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EPIDEMIOLOGY OF TUBERCULOSIS IN INTERNATIONALLY DISPLACED CHILDREN RESETTLING IN HARRIS COUNTY

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EPIDEMIOLOGY OF TUBERCULOSIS IN INTERNATIONALLY DISPLACED
CHILDREN RESETTLING IN HARRIS COUNTY

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CHILDREN RESETTLING IN HARRIS COUNTY

by

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MD, Baylor College of Medicine, 2013

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EPIDEMIOLOGY OF TUBERCULOSIS IN INTERNATIONALLY DISPLACED CHILDREN RESETTLING IN HARRIS COUNTY

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The University of Texas
School of Public Health, 2019

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Abstract:

Background

More than 300,000 refugees arrived in the United States (U.S.) from 2010-2015, and Texas accepts the 2nd highest number of refugees. Texas also accepts large numbers of asylees, parolees, and special immigrant visa holders. Additionally, a large proportion of trafficked persons in the U.S. live in or pass through Texas. Foreign-born children are disproportionately affected by tuberculosis (TB) and account for two-thirds of U.S. childhood TB cases. Children are at greater risk for progression from TB infection to disease and experience greater morbidity and mortality from TB disease. This makes screening for and treatment of TB infection in children from high-prevalence areas an important public health intervention. Since 2007, children 2-14 years old emigrating from high-prevalence countries (TB incidence >20 cases /100,000 persons) have been tested for TB infection. Children ≥15 years old are additionally screened with a chest radiograph. The Centers for Disease Control and Prevention (CDC) recommends treatment of children with TB infection, as treatment reduces the risk of life threatening disease and prevents future transmission. There are few studies describing the epidemiology of TB in internationally displaced children relocating to the U.S.; there have been no studies centered on Texas. We describe the secular trends and comparative epidemiology of positive TSTs and IGRAs in children of different immigration statuses cared for through the Houston-area public health program.

Methods

This was a retrospective cross-sectional study of children <18 years-old evaluated by the Harris County Public Health Refugee Health Screening Program between January 1st, 2010 and December 31st, 2015 with the following immigration statuses: refugee, asylee, parolee, special immigrant visa holder, or victim of human trafficking. We analyzed factors associated with TB test positivity, infection and disease for children with these immigration statuses. Data are from the U.S. Committee for Refugees and Immigrants (USCRI), the Harris County Public Health Refugee Health Screening Program, and the Texas Children's Hospital TB clinic. Chi-square test or Fisher's exact test were used for dichotomous variables, one-way

ANOVAs for univariate analyses, and Wilcoxon rank sum or Kruskal-Wallis for continuous variables. Multivariate logistic regression was performed to further analyze factors associated with TB test positivity. To assess secular trends in usage and positivity, monthly totals were analyzed using linear regression and the Wilcoxon Sign Rank test. A p-value <0.05 was considered significant. Children < 5 years were typically tested using tuberculin skin test (TSTs) and older children typically using interferon-gamma release assays (IGRAs). The primary outcome was a positive test of TB infection (TST and/or IGRA). Children who were TST+/IGRA- with no known contacts, a normal chest radiograph and no signs or symptoms consistent with TB disease were typically considered uninfected. However, there were some children who met these criteria who were considered to have TB infection and were treated as such –this typically occurred earlier in the study period, and was most commonly due to young age (< 2 years old) or some variability in provider practice.

Results

The program evaluated 5,990 children, of whom 5870 (98%) were tested, predominantly (64%) with an IGRA alone. During the study period, IGRA use increased (p<0.001), though percentages of positive test results (IGRA or TST) did not decline significantly (p=0.10). Overall, 364 (6.2%) children had at least one positive test of infection: 143/1,842 (7.8%) tested with TST alone, 129/3,730 (63.6%) tested with IGRA alone, and 92/298 (30.9%) had at least one positive test result for those tested with both TST and IGRA. Among the 364 children with any positive test of infection, 4 (1.1%) were diagnosed with TB disease, 325 (89.3%) were diagnosed with TB infection, and 35 (9.6%) were considered uninfected. Three factors were significantly associated with a positive TST or IGRA result: region of origin, younger age group, and HIV infection. All children were more likely to have a positive TST compared to IGRA (OR 2.92, 95% CI: 2.37-3.59). Discordant test results were common (20%) and most often were TST+/IGRA- (95.0%). 35/57 (61.4%) of children who were TST+/IGRA- were considered uninfected and did not receive therapy for TB infection; none developed TB disease. The 22/57 (38.6%) TST+/IGRA- children who were treated for TB infection, were treated as such typically due to young age (< 2 years old) or variability in provider practice.

Conclusions

Positive TST results were twice as common as positive IGRA results and discordant TST/IGRA results were common. Positive TST results in BCG-immunized children frequently represent cross-reactivity and false positivity. Use of IGRAs as opposed to TSTs in BCG-immunized children would reduce false positive tests and allow for TB infection therapy to be targeted to those who would most benefit. These findings support 2018 changes in U.S. immigration guidelines that mandate IGRA use for recently immigrated children above 2 years of age.

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BACKGROUND

Literature Review

Epidemiology of Tuberculosis (TB) in Children:

TB remains a significant problem for children throughout the world. The World Health Organization estimates there are 1 million cases and 234,000 deaths from TB annually among children [1]. Recent mathematical modeling studies demonstrated even higher rates with an estimated 67,000,000 children <15-years-old infected with *Mycobacterium tuberculosis* worldwide [2]. In the United States (U.S.), rates of TB disease have been declining in all pediatric age groups. However, non-U.S. - born children are disproportionately affected; foreign-born children 5-9 years old have rates of TB disease 13times higher than U.S.-born children [3]. Given these disproportionate rates, screening of children for TB infection and disease emigrating from high-prevalence areas remains important in the effort to end TB [4].

Tests for TB Infection and Disease

There are two methods for testing for TB infection: the tuberculin skin test (TST), and interferon gamma release assays (IGRAs), both of which are indirect methods to detect infection with *Mycobacterium tuberculosis* that depend on the cellular immune response [5]. The tuberculin skin test (TST) depends on a delayed-type hypersensitivity reaction (a type of immune response) [5]. Purified protein derivative (PPD) is injected under the skin, and the area of induration is assessed at 48-72 hours [5]. It should be administered and read by a health care provider with experience, or the interpretation can be inaccurate [5]. In children emigrating from high incidence countries (>20 cases/100,000 persons), the test is considered positive if a child develops induration that is 10 mm or greater [5]. Children who have been vaccinated with bacille Calmette-Guerin (BCG) can have falsely positive TSTs due to cross-reactivity [6]. It is thought that this cross-reactivity decreases with age; however, the reaction can be boosted in those who have repeated skin testing [7, 8].

There are two FDA approved IGRAs: the QuantiFERON TB GOLD (Qiagen, Hilden, Germany) and the TSPOT.TB (Oxford Immunotec, Abingdon, UK) [5]. Both tests measure interferon-gamma [IFN- γ] production from T lymphocytes in response to *M tuberculosis* antigens [5]. These tests can result as positive, negative, or indeterminate/invalid [5]. The 2018 edition of the American Academy of Pediatrics Redbook [5] recommends use of IGRAs as the preferred method for TB testing in children ≥ 2 years-old; however, during the years of the proposed study period, IGRA testing was recommended for children ≥ 5 -years-old [5, 9].

Important Definitions – Distinguishing Positive Tests of Infection from TB Infection and Disease

A child is determined to have TB infection based on a positive TST or IGRA with a normal chest radiograph and no signs or symptoms of disease (described below) [5]. However, at the Texas Children's Hospital TB Clinic children ≥ 2 -years-old who have received a BCG vaccine and have a positive TST result but no known contact with a

person with pulmonary TB disease, are asymptomatic and have a normal chest radiograph are re-tested with an IGRA, most commonly QuantiFERON TB GOLD (Qiagen, Hilden, Germany). If the IGRA is negative, the “positive” TST result is most likely false (caused by the BCG vaccination), the child is considered uninfected and is not treated with anti-TB medications. If the IGRA is positive, the patient is considered to have TB infection and is offered treatment.

A child with TB disease is defined as one who has a positive test of TB infection, signs and symptoms of disease or a chest radiograph consistent with pulmonary TB, or physical exam findings consistent with extra pulmonary TB [5]. TB disease manifestations include: fever, prolonged cough, hemoptysis, and night sweats [10]. The most common sites of disease include: the lungs (pulmonary and pleural), the central nervous system, lymph nodes, and bones/joints [10].

Internationally Displaced Children and Their Risk-Factors for TB:

Internationally displaced children often transit from high-prevalence areas and live in conditions conducive to acquiring and transmitting *M tuberculosis* (the causative agent of TB) [11-13]. Refugees, asylees, and victims of human trafficking (VHTs) are displaced for prolonged periods in difficult contexts that may promote TB transmission. At the end of 2015, most refugees from non-Middle Eastern countries to the U.S. had lived away from their home countries for an average of 10 years [14]. Living conditions for persons with these immigration statuses, and in particular for those living in refugee camps, may be below United Nations Developmental Programme standards in sanitation and housing, access to healthcare, and access to nutrition, thus placing these individuals at increased risk for acquiring TB infection [15]. In contrast, those with special immigrant visas (SIVs) frequently are Afghani or Iraqi nationals (and their families) who served as translators for the U.S. Armed Forces [16]. As this program grew, more upper and middle class persons who likely were at lower risk for acquiring TB infection applied for this immigration status [16, 17]. Those with parole status most commonly emigrated from Cuba, a country with low incidence of TB, making their risk of acquiring TB infection lower [18-20].

