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Epidemiology to Support a Proposed Policy of Latent Tuberculosis Testing and Treatment in Refugee Populations

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Bachelor of the Arts

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2009

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By Marie E. Semple

Foreign-born persons have the highest rate of progression to active Tuberculosis (TB) within the first year of arrival in the United States [1]. Recent studies suggest that TB elimination goals in the United States (incidence of <1 case/million), will not be possible without targeting the foreign-born [2]. Amongst these, those especially vulnerable are refugees arriving from crowded refugee camps in countries with high TB prevalence and incidence rates, increasing the likelihood for latent Tuberculosis infection (LTBI) and progression to active TB. Currently, LTBI screening is not part of formal protocol for refugees. A cross-sectional analysis of these underserved populations was performed using pre-collected, de-identified data from the Georgia Department of Health and the Minnesota Department of Health (n = 14,141). Prevalence of LTBI in refugee populations by region of origin (Africa, Asia, Middle East, Eastern Europe, and Latin America) was determined by positive Tuberculin skin test (TST) results. Conditional logistic regression was performed conditioning on state (Minnesota and Georgia) with region of origin as the primary predictor of interest. Gender and age, as well as their interactions with region were considered as covariates. A separate analysis was performed with Georgia Department of Health data, since they provided additional health condition information. An unconditional logistic regression model was fit to determine which health indicators were associated with a positive TST. The unadjusted proportion of refugees arriving from African, Asian, Middle Eastern, Eastern European, and Latin American countries who had a positive TST upon screening in the United States was 53.6%, 35.5%, 23.7%, 42.1% and 20.8% respectively. The multivariate analysis showed that sex, age, region, and the interaction between age and region were significant predictors of a positive TST. In the Georgia data sub-analysis, it was observed that in addition to age, sex, and region, testing positive for hepatitis B surface antigen (HBsAg) and hepatitis B vaccination status were associated with a positive TST amongst refugees. Given the prevalence of LTBI in refugee populations and associated co-infections, we suggest screening and prophylactic treatment of LTBI prior to arrival in the United States.

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Background

The Immigrant, Refugee and Migrant Health Branch (IRMHB) of the Division of Global Migration and Quarantine (DGMQ) at the Centers for Disease Control and Prevention (CDC) issues technical instructions (TI) that set the standards for the overseas medical screening of immigrants and refugees bound for the United States. A separate government agency, the Department of State, funds refugee medical screenings by contracting with the International Organization of Migration (IOM) and other country-specific physicians and medical groups to carry out these medical screenings. There is ongoing discussion between the many stakeholders interested in the quality of refugee healthcare regarding the standards that should be set for tuberculosis (TB) and latent tuberculosis (LTBI) screening and treatment.

The current Tuberculosis Technical Instructions (TBTIs) issued by the CDC require that all immigrant and refugee adults (15 years of age and older) immigrating to the United States be screened for pulmonary TB using chest X-ray. If the chest X-ray is abnormal, these persons supply a sputum smear and culture to identify cases of active TB disease. As a provision of the TBTIs, children under the age of 15 are screened using a TST and if found positive, are referred for a chest X-ray to diagnose active TB disease. LTBI, however, is not a current priority of these screenings for reasons that will be discussed briefly.

Currently, there is an on-going study at CDC analyzing the costs and benefits of a newly proposed screening and treatment protocol in response to the FDA approval of a new chemoprophylaxis treatment regimen for LTBI. This larger CDC study will use the results of the study of the new chemoprophylaxis treatment and data regarding the prevalence of LTBI in refugees to analyze the benefits of potentially expanding the current TBTIs to increase the population voluntarily screened for LTBI and implement new treatment standards prior to arrival in the United States. As a portion of this larger project, this epidemiology thesis will provide needed parameter values for the larger economic analysis and will drive decisions for model development by obtaining prevalence estimates of LTBI in various refugee populations and other

demographic and health-related factors associated with LTBI using conditional and unconditional logistic regression. It will also be argued that given the prevalence of LTBI in various refugee populations, in addition to associated health risk factors found in these communities, that screening for LTBI and treatment prior to arrival in the United States would be of personal benefit to refugees in addition to the societal value of treatment.

TB disease most often affects the lungs, but the bacteria can affect any part of the body. As pulmonary TB, it is often considered contagious if the person is able to produce sputum containing the bacteria. LTBI, however, is rarely contagious, simply means that a person has been exposed to the bacteria and that the body's immune system is able to keep the bacteria under control in a dormant state. Largely due to the difference in contagiousness, studies that have been conducted in the United States more often focus on immigrants and foreign-born persons as relates to TB disease and there is much less data regarding the prevalence of LTBI. While data from NHANES has been used to estimate the prevalence of LTBI amongst the foreign-born in the United States, this number groups people originating from all regions of the world. Some state and local health departments have published data about TB prevalence in their individual refugee or immigrant populations, but these samples rarely capture more than a single culture or world region.

Invariably, world regions, if not individual countries, often have a different population prevalence of LTBI. Refugees in particular, often live in camps that function like crowded cities with large families living within confined spaces. Such conditions are optimal for the proliferation of TB. Therefore, knowing the prevalence of LTBI amongst the refugee populations most commonly arriving in the United States and which specific refugee populations to target is essential for TB prevention strategies.

Refugee Status and the Resettlement Process

The United Nations established the United Nations High Commission on Refugees (UNHCR) in their 1951 Refugee Convention. In this convention, a refugee was defined by the

United Nations as someone who "owing to a well-founded fear of being persecuted for reasons of race, religion, nationality, membership of a particular social group or political opinion, is outside the country of his nationality, and is unable to, or owing to such fear, is unwilling to avail himself of the protection of that country" [3]. The United States Department of State follows these same guidelines, with the exception of allowing persons from the former Union of Soviet Socialist Republics (USSR) and the Middle East to file from within their country of nationality.

The basic process for a refugee to resettle from a temporary refugee center to a permanent location in another country is a follows: First, they file for refugee status with the UNHCR. Then the UNHCR evaluates the best option for a permanent location for the refugee, including potential resettlement to a secondary country that is not their original or temporary location. If it is determined that resettlement in a secondary country is the best option, the UNHCR will submit a request to that country. If the request is sent to the United States, the Department of State conducts necessary screening processes to determine whether or not to accept the refugee's application for resettlement. Part of the screening process is a medical examination to identify or rule out infectious diseases that present a public health threat to the United States population or diseases that may make the refugee unfit for travel. One of the primary infectious diseases of concern is TB and a large portion of the medical screening is devoted to ruling out this disease as defined in the next section.

Tuberculosis Disease Process

TB is caused by the bacteria *Mycobacterium tuberculosis*. This disease is airborne and is spread through coughs, sneezes, or respiratory droplets [4]. A person must inhale droplet nuclei which then must reach the alveoli of the lungs to become infected [4]. Within 2 to 8 weeks, the immune system forms a shell around the TB bacilli called a granuloma[4]. The shells keep the bacteria under control resulting in LTBI. When the immune system cannot keep the TB bacilli controlled, bacilli can multiply resulting in active TB, also called TB disease [4]. Once a person is infected, there is a 10% lifetime chance that the disease will progress to active TB [4]. As much as

one third of the world's population is purported to have LTBI that has not progressed to active TB. Persons with LTBI serve as a reservoir for resurgence of the disease, especially when immune systems are compromised by other diseases or age, and can no longer control the bacteria. Most people with LTBI will never progress to develop TB disease, but because a third of the world's population carries the latent infection, the magnitude of the likelihood of TB resurging remains strong.

