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Mortality Hazard and Survival After Tuberculosis Treatment

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Abstract

Objectives—We compared mortality among tuberculosis (TB) survivors and a similar population.

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Contributors

T. L. Miller led the authorship of the article. T. L. Miller and F. A. Wilson led the analytical design, analysis, and interpretation of findings. T. L. Miller, J. W. Pang, and S. Beavers led the methodological design and data collection. T. L. Miller, J. W. Pang, and S. E. Weis conceptualized the project. S. Hoger and M. Pagaoa contributed to the methodological design and data collection. J. W. Pang, S. Hoger, M. Pagaoa, D. J. Katz, and S. E. Weis contributed to the analytical design, analysis, and interpretation of findings. All authors contributed to the writing of the article.

Human Participant Protection

The study was approved by the Centers for Disease Control and Prevention's central institutional review board and institutional review boards at sites that did not defer to the central institutional review board.

Methods—We used local health authority records from3 US sites to identify 3853 persons who completed adequate treatment of TB and 7282 individuals diagnosed with latent TB infection 1993 to 2002. We then retrospectively observed mortality after 6 to 16 years of observation. We ascertained vital status as of December 31, 2008, using the Centers for Disease Control and Prevention's National Death Index. We analyzed mortality rates, hazards, and associations using Cox regression.

Results—We traced 11 135 individuals over 119 772 person-years of observation. We found more all-cause deaths (20.7% vs 3.1%) among posttreatment TB patients than among the comparison group, an adjusted average excess of 7.6 deaths per 1000 person-years (8.8 vs 1.2; $P < .001$). Mortality among posttreatment TB patients varied with observable factors such as race, site of disease, HIV status, and birth country.

Conclusions—Fully treated TB is still associated with substantial mortality risk. Cure as currently understood may be insufficient protection against TB-associated mortality in the years after treatment, and TB prevention may be a valuable opportunity to modify this risk.

Elimination of tuberculosis (TB) is an important facet of public health policy in the United States.[1–4] Coordinated and deliberate efforts have steadily decreased TB incidence and mortality to historically low levels: in 2010, 11163 new domestic TB cases were reported and 320 (2.9%) died from TB-attributable causes before or during treatment; treatment was successfully completed for more than 88.0% of persons for whom an initial drug regimen was prescribed.[5]

But meeting the goals of domestic TB elimination will require more than finding and treating TB disease. Substantial reservoirs of latent TB infection (LTBI) exist within the United States; in 1999–2000, projections from the National Health and Nutrition Examination Survey (NHANES) estimated that 11.2 million individuals, two thirds of them foreign-born, had LTBI.[6] These numbers are continuously augmented by global immigration and by transmission from persons with TB. Because treatment levels of TB disease are already very high in the United States, further progress toward elimination will depend largely on prevention through LTBI diagnosis and treatment or other means.[7]

LTBI is frequently found through screening in developed countries, but treatment decisions are often conservative because of diagnostic, clinical, and other factors, and prevention policy and practice in this population is inconsistent.[8–13] Generally, LTBI treatment is recommended only for persons at high risk for developing TB.[9]

These recommendations are grounded partly on cost-effectiveness analyses and clinical considerations of health risks and benefits that include estimates of TB deaths prevented by LTBI treatment. These estimates usually refer only to deaths associated with acute-phase TB disease; some models explicitly assume that survivors of TB disease experience no long-term morbidity.[14]

If these assumptions are incorrect and survivors of TB experience significant long-term morbidity or mortality because of TB, LTBI treatment is undervalued, with important consequences for policy and prevention. Indeed, there is growing evidence of persistent health deficits in some TB patients after successful treatment completion, including

permanent anatomical changes in the lungs and other affected organs that could elevate long-term mortality risk.[15–27] For example, fewer than 40% of patients with a history of meningeal TB and no reported lung involvement remained alive 45 months after completing therapy.[28] Still, long-term survival and mortality risks among patients who complete TB treatment remain unclear.

Evidence of increased mortality among patients considered cured of TB has substantial potential utility. Such evidence, especially when associated with sequelae of acute TB disease, would suggest prevention has value not reflected in current practice. In addition, descriptions of the distribution of mortality risk by readily observable factors would allow more careful targeting of prevention efforts.

We hypothesized that persons who complete adequate therapy for TB disease are at increased risk of subsequent all-cause mortality. We tested this hypothesis using a retrospective comparison of mortality rates and risks of fully treated TB survivors and a comparison group with LTBI but no history of TB disease. We analyzed all-cause mortality after TB cure to identify disproportionate mortality as a potentially modifiable risk factor.

