Title
Risk Factors for All-Cause Mortality during Treatment for Active Tuberculosis in San Francisco, 1995-2004

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Risk Factors for All-Cause Mortality during Treatment for Active Tuberculosis in San Francisco, 1995-2004

by

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UCSF School of Nursing

DISSERTATION

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in the

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of the

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Dedication

I dedicate this work to my life partner, inspiration, and role model, Lauren Cuttler, RN and to Ida Cuttler and Harriet Cuttler, fellow students and the best roommates I've ever had.

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As I thank Robert Sparacino for his accurate and timely editorial services, it is important that I hasten to add that I am alone responsible for the content including errors or omissions of any kind.

RISK FACTORS FOR ALL-CAUSE MORTALITY DURING TREATMENT FOR ACTIVE TUBERCULOSIS IN SAN FRANCISCO, 1995-2004

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BACKGROUND. Death from all causes during tuberculosis (TB) treatment has remained about 10% in San Francisco County. Estimating risk factors for all-cause mortality was this study's aim.

METHODS. A retrospective cohort study design was used to examine 1,730 subjects with TB older than 24 years in San Francisco from 1995 to 2004. The observation period was from the first day of TB treatment to the last day of treatment or death from any cause. Mean follow-up was 35.8 (± 20) weeks. Host characteristics including age, gender, race, immigration, and language; social-environmental factors including residence, incarceration, and unemployment; TB disease characteristics including anatomic site, culture, chest radiograph, resistance, previous TB; comorbid conditions including HIV coinfection and substance use; health care delivery factors including directly observed (DOT) or self-administered therapy (SAT), and public or private TB medical provider were tested for their predictive value on all-cause mortality.

RESULTS. All-cause mortality was 10.6% (184/1730); 50% of deaths (92/184) occurred < 8 weeks of treatment. Statistically significant predictors of all-cause mortality were age 45-64 (OR 2.2, 95% CI: 1.3, 3.9), age ≥ 65 (OR 2.5, 95% CI: 1.3, 4.7); male gender (OR 1.6, 95% CI: 1.1, 2.4); homelessness (OR 2.1, 95% CI: 1.2, 3.5); not working (OR 5.9,

95% CI: 3.0, 11.5); HIV coinfection (OR 8.1, 95% CI: 3.8, 17.0); and private TB medical provider (OR 3.8, 95%CI: 2.6, 5.7). Previous TB was associated with protection from all-cause mortality (OR 0.6, 95% CI: 0.3, 0.9); concomitant extrapulmonary TB was not associated with all-cause mortality (OR 1.3, 95% CI 0.9, 1.8). Subset analysis of patients receiving public TB care showed that SAT (OR 0.5, 95% CI 0.2, 0.9) and a combination of DOT and SAT were associated with a protective effect when compared with DOT only (OR 0.3, 95% CI: 0.1, 0.8).

CONCLUSION. Middle and older age, male gender, homelessness, not working, positive TB culture, and HIV coinfection predict all-cause mortality. Private TB medical provider was predictive of mortality, and the combination of DOT and SAT is beneficial, suggesting that public-private, TB-care partnerships need to be strengthened and that supervision of therapy should be flexible.

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CHAPTER 1

THE STUDY PROBLEM

Tuberculosis (TB) is an important contributor to global mortality. In 2004, nearly 2 million people died from it worldwide (World Health Organization [WHO], 2006). California has an incidence of TB higher than that of the United States (U.S.) as a whole (California Department of Health Services [CDHS], 2006), and San Francisco has the highest per capita rate of TB in the U.S. (Hunger, 2007; San Francisco Department of Public Health [SFDPH], 2006).

Since the resurgence of TB in San Francisco peaked in the mid-1990s, roughly 10% of its TB patients have died while receiving treatment (L.M. Kawamura, personal communication, November 2006). This case fatality rate compares unfavorably with the 4.6% all-cause death rate reported globally (Frieden, 2004; WHO, 2006), and the causes for this disparity have not been identified.

Despite the availability of therapy that can improve survival (Frieden & Espinal, 2004), many individuals die during the course of their TB treatment (Brewer & Heymann, 2005; Dye, 2006). Various characteristics may put a patient at higher risk of death despite receiving treatment. Current research has focused on the vulnerabilities of persons living in poverty (Squire, Obasi, & Nhlema-Simwaka, 2006). Particular populations that have been identified include the aged (Chan-Yeung, Noertjojo, Tan, Chan, & Tam, 2002; Mackay & Cole, 1984); White and non-White groups (DeRiemer, Rudoy, Schecter, Hopewell, & Daley, 1999; Hansel, Merriman, Haponik, & Diette, 2004); immigrants (Cayla et al., 2004; King, 2003); the homeless (Farmer, 1997; Haddad, Wilson, Ijaz, Marks, & Moore, 2005; Tulsky et al., 2004); those living in long-

term care facilities (Daley et al., 1992); unemployed persons (Sterling et al., 2006); incarcerated persons (Bock, 2000; Stead & Dutt, 1995; White et al., 2004); HIV-infected individuals (Nahid et al., 2007; Tacconelli, Tumbarello, Ardito, & Cauda, 1997); and substance users (Cayla et al., 2004). These groups have disproportionately higher rates of TB disease than the general population.

Mortality during treatment for active TB may be affected by dissemination of the disease beyond the pulmonary parenchyma (Tan, Sin Fai Lam, & Chew, 1996; Walpola, Siskind, Patel, Konstantinos, & Derhy, 2003); the bacterial burden (Dewan et al., 2004); the extent of radiographic abnormality (Dewan et al., 2004; Koppaka & Bock, 2004); primary or acquired resistance to antimycobacterial medications (Chiang et al., 2006; Leimane et al., 2005), and prior episodes of TB disease (L'Ecuyer, Woeltje, Seiler, & Fraser, 1998; Santha et al., 2002).

Besides demographic, social-environmental, and disease characteristics, the care environment may contribute to TB mortality. Although research has clearly shown the public health and clinical effectiveness of medical treatment for TB (Frieden, 2004), few studies have investigated the reasons for mortality during treatment (Borgdorff, Floyd, & Broekmans, 2002) and differential care rendered to the public (Khan, Campbell, Wallington, & Gardam, 2006; Uplekar, Pathania, & Raviglione, 2001).

Reichman (1991) expressed the concern that the resurgence of TB in the U.S. might have been related to diminished support for public health programs in the 1980s. In San Francisco, there has been “more than a decade” (L. M. Kawamura, as cited in Russell, 2008) of decreases in public health services to groups at risk of TB infection and disease. From 2006 to 2007, the incidence of active TB increased by 20% in San Francisco

(Russell, 2008). Changes in the care environment are required to improve surveillance, diagnosis, and treatment of active TB, while enhancing methods to target those at highest risk of death.

The Study Goal

The primary goal of this study is to investigate the relationship between risk or protective factors and death during treatment for TB disease. Specifically, the study will assess the effects of host demographics, social-environmental characteristics, TB disease, comorbid conditions, and health care delivery characteristics on all-cause mortality during treatment for TB in a sample of urban participants affected by a high prevalence of homelessness, incarceration, unemployment, HIV infection, immigration, language discordance, and substance use.

The Study's Aims

The study has eight specific aims:

1. To describe host demographic, social-environmental, TB disease, comorbidity, and health care delivery characteristics of the study sample;
2. To describe all-cause mortality during treatment for active TB;
3. To estimate the independent contribution of host demographic descriptors to all-cause mortality;
4. To estimate the independent contribution of social-environmental characteristics to all-cause mortality;
5. To estimate the independent contribution of TB disease characteristics to all-cause mortality;

6. To estimate the independent contribution of host comorbid conditions to all-cause mortality;
7. To estimate the independent contribution of health care delivery characteristics to all-cause mortality; and
8. To estimate the overall all-cause mortality during TB treatment using predictors from Study Aims 4, 5, 6, and 7

CHAPTER 2

THEORY AND LITERATURE REVIEW

Theoretical Framework

The conceptual framework for this study is based on the classic epidemiologic triad of host, agent, and environment (Bailey, Vardulaki, Langham, & Chandramohan, 2005; Rossignol, 2007; Valanis, 1999), the host being a person, the agent being TB disease, and environment being the social milieu. How the demographics of a human host interact with the characteristics of TB disease within an encompassing social environment is illustrated in Figure 1. There are five host demographic variables (age, gender, race, immigration, and language); four social-environmental variables (residence in a long-term care facility, incarceration, homelessness, and working); five manifestations of TB disease (disease site, TB culture, chest x-ray, antibiotic resistance, and previous TB disease); and four comorbid conditions (HIV, excessive alcohol use, intravenous drug use (IVDU), and non-intravenous drug use (non-IVDU), that is, use of noninjectable drugs. Health care delivery refers to the health care system that screens, diagnoses, and treats individuals. Two variables relate to health care delivery: private or public medical management and supervision of TB treatment. Variables were selected according to this conceptual framework to meet the objectives of this investigation.

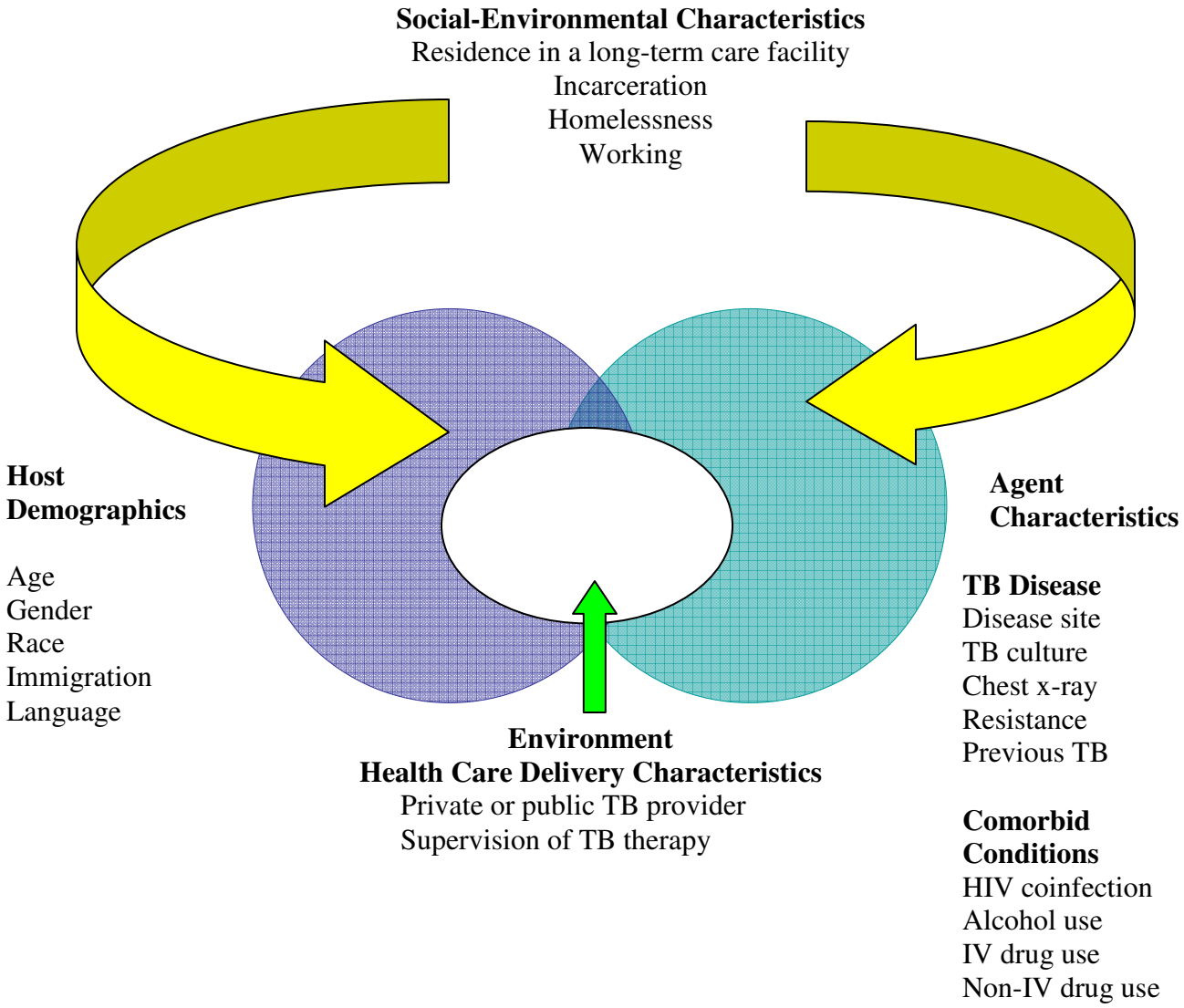

Figure 1. Conceptual framework of all-cause mortality during treatment for active tuberculosis (TB). HIV = human immunodeficiency virus; IV = intravenous.

Literature Review

The scientific literature reviewed for this study consists of journal articles, government reports, books, and treatment guidelines that focus on mortality during TB treatment. A search of the PubMed database in the National Library of Medicine

identified 366 articles about TB written in English with *mortality* as a major heading. The earliest report was published in 1966. The review was conducted to evaluate the possible contribution of variables theoretically relevant and feasible for the proposed study. The literature summarized below is divided into five categories: host demographics, social-environmental characteristics, TB disease characteristics, comorbid conditions, and health care delivery characteristics. Finally, the most current relevant research on characteristics of mortality during TB treatment in the U.S. is summarized.

Host Demographics

Age

Advanced age is generally associated with a higher incidence of TB and TB-treatment mortality. English researchers found that TB disease among younger persons was associated with lower mortality (Martineau, Lowey, Tocque, & Davies, 2004). Conversely, an examination of U.S. death certificate data in 1990 found that mortality from TB peaked among persons aged 25 to 44 (White & Portillo, 1996). Belgian researchers compared younger and older patients with TB and found death to be more frequent among the older group (Van den Brande, Vijgen, & Demedts, 1991).

Gender

Gender disparities have been observed in rates of TB and associated mortality worldwide, although the reasons for this are unclear (Thorson & Diwan, 2003). For example, some studies have shown higher treatment mortality among women (Sacks & Pendle, 1998). Yet more than three quarters of all TB deaths reported in Rio de Janeiro were among men (Selig et al., 2003). Although gender-specific strategies have been

recommended by the WHO (The Stop TB Partnership, 2006), it is unknown if men or women are at greater risk of death during treatment.

Race and Ethnicity

Although race and ethnicity have long been associated with variations in rates of TB disease and mortality (Byrd & Clayton, 2002; Craddock, 2000; King, 2003), it is unknown if race independently predicts death during TB treatment. Although some thought this was due to an inherent biologic characteristic (Gandy, 2003), researchers now understand health disparities in the context of the marginalization that occurs with discrimination (Byrd & Clayton, 2002; Doherty, Munk, & Andersen, 2003). Recent investigations suggest that racial associations with TB mortality may have been spurious. Non-White race was not found to be an independent predictor of hospital mortality among patients being treated for TB in the U.S. (Hansel et al., 2004). In San Francisco from 1986 to 1995, White race was independently associated with TB diagnosed after death (DeRiemer et al., 1999). During this period, the incidence of AIDS in San Francisco peaked (Nahid et al., 2007; SFDPH, 2003). In San Francisco, AIDS was initially concentrated in White men who have sex with men. Reported cases of AIDS among non-Whites did not increase proportionately until the mid-1990s (SFDPH, 2003).

In addition, the relationship between race and educational level has not been assessed by most studies. A mortality study in Mexico indicated that the risk of death during treatment was twice as high among individuals with less than six years of formal education (Garcia-Garcia et al., 2002), and conversely completion of secondary education in Peru showed a protective effect against all-cause mortality during treatment for TB

(Bernabe-Ortiz, 2008). Because few studies collect data on education and other measures of disparity, interpreting any racial or ethnic differences is difficult (Krieger, 2005).

Immigration

Immigration is associated globally with increased risk for TB infection and disease and is thought to be related to poverty and refugee status (Gandy, 2003; King, 2003). Researchers in Spain found that immigrants were nearly nine times more likely than native Spaniards to discontinue treatment (Cayla et al., 2004). In San Francisco, many cases of active TB have been found among persons who were born in one of the 22 countries that the WHO has identified as accounting for 80% of the world's incident cases (WHO, 2006). The stress associated with immigration may be reflected in the higher incidence of TB disease seen among recent arrivals (Gandy, 2003). Nonetheless, differential mortality during treatment for TB based on birth in the U.S. or in another country has not been studied.

Language

Without appropriate translation services, individuals who do not speak English or who have limited English proficiency may encounter difficulties in obtaining an appropriate diagnosis and accessing care (Karliner, Jacobs, Chen, & Mutha, 2007). This problem manifests itself in both foreign-born and U.S.-born individuals who primarily speak their native language. It has not been reported if language discordance is associated with higher or lower mortality during treatment for active TB.

Social-Environmental Characteristics

Long-term Care Facilities

Long-term care facilities refers to nursing homes and drug and mental health facilities. This environmental characteristic is associated with increased rates of TB transmission and rapid disease progression (Daley et al., 1992), as shown by a TB outbreak in an HIV residence in San Francisco (MMWR, 1991).