Pulmonary TB disease is considered to be the most common, although TB can affect body organs other than the lungs, resulting in what is called extrapulmonary TB. Pulmonary and laryngeal TB (TB of the larygnx) are considered to be the most contagious forms of active TB while extrapulmonary TB is rarely determined contagious.

There are a few important differences between active and latent TB which guides the policy decision to make active TB a disease of public health significance that requires mandatory screening and LTBI a disease for which screening and treatment is recommended and considered voluntary. With LTBI, the bacteria are considered to be alive, but in a dormant state in which the TB bacteria are non-infectious. Therefore, LTBI is rarely contagious, and is not a public health threat. For this reason, there is no mandatory screening for LTBI. On the contrary, persons with TB disease are often infectious and may feel sick, which is why screening is mandatory.

Tuberculin skin test (TST) is the most commonly used initial screening measure to determine exposure to *Mycobacteria tuberculosis* and both LTBI and TB can spur positive results. The standard follow-up to a positive TST is a chest X-ray, which, if positive, can be used to diagnose active pulmonary TB disease. If the chest X-ray is normal despite a positive TST, then the diagnosis is usually LTBI. If the chest X-ray is abnormal, sputum smears and cultures are taken and, if positive, confirm a diagnosis of TB disease. Therefore, chest X-rays and sputum smears and cultures are used to diagnose the difference between active TB disease and LTBI as a follow-up to positive TSTs. If diagnosed with LTBI, the next consideration on behalf of the patient is prophylactic medication to prevent the development of TB disease.

The efficacy of screening measures and long duration and side effects of LTBI prophylactic treatment have, until recent developments, been considered barriers to LTBI screening and treatment programs in immigrant populations [5]. Approximately 10% of those tested with TST would result in false positives reactions[5]. Furthermore, LTBI treatment up until recently required six to nine months of treatment with daily isoniazid, which, aside from the length of treatment, has problems of hepatoxicity and compliance issues [5].

Taking these barriers into consideration and since LTBI is not considered contagious, the current TBTIs issued by CDC for immigrant and refugee overseas medical exams do not require screening or treatment for LTBI prior to entry to the United States. Only treatment for TB disease is required for entry to the United States, although experts continue to argue that prophylactic treatment for LTBI is essential for lowering the numbers of incident cases of TB in the United States by lowering the rate of disease progression from latent to active TB[2].

In CDC's opinion, prevention of TB through LTBI treatment has the potential to greatly enhance current TB control efforts. Recent FDA approval of a three month, once weekly, rifapentine and isoniazid LTBI treatment has demonstrated increased compliance since it is easier for patients to follow and shows promise of less hepatoxicity[6]. Considering these new research developments, the potential implementation of a voluntary screening and treatment program may have strong results in stopping the spread of TB in refugee populations.

Tuberculosis Epidemiology in the United States

In 1989, the CDC established plans for TB elimination in the United States (defined as an annual incidence of < 1 case/million) [7]. This section reviews recent studies which indicate that expanding treatment for LTBI, especially amongst the foreign-born, can achieve CDC goals for TB elimination faster than increasing current practices of TB contact tracing and treatment.

TB disease disproportionally affects the foreign born. In 2011, persons born outside the United States and who did not have at least one American parent, had a rate of incident TB 12 times greater than persons born within the United States resulting in an incidence of 17.3 per

100,000 amongst the foreign born [8]. While this rate is much higher than amongst those born in the United States, this marks a 4.8% decrease in TB disease incidence between 2010 and 2011 amongst the foreign born and an overall 49% decrease in TB disease incidence between the years of 1993 and 2011 for the same population[8].

A recent 2008 study by Cain et al. looked at sub-groups of the foreign born and determined that 53% of the cases of TB disease between 2001 and 2006 in the United States occurred in individuals originating from countries in sub-Saharan Africa and Southeast Asia [1]. The publication reported results of a study that demonstrated that even amongst the foreign born stratified by country of birth, recent immigrants had 3 to 7 times higher TB disease incidence compared to non-recent immigrants[1]. For example, between the years of 2001 and 2006, Somalia, a country in the top ten for sending refugees in 2011[9], had a TB case rate as high as 889 per 100,000 for the first two years after arrival [1].

Typically, TB disease prevention in the United States has focused on contact tracing and treatment of recent contacts instead of screening and treatment of LTBI[1]. This works for persons who were recently exposed to TB in the United States, but does not help to identify immigrants or refugees who were exposed abroad or who had lived in a TB endemic country prior to arrival. Furthermore, molecular genotyping has shown that TB disease amongst the foreign born is usually due to progression of LTBI to active disease [1,10]. This means that the foreign born often develop the disease after a period of latency, often termed "reactivation TB", instead of TB disease due to a recent contact with an infectious individual. Additionally, a recent study showed that this reactivation amongst the foreign-born is most likely to occur within the first two years after arrival in the United States[10] indicating that early prevention efforts may be most effective.

Molecular genotyping has been able to determine the proportion of reactivation TB amongst the foreign born. Persons arriving from Myanmar, Nepal, Thailand, Ethiopia, and Somalia respectively have 93.3%, 90.3%, 86.8%, 81.3%, and 78.6% of genotype -determined reactivation TB [10]. Therefore, contact tracing is unlikely to identify these individuals with LTBI

and they would unlikely be offered latent treatment if the primary method of identifying LTBI were contact tracing. Since LTBI leads to such high incidence of TB disease within two years of arrival, and was likely acquired prior to arrival in the United States, multiple sources suggest targeting particular foreign born groups for LTBI screening and treatment, specifically persons from sub-Saharan Africa and Southeast Asia [1,10].

Furthermore, a recent mathematical model of TB trends in the United States showed that since early identification and treatment of TB disease cases is already high in the United States, additional disease treatment is unlikely to substantially decrease TB incidence[2]. They found, however, that time to TB elimination goals can be reduced by about 20 years if treatment for LTBI is doubled in the United States. The authors of the math model note that LTBI treatment is important amongst the foreign-born since quadrupling the LTBI treatment in this population would expect to cause a decrease from 17.7 per million TB incidence in 2100 to 5.7 per million [7]. Further, a continuing challenge to decrease incidence amongst the foreign-born is the continual arrival of new immigrants and refugees. This mathematical model supports the conclusions of other published work that targeted testing and treatment of LTBI amongst the foreign-born is essential to reaching TB elimination goals[10].

Current United States Tuberculosis Screening Program for Refugees

As described above with the TBTIs, refugees are routinely screened for active TB overseas; with adults receiving chest X-rays and children (<15 years of age) receiving a TST first and then chest X-rays if TB disease is suspected. The TST was implemented as standard screening for children in the updated 2007 version of TBTIs issued for countries with a high burden of TB. Even though LTBI is not a disease that prevents entry to the United States, this new procedure of administering TSTs in children prior to X-rays screens for LTBI as a byproduct of determining whether or not the children also need chest x-rays to rule out active TB while avoiding exposing children who test negative to unnecessary radiation. If a child tests positive with TST and is determined non-infectious and fit for travel, he/she is referred for follow-up in

the United States. However, since screening with TST is not a part of the formal medical protocol for adult refugees age 15 and older, many adults enter the United States not knowing they have LTBI and that they should follow-up for diagnosis and treatment.

A large proportion of refugee populations come from countries with high TB prevalence and incidence rates, implying an increased chance of LTBI and subsequent progression to active TB once in the United States. As discussed previously, foreign-born persons have the highest rate of progression to active TB within the first years of arrival in the United States[1,10]. While refugees are supposed to be screened for LTBI upon arrival in the United States as part of their follow-up health screening, individual states have different protocols, and this process does not always function as efficiently as intended. Even current guidelines where screening should take place within 90 days after arrival in the United States leaves a gap of time from screening abroad (up to 6 months prior to departure under current protocol) until screening in the United States in which persons with LTBI can progress to active TB. This gap in time is particularly critical because the likelihood of progression to active TB is higher in the first couple of years after arrival.

