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Factors that Influence the Prevalence of Latent Tuberculosis Infection among Healthcare Workers in Thailand

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B.A., Lewis and Clark College
2012

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ABSTRACT

Factors that Influence the Prevalence of Latent Tuberculosis Infection among Healthcare Workers in Thailand

By Michelle Leisner

Background Healthcare workers (HCWs) are at a higher risk for latent tuberculosis infection than the general population. As individual-level personal protective equipment is regularly not available, environmental factors should be understood to determine mechanisms by which the facility can affect the prevalence of infection among healthcare workers. Therefore, it is important to understand both the individual- and facility-level factors that influence the prevalence of LTBI among HCWs. The present analysis aimed to determine the association between HCW characteristics and facility-level infection control measures and the prevalence of LTBI.

Methods Data were obtained from the "Enhanced Tuberculosis Infection Control Intervention (EnTIC Trial)." 3,835 HCWs from 10 facilities in Thailand were screened for LTBI. At the time of screening, demographic information was obtained on each participant. Facility level information on demographics and infection control measures were also obtained. Bivariate analysis was performed to determine the association of individual level factors with LTBI. Multivariate analysis was utilized, first to create a best-fit individual level model, and then to further evaluate the association between facility-level variables and LTBI. Bonferroni Corrections were utilized to account for multiple-testing. Results of the analysis were reported as prevalence ratios (PRs) accompanied by the corresponding 95% confidence intervals (CIs).

Results The prevalence of LTBI was highest among HCWs aged 40-45, where the prevalence for this age group was over 2 times the prevalence of LTBI among those aged 18-24 (PR=2.13; 95%CI=1.68, 2.70, $p<0.05$). Duration of exposure, as evaluated by years working in the facility, hours worked per week, and years working in the current occupation were all associated with LTBI in bivariate analysis. Multivariate analysis showed that age, having respiratory hygiene posters in units, working more hours, direct patient contact and position were statistically associated with LTBI at the alpha=.05 level of significance; however, only age was statistically significant when applying Bonferroni corrections. (PR=1.04, 95% CI 1.03, 1.05, $p<.001$)

Conclusion Age is significantly associated with the prevalence of LTBI among HCWs. Further research needs to be done on how environmental factors influence infection; the scope of an intervention that targets facility level change will have broad reach with intervention.

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Abbreviations

BCG: Bacillus Calmette–Guérin

CI: Confidence Interval (95% CI)

HIV: Human Immunodeficiency Virus

LMICs: Low- and Middle-Income Countries

LTBI: Latent Tuberculosis Infection

PR: Prevalence Ratio

SD: Standard Deviation

TB: Tuberculosis

BACKGROUND

Overview of Tuberculosis

Tuberculosis (TB) is a disease caused *Mycobacterium Tuberculosis*, a bacterium which commonly affects the lungs [1]. TB is spread person-to-person through airborne transmission, whereby droplets containing the bacteria are expelled from the body either through sneezing, coughing or spitting. TB exists in two forms: the active form and the latent form. The active form is symptomatic and is considered the disease form of the infection. The latent form, latent tuberculosis infection (LTBI), exists when a person has been infected with the bacteria, but does not have any symptoms [2]. Transmission can only occur when the infected person has the active form of the disease, not the latent form of the disease.

LTBI is the predecessor of the active form of TB. LTBI can progress into TB in circumstances where the body has lost its inability to combat the infection, usually through a weakening of the immune system. Weakening of the immune system can occur through aging or co-morbidity with another disease such as human immunodeficiency virus (HIV). It is estimated that 5-10% of people with latent TB infection (LTBI) will develop TB disease at some point in their lives; the risk for converting from LTBI to active TB disease is greatest within the first 2 years after becoming infected[3].

Tuberculosis as a Global Health Problem

In 2013, there were an estimated 9 million incident cases of TB disease globally, equating to 126 cases per 100,000 persons in a given population [4]. The high level of disease is concerning as disease is the necessary first step of transmission to uninfected

populations. An estimated 1.5 million deaths were attributed to active TB disease in 2013. This high level of mortality has consistently placed TB in the top 15 causes of global mortality [5].

Prevention of LTBI is possible through biological interventions. Bacillus Calmette–Guérin (BCG) is a live, attenuated vaccine that is highly utilized in areas where TB is endemic [6]. Efficacy of the vaccine is variable across studies, with a low of 0% and high of 80%, leading to an estimated average efficacy of 50%, with variation due to differences in geographical location and study-design [7, 8]. Efficacy, however, has been consistently shown to wane substantially beyond infancy and is therefore not considered protective in older children and adults [9, 10].

Prevention may also be possible at the environmental level. Environmental factors that influence risk of TB transmission range in type and efficacy. Simple interventions, such as opening windows in places where there are active TB cases to increase ventilation, providing the ill with masks and teaching persons with TB disease to follow good cough etiquette so that they do not sneeze or cough into their hands helps reduce the risk for transmission [11]. Other factors that may influence transmission patterns are related to inadequate cleaning and disinfection of medical equipment, improper procedures in handling specimens, recirculation of infected air, and many more. The efficacy of most environmental interventions are uncertain [3].

While limited research has been done on TB, in specific, literature has shown efficacy of environmental factors with other airborne pathogens which affect the respiratory system. Adequate ventilation has been shown to be an effective way of reducing transmission of other respiratory illnesses, such as influenza [12]. Other studies

have eluded to mechanisms of prevention, via modeling, and come to conclusions that using biocides on surfaces may influence transmission risk [13]. However, while few studies have determined which factors influence respiratory illness, even fewer have determined what factors influence the prevalence of LTBI.

Moreover, environmental factors are important to evaluate due to their ability to influence infection on a broader scale. Environmental factors may be an important mechanism of combatting LTBI, particularly in low resource settings, due to limitations in personalized infection control methods.

Latent Tuberculosis Infection Prevention

LTBI does not contribute to the global mortality rate as LTBI is the asymptomatic, non-transmissible form of the infection. However, this fact does not make LTBI any less important, as it is a necessary predecessor to the disease. In order to effectively change the mortality rate due to TB, objectives for interventions should include appropriate treatment of the disease, preventing transmission, and preventing LTBI progression to disease, all of which are centered on targeting LTBI for intervention [14].

Prophylaxis can be utilized to decrease risk of conversion to TB disease but is not a guaranteed cure. Prophylaxis for LTBI ranges from 3-9 months, depending on drug type or combination of drug types [15]. This, also, regularly can lead to non-compliance in treatment, which can negatively affect how well the drugs inhibit the bacterial growth. A study among HCWs in Saudi Arabia showed that non-compliance was as high as 83% [16].

If LTBI progresses to TB disease, treatment is also available at this stage. However, again, life-long treatment and maintenance of health is not guaranteed. Treatment for the disease lasts between 6-9 months, and with such a long duration, non-compliance occurs regularly. Non-compliance can lead to patients re-establishing symptoms as well as acquiring drug resistant bacteria [17].However, even in populations that complete treatment, and are considered to have successfully recovered, relapse is still possible which can ultimately lead to death. A study in northern Vietnam indicated that 15% of the patients who had been successfully treated for TB had relapsed or died [18]. Fully treated TB, therefore, still poses substantial risk for morbidity and mortality [19].

With the understanding that prophylaxis for LTBI or treatment for LTBI is not a guaranteed lifelong solution and as a result, mortality is bound to happen, focus should be placed on prevention of LTBI. In order to most effectively prevent infection, it is quintessential to determine risk factors associated with acquisition of LTBI.

Risk Factors for LTBI and Subsequent TB Disease

There are certain populations that are at a higher risk for contracting LTBI than others. According to WHO, persons who fall into the following categories are at highest risk for LTBI: those with HIV infection, contact with infectious person, initiation of an anti-tumor necrosis factor treatment, receiving dialysis, receiving an organ or hematologic transplant, silicosis, or those who are in prison, an immigrant, homeless or an illicit drug user [20]. These populations are at a higher risk due to either close confines with potentially infectious persons or lowered immunity due to comorbidity.

Moreover, there are certain populations that are at a higher risk for conversion from LTBI to TB. The 5-10% of LTBI cases, to whom this occurs, have delineated risk

factors that place these populations at a higher risk for the disease and therefore mortality, than other populations who do not possess these characteristics.

Limited immunity has been proven as a significant risk factor for the development of disease. HIV, which targets the immune system, leads to an inability for the body to combat other illnesses. For this reason, it is estimated that persons who are co-infected with HIV have a risk between 26 and 31 times greater for the development of tuberculosis compared to populations without HIV infection [21]. This increased risk led to an estimated 1.1 million cases of TB existing among people co-infected with HIV, out of the 9 million cases of TB that occurred in 2013 ([21].

Children under 5 years of age also have immature immune systems and are also at a higher risk of developing TB disease if they have been infected [3]. The World Health Organization, the International Union against Tuberculosis and Lung Disease and the International Standards for Tuberculosis Care all recommend the screening of children under 5 for TB disease, given their susceptibility to disease and mortality [22].

Lack of immunity can also occur as a result of immunosuppressive drugs that are provided to treat medical conditions. Patients with Crohn's Disease, Arthritis and several other diseases utilize TNF- α blockers in treatment; these immunosuppresive drugs have been reported to put populations with these illnesses at a higher risk [23]. Other clinical conditions that increase risk for conversion from LTBI to TB disease include scoliosis, diabetes mellitus, chronic renal failure, cancer, and solid organ tranplantation [24]. Malnutrition, as associated with lack of immunity, can also be a risk factor for progression to TB disease [25].

Therefore, the mechanisms in prevention of mortality due to TB are complex. Prevention can occur either before infection or before development of disease, but are offset by a variety of risk factors at both of these stages. Prophylaxis or treatment, as well, can be utilized when a patient has LTBI or TB, but, again, recovery is not guaranteed and relapse may still occur. Taking this into consideration, the only true mechanism of preventing mortality is to prevent the infection from occurring in the first place. Interventions should emphasize preventative over reactive interventions, specifically targeting those at the highest risk.

Healthcare Workers as a High Risk Population

Healthcare Works (HCWs) are of particular interest due to their high exposure to cases within the healthcare setting. Many studies have shown that the incidence of TB cases among healthcare workers is higher than in the general population, irrelevant of overall country burden. The relative risk, however, is reflected in the burden of the country, type of institution, and resources of the country and institution; that variability can be shown through a study Turkey, which indicated a 3-fold risk for HCWs in comparison to the general population, while a study in Malawi indicated a 40-fold relative risk in comparison to the general population [26, 27] Furthermore, studies have shown that this risk is due to exposure in the healthcare setting. [28]

Duration of exposure to cases, as usually defined by duration of time working within the facility, has been shown to be associated with higher risk of TB [29]. More so, direct patient contact places HCWs at a higher risk, due the methods by which TB is transmitted. Logically, the closer a person is to the case, the more frequent the person would experience exposure to the bacterium, cumulating in a higher risk for infection.

