# PREVALENCE, RISK FACTORS, AND OUTCOMES OF RIFAMPICIN-SENSITIVE AND RIFAMPICIN-RESISTANT TUBERCULOSIS IN THE SOUTH KIVU PROVINCE, DEMOCRATIC REPUBLIC OF THE CONGO

by

**Jenna A. Nelson**

BA, Elon University, 2016

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This essay is submitted

by

**Jenna A. Nelson**

on

December 1, 2017

and approved by

Essay Advisor:
Nancy W. Glynn, PhD _____
Assistant Professor
Director, Master's Degree Programs
Department of Epidemiology
Graduate School of Public Health
University of Pittsburgh

Essay Readers:
Jean B. Nachega, MD, PhD, MPH _____
Associate Professor
Department of Epidemiology
Department of Infectious Diseases and Microbiology
Graduate School of Public Health
University of Pittsburgh

Linda R. Frank, PhD, MSN, CNS, ACRN, FAAN_____
Professor
Department of Infectious Diseases and Microbiology
Graduate School of Public Health
University of Pittsburgh

Robert M. Boudreau, PhD _____
Assistant Professor
Department of Epidemiology
Graduate School of Public Health
University of Pittsburgh

Nancy W. Glynn, PhD

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Jenna A. Nelson, MPH

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## ABSTRACT

**Background:** Tuberculosis (TB) is one of the top ten killers worldwide. Multidrug Resistant TB (MDR-TB), often defined by Rifampicin-resistant TB (RR-TB), threatens the global TB control strategy. The Democratic of the Congo (DRC) is on the World Health Organization's high burden list. The objective of this study was to estimate the prevalence of RR-TB, explore the risk factors associated with RR-TB, and evaluate the health outcomes associated with different treatment regimens, including a shortened 9-month RR-TB regimen, in the South Kivu Province, DRC.

**Methods:** Active TB patients were identified through active case finding and GeneXpert diagnostic tests via TB REACH. Patients were prescribed an appropriate treatment regimen based on MDR-TB status and clinical presentation. For this study, demographic information, medical history, and TB status data were extracted from 2012 – 2015 for 16,353 community health center patients. Pearson Chi-square tests and multiple logistic regression analyses were used to analyze risk factors and health outcomes.

**Results:** The prevalence of TB among this population was 9.4%; the prevalence of RR-TB was 1.0% in the study population, but 10.2% in TB cases. A positive sputum smear result or being a failed, relapse, or retreatment case were risk factors for RR-TB. 88.4% of RS-TB

patients on the 6-month regimen, 85.7% of RR-TB patients on the 9-month regimen, and 77.9% of RR-TB patients on the 20/24-month regimen had successful outcomes.

**Conclusions:** Results from this study showed a similar TB prevalence rate but higher RR-TB rate with a previous TB REACH study and a higher TB prevalence rate than reported by WHO. The risk factors were consistent with past literature. The 9-month RR-TB regimen's higher success rate is consistent with past literature that this shortened regimen is a feasible and effective way to treat RR-TB. The control of TB depends on the success of high-burden countries implementing efficient diagnosis and prescribing effective treatment. To limit the transmission and virulence of TB and MDR-TB, the implementation of accurate screening programs such as active case finding, testing methods such as GeneXpert, and effective treatment such as the shortened MDR-TB treatment should be a public health priority.

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## PREFACE

I greatly appreciate the guidance and support I have been given by so many people throughout my time at the University of Pittsburgh Graduate School of Public Health. I would first like to thank the faculty from the school, especially those of the Department of Epidemiology who have constantly worked to develop my research skills, intellectual curiosity, and professionalism. I would especially like to thank Dr. Glynn, who has been an advisor and mentor from my start at the school and has continued that mentorship through the development of this essay. Your constant support and knowledge has been influential throughout my time as a student. I would also like to thank Dr. Nachega for not only providing me with the opportunity to complete my internship in South Africa but also for providing the data for this Essay and for being a constant source of support through the entire process. Dr. Frank, thank you for your valuable contributions to my essay including the importance of connecting this research to its policy and programming implications. Lastly, thank you Dr. Boudreau for your statistical expertise and aid in analyzing my data. I am very grateful for all of the support I have received while crafting this essay and while as a student overall.

# 1.0 INTRODUCTION

The overall objective of this essay is to assess the prevalence, risk factors and clinical outcomes of Rifampicin-sensitive and Rifampicin-resistant Tuberculosis in the South Kivu Province of the Democratic Republic of the Congo.

## 1.1 HISTORY OF TUBERCULOSIS

Tuberculosis (TB) is an infectious disease caused by the pathogen *Mycobacterium tuberculosis* (MTB) that has caused morbidity and mortality throughout human history and continues to be among the top ten causes of death worldwide.[1] TB usually infects the lungs, referred to as pulmonary TB, but it can also affect other sites or organs in the body and is then called extrapulmonary TB.[1] TB is spread through airborne transmission and is highly infectious. However, only 5-15% of people who are infected with *M. tuberculosis* (MTB) actually progress to develop active TB.[1]

It is suggested that the genus, *Mycobacterium*, originated more than 150 million years ago and has since killed more persons than any other microbial pathogen.[2] Early Egyptian art from more than 5,000 years ago shows skeletal abnormalities that are typical of TB.[3] Similarly, *M. tuberculosis* has been found in tissues of Egyptian mummies.[3] Stories and descriptions of tuberculosis can be found throughout literature from ancient Indian and Chinese texts to classical

writings by Hippocrates and Aristotle.[2] The large influx of individuals and families moving into cities during the industrial revolution mixed with high rates of poverty proved to be a perfect environment for tuberculosis to spread resulting in death rates of 800-100/100,00 per year in London, Stockholm, and Hamburg.[2] In 1882, Robert Koch revealed that the disease was caused by an infectious agent, *Mycobacterium tuberculosis*.[2] The first vaccine designed to lower the virulence of the bacterium, developed by French bacteriologists Calmette and Guerin, was used in humans in 1921. The Bacille Calmette-Geurin (BCG) vaccine is still used in some parts of the world today to prevent severe forms of TB (e.g. TB meningitis) in children, but it shows limited effectiveness in preventing TB disease in adults.[1,4] The introduction of anti-tuberculosis drugs in 1943 was promising, however resistant mutants quickly began to appear, which endangered the success of the antibiotic therapy.[2] The high infectiousness, the growth of drug-resistant strains, and the lack of newly developed drugs have contributed to endemic and epidemic levels of TB in many developing countries, and the re-emergence of TB in some developed countries.

## 1.2 CASE DEFINITIONS

In the 75-95% of people that are infected with *M. tuberculosis* but never develop active TB, acquired cellular immunity against MTB with granuloma formation in which MTB lie dormant.[4] MTB can stay dormant in granuloma and asymptomatic for many years (latent TB infection) but can progress to active TB disease later in life, often when an individual's immune system is compromised. Approximately one third of the world population is infected with M. tuberculosis.[1] Patients with latent TB will usually have a tuberculin skin test (TST) positive, but will have a normal chest x-ray and negative sputum smear. The high-risk groups for active TB

include those in close contact with active TB, healthcare workers, medically underserved populations, and immunocompromised individuals such as people living with HIV.[1]

Active TB can affect many different sites in the body and therefore can manifest itself through various signs and symptoms. Typical symptoms are chronic cough, weight loss, fever, night sweats, and coughing up blood (haemoptysis).[5]

TB drug resistance is a threat to tuberculosis control strategy and occurs due to spontaneous mutations at predictable rates for each TB drug. To have a case of muti-drug resistant TB (MDR-TB), the TB isolate must be resistant to Isoniazid and Rifampicin.[1] To have a case of extensive-drug resistance (XDR-TB), a patient must be resistant to Isoniazid and Rifampicin as well as resistance to Fluroquinoine and one of the three injectable drugs, Amikacin, Kanamycin, or Capreomycin.[1] Therefore, XDR-TB is a subgroup of MDR-TB. Drug resistance can occur through primary or secondary resistance. Primary resistance is the result of a patient developing MDR-TB due to the transmission from a contact who has MDR-TB. Secondary resistance, also referred to as acquired resistance develops as a result of incomplete or ineffective prior TB treatment.[6] In a 2015 modelling analysis, Kendall, Fofana, and Dowdy found that a median of 95.9% of all incident MDR-TB cases were due to primary (transmitted) infection rather than secondary (acquired) infection.[6] Primary infection often occurs due to delayed diagnosis, a lack of appropriate treatment options, and failure of infection prevention control measures in over-populated clinics that don't allow for isolation, insufficient ventilation, etc.[6]

Quick and precise diagnostic tests for TB are an important part of the TB elimination strategy. The accurate diagnosis of TB or drug-resistant TB followed by proper treatment can significantly reduce morbidity, mortality, and transmission. There are different diagnostic tests

that each offer advantages and disadvantages. To be defined as a definite case of TB according to the WHO's guidelines, an individual has to be:

> A patient with *Mycobacterium tuberculosis* complex identified from a clinical specimen, either by culture or by a newer method such as molecular line probe assay. In countries that lack the laboratory capacity to routinely identify *M. tuberculosis*, a pulmonary case with one or more initial sputum smear examinations positive for acid-fast bacilli (AFB) is also considered to be a "definite" case, provided that there is a functional external quality assurance (EQA) system with blind rechecking.[5]

