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Does Level of Access to Tuberculosis (TB) Treatment Predict Default Patterns? A multilevel analysis.

By

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An abstract of
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Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
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ABSTRACT

Does Level of Access to Tuberculosis (TB) Treatment Predict Default Patterns? A multilevel analysis.

By Stevi Driver-Halley

Setting: KwaZulu-Natal (KZN), a province in South Africa, has one of the highest prevalence of tuberculosis (TB) and multi-drug resistance TB in the world, which presents challenges for effective TB control and treatment outcomes, lending to the highest TB death rate in South Africa. Poor TB treatment outcomes, such as defaulting from treatment, are associated with increased risk for morbidity, mortality, acquisition of drug-resistance, and continued transmission of TB in the community.

Objective: To evaluate the association between access to care metrics (i.e. direct observed therapy, health facility density per population, composite health quality score) and risk for default among persons diagnosed with TB.

Design: A multilevel analysis of existing surveillance and administrative data on all patients registered with active TB and with an available treatment outcome in KZN between 2010 and 2011.

Results: A total of 3,261 (11.3%) TB patients defaulted from treatment during the study period. Patients who received direct observed therapy (DOT) throughout the prescribed treatment and patients who lived in an area with a high density of health facilities were significantly less likely to default than persons without DOT or who lived in areas with a lower concentration of facilities (RR=0.3, 95% CI=0.2, 0.3 and RR=0.4, 95% CI=0.3, 0.5, respectively). However, patients who received DOT during either the intensive or the continuation phase of treatment had an increased risk of defaulting compared to patients who were not provided any DOT during treatment (RR=1.8, 95% CI=1.1, 2.8 and RR=2.1, 95% CI=1.6, 2.8, respectively). There was no association between health quality score and defaulting from treatment.

Conclusions: This study presents key insights on the importance of access to care with regard to defaulting. By linking existing surveillance and administrative data, we demonstrated that consistent provision of DOT and spatial density of health facilities are independent predictors of tuberculosis default. Although this work needs to be replicated, these findings can guide program managers into better understanding the effect of access to care metrics on default patterns in low and middle-income countries.

Keywords: tuberculosis, default, access to care, DOT, South Africa, density of health facilities, health score

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INTRODUCTION

Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis* (1). Globally, TB affects almost 8.6 million people each year and is the second leading cause of death from an infectious disease. Although TB is both preventable and curable, an estimated 1.3 million persons die each year from TB.

One of the greatest challenges to TB control is failure of persons diagnosed with TB disease to adhere to and complete the entire prescribed course of anti-TB treatment. Patients who interrupt treatment for two consecutive months or more are considered to have "defaulted" on their treatment (2). Failing to adhere to TB treatment increases the risk for morbidity, mortality, acquisition of drug-resistance, and continued transmission of TB in the community (1, 3).

Treatment success is a global priority for effective TB control (1), and there have been numerous studies aiming to identify factors that may influence risk for treatment default (4-18). However, an aspect of TB control that has been vastly understudied is access to care, and only a few of these studies have evaluated the association between access to care and default (4, 15-18).

When evaluating access to care in a broad-sense, most researchers have evaluated the relationship between access to care, and treatment adherence in non-TB populations (8, 19-23). The little research that has evaluated the role of access to care and treatment outcomes among persons diagnosed with TB has found that factors, such as economic, geographic, sociocultural and health system/health characteristics, influence poor treatment outcomes, but have been limited by study designs, small sample sizes, and exclusively being evaluated at the individual level (2, 13-16)

The current study aims to: 1) describe and illustrate the proportion of patients who defaulted from TB treatment among persons diagnosed with TB in the largest province of South Africa, KwaZulu-Natal (KZN), in 2011; 2) describe and illustrate indicators of access to care at both the individual and municipality level in KZN, South Africa; and 3) evaluate the association between individual and municipality metrics of access to care and risk of default among persons diagnosed with TB in KZN, South Africa in 2011.

BACKGROUND

General Information about Tuberculosis

Tuberculosis (TB) is a global health problem caused by *Mycobacterium tuberculosis (1)*. Tuberculosis is highly transmissible and is easily spread through the air when persons with active pulmonary TB expel the bacteria by coughing, sneezing, speaking or singing (24). TB typically attacks the lungs (referred to as pulmonary TB) but can affect other sites as well (extrapulmonary TB).

Globally, TB affects approximately 8.6 million people each year and 13% (1.1 million) of persons with TB are also co-infected with the human immunodeficiency virus (HIV) (1). Although TB is preventable and curable, TB is the second leading cause of death worldwide, with an estimated 1.3 million deaths from TB in 2012 alone. Worldwide, the burden of TB is highest in South-East Asia, Africa, and Western Pacific, with almost 40% of the world's cases in India and China, and 27% in Africa (1). Approximately 75% of TB/HIV co-infected persons reside in Africa.

Active Tuberculosis Disease Symptoms

Symptoms of TB disease vary by location of disease (24). Symptoms can include a persistent cough with or without blood (hemoptysis) lasting 2 weeks or more, pain in the chest, weakness or fatigue, weight loss, lack of appetite, chills, fever and night sweats.

Latent Tuberculosis

When exposed, a proportion of people with a robust immune system will develop latent TB infection (LTBI), instead of active TB disease. People with LTBI do not have any symptoms and are not infectious, however LTBI is capable of becoming active if a person's immune system is weakened. Approximately 10% of persons with LTBI will develop active TB disease at some point in their lifetime (25).

Tuberculosis Testing and Diagnosis

There are two types of tests commonly used to determine if a person has been infected with TB bacteria: the tuberculin skin test and TB blood tests (24). A positive TB skin test or TB blood test can only determine that a person has been infected with TB bacteria: it does not differentiate between latent TB and active TB disease. Additional testing, such as a chest radiograph and a sputum sample, are needed to determine whether the person has LTBI or active TB disease. A chest radiograph is used to detect abnormalities that could suggest TB, or rule out pulmonary TB (26). The presence of acid-fast-bacilli (AFB) on a sputum smear often indicates active TB disease, while a culture confirms active TB disease. New tests that are capable of diagnosing TB in the genome are Xpert (27) and Hain (28).

Tuberculosis Treatment

Tuberculosis is a curable disease (29). The current World Health Organization (WHO) treatment guideline for new cases of drug susceptible tuberculosis consists of a 2-month intensive phase daily regimen of four first-line drugs: isoniazid (H), rifampicin(R), ethambutol(E) and pyrazinamide(Z), and 4-month continuation phase of isoniazid and rifampin (2).

With proper treatment around 90% of drug-susceptible cases can be cured with first-line drugs,(30) while without proper treatment, approximately two-thirds of all people infected with TB disease will die (31).

Drug Resistant TB and Treatment

As a result of poor TB treatment compliance, often the first line regimen is ineffective due to drug resistance (29). Two types of drug resistant TB are multi-drug resistant (MDR TB) or extensively drug-resistant (XDR TB). This is of major concern provided that cure rates are much lower than non-drug-resistant TB due to unavailable medications or adverse reactions of medications.

MDR TB is a form of TB caused by bacteria that are non-responsive to at least isoniazid and rifampicin, the two most powerful first-line anti-TB drugs (29). The primary cause of MDR TB is due to an inappropriate TB treatment regimen and can only be cured by an even more demanding treatment plan (32). The current WHO guidelines for MDR TB treatment vary by a patient's specific drug-resistance. For MDR TB treatment, anti-TB drugs are grouped from 1 to 5 according to efficacy, experience of use and drug class (2). Table 1 describes the WHO's current recommended treatment regimen for MDR TB.

The current MDR TB treatment regimen consists of an initial phase of a minimum of 6 months of 5 drugs with the inclusion of an injectable agent 5 times a week while the continuation phase has a minimum duration of 18 months and does not include the injectable (33).

The WHO recommends the following principles for designing an MDR TB treatment regimen: 1) use at least four drugs certain to be effective, 2) do not use drugs for which there is a possibility of cross-resistance, 3) eliminate drugs that are not safe, and 4) include drugs in a hierarchical order based on potency (2).

Of additional concern is extensively drug-resistant (XDR TB), which is a strain of MDR TB that is also resistant to at least one fluoroquinolone and at least one injectable second-line drug (34). The general principles from the WHO also apply to XDR TB, yet the regimen is different. In the case of XDR TB, group 5 drugs are used given that groups 1-4 would provide an inadequate treatment regimen (2).

Treatment Outcomes

For all types of TB, the WHO has standardized tuberculosis treatment outcomes into categories (2). The categories include "cure", "treatment completed", "treatment failure", "died", "default", and "transfer out." A treatment outcome of "cure" is assigned to patients whose sputum smear or culture was positive at the beginning of the treatment but was negative in the last month of treatment and on at least one previous occasion. "Treatment complete" is the category for patients who completed treatment but does not meet the laboratory criteria for establishing cure. "Treatment failure" describes the outcome for patients whose sputum smear or culture is positive at 5 months or later during treatment. Patients who interrupt treatment for 2 consecutive months or more are assigned the outcome of "default." "Transfer out" is the category to describe a patient who has been transferred to another unit with an unknown outcome. Treatment is often considered to be "successful" if patients were either cured or completed treatment.

<u>Tuberculosis Control</u>

In 1993 the WHO developed a "Direct Observed Therapy Short-course (DOTS) strategy" that was comprised of sputum smear microscopy diagnosis, a regular supply of first-line anti-TB drugs, short-course chemotherapy, a standardized system for both TB surveillance and outcomes and political commitment (1). One component of the "DOTS strategy" is directly observed therapy (DOT), an effective strategy to ensure patients adhere to treatment (15, 35). DOT means that a health care worker or other designated individual verifies and records that the patient takes every prescribed treatment dose. In many health departments, DOT is the standard of care. In 2006 the "DOTS strategy" was replaced by the "Stop TB Strategy" (30).

International strategies to control TB, "Stop TB Strategy" and the Millennium Development Goals (MDG), have collaborated to set a target to halt and reverse TB incidence by 2015 (30, 36). Specifically, the aim has two particular goals: 1) to halve TB prevalence by 2015, compared to 1990 levels, and 2) to halve TB mortality by 2015, compared to 1990 levels (30). One primary component is ensuring that patients adhere to and complete treatment through DOT, which is forecasted to be increasingly available with these strategies.

Progress towards worldwide targets for reductions in TB cases and death has improved. Between 1995 and 2012, the MDG's target to halve and reverse the TB epidemic is predicted to be achieved (1). Since 1990, the mortality rate has decreased 45% and the world is projected to achieve the global target of a 50% reduction by 2015. Additionally, targets for 2015 are on track in 11 of the 22 high-burden countries that account for over 80% of the world's TB cases. However, TB still remains a large issue due to poor treatment adherence with almost 25% of TB patients in South Africa with poor treatment outcomes (1). Patients with poor treatment outcomes are at a greater risk for developing drug-resistant TB, leading to poorer health outcomes (i.e. mortality, morbidity) (1, 3).

TB Treatment Compliance as a Threat to TB Control

A critical threat to global TB control is the failure of TB patients to complete the entire prescribed course of anti-TB treatment (1). Although improvements have been made with access to TB treatment, more than one-third of new cases do not participate in global strategy programs (37). A study identified that reported DOTS coverage may not reflect the proportion of patients who are actually receiving treatment with DOT (38). Specifically, the study found that the South Africa

Department of Health reports 100% DOTS coverage in the country, yet this did not mean that all patients are linked to a DOT supporter. One of the key findings was that two hospital sites only had approximately 10% of patients receiving treatment with a DOT supporter, as they had prioritized providing DOT only to patients perceived to be at risk for treatment default. The investigators hypothesized that the reported 100% corresponded to facilities that have resources for the DOTS strategy, but not the actual percentage of patients on treatment with DOT supporters. Without the DOT component, patients are at an increased risk of defaulting from TB treatment (15).

Risk Factors Associated with Treatment Default

Since treatment success is a critical element for effective TB control (15), there have been numerous studies aiming to identify factors that may influence the risk for treatment default (4-14). Figure 1 illustrates demographic, economic, geographical, sociocultural and health system characteristics that have been shown be associated with risk for default.

Demographic Characteristics

Demographics that impact risk of default include age, sex, education, incarceration, homelessness and citizenship (Table 2). The majority of studies have found that ages 20 to 30 years are at an increased risk of default compared to ages younger than 20 years (4-6). However, two studies found no association between age and default (7, 8) and another study found no association between an age of 40 years and older and risk of default (6).

Previous studies that have evaluated the association between sex and risk of default have produced inconsistent results (4-10). A few studies have reported males to be 1.3 to 1.9 times more likely to default from TB treatment than females (5, 6, 9), but the majority of research has failed to identify any association between gender and risk of default (4, 7, 8, 10) .

Studies have reported an inverse association between level of education and risk for treatment default, wherein patients with higher education have a decreased risk for default (4, 6). In addition, patients with a history of incarceration (6, 11), who are homeless (6, 13), who are not literate(4), who are not citizens in the current place in which they reside (6), and who have spent more than three months in the past year outside of country (6) have also been reported to have an increased risk for default.

Economic

Patient characteristics relating to economic status, including employment, salary and occupation, have been reported to be associated with risk of default (Table 3). Most studies have found that unemployment is a risk factor for defaulting from TB treatment when compared to employment (6, 11). However, one study found no significant association between employment status and default (7). Additionally, risk for default is higher among both patients without a salaried income, compared to patients with a salaried occupation (6), and patients who are employed in the farming industry, when compared to students (4).

Geographic

The few studies that have examined the association between geographical factors and TB treatment default have reported inconsistent results (Table 4). A study performed in Moldova found that patients who lived in an urban area were at an increased hazard of defaulting when compared to patients with a rural residency (6). On the other hand, a study in Ethiopia found that patients with urban residency were at a decreased hazard of defaulting from treatment when compared to patients with a rural residency (4).

Sociocultural

Sociocultural factors such as stigma, traditions, and alcohol use are associated with risk of default (Table 5). Patients who defaulted stated that negative stigmas from the community were a main reason for defaulting given that they did not disclose their diagnosis with their support system and, in turn, did not have a TB support system (12). Cultural traditions have also negatively impacted treatment outcome (12). For example, in Uzbekistan, women with TB reported defaulting due to pressure from their spouse to return home. Alcohol use is a risk factor for defaulting impacting negative outcomes for patients who either drink daily (7), a few times a week, or abuse alcohol (11).

Health System and Clinical Characteristics

Health system characteristics that have been studied in the context of default risk include TB/HIV co-infection, the number of drugs during treatment, decentralization of the individual patient, history of a poor treatment outcome and other qualitative risk factors (Table 6). Studies have found that a co-infection of TB/HIV increases the risk of defaulting from TB treatment (6, 9). However one study found no significant association between co-infection and defaulting (10).

Other health characteristic factors that have been evaluated for an association with default include: the amount of drugs a patient is prescribed to take during TB treatment is negatively associated with defaulting from TB treatment (14); a patient who is decentralized from a hospital or clinic to a DOT community center is at a decreased risk of defaulting from treatment; and patients with a history of a poor treatment outcome are negatively associated with treatment default (5). Specifically the team of researchers found that patients with a history of defaulting are at a 7-fold increased risk of defaulting than those without any previous treatment, while a history of failure of TB treatment increases the risk of defaulting by 13-fold.

A study team in Uzbekistan interviewed patients who had defaulted from TB treatment (12). Common reasons for defaulting were due to the side effects of the prescription, insanitary hospitals, poor attitudes from the health care workers and lack of knowledge from the patients.

Access to care

While there have been multiple studies evaluating risk factors for default, default is still a major issue and the studies have yet to evaluate factors related to the overall system of care. Additionally, the previous studies have been limited to individual-level factors of the patient, potentially missing important aspects of population-level statistics. One critical factor demonstrated to have marked effects on overall health and mortality is access to care (39).

Access to care may also be associated with default from TB treatment. Access to care has been defined as a multi-faceted definition that includes availability, accessibility, accommodation, affordability and acceptability (40). Availability is defined as the relationship between volume and type of existing services to the clients' needs. Accessibility is the geographic location of the client in relation to the supply location. Accommodation is the relationship between the resources for the client, and the clients' perceptions of the resources. Affordability is the economic cost of the service. Last, acceptability is the relationship between the client's attitudes of the behaviors associated with the supply. The specific elements of access to care may vary by region and cultural context.

The WHO measures barriers to accessing TB services as falling within one of the following categories: economic, geographical, sociocultural, and health system (39). Economic barriers are significant economic costs on TB patients and households. Geographical barriers are defined by geographic distance to health facility, travel methods, and weather trends throughout the year. Social and cultural barriers for persons with TB relate to the (1) stigma of the disease; (2) lack of knowledge and recognition of TB control as a priority; (3) gender-related barriers to access; and (4) traditional practices and systems. Finally, health system barriers are influenced by a health system's responsiveness to all areas alike, quality of health care, and decentralization. Due to the complexity of the concept "access to care", many poor and vulnerable groups overlap between these constructs and are confronted with more difficulty in overcoming barriers than the non-poor or non-vulnerable groups.

Access to care and treatment adherence

The relationship between access to care and treatment adherence has been previously studied for conditions requiring continuing treatment (8, 19-23). Figure 2 illustrates various measures of access to care and categorizations under the WHO guidelines as they may relate to treatment adherence and default.

