Trends in Tuberculosis Mortality in the United States, 1990–2006: A Population-Based Case-Control Study

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SYNOPSIS

Objective. We assessed demographic and temporal trends of tuberculosis (TB)-related deaths in the United States and examined associated comorbidities listed on death certificates.

Methods. We analyzed TB-related mortality from 1990 through 2006 by examining multiple-cause-of-death data from the National Center for Health Statistics. We assessed age-adjusted mortality rates, secular trends, associations with demographic variables, and comorbid conditions.

Results. From 1990 through 2006, TB was reported as a cause of death among 53,505 people in the U.S. with a combined overall mean age-adjusted mortality rate of 1.16 per 100,000 person-years. The age-adjusted TB mortality rate declined from 2.22 per 100,000 person-years in 1990 to 0.47 per 100,000 person-years in 2006, demonstrating mean annual decline of about 10%. People aged 75 years and older; males; foreign-born people; and those of Hispanic, Asian, black, and Native American race/ethnicity had comparatively elevated TB-related mortality rates. The mortality rate in foreign-born people was more than two times higher than in U.S.-born people. About 89% of deaths among people of Asian race/ethnicity and nearly 50% among black people were foreign-born individuals. Human immunodeficiency virus and selected autoimmune diseases were more common in TB-related deaths.

Conclusions. TB mortality decreased substantially from 1990 through 2006, but remains an important cause of preventable mortality. The observed decrease was more pronounced among U.S.-born people than among foreign-born people. Disparities in TB-related mortality and the identification of important comorbid conditions can inform strategies targeting subpopulations at increased risk for fatal TB infection.

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According to the World Health Organization, in 2007 an estimated two billion people—equal to one-third of the world's population—were infected with the bacterium that causes tuberculosis (TB) infection and disease.[1] In spite of prevention and treatment programs in most nations, TB remains the second leading cause of death (COD) worldwide from infectious disease, exceeded only by human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS).[2] Globally, approximately 9.2 million people become ill from active TB each year, and nearly 1.7 million people die from the disease.[1]

In the United States, TB is sometimes thought of as a disease of the past. In 2007, however, 13,293 people were diagnosed with active and potentially infectious TB disease.[3] Severe cases of TB disease can require hospitalization and are extremely costly to treat, such that estimates of the total charges for the TB hospitalizations in the U.S. in 2000 exceeded $385 million.[4] Although highly curative therapy is available in drug-sensitive cases, in-hospital mortality remains considerably high—ranging from 5% to 28%—and the persistence of multidrug-resistant TB (strains resistant to at least two primary anti-tubercular agents, Isoniazid and Rifampin) combined with the more recent emergence of extensively drug-resistant TB (resistant to almost all the anti-tubercular agents) present challenges to TB-control activities.[3–5] In addition, persistent disparities between white people and racial/ethnic minority groups and between U.S.-born and foreign-born people continue to challenge progress toward TB elimination in the U.S.

Currently, an extensive body of peer-reviewed literature on TB incidence and prevalence is available, but the literature is scarce on the recent burden of TB-related mortality in the U.S.[6,7] Understanding the mortality burden from TB disease can provide support to the funding of prevention, case-finding, and treatment strategies, including enhancing progress toward vaccine development. We analyzed the U.S. multiple-cause-of-death (MCOD) data from 1990 through 2006 to determine population-based estimates of demographic and temporal trends of TB-related deaths and associated comorbid conditions.

METHODS

All 50 states and the District of Columbia mandate mortality reporting using a standard death certificate set forth by the National Center for Health Statistics (NCHS). The death certificate provides information on characteristics of the decedent including age at death, gender, and race/ethnicity, as well as condi-tions that lead to death. The clinician completing the certificate records the CODs, which include immediate and underlying causes and other significant conditions contributing to death. The immediate COD is the final disease or condition leading directly to death, and the underlying COD is the condition that initiated the chain of events resulting in death. Diseases and related conditions reported on the death certificate are coded in accordance with the International Classification of Diseases, Ninth and 10th Revisions (ICD-9 and ICD-10) for 1990–1998 and 1999–2006 data, respectively.[8,9]