Whereas, a case of TB is defined as, "a definite case of TB or one in which a health worker (clinician or other clinical practitioner) has diagnosed TB and has decided to treat the patient with a full course of TB treatment."[5] WHO defines a TB suspect as:

> Any person who presents with symptoms or signs suggestive of TB. The most common symptom of pulmonary TB is a productive cough for more than 2 weeks, 1 which may be accompanied by other respiratory symptoms (shortness of breath, chest pains, hemoptysis) and/or constitutional symptoms (loss of appetite, weight loss, fever, night sweats, and fatigue).[5]

TB patients are classified based on previous TB treatment history. New cases of TB are defined as patients who have never been treated for TB or have taken anti-TB drugs for less than one month.[7] Those that have received one month or more of anti-TB drugs in the past are then broken into three different categories. Relapse cases are those that were previously treated for TB and had a successful clinical outcome (cure or treatment completion) at the end of their most recent course of TB drugs, and they are now diagnosed with another episode of TB.[7] Failure cases are those that were previously treated for TB, but their treatment failed.[7] Retreatment cases or

treatment after lost to follow-up cases are those patients who needed to be retreated due to interrupting their initial TB treatment because of lost to follow-up or other personal reasons.[7]

## 1.3 DIAGNOSTIC TESTS

There are multiple ways to test for active TB. Each of which have their advantages and disadvantages based on sensitivity and specificity as well as the necessary resources such as time, money, and specialized training. Cell culture, sputum smear, and GeneXpert MTB/RIF assay are three tests that are used in a variety of settings to diagnose active TB.

### 1.3.1 Cell Culture

The conventional cell culture test requires the isolation and the identification of the *M. tuberculosis* complex, as well as the testing of strain susceptibility to different anti-TB drugs from a sample of sputum. Sputum is a thick fluid that is produced in the lungs and the airways.[4] Samples of sputum are acquired through expectoration by coughing.[4] The culture can be done on solid media, the Lowenstein-Jensen slope, or in liquid media. Materials on solid media are cheap but labor-intensive. They are less sensitive, but rates of contamination are lower. Inoculate media with processed sputum and can take up to 8 weeks to grow. Cultures done on liquid media uses radioactive or fluorescent markers of MTB and can be completed in a much shorter time, however they are more prone to contamination.[8] Materials and equipment are expensive (i.e. the Mycobacteria Growth Indicator Tubes), but there is less labor involved.

A culture result can take anywhere from 4-8 weeks.[8] This can delay the start of treatment and increase the risk of transmission, morbidity, and mortality. A negative result shows no live tubercle bacilli in the specimen, however it does not rule out TB because there could be bacilli in other parts of the body such as the kidneys or brain.[4] A positive result does confirm the diagnosis of TB. Compared to smears, cultures have higher sensitivity.[8]

### 1.3.2 Sputum Smear

Sputum smear microscopy has been the principal diagnostic method in areas with high rates of TB infection in low-resource health settings.[8] The test is easy to perform, rapid, and specific. It also does not require complex or expensive laboratory methods making it usable in many low and middle-income countries. Each sputum sample is spread as a very thin layer on a glass slide, creating a "smear".[4] A series of stains are applied to the sample and then examined under a microscope for TB bacteria.[8] Smear microscopy has been shown to reflect the extent of the disease with higher smear grades being related to more extensive lung involvement.[8] Since it identifies the most infectious patients and is applicable in various populations, it is an important part of the TB control strategy. Ziehl-Neelsen stained sputum smears are the most widely used testing method for TB in resource-low settings.[8] The test has high specificity but varies in sensitivity from 20% to 80%.[8] Because of the low sensitivity, fluorescent microscopy has been recommended to make the tests more accurate. This method utilizes florescent microscopes illuminated with a quartz halogen or high pressure mercury vapor lamp.[8] This allows a more extensive and rapid examination of each sample. Fluorescence microscopy has been limited historically to well-equipped reference laboratories, but the introduction of light-emitting diode (LED)-based fluorescent microscopes has substantially lowered the cost of this technology and

increased availability in resource-limited areas. Auramine O or auramine-rhodamine dyes are used on concentrated smears and examined under a fluorescence microscope. This technique allows much more rapid screening of slides than the traditional methods, but confirmation of positive results with Ziehl-Neelsen staining is essential, as false-positive fluorochrome results are not uncommon. However, this method is not as applicable in low-resource health settings because it is much more expensive and uses a large amount of electricity.[8] In order to overcome these challenges, light emitting diodes (LEDs) offer a less expensive and safer alternative to fluorescents.[8] Therefore in 2011, WHO recommended that LED microscopy should replace fluorescence microscopy and Ziehl-Neelsen light microscopy.[9]

### 1.3.3 GeneXpert MTB/RIF Assay

The GeneXpert MTB/RIF assay is a highly sensitive nucleic acid amplification test that has the ability to detect TB as well as rifampicin resistance from a sputum sample within two hours of collecting the sample.[8] One advantage of the GeneXpert is that it utilizes pre-loaded cartridges with the necessary reagents to process the sample, extract and amplify the DNA by rapid, real-time PCR, and identify the nucleic acid sequences in the TB genome.[8] This means that the test can be completed with little technical skill and time. Another important aspect of the GeneXpert is that it can be used to identify Rifampicin-resistant strains of TB which is often a sign of MDR-TB. Approximately 95% of Rifampicin resistance is associated with concurrent resistance to isoniazid.[4,8] Therefore, resistance to Rifampicin is often a marker for MDR-TB. In 2010, WHO recommended the use of the GeneXpert for the diagnosis of pulmonary TB in adults, however, since 2013 it has also been recommended for children and some forms of

extrapulmonary TB.[10,11] In March 2017, WHO released new recommendations for the GeneXpert MTB/RIF Ultra assay to be used because it showed significantly higher sensitivity.[12]

Its sensitivity varies from 98 to 100% in smear-positive vs. 57 to 76.9% in smear-negative, culture-positive pulmonary cases; while the test specificity remained at 99% to 100%.[13] GeneXpert can enable a prompt and appropriate initiation of treatment which could prevent morbidity, mortality, and transmission therefore reducing the incidence of TB. The ability to provide a diagnosis of tuberculosis and determine rifampicin-susceptibility within two hours is of enormous importance, and this assay is now being rolled out through much of the world. One main disadvantage of the GeneXpert is the cost. For example, the GX4 edition costs approximately $17,000 for the machine plus additional costs for delivery, installation, service, and the cost of each individual test.[14] However, in 2012, the Bill and Melinda Gates Foundation, the President's Emergency Plan for AIDS Relief (PEPFAR), and the United States Agency for International Development (USAID) secured the price of each test at $9.98.[15] Since 2010, TB REACH, a mechanism through a Global Drug Facility has procured 265 GeneXpert machines and more than 500,000 GeneXpert MTB/RIF cartridges, with 25 more machines and 100,000 cartridges committed for the future.[16] TB REACH awards grants and GeneXpert machines to institutions and organizations that are implementing innovative programs to detect and treat TB cases.Similarly, in 2013, UNITAID, an international drug purchasing facility, and WHO began the largest rollout of GeneXpert by investing $25.9 million to purchase over 200 machines and 1.4 million test cartridges for 21 countries throughout Africa, Eastern Europe, and Asia.[17]

## 1.4 GLOBAL BURDEN OF TUBERCULOSIS

In the Global TB Report of 2016, the World Health Organization (WHO) estimates the global TB incidence rate was 142 cases per 100,000.[1] WHO uses an estimated incidence rather than prevalence rate because the targets set by the End TB strategy set for 2020 are focused on reducing incidence rates and deaths attributable to TB. There were 10.4 million new cases of TB in 2015.[1] Fifty-six percent of these cases were among men.[1] Globally the number of deaths due to TB have fallen by 22% from 2000 – 2015, with a reported 1.4 million people dying from TB in 2015.[1] Due to developed drug resistance, there were an estimated 480,000 new cases of multidrug-resistant TB (MDR-TB) in 2015, and a further 100,000 cases of rifampicin-resistant TB (RR-TB), who are also defined as eligible for MDR-treatment.[1] However, of these 580,000 people eligible for MDR-treatment, only 20% of those patients were actually enrolled.[1] WHO reports a gap of 4.3 million between officially notified cases and the number of estimated cases.[1] This reflects the significance of the underreporting and the under diagnosis of TB. WHO suggests underreporting is a large problem for countries with large private sectors and under diagnosis often occurs to geographic or financial barriers to accessing care.[1] They accounted 77% of this gap to ten countries: India, Indonesia, Nigeria, Pakistan, South Africa, Bangladesh, the Democratic Republic of the Congo, China, the United Republic of Tanzania and Mozambique.[1]

In 2015, 55% of notified TB patients also had a positive HIV test result.[1] Furthermore, one third of the 33 million people living with HIV (PLHIV) are co-infected with TB, and TB is the leading cause of death among PLHIV.[1] The risk of developing active TB increases dramatically for individuals who have an HIV infection and are 20-30 times more likely to develop active TB than those not living with HIV.[18] In order to prevent active TB, WHO

recommends that people living with HIV with an unknown TB status or positive tuberculin skin test (TST) should receive isoniazid preventive therapy (IPT).[19]

In 2014, WHO announced a post-2015 global strategy to end the global TB epidemic with targets to reduce TB deaths by 95%, to cut new cases by 90%, and to ensure that no family is burdened with catastrophic expenses due to TB by 2035.[20] In order to achieve this goal, WHO states that governments, communities, and the private sector must collaborate to expand scientific knowledge to pursue innovative interventions for care and prevention.[20]

Between 2014 and 2015, the rate of decline in TB incidence was 1.5%. In order to reach the milestones outlined in the End TB strategy, this rate needs to accelerate to a 4-5% decline by 2020.[1] However, there are considerable inequalities between developed and developing countries that could slow this decline. In 2015, three new High Burden Country (HBC) lists were outlined to include the 20 countries with the highest number of absolute cases of TB along with ten additional countries with the highest prevalence rates that were not included in the first list of 20.[21] This list allows focused interventions in the countries that contribute 80% of the global burden. There are three lists including TB, TB/HIV, and MDR-TB. Many of the countries, mostly in Asia and Africa, overlap in the three lists.[21] The Democratic Republic of the Congo appears on all three lists.

