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Estimated Latent Tuberculosis Infection Prevalence and Tuberculosis Reactivation Rates Among Non-U.S.-Born Residents in the United States, from the 2011–2012 National Health and Nutrition Examination Survey

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Abstract

Increased testing and treatment of latent tuberculosis infection (LTBI) among US-residents who were born (or lived) in countries with high rates of TB can hasten progress toward TB elimination. We calculated LTBI prevalence using QuantiFERON®-TB Gold In-Tube results from the 2011 to 2012 National Health and Nutrition Examination Survey (NHANES). LTBI prevalence was highest for persons born in India (31.7%, 95% confidence interval [21.2, 44.5]). Non-Hispanic white persons had the lowest LTBI prevalence (6.3% [1.9, 18.9]). TB reactivation rate, defined as the number of TB cases not associated with recent transmission per 100 person-years of life with LTBI, was highest for persons born in Vietnam [0.183 (0.117, 0.303)]. Reactivation rates were lower among persons who had resided in the United States for ≥ 10 years than among those who had resided for < 10 years. Results among high risk populations can guide LTBI targeted testing and treatment among non-U.S.-born residents.

Keywords

Latent tuberculosis infection; LTBI; TB reactivation; Non-U.S.-born

Introduction

Molecular epidemiology studies suggest that the majority of non-U.S.-born tuberculosis (TB) patients likely developed TB disease because of reactivation from TB infection acquired more than 2 years ago rather than through recent transmission from a person with TB disease [1–4]. Strategies to control both recent TB transmission and reactivation of latent TB infection (LTBI) to TB disease have long been considered essential components of TB control and elimination programs [5–7]. However, recent mathematical modeling studies

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suggest that with current TB prevention and control efforts the United States will not reach TB elimination (annual TB incidence less than 1 per million [5]) before the end of the twenty-first century [8, 9]. Increased testing and treatment for LTBI among non-U.S.-born persons in the United States has the potential to be one of the most effective interventions in moving closer to TB elimination [8–10].

In 2011–2012 there were an estimated 4–7 million non-U.S.-born persons in the United States with LTBI [11]. Over half of all non-U.S.-born TB patients reported since 2010 have been from China, India, Mexico, Philippines and Vietnam [12, 13]. The United States Preventive Services Task Force (USPSTF) now recommends targeted testing and treatment for LTBI among high risk populations, including non-U.S.-born persons from countries with elevated TB prevalence [14, 15].

We estimated LTBI prevalence and TB reactivation rates per 100 person-years (PY) among all non-U.S.-born persons as well as specific non-U.S.-born populations, including persons from the five aforementioned countries. Our study is one of several published studies that estimate LTBI prevalence using 2011–2012 NHANES data [11, 16–19]. Unlike previous studies, our LTBI prevalence estimates were adjusted for interferon gamma release assay (IGRA) TB blood test sensitivity and specificity. Additionally, ours is the only study we are aware of that provides LTBI and TB reactivation estimates for persons from China, India, Mexico, Philippines and Vietnam. Because population-level LTBI data by country of birth are not publicly available [20], we also analyzed publicly available data by race/ethnicity in order to assess its use as a proxy for country of birth. The results of this study could be used to determine which high-risk populations should be prioritized for targeted testing and treatment efforts and for informing mathematical models of the effectiveness of such efforts.

Methods

The 2011–2012 NHANES is the most recent cycle to include LTBI testing for all participants ≥ 6 years old [21]. LTBI testing consisted of both a tuberculin skin test (TST) and IGRA blood test (QuantiFERON®-TB Gold In-Tube [QFT-GIT]). TST has been found to have lower specificity and lower positive predictive value than QFT-GIT among non-U.S.-born populations [22]. Therefore, for the purposes of this study we used only the results from the QFT-GIT. Details of NHANES methodology are described elsewhere [11].

QFT-GIT positive was defined according to the manufacturer's guidelines based on the following criteria:

- Nil value ≤ 8.0 international units (IU) gamma interferon/ml AND
- TB antigen value minus nil value ≥ 0.35 IU gamma interferon/ml AND
- TB antigen value minus nil value ≥ 25% of the nil value

We calculated QFT-GIT positive prevalence (QFT-GITpos) by adjusting for the complex survey design using 2-year weights supplied by the National Center for Health Statistics (NCHS). LTBI prevalence was calculated from QFT-GITpos prevalence by incorporating QFT-GIT test sensitivity and specificity. We used the USPSTF systematic review estimates

for QFT-GIT sensitivity of 80% (95% confidence interval [CI] 77%, 84%) and specificity of 97% (94%, 99%) [14]. LTBI prevalence was calculated as:

$$\text{LTBI prevalence} = ([\text{QFT-GITpos}] - [1 - \text{specificity}]) \div (\text{sensitivity} - [1 - \text{specificity}])$$

Standard errors for sensitivity and specificity were estimated by dividing half the CI-width by the standard normal 97.5 percentile of 1.96. CIs for LTBI prevalence were calculated via first-order Taylor series approximation applied to the estimates for QFT-GITpos, sensitivity, and specificity.