We analyzed the 1990 to 2006 U.S. MCOD data files, which were derived from death certificate informa-tion.[10] TB-related death was defined as all observations that assigned any of the following ICD codes as either an underlying COD or a contributing COD: ICD-9 codes of 010-018 (TB), 137 (late effect of TB), and 647.3 (TB complicating pregnancy, childbirth, or the puerperium) or ICD-10 codes of A15-A19 (TB), B90 (sequelae of TB), J65 (pneumoconiosis associated with TB), and O98.0 (TB complicating pregnancy, childbirth, and the puerperium). Other mycobacteria-related deaths, such as those caused by non-tuberculous mycobacteria, were not included in the analyses.

We calculated mortality rates using bridged-race population estimates—an estimate by the NCHS to allow varying multiple-race categories from different data collection systems to be more comparable—from the U.S. Census Bureau for years 1990 through 2006.[11,12] Variables included in the analysis were age, gender, race/ethnicity, year of death, and place of birth. Race/ethnicity was categorized as non-Hispanic white (white), Hispanic, Asian/Pacific Islander (Asian), non-Hispanic black (black), and American Indian/Alaska Native (Native American). Age at death was grouped into people aged <1, 1–4, 5–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and ≥85 years. Anyone born in the U.S. or its associated jurisdictions was clas-sified as U.S.-born. People not meeting this definition were considered foreign-born. Information on place of birth was not available for the years 2005 and 2006.

We calculated age-specific TB-related mortality rates and 95% confidence intervals (CIs) for each age group. Age-adjusted rates and rate ratios (RRs) were standard-ized to the year 2000 U.S. population by gender and race/ethnicity. Temporal trends were modeled by Poisson regression analysis. Premature mortality was measured for all deaths as years of potential life lost (YPLL) before 75 years of age. To assess comorbid conditions, we matched TB-related deaths with ran-domly selected non-TB deaths on age, gender, and race/ethnicity from 1990 through 2006 and computed matched odds ratio (MOR) comparisons of selected

comorbidities. Denominators for computing rates for foreign-born people were obtained from the U.S. Census population estimates.[13–16] We assessed age-specific temporal changes by comparing TB-related deaths for the years 1990, 1995, 2000, and 2005. We used SAS® version 9.2 for all calculations.[17]

RESULTS

From 1990 through 2006, a total of 53,505 TB-related deaths were identified, comprising 0.13% of the 39,694,210 total deaths in the U.S. TB was reported as the underlying COD in 21,285 (39.8%) of these deaths and as one of the contributing causes in 32,220 deaths (60.2%). The age-adjusted mortality rate for TB declined from 2.22 per 100,000 person-years in 1990 (95% CI 2.16, 2.28; $n=5,224$) to 0.47 per 100,000 person-years in 2006 (95% CI 0.45, 0.50; $n=1,468$) with a combined overall mean annual mortality rate of 1.16 per 100,000 person-years (95% CI 1.15, 1.17; $n=53,505$). Poisson regression analysis demonstrated an annually declining temporal trend of 10.44% (95% CI 10.27, 10.60) in TB mortality, but the slope of the decline appeared to be leveling somewhat from the year 2000 forward (Figure 1).

Men were more likely to experience TB-related deaths than women and were predominant among decedents (RR=2.16, 95% CI 2.13, 2.19) (Table 1). The declining trends over time in TB mortality rates for both genders were similar to that of the overall trend.

TB-related deaths among racial/ethnic groups demonstrated substantial disparities. Although the largest proportion of deaths was observed among white people ($n=27,856$, 52.1%), they had the lowest age-adjusted mortality rate (Table 1). Compared with white people, Native American (RR=5.15, 95% CI 5.09, 5.21), black (RR=4.75, 95% CI 4.69, 4.80), Asian (RR=4.17, 95% CI 4.12, 4.22), and Hispanic (RR=2.58, 95% CI 2.55, 2.62) people were more likely to experience TB-related death. When the study years were divided into early (1990–2000) and later (2001–2006) periods for comparison, TB-related mortality among Asian people (from RR=4.23, 95% CI 4.17, 4.28 in the early years to RR=5.88, 95% CI 5.71, 6.05 in the later years) and Native Americans (from RR=5.09, 95% CI 5.02, 5.16 in the early years to RR=6.87, 95% CI 6.68, 7.07 in the later years) increased relative to TB-related mortality among white people.