Individual Risk Factors in HCWs for Latent Tuberculosis Infection

Since initial infection is a requisite precursor to active TB disease, it is important to identify factors associated with risk for infection. Working within a healthcare facility proves to be a substantial risk. Longer employment has been shown to be associated with LTBI, as longer employment would imply longer duration of exposure to infectious agents[30]. Because of this, there is also differential risk across occupational type [31]. History of contact with TB patients and duration of contact with these patients has also associated with higher risk of LTBI infection. [32]. Lastly, a childhood history of BCG vaccination does not protect many adult populations from infection, so while HCWs may have been vaccinated as children, they are still at risk for LTBI infection [33].

Other Risk Factors for Tuberculosis; Facilities and other Environmental Factors

In order to successfully reduce disease burden and transmission, it's essential to look not only at individual characteristics and behaviors of these high-risk populations, but at the environment that surrounds these populations. A highly regarded TB elimination program should encompass multi-level controls: at the administrative level, environmental level and individual level [34]. Many studies have shown that there are various types of interventions that reduce transmission in high resource settings, however few studies have shown what type of interventions could be used in a low-income setting and the effect of these interventions.

Testing for LTBI Infection

There are two commonly utilized types of tests to determine LTBI status: the Tuberculin Skin Test and the Interferon-Gamma Release Assay[3]. The tuberculin skin test utilizes personal immunological response to determine if a person has been infected.

The skin test works via an intradermal injection with a purified tuberculin protein that stimulates an immune response in those that have previously infected or vaccinated. A positive test result is indicated by the size of the inflammatory bubble that arises on the area of injection.

An Interferon-Gamma Release Assay (IGRA) is a test that is performed on whole blood of a given individual. Blood is collected from the patient, and then is processed to determine if there is an immune response that occurs within the blood after exposure to TB proteins [35]. The immune response that occurs is the release of interferon-gamma from immune cells as a response to the presence of TB proteins. These tests are able to differentiate between actual infection and vaccination, which makes them beneficial in societies where BCG vaccine is common.

Tuberculosis as an Issue in Low and Middle Income Countries

Low- and Middle-Income Countries (LMICs) account for 90% of the global burden of tuberculosis [36]. Thailand is an LMICs [37] ranked by the World Health Organization as among the top 22 countries with the highest global burden of TB [4]. LMICs have less access to infection control measures, which makes it difficult to combat the high burden of disease. Measures that may be used to control nosocomial transmission in high-resource settings, such as negative pressure rooms, respirators and infection control procedures, are often not affordable in LMICs [27]. Furthermore, lack of overall healthcare structure has influence the prevalence of TB in LMICs. High levels of TB in LMICs have been attributed to abandonment of vaccination campaigns coupled with poor efficacy of vaccines currently in use. Compounding the issue of vaccination is the lack of efficacy of BCG vaccination in a childhood-vaccinated adult population. [38]

The overall healthcare structure, attributed partially to lack of resources, therefore, culminates in a higher risk of TB transmission and higher overall prevalence.

Thailand as an Example of Where to Begin

With a prevalence of 1.49 cases per 1,000 persons, Thailand is listed on the World Health Organization's 22 Countries with a high burden of Tuberculosis [4]. Listed on the World Bank as a middle-income country [39], Thailand presents an opportunity whereby we can begin to strategize how to effect change in a country that is high-burden but has limited resources to do so. With developing countries attributing approximately 7% of all deaths to TB, and given that the highest risk occurs among healthcare works in a setting where protection is limited, learning about influencing risk factors is key (42). The findings may help guide interventions and policies in Thailand and may also help inform other LMICs.

Objectives

This study aims to determine the individual- and health facility-, or environmental-, level factors associated with LTBI prevalence among HCWs in general provincial or district level healthcare facilities in Thailand.

METHODS

Data Sources

The present study utilized data collected as part of the baseline data collection for a study entitled, "Enhanced Tuberculosis Infection Control Intervention (EnTIC Trial)." The EnTIC Trial aims to examine the impact and cost-effectiveness of an enhanced

infection control package on TB transmission in hospitals and clinics, as measured by the rate of new TB infections among healthcare workers (HCWs). The EnTIC Trial is a randomized cluster study being conducted in healthcare facilities in Vietnam and Thailand; the hospital is the unit of randomization. The current analysis used data obtained from facilities and healthcare workers during the baseline assessment prior to randomization and implementation of the intervention. The present analysis is restricted to data obtained from Thailand.

Health Facilities

Health Facility Eligibility

Health facilities providing inpatient or outpatient care for patients with confirmed or suspected TB were considered for inclusion in the EnTIC Trial. Eligibility criteria included general or provincial hospitals having over 300 beds as a general hospital facility or over 100 beds as a tuberculosis or respiratory hospital, a geographic location within 16 hours proximity of a laboratory, and agreement from the hospital director to commit staff time to participation in the study. Specialty hospitals (e.g., pediatric, infectious disease, maternity) and facilities that had participated in an infection control initiative within the past 3 years were not eligible for inclusion.

Health Facility Recruitment and Selection

To recruit health facilities, study staff made presentations to health facility leaders at a number of venues, including the national Stop TB Partnership meeting, national disease control meetings, and local scientific conferences. Interested parties then contacted the study staff for further information. In addition, investigators and study staff directly contacted hospitals potentially meeting study inclusion criteria. Upon receiving a

note of interest from the facility, the study staff conducted an assessment of the facility to determine eligibility based on the criteria specified above.

A total of ten healthcare facilities in Thailand were enrolled in the EnTIC Trial. The hospital director of each of these ten facilities completed written informed consent prior to the start of the study.

Health Facility Data Collection Procedures

Facility Assessment

A self-administered questionnaire was distributed to an executive healthcare facility employee at each participating facility to obtain information on the health facility characteristics. (Table II) The questionnaire included items on the year the facility was built, number of beds, number of staff by occupation (nurses, physicians), number of admissions and outpatient visits, and number of patients with TB in 2011 and 2012. Information was also obtained on the number of HCWs that had been diagnosed with TB, availability of TB treatment for HCWs, and whether or not records were kept documenting TB disease among HCWs. A facility-level assessment was completed for every health facility enrolled in the study.

Outpatient and Inpatient Infection Control Checklist

In order to determine if infection control practices were being followed at the facility, a designated healthcare employee conducted an assessment using a checklist designed specifically for the EnTIC study; separate checklists were developed for outpatient and inpatient units. Several checklists were completed for each facility, and varied depending on the number of wards or sections that included screening or treatment for persons with suspected or confirmed TB disease. The outpatient checklist was

completed 43 outpatient departments across the 10 healthcare facilities, and included questions pertaining to availability of personal protective equipment for staff and patients, and environmental factors including whether windows were kept open and the availability and use of negative pressure rooms. The inpatient checklist was completed for 132 units across the 10 facilities and included questions relating to airflow of rooms and use of personal protective equipment. The questionnaires were filled out by the designated point-person at each facility; these were generally nurses or physicians. The checklists varied slightly between inpatient and outpatient facilities: however, there were several items that were common to all facilities. The questions that were listed on the two individual checklists were joined for the present analysis. The variables similar to both checklists included items about the availability of soap, alcohol-based hand rubs, examination gloves, masks, respirators, and whether there were respiratory hygiene posters clearly posted outside rooms of patients with suspected or confirmed TB.

Healthcare Workers

Healthcare Worker Eligibility

For this study, a healthcare worker was defined as any person who, paid or unpaid, works in a healthcare facility and is at risk for exposure to infectious agents or materials, patients, contaminated air, or infectious fluids. Medical students, nursing students, pharmacy students and interns who spent >80% of their time outside the classroom were also considered as HCWs for this study. All HCWs at participating facilities between 18 and 45 years of age that worked at least 30 hours per week and who were expected to be working at the participating healthcare facility for at least two consecutive screening rounds (0 and 12 or 12 and 24 months following the baseline assessment) were eligible

for study participation. HCWs that reported a coagulation disorder that could place the participant at higher risk of excessive bleeding during the phlebotomy were excluded to minimize risk.

Healthcare Worker Enrollment Procedures and Analytical Study Population

The designated hospital executive at each facility provided a roster of all HCWs potentially eligible for study participation. A total of 6,847 HCWs from the 10 selected health facilities in Thailand were invited to participate in this study (Figure 1). Of these invited participants, 3,996 (56.4%) presented to recruitment sites. Twelve HCWs were ineligible for the study due to being older than 45 years of age, working less than 30 hours per week, or because they were not planning to continue working at the facility for the next 12 months; 7 additional HCWs refused to participate. A total of 3,977 healthcare workers provided written, informed consent and were enrolled and completed a baseline data collection procedures. Of those enrolled in the study, 137 participants had a previous TB diagnosis, and therefore were not at risk for latent TB infection (LTBI). Five (5) participants had an indeterminate LTBI test result, and therefore were also not included in the analytical sample. The analytical sample, therefore, included a total population of 3,835 HCWs.

Healthcare Worker Data Collection Procedures

All HCWs enrolled in the study were asked to complete a sociodemographic and clinical survey and provide a blood sample for laboratory testing for LTBI. Each participant enrolled had the option to refuse to participate or complete any component of

the study; however all enrolled participants gave a blood sample and filled out the healthcare worker demographic survey.

Sociodemographic and Clinical Survey

All HCW participants were asked to complete a self-administered survey on sociodemographic and clinical information while waiting to undergo screening for LTBI. Results were entered directly by participants into an electronic tablet. The survey included basic demographic information including age, gender, weight and height, and employment history; and information on behaviors and comorbidities that may influence risk for TB infection. Participants were also asked about TB symptoms.

Screening for LTBI

All HCWs enrolled were screened for LTBI with the QuantiFERON®-TB Gold In-Tube assay (IGRA), which utilizes whole blood to test for markers indicative of tuberculosis infection. The assay works by stimulating immune cells, in vitro, from the blood to release interferon-gamma which is then quantified via an enzyme-linked immunoassay (ELISA) [35]. The levels at which the cells release interferon-gamma is indicative of whether or not infection had previously occurred. This assay has a specificity of 98.8% and a sensitivity of 92.6%, indicating that 98.8% of false positives for LTBI are identified as such and 92.6% of true positives for LTBI are identified as LTBI [40]. This assay was utilized in order to reduce false positives due to vaccination with the Bacillus Calmette–Guérin (BCG) vaccination, which is routinely given during infancy in Thailand. The QuantiFERON®-TB Gold In-Tube assay, in contrast to tuberculin skin testing (TST) for LTBI, has no cross-reactivity with the BCG vaccine.

Furthermore, this assay only requires a single visit, so in a larger cohort study such as this one, testing every HCW with IGRA is more feasible than the 2-visit TST.

