Age appropriate treatment of drug-resistant tuberculosis in South Africa

by

Brittney Jayne Sullivan

Department of Nursing
Duke University

Date: _____

Approved:

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Janice Humphreys, Co-chair

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Janet Prvu Bettger, Co-chair

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Susan Silva

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Coleen Cunningham

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Jason Farley

Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor
of Philosophy, in the Department of
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ABSTRACT

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Abstract

Drug-resistant tuberculosis (DR-TB) is a threat to TB control globally. South Africa has the third highest epidemic of DR-TB – following only Russia and China, two much more populous countries. South Africa has stringent guidelines for treating DR-TB; however, little is known about adherence to these guidelines. Additionally, little is known about age appropriate treatment, particularly in youth (13-24 years) who may have differing needs than adults with DR-TB. South Africa also has the world's largest HIV epidemic – nearly 18% of the population is infected with HIV. Individuals with HIV are 26 to 31 times more likely to become infected with TB than individuals without HIV. Among individuals in South Africa with TB, there is a 57-68% HIV coinfection rate.

This dissertation includes a systematic literature review (Chapter 2) exploring barriers to TB treatment initiation in sub-Saharan Africa with an emphasis on children and youth. Additionally, time to treatment was assessed per South African guidelines (i.e. initiating treatment within five days of diagnosis) and total days from DR-TB diagnosis to DR-TB treatment initiation. This analysis included multi-level modeling with fixed patient- (sex, history of TB, HIV coinfection) and system-characteristics (urban-rural location, province) and random effects of treatment site. Guidelines were further evaluated, by assessing through descriptive statistics and logistic regression, receipt of guideline recommended care in terms of correct medications prescribed,

correct dosage prescribed, and correct frequency prescribed at treatment initiation (correct regimen).

Barriers exist for all individuals with TB to initiate treatment regardless of age. These barriers are at the patient- and system-level and include: costs, health seeking behaviors, and infrastructure. More research is needed to identify barriers specifically among children and youth, as only four articles reviewed focused on these vulnerable populations. The time to DR-TB treatment is delayed for 84% of South Africans, and age did not predict delays. Seventeen percent of individuals coinfected with HIV receive care per guidelines compared to 12% of those without coinfection. Additionally, receipt of correct medications was prescribed to 88% of patients; yet, only 33% received correct medications and doses, and still, only 30% received the full correct regimen. Age was not a significant predictor for receipt of correct guideline based treatment. In conclusion, more research must be focused on younger individuals with TB, particularly DR-TB. More research investigating guideline recommended care is essential to improve patient outcomes, prevent the transmission of DR-TB in communities, and to prevent further drug resistance.

Dedication

"A good head and a good heart are always a formidable combination. But when you add to that a literate tongue or pen, then you have something very special."

- Nelson Mandela

This is dedicated to the healthcare providers, researchers, and policy makers working tirelessly to improve the lives of patients with infectious diseases, particularly drug-resistant tuberculosis and HIV. With special thanks and dedication to the participants and the millions of children infected with TB around the globe, especially Ayaba.

Contents

List of Tables

List of Figures

Acknowledgements

First I would like to acknowledge my committee for their continued dedication to my academic and personal success. This dissertation, from the nascent ideas generated from the beginning to this final product, and the life this study has taken on would not have come to fruition without their thoughtfulness, guidance, and wisdom. I would also like to acknowledge all the professors who taught me these past three years. My knowledge base of content as well as research designs and methods has grown substantially and I look forward to the continuation of education throughout my career. To my cohort and classmates – thank you for the numerous edits you have each provided, the stimulating conversations, and the friendship – I do not know what I would do without you. Finally, to my family and friends near and far – thank you for putting up with me during this journey, seeing me at my worst, and possibly also at my best. This labor of love is only just the beginning!

1. Introduction

Mycobacterium tuberculosis (TB) recently surpassed HIV as the leading infectious disease killer in the world (WHO, 2016c). As of 2016, there are 30 high burden countries (HBCs) accounting for 85-89% of TB cases globally (WHO, 2016c). TB claimed the lives of 1.8 million people in 2015, with the highest TB incidence and mortality rate in the African region (WHO, 2016c). Although TB has been treatable since 1943 (with streptomycin antibiotic), it has been difficult to leverage political commitment, healthcare provider knowledge, and public awareness across the globe due to its burden on mostly disenfranchised populations (Buse, Dickinson, Gilson, & Murray, 2009; P. E. Farmer, Nizeye, Stulac, & Keshavjee, 2006). Children and youth infected with TB are especially underrepresented in current TB research (Becerra & Swaminathan, 2014; Jenkins et al., 2014; Sentinel Project on Pediatric Drug-Resistant Tuberculosis, 2013).

Since the inception of the HIV epidemic, researchers and healthcare providers have recognized the dual epidemics of TB and HIV, and substantial funding has been allocated towards eliminating TB in conjuncture with HIV (Global Fund, 2016; WHO, 2015a). The Global Fund has invested nearly $4 billion per year to support partnerships and programs related to HIV, TB, and malaria since 2002. However, there is still a $2 billion annual funding gap for TB control and progress is fragile. This fragility stems from TB being an airborne disease - one infected individual can transmit the disease to 10-15 others within one year if not diagnosed and treated (World Health Organization,

2014b). Adequate diagnosis and treatment has proven incredibly difficult to deliver especially in low- and middle-income countries (LMICs) for economic, infrastructure, educational, and a multitude of other patient and health system barriers (Barter, Agboola, Murray, & Barnighausen, 2012; Langendam, van der Werf, Huitric, & Manissero, 2012; Loveday, Thomson, Chopra, & Ndlela, 2008; World Health Organization, 2009a). There has been a 22% global decline in TB mortality since 2000 and 49 million lives have been saved around the globe between 2000 and 2015 through effective diagnosis and treatment of TB (WHO, 2016c). However, in addition to the funding gap, drug-resistant TB (DR-TB) threatens progress made to date in eliminating TB (WHO, 2016c).

DR-TB, TB that is resistant to first-line medications (including Rifampin Resistant (RR), Multi-Drug Resistant (MDR), pre-extremely drug resistant (pre-XDR), and XDR), spreads due to both individual non-adherence to first-line medications as well as poor provider knowledge leading to inadequate delivery of guideline recommended treatment (Langendam et al., 2012; van der Werf, Langendam, Huitric, & Manissero, 2012). Poor adherence to medication at the patient-level and poor adherence to guidelines at the provider-level causes DR-TB to spread in communities and within hospitals where patients are being treated (Gandhi et al., 2014; Gandhi et al., 2006). HIV also fuels the TB epidemic and complicates treatment as pill burden increases, side effects and toxicities worsen, and concurrent treatment of both diseases can lead to

immune reconstitution syndrome and a heightened immune response potentially worsening disease outcomes (Abay et al., 2015; Swaminathan, Padmapriyadarsini, & Narendran, 2010; Weyer, Brand, Lancaster, Levin, & van der Walt, 2007). Lack of treatment initiation and inadequate treatment of DR-TB or dual therapy of DR-TB and anti-retroviral therapy (ART) for HIV can lead to poor health outcomes for individuals who already have many socially determined barriers to optimal health and spread this more fatal strain in the community (Naidoo et al., 2013; World Health Organization, 2015).

Therefore, the purpose of this dissertation is multifold. It will describe the scope of literature pertaining to treatment initiation in sub-Saharan Africa for children and youth diagnosed with TB. It will examine the treatment provided to people in South Africa with DR-TB with and without HIV, and evaluate the extent to which selected individual- and system-level variables influence the initiation and delivery of guideline-based treatment. This dissertation will use secondary analysis of clinical trial data to examine aspects of how patients and providers must partner together after diagnosis to continue productive interactions to achieve DR-TB treatment initiation as recommended per South African guidelines.

1.1 Health disparities in low and middle income countries

TB is a disease of inequity. It disproportionately affects people in LMICs compared to those in high-income countries (WHO, 2016c). Even within national

borders, TB often affects marginalized populations such as the homeless, the uninsured, and individuals lacking access to quality health services (P. Farmer, 1999; Laokri, Dramaix-Wilmet, Kassa, Anagonou, & Dujardin, 2014; Swaminathan et al., 2010). TB affects the poor and vulnerable for two main reasons. First, TB more easily infects people who are immunocompromised and second, the airborne transmission of TB allows it to spread and thrive in urban slums and overcrowded homes (Kaufmann, 2011).

Individuals who suffer from chronic illnesses are also at increased risk of TB infection (Havlir, Getahun, Sanne, & Nunn, 2008). Individuals with HIV, malnutrition, or vitamin deficiencies - diseases that are under diagnosed and often left untreated in people who lack access to health services – are at higher risk for TB (WHO, 2016c). For example, individuals infected with HIV are 26 to 31 times more susceptible to TB than their non-HIV infected peers (World Health Organization, 2012). Co-morbidity with cardiovascular disease, diabetes, or cancer also increases an individuals' likelihood of being infected with TB due to a weakened immune system. A person with an untreated or mismanaged comorbidity or another infectious disease is unable to mount as an effective immune response to the TB mycobacterium (Havlir et al., 2008; Jeon & Murray, 2008). Thus, individuals with an additional disease burden and poor access to healthcare are at increased risk for TB infection.

TB is spread through airborne droplets of bacilli; therefore, it must be viewed within the social context of overcrowding in intimate living quarters when aiming to

stop the spread of disease in disadvantaged populations. If preventative measures such as improving living conditions and improving nutrition, were taken, reduced levels of TB transmission would occur (Lin, Sattar, & Puckree, 2004). Individuals, such as miners, commercial sex workers, and truck drivers often stay in overcrowded 'hostel' style living arrangements. Crowded living quarters with many individuals in one room with poor ventilation, lack of natural sunlight, and transient patterns encourage bacterial growth and the spread of TB (Dharmadhikari, Smith, Nardell, Churchyard, & Keshavjee, 2013; Gesesew et al., 2016). The migration and transient nature of many workers in LMICs also compounds transmission. For example, many miners contract TB at the worksite and return home to their families and spread the disease when on leave before returning to work (Barwise, Lind, Bennett, & Martins, 2013). Not only are individual immune system functioning and community transmission mechanisms responsible for the spread of TB, but also the social and political context and strength of health care systems also greatly influence health outcomes for those infected with TB.

Unfortunately, financial constraints often create barriers to timely TB diagnosis and treatment. Even though many countries, including LMICs, provide TB services for free, direct (out-of-pocket) and indirect (lost wages) expenditures often place individuals and families in a 'medical poverty trap' due to catastrophic medical expenses (Barter et al., 2012; Laokri et al., 2014; Whitehead, Dahlgren, & Evans, 2001). Catastrophic health expenses are incurred when more than 10% of a family's annual income is spent on

illness-related costs (transport to the hospital, diagnosis and testing costs, additional food, or supplemental medications) (Wagstaff & van Doorslaer, 2003; Xu, 2005; Zhou et al., 2016). When these catastrophes occur, families often resort to selling household assets (i.e. cattle or land), borrowing money, or decreasing household expenses (i.e. housing, education) to cover health expenses (Laokri et al., 2014). In countries where many government facilities are too far to travel to, many people seek care from traditional healers, private pharmacies, and other unregulated healthcare providers (Chimbindi et al., 2015; Storla, Yimer, & Bjune, 2008). Although private healthcare is often thought of as superior in high income countries, there is scant evidence that private facilities provide better services in LMICs, especially for diseases such as TB (Bhattacharyya et al., 2010). Finally, individuals in countries with fragmented healthcare systems with minimal diagnostic and laboratory capacity, poor patient and supply chain management, health workforce training, etc), and with populations in isolated rural villages, or those who lack means of reliable transportation, often lack access to quality health services (P. Farmer, 1999).

Simply put, no rich countries have high TB infection rates and no poor countries have low TB infection rates (Cloney, 2016). Social determinants of health are the "conditions in which people are born, grow, live, work and age" (World Health Organization, 2015). Measuring social determinants of health can be difficult but often help situate how and why a disease is able to affect one group of individuals more than

another. Thus, aspects of social determinants of health, such as poverty, race, age, and gender, have led to TB being frequently referred to as the definitive 'disease of poverty' (Enarson, 2002).

1.2 TB, DR-TB, and HIV pathophysiology

1.2.1 Pulmonary tuberculosis

TB is transmitted via droplets in the air (Centers for Disease Control and Prevention, 2012; Pozniak, 2016). The bacteria enter the respiratory tract and enter the alveoli and lyse macrophages (Figure 1) (Centers for Disease Control and Prevention, 2012). Once an individual has been exposed to TB, the bacteria can be latent (also known as inactive TB). During this period, the infected person is often asymptomatic and cannot transmit TB to others. However; people infected with latent TB have a 10% lifetime risk of having activated TB (or TB disease) (WHO, 2015a). Once TB is activated (when macrophages are ineffective at containing TB bacilli in granulomas), the bacilli spreads to other lung tissue (and possibly other organs) and individuals become symptomatic, often with cough, fever, night sweats, and weight loss (Centers for Disease Control and Prevention, 2012). However; symptoms may be mild for months before a person seeks treatment, and the person can spread TB to ten to fifteen close contacts within one year if not treated (WHO, 2015a). Cavities, or open pockets in lung parenchyma, become spaces where bacteria can replicate and cause major infection, disease, necrosis to lung tissue and this leads to increased infectiousness (Knechel, 2009).

Individuals with poorly functioning immune systems, such as with HIV, have much higher lifetime risks than healthy individuals of having TB activated because their immune system and their immune response (ability to produce and have functioning macrophages and T-cells) is diminished to prevent bacteria replication (Knechel, 2009).

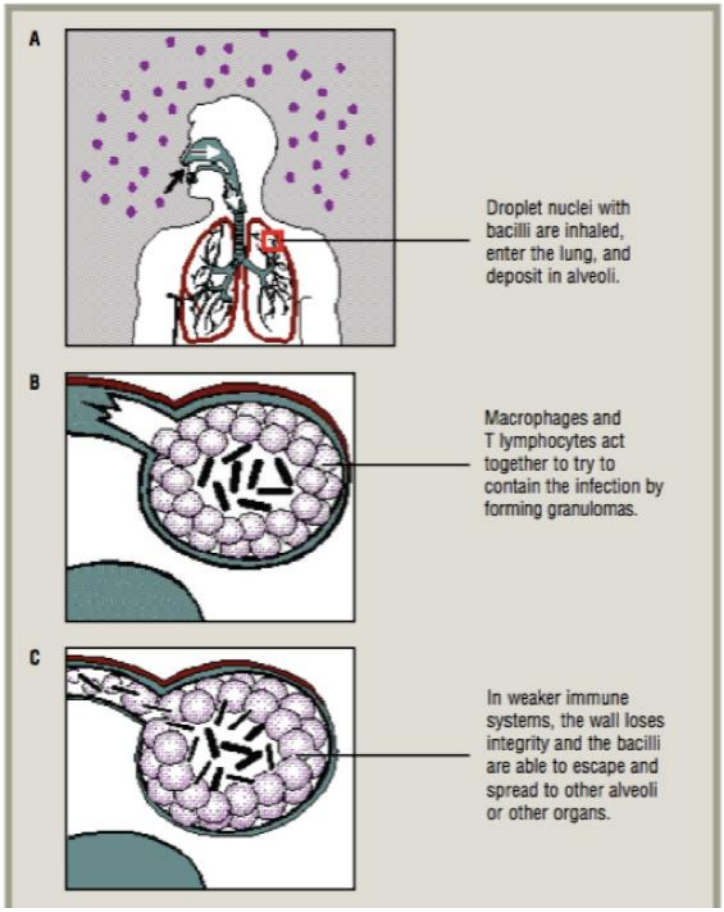

Figure 1: Pathophysiology of tuberculosis. Copyright: Centers for Disease Control and Prevention

1.2.2 Drug-resistant tuberculosis

Although TB is treatable and most TB deaths are preventable, some individuals are infected with resistant organisms. Drug-resistant TB (DR-TB) is especially increasing in the African region (WHO, 2015a; World Health Organization, 2010a). Historically, DR-TB developed only after an individual was treated for drug-susceptible TB and had poor adherence, allowing for drug resistance to develop causing that individual to advance to DR-TB. However, patients with an active DR-TB strain can transmit DR-TB to others, spreading this more difficult and dangerous strain to individuals with no prior history of TB disease (World Health Organization, 2010b). DR- TB is a major concern in South Africa as drug resistance threatens progress made in TB care (Centers for Disease Control and Prevention, 2015).

The development of the Global Fund to Fight AIDS, Tuberculosis, and Malaria in 2002 and the subsequent 2006 extensively drug-resistant TB (XDR-TB) outbreak in South Africa allowed DR-TB to rise on the global policy agenda (Global Fund, 2016; Hafner & Shiffman, 2013; Singh, Upshur, & Padayatchi, 2007; World Health Organization, 2009a). Thus, finding solutions for DR-TB have come to the forefront for research and policy agendas (Ginsberg, 2010; TB Alliance, 2016; Whitehouse, 2015). New medications (such as bedaqueline and delaminid) and repurposed medications (such as linezolid and clofazamine) have recently been developed and more are in the pipeline to improve DR-TB prognosis (Ginsberg, 2010; Meintjes, 2014). Corporations such as Johnson and

Johnson are opening offices in Africa to strengthen their drug research and pharmaceutical activities as well as grow supply chain and other systems necessary to improve long-term treatment capacity (Ginsberg, 2010; Meintjes, 2014; Rockoff & McKay, 2016; TB Alliance, 2016).

Globally, DR-TB continues to emerge and spread due to mismanagement of drug-susceptible TB treatment and person-to-person transmission of drug-resistant strains (Ahmad & Mokaddas, 2014; Mukherjee, Sarkar, Saha, Biswas, & Bhattacharyya, 2009; World Health Organization, 2009a, 2014a, 2014b). Mortality is nearly 44% for patients with DR-TB compared to the 12% mortality among drug-susceptible TB patients (World Health Organization, 2009a, 2014b). DR-TB is also more difficult and more expensive to treat than drug-susceptible TB. The cost of medications needed to treat DR-TB alone is 50 to 200 times higher than DS-TB (World Health Organization, 2014b). Further, although DR-TB cases account for only 8% (18,734 diagnosed and 11,538 treated in 2014 of the entire TB burden in South Africa), the budget allocation for DR-TB is almost 50% of the national TB budget (Pooran, Pieterson, Davids, Theron, & Dheda, 2013). Costs and risk of poor outcomes are even higher for the 70% of DR-TB patients coinfected with HIV (South Africa Department of Health, 2011; World Health Organization, 2012). Thus, DR-TB is a significant public health concern at the individual- and system-level.

1.2.3 DR-TB and HIV co-epidemics

Globally, 12% of all TB cases were among individuals infected with HIV, accounting for an estimated 1.2 million cases, with almost three-quarters of these cases in the Africa region (WHO, 2015). In South Africa, over 18,700 cases of DR-TB were diagnosed in 2014 (WHO, 2015a). Although prevalence has not been reported for DR-TB/HIV co-infection in South Africa, individual studies have found DR-TB/HIV co-infection rates to be 70-77%, much higher than the prevalence of TB/HIV co-infection of 61% (Cox et al., 2014; J. E. Farley et al., 2014; O'Donnell et al., 2013; WHO, 2015a). A lack of population level data yet growing awareness and concern of the convergence of the DR-TB/HIV epidemic indicates more research and attention must be given to this critical area in the future. Outcomes for DR-TB/HIV patients have been worse than individuals who are not co-infected; yet few data exist on the exact mechanisms of poorer outcomes for DR-TB/HIV co-infected individuals. Outcomes may be related to (1) biological (2) poor integration of health services or (3) access to care and appropriate management of dual DR-TB/HIV treatment (Cox et al., 2014; J. E. Farley et al., 2011).

In addition to proper DR-TB treatment, appropriate ART initiation is also critical for individuals coinfected with HIV (Abay et al., 2015). Identifying factors associated with delayed initiation or inappropriate treatment for DR-TB with or without ART is needed to guide development of strategies to improve care and ultimately, improve patient outcomes. In summary, the complexities of DR-TB care in South Africa are

compounded by HIV treatment, medication interactions, national focus and funding. The dual epidemics have created an area for the intersection of HIV where DR-TB testing and treatment could be better integrated (Fairlie, Beylis, Reubenson, Moore, & Madhi, 2011; Rose, Hallbauer, Seddon, Hesseling, & Schaaf, 2012; Weyer et al., 2007). Whether HIV status is associated with DR-TB treatment initiation or adherence to medication, there is a strong overlap of patients co-infected with HIV and DR-TB; therefore, integrating care for both diseases is essential.

1.3 Why Study South Africa?

Sub-Saharan Africa accounts for 78% of the global burden of TB/HIV coinfection. In South Africa specifically, 61% of TB patients are co-infected with HIV and 8% of all TB cases are documented to have drug-resistance (WHO, 2015a). As previously mentioned, South Africa is one of the 27 high burden DR-TB countries around the world (WHO, 2015a). Within South Africa, Kwa-Zulu Natal and the Eastern Cape provinces have the highest total numbers of diagnosed DR-TB in the country accounting for 28% (2032 individuals) and 24% (1782 individuals) of all cases respectively (South Africa Department of Health, 2011).

The level at which TB care, especially DR-TB care is managed is debated at international, national, and local policy levels and must be examined closely within certain contexts. Decentralization can benefit rural areas, and yet it may not be appropriate in urban areas (South Africa Department of Health, 2011). Decentralization

can have major economic and health benefits; one study in Ethiopia found a 63% reduction in cost for community-based programs with similar health outcomes and in South Africa, improved outcomes have also been reported (Cox et al., 2014; Cox, Ramma, Wilkinson, Azevedo, & Sinanovic, 2015; Datiko & Lindtjørn, 2010). Decentralization of care for TB has been recognized for many years, and recently has gained attention for DR-TB (Stop TB Partnership, 2015). As of 1996, directly observed treatment short-course (DOTS) has been implemented in South Africa as recommended by the WHO, and complete coverage was achieved in 2002 (South Africa Department of Health, 2011). Although uptake of the DOTS program in South Africa was rapid, and impacted TB treatment greatly, it is prudent to assume that many rural areas are unlikely to have achieved true complete DOTS coverage.

Guidelines and recommendations are also difficult for healthcare providers to adhere to, as South Africa lacks sufficient numbers of trained healthcare professionals to treat DR-TB (Nkosi et al., 2013; van der Werf et al., 2012). In 2013, of the 26,023 DR-TB cases reported in South Africa, only 10,663 (41%) were started on DR-TB treatment (WHO, 2014b). In 2014, there was a slight improvement with a 39% treatment gap; however fewer cases were diagnosed (18,734 total cases with DR-TB confirmed and 11,538 started on DR-TB treatment) (WHO, 2015a). Figure 2 shows the treatment gap for DR-TB in South Africa in 2009-2014.

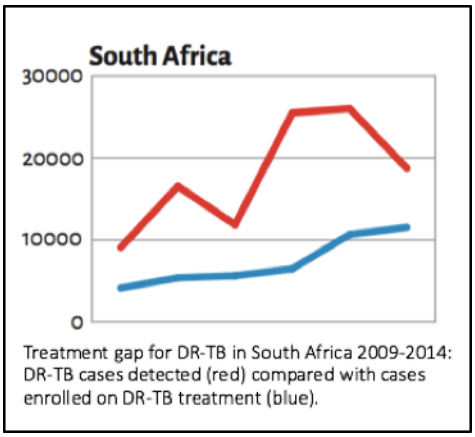

Figure 2: Treatment gap for DR-TB in South Africa 2009-2014 (Copyright: WHO, 2015).

The high co-infection rate in South Africa is unique because many other high DR-TB regions have significantly lower HIV prevalence; therefore, each country's epidemic needs to be studied and strategies must be tailored to the local situation (WHO, 2015a; World Health Organization, 2009b). In addition to knowledge of treatment guidelines, access to proper diagnostics is also critical for improved DR-TB care. As of 2008, routine drug susceptibility testing (DST) was not done on all culture-confirmed TB isolates; rather, DST was performed at the discretion of the treating clinician (Fairlie et al., 2011). Standardization of treatment and care – whether DOTS implementation, adherence to recommended treatment guidelines, or completing DST on all TB samples – will advance the care provided to individuals and encourage providers to systematically improve their care (Diop, Gakiria, Pande, Malla, & Rieder, 2002; Ershova et al., 2014; Langendam et al., 2012; Thongraung, Chongsuvivatwong, & Pungrassamee, 2008).

1.3.1 South African history

To better grasp the underpinnings and social determinants of health as they relate to DR-TB, the context of this dissertation study in South Africa must be understood. South Africa, like most nations, is a society with a rich and complex history of events. British and Dutch immigrants introduced TB to South Africa in the 17th century after the TB epidemic that swept through Europe (Packard, 1987). South Africa experienced the Anglo-Boer Wars at the turn of the twentieth century, the racially separatist Apartheid government from 1948 until 1994, and the world's worst HIV/AIDS epidemic since in the 1990s that is still prevalent today (A. S. S. Karim, Churchyard, Karim, & Lawn, 2009). Currently, there are 6.3 million people in South Africa living with HIV and the adult prevalence is roughly 19% (UNAIDS, 2013). The Apartheid government created structural conditions that segregated communities into living in crowded and poorly ventilated townships (i.e. temporary housing settlements). The thriving mining business in South Africa fueled an 'oscillatory migration' lifestyle which perpetuated the spread of HIV, TB, and sexually transmitted infections. Miners (along with truck drivers, and other migratory laborers) who are away from home for weeks to months at a time were often served by commercial sex workers. Not only are poor living conditions facilitating spread of TB, but working conditions, with silica dust exposure in the mines, also circulating the disease more quickly (Barwise et al., 2013; Dharmadhikari et al., 2013). These social, economic and environmental conditions put in place by

apartheid policies created a systemic break for HIV and TB to thrive even in post-apartheid South Africa (Chopra et al., 2009; A. S. S. Karim et al., 2009; Simelela, Venter, Pillay, & Barron, 2015). The HIV/AIDS and TB epidemics have also effected the health workforce as many health professionals have been infected, stressing the overwhelming burden placed on the health system (Chopra et al., 2009).

South Africa is an incredibly dichotomized socio-economic state (i.e. high levels of extreme poverty contrasted with significant wealth) (Statistics South Africa, 2012). The racial mix of South Africa includes a 79.2% Black African majority, with an additional 8.9% White, 8.9% Colored, 2.5% Indian or other Asian, and 0.5% Other/Unspecified population (Statistics South Africa, 2012). In 2011, South Africa had a Gini index of 63.4; compared to the United States' index of 41.1 in 2013 and Sweden's index of 27.2 in 2011 (Word Bank, 2015). The Gini index is a measure of income distribution among individuals or households within an economy with a 0 representing perfect equality and an index of 100 implying complete inequity (World Bank, 2014). Thus, South Africa has some of the widest wealth and health disparities in the world (ranking 67/67 on the Gini index of all countries measured in 2011) (World Bank, 2015). The wealthiest 10% of the population accounts for 58% of the country's income while the poorest half account for less than eight percent (World Bank, 2014). Consequently, South Africa is an incredibly inequitable society. It is important to note the interactions of these contexts as they all influence the 'person' and the 'system'; in this dissertation, both

levels of context will be studied. These environments serve as a backdrop for understanding the ecological system in which individuals live and develop.

1.4 Youth

Youth, aged 15-24, and adolescents, aged 10-19 years, are a recognized population that often are underrepresented in research by national and international authorities (Gore et al., 2011; Patton et al., 2012; United Nations Department of Economic and Social Affairs, 2013, 2015; WHO, 2013a, 2014a). Studies of DR-TB treatment regimens and co-occurring guideline prescribing behavior in DR-TB and HIV treatment in South Africa to date have primarily focused on either adults or children (Daftary, 2012; Daftary & Padayatchi, 2012; Franck et al., 2014; Seddon, Hesseling, Marais, et al., 2012). Rarely does research disaggregate to the youth population and little is known about this growing marginalized population for whom treatment may be uniquely challenging (Ferrand et al., 2009; Holmbeck, 2002; Seddon et al., 2015). Only as of December 2015 at the latest International Conference on Tuberculosis and Lung Disease, were youth decided to be disaggregated to allow for better tracking of adolescent and youth TB outcomes (Union, 2016).

Youth is a transitional phase between childhood and adulthood characterized by more biopsychosocial changes than any other stage of life excluding infancy (Feldman, 1990; Holmbeck, 2002). Although this period spans many years and is culturally bound through attainment of certain knowledge, skills, and attitudes, this developmental stage

is critical in establishing lifelong self-management and health-related behaviors such as seeking recommended healthcare and treatment (Holmbeck, 2002). Youth is an age of opportunity and linking youth to healthy behaviors is key to creating protective factors for their future health while allowing youth to make poor health decisions can create negative effects in their adult years (WHO, 2013a).

Delayed initiation and inappropriate treatment are major barriers to cure for DR-TB in South Africa, leading to high mortality and widespread DR-TB transmission in the community (Harries et al., 2010; Nkosi et al., 2013; Weyer et al., 2007). Youth are exceptionally vulnerable to delays in diagnosis, linkages to care, treatment initiation, and appropriate treatment for HIV care (Committee On Pediatric, 2013; Ettehad, Schaaf, Seddon, Cooke, & Ford, 2012; Kaufman, 2006; Kendall et al., 2013; Muller, Bode, Myer, Stahl, & von Steinbuchel, 2011; Shisana et al., 2014; United Nations Department of Economic and Social Affairs, 2013, 2015). However, there is a paucity of research specifically pertaining to DR-TB treatment initiation in youth with or without HIV (Desmond Tutu HIV Foundation, 2015; Isaakidis, Paryani, et al., 2013; Shisana et al., 2014). Even the epidemiology of DR-TB and DR-TB/HIV coinfection and treatment in youth remains unclear. Examining the relationship between age (and other covariates such as sex, prior history of TB, HIV serostatus, and treatment center) and receipt of recommended treatment of DR-TB and HIV in South Africa will fill tremendous knowledge gaps.