Trends in Refugee Follow-up

Abroad, refugees are a captive audience awaiting approval for travel to the United States, and are treated at the same time in large groups. The overseas setting may allow for more uniform and complete treatment of LTBI than is available after refugees resettle to the United States. Once in the United States, refugees have a very complex agenda and are searching for employment, finding housing, learning a language and getting children their enrolled in schools. Further, on arrival refugees are distributed to many states, and each state has a different process of medical follow up. For many refugees, medical follow up takes second place to other life priorities such as finding a home or job and not every state emphasizes the priorities of medical follow up.

Using CDC and state department of health data that keeps track of refugee and immigrant health screenings, a few studies have looked to quantify the actual proportion of refugees who obtain suggested medical care. This section looks at the findings of these studies as well as the likelihood that if the person obtains medical follow-up, the likelihood that they will accept medical treatment.

One measure in place to communicate medical findings from overseas to attending physicians in the community of resettlement is the Electronic Disease Network (EDN). The EDN is a notification system and database run by CDC that includes data from overseas panel physicians and local public health departments in the United States. Physicians contracted by the IOM, called panel physicians, input their screening data for all refugees into this system. This system then uses the data from the overseas panel physicians to notify public health departments of recent immigrants with health conditions of concern arriving within the health department's jurisdiction. Refugees with a history of previous TB, suspected TB, or an abnormal chest X-ray are considered at higher risk for active TB and flagged in the EDN. A notice is then sent to the receiving health department. In this notice, the CDC requests that the health department report back to the CDC through the EDN on the results of the refugee's follow-up.

Of refugees flagged in the EDN as being at higher risk for developing active TB, the CDC finds that only 62.3% of refugees complete follow-up for a variety of reasons. The CDC does not hear back from the health departments about the outcome of follow-up for 28.1% of refugees; 6.7% of refugees are documented to have never started the follow-up process; and 2.9% of refugees do not complete the follow-up process. This information from the CDC suggests that follow-up may range between 62.3% -90.4%[11], substantiating the claim that that follow-up for LTBI presents a challenge for refugees once they are in the United States. Not only is follow-up an issue, but acceptance and completion of LTBI prophylactic regimens presents an issue as well.

Treatment Acceptance and Completion

While there are benefits to be gained from LTBI treatment from a societal perspective, the patients for whom treatment is recommended face challenges of compliance or acceptance of treatment and completion of drug regimens. A recent study showed that in the United States and Canada, 23.4% of those that are foreign-born decline prophylactic treatment for LTBI [12]. This study was based upon the commonly offered nine month regimen of isoniazid. 52.5% of these foreign-born persons who accepted treatment did not complete this regimen. While acceptance is relatively high, the authors conclude that completion is low. However, a new, shorter LTBI regimen recently passed clinical trials and was approved by the CDC for use. Due to its shorter treatment duration, it shows promise of increased compliance.

This drug regimen requires that patients take rifapentine and isoniazid once a week, for three months, which is a third of the normal treatment time and only requires one day of treatment a week instead of daily. In contrast to a longer, isoniazid only regimen, this combination drug therapy had 82.1% completion[6]. Additionally, the proportion of patients with hepatotoxicity was lower in the combination therapy group (0.4%) compared to the isoniazid only group (2.7%)[6]. This study shows that making LTBI prophylactic treatment easier to finish boosts compliance and results in more persons protected for the number initially started on treatment. Therefore, if such a regimen were used with refugees, likely more persons from high TB incidence countries would complete therapy.

Additionally, the literature supports the notion that LTBI treatment acceptance and completion may be dependent upon where the treatment is supplied, overseas or in the United States. I would expect that acceptance and completion would be higher if administered abroad in either a refugee camp or refugee urban setting prior to arrival in the United States, due to competing agendas upon arrival in the United States. Some studies abroad have documented higher completion rates, even with the more complex, nine month isoniazid regimen.

Looking at isoniazid completion in Uganda amongst those with human immunodeficiency virus (HIV) positive patients given prophylactic treatment for LTBI, there was overall 89% completion[13]. While this population may not be an appropriate match for a refugee population, this shows the variability in LTBI therapy completion compared to Sterling et al.'s study which was conducted in the United States, Canada, Brazil and Spain[6]. Of the various completion studies, one would expect acceptance and completion to be closer to the study in Uganda since studies administering voluntary ivermectin parasite treatment overseas to refugees showed compliance near 100% (CDC unpublished information).

Further Challenges and Considerations for LTBI Treatment and TB Prevention

One study by Guh et al. interviewed 156 foreign-born persons with TB disease in Connecticut between June 2005 and December 2008[14]. While current recommendations include LTBI screening for foreign-born persons residing in the United States less than 5 years, they showed that only 67% of foreign-born TB cases had been previously screened for LTBI[14]. Of the 48 persons who had a TST and could remember their result, only 48% (12 out of 25 positive persons) of persons with a positive result had reported completing LTBI prophylactic treatment. Furthermore, arriving from Africa, Europe, or Asia was predictive of not having had a prior TST[14]. Similar low compliance was also observed in those born in the United States. As previous studies discussed have shown, two of these regions which often failed to have a prior TST, Africa and Asia, have been shown to be regions of prime concern for reactivation TB [1,10].

Additionally, Slopen et al. have conducted a study in New York City using the New York TB registry to identify TB disease cases they classified as "preventable." "Preventable" cases were defined as "inappropriate screening of contacts and immigrants, inappropriate treatment of persons with prior TB diagnoses, or those who tested positive for latent TB infection (LTBI) as contacts, immigration, or in community settings." [15] The study showed that 47% of the missed opportunities to prevent TB disease was due to failing to start LTBI treatment for patients that had been diagnosed with LTBI [15]. The authors noted that of the foreign-born TB cases

interviewed, only 31% entered the United States with an immigration status requiring screening upon entry. Of these persons, 25% were not screened for TB as part of their medical exam [15]. This highlights the difficulty of domestic screening since these vulnerable persons invariably fall through the cracks in the medical system once they arrive in the United States.

Epidemiologic Methods

There is very little data regarding the prevalence of LTBI in refugees both because the originating countries do not keep the data, and because adult refugees are not tested for LTBI prior to entering the United States. Therefore, this study uses original data from two states that record the results of TSTs administered to refugees after arrival to estimate prevalence of LTBI in refugee populations. The Minnesota and Georgia Departments of Health keep anonymous, refugee TB and LTBI screening data (primarily TST screening data), and provided this de-identified data, along with pertinent demographic information, for use in this study. Since this data was pre-collected and de-identified, this study was ruled exempt from human subject requirements by the Institution Review Boards at Emory University, Georgia Department of Health, Minnesota Department of Health, and CDC.

The Georgia Department of Health had available refugee screening information for the years 2005 through 2011. The Minnesota Department of Health had available data for the years 2006 through 2010. A total of 17,962 persons arriving in the United States fit the definition of refugee status from the Georgia and Minnesota data sets for the years specified. 28.1% of refugees from the Georgia Department of Health and 12.1% of refugees in the Minnesota Department of Health data were excluded from the analysis for incomplete TST results. Of the restricted data for those refugees whose TST result was known (n=14,141), Minnesota (n=6,742) and Georgia (n= 7,399) data were combined for common variables to capture current immigration, disease, and demographic trends of refugees from high TB prevalence countries. Countries of origin were collapsed into regions in order to increase sample sizes within groups

(Africa, Asia, Middle East, Eastern Europe, and Latin America). Basic demographic information was displayed by sex, state the refugee immigrated to, and world region of origin.

