ORIGINAL ARTICLE

The Prevalence of Latent Tuberculosis Infection in the United States

James D. Mancuso[1], Jeffrey M. Diffenderfer[1,2], Bijan J. Ghassemieh[3], David J. Horne[3,4,5], and Tzu-Cheg Kao[1]

[1]Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences, Bethesda, Maryland; [2]Division of Preventive Medicine, Walter Reed Army Institute of Research, Silver Spring, Maryland; and [3]Division of Pulmonary and Critical Care Medicine, Department of Medicine, [4]Department of Global Health, and [5]Firland Northwest TB Center, University of Washington, Seattle, Washington

Abstract

Rationale: Individuals with latent tuberculosis infection (LTBI) represent a reservoir of infection, many of whom will progress to tuberculosis (TB) disease. A central pillar of TB control in the United States is reducing this reservoir through targeted testing and treatment.

Objectives: To estimate the prevalence of LTBI in the United States using the tuberculin skin test (TST) and an IFN-γ release assay.

Methods: We used nationally representative data from the 2011–2012 National Health and Nutrition Examination Survey (n = 6,083 aged ⩾6 yr). LTBI was measured by both the TST and QuantiFERON-TB Gold In-Tube test (QFT-GIT). Weighted population, prevalence, and multiple logistic regression were used.

Measurements and Main Results: The estimated prevalence of LTBI in 2011–2012 was 4.4% as measured by the TST and 4.8% by QFT-GIT, corresponding to 12,398,000 and 13,628,000 individuals, respectively. Prevalence declined slightly since 2000 among the U.S. born but remained constant among the foreign born. Earlier birth cohorts consistently had higher prevalence than more recent ones. Higher risk groups included the foreign born, close contact with a case of TB disease, and certain racial/ethnic groups.

Conclusions: After years of decline, the prevalence of LTBI remained relatively constant between 2000 and 2011. A large reservoir of 12.4 million still exists, with foreign-born persons representing an increasingly larger proportion of this reservoir (73%). Estimates and risk factors for LTBI were generally similar between the TST and QFT-GIT. The updated estimates of LTBI and associated risk groups can help improve targeted testing and treatment in the United States.

Keywords: latent tuberculosis; tuberculosis epidemiology; nutrition survey; tuberculin test; IFN-γ release tests

In 2014, there were 9,412 new tuberculosis (TB) cases reported in the United States (3.0 cases per 100,000 population) (1), a decrease of 48% from the rate in 2000 (5.8 per 100,000) (2). Despite 21 years of declining TB rates in the United States since 1993, the goal of TB elimination, defined as less than one case per million population, is unmet. An Institute of Medicine analysis concluded that continuing at current rates of TB decline, it would take 70 years or more to achieve elimination (3); this was confirmed by an analysis of recent TB trends (4).

Since the 1960s, a central pillar of TB control in the United States has been reducing the reservoir of infection through treatment of latent TB infection (LTBI) (5). Estimates that 80% of cases of TB disease arise from the progression of LTBI to TB disease have been confirmed by the use of genotyping (6–9). The risk of progression is estimated as 2.4% in the first 5 years after infection (10), but risk is higher among children, those coinfected with HIV, and other groups (9, 11). The Institute of Medicine and the Advisory Committee for the Elimination of Tuberculosis have highlighted the importance of preventing TB by targeted testing and treatment of LTBI among groups at high risk of progression to TB disease (3, 12).

Nationally representative estimates of the prevalence of LTBI are important in

(Received in original form August 26, 2015; accepted in final form February 10, 2016)

Partially supported by the Uniformed Services University of the Health Sciences intramural grant R087U7.

The opinions or assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Department of Defense, the U.S. Army, or the Uniformed Services University of the Health Sciences.

Author Contributions: All authors have provided substantial contributions to the conception and design of this work and each has participated in drafting and revising the manuscript. All have given final approval of the version to be published and agree to be accountable for all aspects of the work.

Correspondence and requests for reprints should be addressed to James D. Mancuso, M.D., Dr.P.H., Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814. E-mail: james.mancuso@usuhs.edu

Am J Respir Crit Care Med Vol 194, Iss 4, pp 501–509, Aug 15, 2016

Originally Published in Press as DOI: 10.1164/rccm.201508-1683OC on February 11, 2016
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: In 2000, the prevalence of latent tuberculosis infection in the United States was 4.2% and had declined by 60% during the previous 28 years. However, certain subpopulations, such as close contact with cases of tuberculosis disease and the foreign born, had a high prevalence of infection. Since 2000, the rate of tuberculosis disease in the United States has decreased by 48%, but the current prevalence of latent tuberculosis infection is unknown.

What This Study Adds to the Field: The prevalence of latent tuberculosis in the United States remained constant at 4.4% in 2011–2012 based on a nationally representative survey. This estimate was based on measurement by the tuberculin skin test; the prevalence was slightly higher (4.8%) when measured by an IFN-γ release assay. A large reservoir of infection still exists in the United States (12.4 million people) and foreign-born persons represent an increasingly larger proportion (73%) of this reservoir. This study provides data to guide targeted testing programs, one of the central pillars of tuberculosis control and elimination in the United States.

assessing the burden of disease and changes in these risk groups for targeted testing. The National Health and Nutrition Examination Survey (NHANES) is a large, representative, population-based survey that provides estimates of disease prevalence in the United States. Before 2011–2012, testing for LTBI in NHANES was most recently performed in 1999–2000. That study, which was based on the tuberculin skin test (TST), demonstrated a prevalence of 4.2% and higher risk among foreign-born and certain racial and ethnic groups (13). However, the current prevalence of LTBI is uncertain. Additionally, although the prevalence of LTBI was measured in the 1971–1972 NHANES and again in 1999–2000 using the TST, no nationally representative estimates had been obtained using an IFN-γ release assay (IGRA). The 2011–2012 NHANES again contained an LTBI component that included the TST and an IGRA, the QuantiFERON-TB Gold In-Tube test (QFT-GIT). The primary objective of this study was to provide an updated estimate of the prevalence of LTBI in the United States, and an updated assessment of risk groups. A secondary objective was to compare prevalence estimates and risk groups for LTBI measured by the QFT-GIT with those obtained using the TST.