METHODS

The Tuberculosis Epidemiologic Studies Consortium is a partnership between the Centers for Disease Control's Division of Tuberculosis Elimination and academic and public health collaborators at 20 US sites.[29] We used statewide health authority registries and other records from Texas and Massachusetts and similar local records from Washington's Seattle and King County to create a research database for 2 groups: persons who had completed therapy for TB disease at least 6 years previously and a comparison population of persons with diagnosed LTBI. We used the Centers for Disease Control and Prevention's National Death Index (NDI) to ascertain and compare mortality between the groups while adjusting for available non-TB mortality risk factors.

Health authorities collect and report nationally uniform TB data using the Centers for Disease Control and Prevention's Report of Verified Case of Tuberculosis and other standardized data management tools.[30–32] Although requirements and formats vary, data on incident LTBI were also reported within each of our study areas.[30,33] We standardized data collection for all participants predicated loosely on that available from the Report of Verified Case of Tuberculosis. Patient names and other personal identifiers are not included in national reporting but are collected at the local and state level, and we obtained them from these sources to allow identification using the NDI. Personal identifiers included first, middle, and last names; date of birth; race; ethnicity; gender; last known address; and country of birth. Social security numbers are not consistently available from health authority reports, but we included them when available. HIV status was recorded for all patients, and we collected information on initiation, duration, outcome of treatment, and site of disease (pulmonary, extrapulmonary, or both) for TB patients.

Criteria for inclusion as a TB survivor were

1. patient's TB was diagnosed and reported and treatment completed between January 1, 1993, and December 31, 2002;
2. patient was aged 18 years or older at treatment initiation;
3. patient's treatment was completed within 3 years of initiation;
4. patient was alive at treatment completion;
5. there were sufficiently comparable demographic, clinical, and other selected data on the patient to allow adjusted analyses, and
6. there were sufficient identifiers for the patient for NDI matching.[34]

We used the Centers for Disease Control and Prevention's Link Plus record linkage program to identify patients appearing in both the LTBI databases and TB disease registries; these patients were eligible for inclusion in the TB survivor group only.[35] We used the recorded end of the successful treatment date as the date of enrollment and entry into observation.

Criteria for inclusion in the comparison group were

1. patient had received an LTBI diagnosis recorded by public health authorities during the same 10-year period as cases, regardless of treatment history;
2. patient was aged 18 years or older at diagnosis;
3. patient did not have a documented history of previous TB disease;
4. there were sufficiently comparable demographic, clinical, and other data on the patient to allow adjusted analyses; and
5. there were sufficient identifiers for the patient to determine vital status in the NDI.

We used the first recorded LTBI-positive status during the study period as the date of enrollment and entry into observation.

Power calculations indicated that each cohort would need a minimum of 1836 patients to detect a rate ratio of 1.5 in comparisons of all-cause mortality. Because the availability of administrative records allowed a much larger sample, we selected all TB survivors who met inclusion criteria for the final study cohort. We used random sampling to select an approximately 2:1 oversample of LTBI comparison patients.

We used the NDI to determine vital status as of December 31, 2008, allowing 6 to 16 years of retrospective observation for each patient. The NDI compares user-submitted data with its death records to classify vital status and evaluates robustness of potential matches by the strength and precision of identifying information.[36] Before submission to the NDI, we sought to resolve data discrepancies and strengthen identification and match probability by comparing patients with those in the LexisNexis Accurint database. This commercial service combines multiple individually weak identifier data from public records into a more robust aggregate personal identification.[37]

The NDI classifies patients into groups on the basis of the strength of the match: group 1 matches social security number, full name, gender, and birth state, month, and year; group 2 matches at least 7 digits of social security number but not 1 or more class 1 items; group 3 has an unknown social security number but matches at least 8 of first name; middle initial; last name; birth state, day, month, or year; gender; race; or marital status.[35] We defined patients classified by the NDI as group 1, 2, or 3, with a score above the recommended cutoff threshold as deceased allowing a positive predictive value for mortality of more than 89%.[36,38–43] We de-identified classification final results for analysis.

We used Cox regression to estimate and compare differences in survival between TB survivors and those with LTBI while controlling for gender; age at enrollment and at the endpoints of death or survival through December 31, 2008 (grouped as aged 18–39, 40–64, and ≥ 65 years); race/ethnicity (White, Black, Hispanic, other); HIV status (positive vs negative or unknown); time from enrollment to either death or survival to December 31, 2008; birth country (US- or foreign-born); and site of disease for TB survivors (pulmonary, extrapulmonary, or both). We tested our model's sensitivity to potential nonlinearities between age and outcome using linear and cubic spline and stepwise Cox regressions.