Incarceration

Incarcerated individuals suffer from some of the highest rates of active TB globally (Bock, 2000; Stead & Dutt, 1995). The prevalence of active TB was 72 per 100,000 in the jailed population in San Francisco between 1994 and 1998 (White et al., 2001). By contrast, the U.S. prevalence of TB in the incarcerated population in 2003 was between 24 and 29 cases per 100,000 (MacNeil, Lobato, & Moore, 2005). Researchers have yet to compare mortality during TB treatment in incarcerated and nonincarcerated individuals.

Homelessness

Homelessness was found to be the strongest predictor of death (odds ratio [OR] 9.5, 95% confidence interval [CI] 1.9, 15.9) in a case-control study of TB deaths in Russia (Dewan et al., 2004). This contrasts with a large, U.S., cross-sectional study (Haddad et al.,2005) and a Spanish investigation (Cayla et al., 2004) that found similar rates of death during treatment among homeless and nonhomeless individuals. Studies in San Francisco have identified treatment incentives, such as cash, that have improved completion rates among homeless individuals with TB disease (Tulsky et al., 2004). The

increased surveillance of the homeless (Craddock, 2000) may have contributed to earlier and more successful treatment.

Working

Employment has a generally protective effect on mortality. Working for money may be associated with less poverty and generally improved health (Last, 1998) for two reasons: the "healthy worker effect" and employed persons may be benefiting from health insurance coverage. A Russian study of TB treatment mortality (Dewan et al., 2004) has shown that those who died were five times more likely than survivors to have been unemployed (OR 4.9, 95% CI 1.9, 12.9). A multicenter, longitudinal, mortality study in the U.S. found that unemployment was a significant risk factor (hazard ratio [HR] 1.99, 95% CI 1.2, 3.4) for death during treatment (Sterling et al., 2006).

TB Disease Characteristics

Disease Site

The anatomic site of TB may affect a patient's survival. Pulmonary TB is the most common manifestation and is the focus of TB control efforts because it may be transmissible, while extrapulmonary TB is not. TB of the central nervous system is also associated with a high death rate (Hosoglu et al., 2002; Phypers, Harris, & Power, 2006; Qureshi et al., 2002), and a study has indicated that gastrointestinal TB is associated with high mortality, although all patients were coinfected with HIV (Manosuthi, Chottanapand, Thongyen, Chaovavanich, & Sungkanuparph, 2006). In a study from Malawi, Africa, Harries et al. (2001) found that patients with extrapulmonary TB died sooner after diagnosis than those with pulmonary TB. Extrapulmonary disease, however, was not associated with mortality in another study (Sacks & Pendle, 1998).

TB Culture

A TB smear and culture measure the concentration of mycobacteria in a sputum specimen. High bacterial loads in a smear can be detected by visual microscopy. Smear and subsequent culture positivity correlates with high infectivity and higher mortality (Toman, 2004). Nonetheless, the literature reveals equivocal findings. An African study has shown that smear-negative TB is associated with higher mortality than smear-positive TB (Lawn & Acheampong, 1999). Another study showed that smear-negative TB disease is associated with death in the early phase of treatment (Harries et al., 2001). This association may be confounded by HIV as an atypical low bacterial load may be associated with poorer outcomes among such individuals (Dye, Watt, Bleed, Hosseini, & Raviglione, 2005).

Chest Radiograph

The severity of active TB disease may be detectable on a chest x-ray for individuals with pulmonary and extrapulmonary TB (e.g., pleural effusion or thoracic lymphatic adenopathy). A pulmonary cavitation is associated with high infectivity. A study of individuals in Taiwan, admitted to the hospital for pulmonary TB, showed that those whose chest x-rays revealed consolidation had higher mortality (Lee et al., 2003). Extensive infiltrates on a chest x-ray were also associated with higher hospital mortality in a case-control study from South Africa (Sacks & Pendle, 1998).

Resistance

Five, first-line, antimycobacterial antibiotics are used in San Francisco: isoniazid, rifampin, pyrazinamide, ethambutal, and streptomycin (Centers for Disease Control and Prevention [CDC], 2000). These medications may be given once daily or intermittently

twice a week. Only streptomycin is given parenterally by intramuscular injection. Resistance to an antimycobacterial antibiotic is called monoresistance, while multiple drug resistant (MDR) TB is defined as resistance to isoniazid and rifampin. Polyresistant TB occurs when there is resistance to any two of the first-line antibiotics but not MDR. For example, a polyresistant strain could be resistant to isoniazid and ethambutal.

Several studies have shown that MDR TB is associated with higher treatment mortality (Garcia-Garcia et al., 2002; Manosuthi, et al., 2006; Mathew et al., 2006). Yet a study of a new treatment program for MDR in Latvia reported a low treatment mortality of 7% (Leimane et al., 2005), and a South African hospital study found no association of increased mortality in patients with MDR (Sacks & Pendle, 1998).

Previous TB Disease

Previous TB disease may be associated with poorer outcomes. Prior TB disease can be identified in individuals who have clinical evidence of TB disease or TB disease treatment before the current episode. A study in India showed mortality during treatment of 5%, with previous treatment as a statistically significant independent risk factor for death in that program (Santha et al., 2002). Previous treatment has been associated with treatment mortality in Russia (Mathew et al., 2006) and Ghana (Lawn & Acheampong, 1999). In contrast, newly transmitted disease was found to be a risk factor for death in a Mexican study (Garcia-Garcia et al., 2002).

Comorbid Conditions

AIDS

TB is the leading opportunistic infection in persons with HIV and has been an AIDS-defining diagnosis for many years (CDC, 1986). Coinfection with HIV among TB

patients increases the case fatality rate to as high as 83% in the absence of appropriate treatment for either disease (Dye et al., 2005). In one study, the death rate during TB treatment was 15 times higher among individuals coinfected with HIV (Zvandasara et al., 2006). In an age-adjusted multivariate model, HIV coinfection was an independent predictor of death (HR 5.4, CI 1.1, 26.4; Oursler et al., 2002). A longitudinal cohort study of HIV-infected individuals in Puerto Rico showed extremely high mortality (55%) in the year following diagnosis with TB (Mayor, Gomez, Otero, Vila, & Hunter, 2001). In San Francisco, the prevalence of AIDS among persons with TB is higher than that for California (CDHS, 2006). A comparison of HIV-infected and HIV-negative TB patients from 1990 to 2001 in San Francisco showed that HIV infection was a risk factor for the recurrence of TB disease (Nahid et al., 2007). Highly active antiretroviral therapy has been shown to increase survival even among those with both active TB and AIDS (Nahid et al., 2007).

Substance Use

Substance use is frequently assessed among individuals who are being treated for TB, primarily because it affects patient adherence (CDC, 2003). A large multicenter study in the U.S. (Sterling et al., 2006) found that daily alcohol use was an independent predictor of death during treatment (HR 2.94, $p < .0001$). A study of U.S. death certificates found that substance abuse was associated with TB mortality (White & Portillo, 1996).

Health Care Delivery Characteristics

Public or Private TB Provider

TB care is given by both public health clinicians and private physicians in a variety of settings. An African study has suggested that individuals seeking care for symptoms associated with TB are more likely to visit a private clinician rather than a public health clinician (Kiwuwa, Charles, & Harriet, 2005). If the diagnosis or treatment is inappropriate, this initial visit will contribute to treatment delay. Uplekar et al. (2001) have expressed the view that private practitioners are less knowledgeable about current TB treatments than public health clinicians. Treatment delay in an Ethiopian study was related to private medical treatment and previous attendance at community health posts (Yimer, Bjune, & Alene, 2005). Public-private partnership programs have been evaluated and, in one small study, have been shown to have equivalent treatment completion rates (Balasubramanian et al., 2006). Canadian researchers have found a protective effect when patients receive care from clinicians who have substantial experience in TB treatment (Khan et al., 2006). Although the Stop TB Partnership (2006) advocates more research on provider variables, scant literature has been published on the differences in TB care and their effect on mortality.

Supervision of TB Care

Directly observed therapy (DOT), the principal care variable, requires that medication administration be supervised by a nurse or trained health worker. Although DOT is recommended by the WHO to improve treatment completion (Stop TB Partnership, 2006), supervision has not been consistently associated with improved completion rates when compared with self-administered therapy (SAT) in a meta-analysis

and literature review (Volmink & Garner, 2006; Volmink, Matchaba, & Garner, 2000). A U.S. study found that 24% of urban patients died during treatment, despite almost universal use of DOT (Fielder et al., 2002). At the same time, North American (U.S. and Canadian) studies have identified a protective effect on survival where DOT and SAT have been used (Jasmer et al., 2004; Khan et al., 2006). DOT has not been studied as a method to decrease mortality, but it is used to prevent the emergence of drug resistance and to monitor patients closely for adverse effects that may increase nonadherence (Dhingra et al., 2004).

TB Mortality Research

Few large studies have been conducted on the risk factors for death during treatment of individuals who begin medical treatment for active TB regardless of the susceptibility profile of the infecting mycobacterium, diagnostic method, and disease site. Much of the research on TB and mortality has occurred in countries where the health care system, surveillance, and treatment methods differ substantially from those in the U.S. Of the 366 entries in PubMED, only a few studies examined mortality after initiating TB treatment as a principal outcome (El Sahly, Teeter, Pan, Musser, & Graviss, 2007; Fielder et al., 2002; Oursler et al., 2002; Rao, Iademarco, Fraser, & Kollef, 1998; Sterling et al., 2006).

Rao et al. (1998) performed a historic cohort analysis of individuals (n = 203) admitted to the hospital in St. Louis, Missouri from 1988 to 1996. These researchers found all-cause mortality was 28%. Because TB is primarily managed in the outpatient setting, those who are admitted to the hospital are more likely to be more acutely ill.

Two mortality studies conducted in Baltimore showed high mortality, greater than 20% (Fielder et al., 2002; Oursler et al., 2002). Fielder et al. included 174 sputum-smear-positive subjects with pulmonary TB from 1993 to 1998 in a historic cohort study that found those older than 49 years had a statistically significantly higher (OR 4.6, 95% CI: 2.1, 10.2) all-cause mortality than younger subjects in a multivariate analysis. They found a 24% case fatality rate despite DOT being used for 99% of the subjects. Oursler et.al. studied 139 TB-culture-positive subjects with pulmonary TB. The cumulative mortality for this historic cohort study was 21%, and comorbid conditions found important in an age-adjusted model included HIV coinfection. Because these studies included mostly African Americans receiving treatment exclusively from the public health care system and exclusively by DOT, these findings cannot be generalized to a setting such as San Francisco.

Jasmer et al. (2004) compared DOT and SAT in San Francisco from 1998 to 2000 in subjects (n = 372) who had pulmonary, culture-positive TB and did not have drug resistance. Although the primary outcome being studied was not mortality, it was reported that 11% of the subjects died within one year of treatment initiation. The investigators did not perform a multivariate analysis to control for known confounders, including age. Although the study reported that DOT appeared to be associated with decreased mortality when compared with those assigned to SAT, those assigned to DOT were statistically significantly 10 years younger. Jasmer et al. note that DOT is recommended for patients who are exposed to variables thought to adversely affect survival, such as homelessness, incarceration, substance use, positive sputum smear, MDR, previous TB disease, severe debilitation, and a history of nonadherence (Jasmer et

al., 2004). Because Jasmer et al. excluded those with MDR and culture-negative TB, inferring similar results for groups with all types of TB is not possible.

Sterling et al. (2006) retrospectively studied a large number (n = 1,075) of subjects with pulmonary TB in multiple centers in the U.S. and Canada. HIV coinfection, alcohol use, and unemployment were statistically significantly associated with mortality during and after treatment completion. Although a relatively low (6.6%) mortality was reported, individuals had to have completed 2 months of TB treatment to be included. Because other studies have identified mortality as occurring early in the treatment period (Jasmer, 2004), individuals who survived the early treatment period may have passed the time of highest mortality. In addition, Sterling et al. evaluated a novel treatment drug regimen and their exclusion criteria may limit generalization to other populations. Of greatest importance is the exclusion of subjects with TB drug resistant disease and the comorbidity of HIV because these are variables hypothesized to correlate with increased mortality.

The largest (n = 3,662) recent TB mortality study identified was a Houston, Texas case-control study (El Sahly et al., 2007) of those with central nervous system (CNS) TB (the cases) and those with all other types of TB (the controls). The subjects were enrolled from 1995 to 2004. The follow-up period was 180 days and mortality of the whole population was 8.7% during that time. Survival analysis indicated that mortality was statistically significantly associated with older age (HR 1.06, 95% CI: 1.02, 1.10) and positive TB culture (HR 5.10, 95% CI: 1.06, 24.20).

Bernabe-Ortiz (2008) reported a mortality study in Lima, Peru that used a historic cohort design of 425 subjects from 2000 to 2005. The follow-up period began at

treatment initiation and ended with death, treatment completion, or loss to follow-up. Overall all-cause mortality was the lowest reported at 4.5%. A shorter survival time was statistically significantly associated with HIV coinfection (HR 5.78, 95% CI: 1.10, 29.99). Completion of secondary education was identified as a protective factor with statistically significantly increased survival (HR 0.28, 95% CI: 0.10, 0.83).

This study is novel in examining risk factors for all-cause mortality during TB treatment for all types of TB. The literature reviewed has been generally limited to pulmonary, culture-positive, nonresistant TB. The effects of health care delivery characteristics including type of provider and supervision by DOT or SAT have not been reported.

CHAPTER 3

METHODS

Why San Francisco continues to experience high all-cause mortality during treatment for TB is unknown. Because of the relatively high incidence of TB in San Francisco, evidence from 10 years of newly diagnosed and treated individuals may help inform methods that can improve surveillance, diagnosis, and treatment. The following section describes the research design, study procedures, predictor and outcome variables.

Research Design

This study, a longitudinal retrospective cohort design, used existing data that had been collected as part of the surveillance and reporting function of the San Francisco TB Control Section (TB Control). The cohort design can directly estimate associations between multiple predictors and the relative risk of all-cause mortality. The cohort design is also appropriate and valid because cross-sectional investigations of TB treatment have not been cross-validated with other measures (Youngleson & Joubert, 1991) and is temporally appropriate for causal explanations.

Human Subjects Assurance

The Committee on Human Research at the University of California, San Francisco reviewed and approved this study. Data for the analysis came from the usual care provided by TB Control and other San Francisco medical providers. As a retrospective study of existing medical information, there was no additional physical risk to any of the participants. No attempt was made to contact subjects, their surviving family members, or their TB medical provider. The data provided contained no personal identifiers. And, according to the SFDPH TB Control Research Agreement, the data were

secured on a password-protected computer, the final project data set is archived with TB Control, and all other electronic and paper copies of data with study identifiers were destroyed, as is their usual procedure. Access to the study data was restricted to investigators and Steven M. Paul, PhD, Principal Statistician at the University of California, San Francisco School of Nursing.

Setting

California has 61 local health jurisdictions that are responsible for reporting all cases of active TB. Fifty-eight of these jurisdictions are counties, and three are cities (Berkeley, Long Beach, and Pasadena; CDHS, 2006). As the only reporting jurisdiction that is both a city and a county, San Francisco is unique (CDHS, 2006). TB Control is responsible for compiling and analyzing all cases reported within its jurisdiction (SFDPH, 2003). TB Control provides statistics on surveillance, diagnosis, and treatment to the CDHS, who in turn provides the statistics to the CDC (CDC, 2000). TB is diagnosed and treated by licensed practitioners within TB Control (the public provider) or in other health care settings (private provider).

Sample

This study included all adults with active TB (a) whose active TB case was reported and confirmed in San Francisco between January 1, 1995 and December 31, 2004; (b) who were alive when a TB diagnosis was confirmed; and (c) who commenced antibiotic TB treatment. Cases were excluded if a prior episode of TB was reported in the same period. If two episodes of TB disease occurred during the same period, only the characteristics of the second episode were considered against the risk of death. This avoided counting the same individual twice. TB may be identified after death, but risk

factors for that population in San Francisco have already been described in previous research (DeRiemer et al., 1999).

During the study period (January 1, 1995 to December 31, 2004), 2,009 verified cases of TB were reported. Seven of these represented individuals with two episodes of active TB in the same period; only data from the second episode were included to maintain the independence of measures. Fifty-one patients were dead at diagnosis. Five patients were lost to follow-up before treatment began and, therefore, were excluded. All in all, 1,946 subjects of all ages were initially eligible for inclusion during the 10-year period of this study. Because there were 216 subjects younger than 25 with only one death, those subjects were not included in the data analysis. The final data sample included 1,730 subjects.

Case Definition and Measurement

To be considered a case of active TB, the data were derived from several sources: patient examination and history, laboratory, and radiographic results (CDC, 1997, 2003). The preferred diagnostic measure is a mycobacterial culture showing the growth of any of the following species: *Mycobacterium tuberculosis*, *Mycobacterium bovis*, or *Mycobacterium africanum* (CDC, 2003). Even if a culture is not obtained, the detection of acid–fast bacilli by visual microscopy is considered confirmation (CDC, 2003). The sensitivity of sputum microscopy is estimated to range from 55% to 74% (Brewer & Heymann, 2005), and the WHO reports sensitivity up to 90% with serial sputum samples (Toman, 2004). The cultured specimen has an even greater sensitivity (van Deun, 2004). And, a case of TB can be diagnosed by radiologic signs, symptoms, and a positive skin test (CDC, 2003). Diagnosis of TB disease by chest radiography alone is considered to

have poor reliability (Koppaka & Bock, 2004). The case definition of TB was stable during the period of investigation.

