POST-ARRIVAL SCREENING AND TREATMENT OF FOREIGN-BORN INDIVIDUALS FOR TUBERCULOSIS AND LATENT TUBERCULOSIS INFECTION

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ABSTRACT

Though the total number of tuberculosis (TB) cases reported in the United States (US) is decreasing, persistently high incidence among foreign-born individuals has slowed progress towards national TB elimination. Reducing the overall incidence of TB the US will require enhanced diagnosis and treatment of active TB among the foreign-born, as well as targeting the pool of latently infected individuals who represent an important source of future TB cases. This analysis examines three important aspects of controlling TB in foreign-born individuals. The first study evaluates of efforts by Baltimore City Health Department (BCHD) to screen and treat refugees, non-refugee foreign-born individuals and other patient groups for latent tuberculosis infection (LTBI) and describes factors associated with patient compliance with LTBI evaluation. The second study evaluates post-arrival screening and treatment of high-risk (Class B) immigrants referred to BCHD and assesses whether recent efforts to conduct additional sputa testing on all Class B immigrants resulted in enhanced TB case finding. The third study reviews the importance of LTBI testing and treatment of the foreign-born, and examines ways to equip health departments to complete this important pillar of the US strategy for TB elimination. The results of these studies suggest that local health department efforts to screen and treat foreign-born individuals for tuberculosis and LTBI can be effective in reducing the overall burden of illness within the community. However,

persistent resource limitations and other factors can reduce the effectiveness of these programs.

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CHAPTER 1: BACKGROUND AND INTRODUCTION

Overview of the Current Epidemiology of Tuberculosis in the United States

For the last 20 years, the United States has seen a steady decrease in the annual number of tuberculosis (TB) cases. In 2013, fewer than 10,000 new TB cases were reported across the country—the lowest number of incident cases since reporting began in the 1950s.[1] Despite this welcome progress, the percent reduction in new TB cases has slowed in recent years and the current incidence of TB cases in the U.S. (3.0 per 100,000 population) still exceeds CDC's TB elimination goal of having <1 case per 1 million population.[1] The CDC has estimated that at the rate the TB incidence has been declining in recent years, it may take more than 90 years to achieve TB elimination. [2]

One of the biggest obstacles to eliminating TB from the United States is persistently high incidence of TB among the foreign-born, which is 13 times greater than the incidence among U.S.-born individuals.[1] The majority (65%) of U.S. TB cases now occur among the foreign-born and efforts to reduce incidence in this group have been slow compared to U.S. born. Since 1993, the annual incidence of TB among U.S.-born individuals has decreased by more than 80%., from 7.4 cases per 100,000 to 1.4 per

100,000. But incidence among the foreign-born has been consistently higher—falling from 34 cases per 100,000 in 1993 to 15.9 cases per 100,000 in 2012 (a 53% decline) (Figure 1).

The contribution of foreign-born to TB rates in these states and others are likely to continue to increase, as both the number of and percentage of the US population that is foreign-born persons born abroad has grown steadily since 1970 (Figure 2). Each year, approximately 1 million new immigrants and 173 million foreign-born non-immigrant visitors enter the United States (Table 1). Additionally, it is estimated that 11.7 million foreign-born, unauthorized immigrants currently live in the US.[3] Currently, the states that report the greatest number of TB cases--California, Texas, New York, and Florida—are also those with the highest percentage of foreign-born persons.[1, 4] Combined, these four states accounted for 51.3% of all TB cases reported in 2013 and over half of the number of foreign-born individuals living in the U.S. in 2010. Each of these states has reported more than 500 cases a year since 2008.[5]

US Efforts to Reduce TB among the Foreign-Born

Pre-Arrival Screening of Immigrants

To reduce the chances that TB will be introduced from abroad, the US requires that individuals applying to immigrate to the US undergo a pre-arrival medical exam that includes TB screening. These exams are conducted overseas by US Department of State-appointed panel physicians. The panel physicians conduct TB evaluations according to technical instructions (TIs) developed by the CDC. These instructions require different levels of screening, depending on a patient's age and the TB incidence in the country from which he/she is emigrating (Table 2).

In 2007, CDC published new TIs that included additional screening requirements. Under the revised TIs, the panel physicians must conduct the following: 1) TST or IGRA tests for children (age 2-14) from countries with WHO-estimated incidence ≥20 cases/100,000 population; 2) cultures in addition to smears when sputa testing is indicated; and 3) drug-susceptibility testing for positive isolates.[6] A recent analysis conducted by the CDC estimates that 1,100 cases of TB were diagnosed among applicants in 2012 using the new TIS.[6] Among those cases, approximately 60% of all cases were smear-negative/culture-positive.[7]

Under the current TIs, individuals with evidence of untreated, active, contagious TB are considered to have a Class A condition. Class A applicants are not allowed to enter the United States unless they receive a medical waiver. Individuals with some evidence of radiographic evidence of TB (including extrapulmonary TB that is not laryngeal or pleural), but negative smears and cultures, are designated as Class B1. Individuals who have a positive TST (≥5 mm if individual is contact of known TB case, ≥10 mm for all others) or IGRA, but no other signs of TB are classified as B2. Individuals who are a recent contact of a known tuberculosis case (usually, contacts of individuals who have received an A classification) are designated as B3. Class B immigrants are allowed to enter the US, but are instructed to undergo follow-up examinations within 30 days of arrival in the US.

Post-Arrival Screening and Treatment

The US also maintains programs for post-arrival screening and treatment of foreign-born individuals. When immigrants with Class A and Class B medical conditions enter the United States, CDC notifies health departments of their arrival, so that they may oversee the follow-up examinations of these individuals. In 2009, health departments in 50 states and the District of Columbia were notified of the arrival of 23,321 Class B and 20 Class A (with waiver) immigrants in need of post-arrival tuberculosis examinations.

According to the CDC, across the country, health departments provided follow-up examinations for a median of 75.4% of all notifications for immigrants with suspected tuberculosis classifications.[8]

There are additional efforts to provide post-arrival TB screening for the subset of immigrants that enter the US as refugees. Like other immigrants, refugees undergo a pre-arrival medical examination to determine their eligibility to enter the United States. Those cleared to travel to the US receive a subsequent evaluation upon arrival in the US, which includes tuberculosis screening.

Targeted Testing and Treatment of LTBI

A number of authoritative groups including the American Thoracic Society, the Institute of Medicine and the U.S. Centers for Disease Control and Prevention (CDC) have recommended that there be dedicated programs for testing and treatment of foreign-born individuals for latent TB infection (LTBI). [9-11] Accurate diagnosis and effective treatment of latent tuberculosis infection (LTBI)— having either immunologic or radiographic evidence of TB infection, but no evidence of active TB diseases—can reduce the incidence of TB by shrinking the pool of individuals who represent an

important source of future TB cases. A 9 month course of isoniazid (INH) chemoprophylaxis—has been shown to reduce the risk of active TB in patients with LTBI almost 90%.[12]

Foreign-born individuals have been identified as a priority for LTBI screening and treatment, as they are at high-risk group for progression to TB. Studies suggest that a major contributor to TB cases in the US is the reactivation of infections acquired abroad. Eighty percent of active TB cases reported in the U.S. have been attributed to reactivation of prior infection, rather than newly transmitted infection.[13] The rate of reactivation TB among persons with latent TB infection (LTBI) is higher among foreign-born persons than among persons born in the United States. It has also been shown that the risk of reactivation persists long after arrival in the United States, even though LTBI screening guidelines suggest targeting only those individuals who have been in the country for fewer than 5 years. [14]

Though targeted testing and treatment of LTBI in foreign-born, has been identified as a necessary step to achieve U.S. TB elimination goals, it remains an overlooked component of TB control efforts US.[15] Current guidelines for pre-arrival medical screening do not include LTBI evaluation for adults or other non-immigrant foreign-

born visitors that enter the US. Moreover, efforts to screen and treat foreign-born individuals after arrival in the US are limited. US health departments, which conduct the majority (~80%) of LTBI treatment that occurs in the US, have largely not been able to maintain dedicated programs to test and treat foreign-born individuals for LTBI.[16, 17] Though health departments may require post-arrival LTBI evaluations of the minority of immigrants that enter the US with refugee status, funding restrictions in some areas have limited the type of screening and treatment health departments are able to conduct.[18, 19]

Current Approaches for Diagnosing LTBI

Traditionally, diagnosis of LTBI relied on use of the tuberculin skin test (TST). Though this test is still widely used, TSTs are subject to a number of shortcomings, including cross-reactivity with Bacillus Calmette-Guérin (BCG) vaccine and other Mycobacterium infections. There are also operational challenges associated with administering TST. Interpretation of TST results can be clinically subjective, as it requires healthcare workers to visually measure the size of induration and interpret the results. Guidelines for what is considered a positive result vary by country and the presence and a number of factors, including a patient's immune status. Test administration error can also cause the size of an induration to vary. Administering the TST to an individual requires that

he/she make at least two visits to a health care provider. When individuals are subject to routine screening, two-step testing may be required, which would require an additional healthcare visit to have a TST result read.

In recent years, newer in-vitro methods—called Interferon-Gamma Release Assays (IGRAs)—have become available for diagnosing LTBI. QuantiFERON-TB Gold (QFT-G), QuantiFERON-TB Gold In-tube (QFT-GIT) and the T-SPOT.TB are the three commercially-available IGRA tests that have been approved by the FDA as indirect tests for Mycobacterium tuberculosis infection. IGRAs offer a number of potential advantages over TSTs in diagnosing LTBI. First, unlike the TST, IGRAs have been shown to be specific to infection with M. tuberculosis and do not appear to be influenced by BCG vaccination. Second, interpreting IGRA test results is less subjective than for the TST. Third, administering an IGRA require only one health care visit (versus 2 visits for TST screening of healthcare workers or 3 visits if two-step TST screening is required). Fourth, IGRA test results can be available 24 hours (versus 2-3 days for TST). In light of these advantages, a number of countries have incorporated IGRAs into national guidelines for tuberculosis control.[20]

Despite a number of potential advantages, there are also a number of drawbacks associated with IGRAs. Though several systematic reviews have demonstrated that IGRAs generally have comparable sensitivity and enhanced specificity when compare to TST, there is evidence that IGRA test performance may vary. Different commercial IGRA tests have been shown to have different sensitivities.[21] A small number of studies have found lower IGRA sensitivity when used in high and intermediate TB-burden settings[22, 23] and when used to screen certain populations (e.g., children[22, 24] and HIV+ individuals[25, 26]). Others studies suggest there may be significant within subject variability of IGRA tests when used to serially test individuals.[27]

Baltimore City Health Department's Role in Screening and Treating Foreign-born Individuals for TB and LTBI

TB remains an important public health issue in Baltimore City, Maryland. The annual incidence of reported cases of active TB (3.4 cases per 100,000 in 2013) exceeds the national average, with a large proportion of active TB cases attributable to foreign-born individuals (62% in 2013; BCHD unpublished data). [28, 29] As part of the regional TB control strategy, the Baltimore City Health Department Tuberculosis (BCHD) TB program has historically provided medical evaluation and care services free of charge to Baltimore City residents who are diagnosed with active TB and LTBI.

Overview of this Study

This study describes three important aspects of post-arrival screening and treatment of foreign-born individuals for tuberculosis and LTBI by local health departments.

Chapter 2 presents an analysis of efforts by Baltimore City Health Department (BCHD) to screen and treat refugees, non-refugee foreign-born individuals and other patient groups for LTBI. The aim of Chapter 2 is to provide a better understanding of the factors associated with patient compliance with LTBI evaluation in order to inform patient care for epidemiologically important populations, such as refugees.

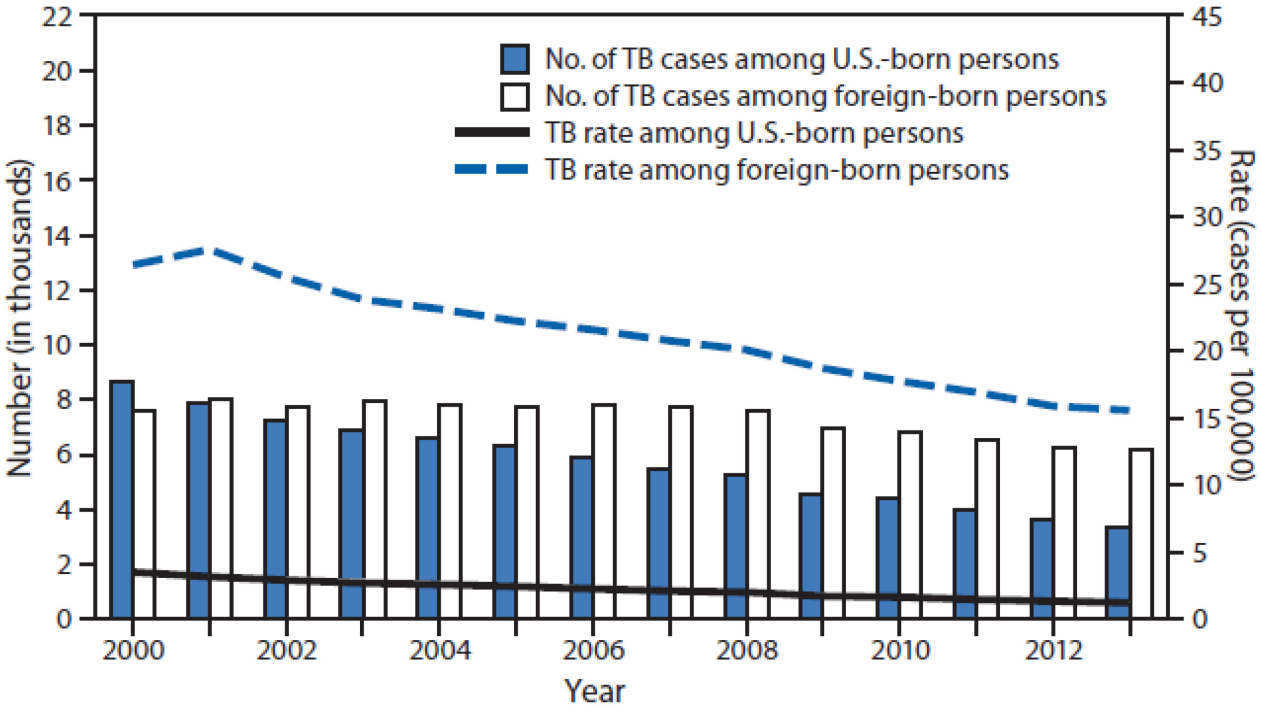
Chapter 3 contains an analysis of post-arrival screening and treatment of Class B immigrants referred to BCHD for follow-up examination. This study describes how Class B immigrants were screened in practice and analyzed the extent to which testing was conducted according to existing protocols. This study also aimed to evaluate whether recent efforts to conduct additional sputa testing on all Class B immigrants resulted in enhanced TB case finding.

Chapter 4 reviews the importance of LTBI testing and treatment of the foreign-born, and discusses ways to equip health departments to complete this important pillar of the

US strategy for TB elimination. This chapter examines the policy landscape surrounding US TB control programs and details current and future challenges that hinder public health departments' abilities to expand LTBI testing and treatment of the foreign-born.