Young children have an increased risk of progression from TB infection to disease compared to adults, and are a specific population of interest in TB eradication [21]. Therefore, effective detection and treatment of TB infection in internationally displaced children remain a priority in order to attain adequate disease prevention and control [22].

Internationally Displaced Children Resettling in Harris County:

Between October 2016 and February 2017, more than 37,000 refugees arrived in the U.S. Texas is the second largest refugee settlement state in the U.S., with Harris County settling the most refugees in Texas. Approximately 8.5% of refugees to the U.S. resettle in Texas annually; 25% of these resettle in Houston [23]. The Harris County Public Health Refugee Health Screening Program serves as the largest health-screening program in Texas [24, 25]. A large proportion of internationally displaced children relocating to the U.S. with the immigration status of asylee, parolee, or SIV

holder also resettle in Texas. Additionally, Texas - and Houston in particular - are considered hubs of human trafficking with more than 300,000 trafficked persons residing in the state [26]. However, despite this tremendous activity, there are minimal published data on childhood TB infection and disease among these populations.

TB Prevalence Among Internationally Displaced Children Resettling in the U.S.

Based mainly on TST results, a recent study demonstrated that 12% of children ages 2-14 years entering the U.S. from high burden countries have TB infection. However, in one study, 64% of those who previously tested positive were re-tested post-immigration and the diagnosis of TB infection was changed from positive to negative for 71% of those re-tested by IGRA [27]. Other studies in refugee children resettling in the U.S. or Australia found rates of TB infection ranging between 9%-35.2% when only the TST was used [28-32].

TB Screening in the U.S.

A recent study evaluating TB screening in refugee children in high-immigration, low-incidence countries found that no two countries had the same approach to TB screening [33].

In 2007, the CDC updated the pre-immigration recommendations for TB screening for immigrants to the U.S. Now, all children ages 2-14 years who live in countries with an estimated incidence rate of >20 cases/100,000 persons are supposed to be screened with either a TST or IGRA [34, 35]; children < 2 years of age receive no screening. However, this does not occur consistently, and results or paperwork are often missing on arrival. As a result, in Houston, the Harris County Public Health Refugee Health Screening Program performs intake TB screening, HIV testing, and pathogenic parasite screening for all refugees, asylees, VHTs (that are identified), parolees, and SIV holders that resettle in the county if this testing was not previously done and/or if there is no documentation of prior testing.

Public Health Significance

Harris County's prevalence of internationally displaced children allows for the study of the prevalence of positive tests of TB infection in this unique population. This study will describe the secular trends, comparative epidemiology of positive TB tests, and will give further insight into the epidemiology of childhood TB infection and disease in internationally displaced children arriving to the U.S. This will allow for further understanding of risk factors for positive TB tests in the pediatric population.

Hypotheses

- 1) Twenty-five percent of high-risk internationally displaced children (refugees, asylees, parolees, SIV holder's and VHTs) age <18 years-old who have resettled in Harris County will have a positive test of tuberculosis infection (either TST or IGRA).
- 2) Presumed higher-risk internationally displaced children (refugees, asylees, and VHTs) < 18 years old who resettled in Harris County between January 1st, 2010

and December 31st, 2015 will have a higher prevalence of positive tests of TB infection compared to presumed lower-risk internationally displaced children (parolees, and SIV holders).

- 3) There will be changes in the composition of the study population over the study period; specifically the proportion of different immigration statuses, and the proportion of persons emigrating from different regions of origin will differ by year.
 - a. There will be a 15% increase in the percentage of children who are tested for TB infection with an IGRA compared to a TST over the study period.
 - b. There will be a 5% decrease in the percentage of children who have a positive test of TB infection over the study period.

Specific Aims

- 1) Describe and analyze the epidemiology of positive tests of TB infection and TB disease among internationally displaced children (refugees, asylees, parolees, SIV holders, and VHTs) age < 18 years who have resettled in Harris County between January 1st, 2010 and December 31st, 2015.
- 2) Compare the prevalence of positive tests of TB infection for those with presumed higher-risk immigration statuses (refugees, asylees, and VHTs) to those with lower-risk statuses (parolees and SIV holders).
- 3) Describe and evaluate secular trends of different immigration statuses over the study period.
 - a. Describe and evaluate secular trends of the types of TB testing performed and the rates of positive tests of infection.

METHODS

Study Design

This is a retrospective cross-sectional study evaluating the epidemiology, secular trends, and variables which may impact rates of positive tests of TB infection among internationally displaced children. Parameters evaluated were: age, sex, year of arrival, region of origin, HIV status, pathogenic parasite status, and other underlying medical conditions. For those with positive TST or IGRA result, we evaluated the size of induration for positive TST, and/or the numerical value of the positive IGRA. TSTs were considered positive if there was ≥ 10 mm of induration unless children were HIV-infected, in which case ≥ 5 mm of induration defined a positive TST result. For the IGRAs, per manufacturers' recommendations: a TSPOT.*TB* (Oxford Immunotec, Abingdon, UK) test was defined as positive if ≥ 8 spots were noted in either well; a QuantiFERON (Qiagen, Hilden, Germany) test was defined as positive if the antigen-nil value was ≥ 0.35 IU/ml [36]. A retrospective review was performed to calculate and compare the prevalence of positive tests of TB infection in presumed higher-risk (refugees, asylees, and VHTs) compared to presumed lower-risk (parolees and SIV holders) internationally displaced children <18 years arriving in Harris County between January 1st, 2010 and December 31st, 2015. A de-identified database which includes the child's sex, age at arrival, country of origin, type of TB test performed and the results, HIV status, and pathogenic parasite status was provided by the U.S. Committee for Refugees and Immigrants (USCRI).

Additional clinical data were abstracted from the Harris County Public Health Refugee Health Screening Program and the Texas Children's Hospital Electronic Medical Records (EMRs) via patient chart review. IRB approval was obtained from the Harris County Health Department and Baylor College of Medicine.

All patients were assigned a study ID number. Study ID numbers that linked the corresponding patient identifying information were stored separately on a Texas Children's Hospital password protected workstation in a locked office.

Study Setting

- 1) Harris County Public Health Refugee Health Screening Program
- 2) Texas Children's Hospital TB Clinic

Study Subjects

Children < 18 years-old evaluated by the Harris County Public Health Refugee Health Screening Program between January 1st, 2010 and December 31st, 2015 with the following immigration statuses: refugee, asylee, SIV holder, parolee and VHT.

Inclusion criteria:

- Refugee, asylee, SIV holder, parolee, and VHT children age < 18 years who have resettled in Harris County between 1/1/2010 and 12/31/2015.

Exclusion criteria:

- Any person > 18 years
- Any person who did not fall under the following classifications: refugee, asylee, SIV holder, parolee, or VHT.

Sample Size

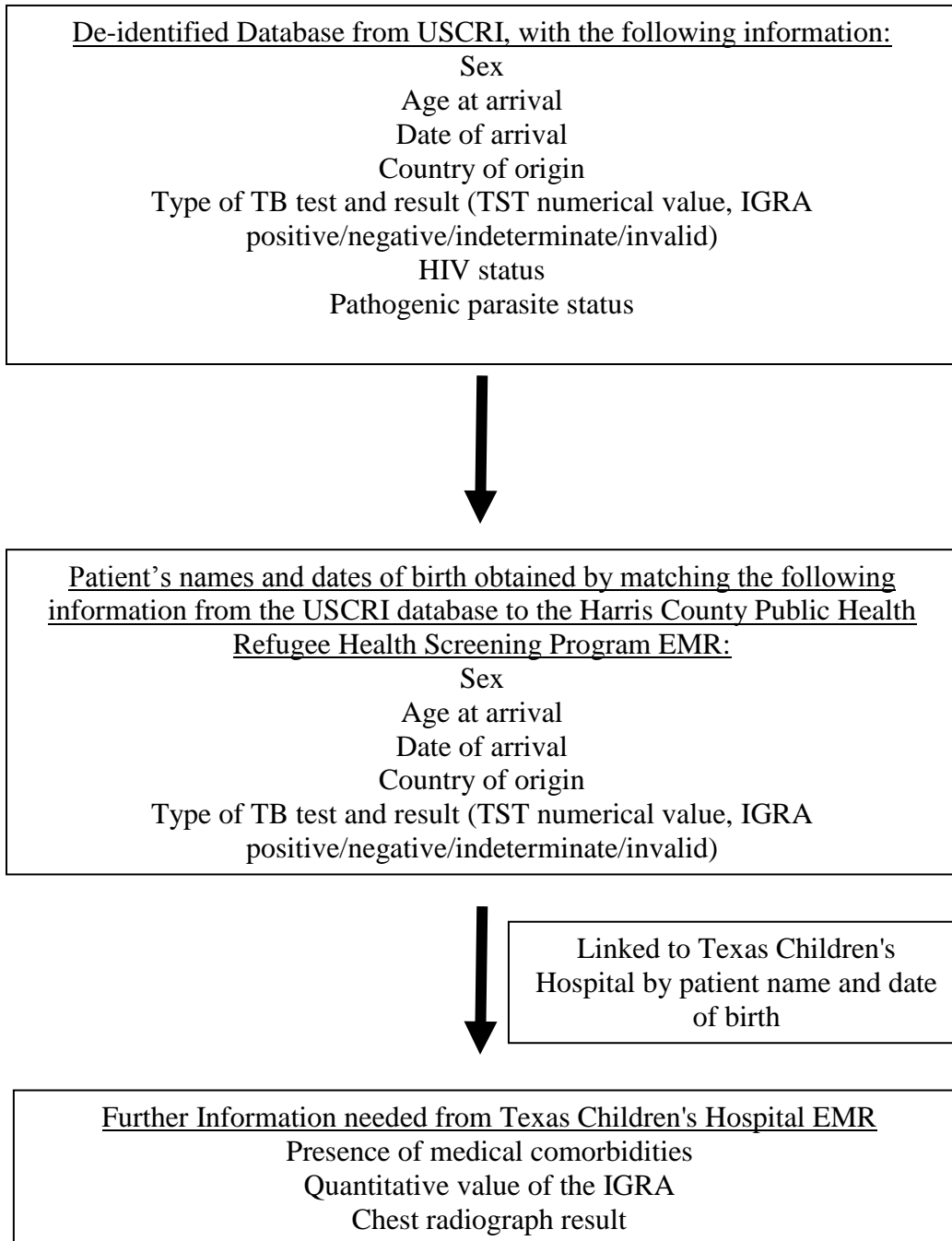
5990 children < 18 years old were evaluated by the Harris County Public Health Refugee Health Screening Program between January 1st, 2010 and December 31st, 2015 with the previously mentioned immigration statuses.