We calculated mortality rates and reported them for patient groups stratified by individual characteristics and by site of TB disease. We did not attempt to determine cause of death. We adjusted estimates for individual characteristics using the sample means for gender, age group, race/ethnicity, HIV status, nativity, and geography. We tested significant differences in the distribution of principal cohort characteristics with χ^2 analysis. We standardized absolute measures (mortality rates, probability of survival, duration of survival) to a population with the same subgroup proportions as the analytic data.

RESULTS

We determined vital status for 12 673 patients. Of these, we censored 1538 (12.1%) records during analysis because of missing data, leaving 3853 TB survivors and 7282 LTBI comparison patients in the final analysis (Table 1). Results represent 119 772 person-years of observation. All 3 sites contributed roughly equal numbers (data not shown).

The TB survivor and LTBI comparison cohorts had similar characteristics, with no significant differences in the distributions of patients by gender, race/ethnicity, HIV status, or birth country. The duration of observation was similar among patients from both groups who remained alive through the study period (data not shown). We found significant differences in the mean age and age distribution of patient cohorts at enrollment, and although there were no significantly different proportions of patients aged 40 to 65 years, fewer TB survivors than LTBI comparison patients were aged 18 to 39 years (21.4% vs 34.1%; $P \leq .001$) and more were older than 65 years (28.9%vs 8.5%; $P<.001$; Table 1).

Unadjusted, observed mortality was more common among TB survivors than among LTBI comparison patients (20.7% vs 3.1%; $P < .001$; Table 1), and of those who died during the observation period, almost twice as many TB survivors (48.3% vs 26.7%; unadjusted $P < .001$) survived 5 or fewer years after enrollment (Table 1). TB survivors who died during the

study period were more often White (43.6% vs 31.1%; $P < .001$) and HIV positive (14.0% vs 7.6%; $P = .016$) and less often Black (21.3% vs 31.6%; $P = .027$) than were deceased LTBI comparison patients.

Mortality rates adjusted for age, gender, race/ethnicity, HIV status, and nativity were 8.8 deaths per 1000 person-years for TB survivors compared with 1.2 per 1000 person-years ($P < .001$) for persons with LTBI (Table 2).

Adjusted mortality hazard for TB survivors averaged 7.6 times that of LTBI comparison patients (Table 3). Mortality hazard was sensitive to age, gender, race/ethnicity, HIV status, and birth country (Table 4). Relative to subgroups of LTBI patients with the same characteristic, mortality hazard tended to be higher among TB survivors who had pulmonary site of disease or were younger than 40 years, female, White, or known to be HIV positive (Table 3).

Survival probability, both as the annual mortality probability and as survival to the end of observation, was lower among TB survivors than among LTBI comparison patients (Figure 1). Cox regression estimates adjusted for age, gender, race/ethnicity, HIV status, and birth country predicted 82.9% of TB survivors would live through the 16-year observation period, compared with 97.4% of LTBI comparison patients (Figure 1). Predicted survival was significantly different among patients who died during the study period for all comparisons ($P < .001$; Table 5).

After multivariate adjustment, TB survivors who died during the study period were predicted to do so an average of 4.1 years after treatment completion, 1.6 years less than decedent LTBI comparison patients (Table 5). Multivariate-predicted survival among TB survivor decedents varied by site of disease, averaging 4.2, 4.0, and 3.7 years for pulmonary only, extrapulmonary only, and both, respectively (Table 5).

DISCUSSION

We traced 11 135 individuals over 119 772 person-years of observation and found all-cause mortality among fully treated TB survivors to be 7 times that of a comparison population with LTBI; 1 in 5 of those with a history of active TB had died an average of just 4.1 years after treatment completion (Tables 2 and 4). Although we could not identify causality, previous studies have identified persistent health deficits in some TB patients after successful treatment completion, including permanent anatomical changes in the lungs and other affected organs.[15–27] How these and other factors may contribute to the excess mortality hazard after TB treatment should be the focus of additional study, but our findings suggest that TB prevention may have population health benefits not currently appreciated.

TB mortality generally describes deaths occurring during the relatively short duration of active illness. Although some TB is diagnosed after death, most persons with TB disease begin treatment. During 2010, 641 (5.9%) all-cause deaths were reported during treatment among the 10 911 individuals with incident TB who were alive at diagnosis. Because of the 6-month duration of treatment, this suggests an all-cause mortality rate of at least 29.4 per 1000 person-years during this acute period.[5]

We have described a previously unreported postacute period of mortality hazard that begins at treatment completion and continues for many years. During this second period of mortality hazard, we found more than 20% (799) of adequately treated TB patients survived an average of just 4.1 years after cure (Table 5). Strikingly, the cumulative mortality burden in our fully treated study population would begin to exceed years lost by those who died during treatment only 3.3 years into this postacute hazard period. TB prevention, primarily finding and treating persons with LTBI, could plausibly have averted much of the postacute mortality hazard among our study patients.