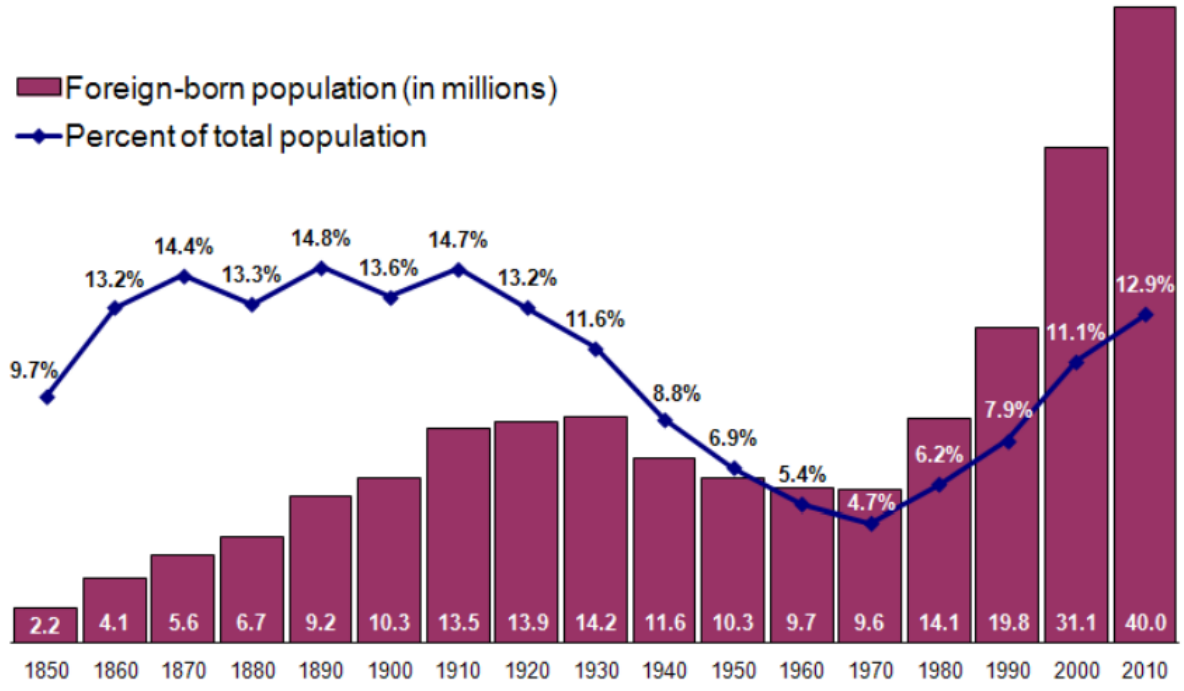
Figures

Figure 1: Number and incidence of tuberculosis (TB) cases among U.S.-born and foreign-born persons, by year reported — United States, 2000–2013



Source: CDC. Trends in Tuberculosis, 2013. 2013. *MMWR*. **63(11);229-233**.

Figure 2: The Number and Percent of the US Population that is Foreign-Born, 1850-2010.



Source: U.S. Census Bureau, Census of Population, 1850 to 2000, and the American Community Survey, 2010.

Table 1: Annual Influx of Immigrants and Non-Immigrant Visitors to the United States*

Year	Immigrants, By Visa Type[‡]				Non-Immigrant Visitors
	Legal Permanent Residents	Refugees	Asylees	Parolees	
2003	703,542	34,362	10,402	4,196	180,500,000
2004	957,883	61,013	10,217	7,121	180,200,000
2005	1,122,257	112,676	30,286	7,715	175,300,000
2006	1,266,129	99,609	116,845	4,569	175,100,000
2007	1,052,415	54,942	81,183	1,999	171,300,000
2008	1,107,126	90,030	76,362	1,172	175,400,000
2009	1,130,818	118,836	58,532	2,385	162,600,000
2010	1,042,625	92,741	43,550	1,592	159,700,000
2011	1,062,040	113,045	55,415	1,147	158,500,000
2012	1,031,631	105,528	45,086	758	165,500,000
Median per year	**1,057,228**	**96,175**	**50,251**	**2,192**	**173,200,000**

*Source: Department of Homeland Security. Yearbook of Immigration Statistics, 2012. http://www.dhs.gov/yearbook-immigration-statistics.

Table 2: Pre-Arrival TB Screening Requirements for Individuals Applying for Immigration to the US

Applicant	Primary Screening Requirement	Secondary Screening Requirement	Tertiary Requirement
≥15 years of age	medical history, physical examination, and CXR	Sputa testing if: CXR with findings suggestive of tuberculosis, *or* has signs and symptoms of tuberculosis, *or* HIV positive	N/A
2-14 years of age, from countries with TB incidence of ≥20 cases/100,000 population	medical history, physical examination, and TST or an IGRA	Chest xray: if TST is ≥10mm or IGRA is positive, *or* has signs and symptoms of TB, *or* HIV infection	Sputa testing: if CXR suggestive of tuberculosis, *or* signs and symptoms of tuberculosis, *or* HIV infection
<2 years of age, from countries with TB incidence of ≥20 cases/100,000 population	medical history, physical examination	Chest xray, TST or IGRA testing, and sputa testing: if signs and symptoms of TB, *or* HIV infection	N/A
<15 years, from countries with TB incidence <20cases/100,000 population	medical history, physical examination	Sputa testing: if HIV+ *or* abnormal CXR	N/A

Source: CDC. CDC Immigration Requirements: Technical Instructions for Tuberculosis Screening and Treatment Using Cultures and Directly Observed Therapy. October 1, 2009. http://www.cdc.gov/immigrantrefugeehealth/pdf/tuberculosis-ti-2009.pdf

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CHAPTER 2: SCREENING AND TREATING REFUGEES AND OTHER PATIENT GROUPS IN BALTIMORE CITY FOR LTBI

Analysis of latent tuberculosis infection treatment adherence among refugees and other patient groups referred to the Baltimore City Health Department TB clinic, February 2009 -- March 2011

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Abstract

Background: We sought to determine the proportion of refugee patients at the Baltimore City Health Department Tuberculosis program (BCHD-TB) successfully completing LTBI treatment, as compared to other referral groups, and to identify factors associated with treatment completion.

Design: Retrospective cohort analysis of individuals referred to BCHD-TB program for LTBI care between February 1, 2009 and March 31, 2011.

Results: Among 841 patients evaluated by BCHD-TB and diagnosed with LTBI, 81% of refugees, 50% of non-refugee foreign-born, and 35% of US-born patients completed LTBI treatment. In multivariate analysis, refugees had greater odds of LTBI treatment completion (Adjusted Odds Ratio: 7.2; 95%CI: 4.2-12.4, $p<0.001$) compared to US-born individuals adjusting for age, gender, and treatment regimen.

Conclusions: Overall, LTBI treatment completion remains suboptimal. At BCHD-TB, LTBI treatment completion was significantly higher among refugees than other referral groups. Additional efforts are needed to optimize LTBI care, and future efforts may need to be tailored for different risk groups.

Introduction

The prevention of active tuberculosis (TB) disease through the identification and treatment of individuals with latent tuberculosis infection (LTBI) is a key component of the United States (US) national strategy to eliminate tuberculosis.[22] While the annual incidence of active TB has continued to decline in the US, national rates (3.2 per 100,000) exceed the goal for TB elimination (less than 1 case per 100,000).[20] Reactivation of LTBI represents a significant source (>70%) of new cases of active TB reported in the US, especially among foreign-born individuals.[23-25] Consequently, the US Centers for Disease Control and Prevention (CDC) recommends targeted testing and treatment of individuals at highest risk for TB infection, such as recent immigrants from TB-endemic regions of the world, including refugees and asylees. [11]

Baltimore City, Maryland, is an urban environment, population approximately 620,000, in which TB remains an important public health issue. The annual incidence of reported cases of active TB (3.5 cases per 100,000 in 2012) exceeds the national average, with a large proportion attributable to foreign-born individuals (36% in 2012).[20,21] As part of the regional TB control strategy, the Baltimore City Health Department Tuberculosis (BCHD) TB program has historically provided medical evaluation and care services free of charge to Baltimore City residents with LTBI or active TB disease. With respect to

LTBI, community sources who suspect that their patients are infected with *M. tuberculosis*, may refer patients with positive test results (typically individuals with a positive tuberculin skin test [TST]) to the BCHD TB program for evaluation and, if indicated, treatment. BCHD receives nearly 500 such referrals each year from heterogeneous community sources including immigration programs, drug treatment programs, homeless services, and federally qualified health centers (FQHC).

The largest source of patient referrals to the BCHD TB program for LTBI care is the state's refugee health program, which is administered by a local FQHC. Each year the State of Maryland screens ~1100 new refugees for M. tuberculosis infection with either a TST or Interferon-gamma-release-assay (IGRA), of which approximately 40% of individuals are sent to local health departments for follow-up evaluations for a positive test result. Refugees referred to the BCHD TB clinic frequently come from countries with high incidence of TB and, therefore, represent a high priority group for LTBI screening and treatment within the city.

Adherence to LTBI treatment is an important determinant of the success of local TB control efforts. A number of studies have examined acceptance and adherence to treatment among patients in the United States. Overall, LTBI treatment completion is

low and has been reported to depend on a variety of social, demographic and clinical factors.[26-30] Few studies have addressed completion rates specifically among refugee populations; two studies from outside of the United States (Canada and Australia) reported that 49% and 44% of refugee immigrants (respectively) completed a full course of prescribed LTBI treatment.[31,32] LTBI treatment success among refugees in the United States has not been previously evaluated.

Our goal was to improve understanding of refugee care within Baltimore City by analyzing the proportion of refugees referred to BCHD for suspected LTBI that complete LTBI treatment. We compared LTBI evaluation and treatment between refugees and other referral groups within Baltimore City, and evaluated factors associated with successful treatment completion. A better understanding of the of the factors associated with patients' reporting to the health department for evaluation and treatment will help to inform efforts to provide better care for this epidemiologically important population.

Methods

Study Design

We performed a retrospective analysis of a cohort of individuals who were referred to the BCHD TB program for LTBI care between February 1, 2009 and March 31, 2011. Patients are referred to the BCHD TB program for LTBI care on the basis of a positive TST or Interferon gamma release assay (IGRA) test result. All individuals referred to the clinic for LTBI evaluation and care were included; individuals with confirmed or suspected active TB disease and their close-contacts were excluded from this analysis.

LTBI Services at BCHD

We reviewed information contained in the BCHD TB Program electronic database (Microsoft Access 2003) and in patients' clinic charts to obtain all clinical and demographic data analyzed in this study. Age, sex, foreign-born status and country of origin information are collected at time of referral for all patients who are referred to BCHD TB program. Individuals that adhere to an initial LTBI evaluation appointment are interviewed by BCHD TB program staff for signs and symptoms of active TB, medical history including TB risk factors, and demographics. All individuals receive a chest x-ray and blood is drawn for liver chemistries; all patients are offered HIV testing. Prior to 2010, BCHD TB ClinicBCHD TB Program staff diagnosed LTBI based on TST or

IGRA results available from the referral source with no further LTBI testing; beginning in early 2010, BCHD performed additional Quantiferon-Gold-In-Tube (QFT-GIT) test on all individuals referred for a positive TST, and determined the final diagnosis of LTBI based on both test results. Individuals with discordant QFT-GIT and TST results were diagnosed with LTBI based on an individualized assessment that included evaluating BCG status, quantitative test results, and other TB risk factors. Individuals with signs and/or symptoms of active TB disease receive further evaluation that includes sputum microscopy and culture and other testing as needed. Individuals diagnosed with LTBI are asked to return for a follow-up visit for treatment initiation.

All patients diagnosed with LTBI in whom active TB has been excluded are prescribed treatment according to current treatment guidelines—either a 9 month course of isoniazid (INH9) or a 4 month course of rifampin (RIF4).[22] The choice of drug treatment regimen (INH9 or RIF4) is based on the judgment of the TB clinician based on a patient's co-morbidities and potential for drug-drug interactions to occur. LTBI treatment initiation was defined as adherence to a follow-up visit at which medications were dispensed; all medications were provided at the clinic, free of charge. The BCHD TB Clinic makes up to three additional attempts to reschedule an appointment in the event that a patient misses their scheduled visit. After treatment initiation, medications

are dispensed by BCHD-TB program staff at monthly clinic appointments. Overall, individuals were considered to have completed treatment if their clinical records indicated that they completed at least 6 months of INH or at least 3 months of RIF and they showed up at BCHD to pick up a final allotment of medicine; we assumed that patients who picked up their final allotment of treatment completed a full course of treatment.

Statistical Analyses

We summarized clinical and demographic factors present among patients who were referred to and/or examined by the BCHD TB program for suspected LTBI. We examined the association of these factors with patients' adherence to LTBI evaluation, treatment initiation, and treatment completion using logistic regression. Variables were included in multivariate logistic regression analysis based on statistical significance in univariate analysis and/or clinical relevance. We used likelihood ratio tests to determine overall p-values for variables included in our regression analyses that had more than two categories. Categorical data were also analyzed using Chi square (χ^2) and continuous variables were analyzed using a non-parametric k-sample test of medians. All data were analyzed using STATA Version 10.1 (StataCorp, College Station, Texas).

Ethical Review

Ethics committees at the Johns Hopkins University School of Medicine (Baltimore, USA) and the Baltimore City Health Department approved this research. This study received a waiver of informed consent.

Results

Referrals and Evaluations

A total of 1,357 patients were referred to the BCHD TB program for LTBI care on the basis of a positive TST or IGRA during the study period (Figure I). Refugees from the State of Maryland's Refugee Health Program accounted for 35% (473/1357) of patients and were the largest single source of patient referrals to the BCHD TB Program for LTBI care; the majority of refugees were of Nepalese or Bhutanese origin (Table I). Non-refugee foreign-born individuals referred from other community sources accounted for 30% (397/1357) of patients referred to the BCHD TB Program for LTBI care, while US-born patients accounted for 36% (487/1357) of patient referrals. Among US-born patients, drug treatment programs and community clinicians accounted for the most common referral sources (48% and 34% of US-born referrals, respectively).

Seventy-five percent [1,019/1357; 95% Confidence Interval (CI) 73%-77%] of all patients referred to the BCHD TB Program adhered to an initial clinic appointment and completed an LTBI evaluation. Adherence to the initial LTBI evaluation appointment differed by referral source: 90% (427/473; 95% CI 87%-93%) of patients referred via the State's Refugee Health program, 71% (281/229; 95% CI 59%-68%) of non-refugee foreign-born and 64% (311/487; 95% CI 59%-68%) of US-born patients completed an evaluation ($p<0.001$).

Table I shows additional demographic and clinical characteristics of refugee, non-refugee foreign-born, and US-born patients who were referred to and evaluated at the BCHD TB Clinic for TB.