Data Collection

A de-identified database which includes all children <18 years-old who were evaluated by the Harris County Public Health Refugee Health Screening Program between January 1st, 2010 and December 31st, 2015 was provided by USCRI. Variables in the database include: the child's sex, age at arrival, date of arrival, country of origin, type of TB test performed and the test results, HIV status, and pathogenic parasite status. Further clinical data were abstracted from the Harris County Public Health Refugee Health Screening Program and the Texas Children's Hospital EMRs via patient chart review. To identify patients by name and date of birth, a retrospective review of the Harris County Public Health Refugee Health Screening Program EMR was performed. Patients were matched to the pre-existing database provided by USCRI by: age at arrival, date of arrival, country of origin, sex, and TB test result (TST induration and if the IGRA result was positive or negative – numerical value not provided). Children were matched in the Texas Children's Hospital EMR by name and date of birth (Figure 1).

Further clinical data from the Texas Children's Hospital needed to complete this project included: presence of medical comorbidities; the quantitative value of the IGRA; and chest radiograph result. IRB approval has been obtained from both of these institutions (Figure 1).

Figure 1. Flow diagram of data-abstraction procedures



Data Analysis

Demographic characteristics among the higher-risk groups and lower-risk groups were compared for statistically significant differences by the Chi-square test or Fisher exact test for dichotomous variables and Wilcoxon rank sum or Kruskal-Wallis for continuous variables. Categorical variables were compared between testing results using Chi-square or the Fisher exact test. Multivariate logistic regression was performed to determine correlates of positive TSTs and IGRAs. Three models were created to determine what factors were independently associated with positive tests of infection: a positive TST result, a positive IGRA result, and any positive TB test result (TST or IGRA). Any factor with a p-value ≤ 0.25 was included in the binary regression model. The final model was created using a backward-step approach. To assess secular trends in usage and positivity, monthly totals were analyzed using linear regression and the Wilcoxon Sign Rank test. A p-value < 0.05 was considered significant.

All analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 25 (IBM Corp.; Armonk, NY). Institutional review board approval was obtained from the Harris County Public Health Department, Baylor College of Medicine, and the UTHSC Committee for Protection of Human Subjects.

Human Subjects Considerations

De-identified patient information was obtained from USCRI. Patient names and dates of birth were obtained from the Harris County Public Health Refugee Health Screening Program in order to link patients between the Harris County Public Health Refugee Health Screening Program and Texas Children's Hospital EMRs. All data were stored electronically and were de-identified by assigning patients a study ID number and having patient identifiers linked to their study ID stored separately on a password protected database. All data were electronic and no physical data exist. All data were abstracted from medical records onto password-protected Texas Children's Hospital workstations located in locked offices. IRB approval was obtained from Baylor College of Medicine, the Harris County Department of Health, and the UTHSC Committee for Protection of Human Subjects.

JOURNAL ARTICLE

Title of Journal Article: Epidemiology of Tuberculosis Infection and Disease in Migrant Children Resettling in Harris County, TX 2010-2015

Name of Journal Proposed for Article Submission: American Journal of Public Health

Abstract:

Background

United States guidelines recommend testing children emigrating from high tuberculosis-incidence countries with tuberculin skin tests (TSTs) or interferon-gamma release assays (IGRAs). We describe a large refugee program's testing results.

Methods

This was a cross-sectional study of all children <18 years old evaluated by a refugee program from 2010-2015. Children < 5 years were typically tested using TSTs and older children typically using IGRAs. The primary outcome was a positive test of TB infection (TST and/or IGRA). Children who were TST+/IGRA- with no known contacts, a normal chest radiograph and no signs or symptoms consistent with TB disease were typically considered uninfected. However, there were some children who met these criteria who were considered to have TB infection and were treated as such – this typically occurred earlier in the study period, and was most commonly due to young age (< 2 years old) or some variability in provider practice.

Results

The program evaluated 5,990 children, of whom 5870 (98%) were tested, predominantly (64%) with an IGRA alone. During the study period, IGRA use increased ($p < 0.001$), though percentages of positive test results (IGRA or TST) did not decline significantly ($p = 0.10$). Overall, 364 (6.2%) children had at least one positive test of infection: 143/1,842 (7.8%) tested with TST alone, 129/3,730 (63.6%) tested with IGRA alone, and 92/298 (30.9%) had at least one positive test result for those tested with both TST and IGRA. Among the 364 children with any positive test of infection, 4 (1.1%) had TB disease, 325 (89.3%) TB infection, and 35 (9.6%) were considered to be uninfected. Three factors were significantly associated with a positive TST or IGRA result: region of origin, younger age group, and HIV infection. All children were more likely to have a positive TST compared to IGRA (OR 2.92, 95% CI: 2.37-3.59). Discordant test results were common (20%) and most often were TST+/IGRA- (95.0%). 35/57 (61.4%) of children who were TST+/IGRA- were considered uninfected and did not receive therapy for TB infection; none developed TB disease. The 22/57 (38.6%) TST+/IGRA- children who were treated for TB infection, were treated as such typically due to young age (< 2 years old) or variability in provider practice.

Conclusions:

Positive TST results were twice as common as positive IGRA results and discordant TST/IGRA results were common. These findings support the 2018 change in U.S. immigration guidelines that mandate IGRA use for recently immigrated children.

Background:

The World Health Organization (WHO) estimated there were 1 million tuberculosis (TB) cases and 234,000 deaths among children in 2017 [1]. An estimated additional 67 million children are infected with *Mycobacterium tuberculosis* [2]. Testing of children emigrating from high- to low-prevalence countries can provide benefit to individual patients (by reducing the risk of progression to disease) and to the community (by decreasing the reservoir for future disease cases).

Not all recently arrived children are at equal risk of TB infection. Refugees, asylees, and victims of human trafficking (VHTs) may be at highest risk, due to prolonged periods of displacement and residence in facilities with crowding, under nutrition, poor sanitation and poor access to medical care [3]. Special immigrant visa (SIV) holders are predominantly children of Afghani or Iraqi nationals who served as military translators and are of higher socioeconomic status (SES) [4-5], potentially placing them less at risk for TB exposure. Those with parole status most commonly emigrated from Cuba, a country with low incidence of TB [6-8].

In 2018, the Centers for Disease Control and Prevention (CDC) updated the pre-immigration guidelines for TB testing for immigrants to the U.S., recommending that children ages 2-14 years who come from high TB-incidence countries (>20 cases/100,000) be tested with an interferon-gamma release assay (IGRA) [9].

Previously, due to resource restrictions, tuberculin skin tests (TSTs) were performed more commonly in many countries, and 9-35% of refugee children tested positive [10-15]. However, in one large study almost two-thirds of children with positive pre-immigration TST results had negative IGRA results on post-immigration testing [11], indicating that many positive TST results likely are caused by prior vaccination with the bacillus Calmette-Guérin (BCG).

Almost 10% of refugees, asylees, parolee, or SIV holders resettle in Texas, with almost 25% of these refugees resettling in Harris County (Houston) [16]. Additionally, Texas is a human trafficking hub, with more than 300,000 trafficked persons passing through the state [17]. We describe the secular trends and comparative epidemiology of positive TSTs and IGRAs in children of different immigration statuses cared for through the Houston-area public health program.

Methods:

The Harris County Public Health Refugee Health Screening Program performs intake TB, HIV, and pathogenic parasite testing for all refugees, asylees, identified victims of human trafficking (VHTs), parolees, and SIV holders resettling in the county. This was a cross-sectional study of 0-18-year-old children evaluated by this program between January 1st, 2010 and December 31st, 2015. We obtained demographics, TB exposure history, symptom screening, and testing results from the refugee program and the U.S. Committee for Refugees and Immigrants (USCRI). These data were linked to data obtained from the Texas Children's Hospital TB Clinic to evaluate testing outcome and diagnoses.

Immigration status was determined by USCRI (**Table 1**). We hypothesized that refugees, asylees, and VHTs would be higher-risk groups for TB infection, as they were more likely to have lived in congregate settings. We predicted the lower-risk groups to be parolees and SIVs due to residence in lower TB-incidence nations and higher SES, respectively. We used WHO definitions for regions of origin [18].

Initial TB testing in the Harris County program typically used TSTs in children < 5-years-old and IGRAs in children \geq 5 years-old. TST results were considered positive if there was \geq 10mm of induration unless children were HIV-infected, in which case the threshold was \geq 5mm of induration [19]. The main IGRA used was the T-SPOT.TB (Oxford Immunotec; Abingdon, UK), which was defined as positive if \geq 8 spots were noted in either well [20]. A positive QuantiFERON Gold-In Tube (Qiagen; Hilden, Germany) was defined as an antigen-nil value of \geq 0.35 IU/ml [20].