The mean age for TB decedents was 65 years (median = 69 years). TB was responsible for a total of 696,782 YPLL. The number of TB-related deaths

Figure 1. Number of TB-related deaths and age-adjusted mortality rates per 100,000 person-years by year, United States, 1990–2006
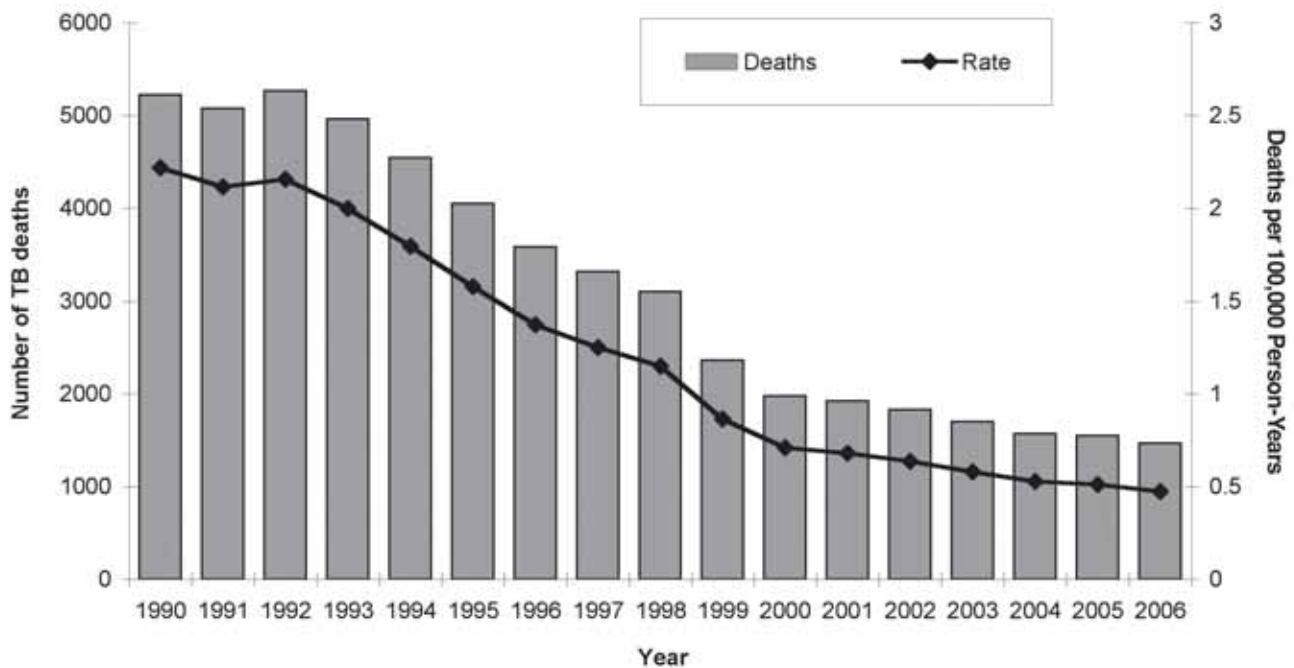
TB = tuberculosis

Table 1. Age-adjusted TB-related mortality rates per 100,000 person-years and mortality rate ratios by gender, race/ethnicity, and age group, United States, 1990–2006

