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Latent Tuberculosis Infection among Immigrant and Refugee Children Aged 2-14 Years Who Arrived in the United States in 2008-2012

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School of Public Health

Public Health Thesis

**LATENT TUBERCULOSIS among
IMMIGRANT and REFUGEE
CHILDREN AGED 2-14 YEARS
WHO ARRIVED in the UNITED
STATES in 2008-2012**

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May 2015

Author's Statement Page

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APPROVAL PAGE

Latent Tuberculosis Infection among Immigrant and Refugee Children Aged 2-14 Years
Who Arrived in the United States in 2008-2012

By

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Abstract

Background: According to Centers for Disease Control and Prevention (CDC) tuberculosis (TB) report TB case rate dropped from 3.2 to 3.0 per 100,000 person in 2013 in the U.S, which was a 4.3% decrease from 2012, but the proportion of total cases occurring in foreign-born persons reached to 65% of the national case total. This proportion has been increasing since 1993. Studies found that progression of latent tuberculosis infection (LTBI) to active TB (reactivation TB) contributed a large proportion to TB cases among foreign-born persons and posed a huge challenge to TB elimination in the U.S. The Division of Global Migration and Quarantine (DGMQ) in CDC provides Tuberculosis Screening and Treatment Technical Instructions (TB TI) for U.S.-bound immigrant and refugee overseas medical screening. The 2007 TB TI made several changes to enhance overseas medical screening for TB. One of them is requiring applicants aged 2-14 years who live in countries with a World Health Organization (WHO)-estimated TB incidence rate equal or higher than 20 cases per 100,000 population to have a tuberculin skin test (TST) or interferon gamma release assay (IGRA) to detect TB/LTBI.

Objectives: To assess LTBI prevalence among immigrant and refugee children aged 2-14 years who arrived in the United States in 2008-2012 and to explore demographic and geographic predictors among LTBI cases.

Methods: Using DGMQ data from 2008-2012, LTBI prevalence was calculated. Regression analyses were used to examine predictors of LTBI risk based upon geographic and select demographic characteristics (country of origin, sex, country-specific LTBI prevalence rate).

Results: LTBI prevalence of all 199 immigrant and refugee arrival countries vs top 16 arrival countries were 6.30% and 8.76%, respectively. Top 16 arrival countries contributed to 68.40% arrivals but contributed to 95.08% of LTBI cases. LTBI prevalence of both populations showed an increasing trend in 2008-2012. The highest five prevalence countries were the Philippines (42.74%) Vietnam (9.35%), Mexico (8.71%), Bhutan (8.31%) and China (7.80%). Regression coefficient estimates (i.e., log odds) for country of origin predictor were significant ($p < .0001$) (all tests $\alpha = 0.05$) for 14 out of 16 top arrival countries. Coefficient estimates for the predictors of female percentage, 2007 TB TI percentage, WHO TB prevalence, female less than 50 percent and its interaction with female percentage were all significant ($p < .0001$).

Conclusions: Diagnosing and treating LTBI and continuing the battle against TB globally are critical to TB elimination in the U.S. 2007 TB TI has contributed to detecting LTBI cases, should be implemented vigorously in immigrant and refugee overseas medical screening. Receiving states should address their follow-up gaps to ensure the completion of TB/LTBI treatment. Resources need to be allocated properly to states with high TB/LTBI burden.

Table of Contents

INTRODUCTION.....	1
Background	1
Objectives	3
Study population	3
Institutional Review Board (IRB) approval	4
REVIEW OF THE LITERATURE	5
TB and LTBI are two related condition	5
TB is a global burden	5
Prevalence of LTBI	6
Reactivation TB	6
Risk factors of LTBI	9
METHODS	12
Data sets	12
Data sources	13
Data analysis software	17
RESULTS.....	18
LTBI prevalence	18
Regression analysis on LTBI prevalence	20
DISCUSSION AND CONCLUSION.....	28
Discussion.....	25
Strength of the study	29
Limitations of the study	29
Recommendations for future studies	29
Conclusions	30
REFERENCES	31

List of Tables

Table 1. Immigrant and Refugee New Arrivals – Total and Aged 2-14 Years.....	4
Table 2. Immigrant and Refugee Children Aged 2-14 Years Who Arrived in the United.....	13
States in 2008-2012 from Top 16 Arrival Countries – Total Arrivals (in descending order)	
Table 3. LTBI Prevalence - All Arrival Countries vs Top 16 Arrival Countries.....	18
Table 4. Arrival and LTBI – Proportions of Top 16 Arrival Countries in	
All Arrival Countries.....	18
Table 5. LTBI Prevalence by Year of All Arrival Countries vs Top 16 Arrival Countries.....	19
Table 6. LTBI Prevalence (in Descending Order) Top 16 Arrival Countries.....	19
Table 7. Odds Ratio Estimates – Top 16 Arrival Countries.....	23

List of Figures

Figure 1. Loess plot female percentage vs logit LTBI prevalence.....	21
Figure 2. Observed Probability.....	24
Figure 3. Predicted Probability.....	24

Chapter 1

INTRODUCTION

Background

Tuberculosis and latent tuberculosis infection

Tuberculosis (TB) is a serious infectious disease caused by a bacterium called *Mycobacterium tuberculosis*. The bacteria mainly attack the lungs as well as other parts of the body. Nodules (tubercles) grow in the tissues. TB can be fatal if left without proper treatment [1].

TB is spread through the air when a person with TB sneezes, coughs, speaks, or sings. People nearby may breathe in these bacteria and become infected [1].

TB bacteria can live asymptomatically in the body. This is called latent TB infection (LTBI). Most of the people infected do not become sick because the body is able to fight the bacteria to stop them from growing. People with LTBI have no symptoms and are not infectious, but if TB bacteria become active in the body and multiply, people with LTBI can progress to TB and become sick and infectious [1]. This is termed as reactivation TB [3] [4] [15].

TB and LTBI among foreign-born persons in the U.S.

