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Socio-demographic and Clinical Risk Factors Associated with Tuberculosis Mortality in the United States, 2009-2013

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Abstract

Socio-demographic and Clinical Risk Factors Associated with Tuberculosis Mortality in the United States, 2009-2013

By Haylea Ariel Hannah

In 2009, the United States National TB Surveillance System (NTSS) was updated to include death attributable to TB. The purpose of our study is to examine factors related to TB mortality and whether they vary between TB-specific mortality and all-cause mortality. The three outcomes of interest were death from any cause (all-cause mortality), TB-specific death, and no death, during January 2009–December 2013. "No death" was used as a control throughout. We used multinomial logistic regression to adjust for risk factors associated with mortality. Stepwise, backwards elimination, and forward selection model techniques were used to determine the best predictive model of the outcome. Statistical significance was assessed at an α=0.001 level. Of the 52,714 TB cases, 2009–2013, 4,331 TB cases resulted in death: 1,404 (32%) TB-specific, 2,413 (56%) all-cause, and 514 (12%) missing cause of death. Following a sensitivity analysis concluding that cases with a missing cause of death did not significantly impact the effect estimates, those 514 cases were excluded. There were 48,358 (92%) TB cases reported as alive. All risk factors were independently associated with TB outcomes in bivariate analyses except for previous episode of TB, homelessness within the past year, and MDR-TB diagnosis. The survival time between TB mortality and all-cause mortality was significantly different ($p<0.0001$). MDR-TB diagnosis, reporting TB symptoms as a reason evaluated, and Hispanic race were all significant risk factors for TB mortality, but not all-cause mortality. Advanced age (45 years and older), male gender, birth in the U.S., being unemployed or retired at the time of diagnosis, the presence of both extra-pulmonary and pulmonary disease, end-stage renal disease, any immunosuppressive risk factors, and reporting an abnormal X-ray as the reason evaluated were all significant risk factors of both TB and all-cause mortality among cases. Being treated with both self-administered therapy (SAT) and directly observed therapy (DOT) was protective against both TB and all-cause mortality. These findings have implications for TB case management and suggest that some high risk groups, such as older TB cases, may need to be followed more closely.

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Chapter 1: Literature Review on Tuberculosis Epidemiology, Control, and Mortality Risk Factors

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I. Natural History of TB

a. <u>Pre-antibiotic era.</u>

With the growing emphasis on industrialization and the rise in immigration across the world, the 19th century was marked by a large migration of people from rural areas into city centers. This led to a large spike in population in very concentrated areas during the beginning of the 19th century. During this migration, people were living in poor, crowded housing conditions with little sanitation. Crowded housing conditions provided the perfect environment for many infectious diseases, including TB. However, at the beginning of the 20th century, the development of public health departments helped create interventions that improved hygiene and sanitation and reduced the impact of infectious diseases, such as Cholera. By 1900, 40 out of 45 of the states in the United States developed public health departments.[1] The development of public health programs allowed for the implementation of TB control programs, which were first funded primarily through Christmas Seal programs. Additionally, as more people moved into city centers, housing conditions were improved to reduce crowding. Both of these developments led to a declining rate of TB mortality even before antibiotic therapy was introduced. In 1900, the TB death rate was 194 per 100,000 among U.S. residents, which drastically declined to 46 per 100,000 persons by 1940, even before the first medications for TB were developed.[1] However, TB still remained a leading cause of death in the U.S. in the 1940s.

In light of a growing epidemic of TB across the world, several key discoveries have helped medical professionals better diagnosis and understand the disease. Koch isolated the causative agent in 1882; Ehrlich discovered the acid-fast nature of the TB bacillus that led to subsequent development of acid-fast stains for diagnosis in 1882; Roentgen discovered X-rays which allowed physicians to observe how TB affects the lungs in 1895; Von Pirquet and

Mantoux developed the tuberculin skin test in 1907-1908; and lastly, Seibert developed a preparation technique of purified protein derivative (PPD) of tuberculin that is used in conjunction with the TST for diagnosis of latent TB infection in 1931.[2] Many of these techniques are still used to diagnose TB today, and control of the epidemic pre-antibiotics would not have been possible without these scientific discoveries.

A key component of pre-antibiotic TB control was isolating infected individuals from crowded areas. The transmission of TB by droplet nuclei was not demonstrated until the 1940s. Wells and Ratcliffe discovered that a drier particle containing a TB bacillus could float in the air for longer periods of time than a moist, heavy droplet, and was thus more likely to result in TB transmission.[3] This knowledge led to targeted TB control measures, such as the use of particulate respirators in hospitals or sanatoriums to isolate infected individuals, to prevent TB droplet nuclei from pervading air spaces.

Several US states demonstrated the success of sanatorium movements in TB control. An idea that open air spaces would reduce TB transmission and improve treatment outcomes led to the development of a sanatorium to house all TB infected individuals in a certain area. New Jersey demonstrated the success of joint efforts to diagnose, treat, and prevent further infections in New Jersey residents in the 1920s. With the implementation of multiple sanatoriums and better diagnosis techniques, the TB death rate in New Jersey dropped by 58% in 25 years. [4] TB mortality was being reduced through control mechanisms long before the introduction of antibiotics and sanatoriums were the treatment facility of choice until the 1940s.

Although multiple techniques were employed to control the growing TB epidemic across the world in the early 1900s, TB still remained a leading cause of death and further control measures were needed to better treat the disease.

b. Post-antibiotic era.

The development of antibiotics in the early 1900s led to substantial improvements in disease control. Physicians now had the opportunity to control disease transmission and treat a disease before it caused mortality. Antibiotics for TB were developed nearly 60 years after Robert Koch isolated the causative agent, *Mycobacterium tuberculosis,* in 1882. [5] In 1942, Selman Waksman discovered streptomycin by isolating anti-microbial agents from soil. [6] This discovery led to the first TB patient being treated for the disease in 1944. The discovery of anti-bacterial agents to treat TB led to better control of the disease and a reduction in disease mortality. Although the TB mortality rate was declining steadily before the discovery of antibiotics, their introduction in the mid-1940s led to a much sharper decline in TB mortality that continued into the 1980s, when HIV/AIDS emerged as a risk factor.[7]

The HIV/AIDS epidemic led to an increase in the incidence of TB in the 1980s and 1990s. The epidemic also impacted the TB mortality rate, which had been declining sharply, because of the virus' impact on the immune system's response to TB. [7] Diagnosis and TB control now depended on simultaneous HIV control and treatment.

The rise of HIV/AIDS in the 1980s paired with patients not taking their antibiotics as directed led to the emergence of multidrug-resistant-TB (MDR-TB) and extensively drug resistant-TB (XDR-TB), which presented unique barriers in TB treatment and completion of therapy. In the post-antibiotic era, TB/HIV co-infection and MDR and XDR-TB are the new challenges to address in TB control.

c. Emergence of Drug Resistant TB

While the development of streptomycin changed the face of TB treatment, doctors soon realized that treating TB with this drug alone was not sufficient. Treatment with a single medication often resulted in treatment failure due to antibacterial resistance.[8] This finding led to the development of isoniazid and para-amino salicylic acid, and the use of multi-drug regimens to treat TB.

Acquired drug resistance is most often associated with failure to take medications regularly, monotherapy, poor drug absorption, improper combinations of active medications in a treatment regimen, and failure to adhere to the prescribed treatment regimen (i.e. taking 2 out of 3 TB medications).[9] During the 1950s and 1960s, TB treatment was primarily monitored in hospitals, and was very successful because hospitals could easily manage adherence and completion of therapy. However, in the 1960s, TB treatment was shifted towards outpatient care because patients on TB therapy were no longer considered a public health threat.[10] This shift has made it more difficult for practitioners to monitor adherence to drug medication and thus drug resistance due to inadherence to treatment has increased.

The Centers for Disease Control and Prevention (CDC) defines multidrug-resistant TB (MDR-TB) as resistance to at least isoniazid and rifampin, two of the most effective drugs in treating TB. Treating MDR-TB can be very cumbersome, and is often only successful when using a multi-drug regimen consistently for 18-24 months. After the emergence of MDR-TB, clinicians began using comprehensive treatment regimens containing multiple antibiotics to treat MDR-TB. Eventually, additional drug resistance developed creating extensively drug resistant TB (XDR-TB). XDR-TB is defined by the CDC as resistance to isoniazid and rifampin, plus any fluoroquinolone and at least one of the three main second-line drugs (amikacin, kanamycin, or

capreomycin). XDR-TB, similar to MDR-TB, results from bacteria with an acquired antimicrobial-resistance being selected for due to ineffective treatment regimens.[11]

Multidrug resistance is also associated with mortality among TB cases. A study conducted in Peru found that MDR-TB was associated with an increased risk in mortality during TB treatment in comparison to drug-susceptible TB cases, even when controlling for several potential confounders.[12] A 1993-2007 study demonstrated that XDR-TB is associated with a higher risk of mortality in the U.S. when compared to both MDR-TB (Prevalence Ratio [PR]: 1.82, 95% CI: 1.10-3.02) and drug-susceptible TB cases (PR: 6.10, 95% CI: 3.65-10.20).[13] An additional study conducted in South Africa in 2010 found that a large proportion of MDR-TB and XDR-TB cases die within 30 days of sputum collection, suggesting that multidrug resistance is also associated with decreased survival among TB cases.[14] It is essential for TB control programs to focus on treatment adherence to address the growing epidemic of MDR and XDR-TB around the world as both are associated with worse treatment outcomes.

II. Present Epidemiology of TB

a. Global epidemiology.

TB remains a significant public health threat globally, with 8.6 million incident TB cases in 2012 worldwide. [15] However, the incidence of TB varies significantly by region and from country to country. For example, the incidence rate of TB is nearly 1,000 cases per 100,000 population in Swaziland, whereas it is fewer than 10 per 100,000 in Japan.

Twenty-two high TB burden countries (HBCs) account for approximately 81% of the world's TB cases. These 22 HBCs include (in alphabetical order): Afghanistan, Bangladesh, Brazil, Cambodia, China, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, the Philippines, the Russian Federation,

South Africa, Thailand, Uganda, the United Republic of Tanzania, Viet Nam, and Zimbabwe. India and China alone account for 26% and 12%, respectively, of global TB cases. [15] These countries often experience increased risk of mortality and adverse outcomes (such as MDR and XDR-TB) among TB cases. Global control efforts target HBCs in order to work towards the target of controlling or eliminating TB.

MDR-TB is still a major public health problem internationally. In 2012, there were 450,000 incident cases of MDR-TB.[15] One of the significant risk factors for MDR-TB in a cross-sectional study conducted in the Republic of Georgia was being a retreatment case (PR: 5.28, 95% CI: 3.95-7.07), which is largely preventable if appropriate treatment is provided when a patient first presents with TB. [16] In order to fully address the growing TB epidemic, adequate treatment and control of MDR-TB is necessary.

b. United States epidemiology

In 2013, 9,588 incident TB cases were reported in the US through the National TB Surveillance System (NTSS), equating to an incidence rate of 3.0 cases per 100,000 persons.[15] Case counts and incidence rates in the US are not homogenous across populations. The proportion of TB cases occurring in foreign-born persons is increasing annually and reached 65% in 2013. In addition, the incident rate of TB was 26 times greater among non-Hispanic Asians than that of non-Hispanic whites. Foreign-born persons account for 88.4% of the 86 reported cases of MDR-TB in the US in 2012. This disproportionate percentage indicates that foreign-born individuals need to be followed more closely to ensure that they do not face worse disease outcomes.

TB incidence is also disproportionate geographically, four states (California, New York, Texas, and Florida) accounted for 51.3% of all TB cases reported to the US NTSS in 2013.[15]

However, the majority of US states are on course with TB control and reducing the disease burden; in 2013, 33 US states had lower incidence rates of TB than the year before.[15] The United States has a low TB incidence relative to high-burden TB countries internationally.

c. TB/HIV Epidemiology

HIV is a significant risk factor for developing TB disease due to immunosuppression. The estimated percentage of TB cases that are co-infected with HIV was 13% in 2012.[13] HIV patients with more immunosuppression have a greater risk of TB, indicating the importance of treating HIV positive patients with antiretroviral therapy (ART) in order to decrease their risk of progression to active TB disease. [16]

The global burden of TB/HIV co-infection is large and is more commonly observed in high-burden areas. Thirteen percent (1.1 million) of the 8.6 million people who were diagnosed with TB in 2012 were HIV-positive.[18] Approximately 75% of the estimated 1.1 million TB/HIV co-infection cases were in the African Region.[13] In South Africa, it is estimated that up to 88% of HIV-infected individuals between 31 and 35 years of age are living with LTBI. [17] Because HIV infection is associated with progressing to active TB disease from latent infection, the proportion of HIV/TB co-infected individuals living with LTBI has important TB control implications.

