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Time Since Infection and Risks of Future Disease for Individuals with *Mycobacterium tuberculosis* Infection in the United States

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Background: Risk of tuberculosis (TB) declines over time since *Mycobacterium tuberculosis* infection, but progression to clinical disease is still possible decades later. In the United States, most TB cases result from the progression of latent TB infection acquired over 2 years ago.

Methods: We synthesized evidence on TB natural history and incidence trends using a transmission-dynamic model. For the 2020 US population, we estimated average time since infection and annual, cumulative, and remaining lifetime risks of progression to TB, by nativity and age.

Results: For a newly infected adult with no other risk factors for progression to TB, estimated rates of progression declined from 38 (95% uncertainty interval: 33, 46) to 0.38 (0.32, 0.45) per 1000 person–years between the first and 25th year since infection. Cumulative risk over 25 years from new infection was 7.9% (7.0, 8.9). In 2020, an estimated average age of individuals with prevalent infection was 62 (61, 63) for the US-born population, 55 (54, 55) for non-US-born, and 57 (56, 58) overall. Average risks of developing TB over the remaining lifetime were 1.2% (1.0, 1.4) for US-born, 2.2% (1.8, 2.6) for non-US-born, and 1.9% (1.6, 2.2) for the general population. Risk estimates were higher for younger age groups.

Conclusions: Our analysis suggests that, although newly infected individuals face appreciable lifetime TB risks, most US individuals with latent TB infection were infected long ago, and face low future risks of developing TB. Better approaches are needed for identifying recently infected individuals and those with elevated progression risks.

Keywords: Latent TB infection; Mathematical modeling; Tuberculosis; United States

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Delayed progression of latent tuberculosis infection (LTBI) is thought to generate most new TB cases in low-incidence countries such as the United States.[1,2] In these settings, treating the population reservoir of LTBI to reduce the risk of progression to TB disease represents a primary strategy for reducing TB incidence.[3–5] However, the large majority of individuals with LTBI will not develop TB in their lifetimes, so a positive test for *Mycobacterium tuberculosis* (*Mtb*) infection alone is a poor indicator of future risk for TB disease; nonetheless, the current US TB prevention policy recommends treating all persons diagnosed with LTBI to ensure that the greatest possible number of persons at high risk for progressing to TB disease are treated. Although estimates of 5%–10% are typically cited for the lifetime risk of TB for newly infected adults, most of this risk occurs in the first few years following infection.[6–9] The remaining lifetime risk of TB for individuals infected many years ago (sometimes called reactivation TB) will be substantially lower.[10] The diagnostic tests currently available to diagnose LTBI—such as interferon-gamma release assays (IGRA)—have imperfect sensitivity and specificity,[11–13] and do not identify those who will eventually develop TB among all those with LTBI,[14] which further limits the effectiveness of efforts to target TB prevention toward those who would benefit most.[15]

Given the importance of time since infection in determining future TB risk and the potential benefits of treatment to prevent TB, we estimated the distribution of time since

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infection in the United States by age and broad population stratum, and calculated the implications of these findings for lifetime TB risk among those with LTBI and those testing positive with current LTBI diagnostics.

METHODS

Data on the timing of *Mtb* infection do not exist for the majority of individuals with LTBI, precluding a direct measurement of study outcomes. Instead, we estimated outcomes using a transmission-dynamic model of TB in the US population. We used this model to synthesize data on population dynamics, TB incidence patterns, and *Mtb* infection test positivity with evidence on TB natural history, *Mtb* infection test performance, and other factors. Using this model, we estimated time since infection and other epidemiologic outcomes for the US population and major population strata in 2020.

Key Data Sources

TB Incidence

We derived TB case data from the National Tuberculosis Surveillance System,[16] which includes all TB cases reported in the United States.[17] We extracted data on total TB cases diagnosed in the United States since 1953, and detailed data on the distribution of TB cases (including age, nativity, and risk group membership) between 1993 and 2018.

Mtb Infection Prevalence

We derived data on IGRA-positivity (a marker of prevalent *Mtb* infection) from the National Health and Examination Survey (NHANES). We used estimates of IGRA-positivity from the last survey cycle to include TB (2011–2012),[18] disaggregated by nativity (US-born vs. non-US-born) and age group (6 years and older).