Methods

Survey Methodology

The study was an analysis of 2011–2012 NHANES data obtained from a publicly available web source (14). The NHANES is a series of cross-sectional, nationally representative surveys. A complex, stratified, multistage probability cluster sampling design was used to select a nationally representative sample of the U.S. noninstitutionalized population. Over-sampled subgroups in the 2011–2012 survey were Hispanic persons, non-Hispanic black persons, non-Hispanic Asian persons, persons at or below 130% of the poverty level, and persons aged 80 years and older (15). Components of the survey interview used in this study included demographic, socioeconomic, and TB questionnaires.

The laboratory component consisted of TB testing using both TST and QFT-GIT. TST measurements were performed for each participant by technicians trained in these guidelines, and Tubersol (Sanofi, Bridgewater, NJ) brand PPD was used for all testing. Although the standard PPD, PPD-Seibert, was used in the previous two NHANES studies, Tubersol has been shown to be equivalent in potency and interpretation of TST results (16). Otherwise, TST methodology was identical to the 1999–2000 NHANES (17), which included a minor modification of CDC guidelines (18); that is, the TST was read 46–76 hours after administration to facilitate patient scheduling. Among participants who had at least one TST result, 46.8% had measurements recorded separately by two or more readers who were blinded to one another's measurements. TST induration was calculated as the average of up to three recorded TST results; if only one TST result was recorded, the single result was used. For comparability with previously published NHANES studies, a positive TST was defined as a reading of induration greater than or equal to 10 mm (13). QFT-GIT was performed and interpreted in accordance with CDC guidelines for the use of IGRAs (19). HIV testing was also performed in the NHANES among the subset of participants aged 18–59 years.

Statistical Analysis

We adapted the analysis plan from the methods used in a previous analysis of NHANES TB data (13). The primary outcome of interest was presence of LTBI as measured by a positive TST or QFT-GIT. To ensure comparability of estimates, only those with valid results for both TST and QFT-GIT were eligible for inclusion in this analysis; an indeterminate QFT-GIT was considered a valid result. Because the TST and QFT-GIT were only performed on participants aged 6 years and older, participants younger than 6 years old were not eligible for inclusion in the analysis. Those with a history of a severe reaction to a previous TST or a severe skin condition (e.g., burns or active eczema) were also excluded from TST. SAS version 9.3 (SAS Institute Inc., Cary, NC) and SAS-callable SUDAAN version 11.0 (RTI International, Research Triangle Park, NC) was used in all analyses. Prevalence estimates for the U.S. population were calculated using NHANES 2011–2012 Medical Examination Center 2-year weight to adjust for probability of selection and nonresponse to the survey. The weights were further adjusted for nonparticipation in TB testing (either TST or QFT-GIT) so that it would represent the applicable study population (20). The missing TST and QFT-GIT data are considered a type of survey nonresponse that can bias the prevalence estimates.

The National Center for Health Statistics recommends the use of weight adjustment to reduce nonresponse bias in the NHANES (21), as was done in previous studies (13, 22). We adjusted the weights using the SUDAAN procedure WTADJUST according to race, age, income, and sex stratified by U.S. born or foreign born. Estimated weighted population or subpopulation (in thousands) or prevalence of LTBI with 95% confidence interval (CI) was reported if applicable. Weighted multiple logistic regression was used to assess the association between potential risk groups and LTBI outcomes

using odds ratios and corresponding 95% CIs; the Wald chi-square test was used to decide if all the subgroups defined by a categorical variable were equal or not. The significance level was set at 5% (or a $P < 0.05$). Analyses were performed separately using LTBI outcomes from TST and QFT-GIT test results, and some models were stratified by birthplace (United States vs. foreign). For comparability with the 1971–1972 and 1999–2000 NHANES prevalence estimates in trend analysis, we also analyzed the subpopulation of all three surveys between the ages of 25 and 74. The study did not require Institutional Review Board approval because it used publicly available, deidentified data.

Results

The 2011–2012 NHANES included 9,756 subjects, of whom 8,161 were ages 6 years and older and thus eligible for the TB testing component of the study. Of those, 7,107 (87%) had a valid QFT-GIT result and 6,128 (75%) had a valid TST result. The 87 (1.4%) of 6,437 respondents who reported a history of a severe reaction to the TST were excluded from testing; the remaining subjects were excluded because of inability to return for TST reading 46–76 hours after administration. Five (0.5%) of those without a valid QFT-GIT result were due to one or more missing values among the three required measurements (TB antigen, mitogen, nil); the remainder were excluded because of refusal of QFT-GIT testing. The 6,083 (75%) who had valid results for both TST and QFT-GIT were the population used in the primary analyses to ensure comparability of the estimates. Without these exclusions, the prevalence estimates would have been slightly lower with the TST and slightly higher with the QFT-GIT, but they did not affect the results or conclusions of the study (data not shown). An additional 19 (0.3%) of the participants had a valid but indeterminate QFT-GIT result.

The prevalence of LTBI in the United States was 4.4% (95% CI, 3.1–6.1%) as measured by a positive TST. Prevalence was slightly higher (4.8%; 95% CI, 4.0–5.8%) when measured by the QFT-GIT. This corresponded to an affected population of 12,398,000 with LTBI by the TST or 13,628,000 by the QFT-GIT. The trend in prevalence of LTBI in the United States using the TST in 25- to 74-year-old population is seen in Figure 1, stratified by location of birth (U.S.- vs. foreign-born). The overall prevalence of LTBI decreased only slightly between 1999–2000 and 2011–2012 (from 5.8 to 5.7%). However, a continued decline was seen among the US born (2.5–1.7%), while remaining relatively constant among the foreign born (21.1–22.3%).

