J Immigrant Minority Health (2016) 18:966–970
DOI 10.1007/s10903-015-0273-2

ORIGINAL PAPER

Latent Tuberculosis Infection Among Immigrant and Refugee Children Arriving in the United States: 2010

Eboni M. Taylor[1,2] · John Painter[1,2] · Drew L. Posey[1,2] · Weigong Zhou[1,2] · Sharmila Shetty[1,2]

Published online: 12 September 2015

Abstract Immigrants and refugees age 2–14 years entering the United States from countries with estimated tuberculosis (TB) incidence rate ≥20 per 100,000 population are screened for TB. Children with TB disease are treated before US arrival. Children with positive tuberculin skin tests (TST), but negative TB evaluation during their pre-immigration examination, are classified with latent TB infection (LTBI) and are recommended for re-evaluation post-arrival. We examined post-immigration TB evaluation and therapy for children arriving with LTBI. We reviewed medical exam data from immigrant children with medical conditions and all refugee children arriving during 2010. Medical examination data were available for 67,334 children. Of these, 8231 (12 %) had LTBI pre-immigration; 5749 (70 %) were re-evaluated for TB post-immigration, and 64 % were retested by TST or IGRA. The pre-immigration LTBI diagnosis was changed for 38 % when retested by TST and for 71 % retested by IGRA. Estimated LTBI therapy initiation and completion rates were 68 and 12 %. In this population, testing with IGRA may limit the number of children targeted for therapy. Increased pre-immigration TB screening with post-immigration follow-up evaluation leading to completion of LTBI therapy should be encouraged to prevent TB reactivation.

✉ Eboni M. Taylor
ETaylor1@cdc.gov

[1] Division of Global Migration and Quarantine, National Center of Emerging Zoonotic and Infectious Diseases, United States Centers for Disease Control and Prevention, 1600 Clifton Road, NE, Mailstop E-04, Atlanta, GA 30333, USA

[2] United States Public Health Service Commissioned Corps, Washington, DC, USA

Keywords Pediatric · Tuberculin skin test · Interferon gamma release assay · Migrants

Background

Despite a 6.4 % decrease in the rate of new tuberculosis (TB) cases in the US from 2010 to 2011, foreign-born person living in the United States continue to be disproportionately affected by TB [1]. In 2011, a total of 6546 TB cases were reported among foreign-born persons, and the rate of incident TB cases among foreign-born persons in the United States was 12 times greater than among US-born persons [1]. Thus, one crucial component of TB elimination in the United States is addressing differences between TB rates in foreign- and US-born persons [1].

In 2011, approximately 80 % of foreign-born persons with TB were diagnosed with TB after being in the United States for more than 2 years, consistent with reactivation of latent tuberculosis infection (LTBI) acquired abroad [1]. Because LTBI treatment reduces the potential for progressing to active disease, LTBI screening and treatment, particularly among foreign-born persons, has become a critical part of the strategy for eliminating TB disease in the United States [2–6].

In 2007, the Centers for Disease Control and Prevention's (CDC) Division of Global Migration and Quarantine (DGMQ) published updated requirements for pre-immigration TB screening in prospective migrants to the United States [also known as the culture and directly observed therapy (CDOT) TB Technical Instructions] which included screening with tuberculin skin test (TST) or interferon gamma release assay (IGRA) for children 2–14 years of age living in countries with an estimated tuberculosis

incidence rate of ≥20 cases per 100,000 [7]. By the end of 2010, 30 countries had implemented these Technical Instructions. This TB screening provides a unique opportunity to diagnose children with LTBI prior to their arrival and increase the number of infected children who can receive preventive TB treatment upon arrival in the United States [7, 8]. We analyzed data from CDC's Electronic Disease Notification System (EDN) to assess post-immigration evaluations and TB therapy for children who entered the United States after being diagnosed with LTBI during the pre-immigration medical examination.

Methods

We obtained data on age, country of origin, pre-immigration screening results, and post-immigration tuberculosis follow-up from EDN, a web-based system that provides state and local health departments with access to the pre-immigration medical exam results. The pre-immigration medical exam is required for all immigrants and refugees immigrating to the United States, but a post-immigration health assessment is only recommended and is suggested to occur within 90 days of arrival. EDN notifications are available for all refugee arrivals. For immigrant arrivals, EDN notifications are only available for those with a medical condition of public health significance, such as LTBI. Health departments report TB evaluation and treatment outcomes to CDC through the TB follow-up module of EDN.