Additional Evidence on TB Natural History

Cross-sectional data on TB incidence and IGRA-positivity do not describe how the risk of developing TB changes as a function of time since infection. Moreover, the small sample size of NHANES means that it provides limited evidence on differences in LTBI prevalence between population strata. For these reasons, we incorporated additional evidence to better describe TB natural history. Data on the risk of progression to TB disease as a function of time since *Mtb* infection was derived from the UK Medical Research Council BCG trials[6] (15 years of follow-up), the placebo arm of the US Public Health Service isoniazid trials[7] (10 years of follow-up), and a long-term follow-up study of TB contacts in the Netherlands[19] (15 years of follow-up). We assumed that progression rates decline monotonically with respect to time since infection, consistent with earlier studies estimating low risk of progression rates for individuals with distant infection,[8] and the possibility that some individuals may eventually clear *Mtb* infection naturally[20] or otherwise experience lower progression rates with distant infection. We derived age-based differences in progression rates for younger age groups from a review of observational studies of pediatric TB,[21] and we also allowed for increases in progression risks in individuals over 65 years of age, conditional on time since infection.[22] We assumed higher risks of progression to TB for individuals living with HIV (stratified by immune status and receipt of antiretroviral therapy),[23–25] and lower risks in individuals with existing infection who are reinfected.[26]

Diagnostic Test Performance

Evidence on test sensitivity and specificity is necessary for estimating *Mtb* infection prevalence from data on IGRA-positive test results,[18] and to estimate progression risks for those with a positive IGRA result. We used sensitivity and specificity estimates for QuantiFERON Gold In-Tube from the CDCs Tuberculosis Epidemiologic Studies Consortium.[11] For adults without HIV, sensitivity was 78.9% for the non-US-born and 78.0% for US-born, and specificity was 98.5% for the non-US-born and 97.9% for US-born. We used an estimate of 67.5% sensitivity and 95.8% specificity for individuals with HIV, and 71.2% sensitivity and 98.9% specificity for children <5 years old, assuming common test performance for the US-born and non-US-born individuals.

Transmission Dynamic Model

We adapted a transmission dynamic model of TB in the United States.[27,28] This model provides a quantitative framework for synthesizing and relating the data sources on TB epidemiology and natural history described above. Model structures used to represent latent infection and risks of progression to TB were consistent with empirical natural history data based on an earlier systematic review.[29]

For the present analysis, we recalibrated the model to recent US TB data[16] (eFigure 1; http://links.lww.com/EDE/B733, which shows model calibration to evidence sources for TB incidence and *Mtb* infection prevalence). We also extended the model to record *Mtb* infection events for successive US birth cohorts and non-US-born immigration cohorts by single year of age and calendar year, as well as to project future outcomes (progression to TB disease or death) among those with prevalent *Mtb* infection in 2020. Among the non-US-born population, most individuals with *Mtb* infection likely acquired infection before entry to the United States,[30] and this introduces substantial challenges for describing the distribution of time since infection for these individuals. Although future risks of progression to TB disease can be inferred indirectly from the time trends in TB incidence rates after entry to the United States, we do not report estimates for time since infection for the non-US-born population.

Study Outcomes

The major study outcomes are shown in Table 1. These outcomes describe risks due to prevalent *Mtb* infection, and exclude TB risks due to new *Mtb* infections acquired in the future. For results describing remaining lifetime TB risks, we assumed that the current US background mortality rates[31] would apply, and for HIV we assumed disease-specific excess mortality rates. All outcomes are estimated for the year 2020.

TABLE 1. Definition of Major Study Outcomes

Category	Outcome
Risks of progression to TB for a known time since infection	Annual rate of progression to TB following *Mtb* infection, as a function of the number of years since infection (per 1000 person–years)
	Cumulative risk of progression to TB following *Mtb* infection, as a function of the number of years since infection (%)
	Remaining lifetime risk of progression to TB for infected individuals who have not yet developed TB, as a function of the number of years since infection (%)
Age at and time since infection	Average age at infection for US-born individuals with prevalent *Mtb* infection (years of age)
	Average time since infection for US-born individuals with prevalent *Mtb* infection (years)
	Average time since infection for US-born individuals developing TB disease (years)
Risks of progression to TB related to prevalent *Mtb* infection	Annual rate of progression to TB for individuals with prevalent *Mtb* infection (per 1000 person–years)
	Annual rate of progression to TB for individuals with prevalent *Mtb* infection who were infected >2 years ago (i.e.,LTBI) (per 1000 person–years)
	Remaining lifetime risk of progression to TB for individuals with prevalent *Mtb* infection (%)
	Remaining lifetime risk of progression to TB for IGRA-positive individuals (%). IGRA-positive individuals include true-positive test results for individuals with *Mtb* infection, and false-positive test results for individuals without *Mtb* infection
	Remaining lifetime risk of progression to TB in the general population (%)

Estimation

We implemented the analysis as a Bayesian evidence synthesis,[32,33] calibrating the model to a variety of demographic and epidemiologic data, with informative prior distributions specified for model parameters.[27] We used Incremental Mixture Importance Sampling[34,35] to draw 5000 parameter sets from the posterior parameter distribution, and used this sample of parameter sets to simulate outcomes of interest. This approach produces a large number of epidemiologic trajectories consistent with prior distributions and calibration data (individual lines shown in Figure 1). We calculated point estimates for each outcome of interest as the mean value across simulation results from all 5000 parameter sets, and calculated 95% uncertainty intervals as the 2.5th and 97.5th percentiles of the distribution of simulation results.

