Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the worldwide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all parts of this thesis or dissertation.

Signature:

_____ _____

Jennifer Anne Whitaker Date

Approval Sheet

High Latent Tuberculosis Infection Test Conversion Rates among Healthcare Workers in the Country of Georgia

By

Jennifer Anne Whitaker
Master of Science

Clinical Research

_____
Henry M. Blumberg, M.D.
Advisor

_____
Igho Ofotokun, M.D., M.Sc.
Committee Member

_____
Mitchel Klein, Ph.D.
Committee Member

Accepted:

_____
Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

_____
Date

Abstract Cover Page

High Latent Tuberculosis Infection Test Conversion Rates among Healthcare Workers in the Country of Georgia

By

Jennifer Anne Whitaker
B.A., Indiana University, 2002
M.D., Indiana University School of Medicine, 2006

Advisor: Henry M. Blumberg, M.D.

An abstract of
A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science
in Clinical Research
2012

Abstract

High Latent Tuberculosis Infection Test Conversion Rates among Healthcare Workers in the Country of Georgia

By Jennifer Anne Whitaker

Background: There are very limited data on serial testing of healthcare workers (HCWs) with interferon gamma release assays (IGRAs) for latent tuberculosis infection (LTBI). The purpose of this study was to determine the prevalence and risk factors for LTBI among Georgian HCWs using the tuberculin skin test (TST) and QuantiFERON-TB Gold In-tube assay (QFT), in addition to determining the rates and risk factors for TST and QFT conversions (change from a negative to positive test result).

Methods: A prospective longitudinal study was conducted among Georgian HCWs.

Results: Among 319 HCWs enrolled, 259 (81%) were female; mean age was 41 years; 285 (89%) reported prior BCG vaccination; 194 (60%) worked in healthcare facilities specializing in TB. HCWs from TB facilities had higher QFT and TST positivity rates than those from non-TB facilities: 107/194 (55%) vs. 30/125 (31%) QFT positive ($p<0.0001$) and 128/189 (69%) vs. 64/119 (54%) TST positive ($p=0.01$). There was fair agreement between the TST and QFT diagnostic tests (70%, kappa=0.42, 95% CI 0.31-0.52). In multivariate analysis, frequent contact with TB patients was associated with increased risk of a positive QFT (OR 3.04, 95% CI 1.79-5.14) but not with positive TST (OR 1.29, 95% CI 0.76-2.18). Age in years was associated with increased risk of positive QFT (OR 1.05 per year, 95% CI 1.01-1.09) and TST (OR 1.05, 95% CI 1.01-1.10). High rates of HCW conversion were seen (QFT conversion rate: 22.8/100 person-years and TST conversion rate: 17.1/100 person-years). TST conversion was associated with working in a TB facility ($p=0.04$), whereas QFT conversion was not ($p=0.43$). In multivariate analysis, female gender was associated with decreased risk of TST conversion (OR 0.05, 95% CI 0.01-0.43) and age in years was associated with increased risk of QFT conversion (1.07, 95% CI 1.01-1.13).

Conclusion: A high prevalence of LTBI was seen among Georgian HCWs, especially those working at TB facilities. Frequent patient contact was associated with increased risk of LTBI when using QFT. High conversion rates were found among Georgian HCWs, particularly at TB facilities. These data highlight the need for effective TB infection control measures.

Cover Page

High Latent Tuberculosis Infection Test Conversion Rates among Healthcare Workers in the Country of Georgia

By
Jennifer Anne Whitaker, M.D.

Advisor: Henry M. Blumberg, M.D.

A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science
in Clinical Research
2012

Acknowledgements

I am grateful to my mentor Dr. Henry Blumberg for providing me the opportunity to travel to the country of Georgia to engage in this research and for his support and guidance throughout the entirety of this project. I am grateful to my Georgian colleague Dr. Veriko Mirtskhulava for providing me the opportunity to collaborate on this project and for her hard work in seeing this project through to completion. I would like to thank Dr. Maia Kipiani for her assistance with the logistics of the study, Dr. Drew Harris for his assistance in testing Georgian healthcare workers, and Dr. Russell Kempker for his support throughout the course of this study. I would like to thank all of the MSCR professors for their instruction in study design, data analysis, and presentation that I will use throughout my future research career and extend specific gratitude toward Drs. Mitch Klein, Igho Ofotokun, John Boring, and John McGowan for their guidance and constructive critique of this work.

Finally, this study would not have been possible without the participation of the Georgian healthcare workers. I would like to thank them for their participation in the study.

TABLE OF CONTENTS

Introduction

Tuberculosis (TB) is a significant occupational health problem for healthcare workers (HCWs), particularly in facilities in low and middle income countries where the greatest burden of disease is found and where often there are limited TB infection control measures (1-3). Most high-income countries (which generally have low incidence of disease) screen healthcare workers periodically for latent tuberculosis infection (LTBI) as part of their TB infection control programs (4, 5). For many years the tuberculin skin test (TST) was the only test available for diagnosis of LTBI. Interferon-γ release assays (IGRAs) are T-cell based assays that provide an alternative diagnostic test for LTBI (6). The lack of a gold standard for LTBI has limited interpretation of IGRA and TST results. Furthermore, data are lacking on the performance of IGRAs in repeated testing, such as the serial testing of HCWs (7, 8). To our knowledge, there has been only one published study of serial testing of HCWs using IGRAs in a high burden TB country (9). While there are CDC and manufacturer guidelines for what constitutes a positive IGRA test (static level), there are no data on what value constitutes an IGRA conversion (which is currently regarded as a change from negative to positive result without an incremental increase), (7) unlike the TST where a conversion is defined as an increase in 10 mm of induration between tests. There are also limited data on the prognostic value of a positive IGRA for the development of active TB disease.

Georgia is a high burden TB country and also a high burden multi-drug resistant TB (MDR-TB) country (10). Medical care for TB in the country of Georgia is provided through the Georgian National Tuberculosis Program (NTP) at inpatient and outpatient facilities, where there have been limited TB infection control measures. Like most low

and middle income countries, there are no routine programs in place in Georgia to screen healthcare workers for LTBI. There has been one study evaluating the rates of LTBI among Georgian HCWs at the NTP (11), but there are no data on the rates of LTBI infection among HCWs at non-TB healthcare facilities. Furthermore, there are no data on rates of conversion for LTBI tests (change from a negative to positive test result) for any HCWs in the country of Georgia.

We performed a prospective longitudinal study of HCWs in TB and non-TB facilities in Georgia using serial testing with the TST and the IGRA QuantiFERON-TB Gold In-tube assay (QFT). The purpose of this study was to determine the prevalence and risk factors for LTBI among these HCWs, in addition to the rates and risk factors for conversion (indicating recent infection among HCWs) of the TST and QFT tests. In the absence of a gold standard for LTBI, it has been proposed that correlation between the degree of TB exposure and IGRA results may be one way to assess IGRA performance (8). We sought to estimate the effect of HCWs' frequency of contact with TB patients at work on the outcome of a positive test for LTBI (TST and QFT) at initial testing and also for the outcome of LTBI (TST and QFT) test conversion. We hypothesized that frequent contact with TB patients is associated with an increased risk of a positive test for LTBI on baseline testing and is also associated with increased risk of LTBI test conversion.

Background

Tuberculosis infection among healthcare workers

Healthcare workers (HCWs), especially those in low and middle income countries where the incidence of TB is generally high, are at increased risk for tuberculosis (TB)

infection due to nosocomial transmission of *Mycobacterium tuberculosis* (1-3). TB is likely the most commonly acquired occupational illness for healthcare workers in low and middle income countries (3). TB transmission in healthcare facilities can be significantly reduced with the implementation of effective TB infection control measures (4, 12-14). The nosocomial transmission of multi-drug resistant (MDR-TB) and extensively drug resistant TB (XDR-TB) further highlights the need for effective TB infection control measures (15-17). While most high-income countries (which now generally have a low incidence of TB) have successfully implemented TB infection control measures (4), TB infection control measures are virtually non-existent in many resource-limited countries (1, 18). Most high income countries include periodic screening of HCWs for latent tuberculosis infection (LTBI) as part of their TB infection control programs (4, 5).

Diagnostics for latent TB infection

Until recently, the only test available for LTBI screening was the tuberculin skin test (TST). Limitations of the TST include: the need for two visits to the healthcare provider for test placement and reading, false positives due to cross-reaction with bacille Calmette-Guérin (BCG) vaccination and non-tuberculous mycobacteria (NTM), subjectivity in reading of test results, and boosting that may occur with serial testing (19, 20) among those with latent TB infection who have not undergone recent testing. Interferon-γ release assays (IGRAs) are alternative diagnostic tests for latent tuberculosis infection. There are two commercially available IGRAs that have been approved for use by the U.S. FDA—the QuantiFERON-TB Gold In-Tube (QFT) assay (Cellestis Ltd,

Carnegie, Australia) and the T-SPOT.TB assay (Oxford Immunotec, Abingdon, UK). IGRAs have several advantages over the TST: they require only one visit, are not affected by BCG vaccination, have less cross-reaction with non-tuberculous mycobacteria, are less subjective in measuring results, and can be repeated without boosting. Studies evaluating the performance of IGRAs for LTBI diagnosis are limited by the lack of a gold standard for LTBI, lack of data on serial testing using IGRAs, and lack of definitions on what constitutes a IGRA conversion.

Using IGRAs for serial testing of healthcare workers

Data are lacking on the use of IGRAs for serial testing of healthcare workers, in particular, how to interpret serial IGRA testing results (7, 8). There are few published studies of serial testing of HCWs with IGRAs (9, 21-26). To our knowledge, there is only one published study of serial testing of HCWs in a high-burden TB country (9). In 2005 US Centers for Disease Control (CDC) recommended that the IGRAs can be used in all settings where the TST has been used, including the serial testing of healthcare workers (27). According to the American Thoracic Society (ATS) and CDC guidelines, a TST conversion for a healthcare worker is a change in induration from <10 mm to $\geq$ 10 mm, with an increase of $\geq$ 10 mm induration within 2 years (6, 28). According to CDC guidelines, a QFT conversion is a baseline interferon-gamma (IFN-γ) <0.35 IU/ml and a follow-up IFN-γ level $\geq$ 0.35 IU/ml, without any consideration of the magnitude in change of the IFN-γ response (6). The updated 2010 CDC guidelines caution that "lenient criterion to define IGRA conversion might produce more conversions than are observed with the more stringent criteria applied to TSTs. Furthermore, an association between an

IGRA conversion and subsequent disease risk has not been demonstrated. The new criteria for interpreting changes in an IGRA that identify new infections remain uncertain" (6). Guidelines from Canada and Australia have been cautious about using IGRAs for HCW screening (29-31), and Canadian guidelines do not recommend the use of IGRAs for serial testing of HCWs (29). According to the World Health Organization (WHO) policy statement on the use of IGRAs in low- and middle-income countries, "data on serial testing and reproducibility of IGRAs, as well as evidence on the predictive value of IGRAs in health care workers (HCWs), are still absent for high-incidence settings. There is no data to suggest that IGRAs are better or worse than the TST for identifying new TB infections after exposure in HCWs, but serial IGRA testing is compounded by a lack of optimum cut-offs and unclear interpretation and prognosis of IGRA conversions and reversions" (32).

