Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature: _____ _____

John Gharbin Date

Prevalence and Treatment Outcome of Tuberculosis and Latent Tuberculosis Infection Among Newly Arrived Refugees in DeKalb County, January 2015-February 2016.

By

John Gharbin

Master of Public Health

Hubert Department of Global Health

_____

Kenneth G. Castro, MD

Committee Chair

_____

Alawode Oladele, MD, MPH

Committee Member

Prevalence and Treatment Outcome of Tuberculosis and Latent Tuberculosis Infection Among Newly Arrived Refugees in DeKalb County, January 2015-February 2016.

By

John Gharbin

Bachelor of Medicine and Bachelor of Surgery, MBChB.

University of Ghana Medical School

2012

Bachelor of Science (Medical Sciences), BSc.

University of Ghana

2008

Thesis Committee Chair: Kenneth G. Castro, MD

An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Global Health

2017

Abstract

Prevalence and Treatment Outcome of Tuberculosis and Latent Tuberculosis Infection Among Newly Arrived Refugees in DeKalb County, January 2015-February 2016.

By John Gharbin

Background: In the United States, tuberculosis(TB) incidence among foreign-born persons (15.1 cases per 100,000) is approximately 13 times compared to incidence among US-born persons (1.2 cases per 100,000). In 2015, approximately 66.4% of new cases of TB occurred in foreign born persons. This has in part been attributed to reactivation of latent tuberculosis infection (LTBI). The Centers for Disease Control and Prevention (CDC) recommend screening and treatment of both active TB and LTBI for newly arriving refugees. However, few studies have evaluated the treatment outcomes of LTBI among newly arrived refugees. We sought to assess TB and LTBI prevalence among recently resettled refugees in DeKalb County and evaluate variables associated with LTBI treatment initiation and completion.

Methods: We did a secondary data analysis of LTBI screening results and follow up logs of 1155 refugees screened at the DeKalb County Board of Health Refugee Health Program between January 2015 and February 2016. A multivariate logistic regression was used to calculate the associations between demographic characteristics and LTBI diagnosis, treatment initiation and completion.

Results: LTBI diagnosis and treatment initiation rates among evaluated refugees were 62% and 85% respectively. Higher completion rates among refugees were associated with Asian origin and with the treatment regimen option of isoniazid and rifapentine combination therapy for 3 months. Compared with other refugees, those from Middle East were less likely to initiate and complete LTBI treatment.

Conclusion: In DeKalb County, public health interventions are required to increase LTBI initiation and treatment completion rates among refugees. Efforts should be aimed at establishing culturally competent and age appropriate interventions for all refugees, especially of Middle Eastern origin and among the 18-34 year age group.

Prevalence and Treatment Outcome of Tuberculosis and Latent Tuberculosis Infection Among Newly Arrived Refugees in DeKalb County, January 2015-February 2016.

By

John Gharbin

Bachelor of Medicine and Bachelor of Surgery, MBChB

University of Ghana Medical School

2012

Bachelor of Science (Medical Sciences), BSc.

University of Ghana

2008

Thesis Committee Chair: Kenneth G. Castro, MD

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

In Global Health

2017

Acknowledgement

I am deeply grateful to my wife, Dr. Maame Adwoa Brago Winful, who has supported me through this journey, providing both requested and unsolicited constructive criticism of this project. The best teacher I will ever have.

I would like to thank Dr. Alawode Oladele of DeKalb County Board of Health, an excellent public health practitioner, physician and a mentor who is constantly dissipating knowledge and helping me actualize this thesis.

My humble gratitude also goes to Dr. Kenneth Castro for accepting to be my thesis advisor and chair and providing such exceptional guidance and direction on this project. A great Academician.

Also to Dr. Sophia Hussen, an inspiration.

And to all who in diverse ways have contributed to making this thesis complete.

Table of Contents

Chapter I: Introduction

Introduction

Tuberculosis (TB) is one of the top ten causes of mortality worldwide, the World Health Organization (WHO) estimates that in 2015,10.4 million people fell ill with TB with a resultant 1.8 million deaths (1) In the United States, the incidence of TB has remained stable at approximately 3.0 per 100,000 persons during 2013-2015, and incidence among foreign-born persons (15.1 cases per 100,000) is approximately 13 times compared to incidence among US-born persons (1.2 cases per 100,000) (2). In 2015, approximately 66.4% of new cases of TB occurred in foreign-born persons (2, 3).

Refugees and immigrants who settle in western countries, including the United States, have been found to have similar incidence of TB comparable to their country of origin. This has been largely attributed to reactivation of latent tuberculosis infection (LTBI) (4, 5).

Applicants for U.S. immigrant visa or refugee status undergo medical screening overseas by panel of physicians appointed by the U.S. Department of State, in accordance with Technical Instructions provided by the Centers for Disease Control and Prevention, Division of Global Migration and Quarantine (DGMQ) (6). Applicants found to have active TB disease receive directly observed therapy (DOT) before being allowed to enter the United States (6). Whilst the treatment of active TB before embarkation is mandatory for resettling immigrants, LTBI treatment is not (7).The CDC therefore recommends screening and treatment of both active TB and LTBI for all newly arriving refugees in the United States as part of post arrival medical screening (8).

The overall prevalence of LBTI in US has been estimated to be 4.4%-4.48% (9, 10).Two studies conducted in Minnesota between 1997 and 2001 that used the tuberculin skin test found the prevalence of LTBI among resettling refugees to be 49.0% and 50.7% (11, 12). Another study

that looked at risk of LTBI among recently arrived refugees in Atlanta with pre-diabetes and diabetes mellitus found an LTBI prevalence of 31.3% (13).Current limited literature on LTBI among refugees mostly focus on sociodemographic characteristics (11-14) with little regard to CDC's treatment recommendations. One study however, examined LTBI treatment initiation and outcome among this subpopulation in San Diego County, California, and found that out of 489 refugees eligible for LTBI treatment, only 76.3% initiated treatment with 58.7% completing LTBI treatment (15).

Over the past decade DeKalb County has historically resettled more than 60% of refugees arriving in the State of Georgia, making it the highest refugee resettlement county in the State of Georgia and also the county with the highest TB case rate of 8.3 per 100,000 in 2014 (16).Evaluating LTBI treatment among recently resettled refugees in this county is therefore essential towards the elimination of TB in the United States as it will inform health policies and interventions aim at reducing the prevalence of TB among this population and in the United States.

This study sought to assess the prevalence of active TB disease and LBTI among refugees recently resettled in DeKalb County from January 1,2015 through February 29,2016 and examine variables associated with initiation and completion of LBTI treatment.

Study Objectives

Increased incidence of TB in foreign-born person has been attributed to reactivation of remote LTBI. Refugees resettling in the US are known to have higher prevalence of LTBI and are at greater risk of developing active TB. CDC recommends that refugees diagnosed with LTBI take one of the following courses for the treatment of LTBI; once daily dose of isoniazid (INH) for 9months; once weekly dose of isoniazid+rifapentine for 3months; or once daily dose of rifampin (RIF) for 4 months.

Objective 1:

To establish the prevalence of active TB and LTBI among refugees arriving in DeKalb County between January 2015 and February 2016, and describe the socio demographic characteristics of LTBI among the sample population.

Objective 2:

To determine the LTBI treatment initiation and completion rate among refugees eligible for LTBI treatment during the study period and identify factors associated with treatment initiation and completion.

Ethical Considerations

Institutional Board Review (IRB) approval was sought from Emory IRB and Georgia Department of Public Health IRB. Study was granted an "Expedited Approval" by both institutions based on the following:

- The project involves access to confidential information held by Georgia Department of Public Health
- The use or disclosure of the confidential information involves no more than minimal risk to the privacy of individuals
- An adequate plan exists to protect the identifiers from improper use and disclosure
- An adequate plan exists to destroy the identifiers at the earliest opportunity consistent with conduct of research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law
- The research could not practicably be conducted without the waiver or alteration
- The research could not practicably be conducted without access to and use of the confidential information.

Definition of Terms

Latent Tuberculosis Infection

Latent tuberculosis infection (LTBI) is a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active TB disease (17). LTBI represents the presence of *Mycobacterium tuberculosis* in the body without signs and symptoms, or radiographic or bacteriologic evidence of tuberculosis (TB) disease (18).

Refugee

A refugee is someone who has fled his or her country because of persecution, war, or violence. A refugee has a well-founded fear of persecution for reasons of race, religion, nationality, political opinion or membership in a social group. Most likely, they cannot return home or are afraid to do so. War and ethnic, tribal and religious violence are leading causes of refugees fleeing their countries (19)

LTBI Treatment Initiation

Refugees detected with LTBI who collected first dose of a chosen or prescribed regimen were considered to have initiated treatment for LTBI.

LTBI Treatment completion

Completion of LTBI treatment was based on a specified number of doses completed within a specified period for each regimen as defined by the CDC and American Thoracic Society (20). For the 9-month daily isoniazid regimen, completion was defined as 270 doses within 12 months; and for 4 months of daily rifampin, completion was 120 doses within 6 months. For

isoniazid and rifapentine combination therapy, treatment completion was defined as receiving ≥11 of 12 scheduled doses via directly observed therapy (DOT) within a 16-week period, based on the PREVENT TB study (21).

A patient achieved treatment completion if the patient was administered with a full course of treatment as defined above.

Background

Global Burden of Tuberculosis

Tuberculosis (TB) is one of the top ten causes of mortality worldwide, the WHO estimates that in 2015,10.4 million fell ill to tuberculosis of which 5.9 million were among men, 3.5 million among women and 1.0 million among children. Overall, 90% of cases were adults and 10% children, and the male: female ratio was 1.6:1 (1). According to the WHO 2016 Global Tuberculosis Report, TB incidence fell globally at a rate of 1.5% per year between 2000 and 2015. Mortality rate also fell by an estimated 47% between 1990 and 2015.That notwithstanding,1.4 million HIV negative people and 0.39 million HIV positive people died from TB in 2015 (1).This calls for enhanced global efforts in addressing this relatively common infectious disease. The End TB Strategy aims at 90% reduction in TB deaths and an 80% reduction in TB incidence by 2030,as part of reaching these goals is optimizing the identification and treatment completion rates of latent tuberculosis infection in low TB burden countries (1).

Tuberculosis in the United States

Information in this section, except otherwise noted, is sourced from the Core Curriculum on Tuberculosis published by the CDC which provide comprehensive reference manual for clinicians and public health professionals (22) and current Reported Tuberculosis in the United States,2015 (23).

*Progress Towards Tuberculosis Elimination in the United State*s

In 1989, the CDC announced a strategic plan for the elimination of tuberculosis in the United States (24).However, the achievement of this goal was undermined by the resurgence of tuberculosis in the late 1980s and early 1990s associated with the occurrence of the human

immunodeficiency virus (HIV) epidemic, increases in immigration of persons from countries where TB disease was common, TB transmission in congregate settings, and outbreaks of multidrug-resistant (MDR) TB in institutional settings (25).