RESULTS

Annual Rates of Progression to tuberculosis Following *Mycobacterium tuberculosis* Infection

Figure 1A shows estimated rates of progression to TB disease over the first 25 years following *Mtb* infection, for an individual infected at age 20 without any risk factors for faster progression. These estimated rates decline from 38 (95% uncertainty interval: 33, 46) per 1000 person–years in the first year after infection, to 3.4 (2.6, 4.0) per 1000 person–years 5 years after infection, 0.76 (0.60, 0.92) per 1000 person–years 10 years after infection, and 0.38 (0.32, 0.45) per 1000 person–years 25 years after infection.

Cumulative risks of progression to tuberculosis following *Mycobacterium tuberculosis* infection

Figure 1B shows estimated cumulative TB risks over 25 years following infection, which increase from 3.8% (3.2, 4.5) at the end of the first year postinfection, to 6.6% (5.8, 7.7) at the end of the fifth year, 7.2% (6.4, 8.3) at the end of the 10th year, and 7.9% (7.0, 8.9) at the end of the 25th year. As the risk of developing TB is concentrated in the years soon after infection, the average time to progression was 7.1 (6.1, 8.1) years for a 20-year-old individual without any known risk factors for faster progression.

Remaining Lifetime Risks of Progression to tuberculosis Following *Mycobacterium tuberculosis* Infection

Figure 1C shows the remaining lifetime risk of developing TB for an individual who has not developed TB by a given year since infection, assuming death at 80 years of age (average age of death for a 20-year-old individual). These estimated risks decline rapidly with increasing time since initial infection, from 8.8% (7.9, 9.9) immediately after infection (representing total lifetime risk of TB following infection), to 2.5% (2.2, 2.9) at the start of the fifth year, 1.7% (1.4, 2.0) at the start of the 10th year, and 1.0% (0.8, 1.2) at the start of the 25th year.

Average Age at Infection and Time Since Infection for US-born Individuals with Prevalent *Mycobacterium tuberculosis* Infection by Age

Figure 2A shows estimates for the average number of years since infection for US-born individuals with prevalent *Mtb* infection in 2020, as a function of current age (red line). These estimates suggest that, for individuals up to 40 years of age, the average age at infection was approximately half their current age. For individuals over 40 years old, the average age at infection was approximately 18–20 years. The average age of the US-born population with *Mtb* infection was estimated to be 62 (61, 63) years, and the average time since infection was estimated to be 44 (43, 46) years, with the average age at infection of 18 (17, 19) years. Estimates for the average age at infection and time since infection for broad age groups are provided in Table 2. Figure 2A also describes the distribution of time since infection for each year of age, with darker blue shading indicating a greater fraction of individuals having been infected a given number of years ago.

Average Time Since Infection for US-born Individuals Developing tuberculosis Disease by Age

Figure 2B shows estimates for the average number of years since infection for US-born individuals who develop

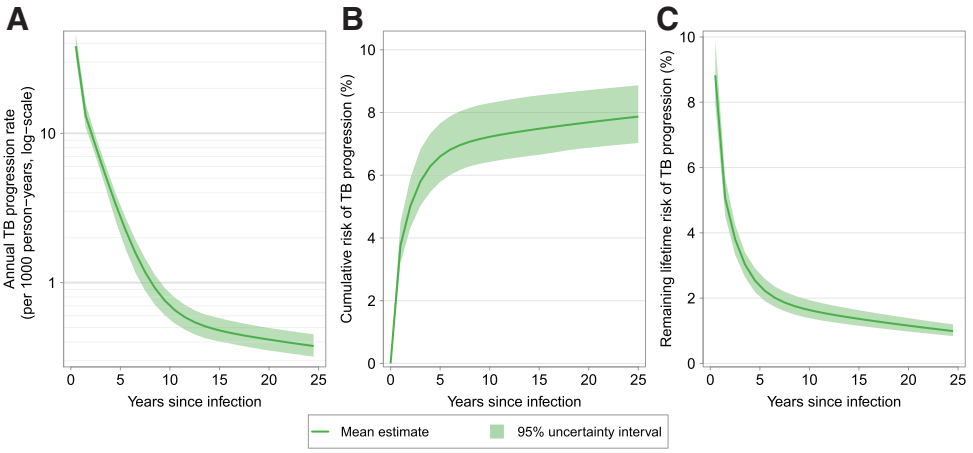

FIGURE 1. Estimated risks of progression to TB as a function of time since infection, for an individual infected at age 20. A, Model estimates for annual rate of progression to TB as a function of time since infection, for an individual infected at 20 years of age with no other risk factors for progression to TB. B, Model estimates for cumulative risk of progression to TB as a function of time since infection, for an individual infected at 20 years of age with no other risk factors for progression to TB. C, Model estimates for remaining lifetime risk of progression to TB as a function of time since infection, for an individual infected at 20 years of age with no other risk factors for progression to TB, and who has not yet developed TB. Estimates assume no reinfection or treatment of *Mtb* infection. Difference between year 1 risk in (C) and final year risk in (B) represents additional risk accruing after 25 years following infection.