In 2013 in the U.S., the TB case rate dropped from 3.2 to 3.0 per 100,000 person, which was a 4.3% decrease from 2012, but the proportion of total cases occurring in foreign-born persons reached to 65% of the national case total. This proportion has been increasing since 1993. TB case rate per 100,000 for U.S.-born persons and foreign-born persons were 1.2 and 15.6, respectively, indicating the rate for foreign-born persons was 13 times of that of U.S.-born

persons [2]. Studies found that reactivation TB contributed a large proportion to TB cases among foreign-born persons and posed a huge challenge to TB elimination in the U.S. [3] [4].

2007 Tuberculosis Screening and Treatment Technical Instructions

Foreign persons who applying for U.S. immigration/refugee status are required to have an oversea medical examination conducted by local panel physicians approved by the U.S. Department of States. The medical screening for TB is essential in the medical examination. The Division of Global Migration and Quarantine (DGMQ) in Centers for Disease Control and Prevention (CDC) provides Tuberculosis Screening and Treatment Technical Instructions (TB TI) for panel physicians to be used in U.S.-bound immigrant and refugee overseas TB screening. Due to the challenges in TB diagnosis, treatment and control the TB TI was designed as a guideline to panel physicians to help detect and treat TB among U.S.-bound immigrants and refugees and prevent the importation of TB into the U.S.

2007 TB TI requires U.S.-bound immigrants and refugees aged 2-14 years living in countries with a World Health Organization (WHO)-estimated TB incidence rate equal or higher than 20 cases per 100,000 population, or having contact with TB or symptoms of TB to have a tuberculin skin test (TST) or an interferon gamma release assay (IGRA) test to detect TB/LTBI and to determine the need for a chest radiograph.

Objectives

To assess LTBI prevalence among immigrant and refugee children aged 2-14 years who arrived in the United States in 2008-2012 and to explore demographic and geographic predictors among LTBI cases.

Study population

The study population was immigrant and refugee children aged 2-14 years who arrived in the United States in 2008-2012. The terms “arrival/arrivals/arrived” used through this study referred to New Arrivals of immigrants and refugees who entered the U.S. as lawful permanent residents (LPRs) or "green card" holders and might live and work permanently in the U.S. The other component of LPRs was Adjustments of Status (AOS) who first entered the U.S. as nonimmigrants and became LPRs through adjustment of status. Refugees also became LPRs through AOS, therefore were included in AOS [6] [7]. AOS (excluding refugees) overseas medical examination data are not available to CDC at present.

In 2008-2012, on average, immigrant and refugee yearly arrivals were approximately 470,000 and 67,000, respectively, immigrant yearly arrivals were about seven times of refugee yearly arrivals. Immigrant and refugee combined yearly arrivals were approximately half million. The yearly arrivals of immigrant and refugee children aged 2-14 years were approximately 88,000 and 16,000, respectively, immigrant children’s yearly arrivals were about five times of refugee children’s yearly arrivals. The combined yearly arrivals of immigrant and refugee children aged 2-14 years were approximately 100,000. Refugee children aged 2-14 years counted for about 25% of the total refugee yearly arrivals and immigrant children aged 2-14 years counted for

about 19% of the total immigrant yearly arrivals. The combined yearly arrivals of immigrant and refugee children aged 2-14 years counted for about 19% the combined immigrant and refugee yearly arrivals (Table 1).

Table 1. Immigrant and Refugee New Arrivals – Total and Aged 2-14 Years

Year	refugee new arrivals			immigrant new arrivals			total new arrivals		
	total	age 2-14	age 2-14 (%)	total	age 2-14	age 2-14 (%)	total	age 2-14	age 2-14 (%)
2008	64737	16924	26.14	458793	87875	19.15	523530	104799	20.02
2009	79941	19940	24.94	466756	88032	18.86	546697	107972	19.75
2010	71361	18158	25.45	494724	93012	18.8	566085	111170	19.64
2011	51456	12658	24.6	466172	85978	18.44	517628	98636	19.06
2012	66285	16263	24.53	481403	85307	17.72	547688	101570	18.55
Grand Total	333780	83943	25.15	2367847	440204	18.59	2701627	524147	19.4
mean	66756	16788.6	25.13	473569	88040.8	18.6	540325	104829	19.4

Institutional Review Board (IRB) approval

This study was approved by the CDC/DGMQ and Georgia State University IRB for use of secondary and aggregate data sources pertinent to study objectives. Detailed descriptions about the data sources were presented in Chapter 3.

Chapter 2

REVIEW OF THE LITERATURE

TB and LTBI are two related conditions

TB and LTBI are related. They both are caused by Mycobacterium tuberculosis bacterium; persons with LTBI get infected by persons with TB and may develop TB later on in their lives and the initial test for TB and LTBI are same [8] [9].

TST or IGRA are two kinds of tests that are used to determine if a person has TB infection. TST performs an injection of a small amount of tuberculin extracted from TB bacteria and measures the size of the swelling in the injection area on the arm. IRGA is a blood test and examines a person's immune system reaction to TB bacteria [9].

A negative test indicates that TB or LTBI is not likely. A positive test indicates that a person has TB infection. It cannot tell whether the person has LTBI or TB. A chest radiograph is needed to determine. If the determination still cannot be made, test of sputum smears or both sputum smears and culture are needed [1] [7]. If no signs and symptoms of TB found, then TB can be ruled out and the person with positive test has LTBI, otherwise, that person has TB [8] [9] [5].

TB is a global burden

TB is deemed as a global burden by WHO [8]. It is the second greatest killer after HIV/AIDS among the infectious diseases worldwide. In 2013, 9 million people became ill with TB and 1.5 million died of TB. 550,000 children fell ill and 80,000 HIV-negative children died from TB. It is the leading cause of death for HIV-positive people and women aged 15 to 44 years. In regard

to geographic distribution of TB low and middle-income countries accounted for over 95% of TB deaths. While a quarter of all TB cases occurred in Africa ranking it as the highest TB case rate per capita, half of all new cases occurred in six Asian countries including Bangladesh, China, India, Indonesia, Pakistan and the Philippines. 425,000 new multidrug-resistant TB (MDR-TB) occurred with the highest rates in the former USSR and China [10] [11].

