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Cost Savings Associated with Implementation of MTBDR*plus* Assay in the Country of Georgia

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Cost Savings Associated with Implementation of MTBDR*plus* Assay in the Country of Georgia

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Abstract

Cost Savings Associated with Implementation of MTBDR*plus* Assay in the Country of Georgia
By Rebecca Ramshaw

A major barrier to the elimination of tuberculosis (TB) in the country of Georgia is the high prevalence of mutli-drug resistant tuberculosis (MDR-TB). Not only does MDR-TB pose a significant threat to public health, it also requires costly treatments that drain limited financial resources. This thesis conducts a cost savings analysis to determine the effect of MTBDR*plus* on overall MDR-TB treatment costs, compared to conventional diagnosis alone. The primary outcome of interest is the potential cost savings associated with implementation of the MTDR*plus* molecular test among adult sputum smear-positive patients with MDR-TB in Georgia. This study is particularly relevant, as Georgia is currently transitioning away from Global Fund financial support and will soon be making important budgetary decisions regarding healthcare spending. Financial information was collected from Georgia's Global Fund office and the National Center for Tuberculosis and Lung Disease (NCTLD) in Tbilisi. Patient data were collected from medical records at the NCTLD. Approximately half of the records pre-dated introduction of MTBDR*plus* testing (March 2009 to May 2010) while the other half were consecutively collected immediately following MTBDR*plus* implementation (June 2010 to October 2012). Compared to conventional diagnosis, the MTBDR*plus* molecular test demonstrated an ability to reduce expenses at several stages of MDR-TB treatment, including hospitalization, outpatient treatment, and TB drug therapy. The median cost of treatment for one pre-implementation patient was significantly higher than the cost of treatment for one post-implementation patient ($13,216.19 compared to $9,320.55, respectively). Importantly, the two largest cost drivers were determined to be hospitalization and second line TB drug treatment. The government of Georgia should continue its investment into MTBDR*plus*; while the molecular diagnostic machine is relatively expensive, subsequent cost savings far outweigh the initial cost. Additionally, as a way to improve clinical outcomes and further reduce healthcare expenses, the government of Georgia should look to emerging global research that documents impact and effectiveness of shortened MDR-TB treatment regimens.

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1. INTRODUCTION

Despite ongoing efforts to eradicate tuberculosis (TB), the disease continues to be a major global health challenge and has recently surpassed HIV to become the leading cause of infectious disease-related mortality worldwide. In 2015, the World Health Organization (WHO) estimated there were 10.4 million cases of active tuberculosis worldwide, and 1.8 million TB-related deaths [1]. However, the global burden of TB is not evenly distributed; 60% of all new cases occur in only six countries which include India, South Africa, Indonesia, China, Nigeria, and Pakistan and the WHO has identified 30 countries that shoulder a disproportionate burden of active TB disease. Beyond mortality, it is important to consider the many other ways in which active TB impacts the livelihood of those affected. Increased incidence of TB leads to loss of income, increased exposure among healthy individuals (especially family members), poor maternal and child health outcomes, and higher school dropout rates among children [2, 3]. These indirect outcomes combined may have a significant impact on a nation's ability to achieve economic success, which in turn can affect the government's ability to support its residents.

A major barrier to achieving effective TB control is the emergence of multidrug-resistant TB (MDR-TB). MDR-TB is defined as *Mycobacterium tuberculosis* which is resistant to at least rifampin and isoniazid, the two most effective anti-TB drugs [4]. In 2015, the WHO estimated there were over 500,000 new MDR-TB cases worldwide, and approximately 250,000 deaths associated with MDR-TB [5]. While drug-susceptible TB is challenging to treat, the treatment for MDR-TB utilizes second-line drugs that are more expensive, have more severe and disabling side effects, are harder to tolerate, and are less effective [6, 7]. Additionally, the total treatment duration for MDR-TB is between 20-24 months as compared to 6 months for drug-susceptible TB. Another major concern regarding the less than optimal available treatment for MDR-TB is the risk

of acquiring further drug resistance and developing extensively drug-resistant TB (XDR-TB). XDR-TB is defined as MDR-TB plus resistance to at least one fluoroquinolone and one second-line injectable agent, the two most important second-line drugs. Both MDR-TB and XDR-TB are of significant public health importance as they have a much lower treatment success rates as compared to drug-susceptible TB [4, 5]. The rate of treatment success among drug-susceptible TB patients in most studies is ≥85% as compared the much lower rates of treatment success among patients with MDR-TB (52%) and for XDR-TB (26%) [4, 5].

A 2015 WHO global TB report placed the country of Georgia among the top 20 MDR-TB (rate per capita) burdened countries worldwide [8]. In 2015, there were a total of 3,611 confirmed cases of active TB in Georgia including 15% of whom had MDR TB [9]. The rate of MDR-TB was much higher among patients previsouly treated for TB as compared to patients with a first-time diagnosis of active TB (33 vs. 12%, respectively). High rates of drug resistance is significant from a financial perspective, as the cost to treat MDR and XDR TB is higher than drug-susceptible TB due to more expensive drugs and longer treatment courses [10-13]. One study found that MDR-TB was approximately 8 times more costly to treat when compared to drug-susceptible TB, and XDR-TB treatment was 3 times more expensive than MDR-TB [14].

Although there are systems in place to support the management of MDR-TB in Georgia, the country's ability to financially sustain current diagnostic and treatment standards remains undetermined. In 2016, Georgia was reclassified by the World Bank from lower middle-income to an upper middle-income country [15]. Prior to reclassification, the country's Ministry of Health (MoH) was eligible for substantial financial support from external sources which may not be available in the future. Based on data reported by the WHO, almost half (44%) of Georgia's TB treatment program was funded by international programs, while 42% was domestically funded,

and 14% was unfunded [9]. Most of the international funding has come from the Global Fund to Fight AIDS, Tuberculosis and Malaria which has played an integral role in developing and maintaining efforts towards treatment and prevention of TB in Georgia. However, the World Bank's reclassification of Georgia to an upper middle-income country has the potential to result in a major loss of financing from the Global Fund [16]. Though there will be a 5-year transition period wherein Georgia's government will gradually take over financial responsibilities, many of the strategic details remain unknown. The current Global Fund grant cycle will finish at the end of 2019, at which point it is predicted there will need to be transitions in TB financing.

The purpose of this thesis is to fill gaps in current knowledge regarding TB financing in the country of Georiga. The overall study goal is that our research findings will assist the Government of Georgia (GoG) in making informed financial decisions when planning future country health budgets. Although Georgia has achieved considerable economic growth since 2000, government budgets for health are not sufficient to meet current needs [17]. Georgia has made meaningful progress in its fight to eradicate TB, but there is still much work yet to be done. Sustainable financing is required to consolidate this progress and to achieve future gains in tuberculosis control.

1.1 Problem Statement

Tuberculosis is an infectious disease that has existed for much of human history, reaching epidemic proportions throughout North America and Europe in the 18th and 19th centuries [18]. However, it wasn't until 1882 that Robert Koch identified the bacteria *Mycobacterium tuberculosis* as the culprit using Koch's postulates, which are still considered a cornerstone of microbiology [18]. In the late 19th century, the use of sanatoria became the most common treatment modality

for TB, due to the belief that rest and clean air would help close cavities in infected lungs. BCG vaccination also became widespread in the early 20th century following World War I. However, it took another two decades before TB treatment entered the modern era with the discovery of streptomycin in 1944 and then isoniazid in 1952 [19].

As is the case with many other bacterial organisms, drug-resistant strains of *M. tuberculosis* emerged not long after the introduction of anti-TB drugs. There are two ways that persons can develop drug-resistant TB: either through primary transmission from someone with drug-resistant disease or by being infected with a drug-susceptible strain and then acquiring drug-resistance. Acquired resistance occurs when a patient's drug treatment regimen is inadequate (i.e., patient does not adhere to medications, the doctor prescribes the incorrect medications, or poor quality drugs are used) or through pharmacokinetic variability. Each scenario leads to low drug concentrations which then select out sponatanesous genetic mutations which are associated with drug resistance [20, 21]. Since the emergence of MDR-TB, there has been debate on how to best focus prevention efforts, which in part stems from the uncertainty whether most cases of MDR-TB arise from primary transmission versus acquired drug resistance [22]. With unlimited resources and reliable support from the WHO, the ideal situation would be for TB prevention programs at the global, national, and local level to focus on both sensitive TB and MDR-TB simultaneously.

The WHO also stresses there is a strong need for high-income countries with low TB burden to contribute financially to the global effort. This is significant especially for MDR-TB, which is more prevalent in low-income countries, but considerably more expensive and requires more resources to manage. Most low-income countries do not have the necessary resources to effectively diagnose and treat all patients with MDR-TB as evidenced by WHO reports which estimate approximately 25% of patients with MDR-TB are diagnosed and only 20% are started on

treatment [1]. This can cause a vicous cycle of undiagnosed or improperly treated patients with MDR-TB who then go on to transmit disease to family members and close contacts. While high-income countries contribute to organizations such as the Global Fund and USAID, TB remains underfunded by approximately $2 billion USD [1]. However, if high-income countries increase financial contributions, their donations would help curb the global outbreak; this should be seen by the international community as a vital investment in global health.

In the country of Georgia, there is an established infrastructure that supports ongoing national efforts to address the epidemic of both sensitive and drug-resistant TB. The National TB Program (NTP) is the governmental agency responsible for coordinating the national response to TB, and it includes the National Center for Tuberculosis and Lung Diseases (NCTLD) as its main center of operations. The NCTLD is located in the capital of Tbilisi and includes hospitals for drug-suceptible, drug-resistant, and pediatric TB patients, and the National Reference Laboratory (NRL). There are 4 additional hospitals through out the country and clinics in each of the 12 regions nationwide. Based on country protocols, all pulmonary TB suspects who present for care have multiple sputum samples collected for testing by conventional acid-fast bacilli (AFB) sputum smear microscopy, AFB culture, and molecular testing methods. Depending on the smear microscopy results, patients will undergo a molecular test with either the Xpert MTB/RIF assay on GeneXpert (Cepheid, USA) or the MTBDR*plus* assay on Genotype MTBDR*plus* (Hain Lifescience, Germany). During our study period, patients who were AFB sputum smear-negative had the Xpert MTB/RIF performed as it has increased sensitivity as compared to the MTBDR*plus* among smear negative patients, while sputum smear-positive patients had the MTBDR*plus* assay. Both assays have been shown to perform well when compared to the gold standard method of drug-resistance detection which consists of AFB culture and drug-susceptibility testing [23].