The IGRA type test cannot, however, differentiate between LTBI and TB disease. [41] However, enrollees were screened for TB symptoms at the time of the blood screening for LTBI. Those with symptoms indicative of TB disease were sent for further evaluation. At the time of this analysis, no HCWs have presented with active TB disease within the first 6 months of follow-up following the baseline evaluation. Therefore, for this analysis, a positive test indicates infection with LTBI and not TB disease.

Blood Collection for IGRA

Written informed consent for the blood draw and testing were obtained at the time of screening. Trained phlebotomists collected 4-5ml of blood on-site. After collection, the blood sample was incubated per manufacturer guidelines and then sent to the Mycobacteriology Laboratory of Thailand, National Institutes of Health in Nonthaburi reference laboratory for analysis. The study staff was responsible for the labeling, packing and shipping of blood samples to the reference laboratory.

IGRA Laboratory Testing

All samples were processed within 16 hours of blood draw as required by this test in order to provide valid and accurate results. The test result of positive, negative or indeterminate was obtained and sent directly to the study staff. All HCWs received the results of their IGRA from the healthcare facility IC focal point person in a sealed envelope to ensure privacy. All HCWs who received a positive test were sent immediately for further screening for TB disease. Participants with indeterminate results were given the opportunity to be rescreened two weeks after the original test. All HCWs

with initial negative LTBI tests will also be rescreened one year after the initial examination.

All HCWs with an initial positive LTBI test who were not diagnosed with TB disease will be re-evaluated at 12 and 24 months following the baseline LTBI test to determine symptoms of TB disease. If at this time, symptoms are consistent with the presence of active TB disease, HCWs will be referred for further diagnostic evaluation as well as HIV counseling and testing.

Data Management

Database

All data collected from the HCW surveys was entered directly into tablets by the HCWs. The survey, electronic and self-administered via tablet, had built-in validation checks for some variables, such as value limits for specific questions (e.g. day of the month only having a range from 1-31). The information on facility level demographics and the inpatient and outpatient checklists were completed as paper surveys; staff at CDC-Thailand single-entered the data into a designated study database. The database was housed at the CDC-Thailand office and was backed up every evening. Data management staff created and followed study-specific standard operating procedures specific to data verification and cleaning for this study to ensure a high level of data quality.

General Data Cleaning Steps

Definitions and Recoding

Primary Outcome

The outcome of interest for this analysis was LTBI. LTBI was defined via the QuantiFERON®-TB Gold In-Tube assay. All values were coded as positive, negative or

indeterminate as reported by the laboratory. HCWs with indeterminate results were not included in this analysis.

Exposures/Potential Risk Factors of Interest and Potential Confounders

For this analysis, all variables were assessed as potential exposure variables to determine associations with LTBI, the outcome of interest. All variables were also treated as potential confounding variables. This dual assessment of each variable was accomplished through building a logistic regression model, described in more detail below. These variables were: age, gender, body mass index (BMI), occupational position within the hospital, variables related to time spent in the facility, with a weekly assessment and a cumulative assessment both considered, as well as contact with TB patients outside of the healthcare facility. A previous diagnosis of diabetes, smoking status of the individual HCW, and exposure to smoking by a family member who resides in the same household as well as smoking in the workplace were also included. Furthermore, all variables were considered as potential confounding variables. Interaction was evaluated between age and number of hours working in a healthcare facility per week, occupation at the healthcare facility, number of years working at the facility, number of years working in the given occupation and known contact with TB positive people in the community. Many studies indicate the importance of age and duration of exposure at risk factors, yet few have evaluated their cumulative effect[29, 42]. As age is highly associated with risk of LTBI and duration of exposure leads to a higher risk of infection, there is biological plausibility that duration and age interact to create a higher level of prevalence among older populations who work longer hours.

Cleaning and Recoding: Healthcare Worker Individual Data

All datasets were analyzed during this analysis for invalid values. Variable values were identified as valid either via a given data dictionary that included possible ranges for variables or based on validity as indicated by the study protocol. The only variables that had invalid responses were the number of hours working at a particular facility and the number of hours working at all facilities per week. All values that indicated working more than 80 hours were changed to 80 hours. For the variable indicating number of hours working at the facility, 263 values were changed to 80 hours. If values were present in the database that were invalid for the established range or defined categories, they were recoded as missing.

For summary purposes, some continuous variables were placed into subgroups for the descriptive statistics and bivariate analysis, but were then left as continuous variables for modeling. All participants were between the ages of 18 and 45: age subgroups were created for participants from 18 to 24, 25 to 29, 30 to 34, 35 to 39 and 40 to 45.

Body mass index (BMI) was calculated from collected variables of height and weight, where height was measured in centimeters and weight was measured in kilograms. Height was then converted into meters and BMI was calculated as kilograms per meters squared ($BMI=kg/m^2$). Subgroups for BMI were then created to indicate underweight (BMI less than 18.5), normal weight (BMI between 18.5 and 24.9), overweight (BMI between 25 and 29.9 or obese (BMI greater than 30) [43].

The variable regarding participant's current occupation at the hospital was categorized into subgroups based on profession and the likely level of exposure to TB patients. Nurses and nurses aids were placed in a "nurses" subgroup; physicians only in the "physicians" subgroup; technicians, orderlies, housekeepers, and phlebotomists were

placed in a “clinical health” subgroup; dental occupations, clerks, dietitians, pharmacy personnel, occupational therapists, social workers, and administrative staff were placed in an “administrative” subgroup; and all others were placed in an “other ” subgroup due either to lack of specified job title or unknown exposure level.

For other continuous variables, subgroups were created based on literature, quartiles, or a combination of both of these classifications. The variables indicating the number of hours worked in the current facility, number of hours worked at all facilities, how long a HCW has worked in current position were all placed in categories based on quartiles, rounding to the nearest whole number. However, variables such as number of years worked in the facility were placed into categories based on both quartiles and literature, given that cases of tuberculosis occur more frequently within the first two years of work, but with less specific time intervals of transmission patterns afterwards [2]. Therefore a subgroup was created for under two years of work within the facility, and for all people above two years, quartile subgroups were used.

Clinical and social variables with responses indicating “Don’t Know/Do Not Prefer to Answer” were placed in the “No” or “Not at All” category, depending on the variable. Responses to questions that asked participants to indicate if they had a previous exposure or comorbidity were originally coded as “Yes”, “No” or “Don’t Know”; due to a large number of “Don’t Know” responses, these questions were recoded to reflect a known exposure. For instance, the question about recent tuberculosis exposure was recoded to reflect “Yes” and “No” to indicate known tuberculosis exposure. This was due to the assumption that those who place themselves within a “Don’t Know” category were unlikely to have had exposure to that variable.

Cleaning and Recoding: Facility Level Data

For facility demographics, each variable was checked for invalid values against an study-specific existing list of potential values. No values were recoded as all values were within specified range.

The Infection Control Assessment was also checked for invalid values. No values were changed as all of the variables were coded with either of the binary options. The information on the Infection Control Assessment was summarized for each health facility to reflect the proportion of checklists with an affirmative answer for a given indicator (e.g., proportion with soap available at all sinks).

Statistical Analysis

All statistical analyses were performed using SAS 9.4 (Cary, NC). Statistical significance was set at alpha=0.05 value for initial analysis. For significance, due to multiple testing, a Bonferroni Correction was applied to reduce the level of significance to a standardized value, decreasing the probability of a type I error. Due to 36 variables initially evaluated for this analysis, the statistical significance level was set at 0.0014, the equivalent of the 0.05 statistical significance level divided by 36.

Descriptives

Descriptive statistics were performed to describe the analytical sample. Frequency procedures were used to determine the proportion of the analytical sample that was defined by a certain characteristic. In reporting information, the number of participants in a given category as well as the percentage of the population that this category represents was determined.

Bivariate

Bivariate analyses were initially performed to assess the association between individual level characteristics and the presence of LTBI.

Prevalence ratios (PRs) and 95% confidence intervals (CIs) were calculated using the GENMOD procedure to determine the magnitude of the association between a given category and LTBI, compared to the reference group. The significance of this ratio was determined after a Bonferroni correction to adjust for multiple comparisons.

Models

Model Selection and Regression Analysis

Model selection and regression analysis was performed via methods that assess for interaction, confounding, collinearity and to create a best fit model [44]. Exposure variables that were originally coded as continuous variables were left as such for the modeling procedures.

Modeling Analysis

I. Modeling Analysis, Overview

All individual-level variables that were shown to be associated with LTBI on bivariate or correlation analyses were considered for the multivariate model. All individual level variables that remained independently significant at an alpha value of 0.05 were left in the model to create a final individual-level model; a few additional variables were also retained in the models if previous studies had consistently reported them as important risk factors for LTBI. Each facility level variable was then tested independently with the best-fit individual level model, accounting for clustering at the facility level via fixed effects. All facility level variables that were significant were left in

the model. The final model including associated individual and facility level factors was reported.

II. Modeling Analysis, Individual Level Factors

Exposure variables at the individual level considered for the multivariate models were informed either by bivariate significance or correlational significance with the outcome of LTBI. Each variable was evaluated by determination of correlation of that model with LTBI. Correlation was considered sufficient for model inclusion when the Rho value was above 0.15 and the variables were below an alpha of 0.05 (46). These variables were then cross-referenced with the results of the bivariate analysis to ensure that all potential exposure variables would be considered. The variables that were correlated with the outcome of interested were then tested individually in a model that included other variables, which included, age, sex, and type of position at the hospital. All variables were left in the model if statistically significant or if previous literature has consistently shown associations with LTBI, regardless of significance: age, gender and occupational position. Regression analysis was then performed on these variables to determine if variation inflation factors indicated any level of collinearity. If the variables were then determined to be significant, non-collinear variables, they were placed in a model to determine their independent association with LTBI. Further confirmation of non-collinearity was performed later in the modeling steps.

To adjust for multiple testing and confirm results of the Bonferroni correction method, F-tests were performed on a group of variables. The groups of variables were tested in a model that included age and sex and were compared to a reduced model that included only age and sex. If the F-Value was not significant, indicating that the reduced

model that included only age and sex was the better-fit model, all the variables were dropped from analysis for the individual level factors. If a group of variables were significant, the individual variable of significance was determined via partial F-tests. This variable was included as a potential variable in the multivariate analysis.

II.i. Testing Collinearity

Collinearity was assessed to determine relationships between variables. Collinearity was tested by looking at Condition Indices. A condition index above 30 could indicate collinearity [44]. Variables were removed if otherwise insignificant, combined to create a new variable, or dropped if equally predicted the same outcome.

II.ii. Testing Interaction

In order to determine if interaction was present, a Likelihood Ratio Test was performed on variables that were not considered to be collinear. Interaction was evaluated for the relationship between age and several variables: occupational position, number of years having worked in the given occupation, number of years having worked in the facility, number of hours working in the facility per week, and known contact with persons infected with tuberculosis in the community. These interaction terms were placed in the model along with the individual factors that were used to create their interaction terms.