Prevalence of LTBI

WHO estimates one-third of the world's population, approximately 2 billion people have LTBI [[12] [13].

A symposium sponsored by WHO on management of LTBI pointed out “Latent TB infection (LTBI) is responsible for most TB cases in low incidence countries. Reactivation TB significantly contributes to transmission in high burden countries” [14].

Reactivation TB

According to a CDC estimate, overall, if no treatment, about 5 to 10% of persons with LTBI will have reactivation TB at some time in their lives, and about half of those with reactivation TB will experience it within the first two years of infection. Persons with HIV infection have considerably higher risk of reactivation TB than those with normal immune systems [8]. WHO has the same estimate and suggests that the majority have reactivation TB within the first five years of infection [12].

A study by Horsburgh reviewed published reports and obtained estimates of the risk of TB among persons with a positive TST, based on these data a model was built to estimate the lifetime risk of reactivation TB among persons with certain medical conditions. The study found that the lifetime risk of reactivation TB was 20% or higher among most persons with a TST being 10 mm of induration or larger; among most persons with HIV infection, and among most persons with evidence of old, healed TB. The lifetime risk of reactivation TB was between 10 and 20% among most persons aged 35 years or younger with a TST being 15 mm of induration or larger and were receiving infliximab therapy; among most persons aged 35 years or younger with a TST being 15 mm of induration or larger and had a recent conversion of TST; and among children aged 5 years or younger with a TST being 10 mm of induration or larger. The author suggested that persons with high risk of reactivation TB should be targeted for testing and full treatment [15].

A cross-sectional study conducted by Ricks et al. used data of patients with an *Mycobacterium tuberculosis* isolate genotyped by the U.S. National TB Genotyping Service in 2005–2009. This service is a surveillance system established by CDC in 2004 and genotypes at least one *Mycobacterium tuberculosis* complex isolate of each TB case in the U.S. The study assumed that TB cases were reactivation TB if they were not included in a localized cluster of cases. This study calculated the overall proportion of reactivation TB in the total foreign-born TB cases, and that for the 25 countries that contributed the largest proportions of reactivation TB. The study found that foreign-born persons accounted for 60% of total TB cases; among these foreign-born TB cases 83.7% were attributed to reactivation TB; Bangladesh was the top one country of origin from which foreign-born persons in the U.S. had the highest proportion (97.6%) of reaction TB

contributed to TB cases, and followed by India (95.2%) and Burma (93.3%). This study analyzed relations between reactivation TB represented by crude odds ratios and 95% confidence interval and select factors represented by the grouped data for age at arrival in the U.S., time interval between arrival in the U.S. and diagnosis of TB, and WHO estimates of TB incidence per 100,000 for the countries of origin. The age groups were 14 years or younger, 15-24 years, 25-44 years, 45-64 years, 65 year or older. The study found that reactivation TB was positively associated with WHO TB incidence, age at arrival in the U.S. and negatively associated with time interval between arrival in the U.S. and diagnosis of TB. The study suggested the strategies to control TB among foreign-born persons in the U.S. should focus on finding and treating LTBI and reducing TB globally [3].

A cohort study done by Walter et al. linked preimmigration data of Filipino visa applicants aged 15 years or older examined in a medical center in the Philippines from 2001 to 2009 to TB cases among Philippines-born persons reported to California TB Case Registry from January 2001 to 2010. Records were matched by last name, first name, date of birth, sex and year of examination. The study defined LTBI reactivation (i.e., reactivation TB) as TB with a normal preimmigration examination and chest radiograph; imported TB as TB occurred no more than six months after arrival in the U.S. with an abnormal preimmigration chest radiography; and reactivation of inactive TB as TB occurred more than six months after arrival in the U.S. with an abnormal preimmigration chest radiography. The study found that within 1 year of preimmigration examination the proportions of each above defined type of TB in total TB cases matched distributed as reactivation TB (6%), imported TB (85%) and reactivation of inactive TB (9%). Within 2-9 years of preimmigration examination, the proportions distributed as

reactivation TB (76%), and reactivation of inactive TB (24%). Because of the high risk of LTBI this study suggested revise current guideline to extend LTBI screening to more than five years after the U.S. arrival [4].

Marais et al. reviewed pre-chemotherapy literature, which they thought documented the natural history of TB in childhood. Most of the studies reviewed defined children as aged less than 15 years, adolescents as aged more than 10 years and primary infection as first time TB infection indicated by TST conversion. They pointed out although in general pulmonary TB in childhood was often considered a benign condition due to little risk to the child and little risk of transmission to the community it could pose a high risk of fatality to the child and a high risk of transmission to the community if it occurred in specific years of age in childhood. According to them the natural history of TB demonstrated that the 1st high-risk period was under 2 years, in which children with primary infection frequently progressed to miliary TB or TB meningitis without significant symptoms. Children aged 2 to 10 years with primary infection rarely developed serious disease and had persistent symptoms. This gave an opportunity for clinical diagnosis. The 2nd high-risk period was adolescence. Children aged over 10 with primary infection frequently progressed to adult-type TB. They suggested early effective intervention for high-risk group to reduce the disease burden and transmission [16].

Risk factors of LTBI

CDC updated guidelines for using IGRA to detect TB/LTBI published in 2010 categorized risk factors for TB and reactivation TB in order to assist targeted testing and selection of persons who were likely to benefit from treatment for LTBI. Persons at increased risk of LTBI included:

those with HIV infection; aged 4 years or younger; receiving immunosuppressive therapy; infected with *Mycobacterium tuberculosis* within the past 2 years; with a history of TB that was not treated or treated inadequately; with diseases including silicosis, diabetes mellitus, chronic renal failure, leukemia, lymphoma, or cancer of the head, neck, or lung; having had a gastrectomy or jejunioileal bypass; with body weight less than 90% of their ideal weight; smoking cigarette or abusing drugs or alcohol; and populations with low-income, inadequate access to medical care and an environment of increase incidence of TB [13].

