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Comparing treatment outcomes among US-born vs. foreign-born patients diagnosed with tuberculosis in the state of Georgia, 2005-2015

By

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Master of Public Health

Epidemiology

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By

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University of Georgia
2014

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2018

Abstract

Comparing treatment outcomes among US-born vs. foreign-born patients diagnosed with tuberculosis in the state of Georgia, 2005-2015

By Nisha George

Elimination of tuberculosis (TB) in the United States necessitates early diagnosis and successful treatment of all cases and the prevention of transmission of *Mycobacterium tuberculosis* to new individuals. Foreign-born individuals bear a disproportionate burden of TB disease in the US, necessitating targeted efforts to minimize TB-related morbidity and mortality and prevent further transmission within this population. We investigated the association between country of birth and unfavorable treatment outcomes (i.e. prolonged or incomplete treatment) among new verified cases in the state of Georgia and sought to identify any risk factors that hinder the timely completion of treatment. We analyzed verified cases reported through the State Electronic Notifiable Disease Surveillance System (SendSS) to the Georgia Department of Public Health (GADPH) during January 2005-December 2015, who were followed through the completion of their treatment or until December 31, 2017, whichever occurred first. We used multivariable logistic regression to assess the association between TB treatment outcomes and country of origin while controlling for sociodemographic and clinical covariates available in case report forms. Of the 4,210 analyzed cases, 547 (13%) experienced unfavorable treatment outcomes, including 253 of 2,347 (11%) US-born cases and 294 of 1,860 (16%) foreign-born cases. After controlling for confounders, the odds of having an unfavorable outcome among foreign-born patients was higher when compared to their US-born counterparts [adjusted OR (aOR) = 1.34; 95% confidence interval (CI): (1.03, 1.74)]. In addition, the covariates that were significantly associated with an unfavorable TB treatment outcome include being male [aOR = 1.45; 95% CI: (1.14, 1.85)], being Hispanic [aOR = 2.13; 95% CI: (1.61, 2.82)], having positive sputum smear [aOR = 1.57; 95% CI: (1.24, 2.00)], being unemployed [aOR = 1.54; 95% CI: (1.23, 1.92)], having extrapulmonary TB disease [aOR = 1.80; 95% CI: (1.33, 2.45)], and having unknown prior history of illicit drug use [aOR = 5.47; 95% CI: (1.81, 16.50)]. Our results suggest that, in addition to clinical risk factors, various sociodemographic and environmental factors might play a role in hampering the success of TB treatment among foreign-born persons. Evidence-based interventions to target and improve treatment outcomes in foreign-born cases are needed to improve control TB in Georgia.

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ACKNOWLEDGEMENTS

This thesis would not have been possible without the patient and diligent guidance and mentorship of Dr. Kenneth Castro, my faculty advisor. It was an incredible opportunity to work with such an esteemed researcher in the field of infectious disease. I am also deeply grateful to Mr. Antoine Perrymon, my field advisor, who worked actively to provide the necessary data and guide me through the analysis in order to complete this project on time. I would like to thank Jasmine Ko for her valuable recommendations for the data analysis. Finally, I would like to thank Dr. Rose Marie-Sales, the former Director of the Georgia TB Program and Chief of the TB Epidemiology Section at the Georgia Department of Public Health, for helping me procure the study data.

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Background and Aims

Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium tuberculosis* organisms [1]. It is one of the top ten global causes of death, particularly among low- and middle-income countries [2, 3]. While pulmonary illness is the most common manifestation of TB disease, *M. tuberculosis* can cause disease throughout the body [1]. Following the inhalation of this pathogen, a person's innate immune system combats the infection, which could result in clearance of the bacilli or establishment of infection [4]. Infection can evolve from containment within the host, wherein the bacteria is isolated within granulomas resulting in latent TB infection, to active disease, during which a patient might exhibit symptoms such as cough, fever, malaise, and weight loss [1]. Active disease will develop in 5 to 15% of individuals with latent infection within a few years of infection, and this percentage increases if they become immunocompromised [1, 4]. TB disease is often fatal; if untreated, about 50% of persons with active TB disease will succumb to it [5].

Even though TB remains relatively forgotten in the national health conversation in the United States of America, it continues to persist with no signs of immediate elimination, despite past commitments to reduce TB incidence to ≤ 1 case/million per year [6]. The overall incidence of TB in the United States experienced an unprecedented increase between 1985 and 1992 [7]. Factors associated with this resurgence have been described and addressed [7]. Subsequently, while TB incidence has been steadily declining throughout the 2000s, with a case rate of 8.5 cases per 100,000 individuals in 1995 to 3.0 cases per 100,000 individuals in 2015, foreign-born individuals in the US remain disproportionately affected by TB [8, 9]. In 2017 the Centers for Disease Control

and Prevention (CDC) reported 9,093 TB cases in the US, and foreign born persons accounted for more than two-thirds of these cases (n = 6,346), with a case rate of 14.6 cases per 100,000 individuals for this population [10]. This was nearly 15 times the TB case rate among US born persons (1.0 cases/100,000 persons), making them an important population of interest in the fight against TB [10].

The state of Georgia is among the top ten states reporting the highest number of TB cases in country, with 321 new verified TB cases and an incidence rate of 3.1 cases per 100,000 persons in 2015 [11]. Of these cases, 149 (46%) are foreign-born individuals, who primarily originated from India (15%), Mexico (14%), and Vietnam (11%), which are countries where TB is an endemic disease [11]. Prior studies have shown that noncitizens, particularly undocumented immigrants, underutilize the healthcare system out of fear of being reported to the authorities, which not only jeopardizes their own health, but in case of tuberculosis also places the health of the general public at risk [12-15]. Hence, the efforts to control and eliminate in the state need to be geared towards understanding the needs of vulnerable population and identifying risk factors that might hinder them from accessing and effectively utilizing available healthcare facilities [15].