LTBI Diagnosis and Treatment Initiation

Among all patients evaluated by BCHD TB Program staff, 83% (841/1019; 95% CI 80%-85%) were ultimately diagnosed with LTBI during the study period (Figure I). Respectively, the proportion of refugees, non-refugee foreign-born and US-born patients who were diagnosed with LTBI was 86% (366/427; 95% CI 82%-89%), 81% (229/281; 95% CI 76%-86%), and 79% (246/311; 95% CI 74%-83%)($p=0.056$).

Overall, we found that 78% percent (652/841; 95% CI 75%-80%) of all patients diagnosed with LTBI returned to the BCHD TB Program to initiate treatment. There was no difference in initiation of treatment between men (78%; 394/505; 95% CI 74%-82%) and women (77%; 258/336; 95% CI 72%-81%; p=0.675), but those initiating treatment were younger [median age 34; interquartile range (IQR) 22-47] compared to those that did not initiate (median age 39; IQR 29-51; p=0.016). Information on treatment regimen was available for 646/652 patients who initiated treatment for LTBI. Among patients diagnosed with LTBI, treatment initiation was highest among refugees (91%; 333/366; 95% CI 88%-94%) compared with non-refugee foreign-born (66%; 152/229; 95% CI 60%-72%) and US-born patients (68%; 167/246; 95% CI 62%-74%; p<0.001)(Figure I and Table II).

Among all patients who initiated therapy, 58% (379/646) were prescribed RIF4 and 41% (267/646) were prescribed INH9 (Table III). Treatment regimen differed with immigration status. Sixty-six percent (220/331; 95%CI 61%-72%) of refugees who initiated treatment were treated with RIF4 (Table II), compared to 68% (101/149; 95%CI 60%-75%) of non-refugee foreign-born individuals and 35% (58/166; 95% CI 28%-48%) of US-born individuals.

In multivariate analysis we found that the odds that patients with LTBI would initiate treatment differed depending on immigration status and age (Table III). Refugees had a significantly higher odds of initiating treatment as compared with US-born individuals (AOR= 4.4; 3.31-5.9; p<0.001), whereas, the odds that non-refugee foreign-born individuals would initiate treatment was not significantly different than that of US-born patients (AOR= 1.2; 0.89-1.6; p=0.264). We also found that the youngest patients (ages 0-14 years) had significantly higher odds of initiating treatment as compared with the reference group (patients ages 25-44) (AOR=2.5; 1.6-3.9; p<0.001). We found no evidence of a difference in treatment initiation between males and females in any of the three immigration status groups (Table 3)(AOR= 0.93; 0.67-1.3; p=0.675).

LTBI Treatment Completion

Overall, only 495 out of the 841 (59%; 95% CI 55%-62%) patients who were evaluated by BCHD TB Program staff and diagnosed with LTBI successfully completed their treatment (Figure I). The overall proportion of individuals who were diagnosed with LTBI that went on to complete treatment differed by immigration status and was 81% (296/366; 95% CI 76%-85%) among refugees, 50% (113/229; 95% CI 43-65%) among non-refugee foreign-born, and 35% (86/246; 95% CI 29%-41%) among US-born (p<0.001) (Figure 1).

When examining only those that initiated LTBI treatment, we found that the overall proportion of individuals who successfully completed LTBI therapy was 76% (495/652; 95%CI 72%-79%) (Figure I and Table II). Among those initiating therapy, refugees were significantly more likely to complete treatment (89%; 296/333; 95% CI 85%-92%) as compared with US-born patients (52%; 86/167; 95% CI 44%-59%) and compared to non-refugee foreign-born (75%; 113/152; 95% CI 67%-81%) ($p<0.001$). This association was observed even after we adjusted for differences in age, gender and treatment regimen (AOR 7.2; 4.2-12; $p<0.001$; Table III). Non-refugee foreign-born patients had a lower percentage of treatment completion compared to refugees ($p<0.001$), but had increased odds of completing treatment as compared with US patients (AOR: 2.8; 1.6-4.9; $p<0.001$).

Among patients initiating LTBI therapy, 80% (302/378; 95% CI 75%-84%) of those prescribed RIF4 completed their treatment compared to 73% (193/266; 95% CI 67%-78%) of those on INH9 ($p= 0.030$); however, this difference was not found to be significantly different in multivariate analysis when adjusting for age, gender, and immigration status (AOR: 1.1; 0.68-1.7; $p=0.725$). Furthermore, we did not find any evidence that of a difference in completion between patients receiving different treatment regimens in our stratified analysis shown in Table 2. Similarly, we found that patients completing treatment were younger (median age 32; IQR 20-45) compared to those failing to

complete treatment (median age 40; IQR 27-50; p= 0.013), but we did not find an association between age and treatment completion in multivariate analysis.

Discussion

Programs to screen foreign-born individuals for LTBI, like those in Baltimore City, are an important component of broader TB control goals. The majority of new TB cases reported in the United States occur among foreign-born individuals. In 2011, the incidence of TB was 12 times greater among foreign-born individuals in the US than it was for individuals born in the US.[33] Therefore, efforts to diagnose and treat LTBI among this high-risk group offer an important opportunity to prevent active TB cases from occurring.

Within Baltimore City, refugees represent a high-risk group in whom LTBI care is particularly important. Our findings suggest that only 81% of refugees diagnosed with LTBI by BCHD-TB program successfully complete therapy. Nonetheless we found that treatment completion among refugees was significantly higher than in other foreign-born or US-born individuals with LTBI (50% and 35%, respectively).

Overall, LTBI treatment completion at BCHD was relatively low (59%), but these results are consistent with those from other settings in the US.[28,30] Interestingly, we found that a major barrier to LTBI care was treatment initiation. Despite adherence to an initial clinic visit, over 20% of individuals evaluated by BCHD who were diagnosed with LTBI failed to return for a follow-up visit for treatment initiation. The reasons for this finding are unclear, but we found that refugees were far more likely to return for LTBI treatment (91%) compared to both US-born (68%) and non-refugee foreign-born patients (66%).

We examined factors associated with successful LTBI care and found that immigration status was the strongest predictor of LTBI treatment completion. Refugees treated by the BCHD TB Program were seven times more likely to complete treatment compared to US-born individuals referred to BCHD with LTBI. We did not find compelling evidence that treatment completion varied according to patient gender or treatment regimen. Although there was some evidence of increased treatment completion among those patients who were treated with the shorter rifampin regimen, this association was not found to be significant when adjusting for immigration status.

This analysis is subject to several limitations. First, we assumed that patients who regularly reported to BCHD to pick up LTBI medications complied with treatment. Therefore, our outcome of interest (treatment completion) may be subject to misclassification bias if patients did not consume medicines as prescribed. Second, because this was a retrospective review, we were unable to conduct patient interviews to ascertain the health-system or patient-specific factors associated with non-adherence with clinic visits. Third, we also had limited data on other factors that have been shown to effect treatment completion in other settings, such as patients' comorbidities (e.g., substance abuse, general health status) and socioeconomic data (e.g., housing or employment status).[34] Therefore, we cannot make any judgments about differences in rates of adverse outcomes or other important factors other than the demographic variables discussed here that may have been related to whether or not a patient complied with treatment. Despite these limitations, this study does have a number of strengths. To our knowledge it is one of the first to evaluate LTBI evaluation and treatment among refugees in the US. Also, the number of patients included in this analysis is larger than many other published studies that have examined LTBI treatment compliance in high-risk patients.

The findings of this analysis are important for public health programs for two main reasons. First, we found that adherence to LTBI evaluation and treatment among all patient groups remains suboptimal. Long duration of treatment, language barriers, and need for frequent clinic visits may represent possible obstacles for patients to successfully complete LTBI therapy. Further research is urgently needed to determine the health system and patient factors associated with lack of LTBI treatment completion among refugees. Second, the significant observed differences in adherence to LTBI evaluation and treatment among refugees, non-refugee foreign-born, and US-born individuals suggests that TB programs may require different strategies to optimize LTBI care among different groups of patients. For example, US-born referrals to BCHD for LTBI care were largely from drug treatment programs or the Department of Corrections—groups that have historically been shown to have low adherence to treatment. Closer collaborations with health providers or staff at these referral sites may be required to improve adherence to LTBI appointments and treatment.

We cannot say with certainty why refugees had higher rates of compliance with LTBI evaluation and treatment than other patients. One explanation may be different administrative mechanisms that oversee healthcare for refugee patients as compared with other foreign-born individuals. In Maryland, a dedicated program exists for

screening and treating immigrants who arrive in the United States as refugees. The Maryland State Refugee Resettlement Program provides social services, financial and medical assistance including health screenings, health insurance, and access to primary care providers through FQHCs to refugees resettled in Maryland. These services are available for all refugees for eight months after their arrival in the US. In some circumstances, refugees may be eligible for state-based services for an extended period of time (up to five years). This support may contribute to enhanced patient follow-up and/or ease other life demands that may prevent other immigrant patients or US-born individuals from accessing care. As such, the provision of these state-based support services may contribute to the higher LTBI treatment completion rates seen in our study. Differences in cultural perceptions may also play a role, as it is possible that refugees have enhanced of awareness of TB and the need for treatment due to high levels of TB disease in refugee camps. Though compliance with LTBI screening and treatment is not a requirement for resettlement, though it is possible that refugees have the perception that compliance is necessary to continue to receive benefits.

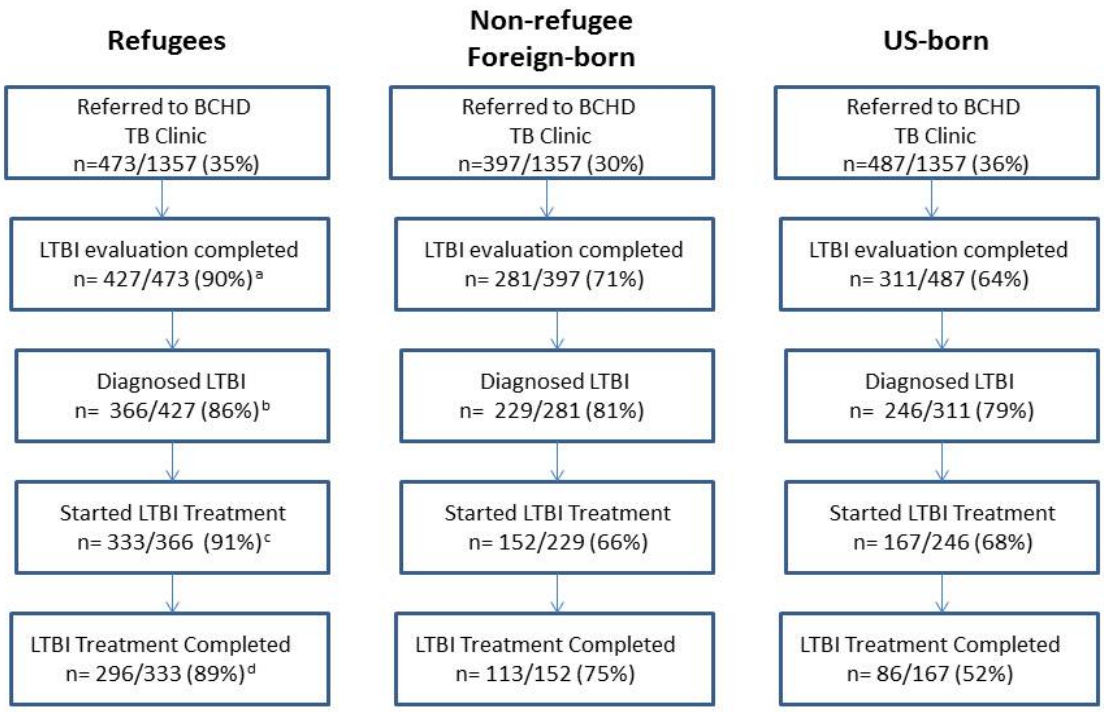
Historically, BCHD has provided all LTBI evaluation, diagnosis and treatment services for refugees living in Baltimore City. However, as of late 2012, BCHD no longer provides LTBI treatment services to individuals with insurance or alternative sources of

care due to budgetary constraints. In light of these changes, refugees with insurance will receive their LTBI care from their primary care providers at a local FQHC. Whether this shift in the locus of care will affect patient compliance with LTBI evaluation and treatment is not yet known.

Our data show that refugee-status may be an important factor in whether or not a foreign-born patient is likely to comply with LTBI screening and treatment. This finding suggests that additional outreach efforts and closer collaboration with patient referral sources may be required for non-refugee patients in order to improve rates of adherence to LTBI screening and treatment. Additionally, incentive programs, case-management or social work support, and perhaps more flexibility in appointment scheduling may enhance LTBI treatment success.

Figures

Figure I. Flow of patients referred to the Baltimore City Health Department for TB screening, February 2009-March 2011 (N=1357).



[a] Among each of the three immigration status groups there was a significant difference in the proportion of patients who reported to the BCHD TB Program for a LTBI evaluation ($p<0.001$).
[b] In an overall comparison of the proportion of patients who were diagnosed with LTBI there was no significant difference between immigrant groups ($p= 0.056$).
[c] Among each of the three immigration status groups there was a significant difference in the proportion of patients who were diagnosed with LTBI that initiated treatment ($p<0.001$).
[d] Treatment completion rates shown here are calculated from among only those patients who initiated treatment. Among each of the three immigration status groups there was a significant difference in the proportion of patients who completed treatment (among those who initiated) ($p<0.001$). Treatment completion among all patients who were eligible for treatment (i.e. all patients diagnosed with LTBI) were as follows: 81% (296/366) for refugees, 50% (113/229) for non-refugee foreign-born, and 35% (86/246) for US-born patients. The proportions of patients who completed treatment among all those who were eligible were significantly different among each of the three immigration-status groups ($p<0.001$)

Table I. Description of Patients Referred to and Evaluated by the BCHD TB Program for latent tuberculosis infection

	Referred to BCHD by TB program			Evaluated by BCHD TB Program		
	Refugees (n=473 referred)	**Non-refugee Foreign-born (n=397 referred)**	**US-born (n=487 referred)**	**Refugees (n=427 evaluated/473 referred)**	**Non-refugee Foreign-born (n=281 evaluated/397 referred)**	**US-born (n=311 evaluated/ 487 referred)**
Gender (%)						
Male	280/473 (59%)	186/397 (47%)	311/487 (64%)	257/427 (60%)	143/281 (51%)	197/311 (63%)
Female	193/473 (41%)	211/397 (53%)	176/487 (36%)	155/427 (40%)	138/281 (49%)	114/311 (37%)
Age (median)	31[e]	32	45	31[f]	32	47[g]
0-14	78/473 (12%)	48/397 (12%)	11/487 (2%)	72/427 (17%)	39/281 (14%)	6/311 (2%)
15-24	92/473 (20%)	67/397 (17%)	56/487 (12%)	85/427 (20%)	41/281 (15%)	32/311 (10%)
25-44	212/473 (45%)	195/397 (49%)	179/487 (37%)	188/427 (44%)	133/281 (47%)	107/311 (34%)
45-64	71/473 (15%)	76/397 (19%)	217/487 (45%)	65/427 (15%)	60/281 (21%)	150/311 (48%)
>65	20/473 (4%)	11/397 (3%)	8/13 (62%)	17/427 (4%)	8/281 (3%)	16/311 (5%)
Country of Birth						
	Nepal/Bhutan 190/473 (44%)	Mexico 54/397 (14%)	--	Nepal/Bhutan 222/427 (52%)	Mexico 38/281 (14%)	--
	Iraq 45/473 (10%)	Honduras 28/397 (7%)	--	Iraq 38/427 (9%)	Honduras 20/281 (7%)	--
	Eritrea/Ethiopia 27/473 (6%)	Philippines 22/397 (6%)	--	Eritrea/Ethiopia 26/427 (6%)	Philippines 17/281 (6%)	--
	Burma 25/473 (5%)	El Salvador 21/397 (5%)	--	Burma 21/427 (5%)	El Salvador 12/281 (5%)	--
	Congo 21/473 (4%)	Nigeria 18/397 (5%)	--	Congo 18/427 (4%)	Nigeria 14/281 (5%)	--
	Other/unknown 124/473 (26%)	Other/unknown 254/397 (64%)	--	Other/unknown 102/427 (24%)	Other/unknown 180/281 (64%)	--
Referral Source						
State refugee program	473/473 (100%)			427/427 (100%)		
Drug treatment program or Department of	--	7/397 (2%)	238/487 (49%)	--	7/281 (3%)	156/311 (50%)

Corrections						
B-waiver[h]	--	55/397 (14%)	--	--	32/281 (11%)	--
Latino health organization	--	59/397 (15%)	--	--	42/281 (15%)	--
Immigration	--	53/397 (13%)	--	--	43/281 (15%)	--
HIV programs	--	5/397 (1%)	19/487 (4%)	--	4/281 (1%)	14/311 (5%)
Other health departments	--	60/397 (15%)	58/487 (12%)	--	52/281 (19%)	31/311 (10%)
Other[i]	--	158/397 (40%)	172/487 (35%)	--	101/281 (36%)	110/311 (35%)

[e] There was a significant difference in median age of patients referred to the BCHD TB program among the three immigration-status groups ($p<0.001$).