### 1.4.1 Background of the Democratic Republic of the Congo

The Democratic Republic of the Congo, often referred to as the DRC is located in central Africa. With a population of 78 million people in 2016, it is the 16$^{th}$ most populated country in the world and the fourth most populated country in Africa. In 2013, 45% of the population was under the age of 15.[22] Thirty percent of the population lives in urban clusters, spread throughout

the country with Kinshasa, the capital, having the largest population.[23] A history of conflict, mismanagement of resources, and political instability have resulted in socioeconomic problems and a lack of infrastructure especially in the health sector.[24] Health services are delivered through 26 provincial health divisions and 515 health zones.[23] The health zones are responsible for the provision of TB and TB-HIV services through diagnostic and treatment centers.[23] There are 472 hospitals, 83% of which deliver TB services, and 8,266 primary health centers in the country.[23] Despite this organizational structure, the health system is fragmented which leads to a lack of access to services for many citizens especially those living in rural areas with limited transport options.[23]

The South Kivu province is located in the eastern side of the DRC and borders Rwanda, Burundi, and Tanzania. It has a population of 6.6 million people, most of which live in rural areas.[24] The province is divided into 34 health zones. Five of the health zones are urban, and 29 of them are rural. Health zones have somewhere between one and six health facilities; each treating a median of 51,500 inhabitants.[24] Eleven of the health zones are extremely hard to reach due to an absence of roads and continued armed-conflict.[24] Going to health facilities is often not feasible for many individuals due to high transportation and clinic costs.[23] Most of the health zones receive external support from non-governmental organizations (NGOs) in order to fund primary healthcare services. In 2013, there were only 408 doctors and 2,862 nurses for the entire population in the province.[24] Therefore, these nurses as well as lab technicians are at the front lines of primary care often seeing patients with conditions they are not trained to recognize or treat.[24]

### 1.4.2 Burden of Tuberculosis in the Democratic Republic of the Congo

In 2015, there were 250,000 new cases of TB and a corresponding incidence rate of 324/100,000 in the DRC.[25] A total of 3.2% of those new cases were MDR or RR-TB, while 14% of previously treated cases were MDR or RR-TB.[25] Eighty-nine percent of the drug-sensitive TB cases put on treatment were successful, while 63% of MDR/RR-TB cases started on second-line treatment in 2013 were successful.[25] There were no XDR-TB cases who began treatment in 2013.[25] The mortality rate excluding patients with co-infected with HIV was 66 per 100,000, while the mortality rate for those with HIV and TB was 21/100,000 resulting in 16,000 deaths.[25] In 2014, there were 436 cases treated by second line treatment, and 93% (N=495) had confirmed Rifampin resistance.[25] The national DRC TB budget was 60 million USD; 3% came from domestic sources, 60% from international sources, and 37% was left unfunded.[25]

In the South Kivu Province 113 of the 500 health facilities provide TB services including Zieh-Nielsen microscopy and first line anti-TB drugs.[24] However, since 2012, ten labs in urban health facilities have been equipped with GeneXpert.[24] The number of TB cases notified within each health facility is variable. Ten percent of health facilities report less than seven cases, while 10% report more than 140 cases.[24] There is a low TB detection rate, with only 41% of estimated cases actually detected.[25] This low detection rate is due to the rural environment of many communities and the lack of diagnostic methods in many health facilities.

## 1.5 TUBERCULOSIS TREATMENT

Research on the natural history of TB has shown that 70% of people with sputum smear-positive pulmonary TB died within 10 years.[26] Therefore, in order to reduce mortality due to TB, patients must be treated with effective drugs and must adhere to their medication.

Directly Observed Therapy (DOT) is an internationally recommended strategy for effective TB control. It consists of five components: political and financial commitment, diagnosis, standardized anti-TB treatment given under direct and supportive observation, a supply of high quality anti-Tb drugs, and standardized reporting.

TB drugs are classified into two categories: first-line and second-line drugs. Normally, first-line drugs are used for those that have drug-susceptible TB, while second-line drugs are used in treatment regimens for those with MDR-TB.

For drug-susceptible TB cases, the treatment includes a six-month regimen of the first line drugs including Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide (Table 1).[27] The WHO reports an 85% treatment success rate for incident cases of drug-susceptible TB.[1]

**Table 1. WHO Recommended Drug-Susceptible Treatment Regimen**

| Intensive Phase (2 months) | Continuation Phase (4 months) |
|---|---|
| Isoniazid (H) | Isoniazid (H) |
| Rifampicin (R) | Rifampicin (R) |
| Ethambutol (E) | |
| Pyrazinamide (Z) | |

(2 H-R-Z-E/4 H-R)

Treating MDR-TB is more challenging and complex than treating drug-sensitive TB. Treatment is often more expensive, more toxic, less effective, and needed for longer. In a study in Namibia 90% of people on MDR-TB treatment experienced side effects, some of which were severe.[28] According to WHO in 2013, 52% of MDR-TB patients had treatment success and 17%

died.[29] The "conventional" MDR-TB regimen consists of an intensive phase lasting up to eight months including four or more second-line drugs and a continuation phase for 12 months or more of three or more second-line drugs (Table 2).[30] Due to this high cost, high toxicity, and long treatment duration, new MDR-TB treatment options were needed.

**Table 2. WHO Recommended Conventional Course Treatment Regimen**

| Steps to Drug Choice | Possible Drugs |
|---|---|
| 1. Choose an injectable (group 2) | Kanamycin (Km)<br>Amikacin (Am)<br>Capreomycin (Cm) |
| 2. Choose a higher-generation fluroquinolone (group 3) | Levofloxacin (Lfx)<br>Moxifloxacin (Mfx) |
| 3. Add group 4 drugs | Cycloserine/erizidone (Cs/Trd)<br>Para-aminosalicylic acid (PAS)<br>Ethionamide/prothionamide (Eto/Pto) |
| 4. Add group 1 drugs | Pyrazinamide (Z)<br>Ethambutol (E) |
| 5. Add group 5 drugs | Bedaquiline (Bdq)<br>Linezolid (Lzd)<br>Clofazimine(Cfz)<br>Amoxicillin/clavulanate (Amx/Clv)<br>Imipenem/cilastatin plus clavulanate (Ipm/Cln + Civ)<br>Meropenem plus clavulanate (Mpm + Civ)<br>High-dose isoniazid ($H_{high\text{-}dose}$)<br>Clarithromycin (Clr)<br>Thioacetazone (T) |

Example 24-month: 6Km-Ofx-Pto-Cs-E-Z/18fx-Pto-Cs-E-Z
Example 20-month: 6Km-Lfx-Pto-Cs-E-Z/14Lfx-Pto-Cs-E-Z

In an observational study from 1997-2007 in Bangladesh, Van Deun et. al found that a nine-month treatment regimen of Gatifloxacin, Clofazimine, Ethambutol, and Pyrazinamide supplemented by a four-month intensive period of Prothionamide, Kanamycin, and high-dose Isoniazid resulted in a relapse-free cure for 88% of 206 patients.[31] These patients also reported fewer adverse outcomes. An updated observational study in Bangladesh showed similar results

with 84.4% of 515 enrolled patients from 2005-2011 having a bacteriologically favorable outcome.[32] Although these observational studies showed efficiency, a randomized controlled trial was necessary in order to diminish the risk of selection bias, to assess the regimen in high-risk populations such as those with an HIV-coinfection, and to provide better evidence for a standard of care.[33] The STREAM trial is a two stage multi-center randomized trial. The first stage aims to compare a nine-month regimen similar to the Bangladesh cohorts with the previously recommended conventional TB treatment.[33] It enrolled patients in 2012, and results are expected in 2018.[33] Stage two will evaluate two new Bedaquiline-containing regimens.[33]

In response to a pooled success rate of 84% (95% CL: 79 - 87%) for patients on short MDR-TB regimens compared to a 62% (95% CL: 53% - 70%) success rate for those on longer regimens in ten observational studies throughout Asia and Africa, WHO issued new treatment guidelines for MDR-TB.[30] Since 2016, WHO recommends the same regimen as in the STREAM trial for some qualifying patients. This means four months of Kanamycin, Moxifloxacin, Protionamide, Clofazimine, Isoniazid, Pyrazinamide, and Ethambutol followed by five months of treatment with Moxifloxacin, Clofazimine, Pyrazinamide, and Ethambutol (Table 3).[30] Although WHO recognizes that the certainty in the evidence is very low due to only having results from the observational studies, these studies did show high levels of success in different settings for both patients and health systems.[30] The shorter drug regimen is also much more cost effective, costing ~€200.[31] In order to qualify for the short MDR-TB regimen, patients cannot have: confirmed resistance or suspected ineffectiveness to one of the drugs in the regimen (except for Isoniazid), exposure to one or more of the drugs in the regimen for more than one month, intolerance to one or more of the drugs in the regimen, a current pregnancy, extrapulmonary disease, or the lack of access to one of the drugs in the regimen.[30]

