Title
Mortality with Tuberculosis in Los Angeles County, 2010-2014: The Effect of Public Health Supervision

Author
Redick, Brittney

Publication Date
2016

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Mortality with Tuberculosis in Los Angeles County, 2010-2014: The Effect of Public Health Supervision

A thesis submitted in partial satisfaction

of the requirements for the degree Master of Science

in Epidemiology

by

Brittney Julia Redick

2016

ABSTRACT OF THE THESIS

Mortality with Tuberculosis in Los Angeles County, 2010-2014: The Effect of Public Health Supervision

by

Brittney Julia Redick

Master of Science in Epidemiology

University of California, Los Angeles, 2016

Professor Roger Detels, Chair

Background: Despite significant public health advancements in prevention, screening and treatment of tuberculosis (TB), mortality with TB remains unacceptably high. The epidemiology of TB mortality is not well understood, and therefore urgent investigation of potentially modifiable aspects of TB care that could inform public health service delivery and improve patient outcomes is needed. The primary aim of this study was to evaluate the relationship between supervision of TB treatment and risk of TB death during TB treatment.

Methods: A retrospective cohort study was conducted to estimate the effect of health provider supervision on the risk of all-cause TB mortality during TB treatment among

clinically and/or laboratory verified active TB cases alive at time of diagnosis and who started treatment in Los Angeles County during 2010-2014.

Results: Of the 3016 TB cases included in the analysis, 283 (9.4%) died. TB treatment was solely supervised by a provider outside of the health department for 508 (19.2%) case-patients. Bivariate analysis revealed significant differences in age, TB disease characteristics and distribution of social, behavioral and common comorbid conditions between patients with TB treatment supervision solely by providers outside the health department (HD), compared to patients who had any HD supervision during their TB treatment. After adjustment for potential confounding factors, patients managed solely by providers outside the HD were found to have increased risk of all-cause mortality during TB treatment, compared to patients who had any HD involvement in the supervision of their TB treatment (adjusted risk ratio [aRR] 2.33, 95% CI 1.80-3.01).

Conclusion: Patients who did not have any HD involvement in their TB treatment supervision experienced over twice the risk of death as those patients with any HD supervision in their TB treatment. Further investigation of TB treatment practices and case management strategies by providers outside the HD is warranted to understand potential mechanisms for the observed increased risk of TB mortality.

The thesis of Brittney Julia Redick is approved.

Marjan Javanbakht

Robert J. Kim-Farley

Sanghyuk Shin

Roger Detels, Committee Chair

University of California, Los Angeles

2016

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ACRONYMS

95% CI	95% Confidence Interval
ACA	Affordable Care Act
ADM	Administrative supervision
AFB	Acid-fast bacilli
aRR	Adjusted Risk Ratio
CDC	Center for Disease Control and Prevention
CHS	Community Health Services
cRR	Crude Risk Ratio
CXR	Chest X-Ray
DM	Diabetes mellitus
DOT	Directly observed therapy
DPH	Department of Public Health
DST	Drug susceptibility testing
EMB	Ethambutol
HD	Health department
INH	Isoniazid
LAC	Los Angeles County
M.tb	Mycobacterium tuberculosis
NAAT	Nucleic Acid Amplification Test
PMD	Private Medical Doctor
PZA	Pyrazinamide
RIF	Rifampin
RIPE	1st line anti-TB drugs: Rifampin, Isoniazid, Pyrazinamide, Ethambutol
SAT	Self-administered therapy
SES	Socio-economic status
TB	Tuberculosis
TBC	Tuberculosis Clinic (public health department)
TBCP	Los Angeles County Department of Public Health Tuberculosis Control Program
TRIMS	Tuberculosis Registry Information System

ACKNOWLEDGEMENTS

First, I'd like to express my deepest appreciation to my faculty advisor, Dr. Sanghyuk Shin. The completion of this thesis paper would not have been possible without his generous support, expert guidance and kind encouragement from the inception of the thesis project.

Furthermore, I am very grateful for the time and guidance of my committee members.

In addition, I'd like to offer my sincerest gratitude to the Los Angeles County Department of Public Health Tuberculosis Control Program for providing access to data, an office workstation, and invaluable guidance and support throughout the development of the thesis project. In particular, I'd like to thank my mentors Dr. Alicia Chang and Dr. Monica Rosales for their input and direction at every stage of the process.

CHAPTER I: INTRODUCTION

The Urgent Need to Reduce TB-related Mortality in the United States

Tuberculosis (TB) is a preventable and treatable disease. In the United States, TB incidence rates have steadily declined since the strengthening of nation-wide tuberculosis control programs in the 1990s (1). However, national rates of deaths by TB have not matched the rate of decline of new cases, and appear to be stagnating in recent years (2). In 2012, 6.0% of TB cases in the United States died during treatment (2). In an era of effective anti-TB therapeutics and chemoprophylaxis, targeted TB screening programs and strong TB Control Programs embedded in communities around the United States, deaths with TB remain unacceptably high. In order to meet the post-2015 global TB target of reducing deaths by 95% by the year 2035, it is imperative that key factors driving the burden of TB mortality are identified (3). By investigating the effect of modifiable factors, tailored programmatic efforts can be implemented to directly address systematic weaknesses in the provision of TB services along the TB care continuum. For active TB cases, the continuum of care spans from diagnosis, successful linkage to TB care services, initiation of TB therapy, regular check-ups with supervising clinician to ensure the effectiveness of treatment, and monitoring patient adherence and occurrence of side effects to guarantee successful treatment completion and clearance of disease. The diverse settings in which a patient-case may be referred to or receive care for their TB diagnosis along the continuum (e.g. community clinics, primary care providers, inpatient wards in a hospital, skilled nursing facilities) underscores the need to better understand the effect of different provider practices and

TB case-management. Improved understanding of the root causes contributing to the TB mortality burden is urgently needed to rectify the pressing public health issue of persistent deaths with a disease that is completely preventable and treatable.

While extensive evaluation of patient and clinical characteristics have been undertaken to identify potential contributors to poor TB outcomes and mortality, there is relatively little understood about the effect of TB treatment practices by health providers. The quality of health provider supervision of TB treatment is a vital component to ensure administration of appropriate anti-TB drug regimens, provide support for patient adherence to TB therapy, manage adverse effects, documentation of key clinical indicators of disease improvement, and ultimately verify completion of TB therapy. However, as TB incidence falls nationally, there are fewer opportunities for health providers to gain experience with TB diagnosis and treatment. As such, providers in the private setting historically have not had the same exposure to diagnosing and treating TB cases; it is estimated that, nationwide, 77% of TB patients are primarily managed by the health department (HD) (4). Studies conducted in a variety of health settings that suggest delays in TB diagnosis and errors in TB treatment by private providers (outside of the HD setting) demonstrate the importance of understanding TB patient outcomes across public and private delivery system settings (5-10).

Illuminating the relationship between health provider supervision of TB treatment and TB patient outcomes, such as mortality, could inform public health evaluation and intervention. Evidence of differences in risk of mortality by type of health provider

supervising TB treatment would inform the development of improved health services strategies to address systemic deficiencies in the provision of TB therapy. With the WHO targets for decreased TB mortality quickly approaching, examination of potentially modifiable TB care practices or management strategies could be an extremely valuable and impactful avenue to rapidly improve patient outcomes with TB. Currently, public health clinics specializing in tuberculosis care coordination are uniquely positioned to provide timely and comprehensive health care. However, with the recent implementation of the Affordable Care Act, the provision of health services has the potential to shift significantly, as a large volume of the previously uninsured obtain coverage either through the health exchange or through the expansion of Medicaid (11). With an increasing likelihood of a larger volume of TB patients to interface with a private sector health provider during the course of TB care, a better understanding of TB outcomes by health providers outside the setting of the health department (HD) is important.

The primary objective of this study is to evaluate the effect of provider supervision of TB treatment on TB mortality. To meet this objective, a retrospective cohort study to evaluate TB mortality during TB treatment in Los Angeles County over a 5-year period was conducted. TB patients alive at diagnosis and who had a record of starting treatment were selected for inclusion in the study cohort. TB cases with any record of TB treatment supervision by the health department were compared to TB cases that were supervised solely by health providers outside of the health department. While previous studies have described an association between private provider supervision of

TB treatment and mortality, none have applied a causal, explanatory modeling approach to investigate this relationship. The present study applies a causal modeling strategy to assess the presence and magnitude of effect of supervision on the risk of TB death between exposure groups.

The Burden of TB Mortality: Global, National and Local Context

Although the advent of effective tuberculosis therapy and an emphasis on treatment for latent TB infection (LTBI) has decreased transmission and mortality with TB over recent decades, death with tuberculosis remains a significant public health concern (3, 12, 13). Worldwide, with an estimated 9.6 million new TB cases, there was an estimated 1.1 million HIV-negative and 0.39 million HIV-positive people who died with TB in 2014 (14, 15). TB is the leading cause of death by an infectious disease, and is one of the top 15 causes of death worldwide (16). With the introduction of the Millennium Development Goals in 2000 by the UN and the Stop TB Partnership, the push to halt TB incidence and reverse other key TB indicators demonstrated a significant decrease in the incidence of TB and similarly stark decrease in mortality rate in the Americas region prior to 2015 (16). The target of decreasing the mortality rate by 50% of the rate in 1990 by 2015 was met well before 2015; in fact, the mortality rate dipped below the target just before 2005 (3, 14, 17).

While TB incidence and mortality is decreasing worldwide, recent statistics indicate that the current status of TB control is at a critical juncture in the United States. Nationally, as a high-income, low TB incidence and HIV prevalence region, there was a 1.5% decline in incidence and 2.2% decline in the national case rate from 2013 to 2014, which was the smallest decrease found in more than 10 years, and the overall incidence stagnating around 3.0 cases 100,000 people from 2013-2015 (1, 2, 18). Interestingly, there was an 8% increase in deaths with TB from 2012 to 2013, from 510 to 555 deaths reported nationwide (2). In all, the annual national death rate due to TB has remained

steady at approximately 0.2 deaths per 100,000 persons since 2003 (the most recent data available is current through 2013) (2).

At the state level, California has the third highest incidence rate of TB nationwide, with a rate of 5.5 cases per 100,000 persons and a total of 2145 cases in 2014, compared to the national incidence rate of 3.0 (1, 2). According to historical data, roughly 10 percent of TB cases die each year, which has remained steady in the state of California since 1993 (19). Of TB cases reported to the state in 2012, there were 212 deaths out of 2188 cases, or approximately 9.7% deaths (19). During this same period, Los Angeles County (LAC) contributed 79 deaths out of 625 cases, or about 12.6% (19). While Los Angeles County contributed roughly 29% of the total TB cases to the state total, LAC contributed about 37% of the total CA state TB deaths for the year 2014 (19-21).

Los Angeles County covers 4,751 square miles has a population of over 10 million persons. It is the most populated county in the United States (22). The population of Los Angeles County is highly diverse, with 44% Hispanic, just over 30% White, and 12% Asian and almost 10% Black persons (23). Covering an expansive area in Southern California, with extensive suburban communities around the densely populated urban core, LAC contains 8 separate Service Planning Areas (SPA), each with a distinct demographic composition (23). The LAC Department of Public Health (DPH) TB Control Program (TBCP) oversees the clinical care of TB patients in 11 community health centers and private medical providers throughout the SPAs (24). Overall, the age adjusted mortality rate in the County has shown a steady decrease of

18% from 2002-2011 (compared to the national decrease of 13%), according to a report released in 2012 (25). However, as mentioned above, the TB mortality rate is higher in LAC compared to overall mortality rates in California and the United States. Therefore, a more in-depth evaluation of mortality related to TB is warranted to understand how to achieve a similar decrease in the TB patient population within the richly diverse demographic, social and health context of a large urban setting such as Los Angeles County.