HIV infection is a risk factor for developing active TB disease. The risk of latent TB reactivation among HIV positive individuals is 20-fold that of reactivation among HIV negative individuals. [19] Additionally, TB is one of the leading causes of death among HIV infected individuals internationally. In 2011, 19% of HIV-positive TB patients died compared to 3% of HIV-negative patients. [13] Understanding the relationship between TB and HIV is necessary to fully explain disproportionate outcomes among special populations infected with TB.

Not surprisingly, TB/HIV co-infection varies geographically. The highest prevalence occurs in the Africa region, ranging from 9.6% of TB patients testing HIV positive in Ethiopia and Angola to 77% testing HIV positive in Swaziland.[13] Efforts to combat the growing dual epidemic need to take geographic variation into account.

TB and HIV co-infection is associated with an increased mortality in the United States. Active TB is associated with an increased risk for death among HIV positive patients in the US, when controlling for age, intravenous drug use (IDU), previous opportunistic infections, baseline CD4+ count, and antiretroviral therapy.[21] However, the mortality among those living with HIV/TB co-infection in the US has been decreasing. In 1993, 950 of 2,337 (41%) patients with TB/HIV died during treatment, in contrast to 131 of 663 (20%) with TB/HIV in 2006. [22] These results suggest that TB may accelerate the natural clinical course of HIV infection and that HIV is influential to health outcomes among TB patients.

III. Measurements and Methods

a. Global Surveillance.

Countries with a high and low TB disease burden estimate the prevalence of TB in various different ways. Countries with a high burden of TB can directly measure the prevalence of TB in the country by using nationwide surveys of a random sample of close to 50,000 people and the cost is between 1 to 4 million US dollars (USD).[23] This method is preferable in areas with a high incidence to ensure that national data are representative of the overall TB prevalence.

Reporting countries and territories send data on TB indicators to WHO using a web-based system in order for WHO to compile the Global TB Report. In 2013, the WHO Global TB Report was based on reports from 179 Member States and 197 countries and territories that comprise over 99% of the world's total TB cases.[13] WHO uses specific surveillance

definitions for their cases and indicator variables, as described in the report Compendium of Indicators for Monitoring and Evaluating National Tuberculosis Programs.[24] Although global surveillance programs are improving, significant changes need to be made in order to ensure all cases are reported to National TB Programs (NTPs), particularly in some of the HBCs. The WHO estimated that there were 2.9 million missed TB cases (defined as those who were either not diagnosed or diagnosed and not reported to NTPs) in 2012. Approximately 75% of these were in 12 countries (in order of total numbers missed): India, South Africa, Bangladesh, Pakistan, Indonesia, China, Democratic Republic of the Congo, Mozambique, Nigeria, Ethiopia, the Philippines, and Myanmar. All of these 12 countries are HBCs and represent the fact that the TB prevalence is being underreported in the areas that need proper reporting most.

The WHO also maintains a passive surveillance of country reports of MDR-TB cases. In 2012, WHO collected information on notification, treatment, enrollment, and outcomes for MDR-TB from 30 countries, which accounted for over 90% of estimated MDR-TB cases. [25] These measurements allow the WHO to track how countries are managing their MDR-TB burden. An underestimation of MDR-TB burden relates to TB mortality, as MDR-TB is a risk factor for adverse outcomes among TB patients.

b. United States Surveillance

TB is on the list of communicable diseases where mandatory reporting is required by clinicians in the United States. U.S. states are responsible for receiving notification of TB cases and generating reports to be sent to the CDC. The CDC is responsible for then collecting all TB cases transmitted by states through the National TB Surveillance System (NTSS). The Report of Verified Cases of Tuberculosis (RVCT) form is used to collect information about each TB case.

This form collects information about the demographics, disease characteristics, treatment, and outcomes of TB cases.

There are three categories that the CDC uses to capture the incident cases of TB: laboratory confirmed cases (positive culture or positive Acid-Fast Bacillus [AFB] smear when culture not obtained), clinical case definition (positive TST or IGRA, symptoms of TB disease, current treatment for TB disease, completed diagnostic evaluation), or provider diagnosis (diagnosed by health care provider and does not fulfill the criteria necessary to meet the other two case verification criteria). If a TB case does not fit these criteria, then it is not counted as an incident case by the NTSS.

Previously, the NTSS captured whether or not a TB patient died, but did not have an indication of the probable cause of death. In 2009, the RVCT form was updated to include several new variables, including variables collecting information about whether a patient died due to TB disease. Collecting information about TB-specific mortality allows the CDC to monitor how many deaths occur due to the disease specifically in the US. Additionally, it gives researchers the opportunity to use this information to determine which factors are more associated with TB-specific mortality. The RVCT is updated periodically to ensure information is captured as TB diagnosis and treatment methods are improved.

IV. **Tuberculosis diagnosis and control**

The gold standard tests used for TB diagnosis include a mycobacterial culture or an acid-fast bacilli (AFB) smear microscopy test. However, several diagnostic techniques allow practitioners to confirm TB diagnoses, including but not limited to the Nucleic Acid Amplification (NAA) test, which allows for rapid diagnosis, the Tuberculin Skin Test (TST) along with an abnormal

chest X-ray, and a sputum culture. Early detection and treatment of TB is necessary in order to improve treatment outcomes.

Because the prevalence of LTBI is unknown and difficult to measure, some believe that the global strategy needs to focus on control rather than eradication. This strategy involves targeting high risk groups, such as those living in congregate settings, to reduce the risk of spreading TB. Additionally, TB among health care workers is a common occurrence internationally. Longer hospital stays in resource limited settings are associated with higher incidence of TB and TB mortality within 12 months. [26] To address these issues, many low resource areas have developed innovative strategies to create an environment where it is more difficult for TB to spread. Negative-pressure isolation rooms are ideal to control TB because the bacteria spread via droplets in the air and can remain suspended in the air for an extended period of time. However, many international settings are resource-limited and may not have the capacity to offer negative-pressure isolation rooms to infectious TB patients. Natural ventilation can provide affordable solutions to TB control in the developing world. A 2007 study conducted in Lima, Peru on 70 naturally ventilated clinical rooms across 8 hospitals found that natural ventilation provided greater ventilation (28 air changes/hour (ACH)) than mechanically ventilated negative-pressure rooms (recommended 12 ACH for high-risk areas).[27] Increased natural ventilation in TB treatment areas can help reduce transmission in high-risk areas, such as hospital waiting rooms, and provide a cost effective TB control mechanism that can improve TB outcomes.

Increased resources and access to treatment, in both patients with active and latent disease, are necessary to improve TB outcomes. A meta-analysis of multiple TB studies revealed that 6-12 months of isoniazid preventive therapy (IPT) was associated with a lower

incidence of active TB among those with a positive TST (RR 0.38, 95% CI 0.54-0.85). [17] In addition, 36 months of IPT among HIV and TST positive patients reduced the TB incidence by 74% in comparison to 6 months of IPT. [17] Adequate screening for LTBI in high risk groups, such as those that are HIV positive, can improve treatment outcomes and reduce mortality among TB patients.

a. United States control

The main priority in the US is to screen high-risk groups, treat active cases, and prevent further infections through contact tracing. Additionally, because TB disproportionally affects certain populations in the US, TB control efforts are targeted towards high risk populations, both demographically and geographically. In 1995, the CDC re-assessed the cost-effectiveness of screening low-risk groups for TB and determined that it is more cost-effective to treat high risk groups for TB infection, including but not limited to: HIV infected individuals, contacts with TB cases, people with medical risk factors known to increase the risk of TB, foreign-born persons, and healthcare workers who work in high-risk client settings.[28] Because of a concerted effort to target these high risk groups, the U.S. has made significant strides in reducing the burden of TB. A total of 6,172 TB cases were reported among foreign-born individuals in the US in 2013, a 19% decline in cases compared to 2000.[15] In 2009, the Advisory Council for the Elimination of Tuberculosis and the National Tuberculosis Controllers Association updated the TB control legal guidelines outlined in a previous 1993 MMWR report to create a handbook including recommendations on laws and policies states should enact and enforce to maintain TB control programs.[29, 30] This report helped solidify TB policies in the US. Adequate TB control is vital in order to prevent the spread of TB and influence treatment outcomes.

V. **Tuberculosis Treatment**

Although TB treatment follow-up needs improvement, the global success rate of TB treatment is improving. In 2011, the percentage of TB patients completing treatment was 87% among new TB cases.[13] However, this still means that 13% of TB cases are not being treated successfully and are more likely to face worse disease outcomes.

Generally, drug-susceptible TB disease cases must take a multi-drug regimen for 6 to 9 months based on CDC recommendations. The US Food and Drug Administration (FDA) has approved 10 drugs for TB treatment. The TB drugs that comprise the first-line treatment of active disease include: isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA). Treatment for active TB disease begins with an initial phase of treatment lasting 2 months, followed by a continuation phase of treatment that can last between 4 to 7 months. The preferred drug regimen, recommended by the CDC, includes an initial phase of daily INH, RIF, PZA, and EMB for 8 weeks, followed by a continuation phase of daily INH and RIF or twice-weekly INH and RIF for 18 weeks. Patients who do not take the full course of their medication are at an increased risk for developing active TB disease again. Patients who do not take prescriptions as directed are at an increased risk of developing MDR and XDR-TB. Directly observed therapy, in which trained healthcare professionals ensure patients take medication as directed and observe them taking the medications daily, is suggested for all TB cases in order to reduce the risk of MDR and XDR-TB, improve treatment outcomes, and ensure treatment completion.

VI. TB Mortality

a. Global Epidemiology of TB Mortality

The TB mortality rate, while still high, has been falling drastically in the past 20 years. By 2012, the global TB mortality rate was reduced by 45% since 1990, from around 25 per 100,000 in 1990 to 12 per 100,000 in 2012.[13] However, In 2012, an estimated 1.3 million people died due to the TB.[13] This mortality varies geographically, with approximately 75% of total TB deaths occurring in Africa or South-East Asia. India and South Africa, alone, comprised of around one-third of total reported TB deaths. [13] Addressing TB mortality globally depends on adequate TB control and treatment in high-burden areas.

b. Global measurement of TB mortality

National Vital Registration (VR) systems are national systems that collect information about causes of death. These are used to assess TB mortality among HIV-negative people. However, in order to be efficient, VR systems must be high coverage and accurately code causes of death by the latest revision of the International Classification of Diseases (ICD-10). [31] The WHO recommends that nations report TB mortality by category of disease, relevant additional medical conditions, age, sex, and geographic location. Despite these recommendations, only 59 of 213 countries in 2005 had TB deaths reported through VR systems, which only accounted for 10% of all estimated deaths due to TB.[31] Increased reporting of TB deaths through VR systems are imperative to determine the magnitude of this public health problem globally.

c. United States Epidemiology of TB Mortality

According to U.S. Vital Statistics Records, TB mortality in the US historically declined rapidly, however, has remained stable for the past 8 years. In 1953 when reporting on TB

mortality began, the mortality rate was 12.4 per 100,000 population, however, this declined rapidly by 1975, when the rate was 1.6 per 100,000 population.[32] The rate has since stabilized to 0.2 per 100,000 population annually since 2003, according to the Annual Reported Tuberculosis in the United States for 2013.[32] The death rate in the US is much higher among certain high risk populations, such as those who are HIV positive. Among patients with TB and HIV in 2006, 20% (131 of 663) died during treatment, in comparison to only 9% (682 of 7,578) of all TB cases during the same year.[22] Further research needs to be conducted to determine mortality risk factors and target public health interventions.

d. **United States measurement of TB mortality**

The U.S. uses a vital registry (VR) system that maintains both death and birth records, however, these can oftentimes be unreliable when provider diagnosis criteria vary and a patient has concurrent infections where it may be difficult to attribute the death to the correct cause. Mortality estimates may also be generated from national TB surveillance, which before 2009 only collected information about all-cause mortality among TB cases. A study conducted in 2012 found that the U.S. surveillance system overestimated all-cause mortality among TB cases in comparison to death certificates extracted from the vital registration system.[7] However, this study focused on the time period from 1990 to 2006, before NTSS began collecting information about TB mortality, specifically, as opposed to all-cause mortality among TB patients. The study demonstrated biases associated with both systems in estimating mortality. Death certificates are more likely to underestimate TB mortality because patients may die long before a diagnosis of TB is confirmed, while NTSS previously only had information about all-cause mortality among TB patients.[7] Both methods present different advantages and disadvantages. The introduction of variables collecting information about TB mortality to the NTSS should

provide more accurate measurements of TB mortality in the U.S. and ensure that the burden of mortality is not underestimated.