To determine the age and country-specific frequencies of arrivals, the numbers were extracted from EDN for refugees and from the Department of Homeland Security (DHS) for immigrants. EDN only includes immigrants with medical conditions, so DHS data were required to obtain the denominators for immigrants [9].

LTBI was defined as having a positive TST result (≥10 mm induration) or a positive IGRA result, normal chest radiograph, and otherwise negative TB evaluation. Post-immigration follow-up was considered reported if a TB follow-up worksheet had been initiated in the EDN system. We reviewed pre-immigration medical exam information and post-immigration TB follow-up data for immigrant and refugee children 2–14 years of age who arrived in the United States during the 2010 calendar year from countries that had implemented the 2007 technical instructions [10].

We calculated the prevalence of LTBI diagnosed during the pre-immigration exam among immigrant and refugee children arrivals in 2010. TB screening results from the post-immigration visit were evaluated for persons with LTBI. LTBI prevalence and demographic characteristics among immigrants and refugees were compared for statistically significant differences by the Chi square test. Analyses were done in SAS Enterprise Guide, version 5.1. Reported p values are two-sided and were not adjusted for multiple testing.

This analysis was determined during human subjects review to be part of CDC's public health surveillance activities and therefore approval by an institutional review board was not required.

Results

During the 2010 calendar year, 67,334 children 2–14 years of age who were screened under the 2007 tuberculosis Technical Instructions arrived in the United States: 53,939 (80 %) were immigrants, and 13,395 (20 %) were refugees. A total of 8231 (12 %) of the 67,334 children included in this analysis were diagnosed with LTBI during the pre-immigration exam (Fig. 1). Overall, LTBI prevalence rates were higher among immigrants (7400/53,939 = 14 %) than refugees (831/13,395 = 6 %) ($p = 0.002$).

Demographic characteristics of children diagnosed with LTBI during their pre-immigration exam are presented by visa type in Table 1. More than half (55 %) of these children were 10–14 years of age, and there was an equal proportion of males and females. Refugees were significantly more likely than immigrants to have been born in a country with a TB incidence ≥100 cases per 100,000 (86 vs. 64 %; $p < 0.0001$).

About 70 % of children who arrived in the United States with a diagnosis of LTBI had a post-immigration follow-up exam reported to CDC, and post-immigration follow-up reporting was similar for immigrants and refugees. Of the 5749 children who arrived with a diagnosis of LTBI and had post-immigration follow-up, 3299 (57 %) were diagnosed with LTBI in the United States at the post-immigration exam. Approximately 0.26 % (15/5749) of children who arrived with a diagnosis of LTBI and had post-immigration follow-up were *Mycobacterium tuberculosis* culture-positive.

The type of TB test conducted in the United States and the post-immigration LTBI diagnosis is shown in Table 2. Of those with LTBI with a post-immigration LTBI evaluation visit reported, 35 % received only a TST, 23 % received only an IGRA, 6 % received both a TST and IGRA, and 36 % had no post-immigration TB test documented. The majority of those retested with TST only (61 %) had their pre-immigration diagnosis of LTBI confirmed in the United States, while 71 % of those retested with an IGRA had their pre-immigration diagnosis of LTBI reversed (Table 2). Seventy-two percent of children who received both tests in the United States had discordant results (a positive TST result and negative IGRA result).