These factors, together with reductions in public health department funding for TB control at the time, retarded public health interventions aimed at tuberculosis control and prevention. Subsequently, the United States renewed its commitment to TB control and mobilized additional resources. In 1999,the elimination goals were reaffirmed for development and rapid implementation of new tools and expand partnerships for diagnosis and treatment of LTBI (26).This new commitment was accompanied with reduction in the number of new cases which has continued to decline (27). Despite unprecedented low rates of TB disease, elimination of TB faces some major barriers including;

- TB disease in high-risk populations where it is difficult to detect, diagnose, and treat;
- Persistence and growth of the global TB epidemic; and
- Limitations of current control measures and the need for new tests and treatments, including an effective vaccine.

The resurgence of TB disease was evident by the increasing number of TB cases starting in 1985 and peaked in 1992. In 1993, a declining trend was noted which has persisted (Figure 1.1). TB incidence rate per 100,000 persons has remained relatively stable at approximately 3.0 since 2013 (3). In 2015, a total of 9,557 TB cases (a rate of 3.0 cases per 100,000 persons) were reported. This represented a 1.6% increase in the number of TB cases compared to 2014.

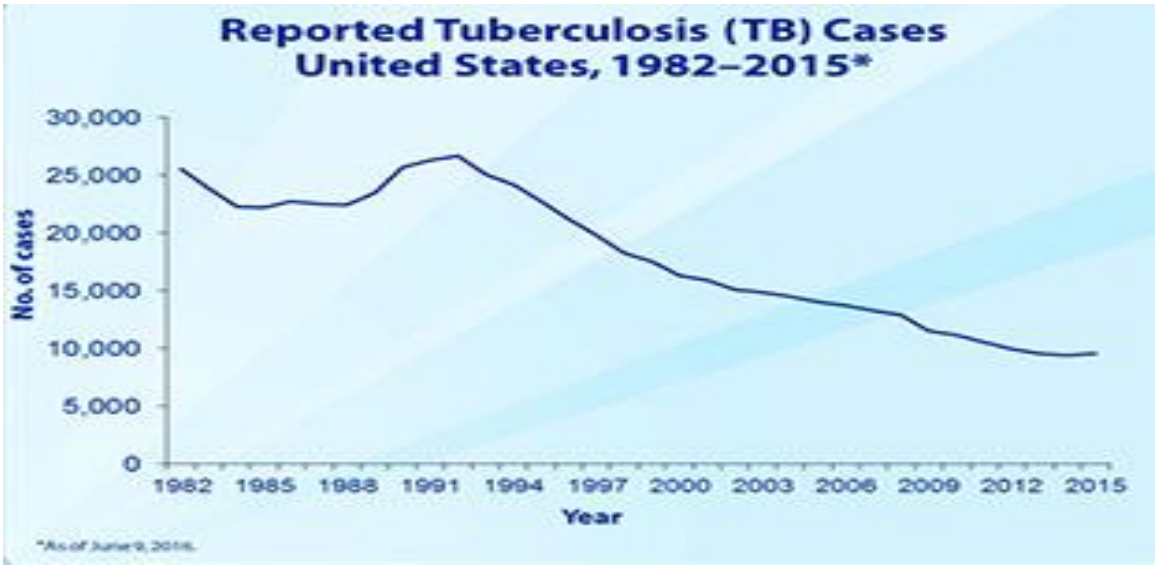


Figure 1.1-TB Disease Trends in the United States,1982-2015, Courtesy of CDC

Case rates appeared to have increased with age, ranging from a low of <1 case/100,000 in children aged 5–14 years to a high of 6.7 cases/100,000 in men aged ≥65 years. Increasing age was associated with increasing case rates among male; the rates among men aged ≥45 years were approximately twice those among women of the same age.

Approximately 85% of all reported TB cases in 2015 occurred among racial/ethnic minorities: Asians-33%; Hispanics-28%; non-Hispanic blacks/African Americans-21%; American Indians/Alaska Natives-2%; and Native Hawaiians/Other Pacific Islanders-1%. In contrast, 13% of cases occurred among non-Hispanic whites. Persons reporting two or more races, not including persons of Hispanic or Latino ethnicity, accounted for 2% of all cases.

TB case rate among foreign-born persons has gradually decreased since 1996, however in 2015, 66.4% of reported TB cases occurred among foreign-born persons. The case rate among foreign-born persons (15.1 cases per 100,000 persons) was approximately 13 times higher compared to U.S.-born persons (1.2 cases per 100,000 persons). Most of these cases are among persons who

have been in the United States 5 years or longer.

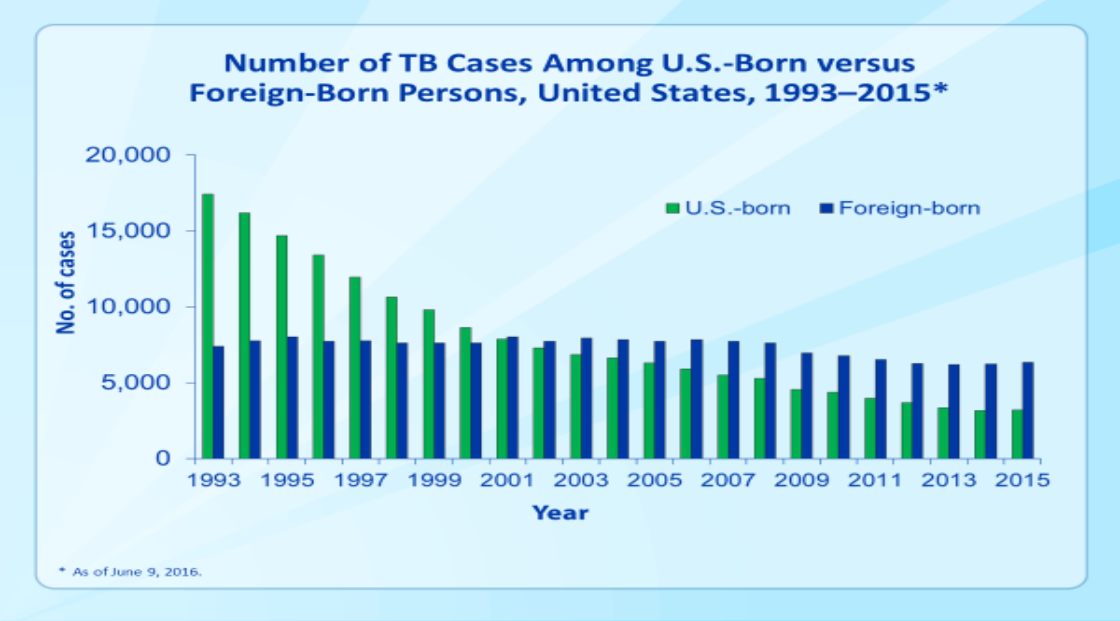


Figure 1.2-TB case rate trends US-born vs Foreign-born persons, Courtesy CDC

Death due to TB has drastically decrease over the past 20 years, recent data available indicates there were 493 deaths from TB in 2014,11% decrease from the 555 TB deaths in 2013. Overall, the number of TB deaths reported annually has decreased by 71% since 1992 (23).

According to CDC, the following persons are increased risk of tuberculosis disease

- Close contacts of persons known or suspected to have TB disease;
- Foreign-born persons from areas that have a high incidence of TB disease (e.g., Africa, Asia, Eastern Europe, Latin America, and Russia);
- Persons who visit areas with a high prevalence of TB disease, especially if visits are frequent or prolonged;
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, long-term care facilities, and homeless shelters);

- Health-care workers who serve clients who are at increased risk for TB disease;
- Populations defined locally as having an increased incidence of latent tuberculosis infection or TB disease, possibly including medically underserved, low-income populations, or persons who abuse drugs or alcohol; and
- Infants, children, and adolescents exposed to adults who are at increased risk for latent tuberculosis infection or TB disease

In 2015, the Department of Homeland Security stated that over 1 million migrants from around the globe, including immigrants from high TB incidence countries (28) acquired legal permanent residency here in the US (29). With an upward migration trend (29), refugee resettlement, global commerce and international travels, the goal to eliminate TB in the United States remains challenging.

Refugee Health-Screening

In the United States, CDC provides comprehensive guidelines for pre-departure and domestic medical screening among refugees (30).These guidelines are implemented by a panel of designated physicians and civil surgeons. A panel physician is a medical doctor practicing overseas who has an agreement with a local U.S. embassy or consulate general to perform immigration medical examinations; more than 760 panel physicians perform these examinations. A civil surgeon is a special designation for a U.S. physician authorized to perform official immigration medical examinations required for adjustment of status (31).

Pre-departure screening activities overseas are carried out by panel of physicians who use the available CDC's Technical Instructions to screen refugees and immigrants for diseases of public health relevance, in accordance with the U.S, immigration law, before arriving in the United

States. Table 1 (in appendix) provides a comparison of the two available Technical Instructions and tuberculosis classifications based on screening test result and clinical evaluation for refugees before arriving in the States. Domestic screening is done by Civil Surgeons, who provide medical screening for immigrants and refugees applying for permanent legal status and persons of foreign birth who entered the country on nonimmigrant visas and want to adjust their immigration status to legal permanent resident (32). Newly arrived refugees are screened for mental health disease, viral hepatitis, HIV infection, intestinal parasites, sexually transmitted diseases, tuberculosis and latent tuberculosis infection. The Guidelines for Screening for Tuberculosis Infection and Disease during the Domestic Medical Examination for Newly Arrived Refugees (8) outlines the diagnostic evaluation for TB and LTBI among refugees based on the Mantoux method for commercially available tuberculin skin tests (TST) or interferon-gamma release assay (IGRA) blood tests, and a chest radiograph. The two Food and Drug Administration (FDA) approved TSTs for use in the U.S. are Tubersol® and Aplisol®. The TST is considered positive if:

- Induration of ≥ 10 mm for all healthy refugees
- Induration of ≥ 5 mm in refugees with HIV, known close contact with someone with infectious TB, chest X-ray consistent with prior TB, organ transplant recipient, or immunosuppressed

The two FDA-approved IGRAs are the QuantiFERON®-TB Gold In-Tube test (QFT-GIT) and T-SPOT®.TB test (T-Spot)(33). Interpretation and use of these tests are based on manufacturer's instructions and the national guidelines (34). A positive IGRA test is interpreted to indicate infection with *Mycobacterium tuberculosis*.

The screening test results together with clinical evaluation and overseas exam classifies refugees

into one of the following;

- Latent Tuberculosis Infection, No Disease
- Tuberculosis, Not Clinically Active
- Suspect or Confirmed Tuberculosis Disease

Refugees suspected or confirmed with tuberculosis diseases should be reported to the local health department within 24hours for immediate public health interventions (26).For an asymptomatic refugee with chest radiograph suggestive of old/healed TB who has documented evidence of previous treatment, no treatment is required.

The treatment of LTBI among refugee is guided by the American Thoracic Society, ATS, Center for Disease Control and Prevention, CDC and the Infectious Diseases Society of America, IDSA treatment guidelines (20).

Chapter II: Literature Review

LTBI Treatment Regimen

Latent tuberculosis treatment is essential towards elimination of tuberculosis in low incidence countries (35). In the United states, a total of 9,557 TB cases were reported in 2015 (2). TB incidence in low-incidence countries such as the United States is mostly attributed to reactivation of remotely acquired LTBI (36-38).Treatment of LTBI, especially among recent immigrants from high incident countries, has been estimated to provide significant cost-saving and quality-adjusted life years saved because of the reduced progression to active TB (39, 40).

