HHS Public Access

Author manuscript

Epidemiology. Author manuscript; available in PMC 2025 March 01.

Published in final edited form as:

Epidemiology. 2024 March 01; 35(2): 164–173. doi:10.1097/EDE.0000000000001707.

Estimated rates of progression to tuberculosis disease for persons infected with *Mycobacterium tuberculosis* in the United States

Mina Ekramnia[1], **Yunfei Li**[1], **Maryam B Haddad**[2], **Suzanne M Marks**[2], **J Steve Kammerer**[2], **Nicole A Swartwood**[1], **Ted Cohen**[3], **Jeffrey W Miller**[4], **C Robert Horsburgh**[5], **Joshua A Salomon**[6], **Nicolas A Menzies**[1,7]

[1.]Department of Global Health and Population, Harvard TH Chan School of Public Health, Boston MA, USA.

[2.]Division of Tuberculosis Elimination, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, U.S. Centers for Disease Control and Prevention, Atlanta GA, USA.

[3.]Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven CT, USA.

[4.]Department of Biostatistics, Harvard TH Chan School of Public Health, Boston MA, USA.

[5.]Departments of Epidemiology, Biostatistics, and Global Health, Boston University School of Public Health and Department of Medicine, Boston University School of Medicine, Boston MA USA.

[6.]Center for Health Policy / Center for Primary Care and Outcomes Research, Stanford University, Stanford CA, USA.

[7.]Center for Health Decision Science, Harvard TH Chan School of Public Health, Boston MA, USA.

Abstract

Background: In the United States, over 80% of tuberculosis (TB) disease cases are estimated to result from reactivation of latent TB infection (LTBI) acquired more than 2 years previously (‘reactivation TB’). We estimated reactivation TB rates for the U.S. population with LTBI, overall, by age, sex, race–ethnicity, and U.S.-born status, and for selected comorbidities (diabetes, end-stage renal disease [ESRD], and HIV).

Methods: We collated nationally representative data for 2011–2012. Reactivation TB incidence was based on TB cases reported to the National TB Surveillance System that were attributed to LTBI reactivation. Person–years at risk of reactivation TB were calculated using IGRA (Interferon-Gamma Release Assay) positivity from the National Health and Nutrition Examination

Corresponding author: Nicolas A Menzies (nmenzies@hsph.harvard.edu), Department of Global Health and Population, Harvard TH Chan School of Public Health, 665 Huntington Ave, Boston MA 02115, USA.

Conflicts of interest: The authors declare no conflicts of interest.

Survey, published values for IGRA sensitivity and specificity, and population estimates from the American Community Survey.

Results: For persons aged ≥6 years with LTBI, the overall reactivation rate was estimated as 0.072 (95% uncertainty interval: 0.047, 0.12) per 100 person–years. Estimated reactivation rates declined with age. Compared to the overall population, estimated reactivation rates were higher for persons with diabetes [adjusted rate ratio (aRR) = 1.6 (1.5, 1.7)], ESRD [aRR = 9.8 (5.4, 19)], and HIV [aRR = 12 (10, 13)].

Conclusions: In our study, individuals with LTBI faced small, non-negligible risks of reactivation TB. Risks were elevated for individuals with medical comorbidities that weaken immune function.

Keywords

Tuberculosis; Latent Tuberculosis; United States; HIV; Diabetes Mellitus; Kidney Failure; Chronic

INTRODUCTION

For persons infected with *Mycobacterium tuberculosis* who do not complete treatment for latent TB infection (LTBI), the risk of progressing to TB disease (i.e., of reactivation TB) extends over the remaining lifetime.[1,2] Consequently, a substantial fraction of incident TB cases can result from previously acquired infections containing viable *M. tuberculosis* organisms, particularly in countries that have reduced TB transmission to low levels. In the United States, nearly 90% of TB cases cannot be attributed to recent transmission, indicating that these cases are likely due to infections acquired >2 years before TB disease diagnosis.[3] For low TB incidence countries like the United States, identifying persons with LTBI and providing treatment for LTBI is a major focus of TB prevention activities.[4,5]

For otherwise healthy individuals, the lifetime risk of progressing to TB disease >2 years after initial *M. tuberculosis* infection is conventionally thought to be 3%–5%,[6] although evidence supporting these values is limited.[7] Within the United States, rates of reactivation TB have been estimated as 0.080–0.083 per 100 person–years for the U.S.-born population,[8] and 0.069–0.114 per 100 person–years for the non-U.S.-born population.[8,9]

Reactivation rates are higher for persons with health conditions such as malnutrition, human immunodeficiency virus (HIV) infection, diabetes, or end-stage renal disease (ESRD), or who take medications that impair immunity (e.g., immunosuppressive therapy).[8,10,11] For this reason, persons with conditions associated with substantial immune suppression may be recommended for screening for LTBI, in addition to persons with factors indicating elevated risks of prior TB infection (e.g., birth in a high-TB incidence country, residence in congregate settings with potential for elevated TB exposure).[4,12] Estimating the potential reductions in lifetime TB incidence that can be achieved by providing treatment to different populations is crucial to evaluate the impact and cost-effectiveness of LTBI screening and treatment strategies,[13,14] and for modeling the relationship between TB incidence and LTBI prevalence.[15]

In this study we estimated rates of TB reactivation in the overall U.S. population, within major population strata (age group, sex, race–ethnicity, and U.S.-born status), and for persons having diabetes, ESRD, or HIV.

METHODS

Analytic approach and study population

We adopted methods used by earlier U.S.-based studies that estimated TB reactivation rates.[8,9] Under this analytic approach, the reactivation rate is calculated by dividing the number of incident TB cases not attributed to recent transmission (assumed to be due to reactivation TB) arising in the population over a given period by the estimated number of person–years at risk for the same population and time period.