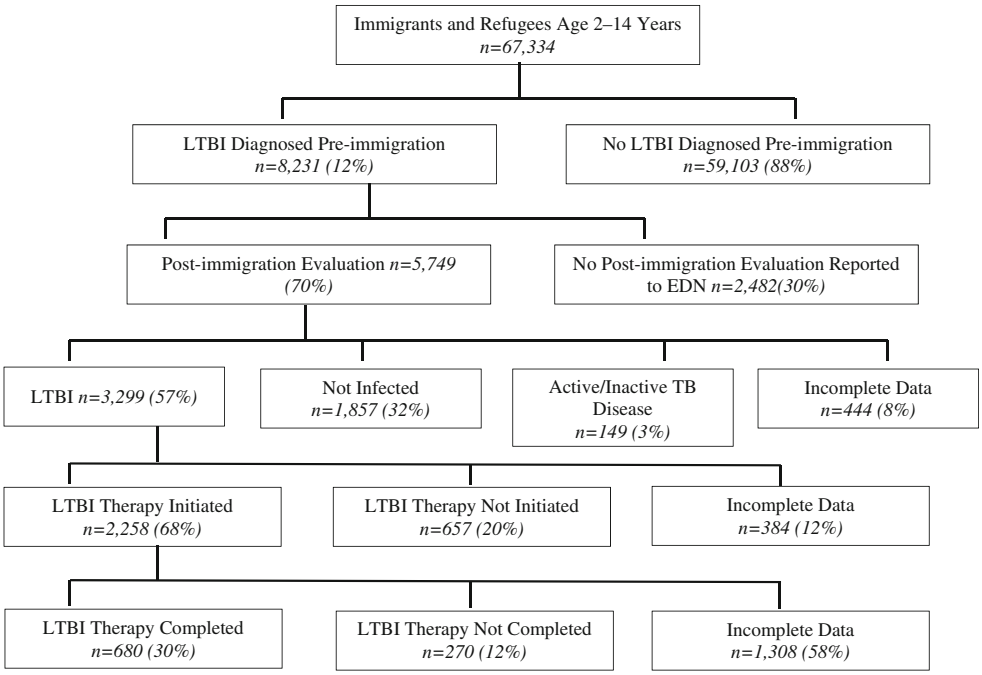

Fig. 1 Post-immigration TB follow-up continuum for immigrants and refugees age 2–14 years diagnosed with LTBI pre-immigration in countries implementing the 2007 TB TIs in calendar year 2010

Table 1 Characteristics of immigrants and refugees age 2–14 years diagnosed with LTBI pre-immigration by visa type (N = 8231)

	Immigrant N = 7400 N (%)	Refugee N = 831 N (%)
Age (years)		
2–4	847 (11)	77 (9)
5–9	2464 (33)	237 (29)
10–14	4089 (55)	517 (62)
Sex		
Male	3741 (51)	441 (53)
Female	3659 (49)	390 (47)
TB incidence in birth country (cases per 100,000)[a]		
20–99	2662 (36)	117 (14)
≥100	4729 (64)	714 (86)
Post-immigration follow-up reported		
No	2207 (30)	275 (33)
Yes	5193 (70)	556 (67)

[a] Effective sample size = 8222; 9 children missing birth country data

We estimated that LTBI therapy initiation and completion rates were 68 and 30 %, respectively (Fig. 1). LTBI therapy initiation was slightly greater among refugees than immigrants, but therapy completion was the same for both groups (data not shown). Of note, 12 % of children had missing data for LTBI therapy initiation, and 58 % had missing data for LTBI therapy completion. On the basis of calculations assuming complete compliance and complete refusal for those with missing data, the true LTBI therapy initiation rate could be 61–72 % and the true LTBI therapy completion rate could be 19–56 %.

Discussion

It is estimated that 4 % of the total US population has LTBI [11], although the rate among newly arriving immigrant and refugee children has been less well described. We found that 12 % of children arriving in the United States during 2010 were diagnosed with LTBI during the pre-immigration medical examination. Foreign-born persons in the United States continue to experience disproportionately higher TB infection rates than persons born in the United States. Pre-immigration LTBI screening combined with follow-up evaluation in the United States presents a unique opportunity to prevent tuberculosis among children arriving from high-TB incidence countries.

Through follow-up with US health providers, 2258 immigrant and refugee children who arrived in the United States with LTBI in 2010 initiated LTBI therapy and more than 600 children had documented completion. Completing therapy for LTBI benefits the infected individual and society as a whole by preventing active, infectious tuberculosis cases from developing [12].

