

## Tuberculosis Mortality in the United States: Epidemiology and Prevention Opportunities

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### Abstract

**Rationale:** More information on risk factors for death from tuberculosis in the United States could help reduce the tuberculosis mortality rate, which has remained steady for more than a decade.

**Objective:** To identify risk factors for tuberculosis-related death in adults.

**Methods:** We performed a retrospective study of 1,304 adults with tuberculosis who died before treatment completion and 1,039 frequency-matched control subjects who completed tuberculosis treatment in 2005 to 2006 in 13 states reporting 65% of U.S. tuberculosis cases. We used in-depth record abstractions and a standard algorithm to classify deaths in persons with tuberculosis as tuberculosis-related or not. We then compared these classifications to causes of death as coded in death certificates. We used multivariable logistic regression to calculate adjusted odds ratios for predictors of tuberculosis-related death among adults compared with those who completed tuberculosis treatment.

**Results:** Of 1,304 adult deaths, 942 (72%) were tuberculosis related, 272 (21%) were not, and 90 (7%) could not be classified. Of 847 tuberculosis-related deaths with death certificates available, 378 (45%) did not list tuberculosis as a cause of death. Adjusting for known risks, we identified new risks for tuberculosis-related death during treatment: absence of pyrazinamide in the initial regimen (adjusted odds ratio, 3.4; 95% confidence interval, 1.9–6.0); immunosuppressive medications (adjusted odds ratio, 2.5; 95% confidence interval, 1.1–5.6); incomplete tuberculosis diagnostic evaluation (adjusted odds ratio, 2.2; 95% confidence interval, 1.5–3.3), and an alternative nontuberculosis diagnosis before tuberculosis diagnosis (adjusted odds ratio, 1.6; 95% confidence interval, 1.2–2.2).

**Conclusions:** Most persons who died with tuberculosis had a tuberculosis-related death. Intensive record review revealed tuberculosis as a cause of death more often than did death certificate diagnoses. New tools, such as a tuberculosis mortality risk score based on our study findings, may identify patients with tuberculosis for in-hospital interventions to prevent death.

**Keywords:** cause of death; risk factors; death certificates

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Americans still die of tuberculosis (TB), a preventable disease (1). On the basis of death certificate data, the TB mortality rate in the United States was 0.2/100,000 population, or 555 deaths, in 2013 and has not changed since 2003 (2). Despite the importance of TB mortality, limited information has been published about patients who die of TB and the frequency of potentially preventable deaths.

Many studies have documented the need for a systematic approach to measure TB-related deaths and determine the role that TB played in death. However, such studies often use death certificates as their main data source. Death certificates can misclassify the cause of death and underestimate the number who died with TB (3–7). One study of death certificates found TB listed as an underlying or contributing cause of death in only 34% of persons who died with TB (4). In a survey of resident physicians, only 33% who completed death certificates believed the death certificates were accurate; 20% who reported entering an incorrect cause of death stated they had done so because they were not familiar with the patient (5). Although some studies have examined TB-related mortality beyond death certificates, many were limited by narrowly defined populations or small size (6, 8–12).

Identifying risk factors for TB mortality could assist in the design of preventive interventions. Our primary objectives were to quantify and assess risk factors for TB-related deaths in the United States.

## Methods

There were 1,304 adults with a verified diagnosis of TB (as reported to the Centers

for Disease Control and Prevention [CDC]) who died in the 15 study catchment areas in 2005 and 2006 (see Table E1 in the online supplement). All patients were included who were reported as dead at diagnosis or if the reason for treatment cessation was “died” on the Report of Verified Case of Tuberculosis form.

For all of the aforementioned study subjects, trained data abstractors from each study site reviewed inpatient and outpatient medical and laboratory records and immediate, underlying, and contributing causes of death from the death certificates and entered into the abstraction form for the patient.

All persons evaluating the TB relatedness of death took a 2-hour training where the TB-relatedness algorithm was reviewed and sample cases were discussed to ensure consistency of review. In addition, all persons performing TB-relatedness determinations referred to a TB-relatedness flowchart and procedural manual to ensure consistency of classification. Two study team members, at least one of whom was a clinician with TB expertise, reviewed each data abstraction form and independently classified each death as possibly or definitely TB related, unlikely or definitely not related, or unclassifiable, using an *a priori* algorithm (Figure E1). Disagreements were resolved by a third independent reviewer. For the final analysis, definitely and possibly TB-related deaths were classified as TB-related deaths, and unlikely or definitely not TB-related deaths were classified as TB-unrelated deaths. This classification is used for all analyses.

A Kaplan-Meier curve was created to compare the time to death for patients who died with a TB-related death and patients who died with a TB-unrelated death.

To study risk factors for TB-related death during therapy, persons who died before diagnosis or treatment initiation were excluded from the cases. Only adults were included because of the small number ( $n = 14$ ) of pediatric (<18 yr) deaths. Control subjects were selected from the group of patients with verified TB reported in the catchment areas from 2005 to 2006, who had completed TB treatment (which may last up to 2 years after treatment initiation; approximately 18,000 patients). Control patients were frequency matched 1:1 to cases by catchment area and age category. As with cases, control medical records were abstracted in each study site by reviewing inpatient and outpatient medical and laboratory records. All available data for each control were entered into the data abstraction form.

All subjects were designated as having severe or extensive TB disease if they had acid-fast bacilli on smear microscopy (smear-positive disease), respiratory failure, bilateral pulmonary disease, extensive pulmonary destruction, pulmonary and extrapulmonary disease, or TB meningitis.