The epidemiology of mortality in patients with tuberculosis is not well understood. The literature spans studies conducted around the world in specific health services settings, which have important considerations for both internal and external validity and generalizability. Due to the unique biological, environmental, social and health system factors that define TB disease progression and care management, the contextual impacts on TB patient outcomes can be significant. Much of the literature has focused on identifying key clinical, demographic, and lab test results that may independent predictors of mortality in patients with TB. However, many of the factors identified are not directly modifiable. Improved understanding of the risk of mortality among patients managed by providers within and outside the HD may help to guide efforts to improve practices along the TB care continuum and provide the impetus to strengthen partnerships between public and private health systems involved in TB case management.

While prior studies in the literature have taken both predictive and explanatory modeling approaches to assess risk factors for TB mortality, the lack of studies utilizing a causal modeling approach often limits the interpretability and generalizability of resulting estimates. For example, some studies have included potential mediators in the model (e.g. directly observed therapy [DOT]), while some studies included covariates in their models that may be highly correlated (e.g. acquired drug resistance, initial drug regimen < 3 drugs) which complicates the interpretation of the resulting estimates of provider effect (6, 9). To understand the effect of supervision of TB treatment from providers within the HD compared to outside the HD, which would have potentially modifiable implications, a causal approach to elucidate the effect of provider supervision on mortality from a source population that reflects the current state of TB care coordination is warranted. In addition, few studies have examined the relationship between provider supervision of TB treatment and TB mortality in a large, metropolitan setting in the United States. The objective of the present study is to understand the effect of supervising provider type on TB mortality in a large county setting with a low-TB prevalence (relative to the global setting) and a strong TB Control Program by using an explanatory modeling strategy that takes into consideration key confounding covariates at baseline.

Primary Research Question

I. Among TB cases reported to the Tuberculosis Control Program in Los Angeles County during the years 2010-2014, do TB cases who have treatment supervision by a provider designated outside the HD system experience an increased risk of dying during the course of TB treatment, when compared to TB cases with primary oversight by a health provider from within the HD?

   I hypothesize that TB patients who initiate TB treatment and have their TB case supervised solely by a health provider outside the HD will have increased risk of death during TB treatment, compared to patients who initiate TB treatment and are primarily supervised by a health provider from within the HD.

CHAPTER II: BACKGROUND

Risk factors for TB mortality

The literature has established well-known risk factors for TB mortality including the very young and very old age groups, social and behavioral factors, comorbid conditions and disease severity near time of diagnosis. While there have been many studies of TB mortality as the outcome, limitations exist in key facets of the study design and selection of patients that could affect the generalizability and understanding of mortality risk. First, many studies limit patient inclusion by primary site of disease. For example, many studies in the literature focus on pulmonary only, culture-confirmed tuberculosis cases (7, 10, 26-31). The majority of tuberculosis patients are diagnosed with pulmonary disease; according to the CDC, almost 70% of TB cases in the United States in 2014 were pulmonary only (2). However, extra-pulmonary and combination extra-pulmonary/pulmonary disease are not insignificant subgroups of patients with TB, with roughly 20% of patients in the US presenting with extra-pulmonary disease with no pulmonary involvement, and 10% of TB patients with both pulmonary and extra-pulmonary sites of disease (2). To provide an understanding of TB disease on the population level, some predictors relevant to patients with pulmonary disease are not applicable to those with extra-pulmonary disease only, due to types of laboratory studies available for particular locations of TB disease. For example, sputum and smear-culture positivity, cavitary and military disease have been shown to be independently associated with increased risk of mortality, and used as proxy measures of disease severity when modeling risk of death with TB (9, 13, 32-34). Of note, patients

with HIV coinfection, the elderly and the very young, who are known to be at higher risk of mortality with TB, may not present with the definitive disease characteristics that are often used as disease severity proxy measures due to unique biological processes (e.g. immune status effects or difficulty producing sputum) (15, 35-39). Few studies have included all sites of TB disease for the evaluation of the effect of provider supervision on TB mortality.

Similarly, many studies investigate TB mortality in the inpatient setting, and tend to focus on specific clinical predictors of death (31, 40-45). However, many of the predictors identified may in fact be exacerbated by the degree of TB disease progression. While helpful to understand potential complications that may arise from inpatient TB care, one can assume that patients requiring admission to the hospital are already very sick. From a programmatic perspective, it would be helpful to understand the avenues for modifiable, improved practices at earlier points along the TB care continuum.

One factor that has been repeatedly associated with increased risk of mortality in patients diagnosed with TB disease is the age of the patient; this factor is likely correlated to the type of health provider supervising the patient case. Younger patients are more likely to be in healthier physical shape, and able to seek care directly at the health department upon referral for TB treatment. Elderly patients, who are guaranteed health insurance coverage under Medicare, may be more likely to seek care in the private health care setting (outside of the health department) with their health benefits.

Likewise, the elderly are more likely to have chronic health conditions that require regular monitoring by health providers, and this may increase the likelihood of having TB treatment supervision by a primary health provider familiar with the entire patient medical history outside the health department. The biological processes of aging can impact not only a patient's susceptibility to infection, but also the immune system's ability to mount a robust defense (46). Increasing age has been shown to be associated with increased risk of mortality in patients with TB across TB disease types, both in inpatient settings and outpatient settings, and in contexts of high and low HIV prevalence (28, 29, 47-49).

Social and behavioral risk factors also identified throughout various studies to be associated with increased risk of death include excess alcohol use, injection and non-injection drug use and recent history of homelessness (9, 32, 33, 47, 50, 51). One hypothesis for why these behavioral health factors demonstrate the associations with mortality in fact may be due in large part to their potential association with the overall socio-economic status (SES) of the patient. SES itself is a key upstream determinant that in turn affects various factors that can impact TB patient outcomes such as access to healthy nutrition options, housing and health care. Patients with known behavioral risk factors such as drug or alcohol abuse may have greater difficulty with adherence to TB therapy due to dealing with addiction or concurrent mental illness, more erratic health seeking behaviors and may have limited comprehension of the long-term treatment management plan required for successful TB treatment. Patients with a history of homelessness in the last year may face particular obstacles with compliance

with monthly standard of care check-ups and TB therapy. This may in reality be related to SES-related factors that are present earlier in the causal pathway that create barriers to accessing reliable health care due to difficulty traveling to the clinic, lack of access to routine, preventative health care or unstable living environment. Much of the TB data, especially in the United States, is reliant on fields available in the surveillance database. SES is difficult to ascertain based on existing fields in the database, and therefore behavioral risk factors and history of homelessness can provide a proxy measure of SES for the patient population. Furthermore, by including behavioral risk factors as a proxy for SES, this can provide some control for this confounding factor, as SES is likely to influence where the patient receives health care as well as may be related to ultimate risk of TB mortality.

Among TB patients, HIV infection has been shown to be a strong predictor of TB mortality (9, 44, 52-54). HIV-associated immune suppression inhibits the immune response to opportunistic infections (55). According to the WHO, it is estimated that the risk of developing TB infection is 26-31 times greater among those who are HIV-positive, compared to those who are HIV-negative (15). HIV is attributed to increased activation of TB disease in those with latent infection, and is associated with a quicker pace of disease progression than in those without HIV infection, which poses challenges to being able to diagnose early in disease development and opportunities for starting effective, early treatment (55). While HIV infection is associated with increased TB mortality, HIV status is also likely to be related to the type of health provider the patient sees to manage their disease therapy. According to a CDC report, 17% of HIV-

positive patients had documented private health insurance coverage, while 30% of HIV-positive patients were found not to have any source of health insurance coverage (56). Federally-funded programs, including Medicaid, Medicare and Ryan White Clinics, have historically provided a large volume of HIV health care to those without insurance, or those lacking sufficient coverage through their established plans (56, 57). As a significant burden of HIV infection has occurred in SPAs with higher levels of overall poverty in Los Angeles County, TB patients with HIV co-infection may be more likely receive some care from the health department due to issues of health care access and coverage (57).

Similarly, other comorbid conditions, including non-HIV-related immunosuppression, diabetes and renal disease have been shown to be associated with increased risk of mortality among patients with TB (32, 50, 54, 58). This is likely due to the impact of having comorbidities on the body's ability to fight and clear the infection, as well as potentially modifying the effectiveness and tolerance to TB treatment regimens, as the patient may also taking other therapies for their comorbid conditions (50, 54, 58) . Having chronic comorbid conditions are also likely correlated with the type of health provider the patient accesses for their TB case management. For example, a patient with end-stage renal disease at any age is eligible for health insurance coverage under Medicare, and most likely will access care outside the health department (59). Likewise, management of chronic comorbidities requires monitoring by a health provider, and these patients may require more acute care procedures and therefore

may be more likely to access private provider care in the hospital setting than a patient without comorbid conditions.

Provider type and TB mortality

Beyond factors related to the patient, a potential risk factor reported across various studies is TB supervision by a provider outside of the HD and overall outcomes for patients with TB. In particular, evaluating the effect of TB supervision from within or outside the HD on poor TB disease outcomes as well as intermediate indicators of therapy progress is important to inform both programmatic objectives in the HD and stimulate further evaluation practices by providers outside the HD. A retrospective case-control study utilizing TB surveillance data for the state of California from 2004-2008 found that, among culture-positive TB cases, primary supervision by a provider outside of the HD was an independent predictor for mortality with TB (aOR 3.08, 95% CI 2.75-3.44) (9). Likewise, Horne et al found that the odds of death was 5 times greater in those who were primarily treated by a provider outside the HD, compared to those who were supervised by providers within the HD (aOR 5.1, 95% 3.5-7.3) (6). In the Netherlands, a study conducted in the mid-1990's found a significant association between type of provider making the diagnosis and risk of mortality; compared to being diagnosed by a TB medical officer, all other types of providers (e.g. chest physician, specialist internal medicine, surgeon) had a statistically significant association with increased risk of mortality (35).

A major limitation of previous studies is that they did not adequately account for differences in general health status between TB patients receiving care at different provider types. This is important because less-healthy patients at baseline TB diagnosis may be more pre-disposed to poor TB outcomes. While previous studies controlled for many important potential confounders, such as primary location of TB disease, radiographic patterns, behavioral risk factors and demographics, they were not able to control for relevant common comorbidities (e.g. diabetes, ESRD, non-HIV immunosuppression) because of limitations of the surveillance data used for the studies. The inclusion of baseline comorbidity status can provide a more complete picture of the patient's health status at the time of TB diagnosis, and allow a more robust proxy measure for degree of general health status near the initiation of TB case management. LAC began routinely collecting common comorbidity status in the Tuberculosis Registry Information System (TRIMS) starting the year 2010, and these fields are available for inclusion in the multivariable model for this analysis.