Correlation with TB exposure gradient

A major challenge in the interpretation of diagnostic tests for LTBI, including IGRA test performance, is the lack of a gold standard for LTBI diagnosis. Various methods have been used to address the lack of a gold standard for LTBI. To determine "true positives" and sensitivity, people with active TB disease have been tested with IGRAs, with the assumption that they should have positive IGRA tests. However, there are limitations to using active TB cases to determine sensitivity, as the immune response to active TB may be different from LTBI, and T-cell responsiveness to the tuberculosis antigens in the IGRA can be reduced as a result of tuberculosis disease or the immunocompromising condition that underlies TB reactivation. To determine true

negative tests, healthy volunteers from low prevalence areas with no known TB contacts, who are assumed to be LTBI free, have been tested. The limitation with this method is that there is no way of knowing that the volunteers are truly LTBI free. Another method has been measuring the degree of concordance with the TST. However, the TST has limitations and is not truly a gold standard. Longitudinal studies following IGRA positive individuals over time to determine the risk of developing active TB disease (in the absence of LTBI treatment) will provide valuable information for the positive predictive value of IGRAs. However, these studies will require long-term follow-up and current data are lacking. An alternative method of assessing the performance of IGRAs is to examine the correlation between positive IGRA results and the levels of exposure to sputum-smear positive active TB cases of the individuals tested (8, 31). The premise of this method is that individuals who are exposed to active smear-positive TB cases are likely to become infected with TB and develop latent infection. Limitations to this approach are that not all individuals closely exposed to active TB cases develop LTBI, and some individuals may have been exposed to active TB cases without their knowledge.

Cross-sectional studies have found good correlation between occupational risk factors for TB exposure and IGRA positivity rates (8). All of these studies were from low- and moderate-incidence countries, with the exception of a study conducted in India (33). A study from the country of Georgia conducted in 2006, found that routine direct contact with TB patients at work was associated with an increased risk of a positive QFT test in univariate analysis. In multivariate analysis, age, gender, occupation, duration of employment as a healthcare worker and BCG vaccine status were included. Employment

in healthcare for >5 years was significantly associated with increased risk of positive TST (OR 5.09, 95% CI 2.77-9.33) and QFT (OR 2.26, 95% CI 1.27-4.01), and age >30 years was associated with increased risk of a positive QFT (OR 2.91, 95% CI 1.32-6.43) (11). In this study, 81% of the HCWs had daily contact with TB patients, and therefore, there may not have been enough HCWs with infrequent contact with TB patients to detect a difference on multivariate analysis (11).

Very few studies have looked at an association between IGRA test conversion and the degree of occupational exposure (8). Two studies found that IGRA conversions were associated with TB exposure, but neither study performed repeat TST and thus comparison of the association for TB exposure and TST conversions could not be made (21, 34). The only published study of serial testing of HCWS using IGRAs in a high-burden TB country did not examine an association with the degree of TB exposure (9).

Tuberculosis in Georgia

Georgia has high rates of TB and has been designated by WHO as a high-burden MDR-TB country(10). In 2010, the incidence of TB in Georgia was 107 cases/100,000 population and prevalence was 118 cases/100,000. Among newly diagnosd TB cases, 9.5% had MDR-TB, and among retreatment cases, 31% had MDR-TB (10). In Georgia, patients with suspected TB are diagnosed and treated in specialized TB facilities organized by the Georgian NTP. Patients with TB generally do not receive care in other healthcare facilities. TB infection control measures in Georgian healthcare facilities have been limited in the past, similar to most resource-limited countries.

This aims of this study were to determine prevalence of LTBI and conversion rates (indicating recent acquisition of infection with *Mycobacterium tuberculosis*) by TST and QFT tests among Georgian HCWs in TB and non-TB health care facilities, to determine the risk factors for LTBI and LTBI test conversion, and to determine the relationship between the HCWs' frequency of TB exposure at work and the outcome of positive QFT and TST.

Methods

Hypotheses and Specific Aims:

Null hypothesis 1: Frequent contact with TB patients is not associated with an increased risk of a positive test for LTBI (QFT, TST).

Null hypothesis 2: Frequent contact with TB patients is not associated with an increased risk of TST or QFT conversion.

Aim 1: To determine the prevalence and risk factors for LTBI among Georgian healthcare workers by positive TST and positive QFT. To determine the concordance between the TST and QFT test in this population.

Aim 2: To estimate the effect of frequency of contact with TB patients at work on positive LTBI test (either test positive, QFT positive, TST positive, discordant positive tests) among Georgian HCWs.

Aim 3: To determine the rates and risk factors for conversion from a negative to a positive test (TST, QFT, either test) for LTBI among Georgian HCWs.

Study Design:

This is a prospective longitudinal study that was conducted from 2009-2011. HCWs from the Georgian NTP, including the National Center for Tuberculosis and Lung Diseases (NCTLD) in Tbilisi, its affiliated outpatient clinics, as well as HCWs from non-TB facilities were eligible to enroll. Inclusion criteria were: age $\geq$ 18 years old, HCW in the country of Georgia, and provision of written informed consent. Exclusion criteria were: history of active tuberculosis and known allergy to the purified protein derivative used in the TST. The study was approved by the Emory IRB and Georgian NCTBLD Ethics Committee. HCWs enrolled into the study provided written informed consent in their native Georgian language of Kartuli and completed a questionnaire with demographic information (date of birth, gender, country of birth, ethnicity), medical history (BCG vaccination, information about household and community TB exposure, history of TST, history of TB disease), and employment history (occupation, number of years in healthcare). BCG vaccination status was also assessed by visual inspection for a BCG scar.

After completing the questionnaire, two diagnostic tests for LTBI were performed: the TST (only if the HCW had no history of a prior positive TST) and the QFT test. After 3 ml of blood was drawn for the QFT test, the TST was placed using 5 tuberculin units (TU) of PPD (Tubersol®, Connaught; Swiftwater, PA, USA). The TST was performed using the Mantoux method (28) and read 48-72 hours after placement.

The QFT test was preformed according to the manufacturer's recommendations and as previously described (35). Because the QFT assay cannot accurately measure absolute IFN-γ values >10 IU/ml, such values were treated as 10 IU/ml. Repeat testing was performed on participants 6-24 months after baseline testing was performed. QFT was performed on all participants who underwent repeat testing. TST was only repeated if the participants had a negative TST result on baseline testing.

Variables

Outcome variables for baseline testing were positive LTBI tests (QFT and TST). As recommended by the manufacturer and by the CDC (6), the QFT result was defined as positive if the response to the TB antigens minus the negative control was ≥ 0.35 IU/ml and > 25% of the negative control, negative if these criteria were not met, and indeterminate if either the negative control had a result of > 8 IU/ml or if the positive control had a result of < 0.5 IU/ml. According to the American Thoracic Society (ATS) and CDC guidelines, for the HCWs the TST was defined as positive if the induration was ≥ 10 mm (28, 36).

Outcome variables for repeated testing were conversion of LTBI tests (QFT and TST). According to CDC guidelines, a QFT conversion is a baseline interferon-gamma

(IFN-γ) <0.35 IU/ml and a follow-up IFN-γ level ≥ 0.35 IU/ml, without any consideration of the magnitude in change of the IFN-γ response (6). According to ATS and CDC guidelines, a TST conversion for a healthcare worker is a change in induration from <10 mm to ≥ 10 mm, with an increase of ≥ 10 mm within 2 years (6, 28).

The primary predictor variable was frequency of contact with TB patients at work. HCWs rated this frequency on a questionnaire at time of LTBI testing. Daily contact was defined as contact ≥ 5 days per week. Frequent contact was defined as contact < 5 days per week and ≥ twice per month. Rare contact was defined as < twice per month and ≥ once per 3 months. Very rare contact was defined as < once per 3 months. The primary predictor variable was later dichotomized into "frequent," defined as contact ≥ twice per month, and "rare," defined as contact < twice per month.

Other covariates considered were age in years (continuous variable), gender (female versus male), number of years in healthcare (continuous variable), occupation (categorized as administrative/technical staff [reference group], medical students, nurses, physicians and other), type of health care facility (categorized as non-TB health facility [reference group], TB inpatient, TB outpatient, medical school, and other), education level (categorized as graduate [reference group], undergraduate, and secondary school or less), and BCG vaccination history (negative versus positive).

Sample Size Calculations

Sample size calculations were determined to measure the prevalence of LTBI among HCWs from TB facilities in Georgia. Initially, HCWs only from TB facilities were going to be enrolled and the prevalence would have been determined for HCWs

who worked in TB facilities in Tbilisi. Sample size calculations were carried out using the following formula for estimating a population proportion with specified absolute precision:(37)

$$n = z^2_{\alpha/2}\, p\,(1-p)/d^2$$

where p= estimated LTBI prevalence, d = absolute precision required on either side of the proportion, z= constant, and α=significance level. Based on a previous study by Mirtskhulava and Kempker of 264 healthcare workers in Georgia, the prevalence of LTBI was 67% for by positive TST, 60% by QFT and 77% for either a positive TST or QFT (11). We anticipated a slightly lower prevalence with this study because we anticipated enrolling more medical students than in the previous study. There are no studies of LTBI prevalence of the general population in Georgia. A study in a refugee population setting found LTBI rates of 50%.(38) In the above equation, estimated prevalence of LTBI among healthcare workers of 60% was used, z=1.96 for 95% confidence interval, and d=0.05. A sample size of 369 was calculated to determine prevalence within 5 percentage points on either side of the estimate with 95% confidence.

Data Management

Study data were collected and managed using REDCap electronic data capture tools hosted at Emory University. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies (39).

Statistical analyses were performed using SAS software version 9.2 (SAS Institute, Inc., Cary, NC, USA).

Data Analysis

Prevalence of QFT positivity and TST positivity was determined for HCWs in non-TB facilities and TB facilities.

Concordance between the two diagnostic tests for LTBI (TST and QFT) was measured using the kappa (κ), where $\kappa > 0.75$ represents excellent agreement, $\kappa = 0.4$-0.75 represents fair to good agreement, and $\kappa < 0.4$ represents poor agreement (40). Only data from participants who had measured TST and QFT values at baseline (n=260) was included for the concordance analysis. Concordance between the two tests was measured for the total population (n=260) and separately for those who had a positive history of BCG vaccine and for those with had a negative history of BCG vaccine.