To implement this analysis, we synthesized data from nationally representative surveys and from the National TB Surveillance System (NTSS), a registry of all verified TB disease cases reported in the United States. The most recent nationally representative data on LTBI prevalence come from the 2011–2012 National Health and Nutrition Examination Survey (NHANES). For this reason, we chose 2011–2012 as the study period. We used the American Community Survey, National Health Interview Survey, and CDC's HIV surveillance summaries to estimate population sizes for the analysis. Using these data, we estimated reactivation rates for the overall population aged ≥6 years as well as by age group, sex, race–ethnicity, U.S.-born status, and for three medical comorbidities. Risk population definitions and analytic methods are described in detail below.

Number of reactivation TB cases (numerator)

We extracted individual-level NTSS data for all persons ≥6 years of age reported as having TB disease during 2011–2012, including both pulmonary and extrapulmonary TB. We retained variables describing demographics and comorbidities as well as a variable calculated by CDC to indicate whether a TB case was estimated to be attributed to recent infection. This recent transmission indicator takes account of possible transmission linkages based on spatial and temporal proximity to other diagnosed TB cases with a matching TB genotype and has been validated against field-based assessment of recent transmission via epidemiologic investigation.[16,17] We categorized age in 10-year age groups, and race–ethnicity as Hispanic, Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian, and Other. The 'Other' category combined smaller racial/ethnic populations with insufficient sample size for estimating separate results. For diabetes, ESRD, and HIV, we counted individuals as having the comorbidity if this was recorded in the checkboxes on the TB case report form, or if the comorbidity was described in a free-text field listing additional risk factors.

Because the recent transmission indicator is only available for culture-positive cases, the indicator was missing for a substantial fraction of persons with reported TB (5,336 individuals, 27.1%) during 2011–2012. We undertook regression-based multiple imputation of these missing indicator values,[18] assuming values were missing at random conditional on demographic variables (age group, sex, race–ethnicity, U.S.-born status), recorded value

for the three medical comorbidities included in the analysis (diabetes, ESRD, HIV), and additional factors associated with recent TB transmission in prior studies (homelessness, excessive alcohol consumption, incarceration, sputum smear positivity, multidrug resistance, history of TB).[17,19,20] We defined reactivation TB as all TB cases not attributed to recent transmission according to the recorded or imputed value. Separately, we used the same regression-based multiple imputation approach to impute HIV status among persons reported as having TB disease but without an accompanying HIV-positive or HIV-negative test result. Reasons for missing HIV status included the test not being offered (1,492 individuals, 7.6%), the test being refused (857, 4.3%), and other reasons (459, 2.3%). We conducted sensitivity analyses with a more conservative assumption that only counted an individual as HIV positive if an HIV-positive test result was recorded.

Prevalence of LTBI and person–years at risk of reactivation (denominator)

We extracted data on LTBI test positivity from the 2011–2012 NHANES. In this survey cycle, LTBI prevalence in the noninstitutionalized civilian U.S. population aged ≥6 years was assessed using both the tuberculin skin test and interferon-gamma release assay (IGRA).[21] We used the IGRA results, based on the higher reported specificity of IGRA in non-U.S.–born persons.[22] We estimated IGRA positivity for the overall population and for demographic strata (by age group, sex, race–ethnicity, U.S.-born status), accounting for NHANES examination weights and survey design, assuming that NHANES data of the noninstitutionalized population can be applied to the whole U.S. population.

To assess IGRA positivity associated with diabetes, ESRD, and HIV, we initially fitted logistic regression models controlling for age group, sex, race–ethnicity, U.S.-born status, and each of the three medical comorbidities. In these models the coefficients associated with each comorbidity were highly imprecise. For this reason, we omitted these comorbidities and assumed IGRA positivity for persons with each comorbidity was the same as in the overall NHANES, conditional on age group, sex, race–ethnicity, and U.S.-born status. In sensitivity analyses we re-estimated results from a regression model including diabetes, based on past research suggesting a positive association with LTBI prevalence.[23]

Unadjusted IGRA positivity can represent a biased estimate of true LTBI prevalence because the test has imperfect sensitivity and specificity. For this reason we refined LTBI prevalence estimates by adjusting for IGRA test performance.[9] For a given population, the relationship between IGRA-positivity and true LTBI prevalence is given by

$$p(igra)_i = p(ltbi)_i * sens_i + (1 - p(ltbi)_i) * (1 - spec_i),$$

where $p(igra)_i$ represents the fraction of analytic stratum i testing positive with IGRA, and $p(ltbi)_i$, $sens_i$, and $spec_i$ represent true LTBI prevalence, sensitivity, and specificity in the same stratum. Based on this relationship we used a Bayesian approach to back-calculate LTBI prevalence for each analytic stratum using published estimates of IGRA sensitivity and specificity[22] and estimated IGRA positivity for each stratum derived from NHANES (details in eAppendix http://links.lww.com/EDE/C99).

For the overall population and demographic strata, we estimated population sizes using American Community Survey data for 2011 and 2012.[24] We calculated population estimates stratified by age group, sex, race–ethnicity, and U.S.-born status, matching the categories of LTBI prevalence estimates. The American Community Survey does not record medical conditions, and the relatively small sample size of NHANES means that medical risk population sizes can only be estimated imprecisely (among 2011–2012 NHANES participants with a recorded IGRA test result, 635 self-reported a prior diabetes diagnosis, 20 met published criteria for ESRD,[25] and 19 tested positive for HIV). For this reason, we estimated medical risk population sizes using the larger samples available in other nationally representative surveys. For persons with diabetes and persons with ESRD, we used the National Health Interview Survey for 2011 and 2012.[26] For persons with HIV we used the CDC's national HIV surveillance reports for 2011 and 2012.[27]

We calculated person–years at risk by multiplying LTBI prevalence by population estimates for each analytic stratum, summing across all strata, and multiplying by 2 to reflect the 2-year study period 2011–2012. From this value we subtracted person–years spent with TB disease, as these persons are not at risk of a new TB diagnosis and should be removed from the denominator. We calculated this value by multiplying the number of TB cases within each stratum by an assumed 24-month duration of disease (taken to include undiagnosed disease, the treatment period, and a 12-month post-treatment period during which any new TB diagnosis would be interpreted as recurrence).