Provider inexperience with recognition and diagnosis of TB is one mechanism proposed as an explanation for the observed association of worse outcomes for patients managed by providers outside of the HD. With the implementation of effective TB Control Programs around the country and subsequent decrease in incidence and prevalence, opportunities to manage TB cases are decreasing. A study conducted in Connecticut to estimate the frequency of "missed opportunities" for TB diagnosis and treatment among active cases found that 94% of patients with TB-related mortality had at least 1 "missed opportunity" identified (defined as a mistake, lapse or delay in diagnosis or treatment)

(60). However, the researchers did not perform an analysis with a control group of TB survivors, as chart review was only performed for those patients who expired. Likewise, among TB cases reported to the state of Maryland over a year and a half period, researchers found that patients who presented initially to a private provider (outside the HD) had significantly longer delays in health care, when compared to patients that first presented to either an emergency department or a HD (median 51 days, vs 18 or 10 days, respectively, $p < 0.05$) (61). Specifically, patients in the study had a median of 2.6 encounters with health providers prior to starting treatment for TB; those receiving an initial diagnosis that was not TB and were started on therapy for the non-TB diagnosis had longer duration of health delay (Relative Hazard Ratio analysis; less than 1 indicates delay, greater than 1 indicates faster than comparison group; RH 0.69, 95% CI 0.49-0.96) (61). Of note, patients who had some form of insurance experienced a longer health delay as well (RH 0.70, 95% 0.48-1.03) (61). Having insurance may be indicative of seeing a provider outside the HD, and therefore interfacing with providers less experienced with tuberculosis cases. However, this study utilized interviews with patients and families to assess explanatory factors for patient delay, and there were no families of deceased patients that agreed to participate. Therefore, the resulting estimates may have limited generalizability for patients who die after diagnosis with TB.

Delays in diagnosis and treatment initiation may have important impacts on TB patient outcomes. One component of provider delay, as related to a public health vs. private setting, is the volume of TB patients seen. A study conducted in the state of California demonstrated that the potential for missed opportunities for TB diagnosis and actual

hospital volume of TB cases was statistically significant and inversely related (rho -0.848, p = 0.0005); as TB case volume went up, the number of potential missed diagnoses decreased (62). This aligns with the notion that in a setting where providers have lower TB patient volume and less experience in TB identification and management, there exists potential for increased likelihood of missed or misdiagnoses in active TB patients.

In addition to possible increased delay in diagnosis among providers outside of the HD, the literature suggests that care by private providers may lead to increased likelihood of incomplete or inappropriate TB therapy regimens. A small retrospective review of culture-confirmed TB cases diagnosed in Baltimore found that of 128 TB patients, 15% had some error in their initial regimen, and 77% of those who had an error in assigned treatment was seen by a provider outside of the HD (10). While this study is suggestive of a higher rate of errors by private providers, the sample size was small, and an analysis of whether the association remained after controlling for potential confounders (e.g. concomitant comorbid conditions requiring therapy, tolerance, allergies) was not conducted. A study out of New Jersey showed similar results; after adjusting for relevant patient characteristics, private providers outside of the HD were found to be 4 to 5 times more likely to order less than 4 drugs for the initial TB treatment regimen, which is the standard care practice for active TB cases, when compared to providers at a public hospital with an established TB Control Clinic as the reference (8). By not starting the patient on an appropriate anti-TB drug regimen, patients are at increased

risk for developing not only more severe disease, but also may require more complicated and intensive anti-TB drug therapies as a result.

A possible consequence of inappropriate initial treatment regimen may lead to extended time to complete TB therapy, and impede treatment progress indicators such as culture conversion within 60 days, as recommended by the CDC's National TB Program Objectives and Performance Targets (18). Ehman et al found that, when evaluating adult, culture-positive pulmonary TB patients in California from 2007-2011, those managed by a private medical provider had 1.37 times risk of not having documentation of culture conversion within 60 days (95% CI 1.25-1.51), as well as a large magnitude of association with a patient not having documented as receiving Directly Observed Therapy (DOT) (aOR 8.56, 95% CI 6.59-11.1; among patient population for whom DOT is highly recommended by guidelines the aOR 6.46, 95% 4.61-9.06) (5). DOT, which is recommended by the CDC as standard practice, is important because it ensures adherence to TB therapy (and prevents the development of drug resistance), monitoring of side effects throughout the duration of therapy and promotes timely completion of treatment (63).

Understanding the effect of provider supervision and TB mortality is particularly relevant to the current political environment in the United States. As the country manages the implementation of the Affordable Care Act, shifts in healthcare coverage will significantly impact health care access, costs and utilization for millions of citizens. With an increase in the number of people gaining coverage in the private market, a subsequent increase

in the likelihood of a patient with TB to present initially to a primary care provider outside the HD may occur. As observed in studies conducted in a variety of health settings, the suggestion of increased delay in TB diagnosis and errors in TB treatment management by providers outside of the HD setting demonstrates the importance of understanding TB patient outcomes across public and private health delivery systems.

CHAPTER III: METHODS

Overall study design

To assess the effect of having TB treatment supervision by a health provider outside the HD (without any involvement by the HD) on the outcome of mortality, a retrospective cohort study examining the relative risk of all-cause mortality among patients with tuberculosis was conducted.

Primary data source

Data were extracted from the Tuberculosis Registry Information Management System (TRIMS). All suspected TB cases are reportable by California State law to the LAC TB Control Program within one business day. Standardized reporting forms completed by health professionals are entered directly into TRIMS. TRIMS, which is managed by the Los Angeles County Tuberculosis Program, contains patient data for all aspects of TB work-up and care management (e.g. demographics, initial reporting information, laboratory tests and results, treatment regimens, hospitalization records, overall case outcomes).

Study population

TB cases verified either by laboratory and/or clinical evidence of active TB, regardless of age, reported to Los Angeles Tuberculosis Control Program and managed under LAC jurisdiction between the January 1, 2010 and December 31, 2014 were eligible for inclusion. The date used to identify TB cases within the specified timeframe was the

date the patient was escalated from Class V TB suspect to Class III TB case. TB cases were defined by the California State TBCP guidelines for reporting. TB cases include those patients with isolation of *Mycobacterium tuberculosis* (M.tb) complex from a clinical specimen, finding of M.tb from a clinical specimen from Nucleic Acid Amplification Test (NAAT), finding of acid-fast bacilli (AFB) in a clinical specimen, or, when laboratory results are not available, satisfaction of all clinical indicators to meet the clinical case definition (evidence of positive TST or positive interferon gamma release assay, symptoms compatible with TB disease or clinical evidence of active disease, and treatment with at least 2 anti-TB drugs) (64).

All TB cases from 2010-2014 who were alive at time of diagnosis and have a start date for anti-TB therapy recorded were eligible (Figure 2). Patients were excluded if they had a TB case closure status of missing, pending or unknown (Figure 2). The patient cohort was further limited to those patients who have a record of starting treatment and a supervising provider type designated in TRIMS. Since estimates range from 60-75% of patients who die with TB die after starting treatment, this was the primary focal group for the multivariable analysis (9, 60, 65, 66). This also allowed for the patient to have had a provider assigned to manage their care, and thereby had been exposed to one of the supervising provider groups of interest.

Primary exposure definition

For the purpose of this analysis, the exposure of interest is the type of provider supervising TB treatment. This was defined as the provider who has primary

responsibility for TB-related clinical decision-making in the outpatient setting (64). Upon review of the entries in the "treatment" table in the TRIMS database (where fields for "Supervising Provider" is recorded), data were extracted for treatment forms where the patient was classified as a "Class III (TB Case)." All entries for supervising providers were reviewed. Patients who were solely managed by the HD or by the administrative office (e.g. jail or other institutional settings) for the duration of their TB case management were classified as "HD Provider." Administrative cases were classified as having a HD provider due to the primary oversight by the LAC TBCP. Patients who had "Private Medical Doctor" for all treatment records on file were classified as "Private provider, outside of the HD." This designation includes any provider outside of the HD (e.g. private medical doctors, providers at public or private hospitals, skilled nursing facilities, assisted living homes, outpatient medical offices in managed care settings, chest clinics). The term "private" does not indicate a public versus private health care setting, but rather that the provider was outside the realm of the HD. Therefore, supervision of TB treatment by providers in publicly funded facilities will be defined as "private" if there was no HD involvement in patient supervision. Patients who had a combination of supervising providers from both within and outside the HD on record were classified as "HD Provider," due to the assumption that having any involvement by the HD was assumed to have the benefit of comprehensive TB care at some point during their care, and indicative of strong linkages between care in the setting of their private health provider and the HD. It should also be noted that any entry for treatment received as an inpatient will be entered in TRIMS as "Private Provider," therefore the

decision was made to collapse those with a combination of care providers from within and outside the HD with the overall “HD” provider category.

Primary outcome definition

The primary outcome of interest was all-cause mortality among tuberculosis cases. Deaths are recorded based on the CDC definition, which is any death that occurs from the time of diagnosis until the time of successful completion of therapy (1). Specific cause of death is not available for this analysis; only data fields available from the TBCP surveillance database were used. Date of death is recorded in TRIMS and is the date that the case is considered closed.

Description of variables

Specific fields were extracted from the TRIMS database to assess patient demographics, clinical characteristics, health status and behavioral factors, and details about initial reporting of the case to TBCP at baseline (See Appendix, Table 5).

Ethics Statement

This analysis was conducted as part of Los Angeles County Department of Public Health Tuberculosis Control Program’s directive to collect and analyze surveillance data for public health purposes.

Statistical Analysis

All analysis was conducted using SAS Enterprise, version 7.1 (SAS Institute Inc., Cary, NC).

Descriptive statistics were used to illustrate patient demographics, disease characteristics, behavioral risk factors and comorbidities for the overall cohort. Continuous variables were described by mean/standard deviation or median/IRQ, according to the distribution. Categorical variables were described by count and percentage. Age, originally continuous, was binned at clinically and historically meaningful cut-points based background review of the literature and expert opinion.

Crude, overall patient demographics, risk factors and disease characteristics were examined using bivariate analysis. The outcome of interest was death during treatment. Crude risk ratios were estimated using modified Poisson regression with robust error variance (67). This regression approach was used because of a desire to estimate relative risks of all-cause mortality in the context of a cohort study. Due to convergence issues with the log binomial regression, the modified Poisson regression approach was selected. This was preferred over estimating odds ratio estimates with logistic regression because OR's are poor proxies for relative risk when the prevalence of the outcome is low, and the study design is appropriate for the direct estimation of relative risks (67). Relative risk estimation enhances the interpretability of the results and, with the additional adjustment for the very conservative confidence intervals that can result from a traditional Poisson regression, the modified approach yields more precise confidence intervals of estimated risk ratios (67).

The exposure variable of interest was indication of TB care management by the HD compared to sole supervision by a provider (or providers) outside of the HD. Using directed acyclic graph (DAG) theory, a model representing the relationship between provider supervision (exposure) to TB mortality (outcome) was constructed in order to guide selection of confounding variables for the final model (Figure 1) (68) Potential confounders, based on review of the literature and prior knowledge, were graphically depicted to understand potential implications and appropriateness of inclusion in the multivariable model. The following parameters measured near baseline TB diagnosis were selected (regardless of statistical significance in the bivariate analysis) to close biasing, backdoor pathways, while avoiding the introduction of collider stratification bias: age, sex, comorbidity composite variable (DM, ESRD, Immunosuppression, HIV), social and behavioral risk factor composite variable (homeless, tobacco smoking, excessive alcohol use, IV and non-IV drug use), disease severity characteristics (primary site of disease, radiographic cavitation, pulmonary/extra-pulmonary/both; culture positivity within 2 weeks of treatment start), history of prior TB, US or foreign born, anti-TB drug resistance, and primary reason for TB evaluation at baseline. In addition, as a proxy for both disease severity and overall health status of the patient, an indicator variable for inpatient care was included in the final model. This indicator variable was generated from the TRIMS treatment table based on outpatient care fields to identify those patients who received a predominance of their TB care as an inpatient (and minimal outpatient care). While there is a risk that this inpatient variable lies on the causal pathway from the exposure provider supervision to the outcome of TB mortality, the potential for bias

by including it is assumed to be outweighed by the bias that could affect the estimates if it were not included in the final model. The indicator of inpatient care provides a tool to control for potentially important differences in general health status that could pre-dispose a patient to worse TB outcomes, while also potentially impacting the supervision status of the patient's TB case management.

