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Neha Patel Date

Factors Associated with Unexpectedly Long Prescribed Therapy for Tuberculosis Patients Eligible for Short-Course Therapy in the United States, 2009 – 2016

By

Neha Patel

Master of Public Health

Epidemiology

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Neela Goswami, MD, MPH
Faculty Thesis Advisor

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By

Neha Patel
B.Sc., Rutgers University, 2013

Faculty Thesis Advisor: Neela Goswami, MD, MPH

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Abstract

Factors Associated with Unexpectedly Long Prescribed Therapy for Tuberculosis Patients Eligible for Short-Course Therapy in the United States, 2009 – 2016

By Neha Patel

Background: Tuberculosis (TB) is a leading cause of death from an infectious agent and among the top 10 of all causes of death globally. TB is a treatable disease with a structured course of antibiotics, however the course can be complicated and long, often ranging from 6 – 12 months. Previous data has shown that TB patients with certain clinical characteristics may achieve comparable clinical outcomes on a shorter four month treatment regimen.

Objectives: Prescription of shorter regimens on a national scale in the US has not been well-studied. This study assesses demographic and clinical risk factors associated with completion of unnecessarily long treatment among patients eligible for a shortened four month treatment course.

Methods: Data collected through the NTSS between 2009 and 2016 were used to look at associations between risk factors and completion of unexpectedly long treatment. Log binomial models were constructed from independent variables significantly associated with our outcome by univariate analysis plus any significant confounders.

Results: Between January 2009 and December 2016, there were 4,572 culture-negative pulmonary TB patients who completed their treatment regimen and met the eligibility criteria to receive a shortened four-month treatment. Asian (aRR: 0.96, 95% CI: 0.93 – 1.00) and black (aRR: 0.94, 95% CI: 0.90 – 0.98) TB patients had a higher likelihood of receiving appropriate shortened therapy compared to white patients ($P < 0.05$). Diabetics had an increased risk of receiving longer therapy compared to non-diabetics, even after adjusting for additional predictors (aRR: 1.04, 95% CI: 1.00 – 1.08). The risk of receiving unexpectedly long therapy was lower among patients in the Northeast, South, and West compared to the risk in patients in the Midwest ($P < 0.05$).

Conclusion: Patient characteristics such as race and ethnicity, US region of diagnosis, and diabetes were found to be significantly associated with completing unnecessarily longer therapy. Results may inform healthcare providers to promote shorter regimens in eligible populations, which may decrease adherence failure and reduce costs for TB treatments, thus decreasing burden on the public health system.

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CHAPTER I: LITERATURE REVIEW

Tuberculosis Transmission, Symptoms, and Diagnosis

Tuberculosis (TB), one of the world's deadliest diseases, is caused by a small aerobic bacillus, the *Mycobacterium tuberculosis* bacterium (1). TB is an airborne disease which can be spread easily from person to person when airborne particles with *M. tuberculosis* is transferred through cough, sneeze, or spit from an infected person (2). Approximately one fourth of the world's population is infected with TB due to its highly infectious nature (3). However, majority of those infected with *M. tuberculosis* are asymptomatic with a latent TB infection (LTBI) where the infection is contained by the immune system, thus preventing the spread of infection to other people. An estimated 5% to 15% of those with LTBI will develop active TB during their lifetime (4). In contrast, immunocompromised individuals, particularly those who are HIV-infected, are 20 to 30 times more likely to develop active TB compared to those with robust immune systems (5).

Unlike a latent TB infection, an active TB infection is highly contagious and can cause severe sickness or death if left untreated (4). The primary site of active TB infection occurs in the lungs, leading to pulmonary TB; however, extra-pulmonary TB can occur when TB infection is spread to other parts of the body, such as the lymph nodes, bones, the central nervous system, the pleura, and the lymphatic system. Active pulmonary TB infection may cause symptoms such as chest pain, bloodied cough or sputum, fatigue, weight loss, and chills (5-7). Presence of TB bacteria and diagnosis of TB infection is determined by combination of symptoms and either a positive Mantoux tuberculin skin test (TST) or a TB blood tests (interferon-gamma release assays – IGRA's) (7-9). A

positive result is then evaluated for latent TB or active TB through chest radiographs and diagnostic microbiology (7). A positive culture for M. tuberculosis confirms diagnosis of TB disease but does not need to be positive for initiation of TB therapy (7).

Global Burden

While slowly declining over the last decade, TB is still the leading cause of death from an infectious agent, and among the top 10 of all causes of death globally (5). In 2016, there were 10.4 million new cases and over 1.3 million deaths attributed to active TB (10). Over 95% of TB deaths occur in middle- and low-income countries, with 64% of total deaths occurring in just seven countries: India, Indonesia, China, Philippines, Pakistan, Nigeria, and South Africa (10). TB is also a leading killer of HIV positive people, accounting for over 40% of HIV deaths. With already high numbers of HIV-infected people, sub-Saharan Africa has been disproportionately affected, with HIV-associated TB accounting for 80% of cases (1).