Estimation of TB reactivation rates and rate ratios

We estimated reactivation rates by dividing the number of reactivation TB cases during 2011–2012 by the estimated number of person–years at risk, for each demographic stratum and medical comorbidity. For age group, sex, race–ethnicity, and U.S.-born status, we calculated rate ratios comparing each covariate level to a reference level, without adjusting for the distribution of other covariates across levels. For diabetes, ESRD, and HIV, we calculated reactivation rate ratios under two approaches: (i) an unadjusted rate ratio comparing reactivation rates in persons with the condition to reactivation rates in the general U.S. population without the condition, which will include differences in reactivation rates due to the condition itself as well as differences due the population distribution of the risk factor by age group, sex, race–ethnicity and U.S.-born status; and (ii) an adjusted rate ratio comparing reactivation rates for persons with/without the condition standardized by age group, sex, race–ethnicity, and U.S.-born status. For these adjusted rate ratios, our basis for standardization was the total population with that medical condition, as derived from the National Health Interview Survey and CDC's national HIV surveillance reports.

For diabetes, ESRD, and HIV, we estimated excess TB cases attributable to each comorbidity over the 2-year period, to quantify the societal impact of these elevated reactivation rates. To do so, we compared observed results to a counterfactual in which we set adjusted rate ratios for reactivation TB to 1.0 for each risk factor and calculated excess cases as the difference in TB cases between the two scenarios for a given comorbidity. We also estimated the population attributable fraction (PAF), calculated by dividing estimated excess cases by total observed cases.

Statistical analysis

We used Monte Carlo simulation to propagate uncertainty in each analytic input through subsequent steps in the analysis.[28] With this approach we simulated 100,000 values for each input and used these to calculate 100,000 estimates for each study outcome. Details on the Monte Carlo simulation approach and equations used to calculate study outcomes are provided in the eAppendix http://links.lww.com/EDE/C99. We calculated point estimates as the median of the simulated values for each outcome, and equal-tailed 95% uncertainty intervals as the 2.5th and 97.5th percentiles of these distributions. These intervals represent the combined uncertainty in all model inputs, imputation of missing data, and Bayesian estimation of LTBI prevalence, as propagated through the analysis via the Monte Carlo simulation. Analyses were conducted in R (version 4.2.2),[29] using the *survey* (version 4.0),[30] *glmnet* (version 4.1–6),[31] and *rstan* (version 2.21.7)[32] packages.

Sensitivity analyses

We conducted sensitivity analyses testing the robustness of results to different assumptions. First, we recalculated results for diabetes allowing for differences in IGRA positivity between the diabetic population and the general population, operationalized by adding a term for diabetes to the regressions of NHANES data. This term was not statistically significant (p=0.22) and so omitted from the main analysis, but diabetes has been associated with elevated LTBI prevalence in other data.[33] Second, we re-estimated ESRD population size using a more inclusive definition (chronic kidney disease Stages 4 and 5 (eGFR<30)). Third, we re-estimated the ESRD population size using data from NHANES cycles 2007–2016 to obtain a more precise estimate of ESRD prevalence, using recommended methods for combining multiple survey cycles.[34] Fourth, we took a conservative approach to estimating HIV status among persons with TB disease, assuming all to be HIV-negative unless recorded as HIV-positive. Fifth, we re-estimated reactivation rates for each comorbidity, omitting persons aged <25 years, in case LTBI natural history is different in younger age groups. Finally, we recalculated rates of reactivation TB for U.S.-born and non-U.S.–born populations for different values of IGRA sensitivity and specificity. We varied these values from the lower to the upper uncertainty bounds reported by Stout et al,[22] to test the sensitivity of reactivation rate estimates to these inputs.

Ethics statement

Apart from National TB Surveillance System data, all data used in this analysis represent deidentified publicly available datasets. TB disease data were used according to the terms of an Assurance of Confidentiality covering TB data shared with the U.S. Centers for Disease Control and Prevention by state health departments (Sections 306 and 308(d), Public Health Service Act, 42 U.S.C. 242k and 242m(d)).

RESULTS

There were 19,729 U.S. persons aged ≥6 years reported as having a verified case of TB disease in 2011–2012. Of these we excluded 9 records (0.05%) due to missing values for age, sex, race–ethnicity, or U.S.-born status. Of the 19,720 persons included in the analysis, 14,384 (72.9%) had a recorded value for the recent transmission indicator, of whom 2,022

(14.1%) were positive and 12,362 were negative (85.9%). There were 19,325 (98.0%) persons aged ≥15 years, who were included in the analyses of TB reactivation rates for diabetes, ESRD, and HIV. Table 1 summarizes TB case data by analytic stratum and recent transmission.

TB reactivation rates based on IGRA positivity

Table 2 reports TB reactivation rate estimates for the overall population and major demographic strata, using IGRA positivity to define the risk population. For the overall U.S. population aged ≥6 years, the reactivation rate was estimated as 0.060 (95% uncertainty interval: 0.051, 0.071) per 100 person–years, with rates of 0.036 (0.027, 0.047) per 100 person–years estimated for U.S.-born and 0.087 (0.075, 0.102) per 100 person–years for non-U.S.–born subpopulations. We estimated reactivation rates to be higher for 25–34-year-olds relative to other age groups, and for minority racial/ethnic populations compared to non-Hispanic White persons. eTables 1–2 http://links.lww.com/EDE/C99 provide results for demographic strata for U.S.-born and non-U.S.–born populations separately.