A case-control study conducted by Saiman et al. analyzed risk factors for LTBI among children in New York City. According to the authors their study “is the largest published study of risk factors for LTBI in young children.” Data were collected from 24 primary care clinics from September 1996 to December 1998. 96 cases and 192 controls were enrolled. Case participants were children aged between 1 to 5 years with LTBI. LTBI case was defined as TST being 10 mm of induration or larger with a normal chest radiograph, and control was defined as TST being 0 mm of induration. Questionnaires in English and Spanish were used to collect demographic and SES information. The demographic characteristics of the subjects were 51% male, 80% Hispanic, 9% black and mean age being 2.9 years. Univariate analysis found no difference between case and control in gender, age, ethnicity/race and language spoken at home and in the proportion of household income less than \$20,000. Logistic Regression Analysis found that having contact with TB or a relative with positive TST, born in a foreign country, traveling to a foreign were predictive of LTBI. Having Bacille Calmette-Guerin (BCG) vaccine for TB, consuming raw dairy products and exposed to persons with history of illicit drug use, homelessness, or incarceration were not predictive of LTBI. The authors pointed out that their

study population had a high proportion of crowding, poverty, lower SES, although these variables were found to be associated with TB by studies, they were not predictive in this study due to case-control matched design being used for the study. This study suggested targeted screening for LTBI should focus on communities with immigrants migrated from countries with high rates of TB and consider LTBI risk factors [17].

Chapter 3

METHODS

Data sets

Two data sets

1st data set included all immigrant and refugee children aged 2-14 years who arrived in the United States in 2008-2012. The total number of subjects in the data set was 524,147 (N=524,147); total number of countries was 199, and the total number of records was 895.

2nd data set included immigrant and refugee children aged 2-14 years who arrived in the United States in 2008-2012 from top 16 arrival countries (ranking by combined immigrant and refugee arrivals in 2008-2012). This was a subset of 1st data set. The total number of subjects in the data set was 358,516 (N=358,516), and the total number of records was 80.

How the two data sets were used

1st data set was used to calculate LTBI prevalence of all arrival countries and to compare that with the top 16 arrival countries. 2nd data set was used to calculate LTBI prevalence of the top 16 arrival countries and to build logistic regress model to assess association between LTBI prevalence (i.e., LTBI/total arrivals) and potential risk factors including country of origin, female percentage, TB TI 2007 percentage and WHO TB prevalence.

The reason why using 2nd data set for analyzing association was because the top 16 arrival countries contributed to 68.40% (358516/524147) arrivals and 95.08% (31418/ 33045) LTBI cases (Table 3, Table 4). It was also because they had complete data while many other arrival countries had missing data in 2008-2012 study period.

Table 2. Immigrant and Refugee Children Aged 2-14 Years Who Arrived in the United States in 2008-2012 from Top 16 Arrival Countries – Total Arrivals (in Descending Order)

Immigrant Refugee Combined Arrival Rank	Country of Origin	Immigrant Refugee Combined Arrivals
1	Mexico	73305
2	Dominican Republic	50405
3	The Philippines	33446
4	Burma	24987
5	China	24271
6	Iraq	22112
7	Vietnam	19325
8	Haiti	18873
9	India	14392
10	Jamaica	13402
11	Bhutan	13331
12	El Salvador	11671
13	Pakistan	11269
14	Bangladesh	10950
15	Ethiopia	9414
16	Somalia	7363

Data sources

U.S. Department of Homeland Security (DHS) immigration data

Data of immigrant arrivals, gender, age, country of birth and type of admission status (New Arrival or AOS) were requested and received by DGMQ from DHS. They were not publically available. Yearbook of Immigration Statistics published by DHS, which is publically available, does not contain data for Lawful Permanent Residents (LRPs) breakdown by New Arrivals and Adjustment of Status (AOS), and breakdown by country and birth for New Arrivals. It also does not contain data for calendar year (only for U.S. federal fiscal year October 1 to September 30).

This study used DHS LPR New Arrivals breakdown by calendar year and country of birth because medical screening data are available to DGMQ at present only for LPR New Arrivals not for AOS. DHS data were used as the denominators for the immigrant part (denominators summed up immigrant and refugee arrivals) when calculating LTBI prevalence.

U.S Department of State (DOS) refugee data

Data of refugee arrivals, gender, age and country of nationality were requested and received by DGMQ from Worldwide Refugee Admissions Processing System (WRAPS) of DOS. They were not publically available. Yearbook of Immigration Statistics contains data (source is DOS) of refugee arrival by country of nationality, but no breakdowns by gender and age and not for calendar year (only for U.S. federal fiscal year October 1 to September 30).

Country of nationality is important information for analyzing LTBI among refugees because for refugees country of birth may differ from country of nationality. For example, many Burmese refugee were born in refugee camps in Thailand. Their country of birth was Thailand while their country of nationality was Burma. Many Bhutanese refugee were born in refugee camps in Nepal. Their country of birth was Nepal while their nationality was Bhutan. Many Somali refugees were born in refugee camps in Kenya. Their country of birth was Kenya while their nationality was Somalia. All these three nationalities were among top 16 arrival countries in this study.

This study used WRAPS country of nationality. WRAPS data were used as the denominators for the refugee part (denominators summed up immigrant and refugee arrivals) when calculating LTBI prevalence.