All interaction terms were tested together at an alpha=0.05 significance level. This procedure was done through a “chunk test” which removes all interaction terms and compares this reduced model to the full model. If the p-value was significant, backwards elimination was to be used to determine which interaction variables should remain in the

model. If the p-value was not significant, all interaction terms were dropped from the model. Further analysis would take place utilizing this new reduced model.

III. Modeling Analysis for Facility Level Risk Factors

Facility level variables were evaluated via alternate methods, due to these individual level procedures not taking fixed effects and clustering into account. The facility level variables were evaluated independently after creation of an individual factor model was finalized.

To determine if facility level risk factors were associated with HCW prevalence of LTBI, the facility proportion of each indicator from the inpatient and outpatient checklist was applied to every HCW who worked in that given facility. Multilevel modeling using GLIMMIX in SAS was used to evaluate the association of facility level factors on LTBI; these models account for clustering across all HCWs within a facility and were specified with fixed effects. Each facility-level factor was added independently to the final multivariate model using individual-level factors (as determined from the steps outlined above).

RESULTS

I. General Descriptive Statistics, Healthcare Worker Demographics

The mean age of participants in the study was 33.6 (standard deviation (SD) 6.3), with 90% of the population aged between 25 and 44 years. Females represented 82% of the study population. (Table II) Almost one-third (29%) of the study population was classified as either overweight or obese based on body mass index (BMI); only 8% were considered underweight.

Nurses and nurses' aids represented the largest proportion of the study population (34%). An additional 35% did not specify their occupation. Most participants had been working at the facility for several years, with only 13% having worked under 2 years within the facility and 61% having worked 6 or more years at the facility. Half (50%) of the population reported working more than 50 hours at all jobs, with 44% reporting more than 50 hours at the current facility. Consistency in the occupational location was also common: only one quarter (25%) of HCWs reported working in a different department within the last year, and only 11% reported they had worked in another facility in the past year.

Fifteen percent of HCWs said they had known contact with members of the community that were positive for TB disease. In terms of symptoms that could reflect TB disease, 25% reported a cough, 12% said they had experienced fever, and only 1reported experiencing night sweats in the previous 2 weeks. However, of those that reported a cough (n=952), only 6% (n=54) reported having a cough that lasted more than three weeks. Diabetes was uncommon in this population (3%).

Most participants reported that they did not currently smoke (94%); however 26% reported sharing a household with a person who smokes daily and 47% reported that another person had smoked indoors in their work area in the last 30 days.

II. *General Descriptive Statistics, Facility Demographics*

All 10 facilities were built between 1935 and 1956, on average being 63.7 years old (SD=6.0) (Table IIII). Each facility had approximately 432 beds (SD=97) and most (n=7; 70%) were teaching facilities.

All facilities enrolled in the study provide inpatient and outpatient care, surgeries, pediatric care, and dialysis (data not shown). All facilities have a ward or unit specifically for suspected or confirmed TB cases. All facilities had an established infection control committee, an infection control focal person, and conducted annual infection control training for HCWs. However, only 6 of the 10 facilities had a written tuberculosis infection control plan. All facilities reported providing respirators to all personnel working on a TB ward; however, none of the facilities provided fit-testing for staff before providing them with a respirator.

The total number of HCWs varied by hospital; the average number of HCWs per facility was 1151 HCWs (SD=260). The proportion of staff at each facility represented by nurses, nurses aids and physicians ranged from 34% to 41%, with a facility average of 29% (SD=4.2) of HCWs in these occupations. On average, each facility had 360 (SD=57) nurses, 37 (SD=16) nurses' aides, and 48 (SD=22) physicians.

All HCWs are annually screened for TB and TB treatment for HCWs is available on site. Eight of 10 facilities reported previous active TB among their HCWs. In 2011, there were an average of 3.1 (SD=3.1) HCWs who developed active TB per facility, and in 2012, there were an average 2.4 cases (SD=1.9) per facility. One facility did not report any information for 2011.

The number of outpatient visits and inpatient admissions varied across facilities. The average daily census in each facility (total number of inpatients plus number of outpatient visits in a given day) had a range of 231 to 550 with a mean of 372 (SD=115). Annually, facilities had a mean overall admission of 28,634 admissions (SD=12,932) in 2012. Of these annual admissions, approximately 206 (SD=121) of them were due to

tuberculosis (average 0.8%, SD 0.4% of all admissions). Annually, outpatient departments saw on average 314,095 patients in 2012 (SD=91,580), with a range between 111,390 and 424,353 patients. Of these patients, an average of 955 (SD=911) of them were seen in the outpatient department for tuberculosis (average 0.4%, SD=0.4 % of all outpatients). The average total number of TB patients managed at the health facilities was 2021 (SD 1343) in 2011 and 1855 (SD 1347) in 2012.

II.i. Facility Safety Measures, Infection Control Assessment

Six facility level variables were evaluated to determine their effect on prevalence of LTBI among HCWs in a given facility. (Table IV) Alcohol-based hand rubs were common in all facilities, with a minimum of 80% of all surveyed units in a given facility providing alcohol-based hand rubs and four facilities providing alcohol-based hand rubs in 100% of their surveyed units. A similar pattern was seen with examination gloves, where two facilities had 100% of surveyed units with easily accessible examination gloves, and one facility providing the minimum of 78% of surveyed units providing easily accessed examination gloves. Masks were also commonly provided on all units, with nine facilities providing masks in every unit, and only one facility providing masks in 92% of surveyed units. Most facilities provided some respirators to their staff, with respirators being, at minimum, available within 62% of surveyed units and a maximum of 91% of units. The availability of soap was variable among facilities with one facility providing soap at 11% at all surveyed units and only two facilities providing soap at 100% of surveyed sinks. Respiratory hygiene posters were also uncommon, with three facilities having no respiratory hygiene posters in any surveyed units, and one facility having the maximum of 60% of surveyed units with hygiene posters. Nine out of the ten

facilities in this study had a maximum of 33% of surveyed units displaying respiratory hygiene posters.

III. Bivariate Analysis

Personal Demographics

Bivariate analysis was conducted to evaluate the association between individual demographic and clinical variables and the presence of LTBI. Age was a significantly associated with LTBI, with the prevalence for LTBI increasing with age. The prevalence of LTBI was highest among HCWs aged 40-45, where prevalence among this age group was over 2 times the prevalence of those aged 18-24 (PR=2.13; 95%CI=1.68, 2.70, $p<0.05$). All age groups showed a significantly higher prevalence for LTBI compared to those aged 18-24, except for the 25-29 age group. There was no significant difference in LTBI prevalence by gender (p=0.63). HCWs that were overweight or obese had a higher prevalence of LTBI compared to HCWs who were underweight [PR=1.28 (95%CI=1.02, 1.61, p=.04) and PR=1.31 (95%CI=1.01, 1.70, p=0.04), respectively].

Occupational Demographics

Nurses had the highest level of prevalence of LTBI (PR=1.42, 95%CI=1.21, 1.66, $p<0.001$) while other clinical health workers also had a significantly elevated risk (PR=1.25, 95%CI=1.02, 1.53, p=0.03) compared to HCWs working in administrative positions. There was no significant difference between the prevalence of LTBI in physicians or HCWs that did not specify their and HCWs in administrative positions.

The number of years working in a given hospital department, a given occupational position and in the current facility were each statistically significantly associated with prevalence of LTBI. HCWs who had worked 6 or more years in the

current department of work were more likely to have LTBI than HCWs who had worked there for 2 years or less (6 – less than 12 years, PR=1.33, 95%CI 1.12-1.59, p=0.0015; ≥12 years, PR=1.49, 95% CI 1.25, 1.77, p<0.001). HCWs working more than 3 years in their current occupation were at a higher risk than those who had worked less than 3 years in their occupation (3 – less than 9 years, PR=1.24, 95% CI 1.04, 1.47, p=.0167; 9 – less 15 years, PR=1.48, 95% CI 1.24, 1.76, p<0.001, >15 years, PR=1.84, 95% CI 1.56, 2.17, p<0.001) HCWs who had worked more than 10 years in the current facility were more likely to have LTBI than those who had worked there less than 1 year (PR=1.62; 95% CI 1.31, 2.03, p=<0.0001); however, HCWs who had worked in the current facility between 1 and 10 years showed no significant difference in LTBI prevalence than HCWs that had worked there less than 1 year.

HCWs that reported working more than 65 hours per week at the current facility or at all facilities were significantly more likely to have LTBI than HCWs who reported working 40 hours or less per week (current facility, PR=1.20, 95%CI 1.03, 1.40, p=.0175 ; all facilities, PR=1.17, 95% CI 1.01, 1.36, p=.0364)

Comorbidities and Increased Risk

Smoking status of the individual, and reported smoking of a family member or within the healthcare facility were not significantly associated with LTBI. Furthermore, known contact with a person in the community who was TB positive also did not place HCWs at a statistically significant higher prevalence of LTBI (PR =1.07, 95% CI .94, 1.23, p=0.296). HCWs with diabetes had a significantly higher prevalence of LTBI than HCWs without a known diabetes diagnosis (PR=1.42, 95% CI 1.11, 1.82, p=0.005).

IV. Model Selection and Regression Analysis

Using correlation to determine association, the following variables either had a Rho value above 0.15 or were statistically significantly associated (alpha=0.05) with the outcome: age, sex, BMI, occupational position at the facility, whether or not they had direct contact with patients, in which unit the HCW works within the facility, and average total hours worked each week in all facilities. These variables were cross-referenced with bivariate analysis to determine if there were other possible associations. These variables were then evaluated for significance in a model that included age, sex, and occupational position at the facility. Variance inflation factors were also considered, whereby none of the variables indicated collinearity. In a model with sex, age, and position, direct patient contact was significant (p=0.01) and average total number of hours worked each week in all facilities was significant (p=0.01). All significant variables were placed in a model, to determine overall significant when controlling for other factors. Age was significant (p=<0.0001), occupational position was significant (p=0.03), direct patient contact was significant (p=.0121) and total number of hours worked at all facilities was significant (p=0.03). Sex was not significant (p=0.50) but was kept in the model.

Evaluation of each facility level variable showed that only one variable was significant; the presence of respiratory hygiene posters outside patient rooms was the only facility level variable significant in this model (p=0.01).

Therefore, the model chosen was:

$$\textbf{Result (LTBI)} = \alpha + \beta_1 \textbf{Position\_Class} + \beta_2 \textbf{Sex} + \beta_3 \textbf{Age} + \beta_4 \textbf{WorkHour} + \beta_5 \textbf{Direct2Patient} + B_{i6} \textbf{Hygiene\_Poster}$$

where:

- α is the intercept of this model, indicating risk of LTBI when all of these

variables are 0

- “i" is the random effect term that allows for Hygiene_Poster to be analyzed at the facility level as a random effect for multi-level analysis
- Position_Class is the variable for occupational position at the facility categorized into 5 subgroups: nurses, physicians, other (clinical health), other (administration), and all others
- Sex is a dichotomous variable with female and male levels
- Work Hour is a continuous variable that indicates the average total number of hours worked per week at all facilities
- TB_Poster is a variable that indicates the proportion of surveyed units that had respiratory hygiene posters posted outside of patient rooms

With this model, all variables were significant at the alpha=0.05 level of significance except for sex (p=0.54). Sex was kept in the model due to literature indicating that this variable is significantly associated with the outcome of interest. However, after taking into account Bonferroni corrections for multiple testing, only age was significant at the alpha=0.0014 level of significance.