Eliminating TB requires the prevention of new cases of infection and disease, which necessitates adequate treatment of all diagnosed TB cases. Treatment of people with drug-susceptible TB can take up to six to nine months, with a regimen of four drugs for the first two months followed by two drugs for an additional 4 months [16]. Drug-resistant TB is characterized by *M. tuberculosis* that is resistant to at least one first-line TB drug [16, 17]. Treating drug resistant TB is complicated, and incomplete or

inappropriate treatment can have severe health repercussions, promote additional antimicrobial resistance, and possibly result in death [16, 17].

There were 4,478 TB cases in Georgia that were diagnosed between 2005 and 2015, and about 85% of them completed their treatment as prescribed [11, 19-20]. Foreign-born individuals comprised 43% of those who completed TB treatment [11, 19-20]. While the overall treatment completion in the state is relatively high, transmission of *Mycobacterium tuberculosis* can be facilitated as long as at least a single infectious case remains untreated or undertreated [21, 22]. Transmission of TB in Georgia and elsewhere can be exacerbated by living in crowded settings as well as experiencing disparities while accessing healthcare [11, 23]. Additionally, partially treated individuals may develop drug-resistant TB, which is more difficult and expensive to treat, and further contribute to the transmission of a more resistant pathogen, worsening the morbidity and mortality associated with TB [17, 24].

Prior studies have shown that certain risk factors are associated with not completing treatment within the prescribed time period. Comorbidities such as diabetes mellitus (DM) and chronic kidney disease and having a history of homelessness have been associated with prolonged treatment and incomplete treatment [25-30]. Prolongation of TB treatment typically occurs when a physician extends the treatment period based on suboptimal response to therapy, or when the treatment is interrupted, while incomplete treatment results from loss to follow-up, migration to another state or country, or refusal to continue treatment.

Living with HIV also affects the TB treatment prescribed to a patient, and active TB disease expedites the progression of HIV infection [31-32]. The outbreak of

isoniazid-resistant TB in 2014 among downtown homeless shelters in Fulton County revealed that transient housing can impede continual, full treatment of TB patients [11, 33]. Lastly, TB cases with a history of substance abuse often experience treatment failure and remain infectious longer since failure extends the period of contagiousness [34-35].

However, specific risk factors that influence treatment outcomes among foreign-born individuals have not been fully explored [36]. This project aims to compare individuals with unfavorable treatment outcomes to those who complete treatment within their designated time period (i.e., favorable treatment outcomes), in order to identify risk factors that are statistically associated with these outcomes among foreign–born and U.S.-born individuals diagnosed with TB within the state of Georgia. If clinical and/or social factors influence patients' ability to adequately complete treatment, these might necessitate the evaluation of public health interventions to improve TB treatment outcomes within the state. It is imperative to understand how TB programs can cater to special needs of TB patients and ensure their successful completion of their treatment.

Methods

Data Source and Study Population

The study population includes all verified cases of TB diagnosed in the state of Georgia and reported through the State Electronic Notifiable Disease Surveillance System (SendSS) to the Georgia Department of Public Health (GADPH). These cases were diagnosed and reported to the Department of Public Health between the years 2005 through 2015 (January 1, 2005 to December 31, 2015), and were followed through the completion of their treatment or until December 31, 2017, whichever occurs first. Documented treatment completion was of key importance to this study and therefore,

cases with missing treatment completion information were excluded from the analyses. Cases with missing country of birth information (i.e. exposure of interest) as well as patients who died during the course of their TB treatment due to causes unrelated to the disease were also excluded from the analysis. The study analyses focus on all the reported cases with accurate TB treatment status and country of origin information.

Variables

The following socio-demographic variables were collected and available in the SendSS system: history of homelessness or transient living, resident of a long-term care facility (e.g. nursing home, correctional facility), country of birth (i.e., U.S.-born or foreign-born), nationality, age, sex assigned at birth, race and ethnicity, history of alcohol or illicit substance use, and employment status. The clinical history variables collected in the case report and requested for this analysis are TB treatment completion status, prolongation of TB therapy if necessary, cause of death, type of therapy administered (directly observed therapy vs. self-administered therapy), reported HIV status, site of disease (pulmonary, extrapulmonary – pleural, lymphatic, bone and/or joint, meningeal, laryngeal, genitourinary, peritoneal TB), initial sputum smear and sputum culture results, nucleic acid amplification (NAA) test results, chest X-ray confirmation regarding TB diagnosis, X-ray evidence of chest cavitation, chest X-ray evidence of miliary TB, immunochromatographic assay (ICT) result, tuberculin skin test result, having a previous TB diagnosis, resistance to anti-TB drugs, and any known co-morbidities such as diabetes, smoking, and end stage kidney disease. For purposes of this analysis, GADPH did not disclose the reported HIV status of the TB cases pursuant to the GA Code § 24-

12-21 (2014), which prohibits the disclosure of AIDS-related confidential information to individuals who are not licensed healthcare providers.

TB treatment outcomes

The main outcome of interest was prolonged or lack of completion of prescribed TB therapy. The following outcomes were assessed for all patients in the database:

Therapy completed: A patient has ingested the total number of prescribed doses of TB drugs within the specified time frame and does not present any evidence of treatment failure. The cases with this outcome were considered to have a 'favorable' TB treatment outcome.

The following nine events relate to prolonged or incomplete TB treatment, and were therefore consolidated and considered as 'unfavorable' TB treatment outcomes:

Adverse treatment event: The patient developed adverse reactions during therapy, resulting in discontinuation of TB treatment.

Adverse drug reaction: The patient developed severe reactions to one or more anti-TB drugs, resulting in extension/prolongation of treatment period.

Death due to tuberculosis: The patient died during treatment and TB was the major contributing cause of death

Lost to follow-up: Patients who did not complete therapy because they could not be located and/or did not return to healthcare facility for follow-up treatment.

Moved: TB patients who transferred out of care before completing treatment and whose treatment outcome is unknown.

Refused or Uncooperative: Patients who refuse to undergo treatment after TB diagnosis

Non-adherence: Patients who did not adhere to prescribed TB treatment regimen, resulting in extension of treatment beyond 12 months.

Rifampin resistance: Patients with *M. tuberculosis* strains that are resistant to the anti-TB drug, rifampin, resulting in longer (i.e., prolonged) treatment periods.