DGMQ Electronic Disease Notification (EDN) data

This data system was developed by DGMQ and put in use in January 2006. It is not publically available (available to immigrant and refugee receiving states). It stores data collected in immigrant and refugee overseas medical examinations. DOS approved local panel physicians conducted medical examinations and entered the data in DOS medical examination forms (MEDICAL EXAMINATION FOR IMMIGRANT OR REFUGEE APPLICANT, CHEST X-RAY AND CLASSIFICATION WORKSHEET, VACCINATION DOCUMENTATION WORKSHEET, MEDICAL HISTORY AND PHYSICAL EXAMINATION WORKSHEET). These forms are made available to DGMQ. DGMQ uses EDN to notify receiving states of the arrivals of all refugees and immigrants who had medical conditions along with their demographic and medical information collected by the DOS forms and stored in EDN. Health Department of the receiving states are required to conduct follow-up medical evaluation of all refugees and immigrants with medical conditions (mainly TB conditions) and follow up on their medical treatment.

This study used EDN LTBI data. Because LTBI is a medical condition these data are captured for both refugees and immigrants.

This study used EDN TB TI form type (2007 vs 1991 TB TI) data. If form type data could not determine whether 2007 or 1991 TB TI was used for medical screening “CoverSheetNotAvailable” (if available then 2007 TB TI) and “TBClassID” variables in EDN were taken into account.

TB TI data are incomplete in EDN because for immigrants only those who had medical conditions were captured in EDN (refugees were supposed to be all captured in EDN). What type of TB TI forms was used for immigrants who did not have medical conditions were unknown. Considering that 2007 TB TI implementation was same or similar in one country this study took immigrant captured in EDN as a simple random sample to make the inference on this variable for the entire immigrant population.

Using TB TI form type and other relevant data in EDN to estimate 2007 TB TI percentage could be more accurate than using 2007 TB TI start date (official start date for a country) because situations happened such as a country still used 1991 TB TI forms even after the 2007 TB TI start date, or used 2007 TB TI forms in a pilot program before the 2007 TB TI start date.

WHO TB Incidence and Prevalence data

WHO TB incidence rates (per 100 000 population per year) was not used in the data sets. It indicates whether test for TB/LTBI is required in immigrant and refugee overseas medical examinations (if incidence rates ≥ 20 in the country). Incidence rates were above 20 or much higher than 20 for 14 out of 16 top arrival countries. Only Jamaica's rates were less than 20 (6.5 in 2008, 6.6 in 2009-2012), therefore, tests for LTBI were not required. Mexico's rates were 20-21 (20 in 2008-2009, 21 in 2010-2012).

WHO TB prevalence rate (per 100 000 population) was used as a predictor in regression model. These data are publically available and were downloaded from WHO website [7].

Match country names used by different data sources

Country of origin is an important variable for this analysis. DHS, DOS, EDN and WHO TB data used different names for a same country for a few countries. For example, North Korea was “Korea, North”, in DHS and DOS data, “KOREA, DEM PEOPLE REP” in EDN data and “Democratic people’s Republic of Korea” in WHO TB data. tblRegions table in DGMQ Information on Migrant Population (IMP) database listed a country with its DHS, DOS, EDN and WHO country names in one record for matching. This study matched DHS, DOS, EDN and WHO country names in their data with their corresponding names in tblRegions and chose WRAPS_nationality (DOS country name) as the name for country of origin to categorize country correctly.

Data analysis software

Microsoft SQL Server 2008 was used to create study data sets. DHS, DOS, EDN and WHO data were stored in Microsoft SQL Server 2008 databases. SQL queries were written to retrieve data for the study data sets.

SAS 9.3 (SAS Institute) was used for statistical analysis.

Chapter 4

RESULTS

LTBI prevalence

Overall prevalence of all arrival Countries vs top 16 arrival countries

Overall prevalence for all arrival countries and top 16 arrival countries were 6.30% and 8.76%, respectively (Table 3). Prevalence of top 16 arrival countries was much higher than that of all arrival countries (199 countries).

Table 3. LTBI Prevalence - All Arrival Countries vs Top 16 Arrival Countries

	All	Top 16
Arrival	524147	358516
LTBI	33045	31418
LTBI Prevalence (%)	6.30	8.76

Proportions of prevalence and arrivals of top 16 arrival countries in all arrival countries

Top 16 arrival countries contributed to 68.40% (358516/524147) arrivals and 95.08% (31418/33045) LTBI cases (Table 4).

Table 4. Arrival and LTBI – Proportions of Top 16 Arrival Countries in All Arrival Countries

	Top 16
In Total Arrival (%)	68.40
In Total LTBI (%)	95.08

Prevalence by year of all arrival countries vs top 16 arrival countries

Prevalence of both all arrival countries and top 16 arrival countries showed an increasing trend over the study period 2008 -2012 (Table 5).

Table 5. LTBI Prevalence by Year of All Arrival Countries vs Top 16 Arrival Countries

Arrival Year	All			Top 16		
	Arrivals	LTBI	LTBI (%)	Arrivals	LTBI	LTBI (%)
2008	104799	1259	1.20	70029	1245	1.78
2009	107972	7356	6.81	75298	7247	9.62
2010	111170	8521	7.66	76651	8227	10.73
2011	98636	7576	7.68	67333	7073	10.50
2012	101570	8333	8.20	69205	7626	11.02

Prevalence of the top 16 arrival countries

The top five prevalence countries were the Philippines (42.74%) Vietnam (9.35%) and Mexico (8.71%), Bhutan 8.31% and China (7.80%). The lowest three prevalence countries were Jamaica (0.00%), Pakistan (0.26%) and El Salvador (0.37%) (Table 6).

Table 6. LTBI Prevalence (in Descending Order) Top 16 Arrival Countries

Rank in Total Arrivals	Country of Origin	Arrival	LTBI	LTBI Prevalence (%)
3	The Philippines	33446	14296	42.74
7	Vietnam	19325	1806	9.35
1	Mexico	73305	6386	8.71
11	Bhutan	13331	1108	8.31
5	China	24271	1894	7.80
4	Burma	24987	1888	7.56

16	Somalia	7363	454	6.17
2	Dominican Republic	50405	2421	4.8
15	Ethiopia	9414	333	3.54
8	Haiti	18873	314	1.66
9	India	14392	175	1.22
14	Bangladesh	10950	92	0.84
6	Iraq	22112	179	0.81
12	El Salvador	11671	43	0.37
13	Pakistan	11269	29	0.26
10	Jamaica	13402	0	0.00

Regression analysis on LTBI prevalence

Regression model

Multiple logistic regression model was built to assess the association between LTBI prevalence and its potential predictors.