TB disease in 2020, as a function of current age. Compared to results for individuals with prevalent *Mtb* infection (Figure 2A), these time since infection estimates are smaller for any given age group—particularly for individuals under 50 years of age—and the average time since infection for the US-born individuals who develop TB disease in 2020 was estimated to be 31 (29, 33) years. As with Figure 2A, Figure 2B shows the distribution of time since infection for each age group. A dark band (indicating a substantial fraction of all individuals) runs along the *x* axis, reflecting the high short-term risk of TB among those initially infected. In both graphs, darker shading can be seen at approximately 30 years since infection, reflecting a temporary increase in the force of infection associated with the recrudescence of TB in the US during the late 1980s and early 1990s.

Annual rates of progression to tuberculosis for individuals with prevalent *Mycobacterium tuberculosis* infection

Among individuals with prevalent *Mtb* infection in 2020 (including those who may have been infected recently), population-average rates of progression to TB were estimated to be 1.19 (1.02, 1.39) for HIV-negative US-born and 0.95 (0.81, 1.12) per 1000 for HIV-negative non-US-born individuals (risk ratio 0.80 [0.70, 0.90] for non-US-born versus US-born). These populations had an average age of 62 (61, 63) and 55 (54, 55), respectively. The average rate was 10.8 (8.8, 13.8) per 1000 person–years for the HIV-positive population, and 1.09 (0.96, 1.28) per 1000 person–years for the general population (average age 57 [56, 58]). Rates were estimated to be higher in younger age groups in which infection is more likely to be recent, with rates of 12.0 (9.8, 13.8) for 0–14 year olds, and 3.0 [2.6, 3.5] per 1000 for 15–24 year olds.

Annual Rates of Progression to Tuberculosis for Individuals Infected More Than 2 Years Ago

When individuals in their first 2 years since *Mtb* infection are excluded, population-average rates of progression to TB were lower, estimated to be 0.79 (0.67, 0.93) for HIV-negative US-born individuals per 1000 person–years and 0.77 (0.65, 0.92) per 1000 person–years for HIV-negative non-US-born individuals (risk ratio 0.97 [0.89, 1.06] for non-US-born vs. US-born). For the HIV-positive individuals, the rate was 7.8 (5.5, 10.4) per 1000 person–years, and for the general population, the rate was 0.82 (0.70, 0.97) per 1000 person–years. These calculations only excluded recent infection within the United States, and did not consider recent infection acquired before US entry for non-US-born individuals. Rates of progression to TB were higher in younger age groups, estimated to be 5.7 (4.5, 7.0) per 1000 person–years for 0–14 year olds and 1.5 (1.3, 1.7) per 1000 person–years for 15–24 year olds.

Remaining Lifetime Risks of Progression to tuberculosis for Individuals with Prevalent *Mycobacterium tuberculosis* Infection by Age

Figure 3 shows estimates for the percentage of *Mtb*-infected individuals who are predicted to progress to TB disease in their lifetime due to this prevalent *Mtb* infection, as a function of age. Values are stratified by nativity and HIV status. These probabilities are substantially higher for younger individuals, due to shorter average time since infection and longer remaining life expectancy, as well as higher risks of