**Table 3. WHO Recommended Short 9-month Course Treatment Regimen**

| Intensive Phase (4-6 months) | Continuation Phase (5 months) |
|---|---|
| Kanamycin (Km) | Moxifloxacin (Mfx) |
| Moxifloxacin (Mfx) | Clofazimine (Cfz) |
| Prothionamide (Pto) | Pyrazinamide (Z) |
| Clofazimine (Cfz) | Ethambutol (E) |
| Pyrazinamide (Z) | |
| High-dose Isoniazid ($H_{high\text{-}dose}$) | |

(4 Km-Mfx-Pto-Cfz-E- Z-H high-dose /5 Mfx-Cfz-Z-E)

## 1.6 PUBLIC HEALTH SIGNIFICANCE

As one of the top ten killers worldwide, tuberculosis is an important public health issue affecting millions of people[1]. It is a public health, health security, and economic development threat. The disease often affects the most vulnerable, financially disadvantaged, and socially marginalized populations. Therefore, 3.6 million cases are missed each year by health systems resulting in millions of people not getting the adequate treatment they need.[1] Furthermore, MDR-TB remains a public health crisis, as only one in four MDR-TB cases is detected and one in two cases is cured.[1] Without treatment, 70% of people with TB die within 10 years.[26] Therefore, in order to reach the Sustainable Development Goal of Good Health and Well-being and the Stop TB strategy to end TB in 2035, national burdens of disease must be understood, risk factors must be minimized, accurate diagnostic tests must be available, and treatment must be feasible and effective. As one of the countries on WHO's TB high burden list, the DRC is an important place to intervene to decrease the spread of TB.

## 1.7 GAPS IN THE LITERATURE

Although the importance of TB control is well discussed in the literature, there is a misconception that drug-resistant TB in Sub-Saharan Africa is only a South African problem due to the limited amount of data available outside of South Africa. Due to limited laboratory infrastructure, little is known about the prevalence, risk factors, and clinical outcomes related to MDR-TB in more rural and post-conflict areas in the DRC. An improved understanding of MDR-TB burden and treatment will assist the South-Kivu Branch of National TB Program in the DRC to plan for MDR-TB services accordingly and begin to fill gaps in the guidelines for the implementation of accurate diagnostic tests and proper care for MDR-TB with the ultimate goal to improve morbidity and mortality of patients.

## 1.8 HYPOTHESES AND OBJECTIVES

The objectives of this essay are to assess prevalence rates detected through GeneXpert of Rifampicin-sensitive TB (RS-TB) and RR-TB the the South Kivu Province, Democratic Republic of the Congo, to assess risk factors for developing RR-TB in the South Kivu Province, Democratic Republic of the Congo and to assess clinical outcomes (i.e. cure, death, loss to follow up). I hypothesized that there would be a relatively high prevalence rate of RR-TB among TB confirmed patients via GeneXpert visiting one of ten urban and rural community health treatment centers from 2012-2015 in the South Kivu Province, Democratic Republic of the Congo, and Rifampicin-resistant TB cases would be associated with a history of previous TB and retreatments following interruptions (non-adherence or lost to follow-up) or failure. I also

hypothesized RR-TB patients on the shorter treatment regimen will have better health outcomes compared to those on the longer treatment regimen.

# 2.0 METHODS

## 2.1 DATA SOURCE

This study utilized existing data collected from ten urban and rural community health treatment centers in South Kivu province, DRC. The records were collected as part of the WHO supported GeneXpert MTB/RIF assay programmatic implementation project through TB REACH. TB REACH is a program within the STOP TB partnership, a collaboration of 1,500 partners combatting TB in more than 100 countries. STOP TB's targets are aligned with the United Nations (UN) Sustainable Development GOALS and WHO's End TB Strategy including their 90-90-90 targets.[34] The goal of TB REACH is "to increase case detection of TB, detect the disease as early as possible, and ensure timely and complete treatment while maintaining high TB cure rates."[16] The program focuses on populations with limited access to TB services and aims to provide innovative ways to control TB.[16] TB REACH requires that funding should be focused on testing patients with suspect TB instead of patients diagnosed with TB and suspected of having MDR-TB.[16]

Clinicians and community health workers (CHWs) screened for TB using active case finding (ACF) by identifying symptoms, suggestive chest x-rays, and/or previous TB treatment. Information, such as age, sex, previous TB, HIV status, and anti-retroviral treatment (ART) status, was collected for patients with a positive screening result. Patients' TB statuses were then

examined via a Ziehl-Neelsen sputum smear test and then evaluated for TB and RR-TB via GeneXpert MTB/RIF. Follow up for treatment outcomes were later assessed. Data was collected between 2012 and 2015, and 16,353 cases were included for analysis.

## 2.2 TB REACH SAMPLE TREATMENT REGIMENS

Based on results from the GeneXpert test, patients were put on one of five treatment regimens. RS-TB patients received either the traditional 6-month regimen (2R-H-Z-E/4R-H) or the 8-month regimen (2S-R-H-Z-E/1R-H-Z-E/5R-H-E). Category I patients described as new TB cases received the 6-month regimen. Category II patients received the 8-month regimen; these patients were usually retreated cases due to relapse, failure, or interruptions. RR-TB cases were treated with one of three regimens. For the purposes of these analyses, patients on the the 6- and 8-month regimens were not combined because Category I patients differ from Category II patients, who are usually problematic TB cases and therefore likely to have less favorable outcomes. Category IV patients, as described as WHO, received the short 9-month regimen, 4 Km-Mfx-Pto-Cfz-E- Z-H/5Km-Mfx-Pto-Cfz-E-Z. RR-TB patients who were not eligible for the shorter course treatment, were prescribed the conventional long regimen. In the past, only available long regimen available in South-Kivu was the 24-month. However, since May 2015 the 20-month treatment has been available. Therefore, if patients were diagnosed prior to May 2015, they were given the 24-month treatment (6Km-Ofx-Pto-Cs-E-Z/18Ofx-Pto-Cs-E-Z), and if they were diagnosed post May 2015, they were given the 20-month regimen (6Km-Lfx-Pto-Cs-E-Z/14Lfx-Pto-Cs-E-Z. For the purposes of this analysis, the patients on the 24- and 20-month

regimens were combined because they were prescribed for a similar type of patient and differ by only one drug (Ofloxacin for the 24-month versus Levofloxacin for the 20-month).

## 2.3 TB REACH SAMPLE TREATMENT OUTCOMES

WHO defines the treatment success as a patient that is cured and/or a patient who completes treatment.[7] Cured is defined as "A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion."[7] Treatment completed is defined as,

> A TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.[7]

For the purpose of this research, Ziehl-Neelsen sputum smear tests were used to evaluate treatment outcomes as cured, treatment completion, treatment failure, death, not evaluated, loss to follow-up, on treatment, or transferred to another Health Zone. In line with the WHO definition, the outcomes cured and treatment completion were combined to signify treatment success.

## 2.4 STATISTICAL ANALYSES

For baseline characteristics, Student T-Tests were performed by comparing the mean of the numeric variables between RS-TB and RR-TB groups. ANOVA was used to compare the mean of numeric variables between TB Negative, RS-TB, and RR-TB. Categorical variables were compared using Pearson Chi-Square test or Fisher's Exact Test if the expected cell count was less than 5. For objective one, incidence rates of TB Negative, RS-TB, and RR-TB were also calculated.

For objective two, univariate analyses were performed to identify the crude association between the potential risk factors and RR-TB. To do this, logistic regression models were fit one covariate at a time. Odds ratios, 95% confidence intervals, and $p$ – values were used to determine the strength and significance of the association. A multiple logistic regression model was then fit using variables that showed a significant association with a staying criterion of $p < .2$ or variables with known clinical importance and previous literature. Odds Ratios, 95% confidence intervals $p$ – values after multiple logistic regression were used to determine the strength and significance of the independent risk factors.

For objective three, univariate analyses were performed to identify the crude associations between potential factors and having a successful clinical outcome. Logistic regression models were fit one potential covariate at a time. Odds ratios, 95% confidence intervals, and $p$ – values were used to determine the strength and significance of the association. Multiple logistic regression was then performed to identify independent risk factors of treatment failure by reporting Odds Ratios, 95% confidence intervals, and $p$ – values after including covariates. Backward selection with a $p < .20$ staying criterion was used for building the best fit model. Patients whose clinical outcome was not yet determined because they were still on continued

treatment were excluded from the objective three analyses. All statistical analyses were performed via Stata SE 14.2 (StataCorp LP, TX, USA), and all data were stored and managed in Microsoft Excel 15.19.1.