Table 1 shows LTBI prevalence according to patient characteristics, comparing the estimates obtained using the TST with those from the QFT-GIT. Findings were generally similar between the two tests. Overall, and among the U.S.-born population, LTBI prevalence estimates were higher using the QFT-GIT compared with the TST. However, LTBI prevalence was lower among the foreign born when using the QFT-GIT versus the TST (15.9 vs. 19.8%). This combination resulted in a higher proportion of foreign born among the TST positives (73%) compared with the QFT-GIT positives (53%). By ethnicity, Asians had the highest LTBI prevalence of any racial or ethnic group, for whom TST estimates were slightly higher than QFT-GIT in this group (21.3 vs. 17.0%). Additionally, although the prevalence of TST positivity decreased in the 65+ age group, the prevalence of QFT-GIT positivity continued to increase in this age group. The effect of birth cohort is shown in Table 2. TST positivity was strongly associated with birth cohort, with a greater risk of infection among earlier birth cohorts. Within each birth cohort, age was also seen to be associated with increased TST positivity up to about age 60, and afterward began to decrease.

Prevalence estimates were stratified by country of birth in Table 3. Again the estimates were generally higher using the QFT-GIT among the U.S.-born population but were higher with the TST among the foreign-born population. TST positivity decreased in the 65+ age group only among the foreign-born population; it remained constant among the U.S. born. In contrast, QFT-GIT positivity continued to increase among both U.S.- and foreign-born populations in this age group. Logistic regression models were performed using both TST and QFT-GIT and are shown in Table 4. The QFT-GIT and TST models were generally similar. The effect of race/ethnicity was attenuated among the foreign born compared with the U.S. born and with the QFT-GIT compared with the TST. The association of increasing age with increasing odds of TST positivity was attenuated in the

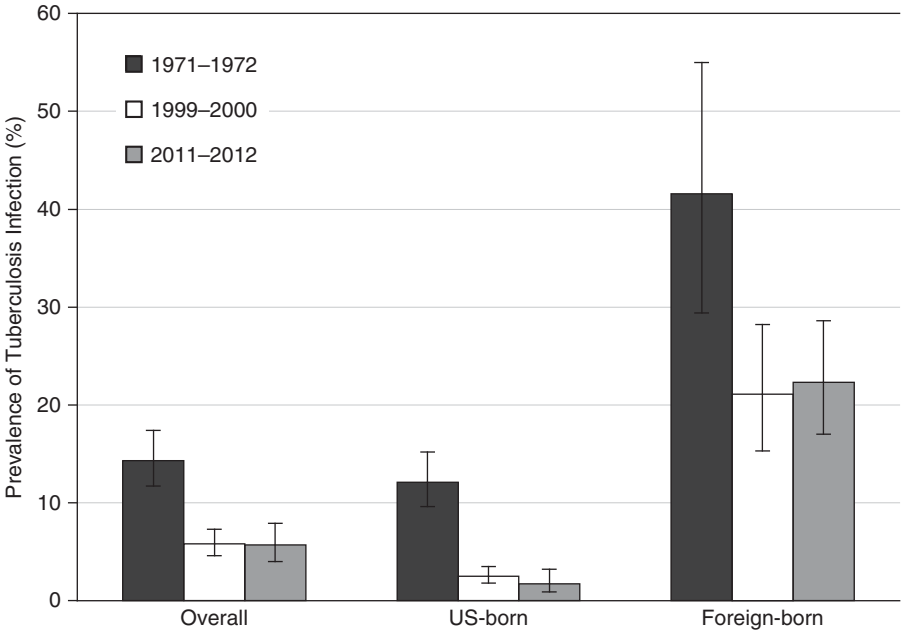

Figure 1. Trend in the prevalence of latent tuberculosis infection in the United States, ages 25–74 years, based on tuberculin skin test reactivity. *Error bars* represent 95% confidence intervals, which were calculated based on SEs incorporating the complex sample design. Latent tuberculosis was defined by a tuberculin skin test reading of greater than or equal to 10 mm induration.

Table 1. Estimated Prevalence and Population with LTBI in the United States, 2011–2012

Characteristics	Estimated Population (*n* [×*1,000*])	TST		QFT-GIT	
		LTBI Prevalence (%) (95% CI)	Estimated Population with LTBI (×*1,000*) (95% CI)	LTBI Prevalence (%) (95% CI)	Estimated Population with LTBI (×*1,000*) (95% CI)
All participants	282,460	4.4 (3.1–6.1)	12,398 (8,869–17,230)	4.8 (4.0–5.8)	13,628 (11,411–16,241)
Sex					
Male	137,320	4.6 (3.2–6.6)	6,378 (4,449–9,091)	5.6 (4.8–6.7)	7,741 (6,536–9,159)
Female	145,140	4.2 (2.9–5.8)	6,020 (4,267–8,447)	4.1 (3.1–5.3)	5,887 (4,499–7,663)
Age group, yr					
6–14	35,584	0.8 (0.4–1.4)	280 (153–512)	0.8 (0.4–1.9)	293 (125–683)
15–24	42,957	2.7 (1.6–4.4)	1,138 (687–1,873)	2.7 (1.7–4.2)	1,142 (726–1,783)
25–44	82,399	5.3 (3.4–8.2)	4,374 (2,793–6,773)	4.3 (3.3–5.4)	3,502 (2,752–4,441)
45–64	84,078	6.1 (4.2–8.6)	5,097 (3,548–7,256)	6.7 (4.9–9.1)	5,617 (4,086–7,668)
⩾65	37,442	4.0 (2.7–5.9)	1,508 (1,018–2,220)	8.2 (6.3–10.7)	3,074 (2,340–4,010)
Race/ethnicity					
Non-Hispanic white	180,506	1.0 (0.5–1.8)	1,726 (903–3,285)	2.6 (1.8–3.8)	4,681 (3,231–6,790)
Non-Hispanic black	34,553	6.3 (4.6–8.4)	2,163 (1,596–2,913)	5.2 (3.8–7.0)	1,780 (1,310–2,408)
Hispanic	45,061	11.7 (8.1–16.5)	5,255 (3,663–7,417)	10.0 (8.4–11.9)	4,495 (3,767–5,344)
Asian	14,403	21.3 (17.5–25.8)	3,072 (2,515–3,714)	17.0 (14.4–19.9)	2,443 (2,074–2,862)
Other	7,936	2.3 (0.5–9.8)	182 (40–775)	2.9 (0.8–9.4)	229 (67–745)
Poverty income index					
⩾1 (nonpoverty)	214,023	3.7 (2.5–5.4)	7,942 (5,393–11,621)	4.3 (3.4–5.4)	9,205 (7,298–11,557)
<1 (poverty)	51,014	6.5 (5.1–8.3)	3,338 (2,612–4,244)	6.3 (5.1–7.7)	3,203 (2,612–3,918)
Education level					
<High school	37,045	11.3 (7.4–17.0)	4,202 (2,745–6,294)	10.7 (8.3–13.8)	3,980 (3,067–5,127)
High school graduate	45,978	4.9 (3.0–7.8)	2,248 (1,393–3,586)	7.4 (5.1–10.7)	3,404 (2,336–4,901)
Beyond high school	143,305	3.7 (2.7–5.1)	5,323 (3,884–7,251)	3.8 (3.0–4.8)	5,416 (4,285–6,821)
Birthplace					
United States	236,725	1.4 (0.8–2.5)	3,379 (1,941–5,823)	2.7 (1.9–3.9)	6,363 (4,427–9,114)
Foreign	45,624	19.8 (15.2–25.4)	9,018 (6,917–11,570)	15.9 (13.3–19.0)	7,264 (6,045–8,678)