Treatment failure: Presence of positive sputum smear or sputum culture for *M. tuberculosis* after 5 months of treatment.

In addition to the above listed outcomes, some cases died due to health reasons other than TB. Since they were not related to tuberculosis therapy, these deaths were excluded from the analysis. Cases with missing treatment completion information were also excluded from the analysis. Following the exclusion of ineligible cases, the remaining cases were classified into two treatment outcome categories - those who successfully completed their prescribed TB regimen (i.e. individuals with favorable outcomes) and those who experienced any of the nine listed adverse TB therapy related events (i.e. individuals with unfavorable outcomes).

Country of origin

All the TB cases in the SendSS system were categorized as either US-born or foreign-born. All cases born in the United States and its insular territories or were born in a foreign country but to a US citizen were considered US-born. Those that did not meet this definition were classified as foreign-born. Individuals with missing or unknown country of origin information were excluded from the analysis.

Statistical Analysis

The outcome was dichotomized into favorable versus unfavorable TB treatment outcomes, as previously described, with favorable treatment outcomes serving as the

reference group. Pearson's chi-square tests and Fisher exact tests (when expected cell counts were less than 5) were used to compare different proportions between treatment outcome groups. Variables that were associated with the outcome of interest (p-value ≤ 0.05) were included in the multivariable logistic regression model. Multivariable logistic regression was used to assess the association between TB treatment outcomes and country of origin while controlling for sociodemographic and clinical covariates. We conducted collinearity diagnostics in order to detect any variables in the model that appeared to have near perfect linear combinations of one another. Variables with a condition index (CI) > greater than 30 and two or more variance decomposition proportions (VDPs) greater than 0.5 were considered to be collinear. We assessed for confounding by sex assigned at birth, age, ethnicity, homelessness, having a prior TB diagnosis, sputum smear, evidence of miliary TB, history of diabetes mellitus and end stage renal disease, employment status and site of TB disease, and those associated with the outcome (p-value ≤ 0.05) were retained in the model. We also conducted a bivariate analysis of the different sociodemographic and clinical covariates with the treatment outcomes stratified by the country of origin. All data analyses were performed using Statistical Analytical Software (SAS) version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics Statement

The data used in the analysis is routinely collected by the Georgia Department of Public Health (GADPH) for TB disease surveillance in the state. Since this study requested sociodemographic patient information, it necessitated Institutional Review Board (IRB) approval due to concerns regarding patient re-identification. The dataset provided by GADPH contained no personal identifiers such as name, dates of birth,

Social Security Numbers (SSN) and excluded HIV status information in accordance with Georgia state law (GA Code § 24-12-21). This project received exempt approval from the Emory University IRB and the GADPH IRB.

Results

A total of 4,478 verified cases of tuberculosis in the state of Georgia were reported to SendSS during January 1, 2005 to December 31, 2015 (Figure 1). Of these, 263 (6%) cases died due to causes unrelated to TB and were excluded from the analysis. Among the remaining cases, 4,210 cases (94%) had valid information regarding their therapy completion status and length of treatment. Following the exclusion of cases with unknown country of origin (n = 3), our final sample size was 4,207 cases. Of these, 2,347 (56%) were US born, while 1,860 (44%) were foreign-born persons. Overall, 547 (13%) cases experienced unfavorable treatment outcomes, which consisted of 9 cases (2%) that experienced adverse treatment event, 137 cases (25%) who had prolonged therapy due to adverse drug reaction, treatment failure, non-adherence and rifampin resistance, 77 cases (14%) who died due to TB disease or therapy, 125 cases (23%) who were lost to follow-up, 26 cases (5%) who refused or were deemed uncooperative with TB therapy, and 149 cases (27%) who discontinued therapy for other or unknown reasons. Two hundred fifty three of 2,347 (11%) US-born cases and 294 of 1,860 (16%) foreign-born cases experienced unfavorable treatment outcomes. Figure 2 shows the annual distribution of unfavorable outcomes by country of origin for TB cases in the state from 2005 to 2015. With the exception of 2014, foreign-born persons had greater or equal numbers of

unfavorable TB treatment outcomes annually than US-born persons throughout that decade.

Table 1 provides the descriptive analyses for the sociodemographic and clinical characteristics for all TB cases and those with unfavorable outcomes, stratified by country of origin. A majority of both US-born and foreign-born cases received directly observed therapy, had pulmonary TB disease and were male. The proportion of African Americans, unemployed individuals, and those with a history of excess alcohol and illicit drug use is higher among US-born individuals ($p \leq 0.05$). Among US-born cases, 1,651 (70%) are African American and 1,179 (50%) are unemployed. Four hundred and ninety (21%) and 375 (16%) US-born cases reported excess alcohol and illicit drug use, respectively. The number of cases identifying as Asian, Hawaiian or Pacific Islander, and those of Hispanic ethnicity represented a relatively large proportion of foreign-born cases. Among foreign-born TB cases, there were 694 (37%) cases identified as Asian, Hawaiian or Pacific Islander and 682 (37%) as Hispanic.

Table 2 provides the results from bivariate analyses that assessed patient sociodemographic characteristics and unfavorable treatment outcomes by country of origin for US-born and foreign-born. The unadjusted odds ratio of the association between being foreign-born and having an unfavorable treatment outcome is 1.6 (95% CI: 1.3, 1.9). In both US- and foreign-born, unfavorable treatment outcomes were associated with older age (>65 years) [US-born OR = 1.7; 95% CI: (1.0, 2.7); Foreign-born OR = 1.7; 95% CI: (0.7, 1.9)], having initial smear positive sputum results [US-born OR = 1.3; 95% CI: (1.0, 1.8); Foreign-born OR = 1.4; 95% CI: (1.1, 1.8)], and being unemployed [US-born OR = 1.4; 95% CI: (1.1, 1.9); Foreign-born OR = 1.3; 95% CI:

(1.0, 1.6)]. Unknown excess alcohol and illicit drug use are associated with unfavorable treatment outcomes among both US-born and foreign-born individuals; however, the positive association between unknown excess alcohol use and foreign-born persons [OR = 11.2; 95% CI: (3.8, 33.1)] is greater than that for US-born persons [OR = 7.5; 95% CI: (3.4, 16.4)]. US-born individuals exhibit a stronger positive association between unknown illicit drug use and unfavorable treatment outcomes [OR = 11.2; 95% CI: (4.1, 30.4)] than foreign-born persons [OR = 5.6; 95% CI: (2.2, 14.2)]. US-born persons were also more likely to have unfavorable treatment outcomes due to end stage renal disease [OR = 2.6; 95% CI: (1.1, 6.0) vs. foreign-born OR = 0.9; 95% CI: (0.1, 7.4)] and extrapulmonary TB disease [OR = 2.0; 95% CI: (1.5, 2.7) vs. foreign-born OR = 1.2; 95% CI: (0.9, 1.7)], while in foreign-born persons, unfavorable treatment outcome was positively associated with being Hispanic [OR = 2.3; 95% CI: (1.8, 2.9) vs. US-born OR = 0.5; 95% CI: (0.2, 1.0)] and having combined pulmonary and extrapulmonary TB disease [OR = 1.6; 95% CI: (1.0, 2.4) vs. US-born OR = 1.0; 95% CI: (0.6, 1.7)].

Table 3 provides the results from multivariable analysis evaluating the sociodemographic and clinical risk factors associated with unfavorable TB treatment outcomes among US-born and foreign-born persons. After controlling for potential confounders during the multivariable analysis, the odds of having an unfavorable outcome among foreign-born patients was higher when compared to US-born individuals [adjusted OR (aOR) = 1.34; 95% CI: (1.03, 1.74)]. This association is statistically significant at $\alpha = 0.05$. There was no significant interaction between country of origin and other covariates included in the final multivariable model. The covariates that are significantly associated with an unfavorable TB treatment outcome include being male

[aOR = 1.45; 95% CI: (1.14, 1.85)], being Hispanic [aOR = 2.13; 95% CI: (1.61, 2.82)], having positive sputum smear [aOR = 1.57; 95% CI: (1.24, 2.00)], being unemployed [aOR = 1.54; 95% CI: (1.23, 1.92)], having extrapulmonary TB disease [aOR = 1.80; 95% CI: (1.33, 2.45)], and having unknown prior history of illicit drug use [aOR = 5.47; 95% CI: (1.81, 16.50)]. Other covariates such as age, race, homelessness, prior history of TB disease, initial sputum culture results, presence of miliary TB, diabetes mellitus, end stage renal disease, and excess alcohol use were also evaluated as potential confounders but did not meaningfully change the odds ratio and were therefore excluded from the final multivariate model.

Discussion

The results of this retrospective study indicate that unfavorable TB treatment outcome in Georgia is statistically associated with being foreign-born, when compared with US-born TB cases. As seen in Figure 2, except for 2010 and 2014, foreign-born persons had unfavorable annual TB treatment outcomes than US-born persons between 2005 and 2015. Foreign born individuals were also less likely to have total directly observed therapy (73% vs. 83%) and fewer cases of pulmonary TB disease (69% vs. 75%). In prior publications, directly observed therapy has been associated with improved treatment outcomes, which could partly explain our observation [37-39]. In addition, we observed that extrapulmonary TB was statistically associated with unfavorable treatment outcomes [40, 41]. The relatively larger proportion of extrapulmonary disease in foreign-born TB cases than in US-born cases might also influence the observed unfavorable treatment outcome [42]. In 2014, US-born individuals had a higher incidence of

unfavorable treatment outcomes, which could be influenced by the occurrence of documented drug-resistant TB outbreaks in homeless shelters in Atlanta [33]. In Georgia, foreign-born TB cases are less likely to have transient housing than their US-born counterparts (4% vs. 14%). These individuals were also less likely to report excess alcohol use and illicit injection and non-injection drug use, risk factors commonly associated with adverse TB treatment outcomes. This suggests that, in addition to clinical risk factors, various social, cultural, environmental, economic, and political factors might play a role in hampering the success of TB treatment among foreign-born persons.

Along with the country of origin, this study also evaluated whether unfavorable treatment outcomes were associated with sociodemographic and clinical covariates. Male sex, Hispanic ethnicity, initial positive sputum smear results, extrapulmonary TB disease, unemployment and having an unknown history of illicit drug use serve as strong predictors of unfavorable treatment outcomes among foreign-born patients. These findings are not surprising since the sociocultural risk factors often characterize marginalized foreign-born persons and the biomedical risk factors make it challenging to diagnose TB or have been associated with unfavorable treatment outcomes.

While males have been documented to be at greater risk than females of being reported with TB, prior studies have also shown that foreign-born males living in low TB burden countries experience unfavorable treatment outcomes [43-44]. These immigrant males were found to have lower rates of treatment and be at greater risk of experiencing therapy failures [44]. The male sex has also been associated with death during treatment [45-46]. Qualitative studies have shown that Mexican males undergoing TB treatment in the United States report feelings of depression during treatment as they may be placed in

isolation while they are infectious or choose to leave or be forced out of their communities [47, 48]. Family support has been identified as a key factor in facilitating drug adherence [49]. Depression and TB have also been associated with low social support and drug side effects, which contribute to delay or stoppage of treatment [47, 48]. This analysis could not assess the role of depression in unfavorable TB treatment outcomes.

Even though Hispanic populations are disproportionately affected by TB, limited research is available regarding barriers to successful treatment completion among them. A study evaluating patient characteristics of foreign-born Hispanic patients undergoing TB therapy reported that about 30% of the patients had a previous history of TB disease and more than a quarter of these patients reported having received therapy outside the United States [50]. However, these numbers could be underestimates of the true proportions given the cultural stigma associated with TB [47, 48]. Fear of deportation could also deter foreign-born individuals with illegal alien status from seeking care at local health departments [47]. Paradoxically, incomplete TB treatment can lead to treatment failure, development of drug resistance, and contribute to ongoing TB transmission in communities [51].