Demographic characteristic	Number of deaths (percent)	Age-adjusted mortality rate (95% CI)	Age-adjusted rate ratio (95% CI)
Gender			
Female	20,539 (38.4)	0.77 (0.76, 0.79)	Referent
Male	32,966 (61.6)	1.67 (1.65, 1.69)	2.16 (2.13, 2.19)
Race/ethnicity[a]			
White	27,856 (52.1)	0.74 (0.73, 0.75)	Referent
Hispanic	5,827 (10.9)	1.91 (1.85, 1.96)	2.58 (2.55, 2.62)
Asian	3,347 (6.3)	3.08 (2.97, 3.19)	4.17 (4.12, 4.22)
Black	15,683 (29.3)	3.50 (3.44, 3.55)	4.75 (4.69, 4.80)
Native American	789 (1.5)	3.80 (3.52, 4.08)	5.15 (5.09, 5.21)
Age (in years)[b,c]			
<1	45 (0.1)	0.07 (0.05, 0.09)	NA
1–4	79 (0.1)	0.03 (0.02, 0.04)	NA
5–14	73 (0.1)	0.01 (0.01, 0.01)	NA
15–24	458 (0.9)	0.07 (0.06, 0.08)	NA
25–34	3,175 (5.9)	0.45 (0.44, 0.47)	NA
35–44	6,014 (11.2)	0.82 (0.80, 0.84)	NA
45–54	5,794 (10.8)	0.98 (0.95, 1.00)	NA
55–64	6,722 (12.6)	1.63 (1.59, 1.67)	NA
65–74	10,500 (19.6)	3.33 (3.27, 3.40)	NA
75–84	13,289 (24.8)	6.60 (6.49, 6.72)	NA
≥85	7,340 (13.7)	10.59 (10.35, 10.83)	NA
Total	53,505 (100.0)	1.16 (1.15, 1.17)	NA

[a]Race/ethnicity was missing for three TB-related deaths.

[b]Age was missing for 16 TB-related deaths.

[c]Mortality rates are age-specific rates, not age-adjusted rates.

TB = tuberculosis

CI = confidence interval

NA = not applicable

increased with age and peaked at people aged 75–84 years ($n=$13,289, 24.8%); the highest age-specific mortality rate was observed among people aged 85 years and older at 10.59 per 100,000 person-years (95% CI 10.35, 10.83; $n=$7,340) (Table 1).

Several diseases/conditions were found to be associated with TB on the death certificate. After adjusting for age, gender, and race/ethnicity, HIV (MOR=8.12, 95% CI 7.57, 8.72) and malnutrition (MOR=4.63, 95% CI 4.21, 5.09) were more likely to be reported on a death certificate that included TB as a cause of death compared with a death certificate of a matched control subject (Table 2). Systemic lupus erythematosus (MOR=3.03, 95% CI 2.40, 3.83) and rheumatoid arthritis (MOR=2.50, 95% CI 2.09, 3.00) also demonstrated a positive association.

We identified 50,487 TB-related deaths from 1990 to 2004 (Table 3; as noted previously, 2005 and 2006 MCOD data did not contain place-of-birth information and so were excluded from the analysis). Of these, 7,777 (15.4%) deaths were among foreign-born people. The percentage of deaths accounted for by foreign-born people increased from 11.1% in 1990 to 22.3% in 2004 (Figure 2). When comparing mortality by place of birth, the majority of the deaths among white ($n=$24,043, 90.9%), Hispanic ($n=$13,802, 92.3%), and Native American ($n=$691, 96.4%) racial/ethnic groups were U.S.-born people. In contrast, the majority of the TB-related deaths among Asian people ($n=$2,628, 88.5%) and nearly half among black people ($n=$2,581, 48.0%) were foreign-born individuals. From 1990 through 2004, the number of TB-related deaths among U.S.-born people decreased by 73.5% (from 4,474 to 1,187) compared with a decrease of 39.7% (from 579 to 349) among foreign-born people (Figure 2). The TB-related mortality rate declined from 1.95 deaths per 100,000 population in 1990 (95% CI 1.90, 2.01; $n=$4,474) to 0.47 deaths per 100,000 population in 2004 (95% CI 0.44, 0.49; $n=$1,187) among U.S.-born people, and from 2.92 deaths per 100,000 population in 1990 (95% CI 2.68, 3.16; $n=$579) to 1.02 deaths

Table 2. Frequency of selected comorbid causes of death and matched odds ratios comparing TB-related deaths with deaths from other conditions, United States, 1990–2006