The first paper to report DR-TB treatment outcomes in the adolescent population was published from India in 2013 and only included 11 adolescents, all of whom were coinfected with HIV and for whom poor outcomes were reported (four died and three defaulted from treatment) (Isaakidis et al., 2015). A second DR-TB study of youth, in South Africa, was published in 2014 with 71 participants (Moyo, 2014). These adolescents (10-19 years) also had poor outcomes with many individuals dying, failing treatment and being lost to follow-up. South African DR-TB guidelines only quote anecdotal evidence that adolescents are at high risk for poor treatment outcomes due to biologic reasons potentially related to delayed diagnosis and initiation of treatment as well as social factors (Department of Health: Republic of South Africa, 2013). The lack of literature pertaining to youth DR-TB is concerning, as 15-24 year olds are a growing demographic in Africa with a doubling of youth expected by 2055 (United Nations, 2015). Additionally, due to the paucibacillary load often seen in children, diagnosing TB is more difficult in children and youth than in adults who are better able to expectorate sputum for samples, and who often have higher bacilliary loads, leading to more accurate diagnostic results (Chang et al., 2013; Moyo, 2014; Seddon, Hesseling, Willemse, Donald, & Schaaf, 2012; Sentinel Project on Pediatric Drug-Resistant Tuberculosis, 2013). Youth also represent large proportions of HIV infected populations who are at-risk for developing DR-TB. In South Africa, female youth have an HIV prevalence of 11.4% while male youth have a prevalence of 2.9% (Shisana et al., 2014).

TB transmission occurs in homes, schools, and communities among HIV-infected and HIV non-infected individuals (Lawn, Bekker, Middelkoop, Myer, & Wood, 2006; Middelkoop, Bekker, Morrow, Zwane, & Wood, 2009). Gendered norms have been linked to varying rates of prevalence, access to diagnosis and initiation of treatment for TB as well as HIV (Ebonwu, Tint, & Ihekweazu, 2013; Franck et al., 2014; Kendall et al., 2013; Shisana et al., 2014). Female youth have much higher rates of HIV than their male peers; in part due to biological transmission as well as environmental and social norms where young females may be expected to have relationships with older men (Shisana et al., 2014). In contrast to the lack of TB research in youth, HIV is a well-defined area of research in South African youth (Cluver, Boyes, Orkin, & Sherr, 2013; Pettifor et al., 2013; Shisana et al., 2014). Poverty (Casale et al., 2015; Cluver et al., 2013; Louwagie, Wouters, & Ayo-Yusuf, 2014; Naidoo et al., 2013), education (Muller et al., 2011; O'Donnell, Wolf, Werner, Horsburgh, & Padayatchi, 2014), and social support (Casale et al., 2015; Louwagie et al., 2014; Munro et al., 2007) are multifaceted and integral factors that similarly impact the lives of individuals with HIV and TB. Both HIV and TB have been tremendously stigmatized in South Africa (Chiu et al., 2008; Daftary, 2012; Daftary, Padayatchi, & O'Donnell, 2014; Harries et al., 2010; Isaakidis, Rangan, et al., 2013; Population Information Program (Johns Hopkins School of Public Health), 1996) leading to delays in diagnosis and treatment. In addition to the complexities of TB and TB/HIV treatment, youth who experience social disparities of poverty, low education, stigma,

and lack of social support may be more likely to delay treatment or receive delayed treatment. Independent of the timing, many factors may be associated with the provision of inappropriate guideline-based treatment for youth. Because of their age, physical development, and oftentimes malnourishment if suffering from chronic disease, weight-based dosing can be challenging for healthcare providers not accustomed to caring for youth (Kaufman, 2006; Satti et al., 2012; WHO, 2013b). HIV literature supports that some adult providers are uncomfortable or unknowledgeable about caring for youth (Committee On Pediatric, 2013; Lee, Rand, Ellen, & Agwu, 2014).

In addition to improving providers' competence to care, youth also need to be active participants in their treatment. Thus, providers should work to empower and motivate youth to adhere to treatment (WHO, 2014a). There has been evidence demonstrating this knowledge-gap in practice and policy, especially in HIV care. Therefore, knowing a context, even within context, is of the utmost importance (World Health Organization, 2009b). The findings from this dissertation will provide evidence for researchers and clinicians in DR-TB care as we try to close the policy-practice gap. Translating the research into practice is vital to impact youth patient outcomes.

Taking a developmental perspective, with age, sex, and cultural setting into consideration, each of these variables is important in the context of DR-TB and HIV treatment. The true incidence (i.e. absolute number of new cases) of DR-TB in South African youth has never been measured, and detection is difficult to predict given poor

notifications of the disease nationwide. Tackling DR-TB from multiple angles – nursing, epidemiology, public health, social services, medical care, etc. is one way in which this epidemic can be challenged. Moving beyond mediocre prevalence estimates towards finding ways to improve care (i.e. diagnostics and treatments) that will save youth lives is critical.

1.5 Health services and systems

Health services and systems affect how people access care, the cost of care, and ultimately influence health outcomes (Academy Health, 2016). Health services vary widely in South Africa as it has a mixed model of public and private healthcare and access greatly depends upon geographic location and financial resources. Barriers within the South African healthcare system coupled with individual barriers can create enormous challenges in TB control as TB management requires intensive resources for DR-TB and HIV diagnosis and treatment, DOTS adherence, and appropriately trained healthcare providers (Cloney, 2016).

1.5.1 South African healthcare system

The availability, accessibility, acceptability, and quality of a workforce is vital to a functioning health system (Global Health Workforce Alliance & World Health Organization, 2013). South Africa has a national health insurance system and aims to provide universal health coverage; however, a 'third epidemiological transition' with a resurgence of infectious diseases (such as DR-TB) due to the inability to treat drug-

resistance as well as accelerating globalization has caused an increase non-communicable and chronic diseases. These health issues include: interpersonal violence, diabetes, cerebrovascular disease, and major depressive disorder (Harper & Armelagos, 2010; Jones et al., 2008; Richardson, Callaghan, & Wamala, 2014). Additionally, South Africa also suffers from high maternal and child mortality due to diarrheal diseases and preterm birth (Institute for Health Metrics and Evaluation, 2010). The nurse to physician ratio is 4.8:1 which is above the Organization of Economic Co-operation and Development (OECD) average. Yet physician density is far below the OECD standard and great variation exists between provinces (Global Health Workforce Alliance & World Health Organization, 2013). Leveraging nurses through task-shifting in HIV, TB, and most recently DR-TB care, has been recognized as one way to facilitate access to healthcare in South Africa (Emdin, Chong, & Millson, 2013; J. E. Farley et al., 2014; Grimsrud, Kaplan, Bekker, & Myer, 2014; IRIN News, 2012; Iwu & Holzemer, 2014).

Currently in South Africa, most patients are diagnosed with TB and DR-TB at primary health centers (PHCs) with GeneXpert MTR/RIF diagnostics (South Africa Department of Health, 2011; World Health Organization, 2014c). This testing of a sputum sample only takes two hours if done at the point of care. After initial diagnosis, a patient can be started immediately on medication per South African guidelines (Department of Health: Republic of South Africa, 2013). Unfortunately, some PHCs do not have MTR/RIF cartridges or GeneXpert machines in the facility and patients must

wait for results to come back from a centralized laboratory. This often results in delayed treatment initiation. At times this delay results in death prior to treatment initiation as many patients do not present to PHCs until advanced disease (Dlamini-Mvelase, Werner, Phili, Cele, & Mlisana, 2014; Finnie et al., 2011; Van Den Handel et al., 2015). Prior to initiation of DR-TB treatment, patients must give a sputum sample for drug susceptibility testing (DST) to allow for a bacterial culture to grow. DST provides information on which medications the bacilli are resistant to, and will allow for individualized treatment after six weeks to three months once DST results are finalized. Some patients are hospitalized and treated for DR-TB inpatient, while many are treated in outpatient facilities and must go to a clinic daily for an injection as part of DR-TB regimens for the first six months of treatment. Awaiting DST results is another point in care that the health system (laboratory services, hospitals, clinics, providers, etc.) loses results or loses an opportunity to provide appropriate care to patients. If a patient is treated with the incorrect medication while awaiting DST results that are available, DR-TB can be transmitted in the patient's home and surrounding environment whether in the hospital or community.

The gap between case detection, patients diagnosed with DR-TB, patients who initiate treatment, and those who complete treatment and are cured is immense. As previously mentioned, less than 30% of patients diagnosed with DR-TB complete treatment or are cured (WHO, 2015a). Diagnosis, initiation, and adherence are major

barriers to DR-TB treatment and control. This cascade of care must be bolstered so that more patients are diagnosed, linked to appropriate care, retained in care, prescribed correct treatment, and achieve DR-TB cure and HIV viral suppression (US Department of Health and Human Services, 2015).

Contact tracing (i.e. identification and diagnosis of persons who had contact with an infected person) and follow-up care (i.e. referral after initial diagnosis for treatment initiation and sustained adherence) are systemic barriers to DR-TB control, which, if improved, could impact the treatment and containment of DR-TB in the community. Throughout the literature, the need for improved treatments cannot be understated – the duration of treatment, medication side effects compounded with HIV therapy, and burden on patients and their families is often too much for patients to endure. As mentioned above, roughly 65% of patients were not started on treatment due to a health system failure to track eligible patients (Ebonwu et al., 2013). A systems-level approach should be adapted to better trace and initiate treatment in DR-TB patients, as well as better follow-up and care during the transition periods between primary health centers, the hospital, and the acute and continuation phase of treatment as the continuation phase is when most patients are lost to follow-up (Kendall et al., 2013).

1.5.2 Provider adherence to guidelines

Due to limited healthcare provider capacity building and many other factors, adherence to TB guidelines are limited. Globally, a systematic review of literature all 31

studies found inappropriate knowledge of treatment regimens or treatment duration (van der Werf et al., 2012). Additionally, in another systematic review of inappropriate TB treatment prescribing, of 37 included studies, 67% studies found inappropriate regiments were prescribed between 0.4 and 100% of the time (Langendam et al., 2012). Specifically, in South Africa, one study found that 64-86% of nurses and physicians in TB hospitals and clinics were unaware of DR-TB guidelines (Nkosi et al., 2013). When inadequate medications are prescribed (such as under-dosing), drug-resistance proliferates; yet overdosing can lead to toxic side effects (Centers for Disease Control and Prevention, 2015; Diop et al., 2002; Gandhi et al., 2006). Thus, provider adherence to guidelines is important to decrease adverse outcomes and increase the probability for improved patient outcomes.

1.5.3 Nurses and DR-TB

Nurses can play a significant role in DR-TB care for all patients, including youth. As treatment can take up to two-and-one-half years, nurses, as case managers, are vital to providing support. The transition phases between diagnosis and treatment initiation, as well as hospital discharge and outpatient treatment should be target areas as these are all vulnerable times when the trajectory for default can be better managed (Gler et al., 2012; Kendall et al., 2013; Rochester-Eyeguokan, Pincus, Patel, & Reitz, 2016).

Another addition to nurses' role in the DR-TB epidemic in South Africa is patient tracing and follow-up for initiation of treatment. Currently nurses are trained in South

Africa to initiate HIV anti-retroviral therapy (ART) and this training is expanding to TB and DR-TB treatment (Green et al., 2014; IRIN News, 2012; Kredo, Adeniyi, Bateganya, & Pienaar, 2014). Evidence shows that non-physician clinicians provide quality care while helping to mitigate the shortage of eligible prescribers in areas with too few physicians (Kredo et al., 2014). Nurses, a cadre of professionals, are capable of reducing the spread of DR-TB via improved health-system processes whether patient-tracing, treatment initiation, care coordination or research (van Oostveen & Vermeulen, 2017).

Coordination of care for DR-TB and HIV services is also another area for future research and implementation of programs. With the dual epidemics and a large proportion of DR-TB patients being HIV positive, ART clinics are well-positioned facilities to test and treat DR-TB. The HIV epidemic also complicates the control of TB as HIV can act as an incubator for the spread of DR-TB (Marais et al., 2014). Patients diagnosed with DR-TB in a hospital laboratory versus clinic were eight times less likely to initiate treatment (Ebonwu et al., 2013). Therefore, coordinating care between hospitals and clinics is vital for treatment initiation. The scenario of clinics referring patients to hospitals is also a place for improved coordination. In Gauteng, South Africa many clinics did not follow up to ensure patients were admitted for DR-TB treatment in the hospital (Nkosi et al., 2013). As South Africa continues to decentralize DR-TB services, nurses are well situated for care coordination at all levels of care as nurses have proficiency in disease management and an understanding of the healthcare system and

areas of care coordination or fragmentation across TB and HIV, maternal and child health and infectious diseases, inpatient, and outpatient care. Better utilization of nurses, both as prescribers and as case managers could improve adherence to guidelines and improve access to care.

1.6 Barriers to treatment

There are numerous barriers to treatment initiation for both TB and DR-TB, thus it is important to cure the disease the first time an individual is diagnosed. Programmatic failures, poor patient management, lack of treatment supervision, interrupted drug supply, poor drug quality, and poor TB control all contribute to the complexity of DR-TB management (Weyer et al., 2007). In addition to numerous personal factors associated with default from treatment (discussed above), Kendall et al. (2013) found access to care is very important in default rates.

There are many barriers to accessing quality TB care to ensure patients are started on the right treatment regimen (Botha, den Boon, Lawrence, et al., 2008; Finnie et al., 2011; Mauch et al., 2011). DR-TB treatment should begin immediately after diagnosis. Rapid molecular diagnostic testing now supports DR-TB treatment initiation within two to 48 hours after sputum production (Hughes & Osman, 2014). Barriers to treatment initiation include cost, patient and health system delays, structural barriers such geography and the availability of services offered at different levels of the health system, and knowledge, attitudes, and beliefs of both patients and providers. Treatment for DR-

TB is challenging, particularly in poorly resourced countries (Van Den Handel et al., 2015).

Early and accurate diagnosis, timely linkage to treatment, and appropriate antibiotic selection increase the likelihood of survival for individuals with DR-TB (Isaakidis et al., 2015). The timeliness and appropriateness of treatment is further complicated for people coinfected with HIV especially with DR-TB (Abay et al., 2015; S. S. A. Karim et al., 2010). South Africa has standardized treatment regimens for DR-TB and HIV (Department of Health: Republic of South Africa, 2013; J. E. Farley et al., 2014; Green et al., 2014; IRIN News, 2012; Kredo et al., 2014). Starting the right patient on the right treatment at the right time can dramatically influence patient outcomes; however, adherence to recommendations for initiation of treatment regimens in South Africa is poorly understood (Loveday et al., 2008; Loveday et al., 2012).

1.7 Theoretical framework

1.7.1 Chronic care model

Chronic illness care has been an area of growing concern for healthcare systems as many individuals are living longer with chronic illness, while not receiving the quality of care they require (Institute of Medicine, 2001). The Chronic Care Model (CCM) depicts the components of a healthcare system that are considered essential for healthcare transformation aimed to improve outcomes (Coleman, Austin, Brach, & Wagner, 2009; Wagner, 1998; Wagner et al., 2001). The CCM as an organizing framework

depicts patient-provider interactions that stem from the health care system embedded in its surrounding community of additional resources and policies. This framework supports both the individual- and system-level analyses proposed for this dissertation focused on the productive interactions between the patient and care providers within the larger South African context of low-resources available in healthcare organizations and communities across the Eastern Cape and KwaZulu-Natal provinces in South Africa (Loveday et al., 2008; Loveday et al., 2012). There are six major concepts described in the CCM: health care organization, community resources, self-management support, delivery system design, decision support, and clinical information system (Wagner et al., 2001).

In 2003, five additional themes were specified under each of the six elements including: patient safety (in health system), cultural competency (in delivery system design), care coordination (in health system and clinical information systems), community policies (in community resources and policies) and case management (in delivery system design) (Improving Chronic Illness Care, 1996). These concepts fall within two broad domains, Community and Health System, where 'functional and clinical outcomes' are measured by the bidirectional productive interactions between patient and practice team. The domains of Community and Health System are recursive and woven together in a nonlinear fashion. Individual, community, and health system factors all relate to DR-TB treatment initiation.

1.7.2 The CCM, ecological systems theory, and the dissertation

This dissertation will examine how patients and providers must partner together after diagnosis to continue *productive interactions* to achieve DR-TB treatment initiation as recommended per South African guidelines. The individual- and system-level analyses leverage both aspects of the CCM providing new knowledge that can improve care and outcomes both at multiple levels. Previously, the CCM as an organizing framework for research on DR-TB/HIV in South Africa has not been applied. Application of the CCM at the individual- and system-level may help identify important opportunities for improving care and outcomes.

Additionally, parts of ecological systems theory will be used to explain the development of individual youth in the context of the individual (in the setting of DR-TB or DR-TB/HIV co-infection), families and peers, community and health system, and South African society. Accounting for the relationships between these levels of influences at the biological, micro-, meso-, and macro-level (and chronosystem) are important because each level contains roles and norms, while the effects of illness, age, and the health system can greatly influence health outcomes for individuals with DR-TB depending on their immediate and more distal surroundings and the relationships between each level (Bronfenbrenner, 1979; U. Bronfenbrenner & Morris, 2006; U. a. Bronfenbrenner, 1981; WHO, 2013a). Taking a developmental perspective to youth is

important. Understanding the differences in their social roles and responsibilities within their environment is important when considering chronic and acute levels of illness.

Chapter two will systematically review pediatric and youth TB care in sub-Saharan Africa and consider cost, delays, health seeking behaviors, and infrastructure at the patient- and health system-level to describe barriers to effective treatment. The CCM and socioecological theory decribe the community with the health system. Each of these four domains (cost, delays, health seeking behaviors, and infrastructure) relate to both the community and health system for individuals with TB. For example, a child with DR-TB who is originally diagnosed at a community primary health center but needs to be referred to a centralized provincial hospital for treatment is influenced by both national policies for pediatric patients as well as community resources (such as transportation and available money to pay for direct and indirect costs associated with TB treatment). The organization of the health system, only providing pediatric DR-TB services at the provincial level, greatly impacts the access and ability of a child to receive care, and may impede treatment altogether (Engelbrecht, Marais, Donald, & Schaaf, 2006; Scott, Azevedo, & Caldwell, 2012; Seddon, Godfrey-Faussett, et al., 2012; Zimri, Hesseling, Godfrey-Faussett, Schaaf, & Seddon, 2012).

In the third chapter, the timing of treatment initiation from DR-TB diagnosis to DR-TB treatment initiation will be explored. Policies, with historical value relating to apartheid, as well as how policies were implemented influence health systems and

communities. For example, when DR-TB care is decentralized, a burden may be shifted away from inpatient hospital units; however, district clinics and community health workers may be challenged with increased workloads. Decentralized care may lead families and individuals to have more access to healthcare as less time off from work and less money for transportation is needed to attend clinic appointments – all of which can facilitate expedited diagnosis and treatment. Considering age and the extra barriers children and youth face in navigating complex health systems, community resources, and support networks, treatment delays may persist. Thus, taking a focused age-appropriate approach to timing of treatment initiation will be the focus of Chapter 3.

We will assess individual patient differences as well as site and provincial differences (Chapter 4) in relation to adherence to treatment guidelines at DR-TB treatment initiation. As stated above, guideline adherence is critical for DR-TB disease cure and to decrease disease transmission. Whether taking a top-down or bottom-up approach, individual patients must adhere to their daily treatment and healthcare providers must adhere to national guidelines (Brugha, Bruen, & Tangcharoensathien, 2014; Walker & Gilson, 2004). Proper education, drug supplies, delivery systems, self-management family and peer support, and ultimate continued and productive patient and provider interactions throughout treatment must be achieved for positive health outcomes. Treatment initiation of correct regimens is just the first step. With the provision of supportive environments on multiple levels - for individuals, communities,

and health systems - chronic illnesses like DR-TB can be well-managed for children, youth, and adults of all ages.

1.8 Research questions

The purpose of this dissertation study has three main aims. First, to describe the scope of the literature pertaining to TB treatment initiation in sub-Saharan Africa for pediatrics and youth, (Chapter 2). Then, through secondary data analysis of an ongoing five year cluster randomized trial investigating the effects of a nurse case management intervention in improving treatment outcomes in individuals older than 13 years with DR-TB in South Africa (R01 AI104488-01A1), we will examine the treatment provided to people in South Africa with DR-TB with and without HIV, and evaluate the extent to which selected patient and site characteristics influence the initiation and delivery of guideline-based treatment. Assessing time to treatment for DR-TB treatment initiation will be vital to learning if age is a factor in treatment delays (Chapter 3). Guideline-based treatment for DR-TB treatment will be assessed at the patient-level and explored at the systems-level by site and province (Chapter 4). The empirical studies specifically aim to:

1. Examine the relationship between age and the number of days from DR-TB initial diagnosis to MDR-TB treatment initiation.

   H_1: Younger patients will have a greater number of days from DR-TB diagnosis to MDR-TB treatment initiation.

2. Compare each individual's prescribed regimen for DR-TB with guideline

recommended treatment and examine the association of age with guideline recommended treatment.

H_2: Younger patients will be less likely to be prescribed guideline-based treatment for DR-TB.

3. Explore whether DR-TB guideline adherence varies by treatment center and whether site characteristics (province, urban/rural site) are associated with guideline adherence after adjusting for patient characteristics (age, sex, prior TB history, and HIV coinfection).

1.9 Conclusion

Overall, the studies for this dissertation aim to provide significant empirical evidence to be used to promote and improve the health of individuals, specifically those with DR-TB and DR-TB/HIV co-infection and improve the understanding of the role communities and health systems have in the provision of DR-TB and HIV treatment. Due to the global burden and communicable nature of DR-TB, the high co-infection rates with HIV, and the social and economic impact of DR-TB on patients and national systems and economies, DR-TB is of global importance. Findings will allow us to better understand behaviors of systems (e.g. family units, populations, and/or organizations) in order to create better, more targeted interventions (National Institute of Nursing Research, 2011). Systematically reviewing literature identifying barriers to pediatric and youth TB treatment initiation in sub-Saharan Africa at both the patient- and system-level will add important knowledge for global TB research. Differences in

DR-TB prescribing patterns (time and specific treatments) identified by this study will support the development of interventions to improve age-specific guideline adherence. This is especially important for youth as the DR-TB Treatment Guidelines of South Africa only quote anecdotal evidence for adolescent care due to the dearth of research in this population (Department of Health: Republic of South Africa, 2013).

To understand the interplay of patients and their interactions with their community and the healthcare system, the broader societal context of DR-TB treatment in which it is occurring must be considered. The focused purpose of this dissertation is to examine the treatment provided to people in South Africa with DR-TB with and without HIV, and evaluate the extent to which age and other patient and site characteristics influence the initiation and delivery of guideline-based treatment. Taking an individual- and system-level approach is important in understanding the context in which DR-TB and HIV affect people of all ages in South Africa. This study is significant, as it will address a critical health problem in a low-resource setting affecting an understudied youth population. Examining the time to treatment initiation and the selection of treatment regimen for DR-TB and ART within the South African context is important so we can address disparities systematically and scale appropriately particularly supporting the vulnerable youth population.

This dissertation will lay foundation for future research in pediatric and youth DR-TB and HIV treatment. Treatment initiation is imperative to prevent disease

transmission and to ensure positive patient outcomes such as treatment completion and disease cure. Initiation of correct treatment is only the beginning of a long journey; yet, it must be taken to disrupt the cycle of drug-resistance.

2. Barriers to tuberculosis treatment initiation in sub-Saharan Africa with an emphasis on children and youth: a systematic review

2.1 Background

Mycobacterium tuberculosis (TB) is the leading infectious cause of death worldwide, surpassing HIV/AIDS (WHO, 2015a). In 2015, TB killed 1.8 million people with 95% of cases and deaths in developing countries (WHO, 2015a). TB is an airborne infectious agent requiring at minimum an intensive six-month medication regimen for bacteriologic cure (WHO, 2015a). Timely initiation and correct treatment of TB are critical to reduce disease transmission and improve patient outcomes. However, barriers to treatment initiation exist at both the patient- and system-levels. Patient-level barriers such as perception of illness, stigma, knowledge about TB, delay in seeking care and initiating treatment, and direct and indirect costs all cause delayed treatment (Finnie et al., 2011; Storla et al., 2008). Health system barriers include resource capacity such as the availability of laboratory tests, accessibility of different levels of care, and costs. Patient costs associated with TB treatment often cause patients and families to fall into a 'medical poverty trap' (Barter et al., 2012; Whitehead et al., 2001).

Pulmonary TB outcomes in children are favorable when treated; however, data are limited regarding outcomes for children (0-18 years) and youth (15-24 years) (Ettehad et al., 2012; Isaakidis et al., 2015; Isaakidis, Paryani, et al., 2013; Moyo, 2014; Seddon, Hesseling, Godfrey-Faussett, & Schaaf, 2014). This research gap is in part due to

lack of standardized definitions of age cohorts (i.e. pediatric, child, adolescent, youth) as well as lack of political and community commitment to this age group (WHO, 2013a). Barriers to involving youth in research, coupled with developmental transitions, additional responsibilities associated with education and employment, and dependence on family commitment, may cause youth to be understudied (Patton et al., 2012).

Pediatric cases (0-18 years) account for 10% of all new and relapse cases of TB in the African region, as compared to 6.5% globally (WHO, 2015a). Additionally, the African region has the highest rate of TB in children and youth compared to any other region (WHO, 2015a). Despite the high burden of disease among younger age groups, barriers are most often studied in adult populations. As a result, barriers to treatment initiation in children and youth are less well understood (Gore et al., 2011; Patton et al., 2012). The objective of this review is to determine patient- and system-level barriers to treatment initiation in sub-Saharan Africa with an emphasis on children and youth diagnosed with TB, through systematic review of the literature.

2.2 Methods

2.2.1 Search strategy

We systematically searched six health databases for literature pertaining to pediatric and youth tuberculosis in sub-Saharan Africa. Specified terms were agreed upon by authors and adapted to each database. The protocol is provided in Appendix A and full search criteria for each database is provided in Appendix B.

2.2.2 Selection criteria

Inclusion criteria was established by the authors a priori based upon preliminary literature searches. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were followed for inclusion and exclusion (Figure 4).

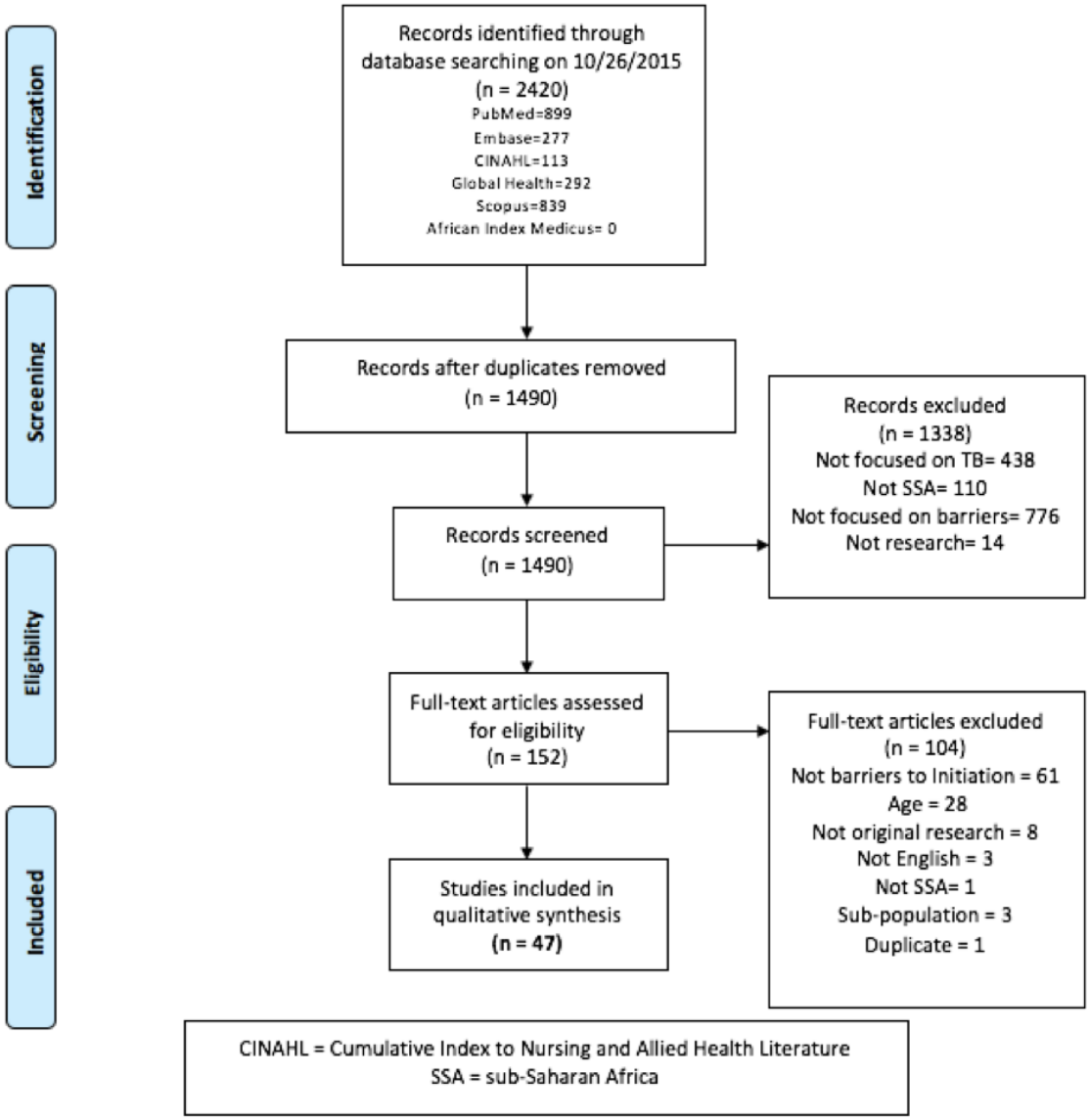

Figure 3: PRISMA flow diagram

Articles were included through October 26, 2015. All potentially eligible original research studies with abstracts in English were reviewed. Inclusion criteria were: a primary or secondary aim of the study addressing barriers to TB treatment initiation for children or youth in sub-Saharan Africa. Definitions of barriers, age groups, treatment initiation, and other variables are provided in Table 1. All publication dates and all study designs were included.