Data Collection Procedures

TB information is recorded on the CDC and CDPH's Report of a Verified Case of Tuberculosis (RVCT; CDC, 2003; see Appendix A for RVCT). The RVCT is used to collect information from all U.S. jurisdictions on the demographics of those diagnosed with TB, the disease characteristics, the environment of diagnosed persons, and some features of their care. It must be completed for all cases of TB, including those diagnosed after death. The RVCT includes three sections: the RVCT; the Initial Drug Susceptibility Report (Follow-Up Report 1), which can only be completed for cases that are culture positive (see Appendix B for Report 1); and the Case Completion Report (Follow-Up Report 2), which is completed for all patients who were alive when TB was diagnosed (see Appendix C for Report 2). There are 41 variables for all reported cases of TB. In 2003, a minor change was made to the form to include multiracial identity.

TB Control is responsible for collecting, compiling, reporting, and storing all of the information requested by the CDHS. All clinicians in San Francisco must report individuals with active TB, be they living or dead. TB Control developed a computerized database known as the Oaxaca data dictionary (data dictionary; Grinsdale, 2006), which includes 366 variables. Ninety-one relevant data variables were selected from the data dictionary to develop predictor and outcome variables.

Data Analyses

Data obtained from TB Control were exported from a Microsoft Excel file and SPSS version 13.0, which was used for all data analyses. The data set was checked for

missing entries and errors. The program manager for TB Control provided missing data in some instances (Grinsdale, 2006). In other instances, missing data were provided by cross-validating the data set. Baseline characteristics of subjects without outcome information were compared with those who completed treatment or died.

The sample was stratified by age-groups. The age-group strata were (a) 0 to 4, (b) 5 to 14, (c)15 to 24, (d) 25 to 44, (e) 45 to 64, and (f) 65 and older. Because there was only one death of a subject younger than 25, only predictors and outcomes for the older three strata were described and evaluated. Summary descriptive measures were calculated for each of the predictors. To describe all-cause mortality, the mean (and its associated standard deviation), median, and modal weeks of therapy were calculated. Bivariate analysis of categorical predictors and the outcome of death or completion of treatment were performed with proportions described by frequency and calculation of ORs and chi-square statistics with their associated 95% CI. With a sample size of 1,730 subjects with $\alpha = .05$ and $ß = .20$, there was a 95% probability of detecting a difference of at least 5% in the all-cause mortality (nQuery Advisor).

Predictor Variables and Conceptual Model

The variables hypothesized to affect survival or death during treatment for active TB were abstracted from the data set, enumerated, and organized into five categories: host demographics, social-environmental characteristics, TB disease characteristics, comorbid conditions, and health care delivery characteristics. Table 1 identifies the predictors that were examined according to their place in the conceptual framework of this study, the possible values for each variable, and their type - categorical or dichotomous.

Table 1
Characteristics of Variables by Conceptual Domain

Characteristics	Possible values	Type of variable
Host demographics		
Age	25-44 years, 45-64 years, and ≥ 65 years	Categorical
Gender	Male or female	Dichotomous
Race/ethnicity	White non-Hispanic Black non-Hispanic Latino Asian Pacific Islander/Native/?	Categorical
Immigration	Born in U.S. or in another country	Dichotomous
Language	English or other language	Dichotomous
Social-environmental		
Long-term care facility	Congregate residence or other	Dichotomous
Incarceration	Incarcerated or not	Dichotomous
Homelessness	Homeless or housed	Dichotomous
Working	Employed or not	Dichotomous
TB disease		
Disease site	Pulmonary only Pulmonary and extrapulmonary	Dichotomous
Sputum smear Culture	Smear (sputum) Culture (any specimen) Positive, negative, not tested	Categorical
Chest x-ray	1. Cavitary 2. Abnormal, noncavitary 3. Normal	Categorical
Resistance	1. MDR 2. Other resistance 3. Pansensitive	Categorical
Prior TB disease	Reported previous TB disease and/or treatment or not	Dichotomous
Comorbid conditions		
HIV	HIV positive, HIV negative, or HIV unknown	Categorical
Substance use	Intravenous drug use Excessive alcohol use	Dichotomous

	Other substance use	
Health care delivery		
Private/public care	Private or public	Dichotomous
Supervision	DOT or SAT or both	Categorical

Note. MDR = multiple drug resistance; TB = tuberculosis; HIV = human immunodeficiency virus; DOT = directly observed therapy; SAT = self-administered therapy.

Study Aim 1: To Describe Host Demographic, Social-Environmental, TB Disease, Comorbidity, and TB Health Care Delivery Characteristics of the Study Sample

Host Demographics

Data elements were available to describe several aspects of individuals initiating treatment for active TB: age, gender, race and ethnicity, immigration, and language.

The host variable of age at date of the TB case report was described by the calculated mean and its associated standard deviation. The remaining host variables of gender, race/ethnicity, immigration, and language are categorical and are described by frequencies and percentages.

Age. The continuous variable of age was created from the raw data (CDC, 2003) by subtracting the birth date of an individual from the date the case of TB was reported (Grinsdale, 2006). Information was complete for all subjects.

Gender. For this study, gender was established as either male or female based on self-report and observation of biologic sex by the reporting clinician (CDC, 2003). There were no missing data for gender.

Race and ethnicity. Race and ethnicity are considered self-defined and self-reported by the CDC (2003), and are abstracted from data dictionary variables 216-219 (Grinsdale, 2006). Although current practice dictates that multiple racial identities be requested and recorded, only one race and one ethnicity per person (e.g., Latino or non-

Latino) were recorded during the period for this study. White race was considered the reference group. The data elements available limit race and ethnicity to any one of the following mutually exclusive categories: American Indian/Native Alaskan, Asian, Black/African American, Native Hawaiian/Pacific Islander, Latino, and White. Eighteen cases (0.9%) lacked race or ethnicity information. Ethnicity was only indicated in terms of Hispanic/Latino or non-Hispanic/non-Latino. Because there is no theoretical, social, or biologic basis for the distinctions between race and ethnicity, one summary variable was created to represent race and ethnicity.

Immigration. This nominal variable is available from the data dictionary (Grinsdale, 2006). A disproportionately large number of active TB cases in San Francisco arise from immigrant populations (CDPH, 2006). This information is requested as the place of birth on the RVCT (CDC, 2003) and is derived from either self-report or by documentation from the country of origin. The data set does not request documentation of an individual's immigration status. The data do not contain information to validate the self-reported country of origin or immigration status.

Language. This data dictionary variable, number 222, is nominal and coded for the many languages spoken by TB patients in San Francisco (Grinsdale, 2006). Twenty different languages (i.e., the primary language spoken by a TB patient) were identified among the study's subjects. Language spoken was missing for 454 cases (23%). No method of imputing these missing data is available. A summary dichotomous variable for English or non-English was abstracted.

Social-Environmental Characteristics

The social-environmental characteristics of residence in a long-term care facility, incarceration, homelessness, and working will also be described with frequency statistics.

Residence in a long-term care facility. Residence in a long-term care facility is addressed by data dictionary variables 46 and 47 (Grinsdale, 2006), which provide the information for completing RVCT variable number 26, "Resident of Long-Term Care Facility at Time of Diagnosis" (CDC, 2003, pp. 20-21). There are data elements for living in a long-term care facility, such as a nursing home, drug treatment center, or residential mental health facility. There were three subjects missing this data that were re-categorized as not living in a long-term care facility. Because of the low frequency of residence in a long-term care facility (48 cases) and because type of facility is not known to correlate with mortality risk, a summary dichotomous variable was created. No other data are available to further characterize the place of dwelling, such as number of inhabitants, size or condition of home, rental or owned, or apartment or single family home.

Incarceration. Data dictionary variables were used to record information if individuals were incarcerated; if so, in what institution; and the county of jurisdiction if located in a county correctional facility (Grinsdale, 2006). Incarceration is defined by the RVCT variable number 25 as having been incarcerated at the time of TB diagnosis (CDC, 2003). Three cases (0.2%) of missing data were recategorized as *not incarcerated* at the time of diagnosis. And, all such cases were diagnosed while the subjects were in San Francisco County jails, so there was no need to further characterize the type or location of the facility (J. Grinsdale, personal communication, January 2006). The length

or frequency of incarceration is unknown. Thus, it is possible for an individual to be diagnosed, commence therapy, or even complete therapy while incarcerated.

Homelessness. Created from data dictionary variable number 148 (Grinsdale, 2006), this variable is used to complete RVCT variable number 24, "Homeless Within the Past Year" (CDC, 2003). Homelessness is defined as having lived in homeless shelters, marginally housed in a single-room occupancy hotel, "doubling up" in apartments, or sleeping in a car, park, or other outdoor location (CDC, 2003). Thirteen cases were missing data (roughly 0 .7%). If this was not indicated on the RVCT, the decision rule was to classify those individuals as not homeless. Homelessness is noted as a dichotomous variable, and thus the type (i.e., location) or duration of homelessness cannot be determined from the data set. Because homelessness is a reason for DOT, such data was used to cross-validate the label of homelessness.

Working. Employment or occupation is noted in the data dictionary as variables 40-42 (Grinsdale, 2006,) and in the RVCT as number 32 (CDC, 2003) and is defined as either unemployed for all of the 24 months preceding diagnosis or working. Although the RVCT includes the categories of "correctional employee" and "migrant agricultural worker" (CDC, 2003, p.24) no such cases were noted during this period (J. Grinsdale, personal communication, January, 2007). Two subjects younger than 65 lacked working information. The decision rule was to recategorize those missing employment information as working

TB Disease Variables

The agent in this study's conceptual framework is active TB disease. The variables examined include anatomic disease site, smear, culture, chest radiograph, antibiotic resistance, and previous TB exposure.

Anatomic disease site. The anatomical disease sites recorded on the RVCT include (a) pulmonary, (b) pleural, (c) lymphatic-cervical, (d) lymphatic-other than cervical, (e) bone or joint, (f) miliary, (g) peritoneal, (h) genitourinary, and (i) meningeal. Pulmonary disease is the most likely to be diagnosed, in part because public health policy requires that all persons suspected of TB disease be offered a chest radiograph (CDC, 2000). The pleural tissue lining the chest cavity also may be a site of disease. Miliary disease, considered a primary site, is characterized by multiple diffuse lesions observed on a radiograph and is diagnostic of disseminated disease (Zahar et al., 2001). Meningeal TB is located in the central nervous system and correlates with a severe symptomatic process associated with poor *sequelae* and often death (El Sahly et al., 2007). Although extrapulmonary manifestations of TB disease can be disabling, some studies show that nonmiliary, nonmeningeal and extrapulmonary disease are less likely to result in death than pulmonary TB disease alone (Martineau et al., 2004).

Sputum smear and culture. This variable is created from the data elements on visual microscopy (sputum smear) and the detection of TB mycobacterial growth (culture). Because a positive smear or TB culture correlates with symptomatic and diagnostic intensity (Toman, 2004), such patients are hypothesized to be the most acutely ill. Those whose sputum smear and culture prove negative for TB disease may thus be

considered as having a less acute phase of their illness when compared with those who have a detectable mycobacterial burden.

Chest radiograph. The detection of pulmonary cavitations on a chest x-ray is a classic sign of active TB disease. The presence of cavitations also correlates with a more acute and infectious state of the TB disease process (Luelmo, 2004). The chest radiograph, however, is neither as sensitive nor as specific as other diagnostic methods (Koppaka & Bock, 2004). Nonetheless, cavitations are related to a patient's risk of death and an increased transmission risk to the community (Tan et al., 1996). A normal chest x-ray is not hypothesized to be a protective factor for survival because with HIV coinfection there is a greater proportion of radiologically negative cases (Manosuthi et al., 2006). Other abnormalities of the lung parenchyma are consistent with a diagnosis of active pulmonary TB. And, mediastinal manifestations of TB may appear on chest films indicating active TB of the thoracic lymph nodes (CDC, 2000). Pleural effusions may appear on chest films and may be associated with extrapulmonary TB of the outer lung membrane (Van den Brande et al., 1991). The only three categories for the chest x-ray variable are (a) normal; (b) noncavitary, consistent with TB; or (c) cavitary, consistent with TB. In this investigation, only the initial x-ray will be considered.

Antibiotic resistance. All culture-positive cases of TB are tested with these first-line antimycobacterial drugs: isoniazid, rifampin, ethambutal, pyrazinamide, and streptomycin. The severity is coded from lowest to highest as (a) pansensitive, no resistance noted; (b) other resistance, resistant to any one or more antibiotics except not both isoniazid and rifampin; and (c) MDR, defined as resistant to at least isoniazid and rifampin (Chiang et al., 2006). Because resistance to any two of the first-line antibiotics

is associated with an extended course of treatment (Leimane et al., 2005), the length of treatment is extended (CDC, 2000). Missing data cannot be inferred to be either resistant or susceptible.

Previous TB exposure. Prior TB infection and/or treatment were indicated by examining several data sources. Researchers have hypothesized that previous TB exposure is correlated with re-infection, relapse, and/or antibiotic resistance (Drobniewski et al., 2002). Yet, patients who have had experience with TB may seek medical care more promptly than those who have not. Those patients identified as having had two episodes of TB during the 10-year period of this study were definitely previously exposed to TB. Although the predictor and outcome variables were only examined for the second episode to maintain independent measures, the previous exposure was noted. And, cases may reveal recorded episodes of TB disease before the period of inquiry and/or previous TB treatment. Some of the information is provided by the patient, although verification should be requested (CDC, 2003). A summary measure will be created for previous TB exposure. This dichotomous measure was coded as no TB history or TB history, defined as any one or more of the following being present: TB disease reported previously, previous TB disease medical treatment, and/or previous diagnosis of TB disease recorded.

Comorbid Conditions

HIV. The source of this data is the CDHS's HIV/AIDS Case Registry. Only confirmed matches are included as HIV positive. Data missing from the data set indicates that these individuals were not tested or there was not a match with the registry. This variable was coded as HIV positive, HIV negative, or HIV status unknown.

Substance use. Substance or drug use is defined as the self-reported excessive use of alcohol (two or more drinks per day) and most nonprescribed drugs including amphetamines, cocaine, marijuana, and opiates, such as heroin. The data set distinguishes the following categories: alcohol (any), excessive alcohol (more than two drinks per day), IVDU (any nonprescribed drugs in year before diagnosis), and non-IVDU (any use of noninjectible drugs not ordered by a clinician; CDC, 2003). Because low alcohol intake (i.e., less than two drinks per day) is not a suspected correlate of differential mortality, only excessive use of alcohol was included as a possible predictor (Sterling et al., 2006). Tobacco use was not included because such data were not required by the RVCT and were not available. Individual cases missing substance abuse data were treated as nonexposed to this risk factor.

Health Care Delivery Characteristics

Public or private management. This variable is not requested by the RVCT but is recorded in the electronic database based on the initial treatment site. TB treatment can be provided by any licensed clinician, but the storage and reporting of the information is the responsibility of the local health department (CDC, 2003). Each case has a unique numerical identifier included in the case-counting code (Grinsdale, 2006) that indicates if clinical responsibility for the case was public (i.e., managed by TB Control) or private (i.e., managed by a clinician in the community). Public management included a hospital-based outpatient clinic and two satellite clinics, one located in the heart of San Francisco (Schecter, 1996) and the other in Chinatown (SFDPH, 2006). There were 13 cases (0.7%) with missing information. If there was no information to indicate type of medical management, the decision to reclassify as either public or private management was based

on the initial referral. There were no known cases of DOT in the private sector (J. Grinsdale, personal communication, January 2007) so such cases were reclassified as public management.

Supervision of therapy This variable was created from the RVCT's Case Completion Report (Follow-Up Report 2), variable number 39 (CDC, 2003) and TB Control's data dictionary variables 351-361 (Grinsdale, 2006). DOT is coded as such if all weekday nonholiday doses are given while being observed by a health worker (CDC, 2003). Therapy may be given intermittently, and all such doses should be given by DOT (CDC, 2000). SAT is to be recorded if all doses were given without observation. Supervision of therapy is classified as DOT, SAT, or both (CDC, 2003; Grinsdale, 2006). The number of cases missing this information was less than 1%. When a data element was blank, it was recategorized as SAT. This decision is based on the fact that individuals on DOT for any length of time are more likely to have multiple indications of DOT in their medical record because the nurse responsible for each patient must document each dose (Jasmer et al., 2004).

Study Aim 2: To Describe All-Cause Mortality During Treatment for Active TB.

The outcome variable was the dichotomous outcome of completion of treatment or death before completion. Cause of death was not available, and all analyses of risk factors are thus estimates of all-cause mortality.