We analyzed categorical variables with the chi-square or Fisher exact test and continuous variables with the Wilcoxon rank sum test. We used the kappa coefficient to compare agreement on TB-related deaths between study algorithm and death certificate.

We assessed risk factors known to contribute to TB-related death from previous studies as well as novel risk factors we hypothesized to be associated with TB-related death. Covariates associated with TB-related death in bivariable models ( $P < 0.2$ ) were included in multivariable logistic regression models. Respiratory failure was excluded from all models because it is on the

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causal pathway for TB-related death (13). If covariates were correlated ( $\phi$  value  $\geq 0.3$ ), only the variable associated with the highest proportion of patients was included in the model. We excluded covariates that represented limited exposure opportunities for patients who died within the first month of treatment (health department monitoring, adverse reactions to TB therapy, treatment interruptions). Age, sex, meningeal TB status, and human immunodeficiency virus (HIV) status were included *a priori* in all models.

Covariates were added in descending order of bivariable odds ratios and were retained if their addition yielded a Wald chi-square  $P$  value  $\leq 0.05$  and 1) changed the adjusted odds ratio associated with meningeal TB or HIV by at least 10% (14), or 2) improved the model fit as indicated by the likelihood ratio test. Interactions that were tested included HIV by meningeal TB, HIV by cognitive impairment, and HIV by sputum smear status, and absence of pyrazinamide in the initial treatment regimen by “liver condition” (defined as patient with cirrhosis or viral hepatitis or

patient reported excess alcohol usage). Data were analyzed using SAS 9.3.

Institutional Review Boards at CDC and each study site approved the study. This study was funded by the Division of Tuberculosis Elimination, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, through a task order announced and managed by the Tuberculosis Epidemiologic Studies Consortium.

### Results

The 1,318 deaths included 14 children and accounted for 52% of all deaths among individuals with TB in the United States during 2005 to 2006. Of the 1,304 adult deaths, 942 (72%) were TB related, 272 (21%) were not, and 90 (7%) were unclassifiable (Figure 1). Review of 331 records indicated 87% agreement between the first and second reviewers on TB relatedness of death. TB-related death occurred during treatment for 705 decedents (75%) and before treatment began

for 237 (25%), of whom 202 (85%) died before diagnosis. Of the 705 who died during treatment, 329 (47%) died within 30 days of diagnosis and 371 (53%) died later; 5 (0.7%) had missing dates (Figure 1). Figure 2 shows that those who had a TB-related death died sooner after their TB diagnosis than those who died of other causes.

Almost all (98%) of the 942 adult patients with TB-related deaths had culture-confirmed TB: 228 of 237 who died before TB treatment, and 692 of 705 who died during treatment. Of the 755 *Mycobacterium tuberculosis* isolates with drug susceptibility results, 58 (8%) were mono-resistant (41 to isoniazid, 16 to pyrazinamide, and 1 to rifampin), 4 (0.5%) were resistant to more than one drug, and 14 (2%) displayed multidrug-resistant TB, defined as resistance to at least isoniazid and rifampin.

Among the 942 patients with TB-related deaths, 789 (84%) had at least one of the following: smear-positive disease (54%), bilateral pulmonary lesions (44%), extensive pulmonary destruction visible on chest image (31%), pulmonary and