Economic

Several studies have identified that costs of accessing treatment and costs associated with treatment are linked with poor treatment outcomes (20, 21, 23); while one study failed to identify any association between cost and treatment adherence (22) (Table 7). HIV-positive patients (21) and focus groups of healthcare workers and community members, found that cost of transportation was a main barrier in adhering to treatment (20). However, among epileptic patients who defaulted from treatment in Ethiopia, transportation costs were not considered to be a main reason for defaulting from treatment (22).

Other economic reasons for defaulting from treatment relate to food security (20, 23). Among 18 focus groups of both health care workers and HIV patients on ART in rural Mozambique, 78% reported that the inability to afford quality or sufficient food was a barrier to ART adherence (20). Supporting these results, another study evaluated reasons why Colombian HIV-positive females had poor adherence to ART and found that 26% of patients interviewed sold medication for food (23).

Geographic

Factors associated with geographic location of health services and means for transport to health services have not been consistently shown to influence treatment adherence (19, 20, 22) (Table 8).

A study in rural Ethiopia reviewed causes of default among patients with epilepsy (22). The researchers found that one-third of patients defaulted mainly due to the distance of travel to the clinics. A study in rural Mozambique reported that two-thirds of healthcare workers and community members who participated in focus groups identified method of transport to the clinic as an important barrier to treatment adherence (20). The authors concluded that this was not due to the cost of transportation; rather it was due to the road quality and unreliability of public transportation. However, in Pennsylvania, patients who traveled at least 50 miles for care did not have a significantly higher risk for a poor treatment outcome (19).

Sociocultural

Sociocultural factors, including beliefs and perceptions, cultural traditions and social behaviors have also been shown to influence treatment adherence (19-23) (Table 9).

Several studies have reported that patient attitudes and beliefs impact adherence to treatment (19-21, 23). Factors reported have included: feelings of guilt for transmitting HIV to their children and therefore prioritizing their children's care above their own adherence behaviors (23); experiencing negative attitudes from healthcare workers(21); feeling stigmatized by the community and healthcare workers(20, 21); and lack of knowledge about efficacy of the medication (19, 20).

Treatment adherence and treatment default may also be affected by patient preferences to utilize traditional healers rather than public or modern care (20, 22). In Mozambique, use of traditional healers for health care was cited by 100% of community health workers and 42% of members of the general community as an important barrier to treatment adherence (20). Additionally, in Ethiopia, 12% reported "traditional remedies preferred" as a main reason for defaulting, while 51% stated it was a contributory reason for defaulting (22).

Social behaviors such as saving pills for other family members (20), alcohol use (19) and lack of social support (19) have also been demonstrated to influence treatment adherence.

Health System Barriers

Health system barriers, including quality of facilities and access to health specialists have been shown to impact poor treatment outcomes (8, 20, 22, 23) (Table 10). Characteristics of health facilities that have been reported as favorable and may optimize patient satisfaction and management have included: options for decentralization of patients to specialty clinics to receive care (8), health care workers that speak multiple languages or dialects (20), staffing and capacity to minimize waiting times (21), external financial support (23) and facilities which enforce patient confidentiality (20). Although many studies have found that health quality and characteristics influence poor treatment adherence, a study among epileptic defaulters in Ethiopia found that only 5% of subjects stated that the quality of the clinic was a reason for defaulting from treatment (22).

Access to care and tuberculosis treatment adherence

To date, few studies have shown the impact of access to tuberculosis care on treatment adherence, specifically treatment default.

Economic

There is a dearth of literature that has examined economic barriers to accessing TB treatment and treatment adherence. The two studies evaluating this association found no significant association between income, employment or reliance on public transportation and TB treatment default (4, 18) (Table 11).

Geographic

Geographical risk factors that have been examined for their association with poor TB treatment outcomes have included the travel distance to the facility, residence characteristics and weather patterns (4, 17, 18) (Table 12). Studies have consistently found than patients who live farther from the health center have an increased risk for poor outcomes compared to patients who live in closer proximity (4, 17, 18). However, a qualitative study performed in Vietnam reported that only 5% of TB patients believed distance to be a main reason for defaulting from treatment (16). A study in Ethiopia found that TB patients that lived in an urban area were at an increased risk for defaulting when compared to patients who lived in more rural settings (4). Rainy weather patterns may also increase difficulty in accessing treatment (17).

Sociocultural Barriers

Sociocultural factors, including knowledge, support, stigma and other various factors have also been shown to influence treatment adherence (4, 17), while factors such as knowledge and stigma were not identified as risk factors (18) (Table 13). Identified sociocultural risk factors were determined to be; an age greater than 25 years old (4); not literate; an occupation as a farmer compared to a student; and seeking traditional healers or self-medicating instead of treatment (17).

Health System and Clinical Barriers

Heath system and clinic-related barriers that may impact risk of default are due to administrative operations, health resources, medication side effects, and DOT (15-18) (Table 14). Administrative issues consisted of unsuitable operation hours (16), complicated administrative processes, long waiting times (18), poor conduct of staff, and minimal communication between the health worker and the patient (17, 18). Other health system barriers that increased risk of a poor treatment outcome relate to the unavailability of medication and side effects of the medication (18). However, DOT was shown to be protective and reduce the risk of defaulting from treatment (15).

Study Objectives

While there has been some progress on determining health care access-related risk factors for defaulting from TB treatment, many gaps still remain. The impact of access to care on defaulting from TB treatment has never been directly studied. Of the studies that have evaluated aspects of access to care, the majority of researchers have performed qualitative studies to determine future directions, some of which included access to care constructs. Additionally, existing epidemiological research evaluating the relationship between access to care and risk of defaulting from TB treatment have been largely restricted to individual-level metrics of access to care. Such studies are unable to distinguish individual-level effects and municipality-level effects. Another gap in current research relates to the study type being predominately qualitative, or survey-based which is difficult to repeat in other high-risk settings.

Epidemiology of Study Location – KwaZulu-Natal

Globally, South Africa has the 2nd highest annual rate of incident TB cases, estimated at 1,000/100,000 persons (0.5 million persons total) in 2012 (1). Of the newly diagnosed TB cases, 8,100 (1.8% of new TB cases) were infected with multidrug-resistant TB (MDR TB); 1,789 retreatment TB patients (6.7% of retreatment cases) also had MDR TB. Approximately 63% of persons with TB in South Africa are co-infected with HIV (TB/HIV).

KwaZulu-Natal (KZN) has the highest burden of HIV in the country, with 15.3% of persons aged 15-24 years of age and 38.7% of antenatal women living with HIV(36). MDR TB is also more common in KZN compared to other provinces, with an estimated 2,032 cases of MDR TB diagnosed in 2010 (41, 42). The high prevalence of TB/HIV co-infection and MDR TB in KZN presents challenges for effective TB control and treatment outcomes, lending to the highest TB death rate in the country (estimated at 197/100,000 population) (1, 43).

The current study aims to:

1) Describe and illustrate the proportion of people who defaulted from TB treatment among persons diagnosed and registered with TB in KZN, South Africa in 2011, overall and by local geographic region (municipality)
2) Define, measure and report indicators of access to care at both the individual level and municipality level, overall and by municipality in KZN

3) Evaluate the association between individual and municipality metrics of access to care (DOT, density of health facilities per population, and health quality score) and risk for treatment default among persons diagnosed with TB in KZN in 2011

METHODS

Setting

In 1996, the Republic of South Africa National Department of Health established a National Tuberculosis Program (NTP) and adopted the DOTS strategy (44). The NTP also implemented a national system for TB surveillance in 2005, the Electronic TB Register (ETR) (42).

KwaZulu-Natal, one of the nine provinces in South Africa, is comprised of 10 districts and 51 local government units, or municipalities (45). KZN is an ideal setting for this research project given it has the highest burden of HIV in the country (36), and a high burden of MDR TB compared to other provinces (41, 42).

Study population

All persons reported from a health facility within KwaZulu-Natal, South Africa and diagnosed with active TB disease and registered in the ETR between January 1, 2010 and December 31, 2011 with treatment outcomes available (excluding persons who transferred or moved) will be included in the present analysis.

Data sources

The current evaluation is a secondary data analysis of previously collected data. This evaluation will utilize several existing data sources:

Electronic Tuberculosis Register (ETR)

The ETR, a surveillance system developed in 2002, was designed to capture patient-based TB data (including HIV surveillance among TB patients) (46). It was developed to provide for more efficient and useful collection, compilation, and analysis of TB data on an on-going basis. Individual patient records are entered directly from the paper TB register; a standard form supplied to all health facilities by the National TB Program, into the ETR at the district (or sub district in other provinces) TB office. Information from the district is provided to each provincial TB office, which in turn provides the data directly to the National Department of Health. The ETR will serve as the only individual-level data source.

2011 Population Census

Population census surveys allow for estimation and enumeration of the population at local and regional levels. Census surveys include questionnaires to detail basic statistics on the population, including measures of income, dwelling type, education level, etc. (47). The 2011 census will provide data for analysis at the municipality level.

2009 KZN Department of Health Medical Health Facility Data and Health Infrastructure Data

The health facility dataset is comprised of specific data on clinics, satellite clinics, community health centers, hospitals, environmental health and emergency and rescue bases within KwaZulu-Natal. This data contains provincial, state-aided, local authority and private medical facilities. Spatial data, specifically the latitude and longitude of each health facility, is included within the dataset. This data is provided at the health-facility level and will be linked to the individuals within the ETR.

Additional data provided by the KZN Department of Health also includes information on type of health facilities. This information was summarized in aggregate for each municipality. Currently operating health facilities, such as a clinic, hospital, and community health center (CHC) were included in the study.

Definitions and coding

The data sources that will be evaluated have been provided at the individual level or municipality level (Table 15).

Outcome: Treatment default

The primary outcome variable for the current analysis is default from TB treatment. Treatment outcomes are assigned and recorded in the ETR for TB patients following the WHO standard outcome definitions for TB treatment outcomes (2). Treatment default refers to a patient who initiated anti-TB treatment and who did not take a treatment dose for at least two months. For the current analysis, each patient included in the study sample will be assigned an outcome of treatment default (1) or as not defaulted from anti-TB treatment (0: including cured, treatment completed, treatment failure, or died). Patients missing a treatment outcome in the ETR (e.g., transferred, moved, or missing) are excluded from the study sample.

Exposure/predictor variables: Access to care

Several measures from the available data sources will be used as metrics or proxies of access to care including:

Individual Level

- DOT provision: DOT provision was provided by the ETR surveillance system and will be evaluated on the individual level. Each patient included in the study sample will be categorized as having one of the following: (1) DOT provisioning during the entire treatment, (2) DOT provisioning during only the intensive phase of treatment, (3) DOT provisioning during only the continuation phase of treatment, and (4) no DOT at any point during treatment. In the ETR, the DOT values were coded as "yes" and missing. Missing values were assumed to be no DOT provision in this analysis. Patients on DOT during the entire treatment will be considered as having the highest level of access to care compared to the other categories.

<u>Municipality Level</u>

- Density of health facilities per population: This variable will be evaluated at the municipality level (n=1,421). Density of health facilities, from the 2009 KZN Department of Health medical health facility data, will be calculated by dividing the total number of facilities in each municipality that is listed in the ETR, by the total population of the municipality provided by the census, then calculated per 100,000 persons. A high level of access to care was defined by a density greater than the median (12.9 per 100,000 persons), while limited level of access was defined by less than or equal to the median health quality score for KZN.
- Health quality: The KZN DOH derived an overall (e.g. not just TB specific) health quality score for each municipality by incorporating several indicators, and rating each on a Likert scale of 1 (least favorable score) through 5 (most favorable) with the maximum possible score of 125. The indicators utilized in deriving the health quality score included: annual antenatal coverage, caesarean section rate, cervical screen coverage, delivery at facility for under 18 year olds, diarrheal incidence, HIV test, antenatal care rate, immunization coverage, male condom distribution, not gaining weight rate, nevirapine uptake, perinatal mortality rate, nurse workload, annual primary care utilization rate for children under 5 years, annual primary care utilization rate, vitamin A rates for children, proportion of households with a child head of household, proportion of households with a female head of household, income, electricity, water, sanitation, employment, social grant, health facilities, roads, and population density. A health quality score greater than the median (80.7) will signify a high

level of access to care, while less or equal to the median will be considered a limited level of access to care. The health quality score will be used in our study to evaluate non-TB indicators of a municipality's overall health which could be useful for assessing the quality of TB care.

Covariates

- Individual level
    - Age: Provided by the ETR, age will be categorized by 0-4, 5-14 years, 15-24 years, 25-34 years, 35-44 years, 45-54 years, 55-64 years, 65-74 and greater than 75 years.
    - Sex: Provided by the ETR, sex will be categorized by female and male. Sex will be evaluated on the individual level.
- Municipality level
    - Race: Provided by the census 2011, race was measured as Black, Colored, White, Indian or Asian and Other. These census counts are aggregated to the municipality level. For our study we will calculate for each municipality the percentage of non-black (e.g. Coloured, White, Indian, Asian and other).
    - Socioeconomic Status (SES) Composite Score: Data for the score was provided by the 2011 census. The score was created by normalizing proportions of the following proportions: low income (approximately less than the national poverty line of 4992 (48), but our cutpoint was 4800 Rand due to census categorization), unemployment, low education (less than 8 years of education), informal dwelling, non-electric heating source, non-electric cooking source, non-electric lighting source, non-flushing toilet,

and non-piped water access. The score ranges from -11.5 to 9.7. A higher score indicates a lower level of SES.

- Usual place of residence: Provided by the 2011 census, usual residence will be categorized by KZN vs. not in KZN. Each municipality will be assigned a proportion of residents with a usual residence that is not in KZN.
- Total population: Provided by the 2011 census, total population will be used to illustrate population by municipality.
- Authority of facility: Authority of each health facility listed in the 2009 KZN Department of Health Medical Health Facility Data will be categorized by "public", "private" or "other". Facilities that were both public and private will be considered as "other". These categories will be evaluated for association with risk of defaulting from TB treatment to see if and how a particular authority type may impact risk of default.
- Type of health facility: Each health facility from the 2009 KZN Department of Health Medical Health Facility Data will be categorized as a "clinic", "CHC", "Hospital" and "other". Type of facility will be evaluated at the individual level.

Statistical analyses

Initially, we will describe the population distribution of residents in KwaZulu-Natal, South Africa. Then we will describe and map proportion of patients who defaulted from treatment among patients diagnosed with TB in KwaZulu-Natal province in 2011, overall and by municipality. Descriptive statistics will be also be applied to summarize and map different indicators of access to care at each level (individual and municipality), overall and by municipality, of each TB patients included in the study sample.

Other factors at each the individual level and municipality level will be considered in models as potential confounders or effect modifiers of the association between measures of access to health care access and TB treatment default. All measures of access to health and other factors will initially be explored for the association with treatment default using univariate models. Factors that are associated with default risk or access to care proxies at an alpha level of ≤0.20 in the current database or that have been demonstrated in previous literature to be important determinants of treatment default will be considered for multivariable models.

In order to answer our research question evaluating the relationship between access to care (DOT, density, and health score) and default, an adjusted generalized estimating equality (GEE) multilevel model will be constructed using factors operating at, first, the individual level and then modifying (by adding and removing) factors at the municipality level to adequately control for confounding and evaluate cross-level interaction. For these models, individuals will be situated within municipalities based on the location of the health facility where they are registered with TB. Risk ratios and 95% confidence intervals (CIs) will be used as the primary measure of association. For the final model, all exposures will be considered in the model but must have an alpha level of <0.05.The estimated risk ratio will be stratified on any effect modifiers with an alpha level of <0.05.

For all analyses, SAS version 9.3 will be used. This software allows for modeling using both linear and non-linear data and allows for estimation of indirect effects and accommodates factors operating at multiple levels.

ETHICAL CONSIDERATIONS

The current evaluation is a secondary data analysis utilizing existing data sources that are part of routine monitoring and evaluation of TB (ETR) and the population and state of health (Census and KZN DOH Databases) in South Africa. This project was reviewed and approved by the Institutional Review Boards for human subjects' research at Emory University and the Centers for Disease Control and Prevention. We also requested permissions and access to all databases through the KZN DOH prior to commencement of the evaluation.

RESULTS

Study Setting

Population size by municipality ranges from 12,898 to 3,442,361 persons (Figure 3). The median population size was 618,536 persons with the majority of people residing in eThekwini metropolitan municipality, which includes the city of Durban. The total population in eThekwini is 3,442,361 persons.

Study Population

A total of 65,535 patients were registered in the KZN ETR during 2011. Of these, 277 persons were excluded because their records indicated they had latent TB infection rather than active TB disease (Figure 4). An additional 36,387 persons were excluded due to having a missing or incomplete outcome or being reported from a facility not identified as a municipality within KZN. The total analytic population included 28,875 individuals diagnosed with active TB disease.

Individual Level Descriptive Results

Demographics

The average age was 33.5 years with a standard deviation (SD) of 13.9 years (Table 16). When age was categorized, most (34.2%) of TB cases were between 25 and 34 years; only a small number of individuals were aged 75 years or older (0.05%). Over half (51.1%) of the patients were male.