Table 1: Definitions used in systematic review

Variable	Definition
Barrier	Obstacle preventing TB treatment initiation and treatment access. Includes: cost, infrastructure, and health-seeking behaviors.
Treatment initiation	TB medication start date.
Child (pediatric)	0-18 (UNICEF)(United Nations Department of Economic and Social Affairs, 2013)
Adolescent	10-19 years (UNICEF, WHO, UNFPA)(United Nations Department of Economic and Social Affairs, 2013)
Youth	15-24 (WHO, UN, UNESCO, UNICEF)(United Nations Department of Economic and Social Affairs, 2013)
Patient-level (P)	Individual-level factors and perceptions. Includes patient costs, health seeking behavior, and internal/external stigma.
System-level (S)	Characteristics of health systems. Includes health system delays, laboratory capacity, geography, health system infrastructure beyond the individual (i.e. information technology systems), and provider attitudes towards TB.
Cost	Direct or indirect economic burden to family, guardian and/or patient associated with TB care. *Part of the cost was incurred *prior to* treatment initiation, i.e. costs incurred while obtaining diagnosis or between diagnosis and treatment were included in analysis.
Direct cost	Out-of-pocket expenses for transportation, food, medicine, etc.
Indirect cost	Lost wages due to time spent seeking care or inability to work
Catastrophic medical expenses	When a household's total out-of-pocket health payments is equal to or exceeds 40% of the household's capacity to pay.(Xu, 2005)
Health seeking behavior	Navigation of the health system. Includes care pathways of providers (formal and informal healthcare providers, private

	and public sector, traditional healers, health extension workers, herbalists, nurses, physicians, etc.) sought prior to appropriate TB diagnosis and treatment. Also includes knowledge, attitudes, and beliefs regarding TB.
Infrastructure	The geography and access to care, laboratory capacity, level of care and health policies (centralized versus decentralized care), health system errors (initial default), and quality of health services delivery.
Initial default	If a patient is diagnosed with TB but does not initiate treatment.

2.2.3 Data extraction and analysis

All search results were entered into EndNote X7 (Thomson Reuters Scientific Inc., Carlsbad, CA, USA) and duplicates were removed. Two authors (BJS and BEE) reviewed titles and abstracts with the aim of removing publications that were unlikely to meet the inclusion criteria. After both authors reviewed 20% of articles and demonstrated greater than 95% inter-rater reliability, the remaining articles were assessed independently. Discrepancies were resolved through discussion with all three authors until agreement was reached.

Garrard's matrix strategy for abstracting was used to build a Microsoft Excel spreadsheet and abstract full texts of the remaining articles (Garrand, 2014). The following data were extracted from the included articles: author, publication year, title, journal, country and setting, study aim and design, outcomes and barriers measured, sample size, covariates, strengths and limitations of each study, 95% confidence intervals and effect sizes (if reported), if HIV was measured as a variable, and if pediatric and youth cases were specifically described in the findings or discussion.

2.3 Results

2.3.1 Study selection

After removing duplicates, a total of 1490 articles were included. There were 1338 articles excluded and 47 articles were retained for full text review (Figure 1). The 47 studies were from 14 countries with 16 studies conducted in South Africa (Table 2). While all 47 studies included children or youth in their sample, only four studies were pediatric-only cohorts (Beyers et al., 1994; Engelbrecht et al., 2006; Seddon, Hesseling, Willemse, et al., 2012; Zimri et al., 2012). Barriers were identified as either patient- or system-level (or both), and whether the barrier related to 1) cost, 2) infrastructure, and/or 3) health seeking behavior (Table 2).

2.3.2 Cost as a barrier to TB treatment initiation

Seven articles identified cost as a barrier to TB treatment initiation. Costs included: direct, indirect, system, or caregiver costs; as well as costs incurred prior to diagnosis and between diagnosis and treatment initiation (Appendix 1) (Abimbola et al., 2015; Datiko & Lindtjørn, 2010; Laokri et al., 2014; Mauch et al., 2011; Umar, Abubakar, Fordham, & Bachmann, 2012; Vassall, Seme, Compernolle, & Meheus, 2010; Yitayal, Aseffa, Andargie, Wassie, & Abebe, 2014). All articles identifying costs cited patient-level costs as a barrier, while only one article considered cost as a barrier from the health system perspective (Datiko & Lindtjørn, 2010).

Table 2: Included articles

Citation	Author	Year	Title/Journal	Country	Type of Barrier and Level of analysis	Pediatric specific
15	Beyers, N., R. P. Gie, H. S. Schaaf, S. van Zyl, E. D. Nel, J. M. Talent and P. R. Donald	1994	Delay in the diagnosis, notification and initiation of treatment and compliance in children with tuberculosis. Tuber Lung Dis 75(4): 260-265	South Africa	Infrastructure (P + S)	Yes
52	Salaniponi, F. M., A. D. Harries, H. T. Banda, C. Kang'ombe, N. Mphasa, A. Mwale, B. Upindi, T. E. Nyirenda, A. Banerjee and M. J. Boeree	2000	Care seeking behaviour and diagnostic processes in patients with smear-positive pulmonary tuberculosis in Malawi. Int J Tuberc Lung Dis 4(4): 327-332	Malawi	Health seeking behavior (P)	No
26	Lienhardt, C., J. Rowley, K. Manneh, G. Lahai, D. Needham, P. Milligan and K. P. McAdam	2001	Factors affecting time delay to treatment in a tuberculosis control programme in a sub-Saharan African country: the experience of The Gambia. Int J Tuberc Lung Dis 5(3): 233-239.	Gambia	Infrastructure (P + S)	No
54	Edginton, M. E., C. S. Sekatane and S. J. Goldstein	2002	Patients' beliefs: do they affect tuberculosis control? A study in a rural district of South Africa. Int J Tuberc Lung Dis 6(12): 1075-1082	South Africa	Health seeking behavior (P)	No
53	Enwuru, C. A., E. O. Idigbe, N. V. Ezeobi and A. F. Otegbeye	2002	Care-seeking behavioural patterns, awareness and diagnostic processes in patients with smear- and culture-positive pulmonary tuberculosis in Lagos, Nigeria. Trans R Soc Trop Med Hyg 96(6): 614-616	Nigeria	Health seeking behavior (P)	No
55	Eastwood, S. V. and P. C. Hill	2004	A gender-focused qualitative study of barriers to accessing tuberculosis treatment in The Gambia, West Africa. Int J Tuberc Lung Dis 8(1): 70-75	Gambia	Health seeking behavior (P + S)	No
27	Martin, A., J. P. Baptiste and G. Krieger	2004	Respiratory infections: SARS and tuberculosis. Clinics in Occupational and Environmental Medicine 4(1): 189-204.	Chad	Health seeking behavior (P), Infrastructure (S)	No
30	Cambanis, A., M. A. Yassin, A. Ramsay, S. Bertel Squire, I. Arbide and L. E. Cuevas	2005	Rural poverty and delayed presentation to tuberculosis services in Ethiopia. Trop Med Int Health 10(4): 330-335	Ethiopia	Health seeking behavior (P)	No

29	Edginton, M. E., M. L. Wong, R. Phofa, D. Mahlaba and H. J. Hodkinson	2005	Tuberculosis at Chris Hani Baragwanath Hospital: numbers of patients diagnosed and outcomes of referrals to district clinics. Int J Tuberc Lung Dis 9(4): 398-402	South Africa	Health seeking behavior (P + S), Infrastructure (S)	No
28	Yimer, S., G. Bjune and G. Alene	2005	Diagnostic and treatment delay among pulmonary tuberculosis patients in Ethiopia: a cross sectional study. BMC Infect Dis 5: 112	Ethiopia	Health seeking behavior (P + S), Infrastructure (P + S)	No
56	Barker, R. D., F. J. C. Millard, J. Malatsi, L. Mkoana, T. Ngoatwana, S. Agarawal and S. De Valliere	2006	Traditional healers, treatment delay, performance status and death from TB in rural South Africa. International Journal of Tuberculosis and Lung Disease 10(6): 670-675	South Africa	Health Seeking Behavior (P + S)	No
31	Dembele, S. M., H. Z. Ouedraogo, A. I. Combary, B. Sondo, J. Macq and B. Dujardin	2006	Are patients who present spontaneously with PTB symptoms to the health services in Burkina Faso well managed? Int J Tuberc Lung Dis 10(4): 436-440	Burkina Faso	Infrastructure (S)	No
16	Engelbrecht, A. L., B. J. Marais, P. R. Donald and H. S. Schaaf	2006	A critical look at the diagnostic value of culture-confirmation in childhood tuberculosis. J Infect 53(6): 364-369	South Africa	Infrastructure (S)	Yes
32	Botha, E., S. den Boon, K. A. Lawrence, H. Reuter, S. Verver, C. J. Lombard, C. Dye, D. A. Enarson and N. Beyers	2008	From suspect to patient: tuberculosis diagnosis and treatment initiation in health facilities in South Africa. Int J Tuberc Lung Dis 12(8): 936-941	South Africa	Infrastructure (S)	No
33	Botha, E., S. Den Boon, S. Verver, R. Dunbar, K. A. Lawrence, M. Bosman, D. A. Enarson, I. Toms and N. Beyers	2008	Initial default from tuberculosis treatment: how often does it happen and what are the reasons? Int J Tuberc Lung Dis 12(7): 820-823	South Africa	Infrastructure (S)	No
34	den Boon, S., S. Verver, C. J. Lombard, E. D. Bateman, E. M. Irusen, D. A. Enarson, M. W. Borgdorff and N. Beyers	2008	Comparison of symptoms and treatment outcomes between actively and passively detected tuberculosis cases: the additional value of active case finding. Epidemiol Infect 136(10): 1342-1349	South Africa	Infrastructure (S)	No
57	Mfinanga, S. G., B. K. Mutayoba, A. Kahwa, G. Kimaro, R. Mtandu, E.	2008	The magnitude and factors associated with delays in management of smear positive tuberculosis in Dar es Salaam, Tanzania. BMC Health Serv Res 8: 158	Tanzania	Health seeking behavior (P + S)	No

	Ngadaya, S. Egwaga and A. Y. Kitua					
58	Dodor, E. A., S. Kelly and K. Neal	2009	Health professionals as stigmatisers of tuberculosis: insights from community members and patients with TB in an urban district in Ghana. Psychol Health Med 14(3): 301-310	Ghana	Health seeking behavior (P + S)	No
20	Datiko, D. G. and B. Lindtjørn	2010	Cost and cost-effectiveness of treating smear-positive tuberculosis by health extension workers in Ethiopia: An ancillary cost-effectiveness analysis of community randomized trial. PLoS ONE 5(2).	Ethiopia	Cost (P + S), Infrastructure (S)	No
51	Yimer, S., C. Holm-Hansen, T. Yimaldu and G. Bjune	2009	Health care seeking among pulmonary tuberculosis suspects and patients in rural Ethiopia: a community-based study. BMC Public Health 9: 454	Ethiopia	Health seeking behavior (P + S), Infrastructure (P + S)	No
35	Sendagire, I., M. Schim Van der Loeff, M. Mubiru, J. Konde-Lule and F. Cobelens	2010	Long delays and missed opportunities in diagnosing smear-positive pulmonary tuberculosis in Kampala, Uganda: a cross-sectional study. PLoS One 5(12): e14459	Uganda	Health seeking behavior (P + S), Infrastructure (P + S)	No
19	Vassall, A., A. Seme, P. Compernolle and F. Meheus	2010	Patient costs of accessing collaborative tuberculosis and human immunodeficiency virus interventions in Ethiopia. Int J Tuberc Lung Dis 14(5): 604-610	Ethiopia	Cost (P)	No
21	Mauch, V., N. Woods, B. Kirubi, H. Kipruto, J. Sitienei and E. Klinkenberg	2011	Assessing access barriers to tuberculosis care with the tool to Estimate Patients' Costs: pilot results from two districts in Kenya. BMC Public Health 11: 43	Kenya	Cost (P)	No
59	Dodor, E. A.	2012	The feelings and experiences of patients with tuberculosis in the Sekondi-Takoradi Metropolitan district: implications for TB control efforts. Ghana Med J 46(4): 211-218.	Ghana	Health seeking behavior (P)	No
36	Ngangro, N. N., D. Ngarhounoum, M. N. Ngangro, N. Rangar, M. G. Siriwardana, V. H. des Fontaines and P. Chauvin	2012	Pulmonary tuberculosis diagnostic delays in Chad: a multicenter, hospital-based survey in Ndjamena and Moundou. BMC Public Health 12: 513	Chad	Infrastructure (P + S), Health seeking behavior (P + S)	No
37	Scott, V., V. Azevedo and J. Caldwell	2012	Improving access and quality of care in a TB control programme. SAMJ - South African Medical Journal 102(11): 837-840	South Africa	Infrastructure (S)	No

17	Seddon, J. A., A. C. Hesseling, M. Willemse, P. R. Donald and H. S. Schaaf	2012	Culture-confirmed multidrug-resistant tuberculosis in children: clinical features, treatment, and outcome. Clin Infect Dis 54(2): 157-166	South Africa	Infrastructure (P + S)	Yes
22	Umar, N. A., I. Abubakar, R. Fordham and M. Bachmann	2012	Direct costs of pulmonary tuberculosis among patients receiving treatment in Bauchi State, Nigeria. Int J Tuberc Lung Dis 16(6): 835-840	Nigeria	Cost (P)	No
41	Cowan, J., J. G. Cowan, S. Barnhart, S. Demamu, D. Fiseha, W. Graham, E. Melese, L. Reason, F. T. Asfaw, G. Feleke and B. Feleke	2013	A qualitative assessment of challenges to tuberculosis management and prevention in Northern Ethiopia. International Journal of Tuberculosis and Lung Disease 17(8): 1071-1075.	Ethiopia	Infrastructure (S)	No
18	Zimri, K., A. C. Hesseling, P. Godfrey-Faussett, H. S. Schaaf and J. A. Seddon	2012	Why do child contacts of multidrug-resistant tuberculosis not come to the assessment clinic? Public Health Action 2(3): 71-75	South Africa	Health seeking behavior (P)	Yes
38	Ebonwu, J. I., K. S. Tint and C. Ihekweazu	2013	Low treatment initiation rates among multidrug-resistant tuberculosis patients in Gauteng, South Africa, 2011. Int J Tuberc Lung Dis 17(8): 1043-1048	South Africa	Infrastructure (P + S)	No
40	Jacobson, K. R., D. Theron, E. A. Kendall, M. F. Franke, M. Barnard, P. D. van Helden, T. C. Victor, E. M. Streicher, M. B. Murray and R. M. Warren	2013	Implementation of genotype MTBDRplus reduces time to multidrug-resistant tuberculosis therapy initiation in South Africa. Clin Infect Dis 56(4): 503-508	South Africa	Infrastructure (S)	No
39	Yassin, M. A., D. G. Datiko, O. Tulloch, P. Markos, M. Aschalew, E. B. Shargie, M. H. Dangisso, R. Komatsu, S. Sahu, L. Blok, L. E. Cuevas and S. Theobald	2013	Innovative community-based approaches doubled tuberculosis case notification and improve treatment outcome in Southern Ethiopia. PLoS One 8(5): e63174	Ethiopia	Infrastructure (S)	No
43	Ansa, G. A., J. D. Walley, K. Siddiqi and X. Wei	2014	Delivering TB/HIV services in Ghana: a comparative study of service delivery models. Trans R Soc Trop Med Hyg 108(9): 560-567.	Ghana	Infrastructure (S)	No
45	Asefa, A. and W. Teshome	2014	Total delay in treatment among smear positive pulmonary tuberculosis patients in five primary health centers, Southern Ethiopia: A cross sectional study. PLoS ONE 9:7 Article Number: e102884.	Ethiopia	Health seeking behavior (P + S), Infrastructure (P + S)	No

60	Biya, O., S. Gidado, A. Abraham, N. Waziri, P. Nguku, P. Nsubuga, I. Suleman, A. Oyemakinde, A. Nasidi and K. Sabitu	2014	Knowledge, care-seeking behavior, and factors associated with patient delay among newly-diagnosed pulmonary tuberculosis patients, Federal Capital Territory, Nigeria, 2010. Pan Afr Med J 18 Suppl 1: 6	Nigeria	Health seeking behavior (P)	No
42	Dlamini-Mvelase, N. R., L. Werner, R. Phili, L. P. Cele and K. P. Mlisana	2014	Effects of introducing Xpert MTB/RIF test on multi-drug resistant tuberculosis diagnosis in KwaZulu-Natal South Africa. BMC Infect Dis 14: 442	South Africa	Infrasturcture (S)	No
23	Laokri, S., M. Dramaix-Wilmet, F. Kassa, S. Anagonou and B. Dujardin	2014	Assessing the economic burden of illness for tuberculosis patients in Benin: determinants and consequences of catastrophic health expenditures and inequities. Trop Med Int Health 19(10): 1249-1258	Benin	Cost (P)	No
44	Makwakwa, L., M. L. Sheu, C. Y. Chiang, S. L. Lin and P. W. Chang	2014	Patient and health system delays in the diagnosis and treatment of new and retreatment pulmonary tuberculosis cases in Malawi. BMC Infect Dis 14: 132.	Malawi	Health seeking behavior (P), Infrastructure (S)	No
46	Virenfeldt, J., F. Rudolf, C. Camara, A. Furtado, V. Gomes, P. Aaby, E. Petersen and C. Wejse	2014	Treatment delay affects clinical severity of tuberculosis: A longitudinal cohort study. BMJ Open 4:6 Article Number: e004818.	Ginea-Bissau	Infrastructure (P + S)	No
47	Yimer, S. A., G. A. Bjune and C. Holm-Hansen	2014	Time to first consultation, diagnosis and treatment of TB among patients attending a referral hospital in Northwest, Ethiopia. BMC Infectious Diseases 14(1): 19-19 11p	Ethiopia	Infrastructure (P + S)	No
24	Yitayal, M., A. Aseffa, G. Andargie, L. Wassie and M. Abebe	2014	Assessment of cost of tuberculosis to patients and their families: a cross-sectional study at Addet Health Center, Yilmana Densa District, Amhara National Regional State. Ethiop Med J Suppl 1: 23-30	Ethiopia	Cost (P)	No
25	Abimbola, S., K. N. Ukwaja, C. C. Onyedum, J. Negin, S. Jan and A. L. C. Martiniuk	2015	Transaction costs of access to health care: Implications of the care-seeking pathways of tuberculosis patients for health system governance in Nigeria. Global Public Health 10(9): 1060-1077	Nigeria	Cost (P), Health seeking behavior (P)	No
49	Cox, H. S., J. F. Daniels, O. Muller, M. P. Nicol, V. Cox, G. van Cutsem, S. Moyo, V. De Azevedo and J. Hughes	2015	Impact of decentralized care and the Xpert MTB/RIF test on rifampicin-resistant tuberculosis treatment initiation in Khayelitsha, South Africa. Open Forum Infectious Diseases 2:1 Article Number: ofv014.	South Africa	Infrastructure (S)	No
61	Cremers, A. L., M. M. de Laat, N. Kapata, R. Gerrets, K. Klipstein-	2015	Assessing the consequences of stigma for tuberculosis patients in urban Zambia. PLoS One 10(3): e0119861	Zambia	Health seeking behavior (P + S)	No

	Grobusch and M. P. Grobusch					
50	Ross, J. M., A. Cattamanchi, C. R. Miller, A. J. Tatem, A. Katamba, P. Haguma, M. A. Handley and J. L. Davis	2015	Investigating barriers to tuberculosis evaluation in Uganda using geographic information systems. American Journal of Tropical Medicine and Hygiene 93(4): 733-738.	Uganda	Infrastructure (S)	No
48	Van Den Handel, T., K. H. Hampton, I. Sanne, W. Stevens, R. Crous and A. Van Rie	2015	The impact of Xpert® MTB/RIF in sparsely populated rural settings. International Journal of Tuberculosis and Lung Disease 19(4): 392-398	South Africa	Infrastructure (S)	No

*Barriers: Cost, Infrastructure, Health Seeking Behavior. Level of analysis: Patient, system

All studies described direct out-of-pocket costs for patients. Five studies described indirect costs (Datiko & Lindtjørn, 2010; Laokri et al., 2014; Mauch et al., 2011; Vassall et al., 2010; Yitayal et al., 2014). One study reported median total of direct and indirect costs was equivalent to 45% of median annual individual incomes ($350 USD) with indirect costs accounting for 85% of total costs (Mauch et al., 2011).

Two articles described costs associated with caretakers in which the cost burden to guardians or caretakers was high (Mauch et al., 2011; Vassall et al., 2010). In addition, one study also measured intangible costs (non-monetary costs affecting quality of life, such as pain, suffering, and social stigma) in addition to catastrophic expenditures (Laokri et al., 2014). Another study measured transaction costs, the difference between total direct costs incurred by a patient and total direct costs incurred prior to the first contact with a National TB Control Program provider (Abimbola et al., 2015). In one of the only intervention studies, Abimbola (2015) cited that interventions for reducing transaction costs should include effective decentralization of services to integrate TB care with primary healthcare. Studies suggested that encouraging the engagement of communities to help address health education and facilitation of referral linkages among formal and informal care providers may reduce costs. None of the cost studies specifically addressed pediatric or youth barriers beyond those of the general population.

2.3.3 Infrastructure as a barrier to TB treatment initiation

Infrastructure as a barrier to TB treatment was included in 29 articles (Appendix E) (Ansa, Walley, Siddiqi, & Wei, 2014; Asefa & Teshome, 2014; Beyers et al., 1994; Botha, den Boon, Lawrence, et al., 2008; Botha, Den Boon, Verver, et al., 2008; Cambanis et al., 2005; Cowan

et al., 2013; H. S. Cox et al., 2015; Datiko & Lindtjørn, 2010; Dembele et al., 2006; den Boon et al., 2008; Dlamini-Mvelase et al., 2014; Ebonwu et al., 2013; Edginton, Wong, Phofa, Mahlaba, & Hodkinson, 2005; Engelbrecht et al., 2006; Jacobson et al., 2013; Lienhardt et al., 2001; Makwakwa, Sheu, Chiang, Lin, & Chang, 2014; Martin, Baptiste, & Krieger, 2004; Ngangro et al., 2012; Ross et al., 2015; Scott et al., 2012; Seddon, Hesseling, Willemse, et al., 2012; Sendagire, Schim Van der Loeff, Mubiru, Konde-Lule, & Cobelens, 2010; Van Den Handel et al., 2015; Virenfeldt et al., 2014; Yassin et al., 2013; S. Yimer, Bjune, & Alene, 2005; S. A. Yimer, Bjune, & Holm-Hansen, 2014). Three of the four pediatric-only studies included infrastructure barriers (Beyers et al., 1994; Engelbrecht et al., 2006; Seddon, Hesseling, Willemse, et al., 2012). Infrastructure includes structural or organizational issues such as geography or distance to TB treatment centers, laboratory capacity, level of service, health services delay or quality of care, and initial loss to follow up (formerly known as initial default)[1]. Fourteen articles described geography and distance as barriers to TB care (Asefa & Teshome, 2014; Beyers et al., 1994; Cambanis et al., 2005; H. S. Cox et al., 2015; Datiko & Lindtjørn, 2010; Dembele et al., 2006; Edginton et al., 2005; Lienhardt et al., 2001; Makwakwa et al., 2014; Sendagire et al., 2010; Van Den Handel et al., 2015; Yassin et al., 2013; S. Yimer, Holm-Hansen, Yimaldu, & Bjune, 2009; S. A. Yimer et al., 2014). Facilities in rural areas with improved TB diagnostic and treatment capacity could reduce diagnostic and treatment delays (S. A. Yimer et al., 2014). Ten articles described laboratory and clinical services offered, such as the impact of drug-resistance testing, and point-of-care testing as barriers to treatment initiation (Cambanis et al., 2005; H. S. Cox et al., 2015; Dembele et al., 2006; Engelbrecht et al., 2006; Jacobson et al., 2013; Makwakwa et al., 2014; Scott et al., 2012; Van Den Handel et al., 2015; Yassin et al., 2013; S. A. Yimer et al., 2014).

Healthcare structures, such as the level of service at which TB disease is diagnosed, where treatment can be initiated, and where treatment can be sustained, was also described as a barrier to treatment initiation in 17 articles (Ansa et al., 2014; Botha, den Boon, Lawrence, et al., 2008; Cowan et al., 2013; H. S. Cox et al., 2015; Datiko & Lindtjørn, 2010; Dembele et al., 2006; Ebonwu et al., 2013; Edginton et al., 2005; Lienhardt et al., 2001; Martin et al., 2004; Ngangro et al., 2012; Ross et al., 2015; Scott et al., 2012; Van Den Handel et al., 2015; Yassin et al., 2013; S. Yimer et al., 2005; S. A. Yimer et al., 2014). For example, Sendigire (2010) found that over 90% of patients visited more than one healthcare provider and had an average of four visits prior to receiving a diagnosis of TB and less than 5% of patients were diagnosed on their first visit to a healthcare provider (Sendagire et al., 2010). Furthermore, fixed primary health care centers (PHCs) and mobile clinics were evaluated to assess the collection and recording process of results, with PHCs having 86% of patients having two sputum samples recorded while only 69% of mobile clinics reported two sputum results (Botha, den Boon, Lawrence, et al., 2008). All but two articles described a health services delay or the quality of care as a barrier to treatment initiation which in some instances prevented treatment initiation (Datiko & Lindtjørn, 2010; Ross et al., 2015). Overall, health service delays often resulted from centralization of health care as well as fragmentation between referrals, diagnostic delays, and hierarchical structures of health care (H. S. Cox et al., 2015; Ngangro et al., 2012; Van Den Handel et al., 2015).

Additionally, initial loss to follow up was considered a structural barrier. When a patient is diagnosed but never initiates TB treatment, often it is the health system's failure to report diagnostic results or make timely follow-up, rather than a patient's unwillingness to start therapy. However, a mixture of lost laboratory results, long wait times between sputum

collection and final culture results, and the number of providers and technicians handling the specimen can all contribute to this initial loss to follow up (Botha, Den Boon, Verver, et al., 2008). Seven studies specifically measured patients with initial loss to follow up, with rates as high as 40% (Botha, den Boon, Lawrence, et al., 2008; Botha, Den Boon, Verver, et al., 2008; den Boon et al., 2008; Dlamini-Mvelase et al., 2014; Ebonwu et al., 2013; Van Den Handel et al., 2015; Yassin et al., 2013). No article described loss to follow up as a function of patient age; however, Yassin, et al. (2013) disaggregated symptomatic patients and smear positive pulmonary TB patients by age and sex for their community-based TB intervention, which benefitted women, children, and vulnerable groups the most.

The three studies of child-only cohorts addressed delays for children and the complexity and value of culture confirmation for children with TB. Waiting for culture confirmation prior to treatment can greatly increase delays in children compared to initiating treatment when a clinical diagnosis is made (median 1 day with clinical diagnosis versus median 40 days with culture diagnosis) (Engelbrecht et al., 2006). Additionally, treatment is delayed in children when an adult source is unknown (median 58 days when adult source is known versus 123 days without a source) (Seddon, Hesseling, Willemse, et al., 2012). Follow-up in urban squatter communities was difficult, causing children in these locations to have significantly worse tracing than children in urban settled areas, rural agriculture areas, and rural settled areas (Beyers et al., 1994). All of these child-only cohort studies were conducted in South Africa.

2.3.4 Health seeking behavior as a barrier to TB treatment initiation

Health-seeking behavior is complex and is influenced by knowledge, attitudes, beliefs, and accessibility of care pathways. Nineteen articles examined health-seeking behaviors specific

to barriers and the subsequent delays they may cause (Appendix D) (Abimbola et al., 2015; Asefa & Teshome, 2014; Barker et al., 2006; Biya et al., 2014; Cremers et al., 2015; Dodor, 2012; Dodor, Kelly, & Neal, 2009; Eastwood & Hill, 2004; Edginton, Sekatane, & Goldstein, 2002; Edginton et al., 2005; Enwuru, Idigbe, Ezeobi, & Otegbeye, 2002; Makwakwa et al., 2014; Mfinanga et al., 2008; Ngangro et al., 2012; Salaniponi et al., 2000; Sendagire et al., 2010; S. Yimer et al., 2005; S. Yimer et al., 2009; Zimri et al., 2012). These behaviors include seeking care from formal and informal sectors, private and public healthcare providers, traditional healers, pharmacies or drug retailers, and private clinics. All 19 articles describing health-seeking behaviors considered patient-level behaviors (i.e. patient knowledge, attitudes, behaviors, and decisions regarding care pathways). Only three studies also considered system-level factors, including stigmatization from healthcare providers as well as provider knowledge of TB acting as barriers against patients seeking care (Dodor et al., 2009; Eastwood & Hill, 2004; Edginton et al., 2005).

All but one article in this category addressed knowledge, attitudes, or beliefs about TB (Barker et al., 2006). All articles but four discussed patient care pathways (Asefa & Teshome, 2014; Cremers et al., 2015; Dodor et al., 2009; Zimri et al., 2012). Eight studies were qualitative, (Dodor, 2012; Dodor et al., 2009; Eastwood & Hill, 2004; Edginton et al., 2002; Edginton et al., 2005; Enwuru et al., 2002; Salaniponi et al., 2000; Zimri et al., 2012) ten were quantitative, (Abimbola et al., 2015; Asefa & Teshome, 2014; Barker et al., 2006; Biya et al., 2014; Makwakwa et al., 2014; Mfinanga et al., 2008; Ngangro et al., 2012; Sendagire et al., 2010; S. Yimer et al., 2005; S. Yimer et al., 2009) and one used mixed methods (Cremers et al., 2015). Patient knowledge of the causes of TB varied between 0% to 63% of patients having 'good' knowledge

of TB (Eastwood & Hill, 2004; Edginton et al., 2005). Stigma was often cited in regards to patients' attitudes and beliefs about TB, and patients often associated TB with HIV/AIDS (Cremers et al., 2015; Edginton et al., 2005). Some studies identified patients who lacked knowledge of TB, yet delayed seeking care because of fear of potential disease or its attached stigma (Dodor, 2012; Salaniponi et al., 2000). Preference for traditional medicine was also cited (Abimbola et al., 2015; Barker et al., 2006; Dodor, 2012). In addition, parents voiced concern about their children being exposed to increased infections while waiting to be seen at healthcare facilities, which significantly contributed to children not receiving care (OR 2.45, 95% CI 1.07-5..60, p = 0.03) (Zimri et al., 2012).