Domestic Burden

There has been a decline in TB case counts and rates in the United States, however the decline has been relatively small. In 2016, 9,272 cases of TB were reported with a case rate of 2.9 per 100,000 persons compared to 9,557 TB cases in 2015, which was a 1.6% increase from 2014 (11). Overall, the TB incidence rate has remained consistent since 2013 at 3.0 per 100,00 persons (3, 11). Four states account for over 50% of all TB cases reported: California, Texas, New York, and Florida, which also account for one-third of the US population (12). Additionally, there are an estimated 13 million residents with latent TB (12). In the US, most TB cases are associated with reactivated untreated LTBI,

particularly among those not born in the US. There is a large disparity in the rates of tuberculosis among US born and foreign-born persons, with 68.5% of cases occurring among foreign born in 2016 (12).

Risk Factors

Risk of TB infection and death can be further complicated by a host of environmental, demographic, and clinical risk factors. Numerous studies have found the risk of infection to be determined by a combination of infectiousness of the source case, proximity to contact, and social and behavioral risk factors (13).

The risk of TB infection is known to be greater in immunocompromised individuals which makes HIV one of the leading risk factors of TB infection (13, 14). HIV infected individuals with associated immunosuppression have an increased susceptibility to a variety of diseases compared to those with healthy immune systems. TB infection and progression is further amplified in those infected with HIV compared to HIV-negative people, making TB the leading opportunistic infection among those with HIV (15, 16).

Diabetes has become a re-emerging risk factor in recent years (17). A systematic review found diabetes mellitus (DM) to increase the risk of TB by three-fold (RR: 3.11, 95% CI: 2.27-4.26 (18). Other clinical studies showed patients with DM to be more susceptible to TB, have more severe TB disease, and higher risk of relapse compared to individuals without DM (19-21).

Illicit drug use has also been cited as another important risk factor for TB disease. Several studies have found associations between drug use and TB disease (22-25). Illicit

drug use impairs immune system function, further increasing TB susceptibility and transmission. Additionally, drug users are also associated with low socio-economic status, unemployment, incarceration, and homeless, further increasing their susceptibility to TB infection and other co-morbidities (26, 27).

Existing Treatments

While latent TB is asymptomatic and unable to be transmitted to others, 5% to 15% of LTBI infected cases can turn into active TB disease. Treatments are prescribed to LTBI patients to prevent development of TB disease as well as prevent the spread of TB. The four core treatment regimens for LTBI are combinations of isoniazid (INH), rifapentine (RPT), or rifampin (RIF) (7). Treatment regimens range from three months to nine months in duration with dosing intervals of daily, once weekly, or twice weekly. Modifications to regimens and dosing intervals are made after considering additional factors such as age, HIV status, and pregnancy.

Unlike a diagnosis of LTBI, active TB can cause severe disease or death if left undiagnosed and untreated. Active TB is caused when the immune system is unable to contain the replication of *M. tuberculosis*. *M. tuberculosis* bacterium can spread throughout the body to cause either or both pulmonary or extra-pulmonary TB disease and can be easily transmitted from person to person. Treatment for active TB is extremely important to both contain the growth and spread of disease within the body as well as prevent the bacteria from developing drug resistance. First line therapy for TB disease is a combination of four main drugs, INH, RIF, ethambutol (EMB), and pyrazinamide (PZA). Treatment regimens for drug susceptible TB total six to nine

months and are split into two phases: an intensive phase of two months, followed by a continuation phase of four to seven months. The preferred treatment regimen for patients with newly diagnosed pulmonary TB is an intensive phase of the four main drugs followed by a continuation phase of INH and RIF, with a total of 182 to 130 doses (7). Completion of therapy for active TB is determined by the number of doses taken over a given period of time and a negative sputum or culture.

Challenges in Treatment Adherence

TB is a treatable disease with a structured course of antibiotics, however the course can be long and complicated. Current guidelines recommend treatment regimens for six to nine months which can be a relatively long course of treatment with a high chance of adherence failure. In high income countries, adherence to long term medication has been estimated to be only 50% (28). Inappropriately prescribed or followed treatment can serve as a cause of drug resistance, resulting in treatment failure, TB relapse, and possibly the spread of drug resistant TB to others (29, 30). A systematic review conducted in 2007 found a host of factors contributing to difficulty in treatment adherence and treatment failure. Attitudes and beliefs, interpretations of wellness, and organization of treatment were all cited as major factors for lapse in treatment (31). WHO cites four main factors that predict adherence to medication, and thus treatment outcomes: “regimen characteristics, various patient factors, the relationship between provider and patient and the system of care” (32).