Length of therapy was calculated by subtracting the date treatment began from the day treatment was discontinued. The RVCT variable 28 (CDC, 2003) requires that this date be documented, preferably by direct observation. Although it is less desirable, the date that TB antibiotics are dispensed or prescribed may be considered the onset of

therapy. These data were recorded in data dictionary variable 344 (Grinsdale, 2006). The end date for therapy is the last day that medication was observed being ingested (preferred) or the date when the final dispensed or prescribed TB antibiotics would have run out (CDC, 2003). This information was recorded on the RVCT Follow-Up Report 2 as variable number 36 (CDC, 2003) and was recorded by the data dictionary as variable number 346 (Grinsdale, 2006). The treatment period encompassed the entire period of treatment for the episode of active TB disease including interruptions in therapy for any reason (CDC, 2003). No data were missing for this variable. One case recorded the conclusion of therapy before treatment began; this error was corrected after TB clinic staff verified the actual dates of therapy (J. Grinsdale, personal communication, January 2007).

Completed therapy is the only desirable category for completion of treatment (CDC, 2003). Other reasons for ending therapy included moved, lost to follow up, uncooperative or refused, not TB, died, other, or unknown (CDC, 2003). Completion of therapy was determined by the treating clinician and may vary in length depending on the disease and treatment regimen. Although completion of therapy implies cure for this episode of disease; follow-up in 6 months and 1 year assesses for relapse (Jasmer, 2004). Because some individuals do not return for follow-up, successful completion of therapy was selected as the outcome for this study and will be compared with those who died or did not complete treatment.

Study Aims 3, 4, 5, 6 and 7: To Estimate the Independent Contribution of Host Demographic, Social-Environmental, TB Disease, Comorbidity, and Health Care Delivery Descriptors to All-Cause Mortality During Treatment for Active TB

The bivariate relationship between categorical predictors and all-cause mortality will be estimated using the descriptive and inferential statistics described previously in data analysis.

Study Aim 8: To Estimate the Overall All-Cause Mortality During TB Treatment Using Predictors From Subset Analyses (Study Aims 4, 5, 6, and 7).

To estimate the effect of two or more predictors on the categorical dichotomous outcome of all-cause mortality or completion of treatment, multivariate logistic regression was used. In both cases, predictors were included when bivariate analysis (Study Aims 4, 5, 6, and 7) showed statistical significance (95% CI does not include one) and/or hypothesized theoretical importance. And, age-group was included in each model as it is a known confounder in mortality studies.

For predictors of mortality, the 1,730 subjects 25 years and older with the outcome of death or survival of treatment were evaluated by multiple logistic regression. The 95% CI was calculated, and a two-tailed alpha < 0.05 constitutes significance, controlling for all the included predictors.

CHAPTER 4

RESULTS

The original data set from the city and county of San Francisco included 1,946 unique subjects with TB disease initiating treatment. Because only one death was reported among all those under 25, the final data set of 1,730 includes only the three older strata of 25 to 44, 45 to 64, and ≥ 65 years old. The 216 subjects under the age of 25 were mostly children and were excluded from further analysis.

A total of 1,730 subjects 25 years and older started treatment for active TB during the enrollment period of January 1, 1995 to December 31, 2004 (see Figure 2). All-cause mortality affected 184 persons (10.6%) during treatment, and 1,473 (85.1%) were reported to have completed treatment successfully, and 73 (4.2%) did not have complete outcome information.

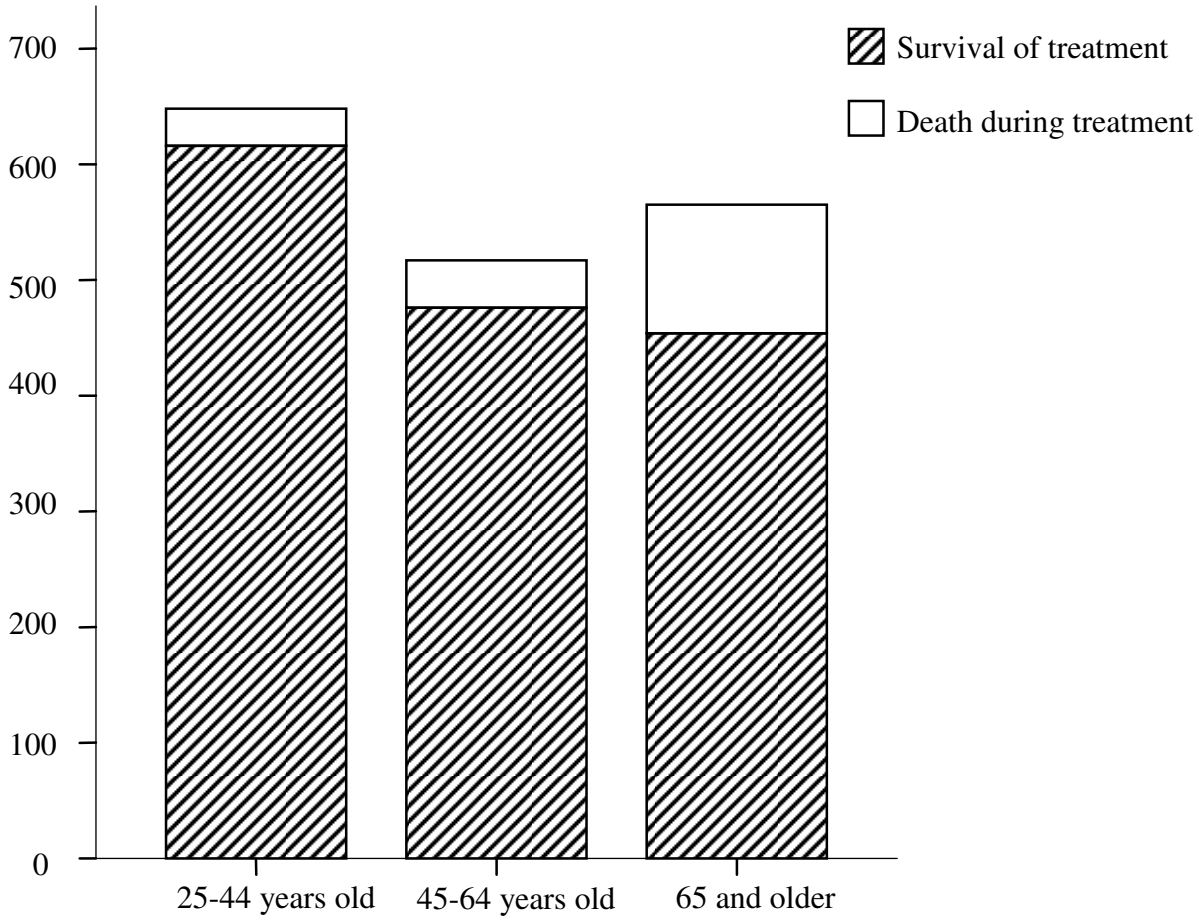

Figure 2. Frequency of subjects initiating treatment for active tuberculosis by age-group, San Francisco, 1995-2004

Study Aim 1: To Describe Host Demographic, Social-Environmental, TB Disease, Comorbidity and Health Care Delivery Characteristics of the Study Sample.

The earliest case began treatment on August 19, 1994. The last case began treatment on November 27, 2004. The latest observation was on May 25, 2006 when the last subject successfully completed treatment. Follow-up of subjects ranged from less than one week

to 141 weeks with a mean of 35.8 weeks (SD ± 20) and mode of 26 weeks (see Figure 3).

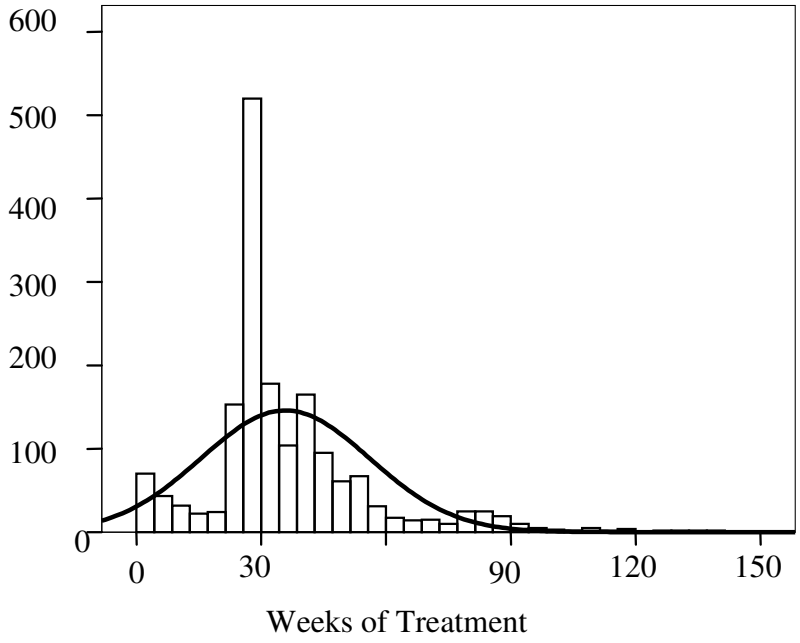

Figure 3. Length of treatment in weeks in subjects with active tuberculosis in San Francisco, 1995-2004.

Host Demographics

The sample for the study consisted of 1,141 men, (66%) and 589 women (34%); their ages ranged from 25 to102 with a mean of 54 years (SD± 18). The racial distribution was 61.5% Asian, 13.8% White, 11.7% Black, 10.9% Latino, and 2.2% Other. The "other" category consisted of 17 subjects without race information, 12 American Indians, and 8 Native Hawaiian/Pacific Islanders. Seventy-three percent declared their place of birth was outside of the U.S., 46.2% spoke a language other than English, and 24.6% were missing information about their language (see Table 2).

Table 2
Demographics of Subjects Initiating Treatment for Active TB by Age-Group, (n = 1,730)

	Total n = 1,730 (100%)	25-44 years n = 648 (%)	45-64 years n = 517 (%)	≥ 65 years n = 565 (%)
Gender				
Male	1,141 (66.0)	417 (64.4)	347 (67.1)	377 (66.7)
Female	589 (34.0)	231 (35.6)	170 (32.9)	188 (33.3)
Race				
White	239 (13.8)	112 (17.3)	79 (15.3)	48 (8.5)
Black	202 (11.7)	102 (15.7)	78 (15.1)	22 (3.9)
Asian	1,064 (61.5)	287 (44.3)	312 (60.3)	465 (82.3)
Latino	188 (10.9)	125 (19.3)	36 (7.0)	27 (4.8)
Other	20 (1.2)	12 (1.9)	8 (1.6)	0 (0.0)
Unknown race	17 (1.0)	10 (1.5)	4 (0.8)	3 (0.5)
Immigration				
U.S. born	469 (27.1)	236 (36.4)	161 (31.1)	72 (12.7)
Non-U.S. born	1,261 (72.9)	412 (63.6)	356 (68.9)	493 (87.3)
Language				
English	506 (29.2)	239 (36.9)	182 (35.2)	85 (15.0)
Not English	799 (46.2)	279 (43.1)	236 (45.6)	284 (50.3)
Unknown	425 (24.6)	130 (20.1)	99 (19.1)	196 (34.7)

Note. TB = tuberculosis; U.S. = United States.

Social-Environmental Characteristics

Table 3 shows the frequency of the social-environmental characteristics: 2.8% lived in a long-term care facility, 1.8% were incarcerated, 16% were homeless, and 64.6% were not working. The method of data collection did not obtain separate data based on “retired” versus “unemployed”.

Table 3
Social –Environmental Characteristics of Subjects Initiating Treatment for Active TB, (n =1,730)

	Total n = 1,730[a] (%)	25-44 years n = 648 (%)	45-64 years n = 517 (%)	≥ 65 years n = 565 (%)
Long-term care residence				
Yes	48 (2.8)	9 (1.4)	10 (1.9)	29 (5.1)
Incarcerated				
Yes	32 (1.8)	25 (3.9)	7 (1.4)	0 (0.0)
Homeless				
Yes	275 (15.9)	158 (24.4)	99 (19.1)	18 (3.2)
Not working				
Yes	1,118 (64.6)	286 (44.1)	292 (56.5)	540 (95.6)

Note. TB = tuberculosis.
[a] Data only shown for positive response.

TB Disease Characteristics

Characteristics of the subset (n = 1,442) of subjects with pulmonary TB are presented in Table 4. A positive sputum smear was found in 37.5%, 80.4% had a positive sputum culture, and the chest x-ray showed cavitary lesions in 15.7%. Other radiographic abnormalities consistent with pulmonary TB were observed in 82.7%. In addition to these pulmonary findings, 22.6% also had involvement in extrapulmonary TB sites. Because some subjects had pulmonary and extrapulmonary disease, neither category was exclusive. A total of 609 subjects had some extrapulmonary TB disease. Of these, 81.8% were culture positive for TB. Pleural TB accounted for the greatest proportion (36.5%) of extrapulmonary sites.

Table 4
Characteristics of Subjects With Pulmonary TB Initiating Treatment (n =1,442)

	Total n =1,442	25-44 years n = 527 (%)	45- 64 years n = 433 (%)	≥ 65 years n = 482 (%)
Sputum smear				
Smear positive	541 (37.5)	218 (41.4)	161(37.2)	162 (33.6)
Sputum culture				
Sputum culture positive	1160 (80.4)	445 (84.4)	331(76.4)	384 (79.7)
Chest x-ray				
Cavitary	226 (15.7)	97 (18.4)	80 (18.5)	49 (10.2)
Non-cavitary	1193 (82.7)	421 (79.9)	343 (79.2)	429 (89.0)
Normal	23 (1.6)	9 (1.7)	10 (2.3)	4 (0.8)
Extrapulmonary[a]	326 (22.6)	114 (21.6)	87 (20.1)	125 (25.9)

Note. TB = tuberculosis.
[a] Frequency of extrapulmonary TB among subjects with pulmonary TB.

Among all cases of TB initiating treatment regardless of anatomic site, 84.5% had a positive TB culture. Drug resistance of subjects with culture-positive TB is depicted in Table 5, showing 16.2% were resistant to one or more of the first-line TB antibiotics, while 82.4% did not show resistance.

Table 5
Resistance Profile of Subjects With Culture-Positive TB (n =1,462)

	Total n = 1,462 (100%)	25-44 years n = 541 (%)	45-64 years n = 421 (%)	≥ 65 years n = 500 (%)
Resistance				
MDR	23 (1.6)	12 (2.2)	8 (1.9)	3 (0.6)
Other resistance	214 (14.6)	97 (17.9)	61 (14.5)	56 (11.2)
Pansensitive	1,205 (82.4)	425 (78.6)	344 (81.7)	436 (87.2)
Not tested	20 (1.4)	7 (1.3)	8 (1.9)	5 (1.0)

Note. TB = tuberculosis; MDR = multiple-drug resistance.

Of note, 20.3% of the subjects reported previous TB disease. The frequency of previous TB increased with age and was 16.8%, 20.9%, and 23.7% for age-groups 25 to 44 years,

45 to 64 years, and ≥ 65 years, respectively. And, there was an association of resistance with previous TB treatment. More than half of those with MDR (12/23) had TB disease before the current episode.

Comorbid Conditions

Table 6 shows comorbid condition; 13.8% (n = 239) had a positive HIV test, while 50.4% were not tested. In the sample, 13.3% reported excessive alcohol use, 12.2% acknowledged non-IVDU, and 7.5% indicated IVDU. And, 7.9% reported use of all three substances (IV and non-IVDU and excessive use of alcohol).

Table 6
Comorbid Conditions of Subjects Initiating Treatment for Active TB, (n = 1,730)

Total n =1,730 (100%)	25-44 years n = 648 (%)	45-64 years n = 517 (%)	≥ 65 years n = 565 (%)	
HIV				
HIV positive	239 (13.8)	172 (26.5)	63 (12.2)	4 (0.7)
HIV negative	619 (35.8)	304 (46.9)	238 (46.0)	77 (13.6)
Not tested	872 (50.4)	172 (26.5)	216 (41.8)	484 (85.7)
Excessive alcohol use				
Yes	230 (13.3)	122 (18.8)	92 (17.8)	16 (2.8)
IV drug use				
Yes	129 (7.5)	77 (11.9)	50 (9.7)	2 (0.4)
Non-IV drug use				
Yes	211 (12.2)	140 (21.6)	68 (13.2)	3 (0.5)
Substances used*				
One	193 (52.6)	105 (49.3)	70 (52.6)	19 (95.0)
Two	145 (39.5)	93 (43.7)	4 (36.8)	1 (5.0)
Three	29 (7.9)	15 (7.0)	14 (10.5)	0 (0.0)

Note. TB = tuberculosis; HIV = human immunodeficiency virus; IV = intravenous.

* Excessive alcohol, IV, and/or non-IV drug use among 367 drug users.

Health Care Delivery Characteristics

As shown in Table 7, health care characteristics, most subjects (54.2%) self-administered their medications, 34.5% received their medications under DOT from the public system, and 11.3% received their treatment under both conditions. Most subjects (68.6%) received their care from a public provider, 30.7% from a private provider. A very small proportion (0.8%) received their care from both public and private providers. Because there were only 13 such cases, they were assigned to either public or private provider by length of time under treatment or by original TB care.

Table 7
Health Care Delivery Characteristics for Subjects Initiating Treatment for Active TB, (n = 1,730)

	Total n =1,730 (100%)	25-44 years n = 648 (%)	45-64 years n = 517 (%)	≥ 65 years n = 565 (%)
Supervision of therapy				
Directly observed	597 (34.5)	280 (43.2)	196 (37.9)	121 (21.4)
Self-administered	938 (54.2)	297 (45.8)	258 (49.9)	383 (67.8)
Combination	195 (11.3)	71 (11.0)	63 (12.2)	61 (10.8)
Provider type				
Private	536 (31.0)	137 (21.1)	111 (21.5)	288 (51.0)
Public	1,194 (69.0)	511 (78.9)	406 (78.5)	277 (49.0)

Note. TB = tuberculosis.