If our findings are generalizable, prevention of TB disease represents an important way to reduce long-term mortality. From 1993 to 2008, 266 512 TB cases were reported in the United States. Of these, 242 979 patients completed therapy.[5] This is not a cause of death study, and we cannot draw conclusions about specific etiologies. However, if our findings accurately represent the posttreatment mortality hazard to this population, an estimated 37 790 of these TB survivors may have died prematurely after their treatment completion, suggesting substantial value for TB prevention or other interventions that could have reduced this large mortality burden.

Individuals treated for TB in the United States benefit from a coordinated public health system that delivers standardized treatment and generally satisfactory short-term outcomes. Most US TB patients can expect an ambulatory course of treatment resulting in cure. Notwithstanding this optimistic prognosis, irreversible medical sequelae are known among TB survivors with little known about associated health burdens.[15–18] TB treatment in the United States is publicly provided and has been generally successful in avoiding the delivery, access, and other systematic disparities found along racial and ethnic lines elsewhere in US health care. However, that may not be the case for long-term survival after cure.

Mortality rate and hazard were predictably higher in TB survivors with physiologic risks such as increased age but were unexpectedly highest in White TB survivors compared with same-race LTBI patients (Table 3). Although data limitations did not allow us to control for important clinical, social, and behavioral factors, these results are consistent with disproportionate pulmonary impairment after TB as well as mortality associated with chronic lower respiratory infections reported among Whites.[22,25,26,42] A finding of White race as a possible marker of increased post-TB mortality hazard suggests the need to more robustly explore pathogen, host, posttreatment patient management, aging, comorbidities, and other potentially explanatory differences.

Prevention is not always possible and does not mitigate post-TB mortality risks among TB survivors. But relatively simple measures such as influenza and pneumococcal immunization have shown survival benefit for patients with other pulmonary disease and could also benefit TB survivors with pulmonary impairment.[18,19,26,27] Determination of risk markers for increased mortality among TB patients who complete treatment could also prompt risk modification through education, referral for follow-up care, or other interventions.[19–23,33]

Limitations

This study has limitations. As a retrospective study it demonstrates association and can suggest but not prove a causal effect. Analytical and sampling challenges inherent to administrative data are well described, and we did not have data to adjust for clinical factors such as diabetes, hypertension, stroke and smoking, cause-specific mortality, and other potentially important contributors to mortality risk.[44] There is a potential for ascertainment bias in our study sample. Individuals at risk for TB in the United States are more likely to have lower socioeconomic status or be foreign-born, and they may be less identifiable in public records such as the NDI.[3]

To reduce this potential bias we included methodology to strengthen and validate identifiers, resulting in vital status and other identifications that were consistent with the NDI's defined standards and others' reports of robust and valid identification.[36,45] TB survivors in our sample tended to be older than were LTBI comparison patients, and we were unable to ascertain and control for specific comorbid conditions correlated with both advancing age and increased mortality hazard.

In addition, there are important limits to the effectiveness of using LTBI-diagnosed populations as comparison groups for populations with TB. These include inconsistencies in how persons diagnosed with LTBI come to the attention of local health authorities and the more systematic and rigorous identification of some risk factors, such as HIV, among TB patients.[3] Still, the significance, general magnitude, and direction of our findings were substantially similar in analyses of relative mortality hazard stratified by age group, and alternative analyses found no confounding from possible nonlinearities for age (results not shown).

Mortality occurring outside the United States is not captured by the NDI database, leading to potential underestimates of mortality among foreign-born persons who complete treatment in the United States and subsequently repatriate. However, such underestimates would also underestimate the mortality risk among treated TB patients, suggesting that our conclusions are conservative. Finally, an alternative conclusion to our findings could be that the excess mortality observed is not caused by TB but that TB is a marker for underlying conditions that predict shorter lifespan. In that case, prevention will not reduce post-TB mortality.

Conclusions

Fully treated TB is still associated with substantial mortality risk. It is plausible that cure as currently understood may be insufficient protection against TB-associated mortality risk in the years after treatment and that TB prevention may represent a valuable opportunity to modify such risk. The clinical and programmatic value of TB prevention usually is calculated on the basis of the morbidity and mortality associated with the short-term period of acute illness.[46]

On the basis of these findings, such an approach does not take into account the substantial long-term mortality risk in TB survivors treated to cure and thus significantly underestimates the long-term health and other benefits of TB prevention. Inclusion of this long-term mortality hazard in cost-effectiveness estimates, programmatic and system priority setting,

and clinical decision-making is likely to better reflect the economic and survival benefit of TB prevention. This in turn could result in superior population health outcomes and more cost-effective policy and funding decisions.