Shortened 4 Month Treatment

In recent years, the TB treatment guidelines put forth by the American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC), and Infectious Diseases

Society of America (IDSA) have recommended a shortened course of therapy for a subset of TB infected patients (7). While culture positivity confirms diagnosis of TB disease, culture negative results can still occur in suspected active pulmonary TB cases. Low bacillary populations or errors in specimen processing can fail to isolate enough organisms and yield culture negative results in active TB patients (33). Approximately 17% of newly reported pulmonary cases have negative cultures in the US (33). In this culture negative population, data has shown that TB patients with certain clinical characteristics may achieve good or comparable clinical outcomes with a shorter regimen of 4 months (34). This four month treatment regimen would consist of an initial phase of two months followed by a shortened continuation phase of two months. In a study done to assess the efficacy of using four months of treatment among smear negative pulmonary TB patients, patients were randomized to receive a daily or combined (daily and intermittent) regimen for a total of four months if culture negative and six months if culture positive (35). When assessed at 30 and 60 months, there was no relapse in the culture negative patients receiving daily treatment and one relapse in the culture negative patients receiving combined treatment (35). The study concluded that a four month regimen is highly effective in the treatment of non-immunocompromised patients with smear- and culture-negative TB (35). Data has also shown that among patients with negative bacteriology, the shortened four month regimen produced similar results as smear- and culture-positive cases on a nine month treatment regimen (36). In a study among 452 TB patients with at least 3 negative smears and cultures, 414 completed a four month treatment regimen. During the follow up period of 6 to 78 months, only five (1.2%) of the 414 patients relapsed (36). The study concluded a treatment regimen with

INH and RIF for four months gave results comparable to those on nine months of therapy. Based on these and other clinical data, the 2016 guidelines recommend the shortened four month regimen may be prescribed to HIV-uninfected patients with a negative sputum culture who have shown symptomatic or radiographic improvement on therapy (7). However, prescription of such shortened regimens in appropriate clinical settings on a national scale has not been well-studied.

CHAPTER II: MANUSCRIPT

While slowly declining over the last decade, tuberculosis (TB) is still the leading cause of death from an infectious agent, and among the top 10 of all causes of death globally (5). Approximately one fourth of the world's population is infected with TB due to its highly infectious nature (3). Tuberculosis is an airborne disease which can be spread easily from person to person when airborne particles with *Mycobacterium tuberculosis* bacterium are transferred through cough, sneeze, or spit from an infected person (1, 2). In 2016, there were 10.4 million new cases and over 1.3 million deaths attributed to active TB (10).

There has been a decline in TB case counts and rates in the United States, however the decline has been relatively small. In 2016, 9,272 cases of TB were reported with a case rate of 2.9 per 100,000 persons compared to 9,557 TB cases in 2015, which was a 1.6% increase from 2014 (11). Overall, the TB incidence rate has remained consistent since 2013 at 3.0 per 100,00 persons (3, 11). Four states account for over 50% of all TB cases reported: California, Texas, New York, and Florida, which also account for one-third of the US population (12). In addition to active TB cases, there are an estimated 13 million residents with latent TB in the US. Unlike an active TB infection, a latent TB infection is contained by the immune system, thus preventing the spread of infection to other people (12). In the US, most active TB cases are associated with reactivated untreated LTBI, particularly among those not born in the US. There is a large disparity in the rates of TB among US born and foreign-born persons, with 68.5% of cases occurring among foreign born in 2016 (12).

Risk of TB infection and death can be further complicated by a host of environmental, demographic, and clinical risk factors. Numerous studies have found the risk of infection to be determined by a combination of infectiousness of the source case, proximity to contact, and social and behavioral risk factors (13).

The risk of TB infection is known to be greater in immunocompromised individuals, which makes HIV one of the leading risk factors of TB infection (13, 14). HIV infected individuals with associated immunosuppression have an increased susceptibility to a variety of diseases compared to those with healthy immune systems. TB infection and progression is further amplified in those infected with HIV compared to HIV-negative people, making TB the leading opportunistic infection among those with HIV (15, 16).

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Illicit drug use has also been noted as another important risk factor for TB disease. Several studies have found associations between drug use and TB disease (22-25). Illicit drug use impairs immune system function, further increasing TB susceptibility and transmission. Additionally, drug users are also associated with low socio-economic status, unemployment, incarceration, and homeless, further increasing their susceptibility to TB infection and other co-morbidities (26, 27).

Treatments

Treatment for active TB is extremely important to both contain the growth and spread of disease within the body as well as prevent the bacteria from developing drug resistance. First line therapy for TB disease is a combination of four main drugs, isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA). Treatment regimens for drug susceptible TB total six to nine months and are split into two phases: an intensive phase of two months, followed by a continuation phase of four to seven months. The preferred treatment regimen for patients with newly diagnosed pulmonary TB is an intensive phase of the four main drugs followed by a continuation phase of INH and RIF, with a total of 182 to 130 doses (7). Completion of therapy for active TB is determined by the number of doses taken over a given period of time and a negative sputum or culture.

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However, prescription of shorter regimens in appropriate clinical settings on a national scale in the United States has not been well-studied. This study assesses demographic and clinical risk factors associated with completion of unexpectedly long treatment among patients eligible for a shortened four month treatment course.