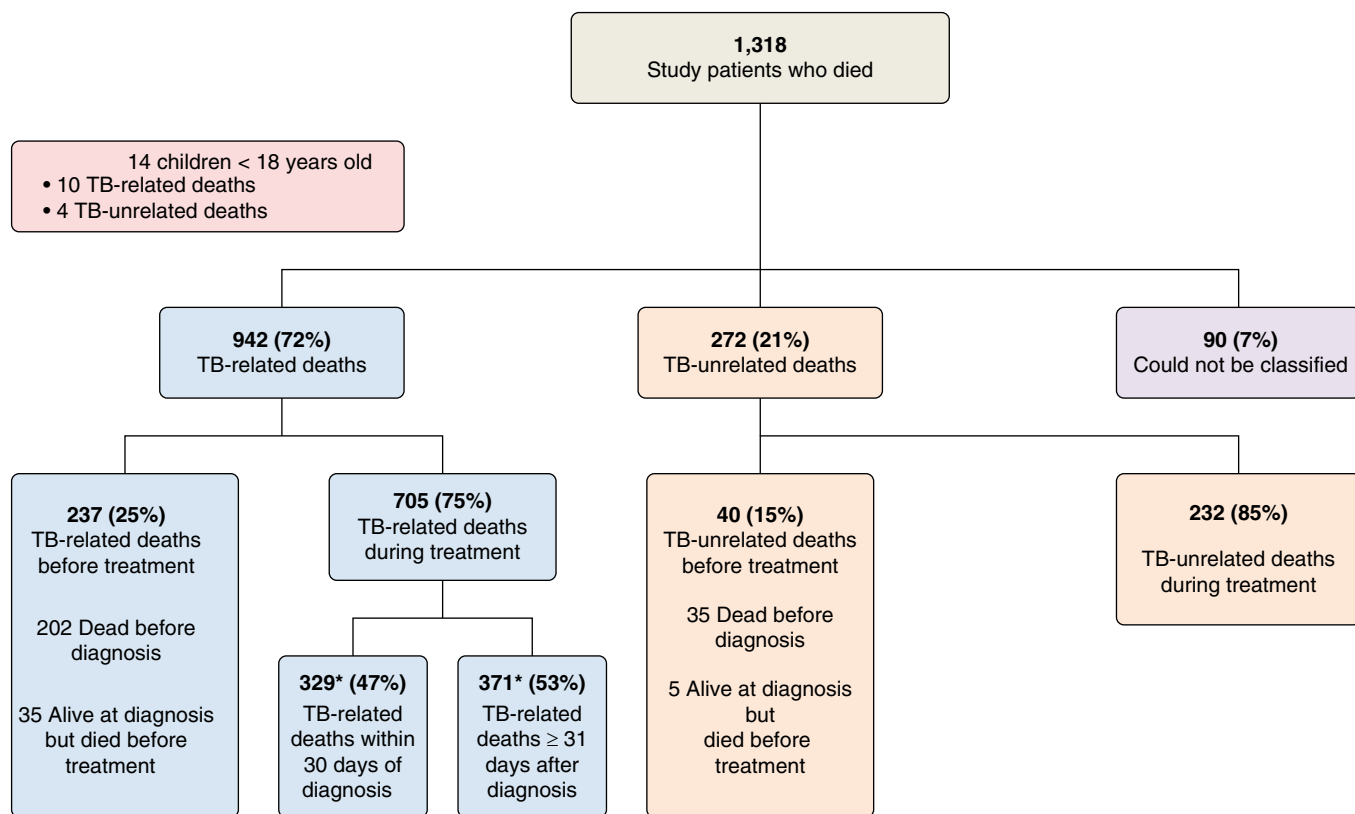
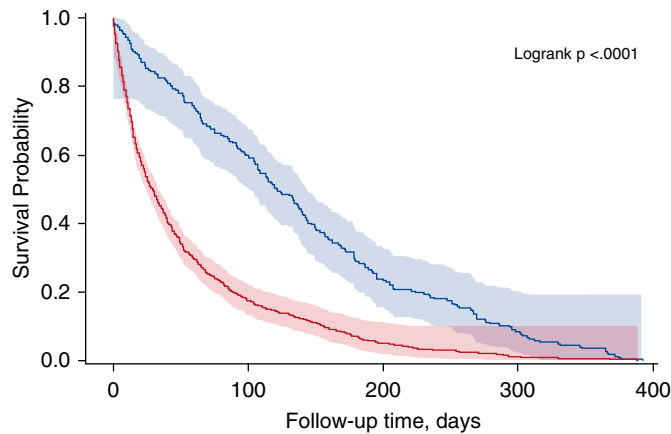


Figure 1. Tuberculosis (TB) relatedness and timing of deaths. \*Five patients’ time-to-death could not be assessed due to missing dates. TB = tuberculosis.



**Figure 2.** Kaplan-Meier curve comparing time to death for patients who died with tuberculosis (TB)-related death to patients who died with TB-unrelated death. The lower line represents the probability of survival for patients with TB-related death. The upper line represents the probability of survival for patients with TB-unrelated death.

extrapulmonary disease (23%), meningeal TB (10%), or miliary TB (7%). Concurrent medical conditions included chronic obstructive pulmonary disease (COPD) (25%), diabetes mellitus (25%), coronary artery disease (20%), viral hepatitis (12%), cancer (11%), and cirrhosis (10%) (Table 1).

Of the 237 cases with TB-related deaths who died before starting treatment, 82% had pulmonary/pleural involvement; 10% had cavitory lesions on chest radiographs. Notably, 40% had an initial diagnosis other than TB, 56% had no TB nucleic acid amplification test performed, and 51% did not have a full TB diagnostic evaluation. Compared with those who died during treatment, cases who died before starting treatment were more likely to have extrapulmonary TB, unknown HIV status, a diagnosis or history of cancer, or no reported TB symptoms (Table 1).

Adults with TB-related death within 30 days after starting TB treatment were older than those who died more than 30 days after starting TB treatment (Table E2).

Death certificates were available for 1,093 of the 1,214 patients whose deaths could be classified as TB related or not using the study algorithm. We classified 847 deaths (77% of 1,093) as TB related and 246 (23%) as TB unrelated. Of the 847 algorithm-defined TB-related deaths, 469 (55%) had TB listed on the death certificate as the immediate, underlying, or contributing cause of death. Among adult patients with TB-related deaths, early death was more common if the death certificate did not mention TB. Almost two-thirds

(66%) of those with no mention of TB on the death certificate died before treatment or within 30 days of treatment start, compared with 54% of those whose death certificates mentioned TB ( $P = 0.0001$ ).

Compared with death determined to be related to TB by the study algorithm, the sensitivity of death certificate data (i.e., TB listed as underlying, immediate, or contributing cause of death) was 55% and specificity was 75%. Agreement between study algorithm and death certificate was modest ( $\kappa = 0.21$ ; 95% confidence interval [CI], 0.19–0.26) (Table E3).

In the case-control study, bivariable analysis showed that cases (adults with TB-related deaths who died during treatment) were more likely than control subjects (adults alive at least 2 years after treatment completion) to have severe or extensive disease: smear-positive disease (60% vs. 41%,  $P < 0.001$ ), respiratory failure (50% vs. 3%,  $P < 0.001$ ), bilateral disease (47% vs. 26%,  $P < 0.001$ ), extensive pulmonary destruction (36% vs. 21%,  $P < 0.001$ ), combined pulmonary and extrapulmonary disease (27% vs. 8%,  $P < 0.001$ ), and meningeal disease (11% vs. 1%,  $P < 0.001$ ).