Patients' decisions of where to first seek care was influenced by numerous factors. These decisions were made by patients themselves, by close family members, or by healthcare workers (Enwuru et al., 2002; Salaniponi et al., 2000). Distance from home and mode of transport also was a factor in where to seek care, with closer proximity to home and walking distance preferred (Salaniponi et al., 2000). However, patients who visited health centers, private facilities, and health posts were more likely to experience delays compared to those who visited hospitals (S. A. Yimer et al., 2014). Eastwood (2004) reported that patients who consulted with pharmacies had diagnostic delays of around one month, while patients who consulted traditional healers had delays of several months. Many studies cited multiple care provider visits prior to diagnosis and appropriate treatment of TB with one study citing upwards of six facilities being visited (Edginton et al., 2005). In cases where the mother was the source of MDR-TB infection, children were almost four times less likely to receive MDR-TB care than if the

mother was not the source of infection (OR 3.78, 95% CI 1,29-11.1, p = 0.02) (Zimri et al., 2012). Thus, children with close house-hold contact to MDR-TB received delayed care.

2.4 Discussion

This review suggests that more research in younger populations is urgently needed related to barriers to TB treatment. Previous studies have described delayed treatment for children and youth with HIV or those with TB (Ettehad et al., 2012; Kendall et al., 2013; Shisana et al., 2014). However, there is a paucity of research specifically pertaining to TB treatment initiation in youth with or without HIV (Desmond Tutu HIV Foundation, 2015; Isaakidis, Paryani, et al., 2013). More specifically, the epidemiology of DR-TB and DR-TB/HIV coinfection and treatment in youth remains unclear. Children and youth are now a priority populations in TB research (WHO, 2016c). Thus, there should be increased research specific to children and youth. Only four of the reviewed studies were specific to children and youth. These four studies focused on barriers to timely treatment initiation with a pediatric lens. Interestingly, most of the same barriers existed for adults and children except for increased social, logistic, and cultural factors contributing to pediatric non-attendance at clinics including the mother also being ill, which likely would not affect adults as much as children (Zimri et al., 2012).

2.4.1 Cost barriers

Both direct and indirect costs pose barriers to TB treatment initiation for individuals of all ages in sub-Saharan Africa. Additionally, intangible costs and costs associated with caretaker burden influence when and where someone seeks TB treatment. Catastrophic medical expenses and poverty can delay, and potentially prevent, individuals from initiating TB treatment (Whitehead et al., 2001). Therefore, community-based TB treatment initiation, and grants and

other resources for transportation, nutrition, and financial services such as through National TB Programs, may enable earlier and more adequate TB treatment. Interestingly, cost barriers were not found to be reported until 2010, suggesting that economic studies have only recently become important to researchers in sub-Saharan Africa.

Costs unique to child and youth TB treatment initiation must be studied more specifically. For example, pediatric drug formulations are often more expensive than standard adult formulations, which may create additional financial barriers for either families if paying out of pocket or health systems if provided by National TB Programmes (TB Alliance, 2015). Additionally, intangible costs such as lost days of school for a child and missed days of work for a parent double the burden. No studies assessed caretaker costs among pediatric cohorts; two studies evaluating these intangible costs only included individuals 15 years and older (Mauch et al., 2011; Vassall et al., 2010). In addition, pediatric TB specialists are often in more centralized or urban areas, creating a heavier financial burden for younger children who must travel further from home, and often must be accompanied by an adult.

2.4.2 Infrastructure barriers

Delays were observed in children from rural or farming areas, and when errors were made by treating physicians (Beyers et al., 1994). Additionally, lack of point of care laboratory capacity and the lack of ability to perform certain diagnostic testing (such as cultures and drug susceptibility testing) often caused treatment delays, especially for drug-resistant TB (Engelbrecht et al., 2006). Thus, starting same-day empiric treatment prior to culture results can greatly reduce barriers to initiating treatment.

Improving health system infrastructure through integrating TB services into existing programs was found to be critical for all ages. Deficiencies of health systems were apparent across multiple settings; application of recommended TB/HIV integration programs should be utilized (World Health Organization, 2012). The level of care at which TB services were available influenced where patients first sought treatment, with centralized services often delaying or inhibiting treatment initiation (Datiko & Lindtjørn, 2010; Ngangro et al., 2012).

Geographic barriers are common and limit access to treatment. Thus, developing diagnostic and treatment options in rural areas, and training health care providers on the signs and symptoms of TB, could remove some geographic barriers to TB treatment initiation (Sendagire et al., 2010; Van Den Handel et al., 2015). Community-based interventions have shown to be cost-effective, such as leveraging health extension workers to educate communities on sanitation and hygiene, debunking TB and HIV myths and lessening stigma, as well as in conducting screenings (Datiko & Lindtjørn, 2010; den Boon et al., 2008). While the public sector is by no means a panacea for TB treatment initiation, it could actively engage and educate traditional practitioners, the private sector, and community partners to improve services to patients closer to their homes and at more affordable costs (Ardian et al., 2007; Magazi et al., 2014). Overall, practical, effective policies to strengthen health systems can create enormous benefits in TB care for all ages, and children in particular.

2.4.3 Health-seeking behaviors

Educating both providers and patients about TB and the importance of timely, effective treatment can greatly improve outcomes. Although Edginton (2005) found that knowledge of TB was good in 63% of patients, 51% of patients were unaware of the cause of TB. Thus, 'good'

knowledge should be interpreted with caution, especially when assessing knowledge across studies using different measures. Similarly, two studies found TB stigma was associated with stigma against HIV in South Africa and Zambia, two high HIV prevalence countries (Cremers et al., 2015; Edginton et al., 2005). Thus, country context also effected health-seeking behaviors. Specific to children, when the source of MDR-TB was from the mother, clinic follow-up attendance was worse (Zimri et al., 2012). Providing patient-centered TB care is one way in which some barriers can be removed from accessing treatment initiation and improving clinic follow-up after diagnosis (Zachariah et al., 2012; Zimri et al., 2012).

Chaotic and uncoordinated services can cause delays and increase costs for patients with TB. A coordinated National TB Program can streamline services, thus improving general health education, promoting TB prevention, and regulating health care providers in both the private and public sectors. On the other hand, decentralized care provided through community-based organizations may facilitate easier, more cost-effective care pathways (Datiko & Lindtjørn, 2010). Decreasing the number of providers' patients visit prior to an accurate diagnosis and effective treatment is one way in which to facilitate more timely treatment initiation. These strategies would have even greater impact upon child and youth cases, though more research in this area is needed.

2.4.4 Limitations

Due to the inclusion of all study designs, there was great heterogeneity of these studies, therefore neither a pooled analysis nor meta-analysis was conducted and no summary measures (e.g. effect size) for specific interventions could be determined. Further, inconsistencies in cost measures was found to be a limitation, as well as differences across

countries. Not all studies captured data in the same manner, nor used the same definitions or timeframes for analysis. However, most articles noted in their limitations the difficulty of getting accurate income data and verifying direct and indirect costs in low-income settings. Although we undertook a systematic literature search, some studies meeting our inclusion criteria may have been missed.

2.4.5 Conclusion

Many patient- and system-level barriers to TB treatment initiation exist among children and youth in sub-Saharan Africa; however, through systematic review of literature, these barriers are more fully described for adults. To our knowledge, no study has correlated barriers to treatment initiation with patient outcomes, and more evidence in this area could benefit TB prevention—and could thereby save lives (Harris et al., 2016). The specific needs of children and youth should be prioritized in research, particularly around enhanced infrastructure such as early diagnosis and treatment initiation and community- and patient-centered approaches. We recommend more standardized language to describe barriers to TB treatment initiation within the TB research and advocacy community, to allow for more unified, collective, and powerful action (Table 1) (Zachariah et al., 2012). Addressing both patient- and system-level barriers is vital to improving patient outcomes, especially among young populations.

[1]NB: Many articles refer to initial loss to follow up as "initial default". Per MacPherson (2014) and Zachariah (2012) the authors have chosen to use the terminology "initial loss to follow up" as default is often considered pejorative and a victimizing word for individuals with TB.

3. Time to drug-resistant tuberculosis treatment in a South African prospective cohort

3.1 Introduction

Mycobacterium tuberculosis (TB) is the leading cause of infectious disease deaths worldwide. Over 95% of TB deaths occur in low- and middle-income countries (LMICs) (WHO, 2016c). Although 83% of patients with drug-susceptible TB are successfully treated or cured, only 28-52% of patients who initiate drug-resistant TB (DR-TB) treatment are successfully treated or cured (WHO, 2016c). DR-TB is a catch all term for TB that is resistant to at least one first line medication. The different types include Rifampin resistant TB, multi drug-resistant TB that is resistant to both isoniazid and rifampicin, and extensively DR-TB which has additional resistance to injectable agents and fluoroquinolones. Regardless of the extent of drug resistance in TB strains, early diagnosis and prompt, accurate treatment initiation is critical to cure, prevention of transmission, and ultimately the prevention of further drug resistance (WHO, 2016c).

South Africa has the world's third highest DR-TB burden (WHO, 2015). South Africa also carries the world's largest burden of HIV infection, with 18% of individuals infected with HIV globally living in South Africa (UNAIDS, 2013). HIV has been a driving force of the resurgence and spread of DR-TB, specifically in sub-Saharan Africa (WHO, 2015). Drug-resistance is a growing problem in South Africa with an estimated 1.8% (279,851) of new TB cases having drug-resistance and an estimated 6.7% (80,580) of TB retreatment cases having drug-resistance (WHO, 2015a). Only 62% of individuals with DR-TB in South Africa initiate treatment (WHO, 2015) in the year of diagnosis. To improve patient outcomes and prevent

transmission of DR-TB, South Africa recommends starting treatment within five days of diagnosis (Department of Health: Republic of South Africa, 2013).

The burden of DR-TB in children and youth is not fully understood. Difficulty in collecting samples, inconsistent definitions of age groups, lack of data disaggregation by age, and the difficulty of conducting rigorous research in highly endemic regions makes measuring DR-TB in children more complex (Becerra & Swaminathan, 2014; Sentinel Project on Pediatric Drug-Resistant Tuberculosis, 2013; WHO, 2016c). Some youth with HIV have been found to delay anti-retroviral therapy; yet, this is less known for youth with TB or DR-TB (Shisana et al., 2014; Storla et al., 2008). There is also inadequate information on individual- and system-level factors associated with treatment initiation for DR-TB and DR-TB/HIV coinfection in South Africa particularly for youth (Ettehad et al., 2012; Lawn et al., 2006).

The purpose of this study was to describe the time from DR-TB diagnosis to treatment initiation for people in South Africa with DR-TB with and without HIV and to evaluate the influence of age on the timing of treatment initiation after controlling for patient and health system characteristics. It was hypothesized that younger patients would have a greater number of days from DR-TB diagnosis to DR-TB treatment initiation.

3.2 Methods

3.2.1 Design

The analysis addressed the extent to which patient age was associated with these two outcomes, after adjusting for clinical characteristics of the patient and healthcare system characteristics that could influence the timing of treatment initiation. This secondary analysis was designed to: (1) determine whether DR-TB treatment was initiated in five or less days from

DR-TB diagnosis as per South African guideline, (2) describe the number of days from DR-TB diagnosis to DR-TB treatment initiation. Data were collected as part of an ongoing 5-year, prospective, cluster-randomized trial investigating the effects of a nurse-led case management to improve treatment outcomes in individuals 13 years of age and older with DR-TB residing in the Eastern Cape and KwaZulu-Natal provinces of South Africa. The study received Institutional Review Board approval from Duke University (Pro00067846) and Johns Hopkins University (NA_00078899/CIR00009135).

3.2.1.1 Parent study

The 5-year parent cluster-randomized trial began in November 2014 and includes 10 treatment sites randomized to either a nurse case management (NCM) intervention or control arm with the primary outcome evaluating the proportion of patients who experience successful treatment outcomes (timeframe: 24-36 months). The NCM intervention consists of a nurse coordinating DR-TB treatment with weekly phone calls and/or visits during the intensive first 6-months of treatment to monitor labs and weight, manage side effects (such as hearing loss), and conduct monthly visits during the subsequent 30-month continuation phase. Patients at control sites receive physician-led standard of care. The parent study clinical trial protocol is described elsewhere (NCT02129244).

3.2.2 Setting and sample

All treatment sites were public facilities in KwaZulu Natal and the Eastern Cape provinces in South Africa, two provinces with high DR-TB incidence (Department of Health: Republic of South Africa, 2013). Participants were generally poor or had exhausted medical aid available in the private sector. Sites did not collect racial statistics; however, most individuals

receiving care in these settings were Black South Africans. All racial groups were screened for eligibility and had equal access to recruitment. Any patient enrolled in another clinical trial was not eligible.

As of November 2016, baseline and medication data were available for 542 individuals 13 years or older with DR-TB who were initiated on DR-TB treatment between November 2014 and August 2016. Participants were eligible if they had initial DR-TB diagnosis, and were consented within seven days of treatment. One participant did not have an initial diagnosis of DR-TB and complete data were unavailable for 20 participants (See Figure 5).

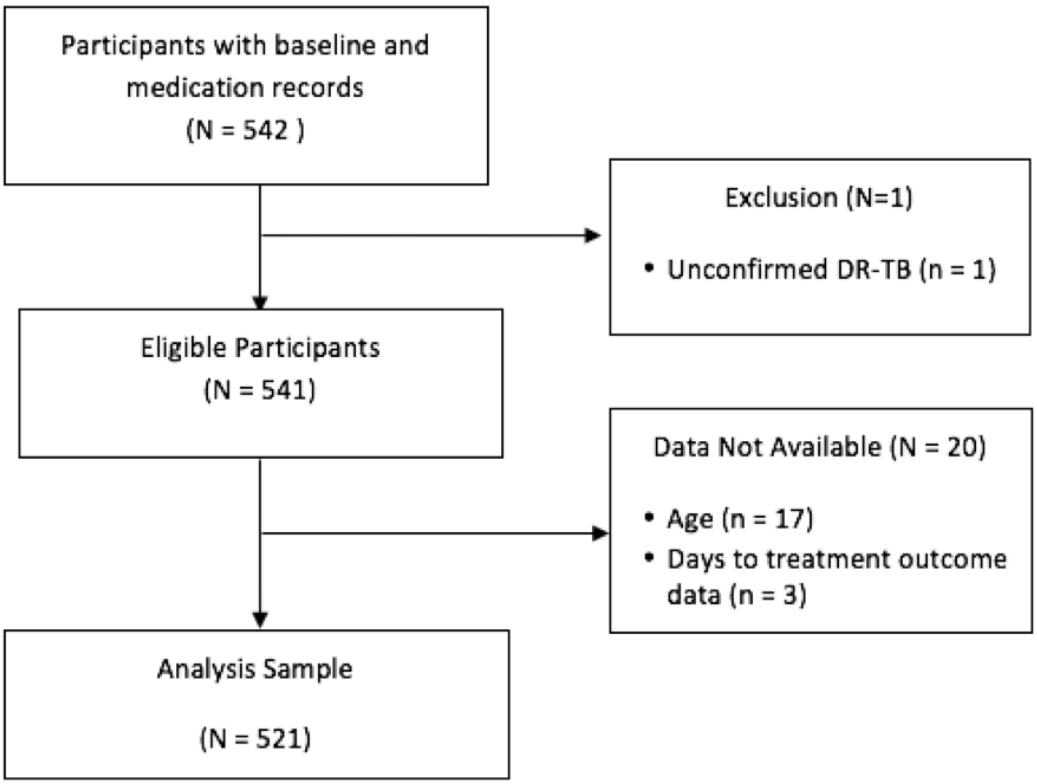

Figure 4: Participant flow diagram

3.2.3 Measures

3.2.3.1 Outcome variables

The time to treatment initiation outcomes were: (1) DR-TB treatment initiated in five or less days from the DR-TB diagnosis, as defined per South African guideline (primary outcome), and (2) days from DR-TB diagnosis to DR-TB treatment initiation. Time to treatment initiation was determined as the time from collection of a sputum sample from which any at least rifampicin resistance was determined to the date second-line anti-TB treatment was initiated.

3.2.3.2 Patient characteristics

Sociodemographic and clinical information were collected by patient interview and medical chart review. Patient-level characteristics included age, sex, history of TB disease, and HIV coinfection. Anti-retroviral treatment (ART), prior exposure to TB. Education level (none, some education, some/complete university), marital status (married/living with partner, single), and employment status (unemployed, employed, student) were obtained and presented as additional descriptive data especially relevant for the adult population.

3.2.3.3 System characteristics

Two system-level characteristics were examined. Urban-rural classification of the hospital or clinic where treatment was provided was designated by the parent study and categorized as urban/peri-urban or rural. Geographic location was defined by treatment site province in either Eastern Cape or KwaZulu-Natal.

3.2.3 Data sources and procedures

Trained study personnel for the parent cluster-randomized trial obtained information by patient interview and medical chart review. Treatment initiation and HIV status were

confirmed in the medical chart and the date of sputum sample for DR-TB diagnosis was obtained from the South African National Health Laboratory System. Data captured concurrent with care were written on paper case report forms. After quality assurance onsite comparing of medical records with paper case report forms, the latter were scanned for storage on a secure server at the parent study's institution. All data were manually entered and stored in REDCap, a web-based application. REDcap data were downloaded into an analytic dataset that was archived on a password protected server at Duke University. These data were cleaned and missing values were entered by verification on original case report forms. Data analysis was conducted using SAS (version 9.3, Cary, NC).

3.2.4 Data analysis

Descriptive statistics summarize the (a) demographic and clinical characteristics of the patients; (b) site characteristics of the healthcare system; and (c) the time to treatment outcome variables. Non-directional statistical tests were performed with the level of significance set at 0.05 for each test. The level of significance was not adjusted for multiple tests and outcomes due to the exploratory nature of this secondary analysis. Effect sizes were used to address clinical significance.

3.2.4.1 Sample characteristics

Descriptive statistics were used to describe the sociodemographic and clinical characteristics for the total sample, adults, and youth. The youth group included individuals between the age of 13 and 24 years. Because it was hypothesized that younger patients (particularly youth) will have a greater number of days from DR-TB diagnosis to DR-TB treatment initiation, the two age groups (youth and adults) were compared regarding

sociodemographic and clinical characteristics. Chi-square tests or Fisher's Exact Tests were used to test for age group differences in proportions for categorical measures and General Linear Models (GLMs, adjusting for sample size differences) were used to test for differences in means for continuous measure. Additionally, descriptive statistics were used to detail the patient sociodemographic and clinical characteristics, site characteristics, and time to treatment initiation outcomes at each of the ten treatment sites.

3.2.4.2 DR-TB treatment initiation in five or less days, per South African guideline

Whether treatment initiation occurred in five or less days from the DR-TB diagnosis, per South African guideline, was coded as 0 (no) and 1 (yes). As a preliminary step, a 4x2 chi-square test was conducted to compare differences in the proportion of patients in which the treatment was initiated within five days in four age subgroups: (1) youth, age 13-24; (2) adults, age 25-35, (3) adults, age 36-50, and (4) adults, age 50 or older (United Nations Department of Economic and Social Affairs, 2013; WHO, 2016a).

For the primary analysis, logistic regression for binary outcomes was used to examine the influence of age on the per guideline outcome and each covariate. Age was included as a continuous variable. Covariates were clinical characteristics of patients (sex, history of TB disease, HIV coinfection) and characteristics of the healthcare system (urban/rural, province). Table 3 includes the set of bivariate models. To address clinical significance, the odds ratio and 95% confidence interval for each explanatory variable was calculated.

3.2.4.3 Days to DR-TB treatment initiation

The outcome for this analysis was days from DR-TB diagnosis to DR-TB treatment initiation. Descriptive statistics for the days to treatment initiation indicated that the data

distribution was severely right skewed (skewness=3.5). A natural log transformation was employed to normalize the data distribution for this continuous outcome. The variable log (days to treatment + 1) was derived for each patient by adding +1 to the days to treatment initial value and calculating the natural log of that value. Adding the constant 1 was necessary because days to treatment value was 0 for some patients (initiation same day as diagnosis, N=2). This "log of days to treatment" variable was used in all subsequent analysis.

The analytic approach applied to days to treatment initiation was the same as the "in five or less days" outcome, except that the analytic tools designed for continuous measures were applied. For the preliminary analysis, days to treatment in the four age groups were compared using a non-parametric Kruskal-Wallis test due to skewness and the means of the log of days to treatment were compared using a GLM to conduct the one-way ANOVA.

For the primary analysis, linear regression models were conducted on the log of days to treatment to evaluate the influence of age and each covariate. Age was included as a continuous variable. The final model included the effects of age, and covariates significant at the $p<0.10$ level on the log of days to treatment outcome.

3.2.5 Power calculation

The primary outcome for this secondary analysis was the binary DR-TB treatment initiation in five or less days as per guideline. The sample size of 521 would be sufficient to provide 80% statistical power to detect an odds ratio of 2.0 for age when applying a logistic regression model for a binary outcome with five covariates and the two-tailed significance level set at 0.05 (Vaeth & Skovlund, 2004).

3.3 Results

3.3.1 Sample

The sample included 542 individuals. Twenty-one were excluded for exclusions or incomplete data (Figure 5). Table 3 summarizes the sample characteristics for the total sample (*N*=521), adults (*N*=434), and youth (*N*=87).

Table 3: Sample characteristics

Baseline Characteristic	**N**	**Total (N=521)**	**Adult (N=434)**	**Youth (N=87)**	***p*-value**
Age, in years	521	35.6 ± 10.9	38.4 ± 9.7	21.7 ± 2.6	<.000
Male sex	521	286 (54.9%)	250 (57.6%)	36 (41.4%)	0.006
Education level	516				0.030
None		24 (4.7%)	24 (5.6%)	0 (0.0%)	
Some education		461 (9.0%)	381 (88.8%)	80 (92.0%)	
Some/complete university		31 (6.0%)	24 (5.6%)	7 (8.1%)	
Employment status	512				<.000
Unemployed		273 (53.3%)	231 (54.4%)	42 (48.3%)	
Employed		199 (38.9%)	187 (44.0%)	12 (13.8%)	
Student		40 (7.8%)	7 (1.7%)	33 (37.9%)	
Living with partner	520	103 (19.8%)	100 (23.1%)	3 (3.5%)	<.000
HIV coinfection	510	384 (75.3%)	343 (80.9%)	41 (47.7%)	<.000
HIV patients on ART	244	202 (82.8%)	186 (83.0%)	16 (80.0%)	0.730
History of TB disease	514	271 (52.7%)	245 (57.4%)	26 (29.9%)	<.000
Prior TB exposure	485	150 (30.9%)	119 (29.5%)	31 (38.3%)	0.117
Exposure drug resistant TB	127	58 (45.7%)	41 (41.4%)	17 (60.7%)	0.070
Eastern Cape province	521	234 (44.9%)	199 (45.9%)	35 (40.2%)	0.336
Urban site	521	242 (46.4%)	199 (45.9%)	43 (49.4%)	0.542
Hospital admission	517	266 (51.5%)	225 (52.2%)	41 (47.7%)	0.443

Youth=Ages 13-24 years; n (%) for categorical variables; mean ± standard deviation for continuous measures; Chi-Square/Fisher's Exact Test for categorical characteristics; General Linear Model (GLM) for continuous characteristics; Employed includes: full time, part time, homemaker, and retired; Some education

includes: some primary, secondary, or technical school complete. Living with partner includes: married, living with boyfriend/girlfriend.

3.3.2 Sample characteristics

The mean age was 35.6 years, with age ranging from 14.0 to 74.9 years. The overall sample composition was 55% male, 5% with no formal education, 53% unemployed, 75% coinfected with HIV, and 53% with a history of TB disease. Fifty-four percent of the patients were treated at rural sites (versus urban/peri-urban), 45% were treated at an Eastern Cape site, and 52% were admitted to the hospital at treatment initiation.

There were 87 youth (17%) in the total sample (Table 1). The comparison of adults and youth indicated that the two groups significantly differed. It was more common for youth to have formal education and be students and for adults to be employed and living with a partner. HIV coinfection was 80.9% among adults and 47.7% among youth (p<0.001) but there was no difference in the percentage of adults versus youth with HIV on ART (p=0.730). History of TB was also higher among adults (57.4%) versus youth (29.9%; p <0.001). Appendix Table 1 details the patient and site characteristics by treatment site.

3.3.3 Timing of treatment initiation

Among the 521 patients enrolled, 82 (16%) received DR-TB treatment in five or less days as per guideline. Table 4 presents the number and percent of the patients who received treatment per guideline recommendations and median number of days to treatment initiation for four age groups. The comparison of treatment initiation within 5 days by age subgroups did not differ significantly (X^2=0.716, df=3, p =0.870). The median number of days to treatment initiation was 11 days (range: 0 to 180). Time to treatment in number of days did not differ by age group (Kruskal-Wallis: X^2=3.841, p =0.279); log of days to treatment (GLM: F=0.89, df=3, 517,

p =0.444).

Table 4: Days to TB treatment: descriptive statistics

		Age Groups				
Time to Treatment	**Total (N=521)**	**13-24 (N=87)**	**25-35 (N=193)**	**36-50 (N=184)**	**50+ (N=57)**	***p*-value**
Per guideline (5 or less days to treatment)	82 (15.7%)	14 (16.1%)	30 (15.5%)	27 (14.7%)	11 (19.3%)	0.8695
Days to treatment						
Mean	17.1	17.2	15.5	19.3	15.3	
Standard deviation (SD)	(18.4)	(19.0)	(14.9)	(21.7)	(15.5)	
Median	11.0	12.0	10.0	13.5	9.0	0.2792
25th, 75th percentile	7.0, 20.0	8.0, 21.0	7.0, 18.0	7.0, 23.0	7.0, 18.0	
Minimum, Maximum	0.0, 180.0	0.0, 142.0	1.0, 87.0	0.0, 180.0	1.0, 77.0	
Log (days to treatment + 1)						
Mean	2.6	2.6	2.5	2.6	2.5	0.4435
SD	(0.8)	(0.8)	(0.7)	(0.9)	(0.8)	
Median	2.5	2.6	2.4	2.7	2.3	
25th, 75th percentile	2.1, 3.0	2.2, 3.1	2.1, 2.9	2.1, 3.2	2.1, 2.9	
Minimum, Maximum	0.0, 5.2	0.0, 5.0	0.7, 4.5	0.0, 5.2	0.7, 4.4	

Log of days to treatment+1 = natural log of (days to treatment +1); Per guideline: p-value for 4 x 2 chi-square test; days to treatment: p-value for non-parametric Kruskal-Wallis Test; Log (days to treatment + 1): p-value for a General Linear Model (GLM).

3.3.4 Age and treatment initiation in five days or less, as per guideline

Table 5 presents the results from the bivariate logistic regression models for the treatment initiation as per guideline outcome. Treatment initiation as per guideline was not associated with age (p =0.795). No covariates were significant at p<0.10 level in bivariate analysis. Thus, no multivariate analyses were conducted.

Table 5: DR-TB Treatment as Per Guideline (Less Than or Equal to Five Days): Bivariate Logistic Regression Models

Variables	*N*	*Wald chi-square*	*df*	OR	OR 95% CI	Model R^2	*p*-value
Age (in years)	521	0.07	1	1.003	0.982-1.025	0.000	0.795
Sex	521	0.57	1	0.944	0.587-1.518	0.000	0.812
History of TB disease	514	2.31	1	1.455	0.897-2.361	0.005	0.128
HIV coinfection	510	1.96	1	1.536	0.842-2.801	0.004	0.162
Urban Site	521	1.50	1	0.741	0.459-1.197	0.003	0.221
EC Province Site	521	1.56	1	1.351	0.842-2.166	0.003	0.212

Age included as a continuous variable from older to younger; EC= Eastern Cape; OR = odd ratio; 95% CI = 95% confidence interval.

3.3.5 Age and days to treatment initiation

Table 6 details the results of the set of bivariate and multivariate linear regression models for the log of days to treatment initiation as the outcome. Days to treatment was not associated with age (p=0.876). Urban site (p=0.000) and Eastern Cape province (p=0.093) were retained for the multivariate model in addition to age. In the multivariate model, only urban site remained significant (p=0.000).

Table 6. DR-TB Treatment in total time to DR-TB treatment: Bivariate and multivariate models

Bivariate Models	*N*	*t-value*	*df*	*p*-value
Age	521	-0.16	1	0.876
Sex	521	0.50	1	0.618
History of TB disease	514	-0.44	1	0.659
HIV coinfection	510	-1.39	1	0.164
Urban Site	521	3.58	1	0.000
EC Province Site	521	-1.68	1	0.093
Multivariate Model				
Age	521	-.10	1	0.924
Urban Site	521	3.64	1	0.000
EC Province Site	521	-1.82	1	0.070

Age included as a continuous variable from older to younger; EC = Eastern Cape; Multivariate model: age and variables significant at p<0.10 level.

3.3.6 Urban site and treatment initiation

Of the covariates examined, only location of care was associated with the timing of treatment and only with median days to treatment. Exploratory analysis of the timing of treatment by location of care found that the median days to treatment initiation for those treated at rural versus urban sites was 10 versus 15 days, respectively (t=3.64, df=1, p=0.000) (Appendix G). Among rural sites, the timing of treatment for youth was 10 days and adults was 10 days. Among urban sites, the timing of treatment for youth was 16 days and adults was 14 days.

3.4 Discussion

Currently little is known regarding the time to DR-TB treatment, and to our knowledge, this has never been assessed specifically for youth and adults in South

Africa. This study of individuals with DR-TB in two South African provinces found treatment to be delayed for 84% of individuals, regardless of age. Only one in six individuals received DR-TB treatment per the timeline specified in the South African guidelines and the median time to treatment from diagnosis was 11 days. Treatment initiation within five days varied from 0-38% across individual treatment locations, with earlier treatment at rural sites. These findings indicate opportunities to improve the timeliness of DR-TB treatment for all ages in South Africa.