Clinical Characteristics

Most (82.4%) of the patients were new TB cases, and over 11% (11.3%, n=3,261) of the patients defaulted from TB treatment. The majority of the patients had pulmonary TB (80.8%), were sputum smear negative (52.2%), and were prescribed the standardized Category I treatment regimen of 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol with 4 months of isoniazid and rifampicin (76.2%).

Of the patients in the ETR, 47.4% (n=13,684) did not receive DOT at any point during treatment, while 29.1% (n=8,413) received DOT during the intensive phase only and 1.2% (n=348) only received DOT during the continuation phase. Twenty-two percent (22.3%; n=6,430) were on DOT throughout the full treatment course (full DOT).

Tuberculosis Testing Results

At baseline, 42.9% (n=9,453) of the patients had a positive microscopy result and 71.3% (n=2,699) had a positive culture. Of the patients with a smear positive baseline result and a follow-up smear reported, 96.7% (n=8,358) converted to a negative smear after the intensive phase of treatment.

Comorbidities

The majority of patients were HIV-positive (n=18085, 76.4%). Of the HIV-positive patients, almost 11% were on ART at the beginning of TB treatment, while 45% were on ART at some point during TB treatment.

Health Facility Characteristics

The majority of patients were diagnosed and registered with active TB disease at a clinic, instead of a hospital or CHC, for TB treatment (49.4%, n=13962), and most visited a facility with a public authority (n=98.9%). Few patients were diagnosed at a TB-specialized clinic (1.7%).

Population Level

The median population of a municipality was 618,536 (interquartile range (IQR): 12,898-3,442,361) (Table 16). Within each municipality, the median proportion of females was 53.2% and the median proportion of employed persons was 62.6%. Of the total population collected on the census, 97.5% were black African and 80.7% were at or below the federal poverty line (4800 Rand). Most (96.5%) of the population lived in a formal dwelling and 84.6% usually resided in KZN. The majority of the population completed more than 8 years of education (57.8%). With regard to housing amenities, a median proportion of 49.5% had an electric cooking source, 35.5% had an electric heating source, 71.9% had an electric lighting source,45.3% had access to piped water, and only 19.4% had a flushing toilet.

Default Status: Descriptive Statistics

The proportion of TB patients registered in the ETR in 2010 and 2011 that defaulted from tuberculosis treatment is illustrated in Figure 5 by municipality. The proportion of patients reported as defaulting from TB treatment ranged from 0 to 25% across municipalities, and proportions appear to be greater in areas that border the ocean or another province. Municipalities located in the northeast corner of KwaZulu-Natal have high proportions of defaulting patients.

Individual-Level Exposure of Interest: Descriptive Statistics

Direct Observed Therapy (DOT)

Figure 6 illustrates the proportion of patients that were on direct observed therapy (DOT) during treatment, as reported in the ETR, by municipality. DOT coverage ranged from 0% to 100%. Areas located in southern KZN, which borders the South African province of Eastern Cape had less DOT coverage.

Population-Level Exposure of Interest: Descriptive Statistics

Density of Health Facilities per Population

Figure 7 depicts the density of health facilities per 100,000 persons by municipality in KwaZulu-Natal, South Africa. The density ranges from 4 facilities per 100,000 persons to 31 facilities per 100,000 persons. The pattern of high and low density are spatially random, as opposed to spatially structured, in KZN.

Health Quality Score

Figure 8 illustrates the health quality score in KwaZulu-Natal by municipality. The health quality was weighted by population per municipality in KZN and ranges from a score of 0.10 to 29.17. The map shows lower health quality scores in the southwestern portion of KZN.

Individual-Level Associations for Defaulting from Tuberculosis Treatment: Bivariate Analysis

When compared to children 4 years or less, persons aged 15 to 24 and 25 to 34 were at an increased risk of defaulting (RR=1.3 and RR=1.2 respectively) (Table 17). Men were significantly more likely to default from treatment than women (RR=1.4, 95% CI=1.4, 1.7).

Re-treatment TB cases were more likely to default than new TB cases (RR=1.7) while TB classification (i.e. pulmonary, extra pulmonary) had no association with defaulting from treatment. When compared to patients with treatment regimen Category I (2 month of isoniazid, rifampicin, pyrazinamide, ethambutol, and 4 months of isoniazid and rifampicin), patients on Category II (2 months of isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin, 1 month of isoniazid, rifampicin, pyrazinamide, ethambutol, and 5 months of isoniazid, rifampicin, ethambutol) were 60% more likely to default from TB treatment (RR=1.6, 95% CI=1.5, 1.7).

When compared to patients that did not receive any DOT during treatment, patients who received DOT throughout the entire course of treatment were significantly less likely to default (RR=0.4, 95% CI=0.3, 0.4), while patients on DOT at only the intensive phase or continuation phase had an increased risk for default (RR=1.8, 95% CI=1.6, 1.9 and RR=3.3, 95% CI=2.9, 3.9, respectively). There was no significant association between baseline (diagnostic) smear microscopy result or culture result and default risk. Patients who converted to a negative smear after the intensive phase of treatment (months 2-3) were significantly less likely to default (RR=0.5, 95% CI=0.4, 0.7).

TB patients co-infected with HIV were at a 10% increased risk of defaulting when compared to patients without HIV (RR=1.1, 95% CI=1.0, 1.2). TB patients with HIV that received ART at some point during treatment were at a significantly decreased risk of defaulting from TB treatment compared to TB/HIV patients who did not receive ART (RR=0.7, 95% CI=0.6, 0.8).

When compared to clinics, patients who were diagnosed at a community health center or a hospital had a significantly increased risk for treatment default (RR=1.3, 95% CI=1.1, 1.4 and RR=2.0, 95% CI=1.8, 2.1, respectively). There was no significant association between diagnosis at a TB-specific facility or type of health authority (private or public) and default risk.

Individual-Level Associations for DOT Provisioning: Bivariate Analysis

Direct Observed Therapy

Factors that influence DOT include demographics, clinical characteristics, comorbidities and health facility characteristics (Table 18a). When compared to children 4 years or less, all age ranges were at a decreased probability of receiving DOT (RR range=0.7-0.9, 95% CI=0.6-0.9). There were no significant differences in DOT coverage by sex.

Patients that were new TB cases were less likely to receive DOT than re-treatment cases (RR=0.9, 95% CI=0.8, 0.9). Patients with extra pulmonary TB were 10% more likely to have received DOT than patients with pulmonary TB (RR=1.1, 95% CI=1.1, 1.1). On the other hand, patients with both pulmonary and extra pulmonary were less likely to have DOT than patients with pulmonary TB, alone (RR=0.8, 95% CI=0.7, 1.0).

Factors associated with receiving DOT consisted of treatment regimen Category II - 2HRZES 1HRZE 5HRE (RR=1.2, 95% CI=1.1, 1.2), and treatment regimen Category III - 2HRZ 4HR (both when compared to Category I) (RR=1.1, 95% CI=1.1, 1.2). Patients that had a positive sputum smear at baseline were less likely to receive DOT (full or partial) during treatment (RR=0.95, 95% CI=0.92, 0.97).

Patients with a positive baseline culture result were more likely to receive DOT than patients with a negative culture (RR=1.1, 95% CI=1.1, 1.1). On the other hand, patients with a baseline positive smear microscopy result were less likely to receive DOT than patients with a negative smear (RR=1.0, 95% CI=0.9, 1.0). Patients with a record of conversion to a negative smear at the end of the intensive phase of treatment (month 2 or 3) were 50% more likely to receive DOT than those that did not convert (RR=1.5, 95% CI=1.3, 1.7).

Patients with TB/HIV co-infection were significantly less likely to receive DOT than TB patients without HIV (RR=0.9, 95% CI=0.9, 1.0). Of the patients that were co-infected, patients who were on ART at the beginning of TB treatment and patients who were on ART at some point during treatment were 10-20% more likely to have DOT than patients that did not receive ART (RR=1.1, 95% CI=1.0, 1.1 and RR=1.2, 95% CI=1.1, 1.2, respectively).

Patients diagnosed with TB at hospitals were 60% more likely to receive DOT than patients diagnosed at community health centers (RR=1.6, 95% CI=1.6, 1.7). Patients that were diagnosed and registered at a TB or MDR TB specialized clinic were 30-50% more likely to receive DOT than patients who were diagnosed at other health facilities (RR=1.3, 95% CI=1.3, 1.4 and RR=1.5, 95% CI=1.3, 1.6).

<u>Population-Level Associations for Health Access Predictors: Bivariate Analysis</u>

Bivariate analyses were performed using the generalized estimating equations.

Density of Health Facilities

There was no significant association between age, sex, and health facility characteristics and density of health facilities (Table 18b). However, when compared to patients who did not receive DOT, patients on DOT during the entire treatment and patients on DOT during the continuation phase only were more likely to live in an area with a lower density of health facilities (RR=0.5 and RR=0.2, respectively). Patients with a baseline positive culture were significantly more likely to have been diagnosed in an area with less health facilities (RR=0.5, 95% CI=0.4, 0.8).

Health Quality Score

Factors associated with a high health quality score are shown in Table 18c. When compared to children 4 years or less, persons aged 5 to 14 and persons aged 55 and older were more likely to have a lower health quality score. There was no significant association between health score and sex.

Clinical characteristics, including case type, diagnostic smear result, treatment regimen, and DOT were significantly associated with health score. Patients who were smear positive at baseline were more significantly more likely to live in municipalities with a health quality score above the median (RR=1.3, 95% CI=1.0, 1.6) (the health quality score was dichotomized by the median). Additionally, when compared to patients who did not receive DOT, patients who received DOT during their entire treatment, patients with DOT only during the intensive phase, and patients who only received DOT during the continuation phase were more likely to have a high health quality score (RR=2.1, 1.3, 2.5, respectively). However, patients who were registered as new TB cases had a lower overall health quality score than re-treatment patients (RR=0.7).

Patients who had a positive smear at baseline had significantly higher health quality scores than patients who were smear negative (RR=1.2). There were no other significant associations between comorbidities, TB testing results, or health facility characteristics and health quality score.

Final Model: Multilevel Associations for Health Access Predictors and Default

The final model used to evaluate the relationship between access to care predictors and defaulting from TB treatment follows:

$$Pr(Y_i)=\beta_0+\beta_1 DOT+\beta_2 density+\gamma_1 age+\gamma_2 sex+\gamma_3 new+\gamma_4 SES$$

where density and SES were evaluated at the municipality level and the other variables were evaluated at the individual level (Table 19).

Direct Observed Therapy

Patients who received direct observed therapy (DOT) during the entire prescribed TB treatment course (instead of partial DOT) were associated with a significantly decreased risk of defaulting from TB treatment when compared to patients that did not receive any DOT, after adjusting for age, sex, registration status (new vs. re-treatment), municipality-level density of health facilities, and municipality-level SES (aRR=0.3, 95% CI=0.2, 0.3). However, patients who were on partial DOT at either the intensive or continuation phase of treatment were at an increased risk of defaulting from TB treatment when compared to patients without DOT (aRR=1.8, 95% CI=1.1, 2.8 and aRR=2.1, 95% CI=1.6, 2.8, respectively).

Density of Health Facilities

Municipalities with a density of health facilities per 100,000 person population greater than the median density (median = 12.9 health facilities per 100,000) had a significantly decreased risk of defaulting from TB treatment when adjusted for age, sex, registration status (new vs. re-treatment), DOT, and municipality-level SES (aRR=0.4, 95% CI=0.3, 0.5).

Health Quality Score

There was no significant association between health quality score and risk for default in the multilevel analysis (aRR=1.0, 95% CI=0.8, 1.3); therefore it was not included in the final multivariate model of factors associated with defaulting from tuberculosis treatment.

DISCUSSION

Our study provides novel evidence that various components of accessing health care influences risk for default from anti-TB treatment. Direct observed therapy (DOT) can help predict an individual's level of access of care, for example, patients with DOT have a greater level of access to healthcare workers, TB services, and organized health resources (49). Patients on DOT during the entire prescribed treatment course were a third as likely to default than patients who never received any DOT, while patients who received DOT only during either the intensive or continuous phase were 1.5 to 2 times (RR=1.8 and RR=2.0) more likely to default from treatment than patients who did not receive any DOT after adjusting for age, sex, new cases, municipality-level facility density, and municipality-level SES. These stratified results denote a differentiation of default risk by the amount of DOT received during treatment. Patients on partial DOT (intensive or continuous) may feel that their sickness has improved once the DOT discontinues and therefore discontinue treatment, putting them at a higher risk for default than patients without any DOT.

Patients who live in municipalities with more health facilities per population, defined as greater than the median, were at a decreased risk of defaulting after controlling for age, sex, new cases, DOT, and municipality-level SES. Patients living in lower density areas were anywhere from 2 to 5 times more likely to default than patients living in a municipality with a higher density. Reasons for this could include that patients living in high density areas have health facilities closer to their residences, while patients living in lower density areas may not have geographical access to their facilities, as well as may not have access to a specialized clinic or highly qualified healthcare workers.

Surprisingly, there was no association between health quality score and defaulting from tuberculosis treatment. Although the scoring system identified various components that compose a health score, the score may not translate to accessing tuberculosis care. Moreover, the score may represent a general well-being of the population, as opposed to a quality of health facilities. Additionally, the health quality score was represented at the municipality level, which may not translate to an individual's level of access.

Strengths and Weaknesses

There are a few potential shortcomings of this study worth noting. The data utilized in this evaluation were from sources that are routinely collected and not intended for research purposes. Therefore, the way in which the information was recorded may not have been standardized or consistent across sites, and the specific variables were limited. For example, we were unable to evaluate socioeconomic status at the individual level, as they are not collected in the ETR. Additionally, many patients in the database were missing values for one of our key factors of interest, DOT. For the analysis we assumed those missing values did not receive DOT; however, this may have introduced a bias in our results. However, we conducted the analysis with a worst-case approach, using patients with a DOT value, as yes, and assumed that patients with missing values did not have DOT. This could lead to misclassification of DOT, resulting in an underestimated true risk. With regard to facility density, this municipality-level exposure was heavily influenced by large municipalities (i.e. eThekwini) due to more ETR patients living in those areas, which would have had a heavier weight on the estimated relative risk. An additional limitation is due to the data sources. Unfortunately we were unable to compile data from 2010 and 2011. The data sources (i.e. ETR, census, DOT datasets) ranged from 2009-2012, which could lead to information bias. Finally, we were unable to evaluate all constructs of access to care. We were only able to evaluate health system barriers and geographical barriers, therefore missing economic and sociocultural barriers in accessing TB services.

Despite these limitations, this study introduces several new dimensions to our current understanding of the social determinants that may influence tuberculosis treatment outcomes. To our knowledge, this study is the first of its kind to evaluate access to care and default using routinely collected data. By performing a multilevel analysis, we have taken into account other levels that if ignored might lead to erroneous variance estimates and type I errors. Additionally, we had a large sample size of approximately 29,000 patients, which was a great representation of our target population. Moreover, with the use of municipality-level data from the census and department of health, we were able to provide an estimate of socioeconomic status and access to health, which is often excluded in epidemiological studies. Also, this study could be easily repeated in other countries using routinely-collected data (i.e. surveillance and census), and therefore could continuously evaluate levels of access to care and risk of default by municipality/state-level.

<u>Future Directions</u>

Future research should evaluate all concepts of accessing care: economic, geographic, socio-cultural, and health system barriers on poor treatment outcomes which may better describe the relationship between accessing care and default. For example, future studies could incorporate economic elements such as TB-related costs to the patients, as well as sociocultural barriers, such as proportion of patients using a traditional healer for care. By implementing this research into other middle-income countries, it would allow countries to evaluate the effects of their level of care on poor treatment outcome with only routinely-collected census and surveillance data. Although this study design evaluated variables at the individual and municipality level, future research could incorporate a mixed effects model to further describe the relationship between access to care and defaulting.

CONCLUSION

This study presents key insights on the importance of access to care with regard to defaulting. By linking existing surveillance and administrative data, we demonstrated that consistent DOT provisioning and spatial density of health facilities are independent predictors of tuberculosis default. This work needs to be replicated, but it provides concrete steps that can be taken to improve quality of care for TB patients in low and middle-income countries.