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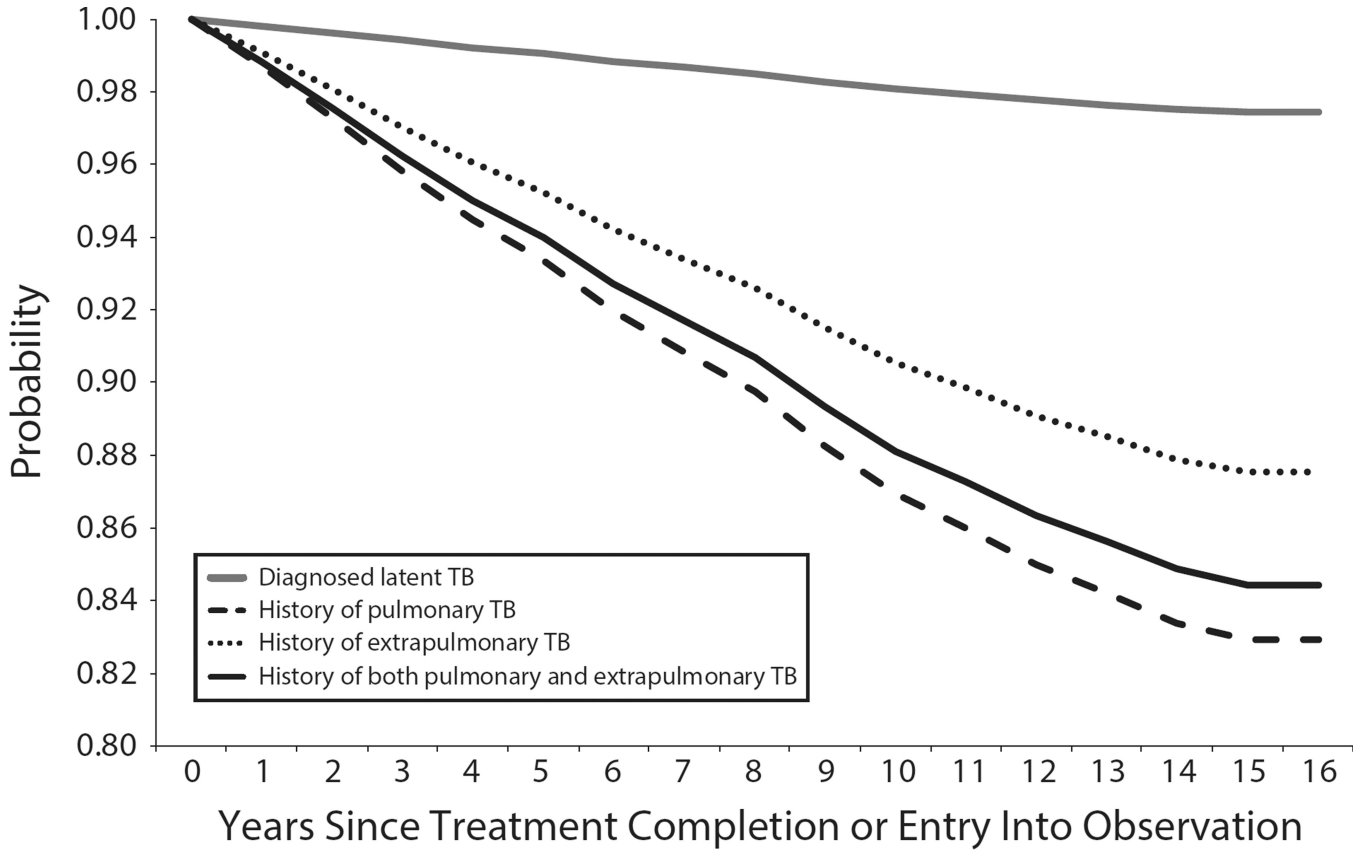

FIGURE 1.

Age, gender, race/ethnicity, HIV status, and nativity-adjusted Cox regression survival probability by tuberculosis history: Centers for Disease Control and Prevention's National Death Index; Texas, Massachusetts, and Seattle and King County, WA; 2008.

Note. TB = tuberculosis. Treatment completion indicates a history of active TB; entry into observation indicates no history of active TB.