Cases were also more likely to have been born in the United States (54% vs. 38%,  $P < 0.001$ ), to have had an initial diagnosis other than TB (43% vs. 27%  $P < 0.001$ ), to have refused treatment at any time during the treatment course (6% vs. 3%,  $P = 0.001$ ), to have cognitive impairment (28% vs. 5%  $P < 0.001$ ), to have had drug interactions with other medications (3% vs. 1%,  $P = 0.02$ ),

to report any TB symptom (93% vs. 85%,  $P < 0.001$ ), and to report weight loss (65% vs. 56%,  $P = 0.001$ ), fever (55% vs. 44%,  $P < 0.001$ ), shortness of breath (49% vs. 29%,  $P < 0.001$ ), or loss of appetite (40% vs. 25%,  $P < 0.001$ ) (Table 2). Cases were more likely to be HIV-positive (20% vs. 5%,  $P < 0.001$ ) or to have unknown HIV status (40% vs. 23%,  $P < 0.001$ ). Cases were less likely to report cough (64% vs. 75%,  $P < 0.001$ ), night sweats (27% vs. 33%,  $P = 0.01$ ), or hemoptysis (11% vs. 16%,  $P = 0.003$ ). There was no difference between the two groups in the proportion of patients with diabetes mellitus (DM) (26% vs. 23%,  $P = 0.11$ ).

Bivariate analyses also showed differences in receipt of health services. Cases were more likely to have been diagnosed as inpatients (89% vs. 54%,  $P < 0.001$ ) and to have received a portion of the intensive phase of TB treatment as inpatients (79% vs. 25%,  $P < 0.001$ ). Cases were less likely to have had a health department home visit, to have been interviewed within a week of the health department's notification of their case, and to have had their home address recorded (11% vs. 1%,  $P < 0.001$ ).

In multivariable analysis, factors associated with TB-related death while receiving TB treatment included receiving a portion of the intensive phase of therapy in the hospital (adjusted odds ratio [aOR], 6.5; 95% CI, 4.9–8.6), absence of pyrazinamide in the initial treatment regimen (aOR, 3.4; 95% CI, 1.9–6.0), cognitive impairment (aOR, 2.8; 95% CI, 1.9–4.2), receiving immunosuppressive medications such as prednisone or tumor necrosis factor- $\alpha$  inhibitors (aOR, 2.5; 95% CI, 1.1–5.6), COPD (aOR, 2.4; 95% CI, 1.7–3.3), bilateral pulmonary disease (aOR, 2.2; 95% CI, 1.6–2.9), no sputa collection for smear microscopy during pulmonary TB evaluation (aOR, 2.2; 95% CI, 1.5–3.3), liver conditions (aOR, 1.9; 95% CI, 1.4–2.7), cancer (aOR, 1.9; 95% CI, 1.9–5.4), and receiving a diagnosis other than TB before the TB diagnosis (aOR, 1.6; 95% CI, 1.2–2.2) (Table 3). None of the interaction terms achieved statistical significance; therefore, they were not maintained in the final model.

## Discussion

Tuberculosis, a treatable and preventable disease, contributed to death in almost

**Table 1.** Characteristics associated with death before or during tuberculosis treatment among 942 adults whose deaths were tuberculosis related

Characteristic	Patients Who Died before Treatment (n = 237)	Patients Who Died during Treatment (n = 705)	P Value
Demographic			
Age, yr, mean, median (IQR)	65.8, 69.4 (50.7–81.5)	64.9, 66.1 (51.9–79.9)	0.3
Age group, yr			0.014
18–44	45 (19)	100 (14)	
45–64	57 (24)	237 (34)	
65–85	96 (41)	284 (40)	
>85	39 (16)	84 (12)	
Male	157 (66)	481 (68)	0.6
White non-Hispanic	95 (40)	290 (41)	0.8
Black non-Hispanic	85 (36)	250 (35)	0.9
Asian	54 (23)	153 (22)	0.7
Hispanic	45 (19)	160 (23)	0.2
U.S. born	124 (52)	378 (54)	0.7
Socioeconomic/behavioral*			
Unemployed	162 (68)	542 (77)	0.01
Homeless	10 (4)	64 (9)	0.02
Incarcerated	5 (2)	17 (2)	0.8
Injection drug use	5 (2)	34 (5)	0.07
Noninjection drug use	13 (5)	75 (11)	0.02
Excess alcohol	35 (15)	126 (18)	0.3
Long-term care facility	29 (12)	110 (16)	0.2
Clinical			
Pulmonary TB only	165 (70)	440 (62)	0.5
Extrapulmonary TB only	43 (18)	74 (11)	0.002
Both pulmonary and extrapulmonary TB	29 (12)	191 (27)	<0.001
Bilateral disease	91 (38)	328 (47)	0.03
Cavities on chest image	24 (10)	180 (26)	<0.001
Effusion	84 (35)	272 (39)	0.4
Hemorrhage	7 (3)	7 (1)	0.03
Meningeal TB	23 (10)	75 (11)	0.7
Gastrointestinal TB	1 (0.4)	28 (4)	0.01
Peritoneal TB	7 (3)	26 (4)	0.6
Miliary TB	20 (8)	48 (7)	0.4
Pneumothorax	3 (1)	25 (4)	0.07
Extensive pulmonary destruction	44 (19)	252 (36)	<0.001
Respiratory failure	97 (41)	352 (50)	0.02
Smear positive <sup>†</sup>	88 (37)	423 (60)	<0.001
Multidrug-resistant TB <sup>‡</sup>	1 (0.4)	13 (2)	0.1
History of TB	9 (4)	56 (8)	0.03
HIV status			<0.001
HIV negative	47 (20)	283 (40)	
HIV positive	29 (12)	141 (20)	
HIV test not offered	42 (18)	98 (14)	
HIV test refused	2 (1)	24 (3)	
Unknown HIV test result	117 (49)	159 (23)	
Coronary artery disease	46 (19)	143 (20)	0.8
Cancer	35 (15)	66 (9)	0.02
COPD	55 (23)	184 (26)	0.4
Condition affecting the liver <sup>§</sup>	59 (25)	215 (31)	0.1
Cirrhosis	24 (10)	70 (10)	0.9
Hepatitis (viral)	23 (10)	90 (13)	0.2
Diabetes mellitus	52 (22)	183 (26)	0.2
Cognitive impairment	61 (26)	198 (28)	0.5
Physical inability to self-medicate	16 (7)	108 (15)	<0.001
Immunosuppressive medications <sup>  </sup>	5 (2)	40 (6)	0.03
No reported TB symptom	50 (21)	48 (7)	<0.001
Reported cough <sup>  </sup>	111 (59)	421 (64)	0.2
Reported fever <sup>  </sup>	83 (44)	358 (55)	0.01
Reported hemoptysis <sup>  </sup>	18 (10)	73 (11)	0.6
Reported night sweats <sup>  </sup>	26 (14)	178 (27)	<0.001
Reported weight loss <sup>  </sup>	81 (43)	424 (65)	<0.001