# 3.0 RESULTS

## 3.1 BASELINE CHARACTERISTICS AND TB PREVALENCE

The prevalence of TB among the study population of suspected TB cases in South Kivu province, DRC was 9.4% (1,531 out of 16,353) from 2012 – 2015. The prevalence of RR-TB was 1.0% for the whole study population, but 10.2% among those positive for TB (Table 4). The median age was 33, but patients in the two TB positive groups were younger. The RS-TB group had a median age of 30, while the RR-TB group had a median age of 30.5. There was no significant association for age and the TB positive groups, however there was a significant association for the age of patients in the TB negative, RS-TB, and RR-TB groups ($p < .0001$). Fifty-five percent of the total patients were male. Within the RS-TB group, 64.9% were male, and within the RR-TB group, 67.5% were male (Table 4).

Table 4 also shows that within the study population among those that reported their HIV status, 990 (62.6%) patients were HIV positive, and 456 (28.8%) patients had an unknown HIV status. Among the RR-TB patients, 72.0% were HIV positive. HIV status was significantly different among TB negative, RS-TB, and RR-TB groups, as well as when comparing only the RS-TB and RR-TB groups.

Seven hundred and eleven patients had a positive sputum smear result, whereas 15,642 had a negative result (Table 4). Out of those that tested negative via GeneXpert, 99.4% of them

also had a negative sputum smear result. Only 36.6% of the patients who were diagnosed with RS-TB had a positive sputum smear result. Whereas 72.3% of patients who were diagnosed with RR-TB had a positive sputum smear result.

**Table 4. Baseline Characteristics by GeneXpert Result Groups**

| | Overall | Tuberculosis Negative | Rifampicin-sensitive Tuberculosis | Rifampicin-resistant Tuberculosis | *p*-value |
|---|---|---|---|---|---|
| **Sample Size** *n* (%) | 16,353 (100) | 14,882 (90.64) | 1,365 (8.4) | 166 (1.0) | |
| **Age**, years median (IQR) | 33 (21-51) | 35 (21-52) | 30 (21-42) | 30.5 (22-40) | 0.76[a]<br><.0001[b] |
| **Sex** *n* (%) | | | | | 0.51[c]<br><.0001[d] |
| Female | 7,327 (44.8) | 6,794 (45.8) | 479 (35.1) | 54 (32.5) | |
| Male | 9,026 (55.2) | 8,028 (54.2) | 886 (64.9) | 112 (67.5) | |
| **HIV Status** *n* (%)* | | | | | .002*[c]<br><.0001*[d] |
| Positive | 990 (62.6) | 29 (48.3) | 843 (62.1) | 118 (72.0) | |
| Negative | 135 (8.5) | 28 (46.7) | 91 (6.7) | 16 (9.8) | |
| Unknown | 456 (28.8) | 3 (5.0) | 423 (31.2) | 30 (18.3) | |
| **Sputum Smear** *n* (%) | | | | | <.0001*[c]<br><.0001*[d] |
| Negative | 15,642 (95.7) | 14,730 (99.4) | 866 (63.4) | 46 (27.7) | |
| Positive | 711 (4.4) | 92 (0.6) | 499 (36.5) | 120 (72.3) | |

[a] Comparison between RS-TB and RR-TB using Student t-test
[b] Comparison between TB negative, RS-TB, and RR-TB using One-way ANOVA test
[c] Comparison between RS-TB and RR-TB using Pearson chi-square test
[d] Comparison between TB negative, RS-TB, and RR-TB using Pearson chi-square test
*Not every patient reported their HIV status. More patients with TB reported their HIV status. 60 TB-negative patients, 1,357 RS-TB patients, and 164 patients reported their HIV status.

Among the TB positive cases, 84.7% were new cases, and 6.9% were relapse cases. There was a significant association between TB category and type of TB ($p < .0001$) (table 5). Of the patients with RS-TB, 89.7% were new TB cases, and 4.80% were relapse cases. Whereas among RR-TB patients, 43.6% were new TB cases, and 23.6% were relapse cases. There was also a significant association between TB episode number and TB type groups ($p < .0001$). For 1,293 (85.9%) patients, this current episode was their first episode of TB. One-hundred and

eighty (11.9%) patients developed TB for the second time, 42 patients had TB for the third time, and one patient had TB for the fourth time. Of the RS-TB cases, 89.9% were TB positive for the first time, and 8.9% had TB for the second time. Of the RR-TB cases, 47.3% of cases developed TB for the first time, 36.4% for the second time, and 15.8% for the third time (Table 5). The one patient who developed TB for the fourth time had RR-TB.

**Table 5. Baseline Tuberculosis Characteristics among Tuberculosis Positive Sub-Population**

| | Overall | Rifampicin-sensitive Tuberculosis | Rifampicin-resistant Tuberculosis | *p* - value |
|---|---|---|---|---|
| **TB Category,** *n* (%) | | | | <.0001*[a] |
| New | 1,286 (84.7) | 1,214 (89.7) | 72 (43.6) | |
| Failure | 69 (4.6) | 38 (2.8) | 31 (18.8) | |
| Relapse | 104 (6.9) | 65 (4.8) | 39 (23.6) | |
| Retreatment | 59 (3.9) | 36 (2.7) | 23 (13.9) | |
| **TB Episode Number,** *n* (%) | | | | <.0001*[a] |
| 1 | 1,293 (85.3) | 1,215 (89.9) | 78 (47.3) | |
| 2 | 180 (11.9) | 120 (8.9) | 60 (36.4) | |
| 3 | 42 (2.8) | 16 (1.2) | 26 (15.8) | |
| 4 | 1 (0.1) | 0 (0.0) | 1 (0.6) | |

[a] Comparison between RS-TB and RR-TB using Pearson chi-square test or Fisher's exact test
* Significant $p < .05$

## 3.2 RISK FACTORS FOR THE DEVELOPMENT OF RIFAMPICIN RESISTANT TUBERCULOSIS

A cutoff point of age 33 was used as it represents the median age for the study population. Univariate analyses showed that an unknown HIV status, a positive sputum smear results, a failure case, a relapse case, a retreatment case, and TB for two or more times were

significantly associated with developing RR-TB (Table 6).

Multiple logistic regression, controlling for age, sex, and the other variables with significant p-values <.2 in the univariate analyses showed having a positive sputum smear result and being a failure, relapse, or retreatment case of TB compared to being a new case of TB were significantly and independently associated with developing RR-TB. TB episode number was not included in the analyses due to collinearity with TB Category. A positive sputum smear result was associated with a 2.31 times higher odds of testing positive for RR-TB via GeneXpert (95% CI 1.55 – 3.45). Failure cases were 10.16 times more likely than new cases to develop RR-TB (95% CI 5.80-17.77). Relapse cases were 7.75 times more likely to develop RR-TB than new cases (95% CI 4.77-12.59). Retreatment cases were 8.95 times more likely to develop RR-TB than new cases (95% CI 4.94-16.21).

**Table 6. Univariate and Multiple Logistic Regression Analysis of Risk Factors for Rifampicin Resistant Tuberculosis (RR-TB)**

| | | Unadjusted | | Adjusted* | |
|---|---|---|---|---|---|
| **Variable** | **n (%) of RR-TB cases** | **Crude Odds Ratio (95% CI)** | ***p* - value** | **Adjusted Odds Ratio (95% CI)** | ***p* - value** |
| **Age,** years | | | | | |
| <33 | 97 (58.4) | Reference | | | |
| ≥33 | 69 (41.6) | 0.95 (0.68-1.32) | 0.78 | | |
| **Sex** | | | | | |
| Female | 54 (32.5) | Reference | | | |
| Male | 112 (67.5) | 1.12(0.80-1.58) | 0.51 | | |
| **HIV Status** | | | | | |
| Negative | 16 (9.8) | Reference | | | |
| Positive | 118 (72.0) | 0.80 (0.45-1.4) | 0.43 | 1.17 (0.62-2.24) | 0.63 |
| Unknown | 30 (18.3) | 0.40 (0.21-0.77) | 0.006 | 0.70 (0.34-1.47) | 0.35 |
| **Sputum Smear Result** | | | | | |
| Negative | 46 (27.7) | Reference | | | |
| Positive | 120 (72.3) | 4.53 (3.17-6.47) | <0.001 | 2.31 (1.55-3.45) | <0.001 |
| **TB Category** | | | | | |

**Table 6. Continued**

| Variable | n (%) of RR-TB cases | Unadjusted | | Adjusted* | |
|---|---|---|---|---|---|
| | | Crude Odds Ratio (95% CI) | *p* - value | Adjusted Odds Ratio (95% CI) | *p* - value |
| New | 72 (43.6) | Reference | | | |
| Failure | 31 (18.8) | 13.76 (8.09-23.38) | <0.001 | 10.16 (5.80-17.77) | <0.001 |
| Relapse | 39 (23.6) | 10.11 (6.37-16.07) | <0.001 | 7.75 (4.77-12.59) | <0.001 |
| Retreatment | 23 (13.9) | 10.77 (6.06-19.14) | <0.001 | 8.95 (4.94-16.21) | <0.001 |
| **TB Episode Number** | | | | | |
| 1 | 78 (47.3) | Reference | | | |
| 2 | 60 (36.4) | 7.78 (5.30-11.45) | <0.001 | | |
| 3 or 4 | 27 (16.4) | 26.29 (13.59-50.83) | <0.001 | | |

* Variables showing significant association during univariate analyses at $p < 0.2$ (TB category, Sputum smear result and HIV status) were used in multiple logistic regression analysis except for TB episode number due to collinearity; Age and sex were also included

## 3.3 TREATMENT CLINICAL OUTCOMES

Figure 1 shows the flow of patients for this TB REACH study sample. Of the patients with TB, 68 died, 1,136 had treatment success, 19 failed, and 111 were lost to follow up. This means that 85.2% of the sample were either cured for finished their treatment. A higher percentage of RS-TB patients experience treatment success (75.4%) than RR-TB patients (59.6%). Similarly, 3.4% of RS-TB patients died, while 13.3% of RR-TB patients died.