Comorbid condition	Frequency of comorbid condition in TB-related deaths N (percent)[a]	Frequency of comorbid condition in matched control deaths N (percent)[a]	Matched odds ratio of condition being reported as a cause of death (95% CI)[b]
Diseases of the heart	21,241 (39.7)	24,505 (45.8)	0.77 (0.75, 0.79)
Chronic lower respiratory disease	10,724 (20.1)	4,667 (8.7)	2.78 (2.67, 2.89)
Respiratory arrest	8,375 (15.7)	3,188 (6.0)	2.94 (2.81, 3.07)
HIV	8,100 (15.1)	1,946 (3.6)	8.12 (7.57, 8.72)
Pneumonia	6,762 (12.6)	4,103 (7.7)	1.75 (1.68, 1.83)
Septicemia	4,177 (7.8)	3,093 (5.8)	1.38 (1.31, 1.45)
Renal failure	3,763 (7.0)	3,949 (7.4)	0.95 (0.91, 0.99)
Diabetes mellitus	3,274 (6.1)	4,942 (9.2)	0.63 (0.61, 0.66)
Respiratory failure	3,398 (6.4)	1,931 (3.6)	1.82 (1.71, 1.92)
Hypertension	3,031 (5.7)	4,159 (7.8)	0.71 (0.67, 0.74)
Malignant neoplasm of trachea, bronchus, and lung	2,866 (5.4)	3,607 (6.7)	0.78 (0.74, 0.82)
Malnutrition	2,391 (4.5)	540 (1.0)	4.63 (4.21, 5.09)
Rheumatoid arthritis	411 (0.8)	166 (0.3)	2.50 (2.09, 3.00)
Systemic lupus erythematosus	288 (0.5)	97 (0.2)	3.03 (2.40, 3.83)

[a]Total *n*=53,486. Three TB-related deaths in people of undetermined race/ethnicity and 16 TB-related deaths in people of undetermined age were excluded from matched analyses.

[b]Adjusted for age, gender, and race/ethnicity

TB = tuberculosis

CI = confidence interval

HIV = human immunodeficiency virus

per 100,000 population in 2004 (95% CI 0.91, 1.13; *n*=349) among foreign-born people.

Figure 3 shows the frequency distribution of TB-related mortality by age group during four separate years: 1990, 1995, 2000, and 2005. The years 1990 and 1995 mark the AIDS epidemic era, and a bimodal age distribution curve, peaking at 35–44 and 75–84 years of age, is observed. By 2000, total TB-related deaths decreased by more than 50% from 1995 (from 4,050 to 1,978), and the peak previously observed at 35–44 years of age had diminished significantly. In 2005, the major change from 2000 was a decrease in the number of deaths in people aged 65–84 years (from 977 to 675); the curve is unimodal with a peak observed at 75–84 years of age (*n*=413). The total count of TB-related deaths in 2005 represented a 70% decrease from 1990 (from 5,223 to 1,550) and a 21% decrease from 2000 (from 4,050 to 1,550).

DISCUSSION

The study findings indicate that TB-related mortality rates in the U.S. declined substantially from 1990 to 2006. Nevertheless, TB remains an important cause

Table 3. Frequency of TB-related deaths by race/ethnicity and place of birth, United States, 1990–2004[a]

Race/ethnicity	U.S.-born (percent)	Foreign-born (percent)[b]	Unknown (percent)	Total (percent)[c]
White	24,043 (90.9)	1,893 (7.2)	520 (2.0)	26,456 (52.4)
Black	2,671 (49.6)	2,581 (48.0)	130 (2.4)	5,382 (10.7)
Hispanic	13,802 (92.3)	649 (4.3)	509 (3.4)	14,960 (29.6)
Asian	319 (10.7)	2,628 (88.5)	22 (0.7)	2,969 (5.9)
Native American	691 (96.4)	23 (3.2)	3 (0.4)	717 (1.4)
Total	41,526 (82.3)	7,777 (15.4)	1,184 (2.3)	50,487 (100.0)

[a]2005 and 2006 multiple-cause-of-death data do not contain place-of-birth information and were excluded from the analysis.