The outcome of interest was a positive TST. Positive TST status was determined by a recorded "abnormal" TST result (based upon 10mm induration or greater) within the Georgia data set (Georgia coded this information as a yes or no categorical variable) or 10mm induration reading and above for Minnesota. In keeping with the literature for estimating LTBI in this population[16-19], a positive TST at 10mm induration or above was considered LTBI.

For refugees who migrated to either Minnesota or Georgia, student T-tests were used to compare means and Satterwaite test statistics were used if variances in the populations compared were unequal. Chi-Square Tests of Significance were used to compare crude data for categorical groups between the two states. Mean age (mean +/- standard deviation), sex (n (%)), and TST status (number positive (%)) was also computed by world region as well as unadjusted odds ratios.

Conditional logistic regression was performed with region of origin as a primary predictor. The model conditioned on state of arrival (Minnesota or Georgia) and considered controlling for gender and age as well as potential interaction between gender and age, gender and region, and region and age. Potential collinearity was assessed by consideration of condition indices (CI) greater than 30 [20] and variance decomposition proportions (VDP) greater than 0.5 [20]. A backwards elimination procedure was used and model parameters were considered statistically significant at alpha = 0.05. Likelihood ratio tests were used to compare models and statistical significance was held at 0.05. A variable was considered to be a confounder if it altered any of the region estimates by greater than 10%.

A second analysis was conducted on the Georgia data since this state provided more health indicators than the Minnesota data set. Frequencies and unadjusted odds ratios were calculated. A subsequent unconditional logistic regression analysis assessed whether or not there was an association between TST and other health indicators, such as pregnancy status, syphilis

status, hepatitis screening (hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis B surface antibody (anti-HBs)), vaccination status for hepatitis B, diabetes status, anemia, and malnutrition. All potential indicators were tested for interaction with region. Again, potential for collinearity was assessed by consideration of condition indices (CI) greater than 30 and variance decomposition proportions (VDP) greater than 0.5. A backwards elimination procedure was used and model parameters were considered statistically significant at alpha = 0.05. Likelihood ratio tests were used to compare models and statistical significance was held at 0.05. A variable was considered to be a confounder if it altered any of the region estimates by greater than 10%. Adjusted odds ratios were obtained from a full model with all variables and the final model with a reduced number of variables after backwards elimination. Unadjusted odds ratios and their confidence intervals were calculated using OpenEpi version 3.0 and all other analyses were performed using SAS version 9.3.

Results

The mean adult refugee age in Minnesota of 31.1 years (SD= 16.3 years; Table 1) and in Georgia of 32.3 (SD = 13.6 years; Table 1) years of age were statistically different (p-value <0.01). Fifty-one percent of adult refugees in Minnesota were male, while in Georgia, 49.0% were male (p-value <0.01). The largest differences, however, are the composition of world regions of origin. Minnesota had 73.1% of persons from Africa, while during a similar time period, only 26.9% of incoming refugees to the state of Georgia arrived from Africa (p-value <0.01). In contrast, 46.5% of the refugees resettled in Georgia were from Asia compared to only 19.7% of refugees in Minnesota (Table 1).

In addition to demographic differences, Minnesota has more refugees that test positive with Tuberculin skin test (TST) compared to Georgia. 46.1% of refugees during this time period tested positive with TST compared to 25.3% in Georgia. However, Georgia has a larger proportion of incomplete TST results; 28.1%, compared to only 12.1% of refugees in Minnesota (Table 1). Although persons missing a TST are not considered further in the analysis, the

prevalence estimates of TST in the two states may not be comparable because of this difference in the prevalence of missing data.

Information was also collapsed on state and stratified by world region to determine demographic differences. The distribution of age groups by region (15-24 years, 25-44 years, 45-64 years, and $\geq$ 65 years) were statistically different. For example, 57.8% of persons from Africa were between the ages of 15 and 24 while only 35.6% of refugees from Asia and 54.9% of refugees from the Middle East fell within the same age category (Table 2). These age groupings allowed for comparison of data to NHANES TST results for 1999-2000.

Within this stratified data by region, crude odds ratios and adjusted odds ratios (adjusted for age category, sex, region, and the interaction between age and region; Table 3b) of age categories by region (ages 15 to 24 as the referent group) showed initial increases in the odds of a positive TST with increasing age. This increase leveled off in the oldest age category for each region. For example, persons between the ages of 25 and 44 in Asia had 2.21 times the unadjusted odds of a positive TST compared to persons in the 15 to 24 age range (CI 1.92-2.54; adjusted odds ratio 2.33; adjusted CI 2.03-2.69). Between ages of 45 and 64, the point estimate slightly decreases and these persons have 2.05 times the odds of a positive TST compared to the youngest age category (Table 2; Table 3b adjusted odds ratio 2.16; adjusted CI 1.78-2.61). Persons in the 65 and older age category in Asia have 1.44 times the odds of a positive TST compared to those between 15 and 24 year old (Table 2; Table 3b adjusted odds ratio 1.48; adjusted CI 1.07-2.05). While there is no consistent trend in unadjusted and adjusted odds ratios of a positive TST by region and age category, the odds of a positive TST tends to increase as a person gets older (Table 2 and Table 3b) as compares to the youngest age category.

The proportion of persons presenting with a positive TST in the combined Minnesota and Georgia Health Department data differed by region (p-value <0.01). The unadjusted proportion of refugees arriving from African countries who had a positive TST upon screening in the United States was 53.6%. Refugees from the Asian region had a proportion of 35.5% positive TST

results. 23.7% of persons from the Middle East had positive TST results while 42.1% of persons from Eastern Europe had positive TST results. This compared to only 20.8% of persons from Latin America with a positive TST (Table 2).

Multivariate Analysis

After backwards elimination conditioning on state (Georgia or Minnesota), the final model included sex, categorical age, region of origin, and the interaction between region and age (Table 3b). The results of the conditional logistic regression show that men are 85% more likely than women to have a positive TST (CI 1.72-1.98; Table 3a). Controlling for state (Minnesota or Georgia), age, and sex, refugees arriving from Africa have 4.16 times the odds (CI 3.03-5.72; Table 3a) of a positive TST compared to persons from Latin America (the region with the lowest crude odds in this analysis). Asia has 2.07 times the odds of positive TST compared to Latin America controlling for the same variables, the Middle East has 1.16 times the odds and Eastern Europe has 2.77 times the odds compared to Latin America (Table 3a).

As age increased (controlling for state, region, and sex), the trend of having a positive TST increased initially compared to the youngest age group then decreased in the highest age group (Table 3a). Refugees in the 25 to 44 year old age category had 1.70 times the odds of a positive TST compared to persons in the 15 to 24 year age group (CI 1.56-1.85), while the 45 to 64 age group had 1.67 times the odds compared to the youngest age group (CI 1.51-1.86). While those greater than or equal to 65 years of age had a point estimate of 1.15 times the odds of a positive TST compared to those in the youngest age group. However, this was not statistically significant likely due to the limited number of persons in the oldest age category (CI 0.96-1.37).

When looking at the effect of region within age groups, Africa, Asia, and Eastern Europe all have statistically significant higher adjusted odds of a positive TST compared to Latin America (adjusted for sex, age category, region, and the interaction between region and age). For example, in the youngest age category, refugees from Africa have 12.6 times the odds of a positive TST compared to Latin Americans in the same age category (CI 3.91-40.73; Table 3b).

The Middle East has adjusted odds of a positive TST higher than Latin America, however, these findings are only statistically significant in the youngest age category.