While it has been shown that current efforts have led to an overall decrease in the prevalence of TB nationwide, there is limited evidence demonstrating cost-savings associated with these diagnostic strategies [24]. It has yet to be explored whether current diagnostic efforts are fully maximizing financial investments. A cost savings analysis is beneficial in this case, because it will allow decision-makers in the GoG and MoH to optimize limited funds while weighing the benefits and drawbacks of each method in regards to cost and public health.

1.2 Purpose Statement

This study leverages a study cohort which was previsouly used to evaluate the impact of MTBDR*plus* implementation by comparing clinical treatment outcomes between patients who received conventional diagnosis (AFB sputum smear microscopy, AFB culture, and DST) and patients who were diagnosed through the use of the MTBDR*plus* molecular assay (and also later had culture and DST confirmation of disease and drug resistance, respectively) [25]. Specifically, this study seeks to evaluate the overall cost savings of these two diagnostic strategies from the perspective of the Georgian health system. Treatment costs were separated into five categories: 1) Diagnosis; 2) Drug treatment; 3) Hospitalization; 4) Outpatient treatment; and 5) Surgery. The cost analysis was used to determine the overall treatment costs for both patients who did and did not receive molecular testing with the MTBDR*plus* assay. Our analysis and findings will allow decision-makers to consider the potential cost savings associated with utilizing one method over another (MTBDR*plus* vs no MTBDR*plus*). This cost analysis study is soley from the perspective of the Georgian health system, and does not include patients' out-of-pocket expenditures.

1.3 Significance

Georgia has recently transitioned from a lower middle-income country to an upper middle-income country. This will result in a potential loss of financial support from the Global Fund to Fight AIDS, Tuberculosis and Malaria, which is a major contributor in Georgia's fight to eliminate TB. While there is a 5-year transition period away from Global Fund financial support, Georgia's MoH is already deliberating on the allotment of GoG funds. It is our hope that this cost savings analysis will assist the MoH in considering important overall financial savings (beyond initial diagnostic costs) associated with the implementation of new molecular tests, and whether the purchasing of these molecular tests is a wise use of resources. The MTDBR*plus* assay was only recently endorsed by the WHO [10], and our study would be the first of its kind evaluating cost savings in the country of Georgia using real data.

1.4 Definitions

- All costs were collected in local currency (GEL) and were then converted to USD using a 2015 average exchange rate from OANDA [26].
- Treatment outcomes: A poor outcome was defined as either loss to follow-up (formerly known as default), death during treatment, or treatment failure. A favorable outcome was defined as cured or treatment completion. [27]
- Poor outcomes include: failure, loss to follow up, and died [28].
    - Failure: A patient whose sputum smear or culture remains positive after month five of treatment, or at any time thereafter.
    - Loss to follow-up: an interruption of TB treatment of at least two months.

    - Died: A patient who dies during treatment for any reason, either before starting treatment or any time throughout treatment
- Favorable outcomes include: cured and treatment completed [28].
    - Cured: A pulmonary TB patient with bacteriologically confirmed TB at beginning of treatment, but who is then smear- or culture-negative at the end of treatment and on at least one previous occasion.
    - Treatment completed: A TB patient who completed treatment without evidence of failure but has no record to show sputum or culture results in the last month of treatment. This individual did have at least one previous smear- or culture result.
- First-line drugs: Patients at the NCTLD are treated with RIPE combined tablets for first line drug therapy. The combined tablet includes 150mg rifampin, 75mg isoniazid, 400mg pyrazinamide, and 275mg ethambutol.
- Second-line drugs: Second line drug therapy for these patients pre-dated introduction of linezolid, delamanid, and bedaquiline and include some combination of ethambutol, pyrazinamide, capreomycin, kanamycin, levofloxacin, moxifloxacin, PAS, cycloserine, and prothionamide.
- Directly observed therapy (DOT): A strategy to ensure TB patients take their medications. The observer is someone who is acceptable to both the patient and healthcare system; this individual will record each dosage of medication taken by the patient [29].
- Treatment duration: Treatment initiation was defined as the date of starting any anti-tuberculosis drug treatment. The end of treatment was defined as the final date of receiving anti-tuberculosis drugs and a final outcome (poor or favorable) was assigned. Treatment duration was then calculated as the difference in time between treatment intiation and end.

- Improper vs. proper cohorting: Improper cohorting occurs when MDR-TB patients spend time in drug-susceptible TB wards. Proper cohorting is best for MDR-TB infection control, and occurs when MDR and drug-susceptible TB patients are isolated from one another.

2. COMPREHENSIVE REVIEW OF THE LITERATURE

This literature review has three main parts: epidemiology of tuberculosis, multi-drug resistant tuberculosis in the country of Georgia, and economic costs. The review will conclude with an assessment of the available cost-effectiveness evidence and will also identify existing knowledge gaps that our study intends to fill.

2.1 Epidemiology of Tuberculosis

The WHO estimates that 10.4 million people worldwide developed active tuberculosis in 2015, and that there were 1.8 million TB-related deaths [1]. Importantly, up to one-third of all people who are newly infected with tuberculosis each year will remain undiagnosed [30]. This translates to roughly 3 million "missed" cases who remain untreated, infectious, and at risk for a poor outcome. The global burden of TB is not evenly distributed; some countries experience low incidence (3 cases per 100,000 population per year in the US) while other countries bear a much higher burden (834 cases per 100,000 population per year in South Africa) [4].

Notably, incidence among men is nearly twice as high when compared to women [31]. However, tuberculosis infection among women remains a signficant challenge. In 2015, 3.5 million women developed active TB and TB remains one of the top five causes of mortality among women aged 20-59 years worldwide [1]. Additionally, there are significant threats to maternal health: the WHO reports that perinatal deaths are six times greater when the mother is exposed to TB, and their newborns are twice as likely to suffer from low birthweight and/or premature birth. Treatment may also be difficult for women to access, due to lack of financial agency resulting from global gender inequality [32]. Inability to access treatment may lead to higher rates of

transmission among a woman's entire family [33]. Furthermore, TB may result in infertility among women, especially in developing countries [34, 35].

A number of factors influence an individual's risk of developing active tuberculosis. Chief among these is HIV infection; while HIV-infected individuals make up only 0.5% of the world's population, 12% of all patients with active TB and one-quarter of all TB-related deaths occur in persons infected with HIV [36]. The majority (75%) of TB-related fatalities among patients infected with HIV occur in Africa [37]. Other significant factors that influence transmission of *M. tuberculosis* include overcrowding, undernutrition, indoor air pollution, diabetes mellitus, excessive alcohol use, and smoking [38-42]. The estimated lifetime risk of developing active TB after exposure and infection with *M. tuberculosis* is between 5-15% [43]. In persons with active TB disease, approximately 50% of cases will result in mortality if treatment is not administered [19].

2.1.1 Epidemiology of Multi-Drug Resistant Tuberculosis

Multi-drug resistant tuberculosis (MDR-TB) is defined as *M. tuberculosis* which is resistant to at least isoniazid and rifampin [4]. The WHO reports in 2015 there were 480,000 new cases of MDR-TB, plus an additional 100,000 cases of rifampicin-resistant TB (RR TB). Notably, only 125,000 of these 580,000 individuals (20%) were initiated on MDR-TB treatment with secondline drugs. This is due to the lack of diagnostic testing resources to detect drug-resistance in most parts of the world. The highest rates of MDR-TB can be found in Eastern Europe and Central Asia; in some regions of Russia and Belarus, up to 35% of new TB cases were classified as MDR-TB [44].

The WHO estimates 3.3% of all new TB cases are multidrug-resistant, and 20.5% of all previously treated cases are multidrug resistant [45]. High prevalence of MDR TB is problematic, because MDR-TB treatment is more complex, lengthy, toxic, and expensive when compared to drug-susceptible TB treatment [1, 6, 7]. In order to administer effective treatment, healthcare providers must first determine which medication will be most successful in killing the *Mycobacterium tuberculosis* strain for their patient. If using conventional culture and DST methods, it can take up to 2 months to get results [23]. Furthermore, treatment of MDR-TB lasts much longer as compared to drug-susceptible TB; wherase drug-susceptible TB treatment lasts for 6-8 months, MDR-TB treatment requires 18-24 months of treatment and also includes up to 8 months of receiving a daily injection intravenously or intramuscularly [46]. Longer treatment is also problematic because second-line TB drugs are highly toxic; therefore, prolonged treatment results in a higher proportion of patients who experience severe negative side effects, such as renal failure, deafness, and hepatitis [47].

Additionally, poor MDR-TB treatment adherence due to intolerability increase the risk of acquired drug-resistance and thus the development of XDR-TB, whose treatment is even more toxic and expensive [48]. XDR-TB has a much lower treatment success rate when compared to both MDR-TB and drug-susceptible TB. In most settings ≥85% of drug-susceptible TB patients will achieve treatment success, while the rate of treatment success is much lower for patients with MDR-TB at 52% and even lower yet for patients with XDR-TB at 28% [1]. Additionally, XDR-TB has a higher case fatality rate (CFR); a 2010 meta-analysis reported that 21% of XDR-TB patients died, while the CFR was 9% for MDR-TB patients [49, 50]. A 2015 study found the CFR among drug-susceptible TB patients seeking treatment at 5%; much lower than both MDR-TB and XDR-TB [6].

2.2 Multidrug Resistant Tuberculosis in Georgia

There is a particularly high incidence of MDR-TB in former Soviet Union countries (FSU), including in Georgia [51, 52]. This is a problem that predates the collapse of the Soviet Union, and was caused by a multitude of factors including suboptimal treatment protocols, low quality drugs, and poor medication adherence. The collapse of the Soviet Union further complicated treatment procedures throughout the region as slowly recovering economies led to poor living conditions, heatlh systems, and broken medical supply chains. The availability of medications was limited and patients were unable to adhere to treatment regimens. These inconsistent treatment patterns caused an alarming increase in the incidence of MDR-TB. During the late 1990s, many patients withTB remained untreated and improperly treated which led to a continued spread of TB and rise in MDR-TB throughout FSU countries [53]. After Georgia gained independence, it struggled to adapt the highly centralized Soviet TB treatment regimens, thus causing further delays to patient treatment and exacerbating the development of drug resistance [54].

MDR-TB in Georgia has remained a significant threat to public health since independence in 1991. In a 2008 multi-site study of 1,422 TB suspects, 64% of patients tested positive for *M. tuberculosis* [55]. Of those who tested positive, 28% had MDR-TB including 11% of newly diagnosed patients and 53% of retreatment cases. A follow up study in Georgia confirmed the prevalence of MDR-TB was higher among retreatment cases than among newly diagnosed first-time cases [56]. While retreatment cases had an MDR-TB prevalence of 27.4%, prevalence among newly diagnosed cases was 6.8% (OR=5.27).