TB reactivation rates based on estimated LTBI prevalence

Table 3 reports TB reactivation rate estimates for the overall population and major demographic strata, using estimated LTBI prevalence after refinement based on IGRA test performance. For the overall U.S. population aged ≥6 years the reactivation rate was estimated as 0.072 (0.047, 0.12) per 100 person–years, with rates of 0.068 (0.029, 0.87) per 100 person–years estimated for U.S.-born and 0.074 (0.058, 0.097) per 100 person–years for non-U.S.–born populations. Rate ratios comparing demographic strata were generally imprecise, although we estimated reactivation rates to be lower for older persons compared to 25–34-year-olds. eTables 3–4 http://links.lww.com/EDE/C99 provide results for demographic strata for U.S.-born and non-U.S.–born populations separately.

TB reactivation rates for persons with diabetes, ESRD and HIV

We estimated reactivation rates for persons with diabetes, ESRD, and HIV to be higher than the general population (Table 4). For the diabetic population with LTBI (adjusting IGRA positivity for imperfect sensitivity and specificity of IGRA), the reactivation rate was 0.075 (0.048, 0.12) per 100 person–years (adjusted rate ratio (aRR): 1.6 (1.5, 1.7), compared to a population matched by age group, sex, race–ethnicity, and U.S.-born status without diabetes). The reactivation rate was estimated as 0.46 (0.22, 1.0) per 100 person–years (aRR: 9.8 (5.4, 19)) for persons with ESRD and LTBI, and 0.69 (0.41, 1.3) per 100 person–years (aRR: 12 (11, 13)) for persons living with HIV and LTBI. Rate ratio results estimated for IGRA-positive persons were similar to those based on LTBI prevalence adjusted for IGRA sensitivity and specificity.

Based on the LTBI results estimated in Table 4, we estimated that there were 1,087 (913, 1,254) excess TB cases during the study period attributable to diabetes [population attributable fraction (PAF) = 6.5% (5.5%, 7.5%)]. For ESRD there were an estimated 413 (358, 463) excess cases [PAF = 2.5% (2.1%, 2.8%)], and for HIV there were 1,074 (1,003, 1,147) excess cases [PAF = 6.4% (6.0%, 6.9%)].

Sensitivity analyses

We re-estimated TB reactivation rates for diabetes, ESRD, and HIV under several alternative analytic assumptions (eTable 5 http://links.lww.com/EDE/C99). Results for diabetes and HIV were robust to these changes, while results for ESRD changed substantially under different analytic assumptions, primarily related to uncertainty in the size of the ESRD population. We also re-estimated results for the population aged ≥25 years (i.e., excluding 15–24-year-olds), and in these results the estimated reactivation rates were similar to those estimated in the main analysis (eTable 6 http://links.lww.com/EDE/C99).

The Figure shows how TB reactivation rates estimated for U.S.-born and non-U.S.–born populations change for different assumptions of IGRA sensitivity and specificity. For sensitivity, estimated reactivation rates increased by 41% (U.S.-born) and 30% (non-U.S.–born) as test sensitivity was increased from the lower bound to the upper bound of the confidence intervals reported by Stout et al.[22] (Figure, Panel A). For specificity, estimated reactivation rates decreased by 93% (U.S.-born) and 20% (non-U.S.–born) as test specificity was increased from lower to upper bound of the reported confidence intervals (Figure, Panel B). Reactivation rate estimates for U.S.-born persons were particularly sensitive to low values of test specificity (reactivation rate estimated as 0.49 (0.10, 13) per 100 person–years for 96% test specificity), as the false-positive rate (1 − specificity) approached the fraction testing IGRA positive in NHANES.

DISCUSSION

In this study, we estimated rates of TB reactivation for persons with LTBI in the United States. For the population aged ≥6 years with latent TB infection, the overall reactivation rate was estimated as 0.072 (0.047, 0.12) per 100 person–years, equivalent to 1 incident TB case for every 1,400 (900, 2,100) person–years at risk. For IGRA-positive persons, reactivation rates were estimated to be lower for older persons, non-Hispanic White persons, and U.S.-born persons. After adjusting for IGRA sensitivity and specificity, these same patterns persisted, but at a smaller magnitude and with lower precision. Age-related declines in reactivation rates were observed for both U.S.-born and non-U.S.-born populations, with the magnitude of these differences greater for non-U.S.-born populations. Similarly, reactivation rates differed by race–ethnicity in both U.S.-born and non-U.S.-born populations. Our study was not designed to reveal the mechanisms behind these differences, but it is possible they result from differences in the distribution of risk factors for progression (more recent infection, comorbidities affecting immune function) by race–ethnicity and age. It is also possible that unquantified differences in factors determining IGRA sensitivity and specificity could produce this finding. In contrast, we estimated minimal (and non-significant) differences in reactivation rates by sex, despite TB incidence rates for men being 50–60% greater than for women. Compared to the general population, estimated reactivation rates were modestly higher for persons with diabetes, and substantially higher for persons with ESRD and HIV, consistent with the magnitude of immune suppression associated with these conditions.

These results are generally consistent with earlier estimates of TB reactivation rates in the Unites States, although our estimated rates are modestly lower. Using data on tuberculin

skin test positivity from NHANES 1999–2000 and an earlier genotype-based approach to estimate which TB cases were not due to recent transmission, Shea et al. estimated an overall reactivation rate of 0.084 (0.083, 0.085) per 100 person–years, compared with 0.072 (0.047, 0.12) in this analysis.[8] Subpopulation point estimates for U.S.-born and non-U.S.–born persons were also 20%–30% higher in the Shea et al. analysis. These differences are likely related to the multiple methodologic differences between these two studies, particularly the use of tuberculin skin test positivity to represent LTBI prevalence. More recently, Yelk Woodruff et al. estimated reactivation rates for the non-U.S.–born population, using similar methods and data as this analysis. They reported a reactivation rate of 0.088 (0.069, 0.11) per 100 person–years,[9] approximately 20% higher than the point estimate in this analysis. This difference is likely due to the lower IGRA sensitivity and higher specificity estimates used in the present analysis (as compared to the earlier study), which produce lower reactivation rate estimates as shown in sensitivity analyses.