In 2011, CDC recommended a combination regimen of isoniazid and rifapentine (3HP) given as 12 weekly under directly observed therapy (DOT) as an equal alternative treatment regimen to 9 months of daily self-administered isoniazid (INH) for treating LTBI in otherwise healthy patients 12 years and above who have a higher risk for progression to TB disease (41) based on The PREVENT TB clinical trials which conducted an open-label, randomized noninferiority trial comparing 3 months of directly observed once-weekly therapy with rifapentine (900 mg) plus isoniazid (900 mg) (combination-therapy group) with 9 months of self-administered daily isoniazid (300 mg) (isoniazid-only group) in subjects at considerable risk for tuberculosis. Subjects were enrolled from the United States, Canada, Brazil, and Spain and followed for 33 months. The trial established that treatment completion were 82.1% in the combination-therapy group and 69.0% in the isoniazid-only group ($P<0.001$) and that use of rifapentine plus isoniazid for 3 months was as effective as 9 months of isoniazid alone in preventing tuberculosis and had a higher treatment-completion rate (21). 3HP is recommended in settings where persons are less likely to complete 9-months of INH (21) and in clinics for recent migrants (41). However, this regimen is not recommended for children ≤ 2years, patients on antiretroviral therapy (ART), presumed INH or rifampin (RIF) resistant *M.tuberculosis*, pregnant women and women

expecting to be pregnant while taking this regimen (18).

The use of INH to treat LTBI relied on evidence from randomized clinical trials and observational studies (42-45) that showed daily INH reduced the incidence of TB by 60% to 90% (46), 9-INH is preferred to 6-months of INH because of increased efficacy even though the latter is more cost effective and has higher adherence rates (18). Daily dosing 9-INH is recommended in children aged 2 to 11years (18). INH associated hepatitis in the treatment of LTBI was found to be age related with a rate 2.3% occurring in persons >50 years, with no occurring cases in persons <20years of age (47).

RIF is used as an alternative for persons who cannot tolerate INH, have been exposed to INH-resistant TB (18). This treatment option was informed by four randomized controlled trials that compared 3-4 moths of RIF alone with 9-months of INH (46, 48-51). A meta-analysis from 53 studies of different LTBI treatment regimens found that the odds of TB incidence was reduced by 59% with RIF alone compared to placebo (46, 52). In the United States, CDC recommends 4-months of daily RIF, however should not be used alone in combination with anti-retroviral therapy (ART) (18). LTBI treatment candidates should be evaluated before initiation of treatment (42), to inform the clinicians' choice of optimal regimen based on: co-morbidities, potential for drug-drug interaction, and drug susceptibility results of presumed source case (18). Evidence for the use INH and RIF combination therapy in the treatment of LTBI has not well been studied in the U.S. A randomized controlled study over a 11-year period (from 1995-2005, inclusive) in children <15 years who fulfilled the criteria for LTBI used by the International Union Against Tuberculosis and Lung Disease, American Academy of Pediatrics, and British Thoracic Society (53-55) compared 3- and 4-month combination regimens of INH and RIF with a 9-month regimen of INH monotherapy for the treatment of LTBI, found that no patient in any

treatment group develop TB disease but radiographic findings suggestive of possible active disease were common in patients who received INH monotherapy, compared to those treated with shorter regimens of INH and RIF. The study concluded that short-course treatment with isoniazid and rifampin for 3–4 months is safe and seems to be superior to a 9-month course of isoniazid monotherapy (56). In 2015, Ena and Valls published a meta-analysis that determined the equivalence of daily short-course therapy with INH and RIF combination therapy for 3 months and standard therapy with INH for 6-12 months, in the 5 trials comprising of 1926 adults from Hong Kong, Spain and Uganda, they found equivalent efficacy, side effects, and mortality (57). The benefits of combination therapy of INH and RIF for LTBI remain inconclusive (46)

LTBI Prevalence and treatment in the United States

In 1989, the first strategic plan for the elimination of TB in the United States was published (24) in the wake TB resurgence which resulted from HIV epidemic, nosocomial transmission of TB and MDR-TB, and increased immigration from high TB burden countries (58). Subsequent strategies (20, 26, 58) have strongly suggested LTBI diagnosis and treatment, especially among individuals at substantial risk for TB disease, as a cornerstone to the elimination of TB in the United States.

In 2008 Bennett et al., published the first survey-based national LTBI estimates since 1971-1972, defining LTBI as TST induration ≥10mm, they estimated LTBI prevalence of 4.2% and found that a total of 63% of LTBI were among foreign-born persons who participated in the National Health and Nutrition Examination Survey (NHANES) during 1999-2000. Out of 25.5% of persons previously diagnosed with LTBI or TB disease only 13.2% had been prescribed treatment at the time (59).

In 2015, Miramontes et al., published another study that analyzed data from NHANES for 2011-2012, and estimated that there was a relatively slight increase in LTBI prevalence from 1999-2000 (4.3% [95%CI:3.5-5.3]) to 2011-2012 (4.7% [95% CI 3.4-6.3]) based on TST positivity. Prevalence of LTBI in foreign born persons was higher (20.5%[95%CI:16.1-25.8) compared to US-born persons (1.5% [95%CI: 0.9-2.6]) (10).

Similarly, in 2016, Marcuso et al., published an analysis of data between 2011-2012 from the same source and estimated prevalence of LTBI in 2011-2012 was 4.4% (95% CI, 3.1–6.1%) as measured by the TST and 4.8% (95% CI, 4.0–5.8%) by QFT-GIT, they estimated a reservoir of 12.4 TB cases in the form of LTBI with foreign-born persons representing 73% (9).

Despite this rate, LTBI was believed to be underdiagnosed, and that fewer people in the United States received any type of LTBI testing (59). With the introduction of IGRA tests, testing rates

for LTBI is expected to increase. To that effect, in 2016, Vozoris and Batt produced a study that evaluated potential changes in the prevalence of LTBI testing in the U.S. following the introduction of IGRA. They sourced data from NHANES, compared self-reported LTBI testing from 1999-2000 and 2011-2012, found that significantly fewer people self-reported testing for LTBI in 2011-2012 compared to 1999-2000 among Hispanic Americans (68.0% vs. 60.7%, $p < 0.0001$) and people with co-morbities (74.7% vs 72.0%, $p = 0.02$) and concluded that LTBI testing occurs less frequently among vulnerable groups (60).

While diagnosis LTBI is essential in the cascade towards elimination of tuberculosis, the impact of efforts can be measured by the completion rate of LTBI treatment. In January 2015, Hirsch-Moverman et al., with the Tuberculosis Epidemiologic Studies Consortium (TBESC) published findings from 12 study sites where they had enrolled participants from both the United States and Canada. They concluded that of the 1515 participants who initiated LTBI treatment, only 46.6% completed and completion was also associated with male sex, foreign birth and having health insurance. Participants who were reminded monthly of their appointment were more likely to complete treatment (61).

Yamin et al., in April 2016, published an article of a retrospective chart review study conducted on patients ≥18years who accepted treatment at the Fulton County Health Department (FCHD) in Atlanta, Georgia from January 2012 to December 2013. Of the 547 patients offered LTBI treatment, 78% accepted. Of those who accepted treatment, 70% successfully completed treatment. Treatment completion was defined as taking ≥88% of prescribed doses within 12 months and 6 months, respectively for 9-months INH and 4-months RIF regimen. For the 3HP regimen, treatment completion was defined as receiving ≥11 of 12 scheduled doses through a directly observed therapy within a 16-week period. Treatment completion among foreign-born

patients was 36% and higher completion rate among patients prescribed with 3HP (79%) was also found (62).

LTBI Prevalence and Treatment Among Refugees

A retrospective study that examined LTBI among 9,842 primary refugees who settled in Minnesota between January 1,1997 and December 31,2001 using TST found LTBI prevalence to be 50.7%, and diagnosis was common in men, older age and refugees of African descent with 116 refugees receiving treatment for active TB [9]. Similarly, another study that only looked at 1999 domestic health screening results for 2,545 newly arrive refugees using TST, again in Minnesota, found LTBI prevalence as 49% using a tuberculin skin test reaction ≥ 10mm. As in the previous study, higher prevalence was associated with male sex and African origin (p=0.006) [8].

Hensel et al. looked at risk of latent tuberculosis infection among recently arrived refugees in Georgia with pre-diabetes and diabetes mellitus and found LTBI prevalence of 31.3% among studied population [10].

While many studies among this subpopulation focus on prevalence of LTBI, little is known among LTBI treatment in the U.S. and among the refugees resettling in the United States.

In 2014, Bennett et al., published on LBTI prevalence and treatment outcome among newly resettled refugees in San Diego county, California. They looked at data on primary refugees aged 13 years and older who were evaluated through the San Diego County Refugee Health Assessment Program (RHAP) between January 1,2010 to October 1,2012, using a positive QFT test and normal chest radiography, they established LTBI prevalence as 89.8% with treatment initiation and completion as 76.3% and 58.7%, respectively, among the studied population. Among this group, refugees from sub-Saharan Africa had a higher LTBI prevalence (43%) and were less likely to initiate treatment (15).

Similarly, In May,2015, Subedi et al published a study that compared evaluation and treatment in refugees seen at the Philadelphia Refugee Health Collaborative(PRHC) clinic and non-PRHC

clinics from 2010-2012, LTBI prevalence of 38.8% among 149 refugees who were seen by the Department of Public Health, no active case was detected and LTBI treatment completion rate was 75.4% (63).

In Canada, where demographics are similar to that of the United States, due to shared geography and geopolitical interests, and where about 65% of TB cases result from reactivation of LTBI among foreign-foreign persons, an evaluation of outcome of LTBI screening and treatment among newly arrived refugees was conducted in Edmonton between January 1, 2009 and December 31, 2011. Of the 147 offered LTBI treatment, 141 (95.9%) and 103 (73.0%) accepted and completed treatment, respectively. Non-adherence to treatment was statistically associated with young age and sub-Saharan Africa origin ($p< 0.005$) (64).

Other studies have examined treatment outcome of LTBI among the general U.S. population and neighboring countries.

In Nov 2008, A systematic review of studies done in the US and Canada for LTBI treatment searched PUBMED, MEDLINE and PsycINFO electronic databases for quantitative studies published between 1997 and 2007 found adherence and completion rates of LTBI treatment were suboptimal across high-risk groups, regardless of regimen and associations between adherence and patient factors, clinic facilities or treatment characteristics were found to be inconsistent across studies. This review found LTBI treatment completion rate among recent immigrants from high endemic regions to varied between 22% and 90% (65).

Chapter III: Manuscript

Abstract

Prevalence and Treatment Outcome of Tuberculosis and Latent Tuberculosis Infection Among Newly Arrived Refugees in DeKalb County, January 2015-February 2016.

Background: In the United States, tuberculosis(TB) incidence among foreign-born persons (15.1 cases per 100,000) is approximately 13 times compared to incidence among US-born persons (1.2 cases per 100,000). In 2015, approximately 66.4% of new cases of TB occurred in foreign born persons. This has in part been attributed to reactivation of latent tuberculosis infection (LTBI). The Centers for Disease Control and Prevention (CDC) recommend screening and treatment of both active TB and LTBI for newly arriving refugees. However, few studies have evaluated the treatment outcomes of LTBI among newly arrived refugees. We sought to assess TB and LTBI prevalence among recently resettled refugees in DeKalb County and evaluate variables associated with LTBI treatment initiation and completion.