Descriptive statistics were used to determine the frequencies of the categorical covariates and distributions of the continuous covariates for the study population.

Logistic regression modeling with outcome of either LTBI test (TST or QFT) positive was used to determine risk factors for outcome of LTBI on baseline testing and to determine the association of frequent contact with TB patients at work on the outcome of LTBI. Logistic regression models with outcome of QFT and with outcome of TST were used to determine the association of frequent contact with TB patients on each outcome. Participants were included in these models if they had measured TST (or documented history of positive TST) and measured QFT. The same participants were included in the models for the outcome of either LTBI test positive, QFT positive, and

TST positive. Additionally, a logistic regression model was used to determine the association with frequent contact with TB patients and the outcome of discordantly positive LTBI tests (QFT positive/TST negative versus TST positive/QFT negative).

To better visualize potential risk factors, causal pathways between the primary predictor and outcome variables causal diagrams were constructed (Figures 1a and 1b).

Univariate analyses were performed to evaluate the odds ratios for the primary exposure variable (dichotomized frequency of contact with TB patients) and each covariate with respect to the outcome variable (positive test for LTBI). The frequencies of exposure variables in cases (HCWs with a positive LTBI test) and controls (HCWs with negative LTBI tests) were evaluated. Additionally, analyses were employed to explore the associations between the primary exposure variable and each of the covariates as part of the assessment for confounding. The Chi-square test was used to test these associations and to assist in identifying potential confounders. A p-value < 0.05 was considered statistically significant. Next, a stratified analysis was performed, controlling for the relationship between the primary exposure variable (dichotomized frequency of contact with TB patients) and the outcome (positive test for LTBI). To evaluate for potential interaction and confounding, stratum-specific odds ratios were calculated. The Breslow-Day test was used to test the homogeneity of the odds ratios (p-value<0.05 was considered statistically significant) to assess for interaction. Adjusted odds ratios (using the Mantel-Haenszel approach) were compared to the crude odds ratio to identify potential confounding.

A modeling approach was used to better visualize the association between the exposure variable and outcome in the setting of the covariates. First, a test model was

generated including numerous covariates that were deemed important based on prior knowledge, biological plausibility, and potential confounders or interaction terms. Collinearity was tested using the Collin Macros by Dan Rosen, with collinearity defined as both a conditional index of ≥ 23 and variance decomposition proportion of ≥ 0.5 (41). Interaction, was evaluated using likelihood ratio test for product terms, where a p-value <0.05 was considered statistically significant. Finally, confounding was evaluated by assessing whether there was a meaningful change (subjectively determined) in the odds ratios in the full versus reduced models. A final model was then constructed to include the predictor variable, outcome variable, identified confounders and interaction terms, and other clinically important covariates.

Incidence rates for TST and QFT conversion (in 100 person-years) were determined by dividing the number of events by the total amount of person-time contributed by those who were negative at time of first testing and accounting for the time to follow-up testing. Risk factors for TST and QFT conversion were determined by using univariate analyses and multivariate logistic regression analysis. Because of the small number of events, only the covariates of gender, age, and frequency of TB contact (primary exposure variable) were included in the logistic regression models.

Cox propotional hazards regression modeling was also used to determine univariate rate ratios for TST and QFT conversion. The use of this type of analysis is prone to error, because participants were not tested at regular intervals, and we did not truly know the time to developing the event (LTBI test conversion). Plots of estimated log-log survival curves were compared stratified on each predictor to assess the

proportional hazards (PH) assumption. If the log-log curves were parallel then the PH assumption was assumed to be valid.

Results

Between March 2009 and July 2011, 320 health care providers were enrolled in the study (figure 2); all enrolled had a QFT performed. One participant was excluded for history of active TB disease. Fifty-nine HCWs did not have a TST performed (48 participants reported a prior positive TST in the past and 11 refused to have a TST done). We were able to confirm documentation of a positive TST for 25 of the 48 HCWs with a prior history of testing positive. Participants with documented past TST and those who had a TST performed in this study (n=285) were included in the analyses for risk factors for positive test for LTBI (Figure 2). For concordance analysis comparing TST and QFT, we only included participants who had TST and QFT performed in our study (n=260). For determination of prevalence of positive TST, we included participants who had TST performed in our study or reported prior history of positive TST (n=308). For determination of prevalence of positive QFT, we included participants who had QFT measured (n=319).

The Study Population

Table 1 denotes the characteristics of the study population (n=319). The majority of the health care workers in our study were from Tbilisi (n=274, 86%) where the NCTLD is located. Approximately 60% (142/319) of the participants worked in TB facilities, and 40% worked in non-TB facilities. Eighty nine percent (285/319) reported

history of BCG vaccine. The majority of the participants were female (n=259, 81%), which represents the demographics of healthcare workers in Georgia. The mean age was 40.9 years (standard deviation 12.6 years). The mean number of years in healthcare was 17.0 (standard deviation was 12.6 years). The majority of our cohort were physicians (n=114, 36%); (94/319) 29% were administrative staff; (14/319) 4% were medical students; (50/319) 16% were nurses; and (47/319) 15% had "other" occupations. Seventy two percent (230/319) of our cohort had graduate level education; 21% (68/319) had undergraduate education, and (21/319) 4% had secondary school education level or less. Thirty-two percent of the participants reported daily TB exposure at work; 18% reported TB exposure < 5 days per week and ≥ twice per month; 19% reported TB exposure ≤ once a month and ≥ once per 3 months; and 31% reported TB exposure < once per 3 months. After TB exposure at work was dichotomized, 49% (158/319) HCWs had frequent contact with TB patients at work (contact ≥ twice per month) and 51% (161/319) had infrequent contact with TB patients (contact ≤ once per month).

Prevalence of TST and QFT Positivity

The prevalence of a positive TST in our cohort was 67% (193/308). The prevalence of a positive QFT in our cohort was 46% (146/319). HCWs from TB facilities had higher QFT and TST positivity rates than those from non-TB facilities. Among HCWs who worked in TB facilities 107/194 (55%) had positive QFT versus 30/125 (31%) of HCWs working in non-TB facilities ($p<0.0001$). Among HCWs working in TB-facilities 128/189 (69%) had positive TST versus 64/119 (54%) of those working in non-TB facilities ($p=0.01$).

Concordance between TST and QFT Results

The concordance of baseline TST and QFT results for the participants who had both tests measured at baseline are shown in Table 2 (n=260). There was fair concordance between the TST and QFT (kappa statistic [κ] =0.42 [95% CI: 0.31-0.52]). Agreement between the two diagnostic tests was 70.4%; with 36% (93/260) of tests concordantly negative, 35% (90/260) tests concordantly positive, 21% (55/260) TST positive and QFT negative, and 8% (22/260) QFT positive and TST negative. Concordance of the baseline TST and QFT results stratified by history of BCG vaccine is represented in tables 3a and 3b. Concordance was higher for the group with no history of BCG vaccine, $\kappa = 0.70$ (95% CI: 0.44-0.97) than for the group with BCG vaccine history, $\kappa = 0.38$ (95% CI: 0.27-0.50).

Comparison of Participants with LTBI versus Those without LTBI

Table 4 shows the results of the analysis for the frequencies of the potential risk factors for LTBI among those with the outcome of either LTBI test positive (QFT or TST) and among those with no test positive for LTBI. A positive test for LTBI was found to be associated with TB exposure frequency with the 4 levels, as previously defined ($p = 0.037$) and for TB exposure frequency dichotomized into "frequent," defined as contact $\geq$ twice per month, and "rare," defined as contact < twice per month ($p=0.006$). Among the cases of positive test of LTBI, 102/191 (53%) had frequent contact with TB patients and 89/191 (47%) had rare contact; among those with no LTBI test positive, 34/94 (36%) had frequent contact with TB patients and 60/94 (64%) had rare contact with TB patients

(Chi-square p-value=0.006). Additionally, LTBI cases were associated with age >30, years in healthcare >15, and type of healthcare facility.

Univariate Analysis of Risk Factors for Positive LTBI Diagnostic Test at Baseline

Using logistic regression, univariate analysis was first performed to determine unadjusted odds ratios for potential risk factors for a positive test for LTBI. These results are summarized in Table 5. Risk factors for the outcome of either QFT or TST being positive (the prevalence of a positive test) that were found to be statistically significant were frequent exposure with TB on the dichotomized definition (OR 2.02, 95% CI 1.27-3.36), age in years (OR 1.03, 95% CI 1.01-1.06), and undergraduate education versus graduate education (OR 2.02, 95% CI 1.05-3.92).

Assessment for Confounding and Interaction Using a Database Approach

To evaluate for confounding, the relationships between the primary exposure variable (frequency of contact with TB patients) and each covariate were analyzed. Frequent contact with TB patients was found to be associated with occupation, education, and type of healthcare facility. However, occupation and education were very strongly associated and provided qualitatively redundant information (table 6a), with nearly all nurses having undergraduate education and physicians having graduate education. Therefore, education and occupation were determined to qualitatively collinear (42), and education was not selected for inclusion in the multivariate model, as it was not thought to provide information beyond the type of occupation. Additionally, healthcare facility and frequency of TB contact were highly associated (table 6b) and determined to be

qualitatively collinear. All HCWs at non-TB facilities had rare TB contact, thus type of healthcare facility was not selected for inclusion in the multivariate model, as it was not thought to provide information beyond the frequency of TB contact. Occupation type and frequent TB contact were associated (table 6c), but each occupation had varying degrees of frequent TB contact and were not determined to be qualitatively collinear. Occupation was also associated with the outcome. Therefore, occupation was identified as a potential confounder and was explored further with a stratified analysis.

Through the stratified database approach (table 7), no interaction was identified between frequency of contact with TB patients and the covariates (Breslow-Day p-value <0.05). The p-value for the Breslow Day test for frequency of contact with TB patients and BCG vaccine history was close to significance (p=0.08), so a product term these variables was created and tested by a modeling approach as described below. Based on the stratified database approach, the only covariate that was identified as a potential confounder was occupation. The Mantel Haneszel adjusted OR for frequent contact with TB patients on outcome of a positive test for LTBI adjusted for occupation was 1.78, which was different than the crude OR of 2.02. Therefore occupation was identified as a moderate confounder.