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FIGURES

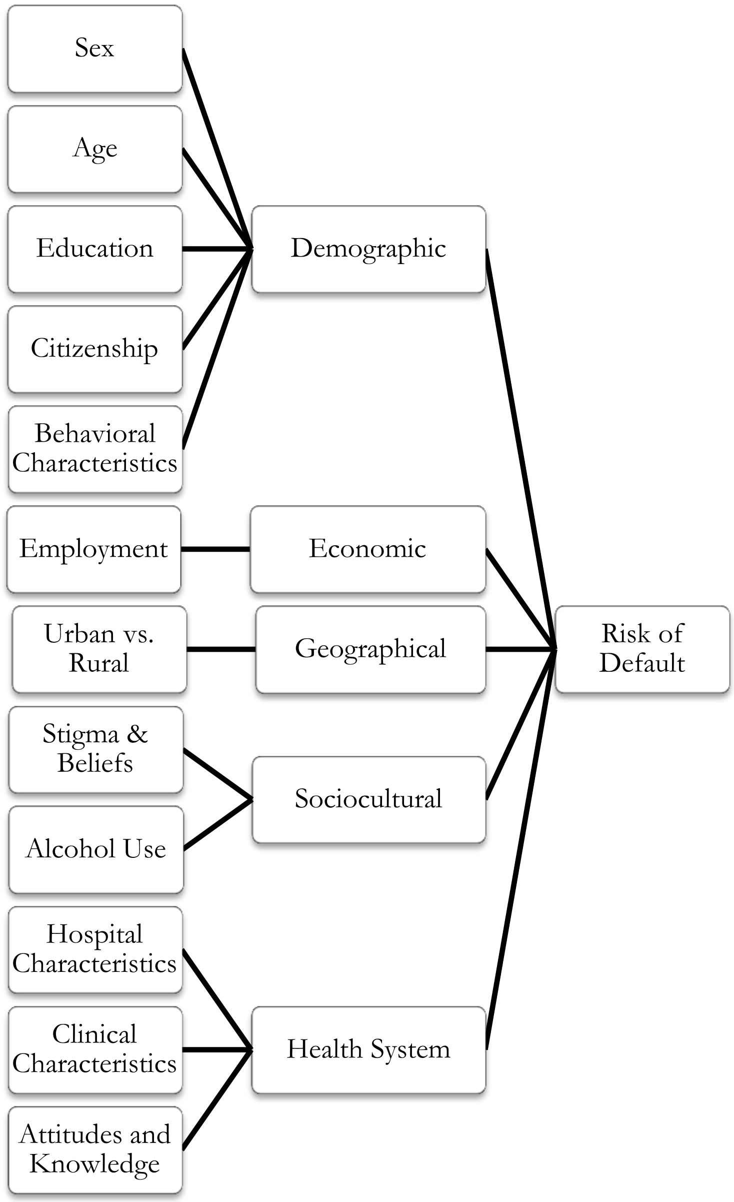

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Figure 1. Risk factors identified by previous studies as impacting risk of default from tuberculosis treatment (4-14)

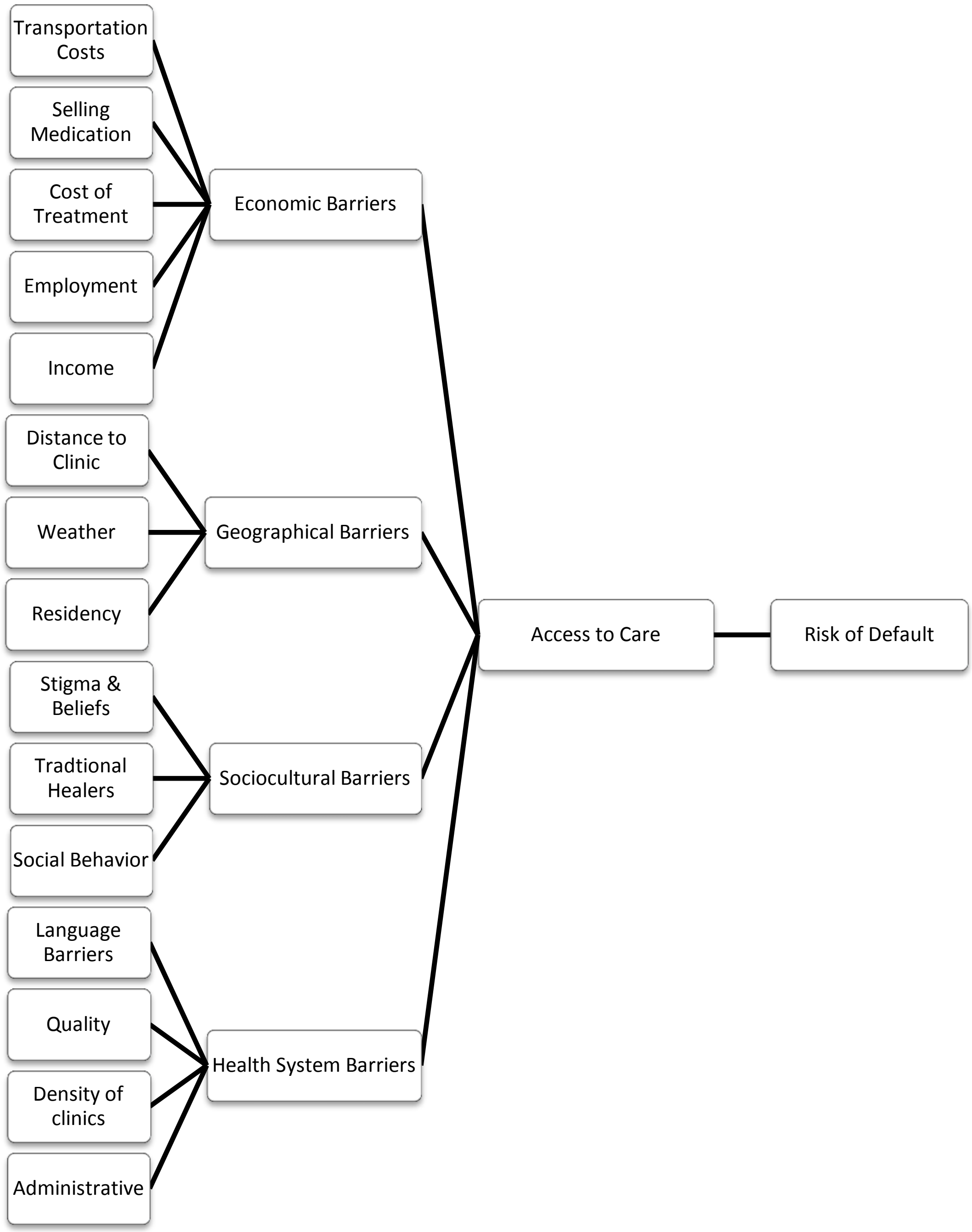

Figure 2: Constructs of access to care and the potential association of factors with risk of TB treatment default (8, 19-23).

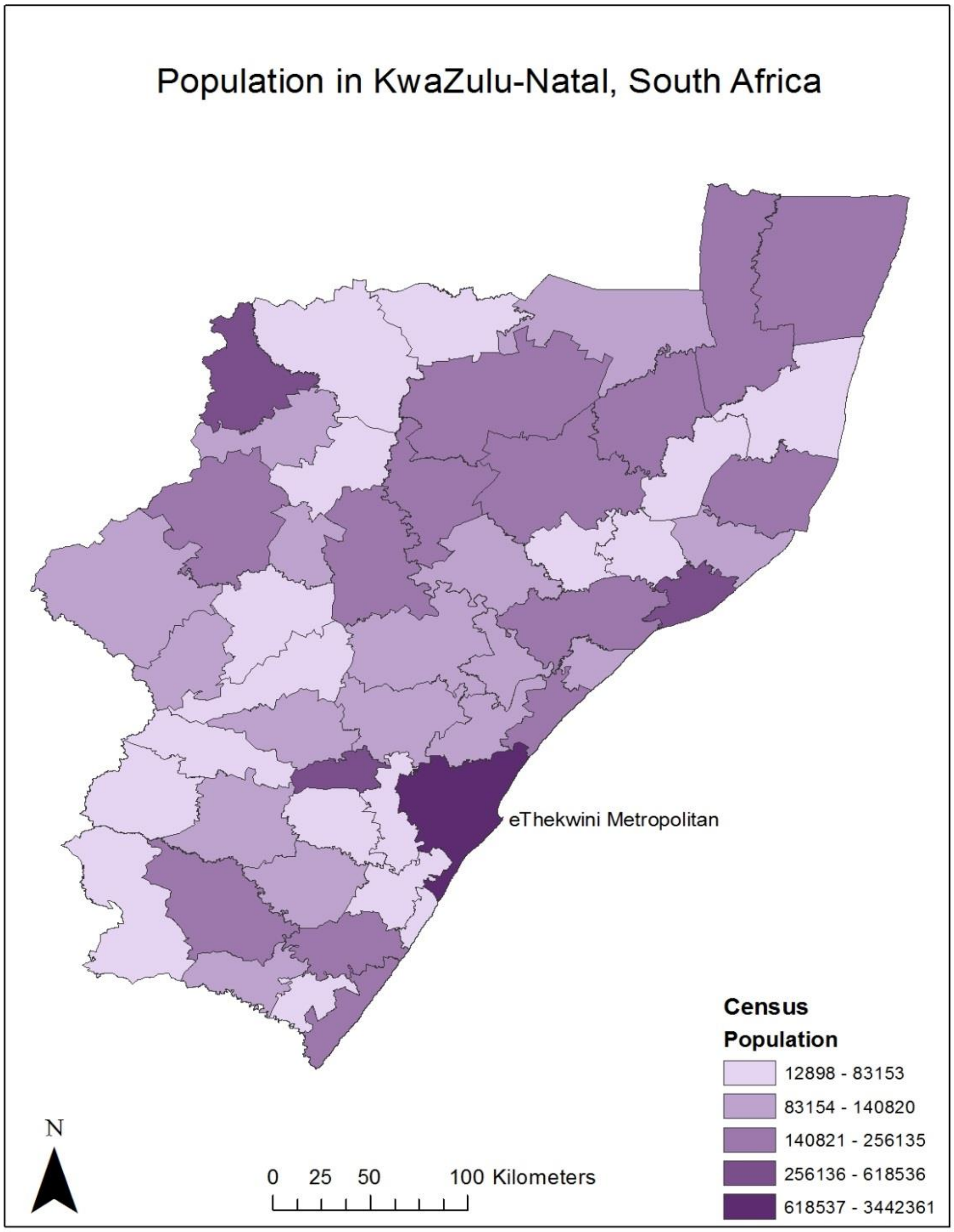

Figure 3. Map of the total population of persons living in KwaZulu-Natal, South Africa in 2011, from the Census.

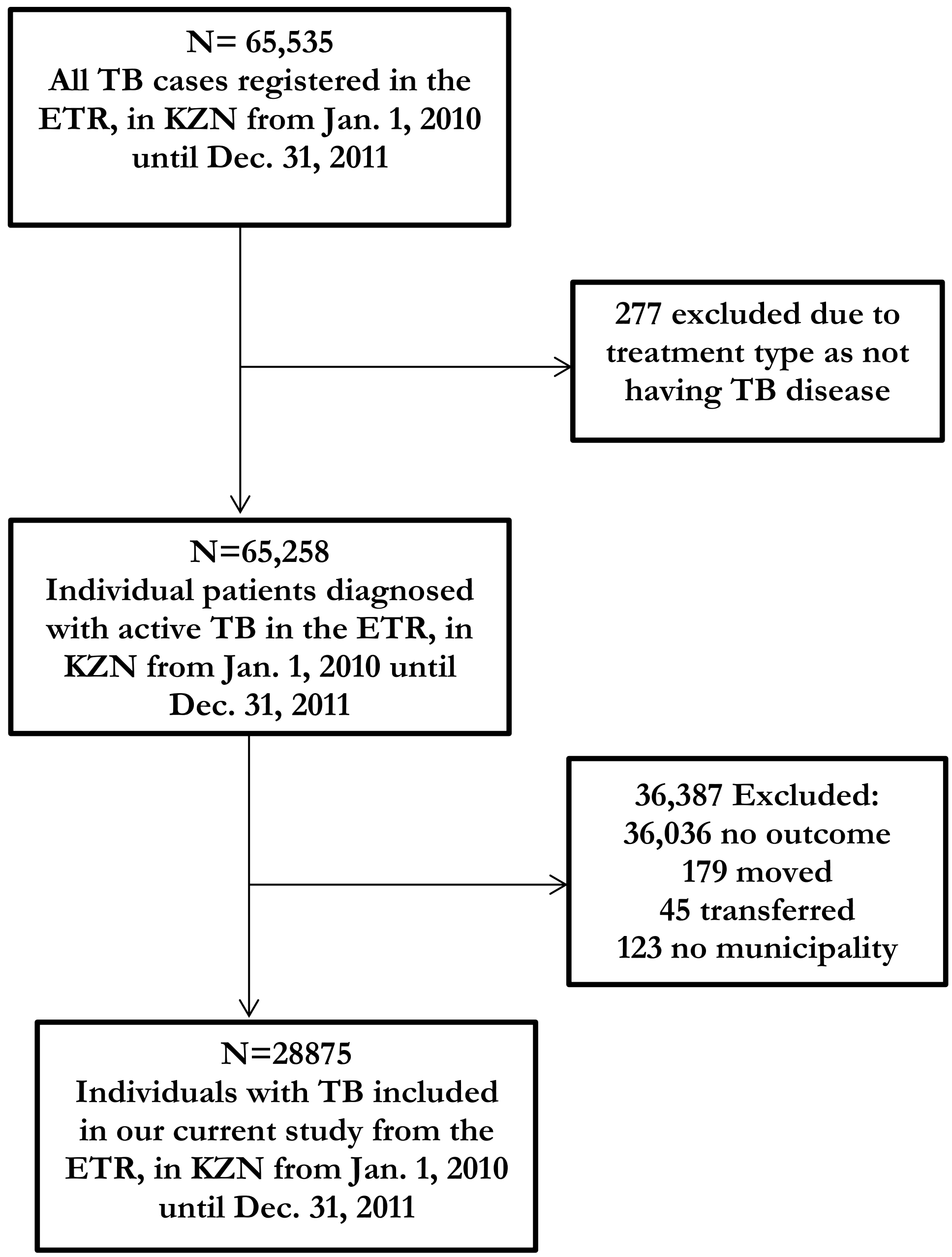

Figure 4: Flowchart of Study Sample from the ETR in KwaZulu-Natal in 2010-2011.

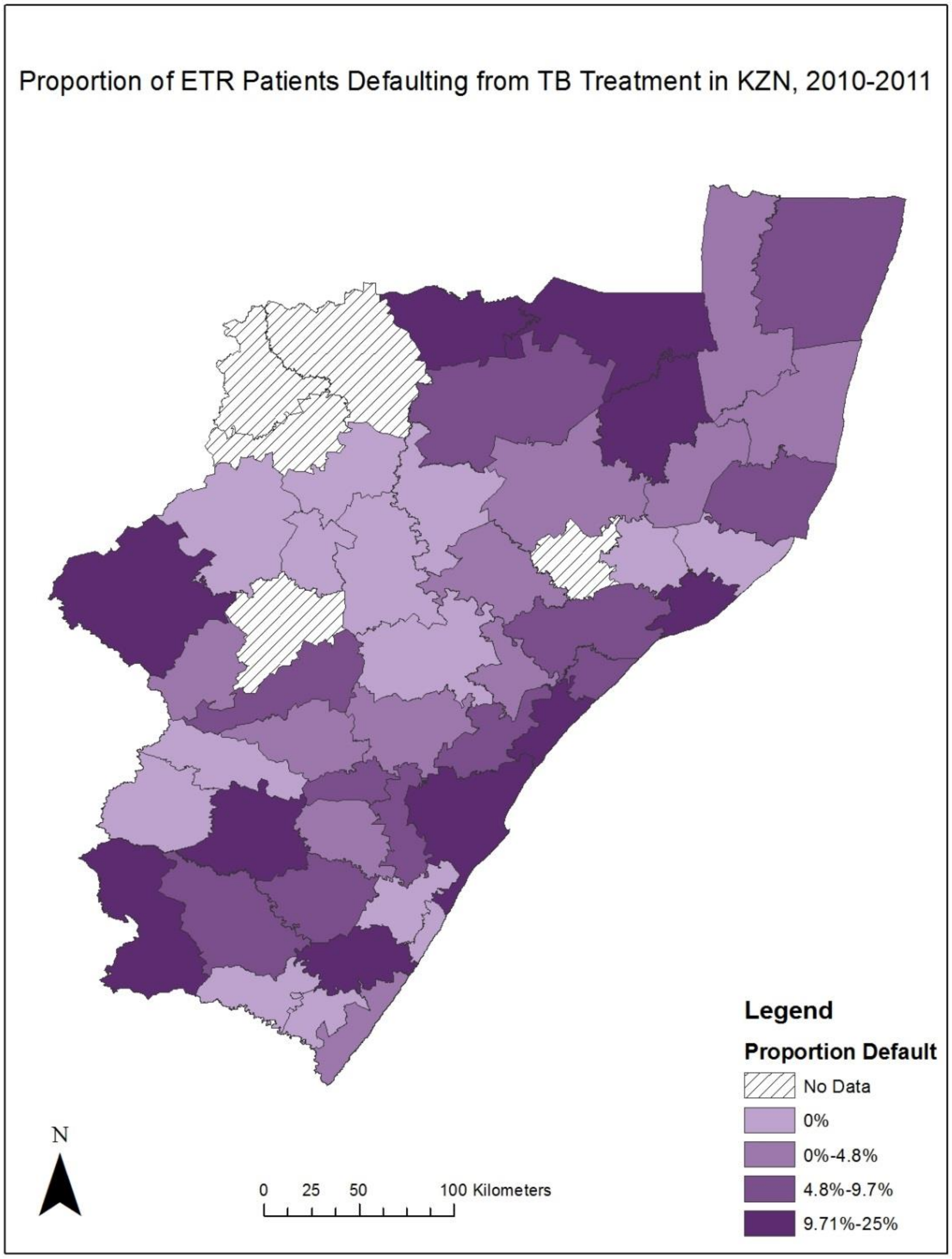

Figure 5. Proportion of Patients Defaulting from TB Treatment by Municipality, in KwaZulu-Natal