Children with positive test(s) of infection were classified as TB infected, TB uninfected, or having TB disease. These classifications were determined by two pediatric TB experts. In the first 2 categories, children had normal physical examinations and 2-view chest radiographs. Children were defined as having TB infection if they had a 1) IGRA+ or 2) TST+ result and no IGRA was done (not all TST+ children had IGRAs performed), or if the IGRA result was indeterminate/invalid. We typically defined children as being uninfected if they had a negative TST and/or IGRA, or received a BCG vaccine, were TST+/IGRA- and had no known contacts with TB disease. However, not all children who were TST+/IGRA- were classified as being uninfected; some of these children were classified as having TB infection (based on TB clinic note)- and were treated as such, most commonly due to young age and some variability on provider practice. TB disease was diagnosed in children with clinical, examination, or radiographic findings consistent with TB [21].

Three models were created to determine what factors were independently associated with positive tests of infection: a positive TST result, a positive IGRA result, and any positive TB test result (TST or IGRA). Demographic characteristics among the higher-risk groups and lower-risk groups were compared for statistically significant differences by the Chi-square test or Fisher exact test for dichotomous variables and Wilcoxon rank sum or Kruskal-Wallis for continuous variables. Categorical variables were compared between testing results using Chi-square or the Fisher exact test. Any factor with a p-

value ≤ 0.25 was included in the binary regression model. The final model was created using a backward-step approach. To assess secular trends in usage and positivity, monthly totals were analyzed using linear regression and the Wilcoxon Sign Rank test. A p-value < 0.05 was considered significant.

All analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 25 (IBM Corp.; Armonk, NY). Institutional review board approval was obtained from the Harris County Public Health Department and Baylor College of Medicine.

Results:

During the study period, the refugee program evaluated 5,990 children (**Table 2**), 98% (5,870) of whom received at least 1 test of TB infection (**Table 3**): IGRA (3,730, 63.6%); TST (1,842, 31.4%); and both TST and IGRA (298, 5.1%). In the latter group, 29/298 (9.7%) were TST+/IGRA+, 57 (19.1%) TST +/IGRA -, 3 (1.0%) TST+/IGRA indeterminate/invalid, and 3 (1.0%) TST-/IGRA + (**Figure 1**). Discrepant test results occurred in 60 (20.0%) of children tested with both a TST and an IGRA. Among children with discrepant test results: 3 (5.0%) were TST-/IGRA+, and 57 (95.0%) were TST+/IGRA-. Overall there were 364 children (6.2%) with at least one positive TB test. Among those children with any positive TB test, 4 (1.1%) children were diagnosed with TB disease, 325 (89.3%) were diagnosed with TB infection, and 35 (9.6%) were considered uninfected (**Figure 1**). The 35 children who were considered uninfected were all TST+/IGRA-. There were additionally 22 (38.6%) children who were TST+/IGRA- that were classified as having TB infection, typically earlier in the study period because of young age (< 2 -years-old), and/or variability in provider practice (**Figure 1**). The Texas Children's Hospital TB Clinic sees most children in Harris County with TB disease, and per chart review, none of these children developed TB disease. Further, we cross-referenced the public health records for Harris County and also found that none of these children had developed disease.

Positive TST results:

Three factors were significantly associated with a positive TST result: region of origin, age group, and HIV infection. Children from Eastern Mediterranean countries (aOR = 0.48 [95% CI 0.33 - 0.70]) and the Americas (aOR = 0.19 [95% CI 0.09 - 0.39]) had reduced odds for a positive TST result compared to children from Southeast Asia (**Table 4**). Children ages 2-5 years had reduced odds for a positive TST result when compared to children < 2 years old (aOR = 0.40 [95% CI 0.26 - 0.61]). On univariate analysis, there were significant differences in positive TST results in children with different immigration statuses; however, these differences were not seen after logistical modeling. Children with HIV had increased odds for a positive TST result (aOR = 2.99 [95% CI 1.01 - 8.87]) (**Table 4**).

Positive IGRA results:

There were two factors associated with a positive IGRA result: age group and region of origin. Children from Eastern Mediterranean countries (aOR = 0.34 [95% CI 0.21 - 0.53]), and the Americas (aOR = 0.12 [95% CI 0.06 - 0.25]) had reduced odds for a

positive IGRA result compared to children from Southeast Asia (**Table 4**). Children ages 2-10 years had reduced odds for a positive IGRA result when compared to children less than 2 years (2-5 years aOR 0.26 [95% CI 0.11-0.60]; 6-10 years aOR 0.41 [95% CI 0.20-0.85]). On univariate analysis, there were significant differences in positive IGRA results in children with different immigration statuses, however, these differences were not seen after logistical modeling. HIV infection was not associated with a positive IGRA result (**Table 4**).

Either positive TST or IGRA result:

Three factors were associated with a positive TST or IGRA result: region of origin, age group, and HIV infection. Children from Eastern Mediterranean countries (aOR = 0.44 [95% CI 0.33 -0.59]) and the Americas (aOR = 0.14 [95% CI 0.08 – 0.23]) had reduced odds for a positive TST or IGRA result compared to children from Southeast Asia (**Table 4**). Children ages 2-14 years had reduced odds for a positive TST or IGRA when compared to children less than 2-years (2-5 years aOR = 0.36 [95% CI 0.24-0.54]; 6-10 years aOR = 0.28 [95% CI 0.18-0.42]; 11-14 years aOR = 0.55 [95% CI 0.48-1.10]). Children with HIV infection had increased odds for a positive TST or IGRA result (aOR = 5.57 [95% CI 2.23 – 13.90]) (**Table 4**). Pathogenic parasite status was not associated with either a positive TST or IGRA result (p=0.36)

Positive results for TST vs IGRA:

Children from all regions and age groups had greater odds of having a positive TST result than a positive IGRA result (OR 2.92 [95% CI 2.79-3.59]). Using the IGRA result as the reference, the odds of having a positive TST result were greater in children from: Eastern Mediterranean countries (OR 3.99 [95% CI 2.59-6.16]), the Americas (OR 4.15 [95% CI 1.62-10.62]); Southeast Asia (OR 2.96 [95% CI: 2.11-4.15]), and Africa (OR 2.74 [95% CI 1.95-3.84]) (**Figure 2a**). Children ages 6-10 years had the greatest odds of having a positive TST result compared to a positive IGRA result (OR 5.47 [95% CI 3.45-8.69]). Children < 2 years had 3.2 times the odds of having a positive TST result compared to the IGRA result (95% CI 1.58-6.48), and those ages 11-14 and >14 years had approximately 2.5 times the odds of having a positive TST result and a negative IGRA result (95% CI 1.60-9.94 and 1.47-4.07 respectively) (**Figure 2b**).

Secular Trends:

Demographic secular trends are shown in **Figure 3**. There was a significant difference between monthly TST and IGRA test results using a matched monthly analysis (Wilcoxon Sign Rank and Paired t-Test). IGRA testing was utilized more often than TST (Median number of tests per month: 61 vs. 25, respectively) (p-value<0.001) (**Figure 4**). Through linear regression modeling, the slope of monthly IGRA tests significantly increased over time ($y = 0.94x + 21.53$) (p-value<0.001) (**Figure 5a**). Percentages of positive results (IGRA or TST) appeared to decrease over time but were not significant ($y = -0.035x + 7.28$) (p-value = 0.10) (**Figure 5b**).

Discussion:

In the U.S., 66% of reported TB cases occur among the foreign-born, a rate 13 times higher than for U.S.-born persons [22]. Previous studies mostly utilizing the TST found a prevalence of TB infection of 9-35% among refugee children [10-15]. However, positive results were less common in our cohort, potentially due to expanded IGRA use and the variety of immigration statuses included.

We found that the prevalence of positive TB test results varied by region of origin, age, and HIV status, and that all children had greater odds of having a positive TST result as compared to IGRA regardless of region of origin or age. We also found discordances between TST and IGRA results across the pediatric age spectrum, suggesting that the impact of BCG vaccination on TST positivity may be more prolonged than often expected.

Region of origin was an important risk factor for positive TB test results: children from Southeast Asia had greater odds of having a positive TST and/or IGRA result compared to children from Eastern Mediterranean countries and the Americas. Presuming positive TB test results represent true TB infection, this is consistent with known epidemiologic risk factors - the prevalence of TB disease in Southeast Asia is higher than in Eastern Mediterranean countries and Cuba (where most children from the Americas region originated) [23].

Age was another important risk factor for positive TB test results. Children <2 years and ≥ 14 years had higher prevalence of positive TST and/or IGRA results compared to those ages 2-14 years. Older aged children (≥ 14 -years) in our cohort had increased prevalence of positive TB test results with both the TST and IGRAs, which more likely represent true TB infection because of the children's greater time outside the home and cumulative exposure to adults with infectious pulmonary TB [24-27]. The higher frequency of positive tests in children <2 years, on the other hand, is more difficult to explain. Higher TST positivity in children <2 years may represent greater cross-reactivity with BCG, given the temporal proximity to vaccination or potential boosting if children have serial TSTs performed (pre and post immigration); however, this cannot explain the increased prevalence of positive IGRAs in these children. Further, these data contradict previous studies which demonstrate that older children are more likely to have TB infection [24-27]. One explanation is that IGRA positive children <2 years in our cohort had more prolonged exposure to an adult family member with infectious pulmonary TB in the home, as very young children spend more time in the home compared to their school-aged counterparts. To date, IGRAs have not been used routinely for the diagnosis of TB infection in children < 2-years-old due to paucity of data for their sensitivity [28]. The relatively high prevalence of positive IGRA results in this age group may provide some insight for the utility of IGRA use in these younger age groups.

