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The Influence of Age at Arrival and Duration of Residence in US on Prevalence of Latent TB Infection

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Abstract

Rationale and Background: Screening for and treatment of latent tuberculosis infection (LTBI) among foreign-born persons living in the United States (U.S.) has been identified as an important public health priority. In order to reach the goal of tuberculosis (TB) elimination in the U.S., screening and treatment of LTBI will need to be expanded.

Objectives: To estimate the relationship between age at arrival in the U.S., among foreign-born persons, duration of U.S. residence and risk for LTBI, simultaneously.

Methods: We examined participants in the 1999-2000 and 2011-2012 NHANES surveys to assess the association between foreign birth, age, and length of time in the U.S. and prevalence of LTBI.

Results: Overall, 1.7% of U.S-born and 19.2% of foreign-born persons had LTBI. In unadjusted regression models, increasing age and shorter length of time in the U.S. were associated with increased prevalence of LTBI: OR=1.3 (1.2, 1.4) for every 10 year increase in age and OR=0.97 (0.84, 1.1) for every 10 year increase in of duration of years in U.S.

Conclusions: Both of these factors should be considered when prioritizing foreign-born populations for LTBI screening and treatment in the U.S.

Background

Reactivation of latent tuberculosis infection (LTBI) is the source of more than 80% of the cases of tuberculosis in the U.S [1,2]. In order to reach the goal of tuberculosis (TB) elimination in the U.S., screening and treatment of LTBI will need to be expanded [3,4]. A prime population for screening and treatment of LTBI is persons born in countries where TB is common, since they have a higher prevalence of a positive tuberculin skin test (TST), and prevalence of TST is a major determinant of the cost-effectiveness of such screening [5]. A recent report has documented that the risk for progression from LTBI to active TB disease among foreign-born persons is highest immediately after arrival in the U.S. but persists for many years after arrival [6]. However, there are no reports examining the relationship between age at arrival in the U.S., duration of U.S. residence, and risk for LTBI, simultaneously. Therefore, we estimated the interactions between age at arrival in the U.S., length of time in the U.S. and prevalence of LTBI.

Additional risk for progression from LTBI to TB disease is conferred by low weight or low body mass index (BMI) [7-9]. Incidence of active TB was found to be higher among underweight navy recruits with a positive TST from 1958-1967 in San Diego, and confirmed in a subsequent cohort of navy recruits [8]. However, it is unclear whether the increased BMI is also a risk factor for LTBI or only a risk factor for progression from LTBI to TB disease. A previous NHANES study did not show an association between BMI and LTBI, but this result could have been confounded by foreign birth [10]. Therefore, we also examined the relationship between BMI and a positive TST while controlling for foreign birth. Because the number of subjects who receive TST in a given NHANES survey is small, we pooled data from the two most recent NHANES TST surveys.

Methods

Study participants

Study participants included all respondents who completed the tuberculin skin testing (TST) component of the NHANES survey during either the 1999-2000 or the 2011-2012 cycles. NHANES survey methodology has been previously described in detail [4,11]. In brief, NHANES is an ongoing series of cross-sectional health examination surveys conducted by the National Center for Health Statistics (NCHS) within the Centers for Disease Control and Prevention (CDC) designed to assess the health and nutritional status of U.S. residents. Every year, approximately 5,000 non-institutionalized civilian U.S. residents of all ages complete detailed health interviews in their homes, and complete a comprehensive physical health examination in a mobile examination center [4,11]. Although each survey year represents a nationally representative sample, data are released in 2-

year cycles to ensure adequate sample size and protect confidentiality. Beginning in 1999, NHANES became a continuous, annual survey making it possible to combine two or more 2-year cycles for analysis. The data presented in this analysis are from the 1999-2000 and 2011-2012 NHANES because these are the two most recent survey cycles that included TB skin testing components.