(Continued)



Table 1. (Continued)

Characteristic	Patients Who Died before Treatment (n = 237)	Patients Who Died during Treatment (n = 705)	P Value
Health care			
Early report**	227 (96)	695 (99)	0.01
No insurance	25 (11)	75 (11)	0.9
Competing diagnosis††	94 (40)	304 (43)	0.3
NAAT not done	132 (56)	337 (48)	0.04
TST not done	185 (78)	341 (48)	<0.001
Incomplete evaluation‡‡	120 (51)	126 (18)	<0.001

Definition of abbreviations: AFB = acid-fast bacilli; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus; IQR = interquartile range; NAAT = nucleic acid amplification test; TB = tuberculosis; TST = tuberculin skin test.

Data presented as n (%) unless otherwise noted.

\*Unemployed included all persons not seeking employment at the time of TB diagnosis; homeless included those without a stable home within 1 year up to TB diagnosis; incarcerated included those who were incarcerated within 1 year up to TB diagnosis; injection drug use, noninjection drug use, excess alcohol use: each involved substances used within 1 year up to TB diagnosis; long-term care facility included those who lived in a long-term care facility within 1 year up to TB diagnosis.

†Smear-positive indicates positive on AFB smear microscopy. Comparison group was negative or unknown results on AFB smear microscopy.

‡Multidrug-resistant group was a subgroup of culture-confirmed cases (n = 920) with known drug susceptibility test results (n = 755).

§Patient had cirrhosis or viral hepatitis or reported using excess alcohol.

||Includes prednisone and tumor necrosis factor- $\alpha$  inhibitors.

¶Denominators are for patients who reported any TB symptom—patients who died: before treatment = 187; during treatment = 657.

\*\*Report case to state TB control program within 10 days of diagnosis.

††A diagnosis other than TB was made before TB diagnosis.

‡‡Patient pulmonary evaluation did not include collection of three consecutive sputum samples for AFB smear microscopy within 4 days of hospitalization, or within 30 days if the patient with pulmonary disease was diagnosed as an outpatient. For patients with extrapulmonary TB only, no imaging or laboratory tests were documented.

three-fourths of persons in our study who died with the disease in the United States. Persons who died from tuberculosis were less likely to have typical symptoms and signs of tuberculosis, yet, paradoxically, they had extensive disease. Clinicians must be aware of atypical presentations of tuberculosis, particularly in persons with extensive disease and in human immunodeficiency virus–infected persons, and have a low threshold for including tuberculosis in the differential diagnosis. For individuals without obvious risk factors for tuberculosis, additional tools are needed to help clinicians focus sooner on the possibility of tuberculosis.

Almost three-fourths of persons with tuberculosis-related death died before diagnosis or within a month after treatment initiation. Many who died did not report tuberculosis symptoms, and few who died before treatment had cavities on chest radiograph, which may have obscured the diagnosis of tuberculosis, an infrequent disease in the United States. Our finding was consistent with other studies that found an association between atypical chest radiographic findings (i.e., noncavitary infiltrate) and death at diagnosis and before treatment (15, 16). In our study, persons with tuberculosis-related deaths were more likely to have had an initial nontuberculosis diagnosis, such as pneumonia. This finding

suggests patients may die or experience increased risk of death while providers pursue other diagnoses.

In a systematic review evaluating risk factors for tuberculosis death during treatment, Waitt and Squire hypothesized that studies demonstrating an association between increased comorbidities, social isolation, and death from tuberculosis may be caused by delays in presenting to a provider with symptoms (17). The role of cognitive impairment in death during tuberculosis treatment may be explained by patient delays in presenting to a provider (8, 17), but could also be independently associated with mortality.