Methods

Data Source

The study population for this analysis was a subset of TB cases reported to the National TB Surveillance System (NTSS) of the CDC. TB surveillance data is collected through the Report of Verified Case of Tuberculosis (RVCT), a standardized reporting form used by all local and state TB programs in the United States. The RVCT form was updated in

2009 to include additional risk factors, new drug treatments, and additional diagnostic tests, thus only reported cases after 2009, and through 2016, were included. TB surveillance data is submitted by 60 reporting regions: the 50 United States, District of Columbia, American Samoa, Guam, Puerto Rico, US Virgin Islands, Commonwealth of the Northern Mariana Islands, Federated States of Micronesia, Republic of the Marshall Islands, and the Republic of Palau.

Inclusion and Exclusion Criteria

Figure 1 describes the exclusion process for our study. Only verified TB cases reported between 2009 and 2016 were used in this analysis. TB cases are marked as verified if they are reviewed by a TB control official and met the laboratory or clinical case definitions (7, 37). In the United States, local and statewide TB programs manage majority of the TB cases. Prior studies have shown that patients managed by private health care providers receive less optimal care than those managed by public health programs therefore our study population only included cases followed by a health department or a TB program, or a combination of health department and private care providers (32, 38). Pediatric cases (under the age of 15) were excluded from our analysis. Cases were further excluded if they did not meet the criteria to receive a shortened TB treatment regimen (7). Reported cases with extra-pulmonary TB, drug resistant TB, positive cultures, HIV, or any other immunosuppression were also excluded from the analysis. Patients reported as illicit drug users were also excluded from our study as drug use impairs immune system function and increases TB susceptibility and transmission, thus putting drug users at higher risk than the average population (22-25). Cases with incomplete TB treatment regimens were also excluded from our analysis.

Outcome and Predictor Variables

The outcome of interest in our analysis is unexpectedly long duration of TB therapy among cases eligible for a shortened treatment regimen of four months. As recommended in prior studies and guidelines, eligibility for a shortened four month treatment regimen was restricted to only those with pulmonary TB with a negative culture, an absence of any drug resistance to the first-line treatment regimen, a HIV negative test, and absence of any other immunosuppression (Figure 1) (7). Consistent with prior studies, our study defined appropriate therapy duration as four months, which included a window of two weeks, totaling 112 to 140 days. Patients who were eligible for a shortened therapy but took longer than four months to complete therapy were classified as receiving unexpectedly long therapy.

Based on prior literature and data availability on the RVCT, a combination of individual, medical, and sociodemographic factors were also considered as predictors for completion of treatment (Table 1). These variables included seven race and ethnicity groups: non-Hispanic White, non- Hispanic American Indian or Alaskan Native, non- Hispanic Asian, non- Hispanic Black or African American, Hispanic, non- Hispanic Native Hawaiian or Pacific Islander, and non- Hispanic multiple races; four age groups: 15 to 24 years, 25 to 44 years, 45 to 64 years, and greater than 65 years of age; sex; birthplace: US born and foreign born; US census region of diagnosis[1]: Midwest, Northeast, South, West, and US Territories; medical risk factors: diabetes mellitus, previous diagnosis and incomplete treatment for latent TB, contact of infectious TB patient, diagnosis of end stage renal

[1] US Region of diagnosis is classified according to US Census Regions

disease or renal failure, a solid organ recipient, and recently receiving TNF-alpha antagonist therapy; social risk factors: residence in a long-term care or correctional facility, homelessness, and unemployment.

Data Analysis

Univariate and adjusted analyses were conducted to determine associations between potential predictors and our outcome. Unadjusted risk ratios and 95% confidence intervals for the association between each predictor variable and the outcome are presented in Table 3. Log binomial regression models were constructed from independent variables significantly associated with our outcome by univariate analysis plus any significant confounders, using backward elimination. Adjusted risk ratios and 95% confidence intervals for the association between significant predictor variables and the outcome are presented in Table 4. Predictor variables race and ethnicity, age, US region of diagnosis, and diabetes status were found to have an association with our outcome and were included in the final model. Sex was kept in the model to correspond with prior literature.

Results

Descriptive Statistics

Between January 2009 through December 2016, 84,149 verified adult cases were reported to the NTSS. After applying exclusion criteria, our final study population included 4,572 patients who completed their treatment regimen and met the eligibility criteria to receive a shortened appropriate treatment.

Among the 4,572 patients who completed treatment and were eligible for a shortened treatment regimen, 3,372 (73.8%) patients were born outside of the United States. Of the patients who completed treatment, 70% were between 25 to 64 years of age. Approximately one-third of TB cases in our study were Asian, followed by Hispanics (26.4%) and Black (21.1%). Approximately half of the TB cases were from the South (45.2%), compared to only 10.1% from the Northeast. Diabetes mellitus was reported in 566 (12.4%) patients and 1,482 patients were reported to have additional medical risk factors.