Multivariate Logistic Regression Analysis of Risk Factors for Positive LTBI Diagnostic Test at Baseline

The initial full model evaluated the relationship between frequency of contact with TB patients and the outcome of a positive test for LTBI at baseline (prevalence of

either QFT or TST positivity), controlling for age, BCG vaccine history, gender, years in healthcare, occupation, and the interaction term "frequent contact with TB patients*BCG vaccine history." These covariates were selected based on biologic plausibility and the analysis described above. The p-value for the likelihood ratio test (LRT) testing the significance of the interaction term was 0.13. Because the significance level was set at α=0.05, this was determined not to be statistically significant, and the interaction term was dropped from the final model. No collinearity was noted in the final model by using the Collin Macros by Dan Rosen (41). The final model can be found in appendix 1. The ORs for the final model are listed in table 8. The same model with the outcomes of either test positive, QFT positive, and TST positive were run. The ORs for each of these models are also listed in table 8.

TB exposure frequency at work, BCG vaccine history, gender, years in healthcare, and occupation were included in the multivariable analysis for outcome of QFT or TST test positivity at baseline (prevalence of positive test for LTBI) (table 8). In multivariate analysis, the OR for frequent versus rare contact with TB patients was 1.77 (95% CI, 1.03-3.05). For the outcome of positive TST, the OR for frequent versus rare contact with TB patients was not statistically significant (OR 1.29, 95% CI 0.76-2.18); however, it was significant for the outcome of a positive QFT (OR 3.04, 95% CI 1.79-5.14). Age in years was found to be significant in multivariate analysis for each of the outcomes (table 8). Occupation as a nurse versus administrative/technical staff was found to be a statistically significant predictor of a positive TST on multivariate analysis.

Additionally, a multivariate logistic regression model was used to determine the association between frequent contact with TB patients and the outcome of discordant

LTBI tests (QFT positive/TST negative (n=22) versus TST positive/QFT negative (n=63)). The same covariates were included in this model, except for occupation. The model became unstable when occupation was included in the model, likely because of the smaller sample size (n=85) and number of events (n=22). The results of this analysis are presented in table 9. The adjusted OR for frequent versus rare contact on the outcome of QFT positive/TST negative among HCWs with discordant results was 3.59 (1.23-10.42).

Serial Testing: LTBI Test Conversion Rates and Risk Factors

Of 154 HCWs who had TST and QFT performed at baseline and repeat testing, 77/154 (50%) were susceptible to QFT conversion (had negative QFT at baseline) and 48/154 (31%) were susceptible to TST conversion (had negative TST at baseline) (figure 3). There were 23/77 (29.9%) QFT conversions, 12/77 (15.6%) QFT reversions (initial value $\geq$ 0.35 IU/ml and second test value <0.35), and 11/48 (22.9%) TST conversions (figure 3). The conversion rate by QFT (regardless of baseline TST result) was 22.8/100 person-years. The conversion rate by TST (regardless of baseline QFT result was 17.1/100 person-years. The conversion rate by either test (QFT or TST) among those who had concordantly negative results at baseline (negative TST and negative QFT) was 26.9/100 person-years (17.3/100 person-years for TST conversion and 13.5/100 person-years for QFT conversion).

Females had decreased risk of TST conversion in univariate analysis by Cox regression (rate ratio 0.18 (95% CI 0.05-0.59) and univariate logistic regression (OR 0.13, 95% CI 0.30-0.59) (table 10). All of the TST conversions occurred in TB healthcare

facilities. TB facility type was significantly associated with TST conversions (Fisher's exact two-sided p-value =0.04). The TST conversion rate for HCWs with frequent versus rare TB contact was not significant in univariate analysis. Frequency of contact with TB patients, gender, and age in years were included in multivariate logistic regression analysis of risk for TST conversion (table 12). Health care facility type (TB versus non-TB) was not included in the multivariate analysis, because the OR was infinity. In multivariate analysis only female gender was statistically significant and was associated with decreased risk of TST conversion (OR 0.05, 95% CI 0.01-0.43) (table 12).

In univariate analysis QFT conversion was associated not found to be associated with frequency of TB contact, gender, age, or TB vs. non-TB facility in Cox regression or logistic regression (table 11). Frequency of contact with TB patients and gender were not associated with QFT conversion in multivariate logistic regression analysis (model including these covariates) (table 12). Only age in years (OR 1.07, 95% CI 1.01-1.13) was associated with increased risk of QFT conversion in multivariate logistic regression analysis. Healthcare facility (TB or non-TB) was not associated with risk for QFT conversion (Fisher's exact two-sided p-value= 0.43). An additional multivariate logistic regression model was run, including TB vs. non-TB facility type, along with the other covariates above, and the OR for TB facility type was not statistically significant.

In univariate Cox regression and logistic regression analysis of conversion of either QFT or TST test among those who had negative TST and QFT at baseline, frequency of contact with TB patients, age in years, gender, and TB facility type were not statistically significant (data not shown). The univariate OR for TB facility type (TB vs. non-TB) was 8.67 (0.97-77.10). A multivariate logistic regression model with the

outcome of conversion of either test (QFT or TST), including frequency of TB contact, gender, and age was run. Only female gender was found to be significant, and it was negatively associated with risk of TB conversion (OR 0.07, 95% CI 0.01-0.63) (table 12). An additional multivariate logistic regression model was run, including covariates above, along with TB facility type, and the OR for TB facility type was not statistically significant (OR 8.79, 95% CI 0.47-165.49).

Discussion

We found a high prevalence of LTBI among Georgian healthcare workers in both TB (55% QFT positive and 69% TST positive) and non-TB healthcare facilities (31% QFT positive and 54% TST positive). HCWs from TB facilities had higher QFT and TST positivity rates at baseline than those from non-TB facilities (respective p-values of <0.001 and 0.01). In multivariate analysis, frequent contact with TB patients was associated with increased risk of a positive QFT (OR 3.04, 95% CI 1.79-5.14) but not with positive TST (OR 1.29, 95% CI 0.76-2.18). Age in years was associated with increased risk of positive QFT (OR 1.05 per year, 95% CI 1.01-1.09) and TST (OR 1.05, 95% CI 1.01-1.10). High rates of HCW conversion were seen (QFT conversion rate: 22.8/100 person-years and TST conversion rate: 17.1/100 person-years). TST conversion was associated with working in a TB facility (p=0.04), whereas QFT conversion was not (p=0.43). In multivariate analysis, female gender was associated with decreased risk of TST conversion (OR 0.05, 95% CI 0.01-0.43) and age in years was associated with increased risk of QFT conversion (1.07, 95% CI 1.01-1.13).

Our study provides valuable data on the rates of LTBI prevalence and LTBI test conversions in the country of Georgia. Prior to this study, there was no data on LTBI prevalence in HCWs from non-TB facilities in Georgia and no data on LTBI test conversions among HCWs from any healthcare facilities (TB and non-TB) in Georgia. Our study used a novel approach in comparing the measure of association between frequency of contact with TB patients and the outcome of positive QFT and TST tests. Additionally, our study performed a unique analysis of the risk factors for discordantly positive QFT and TST tests—an analysis that we have not seen before in the literature. Furthermore, our study is novel in that it assessed the relationship between frequency of contact with TB patients and LTBI test conversions. To our knowledge, there has only been one published study of serial testing of HCWs using IGRAs in a high burden TB country, and this study did not evaluate the relationship between degree of TB exposure and LTBI test conversion (9).

Our results are consistent with a previous cross-sectional study of HCWs at the National TB Program in Georgia that found 67% HCWs had a positive TST and 60% had a positive QFT test (11). There are no prior data regarding LTBI rates in the country of Georgia for HCWs who work in non-TB facilities. Additionally, the prevalence of LTBI in the general population of Georgia is not known. The only available data of LTBI among non-HCWs in Georgia is from a study using TST among internally displaced persons (IDPs) that found a prevalence of 48% among 988 (IDPs) (43). The prevalence of LTBI by QFT in HCWs from non-TB facilities (31%) was similar to the prevalence of LTBI by QFT among Russian primary health care providers (26%) (44).

Three cross-sectional studies have evaluated IGRA performance in high-burden TB countries: India (33), Russia (44), and Vietnam(45). TST and QFT positivity rates were high in HCWs (40-66%). The Russian study did not perform TST. IGRA positivity was slightly lower than TST positivity in the Indian study and was significantly lower in the Vietnamese study. The Vietnamese study reported BCG vaccination rate of 37%, compared to the Indian study, which reported 71% BCG vaccination. In a systematic review by Zwerling et al., among 25 cross-sectional studies from low and intermediate incidence TB countries that compared TST to IGRA, all but one reported lower prevalence of positive IGRA than positive TST (8). Concordance between TST and IGRAs had a wide range with κ values from 0.05 in Denmark (using a 12 mm TST cut off, among HCWs with 76% BCG vaccination rate)(46) to 0.56 in Spain (using 5 mm TST cut off for HCWs with no history of BCG vaccine and cut off of 15 mm for BCG-vaccinated HCWs, among HCWs with 35% BCG vaccination rate) (47).

In our study population, 89% of HCWs reported BCG vaccination. Concordance between the two tests was fair (κ=0.42, 95% CI 0.31-0.52). Concordance increased when tests were compared for only non-BCG vaccinated HCWs (κ=0.70, 95% CI 0.44-0.97). Among BCG vaccinated HCWs, 22% had positive TST/negative QFT results, whereas among non-BCG vaccinated HCWs, 11% had positive TST/negative QFT results. This decrease in positive TST/negative QFT results is partially explained by BCG vaccine, which may cause a positive TST result, but will not affect the QFT tests. However, the remaining 11% of discordant positive TST/negative QFT results among non-BCG vaccinated individuals could be due to other another cause of a false positive TST, such

as non-tuberculous mycobacteria exposure, or they could be the result of a more sensitive TST test.

In multivariate analysis, frequent contact with TB patients (contact ≥ twice per month) was associated with at least one LTBI test being positive (OR 1.77, 95% CI 1.03-3.05). Frequent contact with TB patients was not found to be significantly associated with a positive TST; however, it was associated with positive QFT (OR 3.04, 95% CI 1.79-5.14). This association was not seen on multivariate analysis from the study in 2006 of Georgian HCWs (11). However, all of the HCWs in that study worked in TB facilities, and 81% had daily contact with TB patients. There may have not been enough HCWs with limited contact with TB patients to detect a difference in LTBI rates between HCWs with frequent and rare contact. Other studies have found positive association between occupational TB exposure and IGRA positivity rates (8). Of three cross-sectional studies of IGRAs and TST conducted in high-incidence settings (33, 44, 45), only one study from India evaluated the association between occupational risk factors for both TST and IGRA (33). This study found a stronger, but non-significant, association between occupational risk factors and IGRA positivity than for TST positivity (33). A study of HCWs in Russia did not perform TST, but did find that there was a gradient of LTBI by QFT, proportional to exposure in medical students (10% QFT positive), primary health care providers (26%), and TB physicians (55%), respectively (44). In the systematic review by Zwerling et al., among 22 cross-sectional studies of HCWs in low and moderate incidence TB countries, TST, QFT, and TSPOT.TB correlated well with established indicators of occupational risk of TB exposure, although no test was consistently more often associated with these indicators of exposure (8).

