

Tuberculosis Infection in the United States

National Trends over Three Decades

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Rationale: In 1989, the United States embarked upon an ambitious path to eliminate tuberculosis (TB) nationwide. Although incidence rates of TB disease in the United States are declining, these cases represent only a tiny fraction of all TB infections. Understanding national trends in TB infection may be important in anticipating future trends in TB disease.

Objectives: Describe the epidemiology of *Mycobacterium tuberculosis* infection in the United States in 1971–1972 and 1999–2000.

Methods: We studied nationally representative cohorts of the U.S. noninstitutionalized civilian population participating in the 1971–1972 and 1999–2000 National Health and Nutrition Examination Surveys. Participants were tuberculin skin tested and the epidemiology of TB infection was compared across surveys. Logistic regression was used to identify associations between participant and household characteristics and TB infection.

Measurements and Main Results: In 1999–2000, 4.2% (95% confidence interval [CI], 3.3–5.2%) of the U.S. population aged 1 year or older displayed evidence of TB infection. Among persons aged 25–74, the prevalence of infection decreased from 14.4% in 1971–1972 (95% CI, 11.6–17.7%) to 5.6% in 1999–2000 (95% CI, 4.4–7.1%). Declines in the relative burden of infection among persons aged 25–74 were greater in the United States–born population (12.6 to 2.5%) compared with the nation's foreign-born population (35.9 to 21.3%).

Conclusions: The United States has experienced a substantial decline in the burden of TB infection since the early 1970s. Despite this, the prevalence of infection among the nation's foreign-born population is over eight times greater than that observed in the United States–born population.

Keywords: tuberculosis; United States; public health; emigration and immigration; tuberculin test

In 1989, the United States embarked upon an ambitious path to eliminate tuberculosis (TB) nationwide (1). Although cases of TB disease (TBD) in the United States have declined substantially in recent years (2), these cases represent only the tip of a much larger national reservoir of TB infection (TBI). Because the latency period for TB can be lengthy, changes in the national burden of TBI could go undetected for years before its effects are recognized.

Most recent epidemiologic studies of TBI in industrialized countries are restricted to relatively small samples of foreign-born persons at a single point in time (3–9). These studies tend not to be generalizable, and consequently have limited value in

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Most epidemiologic studies of tuberculosis infection in industrialized countries have been conducted on small populations at a single point in time and consequently have limited generalizability.

What This Study Adds to the Field

The United States has experienced a substantial decline in the burden of TB infection since the early 1970s. Despite this, the prevalence of infection among the nation's foreign-born population is over eight times greater than that observed in the United States–born population.

aiding the development of national TB control and elimination policies. This study, which examines the epidemiology of TBI among two representative cohorts of the U.S. population three decades apart, measures the national reservoir of TBI and determines how it has changed with time.

As local transmission of TB within the United States diminishes (10, 11), immigration from TB-endemic areas of the world has emerged as the primary source of new TBIs. Although the importation of TBI via mass migration is unlikely to have an immediate impact on national incidence rates of TBD, one can reasonably anticipate that about 10% of imported (untreated) TBIs will reactivate over the lifetime of an immigrant cohort (12). Thus, understanding current trends in TBI is important in anticipating future trends in TBD, and consequently vital to national TB control and elimination policies (1, 13, 14).

METHODS

Survey Design and Data Collection

The National Health and Nutrition Examination Survey (NHANES) is conducted periodically by the National Center for Health Statistics, Centers for Disease Control and Prevention, to obtain statistics on the health and nutritional status of the U.S. population (15). This objective is accomplished by conducting household interviews, performing standardized physical examinations, and collecting and testing biological specimens from participants from randomly selected locations across the country. When sample weights are applied, the distribution of participants in NHANES approximates that of the noninstitutionalized civilian population of the United States as a whole. In this analysis, data from two NHANES surveys were analyzed (1971–1972 and 1999–2000), each of which was based on a complex, stratified, multistage, probability-sample design (16, 17).

Data from NHANES 1999–2000 included information on participant characteristics (i.e., age, sex, race/ethnicity, birthplace, education, income, prior household contact with TBD, and bacille Calmette Guérin (BCG) vaccination scar on examination) as well as household factors (i.e., dwelling type and household size). Analyses of self-reported

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education status were restricted to participants 20 years of age or older. Information on prior lifetime household contact with TBD was ascertained via the following question: "Have you ever lived in the same household with someone while that person was sick with tuberculosis or TB?" Analyses distinguishing previously detected and treated from undetected and untreated TBI were performed. Data from NHANES 1971–1972 and NHANES 1999–2000 were compared.