TABLE 1

Cohort Description and Distribution of Age, Gender, Race/Ethnicity, HIV Status, Nativity, and Vital Status (n = 11 135): Centers for Disease Control and Prevention's National Death Index; Texas, Massachusetts, and Seattle and King County, WA; 2008

	Fully Treated TB Survivors				LTBI Comparison			
Characteristic	**All TB Survivors, No. (%)**	**Living, No. (%)**	**Dead, No. (%)**	**% Dead**	**All LTBI, No. (%)**	**Living, No. (%)**	**Dead, No. (%)**	**% Dead**
Sample size	3853 (100.0)	3054 (79.3)**	799 (20.7)**	20.7**	7282 (100.0)	7057 (96.9)**	225 (3.1)**	3.1**
Time observed, y								
< 5	386 (10.0)**	0.0	386 (48.3)**	100.0	60 (0.8)**	0.0	60 (26.7)**	100.0
5–9	1613 (41.9)**	1312 (43.0)**	301 (37.7)*	18.7*	1763 (24.2)**	1656 (23.5)**	107 (47.6)**	6.1*
≥ 10	1854 (48.1)**	1742 (57.0)**	112 (14.0)**	6.0**	5459 (75.0)**	5401 (76.5)**	58 (25.8)*	1.1**
Unadjusted average y observation	9.2	10.3	5.3		11.6	11.7	7.1	
Age at enrollment, y								
18–39	823 (21.4)**	758 (24.8)*	65 (8.1)*	7.9**	2480 (34.1)**	2446 (34.7)*	34 (15.1)*	1.4**
40–64	1917 (49.8)	1610 (52.7)	307 (38.4)**	16.0**	4185 (57.5)	4051 (57.4)	134 (59.6)**	3.2**
≥ 65	1113 (28.9)**	686 (22.5)**	427 (53.4)**	38.4**	617 (8.5)**	560 (7.9)**	57 (25.3)**	9.3**
Gender								
Male	2399 (62.3)	1817 (59.5)	582 (72.8)	24.3**	4157 (57.1)	3990 (56.5)	167 (74.2)	4.0**
Female	1454 (37.7)	1237 (40.5)	217 (27.2)	14.9**	3125 (42.9)	3067 (43.5)	58 (25.8)	1.9**
Race/ethnicity								
White	895 (23.2)	547 (17.9)	348 (43.6)**	38.9**	1590 (21.8)	1520 (21.5)	70 (31.1)**	4.4**
Hispanic	945 (24.5)	768 (25.2)	177 (22.2)	18.7**	2354 (32.3)	2304 (32.7)	50 (22.2)	2.1**
Black	933 (24.2)	763 (25.0)	170 (21.3)*	18.2**	1652 (22.7)	1581 (22.4)	71 (31.6)*	4.3**
Other	1080 (28.3)	976 (32.0)*	104 (13.0)	9.6**	1686 (23.2)	1652 (23.4)*	34 (15.1)	2.0**
HIV status								
Positive	334 (8.7)	222 (7.3)	112 (14.0)*	33.5**	384 (5.3)	367 (5.2)	17 (7.6)*	4.4**
Negative or unknown	3519 (91.3)	2832 (92.7)	687 (86.0)*	19.5**	6898 (94.7)	6690 (94.8)	208 (92.4)*	3.0**
Nativity								
Foreign-born	2257 (58.6)	2051 (67.2)	206 (25.8)	9.1**	4252 (58.4)	4203 (59.6)	49 (21.8)	1.2**

	Fully Treated TB Survivors				LTBI Comparison			
Characteristic	**All TB Survivors, No. (%)**	**Living, No. (%)**	**Dead, No. (%)**	**% Dead**	**All LTBI, No. (%)**	**Living, No. (%)**	**Dead, No. (%)**	**% Dead**
US-born	1596 (41.4)	1003 (32.8)	593 (74.2)	37.2**	3030 (41.6)	2854 (40.4)	176 (78.2)	5.8**

Note. LTBI = latent tuberculosis infection; TB = tuberculosis.

*$P = .05$;

**$P = .01$.

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TABLE 2

Cox Regression-Adjusted Mortality per 1000 Person-Years Among Study Cohort by TB History, Site of Disease, Age, Gender, Race/Ethnicity, HIV Status, and Nativity: Centers for Disease Control and Prevention's National Death Index; Texas, Massachusetts, and Seattle and King County, WA; 2008