2.2.1 Tuberculosis Prevention and Control Efforts in Georgia

The National Center for Tuberculosis and Lung Diseases (NCTLD) is located in Tbilisi and is the main center in Georgia for TB diagnosis and treatment. Individuals who are TB suspects receive a consultation with a TB specialist and a series of laboratory tests. For each TB suspect, two sputum samples are collected for AFB smear microscopy and culture as well as molecular testing (smear-negative patients will receive Xpert TB/RIF, while smear-positive patients will have the MTBDR*plus* performed). If a sputum AFB culture is positive for *M. tuberculosis* the isolates will undergoe first-line DST and if found to have MDR second-line DST is carried out. Sputum samples from regional hospitals are mailed in sealed biohazardous containers to the NCTLD in Tbilisi. These services are provided at no direct financial cost to the patient. The Georgian government provides vouchers that pay pre-determined fees to all service providers involved in the care of TB suspects and patients. However, these vouchers do not cover all costs; Global Fund support helps to pay for expenses related to MTBDR*plus* molecular diagnostic testing and all drug treatment (both first and second line drugs).

The Global Fund plays a major role in financially supporting the fight against TB in Georgia. To date, the Global Fund has committed over $38 million USD to the elimination of TB in Georgia [57]. These funds have supported development and implementation of a Country Coordinating Mechanism (i.e., a strategic infrastructure), Directly Observed Therapy (DOTS), treatment in prisons, NGO support, funding for the NCTLD, and HIV prevention.

2.3 Economic Costs

This section will explore the costs associated with two TB diagnostic methods used in the country of Georgia including 1) AFB sputum smear microscopy, AFB culture, and DST; and 2) AFB sputum smear microscopy, AFB culture, and DST + MTBDR*plus*.

2.3.1 AFB Sputum Smear Microscopy, Culture, and DST

Conventional AFB smear microscopy has historically been the traditional method used in testing tuberculosis suspects. First invented and implemented over 125 years ago, sputum smear microscopy is often combined with chest x-rays to diagnose TB suspects in low-resource settings [58]. Low- and middle-income countries often do not have access to culture and DST when diagnosing TB suspects, due to limited funding and an underdeveloped infrastructure. Even when DST is available, its ability to detect drug resistance in patients is limited to those who have a positive AFB culture.

A 2013 systematic review analyzing 26 published studies from 1995-2012 found the estimated unit costs for smear microscopy, culture, and combined tests: $0.26 to $10.50, $1.63 to $62.01, and $26.73 to $39.57, respectively [59]. Key drivers of cost were consumables, equipment, transportation, and staff. Smear microscopy is considered low cost and requires relatively very little infrastructure [60]. It is also highly specific in areas with high TB prevalence, which is important considering a majority of TB cases occur in low- and middle-income countries with limited resources [61]. However, there are significant drawbacks to the use of smear microscopy including a low sensitivity and its inability to detect drug resistance [62]. The sensitivity of smear microscopy is particularily low in patients with a low sputum bacterial load

which includes children, patients with HIV infection and patients with non cavitary lung disease [60, 63].

DST is an important step in combination with culture as it allows healthcare providers to determine which drugs their patients *Mycobacterium tuberculosis* isoslate is susceptible to and thus how to tailor their treatment regimen. The main drawback of DST is the long turnaround time; in addition to the 6-8 weeks necessary for culture incubation, DST requires another 4-6 weeks (thus total time of 10-14 weeks) before laboratory technicians can determine which line of treatment will be most beneficial for patients [64, 65]. During this period, patients are likely on inappropriate treatment; these patients remain infectious, thereby potentially infecting healthy individuals while awaiting proper treatment assignment [66].

2.3.2 GenoType MTBDR*plus* Assay

Endorsed by the WHO in 2008, GenoType MTBDR*plus* assay is a molecular test that is recommended for use in suspected cases of TB with a positive sputum microscopy result [67]. The MTBDR*plus* assay can be performed in 6 hour and in addition to detecting *M. tuberculosis*, it can accurately detect the most common genetic mutations associated with resistance to rifampin and isoniazid [68, 69]. A major benefit of MTBDR*plus* is its rapid turn around time as compared to culture and DST, which aids in reducing the time that patients are receiving inappropriate thereapy. While the Xpert MTB/RIF assay is used when diagnosing aputum smear-negative patients, the MTBDR*plus* assay can provide additional drug-resistance information for smear-positive TB suspects as it tests for resistance to isoniazied in addition to rifampin resistance [70]. The use of the MTBDR*plus* assay has also led to increased TB diagnoses in some settings; a 2012 study found

that implementation of MTBDR*plus* in South Africa resulted in twice the number of MDR-TB diagnoses when compared to DST alone [71].

The clinical impact of the MTBDR*plus* assay should also be considered when discussing potential economic cost savings. A 2014 Georgian study found that implementation of MTBDR*plus* assay resulted in significantly reduced time to MDR-TB treatment initiation, decreased time to culture conversion, and improved infection control measures [25]. It should be noted that this 2014 Georigan study's data was utlized for our cost savings analysis. A additional study also found that utilizing MTBDR*plus* resulted in reduced time to MDR-TB treatment initiation. Based on this data, it has been demonstrated that implementation of the MTBDR*plus* assay can have significant clinical impact; not only can itt increase the number of cases of MDR-TB detected but if can also decrease the time to receiving appropriate thereapy thereby decreasing the number of days at risk for transmitting disease. By diagnosing more patients and quickly initiating proper treatment, clinicians may be reducing future incidence and decreasing the overall public health burden of TB. Additionally, rapid diagnosis with MTBDR*plus* has led to effective isolation of MDR-TB patients in Georgia [25]. Instead of MDR-TB patients spending several weeks in drug-susceptible TB wards, they were cohorted to the proper drug-resistant TB ward much sooner, which may help reduce nosocomial transmission of MDR-TB.

One study calculated the cost of each MTBDR*plus* test and found the cost per-test to be $23.46 per sputum sample [72] while another study found the average cost to be $67.18 [10]. Since the WHO endorsement of MTBDR*plus* in 2008, there has been only one systematic review/meta analysis conducted that focuses on MTBDR*plus*-related costs; however, these costs are lumped together with GeneXpert and INNO-LiPA [10]. This review measures the costs and cost effectiveness of molecular test diagnosis against conventional diagnosis alone. The analysis

by Drobniewski et al. estimated the treatment costs for patients who did and did not receive molecular testing [10]. For patients who only received conventional diagnostic tests, the total cost ranged from $3,442.29 to $199,038.61. For patients receiving molecular testing, costs were comparable and ranged from $3,567.64 to $201,418.56. Importantly, the systematic review states that molecular testing had a small impact on TB transmission, due to the fact that current prevention practices are already effective in limiting further spread. However, the authors point out that their study was considered only within the context of the United Kingdom, a country with a well-developed healthcare system and infrastructure.

The Drobniewski publication named MTBDR*plus* the most cost-effective diagnostic test in South Asian populations, while GeneXpert was determined to be more cost-effective in all other populations [10]. (Note: all diagnostic tests used smear microscopy, culture, and DST as the baseline comparison.) Beyond this publication, there is a paucity of literature regarding any type of cost-related analysis when utilizing the MTBDR*plus* assay. Additionally, more research is needed to determine the role of MTBDR*plus* in the country of Georgia [73]. To review, this thesis will focus on determining the cost savings associated with the use of MTBDR*plus* assay in detecting MDR-TB as compared to conventional diagnostic methods alone.

2.3.3 Funding Sources

Georgia relies upon the Global Fund for significant financial support in funding their National TB Program. From 2003 to 2016, the Global Fund distributed $38.6 million USD towards helping curb the TB epidemic in Georgia [57]. This funding has helped provide treatment to newly diagnosed cases of TB, and it is estimated has helped to save over 5,000 patient lives [74]. While there is an additional $7.7 million USD due to be disbursed, the Global Fund will

begin reducing its financial presence in the country now that Georgia has been designated an upper middle-income country by the World Bank [15, 57]. Georgia's National Center for Disease Control and Public Health (NCDC) has stated that it is critical for the government of Georgia to begin increasing its financial contributions in order to make up for the inevitable loss of funds [74]. Beyond the direct impact on TB, HIV, and Malaria control, a 2009 Georgian country case summary found that the Global Fund also contributed towards the national development of leadership, governance, health workforce, medical products, and community development [75]. While the transition away from the Global Fund will pose challenges, this marks a significant point in Georgia's history. In order to make smart choices about how to best invest GoG funds, the MoH will require information on the cost of implementing new TB diagnostic and drug-resistance detection testing methods.

3 PROJECT CONTENTS

3.1 Methodology

3.1.1 Introduction

This section will describe the parameters involved in calculating the annual cost of choosing one intervention over the other: conventional diagnosis alone (AFB sputum smear microscopy, AFB culture, and DST) compared to conventional diagnosis + MTBDR*plus* molecular testing. If either the pre- or post-implementation group presents significantly less expensive results, the national cost savings will be calculated. Additionally, this section will describe the study details, including: population, research design, procedures, and data analysis.

3.1.2 Population

The study cohort consists of adult patients with sputum smear and culture positive pulmonary MDR-TB disease who were treated at the NCTLD in Tbilisi, Georgia. The study population is divided into two groups: a pre-MTBDR*plus* implementation cohort (n=76) and a post-MTBDR*plus* implementation cohort (n=73). Pre-implementation patients received AFB sputum smear microscopy, AFB culture, and DST; post-implementation patients received diagnostic testing with the MTBDR*plus* assay in addition to the conventional methods of AFB sputum smear microscopy, AFB culture, and DST. The preimplementation cohort included patients diagnosed from March 2009 to May 2010, while the post implementation cohort consisted of patients diagned from June 2010 to October 2012.

Treatment regimens for patients with MDR-TB were determined by the NCTLD Drug Resistance Treatment Committee; once DST results are complete, the committee individualizes drug treatment regimens using WHO recommendations for guidance [76]. When possible, patients

with MDR-TB were recommended to receive at least four drugs to which their *M. tuberculosis* isolate is susceptible. All patients received a fluoroquinolone, pyrazinamide, and either capreomycin or kanamycin for at least six months. The NCTLD utilizes DOT to help ensure good drug adherence. As per National guidelines, patients were initially hospitalized for treatment and were recommended to stay in the hospital until they achieved sputum smear or culture conversion, and demonstrated clinical improvement [77]. Importantly, the treatment guidelines for patietns with MDR-TB did not change between pre- and post-MTBDR*plus* implementation cohorts; additionally, the same clinicians provided all patient care during both periods. Approval for this study was received from both the Georgian NCTLD and Emory University Institutional Review Board.