The stronger association with frequent contact with TB patients (higher TB exposure risk) and QFT positivity than TST positivity that was observed in our study is difficult to interpret without a gold standard for LTBI diagnosis. In our multivariate analysis of discordantly positive tests (QFT positive/TST negative versus QFT negative/TST positive) controlling for age, gender, years in healthcare, and BCG vaccine, we did see a statistically significant association with frequent TB exposure and QFT positive/TST negative tests versus QFT negative/TST positive tests. This finding suggests that among those with discordant test results, the QFT test has a stronger association with occupational TB exposure. This could indicate that the QFT is more a sensitive test for LTBI among HCWs than TST. However, the positive TST and negative QFT result combination could also be due to non-tuberculous mycobacteria exposure, a cause of positive TST for which we did not test. In a recent study by Mancuso et al., TST positive, IGRA negative discordance was strongly associated with Battey skin test results, a test for reactivity to *Mycobacterium intracellulare* (48). However, BCG vaccination history and positive Battey skin test results, did not explain most of the discordance encountered for TST positive, IGRA negative results (48).

Age in years was a significantly associated with both TST (OR 1.05) and QFT (OR 1.05) positivity on multivariate analysis. Our findings are consistent with other reports that increasing age is a risk factor for LTBI (2, 11). The biological explanation is that with increased age, there has been increased cumulative chance for exposure to tuberculosis to occur.

The most striking findings of our study were the high rates of LTBI test conversion representing recent infection with M. tuberculosis among HCWs. In our

study the TST conversion rate was 22.8/100 person-years, 17.1/100 person-years for QFT, and 26.9/100 person-years for either test conversion among those who had both negative TST and QFT results at baseline. To put these rates into perspective, a study of HCWs in India found TST conversion rates of 2.7/100 person-years and QFT conversion rates of 7.7/100 person-years (9). A study of Malaysian healthcare workers found QFT conversion rates of 9.9/100 person-years (25). Of note, these other studies were of HCWs from hospitals not specializing in TB care, whereas in our study, 60% of HCWs worked in facilities specializing in TB care. Nonetheless, our findings support the need for strengthening of TB infection control measures in Georgian healthcare facilities, particularly those specializing in TB care.

To our knowledge, there has only been one published study of serial testing of HCWs using IGRAs in a high burden TB country, and this study did not evaluate the relationship between degree of TB exposure and LTBI test conversion (9). A study from Japan of serial testing of HCWs with QFT found that HCWs who worked in a TB ward were 20 times more likely to experience QFT conversion than those who did not work in a TB ward. This study did not perform serial TST tests, so no comparison could be made with TST conversions (21). We did not observe an association with TB exposure frequency by our questionnaire and the outcome of TST or QFT test conversion. This may have been a result of our small sample size for serial testing: only 48 HCWs were TST negative on baseline testing and only 77 were negative on baseline QFT testing. However, we did observe that all of the 11 TST conversions occurred in TB health care facilities, and TST conversion was associated with working in a TB facility ($p=0.04$), which indicates that the HCWs who experienced TST conversion did have higher TB

exposure than those who did not convert. Eighteen of the 23 QFT conversions occurred in non-TB health care facilities; however healthcare facility type (TB vs non-TB) was not associated with the outcome of QFT conversion on either univariate or multivariate analysis. The higher rate of QFT conversions could mean that the QFT has a higher sensitivity for detecting LTBI than TST, or it could mean that the QFT has less specificity (is picking up more false positives). We found a higher proportion of TST conversion (100%) among HCWs working at healthcare facilities specializing in TB care, compared to 78% of QFT conversions occurring in HCWs working in TB healthcare facilities. Since Georgia is a high-burden TB country, it is certainly possible that HCWs could have been exposed to active cases of tuberculosis in the community, although none reported known TB contacts.

Our study had several limitations. We had a relatively small sample size of susceptible HCWs who were at risk for LTBI test conversions. This is in part because of the high prevalence of LTBI at baseline among Georgian HCWs. HCWs were enrolled based on convenience sampling, which may introduce selection bias and volunteer bias into the study. Not all of the HCWs enrolled in the study had repeated LTBI tests performed, which could have introduced bias with respect to conversion rates and risk factors. Finally, repeat testing occurred at different time intervals.

Our study provides valuable data regarding serial IGRA testing of HCWs, particularly in a high-burden TB country. Furthermore, we have performed a unique analysis comparing the frequency of contact with TB patients on the outcome of positive TST and QFT tests, which adds unique data to the literature on the performance of IGRA testing for healthcare workers. We observed extremely high TST and QFT conversion

rates, particularly in TB facilities. Our study highlights the need for TB infection control measures in the country of Georgia, particularly for healthcare facilities specializing in tuberculosis care.

References:

1. Joshi R, Reingold AL, Menzies D, Pai M. Tuberculosis among health-care workers in low- and middle-income countries: a systematic review. PLoS Med. 2006 Dec;3(12):e494.
2. Menzies D, Joshi R, Pai M. Risk of tuberculosis infection and disease associated with work in health care settings. Int J Tuberc Lung Dis. 2007 Jun;11(6):593-605.
3. Fennelly KP, Iseman MD. Health care workers and tuberculosis: the battle of a century. Int J Tuberc Lung Dis. 1999 May;3(5):363-4.
4. Jensen PA, Lambert LA, Iademarco MF, Ridzon R. Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005. MMWR Recomm Rep. 2005 Dec 30;54(RR-17):1-141.
5. Guidelines for preventing the transmission of tuberculosis in Canadian Health Care Facilities and other institutional settings. Can Commun Dis Rep. 1996 Apr;22 Suppl 1:i-iv, 1-50, i-iv, 1-5.
6. Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection - United States, 2010. MMWR Recomm Rep. 2010 Jun 25;59(RR-5):1-25.
7. Pai M, O'Brien R. Serial testing for tuberculosis: can we make sense of T cell assay conversions and reversions? PLoS Med. 2007 Jun;4(6):e208.
8. Zwerling A, van den Hof S, Scholten J, Cobelens F, Menzies D, Pai M. Interferon-gamma release assays for tuberculosis screening of healthcare workers: a systematic review. Thorax. 2012 Jan;67(1):62-70.
9. Pai M, Joshi R, Dogra S, Mendiratta DK, Narang P, Kalantri S, et al. Serial testing of health care workers for tuberculosis using interferon-gamma assay. Am J Respir Crit Care Med. 2006 Aug 1;174(3):349-55.
10. WHO. Georgia: Tuberculosis Profile. [cited 2012 February 12]; Available from: https://extranet.who.int/sree/Reports?op=Replet&name=%2FWHO_HQ_Reports%2FG2%2FPROD%2FEXT%2FTBCountryProfile&ISO2=GE&outtype=html.
11. Mirtskhulava V, Kempker R, Shields KL, Leonard MK, Tsertsvadze T, del Rio C, et al. Prevalence and risk factors for latent tuberculosis infection among health care workers in Georgia. Int J Tuberc Lung Dis. 2008 May;12(5):513-9.
12. Blumberg HM, Watkins DL, Berschling JD, Antle A, Moore P, White N, et al. Preventing the nosocomial transmission of tuberculosis. Ann Intern Med. 1995 May 1;122(9):658-63.
13. WHO. Guidelines for the prevention of tuberculosis in health care facilities in resource-limited settings. Geneva, Switzerland: World Health Organization; 1999 [cited 2012 February 12]; Available from: http://www.who.int/tb/publications/who_tb_99_269.pdf.
14. WHO. Tuberculosis infection control in the era of expanding HIV care and treatment. Geneva, Switzerland: World Health Organization; 2006 [cited 2012 February 12]; Available from: http://www.who.int/tb/publications/2006/tbhiv_infectioncontrol_addendum.pdf.

15. Nodieva A, Jansone I, Broka L, Pole I, Skenders G, Baumanis V. Recent nosocomial transmission and genotypes of multidrug-resistant Mycobacterium tuberculosis. Int J Tuberc Lung Dis. 2010 Apr;14(4):427-33.
16. Basu S, Andrews JR, Poolman EM, Gandhi NR, Shah NS, Moll A, et al. Prevention of nosocomial transmission of extensively drug-resistant tuberculosis in rural South African district hospitals: an epidemiological modelling study. Lancet. 2007 Oct 27;370(9597):1500-7.
17. Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet. 2006 Nov 4;368(9547):1575-80.
18. Jones-Lopez EC, Ellner JJ. Tuberculosis infection among HCWs. Int J Tuberc Lung Dis. 2005 Jun;9(6):591.
19. Menzies D. Interpretation of repeated tuberculin tests. Boosting, conversion, and reversion. Am J Respir Crit Care Med. 1999 Jan;159(1):15-21.
20. Farhat M, Greenaway C, Pai M, Menzies D. False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria? Int J Tuberc Lung Dis. 2006 Nov;10(11):1192-204.
21. Yoshiyama T, Harada N, Higuchi K, Nakajima Y, Ogata H. Estimation of incidence of tuberculosis infection in health-care workers using repeated interferon-gamma assays. Epidemiol Infect. 2009 Dec;137(12):1691-8.
22. Chee CB, Lim LK, Barkham TM, Koh DR, Lam SO, Shen L, et al. Use of a T cell interferon-gamma release assay to evaluate tuberculosis risk in newly qualified physicians in Singapore healthcare institutions. Infect Control Hosp Epidemiol. 2009 Sep;30(9):870-5.
23. Lee K, Han MK, Choi HR, Choi CM, Oh YM, Lee SD, et al. Annual incidence of latent tuberculosis infection among newly employed nurses at a tertiary care university hospital. Infect Control Hosp Epidemiol. 2009 Dec;30(12):1218-22.
24. Ringshausen FC, Nienhaus A, Schablon A, Schlosser S, Schultze-Werninghaus G, Rohde G. Predictors of persistently positive Mycobacterium-tuberculosis-specific interferon-gamma responses in the serial testing of health care workers. BMC Infect Dis. 2010;10:220.
25. Rafiza S, Rampal KG. Serial testing of Malaysian health care workers with QuantiFERON(R)-TB Gold In-Tube. Int J Tuberc Lung Dis. 2012 Feb;16(2):163-8.
26. Fong KS, Tomford JW, Teixeira L, Fraser TG, Vanduin D, Yen-Lieberman B, et al. Challenges of Interferon-gamma Release Assay Conversions in Serial Testing of Health Care Workers in a Tuberculosis Control Program. Chest. 2012 Jan 19.
27. Mazurek GH, Jereb J, Lobue P, Iademarco MF, Metchock B, Vernon A. Guidelines for using the QuantiFERON-TB Gold test for detecting Mycobacterium tuberculosis infection, United States. MMWR Recomm Rep. 2005 Dec 16;54(RR-15):49-55.
28. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999,