Characteristic	LTBI Comparison, Person-Years (95% CI)	Any TB, Person-Years (95% CI)	PTB Only, Person-Years (95% CI)	EPTB Only, Person-Years (95% CI)	Both PTB and EPTB, Person-Years (95% CI)
Overall	1.23 (0.72, 1.74)	8.79 ** (4.94, 12.64)	8.31 ** (5.17, 11.44)	6.02 ** (3.34, 8.70)	7.55 ** (3.89, 11.21)
Age at enrollment, y					
18–39	0.86 (0.59, 1.13)	5.89 ** (3.30, 8.47)	5.23 ** (2.74, 7.71)	6.22 ** (2.64, 9.81)	9.74 ** (4.67, 14.81)
40–64	1.60 (0.82, 2.37)	7.27 ** (4.43, 10.11)	8.22 ** (5.06, 11.37)	4.28 * (2.04, 6.53)	5.34 * (2.16, 8.51)
≥ 65	5.09 (2.56, 7.62)	18.33 ** (13.26, 23.41)	18.94 ** (13.77, 24.11)	17.21 ** (11.46, 22.95)	15.05 ** (8.16, 21.94)
Gender					
Male	2.04 (1.12, 2.97)	9.69 ** (5.53, 13.85)	9.32 ** (5.87, 12.76)	5.92 ** (3.13, 8.72)	8.50 ** (4.32, 12.68)
Female	1.14 (0.68, 1.60)	7.63 ** (4.12, 11.14)	7.03 ** (4.18, 9.89)	6.16 ** (3.19, 9.13)	6.36 ** (2.60, 10.11)
Race/ethnicity					
White	1.72 (1.05, 2.39)	11.73 ** (6.85, 16.61)	11.24 ** (7.13, 15.36)	6.96 ** (3.34, 10.58)	12.48 ** (6.25, 18.71)
Hispanic	1.25 (0.61, 1.89)	8.30 ** (4.51, 12.09)	7.99 ** (4.81, 11.17)	6.4 ** (2.89, 9.91)	4.42 (1.17, 7.68)
Black	1.69 (0.84, 2.54)	7.64 ** (4.07, 11.21)	7.17 ** (4.19, 10.16)	4.37 (1.79, 6.95)	8.0 * (3.23, 12.77)
Other	1.96 (1.01, 2.92)	8.28 ** (4.43, 12.13)	7.60 ** (4.38, 10.81)	6.14 * (2.76, 9.52)	7.76 * (2.23, 13.29)
HIV status					
Positive	2.01 (0.80, 3.22)	16.95 ** (10.69, 23.21)	14.61 ** (9.36, 19.87)	20.87 ** (13.24, 28.50)	14.41 ** (7.10, 21.72)
Negative or unknown	1.59 (0.94, 2.24)	8.42 ** (4.69, 12.14)	8.0 ** (4.95, 11.05)	5.53 ** (3.00, 8.06)	7.24 ** (3.66, 10.81)
Nativity					
Foreign-born	0.92 (0.46, 1.37)	5.95 ** (3.08, 8.82)	5.95 ** (3.46, 8.44)	3.63 ** (1.74, 5.53)	4.18 * (1.38, 6.98)
US-born	3.48 (2.24, 4.73)	14.75 ** (9.27, 20.22)	12.98 ** (8.60, 17.35)	11.80 ** (6.97, 16.63)	16.38 ** (9.87, 22.89)

Note. CI = confidence interval; EPTB = extrapulmonary tuberculosis; LTBI = latent tuberculosis infection; PTB = pulmonary tuberculosis; TB = tuberculosis. n = 11 135. Cox regression predicted mortality incidence/1000 person-years. Cox regression adjusts for all variables listed in table and for study site location.

* $P = .05$;

** $P = .01$.

TABLE 3

Relative Mortality HR (95% CI) Among Tuberculosis Survivors by Site of Disease Age, Gender, Race/Ethnicity, HIV Status, and Nativity: Centers for Disease Control and Prevention's National Death Index; Texas, Massachusetts, and Seattle and King County, WA; 2008