Though rare in this cohort, HIV infection was also a significant risk factor for having a positive TST result. Consistent with previously published data, HIV has been associated with increased risk for TB infection and progression to disease [29], and TB remains an

important opportunistic infection, with an incidence of 30% in HIV-infected children in low- and middle-income nations [30]. However, the number of HIV-infected children in this study was very low, making it difficult to draw meaningful conclusions from these data.

Most prior estimates of the prevalence of TB infection in immigrant children used the TST as the test of choice, given an initial paucity of pediatric data and the lack of availability and cost of IGRAs. A more recent study using IGRA testing estimated that 5.6% of immigrant children had TB infection compared to 22% using TST [31], and our findings paralleled these results. More recent AAP guidelines recommend IGRA use down to 2 years of age [28], with some experts using IGRAs in children as young as 1 year of age. Use of IGRAs rather than the TST in this younger cohort would likely reduce false positive tests and allow for TB infection therapy to be targeted to those who would most benefit.

The CDC does not recommend tiered testing for TB infection (that is, obtaining an IGRA if a TST result is positive). However, there are times when the initial test of infection, selected either by choice or by necessity, is not the optimal test, particularly for a BCG-immunized child. In our study, all children had greater odds of having a positive TST result as compared to IGRA regardless of region of origin or age. Additionally, we had almost 300 children in whom both TSTs and IGRAs were obtained, of whom 20% had discordant results. Our findings are consistent with a prior study that demonstrated that for BCG-immunized children who have immigration testing, false positive TST results are common, and IGRAs should be the tests of choice for this patient population [10].

Of note, discordance between TST and IGRA results were seen in all age groups. Typically, the impact of BCG vaccine in causing falsely positive TST results has been thought to be temporally related to when the child received the BCG vaccine, which in most countries is a single dose immediately after birth. However, discordant TST and IGRA results even in older children suggest that either the immunogenicity of some strains of BCG is longer than previously recognized or that the impact of nontuberculous mycobacterial infections, that also can cause a falsely positive TST result, may be underestimated in children from developing nations. Concerns about false positive TST results are considered in updated 2018 guidelines [9] for TB testing prior to immigration, mandating use of IGRAs for all persons 2 years and above.

This study has several limitations. Though we have follow-up data for most children evaluated for a positive test of TB infection, as they were seen in our clinic, we do not have data for some children evaluated post intake-testing at other clinics, or for children whose test for TB infection was negative. BCG vaccination status was not routinely documented, thus the presumption of falsely positive TSTs secondary to cross-reactivity with BCG assumes that the vast majority of children were BCG-immunized as they originated from countries with high BCG-uptake. BCG vaccination is recommended in the national immunization program of 95% of countries from which these children emigrated [32]. HIV infection was rare in this cohort, thus it is difficult to make meaningful conclusions regarding TST and/or IGRA positivity in HIV-infected children

from our data. Finally, these data may not be generalizable to all immigrant children relocating to the United States, as this study predominately included children from TB high-burden countries [9].

Conclusions:

The prevalence of positive TB test results in this cohort of children was lower than previously reported (compared to studies that predominately used the TST), and TB disease was rare. The lower prevalence of positive tests of TB infection in this childhood population likely stems from the predominant use of IGRA testing. Despite these low rates of positive results, it remains important to screen children emigrating from high-burden countries. Region of origin, and age are important risk factors for having a positive TB test. The TST and IGRAs are frequently discrepant, particularly among younger children who have received a BCG vaccine, and those from lower-burden countries. Positive TST results in BCG-immunized children frequently represent cross-reactivity and false positivity. Use of IGRAs as opposed to the TST in BCG-immunized children would reduce false positive test results and allow for TB infection therapy to be targeted to those who would most benefit.

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Figures and Tables:

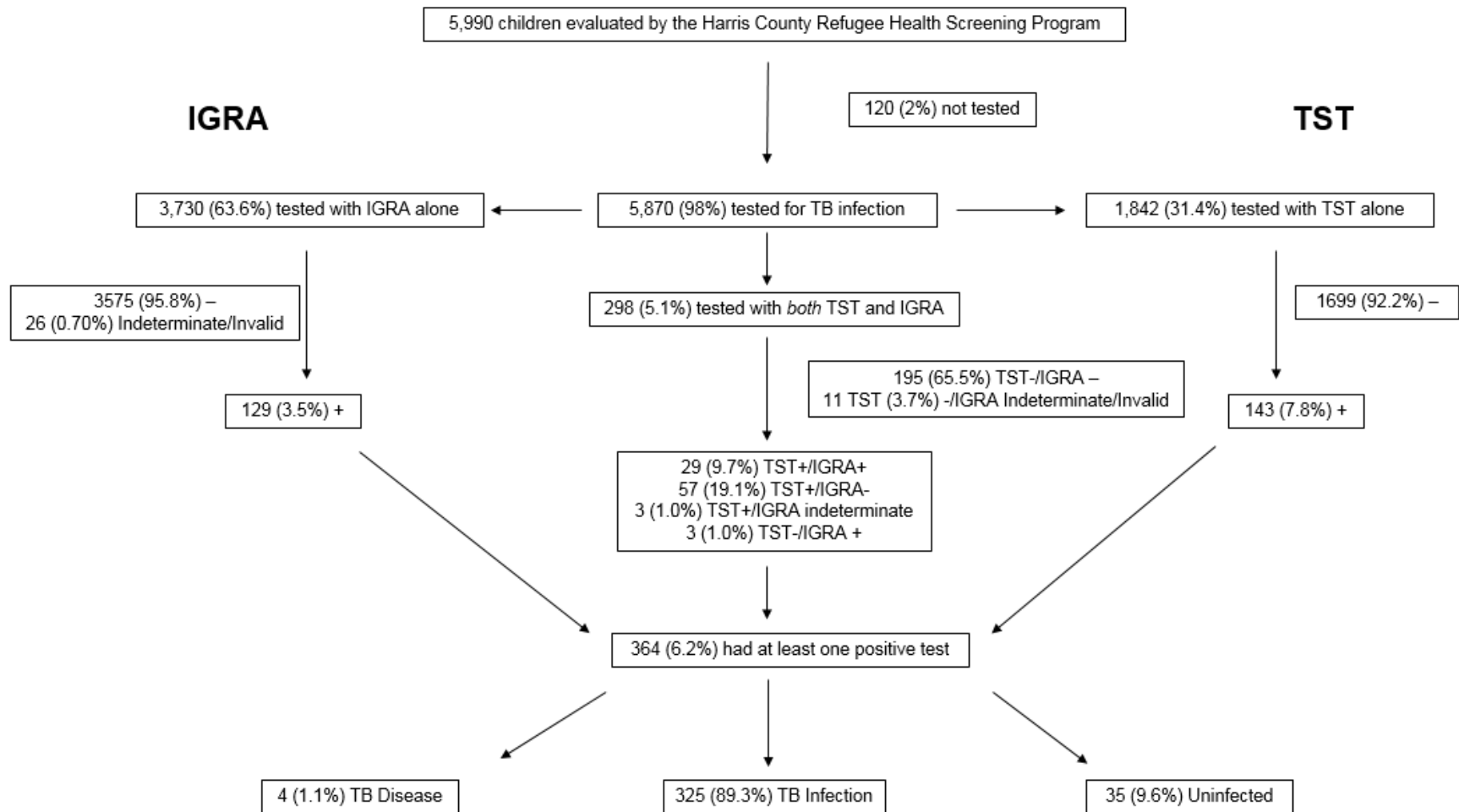
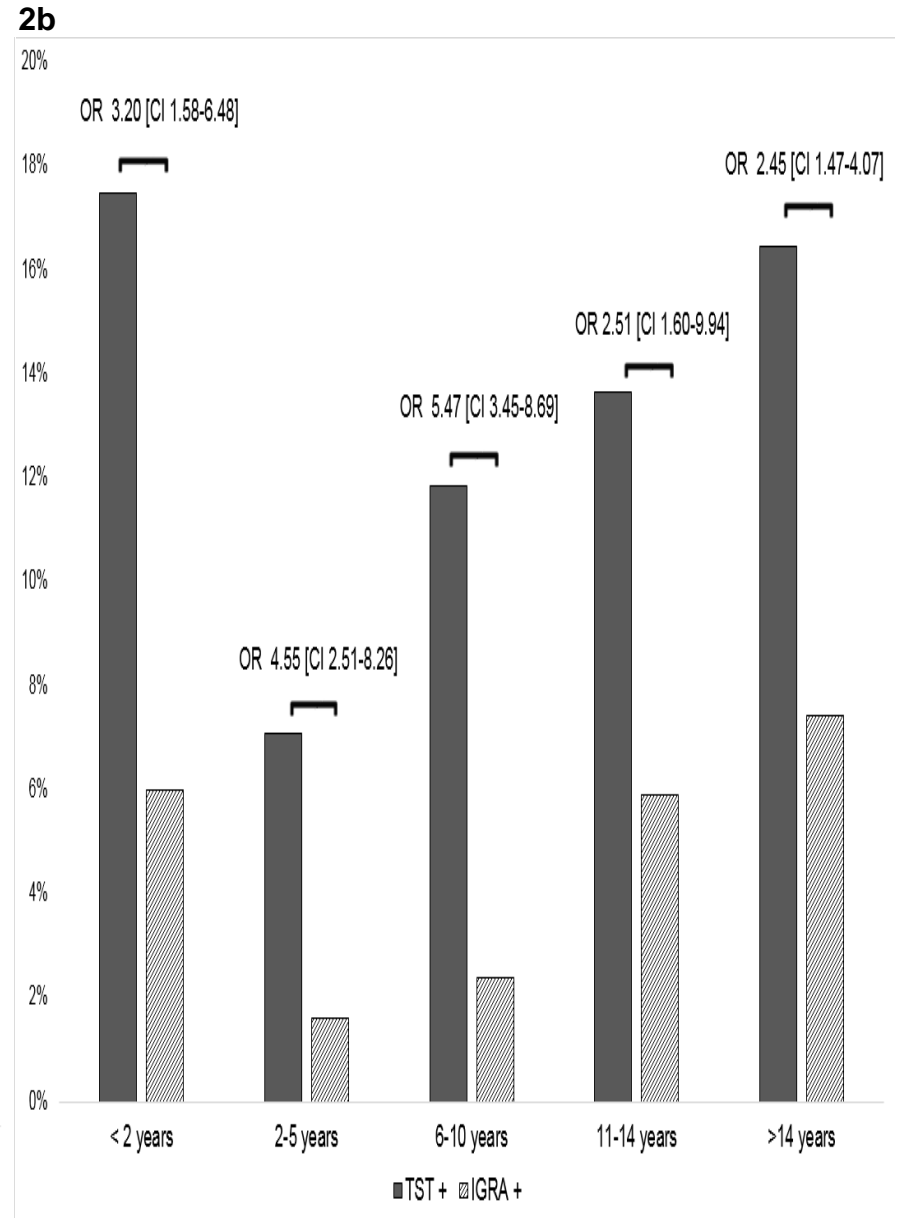
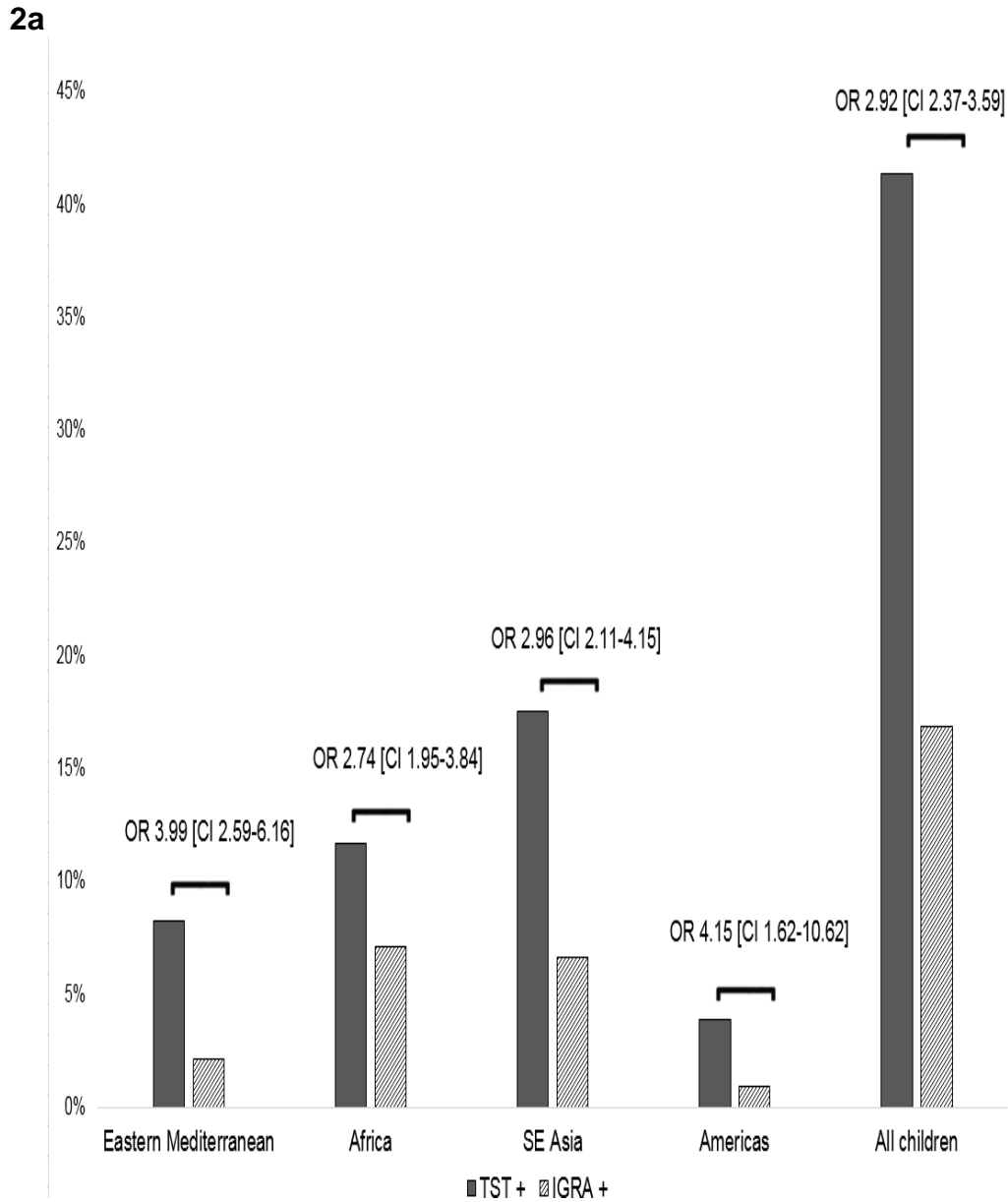