When compared with those dying before diagnosis, cases who died during treatment were more likely to be human immunodeficiency virus–positive, to have pulmonary and extrapulmonary disease, and to have extensive pulmonary destruction and bilateral disease on chest radiograph. Human immunodeficiency virus infection was an independent risk factor for tuberculosis-related death in our study and others (15, 16, 18, 19). However, many decedents had unknown human immunodeficiency virus status, either because the test was not performed or the results were unknown. This finding underscores the importance of human immunodeficiency virus testing of all

patients being evaluated for tuberculosis and extensive pulmonary and extrapulmonary conditions without a definitive diagnosis, because management of both tuberculosis and human immunodeficiency virus concurrently increases the likelihood of a successful outcome (20, 21).

Findings of significant abnormalities on chest radiograph or combined pulmonary/extrapulmonary disease might increase the likelihood that the physician makes a tuberculosis diagnosis sooner. However, consistent with the extensive burden of disease, half the patients who died during treatment did so within a month of starting treatment.

Although previous studies identified diabetes mellitus as a risk factor for death in patients with tuberculosis (13, 22, 23), our study found that diabetes did not contribute to tuberculosis-related death. The literature has been inconsistent about the role of diabetes in tuberculosis treatment outcomes (24, 25).

Of note, 42 persons (6%) starting tuberculosis therapy had severe adverse reactions to antituberculosis medications, which may have exacerbated an underlying condition and led to death. In our study, the most common preexisting condition was liver disease. In a study evaluating mortality of patients with cirrhosis with and without tuberculosis, patients with cirrhosis were

**Table 2.** Comparison of adult patients with tuberculosis-related deaths who died during treatment and control patients who completed treatment

Characteristic	Patients Who Died during Treatment (N = 705)	Control Subjects (N = 1,039)	P Value
<b>Demographic</b>			
Age, yr, mean, median (IQR)	64.9, 66.1 (51.9–79.9)	62.5, 66.9 (50.6–76.4)	0.01
Male	481 (68)	666 (64)	0.08
White non-Hispanic	290 (41)	413 (40)	0.6
Black non-Hispanic	250 (35)	249 (24)	<0.001
Asian	153 (22)	370 (36)	<0.001
Hispanic	160 (23)	206 (20)	0.2
U.S. born	378 (54)	399 (38)	<0.001
<b>Socioeconomic/behavioral</b>			
Unemployed	542 (77)	633 (61)	<0.001
Homeless	64 (9)	56 (5)	0.003
Incarcerated	17 (2)	33 (3)	0.3
Injection drug use	34 (5)	20 (2)	<0.001
Noninjection drug use	75 (11)	60 (6)	<0.001
Excess alcohol	126 (18)	110 (11)	<0.001
Long-term care facility	110 (16)	43 (4)	<0.001
<b>Clinical</b>			
Pulmonary TB only	440 (62)	801 (77)	<0.001
Extrapulmonary TB only	74 (11)	156 (15)	0.006
Both extrapulmonary and pulmonary TB	191 (27)	82 (8)	<0.001
Bilateral disease	328 (47)	269 (26)	<0.001
Cavities on chest image	180 (26)	254 (24)	0.6
Effusion	272 (39)	183 (18)	<0.001
Hemorrhage	7 (1)	4 (0.4)	0.1
Meningeal TB	75 (11)	10 (1)	<0.001
Gastrointestinal TB	28 (4)	14 (1)	<0.001
Peritoneal TB	26 (4)	16 (1.5)	0.004
Miliary TB	48 (7)	4 (0.4)	<0.001
Pneumothorax	25 (4)	2 (0.2)	<0.001
Extensive pulmonary destruction	252 (36)	216 (21)	<0.001
Respiratory failure	352 (50)	27 (3)	<0.001
Smear positive*	423 (60)	423 (41)	<0.001
Multidrug-resistant TB	13 (2)	0	<0.001
History of TB	56 (8)	71 (7)	0.4
<b>HIV status</b>			
HIV negative	283 (40)	758 (73)	
HIV positive	141 (20)	47 (5)	
HIV test not offered	98 (14)	57 (5)	
HIV test refused	24 (3)	57 (5)	
Unknown HIV test result	159 (23)	120 (12)	
Coronary artery disease	143 (20)	109 (10)	<0.001
Cancer	66 (9)	44 (4)	<0.001
COPD	184 (26)	130 (13)	<0.001
Condition affecting the liver <sup>†</sup>	215 (31)	166 (16)	<0.001
Cirrhosis	70 (10)	20 (2)	<0.001
Hepatitis (viral)	90 (13)	65 (6)	<0.001
Diabetes mellitus	183 (26)	235 (23)	0.1
Renal failure	24 (3)	6 (0.6)	<0.001
Immunosuppressive medications <sup>‡</sup>	40 (6)	18 (2)	<0.001
Cognitive impairment	198 (28)	53 (5)	<0.001
Physical inability to self-medicate	108 (15)	27 (3)	<0.001
No reported TB symptom	48 (7)	161 (15)	<0.001
Reported cough <sup>§</sup>	421 (64)	653 (75)	<0.001
Reported fever <sup>§</sup>	358 (55)	383 (44)	<0.001
Reported weight loss <sup>§</sup>	424 (65)	491 (56)	<0.001
Reported night sweats <sup>§</sup>	178 (27)	289 (33)	0.01
Reported shortness of breath <sup>§</sup>	348 (49)	304 (29)	<0.001
Reported loss of appetite <sup>§</sup>	285 (40)	256 (25)	<0.001
Reported chest pain <sup>§</sup>	128 (18)	173 (17)	0.4
Reported hemoptysis <sup>§</sup>	73 (11)	144 (16)	0.003