Univariate and Adjusted Associations

Treatment distribution among the study population and p-values for the crude association between each predictor variable and the outcome are presented in Table 2. In our study, 963 (21.1%) of TB cases completed therapy in the appropriate time compared to 3,609 (78.9%) of cases who took more than four months to complete therapy. Race was found to be significantly associated with completion of longer therapy ($P < 0.0001$). 72% of Black or African Americans completed longer therapy compared to 97% of Native Hawaiian or Pacific Islanders. Less than 23% of eligible cases across all age groups completed the appropriate shortened therapy and age was found to be significantly associated with completion of longer therapy in our univariate analyses. Similarly, only 21% of males and females completed the appropriate shortened therapy, however there was no association between sex and longer therapy completion. US region of diagnosis was significantly associated with longer therapy completion ($P < 0.0001$), with only 6% of those living in the US Territories completing shortened therapy, followed by the Midwest (16%). The South had the highest percentage of TB patients completing

appropriate therapy (26%). Data also showed an association between diabetes mellitus and longer therapy completion ($P < 0.0001$).

Unadjusted and adjusted risk ratios (RR) and 95% confidence intervals (CI) for the association between each predictor variable and the outcome are presented in Table 3 and Table 4, respectively. Both unadjusted and adjusted analyses showed Asian and black TB patients to have a lower risk of completing longer therapy compared to whites, ($P < 0.05$). In our unadjusted analyses, Native Hawaiian or Pacific Islanders had higher risks of receiving longer therapy (RR: 1.19, 95% CI: 1.14 – 1.24), however after adjusting for other predictors, this association was found to be not significant ($P = 0.4840$). Diabetics were at a slightly increased risk of completing longer therapy compared to non-diabetics, even after adjusting for additional predictors (RR: 1.04, 95% CI: 1.00 – 1.08). The risk of completing longer therapy was lower among patients diagnosed in the Northeast, South, and West compared to those diagnosed in the Midwest, even after adjusting for additional predictors ($P < 0.05$). Our adjusted associations showed statistically significant associations between race and ethnicity, US regions of diagnosis, and diabetes and completing longer therapy.

Discussion

Prior studies have shown the efficacy of shortened therapy among a subset of patients diagnosed with TB. Data has shown that a four month regimen is highly effective in the treatment of non-immunocompromised patients with smear- and culture-negative TB (35). Shortened four month regimens produced similar results as smear- and culture-positive cases compared to nine month treatment regimens (36). Based on these and

other clinical data, recent TB guidelines recommend the four month regimen may be prescribed to HIV-uninfected pulmonary TB patients with a negative sputum culture who have shown symptomatic or radiographic improvement on therapy (7).

However, with established recommendations for shortened regimens and comparable outcomes, our study found 78.9% of TB patients to have completed an unexpectedly longer therapy.

US Region of Diagnosis

In both univariate and adjusted analyses, we found US region of diagnosis to be significantly associated with completion of longer treatment among eligible patients. After adjusting for race/ethnicity, age, sex, and medical risk factors, we found the risk of receiving longer therapy was lower among eligible patients in the Northeast, South, and West compared to eligible patients in the Midwest ($P < 0.05$). In a 2006 to 2010 comparison of TB rates between the four regions, the Midwest had an annual TB rate of 2.32 per 100,000 persons, compared to rates between 4.14 and 5.31 per 100,000 in the other three regions (39). In 2016, the Midwest reported TB incidence rates below the national TB incidence rate of 2.9 cases per 100,000 persons (11). With lower incidence of TB compared to the rest of the US, local and state TB programs may have less guidance and evidence based practice to promote shorter treatment regimens among eligible patients. The Midwest also reported greater than 50% of their cases to be among foreign born persons (3, 11). In recent years, the Midwest has settled large numbers of refugees, particularly from countries with high TB and multi drug resistant (MDR) TB, such as Somalia. A nationwide study done in Somalia among 850 TB cases detected

MDR-TB in 5.2% (95% CI: 2.8–7.5) of persons with newly diagnosed TB and 40.8% (95% CI: 24.7–57.0) of persons with previously treated TB (40). As data has indicated higher incidence of MDR-TB in refugee populations, TB programs in the Midwest may have higher suspicion of MDR-TB in their TB cases, thus promoting longer treatment regimens as a precautionary measure.

Race and Ethnicity

Certain racial groups were also found to be significantly associated with completing unexpectedly longer therapy compared to whites. Eligible Asians and black TB patients were found to have a lower risk of completing longer therapy compared to whites. While encouraging, these associations may also be linked to adverse drug events. Adverse drug events from TB therapy can range from mild to serious and can lead to treatment interruption or even discontinuation. Several studies have shown an association between Asian TB patients and adverse drug events (41-43). In a study examining adverse drug events among TB patients, Asians were found to have 2.5 (95% CI: 1.3 – 5.0) times the rate of developing adverse events compared to other race groups (42). Similarly, blacks are also at a higher risk of developing adverse events and having a poorer response to TB drugs (43). Thus, among this population, completion of a shortened treatment regimen may be a result of treatment interruption or discontinuation, instead of new guideline based practices.