IV.i. Interaction Terms

Interaction was evaluated for the relationship between age and variables reflecting how long the HCW had worked in the facility, total hours of work per week working in healthcare facilities, position at the facility and how long they have worked in their current occupation. A likelihood ratio test was performed to look at the difference between the model including the interaction terms (full model) and the model with only the individual factors (reduced model). The likelihood ratio statistic was non-significant,

indicating that the interaction factors were not significantly associated with the outcome (X^2= 5.10, p=value= 0.28).

IV.ii. Collinearity

Collinearity was investigated by creating condition indices for each variable in the model. Condition indices varied from 1 to 1.65, indicating that all variables in the model were not collinear. Therefore, no variables had to be removed or combined, as a result of collinearity, from the model.

V. Multivariate Model Results and Implications

Age was the only variable that remained statically significant in the multivariate model, indicating that for each year of age, the prevalence of LTBI increases by 4% (PR=1.04; 95%CI=1.03,1.05, p<.001). The relationship between LTBI and a given group of HCWs was not significant once controlling for other variables in the model, at the alpha=0.0014 level of significance. The prevalence of LTBI among HCWs with direct patient contact was 19% percent greater than HCWs that that did not report direct patient contact (95%CI=1.04, 1.38, p=0.02) when controlling for other variables in the model. The total number of hours a HCW worked per week in all facilities was not statistically significantly associated with LTBI, where the prevalence of LTBI multiplied by 1.004 for each hour working (95% CI=1.0003, 1.008, p=0.03). The prevalence of LTBI decreased by 31% in facilities that had respiratory hygiene posters on all units versus those that had none (PR=0.69, 95% CI= 0.48, 0.99, p=0.04) However, after Bonferroni Corrections to account for multiple testing, the overall multivariate analysis indicates that for these analyses, age is the only statistically significant variable associated with LTBI.

DISCUSSION

In this study we found that age, sex, work hours at all facilities, position, direct patient contact and respiratory posters were all associated with LTBI. However, due to the large number of variables considered, the model was re-considered via Bonferroni Corrections at the 0.0014 level of significance. At this level of significance, only age was statistically significantly associated with LTBI.

Prior to multivariate modeling, bivariate analysis was performed to determine associations between each variable and LTBI. At the alpha=0.05 level of significance, we found that many time-dependent variables were significantly associated with LTBI, including age, number of years having worked in the unit, number of years having worked in the current occupation and excess work hours per week (>65 hours). When correcting for multiple tests, adjusting the alpha value to 0.0014, these variables were significantly associated in the initial bivariate analysis. These variables are all related to duration and frequency of exposure: more time with exposure and more potential for contact with infectious agents.

Our finding of a linear association between increasing age and increased prevalence of LTBI (4% increase per 1 year increase in age) is consistent with other studies that have shown increasing age as a risk factor for LTBI among healthcare workers in other low-resource settings [42, 45, 46]. It is likely that this association is attributed to waning immunity as an individual grows older, as the immune system is slower to respond and is less effective in the response and reaction to infection [47]. This places older populations at a higher risk for all types of infections, including LTBI. Furthermore, as aforementioned, as time passes, the potential for infection grows as

passing allows for more opportunities for exposure. This finding indicates that controlling for other factors that influence likelihood of infection, age still is the predominate correlate with higher risk of infection.

This study did, however, produce results that differed from results from previous studies related to duration of exposure. Time worked in given occupation, time working at the given facility and number of hours worked per week, both at a given facility and at all job, as well as direct patient contact were significant in bivariate analysis, consistent with the literature [42, 45]. HCWs who had worked in their current occupation for more than 5 years have been reported to be at an elevated risk for LTBI. In the present study, HCWs that had worked in their current occupation for more than 10 or the current facility for more than 9 years had an elevated risk for a LTBI in bivariate analysis, but neither of these exposure-level related factors were independently associated with LTBI in multivariate analysis.

These null results may have to do with the association of age to duration in the healthcare facility, in that time passes equally with each of these variables. The older populations are more likely to have worked longer time than the younger populations and therefore the association of working more than 10 years in a current occupation as well as working more than 9 years in the facility may be due to time passing, whereby age provides more predictive value than the other variables in the model.

Another deviance from the literature occurred when determining the relationship between direct patient contact and LTBI. The literature suggests that direct patient contact, both in frequency and duration, increases the opportunity for infection[3, 31]. The findings in our study could be due to differences in training of staff, availability of

preventative measures, or other infection control procedures that are strongly related to the occupation of the healthcare workers.

Interestingly, however, was that none of the variables that measured duration of exposure were collinear. Years worked in a healthcare facility, years worked in a given occupation and age were not collinear despite all variables having strong correlation, in that they are all related to progression of time. This could be due to the fact that professions in the healthcare setting vary drastically and not all HCWs begin their work within a similar age range, work the same hours, or work in areas in the hospital that provide similar levels of exposure.

Strengths and Limitations

There are a few areas of weakness in this study that are of importance. On the individual level, the outcome of having a positive test was not guaranteed to indicate only LTBI. While HCWs in the parent study were screened for both LTBI and were referred for TB screening if they had a positive LTBI test, TB disease cannot, with perfect precision, be ruled out. However, it should be of note that only 5-10% of LTBI cases ever convert to TB disease and most convert within 2 years of infection [2]. All HCWs have been followed for 6 months following the baseline LTBI assessment and none have been diagnosed with TB disease. Furthermore, coughing for more than 3 weeks is usually indicative of TB disease. In this study, 11/258 (4.3%) of participants with a cough for more than 3 weeks tested positive for LTBI, which was similar to the proportion with a cough for greater than 3 weeks that were negative for LTBI (X^2=1.71, p=.1905). Due to the fact that the prevalence of a persistent cough was not different among those that test positive and test negative for LTBI, and that no HCWs have been identified with TB

disease, we believe the results of the baseline LTBI test as utilized in this analysis are indicative of infection status rather than disease.

Furthermore, some of the individual variables were not specific enough to determine a true association between exposure and LTBI prevalence. For example, the variable that measured whether or not a HCW had direct patient contact was not specific to tuberculosis and the results, therefore, may not be a proper measurement of level of exposure. If a HCW is consistently with patients, none of which present with TB disease, the variable may not be a logical risk factor to incorporate into the model. It would be more effective to evaluate contact with patients presenting with active TB disease to determine the true association between patient contact and risk for LTBI.

This is a similar pattern as seen in the variables that indicate hours worked weekly, total number of years in a given occupation, total number of years in the given facility, in that they are not specific to exposure to TB patients. If a given HCW works more or less in the facility, this does not necessarily indicate that level of exposure to persons with infectious TB disease or infectious materials.

In this analysis, few variables had any missing values; however, not all variables were specifically defined in a way that made analysis interpretable. For example, almost 1/3 of the population listed “other” as a type of occupation, rather than one of the defined categories. Since no information was available to try to extrapolate what “other” indicated for a given individual, associations, or lack thereof, may have been masked by the population that designated their occupation as other. If members of a given occupation were more likely to list themselves as other than another category, this could influence the associations between occupation type and a LTBI. While it is possible

there could be a differential misclassification if one group were more likely to utilize the "other" group than another occupational group, there is no information to suggest this. Therefore, it is likely that misclassification, if existent, was non-differential, which would bias the estimates toward the null.

Furthermore, many of the variables that were listed as dichotomous "Yes/No" variables were originally listed as "Yes, No, Don't Know/ Prefer not to Answer." In the analysis, those who answered Don't Know/Prefer Not to Answer, were placed in to the "No" category, and the questions were phrased in a way that indicated known exposure to a variable rather than actual exposure. However, this could have influenced associations due to information misclassification. While it can be assumed that if a HCW does not know about an exposure, that the exposure would be unlikely, for some variables this is not true. For example, with the variable that indicates exposure to TB cases in the community, those who do not know if they have been exposed, cannot ensure no exposure to TB, particularly in Thailand where the prevalence of TB is so high. Without controlling for contact with persons with TB outside the facility, it can be difficult to evaluate the contribution of healthcare facility exposures on LTBI. Therefore, there is potential for residual confounding as this variable does not truly account for contact with persons with TB disease outside of the healthcare facility or duration of these contacts.

The categorization of occupation into subgroups could potentially be have masked effects for a given group. While evaluation of patient contact was initially used to try to categorize occupation into groups based on exposure level, the only subgroup that was statistically significantly associated with a positive LTBI test was the nurses group. This

association was, however, no longer significant at our corrected level of significance after controlling for age. The literature has reported that radiology technicians, patient attendants, nurses, ward attendants, paramedics, and clinical officers have a higher risk of LTBI in low to middle income countries. The majority of studies in which these associations of LTBI and occupation were identified did not have any infection control procedures in place; in contrast, the health facilities in the current analysis all had infection control plans, which included annually screening of all HCWs, infection control trainings for all HCWs, annually, and mechanisms by which to react to potential TB patients that arrive at the facility, all methods to reduce levels of infection. Moreover, in the current analysis, subgroups were created, where in other studies, occupation was left in the way it was defined. Creating these subgroups could have masked the association that would have been seen, had the groups been left as each individual occupation.

Due to the cross-sectional nature of the study, it is not possible to ascertain temporal relationships between variables. A positive LTBI test does not indicate when exposure occurred, and it is impossible to determine the direction of the association between the defined exposure and the positive test. It is possible that healthcare workers may have been exposed to TB prior to working in the health facility, since Thailand has a high prevalence of TB in the population.

There were also some limitations in our facility level evaluation. While both the inpatient infection control assessment and outpatient infection control assessment evaluated a large number of infection control measures, there were only a few variables that were common to both assessments. This made it difficult to truly evaluate the breadth of facility level factors that may influence individual HCW risk for LTBI. It may

be that infection control measures only effect the prevalence of LTBI when several measures are in place, where a singular given measure is not sufficient for infection control. However, because we were only able to evaluate a few measures, we were unable to determine the overall effect of combined mechanisms of infection control.

Furthermore, the facility level variables regularly measured the presence of an infection control measure, but not use of that control measure. Using these as a proxy for use of infection control measures, without an objective assessment of infection control practices may have influenced why none of the facility level variables were significantly associated with the prevalence of LTBI. Lastly, the low variance in many of the variables made prediction not feasible, low variance in the variable makes it difficult to determine if differences in the outcome are due to that variable. In order to truly evaluate if availability can be used as a proxy for actual use, a study needs to be done among this population to determine the concordance between availability of infection control measures and use of infection control measures. This could include an objective assessment to ascertain information on the correct use of respirators, proper collection methods of sputum including collection in a particular area, efficiency of confirmation of diagnosis and subsequent isolation of infected persons.