VII. Risk Factors associated with TB Mortality

Understanding the risk factors associated with TB deaths can have important public health implications, in terms of treatment, diagnostic procedures, and mortality prevention. Special populations have known risk factors associated with both TB morbidity and mortality. Such special populations are discussed in detail below.

a. Special populations

i. HIV positive

TB is the leading cause of death among HIV positive individuals. HIV status is associated with increased mortality both globally and nationally. HIV is associated with an increased hazard of mortality by 3.89 ($p<0.0001$) among Canadian and US TB patients who completed TB treatment according to a randomized clinical trial.[33] Additionally, a study conducted in New York City in 1996 demonstrated that acquired immunodeficiency syndrome (AIDS) among HIV-infected patients was one of the most important predictors of all-cause mortality among TB cases (Cox relative risk [RR] 7.8 (95% CI: 2.1-29.1).[34] Because HIV leads to immunosuppression, those with the disease are far more likely to both progress to active TB disease and have worse disease outcomes.

HIV is a significant risk factor for TB mortality globally as well. A study conducted in Brazil from 2003-2008 reported an increase risk of death among TB patients comparing HIV positive to HIV negative individuals (RR: 9.24; 95% CI: 8.78-9.72). [35] In 2008, African countries' HIV-positive TB mortality rates were significantly higher than those in non-African

countries (Rate Ratio: 29.9; 95% CI: 16.8-53.4). [36] In addition, a study conducted in South Africa found that low CD4 counts (less than 50 cells/mm^3) were associated with mortality in patients with XDR [HR 4.46, p=0.01] and MDR-TB [HR 4.64, p=0.01]. The same study demonstrated the protective effects of using antiretroviral therapy (ART) [HR 0.34, p=0.009].[37] Treatment of HIV is important in predicting TB outcomes and in preventing mortality, as treatment increases the immune response to TB.

ii. **Immunosuppression**

As demonstrated through worse TB outcomes among HIV positive patients with worse CD4+ counts, immunosuppression due to other causes is also associated with an increased risk for progression to active TB disease and mortality. When a healthy individual becomes infected with TB, his or her immune system normally contains the mycobacteria into a latent state. However, during periods of immunosuppression, these latent bacteria can reactivate in the body and lead to active TB disease. Common associations between immunosuppression and TB include the following diseases: Addison's disease, Goodpasture's syndrome, systemic lupus erythematosus (SLE), polymyositis, polyarteritis nodosa, dermatomyositis, scleroderma, and autoimmune hemolytic anemia. [38] However, further studies are needed to clarify whether these risks are associated with the diseases, themselves, or the medications used to treat these diseases.

Worse TB outcomes generally result as the body's immune system cannot adequately control the growth of the mycobacteria. A study conducted in Helsinki, Finland demonstrated an increased age-adjusted odds ratio for all-cause mortality among immunosuppressed groups in comparison to TB patients with other co-morbidities or no underlying conditions.[39] In addition, multiple clinical regimens as part of a treatment course can be linked to

immunosuppression, and in turn, mortality due to TB. A study conducted among SLE patients in Turkey reported a significantly higher mean daily dose of prednisone in patients who developed TB in comparison to those who did not (27± 22 g versus 16±16 g). [40] The FDA has listed TB disease as a possible adverse outcome as a result of treatment with tumor necrosis factor-alpha (TNF-α) antagonists, which are commonly used to treat rheumatoid arthritis and other autoimmune conditions. Blocking TNF-α can suppress the immune system and allow mycobacteria to re-emerge from a latent state. [41] However, there is not sufficient evidence to suggest that TNF-α antagonists are associated with TB mortality. Understanding how the body responds to infection with *Mycobacterium tuberculosis* and how suppressing the immune system can hinder this response are integral to understand the possible links between these high-risk groups and TB mortality.

b. **Age**

The incidence of active TB disease increases with age, and along with it, so does TB mortality. The rate of TB in the US among those 64 years of age and greater in 2013 was 4.9 per 100,000 population in comparison to 0.8 per 100,000 among those 0-14 years of age.[32] A nearly 6 fold increase in the rate of TB in older populations in comparison to younger populations may be due to the latent period between TB infection and TB disease or the reduction in the immune system that results from aging. A study conducted in Germany corroborated these results in relation to TB mortality and demonstrated that individuals who died due to TB were, on average, older than TB cases who died from other causes.[42] These results have been replicated in US studies. A study conducted in Washington followed 3,451 persons with active TB disease for 13 years and demonstrated that increased age was associated with all-cause mortality among TB patients.[43] All-cause mortality is higher among older TB cases

because they may be dying of old age that is unrelated to TB disease. Age proves to be an important predictor of disease outcomes among TB patients.

c. **Global risk factors**

Men are at highest risk of TB mortality and morbidity. A study in Brazil in 2014 demonstrated that males had a greater odds of death from TB in comparison to females (OR: 1.37, 95% CI: 1.20-1.56). [44] Globally most TB cases and deaths occur among men, however, TB accounts for a significant proportion of mortality among women as well. In 2012, TB was estimated to be one of the top three killers of women; there were an estimated 410,000 TB deaths among women alone.[45] Although TB is a largely treatable and preventable disease, mortality remains high.

All-cause mortality among TB patients is more common than TB mortality. In a study conducted in Taiwan from 2003-2007, 12.4% of TB cases died from any cause (including TB deaths), 82.7% of which were due to non-related TB causes. However, TB mortality was associated with specific time-related factors in this study. Many patients who died of TB in this cohort were diagnosed post-mortem (37.2%). [46] These results suggest that these cases may have died from TB before they were able to begin treatment.

Mortality and recurrence in some high-burden countries is high despite treatment, primarily due to multidrug resistance. Among 213 patients followed for a median of 22 months after diagnosis in Uzbekistan, an average of 15% (95% CI 11-19%) per year died, and out of 99 new cases during this time period, 74% were successfully treated, yet 34% were diagnosed with recurrent TB. Although DOTS is the recommended therapy regimen for high-burden, MDR-TB settings, MDR-TB diagnosis and previous TB treatment predicted unsuccessful DOTS therapy and initial drug resistance contributed to mortality and recurrence among this cohort. [47]

Adequate treatment along with TB control is necessary, particularly in high-burden TB countries, in order to prevent poor outcomes among TB cases.

XDR and MDR-TB present unique challenges in combating TB mortality. A study conducted in South Africa in 2012 found that 63% of 123 patients with MDR-TB and 80% of 139 XDR-TB patients died following diagnosis. [37] XDR and MDR-TB are very difficult to treat and it can take up to 24 months with 12 or more second-line TB medications. This cumbersome regimen often results in treatment failure and worse disease outcomes.

d. **United States risk factors**

Several studies have addressed risk factors for TB mortality and all-cause mortality in the United States among TB patients. Sterling et al. conducted a randomized clinical trial in US and Canada where individuals were enrolled after 2 months after treatment, treated for 4 additional months, and followed for a total of 28 months.[33] Cause of death was determined by death certificate, autopsy, and/or clinical observation. Among their cohort of 1,075 individuals, only 1 death was attributed to TB, suggesting that TB mortality is low in this population. However, it should be noted that the study participants are those who completed 6 months of TB therapy, which may result in better treatment outcomes than the average TB case. Within this study cohort, 6.6% died due to other causes, which were primarily malignancy (hazard ratio [HR] 5.28 $p<0.0001$), HIV positive (HR 3.89 $p<0.0001$), daily alcohol consumption (HR 2.94 $p<0.0001$). Past global studies have demonstrated similar connections between TB mortality and HIV, alcohol consumption, and malignancy. Predictors of all-cause mortality among TB cases may be similar to those of TB mortality because some reported all-cause mortality risk factors, such as age, are associated with mortality in general. Few studies examine TB-specific mortality,

therefore, additional research is needed to determine the similarities and differences between adverse outcomes among TB patients.

A recent study conducted in California suggests that advanced TB disease may be associated with increased TB mortality. Pascopella et al. reviewed California's TB registry from 1994 to 2008 to determine how many TB cases reported to this registry resulted in death and to identify risk factors associated with death.[48] Of the 40,125 patients with culture-confirmed TB reported to the California TB Registry between 1994 and 2008, 4,565 cases resulted in death, with 25% who died before treatment started and 75% who died during treatment. This finding supports past studies that have demonstrated that around a quarter of those with TB are still dying before they are able to be treated.

Specific co-morbidities are associated with all-cause mortality in TB cases. The study conducted on the California TB Registry found the following risk factors to be associated with all-cause mortality among TB patients: acquired multidrug resistance (age-adjusted OR: 4.67 (2.09-10.45)), care in the private sector (age-adjusted OR (aOR): 3.08 (2.75-3.44)), initial treatment regimen of <3 drugs (aOR: 2.07 (1.63-2.64)), HIV co-infection (aOR: 4.39 (3.68-5.24)), disseminated TB (aOR: 2.30 (1.82-2.91)), substance use (aOR: 1.33 (1.14-1.54)), and having an abnormal chest radiograph without cavities during the diagnosis process (aOR:1.58 (1.32-1.90)).[48] A study conducted in Washington found an increasing mortality percentage over time among TB/HIV co-infected patients, from 10.5% mortality one-year from diagnosis to 18.9% three-years after diagnosis.[43] These results suggest that there are several preventable co-morbidities associated with mortality among TB cases in the U.S. and that some of these co-morbidities, such as HIV infection, may decrease survival.

Additional studies have identified specific risk factors associated with TB mortality. A study conducted in 2012 found that anemia (with or without iron deficiency) and iron deficiencies increase the risk of death due to any cause among TB patients. The adjusted risk of death among TB patients with iron deficiency anemia was 2.13 times that of patients without (95% CI 1.10-4.11). [49] A study conducted in New York City from 1991-1994 demonstrated that two of the most important predictors of all-cause mortality among TB cases were multidrug resistance (RR 5.8; 95% CI: 2.3-14.5) and lack of treatment (RR: 3.1; 95% CI 1.0-9.7). [34] However, because this study setting was shortly after the emergence of HIV/AIDS and MDR-TB in the US, these factors were less controlled in this study than they would be currently (i.e. the MDR-TB incidence in the US is currently very low). Understanding what specific co-morbidities increase the risk of death among TB patients can help target public health interventions in the US to those at highest risk.

VIII. **Conclusions**

TB remains a major public health issue, and innovations in treatment, control, and case management are essential to reduce TB incidence and mortality worldwide. TB mortality was initially extremely high across the world. The introduction of public health interventions reduced the mortality somewhat by creating programs that isolated infectious individuals as to prevent additional spread of the disease. TB morbidity and mortality was again drastically reduced with the introduction of antibiotics in the 1940s. However, the emergence of HIV/AIDS, inadequate TB control, surveillance, and treatment programs, and MDR and XDR-TB have contributed to the continued high and disproportional TB morbidity and mortality.

Although studies have been conducted to explore risk factors associated with TB mortality or all-cause mortality, none of them have addressed these risk factors on a national scale among TB

cases with various different attributes (varying treatment durations, ethnicities, etc.). The current study aims to determine what risk factors are associated with TB mortality, specifically, among patients living in this low prevalence setting. The findings from this study have implications for informing TB control programs on how to reduce risk factors among TB patients in order to prevent mortality due to this preventable disease.

Chapter 2. Socio-demographic and Clinical Risk Factors Associated with Tuberculosis Mortality in the United States, 2009-2013

Socio-demographic and clinical risk factors associated with Tuberculosis mortality in the United States, 2009-2013

Abstract

BACKGROUND: Several studies have examined risk factors related to all-cause mortality among TB cases, however, very few have examined those associated with TB-specific mortality. In 2009, the United States National TB Surveillance System (NTSS) was updated to include death attributable to TB. This study examines risk factors related to TB-specific mortality and whether these are different from those associated with all-cause mortality among TB cases.

METHODS: The three outcomes of interest were death from any cause (all-cause mortality), TB-specific death, and no death, during January 2009–December 2013. We used multinomial logistic regression to adjust for other factors associated with mortality. We examined risk factors pertaining to TB-specific mortality as well as those that differed between TB-specific and all-cause mortality.