3.1.3 Research Design

This thesis uses a cost savings analysis to determine whether utilization of the MTBDR*plus* assay will result in cost savings to the health system in the diagnosis and treatment of MDR-TB patients. A cost savings analysis is appropriate because it summarizes healthcare expenditures and compares costs between different interventions. In this thesis, the health intervention is the introduction of MTBDR*plus* (post-implementation group), which is compared to the baseline intervention of no MTBDR*plus* (pre-implementation group). Costs for each intervention group will be compared between five cost categories (diagnosis, drug treatment, hospitalization, outpatient treatment, and surgery); expenses will also be totaled to present a mean and median cost of treatment per patient for both pre- and post-implementation groups. Patient outcomes will also be considered when recommending an appropriate intervention. WHO criteria were used to assign each patient a final treatment outcome. Poor outcomes were defined as one of the following: 1)

Treatment failure; 2) Loss to follow-up (formerly known as default); or 3) Death during treatment. Favorable outcomes were either 1) Cure; or 2) Treatment completion [27].

3.1.4 Procedures

Clinical data including the length of hospital stay and treatment regimen were abstracted from patient medical charts at the NCTLD in Tbilisi. All patients had an AFB sputum smear and culture as well as a DST performed. AFB culture was conducted on both liquid and solid media; DST was also conducted on liquid and solid media to determine susceptibility to both first and second-line drugs. The post-implementation group also had testing performed on their initial sputum sample with the MTBDR*plus* assay.

Financial information was obtained with support from The Global Fund in Georgia and the NCTLD. All costs were collected in local currency (GEL) and subsequently converted to USD using a 2015 average exchange rate from OANDA [26]. Cost information is separated into two main groups: expenses paid for by the Global Fund, and expenses paid for by the Georgian government's voucher program. Voucher prices were determined by obtaining quotes, the lowest of which is then determined to be the amount payable. All financial information was gathered, documented, and then compiled into an itemized cost list and used to calculate expenses for each patient for the following categories: 1) Diagnostis and detection of drug-ressistance 2) Drug treatment 3) Hospitalization 4) Outpatient treatment and 5) Pulmonary surgery. All expenses in these five categories were then added together to receive a total cost of treatment for each patient.

3.1.4.1 Diagnostic costs

Diagnostic costs are paid for by both the Global Fund and the Georgian government's voucher program. While the voucher program covers the cost of performing AFB sputum smear microscopy, AFB culture, and DST, the Global Fund currently pays for all costs related to performing the MTBDR*plus* assay. The MTBDR*plus* costs include the amortized cost of the diagnostic equipment, testing kits, and lab equipment. Diagnosis for both groups include initial consultation, AFB sputum smear microscopy, AFB culture, and DST (for both first and second-line drugs). The initial consultation is paid for by a government voucher, and consists of an x-ray, blood analysis, TST, and an appointment with a TB specialist. Prior to 2014, the NCTLD used two AFB sputum smear microscopy tests in working up TB suspects; each sputum smear microscopy test costs $1.29 USD. The AFB culture is then conducted on both solid and liquid media. The solid culture utilizes the Lowenstein-Jensen method and costs $8.06 USD. The liquid culture utilizes the BACTEC MGIT 960 broth culture system, and costs $12.16 USD per test. Additionally, DST was conducted on both solid and liquid media to determine drug susceptibility to first and second-line drugs. DST for first-line TB drugs on solid media costs $7.50 USD, while first-line DST on liquid media costs $34.96 USD. For second-line drugs, DST conducted on solid media is $8.56 USD and costs $26.59 on liquid media.

Costs of follow-up AFB sputum smear microscopy, AFB culture, and DST were included when calculating each patient's exact cost of laboratory testing. The NCTLD adheres to an algorithm to determine the frequency of follow-up diagnostic tests [77]. During the intensive phase of treatment, which lasts at least six months, sputum samples are obtained monthly for patients with MDR-TB. Second-line DST is performed at baseline and again at month three and six of treatment if cultures remain positive. Once a patient enters the continuous phase, both

sputum smear microscopy and cultures are obtained every three months; if a culture is still positive, second-line DST is again conducted (see Figure 4).

The added costs related to molecular testing (e.g., amortized cost of machines, molecular testing kit, etc.) were factored in to the cost of diagnosis for post-implementation patients. The MTBDR*plus* molecular test is only performed once at baseline, and only for patients in the post-implementation group. Performing one MTBDR*plus* assay costs $43.32 USD; this price includes one test pack, laboratory supplies, and other indirect and equipment service costs. Laboratory technician salaries are not included in this $43.32 price, since they are covered by the government-provided diagnostic voucher (see Table 6). Additionally, the amortized cost of the MTBDR*plus* equipment was included in diagnostic costs for the post-implementation group. The MTBDR*plus* equipment includes the TwinCubator ($2,442.88 USD) and the GTQ-Cycler ($5,102.29 USD) which together total $7,545.17 USD. While other equipment is utilized in the MTBDR*plus* testing system, these machine costs are not included here, as their costs are far below $5,000, the generally accepted threshold for a capital cost. An amortized total was calculated using the following equation[1] $C = \left[P - S\frac{1}{(1+r)^t} \right] [A(t, r)]^{-1}$ [78]. The annuity factor was determined to be 8.5302 using a discount rate of 3% and equipment lifetime of 10 years. The annual cost of this equipment is $658.17. The annual cost ($658.17) was then divided by the 2013 annual incidence of smear-positive patients who were diagnosed in Georgia to calculate a per-patient MTBDR*plus* equipment cost. The per-patient cost was determined to be $0.49, which was then added to the per-test cost of $43.32 for a total per-patient diagnostic test cost of $43.81.

[1] C = annual cost of the unit; P = cost of unit purchase; S = present value of the unit scrap value after n years of service; r = discount rate; A(t,r) = annuity factor

3.1.4.2 Drug Treatment Costs

Drug treatment costs are paid for by the Global Fund and ithey cover a variety of different medications, including both first and second-line anti-tuberculosis drugs. All patients with active MDR-TB disease treated through the Georgian National TB Program are assigned weight-based second-line drug dosages recommended by the WHO guidelines for MDR-TB management [47]. All drug cost calculations multiply the cost of one tablet by the number of tablets required to meet the daily weight-based dosage guidelines. For example, if a patient requires 1200mg of Ethambutol, the cost of one 400mg tablet ($0.041 USD) is multiplied by three, for a total of $0.123 USD. During the period a patient received firt-line drug therapy it was assumed they were receiving a combined tablet containing 150mg rifampin, 75mg isoniazid, 400mg pyrazinamide, and 275mg ethambutol (RIPE). Some patients continued to receive pyrazinamide and/or ethambutol during MDR-TB treatment and the additional costs of these drugs during MDR-TB treatment were taken into consideration when calculating each patient's total drug treatment cost. Once patients were diagnosed with MDR-TB and began second-line drug therapy, their regimen included either capreomycin and/or kanamycin and it should be noted that the cost of kanamycin, capreomycin and streptomycin uses the cost equivalent to 1gram, even when patients received less medication. For example, kanamycin is manufactured in 1gram vials, but patients who weigh 46-50kg receive only 875mg; the additional 225mg is discarded. The drug treatment cost calculations took this into consideration when determining expenses. If a patient received 875mg kanamycin, the cost is actually equivalent to 1 gram kanamycin. This is also the case when totaling drug treatment costs for capreomycin and streptomycin.

3.1.4.3 Hospitalization Costs

Hospitalization costs were calculated using information collected from the Georgian government's voucher program for tuberculosis treatment (see Tables 6-10 for voucher breakdowns). While the Global Fund currently pays for all drug treatment (both first and second-line) and molecular test costs (MTBDR*plus* equipment and test kits), the Georgian government uses a voucher system to pay for all other costs, including inpatient treatment. The inpatient voucher is worth $56.71 USD per day in Tbilisi hospitals, and includes the following items: 1) direct costs (medications unrelated to TB treatment and food); 2) salary for healthcare workers in the hospital (doctors, lab technicians, and nurses); and 3) Incidental expenses. Hospitalization costs are the same for both the intensive phase and continuation phase of MDR-TB treatment.

3.1.4.4 Outpatient Treatment Costs

Outpatient treatment costs are paid by the Georgian government utilizing voucher program and include three main components when determining overall expense. First, patients with MDR-TB receive intensive phase treatment for a minimum of eight months and this treatment phase is covered by a government voucher worth $2.33 USD per day. After the intensive phase of treatmeht, patients move to an continuation phase until treatment completion (overall treatment duration is generally between 20-24 months). The continuation phase is paid with a government voucher worth $1.24 USD per day. Third, some individuals received outpatient treatment for drug-susceptible TB prior to being diagnosed with MDR-TB. These outpatient drug susceptible treatment costs were included when calculating overall outpatient treatment costs. The government voucher for outpatient drug susceptible TB is the same for both the intensive and

continuation phases, and is worth $0.74 USD per day. All per-day outpatient treatment costs were multiplied by the number of days each patient spent, if any, receiving outpatient treatment.

3.1.4.5 Lung Resection Surgery Costs

For patients who undergo lung resection surgery these costs are also paid through the voucher program. General criteria for surgical intervention included MDR-TB, failure of medical therapy (persistent sputum culture positive), a high likelihood of treamtnet failure or disease relapse, localized lesion, and sufficient pulmonary function to tolerate surgery. In our study population, eight patients received lung resection surgery. Each lung resection surgery is covered by a one-time voucher of $1,198.95 USD to cover all surgery related expenses. Related recovery costs are paid with inpatient vouchers (as discussed above). Overall cost for surgery was calculated by multiplying the number of patients who required pulmonary re-section by the one-time cost of $1,198.95 USD.

3.1.4.6 Total Costs

Costs for each of the five categories were added together to calculate the overall treatment cost for each patient and for all patients overall. The total cost was then broken down according to group (either pre- or post-implementation) and also by outcome.