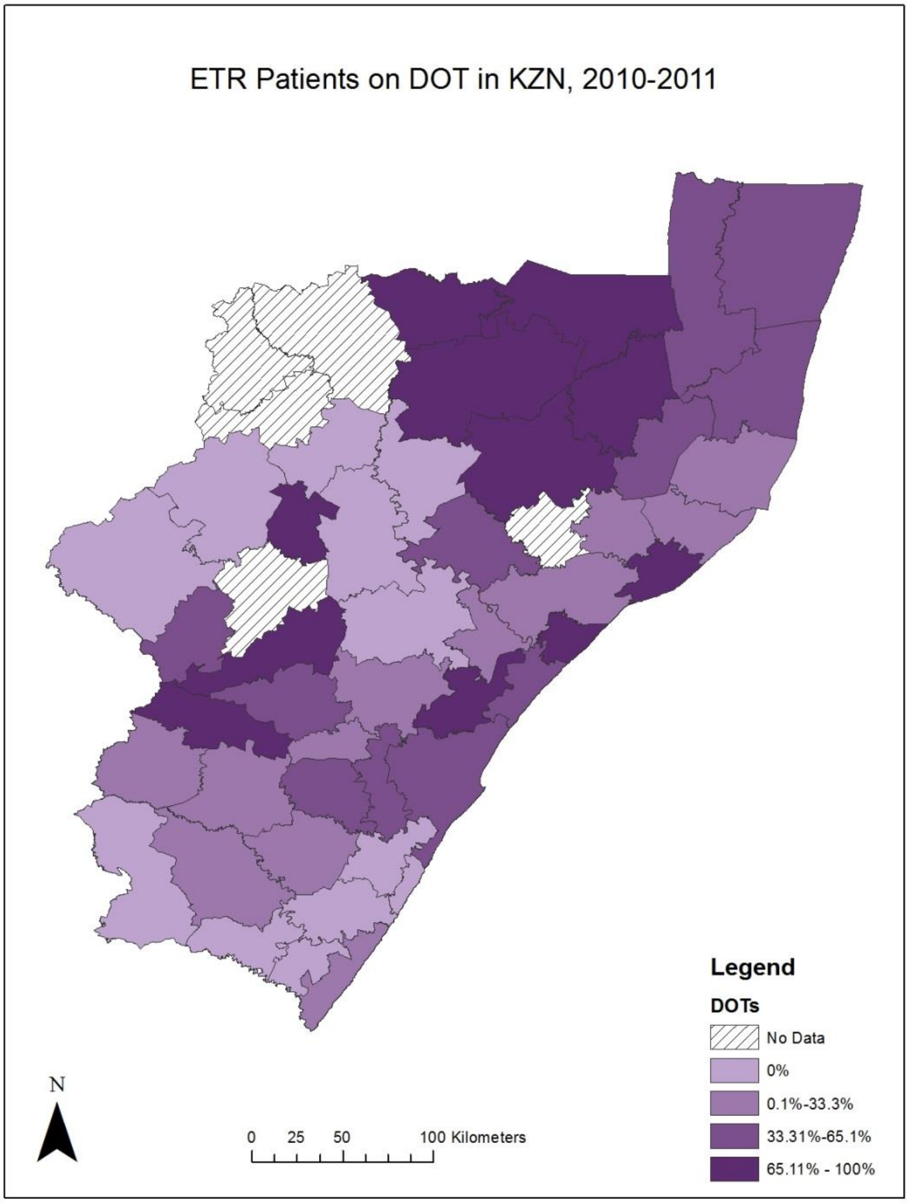

Figure 6: Map of Proportion of ETR Patients on DOT in 2010-2011, in KwaZulu-Natal, South Africa.

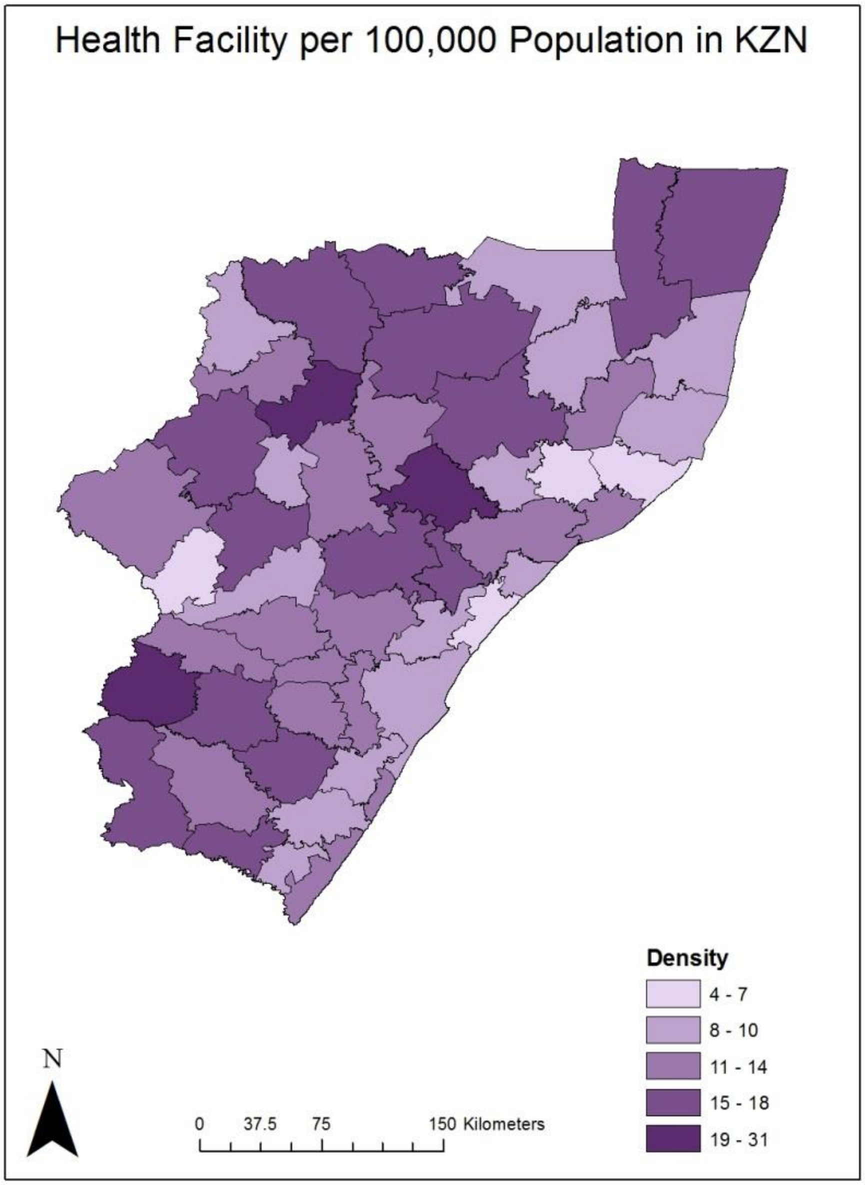

Figure 7: Map of Health Facilities per 100,000 population in KwaZulu-Natal, South Africa

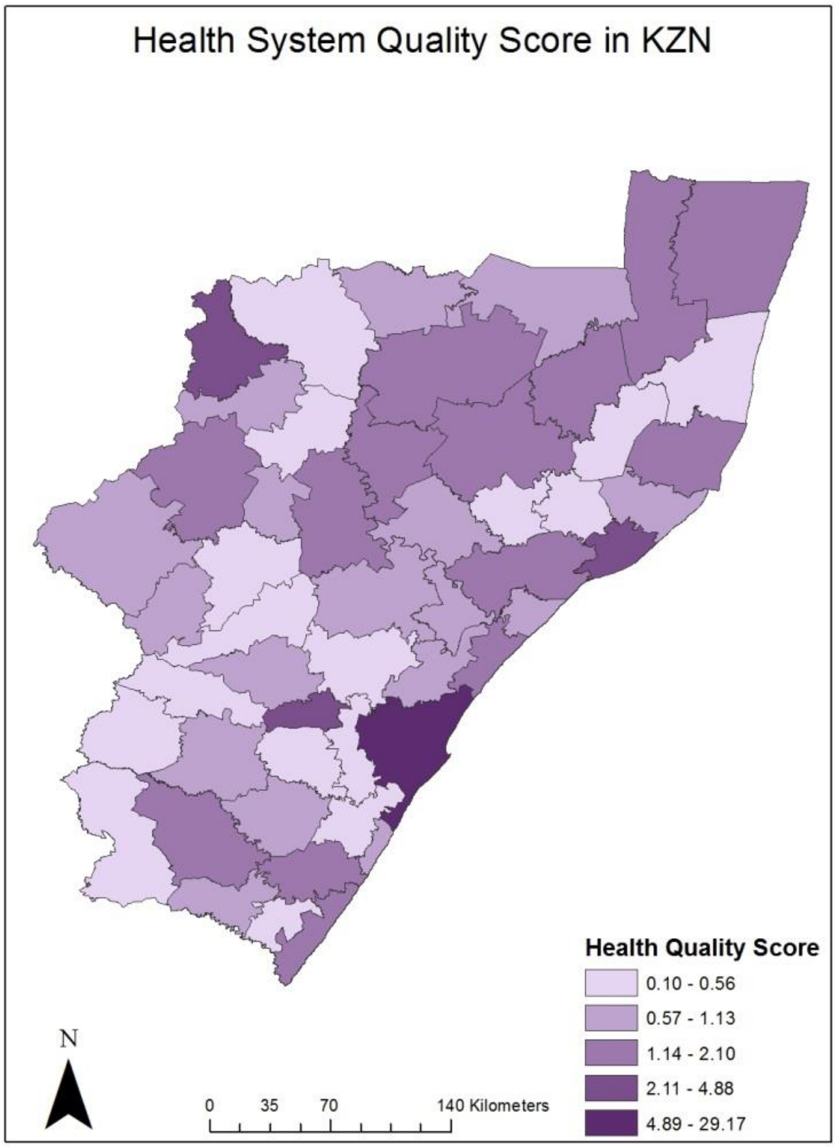

Figure 8: Map of Weighted Health Quality Score in KwaZulu-Natal, South Africa

TABLES

Table 1: World Health Organization classification of drugs to treat MDR TB (2).

Group	**Drugs**	**Uses for MDR TB**
Group 1: *First-line oral agents*	Pyrazinamide, ethambutol, rifabutin	Group 1 drugs are the most potent and best tolerated. If there is good laboratory evidence and clinical history that suggests that a drug from this group is effective, it should be used.
Group 2: *Injectable agents*	Kanamycin, amikacin, capreomycin, streptomycin (S)	All patients should receive a Group 2 injectable agent if susceptibility is documented or suspected.
Group 3: *Fluoroquinolones*	Levofloxacin, moxifloxacin, ofloxacin	All patients should receive a Group 3 medication if the M. tuberculosis strain is susceptible or if the agent is thought to have efficacy.
Group 4: *Oral bacteriostatic*	PAS, cycloserine, terizidone, ethionamide, protionamide	Ethionamide (or protionamide) is often added to the treatment regimen because of its low cost. If cost is not a constraint, p-aminosalicylic acid (PAS) may be added first, given that the enteric-coated formulas are relatively well tolerated and that there is no cross-resistance to other agents.
Group 5: *Agents with unclear role in drug resistant-TB*	Clofazimine, linezolid, amoxicillin/clavulanate, thioacetazone, imipenem/cilastatin, high-dose isoniazid, clarithromycin	Group 5 drugs are not recommended by WHO for routine use in drug-resistant TB treatment because their contribution to the efficacy of multidrug regimens is unclear.

Table 2: Summary of studies evaluating the association between TB patient demographic characteristics and risk for default from TB treatment.

Primary Author, Publication Year	Country	Study Type	Population	Risk Factor	Results:
Brust, 2011 (9)	South Africa	Retrospective Cohort	MDR TB patients admitted from 2000-2003, N=1209, median age=33	Sex	Sex: (male vs. female): OR=1.9, 95% CI=1.2, 3.1, p=NR
Chan, 2010 (8)	Malawi	Retrospective Cohort	ART patients from 2004-2008, N=8093, mean age=33	Age, sex	Age (linear): HR_{adj}=1.0, 95% CI=1.0, 1.0, p=NR (NS) Sex (male vs. female): HR_{adj}=1.0, 95% CI=0.9, 1.1, p=NR (NS)
Farley, 2011 (10)	South Africa	Prospective Cohort	MDR TB patients, N=757, mean age=34.8	Sex	Sex (male vs. female): HR=0.9, 95% CI=0.5, 1.5, p=0.7 (NS)
Hasker, 2008 (11)	Uzbekistan	Case Control	Case=defaulter in 2005, control=patients who completed treatment, in 2005, N=297, median age=37	Imprisonment	Imprisonment (yes vs. no): OR=2.7, 95% CI=0.9, 7.8, p=NR

Jenkins, 2013 (6)	Moldova	Retrospective Cohort	Non MDR TB patients who defaulted, N=4890, mean age=NR	Age, sex, education, citizenship, incarceration	Age (30-39 vs. <30 yrs.): New cases: HR=1.4, 95% CI=1.1, 1.9, p=0.01 Previously treated: HR=1.2, 95% CI=0.8, 1.8, p=0.4 (NS) Age (40+ vs. <30 yrs.): New cases: HR=0.9, 95% CI=0.7, 1.1, p=0.2 (NS) Previously treated: HR=0.8, 95% CI=0.6, 1.2, p=0.3 (NS) Sex (male vs. female): New cases: HR=1.3, 95% CI=1.0, 1.7, p=0.05 Previously treated: HR=1.31, 95%CI=0.89, 1.92, p=0.2 Education (linear for each increase in education level - no education, primary, secondary, specialized secondary, higher.): New cases: HR_{adj}=0.8, 95% CI=0.7, 0.9, p<0.002 Previously treated: HR_{adj}=0.8, 95% CI=0.7, 1.0, p=0.05 Homelessness (yes vs. no): New cases: HR_{adj}=2.3, 95%CI=1.6, 3.3, p<0.0001 Previously treated: HR=1.5, 95% CI=1.0, 2.4, p=0.07 (NS) History of Incarceration (yes vs. no): New cases: HR_{adj}=1.3, 95%CI=0.9, 1.8, p=0.2 (NS) Previously treated: HR_{adj}=1.7, 95%CI=1.2, 2.4, p=0.004 Incarceration (at the time of diagnosis/during treatment vs. never):

					New cases: HR_{adj}=0.04, 95%CI=0.01, 0.3, p=0.002 Previously treated: HR_{adj}= not enough data Citizenship (no vs. yes): New cases: HR=3.2, 95%CI=1.3, 7.8, p=0.01 Previously treated: not enough data Time spent out of country in past year (>3 vs. <3 months): New cases: HR=1.3 95% CI=1.0, 1.6, p=0.05 Previously treated: HR=1.3, 95% CI=0.9, 1.8, p=0.03
Marx, 2012 (5)	South Africa	Retrospective Cohort	TB cases from 2002-2007, N=2166, median age=30	Age, sex	Age (19-39 vs. ≤ 18 yrs.): OR_{adj} 3.5, 95% CI 1.9, 6.6 years, p<0.001 Age (40+ vs. ≤ 18 yrs.): OR_{adj}=1.7, 95% CI=0.9, 3.5, p<0.001 Sex (male vs. female): OR_{adj}=1.8, 95% CI=1.2, 2.7, p=0.003
Sendagire, 2012 (7)	Uganda	Prospective Cohort	TB cases from 2007-2008, N=270, median age=30	Age, sex	Age (30-39 vs. 16-29): OR_{adj}=0.7, 95% CI=0.3, 1.7, p=0.4 (NS) Age (40+ vs. 16-29): OR_{adj}=0.5, 95% CI=0.2, 1.5, p=0.4 (NS) Sex (male vs. female): OR_{adj}=2.0, 95% CI=3.3, 5.0, p=0.1 (NS)
Shargie, 2007 (4)	Ethiopia	Prospective Cohort	Patients diagnosed with TB between 2002-2004, N=404, mean age=NR	Age, sex, literacy	Age (25+ vs. <25 yrs.): HR_{adj}=1.7, 95% CI=1.1, 2.7, p=0.02 Sex (male vs. female): HR=0.8, 95% CI=0.6, 1.3, p=0.5 (NS) Literacy (non-literate vs. literate): HR=1.7, 95% CI=1.1, 2.6, p=0.02

Siemion-Szcześniak, 2012 (13)	Poland	Chart Review	TB cases from 1995-2000 from hospitals and dispensaries, N=708, mean age=49	Homelessness	Homelessness (yes vs. no): N=60 (15 homeless, 45 non-homeless), p<0.0001

ADJ=adjusted
ART=antiretroviral therapy
HR=hazard ratio
MDR TB=multi-drug resistant tuberculosis
NR=not reported
NS=not significant
OR=odds ratio
TB=tuberculosis

Table 3: Summary of studies evaluating the association between TB patient economic characteristics and risk for default from TB treatment.