Despite these limitations, evaluating facility level factors as risk factors on the individual HCW level offers a new opportunity for a novel field of research; if we can identify which facility level factors influence risk, facilities can adjust their infection control practices to incorporate these findings, and provide protection for all of their healthcare workers collectively. Individual level factors for LTBI among HCWs have been studied and published many times in the literature, however associated facility level

factors that influence LTBI prevalence have yet to be determined particularly in high-burden, low resource settings. The importance of this concept of mixed modeling utilizing both individual and facility level risk factors in tandem and determining a concurrent effect of individual demographics as well as environmental elements may provide insight into a new intersection for intervention.

The overall generalizability of the study is limited. The population in Thailand is much different than many other countries that have a high prevalence of TB. Many of the countries that face a high burden of TB regularly combat a high prevalence of HIV. HIV is a risk factor for TB due to the impact HIV infection has on immunity. The prevalence of HIV in Thailand among those aged 15-49, a similar age range to those in the study population is 1.1% (56). The low prevalence of HIV in this population makes it difficult for these results to indicate risk factors among other high burden, low-resource countries that present with higher levels of HIV.

Future Directions

In order to truly understand the extent to which facility level factors can influence an individual HCW's risk for LTBI, first, more directed focus needs to be placed on specific measures that are associated with LTBI. For example, a variable that measures direct patient contact could be more specific in that it measures time in TB wards, time directly in patient rooms who present with TB, and other more directed, specific questions that could provide more specific evidence for these measures being risk factors.

The development of these measures should include a panel of subject matter experts that have experience in risk factors for LTBI, as these experts would be able to present

relevant measures. After the measures have been compiled, they should be validated. A validation study would include piloting them in a smaller facility and determining these measures provide the capacity to relate a variable to LTBI.

Once specific measures have been validated, future studies could thoroughly evaluate these risk factors longitudinally. Future studies could look at level of infection pre-intervention and re-evaluate prevalence of infection post intervention. The study would be a more robust evaluation of low-cost interventions, such as specified sputum collection areas, open windows and specified TB case areas within the facility. The fortuitous component of this being a necessary direction for this field of research is that this is what the EnTIC Trial seeks to understand. Therefore, the results of this study provide evidence that the undertakings of the parent study are both warranted and necessary.

By determining if facility level risk factors can influence individual health and which factors most drastically influence transmission, facilities can begin to implement changes that will directly affect all persons within the healthcare facility without requiring individual behavior change. The scope of an intervention that targets facility level change will have broad reach with intervention. Therefore, further research needs to be done in this area to reduce LTBI and in turn reduce TB disease in an effort to reduce and eventually eliminate mortality due to *M. Tuberculosis.*

APPENDIX I: Tables and Figures

Table I: Surveys Used for Analysis to Determine Factors Influencing Prevalence of LTBI among HCWs in 10 Healthcare Facilities in Thailand

Survey	Population	Number Completed	Survey Type	Question Types	Adjustments
Healthcare Worker Demographics	Healthcare Worker	3,977	Electronic	See Table I	Any person who worked more than 80 hours were re-coded as 80 hours
Facility Demographics	Facility Level	10	Paper	See Table II	None.
Outpatient Department (OPD) Infection Control Checklist	Facility Level	43	Paper	Infection prevention measure availability, both for patient and staff, presence of designated individual to keep windows open, etc.	Components merged with Inpatient Unit-level Assessment Tool and renamed "Infection Control Assessment"
Inpatient Unit-level Assessment Tool	Facility Level	132	Paper	Airflow tests, infection prevention measures availability and locations, are for confirmed or suspected TB cases, etc.	Components merged with Outpatient Department (OPD) Infection Control Checklist and renamed "Infection Control Assessment"

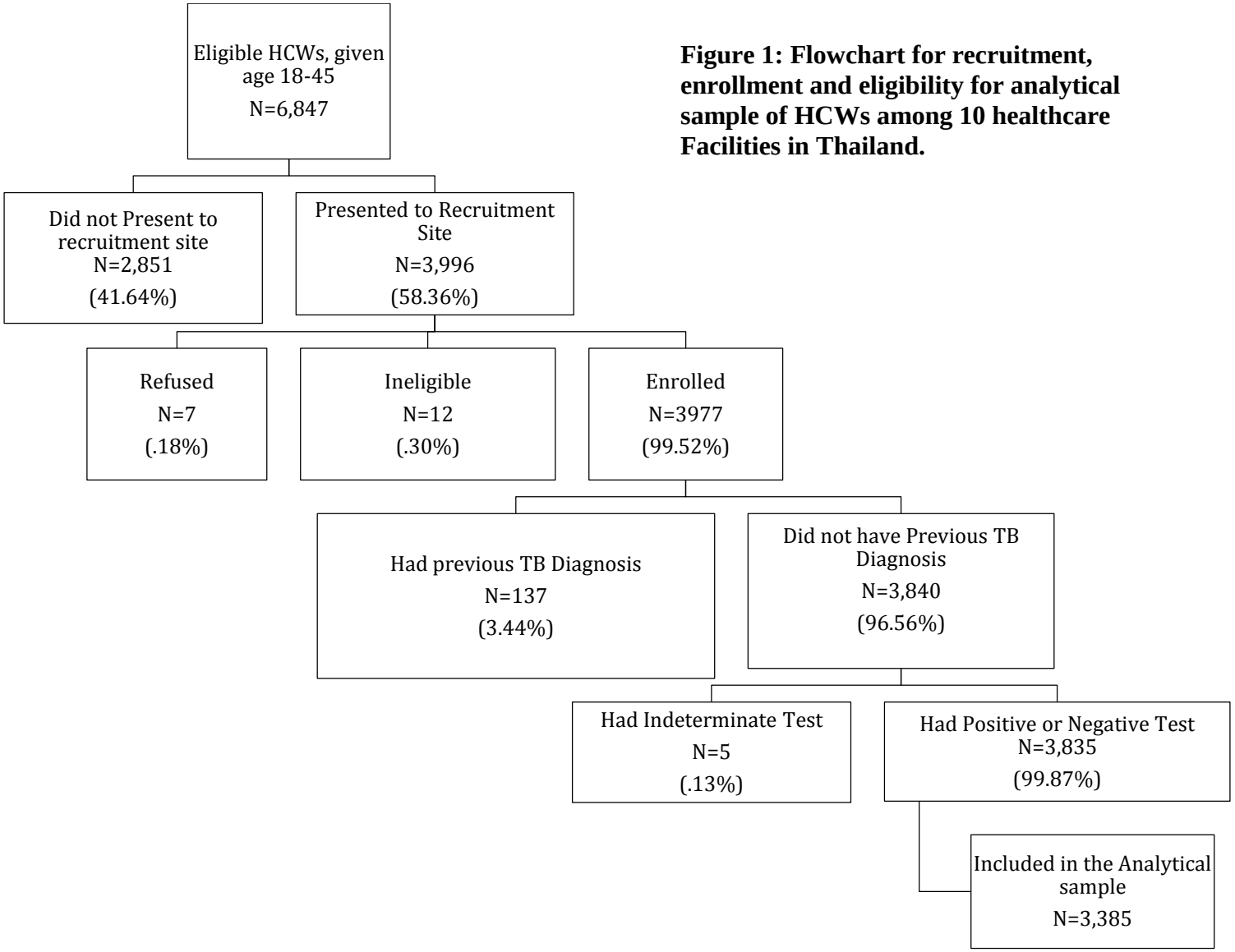

Figure 1: Flowchart for recruitment, enrollment and eligibility for analytical sample of HCWs among 10 healthcare Facilities in Thailand.

Table II: Characteristics of Healthcare Workers Enrolled in the EnTIC Trial from 10 Healthcare Facilities in Thailand (N=3835).

		n	%
Demographics			
Age, years (at enrollment)			
	18-24	396	10.3
	25-29	724	18.9
	30-34	871	22.7
	35-39	1076	28.1
	40-44	768	20.0
Gender			
	Male	678	17.7
	Female	3157	82.3
Body Mass Index			
	Underweight	308	8.0
	Normal	2398	62.5
	Overweight	797	20.8
	Obese	332	8.7
Occupational			
Occupational position			
	Administrative*	692	18.0
	Nurses†	1308	34.1
	Physicians	41	1.1
	Clinical Health††	449	11.7
	All Others	1345	35.1
Duration worked in current occupation, years			
	Less than 3	763	19.9
	3-8.99	1187	31.0
	9-14.99	868	22.6
	15 or more	1017	26.5
Duration worked in the current facility, years			
	Less than 1 year	314	8.2
	1-1.99	174	4.5
	2-4.99	867	22.6
	5-9.99	861	22.5
	10 or more	1619	42.2
Worked at another facility within past year			
	No	3417	89.1
	Yes	418	10.9
Duration worked in current department, years			
	Less than 2	575	15.0
	2 - 5.99	1237	32.3
	6 -11.99	1012	36.4
	12 or more	1011	25.4
Worked in other departments within the past year			
	No	2894	75.5
	Yes	941	24.5
Hours/week working at all jobs			
	40 or less	974	25.4
	>40-50	962	25.1

	>50-65	1163	30.3
	More than 65	736	19.2
Hours/Week Working at the Current Facility			
	40 or less	1130	29.5
	>40-50	1014	36.4
	>50-65	1105	28.8
	More than 65	586	15.3
Primary Work Shift			
	No shiftwork	209	5.5
	Morning	1786	46.6
	Afternoon	35	.9
	Night	24	.6
	Rotation	1781	46.4
Direct Contact with Patients			
	No	837	21.8
	Yes	2998	78.2
Known contact with person with TB at home or in the community			
	No	3244	84.6
	Yes	591	15.4
Symptoms Indicative of Tuberculosis			
Cough in past 2 weeks			
	No	2883	75.2
	Yes	952	24.8
If cough, duration (n=952)			
	Less than 3 weeks	898	94.3
	3 or more weeks	54	5.7
Fever in past 2 weeks			
	No	3371	87.9
	Yes	464	12.1
Night sweats in past 2 weeks			
	No	3789	90.8
	Yes	46	1.2
Lost weight in the last 6 months			
	No	3491	91.0
	Yes	344	9.0
Comorbidities and Behavioral Characteristics			
Known diabetes			
	No	3734	97.4
	Yes	101	2.6
Currently smoke tobacco			
	Not at All	3603	94.0
	Less Than Daily	127	3.3
	Daily	105	2.7
Previous smoking frequency (n=3,672)			
	Not at All	3489	91.0
	Less than Daily	150	3.9
	Daily	33	0.9
Smoking frequency of any household family member			

	Never	2335	60.9
	Less Than Monthly	327	8.5
	Monthly	31	0.8
	Weekly	128	3.3
	Daily	1014	26.4
Smoking exposure in the work area, past 30 days			
	No	2053	53.5
	Yes	1782	46.5

*Includes dental occupations, clerks, dietitians, pharmacy personnel, occupational therapists, social workers, and administrative staff.
†Includes both nurses and nurses' aides.
††Includes technicians, orderlies, housekeepers, and phlebotomists.