[f] There was a significant difference in median age of patients evaluated by the BCHD TB program among the three immigration-status groups ($p<0.001$).

[g] The median age (43) of US-born patients who did not report to the BCHD TB program for an evaluation was significantly lower than those US patients who were evaluated ($p=0.030$). There was no significant difference in median age among patients who were and were not evaluated in the other two immigration-status groups.

[h] Individuals with evidence of inactive TB infection on chest radiographs at the time of immigration.

[i] Other sources refer to those community sources not listed in table who refer patients to the BCHD TB Clinic. In most cases, these sources are individual clinicians in the community.

Table II. Description of Patients who Initiated and Completed Treatment for LTBI According to Immigration Status

	LTBI Treatment Initiation among those Diagnosed with LTBI (n=652 initiated/841 diagnosed)			LTBI Treatment Completion among those that Initiated LTBI treatment(n=495 completed/652 initiated)		
	Refugees (n=333 initiated/366 diagnosed)	**Non-refugee Foreign-born (n=152 initiated/229 diagnosed)**	**US-born (n=167 initiated/246 diagnosed)**	**Refugees (n=296 completed/333 initiated)**	**Non-refugee Foreign-born (n=113 completed/152 initiated)**	**US-born (n=86 completed / 167 initiated)**
Treatment Regimen						
INH	111/331 (34%)[j]	48/149 (32%)[k]	108/166 (65%)[l]	99/111 (89%)	37/48 (77%)	57/108 (53%)
RIF	220/331 (66%)	101/149 (68%)	58/166 (35%)	197/220 (90%)	76/101 (76%)	29/58 (50%)
Gender						
Male	201/220 (91%)	85/124 (69%)	108/161 (67%)	181/201 (90%)	64/85 (76%)	62/108 (57%)
Female	132/146 (90%)	67/105 (64%)	59/85 (69%)	115/132 (87%)	49/67 (73%)	24/59 (41%)
Age (median)	30[j]	30[m]	47	31[o]	29[o]	46[o]
0-14	66/69 (96%)	31/36 (86%)	2/5 (40%)	61/66 (92%)	26/31 (84%)	1/2 (50%)
15-24	64/67 (96%)	23/30 (77%)	16/25 (64%)	55/64 (86%)	18/23 (78%)	9/16 (56%)
25-44	144/160 (90%)	65/108 (60%)	60/87 (69%)	126/144 (88%)	44/65 (68%)	31/59 (53%)
45-64	50/55 (91%)	32/49 (66%)	81/116 (70%)	46/50 (92%)	24/31 (77%)	41/81 (51%)
>65	9/15 (60%)	1/6 (17%)	8/13 (62%)	8/9 (89%)	1/1 (100%)	4/86 (50%)
Country of Birth						
	Nepal/ Bhutan 173/191 (90%)	Mexico 20/30 (67%)	--	Nepal/ Bhutan 167/173 (97%)	Mexico 12/20 (60%)	--
	Iraq 29/31 (94%)	Honduras 7/14 (50%)	--	Iraq 20/29 (69%)	Honduras 4/7 (57%)	--
	Eritrea/ Ethiopia 23/24 (96%)	Philippines 11/16 (69%)	--	Eritrea/ Ethiopia 21/23 (91%)	Philippines 9/11 (82%)	--

	Burma 17/20 (85%)	El Salvador 6/9 (67%)	--	Burma 15/17 (88%)	El Salvador 5/6 (83%)	--
	Congo 16/17 (94%)	Nigeria 10/13 (77%)	--	Congo 10/16 (63%)	Nigeria 9/10 (90%)	--
	Other/ unknown 75/83 (90%)	Other/ unknown 98/147 (67%)	--	Other/ unknown 63/75 (84%)	Other/ unknown 74/98 (76%)	--
Referral Source						
Drug treatment program or Department of Corrections	--	3/5 (60%)	85/127 (67%)	--	2/3 (67%)	44/85 (53%)
Refugee	--	--	--	--	--	--
B-waiver	--	16/23 (70%)	--	--	15/16 (94%)	--
Latino health organization	--	20/32 (63%)	--	--	14/20 (70%)	--
Immigration	--	24/40 (60%)	--	--	19/24 (83%)	--
HIV programs	--	2/2 (100%)	10/11 (91%)	--	2/2 (100%)	5/10 (50%)
Other health departments	--	32/46 (70%)	13/24 (54%)	--	25/32 (78%)	5/13 (38%)
Other*	--	55/81 (68%)	59/84 (70%)	--	36/55 (65%)	32/59 (54%)

[j] Treatment regimen information was only available for 331/333 refugee patients who initiated treatment. Since patients have no knowledge of their treatment regimen assignments prior to showing up to initiate treatment, we used the total number of patients who initiated treatment to calculate the proportion who initiated treatment for each treatment type.

[k] Treatment regimen information only available for 149/152 non-refugee foreign-born patients who initiated treatment.

[l] Treatment regimen information only available for 166/167 US-born patients who initiated treatment.

[m] Among patients who initiated LTBI treatment, there was a significant difference in median age between among the three immigration-status groups ($p<0.000$).

[n] The median age (38) of non-refugee foreign-born LTBI positive patients who did not initiate treatment was significantly higher than the median age among those who of the same immigration-status who initiated ($p=0.001$). There was no significant difference in median age among patients who did and did not initiate treatment within the other two immigration-status groups.

[o] There was a significant difference in median age of those completing treatment between the three immigration-status groups ($p<0.000$). Within each immigration subgroup, there was no significant difference in the median ages of patients who completed treatment and those that did not.

Table III. Analysis of Treatment Initiation and Completion among those Diagnosed with LTBI at BCHD

	Initiated LTBI treatment (n=652 initiated/841 diagnosed)			Completed LTBI treatment (495 completed/652 initiated)		
	n (%)	OR	AOR	**n (%)**	OR	AOR
Treatment Regimen						
INH	267/646 (41%)		--	193/267 (72%)	REF	--
RIF	379/646 (59%)	--	--	302/379 (79%)	1.5 (1.0-2.2; p=0.030)	1.1 (0.68-1.7; p=0.725)
Gender (%)						
Male	394/505 (78%)	REF		307/394 (78%)	REF	REF
Female	258/336 (77%)	0.93 (0.67-1.3; p=0.675)	0.79 (0.63-1.0; p= 0.049)	188/258 (73%)	0.76 (0.53-1.1;p=0.147)	0.70 (0.47-1.0; p=0.081)
Age (median)	34[p]		[q]	32[s]		[t]
0-14	99/110 (90%)	2.9 (1.5-5.6; p=0.002)	2.5 (1.62-3.85; p<0.001)	88/99 (89%)	2.7 (1.3-5.3; p=0.005)	1.9 (0.87-4.2; p=0.105)
15-24	103/122 (84%)	1.7 (1.0-3.0; p=0.05)	1.0 (0.72-1.4; p=0.989)	82/103 (80%)	1.3 (0.75-2.3; p=0.351)	1.3 (0.72-2.5; p=0.352)
25-44	269/355 (76%)	REF	REF	201/269 (75%)	REF	REF
45-64	163/220 (74%)	0.91 (0.62-1.3;p=0.65)	1.2 (0.94-1.7; p=0.127)	111/163 (69%)	0.73 (0.47-1.1; p=0.145)	1.2 (0.72-1.9; p=0.525)
>65	18/34 (53%)	0.10 (0.03-0.28;p<0.001)	0.55 (0.30-1.0; p=0.062)	13/18 (72%)	0.87 (0.30-2.5; p=0.793)	1.4 (0.38-4.8; p=0.637)
Status			[r]			[u]
US-born	167/246 (68%)	REF	REF	86/166 (52%)	REF	REF
Refugee	333/366 (91%)	4.8 (3.4-7.5; 7p<0.001)	4.4 (3.31-5.9; p<0.001)	296/333 (60%)	7.4 (4.7-12; p<0.001)	7.2 (4.2-12; p<0.001)
Non-refugee Foreign-born	152/229 (67%)	0.93 (0.6-1.4; p=0.726)	1.2 (0.89-1.6; p=0.264)	113/152 (75%)	2.8 (1.7-4.5; p<0.001)	2.8 (1.6-4.9; p<0.001)

[p] The median (39) age of those LTBI patients who did not initiate treatment was significantly higher than the median age (34) of patients who did initiate treatment (p=0.020).

[q] Overall p-value for age obtained from likelihood ratio test: p= 0.0003

[r] Overall p-value for immigration status obtained from likelihood ratio test: p<=0.001

[s] The median (40) age of those patients who did not complete treatment after initiation who did not initiate treatment was significantly higher than the median age (32) of patients who did initiate treatment (p=0.017).

[t] Overall p-value for age obtained from likelihood ratio test: p= 0.5216

[u] Overall p-value for immigration status obtained from likelihood ratio test: p<0.0001

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CHAPTER 3: POST-ARRIVAL TB SCREENING OF HIGH-RISK IMMIGRANTS

Post-Arrival Tuberculosis Screening at a Local Health Department of High-Risk Immigrants

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Abstract

Background: As foreign born individuals represent the majority of tuberculosis (TB) cases in the United States, there is an interest in identifying prior to arrival in the U.S., individuals who may be at greatest risk TB. United States (US) policies require individuals who wish to immigrate to the US to be medically evaluated for tuberculosis (TB) by U.S.-designated overseas physicians. Individuals who have some evidence of TB infection, but who are not thought to be contagious, are considered to have a Class B medical condition and are recommended to seek follow-up examination upon arrival to the US. Class B immigrants residing in Baltimore, Maryland receive post-immigration TB evaluation at the Baltimore City Health Department TB program (BCHD). We sought to characterize post-immigration TB care for Class B immigrants at BCHD, and determine the proportion of immigrants with active TB or LTBI in this high-risk population.

Methods: We conducted a retrospective cohort study consisting of a chart review of Class B immigrants who reported to BCHD TB program for post-immigration TB evaluation from 2010-2012.

Results: Among the 205 class B immigrants referred to the BCHD TB program during 2010-2012 for post-arrival screening, we located and evaluated the clinical records of 153 (75%) patients who reported to BCHD. Of these individuals, 144 (94%) completed

BCHD evaluation including medical exam and chest X-ray; 63 (41%) additionally received sputum testing for mycobacterial smear and culture and 108 (71%) received a test for latent infection with either a TST or interferon-gamma release assay. The median time to evaluation after immigration was 75 days (IQR: 55-98). At post-immigration BCHD evaluation, 6 individuals were diagnosed with active TB (4%), and 76 (53%) were diagnosed with latent TB (LTBI). Among the 6 individuals diagnosed with active TB, 6 (100%) were smear-negative, 3 (50%) were culture positive and 4 (67%) were asymptomatic; all 6 received and completed active TB therapy at BCHD. Among the 76 individuals diagnosed with latent TB, 66 (87%) initiated LTBI therapy and 60 (91%) completed treatment.

Conclusions: Despite their having thorough pre-departure medical examinations, we found a high prevalence of active TB and LTBI among Class B immigrants evaluated by the BCHD-TB program. The majority of the active cases did not report any symptoms at their pre-departure examination. These findings underscore the need for post-immigration TB screening for this high risk group despite pre-immigration evaluations, and the challenges in diagnosing active TB in a timely fashion.

Introduction

Efforts by local health departments to screen recent immigrants for TB are an important component of broader TB control goals. Foreign-born individuals represent a significant source of new cases of active tuberculosis reported in the US. In 2012, the incidence of TB was 11.5 times greater among foreign-born individuals in the US than it was for individuals born in the US. [20] It has been estimated that 4 out of 5 active TB cases among the foreign-born is attributable to reactivation of TB that was likely acquired prior to arrival in the US.[35]

Among the foreign born, there is particular interest in identifying prior to immigration individuals, who may be at risk for developing tuberculosis. Persons applying to immigrate to the U.S. are required prior to their arrival to be medically evaluated for TB by U.S.-designated overseas physicians. Individuals who are found to have some evidence of tuberculosis infection but who are not thought to be contagious are designated as Class B immigrants.[36] Applicants whose sputa smears and cultures test negative for TB, but who have some clinical indication of TB (such as an abnormal chest radiograph or TB symptoms) are classified as B1 immigrants. Individuals who are interferon-gamma release assays (IGRA) positive, or have a tuberculin skin test (TST) result of ≥ 10mm but no other indication of active disease, are classified as B2.

Individuals who are a contact of a known TB case are classified as B3 applicants. All Class B immigrants are allowed to enter the country, but are instructed to report to a local health department within 30 days of arrival for follow-up screening and, if indicated, treatment.

Local programs to screen and treat recent immigrants, like those in Baltimore City, are an important component of local TB control goals.[37] Immigrants with Class B medical conditions are considered to be at high risk for tuberculosis. Therefore, efforts to diagnose and treat TB among this high-risk group offer an important opportunity to detect imported cases of TB and to prevent additional cases from occurring domestically.

In Baltimore City, the annual incidence of reported cases of active TB (3.4 cases per 100,000 in 2013) exceeds the national average, with a large proportion of active TB cases attributable to foreign-born individuals (62% in 2013; BCHD unpublished data). [20,21] The Baltimore City Health Department (BCHD) Tuberculosis (TB) program provides clinical evaluation and care services to Class B immigrants that settled within the city. Since 2007, the guidelines for screening Class B immigrants as published by the State of Maryland has required that local health departments perform sputum testing for all

Class B immigrants who, upon evaluation, were found to have a productive cough.[38] In 2012, BCHD changed its protocol for evaluating Class B immigrants to consider sputum testing of all Class B1 immigrants, regardless of whether they had TB symptoms or not.