One additional model was fit to examine the change in estimate when early deaths were excluded. For purpose of this analysis, early deaths were defined as death within 30 days of diagnosis based on review of the literature (6, 27, 40)

CHAPTER IV: RESULTS

Overall, there were 3,226 laboratory and/or clinically confirmed cases of active TB reported to Los Angeles County Tuberculosis Control Program between January1, 2010 and December 31, 2014 (Figure 2). Of these, 21 cases (0.7%) have a pending case closure status, 40 cases (1.2%) were lost to follow-up and 60 cases (1.9%) moved out of LAC jurisdiction, and therefore were excluded from analysis since a determination of TB care outcome could not be ascertained. Furthermore, 59 cases (1.8%) were deceased at time of diagnosis, leaving 3,046 cases alive at diagnosis, and with a known treatment outcome entered in the TRIMS database during this time period.

Additional exclusion criteria were applied in order to subset a cohort of TB cases that were alive long enough to receive treatment and to receive the exposure of having a supervising treatment provider. Among those alive at time of diagnosis, 23 cases (0.7%) died before receiving treatment, 4 cases (0.01%) were recorded as expired post-completion of TB therapy, and 3 patients (0.01%) did not have a recorded start date for treatment.

In all, 3016 patient cases from the years 2010-2014 met final inclusion criteria for the retrospective cohort study (Figure 2). The majority of cases were male (n=1828, 60.6%), the mean age was just over 52 years old (standard deviation 21.4) with a range of 1 to 101 years old, and about 2/3 of cases reported between the ages of 15 and 64 years (Table 1 & Table 5). Asian race/ethnicity accounted for 40.4% of cases, and an

additional 45.1% of cases were Hispanic. Less than 5% (n=149) had a recorded history of previous active TB disease. At the time of diagnosis, 2.9% (n=87) of cases were living in a long term facility, and 2.1% (n=63) of cases were located at a correctional facility. Close to 70% of cases (n=2068) had a primary reason for TB evaluation recorded as due to having TB symptoms, and 1956 cases (64.9%) were first reported directly from a hospital, 480 cases (15.9%) from a private medical office and 299 (9.9%) from a public health clinic. Behavioral and social risk factors for TB were common; 8.3% of patients reported being a current smoker, 6.2% had a recent history of drug use, and 9.7% reported excessive alcohol use within the last year at time of diagnosis. Similarly, comorbid conditions were prevalent. Diabetes mellitus, including both type I and type II, was common and reported by 26.8% of cases (n=807). Immunosuppression, excluding HIV, was prevalent in 7.4% of cases (n=223), while 145 patients (4.8%) were known HIV-positive. Overall, 76.7% (n=2312) were classified at pulmonary only disease; 21.2% (n=639) were found to be extra-pulmonary, and 2.2% (n=65) were diagnosed with both pulmonary and extra-pulmonary disease. Only 62 patients (2.1%) were found to have miliary disease, while 560 patients (18.6%) had radiographic evidence of cavitary disease. Fifteen percent of cases (n=463) were found to have resistance to any of the first-line drugs; however, 20.1% (n=629) of cases did not have drug susceptibility test results available (either due to being culture negative or incomplete laboratory testing). Overall, 88.7% (n=2675) of cases completed treatment, and 9.4% of cases (n=283) expired before completion of therapy.

The majority of patients were supervised only by the HD and/or by TBCP administrative oversight (n=2156, 71.5%). Fewer patients were managed only by a private provider (n=580, 19.2%), and a smaller proportion was managed by a combination of providers within the HD and outside the HD (n=280, 9.3%).

Compared to patients who had any recorded involvement by the HD during treatment, patients who were managed solely by providers outside the HD tended to be elderly, and have a higher likelihood of being non-Hispanic White or Asian race/ethnicity (Table 1). Patients managed by private providers outside of the HD were more likely to be diagnosed while living in a long-term living facility (9.5% vs 1.3%), and more likely to have been evaluated for TB by means of an incidental lab result (e.g. incidental specimen positive for AFB or incidental culture positive for M.tb; when test conducted without suspicion of TB disease or not considered a possible diagnosis) (11.0% vs 4.9%). Privately supervised patients had higher percentage of extra-pulmonary only disease (32.4% vs 18.5%), significantly less likely to demonstrate radiographic evidence of cavitary disease (10.2% vs 20.6%), and higher likelihood of extra-pulmonary sites of TB disease such as TB involving the bone/joints or lymphatic system (8.6% vs 3.2%; 13.6% vs 9.6% respectively). Patients managed solely by non-HD providers were less likely to have sputum smear and sputum culture positivity from specimens within 2 weeks of treatment start date (sputum smear, 33.8% vs 47.3%; sputum culture 52.4% vs 63.7%, respectively); however, culture positivity from other non-sputum samples was higher in privately managed patients (50.0% vs 30.1%). In all, patients supervised by a private provider had higher burden of common comorbidities, as collected by TRIMS

(DM 32.9% vs 25.3%; ESRD 10.7% vs 3.6%; Immunosuppression 12.2% vs 6.2%, respectively).

Patients with sole supervision by provider(s) outside the HD had an unadjusted risk of all-cause mortality during TB treatment that was over 5 times the risk of mortality when compared to patients having a record of any HD involvement in the supervision of their tuberculosis treatment (crude risk ratio [cRR] 5.62, 95% CI 4.52-6.99). After adjusting for potentially confounding covariates selected a priori using background knowledge and directed acyclic graph theory (see: Figures 1. & 2.), the magnitude of the association was significantly reduced. The adjusted risk of all-cause mortality during TB treatment for patients managed solely by providers outside the HD was found to be 2.33 times the risk of all-cause mortality for patients who had a record of involvement by the HD in the supervision of their TB treatment (adjusted risk ratio [aRR] 2.33, 95% CI 1.80-3.01). Other factors independently associated with TB mortality include: increasing age, not having a history of prior TB, presence of common comorbidities (increasing from having one comorbidity to having 2 or more, compared to no reported common comorbidities), culture positivity at baseline diagnosis, being evaluated for TB due to TB symptoms or an incidental lab or abnormal CXR finding (compared to patients identified through routine screening/active case finding), and indication of inpatient care during TB treatment.

In addition, to evaluate the impact of patients who expired within 30 days from date of TB diagnosis, multivariable analysis was repeated with the exclusion of patients who

died early (within 30 days of diagnosis). The adjusted risk of all cause-mortality among patients who lived at least 30 days from diagnosis and who were solely supervised by providers outside the HD remained higher than the all-cause mortality among patients who had HD involvement in their TB treatment management (aRR 2.45, 95% CI 1.78-3.36).

CHAPTER V: DISCUSSION

Patients managed outside of the health department were found to be at a much higher risk of death during TB treatment when compared to patients supervised at any point of their care by the health department. After controlling for significant confounding variables, having no recorded supervision by the health department in a patient's TB treatment management was associated with 2.33 times higher risk of mortality after starting TB treatment, when compared to TB patients with any HD supervision. Previous studies cited earlier found effect sizes of higher magnitude (Pascopella: aOR 3.08, 95% CI 2.75-3.44; Horne: aOR 5.1, 95% CI 3.5-7.3), however it is important to note that OR estimates inflate the interpretation of relative risk (6, 9, 67). The ability to control for relevant comorbid conditions in this analysis may have captured baseline health status of the patient that was not accounted for in the earlier studies (6, 9).

Compared to the cRR of the association between provider supervision and TB mortality, the RR decreased significantly upon controlling for covariates postulated to lie on biasing pathways from provider supervision and TB mortality. The estimate decreased from 5.62 (cRR 95% CI 4.52-6.99) to 2.33 (95% CI 1.80-3.01), indicating that by including the confounding variables in the model (as decided a priori based on DAG theory), substantial bias was removed from the adjusted estimate.

After limiting the cohort to those patients who lived at least 30 days after diagnosis, the risk of death for those patients with no HD involvement remained elevated. It was

hypothesized that by removing early deaths, most likely to be hospitalized and categorized as not having involvement by the HD in their treatment supervision, the resulting estimate would decrease in the direction of the null. Interestingly, the effect estimate remained similar to the primary multivariable analysis that included deaths within 30 days of diagnosis. The finding that the estimate of effect did not change significantly is suggestive of an effect of provider supervision outside the HD to put a patient at a higher risk of death, since eliminating early deaths would have removed patients at high risk of death at baseline.

Due to the large magnitude of the effect estimate, it is unlikely that uncontrolled confounding could explain the entirety of the effect. The results of this analysis is supportive of the original hypothesis that, after controlling for baseline confounding variables, TB patients supervised solely outside the health department are at increased risk of mortality during TB treatment. The results of the secondary analysis further strengthens the case that, even among patients living longer than 30 days, patients managed outside the HD appear to remain at a significant increase risk of death with TB. This analysis was able to control for baseline comorbidities that previous studies were not, and the effect estimate remained large. However, since the crude estimate decreased substantially after the inclusion of baseline confounders, uncontrolled confounding may plausibly account for some of the magnitude of the effect found in both the primary multivariable analysis and the secondary analysis.

Significant differences in the age distribution of patients between exposure groups were apparent. Patients supervised solely by providers outside the HD were much more likely to be elderly, while patients supervised at any point by the HD tended to be younger. While age was controlled for in all models, it may not completely capture all potentially related biological aging processes. Similarly, with the imbalance in age, the risk of all-cause death increases as age increases. Since older patients were more likely to receive provider care outside of the HD, it is possible that this sub-population was less likely to be ambulatory, have other health conditions that could complicate initial TB diagnosis and treatment, and overall be at higher risk of death at the outset (35, 37, 48, 69). This could explain why the aRR did not change significantly with or without the inclusion of early deaths within 30 days of diagnosis; the potential outcomes among patients managed by providers outside of the HD may remain imbalanced compared to patients supervised by the HD due to the inability to fully control for general health status at baseline.

While standard comorbidity data were captured in the multivariable regression model, there may be significant conditions not captured by the fields available in TRIMS. Inflammatory conditions, such as systemic lupus erythematosus and rheumatoid arthritis, have been found to have significantly higher odds of being recorded on a death certificate that included TB as a cause of death, when compared to one of a matched subject without TB disease (53). In addition, malnutrition, anemia, cirrhosis, chronic heart disease, albumin levels and COPD have all been cited as independent clinical predictors of death with TB (32, 42, 70, 71). However, many of these studies were

conducted in a population of TB patients requiring inpatient care, and these fields were available by careful review of a patient's medical record. In fact, a study conducted among pulmonary TB patients requiring inpatient care found that after including anemia, dyspnea, heart disease and malignancy, as well as an indicator for care received in the intensive care unit, age above 65 years was not a statistically significant predictor of mortality (41). This lends weight to the idea that controlling for age may not necessarily capture the full picture of a patient's general health status, and those patients particularly weak or frail may be incompletely characterized by the limited comorbidity data available in TRIMS.