Georgia Sub-Analysis

The sub-analysis for the Georgia data included sex, age category, region, pregnancy status, syphilis status, hepatitis B screening results (HBsAg, HBcAb, anti-HBs), hepatitis vaccination status, hypertension status, diabetes status, as well as anemia test results. Of the unadjusted odds ratios of TST status by the covariates listed above, only two of the three hepatitis B tests (HBcAb and HBsAg), vaccination status for hepatitis B, and diabetes were found to have unadjusted odds ratios that were statistically significant (Table 4a). HBcAb and diabetes were marginally significant (HBcAb crude OR 1.25; CI 1.03-1.52; Diabetes crude OR 2.12; CI 1.06-4.26**).**

After backwards elimination of the unconditional logistic regression model, only sex, region, age group, hepatitis vaccination status, and one of the hepatitis screenings, HBsAg, were significant predictors of a positive TST in the final unconditional logistic regression model. The interaction between age and region were unable to be considered in this model since the model would not converge with these interaction terms included. There was no collinearity observed between the different hepatitis B tests. No significant interactions were observed in this model.

Similar to the combined dataset, male refugees in Georgia were 78% more likely to have a positive TST compared to females. Compared to persons from Latin America and controlling for all variables mentioned above in the final model, refugees from Africa had 6.84 times the odds of a positive TST (CI 2.70-17.37; Table 4b). Persons from Asia had 5.20 times the odds compared to Latin Americans (CI 2.06-13.12) and persons from Eastern Europe had 5.15 times the odds (CI 1.92-13.86) compared to Latin Americans. Middle Easterners did not have a statistically significant difference compared to persons from Latin America, despite and odds of 2.08. The confidence intervals for the Middle East were wide, likely due to sparse data.

Georgia data followed the overall age trend detailed above in that the odds of a positive TST increases with age with 1.59 (CI 1.29-1.94), 1.62 (CI 1.20-2.20) and 1.51 (CI 0.28-8.31) times the odds compared to ages 15 to 24 controlling for the variables in the final model for age groups 25 to 44, 45 to 64 and age group 65 and over respectively (Table 4b).

Interestingly, refugees vaccinated for hepatitis B were 74% more likely to have a positive TST compared to those were not vaccinated (CI 1.25-2.41). Additionally, those positive for HBsAg were 1.61 times more likely to have a positive TST result.

Discussion

The most important results from this study, as measured by usefulness in public health policies and programs, are knowing the prevalence of LTBI among refugee populations arriving in the United States as well as which demographics and health indicators are related to LTBI from the multivariate models. As expected, the refugee populations in Minnesota and Georgia had statistically significant differences in TST results (p-value <0.001; Table 2), in part because refugees in each state come from different regions. Over 50% of refugees from African countries had positive TSTs while refugees from Asian, Middle Eastern, Eastern European, and Latin American countries had positive TSTs of 35.5%, 23.7%, 42.1%, and 20.8% respectively (Table 2). Armed with this knowledge, public health departments can plan on prioritizing resources for LTBI treatment for refugees that may not already be allocated. Additionally, knowing that HBsAg and vaccination status for hepatitis B are related to a positive TST also helps practitioners plan treatment strategies. Additionally, these findings can be compared with other studies.

Bennet et al. published an article comparing the 1999-2000 NHANES data comparing the prevalence of LTBI in the United States to the only other country-wide survey estimate of LTBI from 1971-1972. Here, the findings from Bennet et al.'s analysis of NHANES data are compared to the results of this study to see how the refugee populations studied in this analysis compare to the United States population at large, as well as the overarching foreign-born population in the United States. Similar to this study, the case definition for LTBI in Bennet et al.'s study was a

TST reaction of 10mm or greater[16]. However, they also used an alternative definition of 15mm or greater or between 5mm and 15mm and at least 2 mm greater than a reaction to PPD-B, which has been used to determine if those with a positive TST are more likely to progress to active TB[16]. A limitation of the comparison made here is that this thesis data does not contain information related to the second case definition considered in their study since PPD-B was not used for LTBI screening in either Georgia or Minnesota.

Our study and Bennet et al.'s study arrive at similar results with respect to the effect of age on LTBI prevalence. As persons age, they are more likely to be exposed to TB bacteria and therefore, are more likely to have a positive TST. The general trend in the 1999-2000 NHANES data is that LTBI/TST positive prevalence increases as age increases and then slightly decreases in the highest age group[16]. The crude prevalence of a positive TST across the age categories for Africa, Asia, Eastern Europe and Latin America follow a similar trend as seen in the NHANES data. The Middle Eastern region deviates slightly from the other regions in that the crude prevalence of a positive TST continues to increase in the oldest age category instead of decreasing slightly. While the crude data follows a similar trend as documented in the literature, the overall prevalence estimates in our study are much higher than in the NHANES data with regard to TST prevalence within age categories.

As compared to the United States population at large which includes both domestic and foreign-born individuals, almost every age category within each of the five regions in our study had a much higher positive TST prevalence. In the NHANES data, the highest prevalence of LTBI for the entire United States population was 6.5% occurring between the ages of 45 and 64[16]. This compares to 58.1% in Africa, 40.5% in Asia, 31.5% in the Middle East, 46.7% in Eastern Europe, and 24.6% in Latin America for the same age category. Latin America has the lowest prevalence, but it is still 3.8 times that of the United States population at large for the same age group.

Bennet et al. categorize race and ethnicity as non-hispanic white, non-hispanic black, Mexican American, and other. In our analysis, refugees arriving from Latin America are more likely to have a positive TST compared to the Mexican/Mexican Americans in the 1999-2000 NHANES data. In the NHANES study, 9.4% of Mexicans and Mexican Americans were estimated to have LTBI[16] while those with refugee status arriving from Latin America to either Minnesota or Georgia were estimated to have a 20.8% prevalence of LTBI. When Bennet et al. differentiate between foreign-born and United States born Mexican Americans, those that are foreign-born have a 19.1% prevalence of LTBI, which is similar to the Latin American prevalence in our analysis[16].

Yet another means of comparison between our study and other studies is the effect of gender on positive TST outcomes. In our study, males were 85% more likely than females to have a positive TST controlling for region and age category. This compares to Bennet et al.'s study in which males within the foreign-born population had twice the odds of LTBI compared to females in the same population[16]. Both studies show that males are more likely than females to be exposed to TB bacteria and become infected with TB.

Other studies have estimated the burden of LTBI in various foreign-born, immigrant, and at times, specific refugee populations. While these studies may not be comparable due to different data and different populations, their results support our estimates for LTBI. For example, Varkey et al. found that the prevalence of a positive TST amongst refugees arriving in Minnesota between the years of 1997 and 2001 to be 50.7% [17]. While their analysis does separate the analysis by continents, our analysis updates that information, samples from two states, and incorporates a higher sample size from Latin America and includes the Middle East, which was not sending refugees in high numbers during that time period.

San Diego County Health Department in California analyzed Iraqi refugees arriving between October 2007 and September 2009 [19]. It was reported that Iraqi refugees over 1 year of age had an LTBI prevalence of 14.1% when testing children less than 12 years with a TST and

persons aged 12 and older with Interferon-Gamma Release Assays (IGRA) [19]. This compares to 23.7% positive results for adult Middle Eastern refugees 15 years and older tested with a TST in our analysis. Comparing persons 65 years and older, our analysis had a positive TST prevalence of 34.8% compared to an LTBI estimate of 52.3% in this age category for San Diego County[19]. The difference in prevalence for this age category may be due to the small number of persons in our analysis who fit this description (23 people), the inclusion of other Middle Eastern countries in our data, as well as the different screening type (TST versus IGRA).