Methods: We did a secondary data analysis of LTBI screening results and follow up logs of 1155 refugees screened at the DeKalb County Board of Health Refugee Health Program between January 2015 and February 2016. A multivariate logistic regression was used to calculate the associations between demographic characteristics and LTBI diagnosis, treatment initiation and completion.

Results: LTBI diagnosis and treatment initiation rates among evaluated refugees were 62% and 85% respectively. Higher completion rates among refugees were associated with Asian origin and with the treatment regimen option of isoniazid and rifapentine combination therapy for 3 months. Compared with other refugees, those from Middle East were less likely to initiate and complete LTBI treatment.

Conclusion: In DeKalb County, public health interventions are required to increase LTBI initiation and treatment completion rates among refugees. Efforts should be aimed at establishing culturally competent and age appropriate interventions for all refugees, especially of Middle Eastern origin and among the 18-34 year age group.

Introduction

Tuberculosis (TB) is one of the top ten causes of mortality worldwide, the World Health Organization (WHO) estimates that in 2015, 10.4 million people fell ill with TB with a resultant 1.8 million death (1). In the United States, the incidence of TB has remained stable at approximately 3.0 per 100,000 persons during 2013-2015, incidence among foreign-born persons (15.1 cases per 100,000) is approximately 13 times compared to incidence among US-born persons (1.2 cases per 100,000) (2). In 2015, approximately 66.4% of new cases of TB occurred in foreign born persons (2, 3). Refugees and immigrants who settle in western countries, including the United States, have been found to have similar incidence of TB comparable to their country of origin. This has been largely attributed to reactivation of remotely acquired latent tuberculosis infection (LTBI) (4, 5). Applicants for immigrant visa or refugee status undergo medical screening overseas by panel of physicians appointed by the U.S. Department of State in accordance with Technical Instructions provided by the Centers for Disease Control and Prevention (CDC), Division of Global Migration and Quarantine (DGMQ) (6).Applicants found to have active TB receive directly observed therapy (DOT) before being allowed to enter the United States (6).Whilst the treatment of active tuberculosis before embarkation is mandatory for resettling refugees, treatment for LTBI is not (7). CDC therefore recommends screening and treatment of both active TB disease and LTBI for all newly arriving refugees in the United States as part of post-arrival medical screening (8).

The overall prevalence of LBTI in US has been estimated to be 4.3%-4.48% (9, 10) Two studies conducted in Minnesota between 1997 and 2001 that used the tuberculin skin test (TST) found the prevalence of LTBI among resettling refugees to be 49.0% and 50.7% (11, 12). Another study that looked at risk of LTBI among recently arrived refugees in Atlanta with pre-diabetes and diabetes mellitus found an LTBI prevalence of 31.3% (13). Current limited literature (12-14)

focus on describing the prevalence of LTBI and sociodemographic characteristics in immigrants and refugees who resettle in the U.S, but there are few assessments of implementation of CDC's treatment recommendations. One study, however, that examined LTBI treatment initiation and outcome among this subpopulation in San Diego County, California, found that out of 489 refugees eligible for LTBI treatment, only 76.3% initiated treatment with 58.7% completed LTBI treatment (15).

Over the past decade, DeKalb County has historically resettled more than 60% of refugees arriving in the State of Georgia, making it the highest refugee resettlement county in the State of Georgia and the county with the highest TB case rate of 8.3 per 100,000 in 2014 (16). Evaluating LTBI treatment among recently resettled refugees in this county is therefore essential towards the elimination of TB in the United States, as it will inform health interventions aimed at reducing the prevalence of TB among this population and in the United States. This study sought to investigate active TB and LBTI prevalence among refugees recently resettled in DeKalb County from January 1, 2015 through February 29, 2016, and examined variables associated with LBTI treatment.

Methods

Refugees entering DeKalb County receive domestic medical screening examination within 30 days of arrival through the DeKalb County Board of Health Refugee Health Program. The program screens newly arrived for active TB disease, LTBI, parasites, HIV, hepatitis A, B, and C, and syphilis according to CDC guidelines and recommendations.

The refugee clinic uses commercially available interferon gamma release assays (IGRA), such as QuantiFERON-TB Gold In-Tube (QFT-GIT), to screen for LTBI. In addition, children ≤5 years receive a Tuberculin Skin Test (TST). Due to an ongoing study by the Tuberculosis Epidemiologic Studies Consortium (TBESC), some refugees were also tested with another commercially available IGRA, T-SPOT.*TB* (TSPOT), and TST. Refugees with a positive QFT-GIT (≥0.35IU/ml), TSPOT (Panel A minus Nil Control and or Panel B minus Nil control ≥8 spots), or TST (≥10mm) were scheduled for LTBI clinic. Diagnosis of LTBI was based on any positive IGRA test, or positive TST, normal chest x-ray and no TB symptoms. Those with abnormal chest x-ray or TB symptoms were further evaluated for active TB disease by sputum culture and computerized tomogram (CT) scanning of the chest. A confirmed case of active TB was referred to the TB clinic for further management. Refugees with LTBI were offered one of the following treatment regimens per CDC recommended guidelines: 9 months of once daily dose of isoniazid (INH); 3 months of weekly dose of isoniazid+rifapentine (3HP); or 4 months of once daily dose of rifampin(RIF). In addition, 4 months daily dose of Rifamate (isoniazid+ rifampin) were prescribed to LTBI patients who were close contacts to TB cases. Treatment was voluntary and regimen selection was based on clinical evaluation with relevance to contraindications and patient preference.

This assessment was a secondary data analysis on primary refugees who received TB and LTBI screening and treatment through the DeKalb County Board of Health Refugee Health Program from January 2015 to February 2016.

Outcomes of interest included: diagnosis of LTBI, LTBI treatment initiation, and LTBI treatment completion. LTBI treatment initiation was defined as starting the first dose of a regimen. LTBI treatment completion was also defined as completing a full course of regimen as recommended by the CDC. Demographics such as age, gender, country of birth, IGRA and TST tests results, date of treatment initiation and completion were extracted from the LTBI tracking log. Outcome variable were re-coded as binary variables and country of birth into region of birth. Age was also categorized into <12 years, 13-17 years, 18-34 years, 35-49 years and over 50 years. Indeterminate test results were excluded from analysis.

Data cleaning and analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC) statistical software. Univariate descriptive statistics with frequencies for demographic variables were conducted. Differences in categorical variables were tested using chi-square or Fisher's exact test. A 2-sided $P<0.05$ was considered significant throughout the analyses. A bivariate logic regression model was used to assess association between outcomes and independent variables. Variables with a *P*-value <0.20 were included in the final multivariate logistic regression using the stepwise model selection approach. Interaction terms were included in the final model. Approval for this study was sought from the Georgia Department of Public Health Institutional Review Board and the Emory University Institutional Review Board.

Results

A total 1155 primary refugees were evaluated for LTBI based on a positive IGRA and TST test out of 3118 primary refugees screened through the DeKalb County Board of Health Refugee Health Program between January 1, 2015 and February 29,2016. The mean and median age of refugees evaluated for LTBI was 30 years, range 83 years; 37.8% were between 18-34 years. Males accounted for 57.4% (Table 1). The majority of refugees evaluated for LTBI during the study period were from Asia (n=798, 69.4%); most were born in Burma (n=521, 45.3%) followed by Bhutan (n=227, 19. 8%). Among those from Sub-Saharan Africa, persons from Democratic Republic of Congo (DRC) were the majority and accounted for 14.3% (n=164) of refugees evaluated.

Diagnosis of LTBI

Out of 1155 refugees who were scheduled for LTBI clinic, 720 (62.3%) were diagnosed with LTBI (Fig.1). Ten refugees (0.9%) with abnormal chest x-ray finding were diagnosed of pulmonary TB disease and transferred to DeKalb Board of Health TB Clinic. Diagnosis of LTBI was highest among refugees from Middle East (90.0%) compared with Sub-Sahara Africa (75.8%) and Asia (55.2%) ($P<0.0001$).

In the bivariate analysis, refugees from Middle East were 7 times more likely to be diagnosed with LTBI compared to those of Asian origin (OR=7.32, 95% CI=3.11-17.22), similarly those from sub-Saharan Africa had significantly increased odds to be diagnosed with LTBI compared to those from Asian origin (OR=2.55, 95% CI=1.89-3.43) (Table 2). A comparison of odds showed higher odds of LTBI diagnosis among Middle East refugees compared to Sub-Saharan refugees (OR=2.87, 95% CI=1.19-6.94).

In the multivariate logistic regression using the stepwise model selection approach, statistical significance LTBI predictors were found be age group ($p=0.01$), QFT result ($p<0.0001$) and

TSPOT result (p<0.0001). The likelihood of having LTBI increased with increasing age group (in years), refugees over 50 years were about 5 times likely to be diagnosed LTBI compared to those less than 12 years of age (AOR=5.07,95% CI=1.85-13.96). Interaction for age groups by QFT-GIT, TSPOT and TST results showed no statistical significance.

Treatment initiation

610 refugees started LTBI treatment representing 84.7% of those diagnosed with LTBI. A higher percentage of female compared to males started treatment but there was however no statistical significance (p=0.76). Out of the 110 refugees who did not initiate LTBI treatment; 95 did not keep appointment for LTBI clinic; 6 were pregnant, 4 had HBsAg positive and were referred for specialist consult; and 5 had moved out of state (Fig.1). Most of the refugees with LTBI were started on 4 months Rifampin regimen (72.5%). Bivariate analysis showed that refugees from middle East were significantly less likely to start treatment compared to those of Asian origin (OR=0.20, 95% CI=0.11-0.38) (Table 3). Multivariate analysis only showed significant association between region of birth and initiation of LTBI treatment (p <0.0001). There was no statistically significant interaction between age group and region of birth.

Treatment completion

507 refugees completed LTBI treatment; 83.1% of refugees who started treatment completed. Out of 103 who failed to complete treatment, 83 were lost to follow up or did not return for continuation of treatment after initiation; 12 who moved out state were issued letters to continue treatment in resettling states; 5 reported being pregnant and were referred for OBGYN clearance but failed to report back; 3 refugees had adverse drug effects and stopped medication (Fig.1).

Higher percentage of males completed treatment compared to females (85.2% vs 80.3%, p=0.1). There was a borderline statistically significant difference among age groups (p=0.06) with respect to treatment completion, persons aged 18-34 years were half less likely to complete treatment compared to those aged 35-49 years (OR=0.5, 95% CI=0.95-6.60). Compared to other regions of birth, refugees from Asia were more likely to complete LTBI treatment (Table 4), they were over 3 times more likely to complete LTBI treatment; Asia vs sub-Saharan Africa (OR=3.11, 95% CI=1.96-4.95); Asia vs Middle East (OR=3.49, 95% CI=1.50-8.10). LTBI treatment completion was higher among those who received the 3HP regimen (Fig.1) (Table 4), however, no significant bivariate associations existed between treatment completion and type of regimen (p=0.22)

In the final multivariate logistic regression, using the stepwise model selection method, only region of birth, age group and gender were predictors of completion (Table 4), There was no statistically significant interaction between age group and regimen type in the final model.