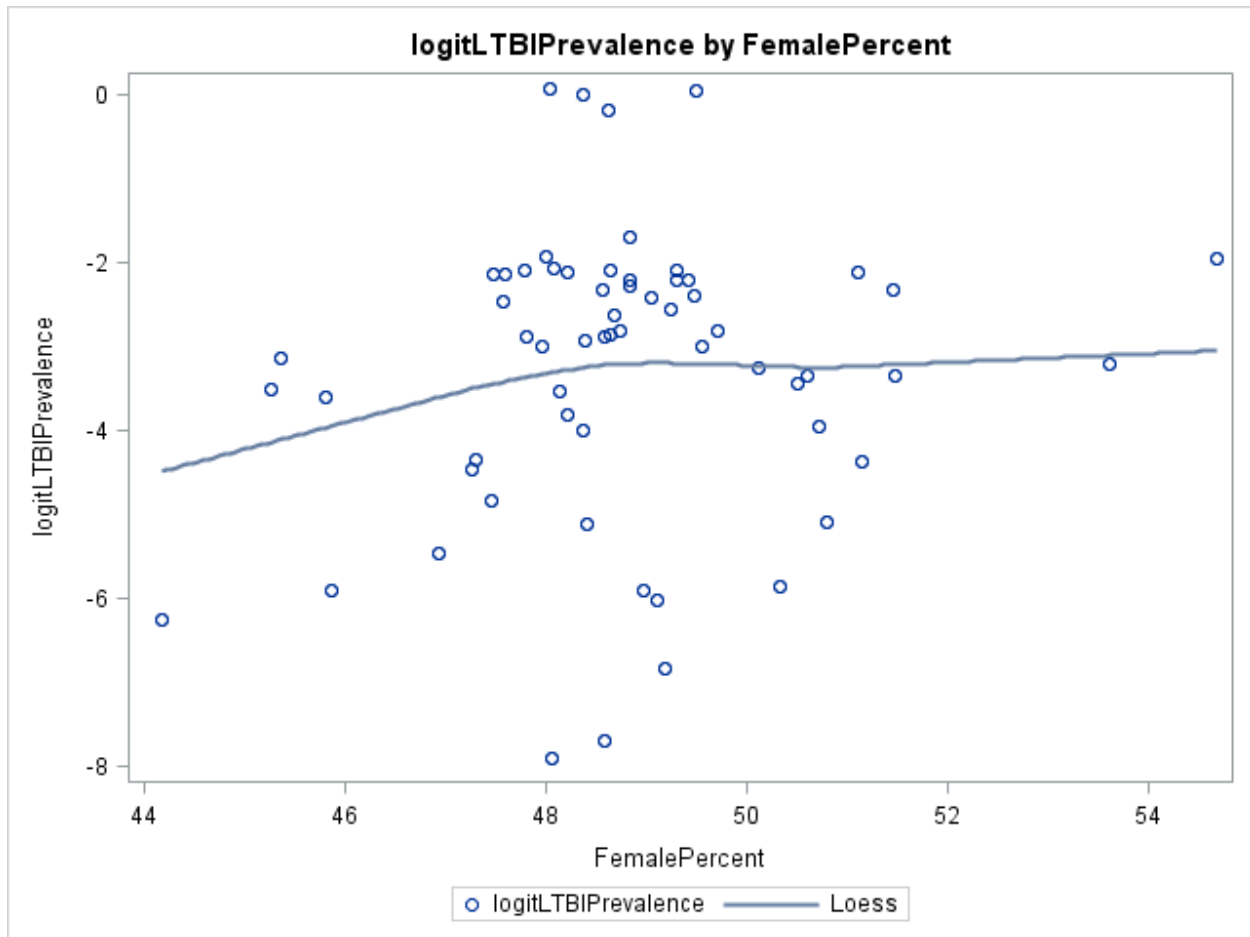
Response variable was LTBI prevalence. It was calculated (LTBI/total year arrivals) and added to the study data set.

Predictors were country of origin, female percentage, TB TI 2007 percentage and WHO TB prevalence.

In addition, female less than 50 percent variable (set based on female percentage and added to the data set) and its interaction with female percentage variable were added to the regression model as potential predictors after the examination of Loess plot between female percentage and log LTBI prevalence (i.e., log odds or logit). Female 50 percent was approximately a dividing

point. The rate of logit LTBI prevalence increased more rapidly before this point than after this point (Figure 1)

Figure 1. Loess plot female percentage vs logit LTBI prevalence



Regression coefficient estimates

Coefficient estimates (i.e., log odds or logit) from SAS output Analysis of Maximum Likelihood Estimates for country of origin predictor were significant ($p < .0001$) (all tests $\alpha = 0.05$) for 14 out of 16 top arrival countries, and not significant for China ($p = 0.1166$) and Jamaica ($p = 0.8296$).

Coefficient estimates for the predictors of female percentage, TB TI 2007 percentage, WHO TB

prevalence, female less than 50 percent and its interaction with female percentage were all significant ($p < .0001$).

Odds ratio estimates

Odds ratio estimates for country of origin showed that compared to Mexico, China (OR = 0.886, 95% CI = 0.762, 1.031) was not significant (CI including 1) and all other countries were significant; the Philippines (OR = 2.437, 95% CI = 1.634, 3.633) had the highest odds of LTBI, which was 2.44 times of that of Mexico and the only country with higher odds of LTBI than Mexico; and Bangladesh (OR = 0.041, CI = 0.028, 0.06) had the lowest odds of LTBI, which was 4.1% of that of Mexico.

Odd ratio estimate for TB TI 2007 percentage (OR = 1.042, 95% CI = 1.041, 1.044) was holding other variables in the model constant with one percent point increase in 2007 TB TI form usage the odds of detecting LTBI increased by 4.2%.