Primary Author, Publication Year	Country	Study Type	Population	Risk Factor	Results
Hasker, 2008 (11)	Uzbekistan	Case Control	Case=defaulter in 2005, control= patients who completed treatment, in 2005, N=297, median age=37	Employment	Unemployment (unemployed vs. employed by gov.) OR_{adj}=2.7 95% CI=1.3, 5.9, p=NR
Jenkins, 2013 (6)	Moldova	Retrospective Cohort	Non MDR TB patients who defaulted, N=4890, mean age=NR	Employment	Unemployment (unemployed vs. employed/retired/disabled) New cases: HR=2.6, 95% CI=2.0, 3.5, p<0.0001 Previously treated: HR=2.2, 95% CI=1.6, 3.1, p<0.0001 Salaried (no vs. yes): New cases: HR=2.5, 95% CI=1.9, 3.3, p<0.0001 Previously treated: HR_{adj}=1.1, 95% CI=0.5, 2.4, p=0.9 (NS)
Sendagire, 2012 (7)	Uganda	Prospective Cohort	TB cases from 2007-2008, N=270, median age=30	Employment	Unemployment (unemployed vs. employed): OR_{adj}=0.9, 95% CI=0.4, 2.1, p=0.8 (NS)
Shargie, 2007 (4)	Ethiopia	Prospective Cohort	Patients diagnosed with TB between 2002-2004, N=404, mean age=NR	Occupation	Occupation (farmer vs. student): HR=2.1, 95% CI=1.2, 4.0, p=0.02.

ADJ=adjusted

HR=hazard ratio

MDR TB=multi-drug resistant tuberculosis
NR=not reported
NS=not significant
OR=odds ratio
TB=tuberculosis

Table 4: Summary of f studies evaluating the association between TB patient geographic characteristics and risk for default from TB treatment.

Primary Author, Publication Year	Country	Study Type	Population	Risk Factor	Results
Jenkins, 2013 (6)	Moldova	Retrospective Cohort	Non MDR TB patients who defaulted, N=4890, mean age=NR	Residency	Residency (urban vs. rural): New cases: HR=1.3, 95% CI=1.1, 1.6, p=0.01 Previously treated: HR=1.4, 95% CI=1.1, 1.8, p=0.02
Shargie, 2007 (4)	Ethiopia	Prospective Cohort	Patients diagnosed with TB between 2002-2004, N=404, mean age=NR	Residency	Residency (urban vs. rural): HR=0.4, 95% CI=0.2, 1.0, p=0.04

HR=*hazard ratio*

MDR TB=*multi-drug resistant tuberculosis*

NR=*not reported*

TB=*tuberculosis*

Table 5: Summary of literature review of studies evaluating the association between TB patient sociocultural characteristics and risk for default from TB treatment.

Primary Author, Publication Year	Country	Study Type	Population	Risk Factor	Results
Hasker, 2008 (11)	Uzbekistan	Case Control	Case=defaulter in 2005, control=patients who completed treatment, in 2005, N=297, median age=37	Alcohol abuse	Alcohol abuse (yes vs. no): OR_{adj}=6.0, 95% CI=1.7, 19.5, p=NR
Hasker, 2010 (12)	Uzbekistan	Qualitative	TB Defaulters, N=32, median age=30	Stigma, cultural differences	Stigma: Many patients did not disclose their diagnosis due to the stigma of TB Cultural: Women with TB reported defaulting due to the pressure to return home from their spouse
Sendagire, 2012 (7)	Uganda	Prospective Cohort	TB cases from 2007-2008, N=270, median age=30	Alcohol	Drinks alcohol (1-3 days/week vs. never): OR_{adj}=2.2, 95% CI=0.8, 5.9, p=0.01 (Daily vs. never): OR_{adj}=4.9, 95% CI=1.8, 13.5, p=0.01

ADJ=adjusted

NR=not reported

OR=odds ratio

TB=tuberculosis

NR=not reported

Table 6: Summary of studies evaluating the association between TB patient health system and clinical characteristics and risk for default from TB treatment.

Primary Author, Publication Year	Country	Study Type	Population	Risk Factor	Results
Brust, 2011 (9)	South Africa	Retrospective Cohort	MDR TB patients '00-03, N=1209, median age=33	TB/HIV co-infection	TB/HIV co-infection (yes vs. no): OR_{adj}=2.0, 95% CI=1.3, 3.1, p=NR
Farley, 2011 (10)	South Africa	Prospective Cohort	MDR TB patients, N=757, mean age=34.8	TB/HIV co-infection	TB/HIV co-infection (yes vs. no): OR_{adj}=1.1, 95% CI=0.7, 1.6, p=0.7 (NS)
Gler, 2012 (14)	Philippines	Retrospective Cohort	MDR TB patients, N=583, mean age=39	Number of drugs during treatment, decentralization	Number of drugs (5+ vs. 2-3): HR_{adj}=7.2, 95% CI=3.3, 16.0, p<0.001 Decentralization (yes vs. no): HR=0.3, 95% CI=0.2, 0.7, p=0.006
Hasker, 2010 (12)	Uzbekistan	Qualitative	Patients who defaulted from TB treatment, N=32, median age=30	Side effects of treatment, unwillingness to be hospitalized, attitudes of workers, patient's lack of knowledge	Side effects: Many patients stated that they defaulted because of side effects of the TB medication Hospitalization: Patients did not want to be hospitalized because of unsanitary conditions Attitudes of workers: Workers believed that they would acquire TB if they treated the patients Lack of knowledge: Patients did not know the duration
Jenkins, 2013 (6)	Moldova	Retrospective Cohort	Non-MDR TB patients N=4890, mean age=NR	TB/HIV co-infection	HIV (yes/untested/unknown vs. no): OR_{adj}=1.6, 95% CI=1.2, 2.1, p=0.002

Marx, 2012 (5)	South Africa	Retrospective Cohort	TB cases '02-07, N=2166, median age=30	Treatment history	History of default (yes vs. no previous treatment): OR=7.6, 95% CI=4.6, 12.6, p<0.001 History of failure (yes vs. no previous treatment): OR=12.8, 95% CI=4.2, 39.4, p<0.001

ADJ=*adjusted*

HR=*hazard ratio*

MDR TB=*multi-drug resistant tuberculosis*

NR=*not reported*

NS=*not significant*

OR=*odds ratio*

TB=*tuberculosis*

Table 7: Summary of studies evaluating economic barriers of accessing care (non-TB patients) and treatment adherence.

Primary Author, Publication Year	Country	Study Type	Population	Access to Care Proxy	Proxy Measurement	Outcome	Results
Arrivillaga, 2011 (23)	Colombia	Qualitative Study	Women with HIV on ART, n=47, mean age=39	Selling Medication	Selling medication in order to eat	Non-adherence to treatment	Percentage reported selling medication instead of adhering: 26%
Berhanu, 2009 (22)	Ethiopia	Qualitative Study	Patients with epilepsy who defaulted from treatment between 1998-2002, N=113, median age=24	Cost of travel and treatment	Self-report	Default	Percentage reporting "cost" as the main reason for defaulting -Cost of travel: 4% -Cost of treatment: 3%
Duff, 2010 (21)	Uganda	Qualitative Study	HIV+ mothers, n=45, mean age=32	Transportation	Cost of transportation	Non-adherence to treatment	Percentage reporting costly transportation as a barrier: 93%
Groh, 2011 (20)	Mozambique	Qualitative Study	Focus groups on ART of healthcare workers and community members with HIV, N=164, mean age=30	Transportation, food security	Inadequate transportation, the inability to afford food	Non-adherence to treatment	Percentage reporting this barrier: - Inadequate transportation: 67% - Food insecurity: 78%

ART=antiretroviral therapy

HIV = human immunodeficiency virus

Table 8. Summary of studies evaluating geographic barriers of accessing care (non-TB patients) and treatment adherence.

Primary Author, Publication Year	Country	Study Type	Population	Access to Care Proxy	Proxy Measurement	Outcome	Results
Berhanu, 2009 (22)	Ethiopia	Qualitative Study	Epileptic Defaulters from 2005, N=113, median age=24	Distance	Self-report	Default	Percentage reporting "distance to clinic" as the main reason for defaulting: 33%
Groh, 2011 (20)	Mozambique	Qualitative Study	Focus groups on ART of healthcare workers and community members, N=164, mean age=30	Inadequate transportation	Self-report	Treatment adherence	12/18 groups (67%) found that inadequate transportation was an important barrier to treatment adherence. This was mainly due to poor quality of the roads and unreliability of transportation.
Zeber, 2011 (19)	USA	Prospective Cohort	Veterans with bipolar disorder, N=435, mean age=49	Distance	Travels 50+ miles for care	Poor adherence	Travel: OR=1.5, 95% CI=0.9, 2.4, p=0.1 (NS)

ART=antiretroviral therapy

NR=not reported

NS=not significant

OR=odds ratio

Table 9. Summary of studies evaluating sociocultural barriers of accessing care (non-TB patients) and treatment adherence.

Primary Author, Publication Year	Country	Study Type	Population	Access to Care Proxy	Proxy Measurement	Outcome	Results
Arrivillaga, 2011 (23)	Colombia	Qualitative Study	Women on ART, n=47, mean age=39	Guilt	Guilt of transmitting the virus so prioritizes child's treatment	Treatment adherence	The investigators concluded that the females often feel guilty for transmitting the virus to their children and therefore prioritize their children's care above their own adherence behaviors.
Berhanu, 2009 (22)	Ethiopia	Qualitative Study	Epileptic defaulters from 2005, N=113, median age=24	Traditional remedies preferred	Self-report	Default	Percentage reporting "traditional remedies preferred" as a main reason for defaulting: 12% contributory reason: 51%
Duff, 2010 (21)	Uganda	Qualitative Study	HIV+ mothers, n=45, mean age=32	Stigma, attitudes	HIV related stigma, negative attitudes of workers	Treatment adherence	Percentage reporting the following as a barrier: stigma: 42% attitudes: 33%

Groh, 2011 (20)	Mozambique	Qualitative Study	Focus groups on ART of healthcare workers and community members, N=164, mean age=30	Saving pills, traditional healer preference, stigma, lack of knowledge	Saving pills for family, preferring traditional healer, stigma of community, concerned with effectiveness of ART	Treatment adherence	Percentage reporting the following barrier: saving pills: 66% traditional healers: 100% (CHWs) 42% (community) stigma: 78% lack of knowledge: 75%
Zeber, 2011 (19)	USA	Prospective Cohort	Veterans with bipolar disorder, N=435, mean age=49	Beliefs, alcohol use, support	Low medication beliefs, binge drinking in past month, poor therapeutic alliance	Poor adherence	Beliefs: OR=2.4, 95% CI=1.2, 3.9, p=0.01 Alcohol: OR=2.0, 95% CI=1.0, 2.9, p=0.03 Support: OR=1.6, 95% CI=0.9, 2.1, p=0.1 (NS)

ART=antiretroviral therapy

HIV = human immunodeficiency virus

NS=not significant

OR=odds ratio

Table 10. Summary of studies evaluating health system barriers of accessing care (non-TB patients) and treatment adherence.

Primary Author, Publication Year	Country	Study Type	Population	Access to Care Proxy	Proxy Measurement	Outcome	Results
Arrivillaga, 2011 (23)	Colombia	Qualitative Study	Women on ART, n=47, mean age=39	NGOs	Self-report	Treatment adherence	The participants believed that NGOs were critical to their success by providing educational components, food, money and transportation.
Berhanu, 2009 (22)	Ethiopia	Qualitative Study	Epileptic defaulters from 2005, N=113, median age=24	Dissatisfaction with clinic services	Self-report	Default	Main reason for defaulting was due to dissatisfaction of clinic services: 5%
Chan, 2010 (8)	Malawi	Retrospective Cohort	ART patients, N=4653, mean age=33	DC	DC to a health center equipped for ART	Default	DC (yes vs. no): OR=0.5, 95% CI=0.4, 0.6, p=NR Time DC: 0-10 months: HR=0.4, 95% CI=0.3, 0.5, p=NR 10+ months: HR=0.6, 95% CI=0.4, 0.8, p=NR
Duff, 2010 (21)	Uganda	Qualitative Study	HIV+ mothers, n=45, mean age=32	Waiting times	Self-report	Treatment adherence	Average waiting time: 4 hours (range 1-24+hours)

Groh, 2011 (20)	Mozambique	Qualitative Study	Focus groups on ART of healthcare workers and communit y members with HIV, N=164, mean age=30	Negative attitudes of workers, language barriers	Self-report	Treatment adherence	Attitudes: Patients expressed that health care workers treated patients poorly and were not confidential Language: Patients expressed that workers did not speak their language and therefore they had to generalize their conditions.
Zeber, 2011 (19)	USA	Prospective Cohort	Veterans with bipolar disorder, N=435, mean age=49	Limited access to a mental health specialist	Self-report	Poor adherence	Limited Access (yes vs. no): OR=1.7, 95% CI=1.1, 2.7, p=0.04

ART=antiretroviral therapy

DC=decentralized

HIV = human immunodeficiency virus

NGO=non-governmental organization

NR=not reported

OR=odds ratio

Table 11. Summary of studies evaluating economic barriers of accessing care (TB patients) and treatment adherence.

Primary Author, Publication Year	Country	Study Type	Population	Access to Care Proxy	Proxy Measurement	Outcome	Results
Elbireer, 2011 (18)	Uganda	Case Control	Cases: TB/HIV defaulters, Controls: TB/HIV patients who completed 8+ months of treatment, N=344, mean age=36	Employed	Employed at time of TB diagnosis	Default	Employed (no vs. yes): OR_{adj}=1.1, 95% CI=0.6, 2.2, p=0.7 (NS)
Shargie, 2007 (4)	Ethiopia	Prospective Cohort	Patients diagnosed with TB between 2002-2004, N=404, mean age=NR	Income, public transportation cost	Family income in Birr, necessity of public transportation for medication	Default	Income (>150 vs.≤150): HR=1.0, 95% CI=0.6, 1.6, p=0.9 (NS) Public transportation (yes vs. no): HR_{adj}=1.6, 95% CI=1.0, 2.6, p=0.06 (NS)

ADJ=adjusted
HIV = human immunodeficiency virus
HR=hazard ratio
NR=not reported
NS=not significant
OR=odds ratio
TB=tuberculosis

Table 12. Summary of studies evaluating geographic barriers of accessing care (TB patients) and treatment adherence.

Primary Author, Publication Year	Country	Study Type	Population	Access to Care Proxy	Proxy Measurement	Outcome	Results
Buu, 2003 (16)	Vietnam	Qualitative Study	Patients diagnosed with TB who did not register in the national TB program, N=166, mean age=NR	Distance	The clinic is too far	Default	Main reason for defaulting: Distance: 5.4% believed the clinic was too far
Elbireer, 2011 (18)	Uganda	Case Control	Cases: TB/HIV defaulters, Controls: TB/HIV patients who completed 8+ months of treatment, N=344, mean age=36	Distance	Distance to the TB clinic	Default	Distance (far - more than 10km vs. near - less than 10 km): OR_{adj}=2.2, 95% CI=1.2, 4.1, p=0.01
Sanou, 2004 (17)	Burkina Faso	Qualitative Study	TB patients, community members and various healthcare workers, N=NR, mean age=NR	Distance, weather	Distance to health center, weather patterns	Accessing treatment	Distance: Geographical distance was a barrier for accessing treatment. This was compounded by lack of transportation. Weather in the rainy season was problematic with regards to getting to the center.

Shargie, 2007 (4)	Ethiopia	Prospective Cohort	Patients diagnosed with TB between 2002-2004, N=404, mean age=NR	Residency, walking distance	Residency= rural and urban, within walking distance to the clinic	Default	Residency (urban vs. rural): HR=2.4, 95% CI=1.0, 5.5, p=0.03 Walking distance (2+hrs vs.≤2hr): HR=3.0, 95% CI=1.9, 4.6, p<0.001

ADJ=adjusted
ART=antiretroviral therapy
HIV = human immunodeficiency virus
HR=hazard ratio
NR=not reported
OR=odds ratio
TB=tuberculosis

Table 13. Summary of studies evaluating sociocultural barriers of accessing care (TB patients) and treatment adherence.

Primary Author, Publication Year	Country	Study Type	Population	Access to Care Proxy	Proxy Measurement	Outcome	Results
Buu, 2003 (16)	Vietnam	Qualitative Study	Patients diagnosed with TB who did not register in the national TB program, N=166, mean age=NR	Knowledge	Unaware of the diagnosis	Default	Main reason for defaulting: Knowledge: 15% were unaware of their diagnosis
Elbireer, 2011 (18)	Uganda	Case Control	Cases: TB/HIV defaulters, Controls: TB/HIV patients who completed 8+ months of treatment, N=344, mean age=36	Knowledge, support, stigma, reminders	Knowledge that TB is curable and the duration of TB treatment, family support, feeling stigmatized, having reminders from support group	Default	Knowledge Curable (no vs. yes): OR_{adj}=44.1, 95% CI=13.7 142.4, p<0.001 Duration of treatment (no vs. yes): OR_{adj}=10.8, 95% CI=5.2, 22.4, p<0.001 Family support (no vs. yes): OR_{adj}=1.1, 95% CI=0.3, 4.1, p=0.9 (NS) Stigmatized (yes vs. no): OR_{adj}=2.0, 95% CI=0.5, 8.1, p=0.3

							(NS) Reminders (no vs. yes): OR_{adj}=1.0, 95% CI=0.5, 2.1, p=.999 (NS)
Sanou, 2004 (17)	Burkina Faso	Qualitative Study	TB patients, community members and various healthcare workers, N=NR, mean age=NR	Traditional healer	Preference of traditional healers	Accessing treatment	Patients reported seeking assistance from traditional healers (rural patients) or self-medication (urban patients).
Shargie, 2007 (4)	Ethiopia	Prospective Cohort	Patients diagnosed with TB between 2002-2004, N=404, mean age=NR	Occupation, age, education, knowledge	Occupation (student, farmer, other), age=NR, knowledge of treatment duration	Default	Occupation (farmer vs. student): HR=2.1, 95% CI=1.2, 4.0, p=0.02 (other vs. student): HR=1.5, 95% CI=0.8, 3.0, p=0.2 (NS) Age (≥25y vs.<25y): HR_{adj}=1.7, 95% CI=1.1, 2.7, 0.02 Education (non-literate vs. literate): HR=1.7, 95% CI=1.1, 2.6, p=0.02 Knowledge of duration (not sufficient vs. sufficient): HR-1.0, 95% CI=0.7, 1.6, p=0.99 (NS)

ADJ=adjusted
HR=hazard ratio
NR=not reported
NS=not significant
OR=odds ratio
TB=tuberculosis

Table 14. Summary of studies evaluating health system and clinical-related barriers of accessing care (TB patients) and treatment adherence.