Discussion

Among this study population, we found a higher LTBI diagnosis among refugees of Middle Eastern origin (90.0%) compared those from Asia (56.2%) and Sub-Saharan Africa (75.8%), (P<0.001). This is in contrast with previous publications where LTBI prevalence was highest among refugees of sub-Saharan Africa (11, 12). This finding, however, is essential as it reflects the demographic of this study group relative to TB prevalence in originating countries and can serve to guide adaptations required in DeKalb County. The current political instability with resultant crowding among Middle Eastern countries creates opportunity for transmission of communicable diseases; TB disease and LTBI could flourish in these settings. Additionally, this finding justifies renewed efforts in pre- and post-embarkation screening among person from this region. While persons of Middle Eastern origin had higher LTBI diagnosis, they were less likely to start and complete LTBI treatment. This may reflect insufficient resources at the refugee health program to provide culturally appropriate care for this group, and is deserving of further attention.

The increasing age association with LTBI prevalence among refugees observed in this study has been well documented in previous studies (11, 12, 15). Our multivariate analysis revealed that increasing age group was associated with higher odds of having latent tuberculosis infection (Table 2). Persons ≥50 years were over 5 times likely to be diagnosed with LTBI compared with person ≤12 years. This finding should ensure older refugees receive LTBI treatment, as aging with decreasing immunity may place them at risk for reactivation of remotely acquired LTBI. Also, a bivariate analysis showed that refugees aged between 18-34 years had significantly higher odds of being diagnosed with LTBI (OR=7.21, 95% CI=4.89-10.61), however this age group had the lowest rate of starting and completing LTBI treatment. This finding reflects the challenges associated with engaging younger age groups, necessitating that Public Health

Departments and agencies serving refugee communities seek ways to provide age appropriate interventions to ensure higher retention and adherence to recommended treatment.

Though not recommended for routine LTBI treatment, it was observed that 22 refugees diagnosed with LTBI were started on Rifamate (INH and RIF combination). Evidence for the use rifamate in the treatment of LTBI remains unclear (17-19). However, some health departments, including the New York City Department of Health and Mental Hygiene (NYCDOHMH), recommend this as alternative regimen for LTBI patients who are contacts of INH- and RIF-resistant TB (20).

With no reference to study designs and sample demographics, 96.7% completion rate among patients offered 3HP was much higher than that found in the PREVENT TB study (82%) (21) and of a neighboring county (79%) (22). Even though higher completion rates have been demonstrated in other studies, a 3HP concurrent study at the clinic during this study period that offered incentives to patients taking 3HP might have contributed to the observed rate. Since the refugee health program reminds clients of appointments, the increased numbers for those who did not keep appointment or were lost to follow up (Fig.1) may be an indication of transportation and telecommunication challenges among these resettling refugee populations.

The overall LTBI treatment initiation and completion rate of 85% and 83% respectively are higher than in previous studies and exceeds CDC's target of 79% treatment complete rate among the general population (23-25).

Limitations

The limited dataset restricted our analysis to only refugees scheduled for LTBI clinic. This prevented us from establishing the baseline demographics of all refugees screened during the study period. The study design also limited our ability to explore clinical risk factors associated with TB reactivation; reasons for not keeping appointments or lost to follow up patients; and treatment interruption. The non-randomization of treatment may have introduced confounders such as clinician preference for a treatment regimen that might have influence our findings. The above listed limitations are not exhaustive given the study design. The findings of this study are not representative of all refugees arriving in the United States, and only reflects the population assessed in DeKalb County during the study period.

Conclusion

We conclude that refugees resettling in the United States have a significantly higher prevalence of LTBI and are a repository of future TB disease if treatment is not tailored to meet their needs during resettlement. The disparity in LTBI prevalence, treatment initiation and completion observed among refugees from the Middle East and persons aged between 18-34years calls for culturally competent and age appropriate public health interventions at our health departments. Efforts may include staffing of interpreters, provision of transportation and telecommunication assistance to resettling refugees. The desirable completion rate among refugees who received short course combination therapy of 3HP given as directly observed therapy should be encouraged for use among refugees given the fluidity of their resettling situation.

The relatively high treatment initiation and completion rate among this study group may also reflect enhanced local efforts by the health department to reduce of TB cases within the county and eliminate TB in the United States.

Tables and Figures

Table 1-Charateristics of Newly Arrived Refugees Evaluated for Latent Tuberculosis Infection(LTBI): DeKalb County, GA; January 2015-February 2016 (N=1155)

Characteristics	No.	(%)
Gender		
Male	663	(57.3)
Female	492	(42.6)
Age Groups(years)		
<=12	187	(16.1)
13-17	98	(8.5)
18-34	436	(37.8)
35-49	286	(24.8)
>=50	149	(12.9)
Region of Birth		
Asia[a]	763	(66.4)
Middle East[b]	61	(5.3)
Sub-Saharan Africa[c]	314	(27.3)
Others[d]	11	(1.0)
QFT-GIT Result		
Positive	674	(58.7)
Negative	473	(41.2)
TSPOT Result		
Positive	184	(31.2)
Negative	372	(63.1)
Borderline	34	(5.8)
PPD Result		
Positive	574	(94.4)
Negative	34	(5.6)

[a] Bhutan, Burma, Malaysia, Nepal, Thailand, Pakistan

[b] Afghanistan, Egypt, Iran, Iraq, Syria

[c] Burundi, Cameroon, Central Africa Republic, Democratic Republic of Congo(DRC), Eritrea, Ethiopia, Gambia, Rwanda, Somalia, Sudan, Togo, Uganda

[d] Cuba, Russia, Turkey

Table 2-Charateristics Associated with Latent Tuberculosis Infection(LTBI) Diagnosis Among Newly Arrived Refugees: DeKalb County, GA; January 2015-February 2016

Characteristics	LTBI Diagnosis, N (%)	OR	(95% CI)	AOR	(95% CI)
Gender					
Female[Ref]	408/655(62.3)	1.00			
Male	312/490(63.7)	0.94	(0.74-1.20)		
Age Groups(years)					
<=12 [(Ref)]	50/185(27.0)	1.00		1.00	
13-17	57/98(58.2)	3.75	(2.24-6.29)	2.43	(0.90-6.52)
18-34	315/433(72.8)	7.21	(4.89-10.61)	3.14	(1.47-6.74)
35-49	197/281(70.1)	6.33	(4.19-9.57)	3.22	(1.46-7.09
>=50	101/148(68.2)	5.80	(3.61-9.32)	5.08	(1.85-13.96)
Region of Birth					
Asia [a(Ref)]	418/758(55.2)	1.00			
Middle East[b]	54/60(90 .0)	7.32	(3.11-17.22)		
Sub-Saharan Africa[c]	235/310(75.8)	2.55	(1.89-3.43)		
Others[d]	8/11(72.7)	2.17	(0.57-8.24)		
	No.Positive/No.Tested (%)				
QFT-GIT Result					
Negative [(Ref)]	93/472(19.7)	1.00		1.00	
Positive	624/666(93.7)	60.54	(41.15-89.06)	14.52	(7.51-28.07)
TSPOT Result					
Negative [(Ref)]	93/372(25.0)	1.00		1.00	
Positive	166/180(92.2)	35.57	(19.64-64.41)	5.56	(2.64-11.74)
Borderline	26/34(76.5)	9.75	(4.27-22.28)	2.81	(1.04-7.58)
PPD Result					
Negative [(Ref)]	15/34(44.1)	1.00			
Positive	266/571(46.6)	1.10	(0.55-2.22)		

[Ref] Reference group

[a] Bhutan, Burma, Malaysia, Nepal, Thailand, Pakistan

[b] Afghanistan, Egypt, Iran, Iraq, Syria

[c] Burundi, Cameroon, Central Africa Republic, Democratic Republic of Congo(DRC), Eritrea, Ethiopia, Gambia, Rwanda, Somalia, Sudan, Togo, Uganda

[d] Cuba, Russia,Turkey

-GIT=QuantiFERON-TB In-Tube; TSPOT=TSPOT.*TB* test; PPD=Purified Protein Derivative; LTBI=latent tuberculosis infection

Table 3-Charateristics Associated with Latent Tuberculosis Infection(LTBI) Treatment Initiation Among Newly Arrived Refugees: DeKalb County, GA; January 2015-February 2016

Characteristics	Prevalence Treatment Initiation, N (%)	OR	(95% CI)
Gender			
Female[Ref]	265/312(84.9)	1.00	
Male	345/408(84.5)	0.97	(0.64-1.46)
Age Groups(years)			
<=12 [(Ref)]	42/50(84.0)	1.00	
13-17	50/57(87.7)	1.36	(0.46-4.06)
18-34	262/315(83.2)	0.94	(0.42-2.12)
35-49	172/197(87.3)	1.31	(0.56-3.11)
>=50	84/101(83.2)	0.94	(0.38-2.36)
Region of Birth			
Asia [a(Ref)]	367/418(87.8)	1.00	
Middle East[b]	32/54(59.3)	0.20	(0.11-0.38)
Sub-Saharan Africa[c]	201/235(85.5)	0.82	(0.52-1.31)
Others[d]	5/8(62.5)	0.23	(0.05-0.99)
Regimen			
Isoniazid(INH)[(Ref)]	116/610(19.0)		
Rifampin(RIF)	445/610(72.5)		
Isoniazid& Rifapentine(3HP)	30/610(4.9)		
Rifamate(RFT)	21/610(3.6)		

[Ref] Reference group

[a] Bhutan, Burma, Malaysia, Nepal, Thailand, Pakistan

[b] Afghanistan, Egypt, Iran, Iraq, Syria

[c] Burundi, Cameroon, Central Africa Republic, Democratic Republic of Congo(DRC), Eritrea, Ethiopia, Gambia, Rwanda, Somalia, Sudan, Togo, Uganda