The TB reactivation rate ratios associated with diabetes, ESRD and HIV are lower than estimated in some prior studies.[8,11,35,36] In addition to any methodologic differences between studies, this finding could reflect improvements in the quality of medical care for these conditions. For example, Shea et al. estimated a reactivation rate of 1.8 (1.7, 1.9) per 100 person–years for persons with HIV in 1999–2000, over twice the 0.69 (0.41, 1.3) that we estimated in this analysis based on 2011–2012. In 1999–2000, U.S. guidelines for HIV care were still in flux,[37] while by 2011–2012, HIV treatment programs were more established and highly effective regimens available. Consistent with this improvement, the number of reported TB cases among persons with HIV listed as a comorbidity dropped by 60% between 1999–2000 and 2011–2012.[38] It is also possible that the lower current reactivation rates reflect declines in the prevalence of old healed TB disease, which confers high relative risks of reactivation.[39]

Strengths of this study include the use of data sources representing the whole U.S. population, rather than specific study cohorts that may not be representative, as well as the availability of spatiotemporal and genomic data to better identify TB cases not due to recent transmission.[16] There are also several limitations. First, we needed to impute the recent transmission indicator variable for 27% of all observations, which reduces the precision of estimated reactivation rates and makes the analysis sensitive to factors not accounted for in the imputation approach. Second, the analysis requires each analytic stratum to be defined consistently across the various datasets used. While this assumption is unlikely to be problematic for demographic strata, definitions of diabetes, ESRD, and HIV might differ across datasets. In particular, our sensitivity analyses showed that alternative approaches to estimating ESRD population size could produce substantially different reactivation rate estimates. Third, while we found no evidence that LTBI prevalence varied between persons with one of the three medical comorbidities and the general population (conditional on other covariates), the small numbers of NHANES participants with both LTBI and one of these conditions provides relatively imprecise estimates of these differences, if they exist. If LTBI prevalence were higher (or lower) for persons with a given comorbidity conditional on other covariates, then our estimated reactivation rates will be biased upwards (or downwards) relative to the true values. For HIV, independent estimates suggest the LTBI prevalence values calculated in our study were reasonable.[40] Fourth, TB reactivation rate estimates

are sensitive to assumptions about LTBI test sensitivity and specificity. Estimates were particularly sensitive to changes in specificity when estimated IGRA positivity was low, where false-positive diagnoses can account for most positive test results. Consequently, uncertainty intervals for estimated reactivation rates tended to be wider in populations with lower IGRA positivity (U.S.-born populations, younger age groups). Moreover, we were unable to investigate changes in IGRA performance with increasing time since infection, though evidence suggests that initially positive individuals may revert to IGRA-negative over time.[41,42] Fifth, care should be taken when interpreting the results of this study causally. As we were not able to control for the full range of risk factors known to affect LTBI reactivation rates, it is possible that differences in the distribution of these factors contributed to the estimates of rate ratios, excess cases, and population attributable fractions. Finally, while this study reported results for a variety of population groups, is it possible that reactivation rates vary considerably within these groups. This variation could relate to differences in time since infection, with recent studies suggesting ongoing declines in TB incidence rates many years after infection.[43,44] It is unclear whether reductions in test reactivity in older populations[45] track with these declines, but evidence suggests that individuals may test positive even after *M. tuberculosis* infection is treated.[46] Variation in reactivation rates could also result from differences in immune function and differences in the duration and quality of care for diabetes, ESRD, and HIV.[47] The NTSS does not record whether individuals are receiving treatment for comorbid conditions and so this could not be considered in the analysis. The population distribution of underlying risk factors may also have changed in the years following the study period (as seen in the change in HIV reactivation rates between earlier studies[8] and this one), meaning that current reactivation rates could differ from those estimated in this study.

In summary, this study estimated TB reactivation rates for multiple demographic strata and risk populations within the United States. These estimates are useful for estimating TB disease risks for persons with LTBI, and for quantifying the potential societal impact and cost-effectiveness of TB prevention interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

We thank Robert Pratt for input on NTSS variable definitions, and Andrew Hill for input on the analytic approach.

Source of funding:

This work was supported by the U.S. Centers for Disease Control and Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention Epidemiologic and Economic Modeling Agreement (NEEMA; #5NU38PS004644), and the National Institutes of Health (R01AI146555–02). The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Data-availability statement:

Apart from National TB Surveillance System data, all data used in this analysis represent deidentified publicly available datasets. National TB Surveillance System data contain information abstracted from the national tuberculosis case report form called the Report of Verified Case of Tuberculosis (RVCT) (OMB No. 0920–0728). These data have been reported voluntarily to CDC by state and local health departments and are protected under the Assurance of Confidentiality (Sections 306 and 308(d) of the Public Health Service Act, 42 U.S.C. 242k and 242m(d)), which prevents disclosure of any information that could be used to directly or indirectly identify patients. For more information, see the CDC/ATSDR Policy on Releasing and Sharing Data (at http://www.cdc.gov/maso/Policy/ReleasingData.pdf). A limited dataset is available at http://wonder.cdc.gov/tb.html. Researchers seeking additional National TB Surveillance System data may request access through the National Center for Health Statistics' Research Data Centers (https://www.cdc.gov/rdc/b1datatype/tuberculosis.htm). Computing code available upon request.