Characteristic	Any TB, HR (95% CI)	PTB Only, HR (95% CI)	EPTB Only, HR (95% CI)	Both PTB and EPTB, HR (95% CI)
Overall	7.63 * (2.32, 12.94)	7.18 ** (2.64, 11.72)	5.10 * (1.68, 8.52)	6.48 * (1.78, 11.19)
Age at enrollment, y				
18–39	9.40 ** (3.74, 15.05)	8.30 ** (3.08, 13.53)	9.97 * (2.53, 17.41)	16.10 * (4.11, 28.08)
40–64	6.28 * (1.95, 10.60)	7.16 * (2.20, 12.11)	3.60 (0.83, 6.38)	4.53 (0.70, 8.37)
≥ 65	5.37 * (1.43, 9.32)	5.59 * (1.48, 9.70)	4.98 * (1.08, 8.89)	4.26 (0.45, 8.08)
Gender				
Male	6.66 * (1.81, 11.51)	6.38 * (2.11, 10.64)	3.93 * (1.08, 6.79)	5.77 * (1.30, 10.25)
Female	9.29 (2.84, 15.75)	8.52 ** (3.10, 13.94)	7.40 * (2.23, 12.57)	7.66 * (1.48, 13.83)
Race/ethnicity				
White	9.79 * (2.94, 16.64)	9.34 ** (3.36, 15.31)	5.56 * (1.43, 9.69)	10.49 * (2.0, 18.97)
Hispanic	9.25 * (2.10, 16.40)	8.88 * (2.50, 15.26)	7.01 * (1.17, 12.85)	4.77 (0.11, 9.42)
Black	6.25 * (1.41, 11.09)	5.84 * (1.61, 10.08)	3.48 (0.55, 6.40)	6.56 (0.65, 12.48)
Other	5.85 * (1.35, 10.35)	5.34 * (1.47, 9.20)	4.26 (0.76, 7.76)	5.46 (0, 10.96)
HIV status				
Positive	12.70 * (1.68, 23.72)	10.69 * (1.83, 19.55)	16.31 * (1.21, 31.40)	10.52 (0.18, 20.87)
Negative or unknown	7.39 * (2.24, 12.53)	7.0 ** (2.57, 11.44)	4.73 * (1.53, 7.94)	6.29 * (1.69, 10.88)
Nativity				
Foreign-born	8.90 * (2.15, 15.66)	8.91 * (2.63, 15.18)	5.33 * (1.25, 9.41)	6.15 (0.60, 11.71)
US-born	6.17 * (1.97, 10.36)	5.33 * (2.04, 8.63)	4.80 * (1.52, 8.07)	6.97 * (1.81, 12.12)

Note. CI = confidence interval; EPTB = extrapulmonary tuberculosis; HR = hazard ratio; LTBI = latent tuberculosis infection; PTB = pulmonary tuberculosis; TB = tuberculosis. Ratio of control is the case hazard rate from multivariate Cox regression.

* $P = .05$;

** $P = .01$.

TABLE 4

Unadjusted, Age-Adjusted, and Multivariate-Adjusted Relative Mortality HR (95% CI) Among Tuberculosis Survivors by Site of Infection: Centers for Disease Control and Prevention's National Death Index; Texas, Massachusetts, and Seattle and King County, WA; 2008

Relative Mortality Hazard	Any TB, HR (95% CI)	PTB Only, HR (95% CI)	EPTB Only, HR (95% CI)	Both PTB and EPTB, HR (95% CI)
Unadjusted	8.12** (6.57, 9.67)	8.69** (7.01, 10.38)	9.94** (7.02, 12.86)	19.93** (11.05, 28.81)
Age adjusted	7.14** (2.97, 11.31)	6.30** (3.48, 9.12)	4.35** (2.21, 6.50)	9.10** (4.46, 13.74)
Multivariate adjusted	7.63* (2.32, 12.94)	7.18** (2.64, 11.72)	5.10* (1.68, 8.52)	6.48* (1.78, 11.19)

Note. CI = confidence interval; EPTB = extrapulmonary tuberculosis; HR = hazard ratio; LTBI = latent tuberculosis infection; PTB = pulmonary tuberculosis; TB = tuberculosis. Ratio of control to case hazard rate from Cox regression. All models adjust for location. Multivariate Cox regression adjusts for age, gender, race/ethnicity, HIV status, and nativity.

* $P = .05$;

** $P = .01$.

TABLE 5

Regression-Adjusted Duration of Survival HR (95% CI) Among Decedents by History of Tuberculosis and Site of Infection: Centers for Disease Control and Prevention's National Death Index; Texas, Massachusetts, and Seattle and King County, WA; 2008

Average Time After Diagnosis or Treatment, Years	LTBI Comparison, HR (95% CI)	TB Survivor, Any Site of Infection, HR (95% CI)	TB Survivor, Pulmonary Site Only, HR (95% CI)	TB Survivor, Extrapulmonary Site Only, HR (95% CI)	TB Survivor, Both PTB and EPTB, HR (95% CI)
Unadjusted	7.1 (6.7, 7.6)	5.3** (5.1, 5.5)	5.3** (5.1, 5.6)	5.2** (4.6, 5.8)	5.3** (4.5, 6.1)
Age–gender adjusted	5.5 (5.1, 5.8)	4.1** (3.6, 4.7)	4.2** (3.5, 4.8)	4.2** (3.5, 4.9)	4.0** (3.3, 4.8)
Multivariate adjusted	5.7 (5.2, 6.3)	4.1** (3.3, 4.9)	4.2** (3.4, 5.0)	4.0** (3.0, 4.9)	3.7** (2.5, 4.9)

Note. CI = confidence interval; EPTB = extrapulmonary tuberculosis; HR = hazard ratio; LTBI = latent tuberculosis infection; PTB = pulmonary tuberculosis; TB = tuberculosis. Age-gender and multivariate-adjusted estimates also adjust for state location.

*$P = .05$;

**$P = .01$.