While patients with smear-positive TB are considered to be more infectious than smear-negative patients, smear positivity can also influence treatment outcomes [52, 53]. Previous research has shown that smear positive patients had a higher proportion of non-adherence to treatment than smear negative persons, which can result in further treatment challenges and increases the risk of death [52]. Patients who continue to remain smear positive at 2 or 3 months of treatment are more likely to fail or default from therapy [53].

As they are more infectious, they also considerably contribute to the airborne transmission of *M. tuberculosis* to other individuals. To improve treatment outcomes, existing guidelines recommend extending the total duration of treatment beyond six months in patients with drug-susceptible TB who remain smear or culture positive after the first two months of treatment [16].

Treatment for extrapulmonary TB is more complicated than that for pulmonary TB because the site of disease influences the nature of the disease [1, 40]. The damage to different organs due to tuberculosis infection affects mortality due to TB [54]. Disseminated, meningeal, and miliary TB are associated with higher rates of mortality [54, 55]. Additionally, antibiotics may not be able to effectively penetrate different affected anatomic sites [54]. This makes it challenging to kill the pathogen, resulting in a higher likelihood of treatment failure and development of drug resistance [54]. Diagnoses such as meningeal TB also require longer treatment periods (12 months or longer), which has been documented to increase the likelihood of patients dropping out of care or experiencing treatment-related toxicities [40, 54, 56].

Low socioeconomic status has been associated with TB disease in both developing countries and in the United States [57]. Having a TB diagnosis can impede a patient's ability to work and provide for their family as head of household [47]. Foreign-born persons often depend on their employment status to be able to live and work in the United States. Poor health and loss of employment could jeopardize their source of income as well as revoke their current immigrant status. A prior publication suggested that Mexican-born TB patients are less likely to report unemployment to TB care providers [58]. Loss of income also prevents these persons from paying for treatments

and diagnostic tests related to their TB care and might prevent them from completing the entire course of their treatment. Additionally, undocumented individuals may not be eligible for health insurance or government health subsidies.

Use of injection and non-injection drugs influences TB treatment adherence and can lead to treatment failures. While illicit drug use has not been typically associated with foreign-born populations reported with TB, marginalized populations overall are at increased risk of drug use [60]. Patterns of substance abuse among immigrant populations in the United States are understudied [61]. As seen in Table 1, foreign-born TB cases reported lower rates or alcohol and drug abuse than US-born TB cases. Other researchers have suggested that even if alcohol and drug use is lower in their country of origin, foreign born individuals might feel pressured into increasing their consumption in order to 'acclimate' into the new society [62]. Prior studies have also shown that Hispanic persons bear a disproportionate burden of substance use-attributable mortality such as suicides [63, 64]. Additionally, environmental stressors such as separation from families while working abroad, traumatic life events (e.g. death, loss of employment), and racial-ethnic discrimination have been linked to increased substance use [65, 66]. While minority groups such as foreign-born Hispanic persons bear a significant burden of substance abuse related conditions, they are also less likely to have utilized any substance abuse treatment programs [67]. We are uncertain how to explain the observation that unknown illicit drug use, instead of reported drug use, is associated with unfavorable treatment outcomes in this population. This could be the result of providers not consistently asking and documenting substance abuse among reported TB cases, cultural

stigmas related to drug use or fears of being reported to the authorities, all contributing to underreporting of drug use by patients and/or providers [68-69].

There are at least three readily identified limitations to this study. First, this is a cohort study that relies on mostly self-reported sociodemographic information (e.g. drug and alcohol use, employment status) collected in TB case report forms and therefore, may underestimate patient comorbidities. In addition, TB patients diagnosed before 2009 may have incomplete information because the SendSS system was updated to include additional TB-related variables.

Second, the SendSS system did not collect information about cigarette smoking among TB cases. Chronic smoking has been associated with extensive pulmonary disease, chest cavitation and having initial positive sputum smear results [70]. Smokers are also more likely to remain smear positive after 2 months of treatment and are significantly less likely to achieve treatment completion in 2 years [71-73]. Hence, smoking is strongly associated with unfavorable TB treatment outcomes and we could not control for confounding by this variable [73].

Third, due to stringent Georgia state policies, we were unable to obtain reported HIV status of the patients and evaluate TB treatment outcomes by HIV infection. About 9% of TB cases in Georgia report TB/HIV co-infection, and the rate of HIV infection among TB patients in the city of Atlanta is one of the highest in the US [18, 74]. HIV co-infected patients experience higher rates of extrapulmonary involvement, which have higher rates of mortality [75, 40-41]. Researchers have found that HIV-positive patients with meningeal TB died at almost 3-times the rate of those without HIV [76]. TB drug resistance can complicate both HIV and TB therapies by increasing the length of TB

treatment and the risk of negative drug interactions with HIV medications. Additionally, HIV-positive individuals who are not on anti-retroviral therapy (ART) during TB treatment experience worse long-term outcomes [79, 80].

To our knowledge, this ten year retrospective cohort study is one of the first to evaluate TB treatment outcomes in the state of Georgia over a decade by country of origin. While foreign-born individuals made up only 10% of the total state population in 2015, they represented nearly half (n = 148, 46%) of the TB cases in the state that year [81]. The top countries of origin for Georgian immigrants include Mexico (26%), India (9%), and Vietnam (4%), which have also been identified as having high rates of endemic TB [81-82]. We also assessed the role of both clinical and sociodemographic variables in our model in order to understand the varied risk factors that influence unfavorable treatment outcomes.

In conclusion, we found that foreign-born TB patients in Georgia are more likely to have unfavorable TB treatment outcomes than their US-born counterparts. Unfavorable outcome was also positively and significantly associated with male sex, Hispanic ethnicity, positive initial sputum smear results, extrapulmonary TB disease, unemployment and having an unknown history of illicit drug use among foreign born persons. These findings suggest that, in addition to clinical factors, sociodemographic and environmental risk factors play a significant role in the achieving TB treatment success among foreign-born populations. The findings can inform future evidence-based actions by GADPH to target and improve TB treatment outcomes in foreign-born TB cases. As insufficient treatment can result in development of resistance to anti-TB drugs and further raise the cost of treating TB disease, understanding the treatment challenges faced by

foreign-born populations will ultimately provide significant public health as well as economic benefits to the state.