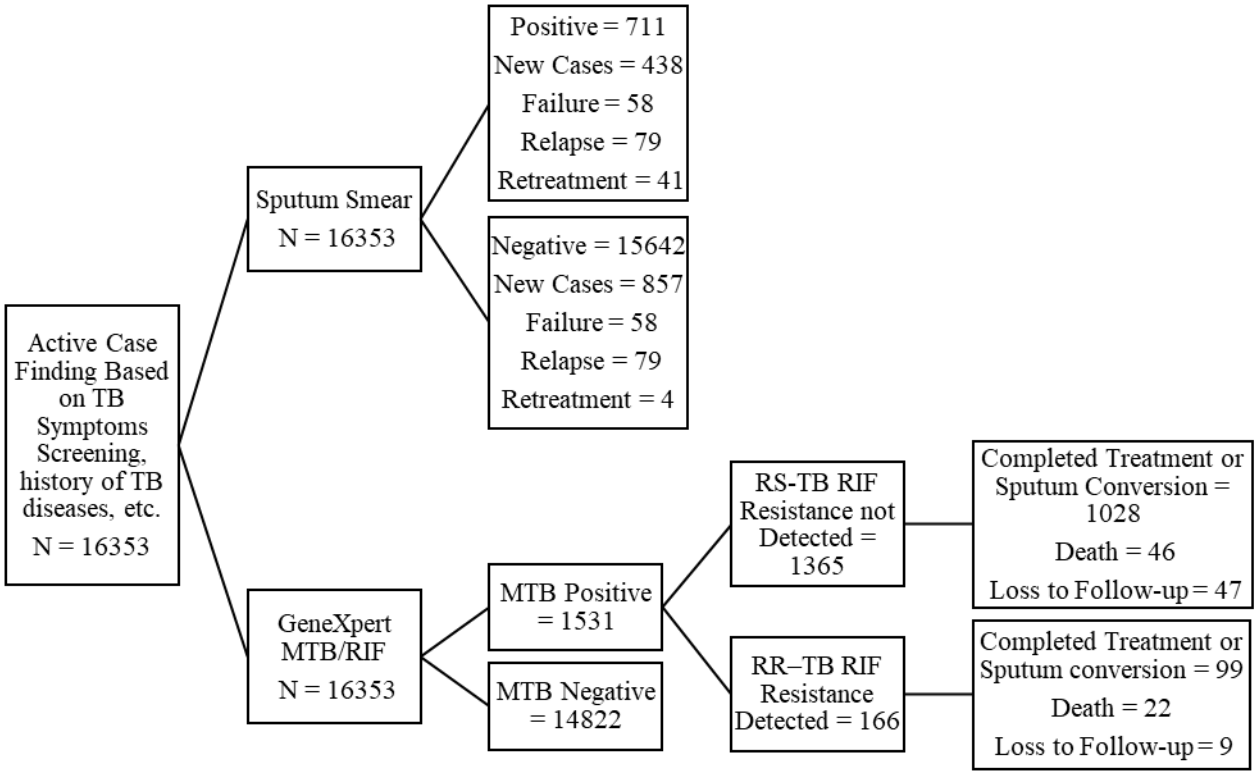


**Figure 1. TB Reach Sample Patient Flow Chart**

In total, 1,497 individuals received treatment. Of the 155 RR-TB patients, 32 qualified for the 9-month treatment, while 123 received the conventional 20/24-month treatment. After including only patients with successful, failure, death, or loss to follow-up outcomes, 104 patients on the 20/24-month treatment and 21 patients on the 9-month treatment were included in the analysis. As shown in figure 2, RR-TB patients receiving the shorted 9-month treatment had an 85.7% success rate, while 14.3% of patients failed their treatment died. However, no patients on the shortened treatment regimen failed, or were lost to follow up. RR-TB patients receiving the conventional 20- or 24-month treatment regimen had a 77.9% success rate and an 8.7% death rate with no treatment failures. Loss to follow up accounted for 11.4% of patients. RS-TB patients on the 6-month regimen had an 88.4% success rate, and RS-TB patients on the 8-month regimen (complicated cases) had a 74.8% success rate (Figure 2).

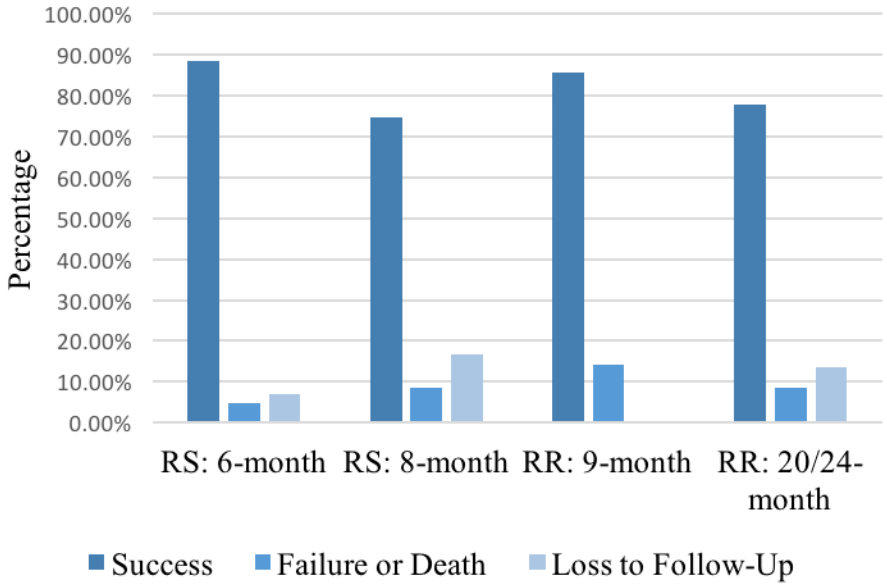


**Figure 2. Clinical Outcome by Type of Tuberculosis and Treatment Regimen for Those with Success, Failure, Death, or Loss to Follow-up Outcomes**

Univariate analyses showed that positive HIV status, unknown HIV status, a positive sputum smear result, a failure or relapse case, having TB for the second or more times, being in the DOT intensive phase, and the DOT continuation phase were all significantly associated with clinical success for RS-TB patients ($p < .2$) and were to be included in the multiple logistic regression (Table 7). The median age of 33 was used to break the age variable into two categorical groups. TB episode number was not included in the analyses due to collinearity with TB Category. Controlling for these factors, as well as age and sex, revealed that a positive HIV status, an unknown HIV status, a positive sputum smear result, being a failure or relapse case, and being in the DOT intensive or continuation phases were significantly associated with clinical success. Failure cases were .22 times less likely to have RR-TB (95% CI 0.08-0.63)), while relapse cases were .15 times less likely (95% CI 0.11-0.56). Patients with a positive sputum smear result were .48 times less likely to have a successful clinical outcome. Those participating

in the DOT intensive phase were 4.85 (95% CI 3.07-7.66) times more likely to have clinical success, and those participating in the DOT continuation phase were 16.85 (95% CI 5.84-48.62) times more likely to have clinical success if patients had RS-TB (Table 7).

**Table 7. Univariate and Multiple Logistic Regression Analysis of Factors associated with Clinical Success for Rifampicin Susceptible Tuberculosis (RS-TB) Patients**

| | | Unadjusted | | Adjusted* | |
|---|---|---|---|---|---|
| **Variable** | **n (%) Successful within each group** | **Crude Odds Ratio (95% CI)** | ***p* -value** | **Adjusted Odds Ratio (95% CI)** | ***p* -value** |
| **Age,** years | | | | | |
| <33 | 593 (87.1) | Reference | | | |
| ≥33 | 435 (85.5) | 0.87 (0.63-1.22) | 0.41 | | |
| **Sex** | | | | | |
| Female | 370 (87.9) | Reference | | | |
| Male | 658 (85.6) | 0.82 (0.57-1.17) | 0.265 | | |
| **HIV Status** | | | | | |
| Negative | 51 (62.2) | Reference | | | |
| Positive | 638 (87.8) | 4.36 (2.65-7.17) | <0.001 | 6.53 (3.28-13.01) | <0.001 |
| Unknown | 339 (89.2) | 5.03 (2.90-8.73) | <0.001 | 12.35 (5.78-26.39) | <0.001 |
| **Sputum Smear Result** | | | | | |
| Negative | 644 (87.6) | Reference | | | |
| Positive | 384 (84.4) | 0.76 (0.55-1.07) | 0.12 | 0.62 (0.40-0.97) | 0.04 |
| **TB Category** | | | | | |
| New | 936 (88.0) | Reference | | | |
| Failure | 26 (72.2) | 0.36 (0.19-0.63) | 0.007 | 0.22 (0.08-0.63) | 0.005 |
| Relapse | 40 (71.4) | 0.34 (0.19-0.63) | 0.001 | 0.25 (0.11-0.56) | 0.001 |
| Retreatment | 26 (81.3) | 0.59 (0.24-1.47) | 0.258 | 0.81 (0.23-2.82) | 0.74 |
| **TB Episode Number** | | | | | |
| 1 | 940 (88.2) | Reference | | | |
| 2 | 79 (73.2) | 0.37 (0.23-0.59) | 0.001 | | |
| 3 or 4 | 7 (58.3) | 0.19 (0.06-0.60) | 0.005 | | |
| **DOT** Intensive Phase** | | | | | |
| No | 288 (73.9) | Reference | | | |
| Yes | 735 (94.6) | 6.20 (4.22-9.10) | <0.001 | 4.85 (3.07-7.66) | <0.001 |