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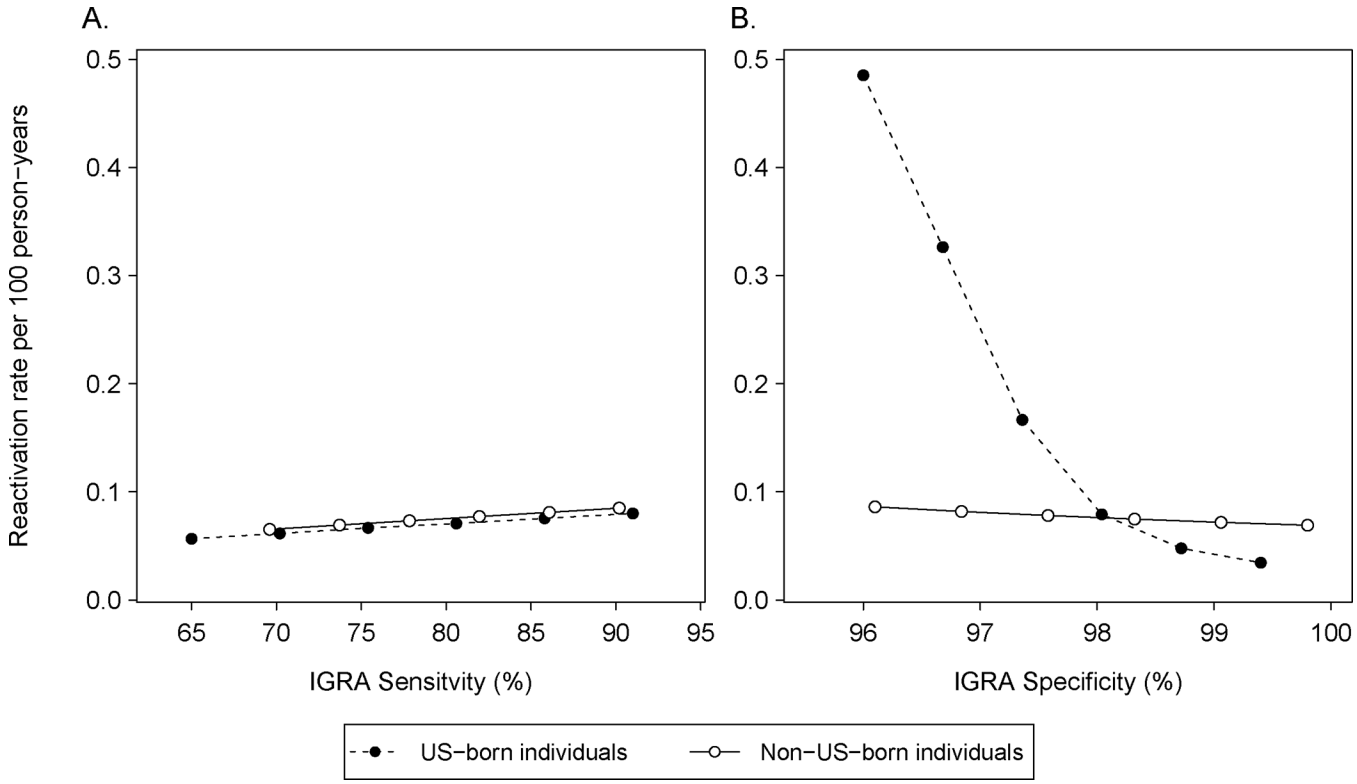

Figure: Change in LTBI reactivation rate for U.S.-born and non-U.S.–born persons for different values of IGRA sensitivity and specificity.

Sensitivity and specificity values varied between uncertainty intervals reported by Stout et al 201822 (sensitivity: 65.0%–91.0% for U.S.-born, 69.6%–90.2% for non-U.S.–born; specificity: 96.0%–99.4% for U.S.-born, 96.1%–99.8% for non-U.S.–born). 'IGRA' = interferon-gamma release assay. 'LTBI' = latent TB infection.

Table 1:

Adult tuberculosis cases among U.S. persons 2011–2012, by analytic strata, medical comorbidity, and recent transmission indicator.

		Classification by recent transmission indicator		
	All cases	**RT**	**Not RT**	**Missing**
All cases	19,720	2,022	12,362	5,336
All cases 15+ years old[a]	19,325	1,993	12,277	5,055
Age group				
Age 6–14 years	395	29	85	281
Age 15–24 years	2,046	284	1,219	543
Age 25–34 years	3,460	322	2,216	922
Age 35–44 years	3,013	326	1,841	846
Age 45–54 years	3,319	469	1,953	897
Age 55–64 years	3,066	359	1,849	858
Age 65–74 years	2,085	142	1,411	532
Age 75+ years	2,336	91	1,788	457
Sex				
Male	12,026	1,365	7,577	3,084
Female	7,694	657	4,785	2,252
Race–ethnicity				
Non-Hispanic White	3,130	298	1,979	853
Non-Hispanic Asian	6,073	311	4,221	1,541
Non-Hispanic Black	4,490	792	2,441	1,257
Non-Hispanic Other[b]	551	116	317	118
Hispanic	5,476	505	3,404	1,567
U.S.-born status				
U.S.-born	6,945	1,300	3,783	1,862
Non-U.S.–born	12,775	722	8,579	3,474
Medical comorbidities				
Diabetes	3,310	327	2,290	693
End-stage renal disease	520	44	337	139
HIV[c]	1,297	205	733	359

‘RT’ indicates cases attributed to recent transmission.

[a]Population used in analyses of reactivation rates for diabetes, end-stage renal disease, and HIV.

[b]Includes all race–ethnicity responses not captured in other categories.

[c]Counts based on non-imputed HIV variable.

Table 2:

Rates of reactivation TB for IGRA-positive persons in the United States, by major population subgroup, 2011–2012.