Another key component that may be amplifying the estimated effect of provider supervision outside the HD is the degree of TB disease severity at time of diagnosis. An attempt to control for TB disease severity near time of diagnosis was performed in this study by including whether the patient was symptomatic as the primary reason for evaluation for TB disease and whether the patient was culture positive (either by sputum or by another type of bio-specimen) within 2 weeks of treatment start, as this can be an indicator of infectiousness. Yet, these indicators may be incompletely capturing TB disease severity around the baseline TB diagnosis. Additional information such as duration from symptom onset to presentation, pneumonic patterns on the CXR, and potentially related hospitalizations or visits to the health provider where symptoms may have been suspicious of TB in hindsight but where a non-TB diagnosis was made prior to TB diagnosis would be informative.

In a similar vein, delays in health seeking behavior by the patient may be influencing the findings of increased risk of death among those patients primarily managed by providers outside the HD. Factors related to delay in seeking health services and TB mortality among TB cases has been found to be related to insurance status, socio-economic status, lack of support network (familial or friends), education level, and health literacy (26, 28, 72, 73). Unfortunately, insurance status and details about early pre-diagnosis patient encounters with the health system were not available. This is particularly pertinent to the current study, as this could impact both the ultimate linkages to TB care and the designated supervising provider type, and likewise be related to disease severity at time of diagnosis. Incomplete control of SES and early health seeking behavior by the patient may therefore be contributing some bias of the resulting estimate of the effect of provider supervision on mortality.

Nevertheless, while incomplete control of confounding factors may explain some of the magnitude, if there is in fact an increased risk of mortality due to the quality of provider care outside of the HD, it is imperative to tease out specific clinical practice patterns that could be related to increased risk of death between exposure groups. From the provider perspective, an evaluation of appropriateness of initial treatment regimens, administration of medication through directly observed therapy when indicated, and timely culture conversion could provide greater information about the potential mechanisms for the observed increased risk of mortality. An assessment of time to completion of therapy would be informative, both to demonstrate percent completing treatment within a year as recommended by the CDC and proportion of patients

requiring greater than a year to complete therapy. In addition, looking at procedures for the adjustment of treatment and appropriateness of the adjusted regimen when patients experience side effects would be useful. Similarly, understanding provider communication of the TB disease treatment plan and availability for consulting the patient should they have questions about their TB care could be helpful. Providers who have less experience managing TB cases may not provide the support services that a patient may need to manage their treatment and remain compliant; likewise, outpatient settings besides the HD may have less resources and manpower to provide comprehensive consultations for patients with active TB disease, and to ensure that patients are adherent with medication. More information about the patient's treatment course in the in-patient setting, whether they received all their TB care there or a portion of care could provide insight; similarly, understanding more about provider practice for TB patients in the institutional setting (e.g. skilled nursing facilities, assisted living) would help develop a more complete picture of potential gaps in practice or communication about care. There may be particular opportunities for greater collaboration between the HD and in-patient and institutional health care settings. Specifically, this could be particularly relevant for private institutions, as public hospitals in LAC are assigned a public health nurse liaison from the TBCP to assist in the care management of TB patients. Based on our findings, future research should examine provider practices and their effect on TB treatment outcomes.

Furthermore, by taking a step back and viewing TB care management from a health systems perspective, a closer look at time to treatment from first suspicion of active TB

and the linkages between health care providers (both in the public and private settings) is warranted. Understanding what is happening earlier along the TB care continuum for a patient may provide insight into additional avenues to improve screening practices, increase alert to TB disease and in turn decrease time to initiating anti-TB therapy for patients with active disease.

It is important to acknowledge limitations of the current study. The exposure categorization was a coarse rendering of the patterns of treatment supervision experienced by the patient cohort. The data field used in this study provided insight as to whether or not the provider was from within the HD or not. The field that would have been preferable to use was the "current supervision" field, which captures the specific location of the provider and health care setting. However, due to the level of missing-ness, this was not possible. Using an arguably rough categorization of provider supervision type may obscure key differences in practice patterns at a more granular level (such as by specific institution, public vs private setting, etc.). Additionally, the lack of dates associated with provider involvement in TRIMS created a challenge to understand what proportion of treatment time could be attributed to a specific provider for patients with a change in provider supervision. Capturing whether a patient moved and had a change of supervision within LAC was not taken into account in this analysis.

Another potential limitation is the patient cohort for analysis was restricted to patients with a known case closure status. Those patients who moved, were lost to follow-up or pending case closure were excluded; while it may be that these patients are more

complicated or unique in some potentially relevant way, because they did not have a closure entered in TRIMS they were removed from the cohort due to incomplete outcome information (n=121/3226, 3.8%). Patients who had an outcome other than completion of treatment or death (n=58/3016, 1.9%) were assumed to have survived; these outcomes included adverse treatment event, refused treatment, and closure status of "other." It was postulated that refusing treatment or having an adverse treatment event may be related to the type of provider supervising treatment, and therefore it was decided to allow this subset of patients to contribute to the multivariable analysis.

This study did not address specific health care practices or intermediate TB indicators (e.g. culture conversion at 60 days) by providers supervising TB treatment. The study is designed to test for the presence and magnitude of the overall effect of having a provider from outside the health department supervise a patient's TB therapy course. Further, more in-depth review of patient medical records would be necessary in order to address whether there is a difference in actual provider practices from within vs. outside the HD.

Lastly, death with TB does not translate to death due to TB. Based on the CDC definition, all deaths that occur after a patient is diagnosed with TB and before they complete (or start) TB treatment is considered a TB death. Therefore, this includes patients that may have died from an unrelated cause. However, the literature has asserted that anywhere from 50-85% of TB deaths are related to the eventual cause of death (29, 47, 60, 71).

The implication of increased risk of death in patients solely supervised outside of the HD has important implications for public health practice. While TB is on the decline, it has not been eliminated and remains a significant contributor of morbidity and mortality in the United States. In particular, the burden of disease disproportionately impacts those born outside the United States, and those with behavioral, social and chronic comorbid risk factors. In the era of the ACA, with a likely influx of previously uninsured patients into the private market, the continued promotion of coordinated of public-private health efforts for conditions like TB that have historically been managed by federally-funded public health programs is imperative.

In summary, patients with TB treatment supervision solely outside of the HD were found to be at over twice the risk of mortality during TB treatment. Similar results were found even after exclusion of deaths within 30 days of TB diagnosis. Recommendations for further study include in-depth examination of specific TB treatment practices by providers outside of the HD. If gaps in care and treatment practices are apparent, there may be a need to improve health provider education about appropriate anti-TB treatment regimens, increase awareness of the epidemiology of TB mortality, and fortify the process for coordinating care between the HD and providers outside the HD. If there is an adverse effect of supervision by providers outside the HD on TB mortality, it begs the question of mandating greater oversight by the HD in all TB case management. Based on findings from this study, additional resources may be needed to support expanded HD oversight of TB case management. Despite waning momentum for TB Control as incidence and prevalence declines, in combination with increasing patients likely to receive care in the

private setting with the ACA, it is imperative that directed efforts to understand treatment practices remain a high priority to ensure robust TB treatment management and improved health outcomes for TB patients.

APPENDICES

Figure 1. Health Provider Supervision and TB Mortality, DAG.

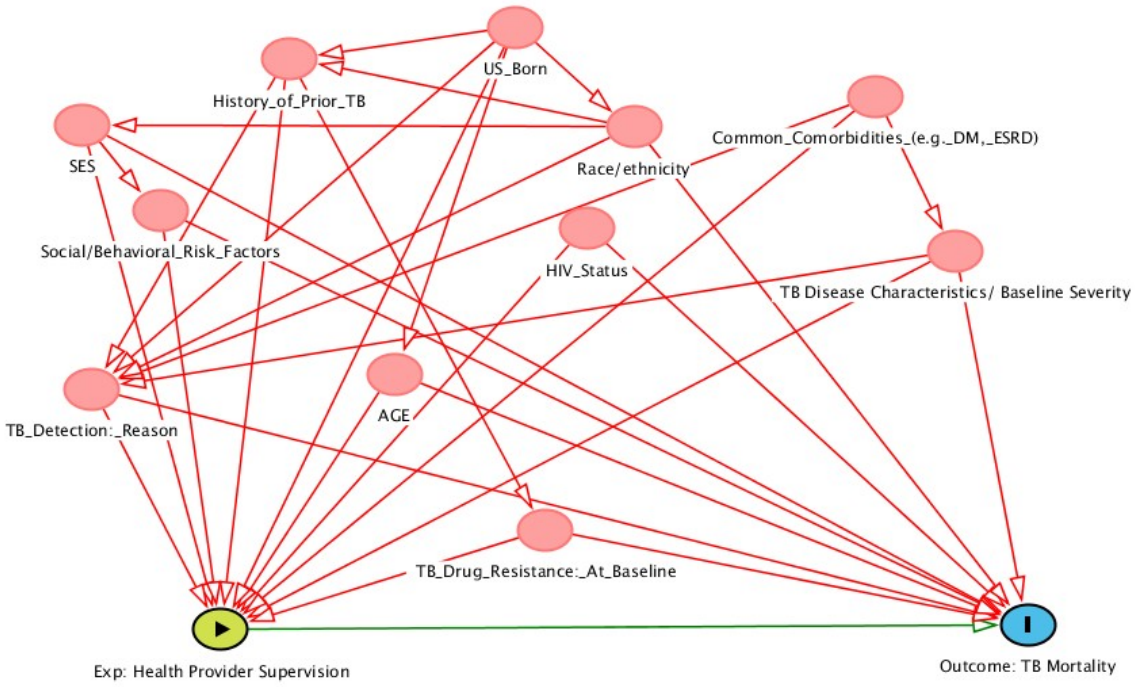

Figure 3. TB Cases Reported to Los Angeles County, 2010-2014.