**Table 7. Continued**

| Variable | n (%) Successful within each group | Unadjusted | | Adjusted* | |
|---|---|---|---|---|---|
| | | Crude Odds Ratio (95% CI) | *p* -value | Adjusted Odds Ratio (95% CI | *p* -value |
| **DOT** Continuation Phase** | | | | | |
| No | 629 (82.2) | Reference | | | |
| Yes | 394 (99.0) | 21 (7.82-58.02) | <0.001 | 16.85 (5.84-48.62) | <0.001 |

*Variables showing significant association during univariate analyses at $p < 0.2$ (HIV status, sputum smear result, TB category, TB episode number, DOT intensive phase, and DOT continuation phase) were used in multiple logistic regression analysis except for TB episode number due to collinearity; Age and sex were also included
**DOT – Direct Observed Therapy

For RR-TB patients, being male, a relapse case, participating in the DOT intensive, or in the continuation phase were statistically associated with having a successful clinical outcome (cure or treatment completion) (Table 8). However, after these factors, as well as age were put into the multiple logistic regression, only those that completed the DOT intensive phase and those that completed the DOT continuation phase were independently associated with clinical success. The median age of 33 was used to break the age variable into two categorical groups. RR-TB patients that completed the DOT intensive phase were 8.84 (95% CI 2.36-33.13) times more likely to have clinical success compared to those that did not participate in the DOT intensive phase. Those that completed the DOT continuation phase were 17.44 (95% CI 2.08-146.42) times more likely to have clinical success compared to those that did not participate in the DOT continuation phase.

**Table 8. Univariate and Multiple Logistic Regression Analysis of Factors associated with Clinical Success for Rifampicin Resistant Tuberculosis (RR-TB) Patients**

| Variable | n (%) Successful within each group | Unadjusted | | Adjusted* | |
|---|---|---|---|---|---|
| | | Crude Odds Ratio (95% CI) | *p* -value | Adjusted Odds ratio (95% CI) | *p* -value |
| **Age,** years | | | | | |
| <33 | 97 (75) | Reference | | | |
| ≥33 | 42 (71.2) | 0.82 (0.38-1.77) | 0.62 | | |
| **Sex** | | | | | |
| Female | 29 (64.4) | Reference | | | |
| Male | 70 (77.8) | 1.93 (0.88-4.24) | 0.10 | 2.53 (0.74-8.64) | 0.14 |
| **HIV Status** | | | | | |
| Negative | 9 (64.3) | Reference | | | |
| Positive | 74 (77.1) | 1.87 (0.56-6.16) | 0.30 | | |
| Unknown | 14 (60.9) | 0.86 (0.21-3.43) | 0.84 | | |
| **Sputum Smear Result** | | | | | |
| Negative | 22 (66.7) | Reference | | | |
| Positive | 77 (75.5) | 1.54 (0.66-3.61) | 0.32 | | |
| **TB Category** | | | | | |
| New | 40 (69.0) | Reference | | | |
| Failure | 22 (78.6) | 1.65 (0.57-4.76) | 0.34 | 0.95 (0.21-4.28) | 0.28 |
| Relapse | 27 (81.8) | 2.03 (0.71-5.76) | 0.19 | 0.38 (0.08-1.82) | 0.94 |
| Retreatment | 10 (66.7) | 0.9 (0.27-3.02) | 0.86 | 0.46 (0.06-3.32) | 0.44 |
| **TB Episode Number** | | | | | |
| 1 | 43 (68.3) | Reference | | | |
| 2 | 38 (77.6) | 1.61 (0.68-3.78) | 0.28 | | |
| 3 or 4 | 18 (81.8) | 2.09 (0.63-6.99) | 0.23 | | |
| **TB Regimen** | | | | | |
| 20/24-month | 81 (77.9) | Reference | | | |
| 9-month | 18 (85.7) | 1.70 (0.46-6.30) | 0.42 | | |
| **DOT** Intensive Phase** | | | | | |
| No | 9 (40.9) | Reference | | | |
| Yes | 90 (86.5) | 9.29 (3.35-25.74) | <0.001 | 8.84 (2.36-33.13) | 0.001 |
| **DOT** Continuation Phase** | | | | | |
| No | 40 (64.5) | Reference | | | |
| Yes | 59 (98.3) | 32.45 (4.20-250.52) | 0.001 | 17.44 (2.08-146.42) | 0.008 |

*Variables showing significant association during univariate analyses at $p < 0.2$ were used in multiple logistic regression analysis except for TB episode number due to collinearity; Age and sex were also included

**DOT – Direct Observed Therapy

# 4.0 DISCUSSION

## 4.1 OVERVIEW OF FINDINGS

As hypothesized, results of this study showed a high prevalence of RR-TB among TB cases. The independent risk factors identified to increasing the odds of patients having RR-TB compared to RS-TB, were a positive sputum smear result via Ziehl-Nelson microscopy or a categorization as a failed, relapse, or retreatment case. Participating in DOT increased RS-TB and RR-TB patients' likelihood of clinical success. Having a positive or unknown HIV status, a positive sputum smear result, or being a failure, relapse, or retreatment case also increased RS-TB patients' likelihood of clinical success. RR-TB patients who were put on the 9-month treatment had a higher success rate than patients put on the traditional 20/24-month regimen.

## 4.2 PREVALENCE OF RIFAMPIN-RESISTANT TUBERCULOSIS

Results from this study demonstrate the impact active TB case finding, diagnosis by GeneXpert, and accurate treatment prescribing can have on health outcomes. This study showed a similar prevalence rate of TB in the South Kivu Province compared to a previous report using TB REACH data. Creswell et al. found that among 6,348 GeneXpert tests, 567 (8.9%) were positive for TB.[14] This is very similar to the prevalence of TB in this study of 8.4%. However,

this study presented a higher rate of RR-TB cases than the study by Creswell et al. They found that 5.3% of TB cases were resistant to Rifampicin, whereas this study showed a two-fold higher prevalence of RR-TB among those that were positive for TB. This difference may be explained by the increased sample size or the extended time frame in this study.

WHO's reported prevalence rate of 576 per 100,000 from 2013 in the DRC was lower than this study's findings.[35] This this study showed a prevalence of 9,362 per 100,000. The increase in number of cases may be due to several reasons. A plausible reason is the differing populations from which the prevalence rates are calculated. WHO's prevalence rate uses the total 2013 DRC population as the denominator, whereas this study uses the population of high-risk individuals identified through active case finding in the South Kivu province. This inconsistency may also be due to the limited laboratory infrastructure available elsewhere in the DRC, which could decrease the reported prevalence.[21] Further, GeneXpert was used as the diagnostic method in this study, which is more sensitive than the Ziehl-Neelson microscopy method that was used in many other areas in the DRC.[13] In this study, sputum smear results revealed a prevalence rate of 4.4% whereas the GeneXpert results showed a prevalence of more than double. Using a less sensitive test, such as Ziehl-Neelsen could lead to underdiagnosis and underreporting. Underdiagnosis and underreporting present a threat to TB control due to the high infectivity of TB. WHO reports that only 10% of the TB case notifications in 2015 were tested with rapid diagnostics at the time of diagnosis.[1] GeneXpert also has the ability to identify drug resistance offering more information on the incidence of drug resistant TB. Boehme et al. reported the GeneXpert identified more than 97% of culture-confirmed TB, and more than 90% of patients with smear-negative disease.[13] Therefore, the use of active case finding and diagnosis through GeneXpert may offer a method to reduce under diagnosis and underreporting.

Compared to the WHO reported case notifications in 2012, this study shows 10% fewer cases categorized as new cases.[35] Therefore, this study shows higher rates of failure, relapse, and retreatment cases than reported by WHO. However, the population from which this data is taken is again an important consideration. Failure, relapse, or retreatment cases may be more likely than new cases to be identified by active case finding. This study also showed that more than 50% of the RR-TB cases had at least two TB episodes including the current episode, compared to only 10% of RS-TB, suggesting secondary transmission of RR-TB.

## 4.3 RISK FACTORS FOR RIFAMPICIN-RESISTANT TUBERCULOSIS

The association between past TB treatment and MDR-TB is well noted in past literature. In a meta-analysis of 30 studies from Sub-Saharan Africa, the risk of having TB resistant to at least one TB-drug was three times higher in individuals who had prior exposure to anti-TB drugs.[36] All but one study in this meta-analysis showed this association.[36] A retrospective chart review in India of 194 patients between 2002 and 2007, showed an increase odds of 18.62 of developing drug resistant TB in patients that had previous TB treatment. Although, the TB episode number was not included in the multiple logistic regression due to collinearity, the univariate analysis did show a significant association between having more than one episode of TB and developing RR-TB. The increased odds were especially true for patients who were experiencing their third or fourth TB episode. This association of past TB and RR-TB is consistent with past literature. In a case-control study of 180 participants in Ethiopia, Workicho, Kasshun, and Alemseged found an adjusted odds ratio of 21 (95% CI: 17.8-28) for developing MDR-TB for participants who reported a previous history of TB compared to those who were

experiencing their first episode of TB. A history of TB can indicate poor immunity or unsuccessful TB treatment. Therefore, these individuals may be more likely to become infected with MDR-TB from people around them through primary transmission or acquire drug resistance due to treatment failure through secondary transmission.