Diabetes

Diabetes status was also found to be significantly associated with completion of longer treatment among eligible patients in both univariate and adjusted analyses. Diabetic

patients in our study had an increased risk of completing unexpectedly long therapy compared to non-diabetics. Studies have shown diabetes to increase the risk of TB by three-fold (RR: 3.11, 95% CI: 2.27-4.26) (18). Additional clinical studies showed patients with DM to be more susceptible to TB, have more severe TB disease, and higher risk of relapse compared to individuals without DM (19-21). These can all be reasons for diabetic patients to be prescribed or take longer to complete TB treatment, even when eligible for shorter regimens.

Limitations

This study has several limitations. This study was retrospective in nature, which limited us to the data available captured by the RVCT. The RVCT does not capture a full clinical history or treatment course, which would include additional relevant information such as all comorbidities, any adverse drug events, treatment interruptions, and follow-up clinical and radiographic data. Furthermore, while all patients who were reported to have completed treatment were included in our study, it is unknown if completion of treatment was patient or provider driven. The generalizability of this study is also limited as this study only included patients who met specific criteria for eligibility for shortened treatment. As recommended in prior studies and guidelines, eligibility for a shortened four month treatment regimen was restricted to only those with pulmonary TB with a negative culture, an absence of any drug resistance to the first-line treatment regimen, a HIV negative test and absence of any other immunosuppression, thus limiting the generalizability of our study. This population was further subset by only including patients followed by health departments or TB programs as data has shown patients to have different health outcomes based on type of provider (38).

Conclusion

Shortened treatment among a subset of patients has been shown to yield comparable outcomes as those on longer treatments. However, factors associated with completing longer therapy when eligible for shortened therapy have not been examined. A shortened treatment regimen may decrease adherence failure and reduce costs for TB treatments, thus decreasing burden on the public health system. Results from our study provide insight into the association of these factors and longer therapy and may encourage health care providers to promote shortened treatment among eligible patients.

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Tables

Table 1: Characteristics of Adult US Tuberculosis (TB) Patients Who Completed TB Therapy and Eligible for a 4 Month Short Course, 2009-2016

	Completed Therapy N = 4,572 No. (%)
Therapy Duration (average days (sd))	199.8 (341.9)
Race	
White	609 (13.3)
American Indian or Alaskan Native	23 (0.5)
Asian	1,394 (30.5)
Black	963 (21.1)
Hispanic	1,206 (26.4)
More than 1 Race	12 (0.3)
Native Hawaiian or Pacific Islander	349 (7.6)
Age Group (years)	
15-24	615 (13.5)
25-44	1,549 (33.9)
45-64	1,663 (36.4)
65+	745 (12.3)
Sex	
Female	1,772 (38.8)
Male	2,800 (61.2)
Birthplace	
US Born	1,192 (26.1)
Foreign Born	3,372 (73.8)
US Census Region **	
Midwest	533 (11.7)
Northeast	461 (10.1)
South	2,067 (45.2)
West	925 (20.2)
US Territories	586 (12.8)
Medical Risk Factors	
Diabetes Mellitus	566 (12.4)
Other Medical Risk Factors §	1,482 (32.4)
Additional Social Risk Factors	
Resident of Long Term Facility **	56 (1.2)
Resident of Correctional Facility **	124 (2.7)
Homeless ***	162 (3.5)
Unemployed ***	1,346 (29.4)

* Appropriate therapy defined as 112-140 days

** At time of Diagnosis

*** Within Last 12 Months

§ Other medical risk factors include: previous diagnosis and incomplete treatment for latent TB; contact of infectious TB patient; diagnosis of end stage renal disease or renal failure; a solid organ recipient; recently receiving TNF-alpha antagonist therapy

Table 2: Percentage of Eligible Patients Completing Appropriate v. Inappropriate Treatment

	Appropriate* Shortened Therapy (%)	Unexpectedly Long Therapy (%)
Provider Type		
Health Department	21.06	78.94
Race		
White	18.23	81.77
American Indian or Alaskan Native	13.04	86.96
Asian	22.6	77.4
Black	27.73	72.27
Hispanic	21.14	78.86
More than 1 Race	8.33	91.67
Native Hawaiian or Pacific Islander	2.87	97.13
Age Group (years)		
15-24	17.24	82.76
25-44	22.92	77.08
45-64	21.89	78.11
65+	18.52	71.48
Sex		
Female	20.99	79.01
Male	21.11	78.89
Birthplace		
US Born	20.55	79.45
Foreign Born	21.29	78.71
US Census Region **		
Midwest	15.95	84.05
Northeast	22.99	77.01
South	25.54	74.46
West	22.81	77.19
US Territories	5.63	94.37
Medical Risk Factors		
Diabetes Mellitus **	15.55	84.45
No Diabetes Mellitus **	21.84	78.16
Other Medical Risk Factors §	20.92	79.08
No Other Medical Risk Factors §	21.13	78.87
Additional Social Risk Factors		
Resident of Long Term Facility **	14.29	85.71
Not Resident of Long Term Facility **	21.16	78.84
Resident of Correctional Facility **	16.13	83.87
Not Resident of Correctional Facility **	21.32	78.68
Homeless ***	22.22	77.78
Not Homeless ***	21.03	78.97