and the sections of this statement. Am J Respir Crit Care Med. 2000 Apr;161(4 Pt 2):S221-47.
29. Updated recommendations on interferon gamma release assays for latent tuberculosis infection. An Advisory Committee Statement (ACS). Can Commun Dis Rep. 2008 Oct;34(ACS-6):1-13.
30. Position statement on interferon-gamma release immunoassays in the detection of latent tuberculosis infection, October 2007. Commun Dis Intell. 2007 Dec;31(4):404-5.
31. HPA Tuberculosis Programme Board. Health Protection Agency Position Statement on the use of Interferon Gamma Release Assay (IGRA) tests for tuberculosis (TB): draft for consultation, October 2007. London: Health Protection Agency; 2007.
32. World Health Organization. Tuberculosis: IGRA TB Tests Policy Statement. The use of TB Interferon-gamma release assays (IGRAs) in low- and middle-income countries. 2011 [cited 2012 February 14]; Available from: http://www.who.int/tb/features_archive/igra_factsheet_oct2011.pdf.
33. Pai M, Gokhale K, Joshi R, Dogra S, Kalantri S, Mendiratta DK, et al. Mycobacterium tuberculosis infection in health care workers in rural India: comparison of a whole-blood interferon gamma assay with tuberculin skin testing. JAMA. 2005 Jun 8;293(22):2746-55.
34. Pollock NR, Kashino SS, Napolitano DR, Sloutsky A, Joshi S, Guillet J, et al. Evaluation of the effect of treatment of latent tuberculosis infection on QuantiFERON-TB gold assay results. Infect Control Hosp Epidemiol. 2009 Apr;30(4):392-5.
35. Ferrara G, Losi M, Meacci M, Meccugni B, Piro R, Roversi P, et al. Routine hospital use of a new commercial whole blood interferon-gamma assay for the diagnosis of tuberculosis infection. Am J Respir Crit Care Med. 2005 Sep 1;172(5):631-5.
36. Blumberg HM, Leonard MK, Jr., Jasmer RM. Update on the treatment of tuberculosis and latent tuberculosis infection. JAMA. 2005 Jun 8;293(22):2776-84.
37. Indrayan A. Confidence Intervals, Principle of Tests of Significance, and Sample Size. In: Medical Biostatistics. Boca Raton: Chapman & Hall/CRC; 2008. p. 388-91.
38. Weinstock DM, Hahn O, Wittkamp M, Sepkowitz KA, Khechinashvili G, Blumberg HM, et al. Risk for tuberculosis infection among internally displaced persons in the Republic of Georgia. International Journal of Tuberculosis & Lung Disease. [Multicenter Study]. 2001 Feb;5(2):164-9.
39. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009 Apr;42(2):377-81.
40. Kraemer HC. Measurement of reliability for categorical data in medical research. Stat Methods Med Res. 1992;1(2):183-99.
41. Rosen DH. The diagnosis of collinearity. A Monte Carlo simulation method. Dissertation. 1999.
42. Kleinbaum DG, Klein M, Pryor ER. Logistic regression : a self-learning text. 3rd ed. New York: Springer; 2010.
43. Weinstock DM, Hahn O, Wittkamp M, Sepkowitz KA, Khechinashvili G, Blumberg HM. Risk for tuberculosis infection among internally displaced persons in the Republic of Georgia. Int J Tuberc Lung Dis. 2001 Feb;5(2):164-9.

44. Drobniewski F, Balabanova Y, Zakamova E, Nikolayevskyy V, Fedorin I. Rates of latent tuberculosis in health care staff in Russia. PLoS Med. 2007 Feb;4(2):e55.
45. Lien LT, Hang NT, Kobayashi N, Yanai H, Toyota E, Sakurada S, et al. Prevalence and risk factors for tuberculosis infection among hospital workers in Hanoi, Viet Nam. PLoS One. 2009;4(8):e6798.
46. Soborg B, Andersen AB, Larsen HK, Weldingh K, Andersen P, Kofoed K, et al. Detecting a low prevalence of latent tuberculosis among health care workers in Denmark detected by M. tuberculosis specific IFN-gamma whole-blood test. Scand J Infect Dis. 2007;39(6-7):554-9.
47. Alvarez-Leon EE, Espinosa-Vega E, Santana-Rodriguez E, Molina-Cabrillana JM, Perez-Arellano JL, Caminero JA, et al. Screening for tuberculosis infection in spanish healthcare workers: Comparison of the QuantiFERON-TB gold in-tube test with the tuberculin skin test. Infect Control Hosp Epidemiol. 2009 Sep;30(9):876-83.
48. Mancuso JD, Mazurek GH, Tribble D, Olsen C, Aronson NE, Geiter L, et al. Discordance among Commercially Available Diagnostics for Latent Tuberculosis Infection. Am J Respir Crit Care Med. 2012 Feb 15;185(4):427-34.
49. Torres Costa J, Silva R, Sa R, Cardoso MJ, Nienhaus A. Serial testing with the interferon-gamma release assay in Portuguese healthcare workers. Int Arch Occup Environ Health. 2011 Apr;84(4):461-9.

Figures:

Figure 1a: Causal depicting potential association between frequent contact with TB patients at work and outcome of positive QFT.

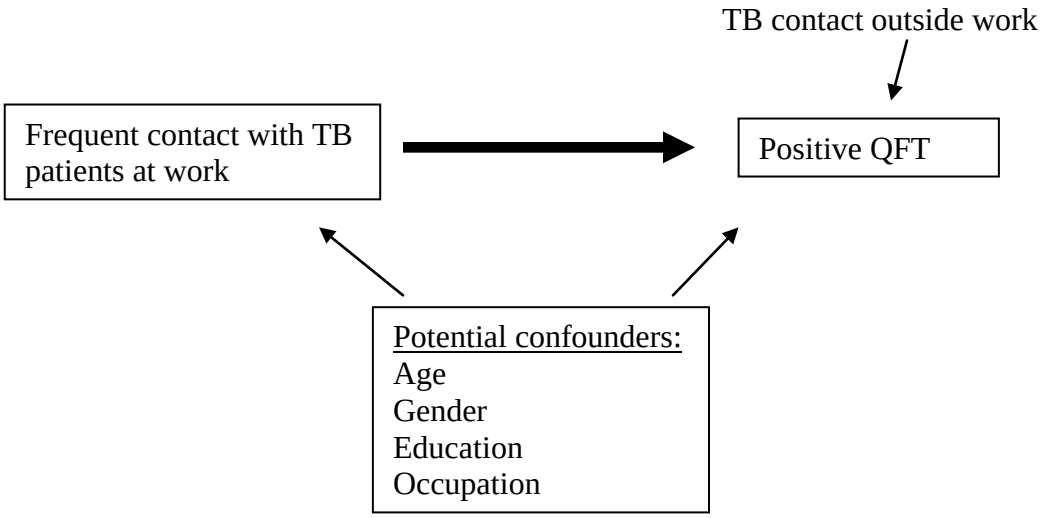


Figure 1b: Causal depicting potential association between frequent contact with TB patients at work and outcome of positive TST.