Odd ratio estimate for WHO TB prevalence (OR = 8.983, 95% CI = 3.826, 21.093) was holding other variables in the model constant with one per 100,000 increase in WHO TB prevalence the odds of LTBI increased by about 8 times.

Odd ratio estimate for Female percent was holding other variables in the model constant, when female in arrivals was minority with one percent point increase of female percentage (OR = 1.196, 95% CI = 1.161, 1.233) the odds of LTBI increased by 19.6%, and when female in arrivals was majority with one percent point increase of female percentage (OR = 1.045, 95% CI = 1.015, 1.077) the odds of LTBI increased by 4.5% (Table 7).

Table 7. Odds Ratio Estimates – Top 16 Arrival Countries

Odds Ratio Estimates			
Effect	Point Estimate	95% Wald Confidence Limits	
CountryOfOrigin Bangladesh vs Mexico	0.041	0.028	0.06
CountryOfOrigin Bhutan vs Mexico	0.375	0.299	0.472
CountryOfOrigin Burma vs Mexico	0.295	0.194	0.448
CountryOfOrigin China vs Mexico	0.886	0.762	1.031
CountryOfOrigin Dominican Republic vs Mexico	0.394	0.364	0.426
CountryOfOrigin El Salvador vs Mexico	0.13	0.096	0.176
CountryOfOrigin Ethiopia vs Mexico	0.339	0.275	0.418
CountryOfOrigin Haiti vs Mexico	0.13	0.099	0.169
CountryOfOrigin India vs Mexico	0.225	0.173	0.292
CountryOfOrigin Iraq vs Mexico	0.692	0.589	0.813
CountryOfOrigin Jamaica vs Mexico	<0.001	<0.001	>999.999
CountryOfOrigin Pakistan vs Mexico	0.06	0.038	0.093
CountryOfOrigin The Philippines vs Mexico	2.437	1.634	3.633
CountryOfOrigin Somalia vs Mexico	0.267	0.174	0.411
CountryOfOrigin Vietnam vs Mexico	0.684	0.571	0.82
TI07Percent	1.042	1.041	1.044
WHOTBPrevalencePerce	8.983	3.826	21.093

Odds Ratio Estimates and Wald Confidence Intervals			
Label	Estimate	95% Confidence Limits	
FemalePercent at FemaleLessThan50Pct=1	1.196	1.161	1.233
FemalePercent at FemaleLessThan50Pct=0	1.045	1.015	1.077

Predicted probability

Predicted probability was calculated by the regression model. In general, predicted probability was close to the observed probability indicating that the predicting power of the regression model was relatively strong.

The observed probability plot (Figure 2) and predicted probability plot (Figure 3) showed similarities, which both showed that the Philippines, Vietnam and Mexico were the three countries with the highest LTBI prevalence, which were consistent with Table 6.

Figure 2. Observed Probability

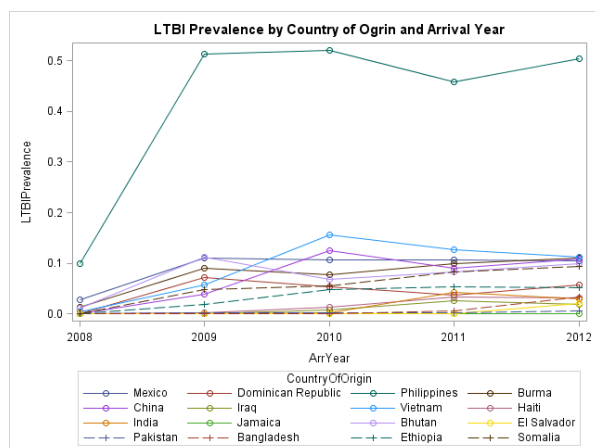
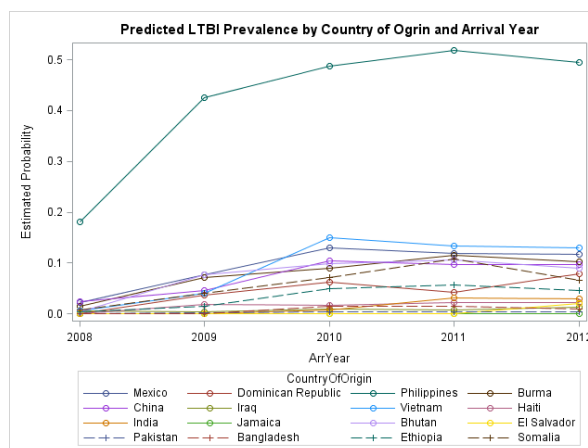


Figure 3. Predicted Probability



Chapter 5

DISCUSSION AND CONCLUSION

Discussion

Applying epidemiologic triad framework to diagnosing and treating LTBI would help address the issue in a more systematic and holistic way.

Agent – LTBI and its interdependence with the host and the environment

As described chapter 1 and 2, TB and LTBI are related. TB is infectious and the mode of transmission is droplet spread. LTBI is asymptomatic and not infectious. But LTBI can progress to TB (reactivation TB), and the host becomes sick and infectious [1] [8].

In general, the chance of reactivation TB is low (5-10%) [8] [15] [21]. This makes the disease easily live in the body of the host without detected and not being dealt with properly by the host and the environment [24] [26] [27].

Host – Immigrant and refugee children resettled in the U.S. and their interdependence with the agent and the environment

Development of LTBI and reactivation TB depends on the immunity, age and environment of the host. Studies found that the risk of reactivation TB was higher for young children, persons with HIV-infections or other particular medical conditions [8] [13] [15]. If infected infants and children aged under 4 years could frequently progress to miliary TB or TB meningitis.

Adolescence could progress to adult-type TB.

Studies also found that the risk of reactivation TB was substantially higher among foreign-born person and reactivation TB contributed a large proportion to the TB cases in the U.S. [3] [4] [22]. This study demonstrated top 16 arrival countries contributed largely to arrivals (68%) and greatly to LTBI cases (95%) (Table 4). LTBI prevalence of all arrival countries and top 16 arrival countries showed an increasing trend in 2008-2012 (Table 5). These LTBI could add to the pool of TB case in the U.S. due to reactivation TB.