3.1.5 Data Analysis

Data analysis was performed using SAS version 9.4 (SAS Inc, Cary, North Carolina). Descriptive statistics were utilized to determine overall treatment costs and compare these costs between the pre- and post-MTBDR*plus* implementation groups. A student's T-test was used to

determine pooled p-values for normally distributed variables in the demographics table. Wilcoxon non-parametric 2-sided p-values (alpha=0.05) were obtained for the cost table, due to the data lacking a normal distribution. Annual expense of treating the absolute number of MDR-TB patients in Georgia is calculated twice. First, the annual absolute number of MDR-TB patients is multiplied by the median cost of treating the average pre-implementation patient. Second the annual absolute number of MDR-TB patients is multiplied by the median cost of treating the average post-implementation patient. Median costs were used in an effort to help offset outliers that skew the mean.

3.2 Results

3.2.1 Patient Characteristics

There were 149 patients with MDR-TB included in our study cohort including 76 and 73 in the pre- and post- MTBDR*plus* implementation periods, respectively. The mean (Interquartile Range, IQR) age was 37.7 (27-46) years. Over two-thirds of the patients were male (72.4%). Both the pre- and post-implementation groups had a similar proportion of previous imprisonment (27.6% and 30.1% respectively). Documented comorbidities include diabetes, HCV, and HIV. Sixty-six patients (44.3%) had a history of prior TB treatment, of which 54 (36.2%) had received previous first-line drug treatment and 12 (8.1%) had received second-line drug treatment.

The mean length of hospital stay (IQR) was 132 (50-165) days, while the mean length of outpatient treatment (IQR) was 522 days (238-733). In total, the duration of treatment lasted an average of 654 days (21.8 months). The pre-implementation group received more follow-up cultures than the post-implementation patients (p=0.0150) but there was no difference in the number of follow-up DSTs between groups. Overall, pre-implementation patients spent more days

on drug therapy for both first line drugs ($p<0.0001$) and second line drugs ($p=0.0394$). Only eight patients received pulmonary resection surgery (5.4%). Overall, 65 patients (43.6%) had a poor outcome after treatment and 84 patients (56.4%) achieved a favorable outcome. There was not a significant difference in treatment outcomes between pre- and post-implementation patients, thus allowing for a direct comparison of cost savings.

Figures 1 and 2 illustrate the complete breakdown of patient outcomes, while Table 3 demonstrates the total cost and significance of each cost category compared between the pre- and post-implementation groups. Lower costs were associated with outpatient treatment for the post-implementation group. This cost difference is explained by two main factors: 1) Compared to the pre-implementation cohort, patients who received MTBDR*plus* testing spent significantly fewer days on drug susceptible outpatient treatment prior to receiving their MDR-TB diagnosis. 2) Post-implementation patients also spent fewer days in intensive phase MDR-TB outpatient treatment. Including both inpatient and outpatient treatment, individuals who were diagnosed using MTBDR*plus* spent 240 fewer days (8 months) being treated for MDR-TB.

3.2.2 Comparing Pre- and Post-MTBDR*plus* Implementation Findings

Patients in the pre-implementation cohort had lower prevalence of HCV co-infection (6.6% vs 17.8%, $p=0.0355$), but both cohorts had comparable rates of HIV (2.6% vs 5.5%, $p=0.5562$) and diabetes (11.8% vs 11.0%, $p=0.8654$). Beyond prevalence of HCV coinfection, there were no other significant differences between the two groups on demographic characteristics. Table 1 shows the demographic characteristics of both cohorts side-by-side for direct comparison.

Outcomes: For both pre- and post-implementation groups, patients who were lost to follow up had lower median costs when compared to patients who died or experienced treatment failure.

Notably, patients who were assigned the 'failure' outcome had the highest costs for both pre- and post-implementation groups. Patients who were classified as cured were more expensive to treat than patients who achieved an outcome of treatment completion; this was true for both the pre- and post-implementation groups. It should be noted that even within the favorable outcome categorizations (cured and treatment completed) the median cost of treatment per-patient for the pre-implementation group remained higher than the median cost for post-implementation patients.

Per-patient treatment cost: On average, one MDR-TB patient from the pre-implementation group cost the healthcare system $13,216.19 to treat (IQR=$9,620.77 - $17,697.63), compared to $9,320.55 (IQR=$6,333.05 - $11,159.65) for one post-implementation patient ($p<0.0001$), a difference of $3,895.64. Patients who did not receive the MTBDR*plus* molecular test in their MDR-TB diagnosis had lower costs associated with diagnosis, but higher costs for every other category. On average, the median diagnostic cost for pre-implementation patients was $35.75 less than the post-implementation patients ($p=0.0031$). Drug costs were on average $1,033.00 (median=$710.30) more expensive for the pre-implementation patients ($p=0.0021$). However, for both groups, there was a similar proportion of costs attributable to first and second-line drugs. Therefore, it may be surmised that increased drug costs for the pre-implementation group are attributable to the greater duration of drug treatment.

Compared between pre- and post-implementation groups, mean hospitalization cost was $2,235.64 (median=$3,345.89) more expensive for the pre-implementation group ($p=0.0020$); this is consistent with the finding that pre-implementation patients spend an average of 43 more days hospitalized during first admission. The mean cost associated with outpatient care for the pre-implementation group was $329.98 (median=$118.82) more expensive than the post-implementation group ($p<0.0001$). Surgery costs were not significantly different between the two

groups; although expenses related to surgery were slightly less on average for the post-implementation group, the median for both groups was $0 (p=0.1678).

Drivers of cost: Key cost drivers for the pre-implementation group's treatment were hospitalization and drug treatment. Hospitalization costs made up over half (58.2%) of the entire cost of treatment, while drug therapy contributed an additional 32.3% of each patient's treatment. Together, hospitalization and drug treatment accounted for 90.5% of treatment costs. The remaining three categories accounted for the following proportions: outpatient follow up costs (7.4%), diagnosis (1.5%), and surgery (0.6%). Similar to the pre-implementation group, the post-implementation group's key cost drivers were drug treatment and hospitalization. Hospitalization costs represented 57.2% of the total treatment cost per patient, and drug treatment accounted for an additional 33.5% of the cost. Together, these two categories made up 90.7% of the overall treatment costs. Outpatient treatment was the third largest proportion of cost (6.8%), followed by diagnostic costs (2.2%) and surgery (0.3%).

3.2.3 Cost Savings Trends by Annual Incidence

Data on the annual incidence of smear-positive TB patients and the absolute number of MDR-TB patients identified in Georgia from 2009 through 2015 was provided by the NCTLD. The annual incidence of MDR-TB patients was used to calculate estimated cost savings for each annual cohort of patients with MDR-TB (Table 5). The main assumption in this section is that patient characteristics and outcomes nationwide do not differ from the thesis study population (N=149). Annual estimated cost savings attributable to the implementation of MTBDR*plus* ranged from $1.8 million USD to $2.9 million USD. In the most recent year calculated (2015) cost savings were estimated at $1.8 million USD. While the incidence of TB has been decreasing throughout Georgia in recent years, MTBDRplus still offers the government of Georgia significant cost savings.

4 DISCUSSION

4.1 Discussion

In our cost analysis study we found a significantly decreased cost to treat patients with MDR-TB if their drug-resistance was detected by the molecular MTBDR*plus* assay as compared to culture and DST. The over $4,000 in savings per patient with MDR-TB is a large cost savings and demonstrates the downstream economic effects of utilizing an upfront expensive molecular test for the rapid detection of *M. tuberculosis* and drug resistance. These costs savings offer an additional incentive to utilize molecular diagnostic testing method on top of the improvements in clinical outcomes that have been shown with implementation of such tests including the MTBDR*plus* [25]. The considerable cost savings estimated in this study present the Georgian government with an opportunity to re-invest into control efforts aimed at curbing the spread of TB, as well as other comorbidities (such as HIV, HCV, and diabetes) that have a synergistic relationship with TB. This would offer the Georgian government the opportunity to be a leader in regional TB prevention efforts. Additionally, lowering the overall cost of MDR-TB treatment would help place Georgia on-par with other upper middle-income countries, which spend $5,284 USD per MDR-TB patient [79].

Our findings are also the first to estimate the cost of treating a patient with MDR-TB in Georgia and help illuminate the specific components responsible for the majority of treatment costs. While the initial cost of MTBDR*plus* may be high, its expense is amortized over the lifetime of the equipment. The MTBDR*plus* diagnostic test clearly demonstrates major health benefits and cost savings over time. If the MoH is looking for areas in which spending could be made more efficient, it should look to inpatient treatment and then possibly drug therapy. In light of the

WHO's recent recommendations to decrease inpatient treatment time, this would be a likely source of further cost savings.

4.1.1 Hospitalization

Because hospitalization was the main cost driver for MDR-TB treatment costs in both the pre- and post-implementation groups, reducing inpatient treatment duration would be an effective way to decrease total treatment costs. This is an important consideration, due to the fact that hospitalization alone contributed >50% towards the total treatment costs for both pre- and post-implementation patients.

Notably, patients from the post-implementation group spent an average of 43 fewer days in the hospital during first admission. This translates to cost savings in the amount of $2,438.53 per-patient, simply due to the introduction of MTBDR*plus* during diagnosis. In addition to cost savings, reduced inpatient time also helps eliminate opportunities for nosocomial transmission, which has historically played a role in contributing towards heightened MDR-TB incidence among both healthcare workers and patients [80, 81]. Considering this, curbing nosocomial transmission will also help prevent these vulnerable patients from experiencing further complications. Increased hospitalization has also been linked to patient productivity losses averaging $700 USD per patient [79].

4.1.2 Drug Therapy

Drug expenses represented the second largest cost driver for both the pre- and post-implementation groups. In MDR-TB treatment, costs between first and second-line drugs are not equal; while first line drugs remain relatively inexpensive, second line drugs contributed >85% of

total drug treatment costs. A key strategy in reducing drug costs will be to decrease the amount of time patients spend on drug therapy. Due to MTBDR*plus*' demonstrated capabilities in decreasing total treatment duration, utilizing this molecular test will result in smear-positive patients spending fewer days on expensive drug therapy. Beyond cost savings, reduced days on TB drugs will also serve to benefit patients' quality of life. The side-effects of second-line drugs can be severe and may result in major decreases in health quality. Patients on second-line drug therapy have reported experiencing indigestion, rash with fever, joint pain, kidney damage, hypothyroidism, hearing loss, hepatitis, and psychiatric disturbances [47, 82-84]. It is possible that these highly toxic drugs may be contributing towards high rates of loss to follow-up among patients with MDR-TB [85]. It is noteworthy that patients in the post-implementation group spent, on average, 99 fewer days in the intensive phase of treatment ($p<0.0001$). While we do not have data available on experiences of negative side-effects such as kidney damage or hearing loss, it may be that the pre-implementation group had a higher incidence of such occurrences [83, 86, 87].