Primary Author, Publication Year	Country	Study Type	Population	Access to Care Proxy	Proxy Measurement	Outcome	Results
Buu, 2003 (16)	Vietnam	Qualitative Study	Patients diagnosed with TB who did not register in the national TB program, N=166, mean age=NR	Operating hours, administrative issues	Operating hours of the TB clinic, complicated administrative process	Defaulting	Main reason for defaulting: Operating hours: 31% believed they were unsuitable Administrative issues: 14% believed it was overly complicated
Elbireer, 2011 (18)	Uganda	Case Control	Cases: TB/HIV defaulters, Controls: TB/HIV patients who completed 8+ months of treatment, N=344, mean age=36	Waiting time, staff conduct, provided counseling and health education, listeners, resources, side effects	Self-report	Default	Waiting Time (4+hours vs. <2hours): OR_{adj}=2.5, 95% CI=1.1, 5.6, p=0.03 (2-4hours vs. <2hours): OR_{adj}=4.2, 95% CI=2.2, 8.0, p<0.001 Conduct (fair vs. good): OR_{adj}=2.7, 95% CI=1.0, 7.3, p=0.05 Received Counseling (no vs. yes): OR_{adj}=1.0, 95% CI=0.4, 2.6, p=0.9 Given a chance to express concerns of TB treatment (no vs. yes): OR_{adj}=3.5, 95% CI=1.7, 7.2, p<0.001 Received health education on risks of defaulting (no vs. yes): OR_{adj}=5.3, 95% CI=1.9, 14.6,

							p=0.001 Medication unavailable at one time (yes vs. no): OR_{adj}=4.8, 95% CI=2.3, 9.8, p<0.001 Side effects (no vs. yes): OR_{adj}=0.2, 95% CI=0.1, 0,4 p<0.001
Garrido, 2012 (15)	Brazil	Case Control	Cases=patients who defaulted from TB treatment, controls=patients who completed TB treatment	DOT	Having DOT	Default	DOT (yes vs. no): OR_{adj}=0.7, 95% CI=0.6, 0.9, p=0.01
Sanou, 2004 (17)	Burkina Faso	Qualitative Study	TB patients, community members and various healthcare workers, N=NR, mean age=NR	Provider behavior	Self-report	Accessing treatment	Behavior: Patients reported that the healthcare workers did not know enough about the illness and would treat them like they had the "plague"

ADJ=adjusted
DOT=direct observed therapy
HIV = human immunodeficiency virus
NR=not reported
NS=not significant
OR=odds ratio
TB=tuberculosis

Table 15: Data provided at the individual-level, from the ETR, and municipality-level, from either the Census or Department of Health

Variable	**Individual-level**	**Municipality-level**
Outcome of Interest		
Default	**X**	
Exposures of Interest		
DOTS provision	**X**	
Density of Health Facilities		**X**
Health Quality Score		**X**
Demographics		
Age	**X**	
Sex	**X**	
Race		**X**
Usual Place of Residence		**X**
Covariates		
Population		**X**
Sputum Collection	**X**	
Type of Facility	**X**	
Authority of Facility	**X**	
SES Composite Score		**X**

DOT=direct observed therapy
SES=socioeconomic status

Table 16. Descriptive Characteristics of patients diagnosed with TB and registered in the ETR and municipality characteristics from the census, in KwaZulu-Natal, 2010-2011 (n=28775).

	n (%)
DEMOGRAPHICS	
Age, in years, continuous mean (SD)	33.5 (13.9)
Age, in years (categorical) (n=28875)	-
0-4	1350 (4.7%)
5-14	951 (3.3%)
15-24	3629 (12.6%)
25-34	9876 (34.2%)
35-44	7637 (26.5%)
45-54	3535 (12.2%)
55-64	1365 (4.7%)
65-74	383 (1.3%)
75+	150 (0.5%)
Sex (n=28875)	-
Male	14747 (51.1%)
Female	14128 (48.9%)
CLINICAL CHARACTERISTICS	
New TB Case (n=28874)	-
No (re-treatment case)	5083 (17.6%)
Yes (new case)	23791 (82.4%)
Classification (n=28874)	-
Pulmonary	23326 (80.8%)
Extra-Pulmonary	5239 (18.1%)
Both	309 (1.1%)
Default (n=28875)	-
No	25614 (88.7%)

Yes	3261 (11.3%)
Smear Positive (n=22015)	-
No	11494 (52.2%)
Yes	10521 (47.8%)
Treatment Regimen (n=28871)	-
2HRZE 4HR - Category I	22012 (76.2%)
2HRZES 1HRZE 5HRE - Category II	4947 (17.1%)
2HRZ 4HR - Category III	1912 (6.6%)
DOT Provision (n=28875)	-
No DOT	13684 (47.4%)
Full DOT	6430 (22.3%)
Intensive DOT only	8413 (29.1%)
Continuation DOT only	348 (1.2%)
BASELINE RESULTS	
Microscopy Result (n=22015)	-
Negative	12562 (57.1%)
Positive	9453 (42.9%)
Culture Result (n=3786)	-
Negative	1087 (28.7%)
Positive	2699 (71.3%)
MONTH 2 or 3 RESULTS	
Smear Conversion (n=8645)	-
No	287 (3.3%)
Yes	8358 (96.7%)
COMORBIDITIES	
HIV Positive (n=23664)	-
No	5579 (23.6%)
Yes	18085 (76.4%)

If Yes (n=18174) - HIV Positive	-
On ART (n=12758)	-
No	7018 (55.0%)
Yes	5740 (45.0%)
On ART at Initiation of TB Treatment (n=18085)	-
No	16100 (89.0%)
Yes	1985 (11.0%)
HEALTH FACILITY	
Authority Type (n=28561)	-
Public	28248 (98.9%)
Private	38 (0.1%)
Other	275 (1.0%)
Facility Type (n=28286)	-
Community Health Center	4310 (15.2%)
Clinic	13962 (49.4%)
Hospital	9951 (35.2%)
Other	63 (0.2%)
TB Specialized Facility (n=28286)	-
No	27810 (98.3%)
Yes	476 (1.7%)
MDR TB Specialized Facility (n=28286)	-
No	28276 (99.96%)
Yes	10 (0.04%)
Summary of KwaZulu-Natal Municipalities (N=51)	**Median (IQR)**
Population (total number of persons)*	618,536 (12,898-3,442,361)
Gender	-
Male	46.8% (46.1-47.8)
Female	53.2% (52.2-53.9)
Employment Status	-

Employed	62.6% (53.2-70.4)
Unemployed	37.4% (29.6-46.8)
Racial Group	-
Black African	97.5% (92.0-99.3)
Non-Black	2.5% (0.8, 8.0)
Income	-
Below or Equal to the National Poverty Line	19.3% (17.5-21.1)
Above the National Poverty Line	80.7% (78.9-82.5)
Housing	-
Formal	96.5% (93.9-98.4)
Informal	3.5% (1.6-6.1)
Usual Place of Residence	-
KwaZulu-Natal	88.9% (79.3-92.3)
Not KwaZulu-Natal	11.1% (7.8-20.8)
Education	-
Less than 8 years/other education	42.2% (34.7-46.0)
More than 8 years	57.8% (54.0-65.3)
Cooking Source	-
Electricity	48.4% (36.2-64.2)
Non-Electric/No Cooking Source	51.5% (35.8-63.9)
Heating Source	-
Electricity	35.5% (25.3-48.4)
Non-Electric/No Heat Source	64.5% (51.6-74.7)
Lighting Source	-
Electricity	71.9% (54.7-80.7)
Non-Electric/No Light Source	28.1% (19.3-45.5)
Water Source	-
Piped	45.3% (38.7-69.1)
Not Piped	54.8% (30.9-61.3)

Type of Toilet	-
Flushing	19.5% (8.0-42.6)
Non-Flushing/No Toilet	80.6% (57.4-92.0)
Low SES Composite Score**	-0.3 (-4.4, 3.5)
Health Quality Score***	83 (79-87)

** Population is a median of total population size*

*** Health Quality Scores ranged from 1-5 (least favorable to most favorable) for each measure, yet total score ranged from 53-88, indicating the least favorable to most favorable circumstance*

**** A high score indicates lower level of SES. This score is comprised of education, employment, income, dwelling type, cook/heat/light/water source and toilet type and ranged from 11.5-9.7*

S=streptomycin, H=isoniazid, R=rifampicin, E=ethambutol, Z=pyrazinamide

Table 17. Bivariate Association of Risk Factors for Defaulting from TB Treatment, in KZN, 2010-2011 (n=28775).

	No Default (n=25614)	Default (n=3261)		
DEMOGRAPHICS	**n (%)**	**n (%)**	**RR (95% CI)**	**P-value***
Age, in years (categorical) (n=28875)	-	-	-	-
0-4	1211 (89.7%)	139 (10.3%)	ref	ref
5-14	873 (91.8%)	78 (8.2%)	0.8 (0.6, 1.0)	0.1
15-24	3150 (86.8%)	479 (13.2%)	1.3 (1.1, 1.5)	**0.01**
25-34	8640 (87.5%)	1236 (12.5%)	1.2 (1.0, 1.4)	**0.02**
35-44	6813 (89.2%)	823 (10.8%)	1.0 (0.9, 1.2)	0.6
45-54	3198 (90.5%)	337 (9.5%)	0.9 (0.8, 1.1)	0.4
55-64	1248 (91.4%)	117 (8.6%)	0.8 (0.7, 1.1)	0.1
65-74	342 (89.3%)	41 (10.7%)	1.0 (0.7, 1.4)	0.8
75+	139 (92.7%)	11 (7.3%)	0.7 (0.4, 1.3)	0.3
Sex (n=28875)	-	-	-	-
Male	12778 (86.7%)	1969 (13.4%)	ref	ref
Female	12836 (90.9%)	1292 (9.1%)	0.7 (0.6, 0.7)	**<0.0001**
CLINICAL CHARACTERISTICS				
New TB Case (n=28874)	-	-	-	-
No (re-treatment case)	4243 (83.5%)	840 (16.5%)	ref	ref
Yes (new case)	21370 (89.8%)	2421 (10.2%)	0.6 (0.6, 0.7)	**<0.0001**
Classification (n=28874)	-	-	-	-
Pulmonary	20732 (88.9%)	2594 (11.1%)	ref	ref
Extra-Pulmonary	4613 (88.1%)	626 (12.0%)	1.1 (1.0, 1.2)	0.08
Both	268 (86.7%)	41 (13.3%)	1.2 (0.9, 1.6)	0.2
Smear Positive (n=22015)	-	-	-	-
No	10212 (88.9%)	1282 (11.2%)	ref	ref
Yes	9354 (88.9%)	1167(11.1%)	1.0 (0.9, 1.1)	0.9
Treatment Regimen (n=28871)	-	-	-	-

2HRZE 4HR - Category I	19759 (89.8%)	2253 (10.2%)	ref	**ref**
2HRZES 1HRZE 5HRE - Category II	4126 (83.4%)	821 (16.1%)	1.6 (1.5, 1.7)	**<0.0001**
2HRZ 4HR - Category III	1726 (90.3%)	186 (9.7%)	1.0 (0.8, 1.1)	0.5
DOT Provision (n=28875)	-	-	-	-
No DOT	12291 (89.8%)	1393 (10.2%)	ref	ref
Full DOT	6182 (96.1%)	248 (3.9%)	0.4 (0.3, 0.4)	**<0.0001**
Intensive DOT only	6911 (82.2%)	1502 (17.9%)	1.8 (1.6, 1.9)	**<0.0001**
Continuation DOT only	230 (66.1%)	118 (33.9%)	3.3 (2.9, 3.9)	**<0.0001**
BASELINE RESULTS				
Microscopy Result (n=22015)	-	-	-	-
Negative	11150 (88.8%)	1412 (11.2%)	ref	ref
Positive	8416 (89.0%)	1037(11.0%)	1.0 (0.9, 1.1)	0.5
Culture Result (n=3786)	-	-	-	-
Negative	908 (83.5%)	179 (16.5%)	ref	ref
Positive	2226 (82.5%)	473 (17.5%)	1.1 (0.9, 1.2)	0.4
MONTH 2 or 3 RESULTS				
Smear Conversion (n=8645)	-	-	-	-
No	250 (87.1%)	37 (12.9%)	ref	ref
Yes	7824 (93.6%)	534 (6.4%)	0.5 (0.4, 0.7)	**<0.0001**
COMORBIDITIES				
HIV Positive (n=23664)	-	-	-	-
No	5064 (90.8%)	515 (9.2%)	ref	ref
Yes	16201 (89.6%)	1884 (10.4%)	1.1 (1.0, 1.2)	**0.01**
If Yes (n=18174) - HIV Positive	-	-	-	-
On ART (n=12758)	-	-	-	-
No	6271 (89.4%)	747 (10.6%)	ref	ref
Yes	5321 (92.7%)	419 (7.3%)	0.7 (0.6, 0.8)	**<0.0001**
On ART at Initiation of TB Treatment (n=18085)	-	-	-	

No	14437 (89.7%)	1663 (10.3%)	1.1 (0.9, 1.2)	0.3
Yes	1764 (88.9%)	221 (11.1%)	ref	ref
HEALTH FACILITY				
Catchment Population (Total numbers of persons)(mean(SD)***	15435.3 (10888.1)	19025.1 (12028.7)	-	-
Authority Type (n=28561)	-	-	-	-
Public	25025 (88.6%)	3223 (11.4%)	ref	ref
Private	37 (97.4%)	1 (2.6%)	0.2 (0.03, 1.6)	0.1
Other	253 (92.0%)	22 (8.0%)	0.7 (0.5, 1.0)	0.1
Facility Type (n=28286)	-	-	-	-
Community Health Center	3867 (89.7%)	443 (10.3%)	1.3 (1.1, 1.4)	**<0.0001**
Clinic	12816 (91.8%)	1146 (8.2%)	ref	ref
Hospital	8329 (83.7%)	1622 (16.3%)	2.0 (1.8, 2.1)	**<0.0001**
Other	57 (90.5%)	6 (9.5%)	1.2 (0.5, 2.5)	0.8
TB Specialized Facility (n=28286)	-	-	-	-
No	24635 (88.6%)	3175 (11.4%)	ref	ref
Yes	434 (91.2%)	42 (8.8%)	0.8 (0.6, 1.0)	0.1
MDR TB Specialized Facility (n=28286)	**-**	**-**	-	-
No	25059 (88.6%)	3217 (11.4%)	-	-
Yes	10 (100%)	0 (0%)	-	-

**P-value derived from chi-square testing*

CI=confidence interval

Ref=reference group

RR=risk ratio

S=streptomycin, H=isoniazid, R=rifampicin, E=ethambutol, Z=pyrazinamide

Table 18a. Evaluation of Individual-Level Factors Associated with Individual-Level Access to Care: Direct Observed Therapy, in KZN, 2010-2011 (n=28775).