	Total reactivation TB cases[a]	IGRA+ prevalence (%)	Population estimate (Mil.)	Person-years at risk (1000s)	Reactivation rate (per 100 PY)	Rate ratio[b]
Total population [c]	17,033 (16,773, 17,294)	4.9 (4.2, 5.8)	288.7 (288.6, 288.8)	28,345 (24,115, 33,534)	0.060 (0.051, 0.071)	---
Age group						
6–14 years	331 (295, 369)	0.7 (0.4, 1.5)	37.1 (37.0, 37.1)	540 (259, 1,145)	0.061 (0.029, 0.13)	0.59 (0.24, 1.4)
15–24 years	1,673 (1,592, 1,755)	2.5 (1.6, 4.0)	43.9 (43.9, 43.9)	2,218 (1,392, 3,547)	0.075 (0.047, 0.12)	0.73 (0.37, 1.4)
25–34 years	3,023 (2,914, 3,133)	3.5 (2.2, 5.6)	41.7 (41.7, 41.8)	2,913 (1,835, 4,652)	0.10 (0.065, 0.17)	Reference
35–44 years	2,581 (2,479, 2,683)	4.6 (3.5, 6.2)	40.9 (40.9, 41.0)	3,749 (2,872, 5,057)	0.069 (0.051, 0.090)	0.66 (0.38, 1.1)
45–54 years	2,716 (2,613, 2,820)	5.4 (3.6, 8.1)	44.4 (44.4, 44.5)	4,769 (3,236, 7,184)	0.057 (0.038, 0.084)	0.55 (0.30, 1.0)
55–64 years	2,607 (2,506, 2,709)	9.3 (7.4, 12)	38.3 (38.3, 38.3)	7,126 (5,696, 9,025)	0.037 (0.029, 0.046)	0.35 (0.21, 0.59)
65–74 years	1,894 (1,808, 1,980)	9.0 (6.6, 13)	23.3 (23.2, 23.3)	4,181 (3,078, 5,866)	0.045 (0.032, 0.062)	0.44 (0.25, 0.76)
75+ years	2,209 (2,117, 2,302)	9.8 (7.7, 12)	19.0 (19.0, 19.0)	3,732 (2,920, 4,661)	0.059 (0.047, 0.076)	0.57 (0.34, 0.97)
Sex						
Male	10,246 (10,045, 10,448)	5.6 (4.8, 6.6)	141.5 (141.5, 141.6)	15,928 (13,583, 18,791)	0.064 (0.054, 0.076)	Reference
Female	6,788 (6,625, 6,951)	4.2 (3.4, 5.4)	147.1 (147.1, 147.2)	12,463 (10,000, 15,810)	0.054 (0.043, 0.068)	0.85 (0.63, 1.1)
Race–ethnicity						
Non-Hispanic White	2,689 (2,586, 2,794)	2.9 (2.2, 3.9)	185.0 (185.0, 185.1)	10,809 (8,000, 14,593)	0.025 (0.018, 0.034)	Reference
Non-Hispanic Asian	5,645 (5,496, 5,795)	17 (15, 19)	14.5 (14.5, 14.5)	4,803 (4,221, 5,445)	0.12 (0.10, 0.13)	4.7 (3.4, 6.6)
Non-Hispanic Black	3,495 (3,377, 3,615)	6.3 (5.2, 7.7)	35.1 (35.1, 35.1)	4,443 (3,623, 5,426)	0.079 (0.064, 0.097)	3.2 (2.2, 4.6)
Non-Hispanic Other	418 (378, 459)	3.3 (1.2, 11)	7.8 (7.8, 7.8)	519 (185, 1,740)	0.080 (0.024, 0.23)	3.2 (0.93, 9.5)
Hispanic	4,786 (4,650, 4,924)	8.5 (7.2, 10)	46.3 (46.2, 46.3)	7,857 (6,647, 9,252)	0.061 (0.052, 0.072)	2.5 (1.7, 3.5)
U.S.-born status						
U.S.-born	5,239 (5,095, 5,386)	3.0 (2.3, 4.0)	246.0 (245.9, 246.0)	14,733 (11,085, 19,480)	0.036 (0.027, 0.047)	Reference
Non-U.S.–born	11,794 (11,580, 12,011)	16 (14, 19)	42.7 (42.7, 42.8)	13,557 (11,612, 15,756)	0.087 (0.075, 0.10)	2.5 (1.8, 3.4)

Values in parentheses represent 95% uncertainty intervals.

[a] TB case counts include imputed values for recent transmission indicator.

[b] Rate ratios not adjusted for the distribution of other covariates across groups.

[c] Total population includes all U.S. residents aged 6+ years. ‘PY’ = person-years. ‘IGRA’ = interferon-gamma release assay.

Table 3:

Rates of reactivation TB for persons with LTBI in the United States, by major population subgroup, 2011–2012.