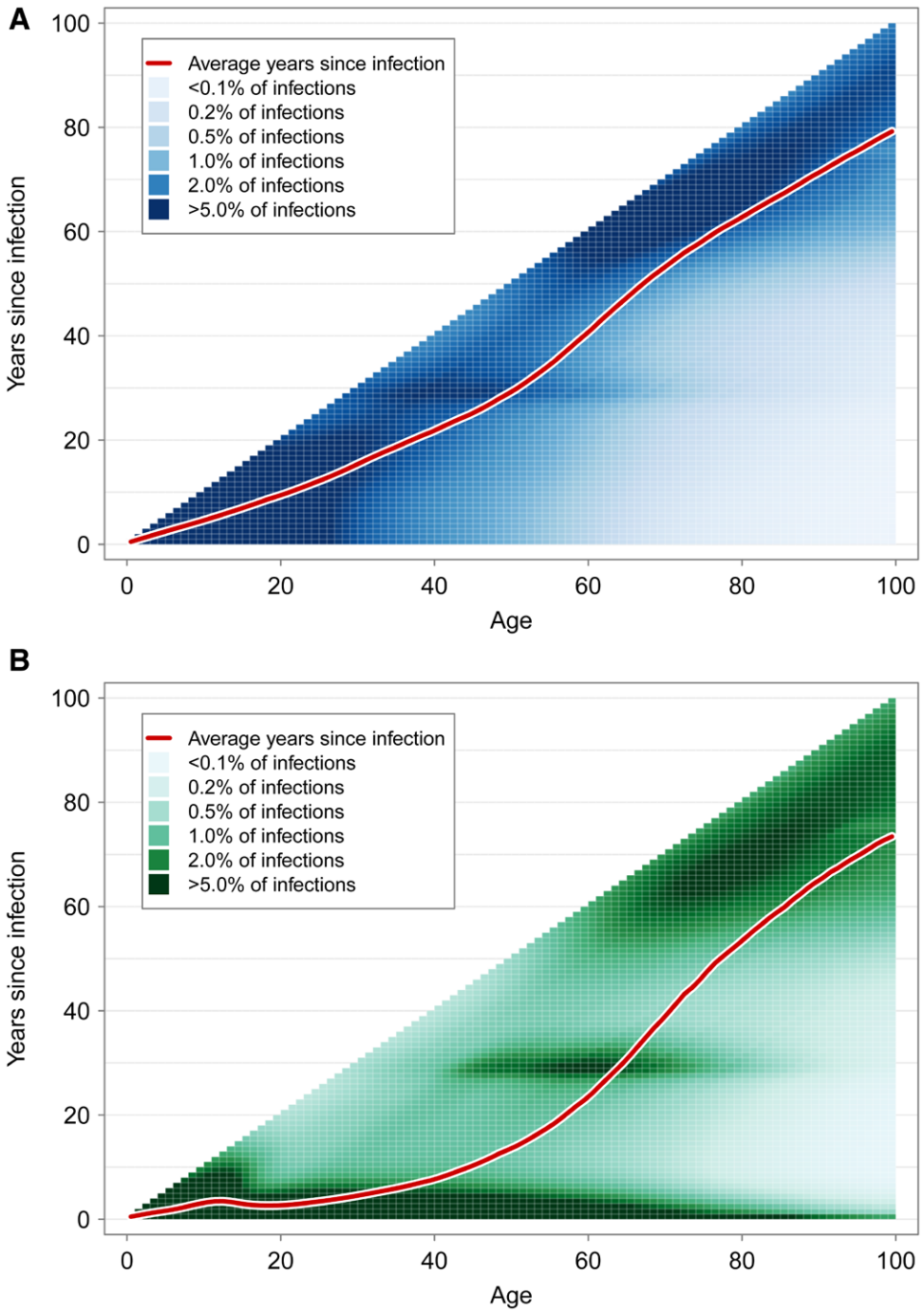

FIGURE 2. Average time since infection for US-born individuals with prevalent Mtb infection and incident TB in 2020, by current age. A, Average number of years since infection and distribution of number of years since infection for US-born individuals with prevalent *Mtb* infection in 2020, by age. B, Average number of years since infection and distribution of number of years since infection for US-born individuals developing TB disease in 2020, by age.

rapid disease progression in young children. We estimated low values for older age groups, which constitute the majority of the US population with *Mtb* infection. Estimates for individuals with HIV were higher than for HIV negative individuals, due to higher risk of progression in this population. The average value was 1.2% (1.0, 1.4) over all ages in the US-born population. The average value was 2.2% (1.8, 2.6) over all ages in the non-US-born population, 1.8 (1.7, 2.0) times higher than that of the US-born population. For the total population with prevalent *Mtb* infection, the average lifetime risk

TABLE 2. Key Measures of the Natural History of Prevalent Mtb Infection, by Age Group and Nativity in 2020.[a]