Table III. Characteristics of Healthcare Facilities in the EnTIC Trial, Thailand (n=10). Numbers are facility mean and standard deviation (SD) unless otherwise specified.

	Mean	SD
Facility Characteristics		
Years Since Facility Built	63.7	6.0
Number of Beds in Facility	432.2	97.8
Total Staff*	1151.3	259.7
Nurses	359.8	56.8
Nurses' Aides	36.7	16.4
Physicians	47.7	21.9
Patients		
Average Daily Census, 2012†	372.2	115.4
Annual Number of:		
Total inpatient admissions	28634.1	12932.4
HIV admissions	251.0	125.2
Pulmonary TB admissions	206.2	121.5
Admissions due to TB, percent	0.8%	0.4%
Outpatient:		
Visits	314095.4	91579.9
HIV visits	2591.5	1261.3
TB visits	955.2	910.7
Tuberculosis Specifics		
Patients with TB disease in 2011	2020.7	1343.3
Patients with TB disease in 2012, (n=9)	1855.1	1347.3
Staff with TB disease in 2011 (n=9)	3.1	3.1
Staff with TB disease in 2012	2.4	1.9

*Includes part time and full time stuff but does not include students or trainees.
†Total number of inpatients plus number of outpatient visits daily.

Table IV: Infection Control Measurement Indicators for the 10 Facilities enrolled in the EnTIC Trial in Thailand

Variable	Total	Yes	
	n	n	%
Is soap available at all sinks?			
Facility 1	19	10	52.6
Facility 2	10	5	50.0
Facility 3	24	24	100.0
Facility 4	21	10	47.6
Facility 5	18	2	11.1
Facility 6	16	13	81.3
Facility 7	12	12	100.0
Facility 8	15	12	80.0
Facility 9	22	15	68.2
Facility 10	16	12	75.0
Are alcohol-based hand rubs available?			
Facility 1	19	19	100.0
Facility 2	10	8	80.0
Facility 3	25	25	100.0
Facility 4	21	20	95.2
Facility 5	18	17	94.4
Facility 6	16	16	100.0
Facility 7	12	11	91.7
Facility 8	15	13	86.7
Facility 9	22	22	100.0
Facility 10	17	16	94.1
Are examination gloves available?			
Facility 1	19	17	89.5
Facility 2	10	8	80.0
Facility 3	25	25	100.0
Facility 4	21	19	90.5
Facility 5	18	14	77.8
Facility 6	16	13	81.3
Facility 7	12	10	83.3
Facility 8	15	15	100.0
Facility 9	22	21	95.2
Facility 10	16	13	81.3
Are masks easily available to staff?			
Facility 1	19	19	100.0
Facility 2	10	10	100.0
Facility 3	25	25	100.0
Facility 4	21	21	100.0
Facility 5	18	18	100.0
Facility 6	16	16	100.0
Facility 7	12	12	100.0
Facility 8	15	15	100.0
Facility 9	22	22	100.0
Facility 10	12	11	91.7

Are respirators available for staff?			
Facility 1	19	17	89.5
Facility 2	10	9	90.0
Facility 3	25	19	76.0
Facility 4	21	13	61.9
Facility 5	18	15	83.3
Facility 6	16	13	81.3
Facility 7	12	9	75.0
Facility 8	15	12	80.0
Facility 9	22	20	90.9
Facility 10	17	13	76.5
Are respiratory hygiene/cough etiquette posters displayed?			
Facility 1	19	0	0
Facility 2	10	6	60.0
Facility 3	25	3	12.0
Facility 4	21	7	33.3
Facility 5	18	3	16.7
Facility 6	16	0	0
Facility 7	12	4	33.3
Facility 8	15	0	0.0
Facility 9	22	1	4.5
Facility 10	17	0	0

Table V. Prevalence Ratios (PRs) and 95% confidence intervals (95% CIs) Prevalence Ratio for the bivariate association between individual level factors and LTBI for healthcare workers enrolled in the EnTIC Trial at 10 health facilities in Thailand (N=3, 835)

		Total	**LTBI (n=1081)**				
			n	%	Prevalence Ratio (PR)	95% CI	p-value
Demographics							
Age, years (at enrollment)							
	18-24	396	67	16.9	Reference (Ref)		
	25-29	724	144	19.9	1.18	0.90, 1.53	0.23
	30-34	871	233	26.8	1.58	1.24, 2.02	0.002
	35-39	1076	360	33.5	1.98	1.57, 2.50	<0.001
	40-45	768	277	26.1	2.13	1.68, 2.70	<0.001
Gender							
	Male	678	186	27.4	Ref.		
	Female	3157	895	28.4	1.03	0.90, 1.18	0.63
Body Mass Index							
	Underweight	308	72	23.4	Ref.		
	Normal	2398	669	27.9	1.19	0.97, 1.48	0.10
	Overweight	797	238	29.9	1.28	1.02, 1.61	0.04
	Obese	332	102	30.7	1.31	1.01, 1.70	0.04
Occupational							
Occupational position							
	Administrative*	692	159	23.0	Ref.		
	Nurses†	1308	427	32.7	1.42	1.21, 1.66	<0.0001
	Physicians	41	10	24.4	1.06	0.61, 1.85	0.83
	Clinical Health††	449	129	28.7	1.25	1.02, 1.53	0.03
	All Others	1345	356	26.5	1.15	0.97, 1.36	0.09
Duration worked in current occupation, years							
	Less than 3	763	153	20.1	Ref.		
	3-8.99	1187	294	24.8	1.24	1.04,1.47	0.02

	9-14.99	868	258	29.7	1.48	1.24, 1.76	<0.001
	15 or more	1017	376	37.0	1.84	1.56, 2.17	<0.001
Duration worked in the current facility, years							
	Less than 1 year	314	68	21.7	Ref.		
	1-1.99	174	33	19.0	0.88	0.60, 1.27	0.48
	2-4.99	867	193	22.3	1.03	0.81, 1.31	0.83
	5-9.99	861	216	25.1	1.16	0.91, 1.47	0.23
	10 or more	1619	571	35.3	1.63	1.31, 2.03	<0.0001
Worked at other facility within past year							
	No	3417	953	27.9	Ref.		
	Yes	418	128	30.6	1.10	0.94, 1.28	0.23
Duration worked in current department, years							
	Less than 2	575	132	23.0	Ref.		
	2 - 5.99	1237	294	23.8	1.04	0.86, 1.24	0.71
	6 -11.99	1012	309	30.5	1.33	1.12, 1.59	0.002
	12 or more	1011	346	34.2	1.49	1.25, 1.77	<0.0001
Worked in other departments within the past year							
	No	2894	791	27.3	Ref		
	Yes	941	290	30.8	1.13	1.01, 1.26	0.04
Hours/week working at all jobs							
	40 or less	974	262	26.9	Ref.		
	>40-50	962	251	26.1	0.97	0.84, 1.13	0.69
	>50-65	1163	336	28.9	1.07	0.94, 1.23	0.31
	More than 65	736	232	31.5	1.17	1.01, 1.36	0.04
Hours/week working at the current							

	40 or less	1130	305	27.0	Ref.		
	>40-50	1014	277	27.3	1.01	0.88, 1.16	0.87
	>50-65	1105	309	28.0	1.04	0.91, 1.19	0.61
	More than 65	586	190	32.4	1.20	1.03, 1.40	0.02
Primary work shift							
	No shiftwork	209	41	19.6	Ref.		
	Morning	1786	501	28.1	1.43	1.08, 1.9	0.01
	Afternoon	35	9	25.7	1.31	0.7, 2.45	0.40
	Night	24	8	33.3	1.70	0.90, 3.18	0.10
	Rotation	1781	522	29.3	1.50	1.12, 1.98	0.006
Direct contact with patients							
	No	837	198	23.7	Ref.	.	
	Yes	2998	883	29.5	0.80	0.70, 0.92	0.001
Known contact with person with TB at home or in the community							
	No	3244	904	27.9	Ref.		
	Yes	591	177	30.0	1.07	0.94, 1.23	0.30
Symptoms Indicative of Tuberculosis							
Cough in past 2 weeks							
	No	2883	813	28.2	Ref.		
	Yes	952	268	28.2	1.00	0.89, 1.12	0.98
If cough, duration (n=952)							
	3 or more weeks	54	257	28.6	Ref.		
	Less than 3 weeks	898	11	20.4	1.40	0.82, 2.40	0.22
Fever in past 2 weeks							
	No	3371	955	28.3	Ref.		
	Yes	464	126	27.2	.96	0.82, 1.12	
Night sweats in past 2 weeks							
	No	3789	1068	28.2	Ref.		
	Yes	46	13	28.3	1.00	0.63, 1.59	0.99
Lost weight in the last 6 months							
	No	3491	1002	28.7	Ref.		
	Yes	344	79	22.80	0.80	0.65, 0.98	0.02

Comorbidities and Behavioral Characteristics							
Known diabetes							
	No	3734	1041	27.9	Ref.		
	Yes	101	40	39.6	1.42	1.11, 1.82	0.005
Currently smoke tobacco							
	Not at All	3603	1012	28.10	Ref.		
	Less Than Daily	127	37	29.1	1.04	0.79, 1.37	0.31
	Daily	105	32	30.5	1.08	0.80, 1.46	0.38
Previous smoking frequency							
	Not at All	3489	985	28.2	Ref.		
	Less than Daily	150	37	24.7	1.04	0.79, 1.37	0.80
	Daily	33	9	27.3	1.08	0.81, 1.46	0.59
Smoking frequency of any household family member							
	Never	2335	679	29.1	Ref.		
	Less Than Monthly	327	93	28.4	0.98	0.81, 1.17	0.81
	Monthly	31	6	19.4	0.67	0.32, 1.37	0.27
	Weekly	128	39	30.5	1.05	0.80, 1.37	0.73
	Daily	1014	264	26.0	0.90	0.80, 1.01	0.07
Smoking exposure in the work area, past 30 days							
	No	2053	558	27.2	Ref.		
	Yes	1782	523	29.4	1.08	0.98, 1.19	0.14

*****Includes dental occupations, clerks, dietitians, pharmacy personnel, occupational therapists, social workers, and administrative staff.95% CI
†Includes both nurses and nurses' aides.
††Includes technicians, orderlies, housekeepers, and phlebotomists.