Figure 1. Consort diagram of TST and IGRA Results in Migrant Children Over a 5-Year Period in Harris County, Texas



Figures 2a and 2b. Comparison of TST and IGRA Results (using IGRAs as reference) in Migrant Children Over a 5-Year Period in Harris County, Texas

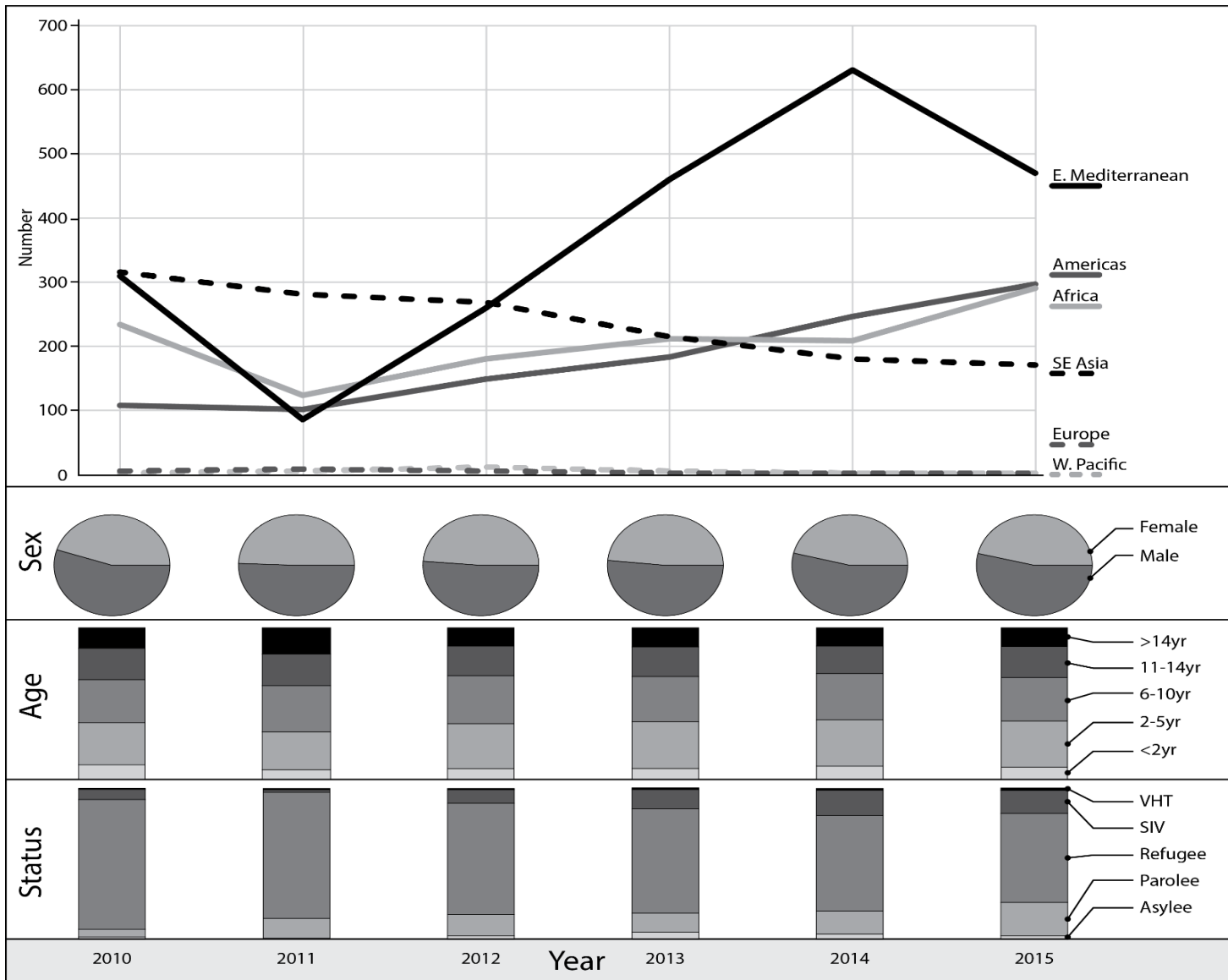


Figure 3. Demographic variables of Migrant Children Over a 5-Year Period in Harris County, Texas