Though US programs for identifying and flagging for post-arrival screening immigrants who may be at high risk for developing tuberculosis, few studies have been published describing efforts by local health departments to evaluate and treat newly arrived immigrants.[39-42] In light of this, we performed a retrospective chart review of Class B immigrants referred to BCHD for TB evaluation between 2010-2012 to describe how Class B immigrants were screened in practice and analyzed the extent to which testing was conducted according to existing protocols. This study also aimed to evaluate whether recent efforts to conduct additional sputa testing on all Class B immigrants resulted in enhanced TB case finding.

Methods

We conducted a retrospective cohort study consisting of a chart review of Class B immigrants who reported to the BCHD TB program for post-immigration TB evaluation in 2010-2012. The study population included all patients who: 1) were classified as a category B immigrant during their pre-immigration medical exam; and, 2) reported to

BCHD for post-immigration screening during the study period. Class B immigrants who were referred to BCHD for post-immigration screening but who did not appear for clinical evaluation (and therefore did not have clinical records) were not included.

We reviewed data from the BCHD's electronic patient database and a state database to identify a list of class B immigrants that may have been evaluated by BCHD during the study period. We then searched BCHD's clinical records to see if charts existed for these individuals. For those charts that we were able to locate, we examined each to confirm that the individual met our inclusion criteria. Once we deemed a chart eligible for inclusion, we abstracted the following information: patient demographic information (from patients' immigration forms); pre-immigration screening information (including clinical and diagnostic results contained in immigration forms and clinician notes from pre-immigration medical examinations); post-immigration TB symptom and diagnostic data (from clinicians' notes and laboratory test reports); clinical diagnosis and treatment data (from BCHD clinicians' notes). Patients were considered to have had a complete medical exam if they received at BCHD a chest xray, a physical exam, and, in some cases, the diagnostic testing necessary to result in a diagnosis of active TB, LTBI or to rule out current active TB or LTBI.

We summarized clinical and demographic factors among individuals included in this study. We examined the association of these factors with patients' pre-immigration screening results, post-immigration diagnosis, treatment initiation, and treatment completion. Categorical data were analyzed using Chi square (χ^2) and continuous variables were analyzed using median tests. All data were analyzed using STATA Version 10.1 (StataCorp, College Station, Texas).

Ethics committees at the Johns Hopkins University School of Medicine (Baltimore, USA) and BCHD approved this research. This study received a waiver of informed consent.

Results

Patient Demographics and Pre-Immigration Screening

Among the 205 class B immigrants referred to the BCHD TB program during 2010-2012 for post-arrival screening, we located and evaluated the clinical records of 153 (75%) patients who reported to the health department for an evaluation (Figure 1 and Table 1). Sixty-four percent (98/153) of immigrants were male and the median age was 33 (IQR: 15-58). Across all years in the study, most immigrants entered the U.S. from Nepal (98/153, 64%), Philippines (19/153, 12%) and Ethiopia (9/153, 6%); however, there was some year to year variation in the immigration patterns (p=0.023).

The majority of immigrants were classified during pre-immigration medical evaluation as category B1 (108/153, 71%) and B2 (43/153, 28%). Among B1 patients, "discrete fibrotic scar or linear opacity" and "infiltrate or consolidation" were the most common categories on pre-immigration medical questionnaires selected to describe the abnormalities found in these patients' chest xray status.

Twenty-one percent (32/153) of all immigrants had documentation of prior TB disease in their pre-immigration screening (Table II). History of TB varied by B waiver category: 27% (29/108) of B1, 7% (3/43) of B2 and 0% (0/2) of B3 immigrants had a prior TB noted in their pre-immigration medical examination paperwork ($p=0.005$).

For all classes of immigrants, the median time period between entry to country and evaluation by BCHD was 75 days (IQR 55-98 days) (Table I). We found that the median time to evaluation of all immigrants varied significantly by year and was highest in 2011 (93 days: IQR: 69-112 days; $p<0.001$). Similarly, the median time that elapsed between immigrants' pre-immigration chest xrays and when they presented to BCHD

for evaluation was 201 days (IQR 169-241) and was also longest in 2011 (224 days; IQR 196-258; p<0.001).

Post-Immigration Evaluation

All 153 immigrants that reported to BCHD received chest xrays at the TB clinic. Abnormalities were found in 43% of all immigrants' xrays (Table II). The highest percentage of abnormalities occurred among Class B1 immigrants; 57% (62/108) of B1 immigrants were found to have abnormal post-immigration chest xrays, as compared to 7% (3/43) of B2 and 0% (0/2) of B3 immigrants (p<0.001).

BCHD performed QFT-GIT testing on 59% (90/153) of immigrants, among whom 53% (48/90) tested positive. Additionally, post-immigration tuberculin skin test (TST) test results were available for 29% (43/153) of all immigrants who reported to BCHD for an evaluation. 91% (39/43) of all those with post-immigration TST results had indurations of ≥10mm. Twenty four immigrants (16%) had both post-immigration TST and QTB results available. For these individuals, 18 were QTB positive and had TST indurations ≥10mm; 5 were QTB negative and had TST ≥10mm, and 1 was QTB negative and had a TST result of <10mm. QTB testing differed between B1, B2 and B3 immigrants, with most tests occurring among B1s (p<0.001).

Overall, 41% (63/153) of immigrants evaluated by BCHD received both sputa smear and culture testing (Table II). Sputa testing was significantly ($p<0.001$) more likely to occur among B1 immigrants, with 71% (60/108) receiving sputa testing, as compared to B2 (3/43; 28%) and B3 (0/2; 0%). Sputa testing also differed between patients who reported symptoms versus asymptomatic patients. 85% (17/20) of all symptomatic patients received sputa testing as compared with 34% of asymptomatic patients ($p<0.001$). The proportion of asymptomatic patients who received sputa testing at BCHD also varied with time. Sputa testing of asymptomatic patients was highest in 2012 (16 out of 39 asymptomatic patients tested; 40%). This proportion was marginally significantly higher than that in 2010, when 9 out of 30 (30%) asymptomatic patients were tested ($p=0.055$).

Post-Immigration Diagnosis

Overall, 94% (144/153) of the Class B immigrants screened by the health department received complete medical evaluations (chest xray and physical exam) that resulted in a diagnosis of either current active TB or LTBI or a rule out of both of those conditions (Figure 1). There were 6 cases of active TB among the 144 (4%) immigrants who received a complete post-immigration medical evaluation (Table III). Half of the active TB cases (3/6) were refugees from Nepal, the remainder from Eritrea/Ethiopia (2/6, 33%)

and Iraq [via Turkey] (1/6, 17%). Eighty-three percent (5/6) of active TB cases were male. Among these 6 active TB cases, 4 (67%) were asymptomatic at time of evaluation but received further evaluation based on their radiographic features or clinical exam. Two of the 4 asymptomatic patients were found to be sputum culture positive, while two were diagnosed clinically based on medical history, exam and xray findings. Among the 2 active TB cases that reported symptoms, 1 was culture positive and one was diagnosed clinically. All newly diagnosed active TB cases completed treatment.

Fifty-three percent (76/144) of Class B immigrants received a diagnosis of latent tuberculosis infection. Thirty-eight patients (50%) were diagnosed with LTBI on the basis of a positive QTB, while 3 (4%) were diagnosed with LTBI based on a positive post-immigration TST. Thirty-five immigrants (46%) were diagnosed and treated for LTBI despite a lack of positive post-immigration TST or QTB on the basis of a pre-immigration TST result or post-immigration chest x ray finding indicative of inactive TB infection. The vast majority of these patients (50/76, 66%) emigrated from Nepal. Eighty-two percent of LTBI patients were <15 years of age and 68% were male. Among those diagnosed with LTBI, 87% (66/76) initiated LTBI therapy, with 91% (60/66) completing treatment. Treatment completion among all those diagnosed with LTBI who were eligible for treatment was 79% (60/76).

Overall, 43% (62/144) of those who completed post-immigration evaluation were found to have no evidence of current active TB or LTBI and were not recommended to complete any further TB treatment. Among these 62 individuals, 40% (25/62) had documentation in their immigration paperwork of prior treatment for tuberculosis, while the remainder (37/62, 60%) had active TB or LTBI excluded on the basis of a combination of QGIT testing (negative QGIT in 32/37, 86%), post-immigration chest xray (no evidence of active or inactive TB in 31/62, 50%), and/or sputum evaluation (negative mycobacterial culture in 100% of the 28/62 (45%) of immigrants tested).

We examined differences among those who reported symptoms at time of examination versus those who did not. Of the 144 patients who received a complete medical examination, only 20 (14%) patients reported having any symptoms at the time of their examination. Active TB, LTBI and no current TB disease or infection were diagnosed in 10% (2/20), 45% (9/20) and 45% (9/20) of symptomatic patients, respectively (p= 0.336). Among the asymptomatic patients, 3% (4/124) were diagnosed with active TB, 54% (67/124) with LTBI and 43% (53/124) with no current TB disease or infection.

Discussion

Despite their having thorough pre-departure medical examinations, we found a high period prevalence of active TB (4%) and LTBI (53%) among Class B immigrants evaluated by the BCHD-TB program. Of the approximately 40 percent of Class B immigrants who were found to have neither current active TB nor LTBI, half did not have abnormalities on their post-immigration chest xray and 40% percent had evidence in their immigration paperwork of having prior treatment for TB.

These findings highlight the difficulties associated with TB diagnostics. Recent (2009) guidance by the CDC has intensified the pre-immigration screening procedures.[6] Class B immigrants arriving in Baltimore during the study period had substantial pre-immigration evaluations, including pre-immigration sputum mycobacterial cultures performed for all those with abnormal chest x-rays (Class B1). Our data suggests that serial testing and evaluation of high-risk individuals, both before and after immigration, is a necessary component to enhanced TB case-finding strategies.

Among the challenges to TB screening and case-finding is the ability to identify sub-clinical or pauci-bacillary disease. Many TB screening algorithms rely upon presence of symptoms to initiate further microbiologic testing or further imaging evaluations. However, our study found that in this high-risk population, two-thirds of the identified

active TB cases reported no symptoms; overall, half of these active TB cases were diagnosed by sputum culture, while the remainder were clinically diagnosed based on imaging, symptoms, and other clinical findings following extensive evaluations. These results offer important insights for policy related to post-immigration examinations for Class B1 immigrants. Given the high proportion of asymptomatic active TB disease identified, clinicians should strongly consider evaluating sputa for AFB smear and mycobacterial culture, along with other directed testing, from high-risk patients with abnormal chest xrays, regardless of pre-immigration microbiologic testing.

Nearly all immigrants diagnosed with either LTBI or active TB completed treatment for their illness. Though these adherence rates observed in this analysis are similar to those in our previous analysis, they are higher than typically reported in the literature.[CITE] High-rates of treatment suggests that local examination and treatment of patients can be effective in reducing the overall burden of TB in the community.

Despite these successes, there remain challenges to local screening efforts. An important issue is the length of time between immigrants' entry to the US and post-immigration evaluation. Nationally, it has been reported that the median time from arrival to post-immigration evaluation for class B immigrants is 39 days[43]. However, at BCHD, we found that the median time to evaluation was 75 days and was longer than these

national survey data, and evaluation was significantly more delayed than CDC's recommendation of 30 days. It should also be noted that there are additional delays generated between the time of pre-immigration clinical evaluation and a patient's arrival in the US. In our study, we found greater than 4 months had elapsed between the time of pre- and post-immigration evaluations; in some cases, greater than 1 year had elapsed. While our study did not directly evaluate reasons for these delays, they are likely multi-factorial and include patient factors as well as health system factors. Individuals, particularly refugees, immigrating to the US may have competing medical appointments and responsibilities which preclude timely participation in health department directed TB evaluations. Resources and staffing at local health departments, including BCHD, are also increasingly becoming limited which may contributed to appointment delays. For example, the median number of days from immigrant entry to BCHD evaluation was highest in 2011; these delays were coincident with a time period when BCHD experienced its highest volume of both active TB and latent TB patients, and had limited staffing. Additional prospective studies are needed to more specifically determine where in the post-immigration time period delays in time to evaluation are occurring.

In light of this, time to evaluation should be considered when defining protocols for domestic screening of Class B immigrants post-arrival. Clinicians may want to consider ordering repeat sputa and other diagnostic tests for immigrants for whom significant time has elapsed since their pre-immigration medical examination. Screening protocols for Class B immigrants should also factor in time to evaluation when defining whether to re-test patients upon arrival, regardless of patients' current symptoms.

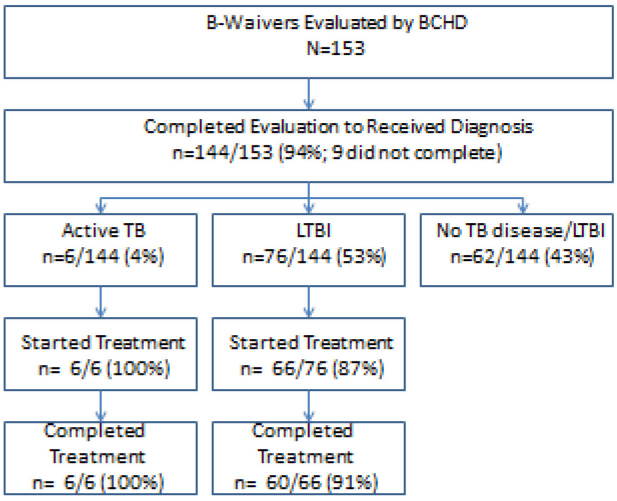
There were some limitations to our study. First, Class B immigrants in Baltimore were largely comprised of refugees from a few specific settings. The high prevalence of active TB in this group, may reflect risk factors specific to the study population that are not generalizable to individuals emigrating from other settings/regions. Secondly, our overall sample size was small which can impact point estimates and may be subject to temporal trends. Nonetheless we are among the first in recent years to report on details of post-immigration TB screening practices at a representative urban local health department across a three year time period, and our period prevalence estimates are consistent with other published data from the state and national level[39,42] [37]. Finally, our study was largely retrospective and long-term follow-up data on class B immigrants was not available; future studies to evaluate incidence of active TB among class B

immigrants over time are warranted to help guide policy regarding further TB screening in this high risk group.

The prevalence of active TB and LTBI observed among Class B immigrants in this study underscore the importance of post-arrival evaluation of this high risk group. Diagnosis is complicated by the absence of symptoms in a majority of active TB cases and long delays between immigrants' entry to the US and post-immigration evaluation. Despite these challenges, high rates of treatment achieved by BCHD suggest local programs to screen and treat recent immigrants can be effective in reducing the burden of TB within the community.

Figures

Figure I. Flow of Class B Immigrants Screened by Baltimore City Health Department for TB, 2010-2012 (N=153).