Demographic variables

In NHANES, participant gender was recorded as "male" or "female", and self-reported race and ethnicity were categorized as "non-Hispanic black," "non-Hispanic white", "Mexican American", or "other Hispanic". Persons who did not fit these categories were classified as "Other Race, including Multi-racial". Although the 2011-2012 NHANES additionally included a category for non-Hispanic Asians, we did not include this category in order to be able to include the 1999-2000 survey cycle in our analyses. Participants' dates of birth were used by NHANES personnel to define participants' age at the time of the household interview, which preceded TST examinations by 2-6 weeks. Age in years is reported for survey participants between 1 and 79 years of age, and age in months is provided for participants less than 2 years old. Because reporting years of age in single years for adults aged 80 years old or older was determined to be a disclosure risk, participants aged 80 years or greater are categorized as being aged "80 years". The ratio of family income to poverty was used as a measure of household socioeconomic status, and was calculated by dividing the household income received in the previous 12 months by the poverty guidelines specific to each survey year set forth by the Department of Health and Human Services (HHS) for determining financial eligibility for certain federal programs such as Head Start and the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC). These ratios were adjusted for average family size for the interview year as determined by the U.S. Bureau of the Census [4]. Education level indicates the highest grade or level of education completed by participants.

Age of arrival in the U.S

Foreign born Survey respondents were asked to indicate the month and or year when they arrived in the U.S., and this information was used by NHANES personnel to categorize each participants' length of time spent in the U.S. into the following: less than 1 year, 1<5 years, 5<10 years, 10<15 years, 15<20 years, 20<30 years, 30<40 years, 40<50 years, and ≥ 50 years. Because the actual length of time spent in the U.S. was not available, we estimated participants' approximate age of arrival in the U.S. by subtracting the minimum, mid-point, and maximum values of their categorized length of time in the U.S. from their age at the time of the survey; we only report results from use of the mid-point value here.

Categorization of body mass index values

All NHANES participants at least 2 of age who participated in the physical examination portion of the survey were eligible for BMI measurement. Among 19,721 total NHANES participants, BMI values were recorded as a continuous variable for 17,059 persons. We examined BMI as a categorical measure, and for those 21 years of age and older, categorized as underweight (<18.5), normal (18.5-24.9), overweight (25-29.9) and obese (>30.0). Those 2 years of age to 20 years of age were categorized in the previously described categories using the CDC-Growth Age BMI charts [12]. The chart uses percentiles, and considers both gender and age. Underweight is defined as less than the 5th percentile, normal as between the 5th and 85th percentile, overweight defined as between the 85th and 95th percentile and lastly, obese as at or above the 95th percentile[12,13].

Identification of latent tuberculosis infection

NHANES survey data collected during 1999-2000 include demographic and TST results for 7,386 participants 1 year of age or older in whom TST was performed in via the Mantoux technique using 0.1 ml of purified protein derivative (PPD) S-1 (PPD-S), the reference standard tuberculin used in the U.S [14]. All TST tests were administered by trained NHANES phlebotomists and read by trained NHANES TST readers 48-72 hours after placement [4,11]. In 2011-2012, 6,128 NHANES participants 6 years of age and older consented to TST, and underwent skin testing with 0.1 ml of the commercially available tuberculin-purified protein derivative (PPD) product Tubersol. Additionally, 2011-2012 NHANES participants were also screened with an FDA-approved blood test, QuantiFERON®-TB Gold In Tube tests (QFT-GIT). NHANES participants from either survey cycle with a TST induration greater than or equal to 10 mm were classified as having LTBI, regardless of HIV infection status (because HIV status was unknown for NHANES participants).

Statistical analyses

The prevalence of LTBI was estimated overall, and by sex, race/ethnicity, age at interview, socioeconomic status, education level, and foreign birth. In addition, we estimated LTBI prevalence by age at interview separately in participants who were born in the U.S. and in those who were not; among those who were not born in the U.S., we also estimated LTBI prevalence by age at arrival. 95% confidence intervals (CI) around LTBI prevalence were estimated.

Next, we estimated crude and adjusted prevalence ratios, and associated 95% CI, describing the association between age at arrival in the U.S. and years in the U.S. among foreign-born persons. We also examined the effect of introducing an interaction term between age in years and years in the U.S.

Analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC). All analyses used methods set forth in the NHANES technical guidelines to account for NHANES sample design and weighting, and we applied the methods described by Bennett et al. to adjust for TST non-participation [4].

Results

Participation in the NHANES medical examination and TST

In the 1999-2000 survey, 8,832 individuals eligible for TST placement participated in the NHANES medical examination and 7,613 (86%) participants had a TST placed. Of those, 7,386 (97%) had their TST reactions read and measured. In the 2011-2012 survey, 7,821 individuals eligible for TST placement participated in the NHANES medical examination and 6,437 (82.3%) participants had a TST placed. Of those, 6,128 (95.2%) had their TST reactions read and measured.