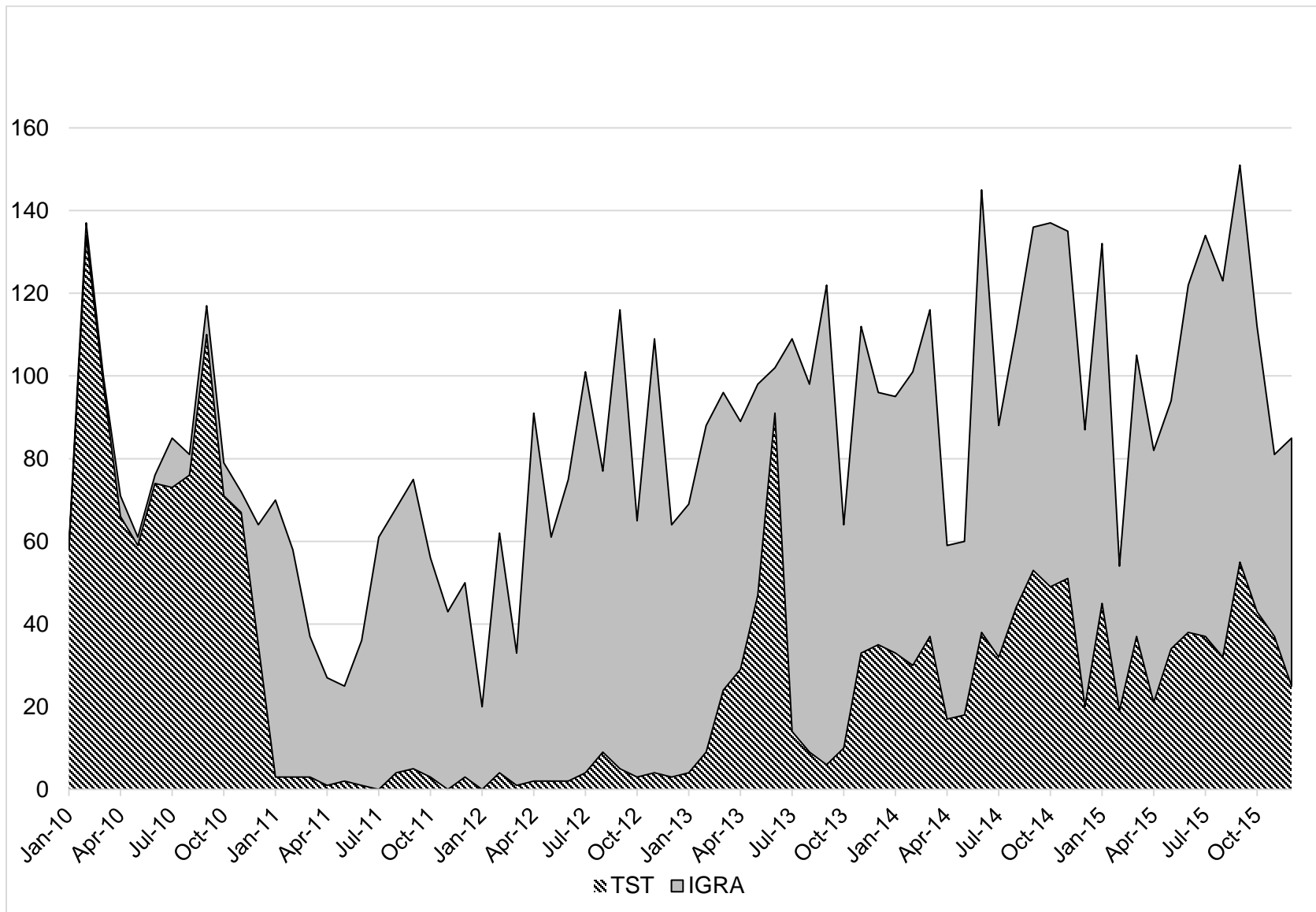
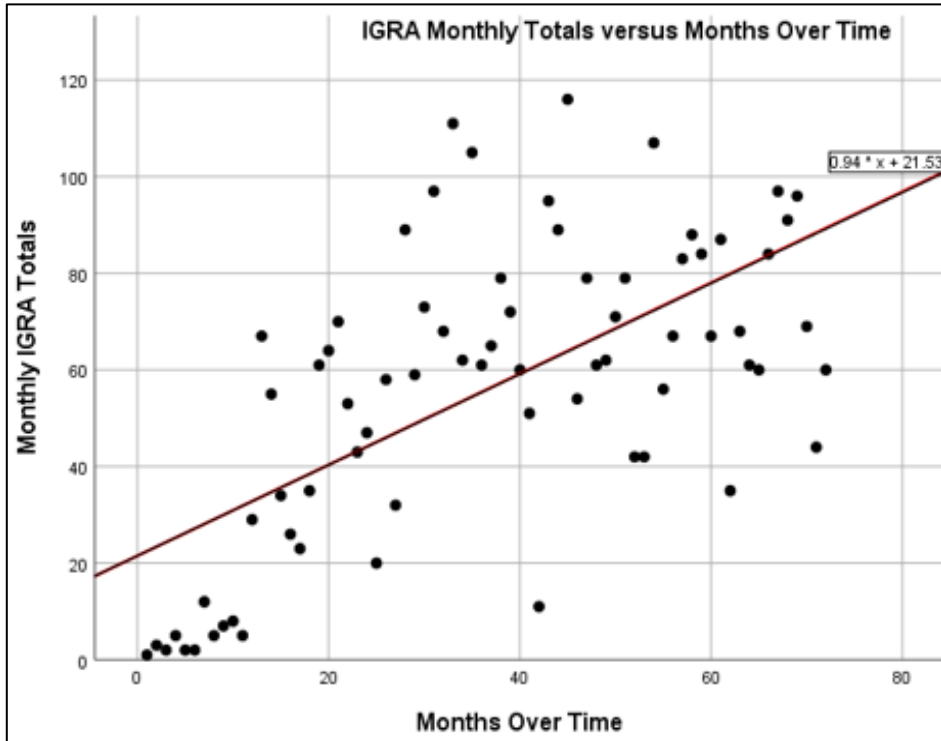


Figure 4. Graph of TST and IGRA Utilization in Migrant Children Over a 5-Year Period in Harris County, Texas

5a



5b

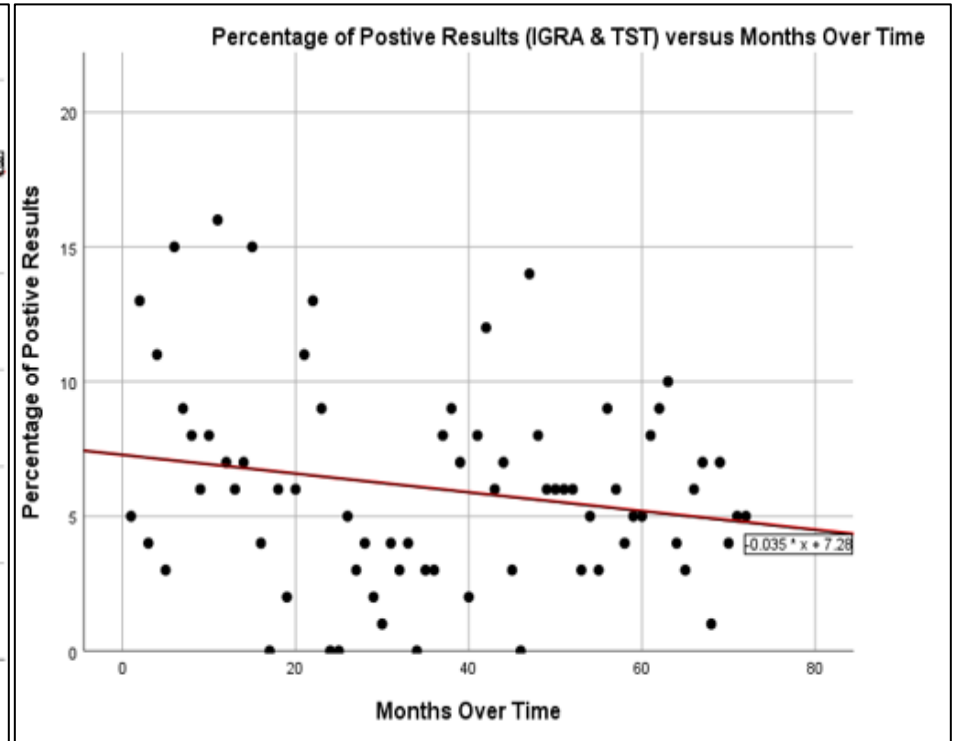


Figure 5a. Graph of IGRA Monthly Totals Overtime and **Figure 5b.** Graph of Monthly Positive TB Results (TST & IGRA) in Migrant Children Over a 5-Year Period in Harris County, Texas

Table 1. Definitions of immigration statuses

Immigration status	Definition
Refugee	A person located outside of the U.S. who demonstrates they were persecuted or have a fear of persecution due to race, religion, nationality, political opinion, or membership in a particular social group and is not firmly resettled in another country [33].
Asylee (Asylum seekers)	Any person who meets the definition of a refugee and is already in the United States or seeking admission at a port of entry [34].
Parolee (The Cuban and Haitian Family Reunification Parole Programs)	Persons from Cuba and Haiti who have family members that are U.S. citizens or lawful permanent residents, who are able to come to the U.S without waiting for immigrant visas to become available [35].
Special Immigrant Visa holders	There are many categories of SIVs, however, the children included in this study are children of Iraqi and Afghan translators are interpreters who have worked with the U.S. Armed Forces or under the Chief of Mission authority at the U.S. Embassy in Baghdad or Kabul [36].
Victim of Human Trafficking	A person who has been recruited, harbored, or transported for compelled labor or commercial sex acts through the use of force, fraud, or coercion [37].