Environment – country of origin and resettlement country and their interdependence with the host

High prevalence of TB in country of origin was the major source of LTBI among the immigrants and refugees resettled in the U.S. According to CDC report Mexico, the Philippines, India, Vietnam, and China were the top five countries of origin of foreign-born persons with TB in the U.S. in 2013 [2]. This study showed the top five countries of origin of LTBI prevalence were the Philippines, Vietnam, Mexico, Bhutan and China. The similarity of these two sets of results indicated the close relationship. This was also found by this study. WHO TB prevalence predictor had the highest odds ratio (OR = 8.983, 95% CI = 3.826, 21.093) among all the predictors. A study found that TB was the most significant predictor of LTBI [17]. Another study pointed out the source that causes TB infection for most children was close contact with adult TB cases [27].

The host was affected by the agent and the environment of the country of origin, and in turn they impacted the environment of the country in which they resettled. The host was also affected by the environment of the resettlement country. Actions should be taken to avert the negative

impacts of agent, host and environment. Progress has been made. The TB death rate dropped 45% between 1990 and 2013 [11]. Awareness of the importance of diagnosing and treating LTBI has increased tremendously. Current LTBI treatment guideline published by CDC in 2011 called treating LTBI “a cornerstone of the U.S. strategy for TB elimination” [20]. Many studies pointed out the imperativeness of treating LTBI among foreign-born persons and its public health and economic benefits [3] [4] [22], and also suggested targeted testing and treatment based on risk factors [13] [15] [16] [17] [18]. IGRA as a new TB/LTBI test method overcame some limitations of the convention test method [13] [25], though more clinical trials are needed [13] and the cost is a concern [21]. Clinical trials indicated that treating LTBI with INH for 6 to 12 month could result in 69% to 93% reduction of TB [24]. Shortened treatment regimen with INH and rifapentine (RPT) weekly for 12 weeks under directly observed therapy (DOT, i.e., give patients the medicine and observe them taking the medicine) was proved by clinical trials as effective as the U.S. standard regimen with INH daily for 9 month without DOT, and has been recommended by CDC since 2011 for LTBI treatment [20]. WHO has similar recommendations [21]. Better access to medical services, more knowledge of the disease, social support, assistance in finding transportation, housing, education and employment opportunities can help host overcome culture barriers, fear and stigma about the disease and being willing to be tested and complete the treatment.

2007 TB TI has led the way in addressing the challenges posed by the agent, the host and the environment. It requires DOT, and culture test. It also requires that children aged 2-14 years from high TB prevalence countries or having contact with TB or symptoms of TB to have TST/IGRA test to detect TB/LTBI. This study showed that 2007 TB TI was effective in

detecting LTBI (OR = 1.042, 95% CI = 1.041, 1.044). Under 1991 TB TI medical screening for children younger than 15 only limited to symptom review, TST or IGRA tests was required only for children with symptoms. Culture test was not required, so smear-negative but culture positive TB could not be detected [28]. DOT helps increase drug adherence and the completion of TB/LTBI treatment. 2007 TB TI requires immigrant and refugee children who diagnosed with LTBI to have preventive therapy, but in general treatment should not be started until the arrival in the U.S. This treatment specification also applies to immigrant and refugees who had TB but completed required treatment, and tests of sputum smears and cultures were all negative. They can travel to the U.S. and continue their treatment after the arrival. Treatment status should be documented to expedite follow-up medical evaluation upon the arrival in the U.S. [5]. These specifications put heavy responsibility on receiving states to ensure the completion of treatment. This is also reflected in the new perspective in the U.S. TB control strategy as stated in ATS/CDC guidelines for treatment of TB “The responsibility for successful treatment is clearly assigned to the public health program or private provider, not to the patient” [19].

Receiving states are required to conduct follow-up medical evaluation on the immigrants and refugees arrived in their states. DGMQ uses Electronic Disease Notification (EDN) to notify states of the arrivals of all refugees and immigrants with medical conditions whose overseas medical examination data are stored in EDN. Receiving state health department and local health clinics have access to EDN. Follow-up evaluation includes TST or IGRA test, chest radiograph (CXR) and other tests and examination. Data of follow-up evaluation are stored in EDN.

In fiscal year 2013 (October 1, 2012 - September 30, 2013), the top five states (ranking by EDN notifications) and their follow-up evaluation percentage out of the total arrivals in the state were California (73%), Texas (69%), New York (79%), Florida (71%) and Illinois (62%). The states with the highest and lowest follow-up percentage were Minnesota (92%) and Hawaii (60%), respectively. These numbers indicate that states should address their follow-up gaps to ensure the completion of TB/LTBI treatment.

Strength of the study

This study has strength. It took advantage of the data resources of DGMQ and combined immigrant and refugee arrival and LTBI data and conducted descriptive and analytic analysis. Most of the LTBI data were collected after 2007, therefore, this is an area lack of study.

Limitations of the study

This study has limitations. As described in data source section, type of TB TI forms used for immigrants who did not have medical conditions were unknown. Inferences were made. Age was no stratified by age groups due to no further breakdown under 2-14 age group for immigrants in DHS data.

Recommendations for future studies

Continue this study. 2007 TB TI has been implemented in almost all panel sites worldwide since October 2013. More LTBI data will be collected. More studies need to be conducted on prevalence and risk factors of LTBI among immigrant and refugee population, which may help future interventions.

Conclusions Diagnosing and treating LTBI and continuing the battle against TB globally are critical to TB elimination in the U.S. 2007 TB TI has contributed to detecting LTBI cases, should be implemented vigorously in immigrant and refugee overseas medical screening. Receiving states should address their follow-up gaps to ensure the completion of TB/LTBI treatment. Resources need to be allocated properly to states with high TB/LTBI burden.

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