	Limited Access to Care (No DOT) (n=13684)	**Access to Care (DOT)* (n=15191)**		
DEMOGRAPHICS	**n (%)**	**n (%)**	**RR (95% CI)**	**P-value****
Age, in years (categorical) (n=28875)	-	-	-	-
0-4	572 (42.4%)	778 (57.6%)	ref	ref
5-14	422 (44.4%)	529 (55.6%)	1.0 (0.9, 1.0)	0.3
15-24	1689 (46.5%)	1940 (53.5%)	0.9 (0.9, 1.0)	**0.01**
25-34	4537 (45.9%)	5339 (54.0%)	0.9 (0.9, 1.0)	**0.01**
35-44	3701 (48.5%)	3935 (51.5%)	0.9 (0.9, 0.9)	**<0.0001**
45-54	1785 (50.5%)	1750 (49.5%)	0.9 (0.8, 0.9)	**<0.0001**
55-64	694 (50.8%)	671 (49.2%)	0.9 (0.8, 0.9)	**<0.0001**
65-74	196 (51.2%)	187 (48.8%)	0.8 (0.8, 0.9)	**0.004**
75+	88 (58.7%)	62 (41.3%)	0.7 (0.6, 0.9)	**0.001**
Sex (n=28875)	-	-	-	-
Male	6946 (47.1%)	7801 (52.9%)	ref	ref
Female	6738 (47.7%)	7390 (52.3%)	1.0 (1.0, 1.0)	0.3
CLINICAL CHARACTERISTICS				
New TB Case (n=28874)	-	-	-	-
No (re-treatment case)	2076 (40.8%)	3007 (59.2%)	ref	ref
Yes (new case)	11608 (48.8%)	12183 (51.2%)	0.9 (0.8, 0.9)	**<0.0001**
Classification (n=28874)	-	-	-	-
Pulmonary	11278 (48.4%)	12048 (51.7%)	ref	ref
Extra-Pulmonary	2230 (42.6%)	3009 (57.4%)	1.1 (1.1, 1.1)	**<0.0001**
Both	176 (57.0%)	133 (43.0%)	0.8 (0.7, 0.9)	**0.01**
Smear Positive (n=22015)	-	-	-	-

No	5189 (45.2%)	6305 (54.9%)	ref	ref
Yes	5035 (47.9%)	5486 (52.1%)	0.95 (0.92, 0.97)	**<0.0001**
Treatment Regimen (n=28871)	-	-	-	-
2HRZE 4HR - Category I	10831 (49.2%)	11181 (50.8%)	ref	ref
2HRZES 1HRZE 5HRE - Category II	2045 (41.3%)	2902 (58.7%)	1.2 (1.1, 1.2)	**<0.0001**
2HRZ 4HR - Category III	807 (42.2%)	1105 (57.8%)	1.1 (1.1, 1.2)	**<0.0001**
BASELINE RESULTS				
Microscopy Result (n=22015)	-	-	-	-
Negative	5723 (45.6%)	6839 (54.4%)	ref	ref
Positive	4501 (47.6%)	4952 (52.4%)	1.0 (0.9, 1.0)	**0.003**
Culture Result (n=3786)	-	-	-	-
Negative	250 (23.0%)	837 (77.0%)	ref	ref
Positive	427 (15.8%)	2272 (84.2%)	1.1 (1.1, 1.1)	**<0.001**
MONTH 2 or 3 RESULTS				
Smear Conversion (n=8645)	-	-	-	-
No	183 (63.8%)	104 (36.2%)	ref	ref
Yes	3893 (46.6%)	4465 (53.4%)	1.5 (1.3, 1.7)	**<0.0001**
COMORBIDITIES				
HIV Positive (n=23664)	-	-	-	-
No	2583 (46.3%)	2996 (53.7%)	ref	ref
Yes	8881 (49.1%)	9204 (50.9%)	0.9 (0.9, 1.0)	**0.0002**
If Yes (n=18174) - HIV Positive	-	-	-	-
On ART (n=12758)	-	-	-	-
No	3653 (52.1%)	3365(48.0%)	ref	ref
Yes	2505 (43.6%)	3235 (56.4%)	1.2 (1.1, 1.2)	**<0.0001**
On ART at Initiation of TB Treatment (n=18085)	-	-	-	-
No	7972 (49.5%)	8128 (50.5%)	ref	ref
Yes	909 (45.8%)	1076 (54.2%)	1.1 (1.0, 1.1)	**0.001**

HEALTH FACILITY				
Authority Type (n=28561)	-	-	-	-
Public	13413 (47.5%)	14835 (52.5%)	ref	ref
Private	25 (65.8%)	13 (34.2%)	0.7 (0.4, 1.0)	0.06
Other	23 (8.4%)	252 (91.6%)	1.7 (1.7, 1.8)	**<0.0001**
Facility Type (n=28286)	-	-	-	-
Community Health Center	2470 (57.3%)	1840 (42.7%)	ref	ref
Clinic	7923 (56.8%)	6039 (43.3%)	1.0 (1.0, 1.1)	0.5
Hospital	2985 (30.0%)	6966 (70.0%)	1.6 (1.6, 1.7)	**<0.0001**
Other	40 (63.5%)	23 (36.5%)	0.9 (0.6, 1.2)	0.3
TB Specialized Facility (n=28286)	-	-	-	-
No	13281 (47.8%)	14529 (52.2%)	ref	ref
Yes	137 (28.8	339 (71.2%)	1.4 (1.3, 1.4)	**<0.0001**
MDR TB Specialized Facility (n=28286)	-	-	-	-
No	13049 (47.4%)	14867 (52.6%)	ref	ref
Yes	9 (90.0%)	1 (10.0%)	0.2 (0.03, 1.2)	0.08

**DOT was condensed to be a patient that had DOT at any given point during treatment*
***P-value is from chi-square testing*
CI=confidence interval
Ref=reference group
RR=risk ratio
S=streptomycin, H=isoniazid, R=rifampicin, E=ethambutol, Z=pyrazinamide

Table 18b. Evaluation of Individual-Level Factors Associated with Population-Level of Access to Care: Density of Health Facilities in KZN, 2010-2011 (n=28775).

	Limited or No Access to Care (≤Median Density)* (n=13611)	**Access to Care (>Median Density)** (n=15264)		
DEMOGRAPHICS	**n (%)**	**n (%)**	**RR (95% CI)**	**P-value****
Age, in years (categorical) (n=28875)				
0-4	697 (51.6%)	653 (48.4%)	ref	ref
5-14	391 (41.1%)	560 (58.9%)	1.2 (0.9, 1.6)	0.1
15-24	1725 (47.5%)	1904 (52.5%)	1.1 (0.9, 1.3)	0.4
25-34	4833 (48.9%)	5043 (51.1%)	1.1 (0.9, 1.3)	0.6
35-44	3611 (47.3%)	4025 (52.7%)	1.1 (0.9, 1.4)	0.5
45-54	1602 (45.3%)	1933 (54.7%)	1.1 (0.9, 1.5)	0.4
55-64	560 (41.0%)	805 (59.0%)	1.2 (0.9, 1.7)	0.3
65-74	143 (37.3%)	240 (62.7%)	1.3 (0.8, 2.1)	0.3
75+	49 (32.7%)	101 (67.3%)	1.4 (0.8, 2.4)	0.2
Sex (n=28875)				
Male	7170 (48.6%)	7577 (51.4%)	ref	ref
Female	6441 (45.6%)	7687 (54.4%)	1.1 (1.0, 1.2)	0.2
CLINICAL CHARACTERISTICS				
New TB Case (n=28874)				
No (re-treatment case)	3140 (61.8%)	1943 (38.2%)	ref	ref
Yes (new case)	10470 (44.0%)	13321 (56.0%)	1.5 (1.0, 2.2)	0.1
Classification (n=28874)				
Pulmonary	10831 (46.4%)	12495 (53.6%)	ref	ref

Extra-Pulmonary	2588 (49.4%)	2651 (50.6%)	0.9 (0.8, 1.1)	0.3
Both	191 (61.8%)	118 (38.2%)	0.7 (0.5, 1.1)	0.1
Smear Positive (n=22015)				
No	4698 (40.9%)	6796 (59.1%)	ref	ref
Yes	5572 (53.0%)	4949 (47.0%)	0.8 (0.6, 1.0)	0.1
Treatment Regimen (n=28871)				
2HRZE 4HR - Category I	9610 (43.7%)	12402 (56.3%)	ref	ref
2HRZES 1HRZE 5HRE - Category II	3052 (61.7%)	1895 (38.3%)	0.7 (0.5, 1.0)	0.1
2HRZ 4HR - Category III	946 (49.5%)	966 (50.5%)	0.9 (0.7, 1.1)	0.4
DOT Provision (n=28875)				
No DOT	5345 (39.1%)	8339 (60.9%)	ref	ref
Full DOT	4613 (71.7%)	1817 (28.3%)	0.5 (0.4, 0.5)	**<0.0001**
Intensive DOT only	3350 (39.8%)	5063 (60.2%)	1.0 (1.0, 1.0)	0.3
Continuation DOT only	303 (87.1%)	45 (12.9%)	0.2 (0.2, 0.3)	**<0.0001**
BASELINE RESULTS				
Microscopy Result (n=22015)				
Negative	5374 (42.8%)	7188 (57.2%)	ref	ref
Positive	4896 (51.8%)	4557 (48.2%)	0.8 (0.7, 1.0)	0.1
Culture Result (n=3786)				
Negative	831 (76.5%)	256 (23.6%)	ref	ref
Positive	2369 (87.8%)	330 (12.2%)	0.5 (0.4, 0.8)	**0.001**
MONTH 2 or 3 RESULTS				
Smear Conversion (n=8645)				
No	121 (42.2%)	166 (57.8%)	ref	ref
Yes	4347 (52.0%)	4011 (48.0%)	0.8 (0.6, 1.1)	0.2
COMORBIDITIES				

HIV Positive (n=23664)				
No	2447 (43.9%)	3132 (56.1%)	ref	ref
Yes	8129 (45.0%)	9956 (55.1%)	1.0 (0.9, 1.1)	0.6
If Yes (n=18174) - HIV Positive				
On ART (n=12758)				
No	3065 (43.7%)	3953 (56.3%)	ref	ref
Yes	2442 (42.5%)	3298 (57.5%)	1.0 (0.9, 1.2)	0.8
On ART at Initiation of TB Treatment (n=18085)				
No	6947 (43.2%)	9153 (56.9%)	ref	ref
Yes	1182 (59.6%)	803 (40.5%)	0.7 (0.4, 1.1)	0.2
HEALTH FACILITY				
Authority Type (n=28561)				
Public	13554 (48.0%)	14694 (52.0%)	ref	ref
Private	19 (50.0%)	19 (50.0%)	1.0 (0.4, 2.1)	0.9
Other	35 (12.7%)	240 (87.3%)	1.7 (0.8, 3.6)	0.2
Facility Type (n=28286)				
Community Health Center	545 (12.7%)	3765 (87.4%)	ref	ref
Clinic	5319 (38.1%)	8643 (61.9%)	-	-
Hospital	7716 (77.5%)	2235 (22.5%)	-	-
Other	0 (0.0%)	63 (100.0%)	-	-
TB Specialized Facility (n=28286)				
No	13457 (48.4%)	14353 (51.6%)	ref	ref
Yes	123 (25.8%)	353 (74.2%)	1.4 (0.7, 2.8)	0.3
MDR TB Specialized Facility (n=28286)				
No	13578 (48.0%)	14698 (52.05)	ref	ref
Yes	2 (20.0%)	8 (80.0%)	1.5 (0.9, 2.6)	0.1

**Median value was 12.9 facilities per 100,000 persons*
***P-value is from chi-square testing*
CI=confidence interval
Ref=reference group
RR=risk ratio
S=streptomycin, H=isoniazid, R=rifampicin, E=ethambutol, Z=pyrazinamide

Table 18c. Evaluation of Individual-Level Factors Associated with Population-Level of Access to Care: Health Quality Score in KZN, 2010-2011 (n=28875).

	Limited or No Access to Care (≤Median Score) (n=15370)	**Access to Care (>Median Score)*** (n=13505)		
DEMOGRAPHICS	**n (%)**	**n (%)**	**RR (95% CI)**	**P-value****
Age, in years (categorical) (n=28875)				
0-4	644 (47.7%)	706 (52.3%)	ref	ref
5-14	555 (58.4%)	396 (41.6%)	0.8 (0.7, 1.0)	**0.02**
15-24	1930 (53.2%)	1699 (46.8%)	0.9 (0.8, 1.0)	0.1
25-34	5074 (51.4%)	4802 (48.6%)	0.9 (0.8, 1.1)	0.4
35-44	4054 (53.1%)	3582 (46.9%)	0.9 (0.8, 1.1)	0.2
45-54	1948 (55.1%)	1587 (44.9%)	0.9 (0.7, 1.0)	0.1
55-64	812 (59.5%)	553 (40.5%)	0.8 (0.6, 0.9)	**0.02**
65-74	248 (64.8%)	135 (35.3%)	0.7 (0.5, 0.9)	**0.01**
75+	105 (70.0%)	45 (30.0%)	0.6 (0.4, 0.8)	**0.01**
Sex (n=28875)				
Male	7712 (52.3%)	7035 (47.7%)	ref	ref
Female	7658 (54.2%)	6470 (45.8%)	1.0 (0.9, 1.0)	0.1
CLINICAL CHARACTERISTICS				
New TB Case (n=28874)				
No (re-treatment case)	1968 (38.7%)	3115 (61.3%)	ref	ref
Yes (new case)	13402 (56.3%)	10389 (43.7%)	0.7 (0.5, 1.0)	**0.05**
Classification (n=28874)				
Pulmonary	12426 (53.3%)	10900 (46.7%)	ref	ref

Extra-Pulmonary	2822 (53.9%)	2417 (46.1%)	1.0 (0.9, 1.1)	0.8
Both	122 (39.5%)	187 (60.5%)	1.3 (0.9, 1.9)	0.2
Smear Positive (n=22015)				
No	6651 (57.9%)	4843 (42.1%)	ref	ref
Yes	4886 (46.4%)	5635 (53.6%)	1.3 (1.0, 1.6)	**0.02**
Treatment Regimen (n=28871)				
2HRZE 4HR - Category I	12498 (56.8%)	9514 (43.2%)	ref	ref
2HRZES 1HRZE 5HRE - Category II	1917 (38.8%)	3030 (61.3%)	1.4 (1.0, 2.0)	**0.05**
2HRZ 4HR - Category III	954 (49.9%)	958 (50.1%)	1.2 (1.0, 1.4)	0.1
DOT Provision (n=28875)				
No DOT	8896 (65.0%)	4788 (35.0%)	ref	ref
Full DOT	1734 (27.0%)	4696 (73.0%)	2.1 (2.0, 2.1)	**<0.0001**
Intensive DOT only	4696 (55.8%)	3717 (44.2%)	1.3 (1.2, 1.3)	**<0.0001**
Continuation DOT only	44 (12.6%)	304 (87.4%)	2.5 (2.4, 2.6)	**<0.0001**
BASELINE RESULTS				
Microscopy Result (n=22015)				
Negative	7058 (56.2%)	5504 (43.8%)	ref	ref
Positive	4479 (47.4%)	4974 (52.6%)	1.2 (1.0, 1.4)	**0.04**
Culture Result (n=3786)				
Negative	264 (24.3%)	823 (75.7%)	ref	ref
Positive	350 (13.0%)	2349 (87.0%)	1.1 (0.9, 1.5)	0.3
MONTH 2 or 3 RESULTS				
Smear Conversion (n=8645)				
No	178 (62.0%)	109 (38.0%)	ref	ref
Yes	3927 (47.0%)	4431 (53.0%)	1.4 (1.0, 2.0)	0.1
COMORBIDITIES				

HIV Positive (n=23664)				
No	3044 (54.6%)	2535 (45.4%)	ref	ref
Yes	10389 (57.5%)	7696 (42.6%)	0.9 (0.8, 1.1)	0.3
If Yes (n=18174) - HIV Positive				
On ART (n=12758)				
No	4273 (60.9%)	2745 (39.1%)	ref	ref
Yes	3411 (59.4%)	2329 (40.6%)	1.0 (0.8, 1.3)	0.7
On ART at Initiation of TB Treatment (n=18085)				
No	9555 (59.4%)	6545 (40.7%)	ref	ref
Yes	834 (42.0%)	1151 (58.0%)	1.4 (0.8, 2.5)	0.2
HEALTH FACILITY				
Authority Type (n=28561)				
Public	14798 (52.4%)	13450 (47.6%)	ref	ref
Private	19 (50.0%)	19 (50.0%)	1,1 (0.5, 2.2)	0.9
Other	240 (87.4)	35 (12.7%)	0.3 (0.04, 1.8)	0.2
Facility Type (n=28286)				
Community Health Center	3049 (70.7%)	1261 (29.3%)	ref	ref
Clinic	9265 (66.4%)	4697 (33.6%)	1.1 (0.3, 4.0)	0.8
Hospital	2434 (24.5%)	7517 (75.5%)	2.6 (0.7, 9.8)	0.2
Other	62 (98.4%)	1 (1.6%)	0.1 (0.01, 0.5)	**0.01**
TB Specialized Facility (n=28286)				
No	14457 (52.0%)	13353 (48.0%)	ref	ref
Yes	353 (74.2%)	123 (25.8%)	0.5 (0.1, 2.3)	0.4
MDR TB Specialized Facility (n=28286)				
No	14802 (52.4%)	13474 (47.7%)	ref	ref
Yes	8 (80.0%)	2 (20.0%)	0.4 (0.1, 1.7)	0.2

**Median score was 80.9*
***P-value is from chi-square testing*
CI=confidence interval
Ref=reference group
RR=*risk ratio*
S=streptomycin, H=isoniazid, R=rifampicin, E=ethambutol, Z=pyrazinamide

Table 19. Final Adjusted Model of an Evaluation of Access to Care's Relationship with ETR Patients Defaulting from TB Treatment in KwaZulu-Natal in 2010-2011 (n=28,875)

	RR_{adj}* (95% CI)	P-value**
DOT***	-	-
Full DOT	0.3 (0.2, 0.3)	**<0.0001**
Intensive DOT	1.8 (1.1, 2.8)	**0.02**
Continuation DOT	2.1 (1.6, 2.8)	**<0.0001**
High Density****	0.4 (0.3, 0.5)	**<0.0001**

** Adjusted for age, sex, new vs. re-treatment, and municipality-level SES*
***P-value is from chi-square testing*
**** Reference group is no DOT provisioning*
***** Reference group is at or less than the median (12.9)*
CI=confidence interval
RR=risk ratio