(Continued)

Table 2. (Continued)

Characteristic	Patients Who Died during Treatment (N = 705)	Control Subjects (N = 1,039)	P Value
Health care			
Competing diagnosis <sup>  </sup>	304 (43)	280 (27)	<0.001
TST not done	341 (48)	332 (32)	<0.001
Incomplete evaluation <sup>  </sup>	126 (18)	110 (11)	<0.001
Treatment characteristics			
Initiated on RIPE	610 (87)	933 (90)	0.04
PZA was excluded from initial treatment regimen	59 (8)	37 (4)	<0.001
DOT was initiated	232 (33)	874 (84)	<0.001**
DOT missing data	414 (59)	46 (4)	
Treatment interruptions	92 (13)	210 (20)	<0.001
SAE from TB meds**	76 (11)	102 (10)	0.5
TB treatment discontinued due to SAE of TB meds	64 (9)	73 (7)	0.1
Drug interactions <sup>††</sup>	19 (3)	12 (1)	0.02
Patient refused treatment at any time during treatment course	42 (6)	29 (3)	0.001
Health department activities <sup>††</sup>			
Lost to follow-up ≥30 d	10 (1.4)	14 (1.3)	0.9

Definition of abbreviations: AFB = acid-fast bacilli; COPD = chronic obstructive pulmonary disease; DOT = directly observed therapy; HIV = human immunodeficiency virus; IQR = interquartile range; PZA = pyrazinamide; RIPE = rifampin, isoniazid, pyrazinamide and ethambutol; SAE = severe adverse events; TB = tuberculosis; TST = tuberculin skin test.

Data presented as n (%) unless otherwise noted.

\*Smear-positive indicates positive on AFB smear microscopy. Comparison group was negative or unknown results on AFB smear microscopy.

†Patient had cirrhosis or viral hepatitis or reported using excess alcohol.

‡Includes prednisone, tumor necrosis factor- $\alpha$  inhibitors.

§Denominators are for patients who reported any TB symptom—patients who died during treatment = 657; control patients who completed treatment = 878.

||A diagnosis other than TB was made before TB diagnosis.

¶Patient pulmonary evaluation did not include collection of three consecutive sputum samples for AFB smear microscopy within 4 days of hospitalization, or within 30 days if the patient with pulmonary disease was diagnosed as an outpatient. For patients with extrapulmonary TB only, no imaging or laboratory tests were documented.

\*\*SAEs documented to be possible due to TB treatment include hepatitis, hepatic failure, seizures, anaphylaxis, thrombocytopenia, severe dermatitis, cardiac event.

††Drug interactions between TB medications and other medications that patient was taking were documented.

‡‡Of patients who died during treatment, 339 (48%) died within 30 days. Patients who died within 30 days had limited opportunity to have a tracking interview or home visit within 30 days.

found to have higher mortality 30 days to 1 year after starting treatment, suggesting that hepatotoxicity from tuberculosis treatment may be a source of higher mortality (26). Careful monitoring of patients with cirrhosis early in their treatment could prevent mortality.

Even after adjusting for age and factors that increased the risk of liver injury, we found that absence of pyrazinamide in the initial treatment regimen was associated with tuberculosis-related death. Clinicians might not prescribe pyrazinamide to patients with risks for liver injury because of its potential hepatotoxicity (27). In fact, 24 of 59 (41%) patients who died during treatment without pyrazinamide had reported excess alcohol use or had viral hepatitis or cirrhosis, and only 3% had a pyrazinamide-resistant *M. tuberculosis* strain. Thus, the absence of pyrazinamide in the regimen may be partially explained by concerns about toxicity in patients with liver conditions, as drug resistance does not

explain it. Further work is needed to understand the mechanism of pyrazinamide efficacy to develop drugs with a similar mechanism but without the toxicity.

As seen in previous studies, our study confirmed that death certificates might incompletely capture tuberculosis disease when it is related to death. As slightly more than half of patients with a death certificate and tuberculosis-related death had tuberculosis listed as an immediate, underlying, or contributing cause of death (55%), the sensitivity of the death certificate to find a tuberculosis-related death was modest (55%). One explanation for the lower detection of tuberculosis-related deaths by the death certificate is that tuberculosis might be diagnosed many weeks after death, when the culture becomes positive and the death certificate has already been completed.

Several features of tuberculosis-related death stand out in this study. Decedents often did not have the classic symptoms

(cough, hemoptysis, cavities on chest radiograph), which made an illness that is uncommon in the United States even easier to miss. Human immunodeficiency virus infection and liver conditions complicate tuberculosis and are also potential markers for increased mortality risk. The risk factors identified in this study may form the basis for the development of a tuberculosis mortality risk score, analogous to those that have been used to predict mortality in patients with tuberculosis in the hospital (28) and intensive care unit (29, 30), which may help with earlier diagnosis, rapid treatment initiation, and enhanced care. A risk score for pulmonary tuberculosis using risk factors (similar to the ones we describe) that was developed using a derivation cohort and tested using a validation cohort was able to differentiate between low-, moderate-, and high-risk patients (31). Bilateral disease on chest radiograph; extensive pulmonary destruction; immunosuppression;