A positive sputum smear result was also significantly associated with RR-TB. RR-TB cases were more likely to be smear-positive than RS-TB cases (72.29% vs. 36.56%). This is consistent with WHO's Treatment of Tuberculosis Guidelines "Patients whose sputum is smear-positive at the end of (or returning from) a second or subsequent course of treatment are … classified by the outcome of their most recent retreatment course: relapsed, defaulted or failed."[5] Therefore, patients that are smear-positive after subsequent TB treatment are categorized into one of the retreatment classifications. In this analysis being in each of these retreatment classifications also increased a patients' odds of developing RR-TB.

The role of HIV as a risk factor for MDR-TB is unclear. In a systematic review of 32 studies assessing HIV as a risk factors for MDR-TB, most studies from North America showed an association between HIV and MDR-TB, however no studies from Africa showed this same result.[37] Similarly, in the meta-analysis of 30 studies from Sub-Saharan Africa, HIV infection was not significantly associated with MDR-TB. [36] However in a case-control study of 180 participants in Ethiopia, HIV was significantly associated with MDR-TB, with an adjusted odds ratio of 3.1.[38] This study did not find an association between HIV and MDR-TB after adjusting for other covariates. The differences between the results of these studies could be methodologic in nature due to study designs or inadequate testing for both HIV and MDR-TB. Therefore, further studies including patient information such as CD4 count and viral load as well as verified testing may offer more insight into the association between HIV and MDR-TB.

## 4.4 HEALTH OUTCOMES

Two factors were significantly associated with an increased likelihood of success for both RS-TB and RR-TB patients. Both of these were related to participating in DOT. No other factors were significantly and independently associated with clinical success for RR-TB patients after adjustment for other factors. However, a positive or unknown HIV status, a positive sputum smear result, and TB category were significantly and independently associated with clinical success for patients with RS-TB. This may be due to a much higher number of patients in this study having RS-TB than RR-TB. Therefore, there was less power to find a difference due to the studied risk factors.

Participating in the DOT intensive phase and participating in the DOT continuation phase were also each independently associated with improved likelihood of clinical success for both RS-TB and RR-TB patients. DOT was recommended for tuberculosis patients by WHO after a synthesis of data from randomized control trials and observational studies. This analysis showed DOT patients had increased rates of treatment success, adherence, and 2-month sputum conversion and a decreased rate of loss to follow-up and acquired drug resistance, compared with patients utilizing self-administered treatment (SAT).[27] However, results also showed that patients on DOT had a slightly higher relapse rate.[27] There was inconsistent evidence of the clear advantage of DOT alone over SAT, however there was evidence that special groups of patients, such as those who had an HIV co-infection were likely to benefit compared to other kinds of patients due an increased risk of drug interactions and severe disease.[27] The effectiveness of DOT is often doubted and presents some ethical and legal concerns, as well as is resource intensive for some health environments.[39] A systematic review published by the Cochran group of 5,662 patients in low, middle, and high-income countries found no statistically significant difference in

clinical success for patients on DOT patients compared to those not enrolled in DOT.[40] They suggested that DOT may be more protective in populations with poorer adherence due to poverty, lower education, higher proportions of minorities, and other factors associated with social exclusion. A meta-analysis analyzing the association between DOT and treatment outcomes in patients with MDR-TB, found that patients reporting utilizing DOT rather than SAT had a higher pooled treatment success rate.[41] Therefore MDR-TB may be one of those vulnerable groups. In a study of over 69,000 patients receiving TB treatment in Brazil, a country with a high proportion of the population being defined as the vulnerable population that may benefit from DOT by the Cochran review, researchers witnessed a 25% reduction of adverse outcomes in patients participating in DOT.[42] Therefore the health barriers present in the DRC and fact that the population included patients identified through active case finding may explain why this study shows such a high increased odds of clinical success for those participating in DOT.

Results showed increased odds of clinical success for RS-TB patients with a positive or unknown HIV status, which is not consistent with past literature. It's been reported that HIV co-infected patients have a higher death rate, increased rate of unfavorable treatment outcome, and decreased rate of treatment success.[43-45] This difference may be due to the study population of those that were found through active case finding or other unknown/unmeasured confounding factors. People living with HIV are a TB high risk group and therefore often screen positive during active case finding. In this study, 62.62% of the patients were HIV positive; there was also a higher number of unknown statuses than HIV negative patients. Therefore, it cannot be generalized that a positive or unknown HIV status increases a drug susceptible patient's odds of clinical success of TB treatment.

As expected, among RS-TB patients, being a failure or relapse case was associated with a

decrease in odds of treatment success. The finding that past TB treatment negatively affects the likelihood of clinical success for TB patients is well defined in the literature. A retrospective cohort study reported a three-fold increase in odds of loss to follow-up. A registry based study in Malaysia, retrospective study in Ethiopia, and systematic review in China showed similar results.[46-48] A positive sputum smear result was associated with a decrease in odds of having a successful clinical outcome in Rifampicin susceptible patients. Melese, Zeleke, and Ewnete showed comparable results with a treatment success rate of 84.0% for smear positive patients compared to 89.5% for smear negative patients.[49]

Although the likelihood of clinical success was not significantly different for patients on the 9-month and 20/24-patient regimens, patients on the 9-month regimen did have a, 8% absolute higher success rate. The lack of significance is likely due to the relatively small number of patients on the 9-month regimen. A reason for this may be that there were no loss to follow-up patients in the 9-month regimen. This is most likely attributable to the shorter time frame that patients must be adherent. This is especially important in a low-resource environment like the DRC. Andre and Mukungo report that loss to follow up is often a large issue in the country due to a lack of clinicians and limited public health infrastructure.[24] Loss to follow-up leads to treatment failure and relapse as well as prolonged infectiousness.[50] These are important risks for patients with drug resistant TB as this could lead to an increase in the primary transmission of MDR-TB. These results further the evidence of the benefits of the 9-month regimen presented by previous studies and consequent recommendations by WHO.[30-33,51,52]

## 4.5 LIMITATIONS AND STRENGTHS

This study has limitations that reduce generalizability. The prevalence ratios do not represent the prevalence ratios in the South Kivu province, but only the prevalence ratios among those found through active case finding. Therefore, this must be taken into account if these data are used to make program planning decisions. Secondly, the success of a program such as this one including GeneXpert and the shortened regimen requires access to modern technology. This may not be feasible in other areas in the DRC or other low-income countries. The sample size of patients who were put on the 9-month treatment was also small. A larger sample size would have increased the power and potentially showed more statistically significant risk factors in developing RR-TB. Lastly, causality cannot be proven due to this study, and further studies must be completed to gain more insight into the risk-factors of RR-TB and TB health outcomes.

However, this study has many strengths that allow it to be used to assist South-Kivu Branch of National TB Program in DRC to plan accordingly for RS- and RR-TB services (program planning), as well as to inform future research. It has a large overall sample size of patients identified through community-based active case finding using GeneXpert. Therefore, this study also shows the positive impact of active case finding matched with timely diagnosis via GeneXpert. It also is the first study looking at RS- and RR-TB data from this post-conflict region in the DRC. It furthers evidence that the 9-month shortened regimen is an effective treatment option for patients with RR-TB. This information is especially helpful for the area of South Kivu because the environment presents many barriers to healthcare. Despite these barriers, the data were complete with demographic baseline data and clinical outcomes, allowing for simple analysis. Therefore, this information can be used in other areas that have vulnerable populations.

## 4.6 CONCLUSIONS

In order to reach USAID's END TB targets to eliminate TB by 2030, knowledge of the incidence of the disease, an understanding of contributing risk factors as well as accurate diagnosis methods, and effective treatment regimens must be available. Therefore, this study is vital in the TB control strategy, especially since the DRC is on WHO's high burden country list. This study documents a high burden of TB in South Kivu province, DRC. However, it shows that the scaling up of diagnosis using active case finding coupled with GeneXpert can allow MDR-TB to be efficiently identified and treated. Shorter treatment also led to better clinical outcomes than the traditional regimen, therefore adding to the limited literature on the feasibility of the shortened treatment. Therefore, this study highlights the need for future funding to scale up testing via GeneXpert as well as prescribing drug regimens that treat patients quickly, effectively, and without adverse effects. It also shows the importance of community health workers in the TB control strategy as they often provide the link between patients and treatment. Community health workers should be trained in active case finding as well as understanding treatment regimens. Community health workers provide the opportunity to prevent loss to follow up by supervising treatment adherence through DOTS. This is especially important in environments like the South Kivu province where there are limited clinicians.

In order to limit the transmission and virulence of TB and MDR-TB, the implementation of accurate screening programs such as active case finding, testing methods such as GeneXpert and effective treatment, such as the shortened 9-month MDR-TB treatment should be a public health priority for both policy and practice.

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