*Treatment completion among all those diagnosed with LTBI was 79% (60/76)

Table I. Description of All B Waiver Patients Seen by the BCHD TB Program for Tuberculosis, by Year (2010-2012)

	Evaluated by BCHD TB Program (N=153)			
	2010 (n=36)	2011 (n=67)	2012 (n=50)	TOTAL (N=153)
Gender (%) (p=0.291)				
Female	9/36 (25%)	26/67 (39%)	20/50 (40%)	55/153 (34%)
Male	27/36 (75%)	41/67 (61%)	30/50 (60%)	98/153 (64%)
Age (median (IQR)) (p=0.033)	30 (15-51)	42 (23-67)	29 (14-47)	33 (14-58)
0-14	9/36 (25%)	16/67 (24%)	14/50 (28%)	39/153 (26%)
15-24	6/36 (17%)	3/67 (5%)	7/50 (14%)	16/153 (10%)
25-44	10/36 (28%)	15/67 (22%)	14/50 (28%)	39/153 (26%)
45-64	7/36 (19%)	14/67 (21%)	10/50 (20%)	31/153 (20%)
>65	4/36 (11%)	19/67 (28%)	5/50 (10%)	28/153 (18%)
Country of Origin/Origination				
Other	9/36 (25%)	4/67 (6%)	5/50 (10%)	18/153 (12%)
Bhutan/Nepal	17/36 (47%)	49/67 (73%)	32/50 (64%)	98/153 (64%)
Philippines	6/36 (17%)	6/67 (9%)	7/50 (14%)	19/153 (12%)
Eritrea/Ethiopia	3/36 (8%)	6/67 (9%)	0/50 (0%)	9/153 (6%)
Dominican Republic	1/36 (3%)	1/67 (2%)	3/50 (6%)	5/153 (3%)
Iraq/Turkey	0/36 (0%)	1/67 (1%)	3/50 (6%)	4/153 (3%)
B Waiver Category (p=0.893)				
B1	25/36 (69%)	49/67 (73%)	34/50 (68%)	108/153 (71%)
B2	11/36 (31%)	17/67 (44%)	15/50 (33%)	43/153 (28%)
B3	0/36 (0%)	1/67 (1%)	1/50 (2%)	2/153 (1%)
Abnormalities Reported in Pre-Immigration Chest X-ray (B1 immigrants only)				
Infiltrate or consolidation	13/25 (52%)	19/49 (39%)	18/34 (53%)	50/108 (46%)
Any cavitary lesion	2/25 (8%)	3/49 (6%)	2/34 (6%)	7/108 (7%)
Nodule with poorly defined margins	1/25 (4%)	4/49 (4%)	2/34 (6%)	5/108 (5%)
Pleural effusion	0/25 (0%)	0/49 (0%)	1/34 (3%)	1/108 (1%)
Hilar mediastinal adenopathy	0/25 (0%)	1/49 (2%)	0/34 (0%)	1/108 (1%)
Linear interstitial markings	1/25 (4%)	0/49 (0%)	1/34 (3%)	2/108 (2%)
Discrete fibrotic scar or linear opacity	11/25 (44%)	35/49 (71%)	23/34 (68%)	69/108 (64%)
Discrete nodule without calcification	1/25 (4%)	2/49 (4%)	1/34 (3%)	4/108 (4%)
Discrete fibrotic scar with volume loss or retraction	2/25 (8%)	4/39 (4%)	3/34 (9%)	9/108 (8%)
Other	5/25 (20%)	15/39 (31%)	9/34 (27%)	29/108 (27%)
History of prior TB (noted in	6/36 (17%)	15/67 (22%)	11/50 (22%)	32/153 (21%)

immigration paperwork) (p=0.624)				
Median Days from Entry to Evaluation by Health Department (range) (p<0.001)	62 (53-77)	93 (69-112)	61 (45-80)	75 (55-98)
Median Days Since Last Pre-Immigration Chest Xray (range) (p<0.001)	194 (167-204)	224 (196-258)	182 (146-217)	201 (169-241)

Table II. Summary of Post-Immigration Examination of All Immigrants for Tuberculosis, By Classification*

	Post-Immigration Screening Results for Immigrants Evaluated by BCHD TB Program			
	B1 (n=108)	**B2 (n=43)**	**B3 (n=2)**	**All Classes (N=153)**
History of prior TB (noted in pre-immigration medical examination paperwork) (p=0.005)	29/108 (27%)	3/43 (7%)	0/2 (0%)	32/153 (21%)
Any symptoms at time of evaluation (p=0.034)	19/108 (18%)	1/43 (2%)	0/2 (0%)	20/153 (13%)
Post-immigration HIV test conducted (p<0.001)	70/108 (65%)	14/43 (33%)	0/2 (0%)	84/153 (55%)
HIV test positive (p=0.001)	0/0 (0%)	2/14 (17%)	0/2 (0%)	2/84 (2%)
Post-immigration TST results available	33/108 (31%)	10/43 (23%)	0/2 (0%)	43/153 (29%)
TST Positive (≥10mm)	29/33 (89%)	10/10 (24%)	--	39/43 (91%)
Received Quantiferon Testing (p<0.001)	78/108 (72%)	12/43 (28%)	0/2 (0%)	90/153 (59%)
Positive	42/78 (72%)	0/12 (0%)	0/2 (0%)	48/90 (53%)
Abnormal Post-Immigration Chest Xray (p<0.001)	62/108 (57%)	3/43 (7%)	0/2 (0%)	65/153 (43%)
Received Sputa Testing ǂ (p<0.001)	60/108 (71%)	3/43 (28%)	0/2 (0%)	63/153 (41%)
Smear Positive	0/60 (0%)	0/43 (0%)	0/0 (0%)	0/63 (0%)
Culture Positive	3/60 (5%)	0/43 (0%)	0/2 (0%)	3/61 (5%)
Completed Medical Evaluation (p=0.136)	99/108 (92%)	43/43 (100%)	2/2 (100%)	144/153 (945)
Active TB (p= 0.724)	5/99 (5%)	1/43 (2%)	0/2 (0%)	6/144 (4%)
LTBI (p<0.001)	39/99 (39%)	35/43 (81%)	2/2 (100%)	76/144 (53%)
No current LTBI/TB disease (p<0.001)	55/99 (56%)	7/43 (16%)	0/2 (0%)	62/144 (43%)

* P values presented in this table represent comparison between b waiver categories for each variable.

ǂ Sputum testing includes acid-fast bacilli (AFB) smear microscopy and mycobacterial liquid culture. Patients received sputum testing on the basis of post-immigration chest x ray, clinical history, or physical exam.

Table III: Characteristics of B Waiver Patients who Received Full Clinical Evaluations, by Diagnosis Category (Active TB, LTBI or No TB Infection)*

	Active TB cases (n=6)	Latent TB (n=76)	No TB Infection of Disease (n=62)
Gender			
Female	1/6 (17%)	24/76 (32%)	26/62 (42%)
Male	5/6 (83%)	52/76 (68%)	36/62 (58%)
Age (median (IQR)) (p=0.021)	29 (14-30)	23 (12-49)	41 (27-59)
Country of Origin/Origination			
Other	0/6 (0%)	7/76 (9%)	10/62 (16%)
Bhutan/Nepal	3/6 (50%)	50/76 (66%)	38/62 (61%)
Philippines	0/6 (0%)	8/76 (11%)	11/62 (18%)
Eritrea/Ethiopia	2/6 (33%)	6/76 (8%)	1/62 (2%)
Dominican Republic	0/6 (0%)	2/76 (4%)	2/62 (3%)
Iraq/Turkey	1/6 (17%)	3/76 (4%)	0/62 (0%)
History of prior TB (noted in pre-immigration paperwork) (p<0.001)	1/6 (17%)	4/76 (5%)	25/62 (40%)
Median days from entry to country to evaluation (IQR)	105 (63-125)	74 (53-98)	76 (57-98)
Abnormal Pre-Immigration Chest Xray (p<0.001)	5/6 (83%)	40/76 (53%)	55/62 (89%)
Infiltrate or consolidation	2/5 (40%)	5/40 (13%)	9/55 (16%)
Any cavitary lesion	0/5 (0%)	0/40 (0%)	2/55 (4%)
Nodule with poorly defined margins	0/5 (0%)	0/40 (0%)	2/55 (4%)
Pleural effusion	0/5 (0%)	0/40 (0%)	0/55 (0%)
Hilar mediastinal adenopathy	0/5 (0%)	1/40 (3%)	0/55 (0%)
Linear interstitial markings	0/5 (0%)	0/40 (0%)	0/55 (0%)
Discrete fibrotic scar or linear opacity	1/5 (20%)	24/40 (60%)	27/55 (49%)
Discrete nodule without calcification	1/5 (20%)	3/40 (8%)	1/55 (2%)
Discrete fibrotic scar with volume loss or retraction	1/5 (20%)	4/40 (10%)	3/55 (6%)
Other	0/5 (0%)	3/40 (8%)	11/55 (20%)
Abnormal Post-Immigration Chest Xray (p<0.001)	5/6 (83%)	23/75 (31%)	31/62 (50%)
Reported Symptoms	2/6 (33%)	9/76 (12%)	9/62 (15%)
Received Sputa Testing	2/2 (100%)	8/9 (89%)	7/9 (78%)
Culture Positive	1/2 (50%)	0/8 (0%)	0/7 (0%)
Did Not Report Symptomsł	4/6 (67%)	67/76 (88%)	53/62 (86%)
Received Sputa Testing	4/4 (100%)	17/67 (25%)	21/53 (43%)
Culture Positive	2/4 (50%)	0/17 (0%)	0/21 (0%) (p<0.001)
Completed Treatment	6/6 (100%)	60/66 (91%)	--

* P values presented in this table represent comparison between diagnosis categories for each variable. Only significant p-values reported.

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CHAPTER 4: LTBI TESTING AND TREATMENT OF FOREIGN-BORN AT US HEALTH DEPARTMENTS

Removing Barriers to TB Elimination in the US: Equipping Health Departments to Conduct Targeted Testing and Treatment of Latent Tuberculosis Infection among the Foreign-born

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Abstract

Though the total number of TB cases reported in the US is decreasing, persistently high incidence among foreign-born individuals have slowed progress towards national TB elimination. Driving down incidence in the foreign born will require going after the pool of latently infected individuals who represent an important source of future TB cases. In light of this, expert groups have called for targeted testing and treatment of LTBI of high-risk individuals, such as the foreign-born, to further US TB elimination goals. However, public health departments, which conduct the majority of LTBI testing and treatment in the United States, have largely not been able to maintain dedicated programs for targeted testing and treatment of foreign-born individuals. In this article, we review the importance of LTBI testing and treatment of the foreign-born, and discuss ways to equip health departments to complete this important pillar of the US strategy for TB elimination.

Introduction

For the last 20 years, the United States has seen a steady decrease in the annual number of TB cases. In 2013, fewer than 10,000 new TB cases were reported across the country—the lowest number of incident cases since reporting began in the 1950s. Despite this welcome progress, the percent reduction in new TB cases has slowed in recent years and the current incidence of TB cases in the U.S. (3.0 per 100,000 population) still exceeds CDC's TB elimination goal of having <1 case per 1 million population.[1] The CDC has estimated that at the rate the TB incidence has been declining in recent years, TB elimination may not be possible until the year 2107.[2]

One of the biggest obstacles to eliminating TB from the United States is persistently high incidence of TB among the foreign-born. The majority of U.S. TB cases now occur among the foreign-born and efforts to reduce incidence in this group have been slow compared to U.S. born. Since 1993, the annual incidence of TB among U.S.-born individuals has decreased by more than 80%., from 7.4 cases per 100,000 to 1.4 per 100,000. But incidence among the foreign-born has been consistently higher—falling from 34 cases per 100,000 in 1993 to 15.9 cases per 100,000 in 2012 (a 53% decline).

Driving down incidence in the foreign born will require going after the pool of latently infected individuals who represent an important source of future TB cases. Studies suggest that a major contributor to TB cases in the US is the reactivation of infections acquired abroad. Eighty percent of active TB cases reported in the U.S. have been attributed to reactivation of prior infection, rather than newly transmitted infection.[3] The rate of reactivation TB among persons with latent TB infection (LTBI) is higher among foreign-born persons than among persons born in the United States. It has also been shown that the risk of reactivation persists long after arrival in the United States, even though LTBI screening guidelines suggest targeting only those individuals who have been in the country for fewer than 5 years.[4]

Though targeted testing and treatment of LTBI in high-risk individuals, such as the foreign-born, has been recognized by the Institute of Medicine and the US Centers for Disease Control and Prevention as a necessary to achieve U.S. TB elimination goals, it remains an overlooked component of TB control efforts in the US. US policies do not require pre-arrival LTBI screening for adult immigrants and foreign-born visitors to the United States. Program objectives and performance targets developed by the CDC to evaluate TB control programs in the US contain no metrics for LTBI screening and care.[5] State and local public health departments, which conduct the vast majority of all LTBI

treatment in the United States, have not been able to maintain dedicated programs to test and treat those at greatest risk for LTBI, such as foreign-born individuals.[6,7] Competing priorities, insufficient funding and other operational obstacles have hindered progress on this front to-date. In this article, we review the importance of LTBI testing and treatment of high risk individuals, such as the foreign-born, and discuss ways to equip health departments to complete this important pillar of the US strategy for TB elimination.

Current Challenges

Declining Funds for TB Control Activities

Though fewer confirmed TB cases have been reported each year, the demands placed on public health departments for TB control activities have remained high. Health departments expend significant effort in managing individuals in whom TB will eventually be ruled out, which is not reflected in annual incidence numbers. The clinical heterogeneity of TB makes its disease presentation difficult to distinguish from several other conditions. As a result, public health departments must be equipped to offer broad diagnostic services, yet only a small proportion of individuals referred for care will ultimately receive a final diagnosis of active TB.[8] For every case of infectious TB diagnosed, public health agencies must also identify people who may have had contact

with the infected individual—on average, 10 contacts per case.[9,10] Public health agencies must locate, interview and evaluate each of these contacts. In total, the number of tests performed can far exceed the number of confirmed cases of active TB. A study conducted in Texas, found that for each case of TB that was confirmed in 2002, 148 cultures were performed on contacts within the community.[11]

Costs associated with providing public health related TB services continue to increase. While the emerging diagnostic tests for TB and LTBI have provided new opportunities for diagnosing infection and active disease, the adoption of new tests places additional demands on public health infrastructure. For example, the CDC now requires that in addition to performing sputa culture, health departments should also perform nucleic acid amplification testing (NAAT) on the sputa from all individuals who are considered to be TB suspects.[12] A recent cost-effectiveness analysis suggested that testing of at least one sputum sample with Xpert MTB/Rif (an FDA- and WHO- endorsed NAAT) would increase laboratory costs by over 60% per patient[13]. These increased costs associated with improved or new technology place added stress on under-funded health departments.