We found the proportion of missing data in EDN increased at each step of the post-immigration TB follow-up continuum, thus our LTBI therapy initiation and completion rates of 68 and 12 %, respectively, are subject to

Table 2 Post-immigration LTBI evaluation and LTBI diagnosis by type of TB test conducted among arrivals with a pre-immigration LTBI diagnosis (N = 5159)

Type of post-immigration test	Post-immigration LTBI evaluation		Final LTBI diagnosis	
	N	(% Total)	N	(% Diagnosed)
TST only	1807	(35)	1108	(61)
IGRA only	1168	(23)	339	(29)
TST and IGRA	317	(6)	79	(25)
No post-immigration test conducted	1867	(36)	1677	(90)

Effective sample size = 5159 with a pre-immigration LTBI diagnosis and post-immigration follow-up reported in EDN; 5749 had post-immigration follow-up reported in EDN; 590 missing diagnosis and/or post-immigration testing information

bias. Approximately 12 % of children with LTBI in our analysis had missing data for treatment initiation and 59 % had missing data for treatment completion. Published estimates of LTBI therapy completion rates among foreign-born and recent immigrant children in the United States vary from 38 to 82 % [13–16], which overlaps with the rates of our sensitivity analysis (19–56 %).

A majority (64 %) of the children included in our analysis were re-tested for TB during their post-immigration exam, most commonly by using a TST. In its guidance on testing newly arrived refugees for TB, CDC advises against repeating a TST if a documented previous positive TST result is available [17]. In 1996, CDC recommended disregarding prior Bacillus Calmette–Guérin (BCG) immunization when interpreting a positive TST [18]. But following the approval by the US Food and Drug Administration of two IGRAs, the recommendation was revised in 2010 to state that IGRAs were the preferred initial test for persons who are likely to have received BCG vaccine [4]. CDC guidance for retesting a BCG-vaccinated patient who has a positive TST with an IGRA is worded cautiously, stating that it may be considered in BCG vaccinated populations where a positive IGRA may encourage compliance with therapy or when a patient has otherwise low risk for progression [4]. In this analysis, most of the TST-positive children retested by using IGRA had a negative IGRA result, possibly due to prior BCG vaccination or other nontuberculous mycobacteria [19, 20]. Through decreased false positive tests, we estimate that IGRA could reduce by 71 % the proportion of children who require LTBI therapy, which may be another important consideration when considering retesting BCG vaccinated populations.

IGRAs are not the preferred testing method for use in children younger than 5 years old [4, 17]. On the basis of the recommendations, we would have expected to see a difference in the type of TB test conducted during the post-immigration exam by age. However, 15 % of children who received an IGRA during their post-immigration exam were in the 2–4 years age group, and the type of test administered during the post-immigration exam did not differ by age.

Our analysis has limitations. First, our results may not be generalizable to all children entering the United States because we only included children who received their pre-immigration medical examination from the 30 countries following the revised 2007 TB TIs as of January 1, 2010; nonimmigrant visitors were also not included. Second, results may be biased by missing data. Because there is no standardized schedule for when to report TB follow-up data to EDN, some states report data when the initial evaluation is completed, while others do not report any information to EDN until follow-up is complete. The low numbers for treatment initiation and completion we observed could either be a true lack of LTBI treatment initiation and completion or a lack of documentation (i.e. missing data). Although CDC DGMQ issues guidelines for US health care providers examining newly arriving refugees [17], post-immigration exams are not required and the content and reporting of these exams varies by state.

CDC is currently working with state and local healthcare providers to improve forms for collecting post-immigration TB follow-up information and develop specific instructions for how and when to report data to EDN. Finally, reasons for not initiating or completing LTBI therapy are not currently captured in EDN, thus we were unable to examine them in this analysis.

By virtue of their young age, children with LTBI have the largest lifetime (i.e., cumulative) risk for activation of latent tuberculosis (assuming no other risk factors), and are therefore an important group to target for preventive therapy. Currently, many immigrant and refugee children with LTBI are not completing preventive therapy. In this population, probably vaccinated with BCG, testing with an IGRA may limit the number of children targeted for preventive therapy.

Acknowledgments We thank the staff of the CDC's Electronic Disease Notification (EDN) team for updating and managing the CDC's notification system for tuberculosis in immigrants and refugees, the staff of CDC's quarantine stations for collecting information about overseas medical examinations, the panel physicians for performing overseas tuberculosis screening, and the staff of state and local health departments for conducting follow-up evaluations.