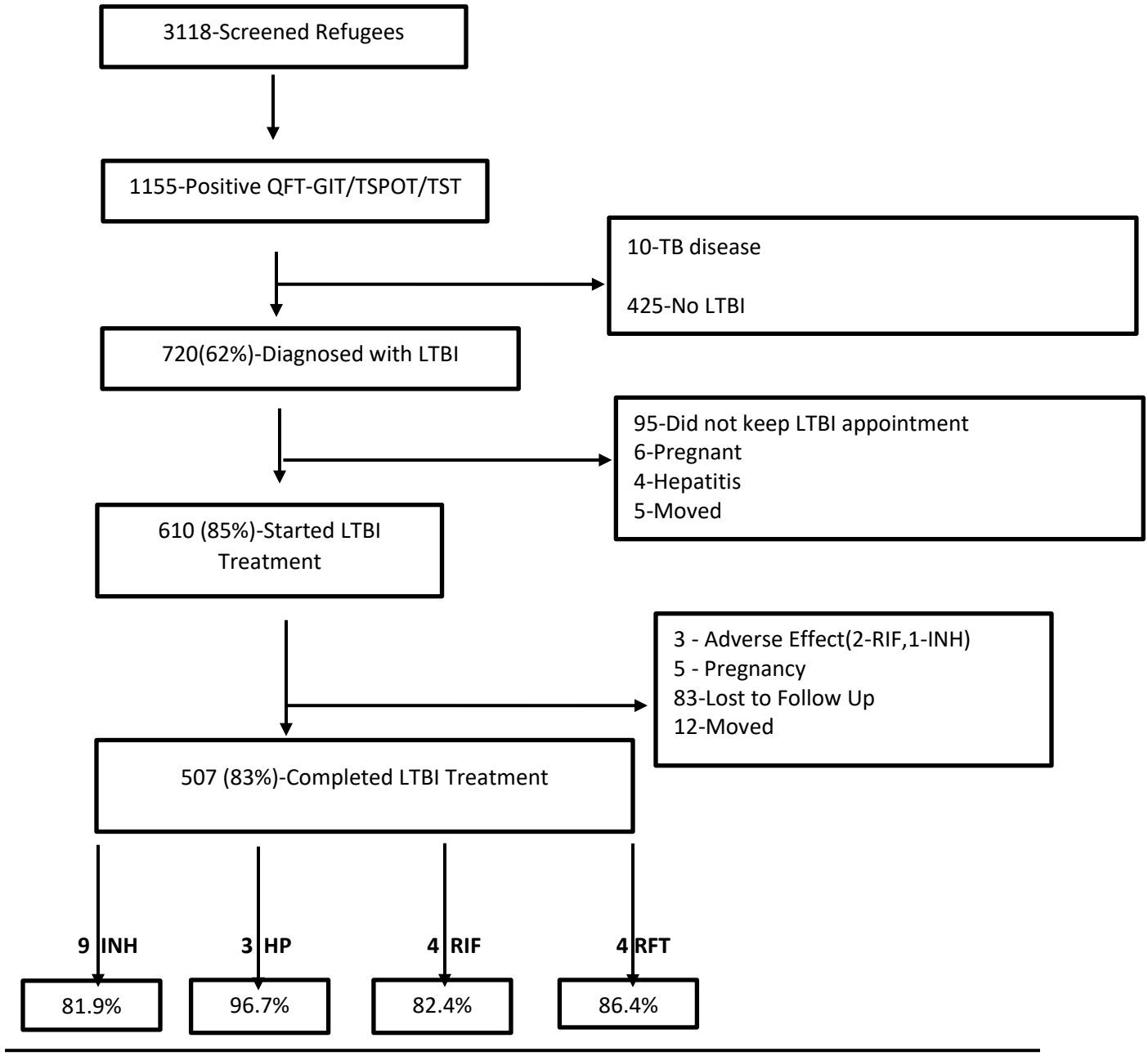
[d] Cuba, Russia, Turkey

Table 4-Charateristics Associated with Latent Tuberculosis Infection(LTBI) Treatment Completion Among Newly Arrived Refugees: DeKalb County, GA; January 2015-February 2016

Characteristics	Prevalence of Treatment completion,N (%)	OR	(95% CI)	AOR	(95% CI)
Gender					
Female[Ref]	213/265(80.0)	1.00			
Male	294/345(85.2)	1.41	(0.92-2.15)	1.63	(1.04-2.57)
Age Groups(years)					
<=12 [(Ref)]	34/42(81.0)	1.00		1.00	
13-17	45/50(90.0)	2.12	(0.64-7.05)	1.97	(0.53-7.33)
18-34	205/262(78.2)	0.85	(0.37-1.93)	0.62	(0.26-1.48)
35-49	151/172(87.8)	1.69	(0.69-4.14)	1.36	(0.53-3.48)
>=50	72/84(85.7)	1.41	(0.52-3.77)	0.79	(0.28-2.24)
Region of Birth					
Asia [a(Ref)]	330/367(89.9)	1.00		1.00	
Middle East[b]	23/32(71.8)	0.29	(0.12-0.67)	0.27	(0.11-0.64)
Sub-Saharan Africa[c]	149/201(74.1)	0.32	(0.20-0.51)	0.30	(0.19-0.49)
Others[d]	2/5(40.0)	0.08	(0.01-0.46)	0.07	(0.01-0.46)
Regimen					
Isoniazid(INH)[(Ref)]	95/116(81.9)	1.00			
Rifampin(RIF)	364/442(82.4)	1.03	(0.61-1.76)		
Isoniazid& Rifapentine(3HP)	29/30(96.7)	6.40	(0.83-49.71)		
Rifamate(RFT)	19/22(86.4)	1.40	(0.38-5.17)		

[Ref] Reference group
[a] Bhutan, Burma, Malaysia, Nepal, Thailand, Pakistan
[b] Afghanistan, Egypt, Iran, Iraq, Syria
[c] Burundi, Cameroon, Central Africa Republic, Democratic Republic of Congo(DRC), Eritrea, Ethiopia, Gambia, Rwanda, Somalia, Sudan, Togo, Uganda
[d] Cuba, Russia, Turkey

Figure 1-Study Cohort Diagram



QFT-GIT=QuantiFERON-TB In-Tube; TSPOT=TSPOT.*TB* test; TST=Tuberculin Skin Test; LTBI=latent tuberculosis infection; TB=tuberculosis; INH=isoniazid; HP=isoniazid & rifapentine; RIF=rifampin; RFT=rifamate

Manuscript References

1. World Health Organization. WHO Global Tuberculosis Report 2016 Geneva [cited 2017 April 16]. Available from: http://apps.who.int/iris/bitstream/10665/250441/1/9789241565394-eng.pdf?ua=1.

2. Salinas JL, Mindra G, Haddad MB, Pratt R, Price SF, Langer AJ. Leveling of Tuberculosis Incidence - United States, 2013-2015. MMWR Morbidity and mortality weekly report. 2016;65(11):273-8. Epub 2016/03/25. doi: 10.15585/mmwr.mm6511a2. PubMed PMID: 27010173.

3. Centers for Disease Control and Prevention. Trends in Tuberculosis 2015 [cited 2017 April 16]. Available from: https://www.cdc.gov/tb/publications/factsheets/statistics/tbtrends.htm.

4. Murray MB. Molecular epidemiology and the dynamics of tuberculosis transmission among foreign-born people. CMAJ: Canadian Medical Association Journal. 2002;167(4):355-6. PubMed PMID: PMC117849.

5. Geng E, Kreiswirth B, Driver C, Li J, Burzynski J, DellaLatta P, et al. Changes in the transmission of tuberculosis in New York City from 1990 to 1999. The New England journal of medicine. 2002;346(19):1453-8. Epub 2002/05/10. doi: 10.1056/NEJMoa012972. PubMed PMID: 12000815.

6. Posey DL, Naughton MP, Willacy EA, Russell M, Olson CK, Godwin CM, et al. Implementation of new TB screening requirements for U.S.-bound immigrants and refugees - 2007-2014. MMWR Morbidity and mortality weekly report. 2014;63(11):234-6. Epub 2014/03/22. PubMed PMID: 24647399.

7. U.S. Department of Health and Human Services. CDC Immigration Requirements:Technical Instructions For Tuberculosis Screening And Treatment 2009 [cited

2017 April 16]. Available from: https://www.cdc.gov/immigrantrefugeehealth/pdf/tuberculosis-ti-2009.pdf.

8. Centers for Disease Control and Prevention. Guidelines for Screening for Tuberculosis Infection and Disease during the Domestic Medical Examination for Newly Arrived Refugees 2012 [cited 2017 April 16]. Available from: https://www.cdc.gov/immigrantrefugeehealth/guidelines/domestic/tuberculosis-guidelines.html.

9. Miramontes R, Hill AN, Yelk Woodruff RS, Lambert LA, Navin TR, Castro KG, et al. Tuberculosis Infection in the United States: Prevalence Estimates from the National Health and Nutrition Examination Survey, 2011-2012. PloS one. 2015;10(11):e0140881. Epub 2015/11/05. doi: 10.1371/journal.pone.0140881. PubMed PMID: 26536035; PubMed Central PMCID: PMCPMC4633161.

10. Mancuso JD, Diffenderfer JM, Ghassemieh BJ, Horne DJ, Kao TC. The Prevalence of Latent Tuberculosis Infection in the United States. American journal of respiratory and critical care medicine. 2016;194(4):501-9. Epub 2016/02/13. doi: 10.1164/rccm.201508-1683OC. PubMed PMID: 26866439.

11. Lifson AR, Thai D, O'Fallon A, Mills WA, Hang K. Prevalence of tuberculosis, hepatitis B virus, and intestinal parasitic infections among refugees to Minnesota. Public health reports (Washington, DC : 1974). 2002;117(1):69-77. Epub 2002/09/26. PubMed PMID: 12297684; PubMed Central PMCID: PMCPMC1497409.

12. Varkey P, Jerath AU, Bagniewski SM, Lesnick TG. The epidemiology of tuberculosis among primary refugee arrivals in Minnesota between 1997 and 2001. Journal of travel medicine. 2007;14(1):1-8. Epub 2007/01/24. doi: 10.1111/j.1708-8305.2006.00083.x. PubMed PMID: 17241247.

13. Hensel RL, Kempker RR, Tapia J, Oladele A, Blumberg HM, Magee MJ. Increased risk of latent tuberculous infection among persons with pre-diabetes and diabetes mellitus. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2016;20(1):71-8. Epub 2015/12/22. doi: 10.5588/ijtld.15.0457. PubMed PMID: 26688531.

14. Taylor EM, Painter J, Posey DL, Zhou W, Shetty S. Latent Tuberculosis Infection Among Immigrant and Refugee Children Arriving in the United States: 2010. Journal of immigrant and minority health. 2016;18(5):966-70. Epub 2015/09/14. doi: 10.1007/s10903-015-0273-2. PubMed PMID: 26364054.

15. Bennett RJ, Brodine S, Waalen J, Moser K, Rodwell TC. Prevalence and Treatment of Latent Tuberculosis Infection Among Newly Arrived Refugees in San Diego County, January 2010–October 2012. American journal of public health. 2014;104(4):e95-e102. doi: 10.2105/AJPH.2013.301637. PubMed PMID: PMC4025726.

16. Georgia Department of Public Health. Georgia Tuberculosis Report 2014 [cited 2017 April 16]. Available from: https://dph.georgia.gov/sites/dph.georgia.gov/files/2014%20GA%20TB%20Report%20FINAL3.pdf.

17. Spyridis NP, Spyridis PG, Gelesme A, Sypsa V, Valianatou M, Metsou F, et al. The effectiveness of a 9-month regimen of isoniazid alone versus 3-and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. Clinical Infectious Diseases. 2007;45(6):715-22.

18. Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. Clinical

infectious diseases : an official publication of the Infectious Diseases Society of America. 2005;40(5):670-6. Epub 2005/02/17. doi: 10.1086/427802. PubMed PMID: 15714411.

19. Fox GJ, Dobler CC, Marais BJ, Denholm JT. Preventive therapy for latent tuberculosis infection-the promise and the challenges. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2016. Epub 2016/11/23. doi: 10.1016/j.ijid.2016.11.006. PubMed PMID: 27872018.

20. New York City Department Of Health. Tuberculosis Clinical Policies and Protocols New York2008 [cited 2017 April 16]. Available from: https://www1.nyc.gov/assets/doh/downloads/pdf/tb/tb-protocol.pdf.

21. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. The New England journal of medicine. 2011;365(23):2155-66. Epub 2011/12/14. doi: 10.1056/NEJMoa1104875. PubMed PMID: 22150035.