Another study in the District of Columbia (DC) analyzed a refugee population in which 93% of the refugees and asylees emigrated from Africa. The DC analysis classified persons as having LTBI with a TST induration greater than or equal to 10mm. Of the refugees in their analysis which included children, 38% were considered to have LTBI[18]. This percentage is between the prevalence for Minnesota (46.1%) and Georgia (25.3%) which further emphasizes that each state/ resettlement area has a different burden of LTBI requiring a different amount of public health planning and resource allocation (Table 1). Furthermore, even estimates for a region can be altered by the inclusion or restriction of children from an analysis due to the greater likelihood of LTBI in older age groups.

Overall, while some regions in this analysis can be compared to other findings in the literature, not one previous study or combination of studies can be directly applied to this analysis. One reason is the differences in screening methods for LTBI, e.g. use of IGRA instead of TST, while other analyses may comprise a separate refugee population or the inclusion of children in the analysis. Our analysis did not include children. Even when screening methods and age categories are the same, the populations studied are different. However, the data in our analysis shows that one can reasonably expect the populations from Georgia and Minnesota to follow similar trends as documented in the literature with regards to age and gender.

Multivariate Analysis

Few other studies have looked at refugees arriving in the United States and their odds of LTBI adjusted for demographic factors and other covariates to determine potential associations between LTBI and other health indicators. The variables age group (defined in this analysis as 15-24; 25-44; 45-64; $\geq$ 65), and sex in the combined Minnesota and Georgia data were significantly related with a positive TST result in a multivariate model, which is comparable to the findings in Bennet et al.'s study [16]. Additionally, our study was able to consider region of origin and found an important interaction between region and age indicating that consideration must be given to the interactive effect of region and age as a predictor of a positive TST. For example, a refugee between the ages of 15 and 24 from Africa has 12.6 times the odds of a positive TST compared to a refugee from Latin America, but within the same age range (Table 3b).

Using the additional information provided in the Georgia data, we were able to determine which health diagnoses were associated with a positive TST. While diabetes, HBsAg, and vaccination for hepatitis B were associated with a positive TST in the crude data as demonstrated by the crude odds ratios and their confidence intervals, only HBsAg and vaccination for hepatitis B were associated with a positive TST in the unconditional logistic regression model controlling for sex, region of origin, and age group.

While HBsAg does not cause a positive TST, this correlation may suggest that those persons exposed to TB bacteria are also being exposed to hepatitis B. Persons with a positive TST may also be more likely to have contact with healthcare systems either domestically or abroad, and may therefore, have been more likely to have received a hepatitis B vaccine.

The findings of this analysis indicate that region of origin, age and sex are all significant indicators of a positive TST and possibly LTBI. Additionally, amongst refugees, persons who are HBsAg positive are 61% more likely to have a positive TST compared to the HBsAg negative. This may have important indications for TB and LTBI treatment. Many of the drugs used for TB

and LTBI treatment can cause inflammation of the liver and hepatoxicity. Knowing that a person is also likely to be HBsAg positive and may already have medical issues with his/her liver may remind physicians to take special precaution when treating TB and LTBI in refugee populations.

For individual patients, such a dual burden of disease can have important implications for successful resettlement and job-seeking in the United States. Many separate doctor appointments for both TB and hepatitis B disease may keep newly-arrived refugees from work or may hinder them from spending time searching for employment. If the person choses work over healthcare appointments, these infections may not receive appropriate medical attention, which may allow for progression of disease or complications later in life. Besides the consequences for the healthcare system, this has potential to affect the refugee and his/her family on a personal level since it may affect a parent's ability to attend work or a wage earner's ability to generate household income. A family illness like TB can be devastating to successful resettlement for people arriving with little more than a couple of suitcases, little to no savings, and the necessity of living from paycheck to paycheck while getting established in a new country.

LTBI Prevalence and Public Health Planning

As discussed briefly above, the prevalence of disease or conditions requiring medical attention can have a significant impact on local public health agencies and planning for building the capacity needed to address such needs. More than 80% of TB cases in the United States are the result of progression of TB bacteria from LTBI to active disease[12]. Historically, TB prevention efforts are focused on TB case finding and contact investigation. As Cain et al. suggest, however, to reach TB elimination goals, it is necessary to target the foreign-borne who most often have LTBI in the United States [2]. Furthermore, the foreign-born TB cases have comprised more than half of the cases of TB in the United States since 2001 and this proportion is increasing [8]. Therefore, a good number of cases of TB in the United States could be prevented by targeting foreign-born populations. One way in which to do so is prophylactic treatment of LTBI amongst the foreign-born.

In TB program planning, it is important to assess how many persons would need to be screened and treated prophylactically for LTBI. Bennet et al. showed using NHANES data from 1999-2000 that the prevalence of LTBI amongst all persons classified as foreign-born is approximately 18.7%[16]. While it is helpful to have an overall estimate of the burden of LTBI in the United States, this number does not allow public health departments to plan to target specific populations within their jurisdiction.

The results in the analysis reported here show that on average, 53.6% of refugees from Africa, 35.5% from Asia, 23.7% from the Middle East, 42.1% from Eastern Europe, and 20.8% from Latin America will test positive with a TST (Table 2). These estimates are limited to refugee populations from these areas and may also be a factor of their exact countries of origin or the conditions under which they lived prior to arrival in the United States.

As this data analysis of refugee populations in Georgia and Minnesota demonstrates, different world populations have varying prevalence of LTBI and that testing for LTBI and TB varies in regularity from state to state. Combined with the differential resettlement patterns by states, these results mean that in planning and building capacity for state and local TB programs, knowing the specific demographic composition of the local refugee populations can help to estimate prevalence of LTBI and aid in subsequent planning and allocation of healthcare resources.

Limitations

Limitations of this study include that: there is no information about BCG vaccination status; no details as to whether or not the person filed for refugee status in an urban environment or a refugee camp; and that the exact country of origin of the refugee had to be collapsed into region of origin. The implications of these limitations will be discussed in more detail.

Concluding that the proportion of positive TST results equals the proportion of persons with LTBI may not be entirely reliable because TST results may be confounded by the unknown BCG vaccination status of the subjects in the dataset. If vaccinated for TB using the BCG

vaccine, it is possible that a TST may result in a false positive[21]. However, vaccination with BCG does not preclude infection with TB bacteria and resultant LTBI, or prevent all cases from progressing to TB disease. Since many foreign countries vaccinate with BCG, some argue that IGRA is a more appropriate screening measure for the foreign-born since this blood test is able to distinguish between LTBI and false positives due to BCG vaccination [21,22]. A drawback of IGRA is that it is much more expensive compared to a TST[21].

Despite recommendations issued that IGRA may be a more appropriate screening measure for the refugee and overall foreign-born population, many states still use TST. Therefore, knowing the number of refugees to expect to test positive with a TST is of value to health departments since it provides an estimate of the number of refugees who are likely to require additional follow-up. Further, there are no other estimates of latent prevalence in these populations that are based on observed data.

Knowing more about living arrangements prior to immigration to the United States might be able to provide reasons as to why some regions, in addition to high TB prevalence, send refugees with high prevalence of LTBI. As mentioned previously, refugee camp settings can often be crowded with large families in single dwelling spaces. Such settings are known to cause the spread of TB.

Additionally, each country, or even sections of countries can have different social and living conditions affecting TB and LTBI prevalence. For example, a Somali refugee who arrived from a camp in Kenya compared to another African refugee who lived in an urban environment may not have the same odds of TB or LTBI, due in part to differences in living conditions. However, given the sparse numbers of refugees arriving from some countries, it was necessary to collapse the data. Despite doing so, there were at times sparse numbers within the age categories which contributed at times to large confidence intervals.