LTBI prevalence

Based on our weighted analysis, we estimate that 4.3% of the civilian, no institutionalized U.S. population aged 6 years of age or older had LTBI in 1999-2000 and 2011-2012. Table 1 presents weighted, cross-sectional prevalence estimates of individuals with LTBI

in 1999-2000 and 2011-2012 overall and by selected demographic characteristics. Foreign born persons were estimated to have a higher prevalence of LTBI than those born in the U.S (19.1% (15.5 – 22.9) vs. 1.7% (1.2, 2.2), respectively). In Table 2, we examine weighted prevalence of LTBI among those who were foreign born, across age categories.

Characteristic	1999-2000 & 2011-2012 NHANES, Combined	
	No. of persons	LTBI Prevalence (%) (95% CI)
All Participants	847	4.3 (3.5, 5.1)
Sex		
Male	485	5.0 (4.0, 5.9)
Female	362	3.7 (2.8, 4.5)
Race/Ethnicity		
Non-Hispanic White	72	1.5 (0.9, 2.0)
Non-Hispanic Black	210	7.0 (5.6, 8.4)
Mexican	287	10.5 (7.3, 13.7)
Other Hispanic	121	12.2 (8.8, 15.6)
Other/Mixed Race	157	12.2 (8.7, 15.6)
Age Group (year)		
6-14	48	1.0 (0.5, 1.4)
15-24	85	2.4 (1.4, 3.5)
25-44	217	5.0 (3.7, 6.2)
45-64	317	6.0 (4.5, 7.5)
≥ 65	180	4.7 (3.4, 6.0)
Poverty Index		
PIR ≥ 1	499	3.5 (2.7, 4.4)
PIR <1	230	6.4 (5.0, 7.8)
Education Level		
<High school	436	7.2 (5.7, 8.7)
High school graduate	125	3.9 (2.8, 5.1)
Beyond high school	252	3.5 (2.8, 4.4)
Birthplace		
U.S.	281	1.7 (1.2, 2.2)
Outside of U.S.	565	19.1 (15.5, 22.9)
BMI*		
Underweight (<18.5)	16	2.6 (0.3, 4.8)
Normal (18.5-24.9)	284	4.0 (3.1, 4.9)
Overweight (25.0 – 29.9)	286	4.8 (3.8, 5.7)
Obese (≥ 30)	255	4.3 (3.1, 5.5)
Length of Time in U.S		
Less than 10 years	173	36.2 (27.2, 45.1)
10 <20 years	152	26.4 (21.9, 30.8)
20 <30 years	115	20.2 (13.5, 26.8)
≥ 30 years	114	17.3 (14.0, 20.6)

*BMI defined by using conventional CDC cut points, except for persons less than or equal to 20 years; BMI in children defined using CDC growth for age and gender charts

Table 1: Proportions of participants with latent tuberculosis infection (LTBI) overall and by selected demographic characteristics, NHANES 1999-2000 and 2011-2012.

Age Group	1999-2000, 2011-2012 NHANES Combined, U.S.-Born U.S Residents		1999-2000, 2011-2012 NHANES Combined, Foreign-Born U.S.Residents	
	No. of persons	LTBI Prevalence (%) (95% CI)	No. of persons	LTBI Prevalence (%) (95% CI)
<10 years	2	0.3 (0.0, 0.9)	3	4.7 (0.0, 12.3)
10<20 years	31	0.4 (0.1, 0.6)	63	9.4 (5.6, 13.3)
20<30 years	16	1.3 (0.5, 2.1)	51	12.6 (7.5, 17.6)
30<40 years	25	1.4 (0.7, 2.1)	90	21.3 (15.2, 27.4)
40<50 years	28	1.5 (0.5, 2.5)	111	23.3 (16.8, 29.9)
≥50 years	179	3.0 (1.9, 3.7)	247	23.4 (18.5, 28.3)

Table 2: LTBI Prevalence among NHANES Participants, by Location of Birth & Age at time of interview 1999-2000 and 2011-2012 Surveys

LTBI and BMI

In univariate analyses, LTBI occurred less frequently among persons with low BMI than among persons with normal or high BMI; this association disappeared, however, after multivariate analyses controlling for age, foreign birth, race/ethnicity and gender. Low BMI was associated with minimal decreased risk of LTBI, but this difference was not statistically significant (OR 0.99 (0.86, 1.14)).

