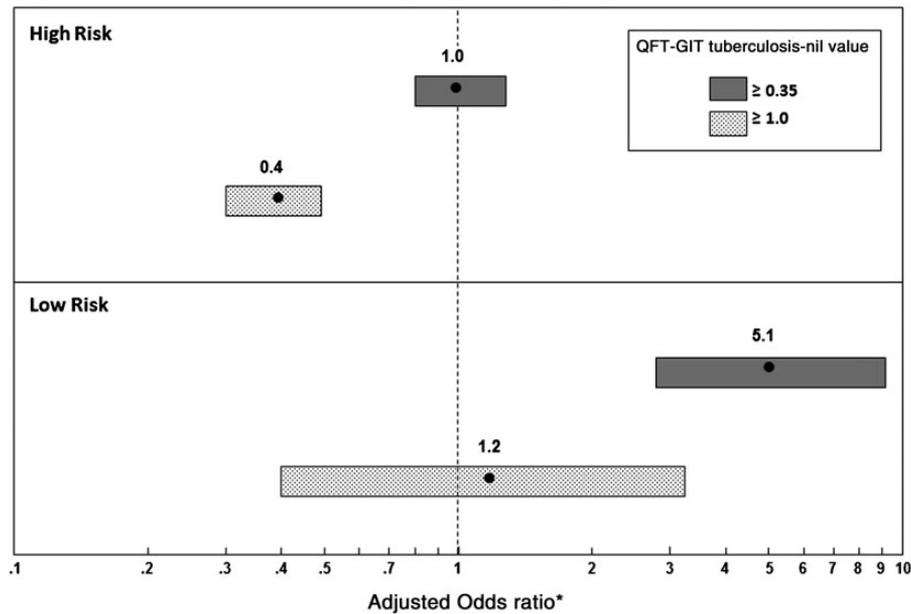
Figure 3. Adjusted odds of positive QuantiFERON-TB Gold In-Tube vs tuberculin skin test by tuberculosis-nil threshold value and student risk of tuberculosis exposure. Abbreviation: QFT-GIT, QuantiFERON-TB Gold In-Tube. *Adjusted odds ratio: odds adjusted for sex, age, academic level, and Asian ethnicity.

testing methods frequently describe IGRA as being more specific than TST due to lack of BCG cross-reactivity with IGRA [6, 8, 17, 25]. However, because BCG has a variable effect on TST [24, 26–28] and cross-reactivity wanes over time [23, 29–31], this potential advantage in specificity should be interpreted cautiously, especially in people who were remotely vaccinated with BCG.

We found the performance of TST and QFT-GIT to be comparable in young adult students who reported having come from a country of high tuberculosis burden and who were therefore more likely to have been vaccinated with BCG. This finding suggests no apparent advantage of QFT-GIT compared with TST in our high-risk student population, which had a mean age of 24 years and reported predominantly Asian (ie, China and India) countries of origin. These countries typically administer BCG in infancy with no subsequent boosting [22]. This finding supports previous studies [23, 29–31] that suggested that remotely administered BCG does not result in a high rate of false-positive TST results. However, we were not able to directly compare tuberculosis test results based on BCG vaccination status because of incomplete ascertainment of vaccination history.

A number of studies have noted the propensity of QFT-GIT results to "wobble" back and forth at the cut-point between positivity and negativity when repeated [3, 4, 18, 32, 33]. Investigators who studied interferon gamma levels of serially tested US healthcare workers found a high reversion rate around the QFT-GIT cut-point of tuberculosis-nil ≥0.35 IU/mL [32] and fewer QFT-GIT reversions when an uncertainty zone was

implemented [34]. The clinical significance of apparent conversions and reversions is not well understood [3, 35].