Table 2. Demographic Variables of Migrant Children Over a 5-Year Period in Harris County, Texas

		Higher-risk groups			Lower-risk groups		P-value
Immigration Status		REFUGEE (N=4,246)	ASYLEE (N=173)	VHT (N=16)	PAROLEE (N=851)	SIV HOLDER (N=704)	
Category	VARIABLE	N (%)	N (%)	N (%)	N (%)	N (%)	
Demographics	AGE (MEDIAN, IQR)	8 (4-12)	9 (5-12)	11.5 (7-15)	9 (5-13)	4 (2-8)	<0.001 ^a
	FEMALE	2,025 (47.7%)	81 (46.8%)	7 (43.8%)	404 (47.5%)	304 (43.2%)	0.281 ^b
WHO Region of Origin	EASTERN MEDITERRANEAN	1,414 (33.3%)	89 (51.4%)	0	0	704 (100.0%)	<0.001 ^b
	SOUTHEAST ASIA	1,416 (33.3%)	7 (4.0%)	1 (6.3%)	0	0	
	AFRICA	1,202 (28.3%)	40 (23.1%)	0	0	0	
	AMERICAS	183 (4.3%)	31 (17.9%)	12 (75.0%)	851 (100.0%)	0	
	WESTERN PAC	18 (0.4%)	2 (1.2%)	1 (6.3%)	0	0	
	EUROPEAN	13 (0.3%)	4 (2.3%)	2 (12.5%)	0	0	
Comorbidities	HIV INFECTED	22 (0.5%)	0	0	1 (0.1%)	2 (0.3%)	<0.001 ^b
	PATHOGENIC PARASITES DETECTED IN STOOL	328 (17.1%)	18 (11.3%)	2 (12.5%)	98 (12.5%)	115 (17.9%)	<0.001 ^b

*% Included reflect those whom the information was available

^a p-value using Kruskal-Wallis

^b p-value using X² test

HIV: human immunodeficiency virus; IQR: interquartile range; PAC: Pacific; SIV: special immigrant visa; VHT: victim of human trafficking; WHO: world health organization

Table 3. Tests TB infection Performed and Test Results by Immigration Status in Migrant Children Over a 5-Year Period in Harris County, Texas

		Higher-risk groups			Lower-risk groups		P-value
Immigration Status		REFUGEE (N=4,246)	ASYLEE (N=173)	VHT (N=16)	PAROLEE (N=851)	SIV HOLDER (N=704)	
test(s) of Infection performed	TST ALONE	1,381 (32.5%)	30 (17.3%)	1 (6.3%)	168 (19.7%)	300 (42.6%)	<0.001 ^b
	IGRA ALONE	2,558 (60.2%)	137 (79.2%)	15 (93.8%)	642 (75.4%)	349 (49.6%)	
	TST AND IGRA	204 (4.8%)	4 (2.3%)	0 (0.0%)	22 (2.6%)	29 (4.1%)	
test results	TOTAL POSITIVE TESTS	311 (7.3%)	9 (5.2%)	0 (0.0%)	10 (1.2%)	34 (4.8%)	<0.001 ^b

IGRA: interferon gamma release assay; SIV: special immigrant visa; TST: tuberculin skin test; VHT: victim of human trafficking

^b p-value using X² test

Table 4. Factors Associated with a Positive TST and/or IGRA Result in Migrant Children over a 5-Year Period in Harris County, Texas (n tested = 5,870)

	TST Only				IGRA Only				TST & IGRA Combined			
	N (%)	aOR	95% CI	P	N (%)	aOR	95% CI	P	N (%)	aOR	95% CI	P
<u>Age (years)</u>												
<2	36 (25.2)	Ref			2 (1.6)	Ref			55 (15.1)	Ref		
2-5	35 (24.5)	0.40	0.26 – 0.61	<0.001	5 (3.9)	0.26	0.11 – 0.60	0.002	81 (22.3)	0.36	0.24 – 0.54	<0.001
6-10	30 (21.0)	0.72	0.42 – 1.25	0.25	31 (24.0)	0.41	0.20 – 0.85	0.02	74 (20.3)	0.28	0.18 – 0.42	<0.001
11-14	23 (16.1)	0.68	0.39 – 1.21	0.19	51 (39.5)	1.05	0.52 – 2.12	0.90	85 (23.4)	0.55	0.37 – 0.83	0.004
>14	19 (13.3)	0.77	0.44 – 1.35	0.36	40 (31.0)	1.35	0.66 – 2.77	0.41	69 (19.0)	0.72	0.48 – 1.10	0.13
<u>Region of Origin</u>												
SE Asia	61 (42.7)	Ref	0.33 – 0.70	<0.001	49 (38.0)	Ref	0.21 – 0.53	<0.001	148 (40.7)	Ref	0.33 – 0.59	<0.001
E Med	41 (28.7)	0.48	0.45 – 1.07	0.10	23 (17.8)	0.34	0.70 – 1.49	0.91	98 (26.9)	0.44	0.61 – 1.09	0.17
Africa	32 (22.4)	0.69	0.09 – 0.39	<0.001	50 (38.8)	1.02	0.06 – 0.25	<0.001	100 (27.5)	0.81	0.08 – 0.23	<0.001
Americas	8 (5.6)	0.19			7 (5.4)	0.12			17 (4.7)	0.14		
HIV Positive	4 (2.8)	2.99	1.01 – 8.87	0.049	1 (0.8)	-	-	-	7 (1.9)	5.57	2.23 – 13.90	<0.001

N = number in group with a positive TB test result

E MED: Eastern Mediterranean; SE ASIA: Southeast Asia

CONCLUSION

TB remains a significant public health issue in the U.S. and globally. In the U.S., 66% of reported TB cases occur among the foreign-born, a rate thirteen times higher than for U.S.-born persons [3]. Previous studies utilizing mainly the TST found a prevalence of TB infection of 9-35% among refugee children [27, 37-41]. However, positive results were less common in our cohort, potentially due to expanded IGRA use and the variety of immigration statuses included.

The prevalence of positive TB test results varied by region of origin, age, and HIV status, and all children had greater odds of having a positive TST result as compared to IGRA regardless of region of origin or age. Additionally, there were discordances between TST and IGRA results across the pediatric age spectrum, suggesting that the impact of BCG vaccination on TST positivity may be more prolonged than often expected.

Most prior estimates of the prevalence of TB infection in immigrant children used the TST as the test of choice, given an initial paucity of pediatric data and the availability and cost of IGRAs. A more recent study using IGRA testing estimated that 5.6% of immigrant children had TB infection compared to 22% using the TST [42]. More recent United States guidelines recommend IGRA use down to 2 years of age [43], with some experts using IGRAs in children as young as 1 year of age. Use of IGRAs rather than the TST in this younger cohort would likely reduce false positive tests and allow for TB infection therapy to be targeted to those who would most benefit.

The CDC does not recommend tiered testing for TB infection (that is, obtaining an IGRA if a TST result is positive). However, there are times when the initial test of infection, selected either by choice or by necessity, is not the optimal test, particularly for a BCG-immunized child. In this study, all children had greater odds of having a positive TST result as compared to IGRA regardless of region of origin or age. Additionally, three were nearly 300 children in whom both TSTs and IGRAs were obtained, of whom 20% had discordant results. These findings are consistent with a prior study which demonstrated that for BCG-immunized children, on immigration testing, false positive TSTs are common, and IGRAs should be the tests of choice for this patient population [27].

Strengths of the study

The strengths of this study include the large sample size, the comprehensive and longitudinal data, and the variety of immigration statuses and countries represented. This study represents one of the largest reports of TB testing among the pediatric age group resettling in the U.S. Additionally, this study is the only one, to my knowledge, that has long term follow up information on these pediatric patients as a result of the relationship between the refugee resettlement program and the TCH TB clinic. This study offers further insight into the epidemiology of TB infection for children with varied

immigration statuses emigrating from high-burden countries, and offers further data on the comparison of TSTs and IGRAs in this largely BCG-immunized population.

Limitations of the study

This study has several limitations. Though follow-up data for most children evaluated for a positive test of TB infection was obtained, there are missing data for some children evaluated post intake-testing at other clinics, or for children whose test of TB infection was negative. BCG vaccination status was not routinely documented, thus the presumption of falsely positive TST results secondary to cross-reactivity with BCG assumes that the vast majority of children were BCG-immunized as they originated from countries with high BCG-uptake. BCG vaccination is recommended in the national immunization program of 95% of countries from which these children emigrated [44]. HIV infection was rare in this cohort, thus it is difficult to make meaningful conclusions regarding TST and/or IGRA positivity in HIV-infected children from our data. Finally, these data may not be generalizable to all immigrant children relocating to the United States, as this study predominately included children from TB high-burden countries.

Conclusions:

The prevalence of positive TB test results in this cohort of children was lower than previously reported (compared to studies that predominately used the TST), and TB disease was rare. The lower prevalence of positive tests of TB infection in this childhood population likely stems from the predominant use of IGRA testing. Despite these low rates of positive results, it remains important to screen children emigrating from high-burden countries. Region of origin, and age are important risk factors for having a positive TB test result. The TST and IGRAs are frequently discrepant, particularly among younger children, and those from lower-burden countries. Positive TST results in BCG-immunized children frequently represent cross-reactivity and false positivity. Use of IGRAs as opposed to TSTs in BCG-immunized children would reduce false positive tests and allow for TB infection therapy to be targeted to those who would most benefit.

Future work:

For future work I plan to further evaluate discrepancies between the TST and IGRAs in BCG-immunized children by expanding the years of the study to include children seen at the TCH TB clinic between 2010 and 2017, specifically evaluating children in whom both a TST and IGRA were obtained to determine test characteristics. I additionally, plan to study factors associated with acceptance and completion of therapy for TB infection in this population.

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