Definition of abbreviations: CI = confidence interval; LTBI = latent tuberculosis infection; QFT-GIT = QuantiFERON Gold In-Tube; TST = tuberculin skin test.

foreign-born population compared with the U.S.-born population, whereas these associations were similar in both populations when using the QFT-GIT.

The prevalence of LTBI was higher in several specific populations as shown in Table 5. Prevalence was higher both using the TST and QFT-GIT among household contacts of a TB case, those who had a prior positive TB test (mostly TST), and among those with a history of TB disease. The estimates among the HIV-infected were unstable because they were based on only 15 U.S.-born participants who were HIV-positive (weighted HIV prevalence, 0.43%) and one foreign born (0.13%); the overall HIV prevalence was 0.37%. Only two of the HIV-positive participants had a positive QFT-GIT; none had a positive TST. Finally, few of those with LTBI had a history of completing TB treatment (data not shown). Of the people with LTBI, 32.8% (17.5–48.2%) of the U.S. born versus 20.7% (16.4–25.0%) of the foreign born had a previous diagnosis of LTBI, and 18.9% (7.9–29.9%) of U.S. born and 10.3% (7.7–13.0%) of foreign born received treatment.

Discussion

This report provides updated estimates of the prevalence of LTBI in the United States and compares them with previous estimates from 1971 to 1972 and 1999 to 2000. The estimated prevalence of LTBI in the United States in 2011–2012 was 4.4% using the TST and 4.8% using the QFT-GIT, corresponding to 12,398,000 and 13,628,000 infected individuals, respectively. This study also compares trends in prevalence over time, changes in risk factors, and the population-level impacts of these temporal changes. Finally, this study estimates the impact of LTBI among high-risk groups in the United States, such as foreign born, close contacts, and certain racial and ethnic groups.

Although the prevalence estimate found in this study is slightly higher than the previous estimate of 4.2% obtained during the 1999–2000 NHANES (13), some of the difference is attributable to the differences in ages of the study participants. For valid comparisons with previous NHANES studies, we compared prevalence estimates using the 25- to 74-year-old subpopulation. Despite a large (60%) decline between 1971 and 1999 (13, 23), TST prevalence decreased by only 3% (from 5.8 to 5.7%) during the 12-year interval between 1999–2000 and 2011–2012. Furthermore, the absolute number of persons infected with LTBI increased by 1.2 million over this interval from 11.2 million to 12.4 million because of overall population increases. Additionally, the proportion of this reservoir existing among the foreign born increased from 63 to 73% over the same interval. This represents a substantial reservoir of infection, which threatens TB elimination efforts in the United States.

Table 2. Prevalence of LTBI with 95% Confidence Interval by Birth Cohort and Age, Using Data from Three NHANES Surveys, Based on Tuberculin Skin Test Reactivity

Birth Cohort (*yr*)	Age in 1971–1972 (*yr*)	Age in 1999–2000 (*yr*)	Age in 2011–2012 (*yr*)	Prevalence in 1971–1972 (%)	Prevalence in 1999–2000 (%)	Prevalence in 2011–2012 (%)
2002–2005			6–9			0.07 (0.01–0.58)
1997–2001			10–14			1.25 (0.66–2.36)
1992–1996		6–7	15–19		0.32 (0.06–1.66)	1.68 (0.97–2.90)
1987–1991		8–12	20–24		1.54 (0.57–4.10)	3.54 (1.90–6.50)
1982–1986		13–17	25–29		1.11 (0.49–2.52)	3.68 (1.80–7.39)
1977–1981		18–22	30–34		3.05 (1.23–7.36)	4.93 (3.60–6.70)
1972–1976		23–27	35–39		2.63 (1.05–6.43)	7.11 (4.35–11.43)
1967–1971		28–32	40–44		3.68 (1.60–8.24)	5.52 (2.78–10.67)
1962–1966		33–37	45–49		6.13 (3.35–10.97)	5.64 (3.86–8.19)
1957–1961		38–42	50–54		6.14 (3.30–11.15)	6.08 (3.65–9.96)
1952–1956		43–47	55–59		4.51 (2.28–8.73)	6.12 (3.37–10.84)
1947–1951		48–52	60–64		7.92 (3.91–15.37)	6.51 (3.65–11.36)
1942–1946	25–29	53–57	65–69	5.46 (1.63–16.74)	8.42 (4.69–14.64)	4.58 (2.73–7.56)
1937–1941	30–34	58–62	70–74	7.74 (3.15–17.77)	5.27 (2.43–11.05)	3.81 (2.13–6.73)
1932–1936	35–39	63–67	75–79	9.29 (4.63–17.78)	5.22 (2.81–9.51)	3.76 (1.93–7.19)
1927–1931	40–44	68–72	80–84	15.11 (9.09–24.07)	8.49 (3.57–18.87)	3.72 (1.72–7.86)

Definition of abbreviations: LTBI = latent tuberculosis infection; NHANES = National Health and Nutrition Examination Survey.