Study Aim 2: To Describe All-Cause Mortality During Treatment for Active TB.

There were 184 deaths (10.6%) in the study population: 4.9%, 7.9%, and 19.6% in age-groups 25 to 44 years, 45 to 64 years, and 65 and older, respectively (see Table 8). Compared with the 25 to 44 year-old group, both the 45 to 64 year-old group [OR 1.66 (95% CI: 1.03, 2.67)] and those older than 65 [OR 4.71 (95% CI: 3.12, 7.10)] were

statistically significantly more likely to experience all-cause mortality. Figure 4 depicts the survival curve by age-group.

All cause mortality was predominant in the early treatment period, with half of all 184 deaths (n = 92) occurring by 8 weeks of TB treatment. Three fourths of all deaths (n = 138) happened before 24 weeks, and the final quartile of deaths (n = 46) were recorded during the period of 24 through 141 weeks.

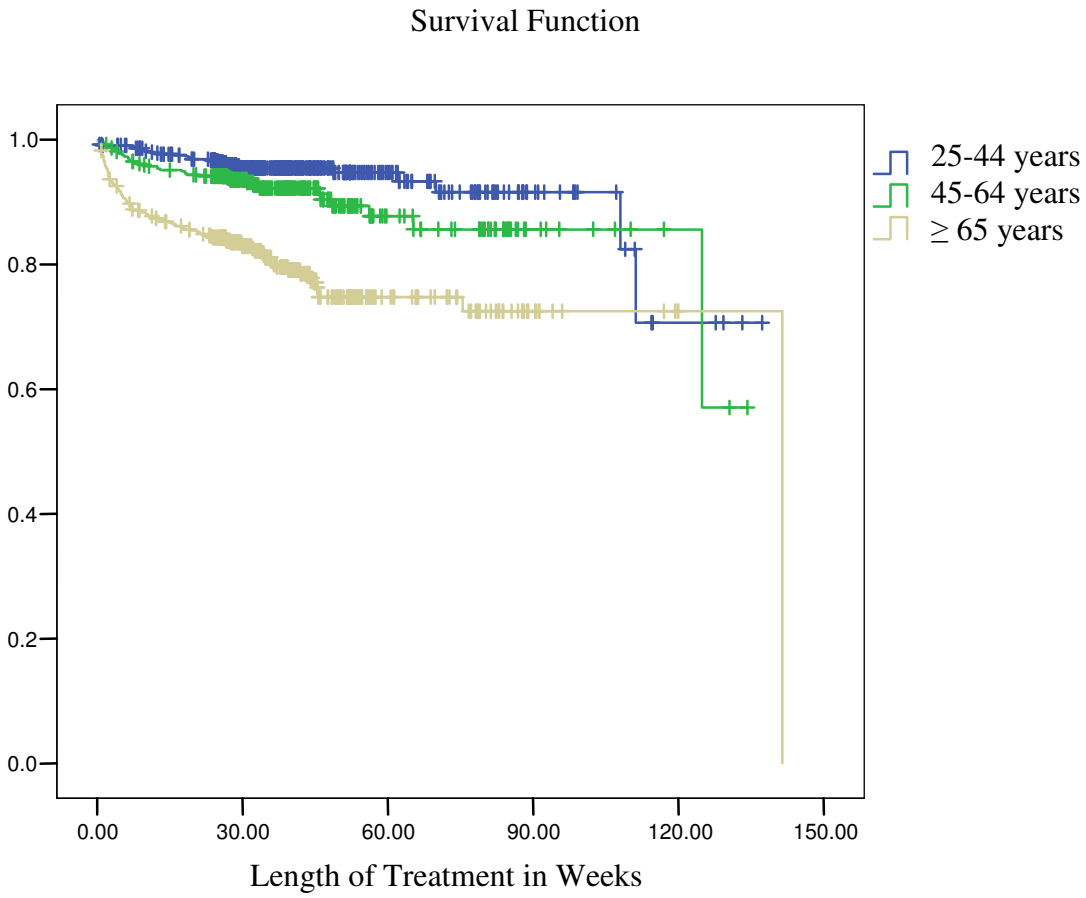

Figure 4. Cumulative survival during treatment for active tuberculosis by age-group.

Table 8
Odds Ratio With 95% Confidence Interval for Age Strata and All-Cause Mortality in Subjects Initiating Treatment for Active TB (n =1,730)

	Death during treatment n (%)	OR	95% CI
Age-group			
25-44 years	32 (4.9)	1.00	
45-64 years	48 (7.9)	1.66	1.03, 2.67
65 and older	111 (19.6)	4.71	3.12, 7.10

Note. TB = tuberculosis; OR = odds ratio; CI = confidence interval; 1.00 = reference group.

There were 73 subjects (4.2%) without complete follow-up information, most of whom (n = 55) moved to another jurisdiction. Those who lacked complete outcome information had received treatment for active TB for an average of 18 (± 15.8) weeks, while the median treatment length was 13.7 weeks. Those with complete outcome information received treatment for 36.6 (± 20.1) weeks with a median treatment length of 30.3 weeks. The mean duration of treatment for those with complete information was 18.6 weeks (95% CI: 13.9, 23.3 weeks) longer than in those with missing information. This difference was statistically significant.

Those without complete outcome information were significantly more likely to be 25 to 44 years old, incarcerated at time of diagnosis [OR 5.62 (95% CI: 2.24, 14.08)], homeless [OR 1.78 (95% CI: 1.03, 3.09)], heavy alcohol [OR 2.20 (95% CI: 1.29, 3.87)] or IV drugs users [OR 2.05 (95% CI: 1.03, 4.10)], and had culture-positive TB [OR 2.57 (95% CI: 1.03, 6.42)].

Study Aim 3: To Estimate the Independent Contribution of Host Demographic Descriptors to All-Cause Mortality.

Table 9 gives the results for gender, race, birth country, and language. Of these, a significantly greater proportion of the men [OR 1.42 (95% CI: 1.04, 1.94)] compared with women died during treatment. Although White subjects had the highest proportion of deaths during treatment (13.4%), only Latinos were significantly protected from all-cause death [OR 0.32 (95% CI: 0.15, 0.70)]. Analysis of subjects by White or non-White race did not show any difference in all-cause mortality [OR 1.36 (95% CI: 0.90, 2.05)]. Country of birth and language were not predictive of all-cause mortality.

Table 9
Odds Ratio With 95% Confidence Interval for Demographic Characteristics and All-Cause Mortality in Subjects Initiating Treatment for Active TB, (n =1,730)

	Death during treatment n (%)	OR	95% CI
Gender			
Male	135 (11.8)	1.42	1.04, 1.94
Female	49 (8.3)	1.00	
Race			
White	32 (13.4)	1.00	
Black	20 (9.9)	0.71	0.39, 1.29
Asian	117 (11.0)	0.80	0.53, 1.22
Latino	9 (4.8)	0.32	0.15, 0.70
Other	6 (16.2)	1.25	0.48, 3.24
Immigration			
U.S. born	56 (11.9)	1.18	0.88, 1.58
Non-U.S. born	128 (10.2)	1.00	
Language			
English	40 (7.9)	0.97	0.67, 1.42
Not English	65 (8.1)	1.00	

Note. TB = tuberculosis; OR = odds ratio; CI = confidence interval; 1.00 = reference group; U.S.= United States.

Study Aim 4: To Estimate the Independent Contribution of Social-Environmental Characteristics and All-Cause Mortality.

Table 10 sets forth the social-environmental factors related to housing, homelessness, incarceration, and work status at initiation of treatment. Those subjects who were living in long-term care facilities were significantly more likely to die during treatment [OR 3.66 (95% CI: 1.93, 6.94)], while homelessness was not associated with all-cause mortality. There were no deaths in those whose TB was diagnosed while they were in jail. As identified earlier, those who were incarcerated at the time of diagnosis (n = 32) were 5.62 times (95% CI 2.24, 14.08) more likely to have incomplete outcome information, while the homeless were 1.78 more likely (95% CI: 1.03, 3.09) to be missing outcome information. Not working in the period before initiating treatment was associated with all-cause mortality 9.09 times more than in those who were employed (95% CI: 5.03, 16.39).

Table 10
Odds Ratio With 95% Confidence Interval for Social-Environmental Factors and All-Cause Mortality in Subjects Initiating Treatment for Active TB, (n =1,730)

	Death during treatment n (%)	OR	95% CI
Long-term care housing			
Yes	14 (29.2)	3.66	1.93, 6.94
No	170 (10.1)	1.00	
Incarcerated			
Yes	0	NA	NA
No	184 (100)	1.00	
Homeless			
Yes	34 (12.4)	1.23	0.82, 1.82
No	150 (10.3)	1.00	
Not Working			
Yes	172 (15.4)	9.09	5.03, 16.39
No	12 (2.0)	1.00	

Note. TB = tuberculosis; OR = odds ratio; CI = confidence interval; 1.00 = reference group; NA = not applicable.

Study Aim 5: To Estimate the Independent Contribution of TB Disease Characteristics to All-Cause Mortality.

Table 11 shows the TB disease characteristics associated with death during treatment. The detection of TB by laboratory culture was associated with a significantly greater death rate (12.2%) than those with culture-negative TB (1.9%) [OR 7.34 (95% CI: 2.99, 18.02)]. The diagnosis of extrapulmonary and pulmonary disease was significantly associated with all-cause mortality when compared with isolated pulmonary disease [OR 1.94 (95% CI: 1.43, 2.64)]. Of the 43 subjects with either miliary or CNS TB disease, 14 died. Chest x-ray status was not associated with all-cause mortality. Prior active TB disease was significantly protective of all-cause mortality during treatment [OR 0.59 (95% CI: 0.39, 0.89)].

Table 11
Odds Ratio With 95% Confidence Interval for TB Disease Characteristics and All-Cause Mortality in Subjects Initiating Treatment for Active TB, (n =1,730)

	Death during treatment n (%)	OR	95% CI
TB culture			
Positive	179 (12.2)	7.34	2.99, 18.02
Negative	5 (1.9)	1.00	
Chest x-ray			
Abnormal	167 (10.8)	1.20	0.71, 2.20
Normal	17 (9.2)	1.00	
Disease site			
Extrapulmonary	91 (14.9)	1.94	1.43, 2.64
Pulmonary only	93 (8.3)	1.00	
Resistance			
Any resistance	23 (9.8)	0.90	0.70, 1.76
No known resistance.	161 (10.8)	1.00	
Previous TB			
Yes	24 (6.8)	0.59	0.39, 0.89
No	160 (11.6)	1.00	

Note. TB = tuberculosis; OR = odds ratio; CI = confidence interval; 1.00 = reference group.

Study Aim 6: To Estimate the Independent Contribution of Comorbid Conditions to All-Cause Mortality.

Table 12 shows the estimate for the comorbid conditions of HIV coinfection and substance use. Those subjects documented to have a positive HIV test [OR 10.78 (95% CI: 5.42, 21.44)] and those missing HIV status [OR 10.04, (95% CI: 5.38, 18.73)] had a statistically significantly greater all-cause mortality. Alcohol and other substance use were not associated with all-cause mortality.

Table 12
Odds Ratio With 95% Confidence Interval for Comorbid Conditions and All-Cause Mortality in Subjects Initiating Treatment for Active TB, (n =1,730)

	Death during treatment n (%)	OR	95% CI
HIV			
Positive	39 (16.3)	10.78	5.42, 21.44
Unknown	134 (15.4)	10.04	5.38, 18.73
Negative	11 (1.8)	1.00	
Excessive alcohol use			
Yes	24 (10.4)	0.99	0.95, 1.05
No	160 (10.7)	1.00	
IV drug use			
Yes	20 (15.5)	1.61	0.97, 2.66
No	164 (10.2)	1.00	
Non-IV drug use			
Yes	23 (10.9)	1.03	0.65, 1.64
No	161 (10.6)	1.00	

Note. TB = tuberculosis; OR = odds ratio; CI = confidence interval; HIV = human immunodeficiency virus; 1.00 = reference group; IV = intravenous; non-IV = non-intravenous.

Study Aim 7: To Estimate the Independent Contribution of Health Care Provider Characteristics to All-Cause Mortality.

Having a private provider was statistically significantly associated with all-cause mortality 4.82 times (95% CI: 3.50, 6.65) that of the public TB provider. Because DOT is offered only by public providers, supervision of therapy was evaluated in the group

receiving treatment by public health providers (n = 1,194). In those who received care by the public provider, there was a statistically significant protective effect in those receiving SAT [OR 0.39 (95% CI: 0.21, 0.71)] and in those receiving a combination of DOT and SAT [OR 0.27 (95% CI: 0.10, 0.76)] when compared with those on DOT.

Study Aim 8: To Estimate the Overall All-Cause Mortality During TB Treatment Using Predictors from Each of the Subset Analyses.

Potential predictors were entered into several different multivariate logistic regression models. First, six demographic variables: age-group, gender, race, immigration, language, and work status were used to estimate all-cause mortality (see Table 13). In the demographic predictor model, the oldest group (≥ 65 years) was 2.42 times (95% CI: 1.48, 3.97) more likely to die during treatment than the 25 to 44 year old stratum; men were 1.55 times (95% CI: 1.08, 2.22) more likely to die than women, while race and immigration were not significant predictors. Although language was a significant factor, those with unknown language had a higher risk of mortality when compared with English speakers [OR 3.05 (95% CI: 1.85, 5.02)]. Not working was the strongest predictor of all-cause mortality in this model [OR 6.06 (95% CI: 3.20, 11.51)].

Table 13

Odds Ratio With 95% Confidence Interval of Multiple Logistic Regression of Demographics and Working Status and All-Cause Mortality in Subjects Initiating Treatment for Active TB, (n =1,730)

	OR	95% CI
Age-groups		
25-44 years	1.00	
45-64 years	1.45	0.88, 2.39
≥ 65 years	2.42	1.48, 3.97
Gender		
Female	1.00	
Male	1.55	1.08, 2.22
Race		
White	1.00	
Black	0.76	0.40, 1.43
Asian	0.73	0.36, 1.50
Latino	0.54	0.22, 1.36
Other	1.05	0.37, 2.94
Immigration		
U.S. Born	1.00	
Non-U.S. Born	0.73	0.37, 1.43
Language		
English	1.00	
Not English	1.43	0.82, 2.51
Unknown	3.05	1.85, 5.02
Working		
Working	1.00	
Not working	6.06	3.20, 11.51

Note. TB = tuberculosis; OR = odds ratio; CI = confidence interval; 1.00 = reference group; U.S. = United States.

The second model tested the comorbid conditions of HIV disease and drug use (see Table 14). Positive HIV status is a strong independent predictor of all-cause mortality [OR 9.73 (95% CI: 4.74, 20.00)], and IVDU is associated with higher mortality [OR 2.05 (95% CI: 1.02, 4.12)]; non-IVDU and excessive alcohol use were not predictive of death.

Table 14
Odds Ratio With 95% Confidence Interval of Multiple Logistic Regression of Comorbidity Predictors and All-Cause Mortality in Subjects Initiating Treatment for Active TB, (n =1,730)

	OR	95% CI
HIV		
Negative	1.00	
Positive	9.74	4.74, 20.00
Unknown	10.65	5.67, 20.02
Alcohol		
None	1.00	
Excess	1.28	0.77, 2.14
IDU		
None	1.00	
Use	2.05	1.02, 4.12
Non-IDU		
None	1.00	
Use	0.74	0.37, 1.35

Note. TB = tuberculosis; OR = odds ratio; CI = confidence interval; HIV= human immunodeficiency virus; 1.00 = reference group; IDU = intravenous drug use; Non-IDU = non-intravenous drug use (substance use other than alcohol or intravenous drugs)

The third model includes the variables of long-term care facility housing and homelessness (see Table 15). Only long-term care facility housing was statistically significantly associated with higher all- cause mortality in this model [OR 3.66 (95% CI: 1.92, 6.96].

Table 15
Odds Ratio With 95% Confidence Interval of Multiple Logistic Regression of Social-Environmental Housing Predictors and All-Cause Mortality in Subjects Initiating Treatment for Active TB, (n =1,730)

	OR	95% CI
Long-term care housing		
No	1.00	
Yes	3.66	1.92, 6.96
Homelessness		
No	1.00	
Yes	1.23	0.82, 1.83

Note. TB = tuberculosis; OR = odds ratio; CI = confidence interval; 1.00 = reference group.

A fourth model tested TB disease and provider variables: TB culture, chest x-ray results, disease site, previous TB disease history, TB drug resistance, and type of TB medical provider (see Table 16). With the exception of drug resistance, each of the variables was a statistically significant independent predictor with positive TB culture, abnormal chest x-ray, disease disseminated beyond the lungs, and private TB medical provider all associated with higher all-cause mortality. In contrast, previous TB disease history was statistically significantly protective for risk of death [OR 0.61 (95% CI: 0.38, 0.96)] compared with a first episode of TB.