LTBI and Age and Length of Time in the U.S

LTBI was found to increase with increasing age among both U.S.- and foreign-born residents, Among U.S.-born residents, the prevalence of LTBI ranged from 0.3% and 0.4% in those aged <10 years and 10<20 years, respectively, to 3.0% in those aged ≥ 50 years. Among foreign-born residents, the prevalence of LTBI ranged from 4.7% and 9.4% to 23.4% among residents in the same age groups.

Increasing age was significantly associated with increased prevalence of LTBI among foreign-born persons: OR=1.3 (1.2, 1.4) for every 10 year increase in age.

Length of time since arrival in the U.S. was also associated with LTBI in univariate analyses in the foreign-born population, with OR=0.97 (0.84, 1.1) for every 10 year increase in of duration of years in U.S.

Interaction between LTBI and age and length of time in the U.S

In logistic regression models examining the association between age and length of time in the U.S and LTBI prevalence, we observed an interaction between age and length of time in the U.S. and LTBI.

Therefore, we present stratified analyses in Table 3. The model shows an increase in the odds of LTBI for shorter amounts of time in the U.S., when examining by age category. For example, in the 20-30 year old age group, the odds of LTBI decrease, as a person stays in the U.S. for longer, by decade of length of time in the U.S. (0.87 (0.36, 2.07) versus 0.15 (0.02, 1.01)).

Age Group	Years in the U.S. (OR (95% CI))			
	0 - 10	10-20	20 - 30	30 – 40
0 - 10	--			
Oct-20	Ref	0.49 (0.28, 0.86)		
20 - 30	Ref	0.87 (0.36, 2.07)	0.15 (0.02, 1.01)	
30 - 40	Ref	0.59 (0.30, 1.17)	0.69 (0.29, 1.60)	0.41 (0.10, 1.65)
40 - 50	Ref	1.32 (0.56, 3.11)	1.27 (0.44, 3.71)	0.54 (0.17, 1.73)
50+	Ref	0.63 (0.28, 1.40)	1.21 (0.55, 2.68)	0.42 (0.24, 0.72)

Table 3: Odds ratios for LTBI, controlling for age, years in the U.S., and the interaction of age and years in the U.S., among Foreign-Born U.S. Residents, NHANES 1999-2000 & 2011-2012.

These prevalences are represented graphically in Figures 1-3. Figure 1 shows the prevalence of a positive TST among foreign-born persons, by age, without regard to time in the U.S. Figure 2 shows the prevalence of a positive TST by age at immigration to the U.S. without regard to age. Figure 3 shows the prevalence of a positive TST at current age, stratified by time in the U.S. As can be seen, LTBI prevalence decreases with increased duration in the U.S. after controlling for age for all age categories.

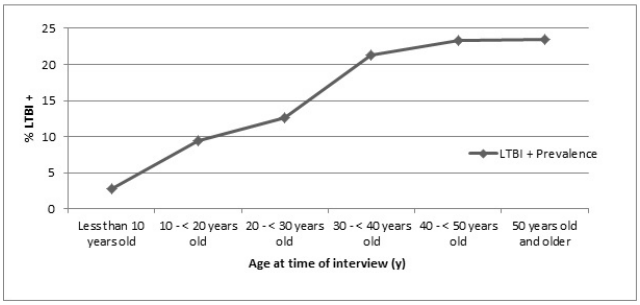

Figure 1: LTBI Prevalence among Foreign-Born U.S. Residents by Age at time of interview 1999-2000 and 2011-2012 NHANES

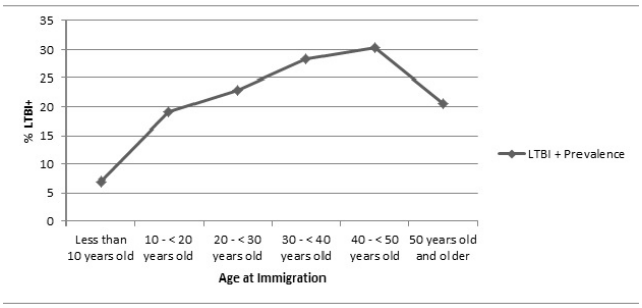

Figure 2: LTBI Prevalence among Foreign-Born U.S. Residents by Age of Arrival in the U.S. 1999-2000 and 2011-2012 NHANES