**Table 3.** Factors associated with tuberculosis-related death on treatment for tuberculosis: multivariate logistic regression comparing patients who died during TB treatment to control patients who completed treatment

Factor	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age*	1.01 (1.002–1.01)	1.01 (1.003–1.02)
Sex (male vs. female)*	1.2 (1.0–1.5)	1.1 (0.8–1.5)
Meningeal TB*	12.3 (6.3–23.9)	13.2 (6.0–29.0)
HIV status* <sup>†</sup>		
HIV positive <sup>†</sup>	8.0 (5.6–11.5)	6.7 (4.1–10.8)
HIV test not offered <sup>†</sup>	4.6 (3.2–6.6)	4.3 (2.6–6.9)
HIV test refused <sup>†</sup>	1.1 (0.7–1.9)	1.4 (0.7–2.7)
HIV status unknown <sup>†</sup>	3.6 (2.7–4.7)	4.2 (2.9–6.1)
Miliary pattern on chest image	18.9 (6.8–52.7)	19.4 (5.4–69.8)
Initiated intensive phase of treatment as an inpatient	11.2 (8.9–14.0)	6.5 (4.9–8.6)
Cognitive impairment	7.3 (5.3–10.0)	2.8 (1.9–4.2)
Diagnosed in long-term care facility	4.3 (3.0–6.2)	2.1 (1.3–3.4)
Immunosuppressive medications <sup>‡</sup>	3.4 (1.9–6.0)	2.5 (1.1–5.6)
COPD	2.5 (1.9–3.2)	2.4 (1.7–3.3)
Pyrazinamide was excluded from initial treatment regimen	2.5 (1.6–3.8)	3.4 (1.9–6.0)
Peritoneal TB	2.4 (1.3–4.6)	3.7 (1.6–8.4)
Cancer	2.3 (1.6–3.5)	3.2 (1.9–5.4)
Condition affecting the liver <sup>§</sup>	2.3 (1.8–2.9)	1.9 (1.4–2.7)
Smear-positive <sup>  </sup>	2.2 (1.8–2.7)	2.5 (1.8–3.3)
Bilateral disease	2.2 (1.7–2.8)	2.2 (1.6–2.9)
Competing diagnosis <sup>¶</sup>	2.1 (1.7–2.5)	1.6 (1.2–2.2)
Incomplete evaluation <sup>**</sup>	1.8 (1.4–2.4)	2.2 (1.5–3.3)

*Definition of abbreviations:* CI = confidence interval; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus; OR = odds ratio; TB = tuberculosis.

\*Covariates were included in the model *a priori*.

<sup>†</sup>Reference category: patients with known negative HIV test results.

<sup>‡</sup>Includes prednisone and tumor necrosis factor- $\alpha$  inhibitors.

<sup>§</sup>Patient had cirrhosis or viral hepatitis or reported using excess alcohol.

<sup>||</sup>Sputum sample demonstrated acid-fast bacilli with smear microscopy.

<sup>¶</sup>A diagnosis other than TB was made before TB diagnosis.

\*\*Patient pulmonary evaluation did not include collection of three consecutive sputum samples for acid-fast bacilli smear microscopy within 4 days of hospitalization, or within 30 days if the patient with pulmonary disease was diagnosed as an outpatient. For patients with extrapulmonary TB only, no imaging or laboratory tests were documented.

meningeal, miliary, or peritoneal tuberculosis; cognitive impairment; and coexisting conditions of obstructive pulmonary disease, cancer, and underlying liver disease should be formally evaluated in scoring and predicting mortality. If scoring becomes routine, a high score could alert clinicians to patients who may benefit from more intensified management and monitoring. Even without a scoring system, when tuberculosis is diagnosed in a hospitalized patient, clinicians should recognize the increased risk of death.

Our study had limitations. We did not assess the impact of smoking on tuberculosis-related death and could not fully assess the impact of health department monitoring, because a large proportion of patients died before there was an

opportunity for such intervention. Because few hospital records noted the provision of directly observed therapy, its potential protective role could not be evaluated. Similarly, we could not evaluate the association between provider type and patient outcome, because patients who died were overwhelmingly cared for in the hospital, with multiple providers during at least some portion of their diagnosis and treatment. Our analysis also assumes that our algorithm for tuberculosis-related death was more accurate than the death certificate. Given that our classification was based on data from an extensive chart review of medical and public health records and multiple independent reviewers, we feel confident that any residual bias is smaller than what might have occurred had the

study been conducted with death certificates only in the classification. Because the study design required extensive medical record review, we were unable to assess risk factors for tuberculosis-related death before presentation to a healthcare provider. Finally, these data were collected on cases reported in 2005 to 2006; because of the extensive nature of the study organization and chart review required, more recent data are not available.

Our study underscores the importance of preventing tuberculosis deaths by preventing tuberculosis disease in the first place. In low-incidence nations with current diagnostic tools, tuberculosis diagnosis is often missed or delayed, and tuberculosis deaths most often occur within weeks of diagnosis. Current tuberculosis treatment regimens are not always sufficient to reverse extensive disease. Finally, many patients who successfully complete antituberculosis treatment often live less robust and shorter lives (32–34).

Fortunately, the public health and medical community have tools (more specific tests in the form of interferon- $\gamma$  release assays and shorter treatment regimens that are more likely to be completed) to identify and treat latent tuberculosis infection (35–37). Increased testing and treatment for latent tuberculosis infection can reduce the number of persons who develop and die of this preventable disease. ■

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