This study provides estimates of LTBI prevalence that are similar to another recent report, which found 4.7% prevalence of positive TST and 5.0% of positive QFT-GIT (22). The slightly higher estimates found in that study resulted from slightly differing methods, in particular the use of model smoothing by reassignment of 9- and 10-mm TST readings. Nevertheless, the overall similarity and consistency of findings between these independently performed analyses using different methodologies suggests that the findings of these studies are robust.

In addition to the foreign born, other factors were found to be associated with LTBI. These included certain racial and ethnic groups, birth cohort, age, household contacts of a TB case, and those with a prior positive TB test. This study also provides estimates of LTBI prevalence among Asians in the United States, which were not available in the previous NHANES. In 2010, 28% of the foreign-born population in the United States was born in Asia (24), and 5 of the 10

Table 3. Estimated Prevalence of LTBI in the United States Stratified by Country of Birth

Characteristics	U.S.-Born Population		Foreign-Born Population	
	% TST-Positive (95% CI)	% QFT-GIT–Positive (95% CI)	% TST-Positive (95% CI)	% QFT-GIT–Positive (95% CI)
All participants	1.4 (0.8–2.5)	2.7 (1.9–3.9)	19.8 (15.2–25.4)	15.9 (13.3–19.0)
Sex				
Male	1.7 (0.9–3.0)	3.2 (2.4–4.4)	20.0 (15.0–26.1)	18.0 (14.7–21.7)
Female	1.2 (0.7–2.1)	2.2 (1.3–3.8)	19.6 (14.6–25.7)	13.9 (10.9–17.7)
Age group, yr				
6–14	0.3 (0.1–0.7)	0.7 (0.3–1.9)	7.4 (2.7–18.8)	2.5 (0.6–10.3)
15–24	0.9 (0.3–2.7)	1.9 (0.9–3.9)	12.7 (7.4–20.9)	6.9 (2.9–15.4)
25–44	1.4 (0.8–2.5)	1.9 (0.9–3.8)	17.9 (12.0–26.0)	12.0 (9.0–15.7)
45–64	2.0 (0.9–4.3)	3.5 (2.1–5.8)	27.9 (21.1–35.9)	23.6 (18.0–30.2)
⩾65	2.0 (1.1–3.5)	5.2 (3.8–7.1)	20.8 (14.5–28.8)	32.3 (23.9–42.0)
Race/ethnicity				
Non-Hispanic white	0.6 (0.3–1.4)	2.3 (1.5–3.6)	9.1 (3.8–20.4)	9.2 (4.0–19.9)
Non-Hispanic black	4.6 (3.1–6.8)	4.3 (3.0–6.2)	26.0 (18.8–34.8)	15.3 (10.3–22.2)
Hispanic	2.9 (2.0–4.3)	3.4 (2.2–5.2)	19.1 (13.0–27.3)	15.6 (12.6–19.1)
Asian	2.1 (0.7–6.0)	2.9 (1.4–5.9)	27.9 (23.6–32.8)	21.8 (18.9–25.0)
Other	2.0 (0.3–12.2)	2.0 (0.3–11.8)	4.5 (1.0–18.3)	9.6 (2.1–34.2)
Poverty income index				
⩾1 (nonpoverty)	1.3 (0.7–2.2)	2.6 (1.8–3.8)	19.6 (14.8–25.4)	15.3 (12.8–18.3)
<1 (poverty)	2.3 (1.2–4.3)	3.4 (2.5–4.7)	19.7 (14.3–26.4)	15.0 (10.1–21.8)
Education level				
<High school	5.2 (2.1–12.4)	5.7 (3.8–8.6)	21.9 (16.4–28.5)	19.4 (15.5–23.9)
High school graduate	2.1 (1.1–3.9)	4.9 (3.1–7.5)	19.3 (11.5–30.7)	20.4 (13.6–29.5)
Beyond high school	1.0 (0.6–1.7)	2.1 (1.2–3.8)	21.5 (15.8–28.5)	14.7 (11.7–18.3)

Definition of abbreviations: CI = confidence interval; LTBI = latent tuberculosis infection; QFT-GIT = QuantiFERON Gold In-Tube; TST = tuberculin skin test.

Table 4. Logistic Regression Models with Risk Factors for LTBI in the U.S. Population, Stratified by Country of Birth*

Factor	U.S.-Born Population [*Adjusted OR (95% CI)*]		Foreign-Born Population [*Adjusted OR (95% CI)*]	
	TST (*n = 4,352*)	QFT-GIT (*n = 4,339*)	TST (*n = 1,274*)	QFT-GIT (*n = 1,270*)
Race/ethnicity				
Non-Hispanic white	1.0	1.0	1.0	1.0
Non-Hispanic black	9.5 (4.3–20.8)	2.3 (1.3–3.8)	3.0 (1.0–8.8)	1.5 (0.5–4.6)
Hispanic	9.5 (3.6–24.6)	2.4 (1.1–5.2)	2.1 (0.8–5.7)	1.7 (0.6–5.0)
Asian	7.6 (1.4–41.3)	2.6 (0.7–9.0)	3.7 (1.5–9.1)	2.5 (1.0–6.5)
Other	4.4 (0.7–28.3)	1.1 (0.2–6.2)	0.5 (0.1–3.9)	0.2 (0.0–3.2)
Wald χ^2_4 (*P* value)	38.39 (<0.0001)	12.59 (0.0134)	17.74 (0.0014)	13.64 (0.0086)
Poverty income index				
⩾1 (nonpoverty)	1.0	1.0	1.0	1.0
<1 (poverty)	1.5 (0.7–3.6)	1.6 (1.0–2.5)	1.2 (0.9–1.7)	1.2 (0.7–2.0)
Wald χ^2_1 (*P* value)	1.21 (0.2708)	3.81 (0.0509)	1.45 (0.2291)	0.27 (0.6047)
Sex				
Female	1.0	1.0	1.0	1.0
Male	1.5 (1.0–2.4)	1.6 (0.9–2.7)	1.1 (0.8–1.5)	1.6 (1.2–2.1)
Wald χ^2_1 (*P* value)	4.02 (0.0449)	3.33 (0.0681)	0.16 (0.6901)	11.32 (0.0008)
Age group, yr				
6–14	1.0	1.0	1.0	1.0
15–24	3.3 (0.8–13.5)	2.7 (0.9–7.7)	1.7 (0.5–6.1)	2.8 (0.5–15.2)
25–44	8.3 (4.0–17.2)	3.8 (1.4–10.4)	2.4 (0.6–9.0)	4.4 (1.1–17.8)
45–64	16.2 (5.8–45.5)	8.1 (2.6–25.0)	4.5 (1.3–14.3)	10.5 (2.5–43.8)
⩾65	18.0 (7.2–45.3)	13.3 (4.4–40.8)	2.9 (0.9–9.8)	17.4 (3.9–77.9)
Wald χ^2_4 (*P* value)	46.48 (<0.0001)	33.71 (<0.0001)	31.07 (<0.0001)	37.77 (<0.0001)