Table 16

Odds Ratio With 95% Confidence Interval of Multiple Logistic Regression of TB Disease Treatment Predictors and All-Cause Mortality in Subjects Initiating Treatment for Active TB, (n =1,730)

	OR	95% CI
TB Culture		
Negative	1.00	
Positive	4.99	2.00, 12.42
Chest x-ray		
Normal	1.00	
Abnormal	2.13	1.20, 3.78
Disease site		
Pulmonary only	1.00	
Any extrapulmonary	1.61	1.14, 2.26
Provider type		
Public	1.00	
Private	4.06	2.91, 5.67
Previous TB		
No	1.00	
Yes	0.61	0.38, 0.96
TB drug resistance		
No	1.00	
Yes	0.92	0.57, 1.49

Note. TB = tuberculosis; OR= odds ratio; CI=confidence interval; 1.00 = reference group.

Final Multivariate Model

A final parsimonious model was created for the entire data set that included those variables that were significant in bivariate analysis: age-groups, gender, homelessness, working, disease site, previous TB disease, and provider type. Homelessness was included because of the high prevalence of this risk factor in this population (15.9%).

The following covariates were excluded: immigration, excessive alcohol use, IVDU, non-IVDU, chest x-ray, and resistance. Incarceration was not included because there were no deaths documented among these subjects. Similarly, race was excluded because subset multivariate analysis failed to show any significant independent association with all-cause mortality. Because only public cases received DOT,

supervision of treatment could not be evaluated in this model. TB culture was excluded because only five subjects with culture-negative TB died, making this measure unstable in multivariate analysis.

The overall model to estimate the OR and 95% CI for all predictors (other than supervision of therapy) statistically significantly associated with all-cause mortality in bivariate analysis is shown in Table 17. The significant predictors in each of the domains of the conceptual model are as follows: host demographics (age-group and gender); social-environmental: (homelessness and working); TB agent (previous TB history) host comorbidity (HIV coinfection); and health care system characteristics (private or public provider). Increased all-cause mortality was associated with age-groups older than 44 years, male gender, homelessness, not working, HIV-positive or HIV status unknown, homelessness, not working, and having a private TB medical provider. A history of TB disease was statistically significant and associated with a protective effect against all-cause mortality.

Table 17
Odds Ratio With 95% Confidence Interval of Final Multiple *Logistic Regression and All-Cause Mortality in Subjects Initiating Treatment for Active TB (n =1,730)*

	OR	95% CI
Age-groups		
25-44 years	1.00	
45-64 years	2.22	1.27, 3.87
≥ 65 years	2.50	1.31, 4.74
Gender		
Female	1.00	
Male	1.61	1.10, 2.36
Homelessness		
No	1.00	
Yes	2.07	1.22, 3.53
Working		
Yes	1.00	
No	5.89	3.01, 11.52
Disease Site		
Pulmonary only	1.00	
Any extrapulmonary	1.30	0.92, 1.85
Previous TB		
No	1.00	
Yes	0.56	0.34, 0.89
HIV		
Negative	1.00	
Positive	8.06	3.82, 17.02
Unknown	4.29	2.12, 8.67
Provider type		
Public	1.00	
Private	3.85	2.61, 5.68

Note. TB = tuberculosis; OR = odds ratio; CI = confidence interval; HIV = human immunodeficiency virus.

Public TB Medical Provider Subset

To evaluate the effect of treatment supervision, a subset analysis was performed on the cases with a public provider of care (n = 1,194). The same predictors significant from bivariate analysis were entered into a multiple logistic regression. In addition, race and ethnicity were controlled for in this model. The results of this model are shown in Table 18.

The subset of cases receiving TB care from the public provider has a set of independent statistically significant predictors that differ from the overall model. Unlike the model that describes all cases, the variables of age-group, gender, homelessness, and previous history of TB are no longer associated all-cause mortality. Yet, extrapulmonary disease is independently significantly associated with a 2.6 times (95% CI = 1.50, 4.50) greater risk of all-cause mortality than those with disease limited to pulmonary TB. Supervision of therapy in the public model is independently significantly associated with all-cause mortality. SAT has a statistically significant independent protective effect compared with DOT [OR 0.48 (95% CI: 0.24, 0.96)]. A combination of SAT and DOT is also significantly independently protective of all-cause mortality for those receiving public TB care [OR 0.27 (95% CI: 0.09, 0.78)].

Table 18
Odds Ratio With 95% Confidence Interval of Multiple Logistic Regression and All-Cause Mortality in Subjects Receiving Public TB Care Initiating Treatment for Active TB, (n = 1,194)

	OR	95% CI
Age-groups		
25-44 years	1.00	
45-64 years	1.95	0.95, 3.98
≥ 65 years	1.70	0.70, 4.17
Gender		
Female	1.00	
Male	1.47	0.78, 2.77
Race		
White	1.00	
Black	0.77	0.32, 1.85
Asian	1.60	0.62, 4.13
Latino	0.99	0.33, 2.98
Other	0.59	0.07, 5.14
Homeless		
No	1.00	
Yes	2.01	0.95, 4.26
Working		
Working	1.00	
Not working	4.00	1.58, 10.12
Disease site		
Pulmonary only	1.00	
Any extrapulmonary	2.60	1.50, 4.50
Previous TB		
No	1.00	
Yes	0.53	0.25, 1.12
HIV		
Negative	1.00	
Positive	5.79	2.26, 14.84
Unknown	5.01	2.10, 11.93
Supervision of therapy		
DOT	1.00	
SAT	0.48	0.24, 0.96
Combination	0.27	0.09, 0.76

Note. TB = tuberculosis; OR = odds ratio; CI = confidence interval; HIV = human immunodeficiency virus; DOT = directly observed therapy; SAT = self-administered therapy.

Private TB Medical Provider Subset

A model of the subset of subjects with private TB medical providers was created including the variables significant from earlier subset analyses (see Table 19). Supervision of therapy is not included because DOT is only available from the public health care system.

As with the overall model, older age-group was associated with greater all-cause mortality: 45 to 64 year olds had mortality 3.72 times (95% CI: 1.29, 10.66) and those older than 65 years 4.70 times (95%CI: 1.51, 14.65) greater than that of those younger than 45 years old. Homelessness is associated with higher all-cause mortality [OR 3.31 (95% CI: 1.07, 10.24)], as is not working [OR 8.06 (95% CI: 2.96, 21.98)].

In subjects receiving care from private providers, gender [OR 1.60 (95% CI: 0.97, 2.62)] and previous TB history [OR 0.62 (95% CI: 0.33, 1.17)] are not associated with a difference in all-cause mortality. Furthermore, subjects with unknown HIV status do not differ in risk of all-cause mortality from HIV negative subjects in this model [OR 3.35 (95% CI: 0.84, 13.27)].

Table 19
Odds Ratio With 95% Confidence Interval of Multiple Logistic Regression and All-Cause Mortality in Subjects Receiving Private TB Care Initiating Treatment for Active TB, (n = 536)

	OR	95% CI
Age-groups		
25-44 years	1.00	
45-64 years	3.72	1.29, 10.66
≥ 65 years	4.71	1.51, 14.65
Gender		
Female	1.00	
Male	1.60	0.97, 2.62
Race		
White	1.00	
Black	0.80	0.26, 2.42
Asian	0.80	0.38, 1.72
Latino	0.28	0.06, 1.26
Other	0.82	0.16, 4.14
Homelessness		
No	1.00	
Yes	3.31	1.07, 10.24
Working		
Working	1.00	
Not working	8.06	2.96, 21.98
Disease Site		
Pulmonary only	1.00	
Any extrapulmonary	0.82	0.52, 1.31
Previous TB		
No	1.00	
Yes	0.62	0.33, 1.17
HIV		
Negative	1.00	
Positive	17.55	3.80, 81.07
Unknown	3.35	0.84, 13.27

Note. TB = tuberculosis; OR = odds ratio; CI = confidence interval; HIV = human immunodeficiency virus.

HIV-Negative Subset

Subjects with a negative HIV test (n = 619) were evaluated for the same predictors used in the final multiple logistic regression and the results are shown in Table 20. Within the HIV-negative subset, there were no deaths in women. Homelessness was

associated with increased all-cause mortality [OR 7.13 (95% CI: 1.58, 32.06)]. Age-group, working status, disease site, previous TB, and provider type were not statistically significantly associated with all-cause mortality during treatment for the HIV negative subjects.

Table 20
Odds Ratio With 95% Confidence Interval of Multiple Logistic Regression and All-Cause Mortality in HIV-Negative Subjects Initiating Treatment for Active TB, (n = 619)

	OR	95% CI
Age-groups		
25-44 years	1.00	
45-64 years	4.34	0.85, 22.28
≥ 65 years	6.10	0.66, 56.67
Homelessness		
No	1.00	
Yes	7.13	1.58, 32.06
Working		
Yes	1.00	
No	1.15	0.24, 5.63
Disease Site		
Pulmonary only	1.00	
Any extrapulmonary	1.69	0.45, 6.43
Previous TB		
No	1.00	
Yes	0.82	0.17, 4.00
Provider type		
Public	1.00	
Private	4.66	0.98, 22.09

Note. TB = tuberculosis; OR = odds ratio; CI = confidence interval; HIV = human immunodeficiency virus.

HIV-Positive and HIV-Status-Missing Subset

HIV-positive subjects and those missing HIV status (n = 1,111) were evaluated together as earlier analyses indicated that both categories were statistically significantly associated with a higher all-cause mortality than the HIV-negative subjects. The analysis of the HIV-positive and HIV-unknown subsets is depicted in Table 21.

Within the subset of subjects with a documented positive or unknown HIV status, the predictors are similar to that of the over-all model. Those 45 to 64 years old [OR 2.06 (95% CI: 1.13, 3.75)] and 65 years and older [OR 2.28 (95% CI: 1.16, 4.48)] were statistically significantly more likely to experience all-cause mortality. Not working [OR 7.44 (95% CI: 3.48, 15.87)] and private TB medical provider [OR 3.76 (95% CI: 2.52, 5.61)] were all statistically significantly associated with a higher all-cause mortality. Previous TB was protective against death during treatment [OR 0.54 (95% CI: 0.33, 0.89)]. Those with a confirmed HIV-positive test were 1.96 (95% CI: 1.05, 3.68) times more likely to experience all-cause mortality during treatment for active TB. Unlike the final multiple logistic regression, in the subset analysis homelessness is not associated with all-cause mortality in the subset with HIV-positive or unknown status.

Table 21
Odds Ratio With 95% Confidence Interval of Multiple Logistic Regression and All-Cause Mortality in HIV-Positive and HIV-Status Unknown Subjects Initiating Treatment for Active TB (n = 1,111)

	OR	95% CI
Age-groups		
25-44 years	1.00	
45-64 years	2.06	1.13, 3.75
≥ 65 years	2.28	1.16, 4.48
Gender		
Female	1.00	
Male	1.48	1.00, 2.19
Homelessness		
No	1.00	
Yes	1.74	0.97, 3.13
Working		
Yes	1.00	
No	7.44	3.48, 15.87
Disease site		
Pulmonary only	1.00	
Any extrapulmonary	1.26	0.88, 1.80
Previous TB		
No	1.00	
Yes	0.54	0.33, 0.89
HIV		
Unknown	1.00	
Positive	1.96	1.05, 3.68
Provider type		
Public	1.00	
Private	3.76	2.52, 5.61

Note. HIV = human immunodeficiency virus; TB = tuberculosis; OR = odds ratio; CI = confidence interval.

Pulmonary TB Subset

The subjects (n = 1,442) with pulmonary TB were analyzed separately using all variables from the overall model with sputum smear status included to evaluate this variable in a multivariate model. The results of this subset analysis are presented in Table 22. In the subset of subjects with pulmonary TB, only homelessness is not statistically significantly associated with all-cause mortality during TB treatment. The association of

increasing age, male gender, not working, HIV positive or unknown status, and private provider type with increased all-cause mortality is similar to that of the overall model. Of note, within the subset of subjects with pulmonary TB, the additional diagnosis of extrapulmonary TB is statistically significantly associated with 1.94 times (95% CI: 1.28, 2.95) the all-cause mortality of those with isolated pulmonary TB. Smear-positive TB disease is associated with 3.63 times (95% CI: 2.42, 5.42) the all-cause mortality of those with smear negative TB disease.

Table 22

Odds Ratio With 95% Confidence Interval of Multiple Logistic Regression and All-Cause Mortality in Subjects with Pulmonary TB Initiating Treatment for Active TB, (n = 1,442)

	OR	95% CI	
Age-groups			
25-44 years	1.00		
45-64 years	2.37	1.27	4.42
≥ 65 years	2.31	1.21,	4.77
Gender			
Female	1.00		
Male	1.60	1.03,	2.50
Homelessness			
No	1.00		
Yes	1.77	0.99	3.17
Working			
Yes	1.00		
No	7.25	3.32,	15.80
Smear			
Negative	1.00		
Missing	1.38	0.58,	3.28
Positive	3.63	2.42,	5.42
Disease site			
Pulmonary only	1.00		
Any extrapulmonary	1.94	1.28,	2.95
Previous TB			
No	1.00		
Yes	0.57	0.34,	0.96
HIV			
Negative	1.00		
Positive	6.56	2.90,	14.83
Unknown	3.97	1.83,	8.60
Provider type			
Public	1.00		
Private	4.42	2.86,	6.86

Note: TB = tuberculosis; OR = odds ratio; CI = confidence interval; HIV = human immunodeficiency virus.

CHAPTER 5

DISCUSSION

The current study of 1,730 subjects initiating treatment for active TB in San Francisco over a period of 10 years was the first to identify predictors of all-cause mortality that included type of medical provider. An epidemiologic, conceptual model identified statistically and clinically significant risk and protective factors from each of the five domains: host demographics, social-environmental characteristics, TB agent characteristics, comorbid conditions, and health care delivery characteristics.

This study reports three new findings and provides further substantiation for several previously documented findings. First, receiving TB care from a private provider was associated with a 385% higher mortality than receiving care from a public provider. Second, a history of prior TB disease was statistically significantly protective of death during TB treatment. Finally, a combination of DOT and SAT was associated with lower mortality when compared with DOT for the duration of treatment.

The study results confirm earlier findings in the literature that all-cause mortality is higher with each age-group (Cayla et al., 2004; Chan-Yeung et al., 2002; Hansel et al., 2004), homelessness (Dewan et al., 2004), not working (Sterling et al., 2006), positive HIV coinfection (Sterling et al., 2006), and concomitant extrapulmonary TB disease (El Sahly et al., 2007).

Sample

The sample consisted of 1,730 subjects, ranging in age from 25 to 102 years. The subjects of this study were predominately male, Asian, non-English speakers, and almost three quarters were born outside of the U.S. The social environmental component of the

model revealed that most subjects were not working, many were homeless, and smaller proportions were living in long-term care facilities or incarcerated. The homeless were mostly distributed in the youngest and middle age-group. Most subjects in long-term care facilities were at least 65 years old. None of the oldest group was incarcerated.

The characteristics of the agent of the model were as follows. Pulmonary TB was the principal site of disease in most subjects, and more than one fifth had a secondary site of disease indicating dissemination. TB was confirmed by culture for the most of the subjects, and a chest x-ray consistent with TB was present in all but a few of the subjects with pulmonary disease.

Those subjects who were resistant to one or more of the first-line TB medications equaled 16.2% of the sample; the proportion with resistance decreased with advancing age. The proportion of MDR subjects was 1.6%. A history of TB disease was reported for about one in five of the study subjects, and this was more likely in the middle and older age-groups (≥ 45 years).

The comorbidity of HIV was present in 27.8% of the subjects who had this data available. Of note, this information was unavailable for 50.4% of the subjects. Those with documented HIV coinfection comprised 13.8% of the total sample, and most were in the youngest age-group. In the substance use category, alcohol was the most commonly used substance. Non-IVDU and IVDU were reported by 12.2% and 7.5% of the subjects, respectively. Substance use was reported almost exclusively in those younger than 65 years.

For supervision of TB therapy, more than half of the subjects received SAT; 34.5% received DOT. More than 1 in 10 received a combination of SAT and DOT. More

than two thirds of all subjects received their care from the public TB provider, while those 65 years and older were equally divided into private and publicly managed TB care.

All-Cause Mortality

Of the 1,730 subjects, 184 (10.6%) died before successful completion of TB treatment. Death was most likely to occur early in the treatment period with half of all deaths occurring before 8 weeks of treatment. For 85.1% of those who began treatment, the outcome was successful completion of therapy. There was missing outcome information for 4.2% of the subjects. Unknown outcome was found more frequently in those 25 to 44 years old, incarcerated, homeless, alcohol and IV drug users, and those with a positive TB culture.

Predictors of All-Cause Mortality

Host Demographic Predictors

The most important host predictor was age, as those older than 65 were nearly five times more likely to die. This is consistent with national and local mortality statistics of increasing death rates in advanced age-groups. TB disease all-cause mortality in San Francisco is concentrated in the oldest age-group with more than 60% (111 of 184) of all the deaths occurring in the group 65 years and older. The age-specific all-cause mortality in this group of 19.6% was nearly five times that of the 25 to 44 year old group. In multivariate modeling that considered other predictors, older age was associated with all-cause mortality except for those in public care and documented to be HIV uninfected.

That older age is positively correlated with all-cause mortality is not surprising. Ischemic heart disease, stroke, cancer, and diabetes are important competing causes of mortality in San Francisco that disproportionately affect older adults (SFDPH, 2003).