RESULTS: Of the 52,714 TB cases, 4,331 TB cases resulted in death: 1,404 (32%) attributed to TB, 2,413 (56%) attributed to other causes, and 514 (12%) missing cause of death. The strongest risk factors for both all-cause and TB mortality were advancing age, end-stage renal disease, any immunosuppressive factors, and HIV. MDR-TB diagnosis (aOR: 3.20, 95% CI: 1.93, 5.92), reporting TB symptoms as a reason evaluated (aOR: 1.64 95% CI: 1.30, 2.07), and Hispanic race (aOR: 1.47, 95% CI: 1.15, 1.87) were all significant risk factors for TB mortality, but not all-cause mortality.

CONCLUSIONS: These findings suggest that some high risk groups, such as older TB cases or those with co-morbidities like end-stage renal disease, may need to be followed more closely by TB control programs.

Key words: Tuberculosis, mortality, risk factors, TB-specific mortality, surveillance

Introduction

In 2013, the World Health Organization (WHO) estimated that 9.0 million people developed TB, 1.5 million of which died. [20] In the U.S., there were 10,509 incident cases of TB and 536 TB deaths in 2011, the most recent year from which death data are available.[17] Some racial and ethnic groups, such as non-Hispanic Asians, Hispanics, and foreign-born individuals, are disproportionally affected by the disease. [17] TB mortality occurred in 5% of U.S. TB cases in 2011, thus, it is vital for TB programs to understand which factors are associated with TB-specific mortality in order to target public health interventions.

There have been very few studies about the risk factors associated with TB-specific mortality in the U.S. A randomized clinical trial observed the outcomes of 1,075 TB patients who completed therapy and only observed 1 death due to the disease. [35] Many TB patients who are at risk for TB-specific death likely never received treatment or only received a short course of therapy, thus, the findings from this study are not generalizable to a broader population. Further research that is applicable to the average TB case is needed to determine which risk factors are contributing to TB-specific mortality observed among U.S. cases.

The majority of studies on mortality in TB cases have studied risk factors associated with all-cause mortality. HIV and multi-drug resistance are important risk factors of all-cause mortality among TB patients. [36, 52, 53] Socio-economic factors that have been related to an increased

odds of death among TB cases are race/ethnicity, country of birth, and homelessness.[50] Results from a recent California study suggest that patients may die before receiving treatment – 25% of 4,565 deaths observed among TB cases died before starting treatment. [50] A New York study corroborated this finding, and reported an increased risk of death in cases not receiving TB treatment. [36] All of these studies fail to distinguish TB-specific from all-cause mortality because the data are not available or were not collected during the study, therefore, it was not possible to determine which factors were associated with cases dying due to a preventable disease.

Despite the multiple strides made in TB control, there were still 536 TB deaths in the U.S. in 2011, indicating that a significant health issue still remains. In 2009, the Report of Verified Cases of Tuberculosis (RVCT), the national TB reporting instrument used by TB programs to report cases to the CDC, was updated to include information on death due to TB in the U.S. Two categories collecting information on the reason a TB patient died were added, one indicating whether TB therapy was stopped because a patient died due to the disease and one indicating death due to TB at time of TB diagnosis. To date, there have been few analyses that examined risk factors related to TB-specific death based on data from the RVCT since this form revision occurred. The current study has two primary goals: to determine what risk factors are associated with TB mortality among patients living in this low prevalence setting and to determine if they differ from those associated with all-cause mortality.

Methods

Setting and Data collection

The current study examines TB and all-cause mortality in comparison to TB cases in the United States from 2009 to 2013. Cases are reported from all 50 U.S. states, U.S. territories, and the District of Columbia (DC) using the RVCT form. All TB cases fit the CDC's verified case of TB guidelines. [32] All TB cases reported to the National TB Surveillance System (NTSS) through the RVCT form are available in a centralized database used for programmatic evaluation and research.

In 2009, two variables collecting information on the reason a TB case died were added to the RVCT form, one indicating whether TB therapy was stopped because a patient died due to the disease, and one indicating death due to TB at the time of diagnosis. These forms are filled out by reporting jurisdictions and TB-specific death is commonly determined by a health professional that reported the TB case to the health department.

Study Population and Definitions

The study population consisted of TB cases reported to NTSS in the U.S. from 2009-2013. All deaths among TB cases reported to NTSS in the United States from 2009-2013 were included in the analysis and considered the cases of interest. TB cases that have a known status at diagnosis of alive and were not reported to have died during therapy were included in this study as controls. The study population was then split into three mutually exclusive categories, alive at report, dead with TB reported as a cause of death (TB mortality), and dead without TB reported as a cause of death (all-cause mortality).

Analysis

Secular trends in reporting TB-specific mortality annually were examined to determine if there may be reduced use of the new variables in the first few years since information about death due to TB was collected for the first time in 2009.

Descriptive statistics in the study population were determined for each risk factor of interest. The median and interquartile range (IQR) were used to describe continuous variables, while frequencies and counts were used to describe categorical variables. Differences in survival time between TB-specific and all-cause mortality were examined by Kaplan-Meir analysis and a log-rank test. The survival time for each observation was defined as the date that the case was counted as a verified TB case (count date) to the death date or study end date (12/31/2013) for those who did not die. A survival time of one day was entered for cases that were dead at diagnosis. Observations were excluded from the survival time analysis if their death date was before their count date or they had a missing death date due to lags in reporting, as the survival time was unable to be estimated.

Bivariate analyses were conducted between the outcome and risk factor variables in order to determine the individual significance of each risk factor. A chi-square test of independence was conducted on each categorical variable including all appropriate two-tailed p-values in order to determine interrelationships between independent variables. All relevant and significant associations will be reported to an $\alpha=0.001$ level of statistical significance.

Multivariate analysis was conducted in order to determine which risk factors predict TB outcomes. In order to assess the risk factors associated with TB mortality, cases with TB as a cause of death during therapy or at time of diagnosis were compared to all TB cases reported to the RVCT.

A polytomous logistic regression analysis was used to determine the effect each predictor variable has on the outcome. The best fit logistic regression model was chosen using stepwise, forward selection, and backwards elimination selection strategies. Every variable had to meet an α=0.001 level of significance for both entry into and to stay in the model, due to the large study sample size.

A sensitivity analysis was performed on 514 individuals in the study population who had a missing cause of death. Crude odds ratio estimates from polytomous logistic regression were compared for when cases with a missing cause of death were added to all-cause mortality, TB mortality, or excluded from analysis. A less than 10% change in the effect estimates indicated that these observations did not have a significant impact on the study results and thus they were excluded from analysis. All statistical analyses were conducted using SAS 9.4 (Cary, NC). The Emory University Institutional Review Board (IRB) declared that the study was exempt from IRB approval.

Results

Of the 52,714 TB cases reported to the CDC in 2009-2013, 52,175 TB cases were eligible for the study [Figure 1]. Of these, 3,817 (7.3%) died, either at the time of diagnosis or on treatment: 1,404 (37%) died due to TB and 2,413 (64%) died due to other causes. There were 48,358 (93%) TB cases reported as alive during this time period. The rate of all-cause mortality remained consistently about 1.8 to 2.1 times higher than the rate of TB mortality across all years of the study (Rate Ratio (RR) was between 1.8 and 2.1 from 2010-2013), except for 2009 (RR 3.1). However, all three outcomes of interest (TB mortality, all-cause mortality, and alive) remained within 2% of the overall proportion of TB cases throughout the study period (TB mortality between 2-3.2%, all-cause mortality between 4.7-6.4%, and alive between 91-92.7%).

The survival time between TB mortality and all-cause mortality were significantly different according to a log-rank test ($p<0.0001$). The median survival time was 9 days (IQR: 1-43 days) among TB mortality cases and 33 days (IQR: 1-102 days) among all-cause mortality cases [Figure 2].

TB cases older than 65 years old were more likely to die of both TB and all-cause mortality. Other factors that were associated with higher proportions of TB and all-cause mortality were birth in the US, white race, not living in a correctional facility at the time of diagnosis, residing in a long term care facility, and being retired [Table 1].

Among clinical characteristics at baseline, end-stage renal disease, any immunosuppression, having a positive or unknown/other HIV status, and not having an MDR-TB diagnosis had higher proportions of TB and all-cause mortality [Table 2]. Contact with a TB case had lower proportions of TB (0.5%) and all-cause (0.8%) mortality than the other reasons that TB cases were evaluated. All of the risk factors of interest were significantly associated with TB outcomes in bivariate analyses except for previous episode of TB and MDR-TB.

All risk factors of interest were selected into the multivariate regression model except for: TB risk factors, duration of time in the US, excessive alcohol use within the past year, resident of a correctional facility at the time of diagnosis, homeless within the past year, and injection drug use within the past year.

Age remains a significant predictor of TB outcomes, even after controlling for immunosuppression and other co-morbidities. Young age is protective against TB mortality, while advancing age is harmful. For the age group 00-14 years old, young age appears to be more protective against TB mortality (OR: 0.08, 95% CI 0.01, 0.60) than all-cause mortality (OR: 0.22, 95% CI: 0.05, 0.91). Advancing age is associated with increased odds of both TB

and all-cause mortality. However, in the 65+ age group, the odds of all-cause mortality in comparison to the 25-44 age group (OR: 8.62, 95% CI: 6.66-11.15) is much higher than the odds of TB mortality in comparison to the 25-44 age group (OR: 5.81, 95% CI: 4.40, 7.66).

The majority of risk factors had a similar effect on TB mortality in comparison to all-cause mortality. However, presence of TB symptoms as a reason a case was evaluated and MDR-TB diagnosis was predictive of TB mortality and not significantly associated with all-cause mortality [Table 3].

The estimated, unadjusted odds ratios did not vary significantly when deaths with missing information on cause of death were combined with TB mortality, all-cause mortality, or excluded from analysis, suggesting that these observations do not significantly impact the study results, thus, they were excluded from analysis.

Discussion

In this study we examined the risk factors associated with both TB-specific and all-cause mortality in all nationally reported cases of TB from 2009-2013 in the U.S. We found that nearly 1 in 30 TB cases in the U.S. died due to TB disease during the study period. On the whole, the risk factors for mortality were similar between TB-specific and all-cause mortality; however, several important, modifiable risk factors differed between the two outcomes. Patients with both extra-pulmonary and pulmonary disease and MDR-TB patients were at greater risk for TB-specific mortality. Some of the risk factors that differ between the two outcome groups are modifiable and do significantly increase the risk of TB mortality; therefore, information about TB-specific mortality should be collected by TB surveillance systems. Otherwise, it may appear that these factors are not associated with mortality among TB cases when they truly are.

There are several risk factors associated with an increased risk of both TB-specific and all-cause mortality. These include advanced age, HIV-infection, having an unknown HIV status, being US-born, being a resident of a long term care facility, having other TB risk factors reported, and an abnormal X-ray indicated as the reason a patient was evaluated. We noticed that not being offered HIV therapy and having an unknown HIV status was associated with both all-cause and TB-specific mortality in this study; however, this may be because these cases died before they had the opportunity to be offered HIV testing. Therefore, it is not possible to determine whether the patient could have received HIV testing, then died, or did not receive testing because they died.

Some factors increase the risk of TB mortality, but do not affect all-cause mortality, including Hispanic race, having both pulmonary and extra-pulmonary disease, and TB symptoms as a reason evaluated. Being evaluated specifically for TB symptoms suggests that the TB case may have been further progressed in their disease, and thus may have been at a higher risk for dying of TB than a patient who was evaluated earlier in the disease course. Additionally, TB cases that experienced all-cause mortality may have died before developing more advanced disease.

Some factors are protective against TB mortality and not all-cause mortality. Residents of long term care facilities are often tested for TB before entering, because of the increased risk of TB at older ages, and thus may be diagnosed and initiated on treatment earlier than individuals who are not residents of a long term care facilities.[45] Having extra-pulmonary disease alone was protective against TB mortality in comparison to pulmonary disease alone, but not all-cause mortality. Medical professionals may be more likely to indicate that TB was a cause of death if a patient had pulmonary TB than if the patient had extra-pulmonary TB. Lastly, the effect of being

on both DOT and SAT is greater for TB mortality than all-cause mortality. This finding is consistent with the fact that more comprehensive therapy has the potential to prevent TB-specific mortality, however, may not influence all-cause mortality among TB cases if they have additional co-morbidities or died due to other causes that are not associated with the disease. Contact with a TB case was protective against all-cause mortality among TB cases, yet did not significantly impact TB-specific mortality. This finding is likely because of low study power as not many individuals in the study sample had contact with a TB case.