22. Yamin A, Bornstein E, Hensel R, Mohamed O, Kempker RR. Predictors of Latent Tuberculosis Infection Treatment After Introduction of a New Regimen: A Retrospective Cohort Study at an Inner City Clinic. Open Forum Infectious Diseases. 2016;3(4):ofw082. doi: 10.1093/ofid/ofw082. PubMed PMID: PMC5066457.

23. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this

statement. American journal of respiratory and critical care medicine. 2000;161(4 Pt 2):S221-47. Epub 2000/04/14. doi: 10.1164/ajrccm.161.supplement_3.ats600. PubMed PMID: 10764341.

24. Hirsch-Moverman Y, Daftary A, Franks J, Colson PW. Adherence to treatment for latent tuberculosis infection: systematic review of studies in the US and Canada. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2008;12(11):1235-54. Epub 2008/10/18. PubMed PMID: 18926033.

25. Hirsch-Moverman Y, Shrestha-Kuwahara R, Bethel J, Blumberg HM, Venkatappa TK, Horsburgh CR, et al. Latent tuberculous infection in the United States and Canada: who completes treatment and why? The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2015;19(1):31-8. Epub 2014/12/19. doi: 10.5588/ijtld.14.0373. PubMed PMID: 25519787; PubMed Central PMCID: PMCPMC5296762.

Chapter IV: Public Health Implications and Recommendations

With current migration crisis resulting from political instability and war in the Middle East, Central Africa and some part of Asia, the goal towards elimination of tuberculosis in developed countries is far from reach. Displaced populations with limited access to clinical care and public health assistance carry with them high burden of communicable and mental health diseases that need to be addressed for successful integration and reduced morbidity.

The findings of this report illustrate a few such needs which require adequate public health interventions. The high LTBI diagnosis rate established for those evaluated for LTBI is indicative of potential reservoir of future TB cases that justifies treatment to prevent TB disease. It is important that treatment be given in a timely manner, immediately after determination, as delays may result in lost to follow-up associated with the mobility of this population after arrival and during resettlement.

While previous studies have found higher LTBI prevalence among refugees of sub-Saharan origin, this study found higher prevalence among refugees of Middle East origin. Health departments that offer TB, LTBI and other health services to refugees such as the DeKalb County Board of Health, may need to adjust their *modus operandi* to provide culturally appropriate interventions that meet the needs of this group and enhance clinical assessment and treatment adherence.

Though LTBI treatment is not mandatory, there appears to be higher acceptance rate among refugees, and this trend should be encouraged. Our study, however, found that the largest number of refugees who did not start LTBI treatment did not keep their clinic appointment for LTBI evaluation and treatment. It is imperative that reminder efforts are made and other measures implemented to ensure and encourage that clinic appointments are kept.

Nonetheless, health departments that send reminders may still encounter clinic absenteeism on

substantial numbers in such a population as observed in this study, probably because of unmet physical needs such as transportation and telecommunication. To bridge this gap, enablers in the form of bus tickets could be allotted to refugees coming for LTBI evaluation and treatment visit, as occasionally done for TB disease patients.

Finally, like previous studies, our study found a higher LTBI treatment acceptance among refugees, when compared with other populations. Treatment completion was much higher in refugees who were prescribed 3months of isoniazid and rifapentine combination therapy (3HP). The relatively short duration of the regimen probably served as an incentive for early completion and clearance. This shortened regimen in this population could be as important as directly observed therapy in TB treatment, as providers are assured that recommended medication is taken. Providers and public health clinicians are therefore encouraged to preferentially prescribe 3HP regimen for LTBI treatment among refugees.

In conclusion, approach to LTBI treatment among high risk populations such as refugees must be evidence based. It should be culturally appropriate, tailored to meet the challenging needs of population and adequate to prevent a future TB reactivation.

References

1. World Health Organization. WHO Global Tuberculosis Report 2016 Geneva [cited 2017 April 16]. Available from: http://apps.who.int/iris/bitstream/10665/250441/1/9789241565394-eng.pdf?ua=1.

2. Salinas JL, Mindra G, Haddad MB, Pratt R, Price SF, Langer AJ. Leveling of Tuberculosis Incidence - United States, 2013-2015. MMWR Morbidity and mortality weekly report. 2016;65(11):273-8. Epub 2016/03/25. doi: 10.15585/mmwr.mm6511a2. PubMed PMID: 27010173.

3. Centers for Disease Control and Prevention. Trends in Tuberculosis 2015 [cited 2017 April 16]. Available from: https://www.cdc.gov/tb/publications/factsheets/statistics/tbtrends.htm.

4. Murray MB. Molecular epidemiology and the dynamics of tuberculosis transmission among foreign-born people. CMAJ: Canadian Medical Association Journal. 2002;167(4):355-6. PubMed PMID: PMC117849.

5. Geng E, Kreiswirth B, Driver C, Li J, Burzynski J, DellaLatta P, et al. Changes in the transmission of tuberculosis in New York City from 1990 to 1999. The New England journal of medicine. 2002;346(19):1453-8. Epub 2002/05/10. doi: 10.1056/NEJMoa012972. PubMed PMID: 12000815.

6. Posey DL, Naughton MP, Willacy EA, Russell M, Olson CK, Godwin CM, et al. Implementation of new TB screening requirements for U.S.-bound immigrants and refugees - 2007-2014. MMWR Morbidity and mortality weekly report. 2014;63(11):234-6. Epub 2014/03/22. PubMed PMID: 24647399.

7. U.S. Department of Health and Human Services. CDC Immigration

Requirements:Technical Instructions For Tuberculosis Screening And Treatment 2009 [cited 2017 April 16]. Available from: https://www.cdc.gov/immigrantrefugeehealth/pdf/tuberculosis-ti-2009.pdf.

8. Centers for Disease Control and Prevention. Guidelines for Screening for Tuberculosis Infection and Disease during the Domestic Medical Examination for Newly Arrived Refugees 2012 [cited 2017 April 16]. Available from: https://www.cdc.gov/immigrantrefugeehealth/guidelines/domestic/tuberculosis-guidelines.html.

9. Mancuso JD, Diffenderfer JM, Ghassemieh BJ, Horne DJ, Kao TC. The Prevalence of Latent Tuberculosis Infection in the United States. American journal of respiratory and critical care medicine. 2016;194(4):501-9. Epub 2016/02/13. doi: 10.1164/rccm.201508-1683OC. PubMed PMID: 26866439.

10. Miramontes R, Hill AN, Yelk Woodruff RS, Lambert LA, Navin TR, Castro KG, et al. Tuberculosis Infection in the United States: Prevalence Estimates from the National Health and Nutrition Examination Survey, 2011-2012. PloS one. 2015;10(11):e0140881. Epub 2015/11/05. doi: 10.1371/journal.pone.0140881. PubMed PMID: 26536035; PubMed Central PMCID: PMCPMC4633161.

11. Lifson AR, Thai D, O'Fallon A, Mills WA, Hang K. Prevalence of tuberculosis, hepatitis B virus, and intestinal parasitic infections among refugees to Minnesota. Public health reports (Washington, DC : 1974). 2002;117(1):69-77. Epub 2002/09/26. PubMed PMID: 12297684; PubMed Central PMCID: PMCPMC1497409.

12. Varkey P, Jerath AU, Bagniewski SM, Lesnick TG. The epidemiology of tuberculosis among primary refugee arrivals in Minnesota between 1997 and 2001. Journal of travel medicine. 2007;14(1):1-8. Epub 2007/01/24. doi: 10.1111/j.1708-8305.2006.00083.x. PubMed

PMID: 17241247.

13. Hensel RL, Kempker RR, Tapia J, Oladele A, Blumberg HM, Magee MJ. Increased risk of latent tuberculous infection among persons with pre-diabetes and diabetes mellitus. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2016;20(1):71-8. Epub 2015/12/22. doi: 10.5588/ijtld.15.0457. PubMed PMID: 26688531.

14. Taylor EM, Painter J, Posey DL, Zhou W, Shetty S. Latent Tuberculosis Infection Among Immigrant and Refugee Children Arriving in the United States: 2010. Journal of immigrant and minority health. 2016;18(5):966-70. Epub 2015/09/14. doi: 10.1007/s10903-015-0273-2. PubMed PMID: 26364054.

15. Bennett RJ, Brodine S, Waalen J, Moser K, Rodwell TC. Prevalence and Treatment of Latent Tuberculosis Infection Among Newly Arrived Refugees in San Diego County, January 2010–October 2012. American journal of public health. 2014;104(4):e95-e102. doi: 10.2105/AJPH.2013.301637. PubMed PMID: PMC4025726.

16. Georgia Department of Public Health. Georgia Tuberculosis Report 2014 [cited 2017 April 16]. Available from: https://dph.georgia.gov/sites/dph.georgia.gov/files/2014%20GA%20TB%20Report%20FINAL3.pdf.

17. World Health Organization. Guidelines on the management of latent tuberculosis infection 2015 [cited 2017 April 16]. Available from: http://apps.who.int/iris/bitstream/10665/136471/1/9789241548908_eng.pdf?ua=1&ua=1.

18. Centers for Disease Control and Prevention. Latent Tuberculosis Infection:A guideline for Primary Healthcare Providers 2013 [cited 2017 April 16]. Available from:

https://www.cdc.gov/tb/publications/ltbi/pdf/targetedltbi.pdf.

19. United Nations High Commissioner for Refugees. Who is a refugee 2017 [cited 2017 April 16]. Available from: http://www.unrefugees.org/what-is-a-refugee/.

20. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement. American journal of respiratory and critical care medicine. 2000;161(4 Pt 2):S221-47. Epub 2000/04/14. doi: 10.1164/ajrccm.161.supplement_3.ats600. PubMed PMID: 10764341.

21. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. The New England journal of medicine. 2011;365(23):2155-66. Epub 2011/12/14. doi: 10.1056/NEJMoa1104875. PubMed PMID: 22150035.

22. Centers for Disease Control and Prevention. Core Curriculum on Tuberculosis 2016 [cited 2017 April 16]. Available from: https://www.cdc.gov/tb/education/corecurr/.

23. Centers for Disease Control and Prevention. Reported Tuberculosis in the United States, 2015 [cited 2017 April 16]. Available from: https://www.cdc.gov/tb/statistics/reports/2015/pdfs/2015_surveillance_report_fullreport.pdf.

24. Centers for Disease Control and Prevention. A strategic plan for the elimination of tuberculosis in the United States. MMWR Morbidity and mortality weekly report. 1989;38(16):269-72. Epub 1989/04/28. PubMed PMID: 2495428.

25. Cantwell MF, Snider DE, Jr., Cauthen GM, Onorato IM. Epidemiology of tuberculosis in

the United States, 1985 through 1992. Jama. 1994;272(7):535-9. Epub 1994/08/17. PubMed PMID: 8046808.

26. Tuberculosis elimination revisited: obstacles, opportunities, and a renewed commitment. Advisory Council for the Elimination of Tuberculosis (ACET). MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports. 1999;48(Rr-9):1-13. Epub 1999/09/15. PubMed PMID: 10485562.