Definition of abbreviations: CI = confidence interval; LTBI = latent tuberculosis infection; OR = odds ratio; QFT-GIT = QuantiFERON Gold In-Tube; TST = tuberculin skin test.
*All logistic models are adjusted for all the variables in the table; Wald chi-square test was used to decide if all the subgroups defined by a categorical variable were equal or not.

leading countries of origin for immigration to the United States were from Asia: China, Vietnam, India, Korea, and Philippines (25), countries that have some of the highest burdens of TB disease worldwide (26). In our study, Asian individuals had the highest prevalence of LTBI among any of the groups studied: 25% had a positive TST and 18% had a positive QFT-GIT. Identifying these high-risk groups is important for surveillance purposes to accurately target testing among these groups over time (3, 12).

Table 5. Prevalence of Positive TST and Positive QFT-GIT among Other High-Risk Populations

Population	No. of NHANES Subjects	TST-Positive		QFT-GIT–Positive	
		Prevalence (%) (95% CI)	Population (×*1,000*) (95% CI)	Prevalence (%) (95% CI)	Population (×*1,000*) (95% CI)
All participants	6,083	4.4 (3.1–6.1)	12,398 (8,869–17,230)	4.8 (4.0–5.8)	13,628 (11,411–16,241)
Household contacts	176	12.8 (7.4–21.2)	904 (524–1,494)	14.4 (8.4–23.6)	1,014 (592–1,661)
HIV-infected*†	16	0 (n/a)	0 (n/a)	7.7 (2.0–25.4)	49 (13–164)
Any previous positive TB test	248	35.5 (27.8–44.0)	2,874 (2,252–3,565)	28.2 (22.3–35.0)	2,285 (1,808–2,831)
Previous positive TST	218	36.3 (28.1–45.3)	2,639 (2,046–3,296)	26.9 (20.3–34.7)	1,956 (1,476–2,524)
Previous positive IGRA*	8	0 (n/a)	0 (n/a)	0 (n/a)	0 (n/a)
Previous positive TB tine*	25	25.7 (11.4–48.4)	235 (104–443)	35.9 (15.3–63.5)	329 (140–581)
History of TB disease	32	47.6 (35.9–59.6)	429 (324–537)	51.5 (31.2–71.3)	464 (281–642)

Definition of abbreviations: CI = confidence interval; IGRA = IFN-γ release assay; NHANES = National Health and Nutrition Examination Survey; QFT-GIT = QuantiFERON Gold In-Tube; TB = tuberculosis; TST = tuberculin skin test.
*Estimates may be unreliable because of small sample size (<10 positives).
†Only includes participants aged 18–59 because only these ages were tested.

This study also compares estimates of LTBI prevalence obtained using the TST with those obtained using an IGRA (the QFT-GIT). These estimates are important because of the increasing use of IGRAs in the United States, particularly among health departments (27–30). Although similar results were obtained for TST and QFT-GIT, use of QFT-GIT resulted in higher overall prevalence estimates among the U.S. born and lower estimates in the foreign born. The finding of lower prevalence of LTBI in the foreign born with the QFT-GIT compared with the TST was expected because of the higher pooled specificity of IGRAs, particularly among persons vaccinated with bacillus Calmette-Guérin (31). The finding of higher estimates among U.S.-born participants with the QFT-GIT was surprising because in low-risk populations, such as this one, highly specific tests are expected to result in less false-positives and lower prevalence estimates (32, 33). It is also concerning because of the greater variability and false-positives that have been reported when using the QFT-GIT in low-risk populations (34, 35). This study supports previous findings that switching to the use of QFT-GIT at health departments may significantly reduce the number of LTBI diagnoses (28), but only when used among foreign-born patients. Further analysis of discordance between TST and QFT-GIT is presented by Ghassemieh and colleagues elsewhere in this issue.

The relationship between LTBI and age is confounded by the strong association of TB with birth cohort (36). Both age and cohort effects were seen in this study. Earlier birth cohorts consistently had higher prevalence than more recent ones, demonstrating cohort effects. Age effects were more complex, with TST reactivity generally increasing up to about age 60 in each cohort and then decreasing thereafter. Because the TST is thought to reflect the cumulative experience with infection since birth (37), this increase in prevalence with age was expected. The decrease in prevalence seen among older age groups is also consistent with the previous literature (13, 38, 39). The reasons for decreasing prevalence with age are complex and multifactorial but may include waning immunologic reactivity; self-cure; preferential survival of uninfected individuals; and the confounding effects of comorbidities, nutritional status, or medications. A previous study using the 1971 and 1999 NHANES showed similar age and cohort effects but suggested that waning reactivity started after age 45 (36), whereas in this study waning did not occur until after about age 60. In contrast to the TST, the prevalence of QFT-GIT positivity continued to increase with age for all age groups, supporting previous suggestions that the QFT-GIT may not be as susceptible to the effect of age compared with the TST. Further research among older adults is needed to determine the significance of this finding.