	Pre-Implementation	Post-Implementation
Proportion of costs attributable to 1st line drugs	12.2%	14.1%
Proportion of costs attributable to 2nd line drugs	87.8%	85.9%

Increasing patients' quality of life will also potentially reduce loss to follow-up. In this thesis study's population, nearly one-third (32.2%) of patients were lost to follow up. While these patients may have received enough treatment to render them effectively cured, it is also likely that they relapsed and remained infectious. A previous study conducted in the country of Georgia found that 40% of patients lost to follow up had not achieved culture conversion [88]. If patients

who are lost to follow up indeed remain uncured, they may go on to develop further drug resistance [89]. Infectivity among MDR-TB patients presents a significant threat to public health, as there may be an increase in the incidence of MDR-TB among newly diagnosed patients.

Looking to the future, there may be an important transition in MDR-TB treatment within Georgia. The WHO now reccommends shorter MDR-TB regimens for both adults and children who meet a specific set of criteria [76]. Patients who have not been previously treated with second-line drugs and who do not have resistance to fluoroquinolones or injectable agents may qualify for 9-12 months of treatment. Patients who have extra-pulmonary TB disease or who are pregnant cannot be considered for shortened treatment [1]. While this shortened MDR-TB regimen has only been implemented in 14 countries, it could still have a positive impact on MDR-TB in Georgia. If patients undergo shorter drug treatment regimens, rates of loss to follow up will likely decrease, thereby lowering incidence and ultimately prevalence as well [88, 90]. However, a recent study found that the shortened MDR-TB regimen is less effective among patients with PZA resistance [91]. Given the high rates of PZA resistance among Georgian patients, this short course regimen would not be recommended for majority MDR-TB patients within the country.

4.1.3 Inpatient vs. Outpatient Treatment

In 2011, the WHO published guidelines stating that healthcare systems should shift towards an outpatient-based model of care. In a 2016 updated guideline, this recommendation remained valid. Considering the Georgian setting – where inpatient treatment is notably more expensive than outpatient care – shortened MDR-TB inpatient treatment would provide the MoH with additional cost savings without compromising patient outcomes. Furthermore, seeking treatment as an outpatient is relatively less burdensome than inpatient treatment. TB patients have

been reported to experience heightened psychological distress due to hospitalization [92-94]. Increased psychological distress is associated with negative treatment outcomes in TB patients [92-94]. Therefore, it is in the best interest of patients to transition towards an outpatient-based model in which patients are afforded a sense of normalcy.

A 2013 systematic review conducted an analysis on the effectiveness of MDR-TB treatment, comparing inpatient and outpatient models [95]. After reviewing 35 studies, it found no statistical differences between the two models at any of the outcomes considered. In 2011 the government of South Africa approved guidelines recommending that smear-negative patients in generally good health be treated as outpatients [96]. While the study population in this present study is smear-positive, the Georgian MoH should still consider outpatient treatment for individuals who have achieved culture conversion (i.e., no longer infectious) and are in otherwise good health; additionally, there should be an assurance of continuation of care and monitoring [97].

4.1.4 Funding Mechanisms and Challenges

4.1.4.1 Transitioning Away from the Global Fund

Due to the World Bank's recent re-classification of Georgia from a lower middle-income country to an upper middle-income country, TB-related financial responsibilities are beginning to shift from the Global Fund to the government of Georgia. When Georgia was officially re-classified as an upper middle-income country in 2016, the country was given a scheduled five-year transition period until total withdrawal of Global Fund financial support. Georgia currently has approximately 3-4 years left to make important financial decisions affecting the control and elimination of MDR-TB within Georgia. While Georgia's MoH already funds certain aspects of

diagnosis and treatment, the Global Fund is still responsible for MTBDR*plus*-related diagnostic costs in addition to all drug costs (both first and second-line). Therefore, the GoG will need to make plans ensuring funds are allocated for molecular testing and anti-tuberculosis drug costs. When designing the national budget, the GoG should take into consideration the cost savings associated with the implementation of molecular diagnostic tests such as the MTBDR*plus* assay.

4.1.4.2 Challenges in Properly Allocating Funds

Funds will need to be allocated carefully and efficiently, due to the many challenges that MDR-TB control poses. As reported by the WHO, up to one-third of MDR-TB cases remain unidentified. These patients pose a significant risk to public health, because they will remain infectious if left untreated. Even patients who are diagnosed and notified of their status need to be linked to care, and then must adhere to an arduous second-line drug treatment regimen. While there is an established cascade of care for MDR-TB patients at the NCTLD (including diagnosis, linkage to care, DOT, and surgery), loss to follow up remains a significant challenge [88]. In this thesis, 41 patients (27.5%) were lost to follow up. It is unknown whether these patients received enough treatment to render them effectively cured, or if they will relapse and become infectious again.

With an annual GDP of $14 billion and a national budget of approximately $4.5 billion, healthcare and social assistance receive 7% of the annual budget ($314 million USD) [98, 99]. Georgia will need to allocate its funds efficiently in the coming years in order to continue to reduce the incidence of MDR-TB nationwide. It is the purpose of this thesis to guide both the NCTLD and policymakers in their efforts to develop realistic budgets over the next 4-5 years that proactively reflect the withdrawal of financial support from the Global Fund. Policy makers need

robust cost and financial projections to guide the government budgeting process. NCTLD will be in competition for resources with other programs in the health sector and the health sector will be in competition with other sectors for its share of the overall budget. An analysis like the one reported on in this study provide the NCTLD the data that it needs for budget negotiation as the country of Georgia makes a broad economic transition. Considering this study's 2015 cost savings estimate of $1.8 million USD, the Georgian government would be wise to re-invest these savings into expenditures that were previously funded by the Global Fund: MTBDRplus molecular testing and TB drugs.

4.1.5 Limitations

When considering costs to the healthcare system, this thesis relies upon an underlying assumption that patient outcomes and characteristics nationwide resemble the study population. The study cohort consisted of consecutively enrolled patients with MDR-TB from Tbilisi, Georgia and thus if there are clinical and/or cost differences between patients with MDR-TB from Tbilisi and outside Tbilisi our results may not be generalizable for the whole country. One know difference that would affect overall costs is the higher cost of hospitalization at the NCTLD in Tbilisi ($56.71 per day) as compared to a regional hospital ($17.69 per day). However, while overall costs savings may be lower among patients hospitalized outside Tbilisi there should still exist a substantial relative cost savings if there remains less time spent in the hospital and fewer days spent on expesnive second-line drugs. Another potential limitation is the use of a historical cohort. However, this potential limitation is mitigated by the fact that there were no changes to the national MDR-TB treatment protocols, NCTLD drug resistance committee, second-line drug regimens, or MDR-TB doctors during the pre and post MTBDR*plus* implemtation period. Our

study was also conducted before the implementation of new drugs for MDR- and XDR-TB and the costs savings of implementing the MTBDR*plus* in the setting of more effective second-line drugs is unclear. The newly introduced drugs have high costs and include linezolid ($5.82 per 600mg), bedaquiline ($4.87 per 100mg) and delamanid ($2.53 per 50mg) [52, 100]. It will be important to conduct future cost savings study in the setting of using these new agents.

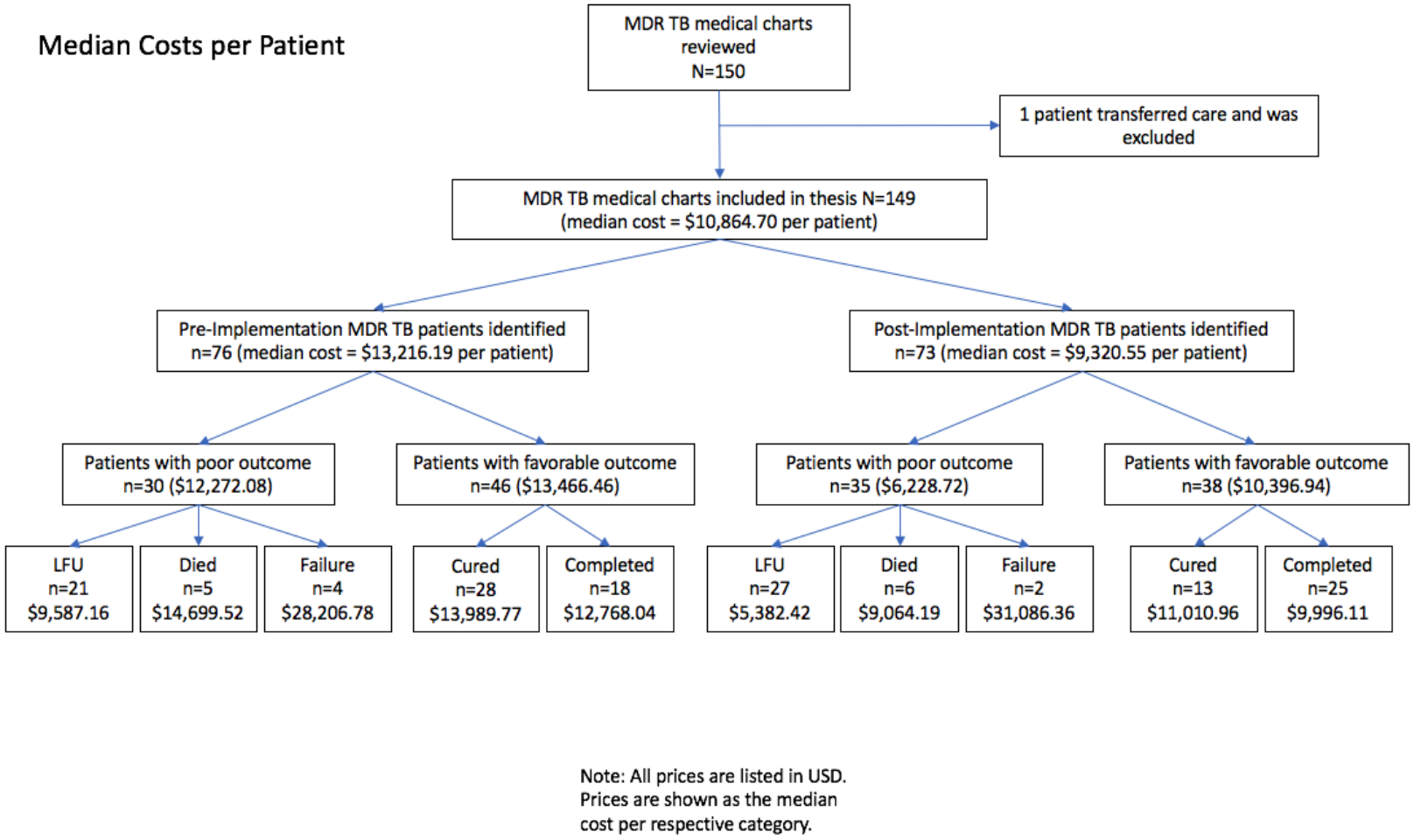
4.2 Conclusion and Recommendations

Based upon the our findings, there is a significant cost savings in the treatment of patients with MDR-TB when using the MTBDR*plus* assay to diagnose *M. tuberculosis* and detect drug-resistance. This finding along with prior data showing the MTBDR*plus* to accurately detect drug-resistance and to be associated with improved clinical outcomes including a faster time to initation of appropriate treatment and decreased time to sputum culture conversion make a strong case for the continued investment in molecular testing for TB diagnosis and detection of drug-resistance [23, 25]. In particular, our results demonstrating a substantial cost savings per patient and per year for each cohort of patients diagnosed with MDR-TB provide important information for the Georgian government and governments in other similar settings to consider when putting together their healthcare budgets. As the Global Fund is transitioning out of Georgia, the optimal use of limited resources takes on a higher level of urgency and importance. The cost savings realized from investing in more expensive TB diagnostic testing methods could be used to fund additional costs associated with TB treatment such as drug costs or to fund other public health programs such as HIV, hepatitis C infection, diabetes, or chronic lung disease. This is especially critical, because comorbidities present unique challenges when treating TB patients. If the prevalence of diseases

like HIV, HCV, and diabetes is reduced, both TB incidence and treatment outcomes will also likely improve.