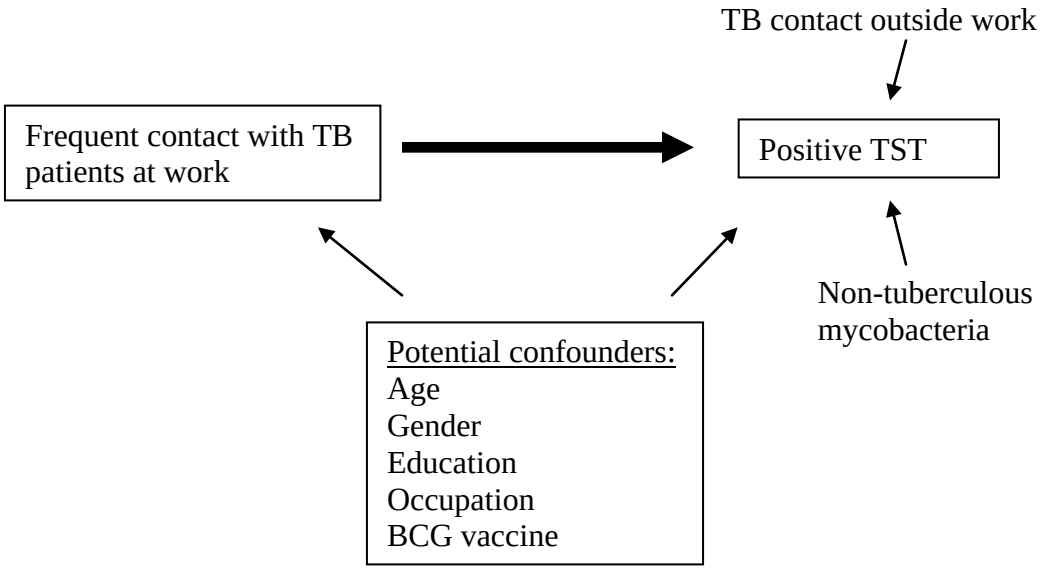


Figure 2: Enrollment and follow-up of participants

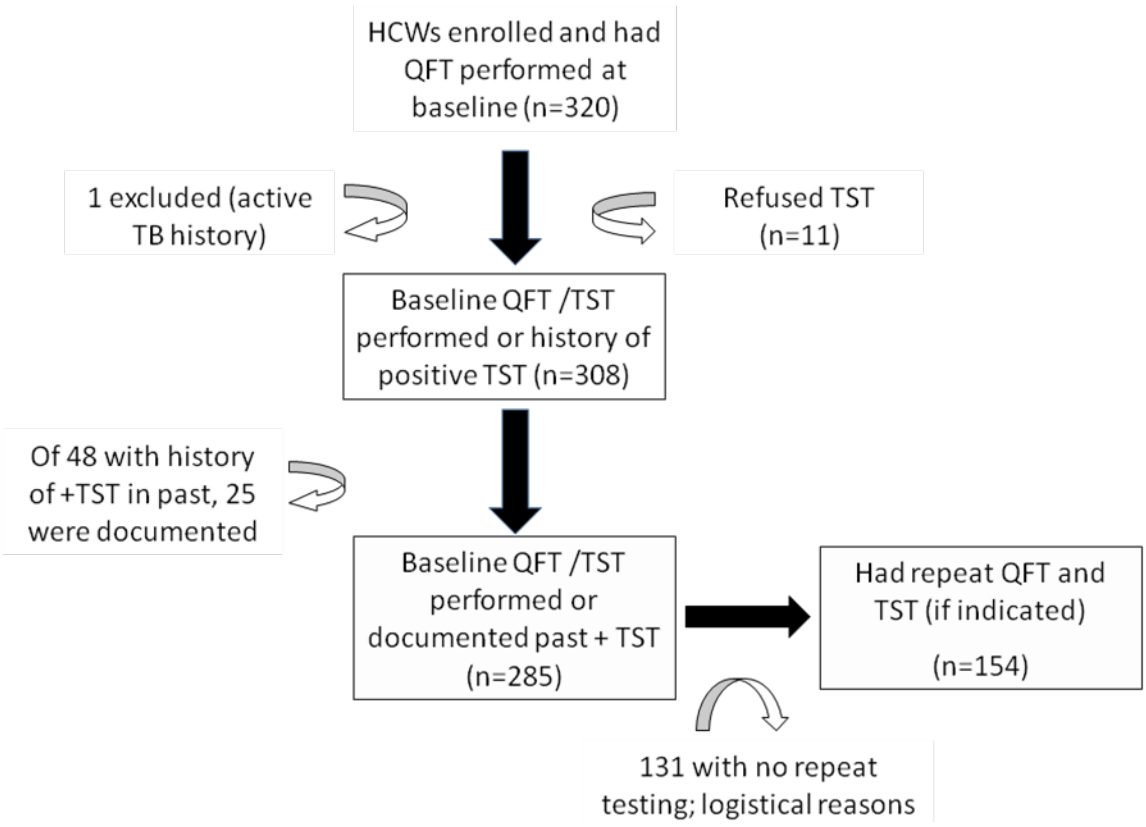
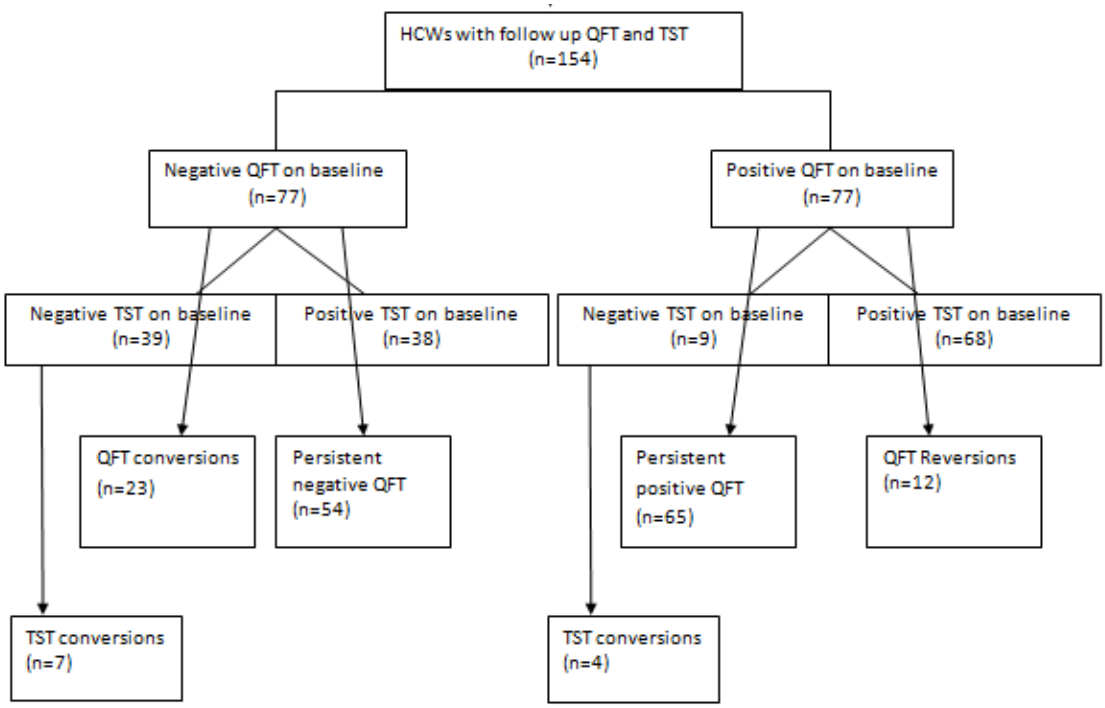


Figure 3: QFT conversions, QFT reversions, and TST conversions



Baseline QFT negative/TST negative (n=39)
- 2nd test: QFT negative/TST positive (n=5)
- 2nd test: QFT positive/TST positive (n=2)
- 2nd test: QFT positive/TST negative (n=7)
- 2nd test: QFT negative/TST negative (n=25)

Baseline QFT negative/TST positive (n=38)
- 2nd test: QFT negative/TST positive (n=24)
- 2nd test: QFT positive/TST positive (n=14)

Baseline QFT positive/ TST negative (n=9)
- 2nd test: QFT negative/TST negative (n=1)
- 2nd test: QFT negative/TST positive (n=1)
- 2nd test: QFT positive/TST positive (n=3)
- 2nd test: QFT positive/TST negative (n=4)

Baseline QFT positive/TST positive (n=68)
- 2nd test: QFT negative/TST positive (n=10)
- 2nd test: QFT positive/TST positive (n=58)

Table 1: Demographic information for healthcare workers (n=319)

Characteristic	*n* (%)
Age, years (median= 41, mean = 40.9, SD = 11.5)	
18-29	64 (20 %)
30-39	83 (26 %)
40-49	98 (31 %)
≥50	74 (23 %)
Gender	
Female	259 (81 %)
Male	60 (19 %)
Georgian ethnicity	305 (96 %)
Location	
Tbilisi	274 (86 %)
Other	45 (14 %)
Positive BCG vaccination history*	285 (89 %)
BCG scar present	242 (76 %)
Healthcare facility	
TB inpatient facility	122 (38 %)
TB outpatient facility	72 (23 %)
Non-TB health facility	70 (22 %)
Medical school	11 (3 %)
Other	44 (14 %)
Years in healthcare (median 15.0, mean 17.0, SD 12.6)	
0-4	70 (22 %)
5-14	83 (26 %)
15-24	72 (23 %)
>25	94 (29 %)
Occupation	
Administrative staff	94 (29 %)
Medical students	14 (4 %)
Nurses	50 (16 %)
Physicians	114 (36 %)
Other	47 (15 %)
Education	
Graduate school	230 (72 %)
Undergraduate	68 (21%)
Secondary school or less	21 (4 %)
TB exposure frequency	
Daily	102 (32%)
Frequent (< 5 days/week and ≥ twice a month)	56 (17 %)
Rare (≤ once a month and ≥ once a quarter)	60 (19 %)
Very rare (< once a quarter)	101 (32 %)
Positive history of TB contact in home	20 (6 %)

*Unknown BCG vaccine history is classified as negative BCG vaccine history

Table 2: Concordance of baseline tuberculin skin test (TST) and QuantiFERON-TB Gold-In Tube (QFT) (n=260)

TST/QFT Results	n (%)
Negative/negative	93 (36%)
Positive/positive	90 (35%)
Positive/negative	55 (21%)
Negative/positive	22 (8%)
Agreement, %	70.4%
Kappa statistic (κ) (95% CI)	0.42 (0.31-0.52)

κ > 0.75 excellent agreement
κ 0.4–0.75 fair to good agreement
κ < 0.4 poor agreement

Table 3a: Concordance of baseline tuberculin skin test (TST) and QuantiFERON-TB Gold-In Tube (QFT) among those with positive BCG vaccine history (n=233)

TST/QFT Result	
Negative/negative	80 (34%)
Positive/positive	80 (34%)
Positive/negative	52 (22%)
Negative/positive	21 (9%)
Agreement, %	68.7%
Kappa statistic (95% CI)	0.38 (0.27-0.50)

Table 3b: Concordance of baseline tuberculin skin test (TST) and QuantiFERON-TB Gold-In Tube (QFT) among those with negative BCG vaccine history (n=27)

TST/QFT Result	
Negative/negative	13 (48%)
Positive/positive	10 (37%)
Positive/negative	3 (11%)
Negative/positive	1 (4%)
Agreement, %	85.0%
Kappa statistic (95% CI)	0.70 (0.44-0.97)

κ > 0.75 excellent agreement
κ 0.4–0.75 fair to good agreement
κ < 0.4 poor agreement

Table 4: Risk factors for a positive diagnostic test for latent tuberulosis infection (LTBI) among Georgian healthcare workers (n=285)

	Positive TST or QFT (n=191)	Negative TST and QFT (n=94)	Chi-square	p-value
Variable	n (%)	n (%)		
TB exposure frequency				
Very rare	56 (29 %)	39 (41 %)	8.46	0.037
Rare	33 (17 %)	21 (22 %)		
Frequent	35 (18 %)	15 (16 %)		
Daily	67 (35 %)	19 (20 %)		
TB exposure frequency				
Very rare/rare	89 (47 %)	60 (64 %)	7.50	0.006
Daily/frequent	102 (53 %)	34 (36 %)		
Age, years				
≤30	29 (15 %)	32 (34 %)	13.3	0.003
>30	162 (85 %)	62 (66 %)		
Gender				
Male	34 (18 %)	21 (22 %)	0.834	0.361
Female	157 (82 %)	73 (78 %)		
BCG vaccine history				
Negative	18 (9 %)	13 (14 %)	1.26	0.261
Positive	173 (91 %)	81 (86 %)		
Healthcare facility				
Non-TB facility	42 (22 %)	22 (23 %)	12.50	0.014
TB inpatient facility	85 (44 %)	29 (31 %)		
TB outpatient facility	40 (21 %)	17 (18 %)		
Medical school	3 (2 %)	6 (6 %)		
Other	21 (11 %)	20 (21 %)		
Years in health care				
≤ 15	96 (50 %)	59 (63 %)	3.97	0.046
>15	95 (50 %)	35 (37 %)		
Occupation				
Administrative staff	56 (29 %)	31 (33 %)	8.54	0.074
Medical students	5 (3 %)	7 (7 %)		
Nurses	37 (19 %)	8 (9 %)		
Physicians	64 (34 %)	33 (35 %)		
Other	29 (15 %)	15 (16 %)		
Education				
Graduate school	127 (67 %)	75 (80 %)	5.41	0.067
Undergraduate	48 (25 %)	14 (15 %)		
≤ Secondary school	16 (8 %)	5 (5 %)		
TB contact in home				
No	178 (93 %)	88 (94 %)	0.02	0.893
Yes	13 (7 %)	6 (6 %)		