The emergence of drug resistant tuberculosis has also placed severe demands on public

health departments tasked with their management. The average costs of treating a single case of MDR and XDR TB, is $131,000 and $430,000, respectively.[14] Since MDR and XDR cases typically occur among indigent patients, public agencies typically bear the burden of treatment costs. The high costs of treating drug-resistant will likely continue, even as new drugs enter the market for the first time in several decades. Bedaquiline, which was recently approved by the FDA for the treatment of MDR-TB, will likely cost the public sector $23,000 for a single treatment course.[15]

Despite persisting demands on public health departments for TB control, there has been decreasing support from federal government via cooperative agreements. For the last 10 years, federal funding for state/local TB control activities has remained constant, which, factoring in inflation, has meant that that the amount of resources available for tuberculosis control have declined substantially (see Figure 1). At the same time, the risk that TB will be imported to the United States persists, as number of legal immigrants (i.e. legal permanent residents, refugees, asylees, parolees), non-immigrant visitors and unauthorized immigrants that enter the US each year has remained stable or increased.[16]

Combined with state budget cuts following the recent recession, declining federal support for TB control has forced health departments to make tough choices. A survey conducted by the National Tuberculosis Controllers Association (NTCA) found that sixty percent of TB control programs have had to eliminate staff as a result of shrinking budgets.[17] Twenty-five percent of programs reported having to restrict some essential TB activities, such as provision of directly observed therapy, contact and outbreak investigations.

The absence of dedicated funding specific for LTBI treatment and evaluation is a further disincentive for health departments to give priority to such activities. Though LTBI treatment and evaluation was once a part of national TB control efforts, budget cuts have forced CDC to focus its efforts on control of active TB cases. [18] Since 2005, there has been no explicit federal funding for LTBI treatment and evaluation and, as a result, many health departments have been able to only offer limited LTBI screening and treatment.[19]

Absent a significant increase in the amount of federal funds allocated to state and local health departments for tuberculosis control activities, the lack of prioritization of LTBI testing and treatment is likely to continue for some time. In 2008, the CDC's Division of

Tuberculosis Elimination in conjunction with the National Tuberculosis Controllers Association began a process to develop new formula to guide allocation of increasingly diminished TB control funding. The new funding scheme, which is to be phased in over the next several years, eliminates base funding to all jurisdictions, in favor of incidence-based funding.[20] Though new the funding formula does contain provisions related to targeted testing and treatment of LTBI, such as the population of foreign-born and high-risk immigrants residing in a location—it does not specifically address LTBI testing and treatment.[21]

Low Adherence to LTBI Treatment

Reviews of initiatives to screen and treat foreign-born individuals have found that effectiveness of these efforts is often compromised by low compliance among patients. A recent systematic review found uptake in all steps of screening and treatment process was suboptimal: frequently, patients fail to complete screening and those that do and are diagnosed with LTBI often do not initiate treatment.[19,22] When patients do initiate treatment for LTBI, completion is generally low. Numerous studies have tried to identify predictors of poor treatment compliance. The results of these analyses have been varied, which suggests that there are many potential factors that contribute to poor adherence.[23] Many of the factors identified in these studies—e.g., age, gender,

employment status, marital support—are difficult to address in the context of traditional models for providing clinical care, which complicates efforts to reduce LTBI.

Innovative approaches are needed to ensure effectiveness of LTBI treatment programs is not marred by poor patient compliance. For example, some programs have employed case management models for administering treatment of LTBI have reported increased compliance with LTBI treatment among high-risk patients such as refugees and homeless individuals. [24-26] At least one study is examining whether employing new technologies, such as mobile phone text messages, may also boost patient adherence.[27]

High Cost of New Regimens

Though new, shorter regimens have been developed to reduce the burden of compliance with LTBI treatment, the high cost associated with these regimens can place them out of reach for many health departments. The CDC has recommended that a combination of INH and rifapentine delivered over three months with directly observed therapy (DOT) is as effective and is associated with greater patient compliance than a 9 month course of INH without DOT.[28] However, the per-patient cost of this new regimen has been reported to be more than 10 times greater than administering 9

months of INH.[29] Moreover, the requirement that DOT be used to administer the regimen also increases the resources drain on health departments.

Lack of Stable Supply Chains for LTBI Testing and Treatment Supplies

Recently, TB control efforts have been slowed by widespread shortages of critical TB medicines and testing supplies. In 2013, the two US-approved manufacturers of tuberculin, the active ingredient used in the Tuberculin Skin Test (TST), reported having insufficient supplies to meet demand.[30,31] A survey conducted by the CDC found that the difficulty in obtaining tuberculin has had a considerable impact on health departments; fifty-six percent of those surveyed by CDC reported that routine TB control activities were being threatened or curtailed by the shortages.[32] At the time of this writing, tuberculin is still in short supply.[33]

The CDC recommended that health departments and clinicians respond to tuberculin shortages by reserving TST testing for those at greatest risk (e.g. TB contact investigations) and substituting IGRA testing where possible. Though many health departments and clinics have already begun using IGRA tests, TST remains an important tool in both outbreak investigations and LTBI screening. First, IGRA testing requires sufficient laboratory infrastructure and material costs of IGRA testing is more

expensive on a per test basis than TST.[34] Both of these traits can make it difficult to switch to or rely more heavily on IGRA testing without additional resources and planning. Second, TST is still routinely used as the preferred means of testing for TB infection in certain patient groups, such as young children.

Control of LTBI has been further complicated by recent shortages in isoniazid (INH)—a critical medicine used to treat both TB infection and active diseases.[35] The shortages, which began suddenly in November 2012, persisted well into 2013 and beyond. A survey of health departments by the CDC determined that 79% of respondents experienced difficulties in procuring INH. Among those experiencing shortages, 68% reported that they were delaying LTBI treatment as a result.

Future Challenges

Changes Associated with the Affordable Care Act

Another question that needs to be answered by public health: What will be the impact of Affordable Care Act (ACA) on efforts to increase targeted testing and treatment of LTBI among high risk individuals? As previously uninsured individuals people gain coverage under the ACA, care of some patients who previously sought treatment at

public clinics will likely shift to the private sector. These changes, along with continued budget cuts and staff losses at public clinics, may change public health's role in being able to provide clinical services like LTBI diagnosis and treatment.

This raises questions about private clinicians' abilities and willingness to offer LTBI screening and treatment. Typically, adherence in private clinics to national recommendations for targeted testing and treatment of high risk individuals for LTBI has been low. [36] Studies have also demonstrated that clinicians outside of the public sector may have low levels of knowledge about and interest in screening patients for LTBI.[18]

For private sector clinicians to assume a greater role in LTBI screening and care, it will likely require additional training regarding the diagnosis of LTBI, treatment regimens. Moreover, since treatment for LTBI is lengthy, the private sector may have to develop plans to provide longitudinal tracking of patients to determine who completes treatment, who experiences adverse outcomes, etc.[37] Moreover, it may not be possible to offer new LTBI therapies that require DOT, unless private clinicians develop a way for patients to report each week to receive medicines.

There are also questions regarding the extent to which LTBI screening and treatment costs will be covered under the ACA's new model of care. For example, costs associated with LTBI screening and treatment may not be covered as a non-cost shared preventative service—that is, without passing along some of the costs to the insured patient.[38] Compliance with LTBI screening and treatment may be reduced if patients are required by their health plans to shoulder some of the costs.

Even with expanded coverage under the ACA, significant numbers of the population that will remain uninsured because they don't qualify for coverage. Many of these patient groups (e.g., undocumented immigrants) are among those who should be targeted for LTBI screening and care. States will have to plan for how to deliver LTBI screening and treatment to those uninsured individuals.

Some public health departments have begun to explore billing for the clinical services that they provide. Though this seems like a promising option for public health jurisdictions that would like to retain oversight and control over LTBI screening and treatment, difficulties in establishing billing procedures and legal restrictions have

proven to be important obstacles in doing so. In Baltimore City, efforts to in-house efforts bill for clinical services have only resulted in 10% of claims being reimbursed.[39]

Measuring Progress

In an era of competing public health priorities and dwindling resources, it is important to measure impact of disease control activities. As TB incidence continues to decline and the work of TB control shifts to LTBI screening and treatment, a fundamental question remains: how will we measure the impact of LTBI testing and treatment? LTBI is not a reportable condition, so it will be difficult to measure the number of individuals diagnosed with LTBI via traditional means of surveillance. Declines in reported active TB is one potential way to measure of community-wide efforts to reduce the pool of LTBI, but it does not directly capture the work that goes into finding and treating LTBI. Ideally, efforts to conduct targeted screening and treatment would be supported by a surveillance system that enumerates the proportion of LTBI-infected individuals who are diagnosed with LTBI and those who initiate and, ultimately complete treatment.

Conducting surveillance for LTBI and measuring progress towards its elimination will be made more difficult if the locus of LTBI screening and treatment shifts from public

health departments to the private sector. Because LTBI is not a reportable condition, it will be difficult for public health to gauge what proportion of infected individuals are being identified and treated outside of public health clinics.

It is possible that the increasing adoption of electronic medical records that is occurring across the country may help with surveillance of LTBI.[40] This will require there be a way to structure or query records to determine who tests positive on TST or IGRA. Additional work will also be needed to track patients to determine who initiates and completes treatment.

Refining Targets

Analyses suggest that efforts to screen and treat LTBI are most cost-effective when they focus on high-risk individuals, such as the foreign-born. However, in the absence of a significant increase in the amount of resources to support expanded LTBI screening and treatment programs, demographic realities suggest that even targeted testing may not be cost-feasible. In 2012, there were close to 41 million foreign-born individuals living in the United States.[41] Over the last 30 years, the percentage of the U.S. population that was born abroad has steadily increased and, absent any major shift in national immigration policy, this trend is likely to persist. What this means is that the number of

potential "targets" for targeted LTBI screening will continue to grow and outpace resources available for screening initiatives.

It would be beneficial to be able to better define who is truly at risk for progressing to disease once infected. On average, 90% of individuals who become infected with tuberculosis will never develop active TB. Additional studies aimed at addressing this question may help improve efforts towards TB elimination.

Conclusions

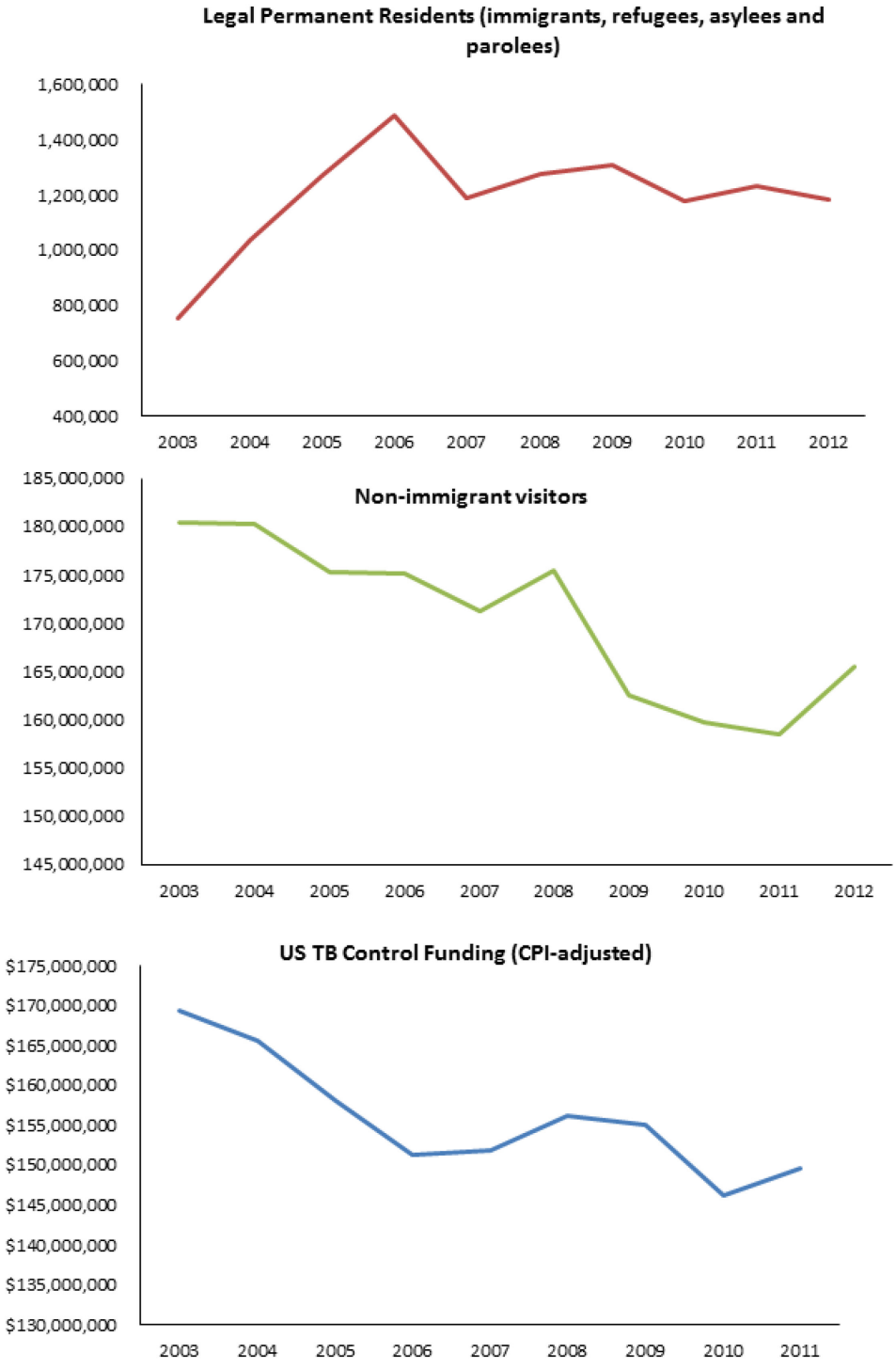
If there is to be meaningful progress towards eliminating TB from the United States, the nation must make a dedicated effort to down TB incidence by reducing incidence of TB among the foreign-born. Limited progress in controlling TB in this group and evidence that the majority of TB cases that arise among the foreign-born is attributed to reactivation of infection likely acquired abroad, strongly support the need for expanded testing and treatment of LTBI of the foreign-born.

Historical trends and documented gaps in knowledge in the private sector indicate that public health departments will for some time have to play a lead role in efforts to reduce LTBI among the foreign-born. However, a lack of sufficient, dedicated funding,

unstable supply chains, and low patient compliance have made it difficult for health departments to give priority within their TB control programs to efforts to conduct targeted testing and treatment for LTBI. In addition, future questions about how the ACA and changing demographics will affect the distribution, surveillance and treatment of LTBI may serve as further disincentives.

Figures

Figure 1. Annual Influx of Foreign-born Individuals to US Compared to Federal TB Control Funding



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CHAPTER 5: CONCLUSIONS

Despite recent successes in reducing the total number of active TB cases reported each year, the US remains far from achieving its TB elimination goal of <1 case per million population. Meaningful progress towards this goal will require expanded efforts to reduce the burden and incidence of TB among the foreign-born. Limited success in controlling TB in this group and evidence that the majority of TB cases that arise among the foreign-born is attributed to reactivation of infection likely acquired abroad, strongly support the need for expanded efforts to conduct post-arrival screening and treatment of active TB, as well as LTBI.