27. Castro KG, Marks SM, Chen MP, Hill AN, Becerra JE, Miramontes R, et al. Estimating tuberculosis cases and their economic costs averted in the United States over the past two decades. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2016;20(7):926-33. Epub 2016/06/12. doi: 10.5588/ijtld.15.1001. PubMed PMID: 27287646; PubMed Central PMCID: PMCPMC4992985.

28. World Health Organization. Use of high burden country lists for TB by WHO in the post-2015 era [cited 2017 April 16]. Available from: http://www.who.int/tb/publications/global_report/high_tb_burdencountrylists2016-2020.pdf.

29. Migration Policy Institute tabulations of U.S. Department of Homeland Security. U.S. Immigration Trends [cited 2017 April 16]. Available from: http://www.migrationpolicy.org/programs/data-hub/us-immigration-trends.

30. Centers for Disease Control and Prevention. Refugee Health Guidelines 2013 [cited 2017 April 16]. Available from: https://www.cdc.gov/immigrantrefugeehealth/guidelines/refugee-guidelines.html.

31. Christine K. Olson WMS, Elizabeth D. Barnett. Newly Arrived Immigrants & Refugees 2014 [cited 2017 April 16]. Available from:

https://wwwnc.cdc.gov/travel/yellowbook/2016/advising-travelers-with-specific-needs/newly-arrived-immigrants-refugees.

32. Recommendations for prevention and control of tuberculosis among foreign-born persons. Report of the Working Group on Tuberculosis among Foreign-Born Persons. Centers for Disease Control and Prevention. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports. 1998;47(Rr-16):1-29. Epub 1998/10/06. PubMed PMID: 9760223.

33. Centers for Disease Control and Prevention. Interferon-Gamma Release Assays (IGRAs) - Blood Tests for TB Infection 2016 [cited 2017 April 16]. Available from: https://www.cdc.gov/tb/publications/factsheets/testing/igra.htm.

34. Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection - United States, 2010. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports. 2010;59(Rr-5):1-25. Epub 2010/06/26. PubMed PMID: 20577159.

35. Lönnroth K, Migliori GB, Abubakar I, D'Ambrosio L, de Vries G, Diel R, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. The European respiratory journal. 2015;45(4):928-52. doi: 10.1183/09031936.00214014. PubMed PMID: PMC4391660.

36. de Vries G, van Hest NA, Baars HW, Sebek MM, Richardus JH. Factors associated with the high tuberculosis case rate in an urban area. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2010;14(7):859-65. Epub 2010/06/17. PubMed PMID: 20550769.

37. de Vries G, Baars HW, Sebek MM, van Hest NA, Richardus JH. Transmission classification model to determine place and time of infection of tuberculosis cases in an urban area. Journal of clinical microbiology. 2008;46(12):3924-30. Epub 2008/10/10. doi: 10.1128/jcm.00793-08. PubMed PMID: 18842933; PubMed Central PMCID: PMCPMC2593293.

38. Kamper-Jorgensen Z, Andersen AB, Kok-Jensen A, Bygbjerg IC, Thomsen VO, Lillebaek T. Characteristics of non-clustered tuberculosis in a low burden country. Tuberculosis (Edinburgh, Scotland). 2012;92(3):226-31. Epub 2012/03/13. doi: 10.1016/j.tube.2012.02.001. PubMed PMID: 22406154.

39. McClintock AH, Eastment M, McKinney CM, Pitney CL, Narita M, Park DR, et al. Treatment completion for latent tuberculosis infection: a retrospective cohort study comparing 9 months of isoniazid, 4 months of rifampin and 3 months of isoniazid and rifapentine. BMC infectious diseases. 2017;17(1):146. Epub 2017/02/16. doi: 10.1186/s12879-017-2245-8. PubMed PMID: 28196479.

40. Porco TC, Lewis B, Marseille E, Grinsdale J, Flood JM, Royce SE. Cost-effectiveness of tuberculosis evaluation and treatment of newly-arrived immigrants. BMC public health. 2006;6:157. Epub 2006/06/21. doi: 10.1186/1471-2458-6-157. PubMed PMID: 16784541; PubMed Central PMCID: PMCPMC1559699.

41. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent Mycobacterium tuberculosis infection. MMWR Morbidity and mortality weekly report. 2011;60(48):1650-3. Epub 2011/12/14. PubMed PMID: 22157884.

42. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Recommendations and reports : Morbidity and mortality weekly

report Recommendations and reports. 2000;49(Rr-6):1-51. Epub 2000/07/06. PubMed PMID: 10881762.

43. Ferebee SH, Mount FW, Murray FJ, Livesay VT. A CONTROLLED TRIAL OF ISONIAZID PROPHYLAXIS IN MENTAL INSTITUTIONS. The American review of respiratory disease. 1963;88:161-75. Epub 1963/08/01. doi: 10.1164/arrd.1963.88.2.161. PubMed PMID: 14045220.

44. Mount FW, Ferebee SH. The effect of isoniazid prophylaxis on tuberculosis morbidity among household contacts of previously known cases of tuberculosis. The American review of respiratory disease. 1962;85:821-7. Epub 1962/06/01. doi: 10.1164/arrd.1962.85.6.821. PubMed PMID: 14476668.

45. Comstock GW, Ferebee SH, Hammes LM. A controlled trial of community-wide isoniazid prophylaxis in Alaska. The American review of respiratory disease. 1967;95(6):935-43. Epub 1967/06/01. doi: 10.1164/arrd.1967.95.6.935. PubMed PMID: 6026165.

46. Fox GJ, Dobler CC, Marais BJ, Denholm JT. Preventive therapy for latent tuberculosis infection-the promise and the challenges. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2016. Epub 2016/11/23. doi: 10.1016/j.ijid.2016.11.006. PubMed PMID: 27872018.

47. Kopanoff DE, Snider DE, Jr., Caras GJ. Isoniazid-related hepatitis: a U.S. Public Health Service cooperative surveillance study. The American review of respiratory disease. 1978;117(6):991-1001. Epub 1978/06/01. doi: 10.1164/arrd.1978.117.6.991. PubMed PMID: 666111.

48. Menzies D, Long R, Trajman A, Dion MJ, Yang J, Al Jahdali H, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis

infection: a randomized trial. Annals of internal medicine. 2008;149(10):689-97. Epub 2008/11/20. PubMed PMID: 19017587.

49. Chan PC, Yang CH, Chang LY, Wang KF, Lu BY, Lu CY, et al. Latent tuberculosis infection treatment for prison inmates: a randomised controlled trial. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2012;16(5):633-8. Epub 2012/03/14. doi: 10.5588/ijtld.11.0504. PubMed PMID: 22410137.

50. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. The American review of respiratory disease. 1992;145(1):36-41. Epub 1992/01/01. doi: 10.1164/ajrccm/145.1.36. PubMed PMID: 1731596.

51. Menzies D, Dion MJ, Rabinovitch B, Mannix S, Brassard P, Schwartzman K. Treatment completion and costs of a randomized trial of rifampin for 4 months versus isoniazid for 9 months. American journal of respiratory and critical care medicine. 2004;170(4):445-9. Epub 2004/06/03. doi: 10.1164/rccm.200404-478OC. PubMed PMID: 15172892.

52. Stagg HR, Zenner D, Harris RJ, Munoz L, Lipman MC, Abubakar I. Treatment of latent tuberculosis infection: a network meta-analysis. Annals of internal medicine. 2014;161(6):419-28. Epub 2014/08/12. doi: 10.7326/m14-1019. PubMed PMID: 25111745.

53. Targeted Tuberculin Skin Testing and Treatment of Latent Tuberculosis Infection in Children and Adolescents. Pediatrics. 2011;114(Supplement 4):1175.

54. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. International Union Against Tuberculosis Committee on

Prophylaxis. Bulletin of the World Health Organization. 1982;60(4):555-64. Epub 1982/01/01. PubMed PMID: 6754120; PubMed Central PMCID: PMCPMC2536088.

55. Control and prevention of tuberculosis in the United Kingdom: code of practice 2000. Joint Tuberculosis Committee of the British Thoracic Society. Thorax. 2000;55(11):887-901. Epub 2000/10/26. PubMed PMID: 11050256; PubMed Central PMCID: PMCPMC1745632.

56. Spyridis NP, Spyridis PG, Gelesme A, Sypsa V, Valianatou M, Metsou F, et al. The effectiveness of a 9-month regimen of isoniazid alone versus 3-and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. Clinical Infectious Diseases. 2007;45(6):715-22.

57. Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2005;40(5):670-6. Epub 2005/02/17. doi: 10.1086/427802. PubMed PMID: 15714411.

58. Taylor Z, Nolan CM, Blumberg HM. Controlling tuberculosis in the United States. Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports. 2005;54(Rr-12):1-81. Epub 2005/11/04. PubMed PMID: 16267499.

59. Bennett DE, Courval JM, Onorato I, Agerton T, Gibson JD, Lambert L, et al. Prevalence of tuberculosis infection in the United States population: the national health and nutrition examination survey, 1999-2000. American journal of respiratory and critical care medicine. 2008;177(3):348-55. Epub 2007/11/09. doi: 10.1164/rccm.200701-057OC. PubMed PMID: 17989346.

60. Vozoris NT, Batt J. Change in the Prevalence of Testing for Latent Tuberculosis Infection in the United States: 1999–2012. Canadian respiratory journal. 2016;2016:1850879. doi: 10.1155/2016/1850879. PubMed PMID: PMC4904560.

61. Hirsch-Moverman Y, Shrestha-Kuwahara R, Bethel J, Blumberg HM, Venkatappa TK, Horsburgh CR, et al. Latent tuberculous infection in the United States and Canada: who completes treatment and why? The International Journal of Tuberculosis and Lung Disease. 2015;19(1):31-8. doi: 10.5588/ijtld.14.0373.

62. Yamin A, Bornstein E, Hensel R, Mohamed O, Kempker RR. Predictors of Latent Tuberculosis Infection Treatment After Introduction of a New Regimen: A Retrospective Cohort Study at an Inner City Clinic. Open forum infectious diseases. 2016;3(4):ofw082. Epub 2016/10/21. doi: 10.1093/ofid/ofw082. PubMed PMID: 27757409; PubMed Central PMCID: PMCPMC5066457.

63. Subedi P, Drezner KA, Dogbey MC, Newbern EC, Yun K, Scott KC, et al. Evaluation of latent tuberculous infection and treatment completion for refugees in Philadelphia, PA, 2010-2012. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2015;19(5):565-9. Epub 2015/04/14. doi: 10.5588/ijtld.14.0729. PubMed PMID: 25868025.

64. Rennert-May E, Hansen E, Zadeh T, Krinke V, Houston S, Cooper R. A Step toward Tuberculosis Elimination in a Low-Incidence Country: Successful Diagnosis and Treatment of Latent Tuberculosis Infection in a Refugee Clinic. Canadian respiratory journal. 2016;2016:7980869. Epub 2016/07/23. doi: 10.1155/2016/7980869. PubMed PMID: 27445565; PubMed Central PMCID: PMCPMC4904499.

65. Hirsch-Moverman Y, Daftary A, Franks J, Colson PW. Adherence to treatment for latent

tuberculosis infection: systematic review of studies in the US and Canada. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2008;12(11):1235-54. Epub 2008/10/18. PubMed PMID: 18926033.