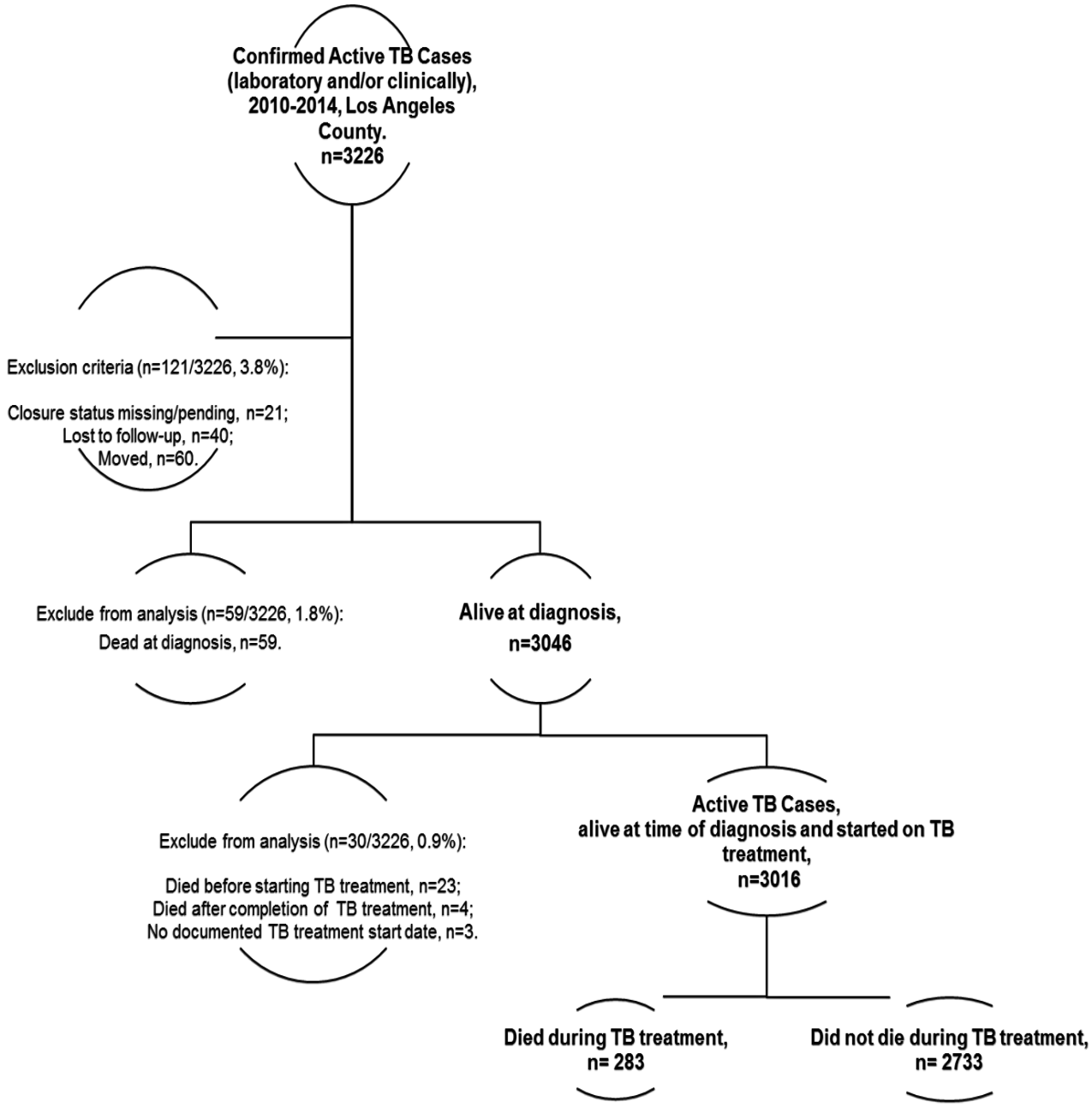

Table 1. Characteristics of TB cases by Supervising Provider, Los Angeles County 2010-2014.

	Overall[1]		Supervising Provider: Any Health Department Involvement		Supervising Provider: Private Provider Only, No HD Involvement	
	N	(Col %)	N	(Col %)	N	(Col %)
Total	3016	(100.0%)	2436	(100.0%)	580	(100.0%)
DEMOGRAPHICS						
Male	1828	(60.6%)	1519	(62.4%)	309	(53.3%)
Age (years)						
0-4 years	74	(2.5%)	66	(2.7%)	8	(1.4%)
5-14 years	47	(1.6%)	41	(1.7%)	6	(1.0%)
15-34 years	547	(18.1%)	496	(20.4%)	51	(8.8%)
35-54 years	898	(29.8%)	776	(31.9%)	122	(21.0%)
55-64 years	533	(17.7%)	445	(18.3%)	88	(15.2%)
65-74 years	402	(13.3%)	294	(12.1%)	108	(18.6%)
75-84 years	316	(10.5%)	213	(8.7%)	103	(17.8%)
85+ years	199	(6.6%)	105	(4.3%)	94	(16.2%)
Race/Ethnicity						
Non-Hispanic White	180	(6.0%)	115	(4.7%)	65	(11.2%)
Hispanic	1360	(45.1%)	1195	(49.1%)	165	(28.4%)
African American	259	(8.6%)	215	(8.8%)	44	(7.6%)
Asian	1217	(40.4%)	911	(37.4%)	306	(52.8%)
US Born	616	(20.4%)	508	(20.9%)	108	(18.6%)
History of Previous TB	149	(4.9%)	123	(5.0%)	26	(4.5%)
Primary Reason for Evaluating Patient for TB						
TB Symptoms	2068	(68.6%)	1677	(68.8%)	391	(67.4%)
Incidental Finding (CXR, lab result)	725	(24.0%)	548	(22.5%)	177	(30.5%)
Active case finding/routine screening	203	(6.7%)	192	(7.9%)	11	(1.9%)
SOCIAL & BEHAVIORAL RISK FACTORS						
Homeless within last year	214	(7.1%)	198	(8.1%)	16	(2.8%)
Drug abuse (IV, non-IV)	187	(6.2%)	174	(7.1%)	13	(2.2%)
Excessive Alcohol Use	292	(9.7%)	266	(10.9%)	26	(4.5%)
Smoking Status: Current	249	(8.3%)	226	(9.3%)	23	(4.0%)
COMMON COMORBIDITY STATUS						
End-Stage Renal Disease	149	(4.9%)	87	(3.6%)	62	(10.7%)
Diabetes Mellitus	807	(26.8%)	616	(25.3%)	191	(32.9%)
Non-HIV Immunosuppression	223	(7.4%)	152	(6.2%)	71	(12.2%)
HIV Status						
Known Positive	145	(4.8%)	131	(5.4%)	14	(2.4%)
Known Negative	2625	(87.0%)	2204	(90.5%)	421	(72.6%)
Not done/Unknown result	167	(5.5%)	75	(3.1%)	92	(15.9%)
Refused	79	(2.6%)	26	(1.1%)	53	(9.1%)
DISEASE CHARACTERISTICS AT BASELINE						
Disease characteristics: site, cavitation						
Pulmonary only and cavitary	558	(18.5%)	499	(20.5%)	59	(10.2%)
Pulmonary only, not cavitary	1754	(58.2%)	1433	(58.8%)	321	(55.3%)
Pulmonary and EP	65	(2.2%)	53	(2.2%)	12	(2.1%)
EP only	639	(21.2%)	451	(18.5%)	188	(32.4%)
Sputum Culture Positive	1856	(61.5%)	1552	(63.7%)	304	(52.4%)
Smear Positive	1348	(44.7%)	1152	(47.3%)	196	(33.8%)
Other Culture Positive	1024	(34.0%)	734	(30.1%)	290	(50.0%)
Greater than one site of disease	379	(12.6%)	307	(12.6%)	72	(12.4%)
ANTI-TB DRUG RESISTANCE AT BASELINE						
Resistant to any first-line drugs (RIPE)	463	(15.4%)	364	(14.9%)	99	(17.1%)
Monodrug resistance: INH	105	(3.5%)	81	(3.3%)	24	(4.1%)
Monodrug resistance: RIF	2	(0.1%)	1	(0.0%)	1	(0.2%)
Monodrug resistance: PZA	122	(4.0%)	93	(3.8%)	29	(5.0%)
Multi-drug resistant TB	31	(1.0%)	29	(1.2%)	2	(0.3%)
TB TREATMENT CHARACTERISTICS						
Received Directly Observed Therapy						
DOT only	1717	(56.9%)	1495	(61.4%)	222	(38.3%)
DOT and SAT	949	(31.5%)	877	(36.0%)	72	(12.4%)
SAT only	349	(11.6%)	63	(2.6%)	286	(49.3%)

[1] Percentages may not sum to 100% due to missing data.

Table 2. Supervising provider type and risk of all-cause mortality, TB cases alive at diagnosis, LAC, 2010-2014.

Characteristic	Died[1] N= 283/3016 (9.4) Died/N (%)		Crude Risk Ratio (cRR)		Adjusted Risk Ratio (aRR)[7]	
	n/N	%	cRR	95% CL	aRR	95% CL
Sex						
Female	93/1188	(7.8)	1.00	--	1.00	--
Male	190/1828	(10.4)	1.33	(1.05-1.68)	1.20	(0.96 - 1.50)
Age (years)						
Less than 35 years	8/668	(1.2)	1.00	--	1.00	--
35-54 years	41/898	(4.6)	3.81	(1.80-8.08)	2.59	(1.25, 5.38)
55-64 years	45/533	(8.4)	7.05	(3.35-14.83)	3.59	(1.72-7.49)
65-74 years	50/402	(12.4)	10.39	(4.97-21.68)	4.67	(2.26-9.64)
75+	139/515	(27.0)	22.54	(11.15-45.53)	6.84	(3.34-14.02)
Race/Ethnicity						
Hispanic	95/1360	(7.0)	1.00	--	1.00	--
African American	18/259	(7.0)	0.99	(0.61-1.62)	0.89	(0.53-1.49)
Asian	143/1217	(11.8)	1.68	(1.31-2.15)	1.04	(0.82-1.32)
Non-Hispanic White	27/180	(15.0)	2.15	(1.44-3.20)	1.24	(0.85-1.80)
US Born						
Yes	43/616	(7.0)	0.70	(0.51-0.95)	0.95	(0.67-1.34)
No	240/2398	(10.0)	1.00	--	1.00	--
History of Previous TB[2]						
Yes	7/149	(4.7)	0.49	(0.24-1.02)	0.38	(0.20-0.71)
No	274/2867	(9.6)	1.00	--	1.00	--
Social/Behavioral Risk Factors[3]						
No behavioral risk factors	242/2528	(9.6)	1.00	--	1.00	--
One behavioral risk factor	33/405	(8.2)	0.84	(0.60-1.20)	1.27	(0.91-1.77)
2 or more behavioral risk factors	20/226	(8.9)	0.92	(0.59-1.42)	1.45	(0.92-2.28)
Common Comborbidity[4]						
No common comorbidity	102/1878	(5.4)	1.00	--	1.00	--
One common comorbidity	125/968	(12.9)	2.38	(1.85-3.05)	1.36	(1.08-1.71)
2 of more common comorbidities	56/170	(32.9)	6.07	(4.56-8.07)	2.29	(1.71-3.08)
Disease Site and Cavitary Status						
Pulmonary only, no cavitary disease	204/1754	(11.6)	1.00	--	1.00	--
Pulmonary only, cavitary disease	32/558	(5.9)	0.49	(0.34-0.71)	0.74	(0.53-1.04)
Extra-pulmonary only	39/639	(6.1)	0.52	(0.38-0.73)	0.70	(0.52, 0.94)
Extra-pulmonary and pulmonary disease	8/65	(12.3)	1.06	(0.55-2.05)	0.78	(0.45-1.34)
Culture Positive at Basline[5]						
Yes	269/2410	(11.2)	4.83	(2.84-8.21)	1.96	(1.24-3.11)
No	14/606)	(2.3)	1.00	--	1.00	--
Primary Reason for TB Evaluation						
TB Symptoms	197/2068	(9.5)	19.34	(2.72-137.24)	8.15	(1.46-45.48)
Incidental finding (e.g. CXR, lab result)	83/725	(11.5)	23.24	(3.26-165.91)	8.34	(1.49-46.79)
Active case finding/Routine screening	1/203	(0.5)	1.00	--	1.00	--
At least 2 disease locations[6]						
Yes	50/379	(13.2)	1.49	(1.12-1.99)	1.19	(0.89-1.59)
No	233/2637	(8.8)	1.00	--	1.00	--
Inpatient Care						
Yes	133/238	(55.9)	10.35	(8.54-12.54)	3.74	(2.94-4.75)
No	150/2778	(5.4)	1.00	--	1.00	--
MDR TB						
Yes	2/31	(6.5)	0.69	(0.18-2.66)	1.49	(0.46-4.85)
No	276/2962	(9.3)	1.00	--	1.00	--
Supervision Type						
Health department involvement	121/2436	(5.0)	1.00	--	1.00	--
Provider outside of HD only	**162/580**	**(27.9)**	**5.62**	**(4.52-6.99)**	**2.33**	**(1.80-3.01)**

[1] Analysis limited to alive at diagnosis, started treatment

[2] History of previous TB determined by patient self-report

[3] Composite variable includes: IV drug use, non-IV drug use, excessive alcohol use, current smoker at diagnosis, homelessness

[4] Composite variable includes: Renal disease, diabetes, HIV, and non-HIV immunosuppression.