* Appropriate therapy defined as 112-140 days

** At time of Diagnosis

*** Within Last 12 Months

§ Other medical risk factors include: previous diagnosis and incomplete treatment for latent TB; contact of infectious TB patient; diagnosis of end stage renal disease or renal failure; a solid organ recipient; recently receiving TNF-alpha antagonist therapy

Table 3. Unadjusted Associations between Unexpectedly Long Therapy and Predictors

	Appropriate * Shortened Therapy N = 963	Unexpectedly Long Therapy N = 3609	RR	95% CI		p-value
Race/Ethnicity						
White[a]	111	498	1			
American Indian or Alaskan Native	3	20	1.063	0.904	1.251	0.4590
Asian	315	1,079	0.947	0.903	0.992	0.0220
Black	267	696	0.884	0.837	0.933	<0.0001
Hispanic	255	951	0.964	0.920	1.011	0.1342
More than 1 Race	1	11	1.121	0.941	1.335	0.2000
Native Hawaiian or Pacific Islander	10	339	1.188	1.139	1.238	<0.0001
Age						
15-24[a]	106	509	1			
25-44	355	1,194	0.931	0.890	0.974	0.0020
45-64	364	1,299	0.944	0.903	0.986	0.0102
65+	138	607	0.984	0.937	1.035	0.5366
Sex						
Female[a]	372	1,400	1			
Male	591	2,209	0.999	0.968	1.030	0.9266
Birthplace						
US Born[a]	245	947	1			
Foreign Born	718	2,654	0.991	0.958	1.025	0.5876
US Census Region **						
Midwest[a]	85	448	1			
Northeast	106	355	0.916	0.861	0.975	0.0057
South	528	1,539	0.886	0.847	0.926	<0.0001
West	211	714	0.918	0.873	0.966	0.0010
US Territories	33	553	1.123	1.077	1.171	<0.0001
Diabetes **						
No[a]	88	478	1			
Yes	875	3,131	1.081	1.039	1.123	<0.0001
Other Medical Risk Factors **						
No[a]	310	1172	1			
Yes	653	2,437	1.003	0.971	1.035	0.8672
Resident of Long Term Facility **						
No[a]	8	48	1			
Yes	954	3,555	1.087	0.976	1.211	0.1293
Resident of Correctional Facility **						
No[a]	20	104	1			
Yes	936	3,455	1.066	0.985	1.153	0.1119
Homeless ***						
No[a]	36	126	1			
Yes	921	3,459	0.985	0.906	1.071	0.7212

[a] Reference group

* Appropriate therapy defined as 112-140 days

** At time of Diagnosis

*** Within Last 12 Months

§ Other medical risk factors include: previous diagnosis and incomplete treatment for latent TB; contact of infectious TB patient; diagnosis of end stage renal disease or renal failure; a solid organ recipient; recently receiving TNF-alpha antagonist therapy

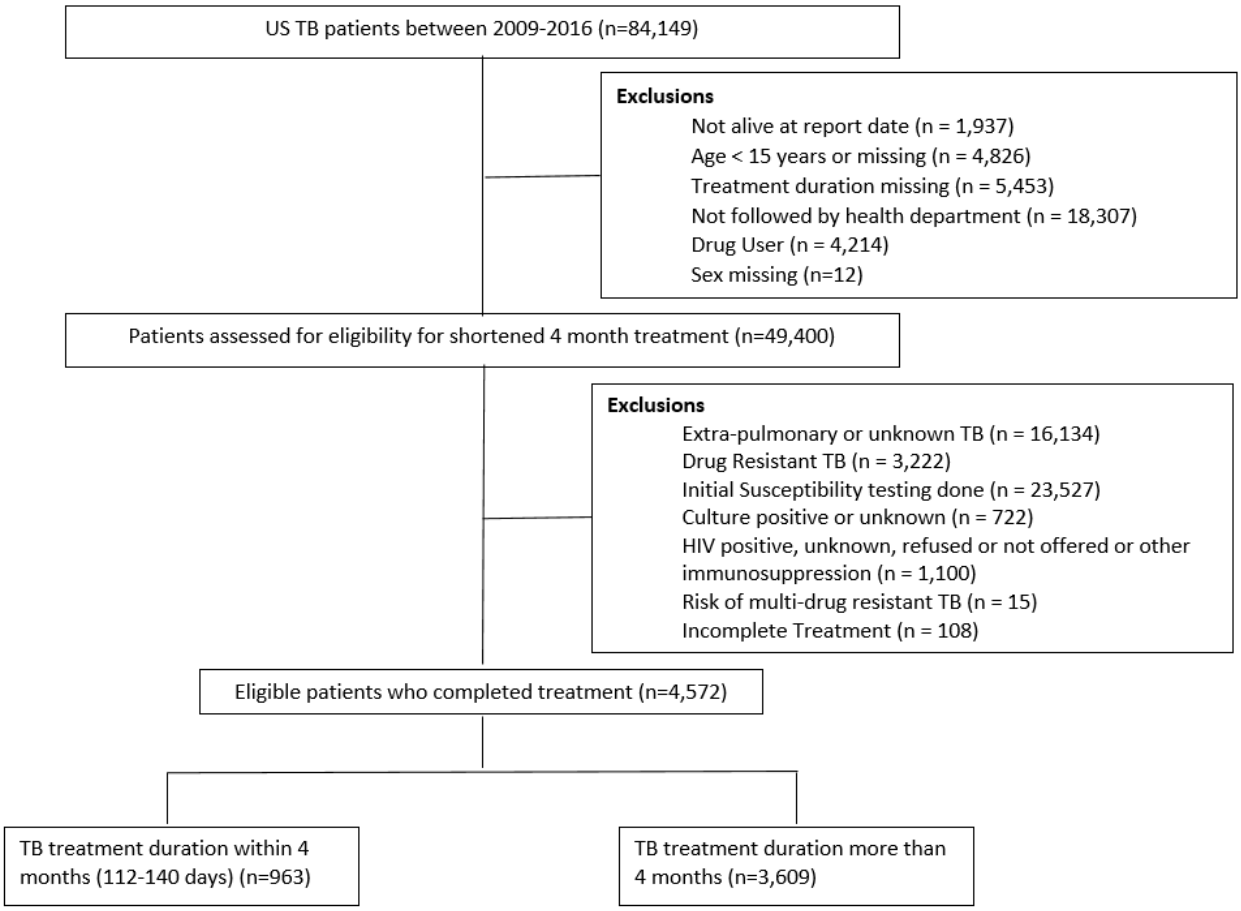
Table 4. Adjusted Associations between Unexpectedly Long Therapy and Predictors