Compared with the South African National TB Program recommendation of treatment initiation within five days of diagnosis, the WHO promotes early treatment initiation within four weeks of DR-TB diagnosis (WHO, 2016d). Given less stringent WHO guidelines, at least 75% of this study's participants (75% of youth and 75% of adults) would have been considered within the recommended period to initiate treatment. Lack of consistent global guidelines for treatment initiation are due to insufficient evidence to support that shorter time from diagnosis to treatment lead to better patient outcomes (Harris et al., 2016; WHO, 2016d). However, because South Africa has access to advanced technology with GeneXpert diagnostics, and they have implemented decentralized care (including both inpatient and community treatment), South Africa clinical and policy experts recommend earlier DR-TB treatment initiation (Department of Health: Republic of South Africa, 2013). Time to treatment initiation of 11 days in this study is shorter than previously reported studies in South Africa

reporting on average of two weeks to greater than two months (Cox et al., 2014; Dlamini-Mvelase et al., 2014; J. E. Farley et al., 2011; Jacobson et al., 2013; Seddon, Hesseling, Willemse, et al., 2012). Delayed initiation and inappropriate treatment are major barriers to cure for DR-TB in South Africa, leading to high mortality and widespread DR-TB transmission in the community (Harries et al., 2010; Nkosi et al., 2013; Weyer et al., 2007). Of note, none of these prior studies specifically compared youth and adult populations.

Although there is little research on DR-TB treatment initiation in youth with or without HIV (Desmond Tutu HIV Foundation, 2015; Isaakidis, Paryani, et al., 2013), youth (15 to 24 years of age) have been identified as being exceptionally vulnerable to delays in diagnosis, treatment initiation, and appropriate treatment for HIV care (Committee On Pediatric, 2013; Ettehad et al., 2012; Kaufman, 2006; Kendall et al., 2013; Muller et al., 2011; Shisana et al., 2014; United Nations Department of Economic and Social Affairs, 2013, 2015). However, in this study age was not a significant predictor of time to treatment initiation. In this study, most youth were in their early twenties and thus the expected delay from previously studied barriers may not have been as prominent. Studies with a larger proportion of the sample of younger youth (13-18 years) may provide more insight into the outcomes in this age group.

Patients treated at urban sites received treatment in significantly more days than patients treated at rural sites. Some urban DR-TB treatment centers are overwhelmed

with the number of referrals they receive and unfortunately must place patients on DR-TB treatment waitlists, which could contribute to longer delays in urban areas. Although our study did not examine availability of diagnostic technologies, healthcare providers or the provision of centralized care, it is possible that our findings were influenced by South African reform initiatives to improve the rural health care workforce for DR-TB care (van Rensburg, 2014).

Recently, the WHO and the South African government have endorsed ambulatory care for DR-TB treatment unless a patient requires hospital level care (Department of Health: Republic of South Africa, 2013; WHO, 2016d). Despite a robust evidence base to recommend early treatment initiation, early diagnosis and treatment can narrow the timeframe for an individual to be infectious; thus, regardless of individual patient outcomes, early treatment should be a public health priority (Harris et al., 2016; WHO, 2016d). Assessing time to treatment, with programmatic differences at the site or system-level, and patient outcomes could provide valuable new knowledge.

Additional research including youth with DR-TB is necessary to examine modifiable factors that may decrease treatment delays (AVERT, 2014; UNAIDS, 2013). Implementation of guidelines is important for healthcare providers since once a patient is able to initiate treatment it must be the correct regimen. Gaining insight into factors related to DR-TB treatment initiation can be informative for TB/HIV care providers as well as policy makers. Although age did not influence time to treatment in this sample,

tailored youth interventions should still be considered and expanded if proven effective (AVERT, 2014; Shisana et al., 2014). Inclusiveness of youth allows for greater generalizability to the South African DR-TB population than many previous reports of only adult populations.

3.4.1 Limitations

This secondary analysis had several limitations. Although there was no evidence that time to treatment was a function of age, this study lacked the range in years of age among those categorized as youth. Also, patients were enrolled at time of treatment initiation rather than when sputum were collected. Thus, the sample inherently lacked any patients lost to follow-up between providing a sputum and receiving a result. Although this issue is common (Botha, den Boon, Lawrence, et al., 2008; Botha, Den Boon, Verver, et al., 2008), including individuals lost to follow-up between diagnosis and treatment initiation would have increased the difference detected, as time to treatment would have never occurred in these patients. As this was a secondary analysis of existing data, this study lacked the opportunity to examine additional factors that may have predicted timing of DR-TB treatment. Patient and provider attitudes and health beliefs towards treatment initiation as well as barriers to treatment initiation could be explored in future research. Additional characteristics regarding the delivery systems differences in each site such as availability of providers and access to relevant resources may be informative. Finally, treatment site could have been incorporated as a

random effect to consider variation in the outcome due to site differences. However, sample size was too small at some sites and we were unable to account for patient clusters.

3.5 Conclusion

This secondary analysis found that the timing of treatment initiation for individuals infected with DR-TB, with and without HIV coinfection in two South African provinces did not differ by age but individuals at rural sites received DR-TB treatment earlier than at urban sites. Only 16% of individuals met the stringent South African guidelines of treatment within five days of diagnosis. Early treatment initiation is critical for improved individual outcomes, prevention of disease transmission, as well as decreasing additional DR-TB resistance in communities. Future research should aim to include more teens and incorporate data regarding patient and provider attitudes and beliefs toward treatment.

4. Prescription of South Africa National Tuberculosis Program standardized drug regimen: influence of individual and health system factors in a prospective cohort

4.1 Background

Treatment oucomes for drug-resitant *Mycobacterium tuberculosis* (DR_TB) remains poor, with only 50% of individuals successfully treated globally (WHO, 2015). The World Health Organization (WHO) Stop TB Strategy has launched an initiative to

engage all care providers to link patients with public sector-based national TB programs (WHO, 2016c). Providers must be aware of guideline recommended treatments for all patients in order to appropriately scale up provision of TB services and treatment. A significant cause of DR-TB is inappropriate treatment (WHO, 2016c). DR-TB (TB resistant to first-line medications) spreads due to non-adherence to first-line medications as well as inadequate delivery of guideline recommended treatment (Langendam et al., 2012). Poor adherence to medication at the patient-level and poor adherence to guidelines at the healthcare system-level causes DR-TB to spread in communities and within hospitals where patients are being treated (Gandhi et al., 2014; Gandhi et al., 2006; Shah et al., 2017).

In South Africa, only 62% of individuals diagnosed with DR-TB initiate treatment (WHO, 2015b). Of those, only half (49%) successfully complete treatment or are cured (WHO, 2015b). Although DR-TB treatment is much more difficult than drug-susceptible treatment – more side effects, longer treatment duration, and more expensive – DR-TB is treatable and curable with second-line medications (Department of Health: Republic of South Africa, 2013). A standardized evidence-based approach has been designed by the Department of Health and communicated to clinicians through national treatment guidelines. However, guidelines must be followed to improve outcomes.

The standardized South African MDR-TB regimen follows WHO

recommendations and includes five antibiotics, amounting to 15 to 20 pills daily plus a daily injection during the initial six-month intensive phase of treatment (Department of Health: Republic of South Africa, 2013; TB Alliance, 2014). South Africa has standard drug formulations to comply with international requirements for minimum, maximum and average doses per kilogram for adults and children over eight years (Department of Health: Republic of South Africa, 2013). The regimen is designed at the national level, based on drug resistance data from prevalence surveys allowing for greater public health benefit and broader access to effective treatment (Department of Health: Republic of South Africa, 2013; Hughes & Osman, 2014). Rates of provider knowledge of DR-TB guidelines is largely unknown, yet from drug-susceptible TB literature, it is known that 67% of incorrect regimens were prescribed, with provider knowledge as a barrier (van der Werf et al., 2012).

Youth (15 to 24 years of age) are exceptionally vulnerable to delays in diagnosis, treatment initiation, and appropriate treatment of HIV (Committee On Pediatric, 2013; Ettehad et al., 2012; Kaufman, 2006; Kendall et al., 2013; Muller et al., 2011; Shisana et al., 2014; United Nations Department of Economic and Social Affairs, 2013, 2015). However, there is a paucity of research specifically pertaining to DR-TB treatment in youth (Desmond Tutu HIV Foundation, 2015; Isaakidis, Paryani, et al., 2013). Even the epidemiology of DR-TB and DR-TB/HIV coinfection and treatment in youth remains unclear. Thus, examining the relationship between age and prescription of

recommended treatment for DR-TB in South Africa will fill important knowledge gaps. The extent to which the guideline recommended treatment for DR-TB is delivered at treatment initiation and its relationship to age has not been previously examined in South Africa.

The overall goal of this secondary analysis of data collected as part of a cluster-randomized trial in South Africa was to (a) describe the prescription of the recommended treatment for DR-TB as per South African guidelines at treatment initiation and (b) evaluate the influence of individual and health system factors on whether the guideline recommended treatment in patients with DR-TB were prescribed. The study's primary aim was to compare individuals' prescribed regimen (medications, dosages, and frequencies) at treatment initiation for DR-TB with guideline recommended treatment and determine whether the patient's age, after adjusting for other factors, was associated with whether guideline recommended treatment was delivered. We hypothesized that younger patients would be less likely to be prescribed guideline recommended treatment for DR-TB.

4.2 Methods

4.2.1 Design

This study examined data collected from a 5-year prospective longitudinal cluster randomized clinical trial investigating the effects of a nurse-led case management (NCM) intervention on improved treatment outcomes in individuals older than 13 years

with DR-TB in the Eastern Cape and KwaZulu-Natal provinces of South Africa (R01 AI104488-01A1; PI: Farley). This secondary analysis was designed to describe if patients received the correct combination of medicines, at the correct doses, and correct frequencies at treatment initiation. The analysis addressed the extent to which patient age was associated with guideline recommended care, after adjusting for clinical characteristics of the patient and healthcare system characteristics that could influence the timing of treatment initiation. The study received Institutional Review Board approval from Duke University (Pro00067846) and Johns Hopkins University (NA_00078899/CIR00009135).

4.1.1 Parent study

The 5-year parent cluster randomized trial began in November 2014. The study includes 10 treatment sites randomized to either a nurse case management (NCM) intervention or observational control with the primary outcome evaluating the proportion of patients who experience successful treatment outcomes. The NCM intervention consists of a nurse coordinating MDR-TB treatment with weekly phone calls and/or visits during the intensive first six months of treatment to monitor laboratory results and weight, manage side effects, and conduct monthly visits during the subsequent 30-month continuation phase. Patients at control sites receive physician-led standard of care without enhanced nurse case management support. The parent

study protocol and the pilot development of the intervention (J. E. Farley et al., 2014) is described elsewhere (NCT02129244) (J. Farley, 2014).

4.2.2 Setting and sample

The study included 10 sites in KwaZulu Natal (KZN) and the Eastern Cape (EC) with high DR-TB burden (Department of Health: Republic of South Africa, 2013). The sites served patients seeking care in department of health clinics, offering free clinical care. Racial statistics are not collected by the sites; however, the majority of individuals receiving care in these settings are known to be Black South Africans.

This study included 542 individuals 13 years of age and older with DR-TB who initiated treatment between November 2014 and August 2016. Study participants were eligible if consented within seven days of treatment initiation. Participants enrolled in a treatment-related clinical trial were excluded. One participant was excluded from analysis for unconfirmed DR-TB. An additional 204 participants were excluded for missing data as well as medical history potentially influencing clinical decision making to start standard regimens. Specifically, participants were excluded if they had: (1) history of liver disease or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >70 (twice the upper limit of normal), (2) history of kidney disease or creatinine clearance (CrCl) <30 (South African definition of impaired renal function), (3) history of psychosis, (4) confirmed hearing loss (<20 decibels (dB)), (5) positive pregnancy test, or (6) history of second-line DR-TB medication. These criteria are known reasons that may

prevent clinicians from following the standardized DR-TB medication regimen (Department of Health: Republic of South Africa, 2013). Medications in the standardized regimen are known to cause liver, kidney, and ototoxicity as well as exacerbate some psychiatric conditions (Keshavjee et al., 2012; Ramachandran & Swaminathan, 2015; Van der Walt et al., 2013). These medications are also contraindicated in pregnancy. Individuals with a history of second-line DR-TB medication were excluded due to their need for an individualized regimen based on previous exposure and potential resistance (Department of Health: Republic of South Africa, 2013). A total of 337 participants were analyzed. See Figure 6 for CONSORT diagram.

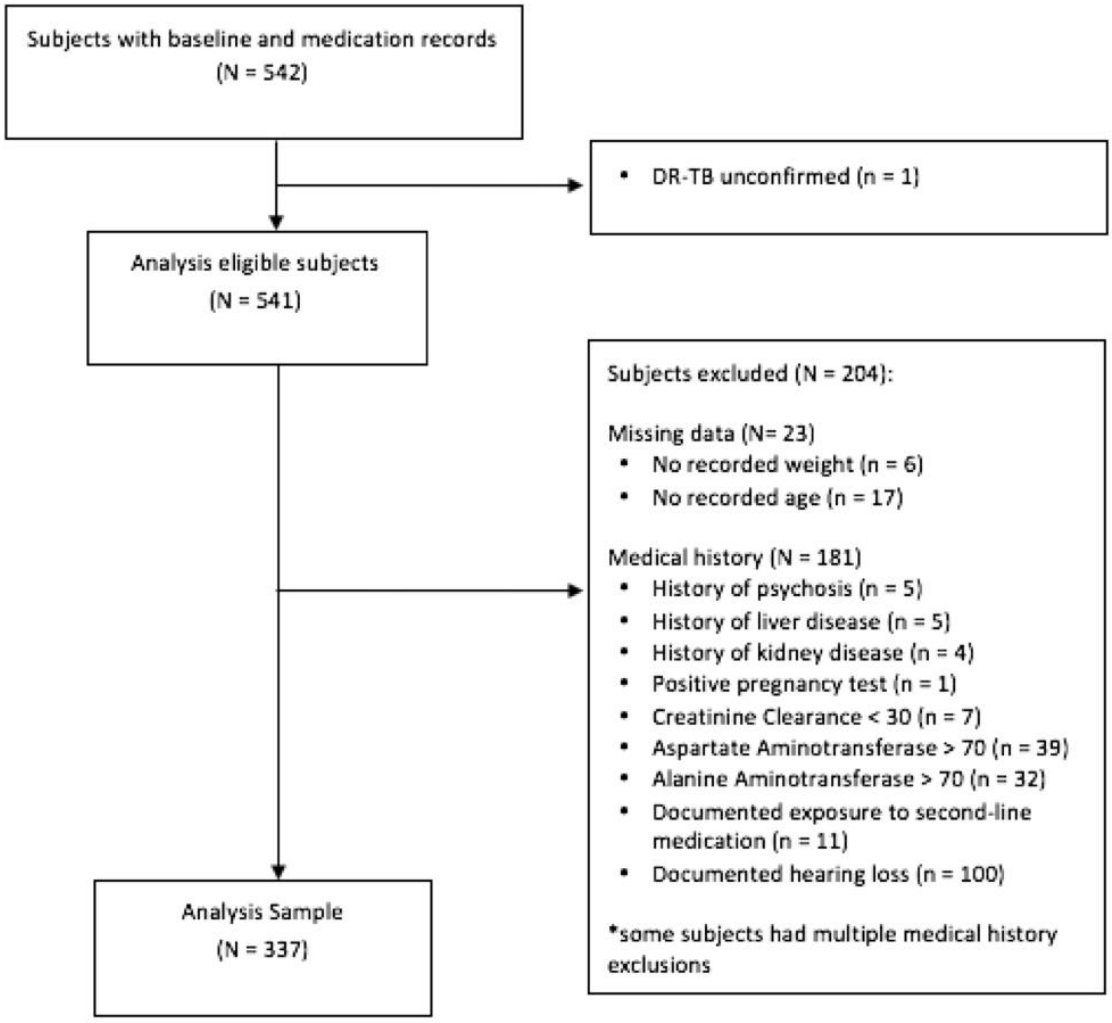

Figure 5: Participant flow diagram

4.2.3 Data sources and procedures

Baseline medications were the first medication prescribed after study enrollment, and within two days of the first prescribed medication. Study documents included all medications, dosages, and frequencies prescribed to each patient. All data were entered and stored in case report binders by trained study personnel concurrent with care. After

quality assurance at each site comparing medical records with case report forms, case report forms were scanned onto the study drive and manually entered into REDCap, web-based application. REDcap data were downloaded into an analytic dataset that was archived on a secure, password protected server at Duke University. Original case report forms were checked for accuracy with REDCap entered data and less than 0.5% of data were incorrect when 10% of charts were checked. Data were cleaned and missing values were entered by verification on scanned case report forms. Data analysis was conducted using SAS (version 9.3, Cary, NC).

4.2.4 Measures

4.2.4.1 Outcome variables

Adherence to MDR-TB treatment consistent with the clinical guideline was the primary outcome variable. To determine adherence (e.g., yes/no) each prescribed DR-TB regimen was reviewed and compared to the standard empiric South African DR-TB treatment which includes at least four oral medications: Moxifloxacin, Ethionamide, Pyrazinamide, Terizidone, and one injectable medication: Kanamycin, Amikacin, or Capreomycin. Adherence to recommended regimen required meeting all the following criteria: a) prescription of all five medications; b) correct weight-based dosage; c) given at the recommended frequency (Table 7). Guidelines state that all medications are to be administered at least six days per week, however due to no clinical availability of weekend administration of injectable agents throughout the country, five days per week

was accepted as adherent to the injectable medication. For each patient, each of the adherence criteria were coded as 0 (not followed) and 1 (followed).

We also examined the individual components of the guideline to better understand which aspects of the recommended treatment presented challenges for providers. The following outcomes were evaluated: (1) medications, defined as recommended combination of oral and injectable medications prescribed; (2) medications and doses, defined as all recommended medications and correct dose of each medication prescribed; and (3) regimen, the primary outcome defined as all recommended medications, all correct doses, and all correct frequencies for each medication prescribed. For each patient, each guideline was coded as 0 (no) and 1 (yes) that specified component(s) of the guideline for DR-TB was prescribed at treatment initiation.

Table 7: Standardized MDR-TB regimen for adults and children 8 years and older

Weight Group	Patient Weight	Medication*	Dosage
1	< 33 kg	Moxifloxacin	400 mg
		Ethionamide	15-20 mg/kg
		Pyrazinamide	30-40 mg/kg
		Terizidone	15-20 mg/kg
		Kanamycin, Amikacin, or Capreomycin	15-20 mg/kg
2	33-50 kg	Moxifloxacin	400 mg
		Ethionamide	500 mg
		Pyrazinamide	750 mg
		Terizidone	750 mg
		Kanamycin, Amikacin, or Capreomycin	500-750 mg, 750-1000 mg, 500-750 mg
3	51-70kg	Moxifloxacin	400 mg

		Ethionamide	750 mg
		Pyrazinamide	1750-2000 mg
		Terizidone	750 mg
		Kanamycin, Amikacin, or Capreomycin	1000 mg
4	> 70 kg	Moxifloxacin	400 mg
		Ethionamide	750-1000 mg
		Pyrazinamide	2000-2500 mg
		Terizidone	750-1000mg
		Kanamycin, Amikacin, or Capreomycin	1000 mg

Developed from Table XVI Intensive Phase: Standardized Regimen for Adult and Children 8 Years and Older (MDR-TB Treatment) from Department of Health: Republic of South Africa. (2013). *Management of Drug-Resistant Tuberculosis*. Pretoria: Republic of South Africa (p. 48. *All medications are oral and required to be prescribed at least six days per week; any injectable (Kanamycin, Amikacin, and Capreomycin) are required to be prescribed at least five days per week.

4.2.4.2 Individual characteristics

Sociodemographic and clinical information was collected by patient interview in the parent study along with medical chart review with data abstraction. Individual-level characteristics included age as well as sex, history of TB disease, HIV coinfection status, and weight. Additionally, anti-retroviral treatment (ART) status, prior exposure to TB, education level, relationship status, and employment status were captured to further describe the sample.

4.2.4.3 Health system characteristics

Two system-level characteristics were examined. The parent study categorized each site as urban/peri-urban or rural. Geographic location was defined by treatment site province (i.e., Eastern Cape/KwaZulu Natal).

4.2.5 Data analysis

Descriptive statistics were used to summarize the (a) demographics and clinical characteristics of the patients; (b) site characteristics of the healthcare system; and (c) prescription of the correct guideline recommended treatment outcomes. Non-directional statistical tests were performed with the level of significance set at 0.05 for each test. The level of significance was not adjusted for multiple tests due to the exploratory nature of this secondary analysis. Only a posteriori results are reported (differences with significant effects), thus a Bonferroni correction was not necessary. Regimen (correct medications, doses, and frequencies) was the primary outcome, while assessing correct medications, and correct medications and doses were secondary outcomes. Effect sizes were used to address clinical significance.

4.2.5.1 Sample characteristics

Descriptive statistics were used to detail the sociodemographic and clinical characteristics for the total sample, adults, and youth. The youth group included individuals between the age of 13 and 24 years. Because the relationship between age and prescription of the correct treatment regimen was of interest, the two age groups (youth and adults) were compared regarding sociodemographic and clinical characteristics. Chi-square tests (alternatively Fisher's Exact Tests) were used to test for age group differences for difference in proportion for categorical measures and General Linear Models (GLMs, adjusting for sample size differences) were used to test for

differences in means for continuous measures. Additionally, descriptive statistics were used to detail patient sociodemographic and clinical characteristics, site characteristics, and prescription of correct medications, correct medications and doses, and correct regimen outcomes at each of the ten treatment sites.

4.2.5.2 Prescription of correct DR-TB regimen, per South African guidelines

The number (n) and percent (%) of patients correctly prescribed the following as per guideline were determined: (a) medications; (b) medications and doses; and (c) regimen (medications, doses, and frequencies). We also examined this information by standard oral and injectable medications, and by treatment site. A logistic regression approach was used to examine the relationship between individual (age along with sex, prior history of TB) and health system (urban/rural, EC/KZN province) characteristics on the primary and secondary outcomes (correct regimen, correct medications, and correct medications and doses respectively).

First, a set of bivariate regression models were created to examine the association between individual and health system characteristics and the primary and secondary outcomes. Next, a multivariable logistic regression model was performed that included age and any individual and/or system characteristics significant at the 0.10 level in the bivariate regression models retained as covariates. This model allowed us to examine the influence of age on each of the guideline outcomes, after adjusting for the effects of individual and system covariates related to the outcomes. To address effect size and

clinical significance, the odds ratio (OR) and 95% confidence interval for each explanatory variable was calculated. Treatment site as a random effect was not evaluated as random effect dues the low sample size and/or lack of variability in the outcome at some sites.

4.2.6 Power calculations

The primary outcome for this secondary analysis was treatment regimen as per guideline. The analysis sample of 337 provided 80% statistical power to detect a statistical significant bivariate association between age as a continuous variable and treatment regimen (coded as 0=incorrect, 1=correct) for two-tailed test with the significance level set at 0.05, assuming a small effect size (defined as an odds ratio of 1.75, which is equivalent to a Cohen *d* =0.31 and r = 0.15) (Demidenko, 2007).

4.3 Results

4.3.1 Sample

The total sample with baseline and medication records included 542 individuals. A total of 205 participants were excluded for various reasons described above (Figure 6).

4.3.2 Sample characteristics

The mean age was 34.8 years (range: 15 to 75 years), with 53% male, 5% with no formal education, 64% unemployed, 73% with HIV coinfection, and 51% with prior history of TB disease (Table 7).

Sixty-four youth (19%) were included in the sample. The comparison of adults and youth regarding sociodemographic and clinical characteristics indicated that, as expected, youth were less likely to be living with a partner or employed. Youth had a significantly lower rate of HIV coinfection and history of TB disease (all $p<0.05$, see Table 8). In terms of sites, 58% of participants were treated at rural sites, 47% were treated at an EC province site. The number of patients enrolled in the cluster randomized trial at each site ranged from 6 to 83 participants (see Table 9).

Table 8: Sample characteristics

Baseline Characteristic	N	Total (N=337)	Adult (N=273)	Youth (N=64)	*p*-value
Age, in years	337	34.8 ± 11.1	37.9 ± 10.0	21.7 ± 2.5	<.0001
Male sex	337	179 (53.1%)	152 (55.7%)	27 (42.2%)	0.0516
Attended university	333	24 (7.2%)	18 (6.7%)	6 (9.4%)	0.4556
Employed	329	120 (36.5%)	110 (41.5%)	10 (15.6%)	0.0001
Living with partner	337	63 (18.7%)	61 (22.3%)	2 (3.1%)	0.0004
Eastern Cape province	337	159 (47.2%)	130 (47.6%)	29 (45.3%)	0.7394
Rural site	337	257 (76.3%)	209 (76.6%)	48 (75.0%)	0.7922
HIV coinfection	332	243 (73.2%)	213 (79.2%)	30 (47.6%)	<.0001
HIV patients on ART	157	135 (86.0%)	122 (85.9%)	13 (86.7%)	1.000
History of TB disease	332	169 (50.9%)	149 (55.6%)	20 (31.3%)	0.0005
Prior TB exposure	317	85 (26.8%)	68 (26.5%)	17 (28.3%)	0.7679
Exposure to drug resistant TB	73	32 (43.8%)	25 (43.9%)	7 (43.8%)	0.9938

Youth=Ages 13-24; n (%) for categorical variables; mean ± standard deviation for age; Chi-Square/Fisher's Exact Test for categorical characteristics; General Linear Model (GLM) for continuous characteristics; Attended university includes: any university, completed university; Employed includes: full time, part time, homemaker, and retired; Living with partner includes: married, living with a partner.

Table 9: Site, patient characteristics and treatment as per guideline by site

Site Characteristics											
Patients enrolled	337	6 (1.8%)	50 (14.8%)	24 (7.1%)	10 (3.0%)	25 (7.4%)	51 (15.1%)	11 (3.3%)	60 (17.8%)	83 (24.6%)	17 (5.0%)
Urban	337	U	U	U	R	R	R	R	R	R	R
Province	337	KZN	KZN	KZN	KZN	EC	EC	KZN	KZN	EC	KZN
Patient Characteristics											
Age, in years	337	38.0 (9.6)	31.7 (8.8)	39.2 (12.9)	33.6 (10.2)	43.9 (14.7)	35.1 (11.3)	34.4 (14.2)	35.8 (10.7)	32.5 (8.7)	31.6 (11.4)
Male sex	337	5 (83.3%)	29 (58.0%)	15 (62.5%)	5 (50.0%)	13 (52.0%)	29 (56.9%)	3 (27.3%)	27 (45.0%)	42 (50.6%)	11 (64.7%)
HIV co-infection	332	6 (100.0%)	37 (74.0%)	20 (83.3%)	8 (80.0%)	20 (80.0%)	31 (64.6%)	8 (72.7%)	47 (79.7%)	54 (65.9%)	12 (70.6%)
History of TB disease	332	3 (50.0%)	16 (32.0%)	13 (56.5%)	5 (50.0%)	17 (68.0%)	20 (39.2%)	3 (50.0%)	29 (58.9%)	49 (59.8%)	11 (64.7%)
Treatment as per South African MDR-TB Guideline											
Sample size	**337**	**6**	**50**	**24**	**10**	**25**	**51**	**11**	**60**	**83**	**17**
Medications		5 (83.3%)	47 (94.0%)	24 (100.0 %)	10 (100.0%)	21 (84.0%)	32 (62.8%)	11 (100.0%)	56 (93.3%)	73 (88.0%)	16 (94.1%)
Sample size	**314**	**6**	**40**	**16**	**10**	**25**	**51**	**10**	**56**	**83**	**17**
Medications & Doses		0 (0.0%)	13 (32.5%)	2 (12.5%)	8 (80.0%)	10 (40.0%)	15 (29.4%)	5 (50.0%)	19 (33.9%)	27 (32.5%)	4 (23.5%)
Regimen		0 (0.0%)	10 (25.0%)	2 (12.5%)	7 (70.0%)	10 (40.0%)	15 (29.4%)	5 (50.0%)	15 (26.8%)	27 (32.5%)	4 (23.5%)

Site 8 and Site 10 combined and represent Site 10; Mean ± standard deviation (SD) for age; n (%) for categorical characteristics; Prescribed DR-TB treatment per guideline = n (%); U=Urban; R= Rural; I=Intervention; C=Control; KZN=KwaZulu Natal province; EC=Eastern Cape province; Regimen = medications, doses, and frequencies per guideline.

4.3.3 DR-TB treatment, as per South African guidelines

Among the 337 patients enrolled, 295 (88%) were correctly prescribed all five standardized medications. Of those 295, 23 patients did not have a documented dose for at least one of the five medications. Thus, 314 patients were evaluated regarding (a) medications and doses and (b) regimen. Among those 314, 103 (323%) were prescribed the correct medications and dosages and 95 (30%) were prescribed the correct full regimen (medications, doses, and frequencies). Table 10, 11, and 12 detail the correct oral and injectable medications, doses, and regimens prescribed. Table 13 provides frequencies of the regimen prescribed by age group.

Table 10: Treatment as per South African MDR-TB guidelines

Guideline Component	Definition	N	Met Guideline Criteria
Medications	All 5 standard medications prescribed (All 4 oral and any injectable standard medications prescribed)	337	295 (87.5%)
Medications and Doses	All 5 standard medications and correct doses prescribed	314	103 (32.8%)
Regimen (medications, doses, and frequencies)	All 5 standard medications, correct doses, and correct frequencies prescribed	314	95 (30.3%)

N = sample size. All 337 patients had medication data. Among the 295 who received the five guideline medications, 23 were missing dose information and the correct dose could not be determined. Thus, the sample size for Guidelines 2 and 3 was 314 participants rather than 337.