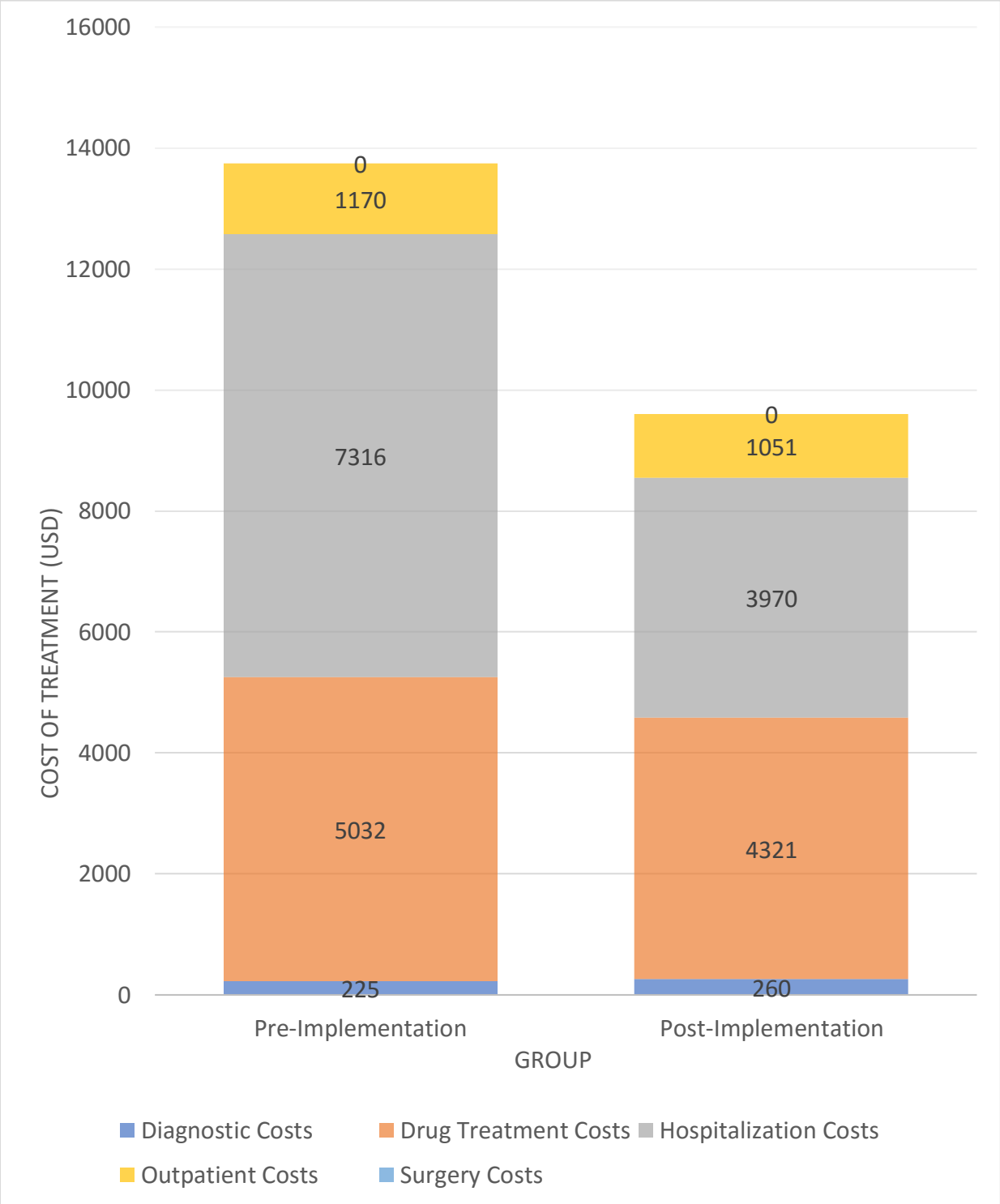
Furthermore, the Georgian government should consider approaches to reduce the amount of time that patients spend hospitalized. Because over half of MDR-TB treatment expenses are attributable to inpatient care, this would be the most effective cost category to focus on if additional cost savings are desired. Shortened MDR-TB regimens should be considered, as this would provide even further cost savings while also reducing the burden of treatment on patients. These recommendations not only reduce treatment costs, but also improve the quality of life for patients and their families.

Figure 1. Flowchart of Treatment Median Costs per patients with MDR-TB by Pre- and Post- MTBDR*plus* Implementation periods (N=149)



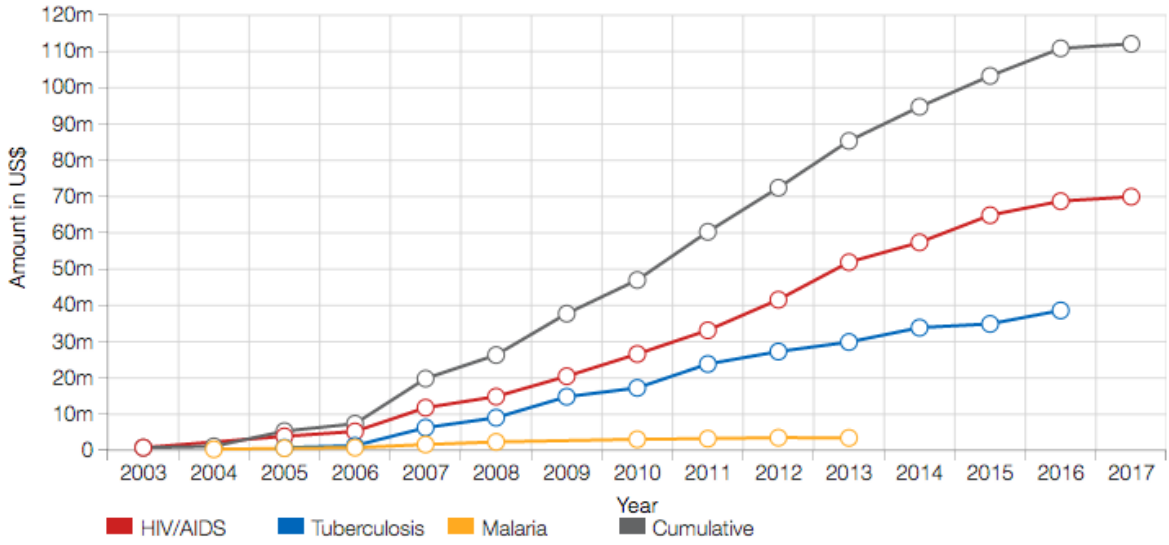
Abbreviations: LFU, lost to follow up

Figure 2. Cost of Treatment per-Patient: Comparing Pre- and Post-MTBDR*plus* Implementation Groups



Note: Few patients received pulmonary re-section surgery, hence the $0 median for both groups.

Figure 3. The Global Fund Disbursements by Component within Georgia (2003-2017)



Source: The Global Fund to Fight AIDS, Tuberculosis and Malaria [57]

Table 1. A Comparison of Characteristics among patients with MDR-TB by Pre- and Post-MTBDR*plus* Implementation Periods (N=149)

	Overall N=149 (%)	Pre-MTBDR*plus* Implementation N=76 (%)	Post-MTBDR*plus* Implementation N=73 (%)	p
Mean age [SD]	37.7 [13.6]	38.9 [15.3]	36.4 [11.5]	0.2714
Male	108 (72.5)	56 (73.7)	52 (71.2)	0.7377
History of imprisonment	43 (28.9)	21 (27.6)	22 (30.1)	0.7358
Diabetes	17 (11.4)	9 (11.8)	8 (11.0)	0.8654
Hepatitis C antibody positive	18 (12.1)	5 (6.6)	13 (17.8)	0.0355
HIV	6 (4.0)	2 (2.6)	4 (5.5)	0.5562
Mean BMI [SD]	20.5 [2.6]	20.5 [2.7]	20.4 [2.6]	0.8804
Prior TB treatment				0.1648
None	83 (55.7)	45 (59.2)	38 (52.1)	
First-line treatment	54 (36.2)	28 (36.8)	26 (35.6)	
Second-line treatment	12 (8.1)	3 (4.0)	9 (12.3)	
Mean follow-up tests [SD]				
Number follow-up cultures	11 [6]	13 [5]	10 [7]	0.0150
Number follow-up DSTs	0.4 [1]	0.4 [1]	0.5 [1]	0.5279
Mean days on drug treatment [SD]				
1st line drugs	49 [43]	82 [37]	15 [10]	<.0001
2nd line drugs	528 [235]	566 [202]	487 [261]	0.0394
Mean overall days	577 [247]	649 [211]	502 [262]	0.0002
Mean days in hospital [SD]				
1st Admission	109 [97]	130 [110]	87 [76]	0.0065
2nd Admission	15 [49]	14 [39]	17 [57]	0.6891
3rd Admission	8 [42]	8 [31]	8 [51]	0.9583
Mean overall days	132 [131]	152 [129]	112 [130]	0.0658
Mean days outpatient treatment [SD]				
Drug susceptible	36 [43]	61 [47]	10 [11]	<.0001
MDR-TB Intensive Phase	271 [151]	320 [144]	221 [143]	<.0001
MDR-TB Continuation Phase	214 [181]	239 [168]	189 [190]	0.0918
Mean overall days	522 [277]	620 [216]	420 [298]	<.0001
Pulmonary Resection Surgery	8 (5.4%)	6 (7.9)	2 (2.7)	0.1629
Mean days treatment duration [SD]	654 [338]	772 [258]	532 [368]	<.0001
Outcomes				0.2972
Poor	65 (43.6)	30 (40.0)	35 (48.0)	
Favorable	84 (56.4)	46 (60.5)	38 (52.1)	