A total of 9,965 individuals, age 1 year or older, participated in NHANES 1999–2000: 7,386 (74.1% of total) had tuberculin skin tests (TSTs) with *Mycobacterium tuberculosis*-derived purified protein derivative product (PPD-S). In NHANES 1971–1972, the TST was only administered to a subgroup of 1,492 participants between the ages of 25 and 74 years.

Tuberculin Skin Testing

In both NHANES 1971–1972 and NHANES 1999–2000, participants were administered a one-step TST using five international units of PPD-S (17). TBI was defined by at least 10 mm of induration (18). In 1971–1972, participants were excluded from testing if they reported a history of a positive TST, prior "prophylaxis" with isoniazid, or a history of TB. In 1999–2000, participants were excluded only if they reported having

a severe reaction to a prior TST. Antigen preparation, administration, and reading of skin tests were similar across the two surveys and performed in accordance with current national guidelines (18).

Statistical Analysis

The prevalence of TBI among participants in each of the two surveys was calculated using SAS version 8.0 (SAS Institute, Cary, NC). Sample weights were applied to project the estimated prevalence of TBI among the noninstitutionalized civilian population of the United States (approximately 227 million people in 1999–2000) while accounting for oversampling and participant nonresponses. To account for the complex survey design, standard errors were calculated with SUDAAN (RTI, Cary, NC) using the Taylor series linearization method (19). For comparisons among subgroups within each survey or changes over time across surveys, data were age adjusted by the direct method to match the Year 2000 U.S. population (20).

Backward elimination logistic regression in SUDAAN was used to identify independent predictors of TBI among participants in the 1999–2000 NHANES cohort. Variables significant at the $P < 0.05$ level were allowed to remain in the final multivariate model. This investigation was approved by St. Michael's Hospital ethics review board.

TABLE 1. PREVALENCE OF TUBERCULOSIS INFECTION* AMONG PERSONS 1 YEAR OF AGE AND OLDER IN THE UNITED STATES BY DEMOGRAPHIC CHARACTERISTICS, 1999–2000

Characteristic	No. Tested [†]	Unadjusted Prevalence (%) with Tuberculosis Infection (95% CI)	Age-adjusted [‡] Prevalence (%) with Tuberculosis Infection (95% CI)	Estimated No. of Persons Infected Nationwide [§] in Millions (95% CI)
All subjects	7,386	4.16 (3.32–5.19)	4.13 (3.32–5.12)	9.47 (7.56–11.82)
Age, yr				
1–19	3,543	1.01 (0.52–1.94)	—**	0.59 (0.31–1.14)
20–39	1,343	4.34 (2.73–6.83)	—	3.21 (2.02–5.05)
40–59	1,102	6.11 (4.53–8.20)	—	3.56 (2.64–4.77)
≥60	1,398	5.73 (4.31–7.58)	—	2.11 (1.59–2.79)
Sex				
Male	3,661	5.14 (4.16–6.32)	5.19 (4.31–6.25)	5.77 (4.67–7.09)
Female	3,725	3.20 (2.25–4.54)	3.14 (2.24–4.39)	3.70 (2.60–5.25)
Birthplace				
United States	5,913	1.81 (1.34–2.46)	1.85 (1.36–2.50)	3.55 (2.63–4.82)
Mexico	927	19.55 (16.40–23.14)	19.38 (16.32–22.85)	1.42 (1.19–1.68)
Elsewhere	502	18.58 (12.05–27.55)	16.74 (11.21–24.25)	4.40 (2.85–6.52)
Race/ethnicity				
Non-Hispanic white	2,489	1.94 (1.28–2.92)	1.84 (1.22–2.78)	3.01 (1.98–4.52)
Non-Hispanic black	1,727	7.3 (5.57–9.52)	8.54 (6.88–10.57)	1.94 (1.48–2.53)
Mexican American	2,516	9.53 (7.72–11.70)	11.56 (9.63–13.81)	1.65 (1.34–2.03)
Other race/ethnic group	654	9.91 (6.71–14.39)	11.04 (7.53–15.93)	2.87 (1.95–4.17)
Poverty				
Below poverty line	1,884	6.04 (4.02–8.96)	7.00 (4.65–10.41)	2.30 (1.53–3.42)
At or above poverty line	4,551	3.32 (2.49–4.41)	3.18 (2.37–4.25)	5.53 (4.15–7.35)
Education				
Less than high school	4,071	5.73 (4.54–7.21)	7.95 (6.16–10.20)	4.70 (3.73–5.92)
High school or equivalent	1,032	3.33 (2.28–4.83)	2.71 (1.83–3.98)	1.55 (1.06–2.24)
More than high school	1,565	3.62 (2.38–5.48)	2.91 (1.93–4.36)	3.11 (2.04–4.70)
Household type				
House	4,893	3.73 (2.76–5.02)	3.65 (2.72–4.88)	5.96 (4.41–8.03)
Apartment or other	2,405	5.30 (4.21–6.64)	5.63 (4.59–6.89)	3.47 (2.76–4.35)
Household size				
One to three rooms	623	7.02 (4.15–11.62)	6.29 (3.72–10.44)	1.13 (0.67–1.87)
Four to six rooms	4,540	4.64 (3.61–5.95)	4.75 (3.69–6.09)	5.95 (4.63–7.63)
Seven or more rooms	2,129	2.88 (1.94–4.26)	2.87 (1.97–4.17)	2.33 (1.57–3.44)
Household contact [¶]				
Yes	233	15.21 (9.31–23.94)	12.58 (7.65–20.00)	1.01 (0.62–1.59)
No	7,113	3.81 (2.96–4.88)	3.81 (3.00–4.82)	8.39 (6.52–10.74)
BCG** scar on exam				
Present	583	11.48 (7.01–18.25)	9.69 (6.66–13.88)	2.54 (1.55–4.04)
Absent	6,801	3.37 (2.60–4.36)	3.49 (2.68–4.54)	6.93 (5.35–8.96)