[b]Race/ethnicity was missing for three foreign-born TB-related deaths.

[c]Row percentage

TB = tuberculosis

Figure 2. Number of TB-related deaths in U.S.-born and foreign-born people by year, United States, 1990–2004[a]
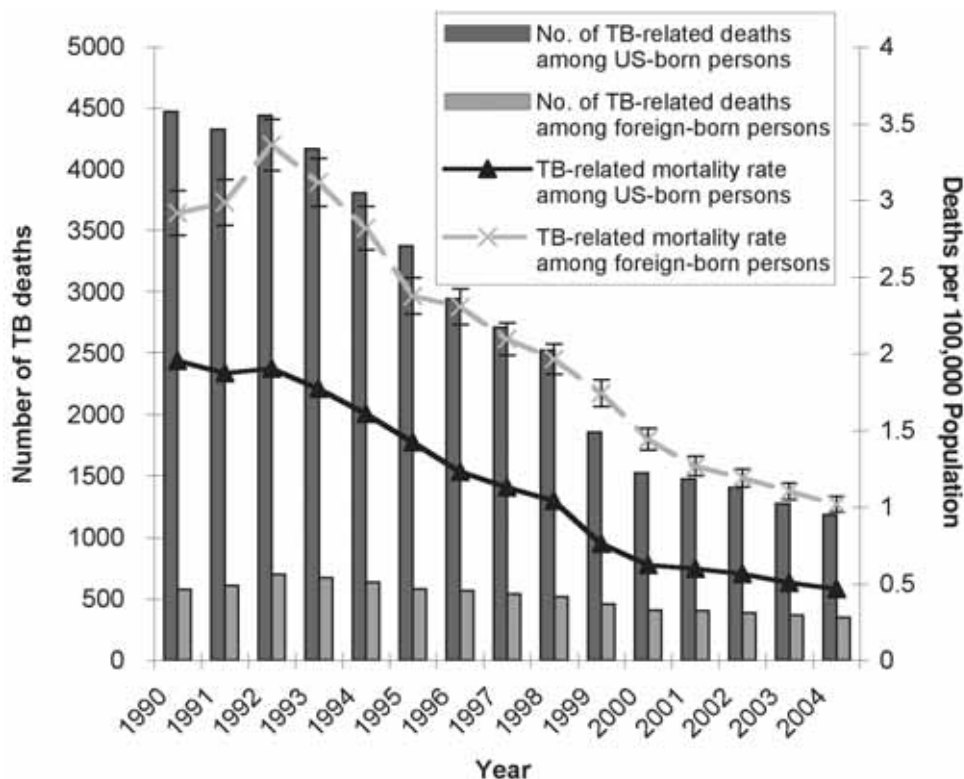
[a]2005 and 2006 multiple-cause-of-death data do not contain place-of-birth information and were excluded from the analysis.

TB = tuberculosis

of preventable death in the U.S., resulting in more than 53,000 deaths throughout the study period. TB mortality rates were comparatively higher in males, ethnic minority groups, foreign-born people, and older people. Positive associations with HIV, malnutrition, and autoimmune conditions were observed.

Consistent with earlier findings, our data indicated significantly higher TB-related deaths among men than women throughout the 17-year study period, and these findings parallel previously reported gender disparities in TB incidence.[4,5,18–21] Higher mortality among men may be, in part, explained by differences in initial exposure to TB infection, as men are at higher risk for TB infection and disease activation because of increased HIV prevalence—the strongest predisposing factor for TB.[22,23] Other studies suggest that differences in notification rates, societal roles that may influence access to care, and/or lifestyle choices such as poor nutrition, smoking, and alcohol consumption between men and women may play a role in the observed epidemiologic differences.[24]

Racial/ethnic minority groups sustained a disproportionate burden of TB deaths during the study period. Although the greatest disparity was observed among Native Americans, black people experienced the greatest burden of deaths. Black people not only had the second highest mortality rate and RR, but also comprised nearly 30% of the total TB-related deaths for the study period, during which they represented approximately 12% of the total population. As racial disparities persistently appear in national TB incidence rates, elevated TB-related mortality rates most likely reflect increased incidence of TB disease among these groups.[3] Socioeconomic status, specifically poverty and disparities in access to health care, may also explain the differences, especially concerning the need for urgent clinical management of fulminant TB disease.[19]