The strengths of this study include its large sample size, generalizability to the overall U.S. population, comparability with previous studies, and ability to compare TST and QFT-GIT prevalence estimates in the same population. However, this study also has several limitations. Selection bias is possible from nonparticipation in the survey or the TB components of the survey, although we attempted to account for this by weighting for the probability of nonresponse and nonparticipation in TB testing. However, NHANES does not include incarcerated or homeless individuals. Because up to 25% of TB is transmitted in a clustered manner (8), particularly in homeless and other difficult-to-reach settings (40), the NHANES sampling methodology may miss individuals within these clusters. Because these are important risk groups for TB control in the United States, their exclusion may have led to slight underestimates of prevalence in this study.

There are potential problems with misclassification of outcome because there is no gold standard for the diagnosis of LTBI. In this study, we were able to compare two commercially available LTBI diagnostics, but neither a positive TST nor a positive QFT-GIT necessarily equate to LTBI. Both tests are known to have substantial variability (34, 41), which may account for some of the discordance between the two tests. Testing of low-risk populations (including much of the U.S. population) may result in a large proportion of false-positives and overestimates of LTBI prevalence (32, 33). Additionally, we used a TST reaction size of greater than or equal to 10 mm to define LTBI to compare the results with previous studies (13, 23). However, this is not the definition recommended by the CDC that is used in practice, which uses a risk-stratified interpretation with different cutoffs for reaction size according to the risk profile (18, 42).

LTBI is mainly a concern because of the risk of progression to TB disease, thus the inclusion of cases with a previous history of TB disease or TB treatment also may have resulted in an overestimate of the population at risk of progression by up to 2 million individuals. We retained these individuals in our estimates of LTBI again for comparability with previous studies and their estimates. NHANES did not capture information on certain well-established risk factors for LTBI that could have been used to target testing, such as immunocompromising medical conditions other than HIV, high-risk occupations, and other groups, such as homeless or prison populations. Information on possible confounders of these associations, such as bacillus Calmette-Guérin vaccination, duration of residence outside the United States, and geographic region of origin among those born outside the United States, was not available, although bacillus Calmette-Guérin had no independent effect on LTBI prevalence in the previous survey (13).

Conclusions

After years of decline, the prevalence of LTBI remained relatively constant between 2000 and 2012. Additionally, the absolute number of those infected increased by 1.2 million to 12.4 million, suggesting that this large reservoir of TB infection will continue to threaten TB elimination efforts in the United States. Targeted testing and treatment of LTBI is a central pillar of TB control efforts in the United States and is critical to the success of the goal of TB elimination. This study provides updated estimates of LTBI among the foreign born and other risk groups in the United States to help guide control programs. Foreign-born persons represent an increasingly larger proportion of the reservoir of LTBI (73%), so programs should continue to increase their focus on this and other high-risk subpopulations through targeted testing and treatment. Finally, as more public health departments and clinicians switch from TST to IGRA testing methods, they should be aware of the differences between these tests when used in specific populations. Further discussion of the significance of the discordance between TST and QFT-GIT is presented by Ghassemieh and colleagues elsewhere in this issue. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Dr. Lara Akinbami and Dr. Brian Kit at the Division of Health and Nutrition Examination Survey, National Center for Health Statistics and Jiayun Lu at the Uniformed Services University of the Health Sciences for their technical assistance.