Conclusions

This study updates and adds region demographics to the current literature surrounding prevalence of positive TSTs which are often defined in the literature as indicative of LTBI. These prevalence findings help to inform local health departments regarding TB program capacity and planning for refugee populations arriving in their jurisdiction.

As demonstrated by this analysis, states typically resettle different proportions of refugees from various world regions. Factors such as age, sex, and region all affect the likelihood of positive TST results. Additionally, it was observed that there is an interaction between age and region, indicating that within each region, age category affects the odds of a positive result.

While each state has their own screening protocol for LTBI, many states, such as Minnesota and Georgia, initiate LTBI screening using a TST. Since TST results can be confounded by previous BCG vaccination or infection with other mycobacterium, it is necessary at times to use a more expensive IGRA to help differentiate between BCG vaccination and LTBI[22]. Regardless of whether or not IGRA or TST are used to screen for LTBI, both tests indicate follow-up in order to rule out active TB. Usually this process involves a chest X-ray and professional determination of active TB, LTBI, or no disease/infection by a physician. Therefore, false positives with an initial screening method, as with previous BCG vaccination, may be costly.

Economic analyses have been done in recent years to evaluate the potential public health outcomes and costs associated with using IGRA for LTBI screening[22]. Less has been done, however, to evaluate the impact of either TST or IGRA for screening and treatment for LTBI specifically for refugees prior to arrival in the United States and its potential impact for public health costs and programming.

While mandatory LTBI screening prior to arrival in the United States cannot legally be implemented since it is not an immediate public health concern, voluntary screening should be offered since knowing one's TST status prior to arrival in the United States may help facilitate

follow-up prior to a refugee securing employment. Offering screening with a TST would build on existing infrastructure for mandatory TST screening with refugee children for active TB. Offering IGRA, however, would require new infrastructure and may prove logistically difficult and costly in a refugee camp environment.

Additionally, offering voluntary treatment for LTBI prior to arrival in the United States would reduce the number of refugees who progress to active TB after arrival. The new, three month rifapentine and isoniazid regimen administered once weekly would be more feasible to administer in a refugee camp compared to nine months of isoniazid. Such a process would be shorter and therefore, easier to complete[6].

Offering such a program for refugees would not only afford persons more time once in the United States to focus on concerns other than healthcare, but would protect public health in the United States as well. Additionally, fewer public health resources would be expended on screening and treating TB disease domestically. To further substantiate this proposed program, we recommend an economic analysis comparing program options. Such an analysis would assess the potential costs and benefits of preventing disease and increasing compliance in addition to quantifying the resources needed to carry out such a project.

Tables

Table 1: Distribution of Age, Gender, Region, and TST Status by State

	Minnesota (6742) Mean (SD) / N (%)	Georgia (7399) Mean (SD) / N (%)	P-value
Age	31.1 (16.3)	32.3 (13.6)	<0.001[c]
Age Categories			
15-24 years	3,771 (55.9%)	2,626 (35.5%)	<0.001[b]
25 – 44 years	1,509 (22.4%)	3,468 (46.9%)	
45-64 years	1,106 (16.4%)	1,088 (14.7%)	
≥ 65 years	356 (5.3%)	217 (2.9%)	
Gender			0.03[b]
Male	3,439 (51.0%)	3,907 (52.8%)	
Female	3,303 (49.0%)	3,492 (47.2%)	
Region			<0.001[b]
Africa	4,931 (73.1%)	1,992 (26.9%)	
Asia	1,327 (19.7%)	3,443 (46.5%)	
Middle East	212 (3.1%)	1,067 (14.4%)	
Eastern Europe	271 (4.0%)	648 (8.8%)	
Latin America	1 (0.01%)	249 (3.4%)	
Tuberculosis Skin Test Status			<0.001[b]
Positive	3,537 (46.1%)	2,606 (25.3%)	
Negative	3,205 (41.8%)	4,793 (46.6%)	
Missing[a]	923 (12.1%)	2,898 (28.1%)	

Abbreviations: SD, standard deviation; N, number of participants with the characteristic
[a] These individuals were excluded from the combined data set. They are shown here to demonstrate the difference in missing data between states.
[b]Chi-Square Test of Significance used to calculate p-values
[c] Satterwaite Test used since variances unequal.

Table 2: Distribution of TST Status by Region, Mean Age, and Age Categories within Region

	TST Positive Mean (SD) / N(%)	TST Negative Mean (SD) / N(%)	Overall Mean (SD) / N (%)	Unadjusted OR (95% CI)
Region				
Africa				
Asia	3,710 (53.6%)	3,213 (46.4%)	-	4.40 (3.25-6.03)
Middle East	1,691 (35.5%)	3,079 (64.6%)	-	2.09 (1.54-2.88)
Eastern Europe	303 (23.7%)	976 (76.3%)	-	1.18 (0.85-1.66)
Latin America	387 (42.1%)	532 (57.9%)	-	2.77 (2.00-3.89)
	52 (20.8%)	198 (79.2%)	-	1.00
Mean Age				
Africa	30.8 (15.6)	29.1 (15.5)	30.0 (15.3)	-
Asia	34.7 (13.3)	31.8 (14.7)	33.1 (14.4)	-
Middle East	35.4 (12.8)	34.9 (15.7)	33.0(12.5)	-
Eastern Europe	36.7 (15.0)	34.9 (15.7)	35.7 (15.5)	-
Latin America	40.6 (10.7)	36.5 (13.7)	37.5 (13.2)	-
Age Groups				
Africa				
15-24 years	2,055 (51.3%)	1,945 (48.6%)	4,000 (57.8%)	1.00
25 – 44 years	881 (56.3%)	683 (43.7%)	1,564 (22.6%)	1.22 (1.09-1.37)
45-64 years	616 (58.1%)	445 (42.0%)	1,061 (15.3%)	1.31 (1.14-1.50)
≥ 65 years	158 (53.0%)	140 (47.0%)	298 (4.3%)	1.07 (0.84-1.35)
Asia				
15-24 years	423 (24.9%)	1,275 (75.1%)	1,698 (35.6%)	1.00
25 – 44 years	926 (42.3%)	1,263 (57.7%)	2,189 (45.9%)	2.21 (1.92-2.54)
45-64 years	280 (40.5%)	411 (59.5%)	691 (14.5%)	2.05 (1.70-2.48)
≥ 65 years	62 (32.3%)	130 (67.7%)	192 (4.0%)	1.44 (1.04-1.98)
Middle East				
15-24 years	68 (18.4%)	301 (81.6%)	369 (28.9%)	1.00
25 – 44 years	169 (24.0%)	534 (76.0%)	703 (54.9%)	1.40 (1.02-1.92)
45-64 years	58 (31.5%)	126 (68.5%)	184 (14.4%)	2.04 (1.36-3.06)
≥ 65 years	8 (34.8%)	15 (65.2%)	23 (1.8%)	2.36 (0.96-5.79)
Eastern Europe				
15-24 years	104 (37.4%)	174 (62.6%)	278 (30.3%)	1.00
25 – 44 years	170 (43.5%)	221 (56.5%)	391 (42.6%)	1.29 (0.94-1.76)
45-64 years	92 (46.7%)	105 (53.3%)	197 (21.4%)	1.47 (1.01-2.12)
≥ 65 years	21 (39.6%)	32 (60.4%)	53 (5.8%)	1.10 (0.60-2.00)
Latin America				
15-24 years	3 (5.8%)	49 (94.2%)	52 (20.8%)	1.00
25 – 44 years	33 (25.4%)	97 (74.6%)	130 (52.0%)	5.56 (1.62-19.02)
45-64 years	15 (24.6%)	46 (75.4%)	61 (24.4%)	5.33 (1.45-19.61)
≥ 65 years	1 (14.3%)	6 (85.7%)	7 (2.8%)	2.66 (0.09-29.47)