	Total reactivation TB cases[a]	LTBI prevalence (%)	Population estimate (Mil.)	Person-years at risk (1000s)	Reactivation rate (per 100 PY)	Rate ratio[b]
Total population [c]	17,033 (16,773, 17,294)	4.1 (2.5, 6.3)	288.7 (288.6, 288.8)	23,589 (14,655, 36,288)	0.072 (0.047, 0.12)	---
Age group						
6–14 years	331 (295, 369)	0.4 (0.0, 1.8)	37.1 (37.0, 37.1)	311 (33, 1,347)	0.11 (0.024, 0.99)	0.79 (0.27, 4.4)
15–24 years	1,673 (1,592, 1,755)	1.5 (0.3, 4.5)	43.9 (43.9, 43.9)	1,354 (289, 3,956)	0.12 (0.042, 0.58)	0.93 (0.42, 2.4)
25–34 years	3,023 (2,914, 3,133)	2.7 (0.8, 7.1)	41.7 (41.7, 41.8)	2,266 (669, 5,889)	0.13 (0.051, 0.45)	Reference
35–44 years	2,581 (2,479, 2,683)	4.3 (2.6, 7.5)	40.9 (40.9, 41.0)	3,535 (2,139, 6,157)	0.073 (0.042, 0.12)	0.54 (0.23, 1.0)
45–54 years	2,716 (2,613, 2,820)	5.3 (2.6, 11)	44.4 (44.4, 44.5)	4,676 (2,265, 9,826)	0.058 (0.028, 0.12)	0.43 (0.21, 0.71)
55–64 years	2,607 (2,506, 2,709)	9.5 (5.3, 15)	38.3 (38.3, 38.3)	7,268 (4,020, 11,242)	0.036 (0.023, 0.065)	0.27 (0.11, 0.51)
65–74 years	1,894 (1,808, 1,980)	9.0 (4.3, 16)	23.3 (23.2, 23.3)	4,183 (2,005, 7,506)	0.045 (0.025, 0.095)	0.35 (0.16, 0.58)
75+ years	2,209 (2,117, 2,302)	10 (5.2, 16)	19.0 (19.0, 19.0)	3,842 (1,965, 6,027)	0.057 (0.037, 0.11)	0.44 (0.19, 0.81)
Sex						
Male	10,246 (10,045, 10,448)	4.9 (2.9, 7.4)	141.5 (141.5, 141.6)	13,838 (8,190, 20,933)	0.074 (0.049, 0.13)	Reference
Female	6,788 (6,625, 6,951)	3.4 (2.1, 5.8)	147.1 (147.1, 147.2)	10,080 (6,087, 16,993)	0.067 (0.040, 0.11)	0.89 (0.53, 1.5)
Race–ethnicity						
Non-Hispanic White	2,689 (2,586, 2,794)	1.6 (0.3, 3.8)	185.0 (185.0, 185.1)	5,850 (1,171, 14,079)	0.046 (0.019, 0.23)	Reference
Non-Hispanic Asian	5,645 (5,496, 5,795)	20 (15, 25)	14.5 (14.5, 14.5)	5,651 (4,466, 7,166)	0.10 (0.079, 0.13)	2.2 (0.48, 4.7)
Non-Hispanic Black	3,495 (3,377, 3,615)	5.6 (2.6, 9.0)	35.1 (35.1, 35.1)	3,955 (1,845, 6,343)	0.088 (0.055, 0.19)	2.0 (0.48, 4.4)
Non-Hispanic Other	418 (378, 459)	4.0 (0.3, 23)	7.8 (7.8, 7.8)	628 (46, 3,558)	0.066 (0.012, 0.91)	1.3 (0.31, 12)
Hispanic	4,786 (4,650, 4,924)	8.7 (5.9, 12)	46.3 (46.2, 46.3)	8,044 (5,443, 11,294)	0.059 (0.042, 0.088)	1.3 (0.30, 2.7)
U.S.-born status						
U.S.-born	5,239 (5,095, 5,386)	1.6 (0.1, 3.6)	246.0 (245.9, 246.0)	7,699 (596, 17,854)	0.068 (0.029, 0.87)	Reference
Non-U.S.–born	11,794 (11,580, 12,011)	18 (14, 24)	42.7 (42.7, 42.8)	15,936 (12,113, 20,371)	0.074 (0.058, 0.097)	1.1 (0.09, 2.4)

Values in parentheses represent 95% uncertainty intervals.

[a] TB case counts include imputed values for recent transmission indicator.

[b] Rate ratios not adjusted for the distribution of other covariates across groups.

[c]Total population includes all U.S. residents aged 6+ years. ‘PY’ = person-years. ‘LTBI’ = latent TB infection.

Table 4:

Rates of reactivation TB for IGRA-positive persons and persons with LTBI, for selected medical comorbidities in the United States, 2011–2012.

	Total reactivation TB cases[a]	IGRA+ / LTBI prevalence (%)	Population estimate (1000s)	Person-years at risk (1000s)	Reactivation rate (per 100 PY)	Unadjusted rate ratio [b]	Adjusted rate ratio [b]
IGRA-positive persons							
General population[c]	16,704 (16,446, 16,962)	5.7 (5.0, 6.6)	251,599 (251,527, 251,670)	28,658 (25,223, 33,009)	0.058 (0.051, 0.066)	Reference	Reference
Diabetes	2,903 (2,797, 3,011)	9.0 (7.8, 10)	20,669 (19,813, 21,563)	3,723 (3,194, 4,343)	0.078 (0.067, 0.091)	1.4 (1.3, 1.6)	1.6 (1.5, 1.7)
End-stage renal disease	461 (419, 504)	11 (7.2, 16)	433 (242, 818)	94 (49, 171)	0.49 (0.27, 0.94)	8.7 (4.8, 16)	9.8 (5.5, 18)
HIV	1,176 (1,105, 1,248)	7.7 (6.4, 9.5)	1,105 (1,041, 1,174)	169 (138, 210)	0.69 (0.56, 0.86)	13 (11, 15)	12 (11, 13)
Persons with LTBI							
General population[c]	16,704 (16,446, 16,962)	5.4 (3.2, 8.7)	251,599 (251,527, 251,670)	27,287 (15,918, 43,818)	0.061 (0.038, 0.11)	Reference	Reference
Diabetes	2,903 (2,797, 3,011)	9.4 (5.7, 14)	20,669 (19,813, 21,563)	3,882 (2,342, 5,991)	0.075 (0.048, 0.12)	1.3 (1.2, 1.4)	1.6 (1.5, 1.7)
End-stage renal disease	461 (419, 504)	12 (5.8, 21)	433 (242, 818)	100 (45, 206)	0.46 (0.22, 1.0)	7.7 (4.2, 15)	9.8 (5.4, 19)
HIV	1,176 (1,105, 1,248)	7.8 (4.3, 12.9)	1,105 (1,041, 1,174)	171 (92, 284)	0.69 (0.41, 1.3)	12 (11, 14)	12 (11, 13)

Values in parentheses represent 95% uncertainty intervals.

[a] TB case counts include imputed values for recent transmission indicator.

[b] Unadjusted rate ratios compare risk population to U.S. general population without the comorbidity. Adjusted rate ratios control for differences in demographic covariates (age group, sex, race–ethnicity, U.S.-born status).

[c] General population and other groups restricted to persons 15+ years old. ‘PY’ = person-years. ‘IGRA’ = interferon-gamma release assay. ‘LTBI’ = latent TB infection.