TB reactivation rates per 100 PY were defined as the number of TB patients reported to the National Tuberculosis Surveillance System (NTSS) [13] in 2011–2012 who were ≥ 6 years old divided by the number of PY at risk for reactivation multiplied by 2 to adjust for the 2-year NHANES cycle:

$$\text{Reactivation rate} = \#\text{ TB cases} \div (\text{population} \times \text{LTBI prevalence} \times 2\text{years})$$

For example, the numerator value for all non-U.S.-born persons was 11,806 TB cases and the denominator values were 39,701,000 non-U.S.-born persons in the population, 0.169 LTBI prevalence (converted from 16.9%) and two person-years for the study period of January 1, 2011–December 31, 2012 ($11{,}806 \div [39{,}701{,}000 \times 0.169 \times 2] = 0.00088$, which we multiplied by 100 to convert to 0.088 per 100 PY). CIs for reactivation rates were obtained by dividing the ratio of cases to population by CI limits for LTBI prevalence.

The number of TB cases (numerator) excludes patients who were not alive at TB diagnosis (and were not likely to have a culture for genotyping), who developed TB disease within 6 months of arrival in the United States, or whose TB disease was attributed to recent transmission (based on a plausible-source case approach described elsewhere) [23]. The numbers of TB patients for all numerators were restricted to match the corresponding population for analyses (e.g., in the United States for less than 10 years or 10 or more years). Population estimates were obtained from the U.S. Census Bureau's American Community Survey, 2011 (Supplemental Table 1) [24]. Both the NHANES and NTSS datasets include information about country of birth and years since arrival in the United States.

We estimated LTBI prevalence for all non-U.S.-born persons and separately for persons born in Mexico, Vietnam, India, China or the Philippines; aggregated for persons born in these five countries; aggregated for non-U.S.-born Hispanic, non-Hispanic Asian, non-Hispanic black or Hispanic persons; and non-U.S.-born non-Hispanic white persons. All analyses of NHANES data involving nonpublic country of birth data were conducted at the NCHS Research Data Center (RDC) in Atlanta, Georgia (https://www.cdc.gov/rdc/index.htm). We analyzed the combined Hispanic, non-Hispanic Asian, non-Hispanic black population as a high-risk comparison group using publicly available data. Due to NCHS confidentiality policy, RDC results were suppressed for all categories and subcategories with a cell size < 5 [20].

LTBI prevalence and TB reactivation rates were calculated for each population stratified by persons in the United States for less than 10 years (which would include all non-U.S.-born persons between the ages of 6 and 9 years old and persons over 9 years old who had been in the United States for less than 10 years) or 10 or more years (includes only non-U.S.-born persons 10 or more years old). Ten years was selected as the cutoff to increase cell sizes and prevent data suppression, and for consistency with another recently published study that examined TB among persons in the United States for less than 10 years or 10 or more years [25].

Relative standard error (RSE) was used as a measure of the reliability of statistical estimates, consistent with other studies that estimated LTBI prevalence using 2011–2012 NHANES data [11, 16–19]. It is defined as the ratio of standard error to point estimate. An RSE > 30% was deemed to indicate an unreliable estimate.

All analyses were conducted using R statistical software [26] and the R survey package [27, 28].

The NCHS Research Ethics Review Board approved NHANES (Protocol #2011-17) [29]. NTSS data were collected as part of public health disease surveillance activities and therefore did not require institutional review board approval.

Results

A total of 9756 noninstitutionalized persons participated in the 2011–2012 NHANES cycle, of which 1955 (20.0%) were non-U.S.-born persons ≥ 6 years old. QFT-GIT results were available for 1788 (91.5%) of these non-U.S.-born participants, of whom 346 (19.4%) had positive results.

During 2011–2012, 20,439 cases of TB were reported in NTSS [12], of which 17,327 met our definition of being presumed reactivated TB cases among persons ≥ 6 years old. Of these, 11,806 (68%) occurred among non-U.S.-born persons.