[5] Any positive culture result within 2 weeks of treatment start date.

[6] Greater than 1 anatomical region indicated in TRIMS

[7] Statistical method: Risk ratios estimated using modified Poisson regression, with robust error variances.

Table 3. Alternative model: Supervising provider type and risk of all-cause mortality, TB cases alive at diagnosis and survived at least 30 days from date of TB diagnosis, LAC, 2010-2014.

Characteristic	Died[1] N= 283/3016 (9.4) Died/N (%)		Crude Risk Ratio (cRR)		Adjusted Risk Ratio (aRR)[2]	
	n/N	%	cRR	95% CI	aRR	95% CI
Alternative Model.[3]						
Survived at least 30 days post-TB diagnosis						
Mortality for overall cohort						
Died within 30 days of diagnosis	173/2906	(5.6)				
Died after 30 days of diagnosis	107/2840	(3.8)				
Supervision Type						
Health department involvement	121/2436	(5.0)	1.00	--	1.00	--
Provider outside of HD only	**162/580**	**(27.9)**	**5.62**	**(4.52-6.99)**	**2.45**	**(1.78-3.36)**

[1] Analysis limited to alive at diagnosis, started treatment and lived at least 30 days.

[2] Statistical method: Risk ratios estimated using modified Poisson regression, with robust error variances.

[3]Controlled for same covariates as final model, but adjusted parameterization of variables.

Table4. Baseline Patient Characteristics, TB cases alive at diagnosis and started treatment, LAC, 2010-2014.

	Overall		Supervising Provider			
			Any Health Department Involvement		Private Provider Only, outside health department	
	N	(col %)	N	(col %)	N	(col %)
Total	3016	(100.0%)	2436	(100.0%)	580	(100.0%)
Source of Initial Report of Suspected TB						
Hospital	1956	(64.9%)	1532	(62.9%)	424	(73.1%)
PMD	480	(15.9%)	378	(15.5%)	102	(17.6%)
PHC	299	(9.9%)	268	(11.0%)	31	(5.3%)
Lab	117	(3.9%)	110	(4.5%)	7	(1.2%)
Correctional	30	(1.0%)	27	(1.1%)	3	(0.5%)
Other	100	(3.3%)	90	(3.7%)	10	(1.7%)
Report Source: Public Institution	1283	(42.5%)	1217	(50.0%)	66	(11.4%)
Primary Reason for TB Evaluation						
Abnormal CXR	542	(18.0%)	429	(17.6%)	113	(19.5%)
Contact Investigation	87	(2.9%)	83	(3.4%)	4	(0.7%)
Employment/Administrative Testing	14	(0.5%)	10	(0.4%)	4	(0.7%)
Health Care Worker	5	(0.2%)	4	(0.2%)	1	(0.2%)
Immigration Medical Exam	68	(2.3%)	68	(2.8%)	0	(0.0%)
Incidental Lab Result	183	(6.1%)	119	(4.9%)	64	(11.0%)
TB Symptoms	2068	(68.6%)	1677	(68.8%)	391	(67.4%)
Targeted Testing (Other)	27	(0.9%)	25	(1.0%)	2	(0.3%)
Completion of TB Treatment	2675	(88.7%)	2270	(93.2%)	405	(69.8%)
Long-term facility at time of diagnosis	87	(2.9%)	32	(1.3%)	55	(9.5%)
Correctional facility at time of diagnosis	63	(2.1%)	55	(2.3%)	8	(1.4%)

[1] Percentages may not sum to 100% due to missing data.

Table5. Continuous descriptive statistics, TB cases alive at diagnosis and started treatment, LAC, 2010-2014.

	Overall						Supervising Provider											
							Any Health Department Involvement						Private Provider Supervision Only, Outside HD					
	N	Mean	StdDev	Median	Min	Max	N	Mean	StdDev	Median	Min	Max	N	Mean	StdDev	Median	Min	Max
Age	3016	52.5	21.4	54	1	101	2436	50	20.8	51	1	101	580	62.8	21.2	66	2	101
Days, diagnosis to death	283	80.5	90	48	0	468	121	110.9	97.5	74	1	421	162	57.8	76.8	34	0	468

Table 6. Description of covariates abstracted from TRIMS database.

Variable	Type	Description	Additional notes
Age	Continuous	At time of diagnosis	Binned for multivariable analysis
Sex	Categorical; Male, Female, no data	At time of diagnosis	
Race/ethnicity	Categorical; Non-Hispanic White, Hispanic, Asian, African American.	Of the patient	Due to small sample size, Native Hawaiian/Alaska Native was collapsed within the Asian category.
US Born	Categorical; Yes, No, Unknown.	Was the patient born in the United States	
History of previous tuberculosis disease	Categorical: Yes, No, Unknown	Previous tuberculosis diagnosis, based on self-report by patient	
Report Source: Public	Categorical: Yes, No, Missing/Unknown.	The health facility that first discovered the patient as a TB suspect. In TRIMS, entered as a specific location (e.g. hospital, clinic, lab)	Recoded as: Public or private institution based on established list available from the County codebook
Report Source: Type	Categorical: Hospital, Private Medical Doctor (PMD), Public Health Clinic (PHC), Lab, Correctional, Other, Missing	The health facility that first discovered the patient as a TB suspect. In TRIMS, entered as a specific location (e.g. hospital, clinic, lab)	
Primary Reason	Categorical: 3-levels; TB Symptoms, Incidental Finding, Active case finding/routine targeted screening	Primary reason the patient was evaluated for TB disease	Raw categories extracted from TRIMS were collapsed accordingly: TB Symptoms (Includes TRIMS categories: TB Symptoms) Incidental finding (Includes TRIMS categories: Abnormal CXR, Incidental Lab Result) Routine targeted screening (Includes TRIMS categories: Employment/Administrative Testing Immigration Medical Exam, Targeted Testing (Other), Targeted Testing (Shelter Referral), Contact Investigation, Health Care Worker)
Long-term care facility	Binary indicator variable; if LT-facility recorded at diagnosis	Did the patient reside in a long-term care facility at time of TB diagnosis	Raw TRIMS Categories: Alcohol/Drug, Hospital-Based, Mental Health, No Data, None, Nursing Home, Other, Residential
Correctional facility	Binary indicator variable created if correctional facility recorded at diagnosis	Did the patient reside in a correctional facility at time of TB diagnosis	Raw TRIMS Categories: Federal Prison, Juvenile, Local Jail, No Data, None, Other, State Prison
Social and Behavioral Risk Factors	Binary: Yes, No	Within the last year, at time of diagnosis. Patient self-report.	Factors: Homeless, Injecting Drug Use, Non-Injecting Drug Use, Excessive Alcohol
Current Smoker	Binary: Yes, No	Smoking status at time of diagnosis	Self-report by patient
End-stage renal disease	Binary: Yes, No	Patient has chronic renal failure or end stage renal disease (ESRD)	
Diabetes Mellitus	Binary: Yes, No	Patient has a diagnosis of diabetes mellitus (I or II) either before or at the time of TB diagnosis.	Diabetes may either be controlled by diet or medication.
Immunosuppression	Binary: Yes, No	Patient has immunosuppression due to either a medical condition or medication (e.g. leukemia, Hodgkin's lymphoma, carcinoma of the head or neck), or immunosuppressive therapy, such as the prolonged use of high dose adrenocorticosteroids (e.g. prednisone).	Not HIV/AIDS or Diabetes or ESRD

Variable	Type	Description	Additional notes
HIV Status	Categorical: Negative, No Data, Not Done, Positive, Refused, Pending, Indeterminate.	The HIV status of the patient	
Site of TB Disease	Categorical: Pulmonary only, extra-pulmonary only, pulmonary and extra-pulmonary.		Pulmonary is defined strictly as pulmonary only, excluding pleural and laryngeal.
Cavitary disease	Binary: Yes, No	Any initial chest radiograph showing abnormalities consistent with TB and marked as cavitary.	Based on results of initial CXR only. Does not include CT results.
Miliary disease	Binary: Yes, No	Any initial chest radiograph showing abnormalities consistent with TB and marked as miliary.	Based on results of initial CXR only. Does not include CT results.
Culture positive (any)	Binary: Yes, No	Based on results from sputum smear, sputum culture, or other type of culture within 2 weeks of start of treatment, if date is available	Provides an indicator of disease severity and degree of infectiousness near baseline time of diagnosis
Sputum Smear Positive	Binary: Yes, No	Smear and Sputum Culture positivity are based on "Sputum" "Direct Sputum" specimens. Based on RVCT definitions.	Smear and Culture information from within 2 weeks of treatment start date.
Sputum Culture Positive	Binary: Yes, No	Smear and Sputum Culture positivity are based on "Sputum" "Direct Sputum" specimens. Based on RVCT definitions.	Smear and Culture information from within 2 weeks of treatment start date.
Extra-pulmonary sites of disease	Binary: Yes, No	Sites: Meningeal, pleural, laryngeal, bone/joint, genitourinary, peritoneal, lymphatic involvement (any)	Composite variable created to capture patients with greater than one site of disease on record (including Pulmonary)
Drug susceptibility testing (DST)	Categorical: Complete DST, does not have complete DST, NA/Culture negative	Complete DST defined as results for INH, RIF, EMB	
Anti-TB drug resistance	Binary indicator variables; Yes, No	Resistance variables based on DST results: • Monodrug resistance • Polydrug resistance • Resistance to first-line TB drugs (RIPE) • MDR	MDR: Defined by CDC; resistance to at least INH and RIF (CDC). Includes those who are MDR only, pre-XRD, and XDR.
Directly observed therapy	Categorical; only directly observed therapy, a combination of directly observed therapy and self-administered therapy, self-administered therapy only, or NA	Did the patient receive directly observed therapy during their treatment course	For analysis, binary indicator variable for any DOT received during treatment course.
Inpatient Care	Binary: Yes, No	Record of inpatient care only during course of treatment	Based on final treatment table entry for patient in TRIMS

REFERENCES

1. CDC. Tuberculosis: Data and Statistics. In; 2015.

2. CDC. Reported Tuberculosis in the United States, 2014. Atlanta: CDC; 2015 October 2015.

3. World Health Organization. Towards tuberculosis elimination: an action framework for low-incidence countries. Geneva; 2014.

4. Balaban V, Marks SM, Etkind SC, Katz DJ, Higashi J, Flood J, et al. Tuberculosis Elimination Efforts in the United States in the Era of Insurance Expansion and the Affordable Care Act. Public health reports 2015;130(4):349-54.

5. Ehman M, Flood J, Barry PM. Tuberculosis treatment managed by providers outside the Public Health Department: lessons for the Affordable Care Act. PloS one 2014;9(10):e110645.

6. Horne DJ, Hubbard R, Narita M, Exarchos A, Park DR, Goss CH. Factors associated with mortality in patients with tuberculosis. BMC infectious diseases 2010;10:258.

7. Kiwuwa MS, Charles K, Harriet MK. Patient and health service delay in pulmonary tuberculosis patients attending a referral hospital: a cross-sectional study. BMC public health 2005;5:122.

8. Liu Z, Shilkret KL, Finelli L. Initial drug regimens for the treatment of tuberculosis: evaluation of physician prescribing practices in New Jersey, 1994 to 1995. Chest 1998;113(6):1446-51.

9. Pascopella L, Barry PM, Flood J, DeRiemer K. Death with tuberculosis in california, 1994-2008. Open forum infectious diseases 2014;1(3):ofu090.