References

1. Scott C, Kirking HL, Jeffries C, Price SF, Pratt R; Centers for Disease Control and Prevention (CDC). Tuberculosis trends—United States, 2014. *MMWR Morb Mortal Wkly Rep* 2015;64: 265–269.
2. Division of Tuberculosis Elimination. Reported tuberculosis in the United States, 2013. Atlanta, GA: Centers for Disease Control and Prevention; 2014.
3. Geiter L. Ending neglect: the elimination of tuberculosis in the United States. Washington, DC: National Academy Press; 2000.
4. Hill AN, Becerra J, Castro KG. Modelling tuberculosis trends in the USA. *Epidemiol Infect* 2012;140:1862–1872.
5. Ferebee SH. The epidemiological basis of tuberculosis control. *Bull Natl Tuberc Assoc* 1967;53:4–8.
6. Suwanpimolkul G, Jarlsberg LG, Grinsdale JA, Osmond D, Kawamura LM, Hopewell PC, Kato-Maeda M. Molecular epidemiology of tuberculosis in foreign-born persons living in San Francisco. *Am J Respir Crit Care Med* 2013;187:998–1006.
7. Ricks PM, Cain KP, Oeltmann JE, Kammerer JS, Moonan PK. Estimating the burden of tuberculosis among foreign-born persons acquired prior to entering the U.S., 2005-2009. *PLoS One* 2011;6:e27405.
8. Moonan PK, Ghosh S, Oeltmann JE, Kammerer JS, Cowan LS, Navin TR. Using genotyping and geospatial scanning to estimate recent mycobacterium tuberculosis transmission, United States. *Emerg Infect Dis* 2012;18:458–465.
9. Shea KM, Kammerer JS, Winston CA, Navin TR, Horsburgh CR Jr. Estimated rate of reactivation of latent tuberculosis infection in the United States, overall and by population subgroup. *Am J Epidemiol* 2014;179:216–225.
10. Sloot R, Schim van der Loeff MF, Kouw PM, Borgdorff MW. Risk of tuberculosis after recent exposure. A 10-year follow-up study of contacts in Amsterdam. *Am J Respir Crit Care Med* 2014;190: 1044–1052.
11. Horsburgh CR Jr. Priorities for the treatment of latent tuberculosis infection in the United States. *N Engl J Med* 2004;350: 2060–2067.
12. Taylor Z, Nolan CM, Blumberg HM, American Thoracic Society, Centers for Disease Control and, Prevention, Infectious Diseases Society of America. Controlling tuberculosis in the United States. Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. *MMWR Recomm Rep* 2005;54:1-81.
13. Bennett DE, Courval JM, Onorato I, Agerton T, Gibson JD, Lambert L, McQuillan GM, Lewis B, Navin TR, Castro KG. Prevalence of tuberculosis infection in the United States population: the National Health and Nutrition Examination Survey, 1999-2000. *Am J Respir Crit Care Med* 2008;177:348–355.
14. National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) 2011-2012. [Accessed 2016 Feb 15]. Available from: http://wwwn.cdc.gov/Nchs/Nhanes/Search/nhanes11_12.aspx
15. National Center for Health Statistics. National Health and Nutrition Examination Survey: sample design, 2011–2014. [Accessed 2015 Jan 24]. Available from: http://www.cdc.gov/nchs/data/series/sr_02/sr02_162.pdf
16. Villarino ME, Burman W, Wang YC, Lundergan L, Catanzaro A, Bock N, Jones C, Nolan C. Comparable specificity of 2 commercial tuberculin reagents in persons at low risk for tuberculous infection. *JAMA* 1999; 281:169–171.
17. National Center for Health Statistics. National Health and Nutrition Examination Survey: Tuberculosis skin test procedures manual. Atlanta, GA: CDC; 2001.
18. Diagnostic Standards and Classification of Tuberculosis in Adults and Children. Diagnostic Standards and Classification of Tuberculosis in Adults and Children. This official statement of the American Thoracic Society and the Centers for Disease Control and Prevention was adopted by the ATS Board of Directors, July 1999. This statement was endorsed by the Council of the Infectious Disease Society of America, September 1999. *Am J Respir Crit Care Med* 2000;161: 1376–1395.
19. Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K, Committee IE, Centers for Disease Control and Prevention. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection—United States, 2010. *MMWR Recomm Rep* 2010;59: 1–25.
20. Heeringa SG, West BT, Berglund PA. Applied survey data analysis. Boca Raton, FL: Taylor and Francis; 2010.
21. National Center for Health Statistics. National Health and Nutrition Examination Survey: analytic guidelines, 2011-2012. [2 May 2014; accessed 2016 Jan 13]. Available from: http://www.cdc.gov/nchs/data/nhanes/analytic_guidelines_11_12.pdf
22. Miramontes R, Hill AN, Yelk Woodruff RS, Lambert LA, Navin TR, Castro KG, LoBue PA. Tuberculosis infection in the United States: prevalence estimates from the National Health and Nutrition Examination Survey, 2011-2012. *PLoS One* 2015;10: e0140881.
23. Khan K, Wang J, Hu W, Bierman A, Li Y, Gardam M. Tuberculosis infection in the United States: national trends over three decades. *Am J Respir Crit Care Med* 2008;177:455–460.
24. Grieco EM, Acosta YD, de la Cruz GP, Gambino C, Gryn T, Larsen LJ, Trevelyan EN, Walters NP. The foreign-born population in the United States: 2010. Washington, DC: US Census Bureau; 2012.
25. Migration Policy Institute. Largest US immigrant groups over time, 1960-present. [Accessed 2015 July 15]. Available from: http://www.migrationpolicy.org/programs/data-hub/us-immigration-trends#history
26. World Health Organization. Global tuberculosis report 2015. Geneva, Switzerland: World Health Organization; 2015.
27. Iqbal AZ, Leighton J, Anthony J, Knaup RC, Peters EB, Bailey TC. Cost-effectiveness of using Quantiferon Gold (QFT-G) versus tuberculin skin test (TST) among U.S. and foreign born populations at a public health department clinic with a low prevalence of tuberculosis. *Public Health Nurs* 2014;31: 144–152.
28. Shah M, DiPietro D, Greenbaum A, Ketemepi S, Martins-Evora M, Marsiglia V, Dorman SE. Programmatic impact of QuantiFERON-TB Gold In-Tube implementation on latent tuberculosis diagnosis and treatment in a public health clinic. *PLoS One* 2012;7:e36551.
29. Grinsdale JA, Ho CS, Banouvong H, Kawamura LM. Programmatic impact of using QuantiFERON-TB Gold in routine contact investigation activities. *Int J Tuberc Lung Dis* 2011;15: 1614–1620.
30. Walters JK, Sullivan AD. Impact of routine quantiferon testing on latent tuberculosis diagnosis and treatment in refugees in Multnomah County, Oregon, November 2009-October 2012. *J Immigr Minor Health* 2015;18:292–300.
31. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med* 2008;149:177–184.
32. Huebner RE, Schein MF, Bass JB Jr. The tuberculin skin test. *Clin Infect Dis* 1993;17:968–975.
33. Rose DN, Schechter CB, Adler JJ. Interpretation of the tuberculin skin test. *J Gen Intern Med* 1995;10:635–642.
34. Dorman SE, Belknap R, Graviss EA, Reves R, Schluger N, Weinfurter P, Wang Y, Cronin W, Hirsch-Moverman Y, Teeter LD, *et al*.; Tuberculosis Epidemiologic Studies Consortium. Interferon-γ release assays and tuberculin skin testing for diagnosis of latent tuberculosis infection in healthcare workers in the United States. *Am J Respir Crit Care Med* 2014;189:77–87.
35. McMullen SE, Pegues DA, Shofer FS, Sheller AC, Wiener EB. Performance of QuantiFERON-TB Gold and tuberculin skin test relative to subjects' risk of exposure to tuberculosis. *Clin Infect Dis* 2014;58:1260–1266.

36. Winston CA, Navin TR. Birth cohort effect on latent tuberculosis infection prevalence, United States. *BMC Infect Dis* 2010;10:206.
37. Rieder HL, Chadha VK, Nagelkerke NJ, van Leth F, van der Werf MJ; KNCV Tuberculosis Foundation. Guidelines for conducting tuberculin skin test surveys in high-prevalence countries. *Int J Tuberc Lung Dis* 2011;15:S1–S25.
38. Dorken E, Grzybowski S, Allen EA. Significance of the tuberculin test in the elderly. *Chest* 1987;92:237–240.
39. Nisar M, Williams CS, Ashby D, Davies PD. Tuberculin testing in residential homes for the elderly. *Thorax* 1993;48:1257–1260.
40. Centers for Disease Control and Prevention (CDC). Notes from the field: tuberculosis cluster associated with homelessness—Duval County, Florida, 2004-2012. *MMWR Morb Mortal Wkly Rep* 2012;61: 539–540.
41. Menzies D. Interpretation of repeated tuberculin tests. Boosting, conversion, and reversion. *Am J Respir Crit Care Med* 1999;159: 15–21.
42. Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR Recomm Rep* 2000;49:1–51.