Younger age-groups were much more likely to be substance users. In San Francisco, drug overdose and alcohol dependence were the two leading causes of death and disability in 1998 (SFDPH, 2003).

Those who died were more likely to be male in the overall model, in the HIV subset analyses, and in those with pulmonary TB. Men were more likely than women to have HIV results. The documented prevalence of HIV coinfection among men was greater than among women subjects. There were no deaths among female subjects documented to be HIV negative.

Asians and Blacks represented 61% and 12% of the sample respectively. According to 2000 census data, Asians and Blacks represented roughly 30% and 5% of the population of San Francisco (SFDPH, 2003). Conversely, White subjects constituted only 14% of the study sample, although they represented more than 45% of San Francisco's population in 2000 (SFDPH, 2003). Although Latinos had a significantly smaller proportion of deaths in univariate analysis, this finding was no longer evident in any of the full prediction models.

TB disease treatment is much more prevalent among the foreign born in San Francisco. About 40% of San Francisco's population was born outside the U.S., while 73% of all TB cases arose from individuals born in other countries. Half of all U.S.-born persons in the sample were in the 25 to 44 year old stratum. More than 36% of the U.S.-born subjects older than 25 years were positive for HIV, while only 5.4% of the foreign-born were found to be coinfected with HIV. It is difficult to detect any effect because 50% of all cases did not have information about HIV status, and the foreign-born were less likely than the U.S.-born to be tested for this factor. Although there may be a

different distribution of predictors between immigrants and U.S.-born subjects, no difference in all-cause mortality was detected. The high proportion of subjects without a language reported prevented any estimation of its effect on all-cause mortality.

Social-Environmental Predictors

The social-environmental characteristics that were significant were not working, living in a long-term care facility, and being homeless. Less than 5% of the TB patients were either living in a long-term care facility, such as a nursing home, or were incarcerated at the time of diagnosis. The number of individuals living in a long-term care facility or incarcerated was quite small. Because of the small numbers at risk and the concentration of subjects in the oldest age-group, long-term care facility was not an important predictor in multivariate modeling. Incarceration was associated with incomplete outcome information (6 of 32 were either lost or moved without follow-up information), suggesting that the lack of any deaths in this group is not meaningful.

The social-environmental factors of housing included the 16% that were homeless during the period one year before their diagnosis. The current study found that homelessness was statistically significantly associated with all-cause mortality more than twice that of those more stably housed. Among those receiving private care, the homeless were 3.3 times as likely to die. In the HIV-negative subset analysis that controlled for age-group, working status, disease site, previous TB and provider type, homelessness was the only statistically significant predictor associated with all-cause mortality at more than seven times that of those housed. In the HIV-infected or unknown subset and pulmonary TB subset analyses, homelessness was not associated with all-cause mortality.

Although homelessness was not predictive of mortality during treatment for TB in Spain (Cayla et al., 2004), researchers in Russia reported homelessness as being statistically significantly (OR 9.5, 95% CI 1.3-70.9), associated with all-cause mortality in an 8 month period of follow-up. The homeless have been the focus of TB control efforts for much of San Francisco's history (Craddock, 2000). It is possible that the all-cause mortality of the homeless would have been worse within the public care subset if not for the housing assistance targeted for homeless TB patients during treatment (L.M. Kawamura, personal communication, 2008).

In the current study, not working was more strongly associated with all-cause mortality than within those employed. In the final model that accounted for age, gender, homelessness, disease site, previous TB, HIV coinfection, and provider type, the mortality of those not working was nearly six times that of those working in the period before TB disease diagnosis and treatment. The negative association of not working and survival during TB treatment was second only to HIV coinfection in the overall model and in the subset analyses of public and private provider. In the HIV-positive/unknown and the pulmonary TB subset analyses, not working was the strongest covariate with all-cause mortality, more than seven times that of those working. Not working was thus consistently found to be a strong independent predictor of all-cause mortality second only to HIV coinfection.

The association of not working and all-cause mortality is confounded by age as the group older than 65 years may be retired from work for reasons other than illness. Nonetheless, it is remarkable that 44% of those 25 to 44 years old and 56% of those 45 to

64 years old were not working in the 2 years before diagnosis. Although there were only 25 subjects 65 years and older working, none of them died before treatment completion.

The association of not working with mortality is consistent with the literature. Unemployment was statistically significantly (HR 1.99, 95% CI: 1.18, 3.37), associated with poorer survival in a large U.S. and Canadian multicenter study (Sterling et al., 2006) and in the Russian study (OR 4.9, 95% CI: 1.9, 12.9; Dewan et al., 2004).

This variable must be interpreted cautiously for several reasons. For one, unemployment is based entirely on self-report, and this may be complicated by fear of detection of undocumented status among immigrants, fear of losing a job, and the possibility that untreated TB illness either preceded or was concomitant with job loss. Nonetheless, the strength of association with this variable, indicative of poverty, has important policy and clinical implications for addressing the risk of death during treatment for active TB.

TB Disease Predictors

Although pulmonary TB disease was predominant, extrapulmonary disease represented a substantial proportion - 609 individuals - of incident TB cases on treatment. Although TB disease beyond the pulmonary parenchyma was not associated with all-cause mortality in the overall model, among those with primary pulmonary TB disease the presence of extrapulmonary disease was associated with all-cause mortality at almost twice the rate of those with isolated pulmonary disease. The same relationship was seen among subjects in the public TB provider subset analysis.

Extrapulmonary disease varies from the less virulent and generally noninfectious lymph node TB disease to the often fatal conditions of TB meningitis and miliary TB. Of

note, 14 of the 46 cases (about one third) with either TB meningitis or miliary TB died before the end of treatment. Although few subjects were affected, this represents a high case fatality rate.

TB smear and culture were important predictors. Although the sputum smear represents respiratory TB disease, the culture is available for all specimens regardless of anatomic location. Because this study involved risk factors for death among all cases of TB initiating treatment regardless of site, this measure was more important than sputum smear and chest x-ray, which are not relevant to all cases. In this study, culture-negative TB is associated with a far better survival of treatment than those who were culture-positive. This finding is consistent with the literature. Having a culture positive for TB was associated with a death rate 4.7 times that of the culture-negative cases in this study. Only about 2% of the culture-negative subjects died during treatment. In the group with pulmonary TB, a positive sputum smear was associated with all-cause mortality more than 3.6 times those with a negative sputum smear in a multivariate model. This data supports the continued use of the mycobacterial smear and culture for diagnosis and effective support for those found to have a positive result.

Only three individuals with MDR TB died during treatment (13%). This is comparable with studies from Taiwan (Chiang et al., 2006) where MDR TB mortality was 9.4%, and Latvia (Leimane et al., 2005) where MDR TB mortality was 7%. There was low attrition in San Francisco with only two MDR TB clients lost to follow-up, while 29% of the Taiwanese subjects and 13% of the Latvian subjects defaulted. Although clinical judgment would predict higher mortality in subjects with MDR because of the more highly toxic and less efficacious drugs used for treatment, this was not the case.

Longer survival in this group may be related to increased medical and nursing effort in their care.

A history of TB disease had an overall protective effect. It is possible that individuals who have had TB disease previously are aware that they are at risk of re-infection or reactivation of latent disease with or without previous treatment. Also, having survived one episode implies that other characteristics that were protective previously may have been again. Health care providers may also be appropriately selecting individuals with reports of previous TB for enhanced surveillance and treatment methods, including a combination of DOT and SAT. And, previous TB is reported by documented immigrants who are required to have their status reevaluated upon arrival in the U.S. Finally, reactivated TB disease occurs in individuals who have already survived and therefore may be more resilient when disease recurs (G. Schecter, personal communication, 2008).

Comorbidity Predictors

The strongest predictor of all-cause mortality was HIV coinfection with a death rate in the final model among the HIV-positive subjects eight times the mortality of the HIV negative. Although the strength of this association varied according to subset analysis, HIV coinfection was consistently associated with increased death rates in all subset analyses. Highly active antiretroviral therapy for AIDS has been available in San Francisco and is associated with improved survival of TB disease (Nahid et al., 2007). Nonetheless, despite an overall decreased incidence of HIV infection in San Francisco, more than 19% of TB cases were coinfected with HIV in 2002. Improved screening and

treatment for this comorbidity is needed in San Francisco and worldwide (Albalak et al., 2007; Brewer & Heymann, 2005).

HIV disease had a serious impact on mortality in San Francisco during the study period. In 2000, AIDS was second only to ischemic heart disease as measured by number of years of life lost (SFDPH, 2003). And, HIV coinfection is one of the strongest predictors of death during TB treatment worldwide (Braun, Cote, & Rabkin, 1993; Elender, Bentham, & Langford, 1998; Lopez, Mathers, Ezzati, Jamison, & Murray, 2006). Both HIV and substance use must be examined as competing causes of mortality. The age-adjusted death rate from drugs in San Francisco was more than three times that of California as a whole during 1999-2000 (SFDPH, 2003).

HIV testing was incomplete, which makes interpreting the findings difficult. Nonetheless, within the subset of subjects with HIV coinfection and unknown HIV status, those with a positive TB test were nearly twice as likely as the unknown TB status subjects to experience all-cause mortality. The importance of HIV as a predictor can be seen as well by examining those documented to be HIV negative. With very few (11/619 or 1.8%) deaths occurring in this group, only homelessness was statistically significantly associated with increased mortality.

Health Care Delivery Predictors

Those receiving care from a private TB medical provider had a higher proportion of all-cause mortality than those receiving treatment from San Francisco's TB public provider. The finding that death outcomes were significantly higher among those receiving care from private providers was strong and sustained even after controlling for age-group and other factors. In the final multivariate model, private TB provider was

independently statistically significantly predictive of all-cause mortality. This relationship was also seen in the subset of subjects known to be HIV positive or unknown coinfection and in those with pulmonary TB.

Comparing the subset analyses of subjects with private and public TB medical providers showed stronger associations with all-cause mortality in the private TB care subset for the predictors of not working and HIV coinfection. Within the public care subset, those who were not working were four times more likely to die than the working population; in private care those not working were eight times more likely to die than the working subjects. Those subjects with HIV coinfection in the public subset were nearly six times more likely to die than the HIV negative, while the HIV-positive subjects in the private subset were nearly 18 times more likely to die during treatment.

Also, the predictors in the public and private subsets were different. Homelessness was not associated with all-cause mortality in those receiving public care. Among those in the private care subset, homelessness was associated with death more than three times that of the more stably housed. Also, advanced age was only associated with death in the private care subset. Yet, within the public care subset, concomitant extrapulmonary disease was associated with 2.6 times the mortality of those with pulmonary TB alone, while there was no association between disease site and mortality in the private subset analysis.

The possible explanations for the decreased all-cause mortality among subjects receiving public TB medical care are several. For one, TB Control specializes in TB treatment, providing expert care and resources that include field and clinic staff, incentives and enablers, and DOT. It is certainly likely that those physicians and nurses

who work with TB Control have more experience with TB. A Canadian study found that physicians' experience with TB patients had a small but statistically significant (HR 0.98, 95% CI: 0.97, 0.99) protective effect against mortality (Khan et al., 2006).

In addition, the public TB provider is part of a wider public health system that includes community clinics and San Francisco General Hospital. It is also possible that medical providers in the private sector are less knowledgeable about recent advances in TB management, have less clinical experience with TB, and are less able to offer comprehensive models of care. The surveillance function of TB Control improves the detection of greater numbers of individuals at an earlier stage of TB disease. In any event, the current investigation appears to be the first to compare the survival experience of individuals on treatment for active TB by private and public TB providers.

Further, within the subset who received public TB care, those who had DOT had higher all-cause mortality than those who received SAT alone or a combination of both approaches. Previous research in San Francisco identified DOT as associated with decreased TB-specific mortality (Jasmer et al., 2004). The value of that study is limited, however, because it excluded subjects who died before completing one week of treatment, subjects without pulmonary and culture-positive disease, and subjects with any resistance (Jasmer et al., 2004). Also, the bivariate model did not allow for control of the known confounder of age and the DOT group was 10 years younger than those assigned to SAT.

DOT has not been shown to be superior to SAT in a Cochrane meta-analysis (Volmink & Garner, 2006). The outcome of interest in that study was not mortality but completion of treatment. In addition, the International Union Against Tuberculosis and

Lung Disease emphasizes that the primary purpose of DOT is to prevent the emergence of MDR TB (Rusen et al., 2007). The current study is the first to examine the effects of DOT, SAT, and a combination of DOT and SAT on all-cause mortality for all subjects who initiate treatment for active TB.

Public TB treatment providers in San Francisco do not use DOT universally. DOT or SAT is prescribed according to the presence of risk factors for non-adherence. Less than half of all cases (45.8%) received DOT for all or part of the duration of treatment. This varied by age-group, for example, only 32% of those at least 65 years old received DOT. Evaluating the effect of supervised treatment on survival is hampered because DOT is only offered by the public health care system and is confounded by its association with known or suspected correlates of poor outcome, such as substance use, homelessness, smear positive, history of previous TB disease, too infirm to self manage, and drug resistant disease, all of which are reasons for offering DOT. Although DOT is not protective against death in any bivariate or multivariate model, the combination of DOT and SAT showed a significant protective effect. This suggests that there may be some advantage to using both strategies during treatment.

Limitations and Strengths of the Study

This study analyzed existing surveillance data. Researchers confront several limitations when using secondary data. In this study, not all desired variables were available or were available in the desired detail. Most important, the lack of information for half of the subjects about HIV infection severely limits inferences about this important predictor. Language was also incompletely recorded. Other hypothesized correlates of mortality during TB treatment include (a) measures of social-environmental status, such as income; (b) TB-related malnutrition, such as weight and serum albumin; (c) symptoms of TB disease, such as cough, fever, and malaise; (d) more information on comorbidity, including concomitant diabetes, cancer, and tobacco use; and (e) health care access, including health insurance, primary care, and history of hospital admissions. More generally, the acuity of illness at initiation of treatment cannot be inferred from this study. Finally, although a data abstraction tool is being developed that may assist discernment of the more important outcome of cause-specific mortality (J. Sprinson, personal communication, 2008), no reliable instrument currently exists.

This study is novel because it included the entire population of individuals with active TB who initiated treatment over a 10 year period, allowing persuasive inferences to be drawn from the results to similar populations. Unlike other studies that have been limited to particular types of TB disease or treatment, the current study included all cases that initiated treatment for active TB over a 10-year period. And, unlike other settings, San Francisco has sufficient variability in TB medical provider types and supervision of treatment to estimate any association with differential all-cause mortality. Finally,

because this study relied chiefly on standardized measures of a disease that is reportable, it should be feasible for researchers to replicate it in other U.S. settings.

The variables that were the most robust estimators in their magnitude and consistency of estimating all-cause mortality were increasing age, male gender, homelessness, not working, HIV coinfection, and private medical care. The protective factors included having experienced a previous episode of TB and, in the subset receiving TB management from TB Control, a combination of DOT and SAT was protective compared with DOT alone.

The new findings that emerged from this study include the association of provider type and degree of medical supervision with the risk of mortality. This has not been reported in the literature. The protective effect of previous TB disease has not been reported.

Further, several results from this study confirm previously reported findings in the literature. This study confirms and substantiates numerous aspects of the epidemiologic conceptual model used for measurement and guidance of this study. Host demographics of increasing age and male gender, socio-environmental variables of being homeless and not working, the TB agent characteristic of a positive TB culture, and the comorbid agent of concomitant HIV infection have all been associated with higher mortality in subjects with active TB receiving treatment..

Conclusion

The predictors shown by this study to affect mortality include host demographics, social-environmental characteristics, TB and comorbid agents, and health care delivery factors. More specifically, in multivariate analysis all-cause mortality was greater among

those older than 44 years, men, homeless, not working, smear or TB culture positive, HIV coinfected, and with a private TB medical provider. In addition, prior TB disease was shown to have a protective effect against death during treatment. Among those receiving varying levels of treatment supervision, the combination of DOT and SAT was protective when compared with either method alone.

This study's findings will be useful to clinicians, health educators, researchers, and health care planners. Further research is needed to corroborate the predictors. It is feasible to perform this analysis in other jurisdictions in California and other parts of the U.S. because the data collection tool (the RVCT) is standardized and used throughout the U.S. The RVCT has been revised and will be available starting in January, 2009. A prospective cohort design would enable calculation of more precise methods to definitively answer research questions.

Clinicians initiating treatment for active TB in San Francisco should consider referring their patients to TB Control, particularly for those who have been shown to be at higher risk of death during treatment: men, age > 44 years, homeless, not working, TB culture positive, and HIV coinfected. DOT and SAT may need to be carefully selected during treatment to optimize the advantages of each during the course of therapy.

Nurses working with clients at risk of TB and HIV need to examine the evidence from the literature to more effectively design individual and population-aggregate treatment plans to maximize the completion of life saving TB treatment. Nurses should work with health policymakers, physicians, social workers, epidemiologists, and communities at risk of TB to improve the ability of health care systems to quickly identify and effectively treat persons with active TB.