In our no-risk population, which consisted predominantly of matriculating healthcare professional students, use of a higher tuberculosis-nil cut-off value of ≥1.0 IU/mL improved the specificity of QFT-GIT from 91.4% to 96.1%, although specificity remained below that of TST. Application of this higher cut-point to the low-risk student population resulted in a substantial improvement in the test performance of QFT-GIT compared with baseline, while the manufacturer's recommended cut-point of tuberculosis-nil ≥0.35 IU/mL yielded results comparable to those of TST in the high-risk group. Such a 2-tiered approach to interpreting QTF-GIT results has been advocated in other populations, including serially tested healthcare workers and US military recruits. Mancuso et al. found a significant dose-response relationship between US military recruits' risk of tuberculosis exposure and their tuberculosis-nil levels, supporting the use of risk-stratified interpretation that incorporates a higher tuberculosis-nil cut-point for students at lower risk of exposure [36]. Among newly hired healthcare workers at the Cleveland Clinic who were tested annually with QFT-GIT over a 3-year period, Fong et al. found a higher conversion rate when QFT-GIT replaced TST as the tuberculosis testing method. The conversion rate decreased when a cut-point of tuberculosis-nil ≥1.0 IU/mL was adopted. As a result of this finding, the Cleveland Clinic implemented a new protocol for treating healthcare workers with latent tuberculosis infection

that uses a higher cut-point of tuberculosis-nil ≥1.0 IU/mL [37]. Our study also supports the use of the higher cut-point of tuberculosis-nil ≥1.0 IU/mL when interpreting QFT-GIT results of students classified as having no or low risk of tuberculosis exposure and limiting the use of the manufacturer's cut-point of tuberculosis-nil ≥0.35 IU/mL to testing of students from high-risk countries.

Cost-comparison analyses have described IGRAs used either in combination with TST or alone as less costly when identifying latent tuberculosis infection than TST alone [38–40]. Similarly, IGRAs have been characterized as contributing to more cost-effective outcomes than TST [40, 41]. However, these conclusions were largely dependent on the assumption that IGRAs are more specific than TST in high-risk populations [42]. Because our study found no difference in performance between QFT-GIT and TST in our high-risk group and because the direct costs of QFT-GIT are higher than those of TST [11, 43], our findings suggest that TST is less costly than QFT-GIT for our student population.

There are several limitations to this study. First, because there is no gold standard reference test for latent tuberculosis infection [3, 7, 16–19], TST and QFT-GIT test sensitivity and positive predictive value cannot be determined. Second, the risk factors we analyzed were self-reported. It is possible that students, many of whom have left home for the first time to come to our university, did not recognize or chose not to report tuberculosis risk factors, resulting in misclassification of tuberculosis risk status. In addition, TST interpreters were not blinded to students' risk factors for tuberculosis infection, and it is possible that access to this information may have influenced their interpretation. Third, QFT-GIT was only available for the final 5 months of the study period and the tuberculosis testing method was chosen by the students, resulting in nonrandom test allocation. Although we adjusted for demographic characteristics, including sex, age, academic level, and Asian ethnicity, there may have been other unmeasured factors that contributed to tuberculosis test selection and risk. Fourth, because we lacked self-reported BCG vaccination status for 75% of our population, we could not directly compare TST and QFT-GIT test performance among BCG recipients. However, since the practice of early childhood BCG vaccination is nearly universal in the countries of high tuberculosis burden that defined our high-risk population, high-risk country status served as a crude proxy estimate of BCG vaccination history in our analysis. Finally, prevalence of positive tuberculosis test results in our low-risk category reporting 1 or more risk factor for tuberculosis exposure may not be generalizable outside of the college student population. For example, students who reported having volunteered or worked in a hospital likely had a substantially lower cumulative risk of tuberculosis exposure than experienced healthcare professionals.

CONCLUSION

Our findings suggest that QFT-GIT performs no better than TST among students who reported having come from a tuberculosis-endemic country and is less specific than TST in our population of US college students. Since QFT-GIT is also more costly, our findings support use of TST for US college student populations who need tuberculosis testing and use of risk-stratified interpretation for students who choose to be tested with QFT-GIT. Such risk stratification could include adopting a higher threshold of positivity of tuberculosis-nil ≥1.0 IU/mL for those at lower risk of exposure to tuberculosis, such as matriculating healthcare professional students from low prevalence countries such as the United States, and the current manufacturer's recommended cut-point of tuberculosis-nil ≥0.35 IU/mL for those at higher risk of exposure, such as students coming from countries with high tuberculosis burden. Randomized studies of TST and QFT-GIT should be performed in college student populations in order to test performance and optimal QFT-GIT interpretive cut-points for those at varying risk of tuberculosis infection and disease.

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