References

1. Miramontes R, Pratt R, Price SF, Jeffries C, Navin TR, Oramasionwu GE. Trends in tuberculosis—United States, 2011. MMWR Morb Mortal Wkly Rep. 2012;61(11):181–5.
2. Al-Orainey IO. Diagnosis of latent tuberculosis: can we do better? Ann Thorac Med. 2009;4(1):5.
3. Linas BP, Wong AY, Freedberg KA, Horsburgh CR. Priorities for screening and treatment of latent tuberculosis infection in the United States. Am J Respir Crit Care Med. 2011;184(5):590–601.
4. Mazurek GH, Jereb JA, Vernon A, LoBue P, Goldberg S, Castro KG. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection, United States, 2010. MMWR Recomm Rep. 2010;59(RR05);1–25.
5. Rose DN. Benefits of screening for latent *Mycobacterium tuberculosis* infection. Arch Intern Med. 2000;160(10):1513.
6. Hill A, Becerra J, Castro K. Modelling tuberculosis trends in the USA. Epidemiol Infect. 2012;140(10):1862.
7. Centers for Disease Control and Prevention. CDC immigration requirements: technical instructions for tuberculosis screening and treatment using cultures and directly observed therapy. Atlanta, GA: US Department of Health and Human Services; 2009.
8. Cohn DL, O'Brien RJ, Geiter LJ, Gordin F, Hershfield E, Horsburgh C. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR Morb Mortal Wkly Rep. 2000;49(6):1–54.
9. US Department of Homeland Security, C.a.B.P. TECS, arrival file: fiscal years 2010 to 2011. Washington: C.a.B.P. US Department of Homeland Security; 2012.
10. Centers for Disease Control and Prevention: Technical instructions implementation. 2011 February 5, 2013; (cited 2013 February 14). http://www.cdc.gov/immigrantrefugeehealth/exams/ti/panel/tuberculosis-implementation.html.
11. Centers for Disease Control and Prevention: Latent tuberculosis infection: a guide for primary health care providers 2010 November 24, 2010; (cited 2013 April 15). http://www.cdc.gov/tb/publications/ltbi/diagnosis.htm.
12. Hirsch-Moverman Y, Bethel J, Colson P, Franks J, El-Sadr W. Predictors of latent tuberculosis infection treatment completion in the United States: an inner city experience. Int J Tuberc Lung Dis. 2010;14(9):1104–11.
13. Coly A, Morisky D. Predicting completion of treatment among foreign-born adolescents treated for latent tuberculosis infection in Los Angeles. Int J Tuberc Lung Dis. 2004;8(6):703–10.
14. LoBue PA, Moser KS. Use of isoniazid for latent tuberculosis infection in a public health clinic. Am J Respir Crit Care Med. 2003;168(4):443–7.
15. Young J, Edick T, Klee D, O'Connor ME. Successful treatment of pediatric latent tuberculosis infection in a community health center clinic. Pediatr Infect Dis J. 2012;31(9):e147–51.
16. Hovell MF, Sipan CL, Blumberg EJ, Hofstetter CR, Slymen D, Friedman L, Moser K, Kelley NJ, Vera AY. Increasing Latino adolescents' adherence to treatment for latent tuberculosis infection: a controlled trial. Am J Public Health. 2003;93(11):1871–7.
17. Centers for Disease Control and Prevention: Guidelines for the U.S. domestic medical examination for newly arriving refugees. 2012 September 24, 1012; (cited 2013 April 15). http://www.cdc.gov/immigrantrefugeehealth/guidelines/domestic/domestic-guidelines.html.
18. Advisory Council for the Elimination of Tuberculosis (ACET). The Role of BCG Vaccine in the Prevention and Control of Tuberculosis in the United States. A Joint Statement by the Advisory Council for the Elimination of Tuberculosis and the Advisory Committee on Immunization Practices. MMWR Recomm Rep. 1996;45(RR-4):1–27.
19. Farhat M, Greenaway C, Pai M, Menzies D. False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria?[Review Article]. Int J Tuberc Lung Dis. 2006;10(11):1192–204.
20. Zwerling A, Behr MA, Verma A, Brewer TF, Menzies D, Pai M. The BCG World Atlas: a database of global BCG vaccination policies and practices. PLoS Med. 2011;8(3):e1001012.