LTBI Prevalence and TB Reactivation Rates

We estimated that 16.9% (95% CI 13.1, 21.5) of the noninstitutionalized, non-U.S.-born population ≥ 6 years old in the United States had LTBI (Table 1). LTBI prevalence point estimates were highest for persons born in India (31.7% [21.2, 44.5]) and lowest for those born in Mexico (15.3% [10.6, 21.6]). The combined non-Hispanic Asian, non-Hispanic black, or Hispanic population had a LTBI prevalence point estimate of 19.1% (15.0, 23.9), whereas for non-Hispanic white persons it was 6.3% (1.9, 18.9).

Using data from NHANES and NTSS, we estimated that the overall reactivation rate for non-U.S.-born persons was 0.088 per 100 PY (0.069, 0.114) (Table 1). Persons born in Vietnam had a reactivation rate of 0.183 per 100 PY (0.117, 0.303), followed by persons from China (0.073 per 100 PY [0.051, 0.110]) and persons from Mexico (0.071 per 100 PY [0.050, 0.102]). Non-Hispanic Asian, non-Hispanic black, or Hispanic population had a reactivation rate of 0.091 per 100 PY (0.073, 0.116). Non-Hispanic white persons had the lowest reactivation rate (0.062 per 100 PY [0.021, 0.203]).

LTBI Prevalence and TB Reactivation by Years in the United States

LTBI prevalence for persons who had been in the United States for < 10 years ranged from 5.9% (1.1, 25.3) among persons born in Mexico to a high of 39.7% (18.9, 65.0) among persons born in the Philippines (Table 2). Among persons in the United States for ≥ 10 years, LTBI prevalence was highest among persons from China (34.8% [26.4, 44.2]) and lowest among non-Hispanic white persons (9.0 [4.5, 17.4]) (Table 3). With the exception of persons from the Philippines or India, prevalence point estimates among persons who had resided in the United States for ≥ 10 years were higher than persons who had resided for < 10 years. Median age was higher among persons who had resided in the United States for ≥ 10 years (Supplemental Table 2).

Among persons who had been in the United States for < 10 years, reactivation rates ranged from a high of 0.367 per 100 PY (0.085, 1.906) among persons from Mexico to a low of 0.116 per 100 PY (0.061, 0.264) among persons from China. Persons from the Philippines had the highest rate of reactivation among persons in the United States ≥ 10 years (0.116 per 100 PY [0.075, 0.192]); reactivation was lowest among non-Hispanic white persons (0.028 per 100 PY [0.014, 0.056]). For all populations, reactivation rates were lower among persons who had resided in the United States for ≥ 10 years than among those who had resided for < 10 years. Reactivation rates among persons who had been in the United States for < 10 years could not be calculated for persons born in Vietnam due to cell suppression or for non-Hispanic white persons because sample size was too small to calculate reliable estimates.

Discussion

Our study provides estimates of LTBI prevalence and TB reactivation in the United States for persons from five high-risk countries using nationally representative data from NHANES. Because NHANES LTBI test data by country of birth are not publicly available and are based on small sample sizes, we also estimated LTBI prevalence and TB reactivation rates from publicly available data for non-U.S.-born non-Hispanic Asian, non-Hispanic black, or Hispanic persons together. We found that although point estimates varied among the top five countries, their combined LTBI prevalence and TB reactivation rates were similar to those for the combined non-Hispanic Asian, non-Hispanic black, or Hispanic population. This suggests that the combined non-U.S.-born non-Hispanic Asian, non-Hispanic black, or Hispanic population may be used as a proxy to estimate LTBI prevalence and TB reactivation rates among non-U.S.-born populations at high risk for TB. Aggregating persons from high risk countries into a single population obscures the differences that can be seen at the country level, but is a reasonable approach given the limitations in obtaining country-specific data.

In order to exclude non-U.S.-born persons who are not from countries with elevated TB disease rates from our high-risk population, we created a separate population for non-U.S.-born, non-Hispanic white persons. Although point estimates for LTBI and TB reactivation were lower among the non-U.S.-born non-Hispanic white than the other respective non-U.S.-born populations, the low number of persons in the former category prevented us from making broader conclusions. However, the difference is notable and demonstrates that although there might be non-U.S.-born, non-Hispanic white persons from high TB burden

countries included in this population, it is more likely that most of the non-U.S.-born, non-Hispanic white population comprised persons from low TB burden countries [15]. For the purpose of our study, exclusion of non-U.S.-born, non-Hispanic white persons from the high-risk population, even if some of them are from countries with a higher TB burden, likely does not affect the LTBI and TB reactivation estimates among high-risk non-U.S.-born populations and allowed for more accurate calculations among high-risk non-U.S.-born persons.