10. Rao SN, Mookerjee AL, Obasanjo OO, Chaisson RE. Errors in the treatment of tuberculosis in Baltimore. Chest 2000;117(3):734-7.

11. Blumenthal D, Abrams M, Nuzum R. The Affordable Care Act at 5 Years. The New England journal of medicine 2015;373(16):1580.

12. Barnes RF, Moore ML, Garfein RS, Brodine S, Strathdee SA, Rodwell TC. Trends in mortality of tuberculosis patients in the United States: the long-term perspective. Annals of epidemiology 2011;21(10):791-5.

13. Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and after tuberculosis treatment. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2011;15(7):871-85.

14. World Health Organization. Global Health Observatory (GHO) data: How many TB cases and deaths are there? In.

15. World Health Organization. HIV/AIDS: Tuberculosis and HIV. In; 2016.

16. World Health Organization. The top 10 causes of death: Major causes of death. In; 2016.

17. World Health Organization. World Tuberculosis Report 2015: WHO; 2015.

18. CDC. National TB Program Objectives & Performance Targets for 2020. In: National Center for HIV/AIDS VH, STD, and TB Prevention, editor.; 2015.

19. Tuberculosis Control Branch. Report on Tuberculosis in California, 2014. Richmond; 2014 August 2015.

20. Tuberculosis Control Branch. TB Fact Sheet 2015: TB in California - A Snapshot. Richmond: California Department of Public Health; 2015 March 24, 2016.

21. Tuberculosis Control Branch. TBCB TB Provisional Annual Report 2015. Richmond: California Department of Public Health; 2015.

22. Los Angeles County Department of Public Health. Community Health Assessment 2015. Los Angeles; 2015.

23. Los Angeles County Department of Public Health. Los Angeles County Population Estimates. In. Los Angeles; 2015.

24. Tuberculosis Control Program. About Us. In. Los Angeles; 2016.

25. Los Angeles County Department of Public Health. Mortality in Los Angeles County 2011: Leading causes of death and premature death with trends for 2002-2011; 2014 August 2014.

26. Demissie M, Lindtjorn B, Berhane Y. Patient and health service delay in the diagnosis of pulmonary tuberculosis in Ethiopia. BMC public health 2002;2:23.

27. Feng JY, Su WJ, Chiu YC, Huang SF, Lin YY, Huang RM, et al. Initial presentations predict mortality in pulmonary tuberculosis patients--a prospective observational study. PloS one 2011;6(9):e23715.

28. Najera-Ortiz JC, Sanchez-Perez HJ, Ochoa-Diaz H, Arana-Cedeno M, Lezama MS, Mateo MM. Demographic, health services and socio-economic factors associated with pulmonary tuberculosis mortality in Los Altos Region of Chiapas, Mexico. International journal of epidemiology 2008;37(4):786-95.

29. Shen X, Deriemer K, Yuan Z, Shen M, Xia Z, Gui X, et al. Deaths among tuberculosis cases in Shanghai, China: who is at risk? BMC infectious diseases 2009;9:95.

30. Sterling TR, Zhao Z, Khan A, Chaisson RE, Schluger N, Mangura B, et al. Mortality in a large tuberculosis treatment trial: modifiable and non-modifiable risk factors. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2006;10(5):542-9.

31. Zahar JR, Azoulay E, Klement E, De Lassence A, Lucet JC, Regnier B, et al. Delayed treatment contributes to mortality in ICU patients with severe active pulmonary tuberculosis and acute respiratory failure. Intensive care medicine 2001;27(3):513-20.

32. Alavi-Naini R, Moghtaderi A, Metanat M, Mohammadi M, Zabetian M. Factors associated with mortality in tuberculosis patients. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences 2013;18(1):52-5.

33. Kourbatova EV, Borodulin BE, Borodulina EA, del Rio C, Blumberg HM, Leonard MK, Jr. Risk factors for mortality among adult patients with newly diagnosed tuberculosis in Samara, Russia. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2006;10(11):1224-30.

34. Xu X, Liu JH, Cao SY, Zhao Y, Dong XX, Liang Y, et al. Delays in care seeking, diagnosis and treatment among pulmonary tuberculosis patients in Shenzhen, China. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2013;17(5):615-20.

35. Borgdorff MW, Veen J, Kalisvaart NA, Nagelkerke N. Mortality among tuberculosis patients in The Netherlands in the period 1993-1995. The European respiratory journal 1998;11(4):816-20.
36. Gadkowski LB, Stout JE. Cavitary pulmonary disease. Clinical microbiology reviews 2008;21(2):305-33, table of contents.

37. Liaw YS, Yang PC, Yu CJ, Wu ZG, Chang DB, Lee LN, et al. Clinical spectrum of tuberculosis in older patients. Journal of the American Geriatrics Society 1995;43(3):256-60.

38. Lin HP, Deng CY, Chou P. Diagnosis and treatment delay among pulmonary tuberculosis patients identified using the Taiwan reporting enquiry system, 2002-2006. BMC public health 2009;9:55.

39. Shafer RW, Bloch AB, Larkin C, Vasudavan V, Seligman S, Dehovitz JD, et al. Predictors of survival in HIV-infected tuberculosis patients. AIDS 1996;10(3):269-72.

40. Kim HJ, Lee CH, Shin S, Lee JH, Kim YW, Chung HS, et al. The impact of nutritional deficit on mortality of in-patients with pulmonary tuberculosis. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2010;14(1):79-85.

41. Kwon YS, Kim YH, Song JU, Jeon K, Song J, Ryu YJ, et al. Risk factors for death during pulmonary tuberculosis treatment in Korea: a multicenter retrospective cohort study. Journal of Korean medical science 2014;29(9):1226-31.

42. Lin CH, Lin CJ, Kuo YW, Wang JY, Hsu CL, Chen JM, et al. Tuberculosis mortality: patient characteristics and causes. BMC infectious diseases 2014;14:5.

43. Liu YC, Lin HH, Chen YS, Su IJ, Huang TS, Tsai HC, et al. Reduced health provider delay and tuberculosis mortality due to an improved hospital programme. The international journal of tuberculosis

and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2010;14(1):72-8.

44. Rao VK, Iademarco EP, Fraser VJ, Kollef MH. The impact of comorbidity on mortality following in-hospital diagnosis of tuberculosis. Chest 1998;114(5):1244-52.

45. Shimazaki T, Marte SD, Saludar NR, Dimaano EM, Salva EP, Ariyoshi K, et al. Risk factors for death among hospitalised tuberculosis patients in poor urban areas in Manila, The Philippines. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2013;17(11):1420-6.

46. Rajagopalan S, Yoshikawa TT. Tuberculosis in the elderly. Zeitschrift fur Gerontologie und Geriatrie 2000;33(5):374-80.

47. Mathew TA, Ovsyanikova TN, Shin SS, Gelmanova I, Balbuena DA, Atwood S, et al. Causes of death during tuberculosis treatment in Tomsk Oblast, Russia. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2006;10(8):857-63.

48. Nguyen LT, Hamilton CD, Xia Q, Stout JE. Mortality before or during treatment among tuberculosis patients in North Carolina, 1993-2003. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2011;15(2):257-62, i.

49. van't Hoog AH, Williamson J, Sewe M, Mboya P, Odeny LO, Agaya JA, et al. Risk factors for excess mortality and death in adults with tuberculosis in Western Kenya. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2012;16(12):1649-56.

50. Fielder JF, Chaulk CP, Dalvi M, Gachuhi R, Comstock GW, Sterling TR. A high tuberculosis case-fatality rate in a setting of effective tuberculosis control: implications for acceptable treatment success rates. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2002;6(12):1114-7.

51. Silva DR, Menegotto DM, Schulz LF, Gazzana MB, Dalcin Pde T. Factors associated with mortality in hospitalized patients with newly diagnosed tuberculosis. Lung 2010;188(1):33-41.

52. Chung-Delgado K, Guillen-Bravo S, Revilla-Montag A, Bernabe-Ortiz A. Mortality among MDR-TB cases: comparison with drug-susceptible tuberculosis and associated factors. PloS one 2015;10(3):e0119332.

53. Jung RS, Bennion JR, Sorvillo F, Bellomy A. Trends in tuberculosis mortality in the United States, 1990-2006: a population-based case-control study. Public health reports 2010;125(3):389-97.

54. Oursler KK, Moore RD, Bishai WR, Harrington SM, Pope DS, Chaisson RE. Survival of patients with pulmonary tuberculosis: clinical and molecular epidemiologic factors. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2002;34(6):752-9.

55. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Archives of internal medicine 2003;163(9):1009-21.

56. CDC. The Affordable Care Act Helps Those Living with HIV/AIDS; 2012 12/1/12.

57. CDC. Prevention Demonstration Project: Los Angeles County; 2010.

58. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lonnroth K, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. BMC medicine 2011;9:81.

59. Health and Human Services. Who is Eligible for Medicare. In: Division DC, editor.: Digita; 2014.

60. Kattan JA, Sosa LE, Lobato MN. Tuberculosis mortality: death from a curable disease, Connecticut, 2007-2009. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2012;16(12):1657-62.

61. Golub JE, Bur S, Cronin WA, Gange S, Baruch N, Comstock GW, et al. Patient and health care system delays in pulmonary tuberculosis diagnosis in a low-incidence state. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2005;9(9):992-8.

62. Miller AC, Polgreen LA, Cavanaugh JE, Hornick DB, Polgreen PM. Missed Opportunities to Diagnose Tuberculosis Are Common Among Hospitalized Patients and Patients Seen in Emergency Departments. Open forum infectious diseases 2015;2(4):ofv171.

63. California Department of Public Health. Information for Physicians Regarding Directly Observed Therapy (DOT) for Active Tuberculosis. In: State of California - Health and Human Services Agency; 2016.

64. California Tuberculosis Control Branch. Tuberculosis Registry Guidelines. Online. Richmond; 2010 February 2010.

65. Marks SM, Magee E, Robison V. Patients diagnosed with tuberculosis at death or who died during therapy: association with the human immunodeficiency virus. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2011;15(4):465-70.

66. Xie HJ, Enarson DA, Chao CW, Allen EA, Grzybowski S. Deaths in tuberculosis patients in British Columbia, 1980-1984. Tubercle and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 1992;73(2):77-82.

67. Zou G. A modified poisson regression approach to prospective studies with binary data. American journal of epidemiology 2004;159(7):702-6.

68. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology 1999;10(1):37-48.

69. Rajagopalan S. Tuberculosis and aging: a global health problem. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2001;33(7):1034-9.

70. Davis CE, Jr., Carpenter JL, McAllister CK, Matthews J, Bush BA, Ognibene AJ. Tuberculosis. Cause of death in antibiotic era. Chest 1985;88(5):726-9.

71. Wu YC, Lo HY, Yang SL, Chu DC, Chou P. Comparing the factors correlated with tuberculosis-specific and non-tuberculosis-specific deaths in different age groups among tuberculosis-related deaths in Taiwan. PloS one 2015;10(3):e0118929.

72. Asch S, Leake B, Anderson R, Gelberg L. Why do symptomatic patients delay obtaining care for tuberculosis? American journal of respiratory and critical care medicine 1998;157(4 Pt 1):1244-8.

73. Bustamante-Montes LP, Escobar-Mesa A, Borja-Aburto VH, Gomez-Munoz A, Becerra-Posada F. Predictors of death from pulmonary tuberculosis: the case of Veracruz, Mexico. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2000;4(3):208-15.