Table 11: Treatment guideline: by medications, medications and doses, and regimen

Guideline	Sample Size (N)	All Four Oral Medications Prescribed	Any Injectable Medication Prescribed	All Four Oral and Any Injectable Medications Prescribed
Medications	337	306 (90.8%)	325 (96.4%)	**295 (87.5%)**
Medications and Doses	314	128 (40.8%)	166 (52.9%)	**103 (32.8%)**
Regimen (medications, doses, and frequencies)	314	99 (31.5%)	97 (30.9%)	**95 (30.3%)**

The sample size is 314 for the medications and doses guideline and regimen guideline due to 23 missing dose information. Thus, correct dosing could only be determined for 314.

Table 12: Summary of medications, doses, and regimen

Summary	Oral Medications Prescribed (N=337)				Injectable Medication Prescribed (N=337)		
Standard medications	**Moxi**	**Eto**	**PZA**	**Teri**	**Kana**	**Ami**	**Capreo**
Medication prescribed	334	310	336	335	245	79	1
Correct Medication Combination			**(N=306)**			**(N=325)**	
Dose missing (N=23)	--	1	11	--	10	--	1
Correct medication and dose	305	252	200	266	147	52	0
Correct Medication Combination and Doses			**(N=128)**			**(N=166)**	
Regimen	127	128	125	128	106	46	0

Moxifloxacin = Moxi, Ethionamide = Eto, Pyrazinamide = PZA, Terizidone = Teri, Kana = Kanamycin, Ami = Amikacin, Capreo = Capreomycin. Regimen = correct medications, doses, and frequencies prescribed.

Table 13. Youth versus adults for regimen

	N	Not Correct Regimen	Correct Regimen
Total sample	314	219 (70%)	**95 (30%)**
Adults	254	174 (69%)	**80 (31%)**
Youth	60	45 (75%)	**15 (25%)**

n (%) provided for categorical variables

4.3.4 Guideline outcomes: relation to individual and health system characteristics

Table 14 shows the set of bivariate logistic regression models for the medications, medications and doses, and regimen outcomes. Age (continuous), HIV coinfection

(yes/no), urban site (urban/rural), and EC province (EC/KZN) were significant predictors of whether the correct medications were prescribed, as per guideline (all $p<0.05$). No variables significantly predicted correct medications and doses or correct regimen.

Table 15 presents the results of the multivariable regression model conducted to examine the relationship between age and medications prescribed as per guideline, after adjusting for individual and system characteristics (covariates). Patients who were younger age (p=0.042), (2) HIV coinfected (p=0.046); (3) treated at a rural site (p=0.017); and (4) treated in the KZN province (p=0.000) were more likely to have correct medications prescribed. The final model explained 10% of the variability of medication outcome.

Table 14: Guideline outcomes: bivariate logistic regression models

Variables	*N*	*Wald chi-square*	*df*	OR	OR 95% CI	Model R^2	*p*-value
Outcome: Medications							
Age (in years)	337	5.439	1	0.969	0.943-0.995	0.015	0.020
Sex	337	0.787	1	1.346	0.698-2.598	0.002	0.375
History of TB disease	332	0.084	1	1.102	0.573-2.119	0.000	0.772
HIV coinfection	332	4.953	1	2.155	1.096-4.236	0.014	0.026
Urban Site	337	9.096	1	0.355	0.181-0.696	0.028	0.003
EC Province Site	337	16.342	1	0.203	0.094-0.440	0.057	<.000
Outcome: Medications and Doses							
Age	314	0.142	1	1.004	0.983-1.025	0.001	0.706
Sex	314	0.204	1	0.897	0.559-1.439	0.007	0.652
History of TB disease	309	0.583	1	0.831	0.517-1.336	0.002	0.445
HIV coinfection	309	1.571	1	0.715	0.423-1.208	0.005	0.210
Urban Site	314	0.432	1	1.173	0.729-1.888	0.001	0.511
EC Province Site	314	0.001	1	0.991	0.619-1.588	0.000	0.970
Outcome: Regimen							
Age	314	0.065	1	0.997	0.976-1.019	0.000	0.798
Sex	314	0.262	1	0.882	0.544-1.429	0.001	0.609
History of TB disease	309	0.574	1	0.829	0.510-1.347	0.002	0.449
HIV coinfection	309	2.556	1	0.648	0.381-1.103	0.008	0.110
Urban Site	314	0.264	1	1.136	0.698-1.847	0.001	0.608
EC Province Site	314	0.914	1	1.266	0.781-2.052	0.003	0.339

Age included as a continuous variable from older to younger; EC= Eastern Cape; OR = odd ratio; 95% CI = 95% confidence interval.

Table 15: Medications guideline: significant bivariate relationships

Explanatory Variable	*N*	Not Correct Medication	Correct Medication
Age	337	**38.6 (13.7)**	**34.3 (10.6)**
HIV coinfection	332		
HIV coinfection	243	24 (10%)	**219 (90%)**
No HIV coinfection	89	17 (19%)	**72 (81%)**
Urban site	337		
Urban	142	27 (19%)	**115 (81%)**
Rural	195	15 (8%)	**180 (92%)**

EC province site	337		
Eastern Cape (EC)	159	33 (21%)	**126 (79%)**
KwaZulu Natal (KZN)	178	9 (5%)	**169 (95%)**

Mean (standard deviation) for age; n (%) for categorical variables.

Table 16: Regimen guideline: significant bivariate relationships

Explanatory Variable	*N*	Not Correct Medication	Correct Medication
Urban site	314		
Urban	62	50 (80.7%)	**12 (19.4%)**
Rural	252	169 (67.1%)	**83 (32.9%)**

n (%) for categorical variables.

Table 17: Primary outcome: correct regimen prescribed: multivariable logistic regression models

Model	*N*	Explanatory Variable	*Wald chi-square*	*df*	*p*-value	OR	OR 95% CI	Model R^2
Model 1	337	Age	0.0652	1	0.7984	0.997	0.976-1.019	0.0002
Model 2	332	Age	0.0869	1	0.7682	0.997	0.975-1.019	0.0150
		Urban site	4.2461	1	0.0393	0.488	0.246-0.966	

Logistic regression models for binary outcomes; OR = odd ratio; 95% CI = 95% confidence interval; Model R^2 = r-squared value for all terms in the model; age included as continuous variable ordered from older to younger; Model 1= bivariate model with age only; Model 2 = multivariable logistic regression model that included age and individual and/or system characteristic covariates significant at the 0.05 level in the bivariate regression models.

4.3.5 DR-TB treatment by site

Table 9 presents the guideline results for each treatment site. There was site variation in the prescription of correct medications, correct medications and doses, and regimen. The percent of correct medication prescribed ranged from 63% to 100% per site, while percent for correct medications and doses ranged from 0% to 32%. Finally, the

percent of sites that prescribed the treatment regimen, as per guideline was also 0% to 32%.

4.3.6 Over and under dosing

For medications with incorrect dosing, this was further explored by medication and weight group to understand if each medication was over or under dosed, independent of all other medications (Table 19). Moxifloxacin was prescribed at the correct dose to 99.7% of participants, while Kanamycin was correctly prescribed to 60.0% of participants. Over dosing occurred in 0% (Amikacin) to 7% (Ethionamide) of participants. Under dosing occurred between 0% (Moxifloxacin) and 34.2% (Amikacin) with Pyrazinamide under dosed 30.4% and Kanamycin under dosed 33.5%. A total of 30 baseline medications were over dosed while 285 baseline medications were under dosed.

Table 18: Over and under dosing for standardized MDR-TB medications

Medications	*N*	Correct Dose n (%)	Over Dose n (%)	Under Dose n (%)	Missing Dose n (%)
Moxifloxacin	**334**	333 (99.7%)	1 (0.3%)		
Weight Group 1		2 (100.0%)	-	-	-
Weight Group 2		101 (99.0%)	1 (0.3%)	-	-
Weight Group 3		187 (100.0%)	-	-	-
Weight Group 4		43 (100.0%)	-	-	-
Ethionamide	**310**	255 (82.3%)	22 (7.1%)	32 (10.3%)	1 (0.3%)
Weight Group 1		2 (100.0%)	-	-	-
Weight Group 2		69 (71.9%)	22 (22.9%)	4 (4.2%)	1 (1.0%)
Weight Group 3		149 (86.1%)	-	24 (13.9%)	-
Weight Group 4		35 (89.7%)	-	4 (10.3%)	-
Pyrazinamide	**336**	222 (66.1%)	1 (0.3%)	102 (30.4%)	11 (3.3%)
Weight Group 1		2 (100.0%)	-	-	-
Weight Group 2		98 (95.2%)	-	1 (1.0%)	4 (3.9%)
Weight Group 3		90 (47.9%)	1 (0.5%)	90 (47.9%)	7 (3.7%)
Weight Group 4		32 (74.4%)	-	11 (25.6%)	-

Terizidone	**335**	292 (87.2%)	1 (0.3%)	42 (12.5%)	-
Weight Group 1		2 (100.0%)	-	-	-
Weight Group 2		66 (64.1%)	-	37 (35.9%)	-
Weight Group 3		183 (97.9%)	1 (0.5%)	3 (1.6%)	-
Weight Group 4		41 (95.4%)	-	2 (4.7%)	-
Kanamycin	**245**	147 (60.0%)	5 (2.0%)	82 (33.5%)	11 (4.5%)
Weight Group 1		1 (100.0%)	-	-	-
Weight Group 2		59 (83.1%)	5 (7.0%)	-	7 (9.9%)
Weight Group 3		56 (40.0%)	-	80 (57.1%)	4 (2.9%)
Weight Group 4		31 (93.9%)	-	2 (6.1%)	-
Amikacin	**79**	52 (65.8%)	-	27 (34.2%)	-
Weight Group 1		1 (100.0%)	-	-	-
Weight Group 2		23 (76.7%)	-	7 (23.3%)	-
Weight Group 3		23 (56.1%)	-	18 (43.9%)	-
Weight Group 4		5 (71.4%)	-	2 (28.6%)	-

4.4 Discussion

Most patients in South Africa receive the correct standardized medication regimens, yet with further evaluation, only 30% receive full guideline adherent treatment. Younger patients, those coinfected with HIV, receiving care at rural sites, and living in the KawZulu Natal province all significantly influenced the likelihood of being prescribed correct medications. Provider adherence to guidelines - including the correct combination of medications, at the correct dose, and at the correct frequency - for all individuals is crucial for positive clinical outcomes.

This study found that younger patients were 1.03 times more likely to be prescribed correct medications than older patients. This could be due to health conditions in older individuals not recorded in the health record, yet clinicians are wary of beginning certain medications in older patients. South African MDR-TB guidelines quote anecdotal evidence that adolescents are at high risk for poor treatment outcomes

due to biologic reasons potentially related to delayed diagnosis and initiation of treatment as well as social factors (Department of Health: Republic of South Africa, 2013). In contrast to the lack of TB research in youth, HIV is a well-defined area of research in South African youth (Cluver et al., 2013; Pettifor et al., 2013; Shisana et al., 2014).Youth is a transitional phase between childhood and adulthood characterized by more biopsychosocial changes than any other stage of life excluding infancy (Feldman, 1990; Holmbeck, 2002). Although this period spans many years and is culturally bound through attainment of certain knowledge, skills, and attitudes, this developmental stage is critical in establishing lifelong self-management and health-related behaviors such as seeking recommended healthcare and treatment (Holmbeck, 2002). Including more youth, specifically younger youth in future DR-TB studies is warranted.

Patients with HIV coinfection were twice as likely to be prescribed correct medications than those without HIV coinfection, clinicians may have been more careful in correctly prescribing to those with HIV. Patients receiving care at rural sites were nearly two and one half times more likely to receive correct medications than those in urban areas and patients in KwaZulu Natal had over four times a greater likelihood of being prescribed correct medications than patients receiving care in the Eastern Cape. Variation in healthcare resourcing of provinces may have influenced the health system variables (van Rensburg, 2014).

Ensuring appropriate use of standard regimens is part of the solution to

managing DR-TB at both the individual- and system-level (Ahuja et al., 2012; Department of Health: Republic of South Africa, 2013; A. S. S. Karim et al., 2009). Before a patient can appropriately adhere to DR-TB treatment, it is essential they are prescribed the correct medications at the correct dose and frequency. However, healthcare infrastructure in South Africa may not adequately support systematic guideline-based care. Hospital and clinic adherence to TB treatment has been shown to have variation in South Africa as well as other countries (Diop et al., 2002; Ershova et al., 2014; Thongraung et al., 2008). One systematic review described health care workers' lack of knowledge of TB regimens ranging between 8% and 93% (van der Werf et al., 2012). Another systematic review described 67% of treatment regimens as inappropriate across 37 studies in 22 countries (Langendam et al., 2012). This study adds to the literature surrounding TB treatment regimens because, to our knowledge, no other studies have specifically evaluated DR-TB treatment regimens inclusive of dosage and frequency in South Africa.

Serious side effects are common with each medication used to treat DR-TB (Hughes & Osman, 2014). Despite the risk of dangerous side effects, under dosing patients with DR-TB medications threatens the ability to fully treat individuals, and can lead to DR-TB transmission in communities. Under dosing potentially leads to ineffective treatment. Pyrazinamide was commonly under dosed which is an important part of DR-TB treatment as it has bactericidal activity to semi dormant mycobacteria and

resistance to Pyrazinamide has been reported in South Africa (Mphahlele et al., 2008). Fluoroquinolones are also an important class of medication for individuals with DR-TB as their use has been shown to improve treatment success and patient survival (Ahuja et al., 2012). Some studies have found that more aggressive regimens shorten the time to culture conversion (Tierney et al., 2014; Yuen et al., 2015).

Effectively changing provider behavior and implementing policies can be difficult. These findings are important due to South Africa expanding prescriptive practice to nurses specially trained in DR-TB treatment and their guidelines moving towards shorter treatment duration, yet increasing the number of medications patients are prescribed (Department of Health: Republic of South Africa, 2013; IRIN News, 2012; WHO, 2016b). There is evidence that non-physician prescribing is equivalent to physician prescribing in HIV care when prescribers are adequately trained and well supported (Kredo et al., 2014). As prescribing expands to more health professionals, ensuring national guidelines are effectively implemented is critical.

4.4.1 Limitations

This study had limitations. This sample only included patients enrolled *after* DR-TB diagnosis, thus limiting the sample to individuals who were tested for DR-TB. Per Mala et. al (2014), lack of dependable diagnostics was one of the most frequent reasons clinicians reported guideline non-adherence. Second, we may have been overly conservative by excluding 204 individuals due to diagnostic and medical history results

which could have unintentionally reduced our sample size as many diagnostic results are not available to prescribing clinicians at treatment initiation. Third, the range of patient ages was not fully inclusive of youth 13-24 years – the mean age of youth was 21.7 years (SD 2.5), thus had younger youth been enrolled, the effect of age may have changed. Forth, correct regimen was assessed in this analysis independent of treatment initiation. Timely initiation is also important in addition to correct regimen prescription. Fifth, correct frequencies may have been negatively biased in the "regimen" outcome since only individuals with the correct dosage were analyzed for frequency. Despite these limitations, this study critically enriches the current literature regarding provider adherence to DR-TB guidelines in low-resource settings.

4.6.2 Conclusion

This study provides evidence that there is poor adherence to national DR-TB guidelines in South Africa for youth and adults. Although most individuals with DR-TB are prescribed the correct combination of medications, few individuals are prescribed correct doses for all medications. Under-dosing is more common than over dosing, which could lead to increased drug resistance. Future research should focus on assessing providers to better understand barriers and facilitators to providing guideline recommended DR-TB treatment. Designing interventions to decrease barriers to appropriate prescribing, especially around dosing, and enhancing providers' ability to

prescribe effective DR-TB treatment can improve patient outcomes, prevent transmission of DR-TB, and prevent further drug resistance.

5. Conclusion

5.1 Introduction

The purpose of this dissertation research is to establish evidence regarding children and youth with tuberculosis (TB) in poor resourced and high TB burden settings. Specifically, this dissertation (1) reviews current literature on the barriers to TB treatment in sub-Saharan Africa; (2) examines the timing of treatment provided to people ages 14 to 75 years in South Africa with drug-resistant TB (DR-TB) with and without HIV; and (3) examines the extent to which age and other patient and site characteristics are associated with the delivery of guideline-based treatment regimens. The main findings from this dissertation include the following. First, barriers to TB treatment initiation among children and youth in sub-Saharan Africa are poorly defined and few studies have specifically examined barriers by age to be able to draw conclusions specific to children and youth. Second, treatment initiation is delayed per South African Multi-Drug Resistant TB (MDR-TB) guidelines (within five days of diagnosis) for most patients in a cohort of South Africans with DR-TB nested within a cluster randomized trial in the Eastern Cape and KwaZulu Natal provinces. Third, only one in three people with initial DR-TB diagnosis (including Rifampin Resistant (RR), MDR, and extremely drug-resistant (XDR) TB) receive correct medications, doses, and frequencies per South African guidelines. Overall, the studies from this dissertation provide significant empirical evidence to promote and improve the health of

individuals, specifically those with DR-TB and DR-TB/HIV coinfection in South Africa. To advance provision of DR-TB treatment in South Africa, a more comprehensive understanding of the role individuals, communities, and health systems play is necessary.

These findings allow us to better understand behaviors of systems (e.g. family units, populations, and/or organizations) to ultimately improve interventions within systems (National Institute of Nursing Research, 2011). Variation in barriers impeding treatment initiation exist across sub-Saharan Africa. Furthermore, once treatment is initiated, barriers likely still exist in providing timely and appropriate treatment at both the individual- and system-level. Understanding and improving DR-TB management should remain a goal in South Africa until the epidemic is controlled and there are zero deaths due to TB.

5.2 Chapter two: barriers to initiating tuberculosis treatment in sub-Saharan Africa: a systematic review focused on children and youth

Timely initiation and correct treatment of tuberculosis (TB) are critical to reduce disease transmission and improve patient outcomes. Barriers to treatment initiation exist at the patient- and system-level for adults and children; however, barriers to treatment initiation in younger individuals are less understood. Therefore, the aim of this study is to determine patient- and system-level barriers to treatment initiation for pediatric and

youth diagnosed with TB in sub-Saharan Africa through systematic review of the literature.

Of 1,490 unique articles identified in the literature, 47 articles are included in the final analysis. Both patient- and system-level barriers exist across sub-Saharan Africa for pediatric and youth diagnosed with TB and impede treatment initiation. Examples of patient-level barriers include limited knowledge, poor attitudes and beliefs regarding TB, and economic burdens causing delays in seeking care for diagnosis of TB symptoms and treatment of TB disease. System-level barriers include laboratory and healthcare provider delays between diagnosis and treatment, lack of integration of TB/HIV services, and lack of flexibility in treatment provision (i.e. centralization of services and directly observed short-course therapy (DOTS)). Barriers to diagnosis were more frequently studied than barriers to treatment initiation. Many barriers for children and youth were the same as barriers for adults. Additional barriers unique to children and youth included having a parent diagnosed with TB and provider difficulty in confirming a TB diagnosis due to delayed or inconclusive diagnostics.

Patient- and system-level barriers to TB treatment initiation are common in sub-Saharan Africa for children and youth. There is a current gap in the literature focusing on pediatric and youth TB treatment initiation and more research aimed at addressing the specific needs of children and youth is urgently needed. Improving the recognition of TB in children and reducing the time from symptom onset to treatment initiation is imperative. Targeting patient- and system-level barriers together must be addressed to improve patient outcomes.

5.3 Chapter three: timing to treatment initiation for drug-resistant tuberculosis in South Africa

This chapter examines the relationship between age and the number of days from initial DR-TB diagnosis to MDR-TB treatment initiation among a prospective South African cohort of youth and adults with DR-TB nested within an ongoing cluster randomized trial. The hypothesis is that younger patients will have a greater number of days from DR-TB diagnosis to DR-TB treatment initiation. Outcomes are treatment initiation within five days of DR-TB diagnosis (consistent with South African National Tuberculosis Program (NTP) guidelines) and days from diagnosis to treatment. Logistic regression models were developed to examine the association between age and outcomes, adjusting for patient (sex, TB history, HIV coinfection) and site (rural/urban, province) characteristics.

Data for 521 study participants with DR-TB, 55% male, 75% with HIV coinfection, and 53% with prior history of TB disease were examined. Age ranged from 14 to 75 years. Eighty-two patients (16%) received DR-TB treatment within five days of diagnosis and met the national strategic plan guidelines for treatment initiation. The median time to treatment for all participants was 11 days (range=0-180). Age was not associated with guideline-recommended treatment initiation (F=0.07, df=1,495, p =0.794) or the number of days to treatment (F=1.42, df=1,489, p =0.233).

Only one in six individuals with DR-TB in this cohort received treatment within five days of diagnosis. Strategies are needed to decrease treatment delays and effectively

implement guidelines. This study shows that few South Africans receive DR-TB treatment within guideline recommended time and that age does not influence time to DR-TB treatment. Although this study did not find a difference in treatment initiation by age, interventions should still be assessed by age as children and youth may have needs beyond those of adults. There is a need for future research in this area in accordance with WHO recommendations.

5.4 Chapter four: prescription of South African national tuberculosis program regimens

This chapter compares each individual's prescribed regimen for DR-TB with guideline recommended treatment and examines the association of age with guideline recommended treatment for 337 patients enrolled in a DR-TB cluster randomized trial in the Eastern Cape and KwaZulu Natal provinces in South Africa. The hypothesis is that younger patients will be less likely to be prescribed guideline-based treatment for DR-TB. Additionally, this study aimed to explore whether DR-TB guideline adherence varies by treatment center.

The prescription of guideline recommended treatment regimen--(1) all medications, (2) all medications at the correct dosages, and (3) all medications at the correct dose and correct frequencies—was examined for 337 people with DR-TB treated at ten treatment sites. Logistic regression methods were used to examine whether age was associated with the prescription of guideline recommended treatment adjusting for patient (sex, history of TB) and health system (urban/rural, province) characteristics.

The sample composition was 53% male, 73% with HIV coinfection, and 51% with prior history of TB disease. Age ranged from 15 to 75 years. Of the 337 patients studied, 87.5% were correctly prescribed the five recommended medications (four oral and one injectable); 32.8% were prescribed the recommended medications at the correct doses for their weight; and 30.3% were prescribed the recommended medications, at the correct doses and frequencies. Younger age, HIV coinfection, and treatment provided in KwaZulu Natal (KZN) province were significantly associated with the prescription of the recommended combination of medications (all $p \leq 0.05$).

These findings indicate that DR-TB patients in South Africa are often prescribed the correct combination of medications recommended as per national guideline. However, the correct dosing and frequencies for medications prescribed rarely meets guidelines. Lack of guideline adherence is a concern for South Africa, the nation with the third highest prevalence of DR-TB globally. Improved prescription of treatment dosages should be implemented, especially as guidelines are rapidly changing and prescriptive practices are expanding to nurse initiated DR-TB treatment.

5.5 Policy and practice implications of the findings from this dissertation

There are numerous policy and practice implications from this dissertation in support of existing policies. First, the amount of TB, and especially DR-TB, research conducted in children and youth is limited. A bigger investment in this vulnerable population is necessary to decrease disease burden and reduce the number of disability

adjusted life years lost. Second, antimicrobial resistance is an emerging global health threat. Improving guideline adherence for diagnosis and treatment is important to support timely, accurate, and holistic treatment of DR-TB. Third, as nurse initiation of DR-TB treatment is trialed in South Africa and the prescriptive practices among non-physicians grows, more research on healthcare provider barriers to, knowledge of, and implementation of, guidelines is warranted. There is a current funding gap in the excess of $8 billion dollars for a global response to end TB epidemics and there is a $43 return on each dollar invested in TB. Thus, an $8 billion investment in TB could potentially save $344 billion (Stop TB Partnership, 2017).

5.5.1 The need for more research in children

Many TB studies, specifically DR-TB quantitative studies that include youth, have been limited in sample size and power (Ettehad et al., 2012; Isaakidis, Paryani, et al., 2013; Rose et al., 2012; Shin et al., 2008). This dissertation contributes important knowledge for global TB research on the barriers to pediatric and youth TB treatment initiation in sub-Saharan Africa identified in previous studies at both the patient- and system-level. Differences identified in this research on DR-TB prescribing patterns (timing of treatment and specific treatment regimens) support the need to develop interventions to improve age (and weight) specific guideline adherence. This is especially important for youth as the DR-TB Treatment Guidelines of South Africa only quote anecdotal evidence for adolescent care due to the dearth of research in this

population (Department of Health: Republic of South Africa, 2013).

5.5.2 Antimicrobial resistance

Antimicrobial resistance is a growing global health threat and DR-TB is especially important to treat rapidly and correctly. In 2015 the United States Whitehouse released a national TB initiative outlining targeted interventions to augment support towards eliminating TB globally (2015). Rates of TB have declined 47% since 1990; however, DR-TB is a serious threat to progress (WHO, 2015a). The economic hazard of DR-TB has given power to push TB up the global political agenda. For bacteriological cure of DR-TB, correct treatment regimens are necessary (World Health Organization, 2014b). Yet, in 2013 it was reported 64-86% of hospital and clinic physicians and nurses were unaware of national guidelines (Nkosi et al., 2013). The standard South African MDR-TB regimen includes five antibiotics, amounting to a daily burden of approximately 15-20 pills plus a daily injection during the six-month intensive phase of treatment that ideally begins immediately after diagnosis (Department of Health: Republic of South Africa, 2013; TB Alliance, 2014). South Africa has simplified regimens across four weight bands for the creation of drug formulations which comply with international requirements for minimum, maximum and average doses per kilogram for adults and children over 8 years of age (Department of Health: Republic of South Africa, 2013). Advances have been made to support political will and progress of TB management; however, there is still significant work to be done to eliminate TB.

Future research should aim to assess adherence to both (1) timing of treatment and (2) appropriate regimen per South African guidelines. Ensuring the timely administration of medication, and appropriate use of standard regimens is part of the solution to controlling DR-TB at both the individual- and system-levels (Ahuja et al., 2012; Department of Health: Republic of South Africa, 2013; A. S. S. Karim et al., 2009).

The growing interest in drug-resistant pathogens and the co-occurring epidemics of TB and HIV has elevated TB on the global health policy agenda (Blondal, 2007; Wellcome Trust, 2016). Rising awareness about antimicrobial resistance and the response to the co-occurring epidemics of HIV and TB has heightened concern that DR-TB is disrupting prior progress addressing TB (Parkhurst & Vulimiri, 2013; Whitehouse, 2015). The most recent global strategy has aimed to eradicate TB by 2050, and eliminating DR-TB is one strategy to reach this goal (WHO, 2015a).

5.5.3 Nurse initiation of drug-resistant tuberculosis treatment

Improving access to services, increasing knowledge of TB among patients and healthcare providers, and decreasing barriers to care could provide improvements for DR-TB care. Increasing nurse prescribing is one example of how to make services more available by increasing the number of healthcare providers able to prescribe DR-TB medication. However, it is essential that guidelines are clear and that clinicians are able to follow guidelines. There is likely a better return on investment to provide interventions for prescribing clinicians than to intervene with individual patients.

Knowledge of guidelines has previously been shown to be low among those treating DR-TB, thus more research perhaps using a pre- and post-test intervention design could be useful (Mala, Moser, Dinant, & Spigt, 2014; Nkosi et al., 2013; Thongraung et al., 2008). Educational tools should leverage what is already known about behavior change in healthcare settings, and should incorporate feasible interventions with existing systems (such as having pharmacists double check dosing). Improving interprofessional relationships between nurses, physicians, and allied health professionals so that individuals are empowered to raise questions if guidelines are not being followed could also be important. Incorporating qualitative methods to learn about provider and patient preferences towards treatment would also be prudent; focus groups with prescribing clinicians could provide necessary information about existing barriers to guideline adherence.

Nurse prescribing has become increasingly common globally, and South Africa has specifically implemented nurse-initiated anti-retroviral therapy in response to the HIV epidemic. Many studies and meta-analyses have shown that with proper training, education, and support systems, non-physician clinicians provide equivalent outcomes as physician providers (Emdin et al., 2013; Grimsrud et al., 2014; Iwu & Holzemer, 2014). Not only does nurse-initiated treatment provide greater opportunities for nurses to practice to the full scope of their license, but it also has been shown to provide improved job morale, and has been associated with improved patient follow-up (Iwu & Holzemer,

2014). With the release of new WHO short-course therapy for some patients with DR-TB, ensuring providers of all types are updated on guideline prescribing is vital.

5.5.4 Prevent transmission of drug-resistant tuberculosis through better tracking and measurement

Although decreasing the time from diagnosis to treatment is important and can decrease disease transmission, there still needs to be more research in understanding the length of time from symptom onset to diagnosis and treatment initiation (WHO, 2016d). Decreasing the time from symptom onset to the time of treatment initiation will likely lead to better patient outcomes and further decrease transmission in communities. Some studies have found that regimen composition can affect the time to sputum conversion (Tierney et al., 2014; Yuen et al., 2015). Additional research assessing the cascade of timing from symptom onset through treatment completion and linking patient outcomes (success, survival) could greatly inform TB care to better position governments to create updated guidelines (Ahuja et al., 2012).

Ultimately assessing the timing of treatment and adherence to guidelines with patient outcomes would provide great insight into DR-TB management. This would allow for the creation of a "TB Care Cascade" similar to what is available now for measuring HIV progress (US Department of Health and Human Services, 2015). Being able to determine the number of individuals with TB infection, TB disease (disaggregated by resistance patterns), the number of individuals diagnosed, on treatment, and effectively treated until disease cure, could improve understanding of the

TB epidemic in individual countries as well as globally. This could help set national and international targets to strengthen the response to combatting TB and DR-TB globally. Due to the global burden and communicable nature of TB, the high co-infection rates with HIV, increasing drug-resistance, and the economic impact of TB on patients and national economies, TB is of major importance to policy makers globally.