The results from this study are corroborated by similar analyses. A study conducted with NTSS data from 1997-2005 also found that HIV-status, race/ethnicity, and country of birth were significant risk factors for all-cause mortality among TB cases.[53] This previous NTSS study found an increased odds of TB diagnosis at death among those with reported Hispanic ethnicity, a 3 times greater odds of death for MDR-TB cases, and an increasing odds of death with advancing age, all of which were replicated in our analysis. However, once controlling for all of the other variables in the current analysis, homelessness was not found to be associated with TB or all-cause mortality, even though it was in the 1997-2005 study.

Another study conducted in New York from 1991-1994 found that all-cause mortality was associated with multidrug resistance. While our study only found MDR-TB to be associated with TB mortality, this may be because the TB-specific deaths were included in the all-cause mortality group of the prior study and drove the observed association. Other risk factors were found to be associated with TB and all-cause mortality in this study. This category includes a wide range of possible values, such as smoking and anemia, which have been found to be associated with all-cause mortality among TB cases in other studies.[51, 54]

These findings have many implications for improving public health programs to better target mortality prevention among TB cases. Long term care facilities may be an important risk factor for mortality among TB cases. Patients in these facilities, because they have the duel burden of advancing age, poorer baseline health conditions, and being in a congregate setting, should be closely followed and regularly screened for TB. TB cases that are 45 years and older should be monitored more closely and started on treatment as soon as possible, as they are at high risk for both TB and all-cause mortality. HIV testing should also be offered to all TB cases and to groups that may be at high risk for both TB and HIV during TB screening. If cases are HIV co-infected, then they can begin treatment sooner and have better disease outcomes. Additionally, several modifiable risk factors are associated with mortality among TB cases. Evaluating high-risk sub-populations before they present with TB symptoms may ensure that treatment has a greater effect and that they have the opportunity to start treatment before dying due to the disease. TB cases with concurrent chronic conditions, such as end-stage renal disease or immunosuppressive disorders, should be followed closely as these factors are risk factors for adverse outcomes among cases. Additionally, cases with MDR-TB need to be started on treatment as soon as possible and followed very closely during treatment to monitor the disease progression and ensure that the treatment is effective.

There are several limitations associated with using data from a passive surveillance system. Some variables, such as diabetes mellitus, may not have been adequately reported or may have been more likely reported in individuals who have access to healthcare or regularly follow their health and would be more likely to have better TB outcomes. However, we do not believe that these variables would be differential by TB specific and all-cause mortality, and thus would not have significantly impacted the study results. Additionally, these data can be updated for several

years, therefore, some of these cases may be misclassified as either TB-specific or all-cause mortality. However, when we restricted the analysis to the middle two years of the study period (2010-2012), it did not significantly impact the study results. Lastly, time on treatment and whether a patient had the opportunity to be treated may play a significant role in TB mortality; however, we did not have an adequate measurement of duration of treatment in this analysis as some TB mortality cases were diagnosed at death and thus never had the opportunity to be treated. However, several other factors were included in the multivariate model that may be a proxy for time on treatment, such as type of treatment.

Identifying risk factors specific to TB mortality help public health programs determine which groups to follow more closely and where to allocate their resources when managing TB cases. Given the increased risk of TB mortality among those with advancing age, HIV, end-stage renal disease, any immunosuppressive risk factors, or residents of a long-term care facility, these individuals should be followed more closely in order to improve TB outcomes. Additionally, treating high risk patients with both SAT and DOT may improve TB outcomes, as having both types of therapy was protective against both all-cause and TB-specific mortality.

Table 1. Descriptive statistics for socio-demographic variables associated with Tuberculosis mortality, 2009-2013

Risk Factor	TB Mortality N=1,404	All-Cause Mortality N=2,413	Alive N=48,358	Total N=52,175	p-value
	n (%) Median [IQR]	n (%) Median [IQR]	n (%) Median [IQR]	n (%)	
Age Categories[1]				52,175 (100)	
0-14	12 (0.4)	6 (0.2)	2,812 (99)	2,830 (5)	<0.0001
15-24	21 (0.4)	16 (0.3)	5,461 (99)	5,498 (11)	
25-44	172 (1)	202 (1.2)	16,561 (98)	16,935 (33)	
45-64	453 (2.8)	746 (5)	14,891 (93)	16,090 (31)	
65+	745 (7)	1,443 (13)	8,630 (80)	10,818 (21)	
Sex[1]				52,156 (100)	
Male	935 (3)	1,597 (5)	29,159 (92)	31,691 (61)	<0.0001
Female	468 (2.3)	816 (4)	19,181 (94)	20,465 (39)	
Country of Origin				51,859 (99)	
Foreign-born	672 (2.1)	1,105 (3.4)	31,041 (95)	32,818 (63)	<0.0001
US-born	727 (3.8)	1,298 (6.7)	17,282 (90)	19,307 (37)	
Duration of time in the US				52,175 (100)	
Less than 1 year	163 (2.3)	243 (3.4)	6,850 (94)	7,256 (14)	<0.0001
1 to 10 years	130 (1.2)	184 (1.6)	10,933 (97)	11,247 (22)	
10 years or greater	384 (2.7)	688 (4.8)	13,293 (93)	14,365 (28)	
US-born	727 (3.8)	1,298 (7)	17,282 (90)	19,307 (37)	
Race/ethnicity[2]					
Asian	307 (2.0)	577 (3.8)	14,266 (94)	15,150 (29)	<0.0001
African American	344 (2.8)	629 (5.2)	11,193 (92)	12,166 (23)	
Hispanic	360 (2.4)	493 (3.3)	14,135 (94)	14,988 (29)	
White	324 (4.0)	636 (8)	7,162 (88)	8,122 (16)	
Other[3] or Unknown	69 (4.0)	78 (4.5)	1,602 (92)	1,749 (3.4)	
Excessive Alcohol Use within the past year				52,109 (100)	
Yes	239 (3.9)	330 (5.4)	5,498 (91)	6,067 (12)	<0.0001
No or Unknown	1,162 (2.5)	2,080 (4.5)	42,800 (93)	46,042 (88)	
Resident of a correctional facility at time of diagnosis				51,993 (99)	
Yes	20 (1.0)	37 (1.8)	2057 (97)	2,114 (4.1)	<0.0001
No or Unknown	1,377 (2.8)	2367 (4.8)	46,135 (92)	49,879 (96)	
Resident of a long term care facility at time of diagnosis				52,111 (100)	
Yes	112 (10)	256 (23)	722 (66)	1,090 (2.1)	<0.0001
No or Unknown	1288 (2.5)	2,151 (4.2)	47,582 (93)	51,021 (98)	
Homeless within the past year				52,112 (100)	
Yes	98 (3.5)	123 (4.4)	2,565 (92)	2,786 (5)	0.02
No or Unknown	1,302 (2.6)	2,284 (4.6)	45,740 (93)	49,326 (95)	
Injecting Drug Use within the past year				52,125 (100)	
Yes	28 (3.7)	53 (7)	672 (89)	753 (1.4)	0.001
No or Unknown	1,374 (2.7)	2,356 (4.6)	47,642 (93)	51,372 (99)	
Primary Occupation					
High Risk Employee[4]	15 (0.8)	22 (1.2)	1,792 (98)	1,829 (3.8)	<0.0001
Not Employed[5]	620 (2.7)	1,088 (4.8)	20,921 (92)	22,629 (47)	
Retired	505 (8)	941 (14)	5,209 (78)	6,655 (14)	
Other or Unknown	235 (1.4)	306 (1.8)	16,661 (97)	17,202 (36)	

[1]Unknown values were excluded from analysis (Age categories: n=4, Sex: n=13); [2]All reported races are non-Hispanic ethnicity
[3]Includes Multi-racial, Native Hawaiian or Pacific Islander, and American Indian; [4]Includes correctional employees or healthcare workers; [5]Includes those not seeking employment and those who are unemployed

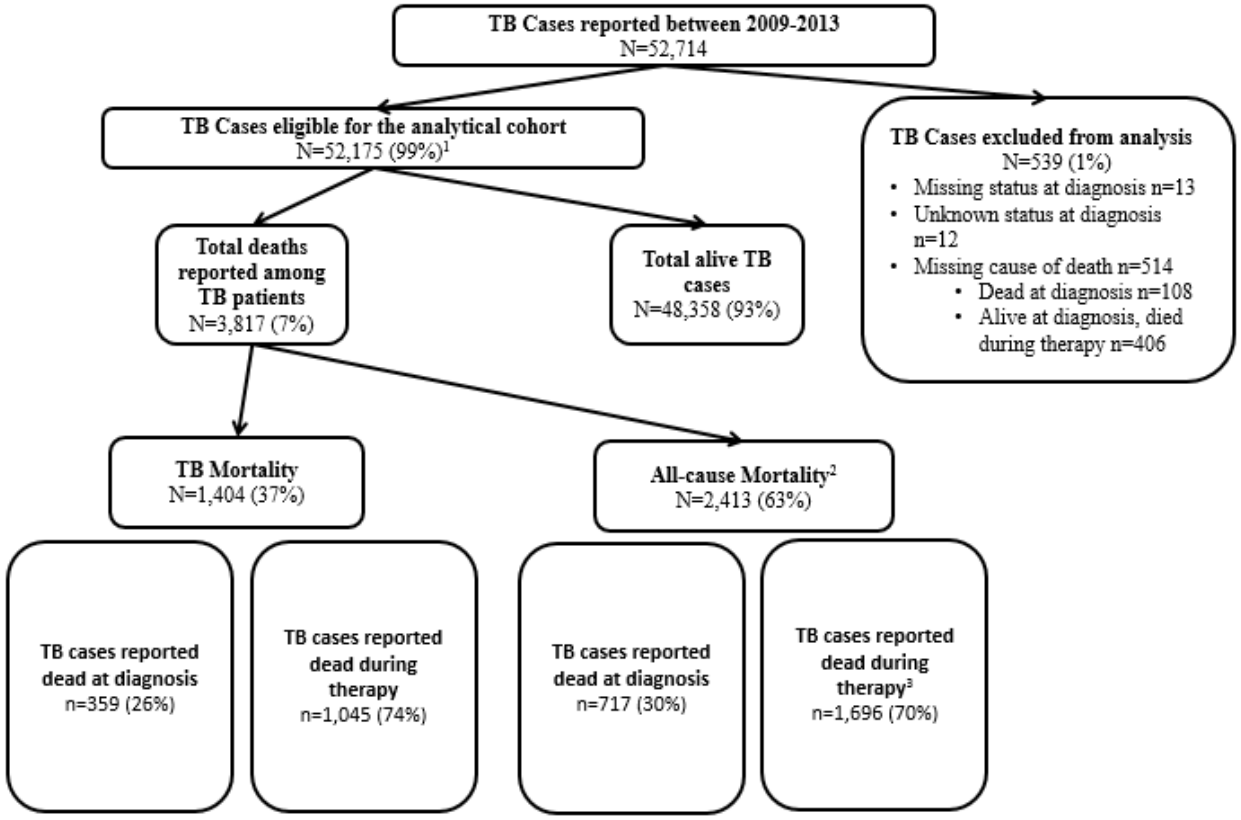
Table 2. Descriptive statistics and bivariate associations for clinical variables associated with Tuberculosis mortality, 2009-2013