The findings of all three studies discussed above suggest that local health department efforts to screen and treat foreign-born individuals for tuberculosis and LTBI can be effective in reducing the overall burden of illness within the community. However, patients' compliance with treatment, persistent resource limitations and other factors can reduce the effectiveness of these programs. New approaches are needed to improve the provision of TB and LTBI care at health departments.

Patient compliance with LTBI therapies represents a key challenge to reducing incidence of TB. Overall, LTBI treatment completion remains suboptimal. At BCHD, LTBI treatment completion was significantly higher among refugees than other referral groups. Additional efforts are needed to optimize LTBI care at BCHD, and future efforts may need to be tailored for different risk groups.

We also found a high prevalence of active TB and LTBI among Class B immigrants evaluated by the BCHD-TB program, despite their having thorough pre-departure medical examinations. The majority of the active cases did not report any symptoms at their pre-departure examination. These findings underscore the need for post-immigration TB screening for this high risk group despite pre-immigration evaluations, and the challenges in diagnosing active TB in a timely fashion.

Though targeted testing and treatment of LTBI in high-risk individuals, such as the foreign-born, has been recognized by the Institute of Medicine and the US Centers for Disease Control and Prevention as a necessary to achieve U.S. TB elimination goals, it remains an overlooked component of TB control efforts in the US. US immigration policies are not sufficient to prevent the introduction of tuberculosis infection into the country; therefore, efforts to conduct post-arrival LTBI screening and treatment of the

foreign-born are important. However, competing priorities at public health departments, insufficient funding and other operational obstacles have hindered progress on this front to-date. Moreover, future trends, such as an increasing proportion of the US population that is foreign born and shifts in the locus of care that may result from implementation of the Affordable Care Act are likely to further complicate public health departments' abilities to prioritize LTBI testing and treatment among TB control activities.

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EDUCATION

- Doctor of Public Health (DrPH), Epidemiology. Johns Hopkins Bloomberg School of Public Health, Expected May 2014.

  - Dissertation Topic: Post-Arrival Screening and Treatment of Foreign-Born Individuals for Tuberculosis and Latent Tuberculosis Infection

- Master of Science (S.M.), Environmental Health, **Harvard School of Public Health**, 2001.

  - Concentration in Water Pollution and Health
  - Major training in infectious disease epidemiology

- Bachelor of Science (B.S.), Environmental Sciences, **Rutgers University,** 1999.

  - Concentration in Pollution Treatment Sciences
  - Minor in Japanese Language

EXPERIENCE

- **Center for Health Security University of Pittsburgh Medical Center (**formerly Center for Biosecurity of UPMC), Senior Associate, July 2010-Present; Associate, July-2008-July 2010; Senior Analyst, July 2006-July 2008; Analyst, June 2003-July 2006.

  - Projects and Areas of Interest: Infectious disease epidemiology; Global and domestic biosurveillance; infectious disease outbreaks and outbreak detection; disease mitigation/ containment strategies; diagnostics; public/private partnerships for public health emergencies; avian/pandemic influenza; drinking water security; international health regulations; public health and business preparedness; healthcare preparedness; mass distribution

- **New York City Department of Environmental Protection**, Public Health Epidemiologist, March 2002-June 2003.

  - Performed epidemiologic surveillance as part of City's interagency Waterborne Disease Risk Assessment Program
  - Managed City's Drug Sale Monitoring Program for syndromic surveillance
  - Reviewed clinical and laboratory data from NYC Department of Health and Mental Hygiene's disease and syndromic surveillance programs
  - Tracked and reviewed legislation and regulations related to drinking water quality
  - Prepared NYC's Cryptosporidium Action Plan
  - Investigated feasibility of conducting epidemiologic study of endemic waterborne illness
  - Evaluated impacts of NYC drinking water quality on sensitive populations
  - Prepared reports for U.S.EPA as required by Filtration Avoidance Determination

- **City of Cambridge, MA**, Researcher, April 2000-June 2001.

  - Coordinated city's Climate Change Program
  - Worked with city council-appointed Climate Protection Taskforce to quantify greenhouse gas emissions reductions
  - Helped Develop city's Climate Protection Plan

- **International Council for Local Environmental Initiatives**, Researcher, June-August 1999.

  - Performed greenhouse gas emissions inventory for City of Cambridge, MA
  - Worked with Cambridge city staff and elected officials to develop emissions reduction target and local action plan
  - Coordinated outreach activities to promote public awareness of climate change issues

- **Environmental and Occupational Health Sciences Institute (Rutgers University)**, Research Assistant, January-May 1999.

  - Investigated bioavailability of heavy metals in soils of varying physical characteristics

- **NASA NSCORT Program (Rutgers University),** Research Assistant, January-May 1999.

  - Performed preliminary investigation for future research regarding pathogen deactivation in compost of bioregenerative life support system using bacteriophage as an indicator organism

- **National Science Foundation Research Program**, Undergraduate Fellow, May-August 1998.

  - Participated in Program on Scientific Research and Public Policy conducted at Howard and New Mexico State Universities
  - Research Title: Concentration of Viral Particles from Environmental Water Samples Using Ultrafiltration

HONORS

- Charlotte Silverman Epidemiology Fellowship (Johns Hopkins School of Public Health), 2007

- Public Health Trainee Grant, 2000-2001

- Dean's List, six consecutive semesters, 1996-1999

- Garden State Scholar, 1995-1999

- Bergen County Utilities Authority Conservation Scholarship, 1993

PEER-REVIEWED PUBLICATIONS

- McNabb SJ, Shaikh AT, **Nuzzo JB**, Zumla AI, Heymann DL. Triumphs, trials, and tribulations of the global response to MERS coronavirus. *Lancet Respiratory Medicine*. 2014 May 1.

- Balkhy H, Miller TL, Ali S, **Nuzzo JB**, Kentenyants, K, El-Saed A, and McNabb SJN. Compliance with Post-exposure Screening and Treatment of Latent Tuberculosis Infection

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- Maldin-Morgenthau B, Toner E, Waldhorn R, **Nuzzo JB**, Franco C, Press D, O'Toole T, Inglesby TV. Roundtable: Promoting partnerships for regional healthcare preparedness and response. *Biosecurity and Bioterrorism.* 2007;5(2)180-185.

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- Winona LJ, Ommani AW, Olszewski J, **Nuzzo JB**, Oshima KH. Efficient and predictable recovery of viruses from water by small scale ultrafiltration systems. Canadian Journal of Microbiolgy. 2001;47:1033-1041.

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- **Nuzzo JB**, Rambhia, K, Morhard RC, Watson M, Adalja AA, Toner E, Cicero AJ, and Inglesby TV. Diagnosing Infection at the Point of Care: How Standards and Market Forces Will Shape the Landscape for Emerging Diagnostic Technologies. August 2013.

- **Nuzzo JB**, Wollner SB, Morhard RC, Sell TK, Cicero AJ, and Inglesby TV. When Good Food Goes Bad. March 2013.

- **Nuzzo JB**. White House Releases Strategy for Biosurveillance. August 2012.

- **Nuzzo JB**, Rambhia K, Wollner S, Adalja A, Toner E, Cicero A, Inglesby T. Diagnostics for Global Biosurveillance: Turning Promising Science into the Tools Needed in the Field. September 2011. Report funded by the U.S. Department of Defense Threat Reduction Agency through the Tauri Group.

- **Nuzzo JB.** Connecting the Dots: Creating a National Biosurveillance Capability. *Crossroads in Biosecurity*. September 8, 2011. Ten-year look back on public health preparedness since 2001.

- **Nuzzo JB**, et al. International Disease Surveillance: United States Government Goals and Paths Forward. June 2010. Report funded by the U.S. Department of Defense Threat Reduction Agency through the Tauri Group.

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- **Nuzzo J**, M Schoch-Spana. 2003. Parity for Mental Health in Public Health Preparedness. *Biodefense Quarterly*. 5(2): 3, 10-11. Accessible at: http://www.upmc-biosecurity.org/pages/news/pdf/quarter5_2.pdf

PUBLICATIONS FOR GOVERNMENT

- Yansen S, Safi B, **Nuzzo J**, Barnett D. *Avian Influenza: Critical Program Issues.* Global Health Technical Brief (Prepared for the United States Agency for International Development). February 2008.

- NYC Department of Environmental Protection. Waterborne Disease Risk Assessment Program 2002 Annual Report. May 31, 2003. Accessible at: http://www.nyc.gov/html/dep/pdf/wdrap02.pdf

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- City of Cambridge (MA). Climate Protection Plan: Local Actions to Reduce Greenhouse Gas Emissions. 2001. Accessible at: http://www.cambridgema.gov/~CDD/et/env/clim_plan/clim_plan_full.pdf

OTHER PUBLICATIONS

- **Nuzzo JB**. The Path Toward Improved Biosurveillance. *Bulletin of the Atomic Scientists*. July 25, 2013;69(4). Invited commentary.

INVITED TALKS

- Taiwan Centers for Disease Control. Guest lecture on U.S. Approaches to Biosurveillance. Taipei, Taiwan. December 4, 2012.

- Georgetown University School of Medicine. Guest lecture on Using Tabletop Exercises for International Public Health Emergencies. Washington D.C. November 7, 2012.

- George C. Marshall European Center for Security Studies. Health Security and Engagement in Military and International Security Operations Conference. *Strengthening Surveillance, Improving Global Security*. Garmisch-Partenkirchen, Germany. July 19, 2012.

- Center for Biosecurity of UPMC. Improving Epidemic Response: Building Bridges Between the U.S. and China. Panel Moderator: *Scientific Innovations to Improve Response to Epidemics.* Washington, DC. May 15, 2012.

- Department of Health and Human Services, Centers for Disease Control/American Public Health Laboratories. Invited participant: *Culture-Independent Diagnostics Forum: Charting a Path for Public Health*. Atlanta, GA. April 25-26, 2012

- Department of Homeland Security, Office of Affairs. Roundtable participant on *National Biosurveillance Integration: Challenges and Opportunities*. Washington, DC. December 16, 2011.

- Georgetown University School of Medicine. Guest lecture on Using Tabletop Exercises for International Public Health Emergencies. September 28, 2011.

- Harvard University School of Public Health. Representative of Class of 2001 (Alumni Weekend) and Guest lecture on Public Health Since 2001. September 24, 2011.

- Columbia University (Hertog Global Strategy Initiative). Guest lecture and facilitated full-day tabletop exercise on pandemic preparedness. August 1-2, 2011.

- George Washington University School of Public Health. Guest lecture on Biosurveillance. Washington, DC. November 15, 2010.

- U.S. Department of Defense: Defense Threat Reduction Agency's Basic and Applied Sciences Division and Advanced Systems and Concepts Office. *Global Biosurveillance Science and Technology Requirements Workshop*. Arlington, VA. September 9, 2010.

- U.S. Department of Defense, Defense Threat Reduction Agency. Countering Biological Threats Working Group Conference. *International Disease Surveillance*. Chantilly, VA. July 15, 2010.

- The Global Green USA Security and Sustainability Program. International Cooperation and Partnerships in C*ombating Biological Threats Seminar*. Situational Awareness and Response to Public Health Emergencies: Lessons from the 2009 H1N1 Influenza Pandemic. Washington, DC. June 2, 2010.

- Trust for America's Health. Working Group on Pandemic Influenza. Panelist: H1N1 Outbreak-Recommendations for Federal Policymakers. Washington, DC. May 27, 2010.

- Homeland Security Outlook. BioDefense 2010 Conference. Panelist: Situational Awareness in a Biological Emergency. Washington, DC. May 3, 2010.

- Center for Biosecurity of UPMC. The 2009 H1N1 Experience: Policy Implications for Future Infectious Disease Emergencies Conference. Panel Moderator: SARS-like Emerging Infectious Disease: What Roles Should Isolation, Quarantine, Travel Restrictions, And Other Disease Containment Measures Play in the Control of International Epidemics? Washington, DC. March 5, 2010.

- Center for Biosecurity of UPMC. Resilient American Communities: Progress in Practice and Policy Conference. Panel Moderator: Action Plan for Making Community Resilience a Reality. Washington, DC. December 10, 2009.

- The Corporate Executive Board Company. Invited teleconference panelist: H1N1 Pandemic Influenza. October 12, 2009.

- Center for Biosecurity of UPMC. Prevention of Biothreats: A Look Ahead Conference. Panel Moderator: Surveillance, Attribution and Deterrence. Washington, DC, October 6, 2009.

- Johns Hopkins University Center for Talented Youth Program. *Odyssey Series*. Lecture on International Public Health. March 28, 2009.

- Johns Hopkins University Center for Communication Programs. Avian Influenza 101 Training Workshop. Lecture on Pubic Private Partnerships. Baltimore, Maryland. January 24, 2008.

- National Committee for Avian Influenza Control and Avian Influenza Preparedness (Republic of Indonesia). National Pandemic Influenza Planning Workshop. Lecture on Public Private Partnerships and Special Session on Disease Mitigation Strategies and Hospital Response. Bogor, Indonesia. August 7, 2007.

- Johns Hopkins Bloomberg School of Public Health. Epidemiology in Evidence-Based Policy Course. Lecture on Avian and Pandemic Influenza. Baltimore, Maryland. June 23, 2006.

SELECTED MEDIA COVERAGE

- Leggiere P. Building Biosurveillance from the Ground Up. *HS Today.US*. February 20, 2011.

- Korade M. Situational Awareness in WMD Attacks Remains a Challenge, Experts Say. *CQ Homeland Security.* May 3, 2010.

- Matthews W. The fire next time. *Government Health IT.* April 20, 2010.

- Guido G. 1957 Asian flu hit area communities hard. *Valley News Dispatch*. October 28, 2007.

- Puko T. Local school districts prepare for flu pandemic. *Pittsburgh Tribune Review*. October 18, 2007.

- Ham B. Want to stop flu? Focus on children's hygiene. *Health Behavior News Service*. October 16, 2007.

- McCall W. Kulongoski says terror exercise will prepare Ore. for other risks. *The Associated Press*. October 4, 2007.

- Miller R. Anthrax has a long history. *Danbury News Times*. September 11, 2007.

- Sandman J. UK pandemic test shows limits of off-site alternatives: Working from home doesn't replicate market activity. *Securities Industry News*. February 5, 2007.

- Mike Moss Show. Discussion of Federal quarantine rules with U.S. Centers for Disease Control and Prevention'S Martin Cetron (Division of Migration and Quarantine). *Washington Post Radio*. April 27, 2006.

- Lafferty M, Doulin T. Sniffling fliers may land in quarantine. *Columbus Dispatch*. April 24, 2006.

- Fiorill J. Hospitals should Streamline Intensive-Care Routines to Enable Treating More Bioterror Victims, Experts Say**.** *National Journal/Global Security Newswire*. November 3, 2007.

- Brenner B. How avian flu could threaten IT security. *SearchSecurity.com*. October 13, 2006.

- Branswell H. Businesses need to do continuity planning for flu pandemic, report suggests. *Canadian Press*. October 11, 2005.

- Hayblower K. Monmouth University Will Track Diseases, Bioterror. *New Jersey Star Ledger*. August 19, 2004

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