Table VI: Analysis and Modeling, Evaluating Demographic Variables for Inclusion

Variable	Correlation Estimate (Rho)	p-value for H_0=Rho	Included as a potential variable in univariate model	Significance in a model that controls for age, position and gender, X^2	Significance in a model that controls for age, position and gender, p-value	Included as a potential variable in multivariate model?	Significance in multivariate model X^2	Significance in multivariate model, p-value	Included in final model
Age	0.157	<0.0001	Yes	Forced inclusion		Yes	94.33	<.0001	Yes
Sex	0.008	0.6306	Yes	Forced Inclusion		Yes	0.46	0.0256	Yes
BMI	.051	0.0018	Yes	2.92	0.09	No			
Position	-.061	0.0002	Yes	Forced Inclusion		Yes	11.08	0.0256	Yes
Diabetes	.047	0.0097	Yes	2.86	0.09	No			
Fever in Last 2 Weeks	-.009	0.5981	No						
Cough in Last 2 Weeks	-.001	0.9770	No						
If you had a cough, has it lasted more than 3 weeks	-0.042	0.1910	No						
Night Sweats in last 2 Weeks	0.001	0.9912	No						
Direct Patient Contact	0.053	0.0010	Yes	7.50	0.01	Yes	6.30	0.012	Yes

Smoking exposure in the work area, past 30 days	0.024	0.1365	No						
Worked on your current area/unit?	0.100	<0.0001	Yes	.08	0.78	No			
Years in current occupation	0.145	<0.0001	Yes	2.09	0.15	No			
Years at this facility	0.145	<0.0001	No						
Hours Work/Week at this facility	0.030	0.06	No						
Lost weight in last 6 months	-0.036	0.02	No						
Currently smoke	-0.009	0.59	No						
Frequency of smoking in the home	0.027	0.09	No						
Smoke in Past	0.0149	0.37	No						
Workhour_80	0.038	0.02	Yes	6.66	0.01	Yes	4.68	0.03	Yes
Contact with TB	0.017	0.30	No						
Work Shift	-0.008	0.62	No						
Worked in Other Department	-0.033	0.04	No						

within Last Year			
Worked in Other Facility within Last Year	-0.019	0.24	No

TABLE VII: Prevalence Ratios of LTBI by Duration Worked in Current Occupation, Stratified by Age

Prevalence Ratios for LTBI by Duration Worked in Current Occupation, Crude Values

Duration worked in current occupation, years		Total	n, positive	Percent	Prevalence Ratio	95% CI	p-value
	Less than 3	763	153	20.1	Ref.		
	3-8.99	1187	294	24.8	1.24	1.04,1.47	0.02
	9-14.99	868	258	29.7	1.48	1.24, 1.76	<0.001
	15 or more	1017	376	37.0	1.84	1.56, 2.17	<0.001

Prevalence Ratios for LTBI by Duration Worked in Current Occupation, Stratified by Age (18-24)

Duration worked in current occupation, years		Total	n, positive	Percent	Prevalence Ratio	95% CI	p-value
	Less than 3	318	57	17.9	Ref.		
	3-8.99	72	10	13.9	.77	0.42, 1.44	0.42
	9-14.99	4	0	0	n/a	n/a	n/a
	15 or more	2	0	0	n/a	n/a	n/a

Prevalence Ratios for LTBI by Duration Worked in Current Occupation, Stratified by Age (24-29)

Duration worked in current occupation, years		Total	n, positive	Percent	Prevalence Ratio	95% CI	p-value
	Less than 3	229	30	13.1	Ref.		
	3-8.99	463	107	23.1	1.76	1.22, 2.56	0.01
	9-14.99	22	5	22.7	1.73	0.75, 4.02	0.20
	15 or more	10	2	20.0	0.42	0.42, 5.51	0.52

Prevalence Ratios for LTBI by Duration Worked in Current Occupation, Stratified by Age (30-34)

Duration worked in current occupation, years		Total	n, positive	Percent	Prevalence Ratio	95% CI	p-value
	Less than 3	115	30	26.1	Ref.		
	3-8.99	338	89	10.2	1.01	0.71, 1.44	0.96
	9-14.99	390	109	28.0	1.07	0.76, 1.51	0.70
	15 or more	28	5	28.0	0.68	0.29, 1.60	0.38

Prevalence Ratios for LTBI by Duration Worked in Current Occupation, Stratified by Age (35-39)

Duration worked in current occupation, years		Total	n, positive	Percent	Prevalence Ratio	95% CI	p-value
	Less than 3	55	15	27.3	Ref.		
	3-8.99	204	56	27.5	1.01	0.62, 1.63	0.98
	9-14.99	353	118	33.4	1.23	0.77, 1.93	0.38
	15 or more	464	171	36.9	1.35	0.86, 2.11	0.19

Prevalence Ratios for LTBI by Duration Worked in Current Occupation, Stratified by Age (40-45)

Duration worked in current occupation, years		Total	n, positive	Percent	Prevalence Ratio	95% CI	p-value
	Less than 3	46	21	45.7	Ref.		
	3-8.99	110	32	29.1	0.64	0.42, 0.98	0.04
	9-14.99	99	26	26.3	0.58	0.36, 0.91	0.02
	15 or more	513	198	38.6	0.84	0.60, 1.18	0.32

TABLE VIII: Prevalence Ratios of LTBI by Duration of Hours Worked at all Jobs, Stratified by Occupation

Prevalence Ratios for LTBI by Duration of Hours Worked at all Jobs, Crude Values							
Hours/Week at all jobs		Total	n, positive	Percent	Prevalence Ratio	95% CI	p-value
	40 or less	974	262	26.9	Ref.		
	More than 40	2861	819	28.6	1.06	0.95, 1.20	0.31
Prevalence Ratios for LTBI by Duration of Hours Worked at all Jobs, by Occupation (Other Administration)							
Hours/Week at all jobs		Total	n, positive	Percent	Prevalence Ratio	95% CI	p-value
	40 or less	240	53	22.1	Ref.		
	More than 40	452	106	23.5	1.06	0.80, 1.42	0.68
Prevalence Ratios for LTBI by Duration of Hours Worked at all Jobs, by Occupation (Nurses)							
Hours/Week at all jobs		Total	n, positive	Percent	Prevalence Ratio	95% CI	p-value
	40 or less	203	67	33.0	Ref.		
	More than 40	1105	360	32.6	0.99	0.80, 1.22	0.91
Prevalence Ratios for LTBI by Duration of Hours Worked at all Jobs, by Occupation (Physicians)							
Hours/Week at all jobs		Total	n, positive	Percent	Prevalence Ratio	95% CI	p-value
	40 or less	8	2	25.0	Ref.		
	More than 40	33	8	24.2	0.97	0.25, 3.71	0.96
Prevalence Ratios for LTBI by Duration of Hours Worked at all Jobs, by Occupation (Other, Clinical Health)							
Hours/Week at all jobs		Total	n, positive	Percent	Prevalence Ratio	95% CI	p-value
	40 or less	90	26	28.9	Ref.		
	More than 40	359	103	28.7	.99	.69, 1.43	0.97

Prevalence Ratios for LTBI by Duration of Hours Worked at all Jobs, by Occupation (All Others)

Hours/Week at all jobs	Total	n, positive	Percent	Prevalence Ratio	95% CI	p-value
40 or less	433	114	26.3	Ref.		
More than 40	912	242	26.5	1.01	0.82, 1.22	0.94

TABLE VII: Prevalence Ratios of LTBI by by Whether or Not they have Direct Contact with Patients, Stratified by Age

Prevalence Ratios for HCWs by Whether or Not they have Direct Contact with Patients, Crude Values

Direct Contact with Patients	Total	n, positive	Percent	Risk Ratio	CI	p-value
No	837	198	23.66	Ref.		
Yes	2998	883	29.45	.80	.70, .92	.01

Prevalence Ratios for HCWs by Whether or Not they have Direct Contact with Patients, By Age, 18-24

Direct Contact with Patients	Total	n, positive	Percent	Risk Ratio	CI	p-value
No	73	11	15.07	Ref.		
Yes	323	56	17.34	1.15	.64, 2.08	.64

Prevalence Ratios for HCWs by Whether or Not they have Direct Contact with Patients, By Age, 25-29

Direct Contact with Patients	Total	n, positive	Percent	Risk Ratio	CI	p-value
No	162	32	19.75	Ref.		
Yes	562	112	19.93	1.01	.71, 1.43	.96

Prevalence Ratios for HCWs by Whether or Not they have Direct Contact with Patients, By Age, 30-34

Direct Contact with Patients	Total	n, positive	Percent	Risk Ratio	CI	p-value
No	213	49	23.00	Ref.		
Yes	658	27.96	75.55	1.22	.92, 1.60	.16

Prevalence Ratios for HCWs by Whether or Not they have Direct Contact with Patients, By Age, 35-39

Direct Contact with Patients	Total	n, positive	Percent	Risk Ratio	CI	p-value
No	215	62	28.84	Ref.		
Yes	861	298	34.61	1.20	.95, 1.51	.12

Prevalence Ratios for HCWs by Whether or Not they have Direct Contact with Patients, By Age, 40-45

Direct Contact with Patients	Total	n, positive	Percent	Risk Ratio	CI	p-value
No	174	44	25.29	Ref.		
Yes	594	233	39.23	1.55	1.17, 2.05	.01

TABLE IX: Risk Ratios for Multivariate Model Predicting Outcome of LTBI among HCWs in 10 Healthcare Facilities in Thailand, Individual Risk Factor Risk Ratios Controlling for Other Variables in the Model [1]

Variable		PR	95% Confidence Interval	P-Value
Age		1.04	1.03, 1.05	<.0001
Sex				
	Male	Ref.		
	Female	1.05	.91, 1.22	.4767
Work Hours at All Facilities		1.00	1.00, 1.00	.0315
Position				
	Other, Administration*	Ref.		
	Nurses†	1.28	1.10, 1.52	.0020
	Physicians	.92	.52, 1.60	.7610
	Other, Clinical Health††	1.13	.82, 1.39	.2453
	All Others	1.19	1.01, 1.40	.0386
Direct Patient Contact				
	No	Ref.		
	Yes	1.19	1.04, 1.38	.0147
Respiratory Hygiene Posters		.68	.48, .99	.0428

[1]Model was built using an alpha value of .05 level of significance. However, to account for multiple testing, significance of multivariate variables after modeling was set at an alpha=.0014 level of significance. Therefore, only age is significantly

associated with LTBI (p<.0001), while all other variables are not associated at this alpha level. Based on Bonferroni correction, significance was determined at an alpha <0.0014.
Modeling selection was based on a p<.05 or through previous literature indicating significance of a given variable.
*Includes dental occupations, clerks, dietitians, pharmacy personnel, occupational therapists, social workers, and administrative staff.
†Includes both nurses and nurses' aides.
††Includes technicians, orderlies, housekeepers, and phlebotomists
§ This is a facility-level factor

APPENDIX II: References

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Ethics

These analyses were performed on a subset of previously collected data. For this reason, this analysis was exempt from Internal Review Board at Emory University as this analysis qualified as non-research.