	Population Prevalence (%)				Remaining Lifetime Risks of Progression to TB (%)[d]		
	Mtb Infection	IGRA-Positive[b]	Average Age at Infection[c]	Average Time Since Infection (Years)[c]	Prevalent *Mtb* Infection[e]	IGRA-Positive[b]	General Population
US-born[f]							
Age 0–4 years	0.02 (0.02, 0.02)	1.13 (0.22, 2.74)	1.4 (1.3, 1.4)	1.6 (1.6, 1.6)	22 (19, 25)	0.38 (0.10, 1.27)	0.004 (0.003, 0.005)
Age 5–14 years	0.08 (0.07, 0.10)	2.15 (0.77, 4.22)	6.0 (5.9, 6.1)	5.2 (5.1, 5.3)	4.5 (3.9, 5.2)	0.16 (0.07, 0.38)	0.004 (0.003, 0.005)
Age 15–24 years	0.22 (0.18, 0.26)	2.25 (0.87, 4.32)	10.8 (10.5, 11.1)	9.8 (9.5, 10.0)	2.7 (2.3, 3.1)	0.24 (0.10, 0.53)	0.006 (0.005, 0.007)
Age 25–44 years	0.66 (0.54, 0.80)	2.6 (1.2, 4.7)	17.0 (16.4, 17.6)	20 (19, 20)	2.0 (1.7, 2.3)	0.44 (0.21, 0.85)	0.013 (0.011, 0.015)
Age 45–64 years	1.9 (1.5, 2.3)	3.5 (2.1, 5.6)	19.7 (18.6, 20.8)	37 (35, 38)	1.3 (1.1, 1.6)	0.57 (0.33, 0.90)	0.024 (0.021, 0.028)
Age 65–84 years	3.3 (2.6, 4.2)	4.6 (3.1, 6.7)	17.0 (15.6, 18.4)	57 (55, 58)	0.73 (0.59, 0.89)	0.42 (0.27, 0.59)	0.024 (0.019, 0.027)
Age 85+ years	4.7 (3.6, 6.0)	5.7 (4.0, 7.9)	18.8 (17.8, 20.0)	72 (70, 73)	0.29 (0.23, 0.36)	0.19 (0.13, 0.26)	0.014 (0.011, 0.016)
All[g]	1.22 (0.98, 1.53)	2.9 (1.7, 4.9)	17.9 (17.0, 18.7)	44 (42, 46)	1.18 (0.98, 1.43)	0.41 (0.22, 0.68)	0.014 (0.012, 0.017)
Non-US-born[f]							
Age 0–4 years	0.92 (0.78, 1.10)	1.76 (0.84, 3.39)	—	—	4.6 (4.0, 5.4)	1.91 (0.85, 3.48)	0.042 (0.037, 0.048)
Age 5–14 years	2.1 (1.8, 2.4)	3.1 (1.8, 5.6)	—	—	3.5 (3.0, 4.2)	2.0 (1.0, 3.2)	0.073 (0.064, 0.085)
Age 15–24 years	4.8 (4.2, 5.5)	5.3 (3.7, 7.6)	—	—	3.3 (2.8, 3.9)	2.4 (1.6, 3.2)	0.16 (0.14, 0.18)
Age 25–44 years	10.4 (9.0, 11.8)	9.6 (7.5, 12.2)	—	—	2.7 (2.3, 3.2)	2.3 (1.8, 2.9)	0.28 (0.24, 0.33)
Age 45–64 years	18 (16, 20)	15 (13, 18)	—	—	2.2 (1.8, 2.6)	2.0 (1.6, 2.5)	0.39 (0.32, 0.45)
Age 65–84 years	25 (22, 28)	21 (17, 24)	—	—	1.5 (1.3, 1.9)	1.5 (1.2, 1.8)	0.38 (0.32, 0.45)
Age 85+ years	29 (26, 32)	24 (20, 28)	—	—	0.72 (0.59, 0.90)	0.69 (0.56, 0.86)	0.21 (0.18, 0.25)
All[g]	14 (12, 16)	12.3 (9.9, 15.0)	—	—	2.2 (1.8, 2.6)	1.9 (1.5, 2.4)	0.30 (0.25, 0.35)
Total population							
All[g]	2.9 (2.6, 3.4)	4.2 (3.0, 5.9)	—	—	1.9 (1.6, 2.2)	1.04 (0.71, 1.43)	0.055 (0.048, 0.062)

Values in parentheses represent equal-tailed 95% uncertainty intervals.
[a]Definitions of measures given in Table 1.
[b]The percentage of individuals expected to test positive with IGRA, including both true-positive and false-positive results.
[c]For individuals with prevalent *Mtb* infection in 2020. These outcomes could not be calculated for non-US-born populations.
[d]Risks attributable to progression to TB from prevalent *Mtb* infection, excludes risks from incident infections in the future.
[e]Values by single year of age shown in Figure 3.
[f]Excludes HIV-positive individuals.
[g]Estimates without age stratification average across all individuals with prevalent infection, with average age 62 (61, 63), 55 (54, 55), and 57 (56, 58) for the US-born, non-US-born, and total population, respectively.

of progression to TB over all ages was estimated to be 1.9% (1.6, 2.2).

Remaining Lifetime Risks of Progression to tuberculosis for interferon-gamma release assay-positive Individuals by Age

Table 2 provides estimates for the percent of IGRA-positive individuals who are predicted to progress to TB disease in their lifetime due to a prevalent *Mtb* infection, by nativity and age group; values in parentheses represent equal-tailed 95% uncertainty intervals. We obtained these results by applying published IGRA sensitivity and specificity values[11] to model-estimated *Mtb* infection prevalence and remaining lifetime TB risks among latently infected individuals (also shown in Table 2). Among the US-born, these values peak in the 45- to 64-years-old age group, with an estimated population average risk of 0.57% (0.33, 0.90). Values were substantially higher in the non-US-born population, with values peaking in the 15–24 age group (2.4% [1.6, 3.2]). Over all ages, the non-US-born average was 1.9% (1.5, 2.4), 5.1 (2.8, 8.7) times higher than that among the US-born (0.41 [0.22, 0.68]). Combining all US-born and non-US-born populations over all ages, the overall average risk among IGRA-positive individuals was 1.0% (0.7, 1.4).

Remaining Lifetime Risks of Progression to Tuberculosis in the General Population

Table 2 shows remaining lifetime risks of TB from prevalent *Mtb* using the entire population as the denominator (i.e., without restricting to *Mtb* infection or IGRA-positives). For this outcome the US-born population average was estimated to be 0.014% (0.012, 0.017). Estimates were much higher for the non-US-born population, with a population average of 0.30% (0.25, 0.35), 21 (17, 26) times higher than that of the US-born. The overall population average was 0.055% (0.048, 0.062).