For additional context we compared our country-specific LTBI prevalence estimates with LTBI estimates in countries of origin. We calculated LTBI prevalence by dividing estimated numbers of persons with LTBI [30] by country-specific population estimates from the World Health Organization [31]. Our estimates of LTBI prevalence among non-U.S.-born persons residing in the United States were similar to in-country LTBI prevalence estimates for China, India, and Mexico (26.1% [21.1, 30.6], 27.2% [26.1, 29.0], 13.3% [7.4, 19.1], respectively). However, for the Philippines and Vietnam in-country LTBI estimates (40.1% [37.1, 43.3], 38.8% [30.1, 44.9], respectively) were considerably higher than our estimated LTBI prevalence among persons from those countries in the United States. Similar to TB disease, for which in-country TB rates among the five countries ranged from 2 times higher in Mexico to 14 times higher in the Philippines than among persons from those countries in the United States [32], in-country populations are not necessarily representative of their U.S.-residing peers.

Our reactivation rates for non-U.S.-born persons are slightly lower than reactivation rates reported by Shea et al. (0.098 per 100 PY [0.096, 0.10]) [33]. Our calculations used NHANES IGRA positivity (rather than TST), which explains our lower estimates. For the sensitivity and specificity values we used, LTBI estimates will be greater than the corresponding IGRA test positivity estimate whenever the latter is > 13%. This in turn results in a lower TB reactivation rate than what would result from using IGRA positivity. A recent model that accounted for declining reactivation over time since infection and higher reactivation rates at older ages reported reactivation rates that are much higher than ours [10]. However, that study was based on four high-burden states with large non-U.S.-born populations (California, Florida, New York, and Texas) and therefore may not be generalizable to the entire U.S. population. Our results indicated that people with the highest reactivation rates among residents who had been in the United States for < 10 years were from Mexico, the Philippines, and India. Furthermore, the highest percentages of TB patients who had been in the United States for < 10 years are from these same countries [25]. Among persons who had been in the United States for ≥ 10 years, we estimated that the highest reactivation occurred among those from the Philippines, Vietnam, and India. The Philippines and Vietnam had the second and third highest percentages (following Mexico) of TB patients who had been in the United States for ≥ 10 years [25].

The LTBI prevalence estimate for all non-U.S.-born persons from our study (16.9%) differs from estimates published by other studies (15.9%) [11, 18] because we adjusted for test sensitivity and specificity whereas the other studies did not. The difference in prevalence estimates is more striking for non-U.S.-born, non-Hispanic white persons (6.3% in our study compared to 9.4% and 9.2% in the other studies) [11, 18]; however, this difference is likely a

combination of small sample size and correction for IGRA sensitivity and specificity which results in an even lower LTBI prevalence estimate.

Our study had several limitations. There were insufficient numbers of non-U.S.-born persons to allow us to obtain prevalence and reactivation rates by risk factor for each population (e.g., persons in the country for < 10 years for Vietnam or non-Hispanic white populations). Analyzing data based on region rather than country might have increased the numbers, however, region information is not publicly available so does not offer a practical solution to the challenge of obtaining restricted NHANES data. Our approach assumed a constant rate of progression from LTBI to TB and did not take into consideration time since or age at infection. When calculating CIs for reactivation rates, we implicitly assumed that NTSS case counts were complete and accurate (based on published estimates stating such [34]) and did not take into account the variability in ACS population estimates as these are typically small compared to the other sources of variability in the calculation. Also, we assumed QFT-GIT sensitivity and specificity did not vary by population. NHANES only collects data from civilian, noninstitutionalized persons; therefore, non-U.S.-born persons who were living in congregate settings are not included in the study.

We used the plausible-source case approach [23] to exclude cases due to recent transmission from our reactivation rate calculation. This approach is based on conventional genotyping methods, which can only be applied to culture-confirmed cases and may have limited molecular resolution for strain discrimination in some areas and populations (e.g., closed, remote populations) [12]. These overestimates of recent transmission would result in underestimates of reactivation. In the U.S.-Mexico border region, whole genome-sequencing results have shown more genetic diversity among *M. tuberculosis* strains than is apparent by conventional genotyping methods [12]. Therefore, our study also may have underestimated reactivation among Mexico-born TB patients residing in the United States.