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Figure 1. Study population flowchart with inclusion and exclusion criteria and number of TB cases in the analysis

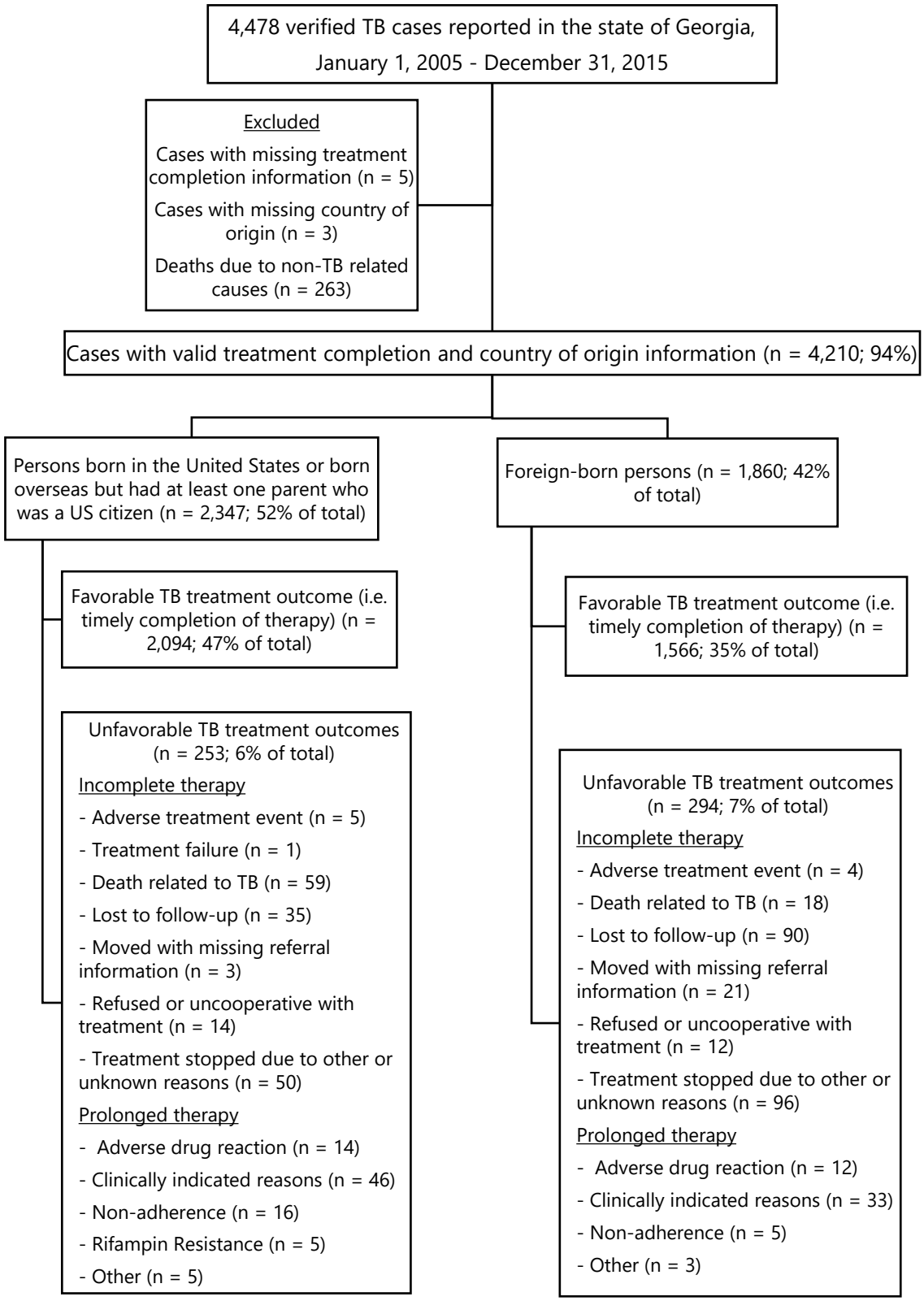

Figure 2. Distribution of cases with unfavorable treatment outcomes (n=547) in Georgia, by year of diagnosis (2005 to 2015) and by country of origin (U.S.-born and foreign-born). Total number of US and foreign-born cases with unfavorable treatment outcomes were 253 and 294, respectively.