Differences in TB mortality were found in relation to place of birth as well. First, the TB-related mortality rate among U.S.-born and foreign-born people declined significantly from 1990 to 2004, but was persistently higher among foreign-born individuals. The percentage of TB-related mortalities accounted for by foreign-born people also doubled from 1990 to 2004, reflecting a similar trend in TB incidence.[13] Second, the magnitude of association between a person's place

of birth and TB-related deaths varied among racial/ethnic groups. For instance, foreign-born Asian people, whose number of TB-related deaths was nearly nine times that of U.S.-born Asian people, had the greatest disparity, also reflecting elevated TB incidence among these people. On the contrary, foreign-born Hispanic people only accounted for 4.3% of the total Hispanic TB-related deaths, while the proportion of their incident TB cases have been steadily rising from 55.4% in 1993 to 77.2% in 2007.[3,13] Such findings suggest that, over time, if the foreign-born proportion of reported Hispanic incident TB cases continues to increase, then it is likely that the proportion of foreign-born Hispanic TB-related deaths will increase as well.

Increased susceptibility to infectious diseases as well as increased risk of activating latent TB infection in people with HIV/AIDS is widely recognized.[25–27] Our data confirm such associations and also support previous studies that reported HIV/AIDS to be an important risk factor for both TB infection and disease.[18,27,28] Similarly, decedents with autoimmune diseases, specifically rheumatologic diseases such as systemic lupus erythematosus and rheumatoid arthritis, had elevated MORs when compared with control subjects. This could be a result of the intrinsic immunosuppressive nature of the autoimmune diseases or the effect of therapeutic drug-induced immunosuppression on TB

infection and disease activation.[29] Although a positive disease association with malnutrition was expected, as numerous studies have shown malnutrition and poverty to be associated with TB susceptibility and death, one must be careful in assessing causality from these data because of inherit temporal ambiguity.[19–21] While people with malnutrition may have a reduced immunological response, making them more susceptible to TB, it is also possible that TB disease itself leads to malnutrition. Our finding, which must be interpreted with caution, may indicate that although diabetes is a recognized risk factor for TB infection, it may not be a risk factor for severe infection and death. Alternatively, our results may be a spurious finding resulting from errors in coding.

When examining temporal changes specific for age groups, a bimodal peak that included younger age groups disappears after 1995. This observation may have been the result of more intense TB and HIV control efforts, including the introduction of highly active antiretroviral therapy in late 1995, as such therapy and subsequent immune reconstitution reduce the likelihood of TB infection, activation, and death.[30] The findings also serve as a follow-up to a previous study by Braun et al. that showed the emergence of bimodal age distribution from 1980 to 1990.[7] In addition, the fact that more than half of the deaths were observed