	RR	Lower	Upper	p-value
Race/Ethnicity				
White[a]	1.00			
American Indian or Alaskan Native	1.04	0.90	1.20	0.5955
Asian	0.96	0.93	1.00	0.0509
Black	0.94	0.90	0.98	0.0014
Hispanic	0.98	0.94	1.02	0.2591
More than 1 Race	1.04	0.79	1.36	0.7917
Native Hawaiian or Pacific Islander	1.03	0.94	1.13	0.4840
Age				
15-24[a]	1.00			
25-44	0.97	0.93	1.00	0.0781
45-64	0.97	0.93	1.01	0.1057
65+	0.99	0.95	1.03	0.6093
Sex				
Female[a]	1.00			
Male	1.00	0.98	1.03	0.7595
US Census Regions*				
Midwest[a]	1.00			
Northeast	0.95	0.91	1.00	0.0531
South	0.94	0.90	0.97	0.0004
West	0.95	0.91	0.99	0.0092
US Territories	1.03	0.98	1.08	0.2418
Diabetes*				
No[a]	1.00			
Yes	1.04	1.00	1.08	0.0449

[a] Reference group

* At time of Diagnosis

Figure 1. Determination of Study Cohort



CHAPTER III: CONCLUSION

This study found positive and negative associations between several clinical, demographic, and social factors and completion of longer therapy among TB patients eligible for shorter therapy in the United States. The risk of completing longer therapy among eligible TB patients living in the Northeast, South, and West was lower than eligible patients living in the Midwest. The risk of completing longer therapy among Asian and Black patients was also lower compared to white patients. Diabetic patients had a higher risk of completing longer therapy compared to non-diabetics.

Shortened treatment among a subset of patients has been shown to yield comparable outcomes as those on longer treatments. However, factors associated with completing longer therapy when eligible for shortened therapy have not been examined. A shortened treatment regimen may decrease adherence failure and reduce costs for TB treatments, thus decreasing burden on the public health system. Results from our study provide insight into the association of these factors and longer therapy and may encourage health care providers to promote shortened treatment among eligible patients.

APPENDIX

EMORY UNIVERSITY | Institutional Review Board

January 2, 2018
Neha Patel
Emory University School of Public Health

RE: Determination: No IRB Review Required
eIRB#: 100867
Title: ***Factors Associated with 4-Month Therapy for Tuberculosis patients in the United States, 2009 – 2016***
PI: Neha Patel

Dear Ms. Patel:

Thank you for requesting a determination from our office about the above-referenced project. Based on our review of the materials you provided, we have determined that it does not require IRB review because it does not meet the definition of research with "human subjects" or clinical investigation as set forth in Emory policies and procedures and federal rules, if applicable. Specifically, in this project, you will seek to identify patient-based and clinical factors associated with three tuberculosis treatment classifications. You will analyze the Report of Verified Case of Tuberculosis (RVCT) data from the U.S. National TB Surveillance System (NTSS) database. All data are de-identified and you will not seek or obtain identifiers.

Please note that this determination does not mean that you cannot publish the results. This determination could be affected by substantive changes in the study design, subject populations, or identifiability of data. If the project changes in any substantive way, please contact our office for clarification.

Thank you for consulting the IRB.

Sincerely,

Tracy Cermak, MA, CIP
Research Protocol Analyst