Risk Factor	TB Mortality N=1,404	All-Cause Mortality N=2,413	Alive N=48,358	Total N=52,175	p-value
	n (%) Median [IQR]	n (%) Median [IQR]	n (%) Median [IQR]	n (%)	
Site of Disease[1]				51,636 (99)	
Pulmonary only	1,003 (2.7)	1,700 (4.7)	33,490 (92)	36,566 (69)	
Extra-pulmonary only	162 (1.5)	456 (4.1)	10,502 (94)	11,203 (21)	<0.0001
Both	239 (5)	254 (5)	4,329 (88)	4,898 (9)	
Previous Episode of TB				51,274 (98)	
Yes	64 (2.7)	119 (4.9)	2,232 (92)	2,415 (5)	0.82
No or unknown	1,331 (2.7)	2,280 (4.7)	45,248 (93)	48,859 (95)	
Type of Therapy[2]					
Self-administered Therapy (SAT)	98 (2.3)	158 (3.7)	4,075 (94)	4,331 (9)	
Directly observed therapy (DOT)	803 (2.8)	1,196 (4.2)	26,322 (93)	28,321 (60)	
Both	81 (0.6)	256 (1.8)	13,580 (98)	13,917 (30)	<0.0001[8]
Unknown	9 (3.3)	13 (4.7)	253 (92)	275 (0.6)	
HIV status at time of diagnosis				47,545 (91)	
Positive	124 (3.9)	233 (7)	2,807 (89)	3,164 (7)	
Negative	649 (1.8)	1104 (3.0)	35,388 (95)	37,141 (78)	<0.0001
Not offered	433 (10)	698 (17)	3,033 (73)	4,164 (9)	
Other[3] or Unknown	123 (4.0)	241 (8)	2,712 (88)	3,076 (6)	
Additional TB Risk Factors[4]					
Diabetes Mellitus	292 (4.4)	519 (8)	5,809 (88)	6,620	<0.0001
End-stage renal disease	114 (11)	244 (23)	690 (66)	1,048	<0.0001
Any immunosuppression[5]	152 (6)	370 (16)	1,852 (78)	2,374	<0.0001
TB Risk Factors[6]	80 (1.5)	101 (1.8)	5,318 (97)	5,499	<0.0001
Other	388 (3.7)	715 (6.9)	9,301 (89)	10,404	<0.0001
None	517 (2.1)	729 (3)	22,884 (95)	24,130	<0.0001
Reason Evaluated				48,618 (93)	
Abnormal X-Ray	320 (3.2)	633 (6.4)	8,988 (90)	9,941 (20)	
Contact with a TB case	12 (0.5)	18 (0.8)	2,356 (99)	2,386 (5)	
TB Symptoms	833 (3.0)	1,173 (4.2)	25,682 (93)	27,688 (57)	
Other[7] or Unknown	219 (2.6)	547 (6)	7,837 (91)	8,603 (18)	<0.0001
MDR-TB diagnosis				39,236 (75)	
Yes	19 (3.6)	14 (2.7)	489 (94)	522 (1.3)	0.02
No or Unknown	1,236 (5)	2,101 (5)	35,377 (91)	38,714 (99)	

[1]40 observations with disease site unknown were excluded from analysis.
[2]Values with unknown type of therapy were excluded from analysis (9 among TB mortality, 24 among all-cause mortality, 253 among alive).
[3]Including indeterminate, refused, and test done but results unknown.
[4]These values were not mutually exclusive, total data counts were not reported.
[5]Including those with immunosuppression, post-organ transplantation, and/or TNF-α antagonist therapy.
[6]Including those who were a contact of an infectious TB patient, had incomplete LTBI therapy, were a contact of an MDR-TB patient, or were a missed contact in a TB cluster investigation.
[7]Including employment/administrative testing, healthcare worker, immigration medical exam, incident lab result, and targeted TB testing.
[8]35% of the data are missing.

Table 3. Adjusted and unadjusted odds ratios for the risk factors associated with mortality in the multivariate model

Risk Factor	TB Mortality		All-Cause Mortality	
	Unadjusted Odds Ratio [OR] (95% CI)	Adjusted OR	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age Categories[1]				
00-14	0.41 (0.23, 0.74)	0.08 (0.01, 0.60)	0.18 (0.08, 0.39)	0.22 (0.05, 0.91)
15-24	0.37 (0.24, 0.58)	0.36 (0.19, 0.69)	0.24 (0.14, 0.40)	0.30 (0.15, 0.63)
25-44		Ref.		
45-64	2.93 (2.45, 3.50)	2.59 (2.02, 3.31)	4.11 (3.51, 4.81)	3.70 (2.92, 4.70)
65+	8.31 (7.03, 9.83)	5.81 (4.40, 7.66)	13.71 (11.81, 15.92)	8.62 (6.66, 11.15)
Sex[1]				
Male	1.31 (1.17, 1.47)	1.36 (1.16, 1.59)	1.29 (1.18, 1.40)	1.41 (1.24, 1.61)
Female		Ref.		
Country of Birth				
US-born	1.94 (1.75, 2.16)	1.42 (1.15, 1.74)	2.11 (1.94, 2.29)	1.22 (1.02, 1.46)
Foreign-born		Ref.		
Race/ethnicity				
Asian	0.48 (0.41, 0.56)	0.93 (0.71, 1.23)	0.46 (0.41, 0.51)	0.94 (0.75, 1.17)
African American	0.68 (0.58, 0.79)	1.07 (0.86, 1.33)	0.63 (0.57, 0.71)	1.03 (0.86, 1.22)
Hispanic	0.56 (0.48, 0.66)	1.47 (1.15, 1.87)	0.39 (0.35, 0.44)	1.03 (0.83, 1.27)
White		Ref.		
Other[6] or Unknown	0.95 (0.73, 1.24)	1.66 (1.14, 2.41)	0.55 (0.43, 0.70)	1.14 (0.81, 1.61)
Resident of a long term care facility at time of diagnosis				
Yes	5.73 (4.66, 7.05)	2.09 (1.56, 2.80)	7.84 (6.76, 9.10)	2.70 (2.15, 3.40)
No or Unknown		Ref.		
Primary Occupation				
High Risk Employee	0.59 (0.35, 1.00)	0.99 (0.51, 1.91)	0.67 (0.43, 1.03)	1.08 (0.62, 1.90)
Not Employed	2.10 (1.81, 2.45)	1.89 (1.52, 2.34)	2.83 (2.49, 3.22)	2.21 (1.82, 2.68)
Retired	6.87 (5.87, 8.05)	1.97 (1.52, 2.56)	9.84 (8.61, 11.23)	2.45 (1.96, 3.06)
Other or Unknown		Ref.		
Site of Disease				
Pulmonary only		Ref.		
Extra-pulmonary only	0.52 (0.44, 0.61)	0.53 (0.40, 0.69)	0.86 (0.77, 0.95)	0.91 (0.76, 1.09)
Both	1.84 (1.60, 2.13)	1.95 (1.60, 2.38)	1.16 (1.01, 1.32)	1.31 (1.09, 1.58)
Type of Therapy				
Self-administered Therapy (SAT)	0.79 (0.64, 0.98)	0.93 (0.72, 1.21)	0.85 (0.72, 1.01)	0.82 (0.66, 1.03)
Directly observed therapy (DOT)		Ref.		
Both	0.20 (0.16, 0.25)	0.20 (0.16, 0.26)	0.42 (0.36, 0.48)	0.47 (0.40, 0.55)
Unknown	1.17 (0.60, 2.28)	0.74 (0.29, 1.93)	1.13 (0.65, 1.98)	0.79 (0.35, 1.79)
HIV status at time of diagnosis				
Positive	2.41 (1.98, 2.93)	2.63 (2.02, 3.42)	2.66 (2.30, 3.08)	2.68 (2.13, 3.37)
Negative		Ref.		
Not offered	7.78 (6.86, 8.84)	4.78 (3.96, 5.77)	7.38 (6.66, 8.17)	3.41 (2.89, 4.02)
Other or Unknown	2.47 (2.03, 3.01)	1.57 (1.18, 2.09)	2.85 (2.47, 3.29)	1.75 (1.42, 2.16)
Additional TB Risk Factors				
Diabetes Mellitus	1.92 (1.69, 2.19)	1.13 (0.94, 1.35)	2.01 (1.82, 2.22)	1.11 (0.95, 1.28)
End-stage renal disease	6.11 (4.97, 7.50)	3.12 (2.33, 4.17)	7.77 (6.67, 9.05)	3.22 (2.54, 4.08)
Any immunosuppression	3.05 (2.56, 3.63)	2.29 (1.82, 2.89)	4.55 (4.03, 5.13)	3.16 (2.66, 3.75)
Other	1.60 (1.42, 1.81)	1.43 (1.22, 1.68)	1.77 (1.62, 1.94)	1.61 (1.41, 1.84)
Reason Evaluated				
Abnormal X-Ray	1.27 (1.07, 1.52)	1.68 (1.29, 2.18)	1.01 (0.90, 1.14)	1.34 (1.10, 1.62)
Contact with a TB case	0.18 (0.10, 0.33)	0.41 (0.17, 1.04)	0.11 (0.07, 0.18)	0.33 (0.15, 0.72)
TB Symptoms	1.16 (1.00, 1.35)	1.64 (1.30, 2.07)	0.65 (0.59, 0.73)	1.12 (0.95, 1.33)
Other or Unknown		Ref.		
MDR-TB diagnosis				
Yes	1.11 (0.70, 1.77)	3.20 (1.93, 5.92)	0.48 (0.28, 0.82)	1.05 (0.48, 2.28)
No or Unknown		Ref.		



[1]Percentage for each category out of the total from which it was derived.
[2]Only including cases where the cause of death was explicitly recorded as not due to TB.
[3]Including cases where the cause of death was due to TB therapy, unrelated, or unknown.

Figure 1. Derivation of the analytical cohort used in the preceding analysis. 539 cases were excluded from analysis and 52,175 were included in the final analytical cohort.

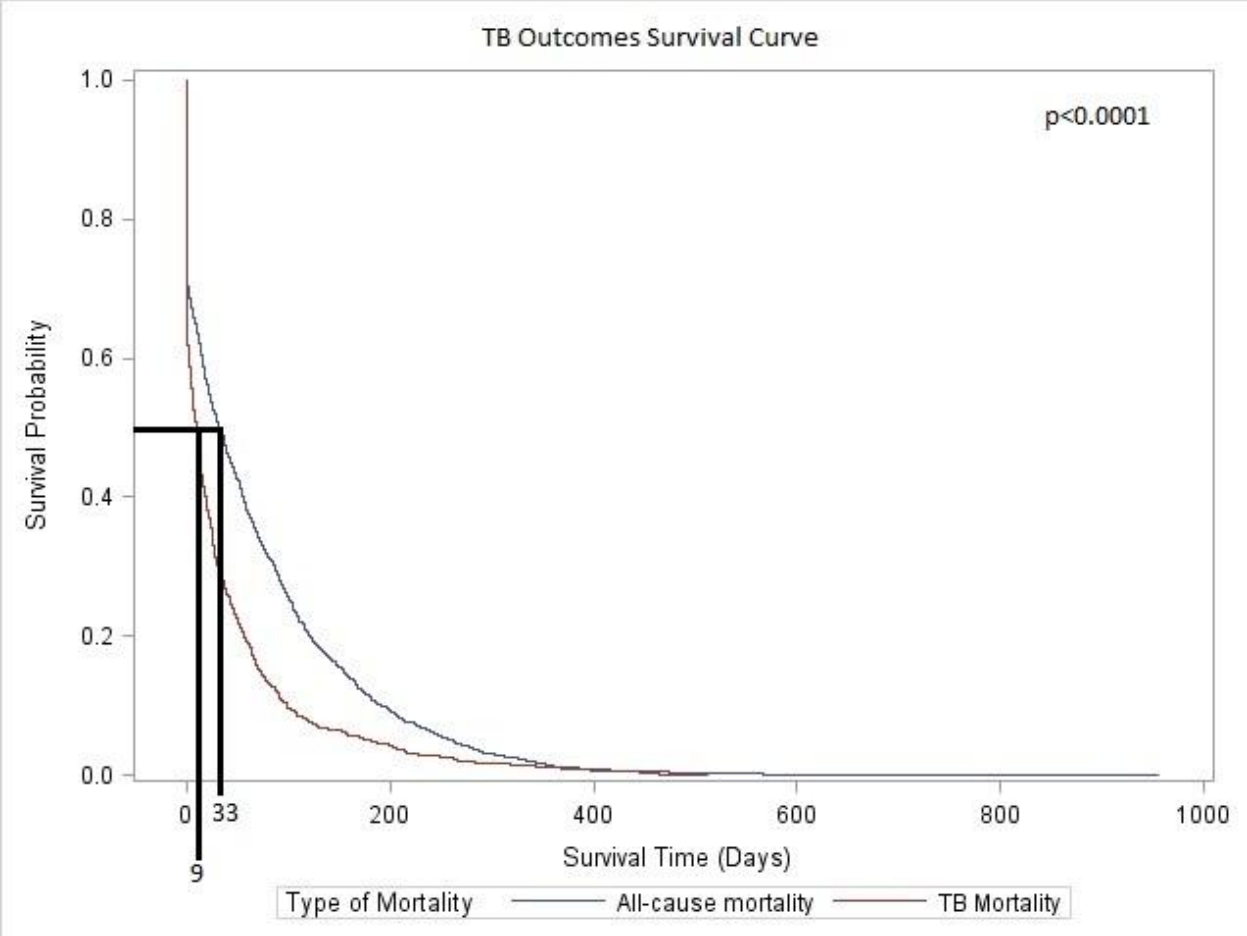


Figure 2. Survival Curve for TB mortality versus All-Cause Mortality for the 2,699 TB cases (975 TB mortality and 1,724 all-cause mortality) included in the survival analysis. The median survival time for each is indicated by the black line and the p-value resulting from a log rank test is displayed in the right corner of the graph. The median survival time among TB mortality cases was 9 days and 33 days among all-cause mortality cases.