DISCUSSION

Most tuberculosis cases in the United States result from the progression of established LTBI. In this context, a granular description of the natural history of *Mtb* infection is useful for understanding the risks faced by infected individuals and interpreting population-level incidence trends. In this study, we used a transmission-dynamic model to estimate time since *Mtb* infection and future TB risks in the

US population. We estimate that US-born individuals with *Mtb* infection were infected an average of 44 (43, 46) years ago. Time since infection was longer for older individuals—estimated as 72 (70, 73) years for individuals >85 years of age. Time since infection estimates were lower for individuals with incident TB (31 [29, 33] years) for each year of age, as TB due to recent infection will represent a greater fraction of incident TB compared to the fraction of individuals with prevalent *Mtb* infection.

Consistent with the extended time since infection for most individuals with prevalent *Mtb* infection, the estimated current and future risks of TB for these individuals were low. We estimated average progression rates as 1.19 (1.02, 1.39) per 1,000 for the US-born, 0.95 (0.81, 1.12) for the non-US-born, and 1.09 (0.96, 1.28) for the general population. The lower progression rate for the non-US-born population compared to the US-born population reflects differences in the distribution of age and time since infection for *Mtb*-infected individuals, as non-US-born individuals spending their early years living outside of the United States will have experienced a different pattern of exposure compared with US-born individuals. Progression rates were lower when we excluded individuals infected within the past 2 years, with a population-average rate of 0.82 (0.70, 0.97) per 1000 person–years. Estimates of annual reactivation risks for latent infection were substantially higher in younger age groups, reflecting shorter average time since infection, and high risks of progression for individuals infected in early childhood.[21]

Our annual risk estimates for established LTBI are consistent with results reported by Shea et al.,[36] who reported a population-average rate of 0.84 per 1000 person–years. This earlier study estimated the progression risks faced by *Mtb*-infected individuals by dividing the number of non-genotypically clustered TB cases during 2006–2008 by the number of person–years at risk estimated from tuberculin skin test positivity in the 1999–2000 NHANES sample. Our results diverged from this earlier analysis for younger age groups, for which we estimated higher average rates (e.g., 5.7 vs. 0.72 per 1000 person–years for 0–14 year olds), possibly related to the imperfect specificity of tuberculin skin test used to define the denominator in the earlier analysis.

Average risks of developing TB over the remaining lifetime were estimated to be 1.2% (1.0, 1.4) for *Mtb*-infected US-born, 2.2% (1.8, 2.6) for non-US-born, and 1.9% (1.6, 2.2) for the general population. For this outcome, higher values were estimated for the non-US-born population (vs. the US-born population), a result of the younger average age of non-US-born individuals with *Mtb* infection, and the longer remaining life expectancy for this group. For both US-born and non-US-born populations with latent infection, remaining lifetime risks of TB were substantially higher for younger individuals, reflecting shorter average time since infection and longer life expectancy.

As compared with those with latent infection, we estimated lower lifetime risks for the IGRA-positive population, for whom imperfect test specificity[11] leads to some individuals