5.6 Limitations

When assessing barriers to TB treatment initiation focused on children and youth from peer reviewed literature, few studies were specific to pediatrics. It was challenging to disaggregate findings by age in studies assessing both children and adults. The use of secondary data limited the ability to assess variables not collected in the parent study. There are likely other modifiable factors causing delays and/or prescription of timely or correct regimens. For example, a deeper understanding of health education and stigma related to treatment initiation could have been useful (Nkosi et al., 2013; Nyasulu et al., 2015; Storla et al., 2008). A measure of individual provider prescribing patterns rather than at the health center (treatment site-level) could have provided insight on healthcare provider behaviors (Chalco et al., 2006; Chiang et al., 2015; Mala et al., 2014). Finally, the focus on youth was limited by the age of patients recruited by the parent study. Youth were mostly in their early twenties rather than teens; thus, youth may not have been fully representative of all youth with DR-TB in South Africa. Although there were

limitations to these studies, the results provide important new knowledge for treatment of individuals with DR-TB.

5.7 Conclusion

The overall goal of the dissertation was to examine the barriers, timing and appropriateness of treatment provided to people in South Africa with DR-TB with and without HIV, and evaluate the extent to which age and other characteristics influence the initiation and delivery of guideline-based treatment. This dissertation lays a foundation for future research in pediatric and youth DR-TB and HIV treatment. Treatment initiation is imperative to prevent disease transmission and to ensure positive patient outcomes such as treatment completion and disease cure. Treatment initiation is only the first step of a long journey; yet, treatment must be initiated to disrupt the cycle of drug-resistance and create a positive health trajectory for individuals and communities.

To understand the interactions of patients with their community and the healthcare system, the broader societal context of DR-TB treatment in which it is occurring must be considered. Taking an individual- and system-level approach is important in understanding the context in which DR-TB and HIV affect people of all ages in South Africa. This study is significant, as it addresses a critical health problem in a low-resource setting affecting people of all ages, including understudied youth. Examining the time to treatment initiation and selection of treatment regimen for DR-TB

within South African is important so we can address disparities systematically and scale appropriately particularly supporting the understudied youth population.

Findings from this study will help inform opportunities for addressing the 45% gap in patients diagnosed with DR-TB who never initiate treatment, those who delay treatment, and those who receive guideline recommended care. A greater understanding of treatment can help direct research and practice aimed to improve patient outcomes and reduce disease transmission in communities. The questions and conclusions are a first step in examining the treatment of DR-TB at both the individual- and system-level. Future research will include provider adherence to guidelines at treatment initiation and throughout treatment until cure. Additionally, more patient, health system, and contextual factors associated with medication adherence should be assessed. Longitudinal adherence throughout the intensive and continuation phase of DR-TB treatment are also critical for disease cure and prevention of disease transmission (Kaufmann, 2011; World Health Organization, 2014b). Ultimately, more robust research that includes the creation of interventions to fit individual patient needs in understudied populations like youth is warranted.

Appendix A. Search protocol

Exclusion Criteria	Explanation:
1. Focus Not TB	Exclude if it's about a disease and TB is only a sub-population (i.e. mental health and TB, HIV and those co-infected with TB)
2. Not SSA	Exclude Europe, MENA, Asia, Americas, Africans outside Africa

3. Not pediatrics	Must include 0-24 years, exclude if only age 18+
4. Not barriers	Must include a specific barrier (i.e. delay, treatment initiation, access to care, location of services, cost, adverse drugs, stigma, fear, perceptions of treatment, etc)
5. Not original research	Exclude reviews, case studies
6. Not English	Exclude if article is not available for full review in English

Appendix B. Full database search

Databases: Pubmed, Embase, CINAHL, African Medicus Index, Global health, SCOPUS

PubMed

Set #		Results
1	"Tuberculosis"[Mesh] OR "tuberculosis"[ti] OR "TB"[ti]	189261
2	"Africa South of the Sahara"[Mesh] OR Africa[tiab] OR African[tiab] OR angola[tiab] OR benin[tiab] OR botswana[tiab] OR burkina faso[tiab] OR burundi[tiab] OR cameroon[tiab] OR cape verde[tiab] OR central african republic[tiab] OR chad[tiab] OR comoros[tiab] OR congo[tiab] OR cote d'ivoire[tiab] OR ivory coast[tiab] OR congo[tiab] OR zaire[tiab] OR Djibouti[tiab] OR equatorial guinea[tiab] OR ethiopia[tiab] OR eritrea[tiab] OR gabon[tiab] OR gambia[tiab] OR ghana[tiab] OR guinea[tiab] OR guinea-bissau[tiab] OR kenya[tiab] OR lesotho[tiab] OR liberia[tiab] OR madagascar[tiab] OR malawi[tiab] OR mali[tiab] OR mauritania[tiab] OR mauritius[tiab] OR Mayotte[tiab] OR mozambique[tiab] OR namibia[tiab] OR niger[tiab] OR nigeria[tiab] OR reunion[tiab] OR rwanda[tiab] OR sahara[tiab] OR saint Helena[tiab] OR sao tome[tiab] OR senegal[tiab] OR seychelles[tiab] OR sierra leone[tiab] OR somalia[tiab] OR south africa[tiab] OR sudan[tiab] OR swaziland[tiab] OR togo[tiab] OR tanzania[tiab] OR uganda[tiab] OR zambia[tiab] OR zimbabwe[tiab]	402257
3	"Delivery of Health Care/supply and distribution"[Mesh] OR "Pharmaceutical Preparations/supply and distribution"[Mesh] OR "Pharmaceutical Preparations/economics"[Mesh] OR "Antitubercular Agents/adverse effects"[Mesh] OR "Antitubercular Agents/economics"[Mesh] OR "Antitubercular Agents/supply and distribution"[Mesh] OR "Attitude to Health"[Mesh] OR "Patient Dropouts"[Mesh] OR "Motivation"[Mesh] OR "Time-to-Treatment"[Mesh] OR "Time Factors"[Mesh] OR "Social Stigma"[Mesh] OR "Social Support"[Mesh] OR dropout[tiab] OR dropouts[tiab] OR refuse[tiab] OR refusal[tiab] OR refused[tiab] OR initiate[tiab] OR initiated[tiab] OR initiation[tiab] OR non-initiation[tiab] OR noninitiation[tiab] OR facilitate[tiab] OR facilitator[tiab] OR facilitated[tiab] OR facilitators[tiab] OR barrier[tiab] OR barriers[tiab] OR uptake[tiab] OR motivat*[tiab] OR delay[tiab] OR delayed[tiab] OR delays[tiab] OR time[tiab] OR supply[tiab] OR stigma[tiab] OR support[tiab] OR economics[tiab] OR pathway[tiab] OR pathways[tiab] OR "side effect"[tiab] OR "side effects"[tiab] OR "adverse effect"[tiab] OR "adverse effects"[tiab]	5558395
4	#1 AND #2 AND #3	**2937**
5	"Focus Groups"[Mesh] OR "Questionnaires"[Mesh] OR "Qualitative research"[Mesh] OR "Observational Study" [Publication Type] OR "Interview" [Publication Type] OR "personal narratives as	7770042

	topic"[Mesh] OR "interviews as topic"[Mesh] OR "Narration"[Mesh] OR "Nursing Research"[Mesh] OR "Anecdotes as Topic"[Mesh] OR "Tape Recording"[Mesh] OR "Observational Study as Topic"[Mesh] OR "semi-structured"[tiab] OR semistructured[tiab] OR unstructured[tiab] OR informal[tiab] OR "in-depth"[tiab] OR indepth[tiab] OR "face-to-face"[tiab] OR structured[tiab] OR interview*[tiab] OR discussion[tiab] OR discussions[tiab] OR questionnaire[tiab] OR questionnaires[tiab] OR survey[tiab] OR surveys[tiab] OR surveyed[tiab] OR "focus group"[tiab] OR "focus groups"[tiab] OR qualitative[tiab] OR ethnography[tiab] OR ethnographic[tiab] OR fieldwork[tiab] OR "field work"[tiab] OR "key informant"[tiab] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR "evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tiab] OR evaluation studies[tiab] OR "intervention studies"[MeSH Terms] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "case-control studies"[MeSH Terms] OR "case-control"[tiab] OR "cohort studies"[MeSH Terms] OR cohort[tiab] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tiab] OR longitudinally[tiab] OR "prospective"[tiab] OR prospectively[tiab] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tiab] OR "follow up"[tiab] OR "comparative study"[Publication Type] OR "comparative study"[tiab]	
6	#4 AND #5	2258
7	"Pediatrics"[Mesh] OR "Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh] OR "Young Adult"[Mesh] OR child[tiab] OR children[tiab] OR infant[tiab] OR infants[tiab] OR pediatric[tiab] OR teenager[tiab] OR teenagers[tiab] OR teenaged[tiab] OR teen[tiab] OR teens[tiab] OR "young adult"[tiab] OR "young adults"[tiab] OR adolescent[tiab] OR adolescents[tiab] OR youth[tiab]	3496121
8	#6 AND #7 [as of 1:45pm on 10.26.15]	923
9	NOT (animals[mh] NOT humans[mh]) NOT (Editorial[pt] OR Letter[pt] OR Case Reports[pt] OR Comment[pt])	**899**

Embase:

Set #		Results
1	'tuberculosis'/exp OR tuberculosis:ti OR TB:ti	266395
2	'Africa south of the Sahara'/exp OR Africa:ti,ab OR African:ti,ab OR angola:ti,ab OR benin:ti,ab OR botswana:ti,ab OR 'burkina faso':ti,ab OR burundi:ti,ab OR cameroon:ti,ab OR 'cape verde':ti,ab OR 'central african republic':ti,ab OR chad:ti,ab OR comoros:ti,ab OR congo:ti,ab OR 'cote divoire':ti,ab OR 'ivory coast':ti,ab OR congo:ti,ab OR zaire:ti,ab OR Djibouti:ti,ab OR 'equatorial guinea':ti,ab OR ethiopia:ti,ab OR eritrea:ti,ab OR gabon:ti,ab OR gambia:ti,ab OR ghana:ti,ab OR guinea:ti,ab OR 'guinea bissau':ti,ab OR kenya:ti,ab OR lesotho:ti,ab OR liberia:ti,ab OR madagascar:ti,ab OR malawi:ti,ab OR mali:ti,ab OR mauritania:ti,ab OR mauritius:ti,ab OR Mayotte:ti,ab OR mozambique:ti,ab OR namibia:ti,ab OR niger:ti,ab OR nigeria:ti,ab OR reunion:ti,ab OR rwanda:ti,ab OR sahara:ti,ab OR 'saint Helena':ti,ab OR 'sao tome':ti,ab OR senegal:ti,ab OR seychelles:ti,ab OR 'sierra leone':ti,ab OR somalia:ti,ab OR 'south africa':ti,ab OR sudan:ti,ab OR swaziland:ti,ab OR togo:ti,ab OR tanzania:ti,ab OR uganda:ti,ab OR zambia:ti,ab OR zimbabwe:ti,ab	491851
3	'drug'/exp/dd_pe OR 'drug industry'/exp OR 'health care distribution'/exp OR 'tuberculostatic agent'/exp/dd_pe,dd_ae OR 'attitude to health'/exp OR 'patient attitude'/exp OR 'patient dropouts'/exp OR 'motivation'/exp OR 'time to treatment'/exp OR 'time'/exp OR 'stigma'/exp OR 'social stigma'/exp OR 'social support'/exp OR dropout:ti,ab OR dropouts:ti,ab OR refuse:ti,ab OR refusal:ti,ab OR refused:ti,ab OR initiate:ti,ab OR initiated:ti,ab OR initiation:ti,ab OR 'non initiation':ti,ab OR noninitiation:ti,ab OR facilitate:ti,ab OR facilitator:ti,ab OR facilitated:ti,ab OR facilitators:ti,ab OR barrier:ti,ab OR barriers:ti,ab OR uptake:ti,ab OR delay:ti,ab OR delayed:ti,ab OR delays:ti,ab OR time:ti,ab OR supply:ti,ab OR stigma:ti,ab OR support:ti,ab OR economics:ti,ab OR pathway:ti,ab OR pathways:ti,ab OR 'side effect':ti,ab OR 'side effects':ti,ab OR 'adverse effect':ti,ab OR 'adverse effects':ti,ab OR motivat*:ab,ti	6815184
4	#1 AND #2 AND #3	**4516**
5	'information processing'/exp OR 'questionnaire'/exp OR 'qualitative research'/exp OR 'observational study'/exp OR 'interview'/exp OR 'literature'/exp OR 'verbal communication'/exp OR 'nursing research'/exp OR 'recording'/exp OR 'semi-structured':ti,ab OR semistructured:ti,ab OR unstructured:ti,ab OR informal:ti,ab OR 'in-depth':ti,ab OR indepth:ti,ab OR 'face-to-face':ti,ab OR structured:ti,ab OR interview*:ti,ab OR discussion:ti,ab OR discussions:ti,ab OR questionnaire:ti,ab OR questionnaires:ti,ab OR survey:ti,ab OR surveys:ti,ab OR surveyed:ti,ab OR 'focus group':ti,ab OR 'focus groups':ti,ab OR qualitative:ti,ab OR ethnography:ti,ab OR ethnographic:ti,ab OR fieldwork:ti,ab OR 'field work':ti,ab OR 'key informant':ti,ab OR 'randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR	13904707

	'clinical study'/exp OR 'clinical trial':ti,ab OR 'clinical trials':ti,ab OR 'controlled study'/exp OR 'evaluation'/exp OR 'evaluation study':ab,ti OR 'evaluation studies':ab,ti OR 'intervention study':ab,ti OR 'intervention studies':ab,ti OR 'case control':ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR 'follow up':ab,ti OR 'comparative study'/exp OR 'comparative study':ab,ti OR 'comparative studies':ab,ti	
6	#4 AND #5	3293
7	'pediatrics'/exp OR 'adolescent'/exp OR 'child'/exp OR 'infant'/exp OR 'young adult'/exp OR child:ti,ab OR children:ti,ab OR infant:ti,ab OR infants:ti,ab OR pediatric:ti,ab OR teenager:ti,ab OR teenagers:ti,ab OR teenaged:ti,ab OR teen:ti,ab OR teens:ti,ab OR 'young adult':ti,ab OR 'young adults':ti,ab OR adolescent:ti,ab OR adolescents:ti,ab OR youth:ti,ab	3546508
8	#6 AND #7	960
9	#8 AND [embase]/lim NOT [medline]/lim	253
	NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp) AND ('humans'/lim)	**217 as of 10/26/15**

CINAHL:

Set #		Results
1	(MH "Tuberculosis+") OR TI (Tuberculosis OR TB)	17151
2	(MH "Africa South of the Sahara+") OR TI (Africa OR African OR angola OR benin OR botswana OR burkina faso OR burundi OR cameroon OR cape verde OR central african republic OR chad OR comoros OR congo OR cote d'ivoire OR ivory coast OR congo OR zaire OR Djibouti OR equatorial guinea OR ethiopia OR eritrea OR gabon OR gambia OR ghana OR guinea OR guinea-bissau OR kenya OR lesotho OR liberia OR madagascar OR malawi OR mali OR mauritania OR mauritius OR Mayotte OR mozambique OR namibia OR niger OR nigeria OR reunion OR rwanda OR sahara OR saint Helena OR sao tome OR senegal OR seychelles OR sierra leone OR somalia OR south africa OR sudan OR swaziland OR togo OR tanzania OR uganda OR zambia OR zimbabwe) OR AB (Africa OR African OR angola OR benin OR botswana OR burkina faso OR burundi OR cameroon OR cape verde OR central african republic OR chad OR comoros OR congo OR cote d'ivoire OR ivory coast OR congo OR zaire OR Djibouti OR equatorial guinea OR ethiopia OR eritrea OR gabon OR gambia OR ghana OR guinea OR guinea-bissau OR kenya OR lesotho OR liberia OR madagascar OR malawi OR mali OR mauritania OR mauritius OR Mayotte OR mozambique OR namibia OR niger OR nigeria OR reunion OR rwanda OR sahara OR saint Helena OR sao tome OR senegal OR seychelles OR sierra leone OR somalia OR south africa OR sudan OR swaziland OR togo OR tanzania OR uganda OR zambia OR zimbabwe)	72414
3	(MH "Health Care Delivery+/UT") OR (MH "Drugs+/SD/EC") OR (MH "Antitubercular Agents+/AE/EC/SD") OR (MH "Attitude to Health+") OR (MH "Patient Dropouts") OR (MH "Motivation+") OR (MH "Time Factors") OR (MH "Treatment Delay") OR (MH "Stigma") OR (MH "Support,	833820

	Psychosocial+") OR TI (dropout OR dropouts OR refuse OR refusal OR refused OR initiate OR initiated OR initiation OR non-initiation OR noninitiation OR facilitate OR facilitator OR facilitated OR facilitators OR barrier OR barriers OR uptake OR delay OR delayed OR delays OR time OR supply OR stigma OR support OR economics OR pathway OR pathways OR "side effect" OR "side effects" OR "adverse effect" OR "adverse effects" OR motivat*) OR AB (dropout OR dropouts OR refuse OR refusal OR refused OR initiate OR initiated OR initiation OR non-initiation OR noninitiation OR facilitate OR facilitator OR facilitated OR facilitators OR barrier OR barriers OR uptake OR delay OR delayed OR delays OR time OR supply OR stigma OR support OR economics OR pathway OR pathways OR "side effect" OR "side effects" OR "adverse effect" OR "adverse effects" OR motivat*)	
4	#1 AND #2 AND #3	**469**
5	(MH "Focus Groups") OR (MH "Questionnaires+") OR (MH "Qualitative Studies+") OR (MH "Nonexperimental Studies+") OR PT interview OR (MH "Storytelling+") OR (MH "Interviews+") OR (MH "Narratives") OR (MH "Research, Nursing") OR (MH "Nursing Administration Research") OR (MH "Clinical Nursing Research") OR (MH "Nursing Practice, Research-Based") OR (MH "Videorecording+") OR (MH "Audiorecording") OR TI ("semi-structured" OR semistructured OR unstructured OR informal OR "in-depth" OR indepth OR "face-to-face" OR structured OR interview* OR discussion OR discussions OR questionnaire OR questionnaires OR survey OR surveys OR surveyed OR "focus group" OR "focus groups" OR qualitative OR ethnography OR ethnographic OR fieldwork OR "field work" OR "key informant" OR motivat*) OR AB ("semi-structured" OR semistructured OR unstructured OR informal OR "in-depth" OR indepth OR "face-to-face" OR structured OR interview* OR discussion OR discussions OR questionnaire OR questionnaires OR survey OR surveys OR surveyed OR "focus group" OR "focus groups" OR qualitative OR ethnography OR ethnographic OR fieldwork OR "field work" OR "key informant" OR motivat*) OR PT randomized controlled trial OR PT clinical trial OR TI (randomized OR randomised OR randomization OR randomisation OR placebo OR randomly OR trial OR groups OR “clinical trial” OR “clinical trials”) OR AB (randomized OR randomised OR randomization OR randomisation OR placebo OR randomly OR trial OR groups OR “clinical trial” OR “clinical trials”) OR (MH "Evaluation Research+") OR TI ("evaluation study" OR "evaluation studies") OR AB ("evaluation study" OR "evaluation studies") OR (MH "Experimental Studies+") OR TI ("intervention study" OR "intervention studies" OR "case-control" OR cohort OR "longitudinal” OR longitudinally OR "prospective" OR prospectively) OR AB ("intervention study" OR "intervention studies" OR "case-control" OR cohort OR "longitudinal” OR longitudinally OR "prospective" OR prospectively) OR (MH "Retrospective Design") OR TI ("retrospective" OR "follow up") OR AB ("retrospective" OR "follow up") OR (MH "Comparative Studies") OR TI ("comparative study") OR AB ("comparative study")	1651496
6	#4 AND #5	376
7	(MH "Pediatrics+") OR (MH "Adolescence+") OR (MH "Child+") OR (MH "Infant+") OR (MH "Young Adult") OR TI (child OR children OR infant	804054

	OR infants OR pediatric OR teenager OR teenagers OR teenaged OR teen OR teens OR "young adult" OR "young adults" OR adolescent OR adolescents OR youth) OR AB (child OR children OR infant OR infants OR pediatric OR teenager OR teenagers OR teenaged OR teen OR teens OR "young adult" OR "young adults" OR adolescent OR adolescents OR youth)	
8	#6 AND #7	**113** **as of 10.26.15**

Global Health:

Set #		Results
1	DE "tuberculosis" OR DE "extrapulmonary tuberculosis" OR DE "miliary tuberculosis" OR TI ("tuberculosis" OR "TB")	36773
2	DE "Africa South of Sahara" OR DE "Central Africa" OR DE "East Africa" OR DE "Sahel" OR DE "Southern Africa" OR DE "West Africa" OR TI (Africa OR African OR angola OR benin OR botswana OR burkina faso OR burundi OR cameroon OR cape verde OR central african republic OR chad OR comoros OR congo OR cote d'ivoire OR ivory coast OR congo OR zaire OR Djibouti OR equatorial guinea OR ethiopia OR eritrea OR gabon OR gambia OR ghana OR guinea OR guinea-bissau OR kenya OR lesotho OR liberia OR madagascar OR malawi OR mali OR mauritania OR mauritius OR Mayotte OR mozambique OR namibia OR niger OR nigeria OR reunion OR rwanda OR sahara OR saint Helena OR sao tome OR senegal OR seychelles OR sierra leone OR somalia OR south africa OR sudan OR swaziland OR togo OR tanzania OR uganda OR zambia OR zimbabwe) OR AB (Africa OR African OR angola OR benin OR botswana OR burkina faso OR burundi OR cameroon OR cape verde OR central african republic OR chad OR comoros OR congo OR cote d'ivoire OR ivory coast OR congo OR zaire OR Djibouti OR equatorial guinea OR ethiopia OR eritrea OR gabon OR gambia OR ghana OR guinea OR guinea-bissau OR kenya OR lesotho OR liberia OR madagascar OR malawi OR mali OR mauritania OR mauritius OR Mayotte OR mozambique OR namibia OR niger OR nigeria OR reunion OR rwanda OR sahara OR saint Helena OR sao tome OR senegal OR seychelles OR sierra leone OR somalia OR south africa OR sudan OR swaziland OR togo OR tanzania OR uganda OR zambia OR zimbabwe)	176608
3	DE "antituberculous agents" OR DE "ethambutol" OR DE "ethionamide" OR DE "minocycline" OR DE "pyrazinamide" OR DE "thioacetazone" OR DE "attitudes" OR DE "consumer attitudes" OR DE "motivation" OR DE "timing" OR DE "time lag" OR DE "social stigma" OR DE "support systems" OR DE "personal support networks" OR TI (dropout OR dropouts OR refuse OR refusal OR refused OR initiate OR initiated OR initiation OR non-initiation OR noninitiation OR facilitate OR facilitator OR facilitated OR facilitators OR barrier OR barriers OR uptake OR delay OR delayed OR delays OR time OR supply OR stigma OR support OR economics OR pathway OR pathways OR "side effect" OR "side effects" OR "adverse effect" OR "adverse effects" OR supply OR motivat*) OR AB (dropout OR dropouts OR refuse OR refusal OR refused OR initiate OR initiated OR initiation OR non-initiation OR noninitiation OR facilitate OR facilitator OR facilitated OR facilitators OR barrier OR barriers OR uptake OR delay OR delayed OR delays OR time OR supply OR stigma OR support OR economics OR pathway OR pathways OR "side effect" OR "side effects" OR "adverse effect" OR "adverse effects" OR supply OR motivat*)	694687
4	#1 AND #2 AND #3	**1811**
5	DE "questionnaires" OR DE "qualitative analysis" OR DE "qualitative techniques" OR DE "interviews" OR DE "medical research" OR DE "video recordings" OR DE "videotapes" OR TI ("semi-structured" OR semistructured OR unstructured OR informal OR "in-depth" OR indepth OR "face-to-face" OR structured OR interview* OR discussion OR discussions OR questionnaire OR questionnaires OR survey OR surveys OR surveyed OR "focus group" OR "focus groups" OR narration OR narrative OR narratives OR anecdote OR anecdotes OR observation OR observations OR observational OR qualitative OR ethnography OR ethnographic OR	698051

	fieldwork OR "field work" OR "key informant") OR AB ("semi-structured" OR semistructured OR unstructured OR informal OR "in-depth" OR indepth OR "face-to-face" OR structured OR interview* OR discussion OR discussions OR questionnaire OR questionnaires OR survey OR surveys OR surveyed OR "focus group" OR "focus groups" OR narration OR narrative OR narratives OR anecdote OR anecdotes OR observation OR observations OR observational OR qualitative OR ethnography OR ethnographic OR fieldwork OR "field work" OR "key informant") OR DE "clinical trials" OR DE "randomized controlled trials" OR TI (randomized OR randomised OR randomization OR randomisation) OR AB (randomized OR randomised OR randomization OR randomisation) OR TI (randomly OR trial OR groups OR "clinical trial" OR "clinical trials") OR AB (randomly OR trial OR groups OR "clinical trial" OR "clinical trials") OR DE "evaluation" OR TI ("evaluation study" OR evaluation studies) OR AB ("evaluation study" OR evaluation studies) OR DE "intervention" OR TI ("intervention study" OR "intervention studies" OR "case-control" OR cohort studies OR cohort OR "longitudinal" OR longitudinally OR "prospective" OR prospectively OR retrospective OR "follow up" OR "comparative study") OR AB ("intervention study" OR "intervention studies" OR "case-control" OR cohort studies OR cohort OR "longitudinal" OR longitudinally OR "prospective" OR prospectively OR retrospective OR "follow up" OR "comparative study") OR DE "longitudinal studies"	
6	#4 AND #5	1811
7	DE "paediatrics" OR DE "adolescents" OR DE "children" OR DE "preschool children" OR DE "school children" OR DE "infants" OR DE "young adults" OR TI (child OR children OR infant OR infants OR pediatric OR teenager OR teenagers OR teenaged OR teen OR teens OR "young adult" OR "young adults" OR adolescent OR adolescents OR youth) OR AB (child OR children OR infant OR infants OR pediatric OR teenager OR teenagers OR teenaged OR teen OR teens OR "young adult" OR "young adults" OR adolescent OR adolescents OR youth)	331165
8	#6 AND #7	**292** as of 10.26.15

SCOPUS:

Set #		Results
1	TITLE (tuberculosis OR tb)	139433
2	TITLE-ABS-KEY (Africa OR African OR angola OR benin OR botswana OR "burkina faso" OR burundi OR cameroon OR "cape verde" OR "central african republic" OR chad OR comoros OR congo OR "cote d'ivoire" OR "ivory coast" OR congo OR zaire OR Djibouti OR "equatorial guinea" OR ethiopia OR eritrea OR gabon OR gambia OR ghana OR guinea OR "guinea Bissau" OR kenya OR lesotho OR liberia OR madagascar OR malawi OR mali OR mauritania OR mauritius OR Mayotte OR mozambique OR namibia OR niger OR nigeria OR reunion OR rwanda OR sahara OR "saint Helena" OR "sao tome" OR senegal OR seychelles OR "sierra leone" OR somalia OR "south Africa" OR sudan OR swaziland OR togo OR tanzania OR uganda OR zambia OR zimbabwe)	910333
3	TITLE-ABS-KEY (dropout OR dropouts OR refuse OR refusal OR refused OR initiate OR initiated OR initiation OR non-initiation OR noninitiation OR facilitate OR facilitator OR facilitated OR facilitators OR barrier OR barriers OR uptake OR delay OR delayed OR delays OR time OR supply OR stigma OR support OR economics OR pathway OR pathways OR "side effect" OR "side effects" OR "adverse effect" OR "adverse effects" OR motivat*)	15281159
4	#1 AND #2 AND #3	**3095**
5	TITLE-ABS-KEY ("semi-structured" OR semistructured OR unstructured OR informal OR "in-depth" OR indepth OR "face-to-face" OR structured OR interview* OR discussion OR discussions OR questionnaire OR questionnaires OR survey OR surveys OR surveyed OR "focus group" OR "focus groups" OR qualitative OR ethnography OR ethnographic OR fieldwork OR "field work" OR "key informant" OR randomized OR randomised OR randomization OR randomisation OR placebo OR randomly OR trial OR groups OR "clinical trial" OR "clinical trials" OR "evaluation study" OR "evaluation studies" OR "intervention study" OR "intervention studies" OR "case-control" OR cohort OR "longitudinal" OR longitudinally OR "prospective" OR prospectively OR "retrospective" OR "follow up" OR "comparative study")	6282153
6	#4 AND #5	1314
7	TITLE-ABS-KEY (child OR children OR infant OR infants OR pediatric OR teenager OR teenagers OR teenaged OR teen OR teens OR "young adult" OR "young adults" OR adolescent OR adolescents OR youth)	6618686
8	#6 AND #7	**839** **as of 10.26.15**

Africa Index Medicus

Set #		Results
1	"Tuberculosis"	355
2	"Africa"	2875

3	"Barrier"	6
	#1 AND #2 AND #3	**0** **as of 10.26.15**

Appendix C. Cost barriers

Citation	Author	Year	Direct costs	Indirect costs	System costs	Carer costs	Costs prior to Diagnosis	Costs Diagnosis - Treatment	Level of analysis	Country	Synthesis
20	Datiko, D. G. and B. Lindtjørn	2010	Y	Y	Y	N	N	N	Patient and system	Ethiopia	Community-based approaches are more cost-effective, than health facility-based approaches. Increased investment in community DOT and health extension workers can remove barriers of cost and distance and thus improve access to TB treatment in rural Ethiopia.
19	Vassall, A., A. Seme, P. Compernolle and F. Meheus	2010	Y	Y	N	Y	Y	Y	Patient	Ethiopia	TB and HIV patients incur major financial losses before and during treatment relative to income levels. For HIV infected patients with TB, delays were longer likely due to smear-negative TB, resulting in increased costs while patients pay for other ineffective treatments. Although TB and ART treatments are free, many patients still spend considerable money on diagnostic tests and drugs. Indirect costs are high during pre-treatment and patients do not turn to TB-HIV services first, leading to treatment delay.
21	Mauch, V., N. Woods, B. Kirubi, H. Kipruto, J. Sitienei and E. Klinkenberg	2011	Y	Y	N	Y	Y	Y	Patient	Kenya	There are substantial direct and indirect costs associated with TB with the majority of costs being indirect (i.e. inability to work). This increases poverty and leads to the 'medical poverty trap'. The Tool to Estimate Patients' Cost analysis is valuable and can be used to help identify

											interventions to lessen financial burdens on TB patients. It can also identify ways to reduce delays in diagnosis, decentralize services, and integrate TB/HIV care.
22	Umar, N. A., I. Abubakar, R. Fordham and M. Bachmann	2012	Y	N	N	N	Y	Y	Patient	Nigeria	Out of pocket spending is catastrophic with 9-39% of per capita GDP being spent on TB medications. This cost may result in delays, poor treatment outcomes, and continued spread of disease.
23	Laokri, S., M. Dramaix-Wilmet, F. Kassa, S. Anagonou and B. Dujardin	2014	Y	Y	N	N	N	N	Patient	Benin	Almost 75% of households in the survey experienced catastrophic expenditures with poorest of the poor having 36 times worse odds of experiencing catastrophic expenses. Lack of financial protection while using free TB services leads to inequities among individuals.
24	Yitayal, M., A. Aseffa, G. Andargie, L. Wassie and M. Abebe	2014	Y	Y	N	N	Y	Y	Patient	Ethiopia	Delays led to increased costs prior to diagnosis, which were much higher than post-diagnosis costs (2569 Birr versus 590 Birr).
25	Abimbola, S., K. N. Ukwaja, C. C. Onyedum, J. Negin, S. Jan and A. L. C. Martiniuk	2015	Y	N	N	N	Y	N	Patient	Nigeria	Referral linkages between formal and informal providers are important to increase early contact with appropriate providers, as transaction costs are a potential financial barrier of access to diagnosis and treatment of TB in Nigeria. Decentralization of services and community engagement may improve earlier contact with National TB Control Programs.