Definition of abbreviations: BCG = bacille Calmette Guérin; CI = confidence interval.

* Defined by a tuberculin skin test with ≥ 10 mm of induration.

[†] Totals vary in accordance with the availability of data. Self-reported education presented in persons 20 years of age and older.

[‡] Reference: 2000 U.S. population. From the 2000 U.S. Census ($n = 227$ million people).

[§] Among the noninstitutionalized civilian population of the United States ($n = 227$ million people).

^{||} As defined by the U.S. Census, adjusting for family size.

[¶] Lifetime household contact of an active tuberculosis case.

** Dashes are shown where age-specific prevalence has been reported.

TABLE 2. RELATIVE ODDS OF TUBERCULOSIS INFECTION* IN THE UNITED STATES AMONG PERSONS 1 YEAR OF AGE AND OLDER, 1999–2000†

Variable	Adjusted Odds Ratio (95% CI)
Age, yr	
1–19‡	1.00
20–39	2.95 (1.46–5.98)
40–59	4.98 (2.56–9.69)
≥60	5.97 (2.57–13.86)
Sex	
Female‡	1.00
Male	1.88 (1.33–2.65)
Birthplace	
United States‡	1.00
Foreign born	10.02 (5.83–17.22)
Race/ethnicity	
Non-Hispanic white‡	1.00
Non-Hispanic black	4.12 (2.71–6.28)
Mexican American	1.90 (1.02–3.54)
Other race/ethnic group	1.64 (0.90–2.98)
Household contact§	
No	1.00
Yes	4.11 (1.75–9.66)

Definition of abbreviation: CI = confidence interval.

* Defined by a tuberculin skin test with ≥10 mm of induration.

† Reported values derived using backward elimination logistic regression.

‡ Reference category.

§ Lifetime household contact of an active tuberculosis case.

RESULTS

In 1999–2000, the estimated prevalence of TBI in the United States was 4.2%, representing approximately 9.5 million TB-infected persons among the civilian noninstitutionalized population of the nation (*see* Table 1). A significantly higher burden of TBI was noted among persons born in Mexico (19.6%; 95% confidence interval [CI], 16.4–23.1%) and other foreign countries (18.6%; 95% CI, 12.1–27.6%) compared with persons born in the United States (1.8%; 95% CI, 1.3–2.5%), and Mexican Americans (9.5%; 95% CI, 7.7–11.7%) and non-Hispanic blacks (7.3%; 95% CI, 5.6–9.5%) compared with non-Hispanic whites (1.9%; 95% CI, 1.3–2.9%). On multivariate analysis, age, sex, birthplace, race/ethnicity, and prior household contact with an active case of TB were independently associated with the presence of TBI (*see* Table 2).