Chapter 3: Implications and Future Directions

The following study provided insight into risk factors associated with worse TB outcomes among cases in the United States. This information can be used by TB programs to follow high risk patients more closely, such as those who have both extra-pulmonary and pulmonary TB, and develop increased TB screening in high risk groups, such as those with end-stage renal disease.

Additional analyses are needed to fully describe some relationships described in this study. For example, it is unclear whether those who were not offered HIV testing were not offered testing because they died and never had the opportunity to be tested. Data imputation techniques may help clarify this relationship and describe more clearly how not being offered HIV testing may affect TB outcomes. Additionally, other risk factors appear to be associated with both TB and all-cause mortality among cases. Multiple different risk factors were reported in this category, including smoking, anemia, and lung cancer. Further analyses are needed in order to determine if some factors reported within this variable explain the association between mortality and other risk factors. Lastly, survival analysis will provide further insight into the importance of some of these risk factors, as they may lead to decreased survival among TB cases.

Future studies are needed to make causal inferences about these risk factors. Because this study was conducted using a national surveillance system, some data may not have been reported correctly or may have been reported differently across local or state TB control programs. An observational, prospective cohort study among TB cases will provide further insight into which risk factors determine adverse outcomes.

References

1. Centers for Disease Control and Prevention (CDC), *Achievements in Public Health, 1990-1997: Control of Infectious Diseases.* MMWR. **48**(29): p. 621-629.
2. Centers for Disease Control and Prevention (CDC), *Historical Perspectives Centennial: Koch's Discovery of the Tubercle Bacillus* MMWR. **31**(10): p. 121-123.
3. Ratcliffe, H.L. and W.F. Wells, *Tuberculosis of rabbits induced by droplet nuclei infection; response to reinfection.* J Exp Med, 1948. **87**(6): p. 585-94.
4. Frankel, E. and H.E. Heyer, *Tuberculous Patients in New Jersey Sanatoriums.* Am J Public Health Nations Health, 1930. **20**(9): p. 969-77.
5. Koch, R., *Die Atiologic der Tuberkulose.* Berliner Klinische Wochenschrift. **15**: p. 221-30.
6. S.A. Waksman, M.T., *The Chemical Nature of Actinomycin, an Anti-microbial Substance Produced by Actinomyces Antibioticus* J. Biol. Chem., 1942. **142**: p. 519-528.
7. Barnes, R.F., et al., *Trends in mortality of tuberculosis patients in the United States: the long-term perspective.* Ann Epidemiol, 2011. **21**(10): p. 791-5.
8. Mitchison, D.A., *Development of streptomycin resistant strains of tubercle bacilli in pulmonary tuberculosis; results of simultaneous sensitivity tests in liquid and on solid media.* Thorax, 1950. **5**(2): p. 144-61.
9. Goble, M., et al., *Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin.* N Engl J Med, 1993. **328**(8): p. 527-32.
10. Iseman, M.D., *Treatment of multidrug-resistant tuberculosis.* N Engl J Med, 1993. **329**(11): p. 784-91.
11. Muller, B., et al., *Programmatically selected multidrug-resistant strains drive the emergence of extensively drug-resistant tuberculosis in South Africa.* PLoS One, 2013. **8**(8): p. e70919.
12. Chung-Delgado, K., et al., *Mortality among MDR-TB Cases: Comparison with Drug-Susceptible Tuberculosis and Associated Factors.* PLoS One, 2015. **10**(3): p. e0119332.
13. Shah, N.S., et al., *Extensively drug-resistant tuberculosis in the United States, 1993-2007.* JAMA, 2008. **300**(18): p. 2153-60.
14. Gandhi, N.R., et al., *HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality.* Am J Respir Crit Care Med, 2010. **181**(1): p. 80-6.
15. WHO, *Global Tuberculosis Report 2013.* Global Tuberculosis Report 2013, 2013: p. 1-303.
16. Mdivani, N., et al., *High prevalence of multidrug-resistant tuberculosis in Georgia.* Int J Infect Dis, 2008. **12**(6): p. 635-44.
17. Negar Niki Alami, M., Courtney M. Yuen, PhD, Roque Miramontes, MPH, Robert Pratt, Sandy F. Price, and M. Thomas R. Navin, *Trends in Tuberculosis — United States, 2013.* MMWR, 2014. **63**(11): p. 229-233.
18. Martin-Echevarria, E., et al., *Development of tuberculosis in human immunodeficiency virus infected patients receiving antiretroviral therapy.* Int J Tuberc Lung Dis, 2014. **18**(9): p. 1080-4.
19. Churchyard, G.J., et al., *Tuberculosis preventive therapy: an underutilised strategy to reduce individual risk of TB and contribute to TB control.* S Afr Med J, 2014. **104**(5): p. 339-43.
20. WHO, *Global Tuberculosis Report 2014.* Global Tuberculosis Report 2014, 2014: p. 1-171.
21. Pawlowski, A., et al., *Tuberculosis and HIV co-infection.* PLoS Pathog, 2012. **8**(2): p. e1002464.
22. Metcalfe, J.Z., et al., *Tuberculosis and HIV Co-infection, California, USA, 1993-2008.* Emerg Infect Dis, 2012. **19**(3): p. 400-6.
23. Whalen, C., et al., *Accelerated course of human immunodeficiency virus infection after tuberculosis.* Am J Respir Crit Care Med, 1995. **151**(1): p. 129-35.

24. S Shah, M., K Cain, MD, S Marks, MPH, MA, J Cavanaugh, MD., *Mortality Among Patients with Tuberculosis and Associations with HIV Status --- United States, 1993--2008.* Morbidity and Mortality Weekly Report (MMWR), 2010. **59**(46): p. 1509-1513.
25. WHO, *Tuberculosis Prevalence Surveys: A Handbook.* Geneva, Switzerland: WHO, 2011.
26. Stop TB Partnership, *Compendium of Indicators for Monitoring and Evaluating National Tuberculosis Programs.* WHO/HTM/TB. **2004.344**.
27. Glaziou, P., et al., *Global epidemiology of tuberculosis.* Semin Respir Crit Care Med, 2013. **34**(1): p. 3-16.
28. Zetola, N.M., et al., *Longer hospital stay is associated with higher rates of tuberculosis-related morbidity and mortality within 12 months after discharge in a referral hospital in Sub-Saharan Africa.* BMC Infect Dis, 2014. **14**: p. 409.
29. Escombe, A.R., et al., *Natural ventilation for the prevention of airborne contagion.* PLoS Med, 2007. **4**(2): p. e68.
30. Alan B. Bloch, M.D., M.P.H., *Screening for Tuberculosis and Tuberculosis Infection in High-Risk Populations Recommendations of the Advisory Council for the Elimination of Tuberculosis.* MMWR, 1995. **44**(RR-11): p. 18-34.
31. Centers for Disease Control and Prevention (CDC), *Tuberculosis control laws—United States,1993: recommendations of the Advisory Council for the Elimination of Tuberculosis (ACET).* MMWR, 1993. **42**(RR-15): p. 1-28.
32. The Advisory Council for the Elimination of Tuberculosis and the National Tuberculosis Controllers Association, *Tuberculosis Control Laws and Policies: A Handbook for Public Health and Legal Practitioners.* 2009: p. 1-44.
33. Korenromp, E.L., et al., *The measurement and estimation of tuberculosis mortality.* Int J Tuberc Lung Dis, 2009. **13**(3): p. 283-303.
34. CDC, *Reported Tuberculosis in the United States, 2013*. Atlanta, GA: U.S. Department of Health and Human Services, CDC.
35. Sterling, T.R., et al., *Mortality in a large tuberculosis treatment trial: modifiable and non-modifiable risk factors.* Int J Tuberc Lung Dis, 2006. **10**(5): p. 542-9.
36. Pablos-Mendez, A., T.R. Sterling, and T.R. Frieden, *The relationship between delayed or incomplete treatment and all-cause mortality in patients with tuberculosis.* JAMA, 1996. **276**(15): p. 1223-8.
37. Sanchez, M., et al., *Outcomes of TB treatment by HIV status in national recording systems in Brazil, 2003-2008.* PLoS One, 2012. **7**(3): p. e33129.
38. Au-Yeung, C., et al., *Tuberculosis mortality in HIV-infected individuals: a cross-national systematic assessment.* Clin Epidemiol, 2011. **3**: p. 21-9.
39. Gandhi, N.R., et al., *Risk factors for mortality among MDR- and XDR-TB patients in a high HIV prevalence setting.* Int J Tuberc Lung Dis, 2012. **16**(1): p. 90-7.
40. Ramagopalan, S.V., et al., *Associations between selected immune-mediated diseases and tuberculosis: record-linkage studies.* BMC Med, 2013. **11**: p. 97.
41. Skogberg, K., et al., *Effect of immunosuppressive therapy on the clinical presentation and outcome of tuberculosis.* Clin Infect Dis, 1993. **17**(6): p. 1012-7.
42. Sayarlioglu, M., et al., *Tuberculosis in Turkish patients with systemic lupus erythematosus: increased frequency of extrapulmonary localization.* Lupus, 2004. **13**(4): p. 274-8.
43. Centers for Disease Control and Prevention (CDC), *Tuberculosis Associated with Blocking Agents Against Tumor Necrosis Factor-Alpha --- California, 2002--2003*, in *Morbidity and Mortality Weekly Report (MMWR)*. 2004. p. 683-686.

44. Forssbohm, M., et al., *[Death due to tuberculosis requiring treatment or an accompanying disease? A contribution to the lethality and mortality of tuberculosis in Germany].* Pneumologie, 2011. **65**(10): p. 607-14.
45. Horne, D.J., et al., *Factors associated with mortality in patients with tuberculosis.* BMC Infect Dis, 2010. **10**: p. 258.
46. Reis-Santos, B., et al., *Treatment outcomes in tuberculosis patients with diabetes: a polytomous analysis using Brazilian surveillance system.* PLoS One, 2014. **9**(7): p. e100082.
47. WHO., *Global Tuberculosis Report 2013.* Geneva, Switzerland: WHO, 2013.
48. Lin, C.H., et al., *Tuberculosis mortality: patient characteristics and causes.* BMC Infect Dis, 2014. **14**: p. 5.
49. Cox, H., et al., *Tuberculosis recurrence and mortality after successful treatment: impact of drug resistance.* PLoS Med, 2006. **3**(10): p. e384.
50. Pascopella, L., Pennan, Barry M., Flood, Jennifer, DeRiemer, Kathryn, *Death With Tuberculosis in California, 1994–2008.* Open Forum Infect Dis 2014. **1**: p. 1-10.
51. Isanaka, S., et al., *Iron deficiency and anemia predict mortality in patients with tuberculosis.* J Nutr, 2012. **142**(2): p. 350-7.
52. Kourbatova, E.V., et al., *Risk factors for mortality among patients with extrapulmonary tuberculosis at an academic inner-city hospital in the US.* Eur J Epidemiol, 2006. **21**(9): p. 715-21.
53. Marks, S.M., E. Magee, and V. Robison, *Patients diagnosed with tuberculosis at death or who died during therapy: association with the human immunodeficiency virus.* Int J Tuberc Lung Dis, 2011. **15**(4): p. 465-70.
54. Alavi-Naini, R., et al., *Factors associated with mortality in tuberculosis patients.* J Res Med Sci, 2013. **18**(1): p. 52-5.
55. *2009 American Community Survey 1-Year Estimates* in *American Fact Finder*, T. S0101, Editor. 2009, U.S. Census Bureau, Population Division.
56. *Annual Estimates of the Resident Population: April 1, 2010 to July 1, 2013, 2013 Population Estimates* in *American Fact Finder*, T. PEPANNRES, Editor. 2014, U.S. Census Bureau, Population Division.

Appendix A: Additional Analyses

a. Secular trends in reporting

There may be a secular trend in reporting because the RVCT was updated and released in 2009 to include information about the cause of death among TB patients. To explore this, the relative proportion of TB outcomes by year [Figure 3] and the rate of TB and all-cause mortality per 100,000 U.S. population for the duration of the study [Table 4] were examined.