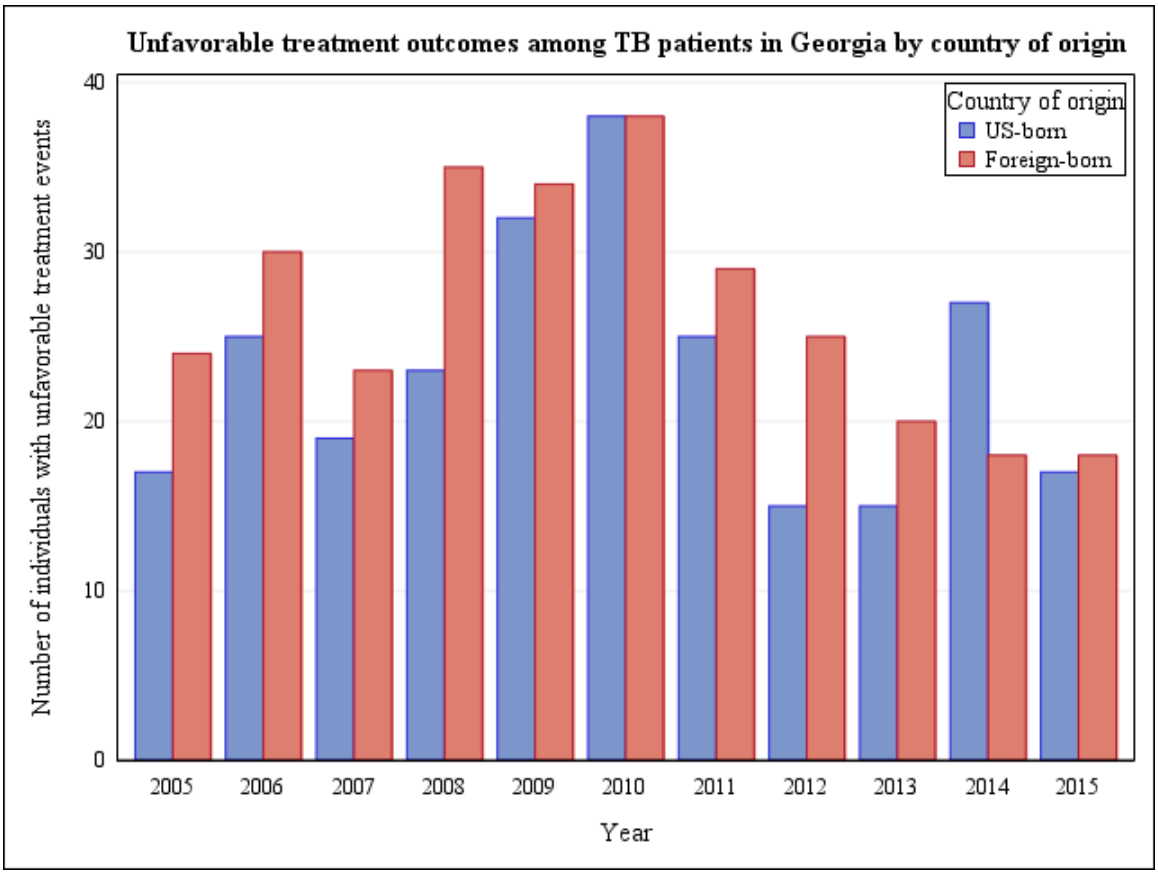

Table 1. Number and percent distribution of sociodemographic and clinical characteristics among total US-born and foreign-born tuberculosis patients and with unfavorable treatment outcomes in Georgia, 2005 – 2015.

Characteristic	U.S.-born		Foreign-born	
	Total (%)	Unfavorable Outcomes (%)	Total (%)	Unfavorable Outcomes (%)
Overall	2347 (55.8)	253 (10.8)	1860 (44.2)	294 (15.8)
Gender[a]				
Male	1525 (65.0)	174 (68.8)	1167 (62.7)	208 (70.8)
Female	822 (35.0)	79 (31.2)	692 (37.2)	85 (28.9)
Age[a]				
≤15 years	276 (11.8)	11 (4.4)	64 (3.4)	0 (0.0)
16-25 years	216 (9.2)	17 (6.7)	353 (19.0)	50 (17.0)
26-35 years	255 (10.9)	28 (11.1)	545 (29.3)	90 (30.6)
36-45 years	402 (17.1)	53 (21.0)	360 (19.4)	64 (21.8)
46-55 years	528 (22.5)	58 (22.9)	241 (13.0)	35 (11.9)
55-65 years	357 (15.2)	33 (13.0)	152 (8.2)	28 (9.5)
>65 years	313 (13.3)	53 (21.0)	145 (7.8)	27 (9.2)
Race[a]				
African American	1651 (70.4)	186 (73.5)	426 (22.9)	55 (18.7)
American Indian/Alaska Native	10 (0.4)	1 (0.4)	64 (3.4)	15 (5.1)
Asian/Hawaiian/Pacific Islander	47 (2.0)	2 (0.8)	694 (37.3)	75 (25.5)
Multi-racial	12 (0.5)	0 (0.0)	13 (0.7)	4 (1.4)
White	624 (26.6)	64 (25.3)	659 (35.4)	145 (49.3)
Ethnicity[a]				
Hispanic	132 (5.6)	7 (2.8)	682 (36.7)	157 (53.4)
Non-Hispanic	2213 (94.3)	245 (96.8)	1177 (63.3)	137 (46.6)
Sputum smear[a]				
Positive	896 (38.2)	96 (37.9)	664 (35.7)	115 (39.1)
Negative	1040 (44.3)	87 (34.4)	1002 (53.9)	130 (44.2)
Directly observed therapy				
Totally directly observed therapy	1958 (83.4)	177 (70.0)	1354 (72.8)	172 (58.5)
Both directly observed and self-administered therapy	260 (11.1)	18 (7.1)	328 (17.6)	47 (16.0)
Totally self-administered therapy	37 (1.6)	3 (1.2)	64 (3.4)	12 (4.1)
Site of disease[a]				
Pulmonary	1753 (74.7)	164 (64.8)	1290 (69.4)	189 (64.3)
Pulmonary + Extrapulmonary	160 (6.8)	15 (5.9)	132 (7.1)	28 (9.5)
Extrapulmonary	433 (18.5)	74 (29.3)	434 (23.3)	76 (25.9)
Homeless				
Yes	331 (14.1)	41 (16.2)	68 (3.7)	16 (5.4)
No	2014 (85.8)	211 (83.4)	1783 (95.9)	272 (92.5)
Employment[a]				
Employed	913 (38.9)	84 (33.2)	1043 (56.1)	150 (51.0)
Unemployed	1179 (50.2)	150 (59.3)	651 (35.0)	114 (38.8)

Unknown	255 (10.9)	19 (7.5)	166 (8.9)	30 (10.2)
Excess Alcohol Use				
Yes	490 (20.9)	53 (21.0)	99 (5.3)	20 (6.8)
No	1831 (78.0)	188 (74.3)	1746 (93.9)	264 (89.8)
Unknown	26 (1.1)	12 (4.7)	15 (0.81)	10 (3.4)
Illicit Drug Use				
Yes	375 (16.0)	43 (17.0)	43 (2.3)	12 (4.1)
No	1956 (83.3)	201 (79.5)	1799 (96.7)	273 (92.9)
Unknown	16 (0.7)	9 (3.6)	18 (1.0)	9 (3.1)
Physical Comorbidity – Diabetes Mellitus				
Yes	144 (6.1)	16 (6.3)	126 (6.8)	25 (8.5)
No	2203 (93.9)	237 (93.7)	1734 (93.2)	269 (91.5)
Physical Comorbidity – End Stage Renal Disease				
Yes	30 (1.3)	7 (2.8)	7 (0.4)	1 (0.3)
No	2317 (98.7)	246 (97.2)	1853 (99.6)	293 (99.7)

[a]Pearson's chi-square test or Fisher exact test ($p \leq 0.05$)

Table 2. Overall univariate crude odds ratio (OR) and 95% confidence interval (CI) for country of birth and unfavorable TB treatment outcomes, and bivariate associations (crude OR and 95% CI) between patient sociodemographic characteristics and unfavorable tuberculosis treatment outcomes, stratified by country of origin.