Among persons aged 25–74 years, the estimated prevalence of TBI in the United States decreased from 14.4% (95% CI, 11.6–17.7%) in 1971–1972 to 5.6% (95% CI, 4.4–7.1%) in 1999–2000 (61% reduction; *see* Table 3). Declines in the burden of TBI were observed in each age subgroup studied, among both males and females, and among persons born in the United States and abroad. Although the absolute decline in prevalence was greatest in the nation's foreign-born population (14.6% reduction compared with a 10.1% reduction in the United States–born population), the relative decline in prevalence was substantially higher in the United States–born population (80% reduction compared with 41% reduction in the foreign-born population; *see* Figure 1).

Among the estimated 1.8% of the United States–born population with TBI in NHANES 1999–2000, 87.4% (95% CI, 79.5–92.6%) reported ever having a previous TST. Of those who had been previously skin tested, 42.2% (95% CI, 30.4–55.0%) reported ever having a positive TST, whereas 42.9% (95% CI, 27.1–60.3%) of TST-positive individuals reported ever having been prescribed medication for the prevention of TBD. Conversely, among the estimated 18.8% of the foreign-born population with TBI in NHANES 1999–2000, 71.1% (95% CI, 64.1–77.2%) reported ever having a previous TST. Of those who had been previously skin tested, 27.3% (95% CI, 16.6–41.6%) reported ever having a positive TST, whereas 58.9% (95% CI, 31.3–81.9%) of TST-positive individuals reported ever having been prescribed medication for the prevention of TBD (*see* Figure 2).

DISCUSSION

In 1999–2000, approximately 4% of persons living in the United States displayed TST evidence of TBI. Increasing age, male sex, race/ethnicity, foreign birth, and prior household exposure to TBD were each associated with TBI on multivariate analysis.

We observed a peak prevalence of TBI among persons 40–59 years of age. Although we anticipated finding the highest TBI prevalence among the eldest age group (*i.e.*, 60+ yr), this was not observed. Instead, we found a slightly higher, but statistically comparable, burden of TBI among persons 40–59 years of age. We speculate that this plateau in TBI prevalence could be due to waning cell-mediated immunity and thus skin test anergy among persons 60 years and older. We also noted a significantly higher

TABLE 3. CHANGES IN THE PREVALENCE OF TUBERCULOSIS INFECTION* IN THE UNITED STATES BETWEEN 1971–1972 AND 1999–2000

Characteristic	1971–1972		1999–2000	
	No. Tested	Prevalence (%) with Tuberculosis Infection* (95% CI)	No. Tested	Prevalence (%) with Tuberculosis Infection* (95% CI)
All subjects	1,492	14.37 (11.56–17.73)	3,012	5.58 (4.41–7.05)
Age, yr				
25–44	492	9.26 (6.69–12.68)	1,343	4.80 (3.60–6.37)
45–54	370	22.21 (16.45–29.27)	550	6.47 (3.70–11.07)
55–64	297	17.20 (12.58–23.07)	560	6.21 (4.42–8.67)
65–74	333	17.73 (13.71–22.61)	559	6.47 (3.14–12.87)
Sex†				
Male	719	17.57 (13.91–21.94)	1,421	7.13 (5.89–8.61)
Female	773	11.68 (8.37–16.06)	1,591	4.09 (2.91–5.71)
Birthplace‡				
United States	1,352	12.58 (9.78–16.04)	2,188	2.47 (1.75–3.47)
Elsewhere‡	129	35.94 (25.01–48.55)	805	21.30 (15.79–28.09)

Definition of abbreviation: CI = confidence interval.

* Defined by a tuberculin skin test with ≥10 mm of induration.

† Age adjusted using the 2000 U.S. population as a reference.

‡ Includes all countries outside of the United States.

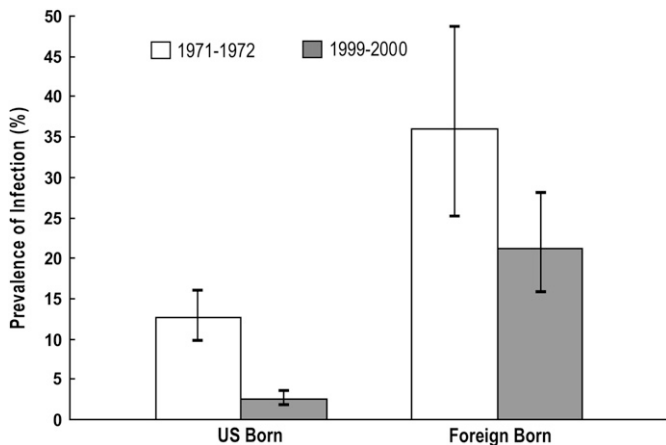


Figure 1. Changes in the prevalence of tuberculosis infection in the United States among persons 25–74 years of age by birthplace, 1971–1972 and 1999–2000. Prevalence is age adjusted using the 2000 U.S. population as a reference. Tuberculosis infection is defined by a tuberculin skin test with ≥ 10 mm of induration. Lines within bars represent 95% upper and lower confidence limits.