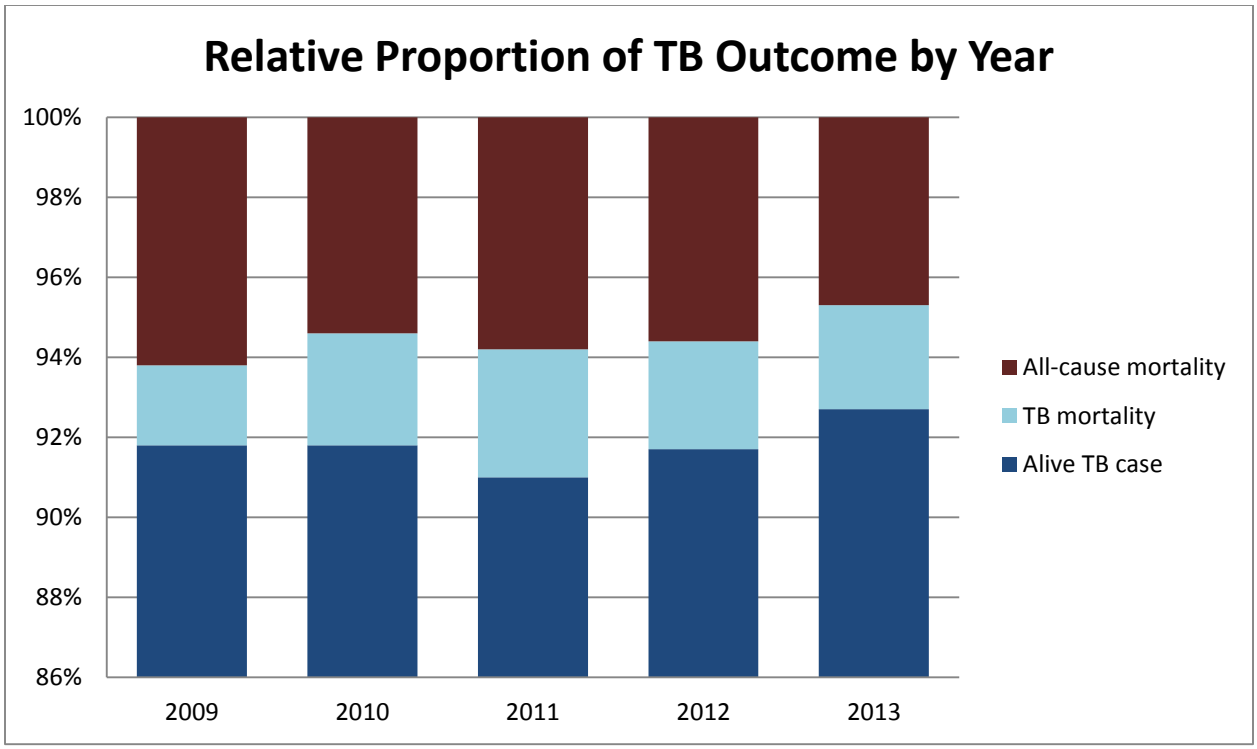


Figure 3. Secular trend of TB outcomes by reporting year, 2009-2013

Alive TB cases remain the majority of TB outcomes throughout the study period, ranging from 91-92.7%. TB mortality increases to around 3% of outcomes in the study population in 2010 from 2% in 2009 and remains stable throughout the study period (ranging from 2.6%-3.2% from 2010 to 2013). All-cause mortality is the lowest during 2013, 4.7%, but otherwise ranges from 5.4-6.4% from 2009 to 2012. All of the outcomes remain within 2% of the overall proportion of TB outcomes throughout the study period, suggesting that a secular trend in reporting does not exist.

Based on census estimates of the US population for 2009-2013[55, 56], the TB mortality and all-cause mortality death rate was calculated for the study population [Table 4].

Table 4. Mortality rates for TB and all-cause mortality among TB cases for the duration of the study period

Year	TB mortality (per 100,000 population)	All-cause mortality (per 100,000 population)
2009	0.076	0.232
2010	0.101	0.195
2011	0.108	0.195
2012	0.086	0.176
2013	0.080	0.142
Total	0.090	0.188

The larger difference between the TB mortality and all-cause mortality rate is likely due to reporting lag as the death due to TB variables were first added to the RVCT form in 2009. Overall, there is about a 2 times higher rate of all-cause mortality in comparison to TB mortality among TB cases.

b. Kaplan-Meir Survival Curves

To determine if there was a significant difference in survival time among different categories of HIV status (positive, negative, not offered, or other), Kaplan-Meir survival curves were generated for TB mortality and all-cause mortality. The results are presented below in Figures 4 and 5.

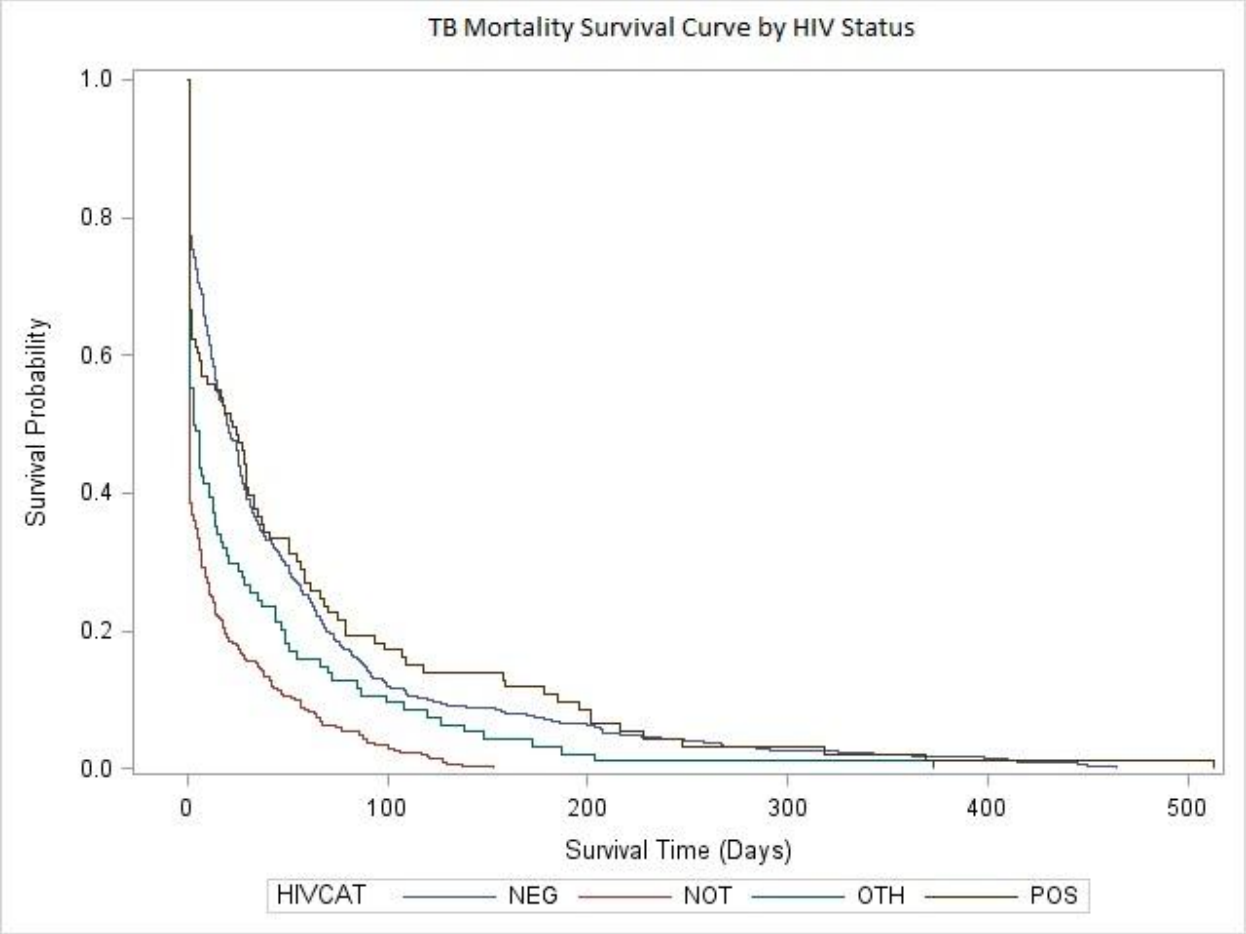


Figure 4. Survival curve for TB mortality among cases stratified by HIV status. The log rank test ($p<0.0001$) suggested that a significant difference in survival exists between the four groups.

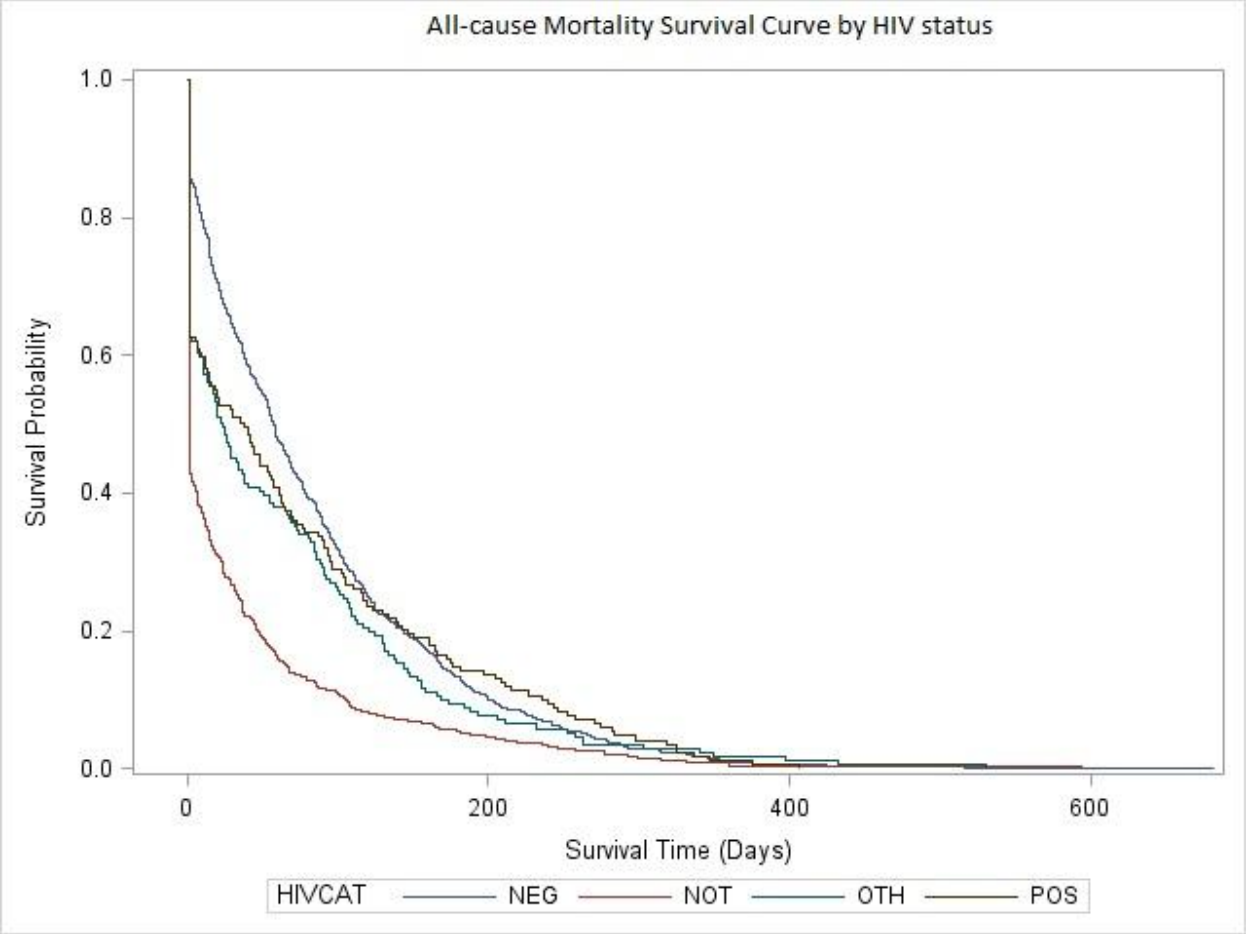


Figure 5. Survival curve for all-cause mortality among TB cases stratified by HIV status. The log rank test ($p<0.0001$) suggested that a significant difference in survival exists among all-cause mortality TB cases by HIV status.

Those who are not offered testing have a much lower survival time [Figure 3, 4] among both TB and all-cause deaths. This finding corroborates the thinking that this group was reported as 'not offered HIV testing' because they did not survive long enough to have the opportunity to be tested. Further analyses will be performed in order to clarify this relationship.