Abbreviations: SD, standard deviation; N, number of participants with the characteristic; OR, odds ratio

Table 3a: Conditional Logistic Regression Model with Risk Factors for Latent Tuberculosis Infection Amongst Refugees Arriving in Minnesota and Georgia[a]

		Adjusted OR (CI)	P-value
Sex			
	Female	1.0	<0.01
	Male	1.85(1.72-1.98)	
Region			
	Latin America	1.0	
	Africa	4.16 (3.03-5.72)	<0.01
	Asia	2.07 (1.51-2.84)	0.01
	Middle East	1.16 (0.83-1.63)	0.38
	Eastern Europe	2.77 (1.98-3.89)	<0.01
Age Group			
	15-24 years	1.0	
	25 – 44 years	1.70 (1.56-1.85)	<0.01
	45-64 years	1.67 (1.51-1.86)	<0.01
	≥ 65 years	1.15 (0.96-1.37)	0.14

Abbreviations: OR, odds ratio; CI, confidence interval

[a]Conditional logistic regression model controls for state, sex, region, and age group

Table 3b: Conditional Logistic Regression Model with Risk Factors for Latent Tuberculosis Infection Amongst Refugees Arriving in Minnesota and Georgia Including Interaction Between Region and Age[a]

Age groupings within Regions	Adjusted OR (CI)	P-value
Africa		
15-24 years	1.0	
25 – 44 years	1.45 (1.28-1.64)	<0.01
45-64 years	1.46 (1.27-1.68)	<0.01
≥ 65 years	1.01 (0.80-1.29)	0.92
Asia		
15-24 years	1.0	
25 – 44 years	2.33 (2.03-2.69)	<0.01
45-64 years	2.16 (1.78-2.61)	<0.01
≥ 65 years	1.48 (1.07-2.05)	0.02
Middle East		
15-24 years	1.0	
25 – 44 years	1.40 (1.02-1.92)	0.04
45-64 years	2.00 (1.32-3.02)	<0.01
≥ 65 years	2.44 (0.98-6.09)	0.06
Eastern Europe		
15-24 years	1.0	
25 – 44 years	1.31 (0.95-1.80)	0.10
45-64 years	0.28 (0.99-2.11)	0.06
≥ 65 years	0.92 (0.50-1.70)	0.80
Latin America		
15-24 years	1.0	
25 – 44 years	5.65 (1.65-19.42)	<0.01
45-64 years	5.26 (1.42-19.46)	0.01
≥ 65 years	2.75 (0.24-31.15)	0.41
Region Interaction with Age Groupings		
Ages 15 – 24		
Africa		
Asia	12.63 (3.91-40.73)	<0.01
Middle East	4.80 (1.48-15.51)	0.01
Eastern Europe	3.54 (1.07-11.73)	0.04
Latin America	9.23 (2.80-30.46)	<0.01
	1.0	
Ages 25-44		
Africa	3.24 (2.14-4.89)	<0.01
Asia	1.98 (1.32-2.98)	<0.01
Middle East	0.88 (0.57-1.35)	0.55
Eastern Europe	2.14 (1.37-3.35)	<0.01
Latin America	1.0	
Ages 45-64		
Africa	3.51 (1.92-6.41)	<0.01
Asia	1.97 (1.07-3.61)	0.03
Middle East	1.34 (0.69-2.62)	0.38
Eastern Europe	2.54 (1.32-4.87)	0.01
Latin America	1.0	
Ages ≥ 65		
Africa	4.65 (0.55-39.59)	0.16
Asia	2.58 (0.30-22.15)	0.39
Middle East	3.15 (0.32-31.40)	0.33
Eastern Europe	3.10 (0.34-28.01)	0.31
Latin America	1.0	

Abbreviations: OR, odds ratio; CI, confidence interval

[a]Conditional logistic regression model controls for state, sex, region, age group, and includes the interaction between age and region

Table 4a: Unconditional Logistic Regression Model for Georgia and Potential Health Conditions Related to TST Status [a]

	TST Positive N (%)	TST Negative N (%)	Crude OR[b] (CI)	Adjusted OR[b] (CI)
Anemia				
Yes	13 (2.0%)	23 (1.3%)	1.62	1.29
No	625 (98.0%)	1794 (98.7%)	(0.82-3.22)	(0.63-2.63)
Hepatitis B (anti-HBs)				
Yes	183 (28.8%)	494 (27.2%)	1.08	1.04
No	455 (71.3%)	1323 (72.8%)	(0.88-1.32)	(0.76-1.40)
Hepatitis B (HBcAb)				
Yes	206 (32.3%)	501 (27.6%)	1.25	0.98
No	432 (67.7%)	1316 (72.4%)	(1.03-1.52)	(0.72-1.33)
Hepatitis B (HBsAg)				
Yes	46 (7.2%)	75 (4.1%)	1.81	1.64
No	592 (92.8%)	1742 (95.9%)	(1.24-2.64)	(1.07-2.51)
Vaccinated for hepatitis B				
Yes	72 (11.3%)	128 (7.0%)	1.68	1.72
No	566 (88.7%)	1689 (93.0%)	(1.24-2.28)	(1.23-2.41)
Diabetes				
Yes	14 (2.2%)	19 (1.1%)	2.12	1.56
No	624 (97.8%)	1798 (99.0%)	(1.06-4.26)	(0.75-3.25)
Hypertension				
Yes	12 (1.9%)	21 (1.2%)	1.64	1.13
No	626 (98.1%)	1796 (98.8%)	(0.80-3.35)	(0.52-2.45)
Pregnant				
Yes	55 (8.6%)	152 (8.4%)	1.03	1.05
No	583 (91.4%)	1665 (91.6%)	(0.75-1.43)	(0.75-1.46)
Syphilis				
Yes	9 (1.4%)	21 (1.2%)	1.22	1.12
No	629 (98.6%)	1796 (98.8%)	(0.56-2.69)	(0.50-2.51)

Abbreviations: OR, odds ratio; CI, confidence interval; HBsAg , hepatitis B surface antigen; HBcAb, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody

[a]The adjusted odds ratios were calculated from the full unconditional logistic regression model which controlled for anemia, Hepatitis B (anti-HBs, HBcAb, HBsAg), hepatitis B vaccination status, diabetes, hypertension, pregnancy status, and syphilis diagnosis status, age group, region of origin, and sex.

[b] "No" is the referent category for all odds ratios in this table

Table 4b: Final Unconditional Logistic Regression Model for Georgia Data

	Adjusted OR (CI)[a]	P-value
Sex		
Female	1.0	
Male	1.78 (0.94-3.34)	0.08
Region		
Latin America	1.0	
Africa	6.84 (2.69-17.37)	<0.01
Asia	5.20 (2.06-13.12)	<0.01
Middle East	2.08 (0.80-5.46)	0.14
Eastern Europe	5.15 (1.92-13.86)	<0.01
Age Group		
15-24 years	1.0	
25 – 44 years	1.59 (1.29-1.94)	<0.01
45-64 years	1.62 (1.20-2.20)	<0.01
≥65 years	1.51 (0.27-8.31)	0.63
Hepatitis Surface Antigen (HBsAg)	1.61 (1.09-2.36)	0.02
Vaccinated for hepatitis B	1.74 (1.25-2.41)	<0.01

Abbreviations: OR, odds ratio; CI, confidence interval

[a]This final unconditional logistic regression model obtained through backwards elimination controlled for hepatitis B surface antigen (HBsAg), hepatitis B vaccination status, age group, region of origin, and sex. All odds ratios in this table control for these variables.

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