burden of TBI among males, which has been reported elsewhere (5, 9, 21) and which may reflect lifestyle behaviors related to TB exposure (22). A greater burden of TBI was also observed among racial/ethnic minorities independent of birthplace.

In 1999–2000, approximately one in five foreign-born persons in the United States displayed evidence of TBI. Worldwide, an estimated one in three persons is considered to have

TBI (23). This difference suggests that immigrants coming to the United States may represent a select and more privileged population than their counterparts back home.

Vaccination with BCG is relatively common among foreign-born persons and may be associated with false-positive TST results (24, 25). In our analysis, participants identified with the presence of a BCG scar on clinical examination were more likely to meet skin test criteria for TBI. However, the observed association between BCG and TBI was negated on multivariate analysis after factors such as participant age and birthplace were accounted for.

Our analysis also examined potential birthplace differences in previously identified and treated TBIs in the United States. Complementing our work is a recent study evaluating the scope and impact of treatment for latent TBI across 19 catchment areas throughout the United States (26).

Although temporal analyses of NHANES data were restricted to persons 25 to 74 years of age, it appears that the national reservoir of TBI in the United States has declined substantially during the past three decades. Overall, the country has witnessed a 61% reduction in the burden of TBI since the early 1970s. However, the relative decline in TBI among the United States–born population has been nearly twice that observed in the nation’s foreign-born population. These findings could be due to shifting immigration patterns, with more recent immigrants entering the United States from Asia, Latin America, and sub-Saharan Africa (27, 28), where TB is endemic and where declines in TBI over the past 30 years may have been outpaced by declines in the United States. Consequently, the ratio of foreign-born to United States–born individuals with TBIs has risen from 2.9 in 1971–1972 to 8.6 in 1999–2000. These findings have important national policy implications for ongoing TB