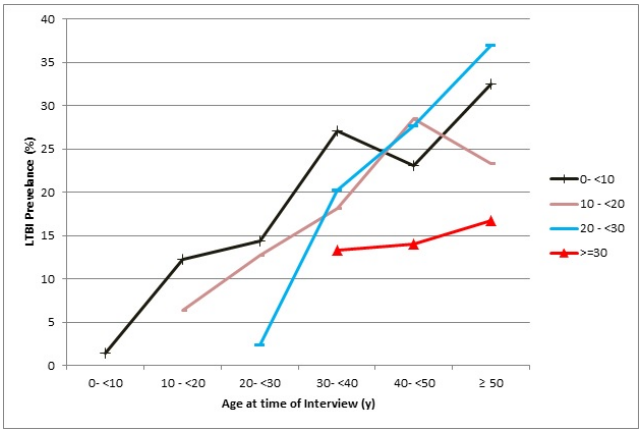

Figure 3: LTBI Prevalence among Foreign-Born U.S. Residents by Age at time of Interview in the U.S., stratified by Length of Time in the U.S. 1999-2000 and 2011-2012 NHANES

Discussion

This report demonstrates that increasing age and shorter length of time in the U.S. were associated with increasing LTBI prevalence among foreign-born persons from a survey-based, representative, national estimate across two different survey samples, 1999-2000 and 2011-2012. In the 1999-2000 and 2011-2012 combined sample, 19.1% of all foreign-born civilian, non-institutionalized persons in the U.S. aged 6 years of age or older had LTBI.

Age and length of time in the U.S. were the strongest predictors of LTBI among foreign-born persons, and had opposing effects. These effects were challenging to evaluate in a multivariate model and required inclusion of substantial interaction terms, resulting in a summary estimate that may not be clinically useful. Therefore, we also present the data graphically, which allows a clearer visualization of the effects. This output facilitates prediction of the likelihood of LTBI in a foreign-born person of a given age and length of time in the U.S. Prediction of the likely prevalence is important, as prevalence is one of the major drivers of the cost-effectiveness of Screening for LTBI [I5].

Although the two combined years of 1999-2000 and 2011-2012 provided approximately 19,700 persons, the prevalence of underweight by BMI classification was very low. We therefore had little precision to estimate the association between low BMI and LTBI. This is consistent with a report from an NHANES survey in 1971-1972 [10].

Our study has several potential limitations. First, we may have included some foreign born participants as having LTBI when in fact the TST reaction of 10 mm or greater was the result of prior BCG vaccination, rather than LTBI. This is of particular concern for children whose BCG was recent [15]. However, our analysis excluded persons under 6 years old, so most of the subjects with a history of BCG vaccination likely had BCG more than 10 years prior to the TST administration [15]. Moreover, in the U.S., the clinical definition of LTBI requiring preventative treatment for those who are foreign born is a TST reaction of 10 mm or greater, regardless of the BCG vaccine history [4]. Second, the use of the NHANES survey across combined years could have introduced bias, but the populations studied were quite similar. In the 1999-2000 survey, Mexican-Americans were specifically oversampled as a subgroup [4], whereas, in the 2011-2012 survey, Hispanics and non-Hispanic black and Asians were oversampled [11]. However, when combined with survey specific weighting, our population reflects the civilian, non-institutionalized U.S. foreign born subpopulation. Therefore, we believe that bias is unlikely. Third, length of time in the U.S. was collected as a categorical rather than a continuous variable and this provides us with a less precise measure of age at immigration. Finally, there is limited information about the country of origin of foreign born participants in the publically available datasets that we used. Therefore, we have a limited ability to determine whether the respondents, across both NHANES data release years, were from low or high TB prevalence countries, and whether they were likely to have received the BCG vaccine.

Despite these limitations, NHANES provides important information on the prevalence of LTBI in foreign-born individuals. The goal of elimination of TB in the U.S. will require increased efforts to diagnose and treat LTBI among the foreign-born, and a better understanding of the relationship between LTBI and age and length of time in the U.S. may contribute to a clearer focus for LTBI screening and treatment programs. Screening for LTBI among the foreign-born is likely to be more productive among foreign-born persons who are adults and have been in the U.S. for shorter periods of time.

Conflict of Interest Statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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