Appendix D. Health seeking behavior barriers

Citation	Author	Year	Country	KAB	Care Pathway	Level of analysis	Synthesis
52	Salaniponi, F. M., A. D. Harries, H. T. Banda, C. Kang'ombe, N. Mphasa, A. Mwale, B. Upindi, T. E. Nyirenda, A. Banerjee and M. J. Boeree	2000	Malawi	Y	y	Patient	Fifty-seven percent (625) of participants thought they might have pulmonary TB prior to diagnosis. 70% of first contact was with professional care, 30% was with traditional healers, grocery shops, or local vendors. Decision of where to seek care was made solely by patient in 45% cases (494); influenced by a close family member in 24% (261); and healthcare worker in 20% (219) of cases.
54	Edginton, M. E., C. S. Sekatane and S. J. Goldstein	2002	South Africa	Y	Y	Patient	Thirty percent (91) of patients believed the cause of TB was unknown; 30% (90) percent believed TB was spread from others/inadequate previous treatment; 24% (71) of patients believed TB was caused by environmental/occupational exposure (e.g. mines); 11% (34) believed cigarette smoking/excess alcohol caused TB; and 6% (21) thought cultural reasons such as disobeying traditional rules or having sex transmitted TB. Thirty-five percent of patients (106) visited district hospitals first, 26% (77) visited traditional or faith healers first, 21% (64) visited district clinics, 10% (30) visited other hospitals, and 8% visited private doctors. *percentages rounded.
53	Enwuru, C. A., E. O. Idigbe, N. V. Ezeobi and A. F. Otegbeye	2002	Nigeria	Y	Y	Patient	Low level of knowledge and awareness of TB led to delays in diagnosis and treatment. Fifty to ninety-seven percent of patients had no knowledge of transmission or etiology of TB or knew the clinic(s) for effective diagnosis and treatment. Private and traditional medical providers are not trained in TB management and may have been a barrier/delay in appropriate management.

55	Eastwood, S. V. and P. C. Hill	2004	Gambia	Y	Y	Patient and system	There is little awareness of disease and knowledge of causes of TB, which creates barriers to treatment initiation. Duration of symptoms prior to presentation at medical facilities varied between four days and three years. Stigma from health care workers was associated with poverty, dirtiness, and prostitution. Many patients felt a lack of privacy in clinics, leading them to hide their diagnosis to avoid gossip.
29	Edginton, M. E., M. L. Wong, R. Phofa, D. Mahlaba and H. J. Hodkinson	2005	South Africa	Y	Y	Patient and system	Knowledge of TB was good in 63% of patients (657 interviews) although 51% did not know the cause of TB. Twenty-five percent of patients felt stigma was attached to TB diagnosis with AIDS as an association. Forty-one percent of patients attended three or more facilities prior to the TB hospital, and 5% had attended six facilities.
28	Yimer, S., G. Bjune and G. Alene	2005	Ethiopia	Y	Y	Patient and system	Patient delays are associated with first visit to a non-formal healthcare provider and self-treatment. Where to seek care was influenced by close family members and friends 89% of the time and health professionals 11% of the time.
56	Barker, R. D., F. J. C. Millard, J. Malatsi, L. Mkoana, T. Ngoatwana, S. Agarawal and S. De Valliere	2006	South Africa	N	Y	Patient and system	Fifty-one percent of patients (68) first visited a traditional healer, 17% (22) first visited a primary health center, 16% (21) visited a mixed traditional/Western medicine facility, 6% (8) visited a general practitioner, 5% (7) visited a faith healer, and 2% went directly to the hospital or it was not known. Patients who consulted traditional healers were more likely to die (31%) 24/77 than patients who went to a government health services (7%) 4/33 (p=0.004). Consulting a traditional healer was associated with death (OR 3.3 95%CI 1.05-10.38) although the effect was lost after adjusting for treatment delay.
57	Mfinanga, S. G., B. K. Mutayoba, A. Kahwa, G. Kimaro, R. Mtandu, E. Ngadaya, S. Egwaga and A. Y. Kitua	2008	Tanzania	Y	Y	Patient and system	Females had significantly more patient delays than males (p = 0.019). Risks for patient delay (not knowing that night sweats and chest pain are TB symptoms, believing that TB is always associated with HIV, being unemployed, and living far from a health facility were more than twice as high for females than males (OR = 2.22, 95% CI 1.14, 4.31). Nearly 37% (232) patients first sought care at dispensaries, 27.5% at district hospitals, 13.6% at health centers, and 13.4% at private facilities.

58	Dodor, E. A., S. Kelly and K. Neal	2009	Ghana	Y	N	Patient and system	There are five inter-related ways in which health professionals may stigmatize patients with TB: through isolation and exclusionary practices; behaviors of health professionals towards patients with TB; public health discourse; food safety and hygiene practices; and prohibition of full burial rites to those who died from TB. Legitimate precautions to prevent the spread of TB and stigmatizing attitudes and behaviors must be separated.
51	Yimer, S., C. Holm-Hansen, T. Yimaldu and G. Bjune	2009	Ethiopia	Y	Y	Patient and system	The median time for first health care action was 30 days (IQR 12-68). Being a dependent (for financial or physical needs) was significantly associated with not taking a health care action (AOR .39, 95%CI 0.2-0.7). Most participants did not receive timely diagnosis or treatment for their symptoms despite contacting a medical provider within a reasonable period of time after the onset of cough (30 days). Of participants who sought care (604), 30% (307) attended facilities that lacked diagnostic equipment.
35	Sendagire, I., M. Schim Van der Loeff, M. Mubiru, J. Konde-Lule and F. Cobelens	2010	Uganda	Y	Y	Patient and system	Patients who knew TB was curable were significantly less likely to have long total delay (AOR 0.28, CI 0.11-0.73) and patients who knew TB was curable were significantly less likely to have long patient delay (AOR 0.36, 95%ICI 0.13-.097). Of 242 patients 231 (95.5%) had seen at least one health care provider before the visit when their diagnosis of TB was made. Most providers the 169 patients visited were: private clinic of nurse or midwives (32.5%), drug shop (21.9%), and private doctor (18.3%). Nine percent already consulted the clinic and 8.3% consulted a hospital.
59	Dodor, E. A.	2012	Ghana	Y	Y	Patient	Patient delays in seeking TB treatment are often caused by lack of knowledge as many patients did not recognize symptoms of TB, and fear of stigma (from families, communities, and health professionals) as well as patient fears of TB itself. Many patients felt health workers' attitudes were demeaning which discouraged them from seeking care at the hospital.

18	Zimri, K., A. C. Hesseling, P. Godfrey-Faussett, H. S. Schaaf and J. A. Seddon	2012	South Africa	Y	N	Patient	Significant risk factors for non-attendance at TB clinics for children were Coloured ethnicity (OR 2.82, 95%CI 1.29-11.1, p=0.02), the mother being the TB source case (OR 3.78, 95%CI 1.29-11.1 p=0.02), and cigarettes smoked in the house (OR 2.37, 95%CI 1.01-5.57, p=0.04). Families who did not bring children to appointments were more concerned about risk of infection while waiting to be seen (OR 2.45, 95%CI 1.07-5.60, p=0.03) and felt like they had to wait a long time to be seen at local clinics (OR 2.47, 95%CI 1.07-5.69, p=0.03). When the mother is the source of TB infection, this can also be a barrier to care. Demographic, social, logistical, and cultural factors all contribute to the complexity of pediatric non-attendance at TB clinic appointments.
36	Ngangro, N. N., D. Ngarhounoum, M. N. Ngangro, N. Rangar, M. G. Siriwardana, V. H. des Fontaines and P. Chauvin	2012	Chad	Y	Y	Patient and system	Low economic status, low level of education, and belief in efficacy of traditional treatments were associated with extended diagnostic delay. In multivariate analysis, an extended patient delay was associated with low health score, an intermediate education level, misconceptions about TB treatment, and having no referral to a hospital. Thirty-three percent of patients sought treatment from a hospital, 22% by buying drugs on the informal market, 21% by visiting a health center, and 13% by using traditional medicine. Less than 8% of patients consulted a private doctor, and 3.5% consulted a pharmacist. Centralization of health care and/or its lack of quality may lead to delays due to the complex 'pathway of care' of referrals, diagnostic delays, and hierarchical levels of care.
60	Biya, O., S. Gidado, A. Abraham, N. Waziri, P. Nguku, P. Nsubuga, I. Suleman, A. Oyemakinde, A. Nasidi and K. Sabitu	2014	Nigeria	Y	Y	Patient	Patients with unsatisfactory knowledge, with multiple-care seeking, and with travel time > 20 minutes were more likely to delay seeking care from DOTS providers. After controlling for travel time and age, multiple care-seeking was independently associated with patient delay (AOR = 2.18, 95% CI = 1.09-4.35). Forty-one percent (66) of patients did not know TB was airborne and 27% (43) of TB patients first sought care from non-medical facilities. Involving traditional and non-medical providers in the referral chain of TB patients to DOTS centers is important to decrease delays.

44	Makwakwa, L., M. L. Sheu, C. Y. Chiang, S. L. Lin and P. W. Chang	2014	Malawi	Y	Y	Patient	Patients' knowledge of TB was significantly associated with patient delay in both new (p=0.007) and retreatment cases (p=0.018). There were significant delays to initiation of TB treatment for both new and previously diagnosed patients, with most delays caused by the health system. The health system delay contributed more than 70% to the total delay. Retreatment cases with smear negative results had even longer health system delays.
45	Asefa, A. and W. Teshome	2014	Ethiopia	Y	N	Patient and system	Gender, perceived stigma, education status and family size significantly contribute to total delay. Being female, having tertiary education, and living in a larger family were less likely to have total delay.
25	Abimbola, S., K. N. Ukwaja, C. C. Onyedum, J. Negin, S. Jan and A. L. C. Martiniuk	2015	Nigeria	Y	Y	Patient	A 17.9% preference for alternative medicine and an 11.5% mistrust of the public sector were reasons patients sought care from care providers outside the public sector. Reducing transaction costs should include effective decentralization of services to integrate TB care with services at the primary health care level and community engagement to help keep informal providers within legal limits and facilitate referral linkages with formal and informal providers to increase early contact with appropriate TB care.
61	Cremers, A. L., M. M. de Laat, N. Kapata, R. Gerrets, K. Klipstein-Grobusch and M. P. Grobusch	2015	Zambia	Y		Patient and system	Eighty-two percent (113/138) patients with TB reported being stigmatized with females having more stigma (OR 5.479, 95%CI 1.51-19.88, p=.010). Stigma related to TB was associated with HIV, immoral behavior, incurability of disease, and traditional myths about TB etiology. Stigma led to patient hospital delays and poor treatment compliance and undermined efforts to screen for TB.

Appendix E. Infrastructure barriers

Citation	Author	Year	Country	Geography	Laboratory Capacity	Level of Care	Initial loss to follow-up	Health Services Delay/Quality	Level of analysis	Synthesis
15	Beyers, N., R. P. Gie, H. S. Schaaf, S. van Zyl, E. D. Nel, J. M. Talent and P. R. Donald	1994	South Africa	Y	N	N	N	Y	Patient and system	Nine percent (16) of children were not notified of TB diagnosis due to physician error. Of 156 notified with TB 26% (25) were not placed on treatment at local health clinics. Children in farming areas had the longest delays.
26	Lienhardt, C., J. Rowley, K. Manneh, G. Lahai, D. Needham, P. Milligan and K. P. McAdam	2001	Gambia	Y	N	Y	N	Y	System	The median number of providers seen prior to starting TB treatment was four (IQR 2–11). The majority of patients (73, 48.6%) were referred to a treatment center by a government nurse or a doctor. Health provider delays caused the majority of the total delay. Those living in rural areas also reported longer delay to treatment. Insufficient knowledge of TB symptoms among health providers of different types significantly contributes to provider delay. Increased awareness of TB among all types of providers and the general population (both urban and rural) is needed.

27	Martin, A., J. P. Baptiste and G. Krieger	2004	Chad	N	N	Y	N	Y	System	Significant treatment delays are caused by patients seeking care from non-medical providers or from "peripheral" hospitals. Total median delay was 75 days (min. 9 days, max. 790 days) with a median patient delay of 45 days (0-730 days) and median physician delay of 3 days (0-270 days).
30	Cambanis, A., M. A. Yassin, A. Ramsay, S. Bertel Squire, I. Arbide and L. E. Cuevas	2005	Ethiopia	Y	Y	N	N	Y	System	Causes for delay greater than four weeks included: rural residence, transport greater than two hours, overnight travel, and use of traditional medicine. Staying away for a night (e.g. for sputum investigation) added to out of pocket expenses.
29	Edginton, M. E., M. L. Wong, R. Phofa, D. Mahlaba and H. J. Hodkinson	2005	South Africa	Y	N	Y	N	Y	System	Forty-six percent (403) of patients reported directly to the hospital without referral, 29% were referred from a clinic, and 15% were referred from a private doctor. There was lack of documentation in hospital notification systems in addition to lack of specific referrals being made by name. Almost half (219 of 443) of patients attending clinics expected problems with continuing TB treatment due to clinic access (106), long wait times (78), and clinic staff problems (35).

28	Yimer, S., G. Bjune and G. Alene	2005	Ethiopia	Y	N	Y	N	Y	Patient and system	Living greater than 10km from a health facility was significantly associated with an increased patient delay (OR =0.42, 95%CI .24, .72). Patients seeking health care from a pharmacy or unregulated retailer or clinician (rather than medical provider) had a four-fold increase in delay. The median health-seeking period was 15 days (IQR 15-21) and health providers' delay was 61 days (IQR 31-116).
31	Dembele, S. M., H. Z. Ouedraogo, A. I. Combary, B. Sondo, J. Macq and B. Dujardin	2006	Burkino Faso	Y	Y	Y	N	Y	System	The case-finding rate was 19.5% which was similar to the national level; and inadequate compared to the 70% WHO target. Case-finding rates varied by health center and did not only depend on patients' geography/health seeking behavior.
16	Engelbrecht, A. L., B. J. Marais, P. R. Donald and H. S. Schaaf	2006	South Africa	N	Y	N	N	Y	System	In the majority of cases (55%) treatment was either not given or initiated without knowledge of the culture result. Delay between admission and clinical diagnosis was a median of 1 day (range 0-21) and treatment was started simultaneously. For children with a culture diagnosis, delay was a median of 40 days (range 16-68). Culture diagnosis may be important as clinical diagnosis, especially in the presence of HIV may be difficult to make. However, the

										majority of cultures add little diagnostic value to children with TB; although DST can only be completed if a culture is available and more drug resistance testing is needed.
32	Botha, E., S. den Boon, K. A. Lawrence, H. Reuter, S. Verver, C. J. Lombard, C. Dye, D. A. Enarson and N. Beyers	2008	South Africa	N	N	Y	Y	Y	System	Only 82% (2037) of the 2484 TB suspects had at least two sputum samples recorded and 18% of TB suspects had deficiencies in the collection process, receiving, and recording of results. Initial defaulters (range 0-40%) with fixed PHC having higher rates (18%) versus mobile PHC (14%).
33	Botha, E., S. Den Boon, S. Verver, R. Dunbar, K. A. Lawrence, M. Bosman, D. A. Enarson, I. Toms and N. Beyers	2008	South Africa	N	N	N	Y	Y	System	Twenty-four percent (14/58) of initial defaulters died, of the remaining 44 patients, 26 could not be found, 18 were interviewed. Fifty-six percent of the reasons for initial default were directly linked to services.
34	den Boon, S., S. Verver, C. J. Lombard, E. D. Bateman, E. M. Irusen, D. A. Enarson, M. W. Borgdorff and N. Beyers	2008	South Africa	N	N	N	Y	Y	System	Of the 20 actively detected cases who started treatment, 16 (80%) were successfully treated, which was a similar proportion as in passively detected cases (OR 1.01, 95 % CI 0.33–3.09). Seven percent (2/27) of the actively detected TB case died,

										compared to 4% (18/473) of passively detected TB cases, however, this difference was not significant (OR 2.02, 95%CI 0.44–9.20).
20	Datiko, D. G. and B. Lindtjørn	2010	Ethiopia	Y	N	Y	N	N	System	Community based DOT involving HEWs cost less than health facility DOTS by 62.6%. In community DOT, 74.8% (172/230) of the patients were cured and 14.3% (33/230) completed treatment. Of the 88 patients treated in Health facilities DOTS, 68.2% (60) were cured and 15.9% (14) completed treatment. The incremental cost-effectiveness ratio of health facility DOT to community DOT was -16.3. Increased investment in Community DOT and HEW's can remove barriers of cost and distance, thus improving access to TB treatment in rural Ethiopia.
	Sendagire, I., M. Schim Van der Loeff, M. Mubiru, J. Konde-Lule and F. Cobelens	2010	Uganda	Y	N	N	N	Y	Patient and system	Over 90% (231) of patients consulted more than one provider before diagnosis of TB was made with a median of four visits per patient (range 1-30). Less than 5% of TB suspects were diagnosed during their first visit to a healthcare provider.

36	Ngangro, N. N., D. Ngarhounoum, M. N. Ngangro, N. Rangar, M. G. Siriwardana, V. H. des Fontaines and P. Chauvin	2012	Chad	N	N	Y	N	Y	Patient and system	Thirty-three percent (95) patients sought treatment from a hospital, 22% (63) by buying drugs on informal market, 21% (60) by visiting a health center, 13% (37) by using traditional medicine, less than 8% (23) by consulting a private doctor, and 3.5% (10) by consulting a pharmacist. Two percent (6) did not seek care. Health system delays were 2.4 times longer than patient delays *No confidence intervals given.
37	Scott, V., V. Azevedo and J. Caldwell	2012	South Africa	N	Y	Y	N	Y	System	Rapid cycle evaluation is important for improving program evaluation and to decrease treatment commencement time. Practical steps to take and includes how to integrate services, especially HIV and pediatric services.
17	Seddon, J. A., A. C. Hesseling, M. Willemse, P. R. Donald and H. S. Schaaf	2012	South Africa	N	N	N	N	Y	Patient and system	Median time to treatment initiation 58 days (IQR 25-120) was shorter when there was a known adult MDR-TB index case than when no adult index case was known (median time 123 days, IQR 67-231, p<.001). Despite advanced disease and extra pulmonary disease in more than 30% of children, 80% had favorable outcomes with 12% (13) overall mortality rate regardless of treatment initiation.

41	Cowan, J., J. G. Cowan, S. Barnhart, S. Demamu, D. Fiseha, W. Graham, E. Melese, L. Reason, F. T. Asfaw, G. Feleke and B. Feleke	2013	Ethiopia	N	N	Y	N	Y	System	Healthcare providers are aware of high success of DOTS but there is no system for follow-up with patients who default. Pharmacists had concerns for shortages of first-line TB medications and lack of pediatric dosages. Many participants reported inadequate prevention of disease transmission and worried about contracting TB themselves and discussed high rates of staff turnover. Many participants were frustrated at the inability to diagnose and treat MDR-TB.
38	Ebonwu, J. I., K. S. Tint and C. Ihekweazu	2013	South Africa	N	N	Y	Y	Y	Patient and system	Only 63% (593) of patients initiated treatment. Of the 37% (349) of patients who did not initiate treatment 84% (293) had previously been treated for TB. Patients referred from a hospital were eight times more likely not to initiate treatment than patients referred from a clinic (aOR 8.2, 95%CI 1.8-37.8).
40	Jacobson, K. R., D. Theron, E. A. Kendall, M. F. Franke, M. Barnard, P. D. van Helden, T. C. Victor, E. M. Streicher, M. B. Murray and R. M. Warren	2013	South Africa	N	Y	N	N	Y	System	MTBDRplus, significantly reduced time from specimen collection to initiation of MDR TB treatment from a median of 80 days to 55 days for patients in a rural Western Cape, South African hospital. The laboratory phase decreased delay from a median 55 days (IRQ 46-66) for culture based testing to median

										of 27 days (IRQ 20-34) when using MTBDRplus. Smear-positive cases took a median of 22 days (IRQ 13-26) to process before resistance was reported compared with a median 29.5 days (IRQ 24-38.5) for smear-negative. Transport for samples remained a median of two days for both DST groups.
39	Yassin, M. A., D. G. Datiko, O. Tulloch, P. Markos, M. Aschalew, E. B. Shargie, M. H. Dangisso, R. Komatsu, S. Sahu, L. Blok, L. E. Cuevas and S. Theobald	2013	Ethiopia	Y	Y	Y	Y	Y	System	HEWs increased case notifications from 64 to 127/100,000 population/year. Distance and accessibility were barriers for patients, especially women, poor, elderly, and the very sick. Lab technicians provided additional training to HEW when smears were of poor quality through QI projects. 100% of patients with TB diagnosed in the intervention zone initiated treatment during the implementation period.
43	Ansa, G. A., J. D. Walley, K. Siddiqi and X. Wei	2014	Ghana	N	N	Y	N	Y	System	The doctor-led approach to ART becomes a barrier to integrating with the decentralized, nurse-led approach to TB treatment. Increasing service integration improved HIV screening but not co-trimoxazole preventive therapy or antiretroviral therapy across three hospitals. There was insufficient data to identify the most effective model of service from the study.

45	Asefa, A. and W. Teshome	2014	Ethiopia	Y	N	N	N	Y	Patient and system	The median patient delay was 30 days (IQR 20.2-60), diagnostic delay 7 (IQR 3-14), treatment delay 3 (IQR 1-4) and total delays measured in days were 45 days (IQR 34.5-69.5). Forty-nine percent (150/306) of patients did not initiate treatment within 45 days of symptom onset.
42	Dlamini-Mvelase, N. R., L. Werner, R. Phili, L. P. Cele and K. P. Mlisana	2014	South Africa	N	N	N	Y	Y	System	Thirty-six percent (98) of patients with confirmed samples were not found on the MDR-TB treatment register within three months of Xpert samples. Of patients initiating treatment, 28% (75) commenced treatment within two weeks, 40% (107) within one month, 21% (56) within two months, and 8% (21) within three months. Three percent (8) of patients never initiated treatment.
44	Makwakwa, L., M. L. Sheu, C. Y. Chiang, S. L. Lin and P. W. Chang	2014	Malawi	Y	Y	N	N	Y	System	There were significant delays to TB treatment initiation for both new and previously diagnosed patients, with most delays caused by the health system. Retreatment cases with smear negative results had even longer health system delays.

46	Virenfeldt, J., F. Rudolf, C. Camara, A. Furtado, V. Gomes, P. Aaby, E. Petersen and C. Wejse	2014	Ginea-Bissau	N	N	N	N	Y	Patient and system	The median delay to treatment decreased during the study period - in the first year median delay was 14.6 weeks (IQR 9.3-26.1) and dropped to 8.6 weeks (IQR 5.7-16.7) in the last year. In linear regression, delay decreased by 10.3% (7.9-12.6%) annually.
47	Yimer, S. A., G. A. Bjune and C. Holm-Hansen	2014	Ethiopia	Y	Y	Y	N	Y	Patient and system	Patients from rural areas had a three-fold increase in patients' delay compared to those from urban areas (aOR 3.4; 95%CI 1.3-8.9). Extra-pulmonary TB more likely to experience delay in seeking treatment compared to PTB (aOR 2.6; 95%CI 1.3-5.4). Improved TB diagnostic and treatment facilities in rural areas could reduce diagnostic and treatment delays.
49	Cox, H. S., J. F. Daniels, O. Muller, M. P. Nicol, V. Cox, G. van Cutsem, S. Moyo, V. De Azevedo and J. Hughes	2015	South Africa	N	Y	Y	N	Y	System	Decentralization and introduction of LPA and Xpert testing reduced time from sputum sample collection to date of second-line anti-TB treatment initiation from a median of 71 days (IQR 49-134, n=158) in 2003-2006 to a median of 8 days (IQR 5-25, n=89) in 2013 (p <.0001).

50	Ross, J. M., A. Cattamanchi, C. R. Miller, A. J. Tatem, A. Katamba, P. Haguma, M. A. Handley and J. L. Davis	2015	Uganda	Y	N	Y	N	N	System	Patients referred for TB evaluation travelled further to care centers than those without referrals for TB; however, longer distance or travel time was not a barrier to evaluation and treatment initiation. Neither distance nor travel time predicted completion of TB evaluation.
48	Van Den Handel, T., K. H. Hampton, I. Sanne, W. Stevens, R. Crous and A. Van Rie	2015	South Africa	Y	Y	Y	Y	Y	System	Decentralization coupled with Xpert testing had the shortest time to treatment initiation. Xpert increased the proportion of cases with bacteriological confirmation, however, point-of-care treatment may resulted in fewer people being evaluated for TB.

Appendix F. Site and patient characteristics, and time to tuberculosis treatment by site

Site characteristics											
Urban	521	U	U	U	R	R	R	R	R	R	R
Province	521	KZN	KZN	KZN	KZN	EC	EC	KZN	KZN	EC	KZN
Patients enrolled	**521**	**16 (3.1%)**	**86 (16.5%)**	**40 (7.7%)**	**27 (5.2%)**	**40 (7.7%)**	**73 (14.0%)**	**21 (4.0%)**	**76 (14.6%)**	**121 (23.2%)**	**21 (4.0%)**
Patient characteristics											
Age, in years	521	37.3 (11.0)	32.8 (8.9)	37.3 (12.4)	35.4 (8.8)	40.2 (13.7)	36.5 (10.6)	35.2 (12.1)	37.1 (11.4)	34.7 (10.1)	31.6 (10.7)
Male sex	521	13 (81.3%)	45 (52.3%)	22 (55.0%)	15 (55.6%)	22 (55.0%)	45 (61.6%)	9 (42.9%)	35 (46.1%)	67 (55.4%)	13 (61.9%)
HIV co-infection	510	14 (87.5%)	65 (75.6%)	31 (79.5%)	23 (85.2%)	34 (85.0%)	46 (66.7%)	16 (76.2%)	60 (81.1%)	79 (67.5%)	16 (76.2%)
History of TB disease	514	6 (37.5%)	30 (34.9%)	23 (59.0%)	17 (63.0%)	24 (60.0%)	31 (42.5%)	13 (61.9%)	37 (52.1%)	77 (64.2%)	13 (61.9%)
Time to treatment											
Per guideline (5 or less days)	521	4 (25.0%)	0 (0.0%)	13 (32.5%)	2 (7.4%)	13 (32.5%)	14 (19.2%)	8 (38.1%)	6 (7.9%)	15 (12.5%)	7 (33.3%)
Days to treatment	521	7 (6, 8)	22 (16-30)	7 (5, 12)	15 (10, 23)	8 (3, 14)	10 (6, 20)	7 (4, 13)	10 (7, 15)	12 (7, 20)	8 (4, 9)

Appendix G. Time to TB treatment by HIV coinfection status

Time to TB Treatment Outcome	Total (N=521)	Rural (N=279)	Urban (N=242)
Days to treatment	11 (7, 20)	10 (6, 16)	15 (8, 23)
Days to treatment (youth)	12 (8, 21)	10 (6.5-17.5)	16 (9, 22)
Days to treatment (adults)	11 (7, 20)	10 (6, 16)	14 (7, 27)

median (25^{th}, 75^{th} percentile) reported.

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Biography

Brittney Jayne Sullivan was born September 24, 1986 in Danvers, Massachusetts, USA. She attended Boston College in Chestnut Hill, MA for her Bachelor of Science and Master of Science degrees in nursing, graduating in 2009 and 2010 respectively. She is a certified pediatric nurse practitioner and practiced pediatric and adolescent medicine in the metro Boston area for three years before moving to Malawi, Africa as part of the first cohort of Seed Global Health/Peace Corps Global Health Service Partnership volunteers. She taught pediatric nursing as faculty at Mzuzu University from 2013-2014. Brittney attended Duke University School of Nursing where she was a Robert Wood Johnson Foundation Future of Nursing scholar. She pursued her PhD as well as doctoral certificate in global health through the Duke Global Health Institute.

Brittney has published in the text book *Primary Care of the Child with a Chronic Condition* with Judith Vessey. Additionally, she has published numerous articles regarding global health. She is a member of: Academy Health, the Association of Nurses in AIDS Care, the National Association of Pediatric Nurse Practitioners, and Sigma Theta Tau International Society of Nursing. Brittney has received awards from: Duke Global Health Institute, Duke Support for Interdisciplinary Graduate Network, Duke Center for International and Global Studies (TB and Migration), Duke University Bass Connections, Duke University Graduate School, Nurses Education Fund, Inc., and Sigma Theta Tau small grant program.