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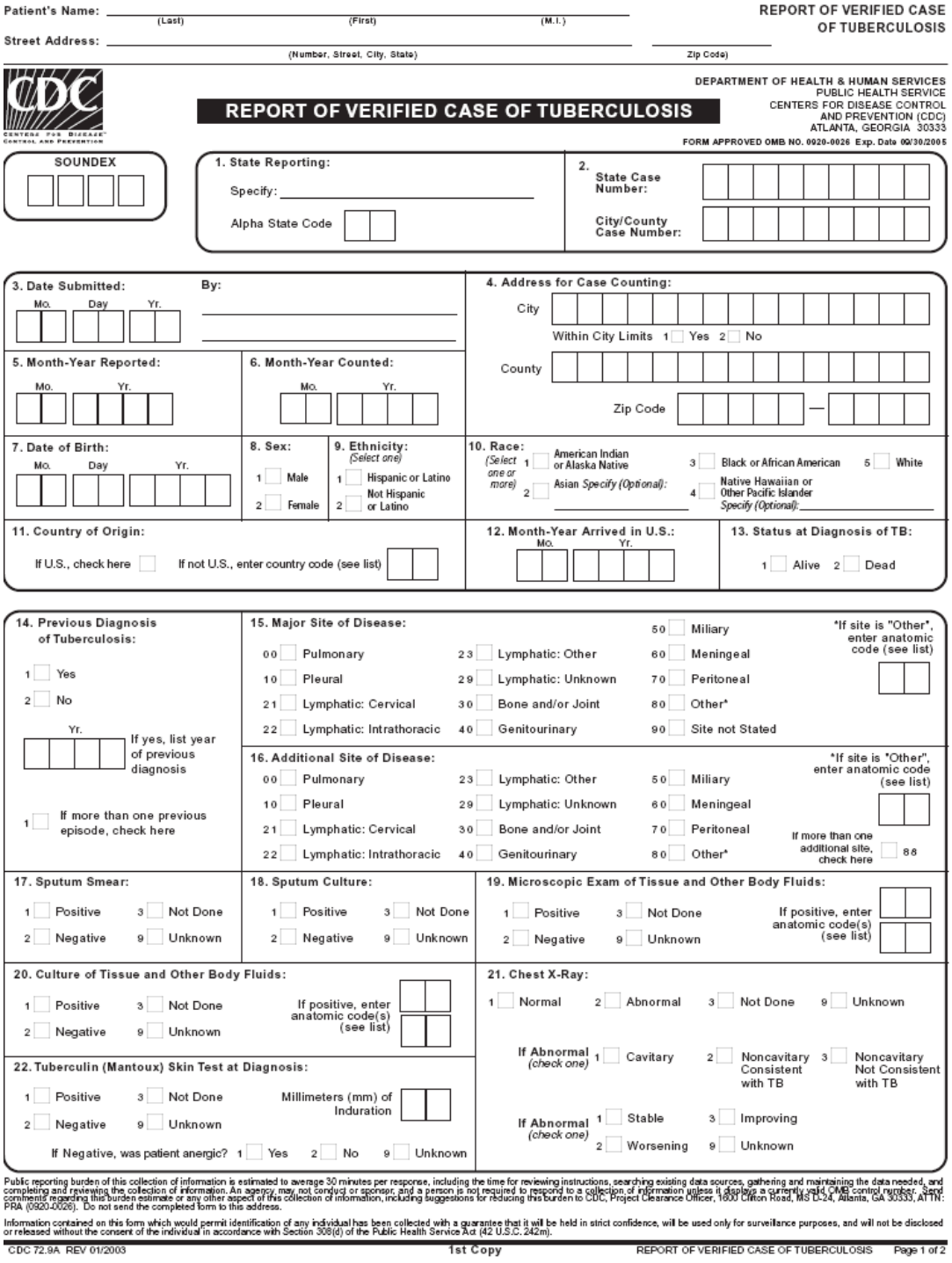
Appendix A

Report of Verified Case of Tuberculosis

Appendix A



Patient's Name: _____ (Last) (First) (M.I.)

Street Address: _____ (Number, Street, City, State) Zip Code)

REPORT OF VERIFIED CASE OF TUBERCULOSIS

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)
ATLANTA, GEORGIA 30333

FORM APPROVED OMB NO. 0920-0026 Exp. Date 09/30/2005

SOUNDEX

1. State Reporting:
Specify: _____
Alpha State Code

2. State Case Number:
City/County Case Number:

3. Date Submitted: Mo. Day Yr.
By:

4. Address for Case Counting:
City
Within City Limits 1 Yes 2 No
County
Zip Code

5. Month-Year Reported: Mo. Yr.

6. Month-Year Counted: Mo. Yr.

7. Date of Birth: Mo. Day Yr.

8. Sex:
1 Male
2 Female

9. Ethnicity: (Select one)
1 Hispanic or Latino
2 Not Hispanic or Latino

10. Race: (Select one or more)
1 American Indian or Alaska Native
2 Asian Specify (Optional): _____
3 Black or African American
4 Native Hawaiian or Other Pacific Islander Specify (Optional): _____
5 White

11. Country of Origin:
If U.S., check here
If not U.S., enter country code (see list)

12. Month-Year Arrived in U.S.: Mo. Yr.

13. Status at Diagnosis of TB:
1 Alive 2 Dead

14. Previous Diagnosis of Tuberculosis:
1 Yes
2 No
Yr.
If yes, list year of previous diagnosis
1 If more than one previous episode, check here

15. Major Site of Disease:
00 Pulmonary
10 Pleural
21 Lymphatic: Cervical
22 Lymphatic: Intrathoracic
23 Lymphatic: Other
29 Lymphatic: Unknown
30 Bone and/or Joint
40 Genitourinary
50 Miliary
60 Meningeal
70 Peritoneal
80 Other*
90 Site not Stated
*If site is "Other", enter anatomic code (see list)

16. Additional Site of Disease:
00 Pulmonary
10 Pleural
21 Lymphatic: Cervical
22 Lymphatic: Intrathoracic
23 Lymphatic: Other
29 Lymphatic: Unknown
30 Bone and/or Joint
40 Genitourinary
50 Miliary
60 Meningeal
70 Peritoneal
80 Other*
*If site is "Other", enter anatomic code (see list)
If more than one additional site, check here 88

17. Sputum Smear:
1 Positive 3 Not Done
2 Negative 9 Unknown

18. Sputum Culture:
1 Positive 3 Not Done
2 Negative 9 Unknown

19. Microscopic Exam of Tissue and Other Body Fluids:
1 Positive 3 Not Done
2 Negative 9 Unknown
If positive, enter anatomic code(s) (see list)

20. Culture of Tissue and Other Body Fluids:
1 Positive 3 Not Done
2 Negative 9 Unknown
If positive, enter anatomic code(s) (see list)

21. Chest X-Ray:
1 Normal 2 Abnormal 3 Not Done 9 Unknown
If Abnormal (check one) 1 Cavitary 2 Noncavitary Consistent with TB 3 Noncavitary Not Consistent with TB
If Abnormal (check one) 1 Stable 3 Improving 2 Worsening 9 Unknown

22. Tuberculin (Mantoux) Skin Test at Diagnosis:
1 Positive 3 Not Done
2 Negative 9 Unknown
Millimeters (mm) of Induration
If Negative, was patient anergic? 1 Yes 2 No 9 Unknown

Public reporting burden of this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to CDC, Project Clearance Officer, 1600 Clifton Road, MS D-24, Atlanta, GA 30333; ATTN: PRA (0920-0026). Do not send the completed form to this address.

Information contained on this form which would permit identification of any individual has been collected with a guarantee that it will be held in strict confidence, will be used only for surveillance purposes, and will not be disclosed or released without the consent of the individual in accordance with Section 308(d) of the Public Health Service Act (42 U.S.C. 242m).

CDC 72.9A REV 01/2003 1st Copy REPORT OF VERIFIED CASE OF TUBERCULOSIS Page 1 of 2

Appendix A

REPORT OF VERIFIED CASE OF TUBERCULOSIS

23. HIV Status: 0 Negative; 1 Positive; 2 Indeterminate; 3 Refused; 4 Not Offered; 5 Test Done, Results Unknown; 9 Unknown

If Positive, Based on: 1 Medical Documentation; 2 Patient History; 9 Unknown

If Positive, List:
CDC AIDS Patient Number [ ][ ][ ][ ][ ][ ][ ] (If AIDS Reported before 1993)
State HIV/AIDS Patient Number [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ] (If AIDS Reported 1993 or Later)
City/County HIV/AIDS Patient Number [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ] (If AIDS Reported 1993 or Later)

24. Homeless Within Past Year: 0 No; 1 Yes; 9 Unknown

25. Resident of Correctional Facility at Time of Diagnosis: 0 No; 1 Yes; 9 Unknown

If Yes, 1 Federal Prison; 2 State Prison; 3 Local Jail; 4 Juvenile Correctional Facility; 5 Other Correctional Facility; 9 Unknown

26. Resident of Long-Term Care Facility at Time of Diagnosis: 0 No; 1 Yes; 9 Unknown

If Yes, 1 Nursing Home; 2 Hospital-Based Facility; 3 Residential Facility; 4 Mental Health Residential Facility; 5 Alcohol or Drug Treatment Facility; 6 Other Long-Term Care Facility; 9 Unknown

27. Initial Drug Regimen:

	NO	YES	UNK.		NO	YES	UNK.		NO	YES	UNK.
Isoniazid	0	1	9	Ethionamide	0	1	9	Amikacin	0	1	9
Rifampin	0	1	9	Kanamycin	0	1	9	Rifabutine	0	1	9
Pyrazinamide	0	1	9	Cycloserine	0	1	9	Ciprofloxacin	0	1	9
Ethambutol	0	1	9	Capreomycin	0	1	9	Ofloxacin	0	1	9
Streptomycin	0	1	9	Para-Amino Salicylic Acid	0	1	9	Other	0	1	9

28. Date Therapy Started: Mo. [ ][ ] Day [ ][ ] Yr. [ ][ ]

29. Injecting Drug Use Within Past Year: 0 No; 1 Yes; 9 Unknown

30. Non-Injecting Drug Use Within Past Year: 0 No; 1 Yes; 9 Unknown

31. Excess Alcohol Use Within Past Year: 0 No; 1 Yes; 9 Unknown

32. Occupation *(Check all that apply within the past 24 months):*
1 Health Care Worker; 2 Correctional Employee; 3 Migratory Agricultural Worker; 4 Other Occupation; 5 Not Employed within Past 24 Months; 9 Unknown

Comments:

.....
.....
.....

Appendix B

Report of Verified Case of Tuberculosis (Follow-Up Report 1)

Appendix B

Patient's Name: _____ (Last) _____ (First) _____ (M.I.)

Street Address: _____ (Number, Street, City, State) _____ Zip Code)

REPORT OF VERIFIED CASE OF TUBERCULOSIS

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

REPORT OF VERIFIED CASE OF TUBERCULOSIS

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)
ATLANTA, GEORGIA 30333

FORM APPROVED OMB NO. 0920-0026 Exp. Date 11/95

Initial Drug Susceptibility Report

(Follow Up Report – 1)

SOUNDEX ☐☐☐☐

State Reporting:
Specify: _____
Alpha State Code ☐☐

Year Counted: ☐☐

State Case Number: ☐☐☐☐☐☐☐☐☐☐
City/County Case Number: ☐☐☐☐☐☐☐☐☐☐

Submit this report for all culture-positive cases.

33. Initial Drug Susceptibility Results:

Was Drug Susceptibility Testing Done: 0 ☐ No 1 ☐ Yes 9 ☐ Unknown

If answer is No or Unknown, do not complete rest of report.

If Yes,
Enter Date First Isolate Collected
for Which Drug Susceptibility Was Done? Mo. ☐☐ Day ☐☐ Yr. ☐☐

34. Susceptibility Results:

	Resistant	Susceptible	Not Done	Unknown
Isoniazid	1 ☐	2 ☐	3 ☐	9 ☐
Rifampin	1 ☐	2 ☐	3 ☐	9 ☐
Pyrazinamide	1 ☐	2 ☐	3 ☐	9 ☐
Ethambutol	1 ☐	2 ☐	3 ☐	9 ☐
Streptomycin	1 ☐	2 ☐	3 ☐	9 ☐
Ethionamide	1 ☐	2 ☐	3 ☐	9 ☐
Kanamycin	1 ☐	2 ☐	3 ☐	9 ☐
Cycloserine	1 ☐	2 ☐	3 ☐	9 ☐
Capreomycin	1 ☐	2 ☐	3 ☐	9 ☐
Para-Amino Salicylic Acid	1 ☐	2 ☐	3 ☐	9 ☐
Amikacin	1 ☐	2 ☐	3 ☐	9 ☐
Rifabutine	1 ☐	2 ☐	3 ☐	9 ☐
Ciprofloxacin	1 ☐	2 ☐	3 ☐	9 ☐
Ofloxacin	1 ☐	2 ☐	3 ☐	9 ☐
Other	1 ☐	2 ☐	3 ☐	9 ☐

Comments:

Information contained on this form which would permit identification of any individual has been collected with a guarantee that it will be held in strict confidence, will be used only for surveillance purposes, and will not be disclosed or released without the consent of the individual in accordance with Section 308(d) of the Public Health Service Act (42 U.S.C. 242m).

Appendix C

Report of Verified Case of Tuberculosis (Follow-Up Report 2)

Appendix C

Patient's Name: _____ (Last) (First) (M.I.)

Street Address: _____ (Number, Street, City, State) Zip Code)

REPORT OF VERIFIED CASE OF TUBERCULOSIS

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

REPORT OF VERIFIED CASE OF TUBERCULOSIS

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)
ATLANTA, GEORGIA 30333

FORM APPROVED OMB NO. 0920-0026 Exp. Date 11/95

Case Completion Report

(Follow Up Report – 2)

SOUNDEX ☐☐☐☐

State Reporting:
Specify: _____
Alpha State Code ☐☐

Year Counted: ☐☐

State Case Number: ☐☐☐☐☐☐☐☐☐
City/County Case Number: ☐☐☐☐☐☐☐☐☐

35. Sputum Culture Conversion Documented:
0 ☐ No 1 ☐ Yes 9 ☐ Unknown

If Yes, Date Specimen Collected on Initial Positive Sputum Culture: Mo. ☐☐ Day ☐☐ Yr. ☐☐

If Yes, Date Specimen Collected on First Consistently Negative Culture: Mo. ☐☐ Day ☐☐ Yr. ☐☐

36. Date Therapy Stopped: Mo. ☐☐ Day ☐☐ Yr. ☐☐

37. Reason Therapy Stopped:
1 ☐ Completed Therapy 3 ☐ Lost 5 ☐ Not TB 7 ☐ Other
2 ☐ Moved 4 ☐ Uncooperative or Refused 6 ☐ Died 9 ☐ Unknown

38. Type of Health Care Provider:
1 ☐ Health Department
2 ☐ Private/Other
3 ☐ Both Health Department and Private/Other

39. Directly Observed Therapy:
0 ☐ No, Totally Self-Administered
1 ☐ Yes, Totally Directly Observed
2 ☐ Yes, Both Directly Observed and Self-Administered
9 ☐ Unknown

If Yes, Give Site(s) of Directly Observed Therapy:
1 ☐ In Clinic or Other Facility
2 ☐ In the Field
3 ☐ Both in Facility and in the Field
9 ☐ Unknown

Number of Weeks of Directly Observed Therapy: ☐☐☐ Weeks

40. Final Drug Susceptibility Results:
Was Follow-up Drug Susceptibility Testing Done? 0 ☐ No 1 ☐ Yes 9 ☐ Unk.
If answer is No or Unknown, do not complete rest of report.

If Yes, Enter Date Final Isolate Collected for Which Drug Susceptibility Was Done: Mo. ☐☐ Day ☐☐ Yr. ☐☐

41. Final Susceptibility Results:

	Resistant	Susceptible	Not Done	Unknown
Isoniazid	1 ☐	2 ☐	3 ☐	9 ☐
Rifampin	1 ☐	2 ☐	3 ☐	9 ☐
Pyrazinamide	1 ☐	2 ☐	3 ☐	9 ☐
Ethambutol	1 ☐	2 ☐	3 ☐	9 ☐
Streptomycin	1 ☐	2 ☐	3 ☐	9 ☐
Ethionamide	1 ☐	2 ☐	3 ☐	9 ☐
Kanamycin	1 ☐	2 ☐	3 ☐	9 ☐
Cycloserine	1 ☐	2 ☐	3 ☐	9 ☐
Capreomycin	1 ☐	2 ☐	3 ☐	9 ☐
Para-Amino Salicylic Acid	1 ☐	2 ☐	3 ☐	9 ☐
Amikacin	1 ☐	2 ☐	3 ☐	9 ☐
Rifabutine	1 ☐	2 ☐	3 ☐	9 ☐
Ciprofloxacin	1 ☐	2 ☐	3 ☐	9 ☐
Ofloxacin	1 ☐	2 ☐	3 ☐	9 ☐
Other	1 ☐	2 ☐	3 ☐	9 ☐

Comments:

Information contained on this form which would permit identification of any individual has been collected with a guarantee that it will be held in strict confidence, will be used only for surveillance purposes, and will not be disclosed or released without the consent of the individual in accordance with Section 308(d) of the Public Health Service Act (42 U.S.C. 242m).

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Sayeri J. Cuda
Author Signature

12/28/08
Date