Abbreviations: IQR, interquartile range; HIV, human immunodeficiency virus; BMI, body mass index; MDR-TB, multi-drug resistant tuberculosis; TB, tuberculosis

Table 2. Itemized Costs for MDR-TB Treatment at the NCTLD in Tbilisi, Georgia

Item	Cost of item per relative unit
Diagnosis Cost	
Initial doctor consultation and work up Consultation ($8.85) Chest x-ray ($6.63) Blood analysis ($2.65) PPD/TST ($1.33)	$19.46
AFB Sputum Smear Microscopy	$1.29
AFB Culture	
Solid media	$8.06
Liquid media	$12.16
Drug Susceptibility Test (DST)	
1st line DST on solid media	$7.50
1st line DST on liquid media	$34.96
2nd line DST on solid media	$8.56
2nd line DST on liquid media	$26.59
MTBDR*plus* test Laboratory equipment ($37.67) Annuitized price of machine ($0.49) Annual servicing cost ($3.77) Other expenses ($1.88)	$43.81
Drug Costs	
RIPE Combined Tablet Rifampicin 150mg Isoniazid 75mg Pyrazinamide 400mg Ethambutol 275mg	1 tablet = $0.058
Pyrazinamide (PZA) 400mg	1 tablet (400mg) = $0.292
Ethambutol 400mg	1 tablet (400mg) = $0.041
Streptomycin	1 vial (1g powder) = $0.265
PAS	1 sachet (4/1.52g) = $1.586
Prothionomide	1 tablet (250mg) = $0.165
Levofloxacin	1 tablet (250mg) = $0.078
Moxifloxacin	1 tablet (400mg) = $0.680
Cycloserine	1 cap (250mg) = $0.381
Augmentin (Amoxicillin/clavulanic acid)	1 tablet (500mg) = $0.178
Clarithromycin	1 tablet (250mg) = $0.275
Clofazimine	1 tablet (100mg) = $2.471
Capreomycin	1 vial (1g powder) = $4.642
Kanamycin	1 vial/ampoule (1g) = $1.937
Hospitalization Costs	
Inpatient: 1 day in hospital	$56.71/day

Outpatient Costs	
Outpatient Intensive Phase (MDR-TB)	$2.33/day ($69.88/month)
Outpatient Continuation Phase (MDR-TB)	$1.24/day ($37.15/month)
Outpatient treatment for drug-susceptible TB	$0.74/day ($22.12/month)
Surgery Cost	
Pulmonary resection surgery	$1,138.95/surgery

Abbreviations: NCTLD, National Center for Tuberculosis and Lung Disease; PPD, purified protein derivative; TST, tuberculin skin test; DST, drug susceptibility testing; RIPE, rifampin, isoniazid, pyrazinamide, and ethambutol

See Tables 6-10 for more further cost breakdowns regarding diagnosis, inpatient treatment, and outpatient treatment

Note: All prices are shown in USD. Average 2015 GEL-USD exchange rate used for cost conversions (1 GEL = $0.44231 USD) [26].

Source: NCTLD data [52]

Table 3. A Comparison of Treatment Costs among MDR-TB Patients by Pre- and Post-MTBDR*plus* Implementation periods (N=149)

	MTBDR*plus* Pre-Implementation period	MTDBR*plus* Post-Implementation period	p-value
Diagnosis			p=0.0031
	Mean cost = $224.42	Mean cost = $250.60	
	Median cost = $224.65	Median cost = $260.40	
	SD = $41.43	SD = $55.45	
	Range = $127.93 – 331.93	Range = $179.80 – 463.40	
Drugs			p=0.0021
	Mean cost = $4,768.10	Mean cost = $3,735.10	
	Median cost = $5,031.76	Median cost = $4,321.46	
	SD = $1,861.41	SD = $2,087.50	
	Range = $633.09 – 9,443.48	Range = $330.26 – 10,676.75	
Hospitalization			p=0.0020
	Mean cost = $8,604.25	Mean cost = $6,368.61	
	Median cost = $7,315.59	Median cost = $3,969.70	
	SD = $7,322.00	SD = $7,396.62	
	Range = $907.36 – 43,723.40	Range = $1,644.59 – 42,022.10	
Outpatient Care			p<0.0001
	Mean cost = $1,086.41	Mean cost = $756.43	
	Median cost = $1,170.05	Median cost = $1,051.23	
	SD = $375.17	SD = $508.87	
	Range = $78.12 – 1,966.52	Range = $0 – 2,026.31	
Surgery			p=0.1678
	Mean cost = $89.92	Mean cost = $31.20	
	Median cost = $0	Median cost = $0	
	SD = $309.17	SD = $187.21	
	Range = $0 – 1,138.95	Range = $0 – 1,138.95	
Total			p<0.0001
	Mean cost = $14,773.10	Mean cost = $11,141.94	
	Median cost = $13,216.19	Median cost = $9,320.55	
	SD = $8,190.58	SD = $9,007.97	
	Range = $3,198.96 – 51,707.60	Range = $2,983.25 – 52,503.27	

Abbreviations: SD, standard deviation; NCTLD, National Center for Tuberculosis and Lung Diseases

p-value in this table is 2-sided Wilcoxon

Table 4. A Comparison of Costs Among MDR-TB Patients from Pre- and Post-Implementation of MTBDR*plus* Using National TB Prevalence Data

Year	Sputum smear-positive TB patients	Sputum smear-positive TB patients enrolled in second-line drug therapy	Total cost of treatment for patients with MDR-TB diagnosed by conventional methods (median =$13,216.19)	Total cost of treatment for patients with MDR-TB diagnosed by the MTBDR*plus* (median= $9,320.55)	Total estimated cost savings when patients are diagnosed using MTBDR*plus*
2009	2,900	636	$8,405,496.84	$5,927,869.80	$2,477,627.04
2010	2,903	634	$8,379,064.46	$5,909,228.70	$2,469,835.76
2011	2,791	743	$9,819,629.17	$6,925,168.65	$2,894,460.52
2012	2,279	666	$8,801,982.54	$6,207,486.30	$2,594,496.24
2013	1,913	526	$6,951,715.94	$4,902,609.30	$2,049,106.64
2014	1,617	502	$6,634,527.38	$4,678,916.10	$1,955,611.28
2015	1,298	466	$6,158,744.54	$4,343,376.30	$1,815,368.24

Incidence data collected from NCTLD [52]

Table 5. Georgian Government Voucher Contents for Costs Related to Outpatient Treatment for Sensitive TB

Item	Price per Unit	Number of units	Total (GEL)
Doctor + Nurse salary	20 GEL	8 visits (4 during intensive phase, 4 during continuation)	160 GEL
X-ray	20 GEL	2 x-rays (Once after intensive phase, once at the end of Tx)	40 GEL
Liver function (ALT, AST), Billirubin, Creatinine	32 GEL	Once during intensive phase, twice during continuation phase	96 GEL
Blood analysis	6 GEL	Once during intensive phase	6 GEL
Total			**302 GEL**
Notes: Outpatient Tx = 6 months (2 months intensive, 4 months continuation) 302 GEL (divided by 6 months) = 50 GEL per month **Outpatient Tx voucher for Sensitive TB (INTENSIVE & CONTINUATION PHASE) = 50 GEL ($22.12 USD) per month ($0.737 USD per day)**			

Source: NCTLD data [52]

Table 6. Georgian Government Voucher Contents for Costs Related to Outpatient Treatment for MDR-TB Intensive Phase

Item	Price per Unit	Number of units	Total (GEL)
Doctor + Nurse	20 GEL	16 visits	320
Specialist visits	20 GEL	2	40
X-ray	20 GEL	2 x-rays	40
Blood analysis	6 GEL	9	54
Urine analysis	6 GEL	9	54
Liver function (ALT, AST), Billirubin, Creatinine	24 GEL	11	264
Serum electrolytes	24 GEL	11	264
Viral hepatitis serology (B &C)	24 GEL	1	24
Creatinine	8 GEL	11	88
Blood sugar	5 GEL	6	30
Total protein	5 GEL	2	10
Serum albumine	5 GEL	2	10
Coagulation	20 GEL	2	40
TSH (Thyroid)	14 GEL	2	28
Total			**1266 GEL**
Note: Outpatient MDR-TB Tx duration = 20 months (8 months intensive, 12 months continuation) 1,266 GEL (divided by 8 months = 158 GEL per month) **Outpatient Tx voucher for MDR-TB INTENSIVE PHASE =** **158 GEL ($69.88 USD) per month ($2.33 USD per day)**			

Source: NCTLD data [52]

Table 7. Georgian Government Voucher Contents for Costs Related to Outpatient Treatment for MDR-TB Continuation Phase

Item	Price per Unit	Number of units	Total (GEL)
Doctor + Nurse	20 GEL	12 visits	240
Specialist visits	20 GEL	2	40
X-ray	20 GEL	2 x-rays	40
Blood analysis	6 GEL	6	36
Urine analysis	6 GEL	6	36
Liver function (ALT, AST), Billirubin, Creatinine	24 GEL	12	288
Serum electrolytes	24 GEL	12	288
Blood sugar	5 GEL	6	30
TSH (Thyroid)	14 GEL	1	14
Total			**1012 GEL**
Note: Outpatient MDR-TB Tx duration = 20 months (8 months intensive, 12 months continuation) 1,012 GEL (divided by 12 months = 84 GEL per month) **Outpatient Tx voucher for MDR-TB CONTINUATION PHASE = 84 GEL ($37.15 USD) per month ($1.24 per day)**			

Source: NCTLD data [52]

Table 8. Georgian Government Voucher Contents for Costs Related to Inpatient Treatment for MDR-TB in Tbilisi

Item	Price per Unit
Direct costs (single-use medical instruments and food)	44 GEL
Medical personnel salary	27.50 GEL
Indirect costs	51.72 GEL
Total	**123.22 GEL ($54.50 USD)**

Source: NCTLD data [52]

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