Characteristic	U.S.-born		Foreign-born	
	Crude OR	$CI_{95\%}$	Crude OR	$CI_{95\%}$
Overall	*Reference*		1.6	1.3, 1.9
Gender				
Male	1.2	0.9, 1.6	1.5	1.2, 2.0
Female	*Reference*		*Reference*	
Age				
≤15 years	0.3	0.2, 0.7	--	--
16-25 years	0.7	0.4, 1.3	0.8	0.6, 1.2
26-35 years	*Reference*		*Reference*	
36-45 years	1.2	0.8, 2.0	1.1	0.8, 1.6
46-55 years	1.0	0.6, 1.6	0.9	0.6, 1.3
55-65 years	0.8	0.5, 1.4	1.1	0.7, 1.8
>65 years	1.7	1.0, 2.7	1.2	0.7, 1.9
Race				
African American	1.1	0.8, 1.5	0.5	0.4, 0.7
American Indian/Alaska Native	1.0	0.1, 7.8	1.1	0.6, 2.0
Asian/Hawaiian/Pacific Islander	0.4	0.1, 1.6	0.4	0.3, 0.6
Multi-racial	--	--	1.6	0.5, 5.2
White	*Reference*		*Reference*	
Ethnicity				
Hispanic	0.5	0.2, 1.0	2.3	1.8, 2.9
Non-Hispanic	*Reference*		*Reference*	
Sputum smear				
Positive	1.3	1.0, 1.8	1.4	1.1, 1.8
Negative	*Reference*		*Reference*	
Directly observed therapy				
Totally directly observed therapy	*Reference*		*Reference*	
Both directly observed and self-administered therapy	0.7	0.5, 1.2	1.1	0.8, 1.6
Totally self-administered therapy	0.9	0.3, 2.9	1.6	0.8, 3.0
Site of disease				
Pulmonary	*Reference*		*Reference*	
Pulmonary + Extrapulmonary	1.0	0.6, 1.7	1.6	1.0, 2.4
Extrapulmonary	2.0	1.5, 2.7	1.2	0.9, 1.7
Homeless				
Yes	1.2	0.8, 1.7	1.7	1.0, 3.0
No	*Reference*		*Reference*	
Employment				
Employed	*Reference*		*Reference*	
Unemployed	1.4	1.1, 1.9	1.3	1.0, 1.6
Unknown	0.8	0.5, 1.3	1.3	0.9, 2.0
Excess Alcohol Use				
Yes	1.1	0.8, 1.5	1.4	0.9, 2.4
No	*Reference*		*Reference*	

Unknown	7.5	3.4, 16.4	11.2	3.8, 33.1
Illicit Drug Use				
Yes	1.1	0.8, 1.6	2.2	1.1, 4.3
No	*Reference*		*Reference*	
Unknown	11.2	4.1, 30.4	5.6	2.2, 14.2
Physical Comorbidity – Diabetes Mellitus				
Yes	1.0	0.6, 1.8	1.3	0.9, 2.1
No	*Reference*		*Reference*	
Physical Comorbidity – End Stage Renal Disease				
Yes	2.6	1.1, 6.0	0.9	0.1, 7.4
No	*Reference*		*Reference*	

Table 3. Multivariable associations between patient characteristics and unfavorable tuberculosis treatment outcomes with corresponding adjusted odds ratio (OR) and 95% confidence intervals (CI).

Characteristic	Adjusted OR (95% CI)	p-value
Country of birth		
Foreign-born	1.34 (1.03, 1.74)	0.03
US-born	*Reference*	--
Gender		
Male	1.45 (1.14, 1.85)	0.0027
Female	*Reference*	--
Ethnicity		
Hispanic	2.13 (1.61, 2.82)	<.0001
Non-Hispanic	*Reference*	--
Sputum smear		
Positive	1.57 (1.24, 2.00)	0.0002
Negative	*Reference*	--
Employment		
Unemployed	1.54 (1.23, 1.92)	0.0002
Employed	*Reference*	--
Site of disease		
Pulmonary + Extrapulmonary	1.35 (0.92, 1.99)	0.1308
Extrapulmonary	1.80 (1.33, 2.45)	0.0001
Pulmonary	*Reference*	--
Illicit Drug Use		
Yes	1.14 (0.80, 1.63)	0.4651
Unknown	5.47 (1.81, 16.50)	0.0026
No	*Reference*	--

Appendix A: Model and Partial SAS Code

This is the final epidemiological model used in the analysis:

$$\ln\left(\frac{p}{1-p}\right) = \alpha + \beta \times FOREIGNBORN + \gamma_1 \times SEX + \gamma_2 \times ETHNIC + \gamma_3 \times SMEAR + \gamma_4 \times UNEMPLOYED + \gamma_5 \times EPTB + \gamma_6 \times DRUGS$$

Final Multivariable Model

```
*Calculating individual odds ratios;
PROC LOGISTIC DATA=THESIS_DATA;
CLASS EPTB (REF = "0")/PARAM = REF;
CLASS DRUGS (REF = "0")/PARAM = REF;
MODEL OUTCOME (EVENT = "1") = FOREIGN_BORN SEX ETHNIC SMEAR UNEMPLOYED
EPTB DRUGS;
CONTRAST 'OR - FOREIGN_BORN - 1/0' FOREIGN_BORN 1/EST = EXP;
ESTIMATE 'OR - FOREIGN_BORN - 1/0' FOREIGN_BORN 1/EXP;
RUN;
```