Our study helps improve the understanding of LTBI and TB reactivation among non-U.S.-born populations residing in the United States. Our results suggest that using publicly available data by origin and race/ethnicity to estimate LTBI prevalence and TB reactivation among a high-risk non-U.S.-born population is as accurate as, and more feasible than, obtaining restricted data by specific country of birth. Additionally, our estimates could be used as parameter inputs in TB modeling studies and provide data that may help TB control programs target high-risk populations for targeted testing and treatment as recommended by USPSTF [14].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

LTBI Prevalence and TB reactivation rates by non-U.S.-born population, United States, 2011–2012

Non-U.S.-born population[a]	LTBI prevalence % (95% confidence interval)	TB reactivation rate (95% confidence interval) per 100 person-years
India	31.7 (21.2, 44.5)	0.087 (0.062, 0.131)
China	30.3 (19.9, 43.1)	0.073 (0.051, 0.110)
Philippines	27.0 (17.8, 38.7)	0.148 (0.103, 0.224)
Vietnam	20.3 (12.2, 31.7)	0.183 (0.117, 0.303)
Mexico	15.3 (10.6, 21.6)	0.071 (0.050, 0.102)
Top 5 countries (Aggregate)[b]	20.0 (15.6, 25.2)	0.091 (0.072, 0.117)
Non-Hispanic Asian, Non-Hispanic Black, or Hispanic	19.1 (15.0, 23.9)	0.091 (0.073, 0.116)
Non-Hispanic White[c]	6.3 (1.9, 18.9)	0.062 (0.021, 0.203)
All non-U.S.-born	16.9 (13.1, 21.5)	0.088 (0.069, 0.114)

[a] Persons ≥ 6 years old

[b] Results for China, India, Mexico, Philippines, and Vietnam as a single population

[c] Relative standard error > 30% indicates an unreliable estimate

Table 2

LTBI prevalence and TB reactivation rates among persons who have been in the United States for < 10 years, by non-U.S.-born population, 2011–2012

Non-U.S.-born population in the United States less than 10 years[a]	LTBI prevalence % (95% confidence interval)	TB reactivation rate (95% confidence interval) per 100 person-years
Philippines[b]	39.7 (18.9, 65.0)	0.187 (0.114, 0.393)
India	34.7 (19.8, 53.3)	0.128 (0.083, 0.224)
China[b]	24.3 (10.7, 46.2)	0.116 (0.061, 0.264)
Mexico[b]	5.9 (1.1, 25.3)	0.367 (0.085, 1.906)
Vietnam[c]	–	–
Top 5 countries (Aggregate)[d]	15.6 (9.5, 24.5)	0.207 (0.132, 0.339)
Non-Hispanic Asian, Non-Hispanic Black, or Hispanic	14.8 (9.5, 22.2)	0.256 (0.170, 0.397)
Non-Hispanic White[c]	–	–
All	12.4 (7.5, 20.0)	0.269 (0.167, 0.448)

[a] Includes all non-U.S.-born persons between 6 and 9 years old and those persons over 9 years old who had been in the United States for less than 10 years

[b] Relative standard error > 30% indicates an unreliable estimate

[c] Results for Vietnam are not available due to cell suppression; results for non-Hispanic white are not available because sample size was too small to calculate estimates

[d] Results for China, India, Mexico, Philippines, and Vietnam as a single population

Table 3

LTBI prevalence and TB reactivation rates among persons who have been in the United States for ≤ 10 years, by non-U.S.-born population, 2011–2012

Non-U.S.-born populations in the United States 10 or more years[a]	LTBI prevalence % (95% confidence interval)	TB reactivation rate (95% confidence interval) per 100 person-years
China	34.8 (26.4, 44.2)	0.045 (0.036, 0.060)
India	29.7 (15.5, 49.4)	0.053 (0.032, 0.102)
Philippines	23.2 (14.0, 36.0)	0.116 (0.075, 0.192)
Vietnam	21.3 (13.2, 32.4)	0.106 (0.069, 0.170)
Mexico	17.8 (12.5, 24.7)	0.043 (0.031, 0.061)
Top 5 Countries (Aggregate)[b]	21.4 (16.8, 26.9)	0.056 (0.044, 0.071)
Non-Hispanic Asian, Non-Hispanic Black, or Hispanic	20.2 (16.2, 24.9)	0.048 (0.039, 0.059)
Non-Hispanic White[c]	9.0 (4.5, 17.4)	0.028 (0.014, 0.056)
All	18.4 (14.4, 23.1)	0.044 (0.035, 0.057)

[a] Includes non-U.S.-born persons 10 or more years old who had been in the United States for 10 or more years

[b] Results for China, India, Mexico, Philippines, and Vietnam as a single population

[c] Relative standard error > 30% indicates an unreliable estimate