TST= Tuberculin skin test
QFT=QuantiFERON-TB Gold In-tube assay

Table 5: Univariate Analysis for Risk Factors for a Positive Test for latent tuberculosis infection (LTBI) among Georgian Healthcare Workers (n=285)

Variable	Odds Ratio (95% confidence interval
TB exposure frequency	
Very rare	1.00
Rare	1.09 (0.55-2.17)
Frequent	1.63 (0.78-3.37)
Daily	2.46 (1.28-4.72)
TB exposure frequency, dichotomized	
Rare	1.00
Frequent	2.02 (1.27-3.36)
Age in years, continuous	1.03 (1.01-1.06)
Gender	
Male	1.00
Female	1.33 (0.72-2.45)
BCG vaccine history	
Negative	1.00
Positive	1.54 (0.72-3.30)
Healthcare facility	
Non-TB health facility	1.00
TB inpatient facility	1.53 (0.79-2.99)
TB outpatient facility	1.23 (0.57-2.65)
Medical school	0.26 (0.06-1.15)
Other	0.55 (0.25-1.23)
Years in health care, continuous	1.02 (1.00-1.04)
Occupation	
Administrative staff	1.00
Medical students	0.40 (0.12-1.35)
Nurses	2.56 (1.06-6.18)
Physicians	1.07 (0.59-1.97)
Other	1.07 (0.50-2.29)
Education	
Graduate school	1.00
Undergraduate	2.03 (1.05-3.92)
Secondary school or less	1.89 (0.67-5.39)
History of TB contact in home	
No	1.00
Yes	1.07 (0.39-2.91)

Table 6a: Association between occupation and education

	Graduate education	Undergraduate Education	High school or less
Administrative/technical	65	9	13
Medical students	12	0	0
Nurses	4	41	0
Physicians	97	0	0
Other	24	8	12

Chi-square $p < 0.0001$

Table 6b: Association between frequency of TB contact and healthcare facility

	Medical School	Non-TB facility	Other	TB Inpatient	TB Outpatient
Frequent contact	0	0	5	77	54
Rare contact	9	64	36	37	3

Chi-square $p < 0.0001$

Table 6c: Association between frequency of TB contact and occupation

	Administrative/ technical	Medical Students	Nurses	Physicians	Other
Frequent contact	31	1	31	25	18
Rare contact	56	11	14	19	49

Chi-square $p = 0.0002$

Table 7: Stratified Analysis: Assessing for interaction and controlling for confounding for covariates on the relationship between primary exposure (frequency of contact with TB patients) and outcome (positive test for LTBI)

		Stratum Specific ORs			
Control variable	Crude OR*	OR_1** (95% CI)	OR_0† (95% CI)	Adjusted OR_{MH} ‡ (95% CI)	p-value Breslow-Day test
Gender (F vs. M)	2.02 (1.22-3.36)	1.86 (1.05-3.29)	2.86 (0.92-8.89)	2.03 (1.22-3.37)	0.51
Age (>30 vs. ≤30)	2.02 (1.22-3.36)	2.07 (1.13-3.77)	1.55 (0.55-4.36)	1.93 (1.15-3.23)	0.64
Years in healthcare (>15 vs. ≤15)	2.02 (1.22-3.36)	2.52 (1.13-5.66)	1.68 (0.87-3.26)	1.98 (1.19-3.30)	0.44
BCG vaccine history (positive vs. negative)	2.02 (1.22-3.36)	1.70 (0.99-2.9)	8.64 (1.45-51.0)	1.99 (1.20-3.30)	0.08
Occupation Med Student vs. Admin Nurse vs. Admin Physician vs. Admin Other vs. Admin	2.02 (1.22-3.36)	---zero cell-- 0.69 (0.12-3.96) 1.86 (0.79-4.36) 2.85 (0.79-10.31)	1.58 (0.61-4.06)	1.78 (1.04-3.00)	0.62

* OR for frequent vs rare contact on outcome of positive LTBI test
**OR for frequent vs rare contact on outcome of positive LTBI test where control variable=1
† OR for frequent vs rare contact on outcome of positive LTBI test where control variable=0
‡ Mantel Haenszel Odds Ratio
Gender: female=1, male=0
Age >30=1, Age ≤30=0
Years in healthcare >15=1, years in healthcare ≤15=0
BCG vaccine history: positive=1, negative=0
Occupation: Admin=Administrative/technical staff (reference group)

Table 8: Odds ratios with 95% confidence intervals (CI) for multivariate logistic regression models with the outcomes of either diagnostic test positive, positive TST, and positive QFT

	Either test (TST or QFT) positive	Positive TST	Positive QFT
Variable	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Frequent vs. rare contact with TB patients	1.77 (1.03-3.05)	1.29 (0.76-2.18)	3.04 (1.79-5.14)
Gender (F vs. M)	1.16 (0.54-2.49)	1.11 (0.53-2.35)	0.55 (0.25-1.20)
Age in years	1.05 (1.01-1.09)	1.05 (1.01-1.10)	1.05 (1.01-1.09)
Years in healthcare (continuous, in years)	0.99 (0.95-1.03)	0.99 (0.95-1.03)	0.99 (0.96-1.04)
BCG vaccine history (positive vs. negative)	1.34 (0.59-3.06)	1.16 (0.51-2.63)	0.84 (0.36-1.94)
Occupation Med Stud vs. Admin Nurse vs. Admin Physician vs. Admin Other vs. Admin	0.65 (0.17-2.40) 1.97 (0.72-5.39) 0.67 (0.30-1.52) 0.67 (0.27-1.63)	0.58 (0.15-2.23) 2.77 (1.01-7.55) 0.42 (0.19-0.95) 0.67 (0.27-1.64)	1.25 (0.28-5.57) 1.75 (0.70-4.32) 0.60 (0.24-1.52) 0.80 (0.35-1.82)

TST= Tuberculin skin test
QFT=QuantiFERON-TB Gold In-tube assay
Frequent =1 is contact with TB patients ≥ twice per month
Frequent=0 (rare) is contact with TB patients < twice per month
Gender: female=1, male=0
BCG vaccine history: positive=1, negative=0
Occupation: Admin=Administrative/technical staff (reference group)

Table 9: Odds ratios with 95% confidence intervals (CI) for multivariate logistic regression model with the outcome of QFT positive/TST negative (n=22) among HCWs with discordant QFT and TST results (n=85)

Variable	Adjusted OR (95% CI)
Frequent vs rare contact with TB patients	3.59 (1.23-10.42)
Gender (F vs M)	0.26 (0.05-1.33)
Age in years	0.96 (0.88-1.04)
Years in healthcare (continuous)	1.07 (0.99-1.17)
BCG vaccine history (positive vs negative)	1.37 (0.13-14.44)

TST= Tuberculin skin test
QFT=QuantiFERON-TB Gold In-tube assay
Frequent =1 is contact with TB patients ≥ twice per month
Frequent=0 (rare) is contact with TB patients < twice per month
Gender: female=1, male=0
BCG vaccine history: positive=1, negative=0

Table 10: Risk of tuberculin skin test (TST) conversion among Georgian health care workers in univariate analysis.

Risk Factor	Number susceptible for TST conversion	TST conversion no. (%)	TST conversion rate/100 person-years	Univariate Rate ratio (95% CI)	p-value for Rate ratio
Total	48	11 (22.9%)	17.1	---	---
Rare contact Frequent Contact	19 29	3 (15.7%) 8 (27.6%	12.6 19.8	1.00 1.55 (0.41-5.86)	0.52
Male Female	11 37	5 (45.5%) 6 (16.2%)	41.9 11.5	1.00 0.18 (0.05-0.59)	0.005
Age ≤ 30 Age >30	10 38	1 (10.0%) 10 (26.3%)	7.2 19.8	1.00 3.33 (0.43-26.0)	0.25
Non-TB TB facility	12 36	0 11 (30.6%)	0 23.4	*p =0.04	---

Frequent contact is contact with TB patients ≥ twice per month
Rare contact is contact with TB patients < twice per month
*Fisher's exact two-sided p-value

Table 11: Risk for QuantiFERON-TB Gold In-tube assay (QFT) conversion among Georgian health care workers in univariate analysis.

Risk Factor	Number susceptible for TST conversion	QFT conversion no. (%)	QFT conversion rate/100 py	Univariate Rate ratio (95% CI)	p-value
Total	77	23 (29.9%)	22.8	---	---
Rare contact Frequent contact	35 42	10 (28.6%) 13 (30.9%)	23.1 22.5	1.00 0.74 (0.32-1.73)	0.45
Male Female	13 64	4 (30.8%) 19 (29.7%)	24.7 22.4	1.00 0.49 (0.16-1.55)	0.23
Age ≤30 Age >30	15 62	4 (26.7%) 19 (30.6%)	21.6 23.0	1.00 0.62 (0.20-1.9)	0.40
Non-TB TB facility	22 55	5 (22.7%) 18 (32.7%)	17.7 24.7	1.00 1.05 (0.38-2.90)	0.92

Frequent contact is contact with TB patients ≥ twice per month
Rare contact is contact with TB patients < twice per month

Table 12: Multivariate analysis for latent tuberculosis infection (LTBI) diagnostic test (QFT and TST) conversion

	QFT conversion (regardless of TST) (23/77)	TST conversion (regardless of QFT) (11/48)	Convert either test from TST-/QFT- (14/39)
	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Frequent vs rare contact with TB patients	1.09 (0.38-3.13)	4.29 (0.63-29.06)	5.61 (0.90-34.8)
Gender (F vs M)	0.67 (0.17-2.68)	0.05 (0.01-0.43)	0.07(0.01-0.63)
Age in years	1.07 (1.01-1.13)	1.05 (0.96-1.14)	1.08 (0.99-1.16)

Frequent contact is contact with TB patients ≥ twice per month
Rare contact is contact with TB patients < twice per month

Appendix 1:

$$Logit\ P\ (QFT\ or\ TST=positive) = \beta_0 + \beta_1 frequentcontact + \beta_2 age + \beta_3 bcg + \beta_4 gender + \beta_5 yearshealthcare + \beta_6 occupation1 + \beta_7 occupation2 + \beta_8 occupation3 + \beta_9 occupation4$$

where :
frequentcontact =1 is contact with TB patients ≥ twice per month
frequent contact=0 is contact with TB patients < twice per month
age=age in years (continuous variable)
BCG vaccine history: positive=1, negative=0
Gender: female=1, male=0
Years in healthcare (continuous variable in years)
Occupation:Administrative/technical staff (reference group)

- occupation1= medical student vs. administrative/technical staff
- occupation2= nurse vs. administrative/technical staff
- occupation3= physician vs. administrative/technical staff
- occupation4= other vs. administrative/technical staff