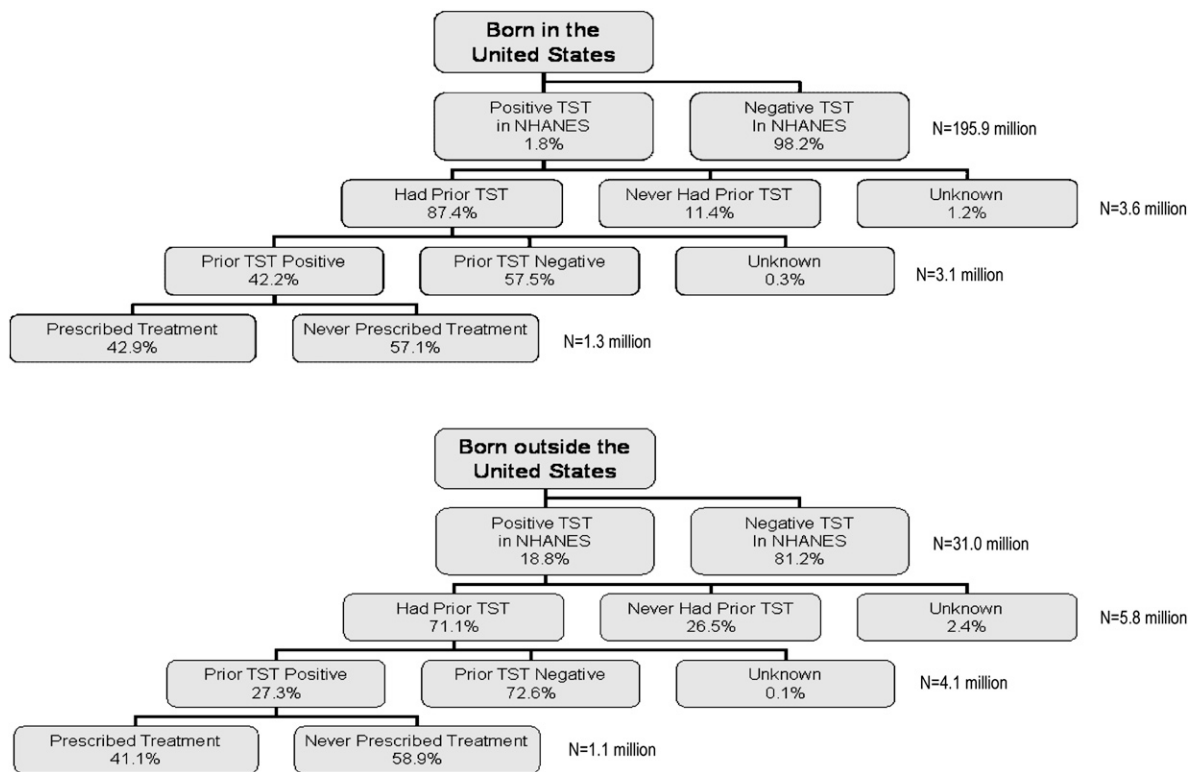


Figure 2. Proportion of previously identified and treated tuberculosis infections in the United States by birthplace, 1999–2000. Tuberculosis infections were defined by a TST with ≥ 10 mm of induration. NHANES = National Health and Nutrition Examination Survey; TST = tuberculin skin test. Note: Numbers represent projected population size.

control and elimination policies (1, 13, 14). Strategies to address this growing disparity could be directed to the detection and treatment of latent TBI among immigrants from TB-endemic countries who have recently entered the United States (12), mass screening and treatment of latent TBI in new immigrants at the time of immigration (13, 29), and/or TB control in high-burden countries themselves (30).

Our analysis has some important limitations that warrant discussion. First, our definition of TBI was based on the TST, which has certain shortcomings (24). False-positive reactions may be associated with BCG vaccination and, to a lesser extent, nontuberculous mycobacteria exposure (24, 25). Conversely, false-negative reactions may occur in persons with suppressed or altered immunity, given that TST reactions are based on a cell-mediated immune response (24).

In our analysis, we defined TBI using a 10-mm threshold for all participants; however, persons with HIV infection or other profound immune compromised states are considered to have TBI at a lower, 5-mm threshold (12). Thus, we may have under-detected TBI in persons with compromised immunity. However, in a subgroup analysis of persons aged 18 to 49 years in whom we were able to evaluate HIV status, we found no HIV-positive individuals with ≥ 5 mm of induration on skin testing. Furthermore, inter- and intrarater variability in placement and interpretation of the TST can affect the reliability of test results (31). However, NHANES used rigorous procedures to ensure that TST placement, reading, and interpretation were performed in a standardized and reproducible fashion, distinguishing it from many other studies of TBI (16, 17).

The exclusion criteria for participants in the NHANES 1971–1972 survey were broader than those in the 1999–2000 survey. This means that the prevalence of TBI in 1971–1972 is likely underestimated to a greater extent than in 1999–2000. Thus, actual declines in the burden of TBI between the two surveys may exceed observed differences in this study. Finally, given that housing is a prerequisite for inclusion in NHANES, homeless persons may not be represented in this study.

In our analysis, we were unable to distinguish between TBD and TBI. This distinction typically requires microbiological evidence and/or histologic findings compatible with active disease. Given that this information was not available in either NHANES survey, we assumed that participants did not have TBD at the time of study. Given that TBD represents an extremely small subset of all TBIs in the United States, we assume that this limitation had no meaningful impact on the outcome of our analysis.

We evaluated temporal changes in the burden of TBI but were restricted to doing so among persons 25 to 74 years of age, as these were the only participants recruited in the NHANES 1971–1972 survey. Furthermore, the smaller number of participants in NHANES 1971–1972 limited our ability to perform detailed subgroup analyses. Definition changes for certain variables also prevented certain head-to-head comparisons across the two surveys. Finally, the most current NHANES data available for this analysis were derived from the 1999–2000 survey, precluding the evaluation of more recent changes in the national burden of TBI.

Despite these shortcomings, we believe our study is of considerable significance, given that it delivers detailed epidemiologic data on two nationally representative cohorts of the U.S. population across a period of three decades. This alone distinguishes it from the vast majority of other studies that are based on one-time convenience samples, with limited generalizability (3–9). Importantly, although our analysis demonstrates that TBI in the United States has declined substantially during the past three decades, a growing divide between the burden of TBI in

the nation's native-born and foreign-born populations is emerging. This finding is particularly noteworthy as it may portend future national trends in TBD and may be informative to policymakers developing national TB control and elimination strategies.

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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