Figure 3. Frequency distribution for TB-related deaths by age, United States, 1990, 1995, 2000, and 2005
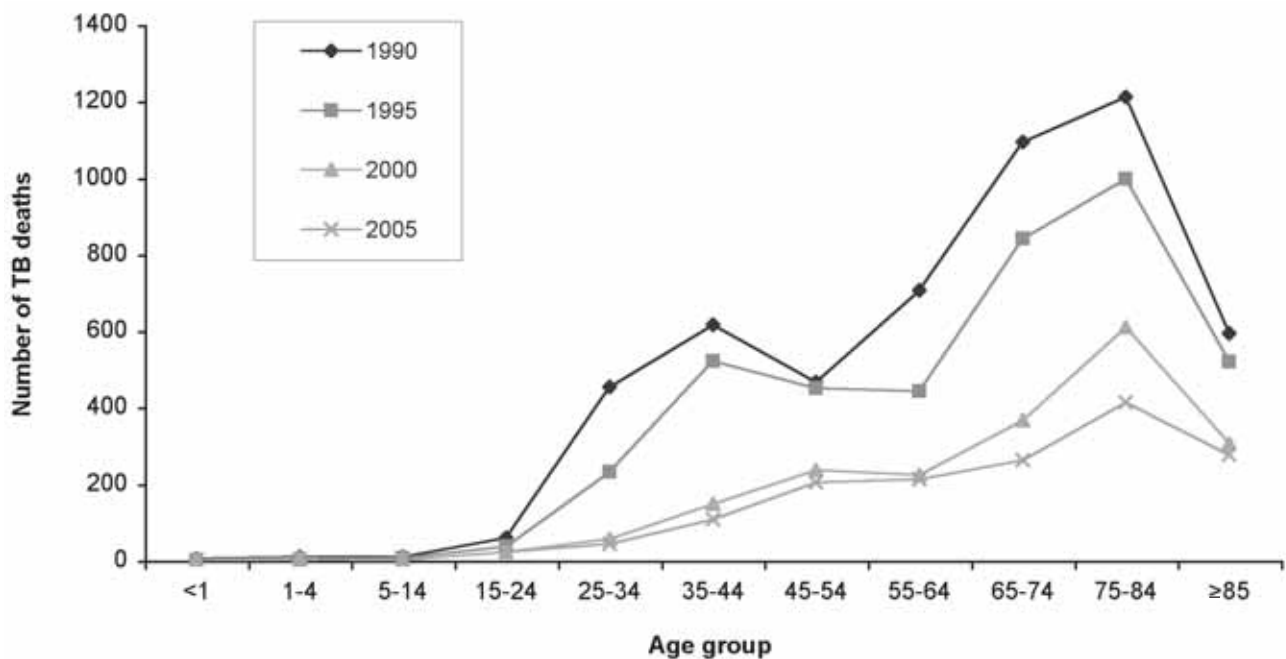
TB = tuberculosis

in people aged 65 years or older compared with approximately 21% of reported TB incident cases in the respective age groups raises public health concerns for elderly populations, given the aging of the American population.[13,31] As higher mortality among older people may be attributed to a greater prior exposure and age-related decreases in immune response, which may trigger subsequent development of active disease from latent TB infection, public health interventions aimed at older people, who disproportionately suffer from greater numbers of comorbid illnesses, will be necessary.[32]

Limitations

The primary strength of this study was the population-based nature of the data. However, several limitations exist in studies based on death certificate data; therefore, findings must be interpreted with caution. Misclassification of variables, including CODs, may occur. A previous study in New York City in 1992 found that 66% (n=206) of 310 people who died with active TB had no mention of TB on the death certificate.[33] Such an error would tend to underestimate the true magnitude of the TB mortality burden, and our findings should be viewed as minimum estimates. Furthermore, death certificate data cannot distinguish between people who die *with* and people who die *from* TB because a clinician who knows that a decedent had TB may be likely to consider it an immediate or underlying COD, even if it is not.

Changes in coding to ICD-10 in 1999 from ICD-9 also suggest that our findings, particularly trends, must be viewed with caution. Demographic information on death certificates and in the census data are subject to bias and error resulting from problems of reporting, classification, and coverage. This issue is especially true for the minority population groups such as Native American, Hispanic, and Asian, as well as foreign-born individuals. Generally, misclassification of deaths (numerator data) results in an underestimation in the death rates, while the undercount of population (denominator data) tends to overestimate the rates. Reporting of country of origin may also be inaccurate and bias the mortality comparisons made between U.S.-born and foreign-born people.

CONCLUSIONS

The results of our study provide information on the burden of TB-related mortality that can assist in shaping more effective TB control and prevention programs. As certain groups including foreign-born Asian, Hispanic, black, and Native American people,

as well as people with HIV and autoimmune diseases, exhibit disproportionately higher TB-related mortality, enhanced prevention efforts, active case-finding, early and adequate treatment targeting these groups, and further investigations to determine whether the observed differences can be attributed solely to the documented higher incidence rate of active disease in these groups are warranted. The continued burden of TB-related mortality underscores the importance of current efforts to develop effective TB vaccines as well as improved treatment.[34]

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