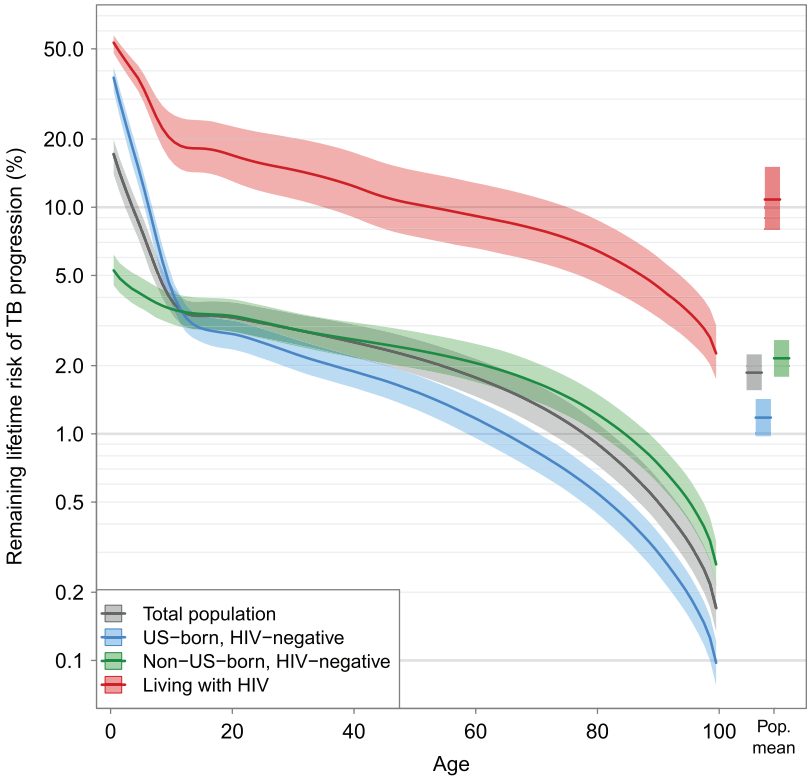

FIGURE 3. Remaining lifetime risk of progression to TB for individuals with prevalent Mtb infection, by age and population group. "Pop. Mean" represents the population-average value for each population group. Estimates not stratified by age include all individuals with prevalent *Mtb* infection, with average age 62 (61, 63), 55 (54, 55), and 57 (56, 58) for US-born, non-US-born, and total population, respectively. Lower risk estimates among non-US-born children reflect longer average time since infection, related to infections acquired prior to entry.

testing positive who do not have *Mtb* infection. For IGRA-positive individuals, remaining average lifetime risks of TB were estimated to be 0.38% (0.32, 0.44) for US-born, 1.92% (1.59, 2.29) for non-US born, and 1.01% (0.87, 1.17) for the general population. These results—in addition to large differences in IGRA-positivity—imply large differences in the risks of progression to TB between US-born and non-US-born individuals, with one in every 340 (290, 400) non-US-born residents who were predicted to develop TB in the future due to prevalence of *Mtb* infection, compared with one in every 7,000 (6,000, 8,300) US-born individuals, and one out of every 1,800 (1,600, 2,100) of the general population.

The low average lifetime risk of progression to TB for prevalent IGRA-positive individuals represents a key challenge for TB prevention programs, with many individuals requiring testing and treatment to avert a single TB case. This confirms the importance of current efforts to target testing and treatment services to individuals with comparatively higher infection prevalence and risks of progression to TB (non-US-born individuals, individuals with immune suppression, individuals with recent infectious exposure, younger populations).[3,4] The low population-average risk of TB—even among *Mtb*-infected individuals—also highlights the need for diagnostics with higher specificity, which would ideally exclude uninfected individuals as well as individuals who would be classified as having *Mtb* infection but for whom long-term TB risks are negligible.[14,15]

The use of mathematical modeling for epidemiologic inference has a long tradition in TB research[8,37,38] due to the slow epidemiologic dynamics and long latency period of TB, and the difficulty of ascertaining the timing of infection and disease progression. Although mathematical modeling can extend the knowledge gained from empirical data, these analyses require assumptions about disease mechanisms that are frequently difficult to validate. Moreover, although models may be complicated (the model for this analysis stratifies the population across 36,300 strata), they simplify the processes being modeled to render the analysis tractable. These assumptions and simplifications may lead to biased inferences, and intervals that do not capture all sources of uncertainty. In our analysis, a potentially influential assumption was the functional form assumed for TB progression rates—we assumed that for individuals of a given age, progression rates would be strictly lower with earlier age of infection. After approximately 15 years since infection, this annual decline in the progression rate converged to a fixed percentage. Our approach is broadly consistent with current evidence on rates of progression to TB up to 15 years after infection, but there is little empirical evidence that describes how rates change for individuals with distant infection, about which there is open debate.[10] More flexible functional forms could produce different results, and wider uncertainty intervals. Although we allowed for elevated progression risks with advanced age[22] (in addition to changes in progression risk during infancy and childhood[21]), we did not explicitly model the comorbidities and immune changes producing these effects. In addition, we did not allow for secular trends in progression rates, apart from those generated by changes in other risk determinants such as age and time since infection. However, it is possible that the population-average rate at which individuals with *Mtb* infection progress to TB has declined over time due to improvements in living standards—if so, the use of historical data[6,7] to parameterize the model introduces additional uncertainty. Another limitation was the use of data from different settings to parameterize the model, which can introduce bias if the underlying populations differ (e.g., representing risk factor distributions different to the current US population). For these reasons, the results of this analysis should be interpreted more cautiously than empirical measures of the same outcomes.

Another limitation is the broad population groups used to stratify results (age, non-US-born vs. US-born status, HIV status). The importance of additional risk groups is reflected in current programmatic guidance,[3,4] and further research is needed to understand future TB risks for these groups. Moreover, large risk differences exist within the non-US-born population,[30] and a more disaggregated description of these differences would allow better targeting of preventive services to those with the highest probability of future TB. Work is also needed to combine epidemiologic evidence with costs and health state preferences, to inform optimal prevention strategy and provide guidance to patients and clinicians interpreting positive LTBI test results.

SUMMARY

For a young adult newly infected with *Mtb,* we estimated lifetime TB risks of 8%–10%, consistent with earlier estimates. However, most individuals with LTBI in the United States were infected many years ago, and face low future risks of progressing to TB. This situation results from the long success of TB control in the United States, with few individuals infected in recent decades compared to historical levels. The low remaining lifetime TB risks present a challenge for prevention programs, justifying the development of better ways to identify TB risk, and the development of more specific diagnostics to identify those at highest risk of future disease.

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